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Individual Differences and Episodic Memory: Examining Behaviour, Genetics, and Brain Activity.

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Declaration

I declare that this thesis was composed by myself, and contains no material previously submitted for the award of any other degree. The work reported in this thesis has been conducted by myself, except where due acknowledgement is made.

Catherine MacLeod

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Abstract

Dual-process models propose that two processes support recognition memory; familiarity, a general sense that something has been previously encountered; and recollection, the retrieval of details concerning the context in which a previous encounter occurred. Event-related potential (ERP) studies of recognition memory have identified a set of old/new effects that are thought to reflect these processes: the 300-500ms bilateral-frontal effect, thought to reflect familiarity and the 500-800ms left-parietal effect, thought to reflect recollection. Whilst the exact functional role of these effects remains unclear, they are widely viewed as reliable indices of retrieval. The ERP literature reviewed in this thesis suggests that the characteristics of these recognition effects vary with task specific details and individual participant differences, suggesting that the recognition effects purported to index retrieval may be conditional on both task and participant. This thesis examined the influence of individual differences on behavioural measures of recognition and the neural correlates of recognition memory, focusing on factors of stimulus material, task performance and participant genotype.

Clear evidence of stimulus differences were found, with pictures eliciting more anteriorly distributed effects than words, and a late onsetting frontopolar old/new effect that was unique for voices. Furthermore, the pattern of ERP activity associated with successful recognition of faces appeared to vary as a function of general face recognition ability, with participants poorer at remembering faces exhibiting a 300-500ms old/new effect not present for those good at remembering faces. The data also suggested that activity over right-frontal electrodes, evident in some previous studies, may be participant specific and could reflect additional retrieval support processes.

Contrary to expectations, behavioural task performance was not found to significantly modulate the 'typical' recognition memory effects. However, a number of genetic polymorphisms were found to significantly influence both behavioural scores and the pattern of ERP activity associated with recognition memory. These results therefore suggest that inherent participant differences influence the neural correlates of recognition memory, in a way that variations in task performance do not.

Overall, the results from this thesis therefore suggest that the 'typical' bilateral-frontal and left-parietal effects thought to index retrieval are not universal. Furthermore the results suggest that the specific processes engaged during retrieval (as indexed by variations in ERP activity) may be dependent on specific task requirements, stimulus material and the genetic makeup of the individual.

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Chapter 1
Episodic Memory

Memory is a fundamental part of our everyday lives. The ability to remember is not only a reminder of who we are and what we have done, but provides us with a reference that shapes our future actions, thoughts and beliefs. Memory is described as constituting three main stages, encoding (the learning of new material), storage (the maintenance of this material for future reference), and retrieval (the recovery of material from storage). Successful memory relies not just on being able to retrieve information but being able to encode information when it is acquired, in a fashion that makes it suitable both for storage and accessible for retrieval. Memory does not serve a single function and can be divided into several different 'types', each having its own distinct characteristics. This chapter will begin with a brief discussion of these different 'types' of memory, describing current thinking on how memory is organised, and characterising the systems and sub-systems that constitute 'memory'.

Whilst each 'type' of memory is important, episodic memory is perhaps most involved in shaping us as individuals. Our different experiences, and the ability to remember these experiences, are a large part of what distinguishes each of us from everybody else. In addition, being able to recognise our friends and family, what we do and don't enjoy, and even where we left our keys the night before, are all fundamental to our functioning in society. It is for these reasons that this thesis focuses on episodic memory.

Consequently, the present chapter will introduce episodic memory in detail, discussing the methods used to investigate this type of memory, before focusing on one particular test of episodic memory – recognition memory. An overview of current theories relating

to the processes involved in recognition memory will be given, with particular emphasis on the anatomical basis of these processes.

1.1 Organisation of memory

Memory can be divided into a series of memory systems and sub-systems that, whilst often considered separately, overlap (Figure 1.1). The division of memory in this way is clearly a vast oversimplification of the processes that are occurring when we remember. However, for the purposes of this thesis the separation of memory, as outlined in Figure 1.1, provides an indication of the type of information and memory process being considered. The first main division comes from multi-store models of memory, such as the Atkinson-Shiffrin model (as cited in Groome, 2004), in which memory is divided into long-term memory (LTM) and short-term memory (STM). LTM refers to information that has been previously experienced and has been stored at an unconscious level to be retrieved at a later stage, whereas STM relates to information recently received that is being consciously attended to.

Evidence to support the existence of separate LTM and STM comes from brain-injured patients who appear to have impairment of one system whilst the other seems to be intact. The fact that the disorder can occur either way round (with STM impaired and LTM spared, or LTM impaired and STM spared) is a double dissociation and provides strong support for the existence of two separate systems (for examples see Scoville & Milner, 1957; Wickelgren, 1968; Warrington & Shallice, 1969).

Within the LTM fraction a further dissociation separates conscious from unconscious memories. Conscious memories are often termed explicit or declarative memories, and refer to intentional memories where specific information is recollected. Unconscious memories, also known as implicit (or procedural/perceptual memories) refer to the

unintentional retrieval of information such as that necessary to perform a task (procedural memory), or improved perception of a word or object due to prior exposure (perceptual memory). Evidence for the existence of unconscious memories comes from tasks such as word-stem completion where participants are primed with a list of words before being asked to complete a series of word fragments (only some of which can be completed with the previously presented words). Findings suggest that participants are more able to complete fragmented words when they relate to the previously presented list, even for words that participants fail to recognise as having been previously presented (Groome, 2004).

Implicit and explicit memories are also influenced differently by factors such as divided attention and retention interval. Divided attention affects the retention of explicit but not implicit memory (Parkin, Reid, & Russo, 1990). Similarly, explicit memory appears to be more sensitive to retention interval than implicit memory, with participant's ability to complete recognition tasks more degraded over time than their ability to complete word fragment tasks (Tulving, Schacter & Stark, 1982). Amnesiac patients provide further evidence to support the existence of separate systems with some patients exhibiting impaired explicit memory and intact implicit memory. This is demonstrated through patient's gradual improvement on tasks such as mirror drawing, despite having no memory of having ever completed the task (Milner, 1962, cited in Squire, 2009).

Explicit memories can be further divided into semantic memories (memory for general facts) and episodic memories (memory for specific experiences or events). For example, neuroimaging data supports the existence of different sub-systems of explicit memory by showing different areas of brain activation for the retrieval of different types of information. Using positron emission tomography (PET) Wiggs, Weisberg and Martin

(1999) found that retrieval of semantic information activated bilateral regions of the temporal and frontal lobes, compared to retrieval of episodic information which activated the medial parietal cortex, retrosplenial cortex, thalamus and cerebellum. The findings from these studies clearly suggest that there is not just one type of explicit memory; also that the neural systems involved differ depending on the type of information being remembered and intended future use of the information.

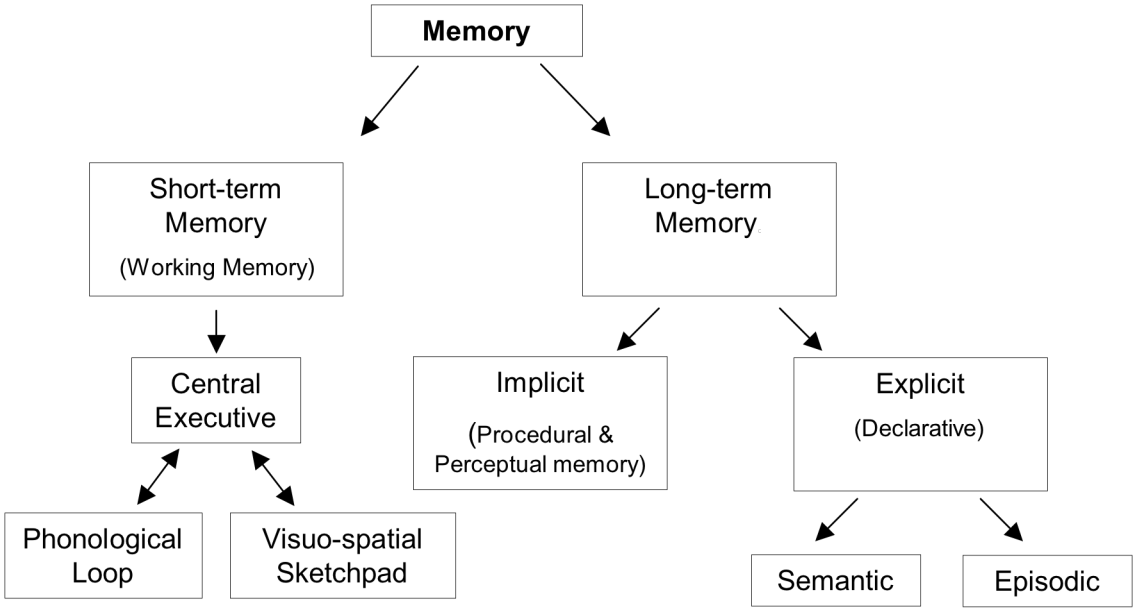


Figure 1.1 Schematic illustration of memory systems.

1.2 Episodic memory

As described above, episodic memory is considered to support memory for experiences and events. Henke (2010) suggests that a key feature of episodic memory is that the components of episodic memories are separable and consequently flexible. That is, episodic memories can be represented as whole events, or via the individual elements that constitute an event (which are stored independently). The independent storage of these individual components allows for flexibility in the way episodic memories are retrieved, with different retrieval cues triggering reactivation of different elements of the memory, allowing retrieval of a particular episode to occur in a variety of situations.

Memory of an evening out could, for example, be retrieved in terms of the restaurant visited, which people were there, the food eaten; retrieval of one of these components may trigger the retrieval of the others. Furthermore, these different components of memory allow selective retrieval, whereby the whole event does not need to be retrieved. Retrieving details of what was eaten may be important if one subsequently feels unwell, but who else was present and the name of the restaurant may not be important in this situation. However, if one is trying to determine whether that particular restaurant is the cause of the sickness, remembering who else was there and the name of the restaurant may be beneficial and all three elements may be retrieved. As this example hopefully makes clear, episodic memories are not simply a straight record of experiences and events, but are a series of individual elements relating to an episode that can be retrieved independently or simultaneously, in a variety of situations.

1.2.1 Studying episodic memory

To investigate episodic memory, experiments typically employ a study-test paradigm in which participants are presented with a series of 'to be remembered' stimuli, which they are later tested on. Investigations into episodic memory tend to look at the encoding and retrieval stages of memory, to try and understand memory processes, with the storage stage being more difficult to monitor. Methods of investigating encoding typically involve manipulation of the type of information being encoded, the conditions under which the information is encoded, and the strategies used by participants during this stage. Whilst holding retrieval conditions constant, comparisons of retrieval success across the different encoding manipulations enable encoding processes to be investigated. Whilst encoding is clearly an important memory stage the focus of the current thesis is on retrieval.

Retrieval is generally investigated using either tests of recall or recognition. Recall tasks involve participants reproducing material previously presented to them and may either involve free recall, where participants are not provided with any information to guide their response; or cued recall, where information that might prompt a response is presented, such as the first word of a pair. By contrast, tests of recognition involve presenting participants with material and asking them to indicate if they have been presented with this information previously, typically using a two choice yes/no judgement. Both types of retrieval test can be presented immediately after the studied information has been presented (immediate recall/recognition) or after a period of time has elapsed (delayed recall/recognition). For a detailed review of encoding and retrieval manipulations used in episodic memory experiments see Yonelinas (2002).

1.3 Recognition memory

Recognition memory tasks assess participants' ability to determine if a stimulus (such as an object, person, or place) has been previously encountered. Participants are presented with a mixture of previously studied (old) items and similar lure (new) items that haven't previously been presented, and asked to distinguish between them. There are two main competing accounts as to how recognition memory works, which are broadly classified as single process and dual process theories. Within each of these frameworks there are many alternative theories (e.g., differences in the way that the processes are characterised, or how they are related). A complete characterisation of the different theories is beyond the scope of this thesis, however the next section will briefly consider three differing accounts of recognition memory, which highlight current debate regarding the mechanisms involved in recognition memory.

1.3.1 Theoretical accounts of recognition memory

1.3.1.1 Dual process theories:

In general, dual process theory suggests that recognition memory involves two separate memory processes, or types of memory[1]: familiarity and recollection. Familiarity is considered to be a general sense that an item has previously been encountered and involves the assessment of the similarities between an item and information stored in memory about previous items. Recollection involves the recovery of details about a previous encounter with an item, such as contextual information about the event in which the item was previously encountered, or additional information relating to the item. The distinction between these two processes is perhaps best illustrated by the common experience of seeing a person and finding them familiar but not being able to recollect whom the person is or where they are from (Mandler, 1980).

The summary of dual process theory described above does not represent one dual process theory but it accurately describes the essence of dual process theory. Each individual dual process theory suggests a contribution of both recollection and familiarity to recognition memory, however they differ in the details of how these processes interact and operate. For example, the Atkinson and Juola (1974 cited in Yonelinas, 2002) model suggests that familiarity is the primary process engaged during recognition, in which items exceeding a set memory strength criterion are considered 'old' and those below a set lower criterion 'new'. The Atkinson and Juola model

[1] As evident from the title, 'dual-process theory' defines familiarity and recollection as processes, however this characterisation is perhaps misleading, suggesting that familiarity and recollection are 'individual' isolated processes, rather than distinct 'memory processes'. As memory processes familiarity and recollection are comprised of a number of processes related to other cognitive functions such as attention and perception, and are perhaps best thought of as different types of memory. It is therefore important to note that discussion of familiarity and recollection as processes in this thesis refers specifically to them as 'memory processes' rather than being singular isolated processes that do not incorporate other cognitive functions.

suggest that recollection is only engaged when the elicited activation of an item is between these two criteria, and additional information is required to make a memory decision. In contrast, the Mandler (1980) model suggests that familiarity and recollection are independent processes acting in parallel, with either process potentially leading to a recognition decision.

The Jacoby and Dallas (1981) model also suggests that familiarity and recollection are independent processes that operate in parallel. In this case however, familiarity is described as an automatic process based on the assessment of perceptual fluency of an item, whereas recollection is considered a more controlled process. Similarly, the Yonelinas (1994) model again supports the idea of two independent processes, but adds an additional mechanistic distinction. Whilst familiarity is based on the assessment of continuous memory strength, in which all items have some degree of familiarity and those recently encountered will be more familiar than those not studied, recollection is suggested to be a thresholded process. In contrast to familiarity, not all items elicit a degree of recollection; that is recollection involves the retrieval of qualitative information about an item or event and in some instances the amount of retrieved qualitative information is not sufficient to discriminate previously studied items or events from those not encountered previously.

In general, therefore, dual process theories suggest that two processes (recollection and familiarity) contribute to recognition memory and that these processes support recognition independently. Furthermore familiarity is generally considered to be a faster process than recollection and is thought to reflect memory strength, whereas recollection is a slower more controlled process involved in the recovery of additional

information about the item or event (for a more detailed review of dual process models see Yonelinas, 2002).

1.3.1.2 Single process theories:

In comparison to dual process theories, single process theories suggest that recognition memory is supported by a single assessment of memory strength, which varies along a continuum resulting in different phenomenological experiences. The simplest form of single process models characterises memory in terms of signal detection theory (Banks, 1970; Wixted, 2007). In this view, recognition decisions are based on an assessment of the memory strength evoked by a stimulus in relation to a set decision criterion. Items evoking a strong signal are classified as 'old' and items with a weak signal are classified as 'new'. Memory errors occur when an unstudied item induces a strong memory signal (false alarms) and when previously studied items evoke a weak signal (misses). Changes in decision criterion (the level of memory strength required to make an 'old' decision) will alter the distribution of responses, with a more conservative criterion (a greater degree of memory strength required to respond 'old') increasing the number of miss items and reducing the number of false alarms; whereas a more liberal criterion (lower memory strength) will have the opposite effect, with greater false alarms and fewer misses.

A second form of single process model can be characterised as a blend between dual-process and 'purer' single process theories. According to Wixted (2007) familiarity and recollection both exist, but an additive combination of the two produces a single memory strength variable that forms the basis for recognition memory decisions. This model assumes (in contrast to Yonelinas) that recollection is a continuous process in which information can be recollected to differing degrees. If both familiarity and

recollection are continuous processes the additive combination of these two continuous signals may lead to a single memory strength signal on which recognition decisions are based. If the two processes can be combined into a single strength signal, then some of the evidence that supports a dual process model over a single process (such as explaining patterns of Receiver Operating Characteristic curves, Yonelinas 1994) could also support a single process model, indicating that familiarity and recollection are not necessarily independent processes (Wixted, 2007).

1.3.1.3 Theoretical account summary:

In summary, whilst it is generally accepted that recognition memory can involve both experiences of familiarity and recollection, there is currently a firm division in the literature as to whether recognition is supported by a single process (e.g., as described by Banks, 1970 & Wixted, 2007), by separate familiarity and recollection processes (as indicated by dual process models (e.g., Yonelinas, Aly, Wang & Koen, 2010), or if two processes exist and are combined to support recognition (as suggested by the memory strength single process models, e.g., Wixted, 2007). Given the extent of research investigating recognition memory it is clear that the differences of opinion in the field are unlikely to be easily resolved. Whilst it is important to place the current thesis in this context, the dual process view is dominant within episodic memory research. Consistent with this, the work presented in this thesis is based on a dual-process perspective and the next sections will therefore consider methods of measuring the two recognition processes, as well as the anatomical basis of recognition memory.

1.3.2 Measuring recollection and familiarity

The basic old/new recognition memory paradigm, described in section 1.2.1 does not allow the contribution of recollection and/or familiarity to a successful recognition

decision to be directly assessed[2]. Thus to evaluate the relative contributions of the two processes to recognition memory, a number of paradigms have been designed that either aim to isolate one of the two processes (task dissociation methods), or allow estimates of the contribution of the different processes to be made (process estimation methods).

An example of a task dissociation method is the comparison of item and source recognition. In a typical source recognition task, participants are shown a series of study words presented in different locations on the screen. At test, participants are initially presented with a word and asked to indicate if the word is 'old' or 'new'. 'Old' responses are followed by a second question asking participants to indicate the location of the word presentation. Dual process theory suggests that only recollection involves the retrieval of contextual information about a previous encounter with an item/event. Source recognition paradigms that ask participants to report this additional information are therefore able to assess recollection by comparing trials in which participants were successfully able to recall or identify the additional information, with those that weren't.

Whilst task dissociation methods such as the comparison of item recognition with and without correct retrieval of source information are widely used in the literature to separate the two processes, particularly in combination with imaging methods such as event-related potentials (ERPs; see Chapter 2), one criticism of such methods is that the process estimates are imprecise. In particular, incorrect source judgements do not necessarily indicate a decision based solely on familiarity because participants may recollect other information related to the previous encounter, information not asked for during test. Furthermore, it may be wrongly inferred that a decision was made on the basis of recollection because source memory was correctly identified, when the decision

[2] Dobbins et al (2000) have suggested that false alarm responses (in which 'new' items are incorrectly classified as 'old') provide some insight into familiarity, although Gallo (2004) suggests that false alarm responses can also occur as a result of recollection.

was actually based on associative familiarity, in which an assessment of how familiar the item feels with each source directs the source judgement decision. Pairing each item with a unique second item that participants are asked to recall following identification of the first item as 'old', can reduce the contribution of associative familiarity, with successful recall of the second item from the pairing suggesting recollection based retrieval. Whilst the paired-associate memory paradigm negates the issue of associative familiarity, the first problem remains: that of underestimating the contribution of recollection due to unmeasured retrieval of details other than the associated secondary item.

A modification of the item/source recognition comparison is the process dissociation paradigm (Jacoby, 1991). The process dissociation procedure involves the completion of two recognition memory tasks under slightly different conditions. For example, if words are presented on either the left of the screen or on the right, participants may be asked in one condition to indicate all previously studied words as 'old' (inclusion condition), whereas in a second condition participants may be asked to only report words presented on the left side of the screen as 'old' (exclusion condition). The assumption in the process dissociation procedure is that recognition responses in the inclusion condition can be based on either familiarity or recollection. By contrast, in the exclusion condition participants need to engage recollection to successfully complete the task, as all previously seen words will elicit the same feeling of familiarity. As for the item/source paradigm discussed above however, the process dissociation paradigm can also be criticised for characterising recollection engagement as the ability to retrieve a specific type of information. Items in the exclusion task may still evoke recollection even when participants incorrectly categorise the item as 'new' because they are recognised on the basis of different contextual information.

Another method used to gain estimates of recollection and familiarity is the 'Remember/Know' (R/K) procedure, initially proposed by Tulving (1985). The R/K procedure asks a participant to make a subjective judgement about a memory decision they have made, in which they indicate if they actually 'remember' a previous encounter with an item, or if they simply 'know' that it had previously occurred. Tulving suggests that the 'remember' responses provide an estimate of the engagement of recollection. One benefit of using subjective judgements is that recollection responses are not restricted to retrieval of specific information, as is the case for the previous two methods. The R/K procedure does, however, have an alternative problem: difficulty isolating the contribution of familiarity.

Whilst 'remember' responses in the R/K paradigm are thought to reflect recollection, the use of 'know' responses to infer familiarity (Gardiner, 1988) has been criticised because of the forced choice nature of the task. In practice, participants are limited to only two responses, either that the item is recollected or that it is not (as opposed to the item being familiar), resulting in a marked under-estimation of the contribution of familiarity. Yonelinas and Jacoby (1995) suggest that R/K data be rescaled to account for items that are both recollected and familiar, and will consequently have received a 'remember' response. They propose that the proportion of 'know' responses be divided by the opportunity to make a 'know' response (1-R), to correct the estimations of the proportion of familiar items. This calculation: $F=K/(1-R)$, is known as the Independence Remember/Know procedure (IRK procedure).

Another problem with the forced choice nature of the task is that when participants are unsure if they have seen the item before they may have guessed whether the item was 'old' or 'new'. Such guess responses would necessarily influence R/K process

estimates, particularly in terms of the 'know' responses often interpreted as reflecting familiarity. A third response option, a 'guess' response, can also be included in the R/K procedure (Gardiner, Ramponi & Richardson-Klavehn, 1998) to filter out trials in which participants were guessing.

An alternative method used to gain accurate estimates of familiarity is the modified R/K procedure (Montaldi, Spence, Roberts & Mayes, 2006). A criticism of the original R/K procedure is that participants are trained to indicate if they recognise stimuli because they recollect information, or if the stimuli are familiar but no information is recollected. That is, the emphasis is on recollection and participants will respond 'know' on the basis of unsuccessful recall, rather than on the basis of the item feeling familiar. The modified R/K runs familiarity and recollection conditions separately in two different procedures. In the familiarity only procedure, participants are instructed to focus on familiarity judgements and to report recollection if it occurs, but they are instructed not to actively try to recollect. In the recollection only procedure, participants are instructed to actively try to recollect and indicate if they successfully recollect information and 'recall-to-accept' – report that the item has been previously encountered on the basis of recollected information, or recollected and 'recall-to-reject' – information was recalled and was judged not to have been previously studied (Mayes, Montaldi & Migo, 2007). More accurate estimates of familiarity and recollection can be obtained by emphasising the different processes in the two procedures, allowing a more accurate examination of neural activity associated with each process. However, because the two processes are measured separately, the modified R/K procedure does not allow estimates of how the two processes contribute to performance on a single task, the basis of a single memory decision, or how the processes interact.

Another criticism of the R/K procedure is that, in practice, participants use the response options as a confidence indicator, with 'remember' responses reflecting high confidence decisions, and 'know' responses as low confidence decisions (Yonelinas, 2002). For example, Wixted (2010) suggests that R/K judgements may not be dissociating recollection and familiarity but reflect differing degrees of memory strength, with participants setting separate response criteria for R and K responses.

The final process estimation method considered here is the use of confidence judgments. In a confidence task participants are asked to rate how confident they are in each recognition decision (e.g., using a 5-point rating scale). It is assumed that memory responses based on recollection will be accompanied by a higher confidence rating compared to familiarity based decisions. Confidence judgements can be used in conjunction with hit and false alarm rates to generate Receiver Operating Characteristic (ROC) curves that can, in turn, be used to estimate the contributions of recollection and familiarity to recognition memory (for a discussion of the use of confidence judgements to plot ROC curves see Yonelinas & Parks, 2007). Whilst ROC curves can be used to gain estimates of familiarity and recollection, the results are not straightforward with the outcome dependent on the confidence scale used and the assumptions of the model used to extract estimates (see Wixted, 2007 for examples). That is, the theoretical interpretation of the same ROC data can differ depending on the model used.

In sum, there are several different methods that can be employed to try and separate the contributions of familiarity and recollection to recognition memory. Each method has its own benefits and flaws; even with the many available methods it remains difficult to obtain definite estimates of the two processes. In many respects the complexity of the human mind and memory systems mean that obtaining process purity (i.e., successfully

isolating one of these processes) is very unlikely. Tulving (2002) emphasises the importance of understanding that episodic memory is a hypothetical memory system and that whilst tasks may be designed with the intention of investigating a particular system they will engage other systems in the process of task completion. That is, Tulving highlights that episodic memory is not just one type of retrieved information or one type of experience, but a combination of components from more than one system. In this regard, it is not possible to completely isolate one process from another as they are inherently intertwined by the contributions made by other systems when they are engaged. However, whilst it may not be possible to completely isolate familiarity and recollection, the methods described above each provide valuable estimates of the two processes that can be used to aid our understanding of episodic memory.

1.3.3 Anatomical basis of episodic memory

The preceding sections highlight the key position that dual process theories play in accounting for episodic memory, a perspective that has been developed within the cognitive behavioural literature. In a recent seminal review Yonelinas (2002) extensively reviews evidence for dual process theories, of which a substantial amount comes from patient data, neuroimaging studies, and animal brain lesion studies. These different types of data all support the theory of two independent recognition memory processes by demonstrating anatomical differences between them. This section briefly reviews the anatomical basis of episodic memory with a particular focus on the role of the medial temporal lobe (MTL) in recognition memory, highlighting evidence to indicate that recollection and familiarity are independent processes that are anatomically dissociable.

The MTLs were initially highlighted as being important for episodic memory by the case of patient HM, who suffered anterograde amnesia following surgery to remove large sections of MTL regions. The surgery involved the bilateral removal of most of the hippocampus, uncus and amygdala, and the resulting amnesia in HM (and in other similar patients) led Scoville and Milner (1957) to surmise that the hippocampal complex was important for normal memory functioning. More recent animal lesion work has suggested that it is not only the hippocampus that is important for memory, in particular the perirhinal cortex is considered critical. Brown and Aggleton (2001) review a series of animal lesion, immediate early gene and neuronal recording studies that use rats and monkeys, concluding that the hippocampus plays an important role in memories involving associative or spatial information, and the perirhinal cortex is important for object based information. In terms of the processes supporting performance on recognition memory tests, these results suggest that the hippocampus is important for recollection and the perirhinal cortex for familiarity.

Neuroimaging studies of healthy human participants have also found dissociable patterns of neural activity associated with recollection and familiarity. In an early study, for example, Henson, Rugg, Shallice, Josephs and Dolan (1999) measured haemodynamic response using functional magnetic resonance imaging (fMRI) whilst participants completed a word recognition task in which they had to indicate if they 'remember' the word, 'know' the word, or if the word was 'new'. In comparison to K judgments, R judgements showed greater responses in the anterior left prefrontal, left parietal and posterior cingulated brain regions at retrieval. As discussed in section 1.3.2 'remember' responses are thought to reflect recollection engagement and 'know' responses recognition without recollection. The study by Henson and colleagues indicates that recognition with and without recollection are reflected by different brain

activation patterns. In a similar R/K experiment, Eldridge, Knowlton, Furmanski, Bookheimer and Engel (2000) also report different patterns of fMRI activity across remember and know judgements, with R judgements showing greater MR signal in the left hippocampal region than K judgments. The studies by Henson et al. (1999) and Eldrige et al. (2000) provide two examples from the large amount of fMRI research that suggests different patterns of activity for successful recognition memory with and without recollection, substantiating the theory that recognition memory is supported by more than one independent process[3].

Further supporting evidence of hippocampal involvement in episodic memory comes from neuropsychological evidence, such as the patient study presented by Vargha-Khadem et al. (1997). Vargha-Khadem and colleagues discuss three brain injured patients who all suffered very early onset bilateral hippocampal pathology and episodic memory amnesia. In addition, on tests of recognition memory the patient group were found to perform significantly poorer on voice-face and object-place associative recognition compared to controls. No group differences were found for one-trial recognition for lists of words, non-words, familiar faces, unfamiliar faces, word pairs, non-word pairs, familiar face pairs, unfamiliar face pairs; nor multi-trial associative recognition of non-word pairs or face pairs. The presence of impairment on the voice-face and object-place tasks and not on the other associative tasks suggest that hippocampal damage does not simply impair all types of associative recognition, but results in a more specific impairment of cross-domain associative recognition. A similar case is also presented by Mayes et al. (2004) who found impaired associative recognition for different types of information (i.e. face-voice), but not for associations

[3] In addition to fMRI studies, a large number of ERP studies provide evidence to support dual-process theory and will be discussed in Chapter 2.

of the same type of information (i.e. face-face), in a patient with selective hippocampal damage.

The results from both Vargha-Khadem et al. (1997) and Mayes et al. (2004) suggest that not all associative memory is driven by the hippocampus, but that hippocampal engagement is only necessary when the types of information to be remembered differ (e.g., in modality). The neuroanatomical evidence has also inspired a number of more detailed theories that attempt to account for the different patterns of findings across MTL regions. For example, one influential suggestion by Mayes, Montaldi and Migo (2007) is the domain dichotomy framework, a functional/anatomical account of difference in associative retrieval. It is theorised that within-domain items share characteristics that make them more likely to activate the same sets of neurons (or neurons within a close proximity) in the perirhinal cortex, compared to between-domain associations. Between-domain associative items have less overlapping characteristics and therefore will be represented by more distal regions. Mayes and colleagues suggest that representations will occur in the perirhinal cortex for within-domain items in much the same way that the individual features of a single item converge - binding together common features. In contrast, each item in a between-domain association is represented separately during binding, a process thought to involve the hippocampus. The differences in the way features and associations are bound lend themselves to different engagement of recognition processes, with common feature binding more applicable to familiarity and separate representations of an item to recollection (although for behavioural evidence against this view see Harlow, MacKenzie & Donaldson, 2010).

Whilst there are many studies suggesting that recollection and familiarity engage different anatomical regions, as in the behavioural literature not all researchers accept

the dual process view of episodic memory. For example, a recent article by Wixted and Squire (2011) suggests that fMRI studies typically confound the two processes with differences in memory strength. A number of studies are reported (such as Wais, Squire & Wixted, 2010), suggesting that when memory strength is controlled, recollection and familiarity are both supported by the hippocampus, which encodes multi-attribute stimuli (although see Diana & Ranganath, 2011; and Montaldi & Mayes, 2011, for strong arguments against this view).

Nonetheless, even those arguing for a single hippocampal account of episodic memory appear to accept that distinctions must be drawn between recollection and familiarity, either at a purely phenomenological level, or via the involvement of additional cortical regions. For example, neuropsychological evidence suggests that in addition to the MTLs, the frontal cortex is involved in episodic memory with patients suffering frontal lobe damage exhibiting episodic memory deficits in tasks of recall and recognition (for a review see Wheeler, Struss & Tulving, 1995). The frontal lobes are thought to be involved in episodic memory by the mediation of MTL processes through executive functions such as working memory, planning and strategy use. Whilst discussion of the role of the frontal lobes in episodic memory is beyond the scope of the current review, the frontal lobe literature has been extensively reviewed elsewhere (Fletcher & Henson, 2001).

1.4 Summary

Memory is a complex system made up of multiple interacting components. The current thesis focuses on episodic memory, a subcomponent of declarative and long-term memory, often studied using tests of recognition. There are many theories as to the mechanisms involved in recognition memory but the main competing theories can

generally be divided into two groups: dual-process models in which recognition memory is supported by two independent processes, recollection and familiarity; and single-process models in which recognition is thought to be based on one process, such as a variable memory strength signal, with different phenomenological experiences resulting from where along the continuum the memory signal falls.

Several different paradigms have been employed to investigate recognition memory processes, including comparisons of item and associative/source memory, inclusion/exclusion tasks, R/K/G tasks, and confidence judgments. Each method has its strengths and weaknesses and there does not currently appear to be a single ideal method with which to accurately estimate the contribution of recollection and familiarity to recognition, nor to entirely isolate either process. The final section of this chapter briefly discussed evidence to indicate anatomical dissociations between recollection and familiarity, particularly in the MTL. Current research suggests the hippocampus supports recollection, particularly for between-domain associations, and the perirhinal cortex supports familiarity, particularly for item and within-domain associations. Even within the neuropsychological literature however the picture is not straightforward with many other regions of the brain playing a role. For example, the frontal lobes have been strongly implicated in episodic memory and are thought to mediate MTL processes through executive functions.

Whilst the current chapter only provides a very brief overview of memory and recognition, the aim is to have provided the necessary background information to place this thesis in context. The principles on which the current work is based are taken from dual process theory and the importance of MTL structures in episodic memory. The next couple of chapters will discuss in greater detail the background to the current

thesis, looking at the different processes involved in successful recognition memory retrieval, presenting evidence from ERP studies of dissociable recognition processes (Chapter 2). This will be followed by a discussion of how individual differences influence memory performance and the associated neural activity (Chapter 3). An outline of the full thesis aims will be presented at the end of Chapter 3.

Chapter 2
ERPs and Recognition Memory

The previous chapter introduced episodic memory, outlining current thinking concerning the conceptualisation, organisation, and understanding of memory, with particular attention paid to dual-process theory and recognition memory. The current chapter expands on this introduction, discussing ERP evidence of dissociable cognitive operations involved at the retrieval stage of memory, looking at the processes engaged during retrieval attempt, retrieval success and post-retrieval monitoring. Whilst descriptions of the technical procedures involved in recording, processing and analysing ERPs will be given in the General Methods (Chapter 4), the current chapter will start with a basic introduction to the underlying theory of ERPs and how they compare to other neuroimaging methods, before discussing the sorts of inferences that can be made from ERPs and the use of ERPs to investigate recognition memory.

2.1 Event-related potentials

An ERP is the electrophysiological activity produced by the brain, in relation to a particular event or stimulus. In order to measure the electrophysiological activity from the brain, voltage changes between an active electrode and the ground electrode are recorded and changes in this voltage are plotted over time (the electroencephalography recording - EEG). The electrical activity relating to a specific event, such as a stimulus presentation, is embedded in the EEG and is extracted by dividing the EEG into epochs, time-locked to the event of interest and averaging together many trials of this event to remove background noise. Noise relating to individual participant variation is then minimised by creating grand-averages in which ERPs from each participant are

averaged together, enabling activity related to the event of interest that is present across participants, to be examined.

In comparison to other experimental measures, such as behavioural measures and other types of neuroimaging, ERPs are a particularly useful tool for investigating cognitive operations because they provide a continuous measure of processing from the point at which a target or stimulus is presented, through until the participant makes a response, or further if post-response activity is of interest. ERPs can also be used to look at activity relating to the processing of stimuli where no behavioural response is required. Whilst this later point may also be true for other types of neuroimaging, such as haemodynamic measures (i.e. PET or fMRI); the key advantage of ERPs is the instantaneous and continuous nature of the signal, providing ERPs with an excellent temporal resolution of around a millisecond (ms). Due to the slow nature of the haemodynamic response other neuroimaging tools such as PET and fMRI cannot match the temporal resolution of ERPs, with such haemodynamic measures having a temporal resolution of several seconds. Conversely, the spatial resolution of ERPs is comparatively poor, with haemodynamic measures having a spatial resolution of around a millimetre. As will become clear in the next section, there are many different neuronal configurations that could give rise to the ERP patterns exhibited, making it very difficult to localise the source of the ERP generator, resulting in poor spatial resolution. Therefore, whilst ERPs allow accurate temporal characteristics of task processes to be observed, the spatial characteristics observed from ERPs are less valuable in terms of understanding the underlying cognition associated with a particular event.

Voltages recorded at the scalp are mostly postsynaptic potentials (as opposed to action potentials), which are caused by the release of neurotransmitters by the presynaptic

neuron that bind to the receptors on the postsynaptic terminal. The binding of these neurotransmitters causes the opening/closing of ion channels in the postsynaptic neuron, resulting in ions entering/exiting from the cell, which in turn changes the potential across the cell membrane. The negativity/positivity at the dendrites and the counterpart positivity/negativity at the cell body form a small dipole, generating the signal recorded by the electrodes. However, the signal generated by the dipole of a single neuron is not detectable by scalp electrodes and it is the capacity for postsynaptic potentials to summate which allows these voltage changes to be recorded at the scalp. Postsynaptic potential summation can occur when a cell receives two or more inputs in close proximity, whether this is spatial proximity from two closely positioned synapses, or temporal proximity where two inputs occur in quick succession. Importantly, these inputs need to be synchronous (i.e. either all excitatory or all inhibitory potentials) if they are to summate, asynchronously activated neurons (i.e. if the cell receives both an excitatory and an inhibitory potential) will simply cancel each other out, resulting in no voltage being recorded (Luck, 2005).

As discussed above, in order for the signal to be detectable at the scalp thousands of synchronously active neurons are required, in addition to which the neurons need to have a similar orientation with the dipoles spatially aligned. Furthermore, as described for input synchronicity, neurons which are randomly oriented in relation to each other may cancel out since the positivity at the dendrites of one neuron may be next to the negativity of the cell body of another neuron, resulting in no voltage being recorded as the net dipole moment of the neurons is equal to zero, known as a ‘closed field’ (Kutus & Dale, 1997). Therefore for scalp electrodes to be able to successfully record postsynaptic potentials thousands of neurons need to be active with similar synaptic

inputs and similar orientations in order for these potentials to summate and produce a voltage strong enough to be detected at the scalp.

With these conditions in mind it is important to recognise that the recordings taken from scalp electrodes are also dependent on how the dipole generating the signal is positioned and orientated. A key consideration that follows is that in terms of investigating cognitive processes, a lack of visible ERP differences between conditions does not necessarily reflect an absence of differences in how the brain is processing the conditions, but could instead be that any processing differences are being generated by a population of neurons in a closed field and are therefore not detected by scalp electrodes. Furthermore, the numerous different dipole configurations, coupled with the differing shape and levels of resistance of each element of the head, such as differences in skull thickness, make it impossible to say which population of neurons are responsible for the voltage distribution evident at the scalp. That is, ERPs that are being generated by one part of the brain may appear as increased voltages at electrodes placed at completely different locations, making it difficult to interpret ERP results with respect to the underlying structure of the brain and how cognitive functions may map on to this.

As well as providing a useful tool to investigate the neural basis of cognitive processes, there has been increasing interest in the use of ERPs as biomarkers to predict and monitor disease progression and treatment effectiveness. In the last decade a number of studies have proposed the use of ERPs as biomarkers for a range of diseases, including mild cognitive impairment (Olichney et al., 2002), Alzheimer's disease (Olichney et al., 2006), psychosis (Bramon et al., 2008), and Schizophrenia (Luck et al., 2011); reporting abnormal presentation of an ERP component, such as the absence or reduction in the

magnitude of an expected effect, as indicators of impairment in neural functioning. By measuring the electrical signal produced during neurotransmission, ERPs may provide a more direct measure of changes in the underlying biology than is evident from clinical symptoms and compared to other neuroimaging methods is relatively cheap. Whilst ERPs have the potential to be effective biomarkers a recent article by Luck et al. (2011) highlight four key issues that need to be addressed before ERPs can be validated and widely used as disease biomarkers; 1) specific ERP components need to be identified that can be linked to transmitter-receptor systems; 2) individual differences need to be reliably measured and components predictive of behaviours and possible treatment response; 3) animal homologues to the ERP components should be identified to facilitate drug development; 4) standards to assess the quality of data collected for clinical purposes should be developed. Although the focus of Luck's article is on the use of ERP biomarkers for Schizophrenia, the same points are applicable for their use in relation to other diseases.

2.2 ERP investigations of recognition memory

ERPs can provide information about cognitive processes that cannot be gained from behavioural measures or haemodynamic imaging and have readily been used to investigate episodic memory. As discussed in Chapter 1, episodic memory can be broken down into many constituent parts and whilst there is a wealth of research looking at the encoding of episodic memories, the focus of this thesis and consequently this chapter, is episodic memory retrieval. With this in mind the aim of this section is to provide a review of the key ERP components of retrieval, looking at pre-retrieval processes, retrieval success and post-retrieval processes.

2.2.1 Pre-retrieval processes

The first step in memory retrieval is the initiation of a retrieval attempt. In order to successfully retrieve an episodic memory there must be an interaction between the retrieval cue (whether an internally generated prompt or an external environmental prompt) and previously encoded memory representations. The degree to which the retrieval cue reactivates the processes engaged at the time of encoding is thought to influence the level of retrieval success (Tulving, 1983). The likelihood of attaining such a successful interaction is thought to vary in relation to three key processes. Firstly, the cognitive state in which these retrieval cues are approached - known as the *retrieval mode*; *retrieval orientation* - the ability to adjust the type of cue processing to match the retrieval goal; and finally the engagement of processing resources when making a retrieval attempt, or *retrieval effort* (Rugg & Wilding, 2000).

2.2.1.1 Retrieval mode:

Retrieval mode is a cognitive state entered into when trying to retrieve episodic memory that ensures retrieval cues are processed as memory probes (Tulving 1983). Studies investigating the neural activity associated with different retrieval modes compare neural activity when participants are completing one type of memory task, i.e. a semantic task, with the activity during another, i.e. an episodic task. Düzel et al. (1999 & 2001) conducted an experiment in which participants were given a series of study-test blocks with some test blocks requiring them to make old/new judgments (the episodic memory task), and other blocks requiring them to make living/non-living judgements (the semantic memory task). Participants were cued at the start of each block as to which task was required for the forthcoming block. Analysis of the ERP data showed a sustained increase in positivity for the episodic task compared to the semantic task over

right-frontopolar electrodes, a difference maintained throughout the retrieval episode. This finding of increased activity over right-frontal scalp sites for the episodic task was supported by additional PET data showing increased blood flow in the right-frontal lobes during the episodic memory task, which was not present during the semantic task. The authors conclude that these differences in neural activity between the two tasks indicate retrieval mode, with the right-prefrontal region mediating a neurocognitive set for episodic memory retrieval, a finding supported by similar functional neuroimaging data reported by Lepage et al. (2000).

Additional supporting evidence for a right frontal correlate of episodic retrieval mode comes from studies looking at trial-by-trial cues, where the judgment prompt is given at the start of each trial, rather than at the beginning of a block. Both Morcom and Rugg (2002), and Herron and Wilding (2004) reported right-frontal positivities for episodic tasks compared to semantic tasks (onsetting at 500ms after cue presentation and sustained until the presentation of the test item in Morcom & Rugg, 2002; and onsetting at 800-1900ms after cue presentation in Herron & Wilding, 2004). However, Morcom and Rugg (2002) note that this difference between the two types of task is only evident on trials that follow one of the same cue type. To exclude the possibility that this delay in the onset of task differences was not caused by a preparatory time constraint at the start of the trial, Herron and Wilding (2006) increased the time between the cue presentation and the word from 2000ms to 4000ms. The results showed that task differences were still only apparent on secondary same cue trials despite the increase in delay, indicating that retrieval mode processes are only engaged following completion of at least one episodic retrieval trial.

In addition to the finding that some prior retrieval is needed to engage retrieval mode, Herron and Wilding (2006) show that for trials in which retrieval mode was successfully implemented, a partial increase in accuracy, limited to context judgments and reduced reaction times, was evident; supporting the hypothesis that the degree to which pre-retrieval processes are engaged influences resulting retrieval success. The restriction of accuracy improvement to trials with correct context judgments is consistent with the view of Morcom and Rugg (2002), who proposed that successful adoption of retrieval mode is only beneficial to recollection based trials. Importantly however, the authors note with caution that the occurrence of the +1 phenomena (that is the presence of differences in neural activity between tasks only on successive trials of the same type) suggests that the presence of retrieval mode is not necessary for successful retrieval and therefore cannot be a pre-requisite.

In sum, episodic retrieval mode has been associated with activity over right-frontal regions and is a process sustained throughout the retrieval period. Furthermore this difference in activity does not appear to be specific to a particular type of episodic memory task; however, it is only present when preceded by trials of the same type, suggesting that whilst beneficial it is not necessary for successful retrieval to take place.

2.2.1.2 Retrieval orientation:

The second pre-retrieval process is retrieval orientation, which establishes the specific type of processing applied to a retrieval cue, and is often investigated by contrasting neural activity associated with memory searches for different kinds of information from the same type of retrieval cue. Such experiments typically compare activity from ‘new’ items in the different conditions to reduce the risk of confounding results with retrieval success (Rugg & Wilding, 2000).

Ranganath and Paller (1999), compared specific and general retrieval in which participants had to differentiate between same, perceptually similar, and 'new' items. The specific task required participants to respond 'old' only to items that were the same as those presented during study, and in the general task to respond 'old' to any items presented in the study phase regardless of any modifications, i.e. to same and perceptually similar items. ERPs to both types of 'old' items and, of particular interest here, to 'new' items presented in the specific retrieval task were found to be more positive going than items presented in the general retrieval task; a difference greatest over left-frontal electrodes between 500-1200ms. Similar left-frontal activity was also found by Rugg, Allen and Birch (2000), with more positive going ERPs for 'new' words presented in a block of shallowly studied words than in a block containing deeply studied words, during a yes/no recognition test. These studies suggest that differential engagement of retrieval strategies are reflected by differences in activity over left-frontal electrodes.

Robb and Rugg (2002) found more widespread effects when manipulating retrieval orientation by varying the type of material presented at study (blocks of words or pictures) to see if the same type of retrieval cue (words) was processed differently depending on the type of information encoded. ERPs to 'new' words from the word encoded block showed more positive going activity than 'new' words from the picture encoded block between approximately 300-1800ms across midline electrodes at frontal, central and parietal locations. A similar finding is also reported by Herron and Rugg (2003), who mixed pictures and words together during study (in contrast to the blocked approached used by Robb & Rugg, 2002), and asked participants to respond 'old' to either words or to pictures at test, depending on which modality was specified as target stimuli. In addition to replicating the findings of Robb and Rugg (2000), the findings

from Herron and Rugg (2003) show that retrieval orientation effects are exhibited when both task-relevant and task-irrelevant items are encoded at the same time. Whilst it appears that a retrieval cue can be processed differently depending on the type of information being retrieved and that this difference is reflected in the ERPs, early studies have been criticised (Rugg & Wilding, 2000) for comparing conditions that vary in task difficulty, which means the contributions of retrieval effort[4] and retrieval orientation cannot be disentangled.

In order to investigate the relationship between task difficulty and retrieval orientation effects Dzulkifli, Sharpe and Wilding (2004) compared unstudied items in two retrieval conditions (phonologically encoded versus semantically encoded) across high and low relative difficulty groups. The findings indicate that retrieval orientation effects (a difference between 300-1400ms that was greatest across anterior electrodes) were only evident for the high relative difficulty group, suggesting that retrieval orientation effects are only exhibited when comparative tasks vary in difficulty. However, this finding is in contrast to that of Robb and Rugg (2000), who found that retrieval orientation effects did not vary as a function of task difficulty, showing that effects relating to task difficulty were limited to a time-window (0-300ms) prior to the onset of orientation effects; and to Hornberger, Morcom and Rugg (2004) who found retrieval orientation effects despite no significant difference in behavioural performance. The cause of the discrepancy between these studies may relate to differences in the type of difficulty comparisons conducted, with Robb and Rugg (2000) and Hornberger, Morcom and Rugg (2004) conducting within-participant comparisons, whereas Dzulkifli, Sharpe and Wilding (2004) employed a between-participant comparison. As is the case with other retrieval effects, it is currently not clear what role individual differences play in the

[4] Retrieval effort is the engagement of processing resources during retrieval attempt and is discussed in greater detail in the next section.

ability to adopt different retrieval orientations or how these are reflected in the ERPs. The differences evident across studies may therefore be caused by between-participant factors that mask or accentuate the presentation of retrieval orientation effects in different studies.

Following on from the studies by Robb and Rugg (2002), and Herron and Rugg (2003), Hornberger, Morcom and Rugg (2004) extended the paradigm to determine if the retrieval orientation effects observed in the earlier studies were dependant on the similarity of the retrieval cue to the information being retrieved. These earlier studies demonstrated ERP differences for 'new' words, when trying to recover information relating to previously presented pictures compared to information relating to previously presented words. One criticism of this approach is that it is not possible to separate out the contribution of the differing types of material being retrieved, from variance in the similarity between the retrieval cue and retrieval information. Hornberger, Morcom and Rugg (2004) therefore included an additional picture retrieval cue condition to investigate the importance of retrieval cue similarity. The findings replicated the earlier studies, showing more positive going ERPs for words than pictures when using a word retrieval cue (a difference onsetting around 300ms, which is widely distributed with a diffuse maximum over central electrodes) but also revealed that the ERP pattern is reversed when the cue is a picture (with more positive ERPs for pictures than words). These results suggest that the similarity between the cue and information being sought is important, rather than the type of material per se. The authors suggest that the ERP effect reflects the different processing required to maximise the overlap between the cue and retrieved information for the different types of material.

The results of studies looking at retrieval orientation effects therefore suggest that there is a difference in neural activity when preparing to retrieve different types of episodic information. When investigating these effects with a single type of material (i.e. words) and varying conditions through the types of judgment made at study, or the inclusion/exclusion of similar stimuli at test, the retrieval orientation effects appear to have an anterior distribution, which in some studies appears to have a left hemispheric bias. In other studies, where comparisons are made on the basis of differing types of study material (i.e. words versus pictures), the distribution of retrieval orientation effects appears to be more widespread, in some cases with a central maximum. It is not clear whether these are real distributional differences or simply the impression given as a result of differences in how the data is presented across studies. It is unlikely that these distributional differences are simply material specificity effects since the studies using a single type of material include both words (Rugg, Allan & Birch, 2000; Dzulkifli, Sharpe & Wilding, 2004) and pictures (Ranganath & Paller, 1999), although it is interesting to note these differences in terms of possible material specificity differences evident during retrieval success (see below). Despite possible distributional differences, in all cases the retrieval orientation effect appears to be fairly sustained throughout the retrieval period, onsetting as early as 300ms and lasting up until 1800ms in some studies.

One of the problems in investigating retrieval orientation effects is separating out the contributions of retrieval orientation and variation in task difficulty, which may influence retrieval effort. The relationship between these two processes is a complex one and there are conflicting results in the literature as to how task difficulty affects retrieval orientation effects. With this in mind, the next section discusses retrieval effort

in more detail, outlining studies that have tried to investigate retrieval effort, often in conjunction with retrieval orientation.

2.2.1.3 Retrieval effort:

The final pre-retrieval process discussed in this chapter is retrieval effort, the engagement of processing resources when attempting to retrieve information. There are less ERP studies investigating retrieval effort than are apparent for other pre-retrieval processes and consequently the current understanding of retrieval effort is much more limited. Whilst studies described above, such as Ranganath and Paller (1999), and Rugg, Allan and Birch (2000), discuss their findings in relation to retrieval effort these results are thought to be confounded by retrieval orientation, with neither process being varied systematically, making it difficult to draw any conclusions from these studies about retrieval effort per se (Dzulkifli, Sharpe & Wilding, 2004).

The study by Robb and Rugg (2002), discussed above in relation to retrieval orientation, also investigated retrieval effort by varying task difficulty, using both study list length and study-test delay. They reported a small early onsetting (i.e. 0-300ms) ERP difference with more positive going 'new' waveforms for the easy compared to the hard condition at frontal electrodes and more positivity for the hard condition compared to the easy condition at central and parietal electrodes. However, the authors expressed caution in interpreting their data, stating that the ERP effects relating to task difficulty were of "modest statistical significance" (Robb & Rugg, 2002: p.588) and required replication before functional interpretations could be made. To date, however, the results have not been replicated; between participant comparison looking at high and low relative difficulty groups by Dzulkifli, Sharpe and Wilding (2004) found no reliable 'new' test word differences in the 0-300ms period.

In sum, therefore, current studies provide us with little insight into the neural activity associated specifically with retrieval effort, with the few studies that have looked at retrieval effort finding it difficult to tease apart this process from other pre-retrieval processes. Nonetheless, on the basis of the studies described above, there is evidence to suggest that retrieval effort, or some such task difficulty related process, does interact with other pre-retrieval processes.

2.2.1.4 Pre-retrieval processes summary:

The above sections discuss work investigating three key pre-retrieval processes that are thought to aid episodic memory retrieval. The first process was retrieval mode, the cognitive state in which a retrieval cue is approached. In comparison to semantic retrieval ERPs for episodic retrieval were found to be greater over right-frontal electrodes, a difference maintained throughout the retrieval period. The second process was retrieval orientation, which relates to the way a retrieval cue is processed depending on the overall goal of the retrieval attempt. The ERP effects for retrieval orientation were more complex than for retrieval mode, with studies often comparing tasks that varied in task difficulty leading to possible confounds with retrieval effort. Overall differences in retrieval orientation appeared to be reflected by differences over anterior electrodes, although in some cases these effects appeared to be more widespread and were sustained between approximately 300-1800ms. The final pre-retrieval process examined was retrieval effort and as per retrieval orientation the findings were often entwined with other pre-retrieval processes, making it difficult to make any strong claims regarding the neural activity associated with variation in retrieval effort. There was some evidence of an anteriorly distributed difference, but the size of this effect was

modest and has not been replicated; there is, however, evidence to suggest an interaction between retrieval effort and retrieval orientation.

2.2.2 Retrieval success processes

As described above, where there is an overlap between retrieval cue and previously encoded information successful memory retrieval may occur. Whilst not always attainable, successful memory retrieval is the desired outcome of a retrieval attempt. Chapter 1 discussed theories relating to the processes involved in this interaction between retrieval cue and memory representations, with dual process models the most widely accepted view. Within this framework it is thought that recognition is dependent on the processes of familiarity and recollection and this section will briefly discuss the pursuit of neural correlates of these two core retrieval processes.

Investigations of recollection and familiarity processes are typically conducted using study-test paradigms in which participants are presented with a series of stimuli to be remembered and are subsequently tested by presenting a mixture of previously studied ('old') items and previously unstudied ('new') items. Participants indicate during the test phase whether or not each item was previously presented, discriminating between 'old' and 'new' stimuli. ERPs to correctly identified 'old' items (Hits) are contrasted with ERPs to correctly identified 'new' items (Correct Rejections, CRs), with the difference between these two types of trial providing an indication of the neural activity associated with successful memory retrieval. As evident from the review of pre-retrieval processes, and as discussed by Rugg and Henson (2002), functional interpretation of ERP differences should be made with caution as processes other than those of interest will contribute to the resulting product. With this in mind the studies discussed in this

next section will consider evidence for the existence of neural correlates of two core retrieval processes, recollection and familiarity.

2.2.2.1 Recollection:

The first chapter reported that recollection is considered to be the process by which details about previous encounters with an item are recovered. It is not simply the retrieval of information indicating a previous encounter but also information relating to the context of that encounter. ERP studies have shown what is believed to be a distinct neural signature of recollection termed the 'parietal' or 'left-parietal' old/new effect (Figure 2.1), in which there is a temporary positive increase in amplitude for 'old' items compared to 'new' items; maximal over parietal electrodes, typically with a left sided distribution, onsetting around 400-500ms post stimulus and lasting until approximately 800ms (Rugg *et al.,* 1998; see Rugg, 1995; Allan, Wilding & Rugg, 1998 or Curran, Tepe & Piatt, 2006 for a review).

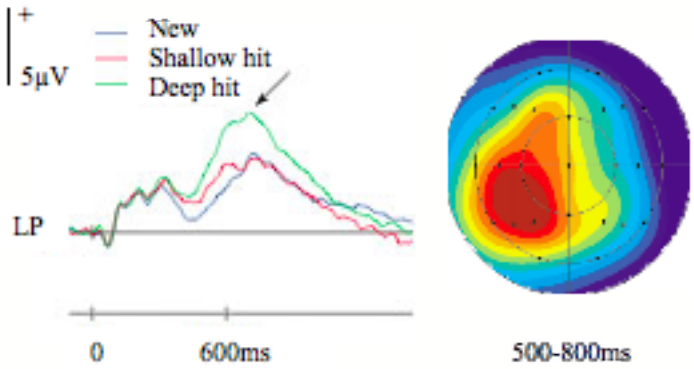


Figure 2.1 ERP waveform of the putative correlate of recollection – the left-parietal old/new ERP effect. The waveforms on the left are shown for 'old' items incorrectly identified as 'new', Hits to shallowly encoded items and hits to deeply encoded items, at a left-parietal electrode. The waveforms show a divergence of deep hits from the other two conditions between approximately 500-800ms. The topographic map on the right shows the left-parietal distribution of the difference between deep hits and shallow hits (figure adapted from Rugg & Yonelinas, 2003).

Evidence that the left-parietal effect is a neural correlate of recollection comes from attempts to modulate the size of the effect by manipulating recollection, such as with a depth of processing paradigm, or by assessing the contribution of recollection to retrieval using paradigms like the remember/know procedure. As discussed in Chapter 1, the remember/know paradigm is often used as a behavioural indicator of the degree to which responses are based on recollection or familiarity. Whilst the subjective introspection required in making these judgements make it in some ways a crude measure of familiarity and recollection, it provides a useful tool for investigating the neural contributions to these processes. Using word stimuli, both Smith (1993) and Düzel et al. (1997) found that the parietal old/new effect was modulated by participants' subjective reports of 'remembering' and 'knowing', with 'remember' responses exhibiting a larger old/new effect than 'know' responses over parietal electrodes. Furthermore using picture stimuli with a modified remember/know paradigm, in which the remember judgement was divided into two separate judgements, 'R1' and 'R2'[5], Vilberg, Mossavi and Rugg (2006) found that the magnitude of the left-parietal effect varied with regards to the amount of recollected information; that is 'R2' trials were more positive going than 'R1' trials, both of which were greater than 'new' trials, over left-parietal electrodes. These studies suggest that the size of the left-parietal effect is modulated by reports of 'remembering' and 'knowing', with 'remember' responses exhibiting a larger left-parietal effect than 'know' judgments.

As previously discussed one of the core functional differences between recollection and familiarity is that recollection involves the recovery of details about previous encounters

[5] The modified remember/know paradigm used by Vilberg, Mossavi and Rugg (2006) enabled participants to make one of four judgments during the test phase, 'new' for items not presented in the study phase, 'know' when the item was very familiar, but no details about it could be recollected, 'Remember 1' (R1) for partial retrieval of a study episode where details of the study episode could be recollected but not the associated picture, and 'Remember 2' (R2) for trials where sufficient details about the episode could be retrieved to enable the picture paired with the test picture to be identified.

with an item. A series of studies in the later 1990's, predominately by Wilding et al. (Wilding, Doyle & Rugg, 1995; Wilding & Rugg, 1996; Trott, Friedman & Walter, 1997; Wilding, 2000), used a source memory paradigm in which memory for study context was tested alongside recognition memory. During a source memory task participants are presented with a series of study items presented in one of two formats, such as auditorily presenting words in either a male and female voice. During the test phase participants are then presented with words visually and asked to make an old/new judgment; if an 'old' response is made participants are then asked to indicate if the word was presented in a male or female voice at study. The idea behind such source memory paradigms is that they attempt to directly assess memory for study context, allowing trials to be separated into those with and without retrieval of study context, reflecting retrieval success with and without recollection.

Studies that have used source memory paradigms to investigate the ERP correlates of recognition memory have found that parietal old/new effects for correct recognition with accurate source judgments were larger than for correct recognition judgments made without accurate source memory (Wilding, Doyle & Rugg, 1995; Wilding & Rugg, 1996; Trott, Friedman & Walter, 1997). The modulation of the parietal old/new effect by successful study context retrieval provides strong support for the notion that it reflects the process of recollection. It is important to note however, that the paradigm has been criticised for its failure to take into account recollection based on factors other than those being explicitly tested by the paradigm (Wilding, 2000). Trials in which information regarding study context is retrieved but not directly tested by the paradigm, such as noting during study that the word is in the title of a book currently being read, (rather than the gender of the speakers voice) are therefore misclassified as recognition without correct source retrieval. This misclassification of trials could be distorting our

understanding of how recollection works, and how recognition processes affect the left-parietal effect.

Wilding (2000) looked to see if the magnitude of the left-parietal effect varied in relation to the number of correct source judgments made. Participants were presented with a series of words spoken in either a male or a female voice at study and were asked to make either an active/passive or a pleasant/unpleasant judgment about each word. During the test phase words were visually presented and participants made an old/new judgment to each word and were then asked to make a task judgment (action/liking) and a voice judgement (male/female). The findings showed that parietal old/new ERP effect magnitude varied with the number of correct source judgments made, with ERPs for trials in which two correct source judgements were made showing larger old/new effects then trials where only one correct source judgment was made. These findings suggest that the parietal old/new effect is modulated, not only by recognition trials where recollection occurred, but also by the amount of information that is recollected.

Additional evidence to suggest that the parietal old/new effect is modulated by the amount of information recollected comes from a study by Vilberg and Rugg (2009), in which the amount of recollected information was manipulated by varying study presentation times. Increased study duration is known to increase recollection estimates (see Yonelinas, 2002, for a discussion) and using presentation times of 1 and 6 seconds Vilberg and Rugg manipulated the proportion of responses based on recollection (as indicated by remember/know judgments), and the amount of information recollected, (as measured by post-test recall). Comparing ERPs for correct ‘remember’ responses to correct ‘new’ responses across the two study presentation times, indicated that the size of the left-parietal old/new effect was modulated by study duration, with items

presented for 6 seconds showing a greater left-parietal effect than items presented for 1 second. Since more information about the study episode was recalled from items presented for 6 seconds the authors suggest that the left-parietal effect is modulated by the amount of information recollected, consistent with the findings of Wilding (2000).

Whilst the study by Vilberg and Rugg (2009) suggests that differences in study duration changed the degree to which recollection was engaged and subsequently modulated the magnitude of the left-parietal effect, the authors noted that increased study duration also increases the proportion of familiarity responses made (see Yonelinas, 2002). Therefore, whilst increased study duration lead to an increase in the amount of information about each study episode recalled post-test, and therefore the amount of recollection, the contributions of familiarity to recognition would also have increased between 1 and 6 seconds suggesting that this is not a pure measure of an increase in recollection. Despite the possible confound of familiarity, this study still provides evidence to support the conclusion that the left-parietal effect not only indexes recollection, but also that it is modulated by the amount of information recollected.

In an attempt to isolate the neural activity relating to recollection, Curan (2000) presented participants with a series of pluralizable concrete nouns at study, half being presented in the singular and half in the plural form. At test participants made old/new style judgments to studied, similar (switched plurality), and ‘new’ words; a task requiring recollection in order to discriminate between studied and similar words, which would elicit similar levels of familiarity. The parietal effect was found to be larger for correctly identified studied words than for similar words that were incorrectly classified as previously studied (false alarms), suggesting that it is modulated by the process of recollection. The parietal effect has also been shown to be sensitive to associative

recognition memory, with word pairs rearranged at test exhibiting a smaller left-parietal effect than words presented in the same pairings as at study (Donaldson & Rugg, 1998); and to depth of processing manipulations, with ERPs to deeply studied words differing from both shallowly studied and 'new' words from 500ms post-stimulus (Rugg et al., 1998, see data presented in Figure 2.1).

In sum, these studies show that remember/know judgments, retrieval of source information, the quantity of remembered information, 'old' judgement accuracy, associative memory, and depth of processing all modulate the parietal old/new effect. Collectively these findings provide strong evidence to suggest that the parietal old/new effect reflects activity relating to the process of recollection and that this effect is often maximal over the left hemisphere. Whilst these studies provide evidence to suggest that the left-parietal effect does reflect recollection, they do not directly provide support for the view that recollection and familiarity are dissociable processes. Factors that are thought to reflect familiarity, or recognition without recollection, such as 'know' responses, have thus far been discussed in relation to a reduction in the size of the left-parietal effect. This in itself is not evidence of a dissociable recollection process, but could simply reflect a reduced left-parietal effect for recognition in the absence of recollection. In order to demonstrate that familiarity and recollection are dissociable a qualitative difference (i.e. in scalp distribution) between the two processes is needed.

2.2.2.2 Familiarity:

In contrast to recollection, familiarity is thought to be a fast automatic process in which the similarities between the item and information stored in memory about previous items are assessed; it is a general sense that an item has been previously encountered. Identification of the neural activity associated with familiarity has been more elusive

than for recollection, with a large proportion of the evidence based on deductive reasoning rather than exploration through direct process manipulation. That is to say that generally familiarity is less sensitive to retrieval manipulations than recollection; inferences about the neural correlates of familiarity are often made when a retrieval effect is found to be insensitive to manipulations of recollection, returning to the idea that retrieval can occur with or without recollection and that successful retrieval without recollection is based on familiarity.

The first indication that familiarity and recollection may exhibit different patterns of neural activity came from a study by Düzel, Yonelinas, Mangun, Heinze and Tulving (1997) who found different ERP effects for 'remembered' words and words associated with a 'know' response, when compared with CRs, with a widespread bilateral-frontal and left-temporoparietal difference between 600-1000ms for 'remember' responses, and a bilateral temporoparietal positivity between 300-600ms, followed by a frontocentral negativity for 'know' responses. An early (300-500ms) old/new effect in which 'old' items were more positive going than CRs was also found by Rugg et al. (1998); however in contrast to the effect reported by Düzel et al., the old/new effect had a frontal maximum. Furthermore, this frontal effect was found to be insensitive to a depth of processing manipulation, in contrast to a later parietal effect modulation, leading the authors to suggest that the early frontal effect reflected familiarity based retrieval (Figure 2.2).

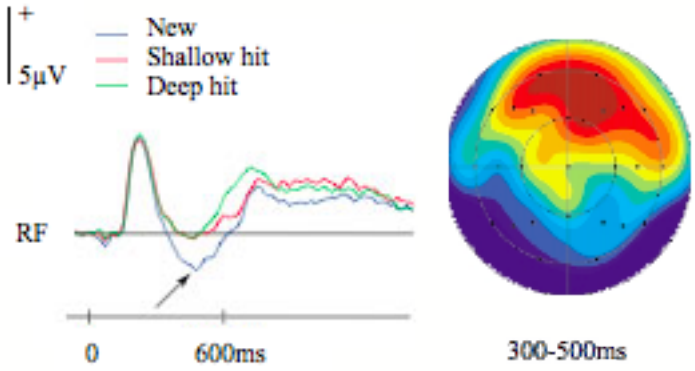


Figure 2.2 ERP waveform of the putative correlate of familiarity – the frontal old/new ERP effect. The waveforms on the left are shown for items incorrectly identified as 'new', hits to shallowly encoded items and hits to deeply encoded items, at a right frontal electrode. The waveform shows the divergence of deep and shallow hits from 'new' items between approximately 300-500ms. The topographic map on the right shows the frontal distribution of the difference between shallow hits and shallow misses/'new' items (figure adapted from Rugg and Yonelinas, 2003).

Support for the hypothesis that the 300-500ms frontal old/new effect indexes familiarity comes from work comparing 'studied' items with similar 'lures' and 'new' items. Using words differing in plurality as similar lures, Curran (2000) found that the early frontal effect (sometimes referred to as the FN400 because of its similarity to the N400 effect observed for incongruous stimuli; for a review of the N400 effect see Kutas & Federmeier, 2011) did not differ between correctly recognised studied words and falsely identified similar words, in contrast to the later parietal recollection effect. Curran (2000) proposed that recollection was needed to discriminate studied from similar words (a difference evident in the parietal old/new effect), but that both classes of word would be more familiar than 'new' words, resulting in the similar ERP effects for studied and falsely recognised lures over frontal electrodes. Similarly, Nessler, Mecklinger, and Penny (2001) found that a 300-500ms fronto-medial old/new effect did not differ between true recognition and false recognition of conceptually similar lures, but when attention at encoding was directed towards item specific information, the early frontal effect for false recognition was no longer evident. Nessler et al. (2001) suggest

that the conceptual similarity of stimuli enhances the feeling of familiarity for similar lures in a way that item specific information does not. Using the same type of old/similar/new paradigm, Curran and Cleary (2003) showed that this pattern of activity is not restricted to words, with similar frontal activity evident for studied pictures and mirror-reversed similar lures, both of which differed from 'new' pictures.

The studies discussed in the previous paragraph included stimuli that were selected or generated for their similarity to studied words, however the 300-500ms frontal effect has also been found for false recognition of stimuli without directly manipulating similarity (Wolk et al., 2006). In addition Wolk and colleagues showed that the frontal effect between 'know' and CRs was maintained over both short (~39 minute) and long (~24 hour) study-test delays, consistent with the hypothesis that the effect reflects familiarity rather than short-term memory. The frontal effect has also been shown to be graded by the degree of familiarity, with confident 'old' responses more positive going than unconfident 'old', unconfident 'new' and confident 'new' responses (Woodruff, Hayama & Rugg, 2006). In this study the magnitude of the frontal effect was comparable for recollection and confident 'old' (most familiar) responses.

One of the few studies that have attempted to directly manipulate familiarity was conducted by Azimian-Faridani and Wilding (2006). The response criterion used to make a decision was manipulated by changing the emphasis of when to use the 'old' and 'new' response, either informing participants to respond 'old' only when confident that the stimulus was 'old' (a conservative bias), or respond 'new' only when confident of an items 'new' status (a liberal bias). Azimian-Faridani and Wilding (2006) proposed that the level of familiarity required to make an 'old' decision would vary depending on the response criterion used. That is, the level of familiarity accepted as indicating that

the item is 'old' would be lower in the liberal bias condition than the conservative bias condition. In accordance with the hypothesis that the frontal old/new effect reflects familiarity, the magnitude of the effect varied with changes in response criterion, with trials engaging a conservative bias (where the sense of familiarity would be strongest) showing more positive going ERPs than trials engaging a liberal bias over mid-frontal electrodes.

Therefore, overall, the studies presented in this section suggest that an early frontal old/new effect between 300-500ms (Figure 2.2), sometimes referred to as the 'mid-frontal' or 'bilateral-frontal' effect, reflects familiarity. However, there is another line of argument suggesting that this effect actually reflects the differential processing of an item because of previous encounters with the item, reflecting processes supporting conceptual priming, rather than processes relating to active retrieval per se.

2.2.2.3 Conceptual priming:

Conceptual priming relates to the unconscious differential processing of an item because of prior experience with it, particularly in terms of access to semantic information associated with the item. It has been argued that the duplication or overlap of items between study and test in a standard recognition memory paradigm induces conceptual priming, with 'old' items being treated differently from 'new' items at test because of repeated access to semantic information relating to the item, rather than simply from an explicit memory of having previously experienced the event (Paller, Voss & Boehm, 2007).

Yovel and Paller (2004) highlighted the potential relationship between the 300-500ms bilateral-frontal old/new effect and conceptual priming when discussing the absence of such an effect in their familiarity contrast during a face recognition task (see material

specificity section below for more details). They suggested that nonverbal stimuli such as faces do not contain the same level of semantic information as verbal stimuli such as words, and therefore tasks using nonverbal stimuli do not engage conceptual priming and subsequently do not exhibit the early bilateral-frontal effect typically associated with familiarity. In line with this argument, Voss and Paller demonstrate across a series of studies that the bilateral-frontal old/new effect is present in conditions where conceptual information about an item is available, but is not exhibited in conditions with no conceptual information. These studies have included primed compared to unprimed famous faces (Voss & Paller, 2006), showing greater positivity over frontal electrodes between 300-500ms for famous faces primed with correct biographical information than unprimed famous faces in which incorrect biographical information was given; uncommon English words varying in the degree of meaningfulness (Voss, Lucas & Paller, 2010) where the bilateral-frontal effect was only present for words that elicited meaningful associations; kaleidoscope images (Voss & Paller, 2009) in which no bilateral-frontal effect was evident for the familiarity contrast, and the exhibited ERP effects for recollection and familiarity between 300-500ms did not differ; and minimalist geometric shapes/squiggles (Voss, Schendan & Paller, 2010) where bilateral-frontal effects were only evident for shapes rated as highly meaningful and not for shapes given low meaning ratings.

It is important to note that the conceptual priming distinction is not simply a linguistic versus pictorial one as bilateral-frontal old/new effects have been reported for pictures (Curran & Clearly, 2003), but the distinction is between stimuli where semantic information can and cannot be accessed (i.e. a squiggle versus a photograph of an object). Whilst there is some evidence to suggest that the bilateral-frontal effect does relate to conceptual priming, Curran (1999) reports a bilateral-frontal old/new effect

between 300-500ms for recognition of pseudo-words, and Groh-Bordin, Zimmer and Ecker (2006) show an early bilateral-frontal effect for nonsense figures; both of these results are difficult for a conceptual priming account. In addition, Groh-Bordin et al. (2006) demonstrated that the bilateral-frontal effect was modulated by perceptual manipulations, a finding that is clearly incongruous with the conceptual priming hypothesis.

An additional study designed to investigate the familiarity and conceptual priming hypotheses was conducted by de Chastelaine, Friedman, Cycowicz and Horton (2009), who used unfamiliar and unnameable symbols learnt over a series of 4 study-test blocks. It was hypothesised that familiarity with the stimuli would increase across the blocks, as stimuli were repeated, and that the magnitude of the recognition memory effects would therefore also increase. Whilst an increase in effect magnitude across blocks was evident for the 500-700ms parietal effect, this was not the case for the 300-500ms frontal effect, suggesting that the frontal effect does not reflect familiarity. To test the conceptual priming hypothesis a stimulus naming task was included, in which participants were asked if they had named the symbol or if it reminded them of another object. It was hypothesised that if the frontal effect reflected conceptual priming then there would be a greater effect for repeated items that had been conceptually processed, as indicated by the naming task. Contrary to the conceptual priming hypothesis, however, symbols that were conceptually processed did not exhibit a greater frontal old/new effect than nonconceptually processed symbols, suggesting that the 300-500ms effect neither reflects familiarity nor conceptual priming. The authors instead suggest that it may reflect control processes that are engaged when the memory trace is weak.

Consequently, whilst the conceptual priming hypothesis has its merits and highlights fundamental problems with the association between familiarity and the bilateral-frontal effect, it is not itself without complications. Therefore, at present, the functional significance of the bilateral-frontal old/new effect remains unclear. It is, however, generally believed to reflect familiarity processes to which conceptual and perceptual information both contribute (Groh-Bordin et al., 2006).

2.2.2.4 Material specificity:

The majority of evidence for the neural correlates of familiarity and recollection discussed above come from studies that have used word stimuli. These studies suggest that recollection is characterised by more positive going ERP activity for correctly identified 'old' items compared to correctly identified 'new' items, a difference maximal over parietal electrodes between approximately 500-800ms, typically showing a left hemispheric distribution. Activity thought to relate to familiarity is an earlier (300-500ms) old/new effect that has a maximal distribution over bilateral-frontal electrodes. Recently several studies have investigated these old/new recognition memory effects using different stimulus materials and have found variation in the distribution of these recognition memory effects with different stimuli types.

There is emerging evidence to suggest that pictorial stimuli may exhibit more anterior going recollection effects than verbal stimuli. Studies that have investigated recognition memory for pictures of objects have shown old/new ERP differences that resemble the parietal old/new effect described for words (Curran & Cleary, 2003; Duarte, Ranganath, Winward, Hayward & Knight, 2004; Galli & Otten, 2011; Schloerscheidt & Rugg, 1997, 2004; Vilberg, Moosavi & Rugg, 2006; Vilberg & Rugg, 2009). However, some of these studies have shown additional or overlapping frontal activity that was

associated with recollection (Cycowicz, Friedman & Snodgrass, 2001; Duarte et al., 2004; Schloerscheidt & Rugg, 1997). Furthermore, in a study that directly compared words and pictures, Galli and Otten (2011) reported more anteriorly extending parietal effects for pictures of objects (compared to words).

In addition to the evidence suggesting more anteriorly distributed effects for pictures of objects, ERP studies looking at recognition memory for pictures of faces[6] have shown similar results. Curran and Hancock (2007), MacKenzie and Donaldson (2007), and Yick and Wilding (2008), have all shown a parietal old/new ERP effect associated with recollection of faces on-setting around 500ms; and, as evident in studies using pictures of objects, an additional or overlapping old/new difference over frontal electrodes has also been reported by MacKenzie and Donaldson (2007), and Yick and Wilding (2008). It is evident, although not discussed, in data presented by Curran and Hancock (2007). In a similar fashion to data reported by Yick and Wilding (2008), Galli and Otten (2011) reported the posterior old/new effect for faces as extending more anteriorly than is evident for word recognition. In addition, MacKenzie and Donaldson (2009) showed that correctly identified 'old' faces reported as 'remembered' (as opposed to 'familiar') showed frontally distributed old/new effects, 500-700ms after stimulus onset, not present for 'remembered' names that had been paired with these faces at study. Neural activity consistent with the parietal old/new effect was evident for 'remembered' names in the 500-700ms time window, an effect not apparent in the 'remembered' faces condition. These results therefore suggest that recollection of faces is associated with a frontal distributed ERP effect that is not present for words.

[6] It is important to note here that in the context of this thesis 'recognition of faces' refers to recognition of pictures that are of faces, rather than recognition of faces per se. That is the 'face recognition' tasks require participants to say if the picture presented at test is new or if it was presented at study. This is in contrast to recognition of a face in which participants may be presented with different pictures of a person's face at study and test (such as photographs taken from different angles or at different times), and are asked to indicate if they have seen this person before.

In relation to familiarity effects for faces the evidence is a little more confusing. Yovel and Paller (2004) report no familiarity effects for faces between 300-500ms, but show a bilateral-parietal old/new effect between 500-700ms which is smaller in amplitude and shorter in duration for the familiarity contrast compared to the recollection contrast. This evidence is further supported by MacKenzie and Donaldson (2007) who also report no significant differences between the familiarity and recollection contrasts in the 300-500ms time window, but report posterior old/new effects in the familiarity condition. In contrast to these findings, Curran and Hancock (2007) report a bilateral-frontal old/new effect between 200-500ms that did not differ between familiarity and recollection contrasts. Galli and Otten (2011) report more anteriorly distributed effects for faces, and pictures of objects, compared to words, in the 300-500ms time window for their recollection contrast (as indexed by correct source judgments), but unfortunately do not report effects for a familiarity contrast.

Therefore the findings from these studies suggest that recognition memory effects for different types of stimuli may differ both quantitatively and qualitatively. The current evidence suggests that recollection related effects are more anterior going for pictorial stimuli than for verbal stimuli, with some studies suggesting an additional frontal component for pictorial stimuli that is not present for verbal stimuli. At present it is not clear what is driving these stimulus differences. One theory is that these ERP differences relate to the perceptual complexity of these different stimulus types. With the exception of two studies (Curran & Cleary, 2003; Cycowicz et al., 2001), all of the studies described above looking at pictures have used photographs of objects and faces, which are perceptually more complex than words (Galli & Otten, 2011). The two other pictorial studies used line drawings, with Cycowicz et al. (2001) reporting data consistent with the theory that pictorial stimuli results in frontal recollection related

activity, whilst Curran and Cleary (2003) show data consistent with the parietal old/new recollection effect seen for words.

The apparent differences between pictorial and verbal stimuli may also be driven by the differences in relation to spatial information, in that pictures of objects and faces both contain spatial information and configuration information not present for verbal stimuli such as words (Yick & Wilding, 2008). Furthermore these different stimulus types also vary in task difficulty, which may cause differences in ERP effect magnitude and distribution, although typically performance is better for pictures of objects than words, and performance for words is better than faces, suggesting that these performance differences are unlikely to be causing the apparent pictorial/verbal differences that are evident. Further investigation of recognition memory effects for different stimulus materials is therefore necessary in order to understand what is driving these different patterns of neural activity between stimulus types and examination of performance differences are needed to fully understand the interaction between the two factors.

2.2.2.5 Retrieval success processes summary:

Previous literature suggests there are distinct neural correlates of recollection and familiarity, with recollection typically associated with a 500-800ms left-parietal old/new effect and familiarity with a 300-500ms bilateral-frontal old/new effect. There is some contention in the literature as to whether the early bilateral-frontal effect actually reflects conceptual priming rather than familiarity, or if it reflects neither of these, and in fact relates to broader control processes engaged when the memory trace is weak. Furthermore there is evidence to suggest material specificity, with more anteriorly distributed effects evident for pictorial compared to verbal stimuli, and in some cases additional frontal effects, suggesting that details relating to the type of

information being retrieved are important in understanding the neural correlates of retrieval success processes.

2.2.3 Post-retrieval processes

After information has successfully been retrieved there may be a requirement to further evaluate or monitor this information, depending on the intended purpose of the retrieval. For example, the relevance of the retrieved information may need to be evaluated if the source of the information needs to be reported. An old/new ERP effect over right-frontal electrodes has been associated with post-retrieval processes and has been shown to onset as early as 400ms (Wilding & Rugg, 1996) or as late as 1300ms (Donaldson & Rugg, 1999).

One of the first discussions of the right-frontal old/new effect was by Wilding and Rugg (1996) who showed a sustained old/new effect, in which hits were more positive than CRs between 400-1400ms, an effect modulated by source judgement accuracy. Given the sensitivity of the effect to the retrieval of source information it was hypothesised that the effect was related to the explicit requirement to retrieve contextual information. However, subsequently there has been evidence of a right-frontal effect in old/new recognition tasks in which the retrieval of contextual information was not an explicit requirement (Allan & Rugg, 1997; Donaldson & Rugg, 1998; Rugg, Allan & Birch, 2000). In a subsequent study Wilding and Rugg (1997) further demonstrated that not only was explicit contextual retrieval unnecessary for the exhibition of the right-frontal old/new effect, but that successful retrieval was not a requirement. When comparing correctly identified non-targets and 'new' items, Wilding and Rugg (1997) found no evidence of a right-frontal effect, despite the presence of a left-parietal effect that was indicative of the engagement of retrieval processes. The absence of a right-frontal effect

in the presence of a left-parietal effect prompted the hypothesis that whilst the right-frontal effect may be related to recollection processes, it was not necessary and may reflect more controlled strategic processing of retrieved information.

In support of a strategic processing hypothesis the right-frontal effect has been shown to be insensitive to the accuracy of source judgements (Senkfor & Van Petten, 1998), and to be larger for shallowly encoded items than to deeply encoded items, a finding in direct contrast to the pattern of activity seen for the left-parietal effect (Rugg, Allan & Birch, 2000). Whilst the modulation direction of the right-frontal effect appears initially surprising, Rugg, Allan and Birch (2000) suggest that the larger effect for shallowly processed items reflects greater engagement of evaluative processes when information pertaining to previous encounters with an item is particularly poor, such as shallowly encoded items. This hypothesis stems from fMRI research conducted by Henson, Rugg, Shallice, Josephs, and Dolan (1999) showing greater prefrontal activation for items accompanied by 'know' responses compared to 'remember' responses, which was hypothesised to reflect variation in the quality of retrieved information associated with the two subjective judgments.

An additional study looking at the quality of retrieved information was conducted by Kuo and Van Petten (2006), which further investigated the idea of greater prefrontal cortex engagement during retrieval of poorly encoded associations, using objects and colours. When attention at study was directed only to the object, i.e. attention was not drawn to the colour of the object during the study judgement, and hence information relating to the object/colour association was weak, retrieval of object/colour associations exhibited a right-frontal effect. By contrast, however, when the study task involved making a judgment about the object/colour association, no right-frontal

retrieval effect was evident. In a subsequent study Kuo & Van Petten (2008) demonstrated that these differences in the right-frontal effect did not simply reflect general differences in task difficulty, showing that a perceptual manipulation of task difficulty did not modulate the magnitude of the right-frontal effect, therefore suggesting that the cause of task difficulty variation was important. In addition, Cruse and Wilding (2009) found that the magnitude of the right-frontal effect was positively correlated with the proportion of low confidence judgments made, which are theorised to reflect the quality of retrieved information. These findings further support the hypothesis that the right-frontal effect reflects the engagement of processes related to retrieval monitoring and evaluation when the quality of information retrieved is poor.

Whilst all the studies discussed above relate to episodic memory, Hayama, Johnson and Rugg (2008) showed that the right-frontal effect is not only present for episodic retrieval, but also for semantic retrieval. In addition, they demonstrated that the class of item is not necessarily the important factor in the production of a right-frontal effect; rather, the requirement to make an additional judgement is key. Hayama et al. (2008) found that 'old' images were more positive going than 'new' items over right frontal electrodes when participants were required to make a semantic judgment about previously seen items. However, when the additional judgment was required on unseen images, the ERPs to 'new' images were more positive going than 'old' images. This result suggests that the right-frontal effect is not specific to episodic memory, nor previously encountered stimuli, but reflects more general information monitoring processes.

The studies discussed above therefore suggest that, particularly in cases where retrieved information is of poorer quality, additional post-retrieval processes are engaged to

evaluate and monitor the retrieved information. These post-retrieval processes appear to be reflected by an old/new ERP effect in which stimuli requiring additional monitoring (which can be 'old' or 'new' stimuli depending on the task), is more positive going than its counterpart over right-frontal electrodes, an effect onsetting as early as 400ms and sustained over time. Whilst the focus of this thesis is on episodic memory, it is important to note that the right-frontal effect is not confined to episodic memory, with evidence indicating the presence of this effect during the retrieval of semantic information.

2.3 Conclusion

ERPs provide a continuous measure of processing, with excellent temporal resolution, making them a useful tool for investigating cognitive processes such as those involved in episodic retrieval. However, due to the many different neural configurations and differing conductivity of different parts of the head, the spatial resolution of ERP data is relatively weak compared to other neuroimaging methods. Despite this limited spatial resolution ERPs can be used to help understand the neural activity associated with different cognitive processes and there has been recent interest in using ERPs as biomarkers of diseases that produce cognitive decline.

This chapter summarised key ERP components associated with episodic memory retrieval, looking at pre-retrieval, retrieval success and post-retrieval processes. In general pre-retrieval processes were associated with activity over anterior electrodes with retrieval mode exhibiting a right hemispheric bias. The evidence for specific retrieval orientation and retrieval effort effects was less compelling, with studies struggling to separate out the two processes. However, both processes were shown to

exhibit anterior effects, with some studies indicating a left hemispheric bias in relation to retrieval orientation.

The evidence for dissociable retrieval success effects is more convincing, showing a left-parietal old/new effect between 500-800ms associated with recollection, and a bilateral-frontal old/new effect between 300-500ms for familiarity. There is, however, some debate in the literature as to whether the bilateral-frontal effect genuinely reflects familiarity or if it actually reflects conceptual priming. At present it is not clear which, if either, interpretation is correct, although the familiarity hypothesis appears to be more widely accepted. Much of the early evidence for distinct neural correlates of recollection and familiarity comes from studies using word stimuli; recent studies suggest there may be material specific retrieval effects, with pictorial stimuli exhibiting more anteriorly distributed parietal effects than verbal stimuli, and faces exhibiting additional frontal differences. Finally, activity over right-frontal electrodes is thought to reflect post-retrieval processes relating to the monitoring of retrieved information, although this effect does not specifically relate to episodic memory, with evidence of an equivalent effect for semantically retrieved information.

Whilst a vast amount has been learnt about recognition memory processes from ERPs, it is evident from this review that the processes involved in episodic retrieval, and the associated ERP effects, are not yet fully understood. As discussed at the beginning of the chapter, ERPs have the potential to be useful disease biomarkers, including those relating to memory disorders. Some studies (Olichney et al., 2002; Olichney et al., 2006) have already identified ERP components relating to episodic memory as potentially useful biomarkers for memory disorders, including a word repetition effect (the Late Positive Component/P600) that resembles the left-parietal recollection effect

discussed above. However, before these retrieval effects can be successfully implemented as biomarkers, a greater understanding of the variation evident in these effects is needed, including task differences, such as stimulus materials; and individual participant differences, such as strategy use or genetic makeup. Overall this chapter outlines the current understanding of episodic retrieval effects and provides the base from which the research in this thesis aims to explore such individual differences in episodic memory.

Chapter 3
Individual Differences and Episodic Memory

Chapter 2 summarised the literature on ERPs and recognition memory retrieval effects, identifying neural activity involved in three key stages: retrieval attempt, retrieval success and post-retrieval monitoring. In general, when trying to isolate activity relating to a particular cognitive operation, ERP activity is averaged across participants who meet predetermined criteria relating to factors such as handedness, sex, neurological health, etc., and these findings are then generalised to the wider population. However, whilst it is important to include such control factors in the design, to understand underlying cognitive processes, this approach raises the question as to whether the ERP effects identified in this way are reflective of the activity and processes engaged by all individuals?

The current chapter discusses evidence of individual differences in episodic memory, considering the influence of biological variations on memory ability and neural activity associated with memory encoding and retrieval. Whilst there is a considerable literature on the influence of ageing on memory (for a review see Friedman, 2000), this chapter will focus on less transient factors, looking at the more stable variables of sex and genetic polymorphisms. Following discussion of sex differences in memory, a brief introduction to genetics will be given before reviewing the literature relating to memory and four different genetic polymorphisms: APOE, BDNF, COMT, and KIBRA. The chapter will conclude with a consideration of the overall thesis aims, discussing the motives for the current project, and outlining the empirical work that will be presented.

3.1 Sex differences

Several studies have reported behavioural differences in episodic memory as a function of sex, with females performing better than males on a variety of episodic memory tasks, including recall and recognition of words, faces, pictures, and stories (Guillem & Mograss, 2005; Herlitz, Airaksinen & Nordström, 1999; Herlitz, Nilsson & Bäckman, 1997; Herlitz & Yonker, 2002; Maitland, Herlitz, Nyberg, Bäckman & Nilsson, 2004; Ragland, Coleman, Gur, Glahn & Gur, 2000). By contrast, a number of imaging studies have failed to find significant behavioural differences between sexes (Ino, Nakai, Azuma, Kimura & Fukuyama, 2010; Nyberg, Habib & Herlitz, 2000; Taylor, Smith & Iron, 1990), although in each case these studies nonetheless found differences relating to the neural activity underlying memory.

In particular, there is evidence of sex differences in episodic memory ERP effects. For example, Taylor, Smith and Iron (1990) reported larger hit amplitudes for females than males, around 300ms and 550ms, over anterior electrodes in a nonverbal recurring figures task (including geometric and curvilinear abstract figures), around 300ms, 550ms and 750ms, over posterior electrodes in a verbal recurring task (stimuli included words, pronounceable nonwords and 3-digit numbers). In contrast, males showed the reverse pattern, exhibiting larger hit amplitudes anteriorly for verbal stimuli (around approximately 300ms), and posteriorly for figures (also around approximately 300ms). Direct comparison of the old/new difference activity across the sexes in the figures task revealed more anteriorly distributed effects for females and posteriorly distributed effects for males (around approximately 400ms and 550ms). Whilst there was evidence of ERP differences between males and females in this study, behavioural performance

in these tasks did not differ, suggesting differential engagement of memory processes by males and females in reaching the same outcome.

In support of the findings of Taylor, Smith and Iron (1990), Guillem and Mograss (2005) also found ERP sex differences over anterior locations in a recognition memory for faces task. Females exhibited a larger old/new effect than males over anterior electrodes, starting at approximately 400ms and continuing until 500ms, with the data showing a similar trend until approximately 700ms. The findings from both Taylor, Smith and Iron (1990), and Guillem and Mograss (2005), suggest that for pictorial stimuli, females exhibit more anterior ERP activity than males, a difference that Guillem and Mograss (2005) suggest may reflect different retrieval strategies. Females were hypothesised to process intrinsic contextual attributes more than males, and consequently form more distinct representations of each stimulus. This richer representation would therefore allow better discrimination between 'old' and 'new' items, resulting in the different behavioural outcomes between males and females evident in studies, including the study by Guillem and Mograss (2005).

The studies discussed above provide convincing evidence for sex differences in memory retrieval, showing both behavioural and ERP differences. In particular females appear to perform better than males on episodic memory tasks, hypothesised to stem from differential engagement of strategic processes. In addition to ERP differences several other neuroimaging studies have found sex differences in neural activity associated with memory, including PET (Nyberg, Habib & Herlitz, 2000; Ragland et al., 2000) and fMRI (Ino et al., 2010) studies, highlighting the possibility of functional differences between males and females. The interactions between sex, ERP effects and stimulus materials further highlight the importance of understanding the influence individual

differences have on memory, including the need to characterise the processes engaged and associated changes in neural activity.

3.2 Genetic differences

Adoption and twin studies have shown that many human characteristics are highly heritable, including cognitive abilities. A twin study by McClearn, et al. (1997) estimates the heritability of memory performance to be as high as 52%, with 38% of memory performance variance estimated to be related to non-shared environment, and 0% to shared environment (assuming a measure reliability rate of 90%). The focus in cognitive genetic research is now beginning to move away from twin studies, to association and candidate gene work, in which attempts to identify specific genes and genetic polymorphisms that influence specific cognitive abilities and cognitive diseases are being made. In a similar way to which animal models are used to try and understand the biological underpinnings of cognitive operations, genetic analysis provides a direct insight into the biological foundations of individuals, and may allow a greater understanding of the biological contribution to cognitive abilities.

3.2.1 Introduction to genetics

Each human cell contains a set of instructions that indicates their function and activity in the form of chromosomes, organised structures of deoxyribonucleic acid (DNA). Humans have 23 different chromosomes in each cell, with two copies of each kind (one maternal and one paternal) making a total of 46 chromosomes. DNA is made up of a series of alkali bases, or nucleotides, of which there are four types: adenine (A), thymine (T), guanine (G) and cytosine (C). The DNA molecule is made of two twisted strands of nucleotides joined together by hydrogen bonds. The pairing of these nucleotides (also known as base pairing) is very specific, with A only binding with T,

and C only with G. The sequence of these nucleotides provides a template for making proteins. Three nucleotides (a codon) create a template for an amino acid, and a series of codons creates a chain of amino acids, which fold into the specific 3-D structure of the proteins coded for by the amino acid sequence. The specific sequences of nucleotides that code for proteins are referred to as genes, and the structure of a protein, and hence its function, is defined by the sequence of amino acids, as per the instructions encoded in the gene. Only approximately 2% of human DNA is thought to make up protein coding genes (Pennisi, 2007), but in general the role of the remaining 'non-coding DNA' is currently unclear.

It is estimated that the human genome contains between 20,000 and 25,000 protein-coding genes with the number of nucleotides currently estimated to be upwards of 2,850,000,000 (International Human Genome Sequencing Consortium, 2004). The DNA sequence of all humans is 99.9% the same; however, that small 0.1% difference goes some way towards accounting for the variations that exist between individuals. There are two main types of genetic mutation that occur, point mutations and chromosome mutations. Chromosome mutations tend to be large-scale mutations affecting large areas of the chromosome, and include deletion, duplication, inversion, insertion and translocation mutations (see Figure 3.1a). By contrast, point mutations are much smaller, in some cases involving only a single nucleotide. There are three main types of point mutation; insertion, where a nucleotide is added; deletion, where a nucleotide is lost; and substitution, where a nucleotide base is replaced by another (see Figure 3.1b). The existence of more than one possible sequence variation at a specified location, and the fact that these mutations only occur on one nucleotide, is referred to as a single nucleotide polymorphism (SNP). The number of SNPs that have been identified in the human genome is approximatley 1.4 million (Kruglyak & Nickerson, 2001),

however these SNPs may not all be functional. This means that although different sequence variations may occur, the different polymorphisms may not all have significant consequences for the protein. It is not yet clear what proportion of SNPs are functional however, nor how many of these will affect cognition. Nonetheless, given the importance of proteins in the brain, it is clear that polymorphisms that do affect the behaviour and expression of proteins may also affect cognitive processing.

At an individual level an organism's genotype is the combination of allelic variations and mutations that it possesses, the genetic makeup of the organism. The observable characteristics such as morphology, behaviour and development are referred to as the organism's phenotype. The phenotype can be affected by both genetic and environmental factors, and research is beginning to be undertaken to try and understand the separate contributions of these factors to different phenotypes. The phenotype of interest in this thesis is episodic memory capability, and in an attempt to begin to understand the role of genetics in episodic memory, research investigating four SNPs (APOE, BDNF, COMT and KIBRA) will be considered. These SNPs are not, of course, the only possible candidates - with estimates of 1.4 million SNPs in the human genome there are no doubt many more which may affect episodic memory. The choice of these SNPs is driven by their having been the focus of recent research, with evidence for their involvement in memory and memory disorders. Below a brief review is provided of existing evidence for each SNPs contribution to memory.

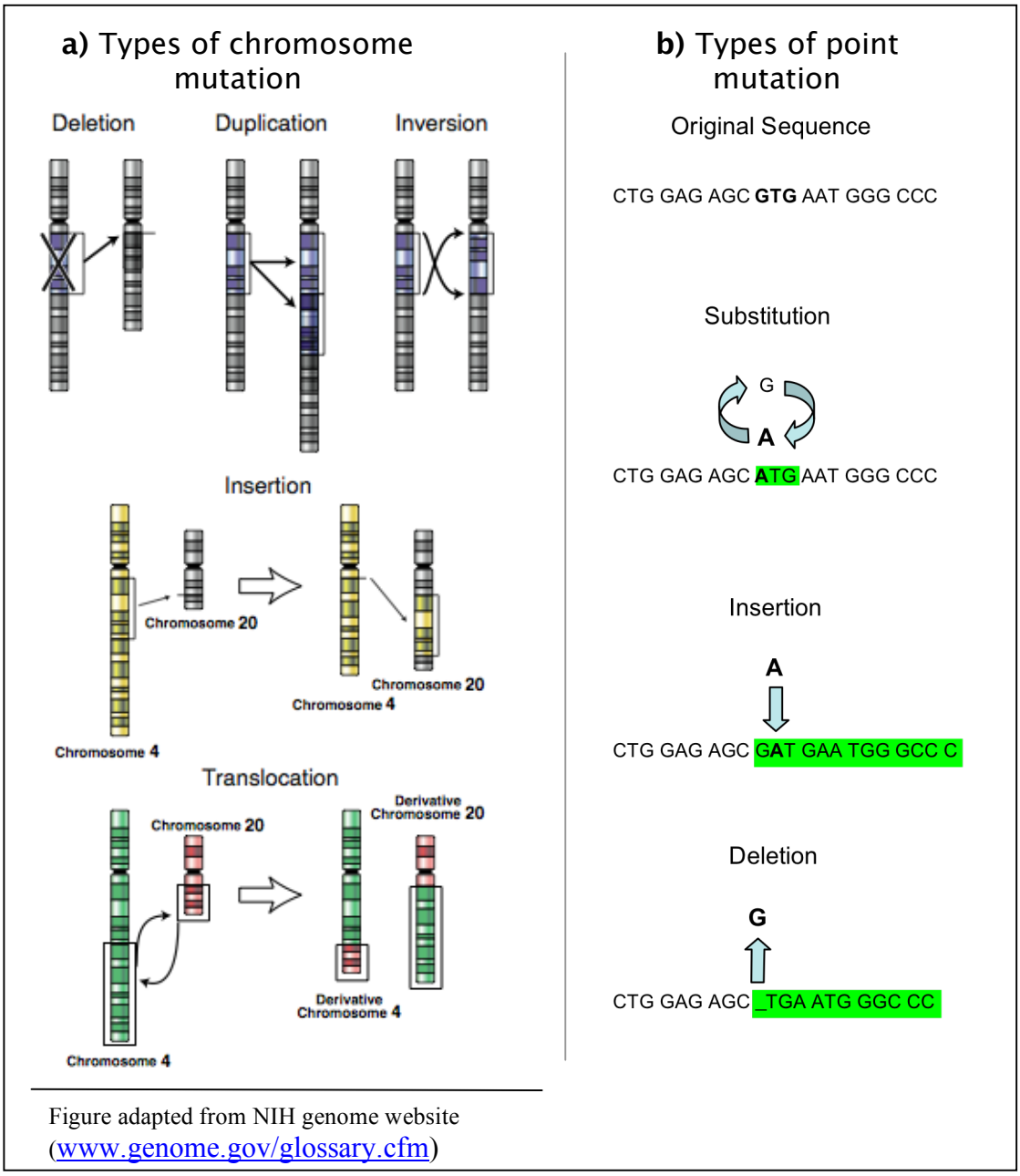


Figure adapted from NIH genome website (www.genome.gov/glossary.cfm)

Figure 3.1 Schematic diagram illustrating types of chromosome and point mutations. The size of the mutated DNA section can range from a single nucleotide base to a whole chromosome. (a) Types of chromosome mutation; deletion (the loss of a section of DNA from the chromosome), duplication (a reproduction of a piece of DNA is added to the chromosome) inversion (the reversal of a DNA segment in the chromosome) insertion (the addition of extra DNA into the chromosome) and translocation (the removal of a section of DNA from one chromosome and the attachment of this segment to another chromosome). (b) Types of point mutation; substitution (the replacement of one nucleotide with another), insertion (addition of a nucleotide) and deletion (loss of a nucleotide). The substitution mutation will only affect one codon, however, both the insertion and deletion mutations will also affect all the codons after the point of mutation.

3.2.2 SNPs and memory

Apolipoprotein E (APOE)

One of the most studied SNPs in relation to memory is APOE. APOE is an apolipoprotein typically known for its role in lipid metabolism (Tsai, Hong, Yu & Chen, 2004) and is thought to play a part in many different metabolic functions in the brain (Strittmatter & Roses, 1995). The APOE gene, located on the long arm (q) of chromosome 19, is polymorphic with three main alleles, ε2, ε3 & ε4. These alleles differ from each other by two single nucleotide substitutions, one at position 112 and one at position 158 (Figure 3.2). These substitutions result in an amino acid change from arginine to cysteine at position 158 in the ε2 variation, and from cysteine to arginine at position 112 in the ε4 variation (Weisgraber, Rall & Mahley, 1981). The proportion of people with each genotype in Caucasian populations is approximately 2% C/C, 26% C/T, 71% T/T for the APOE rs429358 SNP, at position 112 (dbSNP ss76884559) and 89% C/C, 10% C/T, 1% T/T for the APOE rs7412 SNP, at position 158 (dbSNP ss107936539, www.ncbi.nlm.nih.gov/projects/SNP). The ε3 variant is the most common, and therefore considered the 'wild type' isoform, accounting for approximately 78% of all chromosomes, the ε4 variant represents approximately 15% and the ε2 variant approximately 7% (Strittmatter & Roses, 1995). Whilst the ε3 allele is considered normal, the ε2 and ε4 alleles are considered dysfunctional and have been associated with several disorders including Alzheimer's Disease (AD).

AD is the most common form of dementia (Lahiri, Sambamurti & Bennett, 2004). It is a debilitating neurological disorder characterised by extracellular amyloid plaques, intracellular neurofibrillary tangles, leading to neuronal dysfunction and ultimately death. AD results in progressive loss of cognitive function with one of the earliest signs

being difficulty in retrieving episodic memories (Lahiri, Sambamurti & Bennett, 2004; Driscoll, McDaniel & Guynn, 2005). Research suggests that possession of an ε4 allele increases the likelihood of an individual developing Alzheimer's, with those from Caucasian populations homozygous for the ε4 variant having an odds ratio (OR) for developing AD of 12-15, and those heterozygous for the ε4 allele with an OR of 1-3. The increased risk of Alzheimer's is of course relative to the ε3/ε3 reference group, which are assumed to have an OR of 1 (Farrer et al., 1997). In addition there is some suggestion that the ε2 allele can actually reduce the risk of AD (Corder et al., 1994), with an OR of 0.6-1 for ε2/ε2 and ε2/ε3 carriers, and OR 1-3 for ε2/ε4 carriers (Farrer et al., 1997).

Although variations in the APOE allele have been clearly linked to changes in Alzheimer's risk the underlying cause of the link between APOE SNP and AD remains unclear. Savitz, Solms and Ramesar (2006) summarise the main theories. The essence of these theories relates to the efficiency/inefficiency of the ε4 isoform to bind to β-amyloid peptides and microtubule-associated protein tau (Mapτ), as well as the deficiency and inhibitory effect of the ε4 isoform on neuronal repair. AD is not the focus of this thesis, and therefore details of these theories will not be discussed here. However, given the link between AD and memory the question of how APOE SNPs affect episodic memory in healthy populations arises.

a)

Allele	Position 112 (rs429358)	Position 158 (rs7412)
ε2	Cysteine (**T**GC)	Cysteine (**T**GC)
ε3	Cysteine (**T**GC)	Arginine (**C**GC)
ε4	Arginine (**C**GC)	Arginine (**C**GC)

b)

Genotypes				
		Chromosome (Maternal)		
		ε2	ε3	ε4
Chromosome (Paternal)	ε2	ε2/ε2	ε2/ε3	ε2/ε4
	ε3	ε3/ε2	ε3/ε3	ε3/ε4
	ε4	ε4/ε2	ε4/ε3	ε4/ε4

Figure 3.2 a) Indicates the SNP variants for APOE. The change in nucleotide (indicated by the bold letter) at each position is listed with the corresponding allele label. b) Indicates the possible genotypes for APOE. Although there are nine different allele combinations the heritage (maternal/paternal) of these alleles is irrelevant for the current discussion and therefore people will have one of six genotypes, ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, or ε4/ε4.

The role of APOE ε4 in the predisposition of AD has led to an increased interest in healthy ε4 carriers, with a particular focus on the effect of the APOE ε4 allele on cognition in the normal aging. Small et al. (2000) report similar levels of performance across several tests of cognition, including episodic memory, in both ε4 and non-ε4 carriers aged 60-84 years, suggesting that the ε4 allele is not related to cognitive functioning in normal aging. Similar findings are also reported by Jorm et al. (2007) who tested three different age groups (20-24, 40-44 and 60-64 years) and found no overall interaction between APOE genotype and episodic memory performance.

In contrast, a study by Wilson et al. (2002b) found that the rate of decline in all forms of cognition was associated with the APOE ε4 allele in participants aged over 65. Moreover, the effect on episodic memory was more pronounced compared to other types of cognition, with the rate of decline (as measured by the amount a composite score of episodic memory performance changed over time) three times faster for ε4 carriers compared to non-carriers. The composite score was calculated from a series of episodic tasks including word list memory; recall and recognition; immediate and

delayed recall of the East Boston Story, and Story A from Weschler Memory Scale - Revised (WMS-R) logical memory. These findings are supported by Nilsson et al. (2006) who found a significant decrease in episodic memory performance, again defined by a composite score (see Table 3.1), for ε4 carriers aged 70-85 compared to non-carriers in the same age group. Furthermore, Nilsson et al. (2006) reported that the APOE ε4 effect was more pronounced in tests of episodic recall compared to tests of recognition.

An interesting twist in the story also comes from Nilsson et al. (2006) who found that the composite episodic memory score of participants aged 55-65 years was superior for participants with one ε4 allele. That is, participants with a ε3/ε4 genotype exhibited better episodic memory performance than those with a ε3/ε3 genotype. However, those homozygous for the ε4 allele in this age group still showed the poorest performance on the episodic memory test. Nilsson et al. (2006) also report a similar, although less pronounced, pattern for the 35-50 year age group. This later study therefore suggests that possession of one ε4 allele can have a positive effect on memory, whilst having two ε4 alleles is detrimental to memory.

At this point, based on studies focusing on episodic memory, there appears to be evidence suggesting that a) the APOE ε4 allele does not effect episodic memory across any age range - from 20 to 84 years (Small et al., 2000; Jorm et al, 2007); b) that it can increase the rate of episodic memory decline after the age of 65 (Wilson et al., 2002b); and c) that it can decrease episodic memory decline over the age of 70 (70-85 years), but prior to that age only possession of two ε4 alleles results in negative performance, whereas carriers of a single ε4 allele perform better (Nilsson et al., 2006). Therefore, the

findings presented so far provide a confusing picture as to the role of APOE ε4 in memory in healthy participants.

More broadly, Savitz, Solms and Ramesar (2006) examined 45 studies investigating APOE and cognitive function. Despite finding that elderly and middle-aged non-demented individuals with a ε4 allele performed more poorly on neuropsychological tests than those with no ε4 allele, Savitz and colleagues (2006) concluded that this decrease in performance, is likely to be the result of ε4 carrying individuals being in the initial stages of AD. Consistent with this view the existence of preclinical episodic memory deficits in individuals several years before an AD diagnosis is made (Bäckman, Small & Fratiglioni, 2001) is a recognised problem when testing older populations. Thus, whilst it is clear that there is a relationship between the ε4 variant and AD, this association is not yet well understood, making it difficult to assess the relationship between the ε4 allele and normal cognitive aging.

Due to the link with AD there has been a tendency in previous research to group people into two categories, ε4 and non-ε4 carriers, with little research on the effect of the ε2 and ε3 alleles. However, Wilson, Bienias, Berry-Kravis, Evans and Bennett (2002a) found that decline in episodic memory performance over an 8 year period (i.e. a change in composite score over time), was reduced for participants aged over 65 years with at least one ε2 allele compared to those homozygous for the ε3 allele. Like those of Wilson et al (2006) these findings suggest that the ε2 allele may protect against episodic memory decline. Participants with at least one ε4 allele on the other hand showed greater episodic memory decline compared to the reference group (ε3/ε3). Again, however, despite the apparent protection against episodic memory decline, the potential

role of the ε2 allele in reducing the risk of AD in later life (Corder et al., 1994), makes it difficult to draw any firm conclusions about the role of APOE ε2 in normal aging.

Finally, it is important to recognise that the link between APOE and AD means that in research investigating the effect of APOE genotype on episodic memory, there has been a tendency to focus on aging populations. However, a study by Mondadori et al. (2006) with a young population (mean age 22.8 years) produced some fascinating findings. Mondadori et al. (2006) found that for young participants the ε4 allele is advantageous, with ε4 carriers performing better at delayed recall for words than ε2 and ε3 carriers. In addition, over successive learning trials, for both single faces and face-profession associations, ε4 carriers showed decreased neural activity (measured using fMRI), whereas ε2 and ε3 carriers showed increased activity, despite being matched on performance level. These genotype differences were evident in bilateral hippocampus, left orbital gyrus, and left posterior middle temporal cortex in the face-profession association task, and in the left hippocampus and middle frontal gyrus in the single-item face task. Therefore, better retrieval performance (correctly remembered associations and correctly remember faces) was associated with a decrease in activity over learning trials for ε3/ε4 genotypes, but an increase in activity for ε3/ε2 genotypes. Furthermore, during retrieval, ε3/ε4 genotypes showed reduced neural activity compared to ε3/ε2 genotypes - despite being equated for performance. Specifically, ε3/ε4 carriers exhibited a smaller increase in activity over the right hippocampus and left fusiform gyrus for associations (comparing activity for the association and single-item tasks) than ε2/ε3 carriers, and a smaller increase over the right middle and superior frontal gyri, and right precuneus in the single-item task compared to baseline. Mondadori, et al. (2006) therefore suggest that, for young individuals, ε4 carriers have better episodic memory, and a more economic use of memory-related neural resources.

As for other populations, however, the results from studies of young populations are not consistent. For example, in a group of young adults (aged 20-35years) Filippin et al. (2009) report greater hippocampal activation for ε4 carriers compared to homozygous ε3 carriers during encoding of pictures, a difference that could not be explained by differences in recognition memory performance. Consistent with this, Dennis et al. (2010) found greater activation of bilateral MTLs for ε4 carriers compared to non-ε4 carriers during picture encoding, despite matched performance on a 24 hour delayed recognition task of representative words. In this study, however, ε4 carriers were also found to have reduced functional connectivity in MTL regions compared to non-ε4 carriers. The confusing picture emerging from fMRI data is highlighted in a review by Tractenberg, Filippini and MacKay (in press) looking at BOLD response and APOE ε4 genotype – notably the authors reveal discrepancies in the literature regarding both the directionality and location of the change in activity between genotypes.

In sum, research into the effect of APOE and episodic memory strongly indicates a link between APOE and AD, with ε4 carriers more predisposed to AD than ε3 carriers, and with a reduced risk for carriers of the ε2 allele. The relationship between APOE genotype and normal cognition is less clear. The ε2 and ε4 alleles again appear to have opposing effects in relation to both neuronal activity in the young, and also rate of cognitive decline in the elderly. It is difficult, particularly with the older populations, to disentangle the effect of APOE genotype on normal cognition, and its influence on AD. At this point, it is really only possible to conclude that there is an interaction between APOE genotype, episodic memory, age and AD, but despite recent research efforts the details of this interaction are not yet clear.

Research	Population	Measures	Tasks
Bäckman, et al. (2001)	Swedish 75 yrs +	- Number of words recalled. - Discrimination index for recognition (hits -false alarms).	Word recall and recognition
Dennis et al. (2010)	Young adults ε4+: 21.8 yrs ± 3 ε4-: 20.8 yrs ± 3	- Animacy decision accuracy and reaction time. - Subsequent item memory hit rate and false alarm rate.	- Animacy decision at encoding. - 24hr delayed recognition memory task, with confidence 6 point judgements. - Pictures presented at study followed by representative words at test.
Filippini et al. (2009)	UK 20-35 yrs	- % of correct responses (global performance, familiar items, distractors). - Resting state activity (fMRI). - Encoding related activity (fMRI).	Single-item recognition of pictures ~50 minutes after encoding.
Jorm et al. (2007)	Australian 20-24 yrs 40-44 yrs 60-64 yrs	- Number of words recalled.	- California Verbal Learning Test: Immediate and delayed recall of nouns.
Mondadori et al. (2007)	Large sample: 22.8 yrs ± 4 Small sample: 22.3 yrs ± 3	Large sample: - Number of words recalled. Small sample (fMRI): - Encoding related activity. - Retrieval related activity. - Number of remember (hits - false alarms) and know (hits - false alarms) responses. - Number of remembered associations.	Large sample: - Immediate and delayed free recall of words. Small sample (fMRI): - Single face recognition and remember/know judgements. - Face-profession association including face recognition and profession cued recall by category selection (academic or workman).
Nilsson et al. (2006)	Swedish Middle age (35-50 yrs) Young-old (55-65 yrs) Old-old (70-85yrs)	Composite score.	- Immediate free recall of words, and short sentences with and without enacting at encoding; cued recall of short sentences. - Free-choice recognition of faces and nouns from short sentences; forced-choice recognition of names. - Source recall of sentences (enacted/non-enacted). - Memory for activities. - Prospective memory with and without cueing.
Small et al. (2000)	USA 60-84 yrs	- Number of words recalled. - Discrimination index for recognition (hits - false alarms).	- Hopkins Verbal learning Test: Immediate recall, delayed free recall, cued recall, recognition.
Wilson et al. (2002a) Wilson et al. (2002b)	USA 65 yrs +	Composite score.	-Word list memory. - Recall and recognition from the Consortium to Establish a Registry for Alzheimer Disease neuropsychological battery. - Immediate and delayed recall of East Boston Story, and Story A from logical memory (WMS-R).

Table 3.1 Summary of measures used to assess episodic memory function in relation to APOE. Table lists details of the populations tested, measures reported and tasks used for each study described above.

Brain-derived neurotrophic factor (BDNF)

A second SNP investigated in relation to episodic memory is a variation in the genetic sequence for Brain-Derived Neurotrophic Factor. BDNF is a protein involved in the regulation of cell survival, multiplication and synaptic growth in the central nervous system. BDNF is also important in the modulation of synaptic changes including hippocampal Long-Term Potentiation – LTP (Poo, 2001), a process important in learning and memory. The gene for BDNF has been located on the short arm (p) of chromosome 11, and a SNP has been identified at codon 66 of the DNA sequence. The SNP (val^{66}met) is a valine (G) to methionine (A) amino acid substitution caused by a nucleotide change from guanine to adenine on the 196th nucleotide base of the sequence. The proportion of people with each BDNF genotype in Caucasian populations is approximately 3% A/A, 34% A/G, 64% G/G (dbSNP ss12586728, www.ncbi.nlm.nih.gov/projects/SNP), with G/G the 'wild' type isoform.

The valine to methionine SNP does not directly affect the mature BDNF protein, but affects the precursor peptide of BDNF (pro-BDNF), an inactive form that is activated by a type of post-transcriptional modification. The SNP has been shown to alter the intracellular distribution and packaging of pro-BDNF, which in turn can affect the secretion of the mature BDNF peptide (Egan et al., 2003).

Research has also shown that the val^{66}met SNP can affect the morphology of the brain. Compared to homozygous val carriers, carriers of the met allele show a) a reduction in hippocampal formation volume (Pezawas et al., 2004; Szeszko et al., 2005; Bueller et al., 2006; although Richter-Schmidinger et al., 2011, found no difference in hippocampal volume between genotypes); b) a decrease in the volume of grey matter in

the cerebral neocortex - predominantly in the lateral convexity of the prefrontal cortex (Pezawas et al., 2004), the left uncus, right inferior parietal lobule, inferior temporal cortex, left occipital lobe (Eker et al., 2005), left parahippocampal gyrus, and bilateral heads of the caudate nucleus (Nemoto et al., 2006); and c) an increase in grey matter volume in the right inferior frontal gyrus and left temporal gyrus (Eker, et al., 2005). Furthermore, a significant interaction between aged related volume reduction and genotype has also been found with age related reduction in the volume of the Dorsolateral prefrontal cortex (DLPFC) greater for met carriers than homozygous val carriers (Nemoto et al., 2006).

In relation to memory performance Egan et al. (2003) found met carriers had poorer performance on episodic memory tasks than homozygous val carriers, when tested on the WMS-R delayed and immediate recall of two stories. In addition, Egan and colleagues showed that met carriers exhibited abnormal hippocampal activation, with increased caudal hippocampus activation bilaterally for met carriers compared to the more typical decreased activation shown in val homozygotes, when completing a working memory task. Interestingly, however, there was an absence of an association between BDNF genotype and behavioural performance on working memory and semantic memory tasks in the study by Egan et al. (2003), although Richter-Schmidinger et al. (2011) found met carriers performed significantly poorer than non-met carriers on a working memory task.

In relation to hippocampal functioning in episodic memory, Hariri et al. (2003) found that met carriers (compared to val/val genotypes) exhibited diminished hippocampal engagement, during both encoding and retrieval in a recognition task of novel, complex scenes. Furthermore, Hariri and colleagues found reduced recognition accuracy for met

carriers, supporting the findings of Egan et al. (2003). This finding of episodic memory impairment in met carriers is further supported by research conducted by Dempster et al. (2005) and Goldberg et al. (2008), although in contrast to Hariri et al. (2003), Goldberg et al. (2008) found that this impairment was limited to 'Hit' responses finding no impairment in CRs. In addition, Goldberg and colleagues also found that neither levels of encoding nor retrieval delay interacted with BDNF genotype, both of which would be expected if BDNF impacts core episodic memory processes. Nonetheless research clearly indicates an association between episodic memory and BDNF genotype in normal populations, with met carriers exhibiting poorer performance than val homozygotes.

In contrast to the findings in healthy participants, research into the effect of the BDNF val^{66}met SNP on AD has lead to conflicting findings. For example, Ventriglia et al. (2002) found an increased risk of developing AD for homozygous val carriers (independent of APOE genotype). By contrast, other research investigating the BDNF val^{66}met SNP as a susceptibility factor has found no difference between AD and controls in terms of allele frequencies or genotypes (Combarros, Infante, Llorca & Berciano, 2004; Nacmias et al., 2004; Akatsu et al., 2006).

A second BDNF SNP (C270T), a cytosine (C) to thymine (T) nucleotide substitution at position 270, has also been investigated in relation to AD. Research suggests that carriers of the T allele have a higher risk of developing AD then C allele carriers (Riemenschneider et al., 2002; Kunugi et al., 2001). There is, however, inconsistency with regards to time of disease onset, with research by Riemenschneider et al. (2002) suggesting BDNF C270T is a particular risk factor for early onset AD, and Kunuigi et al. (2001) finding no susceptibility for early onset AD, but a higher risk for late onset

AD. Therefore, whilst a clear conclusion about the role of BDNF polymorphisms on AD is not yet possible, it is apparent that BDNF genotype may play a role.

The BDNF SNP raises key issues that must be taken into account when assessing gene studies. As with all research into the effects of SNPs it is not possible to identify one SNP and test it in isolation. Effects that are identified with particular SNPs may in fact be the result of another SNP nearby, which may or may not have been identified. With this in mind, it is necessary to exercise caution with regard to the effect of these BDNF polymorphisms on susceptibility to AD. The differences in research results may suggest that the variation found between homozygous val carriers and met allele carriers by Ventriglia et al. (2002) is actually a function of the C270T SNP that occurs further along the DNA sequence, or vice versa. Thus, at this stage in the investigation of these effects it is not possible to say, with any certainty, the effect of BDNF SNPs on AD.

Nonetheless, in sum, it is apparent from the research reviewed above that BDNF val^{66}met SNP does have an effect on episodic memory and the functioning of the hippocampus. Met carriers were found to exhibit poorer performance on episodic memory tasks, and overall show diminished hippocampal engagement and reduced hippocampal volume compared to val homozygotes. The effect of the SNP on AD is less conclusive, but there is a clear suggestion within the literature that both val^{66}met and C270T BDNF SNPs may influence the development of AD in some way.

Catechol-O-methyltransferase (COMT)

COMT is an enzyme involved in the degradation of neurotransmitters such as dopamine, epinephrine and norepinephrine. The gene for COMT has been located on the long arm of chromosome 22, and a SNP has been identified at codon 158 of the genetic sequence. This SNP (val^{158}met) is a valine (G) to methionine (A) amino acid

substitution. The COMT val^{158}met SNP affects the activity level of the enzyme in the brain with approximately 40% more COMT activity associated with the val allele compared to the met allele in the DLPFC. This suggests that val allele carriers will catabolize dopamine faster than met allele carriers, and therefore reduce the amount of dopamine signalling in the DLPFC (Chen et al., 2004). The proportion of people with each COMT genotype in Caucasian populations is approximately 25% A/A, 46% A/G, 29% G/G (dbSNP ss76883807, www.ncbi.nlm.nih.gov/projects/SNP).

In relation to episodic memory de Frias et al. (2004) found that homozygous met carriers performed better than val carriers on tests of episodic recall. In this case a composite score of episodic recall was calculated from tests of free recall, cued recall and source recall of verbs and nouns; from sentence learning both with and without enactment; word recall with and without a concurrent card sorting task at study or test; memory for activities; and prospective memory. By contrast, no difference between genotypes was observed for tests of recognition (a composite score of episodic recognition calculated from tests of face, name and noun recognition). As for other SNPs, however, results are variable. For example, Schott et al. (2006) did not find a performance difference between genotypes on a word recall task, nor did they find an association with levels of processing. However, when comparing the fMRI results of val carriers and met homozygotes Schott and colleagues observed increased activation of the left fusiform gyrus and right-prefrontal cortex during deep versus shallow processing. The met homozygotes on the other hand showed increased activation of the posterior cingulate. In addition, during encoding, Schott et al. (2006) noted that val homozygotes exhibited stronger functional connectivity between the prefrontal cortex and the hippocampus.

In addition to the findings of de Frais et al. (2004) and Schott et al. (2006), Bertolino et al. (2006) found that recognition performance for novel complex scenes was better for met carriers than homozygous val carriers, in terms of number of correct responses. As for APOE and BDNF therefore, the findings with regards to the association between COMT val^{158}met and episodic memory performance are inconclusive, with evidence for and against an effect with both memory recall and memory recognition. By contrast there is greater correspondence in relation to neural activity. Supporting the findings of Schott et al. (2006), Bertolino et al. (2006) also reports reduced hippocampal and ventral lateral prefrontal cortex (VLPFC) functional coupling for met carriers. In addition for val homozygotes, Bertolino and colleagues found increased activation of the VLPFC during encoding and retrieval, again supporting the findings of Schott et al. (2006), and also reduced neuronal activity in the hippocampal formation in both these memory stages.

Taken together current COMT findings suggest that the val allele results in increased activation of the prefrontal cortex. Given the increase in catabolism of neurotransmitters in val carriers this increase in activation may be necessary to reach the same level of postsynaptic stimulation as the met variant. The research also suggests that carrying two val alleles reduces the functional connection between the hippocampal formation and the prefrontal cortex at encoding, and reduces hippocampal activity during both encoding and retrieval. By contrast, however, the findings with regard to the effect of the val^{158}met SNP on behavioural memory performance remains inconclusive, although the results do provide some evidence for a possible association between performance and genotype.

Kidney and brain expressed protein (KIBRA)

KIBRA, also known as WWC1 (WW domain-containing protein 1), is a signal transducer, which interacts with protein kinase C (PKC), specifically with the PKC zeta isoform (Büther, Plaas, Barnekow & Kremerskpthen, 2004). Protein kinases are enzymes involved in the phosphorylation of proteins in the cAMP pathway (discussed in Chapter 8) and consequently in LTP. Therefore, in association with PKC, KIBRA is potentially important in synaptic plasticity and memory formation. The gene for KIBRA has been located on the long arm of chromosome 5, and a SNP has been identified in which a thymine (T) nucleotide is substituted for a cytosine (C) nucleotide in the ninth intron[7] of the gene. The proportion of people with each KIBRA genotype in Caucasian populations is approximately 47% C/C, 43% C/T, 11% T/T (dbSNP ss11699008, www.ncbi.nlm.nih.gov/projects/SNP).

A study by Papassotiropoulos et al. (2006) highlighted the functional importance of KIBRA in memory, showing 24% better free recall performance for T allele carriers compared to non-T carriers, when recalling words from a 30 word list, after a 5 minute delay. This initial sample included 341 Swiss participants aged 18-48 years, and the findings were validated by a second sample of 256 American participants aged 20-81 years, which again showed better performance for T allele carriers, this time on the Buschke's Selective Reminding Test and Rey Auditory Verbal Learning Test (AVLT). In a follow-up fMRI study Papassotiropoulos et al. (2006) matched T carriers and non-T carriers for performance on the 5 minute delayed recall task, and found increased

[7] An intron is a section of DNA sequence that does not code for the amino acids used to make proteins. A gene is made up of intersecting introns and exons, which are nucleotide sequences that code for amino acids and consequently sections of the final proteins. Whilst introns are considered 'non-coding' sections of DNA, they may still be functional, potentially influencing the expression of the 'host' gene (Cooper, 2010).

activation of the MTL, frontal cortex, medial frontal gyrus and parietal cortex for non-T carriers compared to T carriers during face-profession associative retrieval. Papassotiropoulos et al. (2006) suggest that the increased activation of retrieval related brain regions for non-T carriers is necessary for non-T carriers to achieve the same level of performance as T carriers. No differences in neural activity between genotypes were found during encoding however, suggesting that the genotypic differences are specific to retrieval related processes.

In a large behavioural study of 2230 participants Kauppi, Nilsson, Adolfsson, Eriksson and Nyberg (2011) found increased memory performance for T-carriers compared to non-T carriers in an immediate free recall task for words, replicating the findings of Papassotiropoulos et al. (2006). However, in contrast to Papassotiropoulos et al. (2006), Kauppi et al. (2011) found increased hippocampal activity for T carriers compared to non-T carries during a face-name associative memory task (n=83); a difference that remained after matching the two genotype groups for age, sex and performance (n=64). Kauppi et al. (2011) conclude that better memory performance is mediated by increased hippocampal activation for T-carriers, in contrast to the hippocampal compensation theory suggested by Papassotiropoulos et al. (2006); in which increased hippocampal activity is needed in non-T carriers to reach the same level of performance as T-carriers.

The behavioural findings of Papassotiropoulos et al. (2006) have also been replicated by Schaper, Kolsch, Popp, Wagner and Jessen (2008) who found T carriers performed better than C carriers in tests of both recall and recognition, in a sample of 64 participants, and in a larger sample of 383 participants by Preuschhof, Heekeren, Li, Sander, Lindenberger and Bäckman (2010). Preuschhof et al. (2010) further demonstrated that the effects of KIBRA genotype change with the associative demands

of the task, with T carriers showing greater performance benefits when required to remember words as pairs rather than as two single items. Furthermore, Preuschhof et al. (2010) found an interaction with a second SNP, CLSTN2 (rs6439886), in which KIBRA T allele carriers who also carried a CLSTN2 C allele, performed better than other genotype combinations (i.e. C/C-T/T, T-T/T, C/C-C), highlighting the importance not only of KIBRA in memory performance, but that the interaction of SNPs are important.

Whilst the studies by Schaper et al. (2008), Preuschhof et al. (2010), and Kauppi et al. (2011) provide support for the findings of Papassotiropoulos et al. (2006), that the T KIBRA allele is beneficial to memory performance, a number of other studies find no such association. Need et al. (2008) found no association between KIBRA genotype and memory performance in two large European cohorts, looking at the Verbal Recognition Memory test from the CANTAB battery (n=319), and the AVLT (n=365), as per the Papassotiropoulos et al. (2006) study. Similarly, neither Burgess et al. (2011), with a sample of 2842 participants nor Wersching et al. (2011), with a sample of 545 participants, found an association between KIBRA genotype and performance on the AVLT. However, a study by Bates et al. (2009) only found an association between AVLT delayed memory scores and KIBRA after controlling for initial learning rates, suggesting that KIBRA may be associated with processes relating to forgetting rather than learning (as indicated by the fMRI study reported by Papassotiropoulos et al., 2006), and that genotypic differences in the studies of Need et al. (2008), Burgess et al. (2011), and Wersching et al. (2011) could be masked by differences in the degree to which information was initially learnt.

In relation to pathology, the KIBRA SNP has been shown to be associated with lower glucose metabolism in the posterior cingulate and precuneus brain regions for cognitively healthy, middle-aged, non-T allele carriers, and also with increased risk of late onsetting AD (Corneveaux et al., 2010). An additional large sample study (n=2571) by Burgess et al. (2011) supports the association between KIBRA genotype and AD, with the T allele again having a protective effect for late onsetting AD. The results in the Burgess et al. (2011) are strongest for African-American participants, with only a trend evident for Caucasian participants, suggesting a rather modest association between KIBRA and AD. A meta-analysis of over 8000 participants also suggests that the KIBRA T allele may be a protective factor against late onsetting AD, although again the statistical analysis suggests a modest association (Burgess et al., 2011).

Overall the general trend in studies finding associations between KIBRA and episodic memory indicate that the T allele boosts memory performance and can act as a protective factor against late onsetting AD. However, as with the other SNPs discussed, for every study showing an association between SNP and memory performance, there is another finding no association. The absence of an association in some studies may reflect greater differences in genetic makeup across samples, as indicated by the SNP-AD effect differences evident between African-American and Caucasian participants in the Burgess et al. (2011) study. However, in contrast to the other SNPs, the direction of the KIBRA- memory association is largely consistent across studies, with T carriers performing better than non-T carriers.

3.3 Conclusion

This chapter has discussed some of the biological differences that have been shown to influence memory, both in terms of performance differences and the neural activity

associated with memory encoding and retrieval, finding significant differences as a function of sex and genetic polymorphism. These individual differences highlight the importance of understanding factors that are formative in the outcomes of memory tasks, behaviourally and in the results from neuroimaging techniques, before employing these sensitive measures as biomarkers of disease.

In relation to the genetic research current work is trying to understand each SNP in isolation. When considering and evaluating these findings, it is important to consider the role of potential interactions between different SNPs. Interactions between genes are clearly an important factor in the resulting phenotype of an organism, and have been shown to influence memory performance (Preuschhof et al., 2010). Despite the importance of these interactions however, there is not currently an economically viable way in which detailed investigations of the impact of numerous SNPs on cognitive functions can be conducted. Whilst the figures relating to the population density of different combinations of genes is not currently available, we know that for the KIBRA SNP the proportion of each genotype in Caucasian populations is approximately 47% C/C, 43% C/T, 11% T/T (dbSNP ss11699008, www.ncbi.nlm.nih.gov/projects/SNP) and for the BDNF SNP 3% A/A, 34% A/G, 64% G/G (dbSNP ss12586728). Given that the proportion of the population with the rare BDNF SNP is only 3% it is currently difficult to investigate the met/met (A/A) genotype in isolation, if this is combined with the three KIBRA variants, where the rare variation has a population frequency of 11%, the number of participants needed for a successful study are substantial. Assuming that the probability of carrying the rare BDNF genotype is unrelated to the probability of carrying the rare KIBRA genotype (data relating to the probability of carrying combinations of genes are currently not available), then 0.03 (probability of rare BDNF genotype A/A) x 0.11 (probability of rare KIBRA genotype T/T), the probability of

carrying BDNF A/A and KIBRA T/T = 0.0033. Therefore, in theory, to have a sample of 33 participants with BDNF A/A and KIBRA T/T genotype, 10,000 people would need to be screened.

Studies such as Preuschhof et al. (2010) that investigate the interactions of at least two SNPs (although not necessarily all genotypes of these SNPs) in large samples of several hundred participants are beginning to emerge. It is important to acknowledge however that the effects of genes on episodic memory are unlikely to be limited to the interaction between two genes anymore than they are one. In practice the number of participants needed to investigate all such genetic interactions would clearly make it impractical to carry out such research. Even if completed, the number of variations that exist would make the findings so detailed and specific that the conclusions that could be drawn from the study would be severely limited and difficult to generalise to the population in any way. Therefore, as with much of science, researchers must compromise between the level of detail that is useful, and that which is not. Whilst the interactions between genes are ultimatley important it is first necessary to investigate which specific genetic variations are involved in episodic memory before investigating the different combinations of genes that are likely to have the largest combined impact. Investigating SNPs in isolation is therefore the immediate aim of genetics research. Nonetheless, because our understanding of how genes interact with each other and with memory remains limited, it is important to continually be aware of potential interactions and consider the impact they may be having.

It is clear from the research reviewed above that there are associations between SNPs and episodic memory, but the details of these associations remain somewhat ambiguous. Whilst it is necessary to investigate the effects of single genetic variations

in order to further understand the biological and functional mechanisms that underlie memory, it is imperative that the bigger picture, involving the interactions of thousands of genes at numerous levels, is not forgotten. Additional factors such as ethnic group and environmental factors will also affect the interactions between genes and cognition, with each case described above really indicating a trend or predisposition.

The inconsistencies evident in the literature discussed above may relate to a number of different factors that resulted in a failure to replicate. These include differences in sample size, and consequently statistical power; ethnicity of the studied population, with different genetic polymorphisms known to exist in different ethnic groups (known as ancestry informative markers), which may interact with the candidate gene and therefore show different results across studies; geographic location of the studied population, differing geographic locations will vary in the environmental pressures exerted; similarly special populations, such as studies of nuns and priests, will have differing environmental influences to a more general, varied population.

There is no hard and fast rule stating that possession of a particular SNP will result in a particular outcome, and identical genotypes do not need to result in identical phenotypes. The relationship between genotype and phenotype is nicely illustrated by Mitchell's (2007) interpretation of Waddington's (1957, as cited in Mitchell, 2007) epigenetic landscape, in which he describes an organism as a ball moving through a landscape of valleys, the shape of which is determined by an individual's genotype. The valleys in this analogy represent different phenotypic states. Given the same landscape (or genotype) two runs of the ball (A and B) will not necessarily follow the same path, and therefore may end up in different valleys (with different phenotypes). The differences in paths taken may be the result of chance events or environmental effects

which influence the direction taken (Figure 3.3). Phenotypic variations caused in this manner cannot be investigated through genetics, but what genetic analysis can provide is a landscape that suggests the possible paths that may be taken.

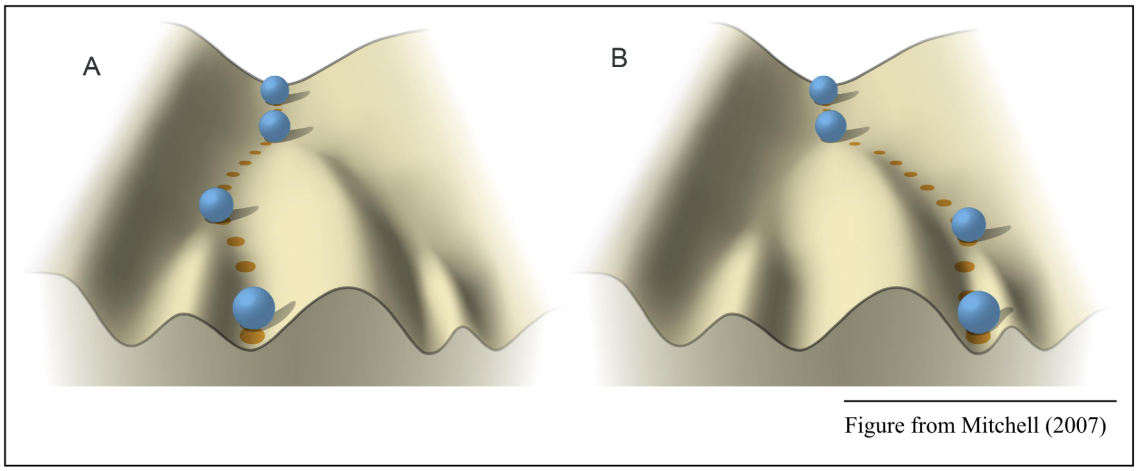


Figure 3.3 Schematic illustration of Waddington's Epigenetic Landscape (1957, as cited in Mitchell, 2007). This diagram represents the relationship between genotype and phenotype. The ball represents the organism rolling around a landscape (the genotype). Despite the identical landscapes in parts A and B the path the ball takes in each image differs. This demonstrates how differing phenotypes can manifest despite identical genotypes, as is the case in monozygotic twins.

3.4 Thesis aims

It is well known that memory ability differs between individuals with the majority, if not all, studies showing variability in task performance, response times and decision bias between participants. Furthermore evidence presented in the current and previous chapters suggest ERP recognition memory effects vary with task specific details, such as stimulus material (Galli & Otten, 2011; Mackenzie & Donaldson, 2007, 2009; Yick & Wilding, 2008), and individual differences, such as participant sex (Taylor, Smith & Iron, 1990; Guillem & Mograss, 2005). Taken together these findings suggest that the bilateral-frontal and left-parietal old/new effects typically associated with recognition memory processes may only occur under specific conditions, in relation to the task completed and the individual completing the task. Furthermore, more broadly, there is evidence to suggest differences in memory performance and neural activity as a

function of genotype, with several SNPs revealing significant behavioural and fMRI differences, as discussed above.

As discussed in Chapter 2, in ERP research grand average waveforms are made to reduce the influence of individual participant variation on the activity of interest. Whilst averaging is an important step towards universally understanding the neural activity relating to an event of interest, the question arises as to whether the final pattern of activity seen in grand averages accurately reflects the true pattern of activity exhibited by individuals. The issue of individual differences is of particular significance in understanding the development and progression of memory disorders. There has been a recent surge in interest in using ERPs as a biomarker of disease, to monitor disease progression and treatment outcome. Clearly, however, to use ERPs as a tool to understand disease progression it is firstly important to understand how ERP effects vary in healthy participants, and whether or not the selected ERP component is predictive of behavioural outcome. Despite evidence of task and individual differences in relation to ERP recognition memory components, some studies have already suggested using episodic memory ERP components, such as word repetition effects (Olichney et al., 2002; Olichney et al., 2006), as a biomarker of memory disorders. Therefore, a key question for researchers understanding memory processes and the associated ERP effects, is in what way do memory performance and ERP effects differ between individuals, and perhaps more importantly, why do they vary?

The focus of this thesis will be on episodic retrieval success, looking in particular at the ERP effects associated with familiarity and recollection. As outlined in Chapter 2, of the ERP retrieval effects, success effects are the best characterised and most robust memory effects, making them ideal for studying individual differences in episodic

memory. Material specific recognition effects will be investigated in relation to four different stimulus materials (words, pictures, faces and voices) using a simple old/new recognition task. The intention is to add to the current material specificity literature by including a homogenous verbal condition (voices) to match the homogenous pictorial stimuli (faces), further investigating the idea that faces are in some way special, or whether it is the homogeneity of the stimuli that is important. Therefore comparisons in this thesis will be made between two types of verbal stimuli, one heterogenous (words) and one homogenous (voices), and two types of pictorial stimuli, one heterogenous (pictures) and one homogenous (faces).

In relation to recognition memory for faces, there are clearly discrepancies in the literature as to the associated ERP correlates (Donaldson & Curran, 2007). One of the aims of this thesis is therefore to further investigate face recognition memory effects; through the single-item recognition for faces task, and using a source memory task for faces and verbal phrase pairs. Analysis of ERP recognition effects for faces will be made contrasting face recognition effects a) with and without successful retrieval of source information, b) with and without additional source retrieval task demands, and c) in participants considered good at remembering faces, as indexed by the single-item recognition for faces task, with those who struggled with the task. Through such analyses it is hoped that a better understanding can be gained of the reasons behind the discrepancies within the literature.

In addition to task related differences, this thesis also aims to investigate individual differences, examining the relationship between behavioural performance and ERP old/new recognition effects. A crucial criterion in using an ERP correlate as a disease biomarker is that the ERP effect is predictive of the behavioural outcome, and is

therefore an index of the process being monitored. ERP studies of recognition memory have identified a set of old/new effects that are thought to reflect the processes of familiarity (the 300-500ms bilateral-frontal effect) and recollection (the 500-800ms left-parietal effect). Whilst the exact functional role of these effects remains unclear, they are widely viewed as reliable indexes of retrieval, with previous evidence suggesting that variation in the magnitude of the left-parietal effect reflects changes in the amount or quality of information retrieved during source memory tests (Chapter 2). It is therefore expected that these old/new effects will be good predictors of memory performance, and reliable across tasks, predictions that will be tested in this thesis.

Finally, as discussed in the current chapter, there is evidence indicating genetic differences in both memory performance and neural activity associated with memory. To date however, there does not appear to be any published studies examining genetic variation in relation to ERP episodic memory effects. Thus, a further aim of this thesis is to investigate a number of candidate SNPs in relation to both behavioural and ERP measures, to see if the ERP correlates of recognition memory are modulated by an individual's genetic makeup. Through such analyses a greater understanding of the influence of biological variables on these measures of recognition memory will be gained, and the reliability of these ERP effects at the individual level will be tested.

3.4.1 Summary of research aims

Overall this thesis aims to investigate individual differences in episodic memory, looking at behavioural and ERP measures in an attempt to gain a greater understanding of how episodic memory differs as a function of stimulus material, task performance, and genetic polymorphisms. The research aims to address four main questions:

1. **Do the neural correlates of episodic memory vary with stimulus material, and what drives material specificity effects? (Chapter 5)**
    a) Are differences in the pattern of ERP activity across stimulus materials driven by stimulus type (i.e. verbal versus pictorial)?
    b) Are differences in the pattern of ERP activity across stimulus materials driven by stimulus homogeneity (i.e. faces versus pictures)?

2. **What factors cause face recognition effects to vary? (Chapter 6)**
    a) Are the ERP correlates of face recognition memory sensitive to successful source retrieval in a face-verbal phrase pairs task?
    b) Do the ERP correlates of face recognition vary in relation to task demands (i.e. item v. source)?

3. **Are the bilateral-frontal and left-parietal old/new effects good predictors of memory ability? (Chapter 7)**
    a) Does behavioural performance modulate the bilateral-frontal effect?
    b) Does behavioural performance modulate the left-parietal effect?

4. **Is recognition memory sensitive to genetic variation? (Chapter 8)**
    a) Do behavioural measures of recognition vary with genotype?
    b) Do the ERP correlates of recognition memory vary across genotype?

Chapter 4
General Methods

This chapter describes the methods used in this thesis providing details concerning participants, stimulus materials, procedures, data processing, and analyses used. The aim of the thesis is to investigate individual differences in episodic memory, looking at the influence that a variety of different individually varying factors have on behavioural and electrophysiological measures of episodic memory. All participants completed the same series of experiments, referred to as the 'study', providing a wealth of information about each participant, and allowing the influence of several key factors (relating to variation in experimental, biological and cognitive function) to be investigated. Whilst this chapter describes the fundamental methodological aspects of the study, specific details regarding participant inclusion and analyses at the level of each factor under investigation are included in the relevant experimental chapters.

4.1 Study Participants

The Department of Psychology's Ethics Committee at the University of Stirling gave ethical approval for the study, and participants were recruited from the University of Stirling. One hundred and twenty nine participants took part in the study and all reported being aged between 17-35 years, right-handed, native English speakers, with normal (or corrected to normal) vision, with no history of colour blindness, hearing difficulties, dyslexia, neurological problems, brain injury, CNS infection, drug or alcohol abuse, and had not or were not currently receiving treatment for a psychological illness. Participants were reimbursed for their participation at a rate of £5 per hour.

Those participants on undergraduate psychology courses were given the option of receiving two credits for the first hour of each session (instead of the £5 reimbursement) to satisfy requirements on these courses. Informed consent from all participants was obtained prior to participation in each part of the study, and participants were fully debriefed at the end of the last session.

4.2 Overall procedure

A brief overview of the experimental procedure is given here to provide an idea of the overall structure and time-line of testing sessions before going on to discuss each section in more detail. The experiment consisted of three main stages, an initial screening, an ERP experimental session, and a psychometric/neuropsychological assessment session. Firstly participants were emailed a background details questionnaire to obtain some descriptive information about them (e.g., age and gender), and were re-sent the exclusion criteria to provide an extra check as to their suitability to participate in the study. Participants subsequently visited the lab on two occasions that were typically within seven days of each other, with an average of 4 days (s.d. 3 days). In the first session participants were fitted with an EEG cap and completed a series of single-item recognition memory tasks (using faces, pictures, words and voices) and a source judgment memory task looking at memory for face-verbal phrase pairs. After completion of the memory tasks and the termination of the EEG recording a DNA sample was collected from each participant. In addition, participants then completed two questionnaires: the Psychiatric Diagnostic Screening Questionnaire: PDSQ (Zimmerman, 2002) and the Eysenck Personality Questionnaire – Revised edition: EPQ-R (Eysenck & Eysenck, 1991).

The second session comprised a variety of psychometric and neuropsychological test batteries including the Wechsler Memory Scale third edition (UK): WMS-III^{UK} (Wechsler, 1998), Wechsler Abbreviated Scale of Intelligence: WASI (Wechsler, 1999) and seven tasks from the Cambridge Neuropsychological Test Automated Battery - eclipse version 3: CANTABeclipse (Cambridge Cognition Ltd, 2006). Additional brief PDSQ follow-up questions were asked if analysis of the questionnaire indicated a follow-up was required (see Figure 4.1 for an overview of the procedure).

Procedure Overview

- Participants sign up for study and are allocated a participant number.
- Participants are asked to complete a background details questionnaire prior to experimental sessions.
- Session 1
  - Background details questionnaire verified.
  - Single-item recognition memory tasks (including recognition for faces, pictures, words and voices) completed.
  - Source judgment memory task (face + verbal phrase pairs) completed.
  - DNA sample collected.
  - PDSQ completed.
  - EPQ –R completed.
- Session 2
  - WMS-III^{UK} completed.
  - WASI completed.
  - CANTABeclipse completed:
    - MOT
    - IED
    - RVP
    - SOC
    - SRM
    - SSP – Forwards
    - SSP – Backwards
    - SWM.
  - Brief PDSQ follow-up if required.

Figure 4.1 Procedure overview.

4.3 Background details questionnaire

Prior to the first experimental session participants were asked to complete a background details questionnaire. This questionnaire provided information about participants

relating to age, sex, handedness, native English speaker status, ethnicity of self and parents, and familial history of AD. Participants were also asked to indicate any factors they thought may influence the EEG recording and to list any current use of medications. As well as providing basic demographic data about participants, this information allowed the participants' suitability to take part in the study to be checked. The questionnaire confirmed eligibility to take part and no participants were rejected on the basis of the questionnaire.

4.4 Stimulus materials

Five different categories of stimuli were used in the experimental tasks; the single-item recognition tasks included face, picture, word and voice stimuli types (illustrated below in Figure 4.2), and the source-judgment task used face and verbal phrase stimuli (illustrated below in Figure 4.3). Details relating to the acquisition and preparation of each stimuli category will now be discussed.

4.4.1 Pictures:

Picture stimuli consisted of 108 pictures taken from the International Affective Picture System (IAPS, National Institute of Mental Health Center for the Study of Emotion and Attention, 1999), consisting of photographs of a variety of subjects including animals, people, sport, landscapes and inanimate objects. Pictures were selected from the IAPS set based on valence and arousal scores, and were hand-filtered to remove unsuitable images, either in terms of content (i.e. an image of the twin-towers where arousal ratings are likely to have changed since the release of the stimuli set), or due to variations in presentation styles (i.e. presence of black borders surrounding the picture). Eight pictures were randomly selected for use during practice trials and the remaining 100 in experimental trials. The images selected for use in experimental trials had a mean

valence rating of 6.95 (s.d. 0.70) and a mean arousal rating of 4.62 (s.d. 1.00). The 100 pictures were sorted by valence and then arousal before alternately assigning pictures to one of two lists, to be used as studied and unstudied pictures. List A had a mean valence rating of 6.37 (s.d. 0.42) and a mean arousal rating of 4.44 (s.d. 0.99). List B had a mean valence rating of 7.52 (s.d. 0.36) and a mean arousal rating of 4.81 (s.d. 0.98). The presentation of each list as studied or unstudied was counterbalanced across participants.

4.4.2 Faces:

Six hundred and seventy six photographs of faces, of which 341 were female, were taken from a series of smaller stimuli sets used by the Department of Psychology at the University of Stirling. Face photographs were hand-filtered, selecting Caucasian individuals who did not have any distinguishing features such as jewellery, glasses or facial hair. An average image of each stimuli set was made using Psychomorph software (Tiddeman, Burt & Perrett, 2001), and all images were eye aligned using this set average. Images were also morphed 25% towards the colour of the set average image to reduce significant differences in the brightness of images. Using individual facial templates (which mark the features of each individual face) images were masked to conceal background, hair and ears, creating an image of a face devoid of heavily distinguishing features on a black background. Images were resized to ensure that each picture was the same size (although some variation in the size of the face on the background remained, the overall size of the picture was kept constant).

Three hundred and forty of the original set were used in the study, with 108 randomly allocated to the single-item recognition memory task and 232 to the source judgment task. The stimuli used in each task were kept consistent across participants. As

described with other stimuli sets eight of the 108 face images in the single-item task were used during practice trials and 100 in the experimental trials. The 100 experimental face image set was sorted by file name, set and gender and then divided into groups by alternately assigning images to one of two lists, to be used as studied and unstudied images. A similar method was used to divide the 232 face images in the source judgment task into studied and unstudied lists, as well as into blocks. An equal number of male and female face images were used in studied and unstudied lists across both tasks. The presentation of the studied and unstudied lists was counterbalanced across participants

4.4.3 Words:

Three hundred, six-letter words with a Kücera-Francis written frequency of 10-20 per million were randomly selected from the MRC Psycholinguistic database (Coltheart, 1981). Words with a Kücera-Francis written frequency (Kücera & Francis, 1967) of more than 13 per million were then removed leaving a list of 148 six-letter words with a Kücera-Francis written frequency of 10-13 per million. This list was subsequently hand-filtered to remove unsuitable words such as identifiers (i.e. EIGHTY, ANDREW), emotive or arousing words (i.e. NIGGER, BREAST), and visually similar words (i.e. MORTAR when MORTAL was present). Forty words were removed during hand filtering leaving 108 words, of which eight were to be used during practice trials and 100 in the experimental trials. The 100 experimental word set was alphabetised and then divided by alternately assigning words to one of two lists, to be used as studied and unstudied words. These two word lists, consisting of only six-letter words, were matched for frequency (mean Kücera-Francis written frequency for list A = 11.16, for list B = 11.24) and their presentation was counterbalanced across participants.

4.4.4 Audio stimuli:

Audio files were recorded using an Olympus WS-320M digital voice recorder and Sony microphone. Six hundred and sixty volunteers were recorded reading aloud five everyday greetings ('Hello', 'Good morning', 'How are you', 'Pleased to meet you' & 'Thanks') to create a pool of previously unheard voices. Volunteers were members of the public most of whom were visiting either University of Edinburgh Students Union or Glasgow Science Centre at the time of recording. A variety of ages (range 15-77 years) and nationalities were recorded with 351 of the volunteers being female.

Recordings were cropped using Praat software (Boersma & Weenink, 2008) to remove noise artefacts (such as breaths, pauses, clicks, etc) and delays at the start and end of recordings. The audio files were then processed using Wavosaur audio editor software (Wavosaur: www.wavosaur.com). Files were converted from stereo files to mono files using 50% from both the left and right channels. Bit depth was converted to 16 bits per sample and files were re-sampled at a rate of 22050 samples a second. A simple DC remover filter was run on all files to compensate for DC offsets that may have occurred. Finally, files were normalised to 0 decibel (dB) and auto-trimmed at -50dB.

One hundred and eight recordings of the 'Pleased to meet you' phrase, half female, were chosen for use in the single item recognition memory task for voices. A sub-set of the original stimuli set was selected in which all files were recorded in the same location (Glasgow Science Centre). The average length of a recording was 801ms (s.d. 69ms). These auditory files were hand-filtered to select the 108 clearest recordings from native English speakers, who had an age range of 17-68 years with a mean of 39.5 years. Eight of these voices were used for the practice trials with the remaining 100 used in the experimental trials. As with face stimuli, voice stimuli were organised by file name and

gender and were alternately assigned to one of two lists, to be used as studied and unstudied voices. These two voice lists were matched for recording time (mean for list A = 799ms, s.d. 68ms; for list B = 804ms, s.d. 70ms) and their presentation was counterbalanced across participants.

For the source judgment task verbal phrase stimuli were recordings of 'Hello' and 'Thanks' from one male and one female volunteer that had not been used in the single item recognition memory for voices task. The recordings selected were considered to be clear recordings from native English speakers that were rated by 12 participants as moderate on a scale of low to high distinctiveness.

4.5 Experimental tasks

All experimental tasks were run using E-prime software (version 1.1, Psychology Software Tools Inc: www.pstnet.com). Visual stimuli were presented on a 15" flat screen computer monitor positioned on top of a desk approximately one meter away from participants. Auditory stimuli were presented using loud speakers at a volume that participants were comfortable with. Participants responded using a PST Serial Response Box positioned on the desk in front of them.

4.5.1 Single item recognition memory tasks:

Participants completed four single item recognition memory tasks, each following the same procedure, which looked at recognition memory for pictures, faces, words and voices (Figure 4.2). Participants were instructed that they were going to be presented with stimuli that they should focus on and to try to remember for a later recognition memory test. Fifty items were presented during the study phase for 1000ms each, preceded by a fixation cross that was presented for 2000ms. In an attempt to ensure

participants were not relying on working memory, a one minute break between study and test was included, in which participants were instructed to relax and rest their eyes. During the test phase participants were presented with 100 stimuli to which they had to indicate using a five key button box if they had been presented with the stimuli in the previous phase (old) or not (new). Participants selected one button, either '1' or '5', to indicate an 'old' item and the other to indicate a 'new' item, the relationship between response and button press was counterbalanced across participants. Stimuli were presented for 1000ms each during the test phase and were followed by an infinite blank screen. Participants could respond either during the presentation of the stimuli or when the blank screen was displayed. When a response was made the trial ended and the next trial began. Participants were instructed to respond as quickly and accurately as they could, making their response as soon as they had made a decision. A fixation cross, presented for 2000ms, preceded each item and indicated the start of a new trial.

Stimuli were divided into two lists as detailed above. Presentation of stimuli within these lists was randomised, with studied and unstudied lists counterbalanced across participants. All stimuli were presented in the centre of the screen against a black background. Based on a viewing distance of approximately 100cm picture stimuli subtended a vertical visual angle of approximately 5.1˚ and a horizontal visual angle of approximately 6.4˚. Face stimuli subtended a vertical visual angle of approximately 10.9˚ and a horizontal visual angle of approximately 9.1˚. Word stimuli were presented in white, bold, 18 point Courier New font. During presentation of the voice stimuli a blank screen was presented. In an attempt to reduce EOG artefact a white fixation cross (+) was used between trials in all tasks to encourage participants to fixate their gaze in the centre of the screen. The order in which the four tasks were completed was counterbalanced across participants.

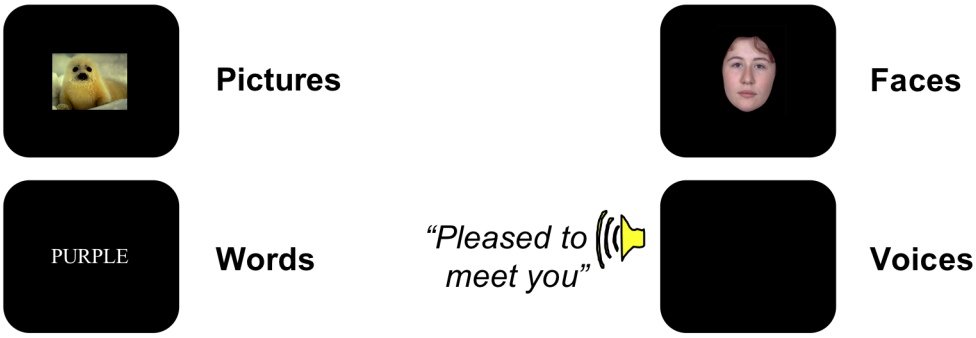


Figure 4.2. Schematic illustration (not to scale) of the four stimuli types – pictures, faces, words and voices.

4.5.2 ***Source Judgment task:***

After completing four single item recognition memory tasks participants completed a source judgment task involving face-verbal phrase pairs. This task was presented in eight short study/test blocks of 14 study pairs and 28 test pairs (the size of these blocks was determined by a series of pilot studies). Participants were presented with a picture of a face, accompanied by a verbal phrase of either "Hello" or "Thanks". Faces were presented for 1000ms and were preceded by a fixation cross presented for 2000ms. Participants were instructed to focus on each face as it was presented and to try and remember which phrase was paired with the face. In an attempt to ensure participants were not relying on working memory, a one minute break between study and test was included. During the break participants were instructed to relax and rest their eyes.

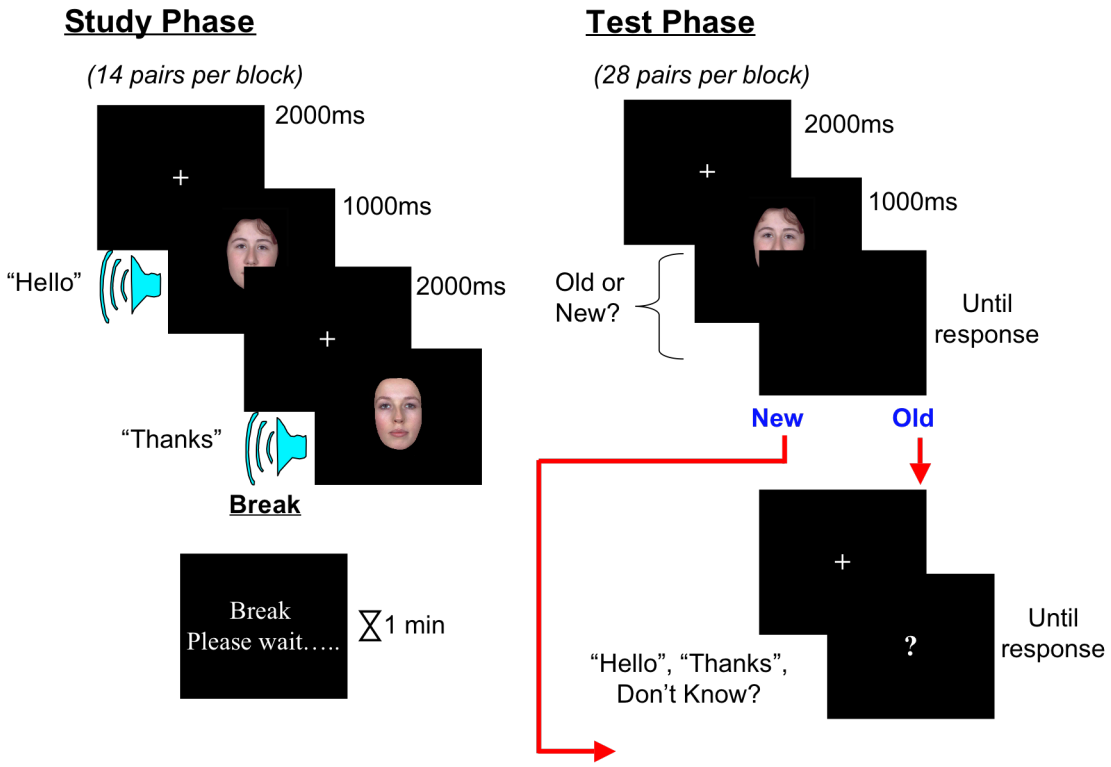


Figure 4.3. Schematic illustration of the source judgment task.

After the break participants were presented with the test phase during which 28 faces were shown and participants were asked to make old/new judgements, as per the single item recognition memory tasks. Faces were shown for 1000ms each and were followed by a blank screen that was present as long as required for the participant to respond. Participants were able to respond either whilst the face was being presented or during the blank screen that followed. Once a response was made the experiment moved on to either the next trial if a 'new' response was made, essentially terminating the trial, or to a fixation cross followed by a question mark (?) if an 'old' response was made. The question mark was a signal for participants to indicate with a button press if the phrase was 'Hello', 'Thanks', or that they did not know, and remained on the screen until participants responded. The buttons used to represent 'Hello' and 'Thanks' were 1 and 5, counterbalanced across participants. Button 3 always represented a 'don't know' response (see Figure 4.3 for an illustrative summary of the source judgment task).

4.5.3 Counterbalancing

As discussed in the proceeding sections the order of single item task presentation, the use of 'old' and 'new' lists, the allocation of old/new response keys and hello/thanks response keys were all counterbalanced across subjects. There are 192 possible combinations of these factors meaning that it was not possible to fully counterbalance all these factors with the sample size collected. Fully counterbalancing the old/new list, old/new response key and hello/thanks response key (the response factors) resulted in eight possible variations, with an additional 24 task order variations. Counterbalancing was therefore split into blocks of 24 with all possible task order variations randomised and then combined with three counterbalanced sets of response factors, the arrangement of which were also randomised. This counterbalancing process was then repeated for each block of 24 until there were enough trials for the number of participants tested.

4.6 Data processing and analysis

An initial analysis of data for each memory task was conducted looking at the overall behavioural and ERP effects for each task, across all participants. Data from each participant was then divided into a series of groups based on their individual characteristics (i.e. gender, performance, SNP variant, etc) for comparison. The method of allocation to each group will be discussed in the respective chapters.

4.6.1 Behavioural data

Accuracy (relating to the proportion of hit and false alarm responses made) and response times are reported in each empirical chapter for each comparison group and task. Behavioural and ERP data was filtered for markedly quick or slow response times,

excluding trials below 300ms and above two times the overall mean response time for each condition. Furthermore estimates of discrimination accuracy were calculated using a two-high threshold model (Snodgrass & Corwin, 1988). The discrimination index (*Pr = pHit - pFA*) was used to correct scores for guesses, and the bias index (*Br = pFA/[1-Pr]*) was used to estimate the probability of guessing 'old' when uncertain. Although Pr and Br are standard measures they are inherently vulnerable; in cases where participants make no errors in their recognition judgments *Pr* would be equal to 1, resulting in the division of the proportion of false alarms by 0 in the calculation of Br. To correct for this mathematical impossibility Snodgrass and Corwin (1988) suggest adjusting all hit and false alarm rates before calculating *Pr* and *Br* so that the hit rate equals (*number of hits +0.5)/(the number of old stimuli +1)*, and false alarm rate equals (*number of false alarms +0.5)/(the number of new stimuli +1)*. All Pr and Br values reported in this thesis are adjusted in this manner to take into account the possibility of a 0% false alarm rate. Specific analyses of the behavioural data for each characteristic analyzed will be described in individual empirical chapters.

4.6.2 EEG recording:

As discussed in Chapter 2, the EEG signal is a recording of changes in voltage produced by the brain, plotted over time. Voltage actually reflects the potential for electrical current to move between one place and another; consequently, to record this potential, it is necessary to have at least two electrodes, the active electrode and the ground. Whilst the voltage being generated by the brain can be recorded with these two electrodes, any environmental electrical activity being picked up by the ground will also be recorded. To eliminate this ground noise an additional reference electrode is used, and the ground voltage is subtracted from both the active electrode and the reference electrode, which

are then compared ([Active-Ground] - [Reference-Ground]). This difference, which is essentially the difference between active and reference electrodes, provides a measure of electrical activity from the scalp free from background electrical noise being picked up by the ground circuit (Luck, 2005).

Using the principles described above additional active electrodes can be placed at different locations on the scalp to simultaneously record activity from multiple locations. In doing so the distribution of voltage across the scalp can be characterised (see Chapter 2 for a discussion about the types of inferences that can be made from EEG and ERPs). The most common system for electrode placement is the 10/20 system (Jaspers, 1958) in which the location of an electrode is specified in relation to its proximity to a particular region of the brain (frontal pole, frontal, central, parietal, occipital, temporal), and the distance it is positioned from the midline (Z), the line running between the nasion and the inion. Electrodes on the left of the midline are labelled with odd numbers, and electrodes on the right with even numbers. The reference electrode should be positioned at a relatively neutral site that does not bias one hemisphere over the other. Whilst a variety of sites could and have been used to position the reference electrode the most common locations are the ear lobes or mastoids (the bony protrusion just behind the ear). To ensure the reference electrode is not biased towards one hemisphere, two electrodes are used, one on either ear lobe or mastoid, and the average of these two electrodes is calculated and re-referenced offline.

In this study scalp voltages were collected using 62 silver/silver chloride electrodes mounted in an elastic cap (QuickCap, Neuromedical Supplies: www.neuroscan.com) in accordance with an extended version of Jaspers (1958) international 10/20 system (FP1, FPZ, FP2, AF3, AF4, F7, F5, F3, F1, FZ, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FCZ,

FC2, FC4, FC6, FT8, T7, C5, C3, C1, CZ, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPZ, CP2, CP4, CP6, TP8, P7, P5, P3, P1, PZ, P2, P4, P6, P8, PO7, PO5, PO3, POZ, PO4, PO6, PO8, CB1, O1, OZ, O2, CB2) shown in Figure 4.4 below. Eye movements and blinks were monitored using electrodes placed above and below the left eye (Vertical EOG) and on the outer canthi of each eye (Horizontal EOG). All electrodes were referenced during recording to an additional electrode (REF) positioned in between the CZ and CPZ electrodes, and two additional electrodes were placed on the mastoids (M1 & M2), which were used to re-reference the data offline to represent linked mastoid recording, as described below. The ground electrode was positioned on the midline between electrodes AF3 and AF4.

Prior to recording conductive gel was used to form an electrical connection between the electrode and the scalp, and because electricity follows the path of least resistance impedances between them were kept low. This was achieved by removing the outer layer of dead skin cells with the wooden end of a small cotton-tipped swab until the impedances at each electrode were below 5kΩ. An impedance check was carried out half way through the study, before the start of the source judgment task, to ensure a good connection was sustained throughout the experiment.

Due to the very small voltages detected at the scalp the recording needs to be amplified, and to enable storage and processing the signal must be converted from analogue to a digital signal. According to the Nyquist Theorem it is possible to convert the voltage fluctuations into numerical representations without losing information, as long as the digitisation rate is at least twice as high as the highest frequency being digitised, and the original signal contains frequencies twice as high as the digitisation rate. Violations of this rule can cause high frequencies to appear as low frequency components in the

digitized waveforms, a phenomenon known as aliasing. To try and prevent such aliasing a low-pass filter is used to attenuate high frequencies that are more than half the digitisation rate (see Luck, 2005, or Handy, 2005, for a greater discussion of filtering and the Nyquist Theorem).

Filtering can also be used to reduce the noise present in the data. High frequency noise such as those caused by muscle movements (in the region of 100Hz) or electrical appliance noise (50Hz) can be filtered using the low-pass filter that helps to prevent aliasing. An additional high-pass filter can also be used to address low frequency noise, such as that caused by sweating and impedance drift (in the region of 0.01Hz). The current study used a SynAmps2 amplifier and Neuroscan 4.3 software (Neuromedical Supplies) for recording. Data was digitised at a rate of 250Hz, sampling at 4ms/point, and a band-pass filter of 0.1-40Hz was used to attenuate both high and low frequencies. Signals were amplified with a gain of 2010.

4.6.3 ERP processing:

The previous section discussed filtering methods used during EEG acquisition to try and reduce noise contamination in the EEG signal. Some of the main causes of noise include muscle activity, skin potentials, repositioning of electrodes and ocular artefacts. Whilst using the band-pass filter and trying to minimise participant movements are successful strategies for reducing EEG artefacts they are by no means foolproof. A series of additional steps are therefore typically taken during processing to try to minimise noise contamination including visually inspecting data after recording to identify and reject particularly noisy or saturated segments.

Ocular artefacts, caused by blinking and eye movements, are a main source of EEG contamination and are most evident at frontal electrodes. An important way to minimise eye movements is to encourage participants to focus on the centre of the screen with the use of fixation crosses, and screen centred stimuli. Furthermore, demonstrating the effects of eye movements on the EEG signal to participants before recording further emphasises the importance of minimising eye movements. All paradigms used in the current study included fixation crosses and screen centred stimuli to reduce eye movements, and participants were shown EEG noise properties before recording began.

Despite attempting to reduce artefacts, the recorded EEG nonetheless contains some remaining noise. The effects of blink artefacts can be reduced through a variety of methods. One possibility is to include specific blink steps in the experiment where participants are asked to refrain from blinking during critical periods and encouraged to blink at set times, allowing blink artefacts to be easily identified and excluded from the data. However, creating 'structured blinking' in this way can add additional artefacts to the data, for example increased muscle tension around the eyes caused by the suppression of blinks, and increased cognitive demand as a function of executing a simultaneous blink monitoring task. Discarding trials containing blinks, or eye movements, in this way could vastly reduce the number of artefact free trials, and those remaining maybe misrepresentative of the complete data set.

Another approach is to correct ocular artefacts. There is a relationship between the recorded electrooculogram (EOG) and EEG that can be used to predict the degree to which the EEG is distorted by the EOG, or ocular artefacts. The assumption is that the voltage recorded at a specific scalp electrode is EEG activity plus a proportion of the voltage generated by the eyes, as measured by the eye electrodes. The proportion of

EOG contributing to each scalp electrode can be calculated, using linear regression techniques, and then subtracted from the recording at each scalp electrode. Whilst this correction allows for the retention of more trials than other methods, it is limited in that just as the scalp electrodes can record ocular activity, the eye electrodes can record brain activity that is subsequently subtracted from the scalp electrode recordings. Despite its limitations it is this last method that was deemed most appropriate for the current study, which used the ocular artefact reduction procedure in Neuroscan Edit software (version 4.3).

Probably the best method for eliminating background noise from data is to average together many trials of the same condition. In most cases the EEG noise makes it too difficult to see the activity relating to a single trial event, so trials that replicate the same experimental conditions are averaged together to reveal the event-related activity. The first stage in this process is to epoch the data around a specific event, such as a stimulus presentation, and then to align (i.e. time-lock) these epochs based on this common event. By averaging together a series of trials the background noise in the EEG (which is assumed to be unsystematic) will be averaged out, leaving only the ERP activity. Although the basic principle of averaging is straight forward, in practice it is not quite this simple – as is discussed below.

There are two main complications with averaging. First it is assumed that background noise is irregular, and occurs on every trial. Whilst there are likely to be many cases of irregular background noise it is also possible that noise may become more prominent at certain times, for example during particularly tedious parts of the experiment, towards the end of the experiment when participants become tired and uncomfortable, or during periods where there is a sudden change in temperature. These changes in circumstance

mean that the chance of artefacts, from for example eye movements, muscle activity or sweating, are not random and may be more prominent in one condition than another. Intermixing conditions where possible can reduce the likelihood of condition-biased noise occurring by equating the chance of such artefacts being present in all conditions.

A second assumption is that the EEG signal will be the same for every single trial of a condition, and that only noise varies. Unfortunately, in practice, this is not likely to be the case as trials vary from each other in terms of both signal amplitude and latency. Whilst variation in amplitude is not a substantial problem, as the averaged ERP will simply reflect the average amplitude, inter-trial variations in terms of latency can be much more problematic. If there are large latency variations between trials the average waveform will not only appear to have a broad temporal distribution, but it will also exhibit a smaller peak amplitude compared to waveforms that are much more closely aligned in time. There are two ways to counter this amplitude reduction; firstly by comparing area amplitude rather than peak amplitude, this measure will be equivalent for both the averaged ERP and the average of all the individual trials; and secondly by increasing the number of trials contributing to the average signal and thereby enhancing the signal-to-noise ratio.

Averaging trials from individual subjects to make a grand average waveform, in addition to averaging individual participant trials, can help to reduce the impact of subject specific variations that might confound the results. Typically a trial number criterion is also set to ensure a good signal-to-noise ratio, excluding participants with an insufficient number of trials from final averages. In doing so the quality of data contributing to the grand averages is known to be of a certain standard. All analyses presented in this thesis have a criterion of at least 16 good trials per condition, and

participants with less than 16 trials in any of the relevant comparison conditions were excluded from that analysis.

In the lead up to making averages, the EEG data in the current study was averaged time-locked to stimulus onset over epochs of -100ms to +2000ms. Additional filters were applied to detect artefacts due to drift, caused by changes in impedance (typically resulting from repositioning of electrodes because of participant movement) or decreases in skin impedance as a result of sweating. Trials where drift was greater than ±75μV on any electrode were detected and excluded, as were trials where the signal exceeded ±100μV. As discussed in the previous section data was re-referenced off-line to re-create a linked mastoid recording. In addition each trial was baseline corrected by subtracting the amplitude from a "neutral" baseline period from the entire epoch, to ensure that all trials had the same starting amplitude. A pre-stimulus period of -100 to 0ms was used for baseline correction as it was assumed that activity in this period would not be specific to the trial condition. Finally, data was smoothed using a rolling average, over successive 5 point smoothing window.

Averages were made for each participant using responses to 'old' items correctly identified as 'old' (Hits) and 'new' items correctly identified as 'new' (CRs) Trials exceeding the upper and lower reaction time limits were excluded from these averages. Individual participant ERP waveforms were then averaged together to produce grand-average ERPs for each condition in each task. In addition to splitting the data into hit and CR response groups, hit responses were further broken down into Hit/Correct and Hit/Incorrect groups in the source judgement task. Hit/Correct responses are trials where participants correctly identified the face as 'old' during the initial judgement, and also identified the correct phrase that accompanied the face during the study phase.

Trials in which the participants correctly identified the face as 'old' but failed to correctly identify the associated phrase (i.e. either responded incorrectly or made a 'don't know' response) were classified as Hit/Incorrect responses.

4.6.4 ERP analysis

The general aim of most ERP experiments is to gain some understanding about the neural activity associated with a specific cognitive function. The average waveform generated by a single condition represents all the processes engaged during this condition, making it impossible to isolate the activity relating to a specific cognitive process of interest. Consequently ERP experiments typically make comparisons of matched conditions that do and do not engage the specific process of interest to provide insight into the associated neural activity that is revealed by the method of subtraction (see Chapter 2 for a detailed discussion of the inferences that can be made from ERPs).

In broad terms successful memory retrieval was the process of interest in the current study, and ERPs for correctly remembered stimuli were compared to correctly identified 'new' stimuli to determine if the amplitudes of each condition were significantly different, providing a clear operational definition of successful retrieval from memory. Single-item contrasts were made between hit and CR ERPs, with an additional Hit/Correct, Hit/Incorrect and CR comparison for the source judgment task. The initial analysis focused on the 300-500ms and 500-800ms time periods, typically identified as capturing the neural correlates associated with familiarity and recollection. The mean amplitude recorded during each of these time-windows for the different electrodes and conditions were calculated and analysed using a repeated measures ANOVA. Initial analyses were conducted using the factors of condition (Hits/CRs), location (frontal/frontocentral/central/centroparietal/parietal), hemisphere (left/right), and

electrode site (inferior/medial/superior) to determine if there was a difference between the two conditions, and whether any such differences varied across the scalp. This initial ANOVA was run on data from electrodes F1, F2, F3, F4, F5, F6, FC1, FC2, FC3, FC4, FC5, FC6, C1, C2, C3, C4, C5, C6, CP1, CP2, CP3, CP4, CP5, CP6, P1, P2, P3, P4, P5, and P6 (as shown in Figure 4.4). The layout of the electrodes in the cap mean that the co-variance between each electrode is not homogenous, with electrodes adjacent to each other sharing greater co-variance compared to those further away, breaking the sphericity assumption of the ANOVA. Where necessary ANOVA results were therefore corrected for non-sphericity using the Greenhouse-Geisser correction and corrected degrees of freedom are reported.

The initial ANOVA described above assesses differences in amplitude between conditions and whether any differences vary across the scalp. However, differences evident across the scalp in this initial analysis may be caused by differences in generator strength rather than by differences in the distribution of underlying generators. If the difference is caused by a single generator then the change in generator strength between conditions results in a multiplicative effect across electrode sites, for example if the generator strength in condition A is twice that in condition B, the voltage recorded at electrode sites in condition A will be double those recorded in condition B.

In order to determine if different generators, rather than differences in generator strength, cause the different scalp distribution, McCarthy and Wood (1985) suggest that the data is normalised (or rescaled) so that differences in amplitude across conditions are removed. Data are rescaled using the max/min method in which the smallest (minimum) amplitude in the condition is subtracted from the original value for that electrode, and this new figure is divided by the difference between the largest

(maximum) and smallest values [i.e. Rescaled value = (original value – minimum value) / (maximum value – minimum value)]. By rescaling the data in this way the values at each electrode will range between 0 and 1, and amplitude differences between the two conditions will no longer be distorted by the multiplicative effect, indicating that significant condition by location/hemisphere/site interactions are not caused by the difference in generator strength between conditions, but reflect activation from different generators (although see Urbach and Kutas, 2002 for a discussion of the effectiveness of this method). Significant condition by location/hemisphere/site interactions are therefore followed up with a second ANOVA, using the same factors as in the initial analysis, conducted on data rescaled in accordance with the max/min method.

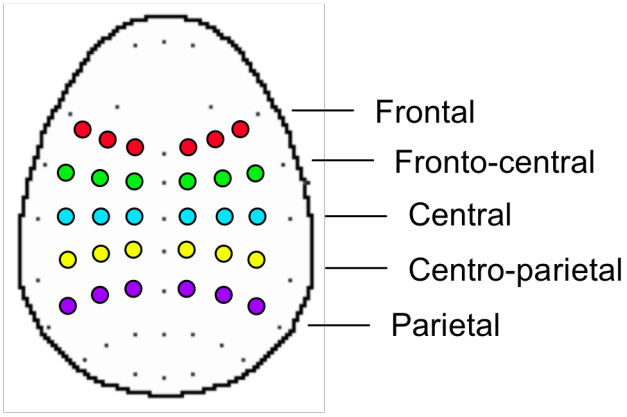


Figure 4.4. Layout of the scalp electrodes. Coloured electrodes represent those used in the initial ANOVA. Horizontally from left to right electrodes on the left are electrode numbers 5, 3, 1, and on the right are numbers 2, 4, 6.

4.7 DNA collection and processing

Following termination of the EEG recording DNA samples were collected from each participant in the form of saliva samples using Oragene OG-100 DNA collection vials (DNA Genotek Inc: www.dnagenotek.com). In accordance with Oragene guidelines samples were stored at room temperature for approximately one year, and were sent to the Welcome Trust Clinical Research Facility, Edinburgh (WTRCF Edinburgh:

www.wtcrf.ed.ac.uk) for processing. DNA was extracted from the saliva using Oragene Purifier OG-L2P-5 and quantified using Picogreen dye. SNP genotyping was conducted using an Applied Biosystems 7900HT Fast Real-Time PCR system, with Taqman SNP assays rs6265, rs17070145, rs7412, rs429358, rs4680, rs263249, rs8074995, rs3730386 (Applied Biosystems: www.appliedbiosystems.com).

4.8 Mental health and personality assessment.

Participants completed the PDSQ (Zimmerman, 2002), a brief self-report questionnaire used to screen for DSM-IV Axis I disorders, to ensure participants were not suffering from undiagnosed mental health problems that may influence the outcome of the study. Participants who scored above the cut-off point on the following subscales (Major Depressive Disorder/Suicidality, Bulimia/Binge-Eating Disorder, Obsessive-Compulsive Disorder, Panic Disorder, Psychosis, Agoraphobia, Social Phobia, Alcohol Abuse/Dependence, Drug Abuse/Dependence, and Generalised Anxiety Disorder) were asked some brief follow-up questions to supplement the initial PDSQ questionnaire. If responses indicated that the individual may be affected by one of these conditions or (any other equivalent indication was given at any point during the study) participants data was excluded from any investigations in to biological variations; this exclusion criteria was intended to remove possible confounds with neurotransmitter or hormone levels. Participants scoring above threshold on the Post Traumatic Stress Disorder subscale were automatically excluded from biological variation analysis as no follow-up on this subscale was conducted. Finally, at the end of the first session, participants completed the EPQ-R (Eysenck & Eysenck, 1991) providing measures of nine personality traits: Psychoticism, Extraversion, Neuroticism/Emotionality, Lie, Addiction, Criminality, Impulsiveness, Venturesomeness, and Empathy.

4.9 Psychometric/Neuropsychological tests

Participants completed three psychometric/neuropsychological test batteries in the second session, WMS-III^{UK} (Wechsler, 1998), WASI (Wechsler, 1999) and CANTABeclipse (Cambridge Cognition Ltd, 2006). The WMS-III^{UK} (Wechsler, 1998) is a tool used to measure specific memory functions with a focus on immediate, delayed and working memory, using tests of both recognition and recall across both auditory and visual modalities. Participants completed the six primary subtests (Logical Memory I & II, Verbal Paired Associates I & II, Letter-Number Sequencing, Faces I & II, Family Pictures I & II, and Spatial Span) and two additional optional subtests (Digit Span and Visual Reproduction I & II). The second test battery was the WASI (Wechsler, 1999), a four-subtest assessment (tests of Vocabulary, Block Design, Similarities, and Matrix Reasoning) that generates Verbal, Performance and Full Scale IQ scores allowing estimates of verbal, non-verbal, and general cognitive functioning to be made.

Finally, the CANTABeclipse (Cambridge Cognition Ltd, 2006) is a computerised battery of non-linguistic tasks designed to target a series of cognitive functions. Participants completed six tasks from the CANTABeclipse (Intra-Extra Dimensional Set Shift [IED], Rapid Visual Information Processing [RVP], Stockings of Cambridge [SOC], Spatial Recognition Memory [SRM], forwards and backwards Spatial Span [SS], Spatial Working Memory [SWM]) providing an assessment of attention, executive function and visual memory. All instructions for the administered tasks were taken from the manuals provided with each test battery.

4.10 Overview of general methods

One hundred and twenty nine participants completed two experimental sessions lasting approximately four hours each. Participants completed a series of ERP memory tasks, psychometric and neuropsychological tests, and provided a sample of DNA in the form of saliva. Data from all participants were collated and subsequently divided into groups to analyse various factors that were hypothesised to influence memory performance and the neural activity associated with recognition memory. Details pertaining to the division and analysis of data with regards to specific factors will be discussed in the relevant empirical chapters. Due to the large number of possible varying factors that were investigated the data was re-pooled after each analysis of an individual characteristic. This re-pooling means that data from a participant could be re-sampled multiple times in the analyses of several different characteristics and interpretation of the data and any findings should bear this in mind. Where possible some characteristics (e.g. behavioural performance) were controlled for, and any instances where factors have been controlled will be highlighted in the relevant empirical chapters.

Chapter 5
Single Item Recognition Memory

This chapter presents the overall behavioural and ERP results from the four single item recognition memory tasks completed in session one (described in Chapter 4). The purpose of this chapter is to understand both the behavioural and ERP effects produced by the tasks, before looking at the impact various individual differences have on these outcomes in subsequent chapters. A brief summary of the ERP findings from recognition memory studies presented in Chapter 2 will be given, leading to an outline of the current hypotheses. The chapter will then go on to discuss the criteria used to select the contributing data and present the findings from each single item recognition memory task (words, pictures, faces, and voices), as well as an analysis of material specificity effects. Finally, the findings will be considered in relation to previous literature.

5.1 Introduction

As outlined in Chapter 2, studies investigating recognition memory using ERPs have shown a series of old/new effects that are thought to reflect underlying recognition memory processes. Whilst there is some variability in the findings reported, it is generally accepted that studies using words have identified a set of successful recognition memory old/new effects including putative correlates of familiarity (the 300-500ms bilateral-frontal effect) and recollection (the 500-800ms left-parietal effect). There is also increasing evidence to suggest material specific differences in the neural correlates of recognition, with pictorial stimuli (i.e. line drawings and photographs of objects, scenes and faces) generally exhibiting more anteriorly distributed effects than

verbal stimuli (i.e. words). More specifically, studies using pictorial stimuli have shown the parietal recollection differences seen for words, but the overall topography of this old/new effect extends more anteriorly then is typically seen for word stimuli (Yick & Wilding, 2008; Galli & Otten, 2011).

In addition to the parietal old/new differences discussed above, several studies have reported additional frontal differences associated with recognition memory for faces (MacKenzie & Donaldson, 2007, 2009; Yick & Wilding, 2008; and evident, although not discussed, in the data presented by Curran & Hancock, 2007). This additional frontal old/new effect is maximal between approximately 500-700ms (although there is evidence to suggest an onset as early as 300ms, see Yick &Wilding, 2008), and is present on trials where correct associated information is reported, but not on trials where no associated information is reported (MacKenzie & Donaldson, 2007), suggesting that it may reflect recollection processes. Whilst at first glance this late frontal effect may resemble an early onsetting late right frontal effect, associated with post-retrieval monitoring (Wilding & Rugg, 1996), MacKenzie & Donaldson (2007) consider this additional frontal effect for faces to be independent, firstly because of the differing topographies of the two effects, and secondly because the face frontal effect is modulated by the type of information recollected (i.e. retrieval of associated names results in a larger effect than retrieval of other details), which is not the case for the late right frontal effect.

In relation to familiarity effects for faces Yovel and Paller (2004), and MacKenzie and Donaldson (2007) report posterior effects for their familiarity contrast, whilst a bilateral-frontal familiarity effect, consistent with findings from word studies, has been reported by Curran and Hancock (2007). The distributional differences of the familiarity

effects observed in these studies may relate to the heterogeneity of stimuli, with Yovel and Paller (2004), and MacKenzie and Donaldson (2007) both using stimuli that were more homogenous in appearance than Curran and Hancock (2007). These differences in stimulus heterogeneity may influence the degree to which familiarity and/or recollection is used as a basis for discerning if the face is 'old' or 'new', resulting in different distributions across studies (Donaldson & Curran, 2007). These studies clearly show material specific differences in the ERP effects associated with successful recognition memory, however the parameters of the material specificity remains unclear (e.g. in terms of the exact stimuli variations resulting in such differences).

The current study employed four single item recognition memory tasks, looking at memory for verbal stimuli (visually presented words and auditorily presented voices) and pictorial stimuli (pictures and faces - both presented in a photographic format). These four tasks were selected to allow for a comparison across stimuli types, providing two tasks rich in semantic content, with a high degree of heterogeneity between stimuli, one verbal (words) and one pictorial (pictures), and two tasks semantically impoverished, with a low degree of heterogeneity between stimuli, one verbal (voices) and one pictorial (faces).

It is hypothesised that, for words, the results from this study will be consistent with the wider literature, showing an early bilateral-frontal old/new effect, followed by a later left lateralised parietal old/new effect. For the picture stimuli it is expected that there will also be an early bilateral-frontal old/new effect followed by a later parietal effect, although it is hypothesised that this parietal effect will be more anterior than the word equivalent. The stimuli used in the face task overlap with those presented in MacKenzie and Donaldson (2007, 2009) and the current study is therefore predicted to replicate

their findings, showing early frontal and parietal old/new differences, and a later parietally distributed old/new effect, with an additional anterior old/new effect in the 500-800ms time-window, as discussed above (not to be confused with the late right frontal effect associated with post-retrieval monitoring discussed in Chapter 2).

Despite the existence of a substantial number of studies investigating successful recognition memory none have employed recognition of voices. ERP studies using voice stimuli have restricted their use to a single male and female voice in a source judgement task, presenting words auditorily in either voice and instructing participants to remember both word and presenter gender (Wilding & Rugg, 1996; Senkfor & Van Petten, 1998). A recent study using fMRI by Stevens (2004) looked at short-term memory for voices, however, comparing neural activity for voices, words and tones using a two-back task[8]. Stevens (2004) found distinct patterns of neural activity for voices (greater effects in the left-temporal, right-frontal and right-medial parietal areas) compared to words (effects in left-frontal and bilateral-parietal areas), suggesting differences between voice and word stimuli in relation to short-term working memory. Whilst this study does not look at longer-term recognition memory for voices and it only used six voices (three male and three female), it does suggest that there may be differences in the neural processes involved in voice and word recognition. It is therefore hypothesised that the ERP correlates for voice recognition will be distinct from those for word recognition, however it is not obvious from previous literature how these correlates will differ.

Analysis of the data from the current study will initially focus on each of the four single item tasks individually, starting with words followed by pictures, faces and voices. A

[8] The two-back task employed by Stevens (2004) involved participants indicating if a presented stimulus matched the stimulus presented two trials previously, i.e. was it the same voice, or in the word condition the same word, as presented before.

more detailed investigation into material specificity effects will then be conducted with an overall comparison of the different stimulus materials. Before presenting these results a brief overview of the inclusion criteria and analysis strategy will be given in the following methods section.

5.2 Methods

All details pertaining to participant recruitment, experimental procedures, and EEG procedures are reported in the General Methods (Chapter 4). A performance criterion of $Pr \geq 0.2$ was set per condition, with participants with a $Pr < 0.2$ excluded from the analysis, this ensured participants scored at least 20% above chance, and were therefore likely to be basing decisions on some degree of memory retrieval rather than simply making guess responses. Initial examination of the data included 'all participants' who met these criteria for each task separately (Words n=122, Pictures n=128, Faces n=52, Voices n=29), followed by an analysis of possible material specificity effects conducted with participants who met the inclusion criterion across all four single item tasks (n=18).

Behavioural results for average recognition response rates (rounded to the nearest integer), discrimination measures, and response times (rounded to the nearest integer) are reported for each comparison group and task, with standard deviation scores given in brackets. Preliminary ERP analysis for each single item task follows the procedure outlined in the General Methods (Chapter 4). Details of any subsidiary analysis conducted are provided alongside the associated results, with only the highest level interaction reported for these subsidiary analyses.

5.3 Results

5.3.1 Word old/new recognition task:

5.3.1.1 Behavioural results

Participants were successfully able to complete the word task with an average hit rate of 73% (s.d.12%), and a false alarm rate of 18% (s.d.11%). Mean discrimination accuracy (*Pr* = 0.54, s.d. 0.17) was above chance level [$t(121)=34.53$, $p<0.001$], and overall participants exhibited a conservative decision bias with a mean *Br* of 0.39 (s.d. 0.16). Mean response times for hits were 823ms (s.d. 138ms), and 898ms (s.d. 157ms) for CRs.

5.3.1.2 ERP results

Figure 5.1 shows grand-average ERPs for word hit and CR responses at representative electrode sites across frontal, central and parietal locations; the largest old/new difference appears to be over left-parietal sites. The distribution of the old/new difference for the 300-500ms and 500-800ms time-window is illustrated in Figure 5.2, showing that the difference is centrally distributed in the 300-500ms time-window followed by a left-parietal distribution in the 500-800ms window.

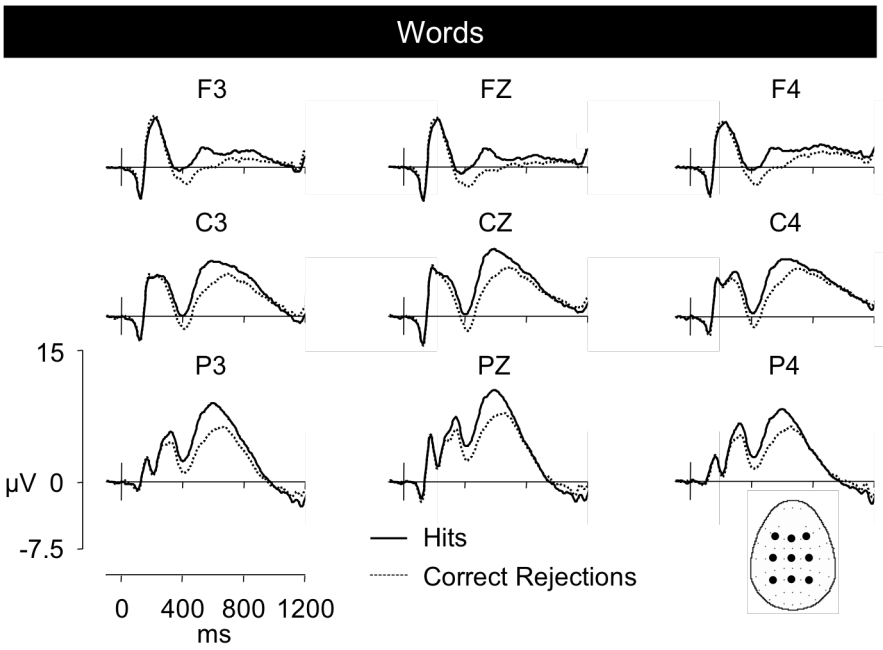


Figure 5.1 Grand average ERP waveforms for the recognition memory for words task, at representative frontal, central and parietal electrode sites, for hit and CR responses. Waveforms generated from 'all participants' who met the inclusion criteria (n=122). The vertical scale indicates electrode amplitude, measured in microvolts, whilst the horizontal scale indicates change in time, measured in milliseconds.

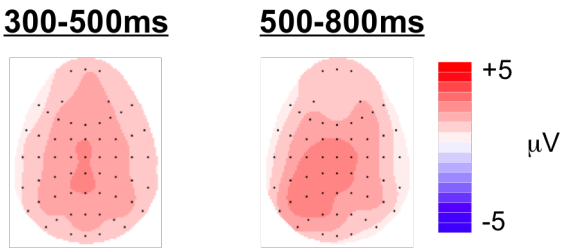


Figure 5.2 Topographic maps showing the distribution of the old/new differences for the word recognition task, Two latency regions are shown, 300-500ms and 500-800ms, along with scale bars to show the size of the old/new difference. Maps show the subtraction of the grand average ERP for CRs from grand average ERP for hits.

Analysis from 300-500ms:

The ERP data were analysed using ANOVA, with factors of condition (Hits/CRs), location (frontal/frontocentral/central/centroparietal/parietal), hemisphere (left/right), and electrode site (inferior/medial/superior) as outlined in Chapter 4. Analysis of the 300-500ms time-window with a global ANOVA revealed a main effect of condition

[F(1,121)=42.27, p<0.001], indicating that hit responses exhibit significantly more positive going activity than CRs. A significant condition by site interaction was also found [F(1,127)=32.37, p<0.001], indicating old/new effect magnitude was larger at superior electrode sites. As is evident from the topographic map, the early effect seen for words is broadly distributed, bilaterally across the scalp, with a central rather than frontal maximum. Visual inspection revealed the old/new difference to be maximal at electrode CPZ in the 300-500ms time-window, with a t-test confirming that the difference between conditions at this electrode was significant [t(121)=6.87, p<0.001].

Analysis from 500-800ms:

Analysis of the 500-800ms time-window revealed a significant main effect of condition [F(1,121)=42.55, p<0.001], and a significant interaction between condition, location and hemisphere [F(1,160)=6.87, p=0.005] reflecting the presence of positivity for hits that is larger over left than right hemisphere electrodes at posterior locations, but bilaterally distributed over frontal and central locations. There was also a significant condition by site interaction [F(22,129)=21.86, p<0.001], indicating that the old/new effect was largest at more superior electrode sites; and a condition by location by site interaction [F(2,266)=6.69, p=0.001] indicates that this is only the case at central locations. Finally a significant four-way (condition, location, hemisphere, site) interaction was found [F(3,395)=10.16, p<0.001], reflecting the fact that the old/new effect is maximal over the left hemisphere at centroparietal and parietal electrodes (and largest at medial sites) whereas at frontal and central locations the old/new effect is bilaterally distributed (and maximal at superior sites). Visual inspection of the data showed that the size of the old/new effect was maximal at electrode P3 in the 500-

800ms time-window, with a t-test confirming that the difference between conditions at this electrode was significant [$t(121)=7.7$, $p<0.001$].

Analysis comparing the old/new effects in the two time-windows revealed a significant time by location by hemisphere by site interaction [$F(3,316)=9.45$, $p<0.001$]. As the preceding analyses show, this reflects the change from a central maximum to a left-parietal old/new effect. Importantly, follow-up topographic analysis using data rescaled to take account of overall differences in amplitude between the two conditions (McCarthy and Wood, 1985), also revealed a significant four-way interaction between time, location, hemisphere and site [$F(3,324)=7.63$, $p<0.001$], suggesting that the topographically distinct effects in the 300-500ms and 500-800ms time-windows are a reflection of distributional rather than just magnitude differences.

5.3.1.3 Discussion

The present experiment required participants to complete a simple old/new recognition task for words. The behavioural results show that participants were successfully able to complete the task and overall exhibited a conservative bias, indicating a tendency to respond 'new' if unsure. Response times indicate that on average participants were slightly quicker to make correct 'old' judgements than correct 'new' judgements.

ERPs for hit and CR responses were contrasted in two time-windows (300-500ms and 500-800ms) that are thought to best capture the ERP neural correlates of familiarity and recollection. The ERP waveforms (Figure 5.1) and topographic maps (Figure 5.2) show clear old/new differences for successful recognition memory of words in these time-windows. Statistical analysis revealed significant differences in the 300-500ms time-window with hits exhibiting more positive activity than CRs, a difference greater over superior electrode sites. However, this old/new effect was found to be maximal at

electrode CPZ rather than bilateral-frontal electrodes suggesting relatively weak evidence for a contribution of familiarity to retrieval. By contrast, data from the 500-800ms time-window revealed clear evidence of a left-parietal old/new difference, maximal at electrode P3. Importantly, comparisons of the two time-windows revealed a statistically significant change in distribution, from a widespread bilateral effect initially, to the left-parietal effect becoming prominent in the later time window.

The early old/new effect is less frontally distributed then is often reported in the literature, which may be due to temporal overlap with the onset of the left-parietal old/new effect evident in the later time-window. Alternatively, the more widespread effect may reflect less engagement of familiarity than is typically seen in recognition tasks, and a heavier reliance on recollection. Unfortunately, estimates of familiarity and recollection cannot be made with the current paradigm, making it difficult to assess the contributions of either process. However, overall these results generally replicate the findings reported in the literature for word stimuli, which show an early ~300-500ms bilateral-frontal effect, followed by a later ~400-800ms left-parietal effect (for a review see Rugg & Curran, 2007).

5.3.2 Picture old/new recognition task:

5.3.2.1 Behavioural results

Performance on the picture task was better than for words, with a mean hit rate of 83% (s.d.12%), and a false alarm rate of 7% (s.d. 6%). Mean discrimination accuracy (*Pr* = 0.76, s.d. 0.15) was above chance level [$t(127)=59.33$, $p<0.001$], and participants again showed an overall conservative decision bias (*Br* = 0.26, s.d. 0.18) indicating a tendency for participants to respond 'new' if they were unsure. Mean response times

were slightly quicker for the picture task than the word task with a mean hit response time of 802ms (s.d. 136ms), and a mean of 852ms (s.d. 146ms) for CRs.

5.3.2.2 ERP results

Figure 5.3 shows grand-average ERPs for picture hit and CR responses. A divergence between conditions is evident across all electrodes starting at approximately 300ms, with hits becoming more positive going than CRs, tailing off between approximately 700ms and 1000ms (depending on electrode site). The distribution of this old/new difference can be seen from the topographic maps presented in Figure 5.4, which shows an early anterior distribution, followed by a more centrally distributed difference.

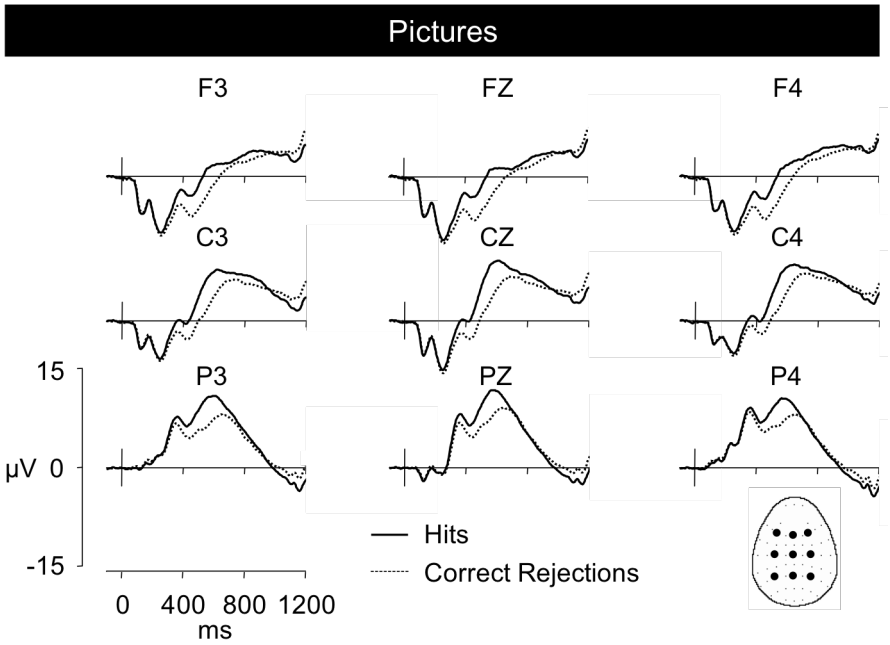


Figure 5.3 Grand average ERP waveforms for the recognition memory for pictures task (n=128). Data shown as in Figure 5.1.

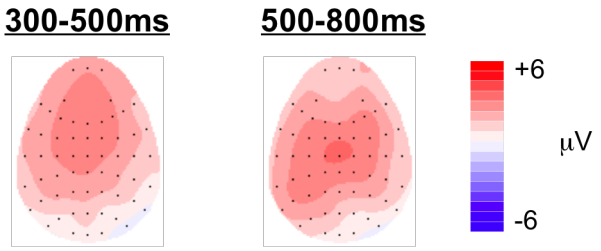


Figure 5.4 Topographic maps showing the distribution of the old/new difference for the picture recognition task. Data shown as in Figure 5.2.

Analysis from 300-500ms:

A main effect of condition [$F(1,127)=106.94$, $p<0.001$] was found between 300-500ms, illustrating that hits were more positive going than CRs. A significant condition by location interaction [$F(1,149)=12.7$, $p<0.001$] indicates that the old/new difference was greatest at anterior sites; a condition by hemisphere interaction [$F(1,127)=4.52$, $p=0.036$] shows that the difference was largest over the left hemisphere; and a condition, location, hemisphere interaction [$F(2,206)=8.91$, $p=0.001$] indicates that the difference in the size of the old/new effect between hemispheres became larger the more posterior the location. A condition by site interaction [$F(1,140)=69.75$, $p<0.001$] was also evident, showing that the old/new effect was largest at superior sites; and a condition, hemisphere, site interaction [$F(1,156)=5.41$, $p=0.016$] indicates that there was greater variability in the magnitude of the effect across sites in the right hemisphere than across sites in the left hemisphere. Finally, there was also a significant interaction between condition, location, hemisphere and site [$F(4,481)=3.59$, $p=0.008$]. The 4-way interaction indicates that hemispheric differences in old/new effect magnitude were only evident over more posterior locations, but in addition, whilst a relatively symmetrical hemispheric distribution is found over frontal locations (where effect size is maximal at superior sites and becomes smaller at inferior sites) over posterior locations the degree of asymmetry varies as a function of site (with the magnitude of the old/new difference much more uniform across left hemisphere sites than right hemisphere sites).

Subsidiary analyses of the data with a three-way ANOVA looking at factors of condition, hemisphere and site at each of the five electrode locations (frontal, frontocentral, central, centroparietal and parietal) support the interpretation of the four-way interaction. Significant condition by site interactions were found for both the

frontal [F(1,142)=49.08, p<0.001] and frontocentral [F(1,145)=46.04, p=<0.001] locations, indicating that the difference between hits and CRs was largest over superior sites, and that there was no significant hemispheric differences at these locations. Significant condition by hemisphere by site interactions were then found for central [F(2,195)=4.89, p=0.015], centroparietal [F(1,166)=10.6, p<0.001] and parietal locations [F(1,157)=8.69, p=0.002], indicating hemispheric differences in the size of the old/new effect (where the effect was biggest over the left hemisphere), and that whilst the effect was still greatest at superior sites the effect distribution over left hemisphere sites were more uniform than over right hemisphere sites. Finally, visual inspection of data revealed that the old/new effect in the 300-500ms time-window was maximal at electrode FCZ and a paired-samples t-test showed that the difference between hits and CRs at this electrode was significant [t(127)=10.22, p<0.001].

Analysis from 500-800ms:

A main effect of condition [F(1,127)=95.72, p<0.001] was also evident in the 500-800ms time-window, again showing that, overall, hits were more positive going than CRs. A significant condition by location interaction [F(1,153)=4.29, p=0.033] indicates that the size of the old/new effect was largest at the central electrodes; and a significant condition by location by hemisphere interaction [F(1,165)=8.06, p=0.002] indicates hemispheric differences in the size of the old/new effect at different locations, with the old/new effect largest over the right hemisphere at frontal electrodes, but becoming progressively larger over the left hemisphere the more posterior the electrode. The global ANOVA further revealed a significant condition by site interaction [F(1,138)=31.86, p<0.001], indicating a larger old/new effect over superior electrodes; a significant condition by location by site interaction [F(2,262)=9.14, p<0.001] shows that

old/new effect magnitude is largest at superior sites, with greatest variation between sites at central locations; and a significant condition by hemisphere by site interaction [$F(1,173)=5.47$, $p=0.012$] shows that the size of the old/new effect is greater at superior sites, with more variation between sites over the right hemisphere. Finally a significant interaction between condition, location, hemisphere and site [$F(3,368)=7.74$, $p<0.001$] reveals a bilateral distribution over anterior locations with greater hemispheric asymmetry over posterior locations, where the effect was greatest at medial sites in the left hemisphere.

A subsidiary three-way ANOVA was conducted looking at factors of condition, hemisphere and site at each of the five electrode locations (frontal, frontocentral, central, centroparietal and parietal). Significant condition by site interactions were found for both frontal [$F(1,145)=12.61$, $0<0.001$] and frontocentral [$F(1,141)=28.72$, $p<0.001$] locations, indicating that the old/new effect was greater at superior sites over anterior locations. As in the 300-500ms time-window significant condition by hemisphere by site interactions were found for central [$F(2,211)=5.27$, $p=0.009$], centroparietal [$F(1,174)=11.19$, $p<0.001$], and parietal [$F(1, 150)=17.39$, $p<0.001$] locations. As described above the old/new effect size at posterior locations is maximal at medial sites in the left hemisphere and is much more uniform in distribution across sites than in the right hemisphere. The old/new difference over the right hemisphere is maximal at superior sites and more graded than over the left hemisphere, becoming smaller towards inferior sites. In the 500-800ms time-window visual inspection indicated that the old/new effect was maximal at electrode CZ. A t-test confirmed that the difference between conditions at this electrode was significant [$t(127)=10.3$, $p<0.001$].

As can be seen in Figure 5.4 the analyses described above demonstrate that there are significant old/new differences for picture recognition in both 300-500ms and 500-800ms time-windows for the 'all participants' group. An additional four-way ANOVA including factors of time (300-500ms/500-800ms), location (frontal/frontocentral/central/centroparietal/parietal), hemisphere (left/right) and site (inferior/medial/superior) was conducted on *old/new difference scores* to see if the effects found in the two time-windows were different from each other. A significant time by location by hemisphere by site interaction [$F(3, 313)=3.70$, $p=0.018$] was found, indicating that across the two time-windows the distribution of the old/new effects differed.

The analysis comparing effects in the two time-windows was repeated using rescaled data, revealing a significant four-way time by location by hemisphere by site interaction [$F(3,313)=3.77$, $p=0.017$], confirming that the old/new effects found in each of these time-windows were topographically distinct. As the preceding analysis demonstrates, over the majority of locations the old/new effect size is largest in the 500-800ms time-window, with the exception of the frontal location where the effect is largest in the 300-500ms window reflecting the presence of an early bilateral-frontal old/new effect. Moreover, whilst the pattern of activity appears fairly consistent across the two hemispheres between 300-500ms, there is a clear asymmetry over posterior locations in the 500-800ms time-window consistent with the emergence of a left-parietal old/new effect. Whilst a left-parietal old/new effect may be present during the later time window, the distribution of the effect is more anteriorly focused than would be expected for a left-parietal effect. However, the analyses clearly support the traditional view that two temporally and topographically dissociable old/new effects are elicited by recognition memory for pictures.

5.3.2.3 Discussion

As with the previous task participants completed a simple old/new recognition task, this time looking at successful recognition memory for pictures. The behavioural results again indicated that participants were able to perform the task well, with high hit rates and low false alarm rates resulting in high discrimination accuracy scores. Overall hit responses were made quicker than CR responses, and as per the word task decision bias scores indicated a conservative bias.

Statistical analysis of the ERPs indicated an early bilateral-frontal old/new effect followed by a more posterior old/new effect that had a clear left hemisphere distribution. The early 300-500ms effect was maximal at FCZ, and the 500-800ms effect at CZ. Topographic comparisons of the two time-windows revealed that overall old/new effect magnitude was greater in the later time-window, except at frontal electrodes where the effect was largest in the 300-500ms window. In addition the old/new effect was more bilateral in the early time-window with much greater asymmetry across locations between 500-800ms.

Previous literature suggested that old/new ERP differences for pictures exhibit an early bilateral-frontal old/new effect between approximately 300-500ms and a later parietal old/new effect in the 500-800ms time-window (Curran & Cleary, 2003; Duarte, Ranganath, Winward, Hayward & Knight, 2004; Galli & Otten, 2011; Schloerscheidt & Rugg, 1997, 2004; Vilberg, Moosavi & Rugg, 2006; Vilberg & Rugg, 2009). The early bilateral-frontal old/new difference in the 300-500ms time-window in the current study is consistent with this literature. In addition, statistical analysis confirms that the current findings in the 500-800ms time-window are also consistent, with a more posterior left hemispheric old/new difference. Although the topographic maps shown in Figure 5.4

indicate a centrally distributed old/new difference, with the statistical maxima at electrode CZ in the 500-800ms time-window, this central maximum appears visually very similar to the anteriorly extended parietal effect reported by Galli and Otten (2011).

In sum, the results from the current study indicate that successful recognition memory for pictures results in an early bilateral-frontal old/new effect in the 300-500ms time-window followed by a more posterior old/new effect with a left hemispheric bias in the 500-800ms time-window. Overall the results are consistent with previous findings, although the old/new effects in the 500-800ms time-window in the current study appear to have a more anterior distribution than is typically reported.

5.3.3 Face old/new recognition task:

5.3.3.1 Behavioural results

The mean hit rate for the face task was 61% (s.d. 9%), with a comparatively high false alarm rate of 33% (s.d. 8%). Mean discrimination accuracy (*Pr* = 0.28, s.d. 0.07) was above chance level [$t(51)=29.30$, $p<0.001$], with participants showing an overall neutral decision bias (*Br* = 0.46, s.d. 0.10). In comparison to the word and picture tasks participants took considerably longer to make their response, with a mean hit response time of 1015ms (s.d. 191ms), and a mean of 1105ms (s.d. 240ms) for CRs. These extended response times reflect the poorer performance seen for faces indicating that participants found this task more difficult than the words and pictures.

5.3.3.2 ERP results

Hit and CR ERP waveforms from the face task are shown in Figure 5.5. The differences between hit and CR responses are much smaller than in the previous picture task,

however, starting around 500ms hits are slightly more positive going than CR responses. This divergence is evident until approximately 800ms, when CR responses appear more positive going than hits, especially over parietal electrodes. The distribution of the old/new difference can be seen in the topographic maps shown in Figure 5.6. There appears to be little old/new difference in the 300-500ms time-window, but a left parietally distributed old/new effect between 500-800ms.

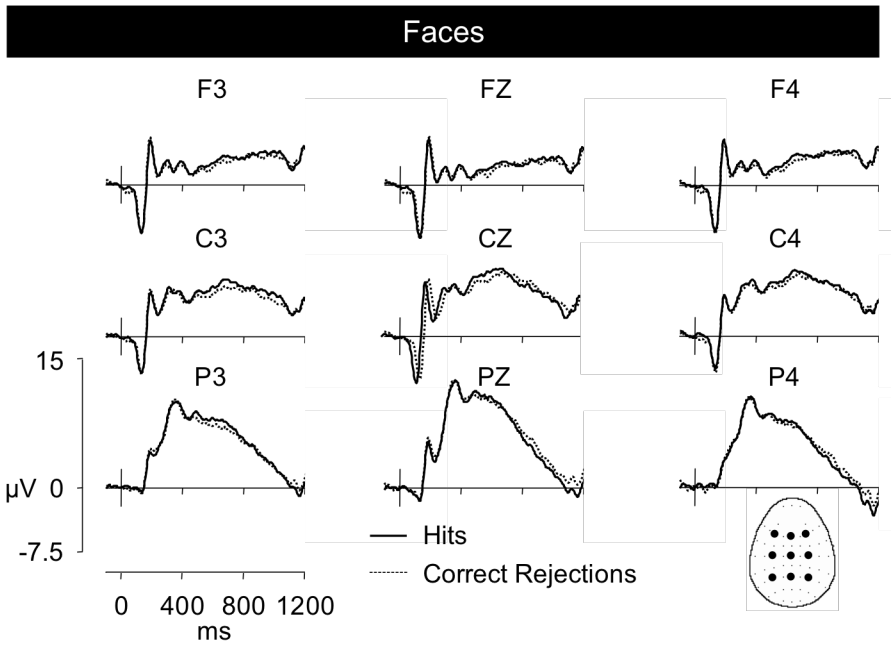


Figure 5.5 Grand average ERP waveforms for the recognition memory for faces task (n=52). Data shown as in Figure 5.1.

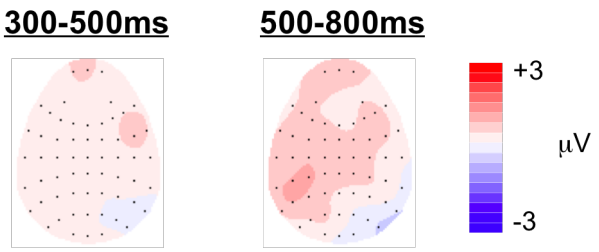


Figure 5.6 Topographic maps showing the distribution of the old/new difference for the face recognition task. Data shown as in Figure 5.2.

Analysis from 300-500ms & 500-800ms:

No significant differences between hit and CR responses were found from 300-500ms. By contrast from 500-800ms there was a significant interaction between condition, location, hemisphere and site [$F(3,174)=2.6$, $p=0.046$]. Subsidiary analysis was conducted to break down the four-way interaction, with an ANOVA performed on factors of condition, hemisphere and site, at each location. No significant effects were found for the frontal, frontocentral, central, or centroparietal locations. However, the parietal location revealed significant interactions between condition and hemisphere [$F(1,51)=4.34$, $p=0.42$] and condition, hemisphere and site [$F(1,62)=4.38$, $p=0.033$]. These interactions indicate that over parietal electrodes a positive going old/new effect is present, an effect which is larger over the left than right hemisphere, increasing in size at more lateral electrodes. Consistent with this, visual inspection of the data indicated that the maximal old/new effect for the 500-800ms time-window was electrode CP5, with a t-test showing that the difference between conditions at this electrode was significant [$t(51)=2.04$, $p=0.047$].

5.3.3.3 Discussion

The present task investigated successful recognition memory for faces. Performance on this task was much poorer than in either the word or picture task with low hit rates and high false alarm rates resulting in low discrimination accuracy, and considerably longer response times than were seen in the previously reported tasks. Decision bias was also higher than for the word and picture tasks, indicating participants exhibited a neutral bias in which they were equally likely to respond ‘old’ as ‘new’ if unsure. There was a large reduction in the number of participants who met the inclusion criteria for the faces

task, with less than half the participants from the word and picture tasks meeting criteria, reflecting the difficult nature of this task.

As per the previously reported tasks, ERP activity for correctly recognised 'old' and 'new' faces were analysed in the 300-500ms and 500-800ms time-windows. The differences between hit and CR responses for face stimuli are much smaller than was evident for the word and picture stimuli. Statistical analysis of the data did not show any significant differences between the two conditions in the 300-500ms time-window, however in the 500-800ms time-window there was a significant left hemispheric difference over the parietal location with hits more positive going than CRs, a difference maximal at inferior sites.

Previous literature on face recognition memory has suggested a parietal old/new effect on-setting at approximately 500ms (Curran & Hancock, 2007; MacKenzie & Donaldson, 2007; Yick & Wilding, 2008), with some studies reporting an additional overlapping frontally distributed ERP effect (MacKenzie & Donaldson, 2007; Yick & Wilding, 2008). The left parietal old/new effect seen in the 500-800ms time-window in the current study is consistent with previous findings, although there was no statistical evidence to suggest an additional frontal effect. Visual inspection of the topographic maps (Figure 5.6) does however indicate a spread of activity from the left parietal electrodes over to frontal electrodes between 500-800ms.

The absence of significant anteriorly distributed old/new differences in the 500-800ms time-window that have been reported by some studies, may relate to the poor performance on this task. Discrimination accuracy scores for the current study were lower than those reported in previous studies, most likely a result of the larger study/test block used in the current study compared to previous studies. MacKenzie and

Donaldson (2009) report a frontally distributed effect for faces, not evident for names, in their recollection contrast. If the additional frontal effect relates in someway to the process of recollection, than the absence of this additional frontal effect in the current study, coupled with the poor performance, suggests that participants were basing their responses predominately on familiarity. However, the presence of a significant left-parietal old/new effect in this time-window, which is typically thought to reflect recollection, would suggest otherwise.

The absence of a significant old/new effect in the 300-500ms time-window is also interesting to note. Typically (in particular relating to word stimuli) a bilateral-frontal old/new difference is evident in the 300-500ms time-window and is thought to reflect familiarity. The current study shows no statistical evidence of a bilateral-frontal old/new effect, nor any visual evidence to suggest the presence of a statistically weak bilateral-frontal old/new effect (as was the case for the single item words). Previous face recognition memory studies present a mixture of results, with some studies reporting old/new differences in the 300-500ms time-window (Curran & Hancock, 2007; Galli & Otten, 2011; MacKenzie & Donaldson, 2007; Yick & Wilding, 2008), and others showing no early effects in some conditions (Yovel & Paller, 2004). Yovel and Paller (2004) report a frontally distributed old/new difference between 300-500ms for the recollection contrast but not for the familiarity contrast[9], suggesting that for faces the earlier frontal old/new effect relates to recollection. If the early frontal old/new effect for faces relates to recollection this may explain the absence of early old/new differences in the current study, assuming (based on poor discrimination accuracy) that participants are predominately basing their responses on familiarity. Unfortunately, as

[9] Yovel and Paller (2004) report no early frontal old/new ERP differences in their familiarity contrast, but a frontally distributed old/new effect for their recollection condition. However, they also report no topographic difference between the familiarity and recollection contrasts in the 300-500ms time-window.

per the word and picture tasks, the current paradigm does not allow estimates of the contribution of familiarity and recollection processes to be made, making it difficult to interpret these differences.

5.3.4 Voice old/new recognition task:

5.3.4.1 Behavioural results

The voice old/new recognition task was a particularly difficult task, which participants clearly struggled with; as a result only 29 participants met the inclusion criteria. The mean hit rate for the voice task was 64% (s.d. 8%), with a false alarm rate of 38% (s.d. 8%). The mean discrimination accuracy score was 0.25 (s.d. 0.05) which, although the lowest score from the four tasks, was above chance level [$t(28)=25.53$, $p<0.001$]. Participants had a mean decision bias score of 0.51 (s.d. 0.10) indicating an overall neutral bias. Finally, response times were considerably longer than in the other three tasks, with a mean hit response time of 1398ms (s.d. 209ms), and a mean of 1506ms (s.d. 271ms) for CRs.

5.3.4.2 ERP results

Representative hit and CR grand average ERPs for the voice recognition task are presented in Figure 5.7. There appears to be little difference between hits and CRs at these electrodes, however hit responses look slightly more positive than CRs between approximately 600-1200ms at the P3 electrode, and onsetting at approximately 900ms until the end of the epoch at the FZ electrode. Topographic maps in Figure 5.8 show the distribution of the old/new differences. Whilst the differences between hits and CRs is very small in the 300-500ms time-window there appears to be some difference over frontopolar electrodes, and an additional difference over parieto-occipital electrodes,

neither of which could be seen in the representative electrodes selected in Figure 5.7. Similarly in the 500-800ms time-window the topographic maps suggest slightly stronger old/new differences over frontopolar electrodes, and again over parieto-occipital electrodes.

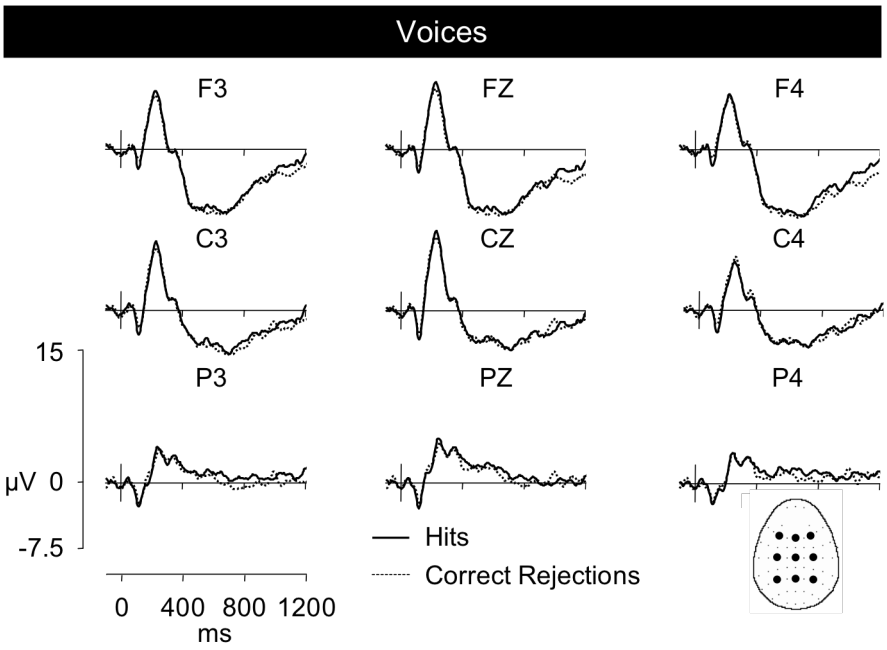


Figure 5.7 Grand average ERP waveforms for the recognition memory for voices task (n=29). Data shown as in Figure 5.1.

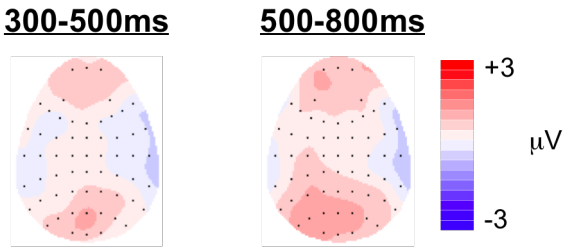


Figure 5.8 Topographic maps showing the distribution of the old/new difference for the voice recognition task. Data shown as in Figure 5.2.

Analysis from 300-500 & 500-800ms:

No significant differences were found in either the 300-500ms or 500-800ms time-windows when analysed using a global ANOVA. This outcome suggests that there is minimal difference in the ERP activity between hit and CR responses in the traditional time-windows.

Additional analysis:

As described above, the topographic maps in Figure 5.8 suggest that the old/new differences are strongest over frontopolar and parieto-occipital electrodes. Figure 5.9 shows the ERP waveforms over representative frontopolar electrodes and Figure 5.10 shows parieto-occipital electrodes, the time-window has been extended to 2000ms in both figures to best capture the effect evident over frontopolar electrodes. The frontopolar electrodes show that hits are slightly more positive going than CRs between approximately 1000-1800ms. Parieto-occipital electrodes also show that hit responses are slightly more positive going than CRs, but with an earlier onsetting divergence from approximately 300ms until approximately 900ms. Topographic maps showing the distribution effects in the additional 300-900ms and 1000-1800ms time-windows are presented in Figure 5.11.

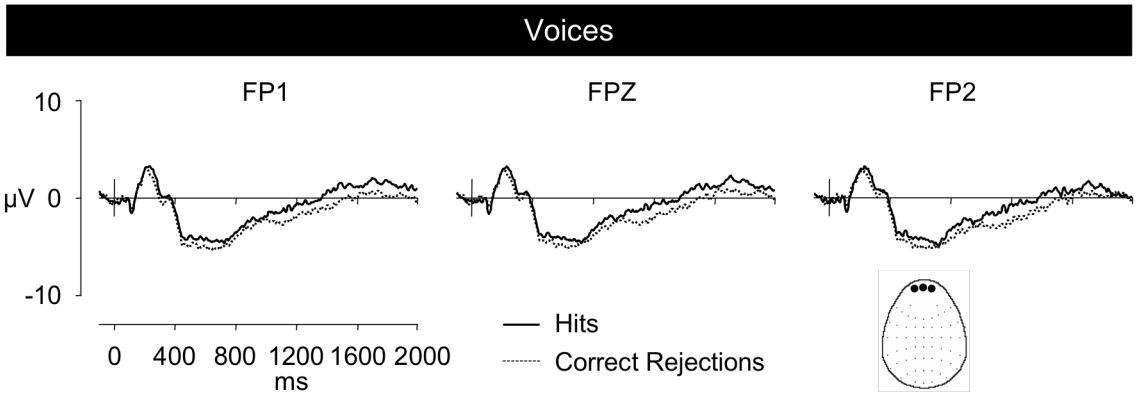


Figure 5.9 Grand average ERP waveforms for the old/new recognition memory task for voices at frontopolar electrodes (n=29).

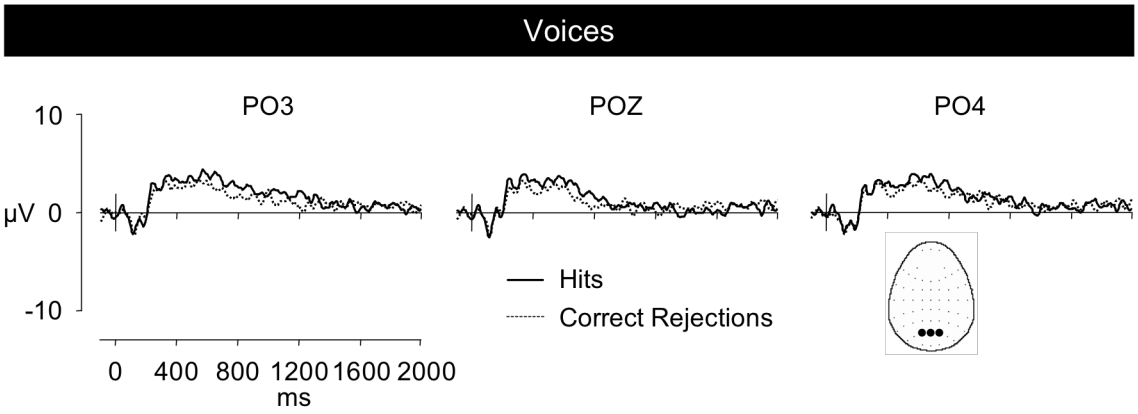


Figure 5.10 Grand average ERP waveforms for the old/new recognition memory task for voices at representative parieto-occipital electrodes (n=27).

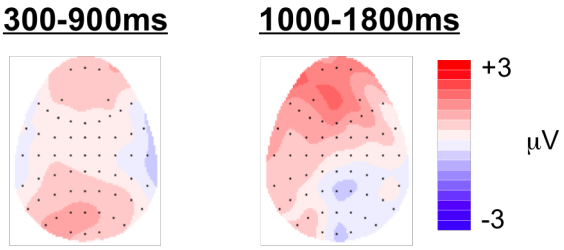


Figure 5.11 Topographic maps showing the distribution of the old/new difference for the voice recognition task. Two latency regions are shown, 300-900ms and 1000-1800ms. Data shown as in Figure 5.2 (n=29).

Analysis from 300-900ms:

As described above visual inspection of the data indicates that the old/new differences are maximal at the parieto-occipital electrodes between approximately 300-900ms, suggesting that the global ANOVA is inadequate for capturing condition differences that may exist. A more focused analysis was therefore conducted targetting the parieto-occipital electrodes in the 300-900ms time-window. An ANOVA with factors of condition (Hits/CRs), location (frontal/parietooccipital), hemisphere (left/right) and electrode site (inferior/medial/superior) was run on electrodes F3, F4, F5, F6, F7, F8, PO3, PO4, PO5, PO6, PO7 and PO8 in the 300-900ms time-window. Due to bridging of parieto-occipital electrodes two participants were excluded from additional analyses that

included these electrodes. Despite the impression given by Figure 5.10 no significant results were found with this re-analysis in the 300-900ms time-window.

Analysis from 1000-1800ms:

Visual inspection of the data also indicates that in the 1000-1800ms time-window the old/new difference appears maximal over the frontopolar electrodes. Re-analysis of the data over a 1000-1800ms time-window was conducted using an ANOVA with factors of condition (Hit/CR), location (frontopolar/parietal) and electrode site (left superior/midline/right superior). Electrodes FP1, FPZ, FP2, P1, PZ and P2 were included in the analysis. The results revealed a significant condition by location interaction [$F(1,28)=4.39$, $p=0.045$] indicating that hits were more positive going than CRs over frontopolar electrodes, with the reverse pattern evident over parietal electrodes, in the 1000-1800ms time-window.

5.3.4.3 Discussion

The behavioural results for the voice task were poor, with low hit rates and high false alarm rates resulting in low discrimination accuracy scores. Decision bias scores indicated participants had a neutral response bias for this task; participants were just as likely to respond ‘old’ as ‘new’ if they were unsure. Response times were the longest of the four recognition tasks, but follow a similar pattern, with CR responses taking longer than hit responses. The number of participants who met the inclusion criteria for this task was very small, with 100 participants excluded from the analyses, reflecting the difficult nature of the task.

ERP analysis of the old/new recognition task for voices initially focussed on the 300-500ms and 500-800ms time-windows, as in previous tasks. However, the global

ANOVA revealed no significant differences between hits and CRs in either time-window. Nonetheless visual inspection of the data indicated the presence of some small differences between conditions that were located out-with the electrode sites included in the global ANOVA, and that did not appear to fit the pre-determined time-windows. A more focused analysis was therefore conducted to investigate these effects, comparing conditions across the frontal and parieto-occipital locations in the 300-900ms time-window and the frontopolar and parietal locations in the 1000-1800ms time-window.

Targeted statistical analysis of the 300-900ms time-window did not reveal any significant differences. However, between 1000-1800ms a significant old/new difference was found that was largest over frontopolar electrodes. Therefore, whilst small, there are significant differences in the neural activity for successful recognition memory of voices.

Previous literature relating to recognition memory for voices appears limited, with studies restricting their use to recognition of voice gender in source retrieval tasks. As noted earlier, however, an fMRI study by Stevens (2004) looked at short-term memory for voices and words, finding differences in neural activity for each stimulus type. The lack of previous studies on recognition memory for voices limited the predictions that could be made about the pattern of ERP effects that would be seen. Arguably, therefore, the best platform for investigating recognition memory effects for voices was to look at the effects seen for other stimulus materials. Looking at the 300-500ms and 500-800ms time-windows used in the previous analysis failed to find any significant old/new differences. The topographic maps for both the 300-500ms and 500-800ms time-windows (Figure 5.8) did indicate the presence of small old/new differences over frontal and parietal electrodes, in which hits were more positive going than CRs, however

equally there was evidence of CRs being more positive going than hits over right central electrodes.

The focused analysis did reveal statistically significant old/new differences between 1000-1800ms, although the effects were small. Despite consistency in the paradigm designs across the four single-item recognition tasks, the nature of voice recognition task is inherently different from the other three tasks. With auditory stimuli it is not possible to present all the information at the same time, with it taking approximately 800ms for the whole voice recording to be presented in the current study, during which time participants need to continuously process the information. Similarly it is not possible for participants to go back and review a particular part of the stimulus as is possible, within the 1000ms presentation time, with visual stimuli. Clearly, this difference in presentation style may alter the typical patterns of ERP activity associated with recognition memory since all stimulus information was not available at the point of stimulus onset, and may explain the prolonged time-windows needed to capture the old/new effects that were present.

Looking more broadly at the ERP literature, longer response times and prolonged neural responses are not unusual for auditory stimuli. For example, Kayser, Fong, Tenke and Bruder (2003) reported longer response times and longer peak latencies for the P3 component with auditorily presented words compared to visually presented words, despite there being no statistical difference in task performance accuracy. Interestingly, in contrast to the typical ERP old/new recognition effects seen for words and pictures, the old/new effect for voices seen in the current study appears to be a late onsetting

frontopolar old/new effect[10]. Whilst late post-retrieval processes (onsetting around 900ms) found in recognition memory studies for words are frontally distributed, these effects tend to have a right hemispheric distribution, whereas the late frontal old/new effect seen in the current study for voices appears to have more of a central distribution, suggesting that it should not be interpreted as a classic "late right frontal" post retrieval ERP effect.

In summary, performance in the voice recognition memory task was poor and old/new effects were small making it difficult to draw strong conclusions about the functional significance of the ERP effects of successful voice recognition. Regardless, the results do suggest a unique set of old/new effects are elicited by recognition memory of voices.

5.3.5 Old/new recognition task material specificity:

The aim of the current section is to look at possible material specificity effects by comparing the old/new ERP effects from each single item recognition task. The results presented above have included all participants who met the inclusion criteria for each stimulus type. However, in order to directly compare the four tasks, the material specificity analysis will only include participants who met the inclusion criteria for the tasks being compared. An initial 'all category performers' analysis will be conducted with the 18 participants who met criteria for all four tasks, followed by a more focussed comparison of the word and picture stimuli with all 122 participants who met the criteria for these tasks. Analysis will focus on the traditional 300-500ms and 500-800ms time-windows described at the beginning of this chapter.

[10] Visual inspection of the ERPs for words, pictures and faces in the 1000-1800ms time-window do not show similar patterns of activity to that seen for voices. Words and pictures show a reversal in polarity, from approximately 1200ms, with CRs more positive going than Hits, and little difference can be seen between conditions for faces. This suggests that the late onsetting frontopolar difference seen in the current study is unique to voices.

5.3.5.1 Analysis of all four single item tasks:

Behavioural results:

Table 5.1 shows the behavioural results for the four single items tasks for the 'all category performers' group. Recognition performance (as indexed by Pr) varies between stimulus types, and as can be clearly seen in Figure 5.12, performance was highest for the picture task and lowest for the voice task. A repeated measures ANOVA confirmed that performance differed between stimulus materials [Greenhouse-Geisser corrected $F(1,28) = 86.48$, $p<0.001$], and paired samples t-tests revealed significant differences between each stimulus type (pictures-faces [$t(17)=16.57$, $p<0.001$], pictures-words [$t(17)=3.53$, $p=0.003$], pictures-voices [$t(17)=17.51$, $p<0.001$], face-words [$t(17)=-6.99$, $p<0.001$], faces-voices [$t(17)=2.27$, $p=0.037$], words-voices [$t(17)=7.82$, $p<0.001$]).

Participants also showed varying degrees of decision bias between different stimulus types. Overall participants exhibited a conservative – neutral response bias in all tasks, however a repeated measures ANOVA indicated that there were significant differences in bias scores between stimulus materials [Greenhouse-Geisser corrected $F(2,25) = 9.48$, $p=0.001$] (Figure 5.12). Follow-up paired samples t-tests revealed that a significant difference in bias scores was evident between all stimulus types (pictures-faces [$t(17)=-3.07$, $p=0.007$], pictures-words [$t(17)=-2.83$, $p=0.012$], pictures-voices [$t(17)=-3.71$, $p=0.002$], faces-voices [$t(17)=-2.74$, $p=0.014$], words-voices [$t(17)=-2.93$, $p=.009$]), with the exception of face and word stimuli which was not significantly different [$t(17)=0.96$, $p=0.35$].

All category performers (n=18)	Hit rate (%)	False alarm rate (%)	Pr	Br	Hit RT (ms)	CR RT (ms)
Words	77 (14)	16 (10)	0.60 (0.20)	0.42 (0.15)	846 (140)	921 (155)
Pictures	86 (15)	5 (3)	0.81 (0.14)	0.29 (0.25)	801 (173)	842 (181)
Faces	62 (9)	32 (6)	0.29 (0.08)	0.46 (0.08)	1013 (183)	1079 (219)
Voices	65 (10)	40 (9)	0.25 (0.06)	0.53 (0.11)	1411 (228)	1544 (288)

Table 5.1 Behavioural results for the participants who met inclusion criteria in all four old/new recognition types (words, pictures, faces and voices). Table shows mean hit and false alarm rates in percentages, mean discrimination accuracy, mean decision bias, and mean response times for hit and CR responses in milliseconds. Standard deviations for each measure are given in brackets.

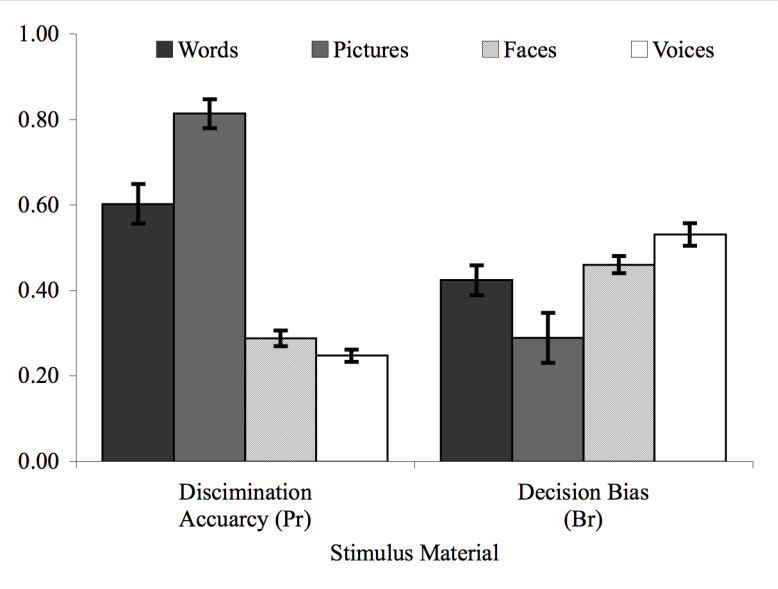


Figure 5.12 Discrimination accuracy (Pr) and decision bias (Br) scores across stimuli types (words, pictures, faces and voices) for participants who met inclusion for all four single item old/new recognition tasks. Data shows that the tasks varied in difficulty, with participants performing better on the picture and word tasks compared to the face and voice tasks. Overall participants showed a conservative-neutral decision bias in all four tasks, although the degree of bias varies between stimulus types.

Response times for both hits and CRs also vary in relation to stimulus material, revealing a pattern consistent with task performance. As discrimination accuracy increases, response times for both response categories decreases, with pictures showing the quickest response times, followed by words, faces and voices. In all tasks hit responses were quicker than CRs.

ERP results:

Topographic maps showing the distribution of old/new effects for the 'all category performers' across stimulus type are presented in Figure 5.13. Statistical analysis of these four stimulus types for the 'all category performers' found significant old/new differences for words[11], which showed that hits were more positive going than CRs, a difference largest over the frontal and central locations in the earlier time-window, and that were greater at superior and medial electrode sites in both time-windows; and pictures[12], suggesting a widely distributed old/new effect with hits more positive going than CRs, a difference maximal over superior electrode sites that did not differ across time-windows. No significant effects were found for either faces or voices for the 'all category performers'.

Given the absence of significant old/new effects for the face and voice tasks, for this analysis group, these stimuli were not included in the material specificity analysis. A comparison was therefore made of the old/new effects for picture and word stimuli. Data was rescaled to take account of overall amplitude differences between the two tasks (McCarthy and Wood, 1985) and then analysed using a repeated measures ANOVA, with factors of stimuli (pictures/words), location

[11] Analysis of the word data for the all category performers group revealed a main effect of condition [$F(1,17)=12.26$, $p=0.003$], a significant condition by site interaction [$F(1,18)=21.39$, $p<0.001$], and a significant condition, location, site interaction [$F(2,38)=3.28$, $p=0.044$] in the 300-500ms time-window. Analysis of the 500-800ms time-window again revealed a main effect of condition [$F(1,17)=24.82$, $p<0.001$], and a significant condition by site interaction [$F(1,18)=5.61$, $p=0.029$]. Due to the absence of location interactions in the 500-800ms time-window no follow-up analyses contrasting effects in the two time-windows were conducted.

[12] Analysis of picture data for the 'all category performers' in the 300-500ms time-window revealed a main effect of condition [$F(1,17)=60.44$, $p<0.001$], and a significant condition by site interaction [$F(1,20)=25.3$, $p<0.001$]. The 500-800ms time-window revealed a main effect of condition [$F(1,17)=28.35$, $p<0.001$], a condition by site interaction [$F(1,19)=9.96$, $p=0.004$], and a significant condition, location, site interaction [$F(3,42)=3.27$, $p=0.038$]. Analysis of the old/new difference across time-windows did not reveal any significant effects. The absence of significant effects suggests that there were no reliable change in magnitude or distribution across time-windows.

(frontal/frontocentral/central/centroparietal/parietal), hemisphere (left/right) and site (inferior/medial/superior). No significant differences between stimulus types were found in either the 300-500ms or the 500-800ms.

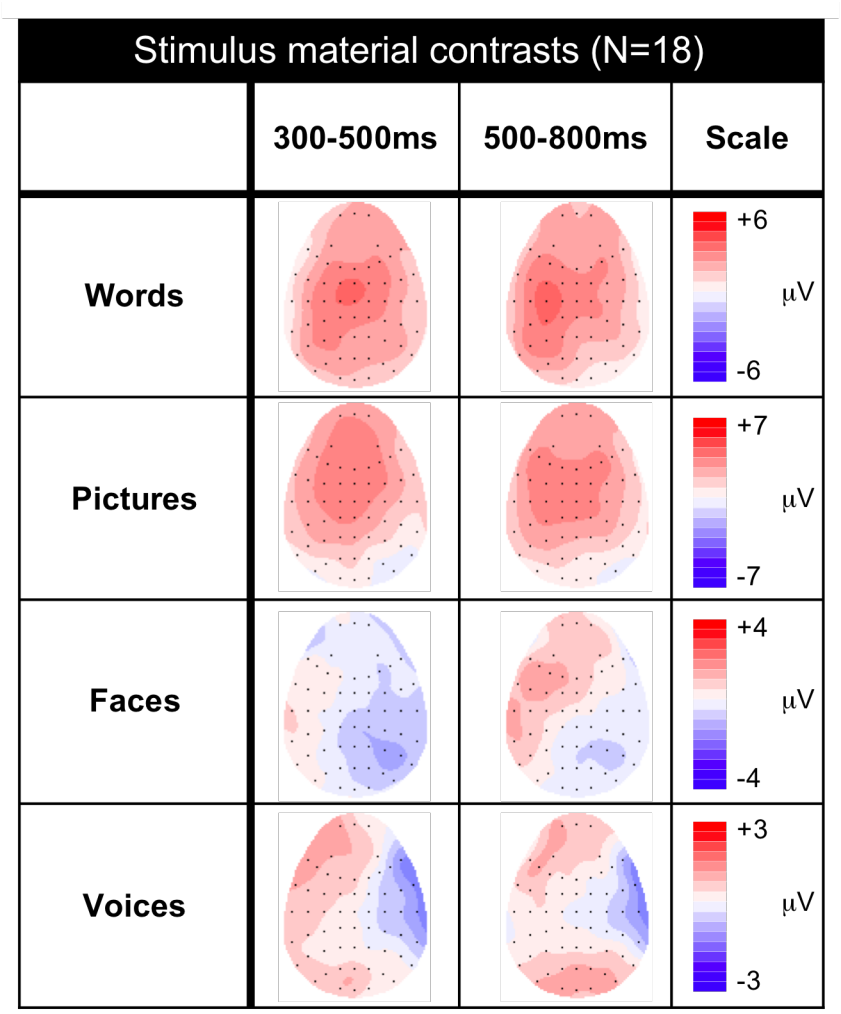


Figure 5.13 Topographic maps showing the distribution of the old/new differences across each of the four stimulus types (words, pictures, faces and voices). Two latency regions are shown, 300-500ms and 500-800ms, along with scale bars to show the size of the old/new difference. Maps show the subtraction of the grand average ERP for CRs from the grand average ERP for hits, generated from the 18 participants who met inclusion criteria in all four old/new recognition tasks.

The 'all category performers' group consisted of all 18 participants who met the inclusion criteria for all four old/new recognition tasks. Whilst old/new effects were found in this group for both the picture and word task, stronger effects were identified in the analysis of all participants from the individual task analysis. Since the face and voice tasks were excluded from the material specificity analysis re-examination of the

data identified 122 participants who met the inclusion criteria for both the pictures and words tasks. With this considerable difference in statistical power, a re-analysis of the material specificity effects was conducted.

5.3.5.2 Word and picture material specificity analysis:

Behavioural results:

The behavioural results for 122 participants who met the inclusion criteria in both the word and picture tasks are presented in Table 5.2. Recognition performance (as indexed by Pr) was clearly better for pictures than words, a paired samples t-tests revealed that the difference between the two tasks was significant [$t(121)=-13.69$, $p<0.001$]. Participants exhibited a conservative decision bias in both tasks, although they were significantly more conservative for the picture stimuli than for words [$t(121)=8.54$, $P<0.001$]. As with the previous sets of analyses hit responses were made quicker than CRs for both groups, and as would be expected from the performance figures overall participants were slightly quicker in the picture task than in the word task.

Words & Pictures (n=122)	Hit rate (%)	False alarm rate (%)	Pr	Br	Hit RT (ms)	CR RT (ms)
Words	73 (12)	18 (11)	0.54 (0.17)	0.39 (0.16)	823 (138)	898 (157)
Pictures	83 (12)	6 (6)	0.77 (0.15)	0.26 (0.18)	800 (137)	850 (145)

Table 5.2 Behavioural results for the participants who met inclusion criteria in both the word and picture tasks. Data shown as in Table 5.1.

The same subset of participants used in the initial word analysis is also used here, and the majority of participants from the initial picture analysis are also included. The behavioural data for the picture task presented here reflects that presented in the earlier discussion of picture effects.

ERP results:

Figure 5.14 shows the ERP *difference waveforms* for the picture and word tasks; the positive going old/new difference for the picture task is clearly larger compared to the word task between approximately 400-700ms, particularly over the frontal electrodes. The distribution of the old/new effects for each stimulus type (words are shown in the top row, and pictures in the middle row), as well as the difference in distribution between the material types (bottom row), can be found in Figure 5.15. These topographic maps suggest a more anteriorly distributed effect for the picture task in comparison to the word task, a pattern that is apparent across both time-windows.

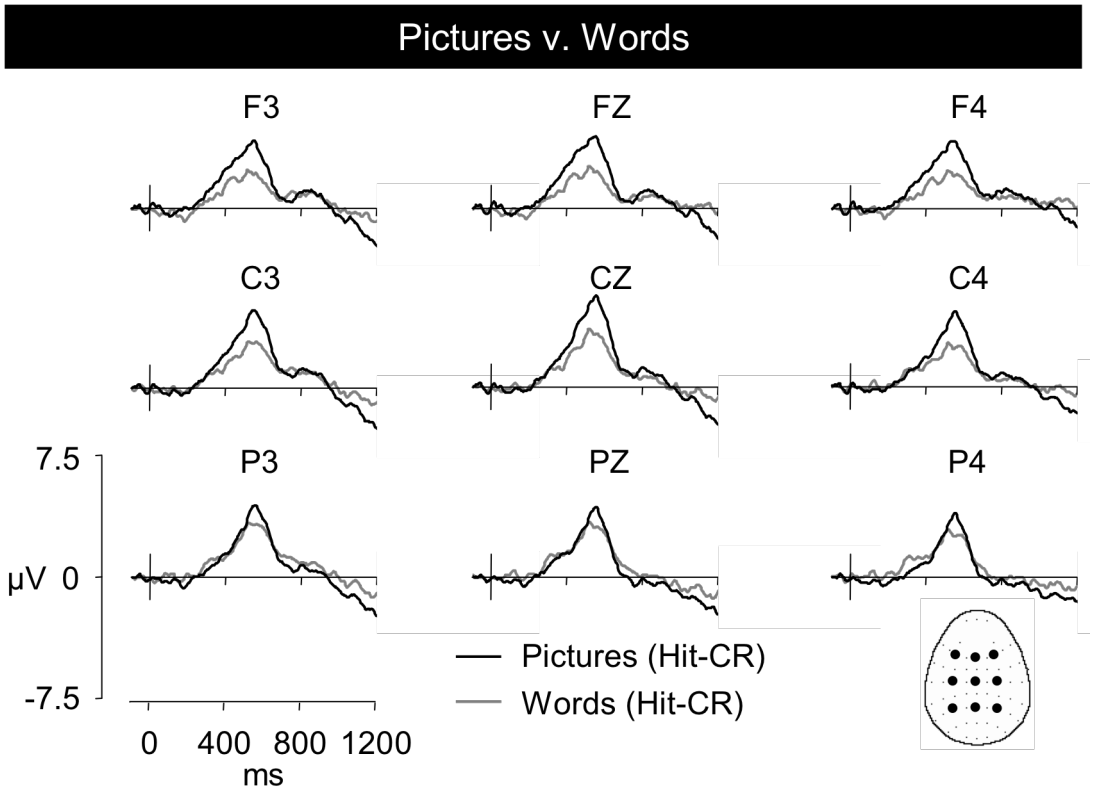


Figure 5.14 Grand average ERP difference waveforms (Hits-CRs) at representative frontal, central and parietal electrode sites, for the picture and word recognition tasks. Waveforms generated from 'all participants' who met the inclusion criteria for both tasks (n=122).

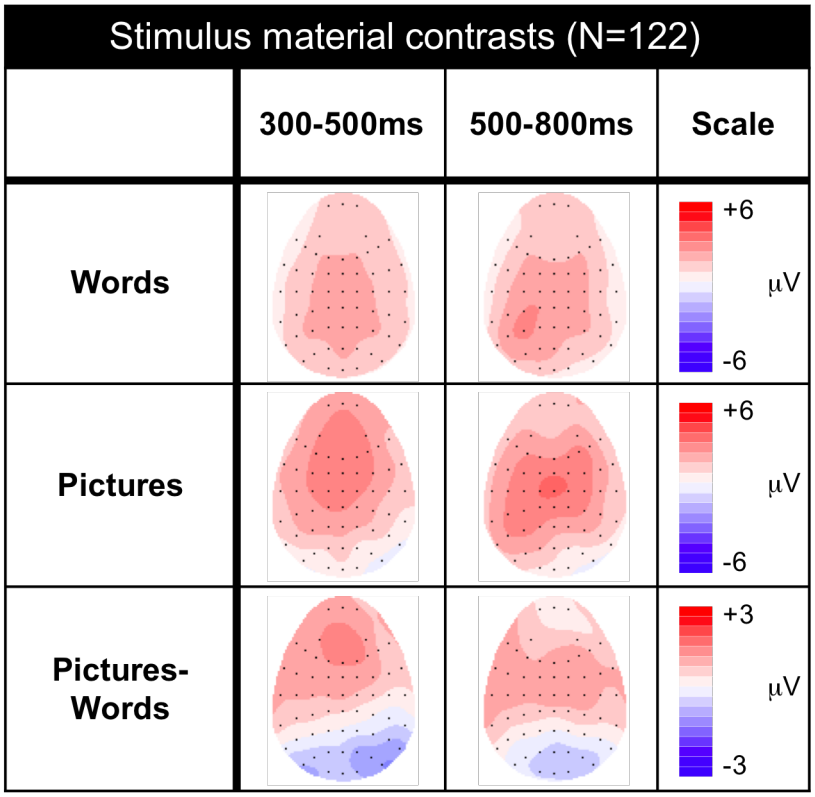


Figure 5.15 Topographic maps showing the distribution of the old/new differences across word and picture tasks for all 122 participants who met the inclusion criteria both recognition tasks. Maps in the top two rows show the subtraction of the grand average ERP for CRs from the grand average ERP for hits, for words and pictures. The maps in the bottom row represent the difference between the picture and word tasks, which were generated by the subtraction of the word difference waveform from the picture difference waveform. Two latency regions are shown, 300-500ms and 500-800ms, along with scale bars to show the size of the difference.

Statistical analysis comparing the two types of stimuli was conducted on rescaled data as per the 'all category performers' analysis. The 300-500ms time-window revealed a significant stimulus by location interaction [$F(1,145)=7.26$, $p=0.005$] indicating that over more anterior locations the old/new effect was larger for the picture task than the word task, a pattern that reversed over more posterior locations. This cross-over of effect magnitude across locations can clearly be seen in Figure 5.16a. Additionally a significant stimulus by hemisphere by site interaction was found [$F(1,140)=4.65$, $p=0.028$], indicating that the difference in the old/new effect is greatest at superior electrodes over the left hemisphere, with an overall equal distribution across sites over the right. In the 500-800ms time-window a significant stimulus by location interaction

was also found [F(1,143)=3.97, p=0.041], indicating that the picture task exhibited a larger old/new effect than words and that, as per the earlier time-window, the difference in effect magnitude was progressively larger the more anterior the location, with words exhibiting a slightly larger effect over parietal electrodes (Figure 5.16b).

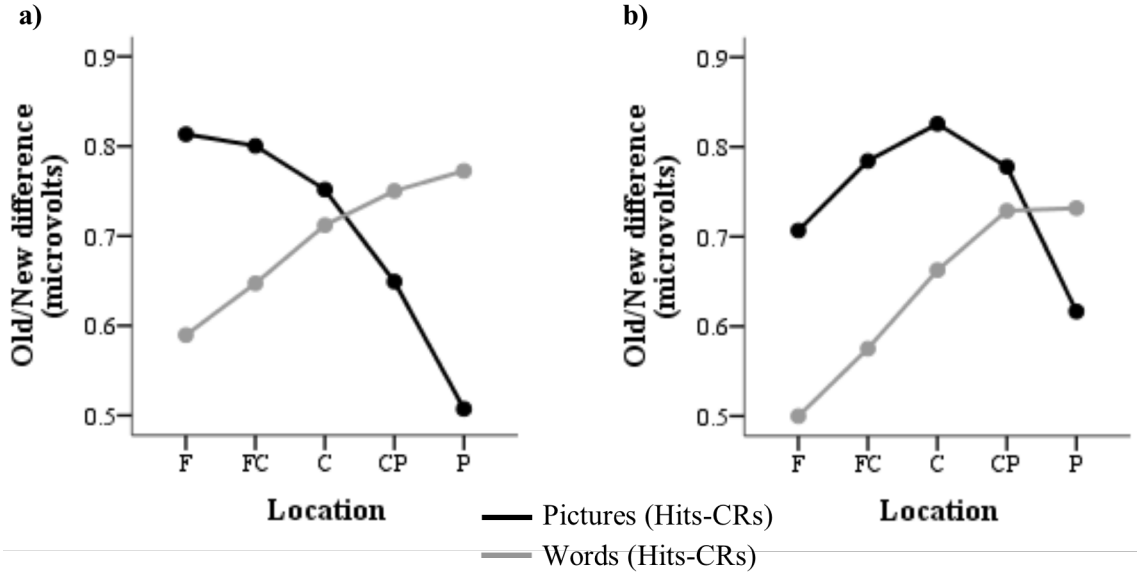


Figure 5.16 Plots showing average old/new effect magnitude (data rescaled to control for overall magnitude differences) for both picture and word stimuli across locations (frontal, frontocentral, central, centroparietal and parietal) for the 300-500ms (a) and 500-800ms (b) time-windows (n=122). Significant stimuli by location interactions were found for both time-windows indicating distributional differences in the old/new effect across stimuli types.

5.3.5.3 Discussion

The purpose of this last results section was to investigate material specificity in relation to ERP recognition memory effects. Eighteen participants met the inclusion criteria for all four single-item recognition tasks. The behavioural results showed significant differences between tasks in performance, decision bias, and response times, with participants clearly finding the picture task easiest, with higher discrimination accuracy and quicker response times then the other tasks. The word task showed the next highest performance scores, followed by the face task, and finally the voice task.

It was also evident from the behavioural data that variation in decision bias across stimulus material was related to task difficulty, with bias scores increasing (i.e. becoming more neutral in nature) the lower the mean discrimination accuracy of a task (see Figure 5.12). This change in decision bias may represent a shift in response strategy based on task difficulty, with participants responding more liberally on tasks which they are struggling with. If participants feel confident in their ability to complete the task their criteria for selecting an item as being previously presented, and responding 'old' is much more stringent than on a task where they are less confident. Furthermore, if participants find a task particularly difficult, such as the voice task, then a neutral bias will allow for a much more equal distribution of responses than a conservative or liberal bias. Interestingly in the current study, overall, participants tended to exhibit either a conservative or neutral bias with a minority showing a liberal bias, although as indicated by the average bias scores, the number of participants with a liberal bias did increase with task difficulty.

ERP analysis was limited to the picture and word tasks due to the absence of significant old/new differences for the face and voice 'all category performers groups'. Unfortunately, however, no significant differences between picture and word effects were found in either the 300-500ms or 500-800ms time-windows when comparing the 'all category performers'. This finding stands in stark contrast to previous literature, which suggests that there are material specific effects, with pictorial stimuli exhibiting more anterior effects than words, particularly in the 500-800ms time-window. Moreover, visual inspection of the data suggested that there may be differences in the ERP effects of pictures and words, the failure to find any statistical effects was therefore surprising. It was hypothesised that this lack of significance differences between words

and pictures may be due to low statistical power in the 'all category performers' sample, with analysis restricted to only 18 participants.

Analysis of all 122 participants who met the inclusion criteria for the picture and word tasks was therefore conducted. Significant differences were found in the distribution of old/new effects across stimuli type, with pictures showing larger anterior effects than words and words showing larger posterior effects than pictures. This pattern of a stronger frontal distribution was evident in both time-windows. These results strongly suggest that there are significant differences in the distribution of the ERP old/new effects exhibited by successful recognition memory for pictures and words, and are consistent with previous literature suggesting that pictures exhibit more anterior ERP old/new effects than words (Galli & Otten, 2011).

Galli and Otten (2011) hypothesise that pictorial stimuli exhibit more anterior ERP effects than verbal stimuli due to the reinstatement of encoding activity, with pictures requiring greater perceptual analysis than words. Galli and Otten (2011) argue that the degree of perceptual analysis could explain discrepancies in the literature relating to line drawings and photographs, with photographs requiring more perceptual analysis. In accordance with this perceptual complexity argument Kayser *et al.* (2003) found different scalp topographies with ERP old/new effects for auditorily and visually presented words, with auditory words exhibiting old/new effects that were largest at posterior locations, and visual words at frontocentral locations.

A second hypothesis is that the different ERP effect distributions seen in the current study may also be related to the variation in decision bias across tasks discussed above. Controlling for task accuracy Windmann, Urbach and Kutas (2002) compared recognition memory ERP effects for verb stimuli, in participants with a high (liberal)

and low (conservative) bias, showing that participants with a low bias exhibited an old/new effect over frontal sites between 300-500ms that was absent for those with a high bias. No significant group differences were found between 500-700ms. Windmann *et al.* (2002) suggest these differences across frontal sites reflect the criterion setting functions of the prefrontal cortex, which they argue is used to maintain a description of the information being sought during memory retrieval and to inhibit memory traces that do not match. The different bias groups are therefore thought to vary in terms of what is consider relevant/irrelevant to the task, with low bias groups endorsing information signalling newness over information suggesting that the item is familiar, therefore facilitating participants in making 'new' responses and inhibiting 'old' responses. In comparison participants with a high bias have less inhibitory control increasing the likelihood that they will respond 'old', and engaging the prefrontal cortex less than the low bias group.

The distributional differences seen in the current study, particularly in the early time-window, may reflect a relaxation of inhibitory control by participants on tasks which are more difficult, perhaps in an attempt to even out the number of 'old' and 'new' responses being made. The findings of Windmann *et al.* (2002) suggest we should see greater old/new effects over anterior sites between 300-500ms for tasks where participants exhibit an overall lower/more conservative bias. In the current study participants were most conservative on the picture task, followed by words, faces and voices. There is clear evidence that the ERP effects for the picture task are more anterior in distribution than the word task, and the absence of significant old/new effects in the 300-500ms time-window for either the faces or voices may reflect the neutral bias exhibited by participants during these tasks.

It is not possible to discern from this study which, if either, hypothesis is correct. The four tasks presented in this chapter differ from each other not only with regard to the stimulus material, but also in relation to task performance, and response bias. The paradigm was kept identical across all four types of stimulus for control, to ensure that any differences evident across stimuli were not a function of paradigm differences, but related to the stimuli. However, the downside of a controlled paradigm design is that performance differed across the tasks, as the inherent properties of the each type of stimulus changed the difficulty of the task. It is possible that a combination of task performance and response bias contributes to the variations in ERP effects seen, and more detailed analysis of the influence of performance and decision bias on ERP effects is needed to unpack this.

5.4 General Discussion

The current chapter examined single-item recognition memory for pictures, faces, words, and voices, with the principal aim of understanding the behavioural and ERP effects produced by these tasks, before going on in later chapters to look at the impact of various individual differences on recognition memory. In addition a material specificity analysis was conducted, to see how differences in stimulus type influenced behaviour and ERP effects. There was some evidence of old/new ERP differences in all four tasks. Particularly strong evidence for an ERP effect for pictures was found, with successful recognition memory exhibiting an early bilateral-frontal old/new effect between 300-500ms, followed by a more posterior left hemispheric old/new effect in the 500-800ms time-window, albeit with clear evidence for continued activity over frontal sites during the later time-window. There was also strong evidence for ERP neural correlates of successful recognition memory for words, with an early bilateral old/new

difference that was more anterior in distribution than the later 500-800ms left parietal old/new difference. Overall, therefore, ERP effects observed for pictures and words appear to be consistent with the findings reported in the literature. Importantly the material specificity analysis suggested that the ERP effects for the two stimulus types are topographically dissociable in both the 300-500ms and 500-800ms time-windows, with pictures exhibiting more anteriorly distributed effects then words, adding weight to the conclusions of Galli and Otten (2011).

The results from the faces and voices tasks do suggest that there are ERP old/new differences, however the size of these effects make it difficult to draw strong conclusions. The faces data in particular indicated the presence of an old/new difference over left parietal electrodes in the 500-800ms time-window, consistent with previous studies. However, whilst visually there are differences between the ERPs for 'old' and 'new' responses over frontal electrodes, statistically these differences were not robust, making it difficult to draw conclusions with regards to additional frontal activity for faces that has been reported in some studies. The different distributions of face recognition effects evident across studies may indicate strategic differences. Further investigations of face effects with a face-verbal phrase source task, will be discussed in Chapter 6, allowing the contributions of familiarity and recollection to be assessed.

The ERP data for the voices task also showed evidence of old/new ERP differences, however these did not fit with the pre-selected time-windows or electrode array. The lack of previous studies looking at old/new recognition memory for voices makes it difficult to interpret the data definitively, with no clear platform from which to base the analysis. In particular, the different nature of the voice task compared to the other three tasks, with a slow release of information over 800ms rather than instantly presenting all

the information, further complicates the analysis strategy and interpretation. Nonetheless, in all other respects the voices task was identical procedurally to the other single item tasks, rendering the ERP contrasts valid as an operational definition of episodic retrieval. Given this, the fact that the data from the current study did indicate a later frontopolar old/new effect between 1000-1800ms (although visual inspection of the data suggest that this anterior effect may onset as early as 300ms), an effect not present in the other tasks, provides strong evidence of material specific differences. The absence of early bilateral-frontal and later left-parietal old/new effects, typically seen in recognition memory studies, suggests that material specific differences are not limited to a change in the expression of these typical effects, as seen for pictures (Galli & Otten, 2011), nor to the presence of old/new effects that are 'additional' to the typical effects, as appears to be the case for face stimuli (MacKenzie & Donaldson, 2007, 2009; Yick & Wilding, 2008). At least for voices, the current data suggest that successful recognition memory can occur in the absence of these typical ERP effects, and instead exhibit a sustained old/new difference over frontopolar electrodes.

The most apparent difference between the tasks that exhibit strong ERP effects (pictures and words), and those showing weaker ERP effects (faces and voices) is the difference in performance. Behaviourally the picture and word tasks show higher hit rates, lower false alarm rates, higher discrimination accuracy, and shorter response times than the face and voice tasks. Whilst participants performed above chance in all groups, in all four tasks, the differences observed between stimuli types suggests that performance may be an important factor in determining the pattern of ERP correlates. Critically, changes in decision bias may be indicative of differences in response strategy, which may influence the observed ERP effects. Exactly what these different strategies are, and how they differentially support recognition memory remains an open question.

The interpretation of the functional significance of the distributional differences evident across stimuli is limited by the lack of independent estimates of recollection and familiarity. One possibility is that the differences in both performance and distribution reflect variable reliance on these two processes. However, the unique effects found for voice recognition, which resemble neither the bilateral-frontal familiarity effect nor the left-parietal recollection effect, are hard to reconcile with the idea that material specific differences simply reflect differing contributions of recollection and familiarity, and therefore provides strong evidence for material specificity.

A number of different methods that allow independent estimates of familiarity and recollection to be made were discussed in Chapter 1, however each method changes the nature of the task, and the way they are completed. Asking participants to rate how confident they are in a response, or to subjectively evaluate their retrieval (R/K paradigms), imposes criteria on the old/new judgment that may change the way they respond. Source tasks provide stronger estimates of recollection and familiarity than confidence or R/K judgments, but include additional stimuli. The single-item recognition paradigm was designed to provide a series of short tasks that would allow the evaluation of basic stimulus differences (in the style of Yick & Wilding, 2008), that were not confounded by a secondary task or additional stimuli. Participants also completed a separate source memory task, which allows estimates of familiarity and recollection to be made with regards to face recognition that will be discussed in Chapter 6.

In sum, across the four tasks there do appear to be material specific effects, with a unique late onsetting frontopolar old/new effect for voices, as well as clear evidence of material specific effects for pictures and words. The results also highlight the possible

importance of performance measures in investigating the functional significance of material specific effects, and the need for further investigation of the influence of behavioural performance and decision bias on the neural correlates of recognition memory. To further understand how task performance influences ERP old/new recognition effects, analysis of performance differences in the word and picture tasks will be presented in Chapter 7.

Chapter 6

Source Memory for Faces and Verbal Phrases

6.1 Introduction

The previous chapter looked at the neural correlates of single item recognition memory, identifying an early (300-500ms) bilateral-frontal old/new effect and a later (500-800ms) left parietal old/new effect for pictures and words, with evidence of the later left-parietal effect also evident for faces. These ERP effects are consistent with the putative neural correlates of familiarity and recollection reported in the literature. The single item recognition memory paradigms employed in the previous chapter are, of course, necessarily limited by the absence of a behavioural measure that allows the contribution of familiarity and recollection processes to be estimated. Therefore, whilst we find ERP effects that reflect those of familiarity and recollection, it is not possible to independently ascertain the degree to which the two processes generate these effects.

A key component of understanding the influences of individual differences on recognition memory is to understand how these variances may influence the contribution of familiarity and recollection, and the associated ERPs. Therefore an additional recognition memory task that allowed familiarity and recollection estimates to be made was also included in the study. As discussed in Chapter 1 there are several methods that can be used to obtain estimates of familiarity and recollection, and the current study employed a source memory task. Participants were required to remember a face and a simultaneously present verbal phrase of either “hello” or “thanks”. It was hypothesised that trials in which participants were able to correctly identify the face as ‘old’ and remember the associated phrase - Hit/Correct responses (HC), would be

recollection-based judgements whereas trials in which the phrase could not be remembered – Hit/Incorrect responses (HI), were more likely to based on the process of familiarity[13].

As discussed in the previous chapter there is some discrepancy in the literature with regards to recognition memory ERP effects for faces, particularly with regards to the familiarity-based recognition. Curran and Hancock (2007) report a bilateral-frontal old/new effect between 300-500ms, resembling the effect typically seen for word stimuli, an effect that is present irrespective of whether specific details relating to the episode are recollected, whereas Yovell and Paller (2004) and MacKenzie and Donaldson (2007) both report posterior familiarity effects. In relation to recollection-based recognition Curran and Hancock (2007), MacKenzie and Donaldson (2007 & 2009), and Galli and Otten (2011) all report a posterior old/new effect between 500-700ms, with additional overlapping frontally distributed activity reported by MacKenzie and Donaldson (2007 & 2009).

Whilst conflicting results are presented in the literature, it is expected that the current study will show effects reflecting the findings from MacKenzie and Donaldson (2007) due to the many similarities between the two tasks. Both tasks present participants with a photograph of a face with masked hair and ears, in both tasks the face is accompanied by auditorally presented information, and furthermore, there is an overlap in the stimulus set used. It is therefore hypothesised that the current study will show a posterior old/new effect for HI responses and a later onsetting postieror old/new effect accompanied by an overlapping anterior effect for HC responses.

[13] Although it is expected that there will be greater involvement of recollection in HC trials than in HI trials, this is not to say that HI trials will be solely reliant on familiarity processes, simply that recollection will be involved to a lesser extent.

6.2 Methods

Details concerning participant recruitment, as well as experimental and EEG procedures, are reported in the General Methods (Chapter 4). As per the single item recognition memory tasks participants were excluded from analysis if they had fewer than 16 good ERP trials per condition, or if they had an old/new face recognition performance of Pr <0.2. Fifty-four participants met the inclusion criteria for the source memory task and were therefore included in the initial analysis.

As detailed in the General Methods the source memory task comprised a series of "face-verbal phrase" pairs during study, followed by a two step retrieval task in which participants first had to make an old/new recognition judgment to a presented face, and then, for faces classified as 'old', to indicate if the face was presented with the phrase 'hello', 'thanks' or that they did not know the phrase. Use of the 'Don't Know' response during the second part of the retrieval task was inconsistent across participants, with some making 'Don't Know' responses and others (n=23) not. The highest utilisation of the 'Don't Know' response by a participant was 24% of source trials, however of the 31 participants who used the 'Don't Know' response only 8 participants used this option on more than 10% of source trials. Due to the overall minimal and inconsistent use of the 'Don't Know' response, these trials were collapsed with 'Source miss' trials in to a 'Source Incorrect' condition for behavioural and ERP analysis. ERP analysis was therefore conducted on three conditions, CRs (faces correctly identified as new), HC (correctly identified 'old' faces with correct identification of the paired phrase), and HI responses (correctly identified 'old' faces without correct identification of the phrase); contrasting HC and CRs, HI and CRs, and HC and HI responses.

In addition to average recognition response rates, discrimination measures and response times, source accuracy is also reported in the behavioural results, with standard deviations given in brackets. ERP analysis follows the procedure outlined in the General Methods (Chapter 4) with any additional subsidiary analysis described alongside the results in the relevant section.

6.3 Results

6.3.1 Source memory task:

6.3.1.1 Behavioural results

Participants were able to successfully complete the initial old/new recognition memory task with a mean hit rate of 64% (s.d. 11%), and a false alarm rate of 29% (s.d. 12%). Mean discrimination accuracy (*Pr* = 0.34, s.d. 0.10) was above chance (zero) [$t(53)=24.44$, $p<0.001$], and participants showed an overall neutral decision bias, indicating participants were equally likely to respond 'old' as 'new' when unsure (*Br* = 0.45, s.d. 0.15). Mean response times for hits were 1191ms (s.d. 292ms), and 1157ms (s.d. 284ms) for CRs. Correct identification of the paired phrase on hit trials (HC responses) was above chance (50%) [$t(53)=10.87$, $p<0.001$], with an average score of 58% (s.d. 6%).

6.3.1.2 ERP results

Figure 6.1 shows the grand-average ERP waveforms for HC, HI and CR responses from representative electrodes at frontal, central and parietal locations. There is a clear divergence of HC and HI waveforms from CRs, starting at approximately 400ms and lasting until approximately 800ms, with hit responses more positive going than CRs. There is no evidence of a difference between hit responses (HC and HI responses) over

posterior electrodes, however, there does appear to be a small divergence over frontal electrodes between approximately 600-1000ms, with HC responses more positive going than HI responses.

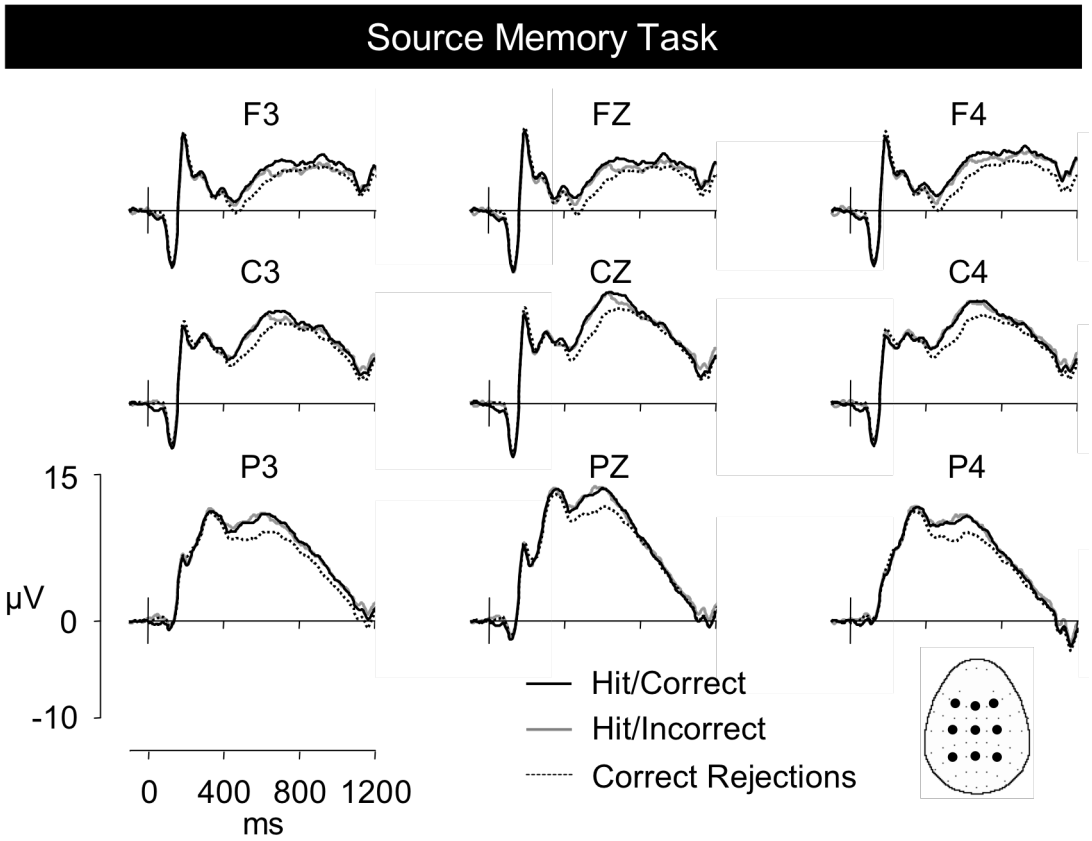


Figure 6.1 The grand average ERP waveforms for the source memory task, at representative frontal, central and parietal electrode sites, for HC, HI and CR responses. Waveforms generated from 'all participants' who met the inclusion criteria (n=54). The vertical scale indicates electrode amplitude, measured in microvolts, whilst the horizontal scale indicates change in time, measured in milliseconds.

As per the single-item task preliminary analysis of the ERP data from the source judgement task focused on the 300-500ms and 500-800ms time-windows identified in the literature. The distribution of the difference in activity between the three conditions is shown in Figure 6.2, across both the 300-500ms and 500-800ms time-windows. The topographic maps suggest a widespread bilateral difference between HC and CR responses, maximal along midline electrodes (top row of Figure 6.2), in the early 300-500ms time-window, becoming more right lateralised at frontal locations and left lateralised at parietal locations, in the 500-800ms time-window. The difference in

activity between HI and CRs (middle row of Figure 6.2) shows a bilateral distribution over parietal locations in the 300-500ms time-window, becoming stronger between 500-800ms. In addition, the maps suggest a weaker right-frontal difference between 500-800ms, that is not present in the previous time-window. Finally, the topographic maps in the bottom row of Figure 6.2 show the difference between HC and HI responses. Whilst the difference between the two hit categories appears to be relatively small, HC responses are clearly more positive than HI responses over frontal electrodes, an effect which becomes stronger between 500-800ms.

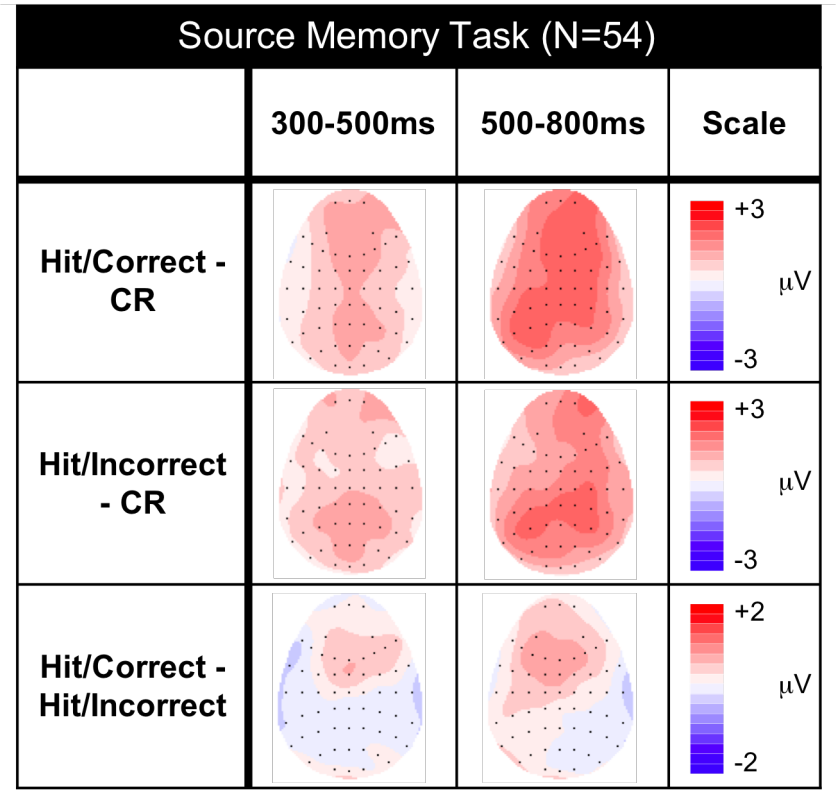


Figure 6.2 Topographic maps showing the distribution of the old/new difference for the source memory task, across all 54 participants who met the inclusion criteria. Two latency regions are shown, 300-500ms and 500-800ms, along with scale bars to show the size of the old/new difference.

Hit/Correct vs Correct Rejection:

Analysis from 300-500ms:

ERP data was analysed using ANOVA, with factors of condition (HC/CRs), location (frontal/frontocentral/central/centroparietal/parietal), hemisphere (left/right), and electrode site (inferior/medial/superior) as outlined in Chapter 4. Analysis of the 300-500ms time-window showed a main effect of condition [$F(1,53)=5.1$, $p=0.028$], showing that overall HC responses were more positive going than CRs. A significant condition by site interaction [$F(1,61)=7.07$, $p=0.008$] indicates that the old/new difference was greatest at superior electrode sites, suggesting a widespread old/new effect across midline electrodes. Visual inspection of the data revealed that the difference between HC and CR responses in the 300-500ms time-window was maximal at electrode FZ, and a paired-samples t-test showed that the difference between conditions at this electrode was significant [$t(53)=2.14$, $p=0.037$].

Analysis from 500-800ms:

In the 500-800ms time-window a significant main effect of condition [$F(1,53)=16.53$, $p<0.001$] and a significant condition by site interaction [$F(1,59)=4.74$, $p=0.03$] were found, indicating that HC responses were more positive going than CRs, a difference largest over superior electrode sites. In addition, there was a significant condition by location by hemisphere by site interaction [$F(3,165),=5.06$, $p=0.002$].

Subsidiary analysis was conducted to further understand the four-way interaction, using ANOVA that included factors of condition, hemisphere and site at each of the five locations (frontal, frontocentral, central, centroparietal and parietal). A significant main effect of condition was found at the frontal location [$F(1,53)=12.07$, $p=0.001$], and

significant condition by site interactions were found at frontocentral [$F(1,61)=4.39$, $p=0.035$] and central [$F(1,60)=5.92$, $p=0.015$] locations, reflecting the presence of positivity for HC responses that is largest over superior electrodes, at central and anterior locations. By contrast, at centroparietal electrodes there was a main effect of condition [$F(1,53)=16.73$, $p<0.001$], with a marginally significant condition by hemisphere by site interaction at the parietal location [$F(1,66)=3.66$, $p=0.051$], indicating that the old/new effect is larger in the left hemisphere (where the distribution across sites is constant) than in the right hemisphere (where the difference is greatest at superior electrode sites). Visual inspection of the data revealed that overall the maximal old/new difference between 500-800ms was at electrode F4, a difference significant at this electrode [$t(53)=3.86$, $p<0.001$].

Comparison of the 300-500ms and 500-800ms time-windows:

The above analyses indicate significant differences between HC and CR responses in both the 300-500ms and 500-800ms time-windows. Additional analysis comparing effects across time-windows was conducted on differences scores (HC-CR), using ANOVA with factors of time (300-500ms/500-800ms), location (frontal/frontocentral/central/centroparietal/parietal), hemisphere (left/right) and site (inferior/medial/superior). The ANOVA identified a significant time by location by hemisphere by site interaction [$F(3,161)=5.79$, $p=0.001$], reflecting the change from a widespread bilateral old/new effect between 300-500ms to a more focused left-parietal effect in 500-800ms time-window. Importantly, follow-up topographic analysis using rescaled data also revealed a significant interaction between time, location, hemisphere and site [$F(4,184)=2.73$, $p=0.037$], suggesting that the distinct effects seen in the two time-windows are different in distribution and not just magnitude.

Hit/Incorrect vs Correct Rejection:

Analysis from 300-500ms:

Analysis of the HI and CR responses in the 300-500ms time-window revealed a main effect of condition [$F(1,53)=4.25$, $p=0.044$], indicating a widespread old/new effect in which HI responses were more positive going than CRs. Visual inspection of the data indicated that the difference was maximal at electrode CPZ, and a paired-samples t-test found this difference to be significant [$t(53)=2.69$, $p=0.01$].

Analysis from 500-800ms:

Analysis of the 500-800ms time-window revealed a main effect of condition [$F(1,53)=10.35$, $p=0.002$], indicating that HI responses were more positive going than CRs, along with a significant condition by location by hemisphere by site interaction [$F(4,183)=3.45$, $p=0.013$]. As shown in the central row of Figure 6.2, the distribution of the old/new effect is widespread, with a posterior maximum. However, subsidiary analysis of the data at each location using ANOVA (including factors of condition, hemisphere and site) revealed a significant condition by hemisphere by site interaction [$F(1,74)=3.8$, $p=0.041$] at the frontal location. This interaction indicates that the old/new difference was greatest in the right hemisphere over more lateral sites, with asymmetry across the hemispheres most evident at inferior sites. Main effects of condition were evident at frontocentral [$F(1,53)=5.89$, $p=0.019$], central [$F(1,53)=9.07$, $p=0.004$], centroparietal [$F(1,53)=13.18$, $p<0.001$], and parietal [$F(1,53)=15.38$, $p<0.001$] locations, indicating that overall HI responses were more positive going than CRs. Visual inspection of the data showed that the maximal difference between conditions in the 500-800ms time-window was at electrode CP2, a difference that was significant at this electrode [$t(53)=3.91$, $p<0.001$]. These results therefore indicate that whilst the

old/new effect is greatest at posterior locations, there is a weaker right frontal effect evident between 500-800ms.

Comparison of the 300-500ms and 500-800ms time-windows:

Analysis of the HI and CR data revealed significant old/new ERP effects in both the 300-500ms and 500-800ms time-windows. Additional analysis comparing the ERP effects across the two time-windows was conducted on difference scores (HI-CR) using ANOVA, (looking at factors of time, location, hemisphere and site) revealing a significant interaction between all four factors [F(4,185), 7.8, p=0.001]. As is evident from the preceding analyses, this interaction reflects the presence of a right frontal effect between 500-800ms that was not present between 300-500ms. Repeating the analysis on rescaled data also revealed an interaction between all four factors [F(3,178)=4.56, p=0.003] showing that the ERP effects across time-windows are topographically distinct, and that the differences are not simply a result of overall magnitude variation.

Hit/Correct vs Hit/Incorrect:

Analysis from 300-500 & 500-800ms:

Analysis of the difference between HC and HI responses did not reveal any significant effects in either the 300-500ms or 500-800ms time-windows. The absence of statistically significant differences suggests that the divergence between conditions

visible in Figure 6.1 and the bottom row of Figure 6.2 were not statistically reliable, suggesting variability across participants.[14]

6.3.1.3 Discussion

Behavioural performance on the old/new recognition task is consistent with the performance seen in the single-item recognition memory for faces task, presented in the previous chapter, with participants able to successfully identify previously presented faces. Although participants generally found the source task difficult, approximately half the study sample (n=54) met the task inclusion criteria and overall correct identification of the paired phrase was above chance level. Comparisons of the ERPs for HC, HI and CR responses were made in both the 300-500ms and 500-800ms time-windows.

Statistical analysis of HC and CR responses revealed a widespread bilateral old/new effect between 300-500ms, with a more focused frontocentral/central bilateral difference in the 500-800ms time-window, alongside a left lateralised parietal effect which was not present in the earlier window. Comparing HI responses and CRs revealed an overall significant difference between the two conditions between 300-500ms, although no interactions with location, hemisphere or site were found. This widespread old/new difference continued into the later time-window, with the development of a large asymmetry between anterior and posterior locations across the left hemisphere, with the old/new effect greatest at posterior locations. There was also evidence of a right frontal old/new effect between 500-800ms that was not present in the 300-500ms time-window.

[14] Additional analysis using the global ANOVA comparing HC and HI responses in the 600-1000ms time-window, identified as best capturing the difference between HC and HI responses from visual inspection of the waveforms presented in Figure 6.1, also failed to find significant differences between the two conditions.

Whilst no significant differences were found directly between the two types of hit response, the relationship between each type of hit response and CRs was subtly different. HC responses appeared to show a more left lateralised posterior effect than was evident in the HI response comparison, which in turn exhibited a more right lateralised old/new difference over frontal sites than was evident in the HC comparison.

The widespread bilateral old/new effect between 300-500ms seen in the 'recollection' contrast resembles the bilateral-frontal old/new familiarity effect reported by Curran and Hancock (2007). The presence of a familiarity effect in the 'recollection' contrast is not in itself unusual or unexpected, however the overall weaker, or at least more poorly characterised effect, seen in the 'familiarity' contrast is more curious. Considering the pattern of activity evident in terms of the location of maximal old/new difference, the frontally maximal 'recollection' effect and more centrally maximal 'familiarity' effect is perhaps more reflective of the activity seen in MacKenzie and Donaldson (2007). However, despite apparent differences in the distribution of the old/new effects in the two hit conditions, it should be noted that direct comparison of the HC and HI responses were not significantly different, in either the current study or in the rescaled name/no specifics topographic comparisons of MacKenzie and Donaldson (2007).

In relation to the later time-window previous studies looking at old/new recognition memory for faces have identified a parietally distributed old/new effect, between approximately 500-700ms (Curran & Hancock, 2007, MacKenzie & Donaldson, 2007; Yick & Wilding, 2008), similar to that seen for words. In addition some studies have reported overlapping frontally distributed activity (MacKenzie & Donaldson, 2007 & 2009; Yick & Wilding, 2008), thought to reflect recollection processes, and posteriorally distributed effects associated with familiarity (Yovel & Paller, 2004;

MacKenzie & Donaldson, 2007). The data presented here is consistent with the literature in terms of the presence of a left-parietal effect between 500-800ms, and there is also some evidence to suggest some additional overlapping anteriorly distributed activity similar to that seen in MacKenzie and Donaldson (2007 & 2009).

In contrast to MacKenzie and Donaldson (2007 & 2009), however, here the anterior activity is evident in both the recollection (HC) and familiarity (HI) contrasts. The inconsistency in the pattern of the late anterior activity with that shown in MacKenzie and Donaldson (2007 & 2009) may of course be caused by the capturing of recollection related activity in the familiarity contrast. In the current study participants found the source task difficult, and may have recollected other details about the faces that were not measured. Whilst the presence of anteriorly distributed activity in the 'familiarity' contrast between 500-800ms is perhaps surprising, the widespread posterior activity evident in this contrast is consistent with the findings of Yovel and Paller (2004) and MacKenzie and Donaldson (2007).

The current study therefore indicates that recognition memory for faces is associated with a late onsetting left-parietal old/new effect and, although weak, goes someway to support the idea of some additional anterior activity. One theory put forward to account for the inconsistency in the distribution of the ERP effects presented in the literature, concerns the heterogeneity of the stimuli (Donaldson & Curran, 2007); the stimuli used by Yoval and Paller (2004) and MacKenzie and Donaldson (2007) were more homogenous than those used by Curran and Hancock (2007). The stimuli used in the current study closely resembled those used by MacKenzie and Donaldson (2007) which would be consistent with the idea that the differences seen between studies relates to specific aspects of the stimuli.

Although the preceding account is reasonable, one serious challenge to this view exists. In the previous chapter results were presented for a single-item recognition memory for faces task, which used the same style of facial stimuli used in the current source memory task (photographs of Caucasian faces, with hair and ears masked). Whilst a left-parietal old/new difference was found between 500-800ms, there was no evidence of any overlapping anterior activity, suggesting that the use of these stimuli per se does not fully explain the pattern of effects. There could be several reasons for this difference in effect distributions, primarily that the single-item task did not require participants to make any associations with other material. Assuming that in the source memory task participants were recollecting in the HI contrast and that the overlapping anterior activity does relate to recollection, as indicated in the previous literature, then it may be that participants were more reliant on familiarity processes to complete the single-item task, explaining the absence of activity believed to reflect recollection. The use of a large study-test block in the single-item memory task, which was more than four times the size of a block in the source memory task, would support the hypothesis that participants were more reliant on familiarity[15].

In addition to the various procedural differences that exist between the two tasks, another potentially important difference is the selection of participants included in the analyses, a variation that is equally applicable to the previous literature, raising the question of whether the presence/absence of overlapping anterior activity is participant specific. Of the 54 participants analysed in the current source memory task 27 were also

[15] Whilst investigating the effect of list length and recognition mirror effects Cary and Reder (2003) show that participants make less recollection-based responses (as indicated by the proportion of 'remember' Hits) and more familiarity-based responses ('know' Hits) for words in longer lists than those in shorter lists. Cary and Reder (2003) suggest that if participants are aware of the proportion of 'old' and 'new' items they will try to produce corresponding numbers of 'old' and 'new' responses. Subsequently if the number of recollection-based responses is reduced (i.e. through manipulation of task difficulty such as increasing the number of items to be remembered) participants will lower their familiarity criterion to achieve more 'old' responses.

included in the analysis of the single-item memory task. Therefore, to investigate the possible effects of the choice of participant an additional set of analyses was conducted comparing the old/new effects from the two tasks in the same sub-set of 27 participants. HC and HI responses from the source memory task were collapsed together to form 'Hit responses'[16] to make the comparisons equivalent across tasks. Therefore, comparisons of hits and CRs will be made for both the single-item and source memory tasks.

6.3.2 Single-item and source old/new recognition memory effects for faces:

6.3.2.1 Behavioural results

The behavioural results for the 27 participants who met the inclusion criteria in both the single-item recognition memory for faces task (Chapter 5) and the source memory task for face and verbal phrase pairs are presented in Table 6.1. Recognition memory for faces (as indexed by Pr) was better for source memory than single item memory [$t(26)= -5.21$, $p<0.001$], but in both tasks participants exhibited a neutral decision bias. Participants made more hit responses in the source memory task, than in the single-item task [$t(26)= -3.46$, $p=0.002$], but there were no significant differences between tasks in the number of false alarms. In relation to responses times participants were significantly quicker at hit responses than CR responses in the single-item task [$t(26)= -4.75$,

[16] As expected collapsing the two types of Hit response did not significantly change the distribution of the ERP effects between 500-800ms, with analysis of the full sample showing a widespread old/new difference across posterior sites, and right lateralised at frontal sites. Statistical analysis revealed a significant main effect of condition [$F(1,53)=16.46$, $p<0.001$] and a condition by site interaction [$F(1,59)=4.11$, $p=0.043$], indicating that Hits were more positive than CRs, a difference largest at superior sites. Finally there was a significant condition by location by hemisphere by site interaction [$F(3,162)=5.28$, $p=0.002$], which when broken down with a 3-way ANOVA at each location revealed a significant condition by hemisphere by site interaction [$F(1,74)=4.17$, $p=0.032$] at the frontal location, indicating that the old/new difference was largest in the right hemisphere where the difference was uniform across sites, and greatest at superior sites in the left hemisphere; there was a main effect of condition [$F(1,53)=11.14$, $p=0.002$] at the frontocentral location, indicating a widespread old/new difference in which Hits were more positive than CRs; a condition by site interaction at both central [$F(1,60)=5.35$, $p=0.021$] and centroparietal [$F(1,60)=4.56$, $p=0.032$] locations indicating a bilateral old/new effect at these locations with the difference greatest at superior sites; and a main effect of condition [$F(1,53)=20.35$, $p<0.001$] at the parietal location, again indicating a widespread effect in which Hits were more positive than CRs.

p<0.001], but there was no significant difference in response times between hits and CRs in the source memory task [t(26)=1.78, p=0.087]. Overall participants responded quicker in the single item task than in the source task, a difference that was significant for both hits [t(26)=-5.52, p<0.001] and CRs [t(26)=-2.2, p=0.037]. Finally, in the source memory task participants identified the correct paired phrase on 59% (s.d. 7%) of trials, which was above chance level (50%) [t(26)=7.31, P<0.001].

Single-item and source task participants (n=27)	Hit rate (%)	False Alarm rate (%)	Pr	Br	Hit RT (ms)	CR RT (ms)
Single-item face recognition	63 (8)	33 (8)	0.29 (0.08)	0.47 (0.10)	1039 (217)	1132 (246)
Source memory task face recognition	70 (9)	30 (11)	0.40 (0.10)	0.49 (0.13)	1274 (282)	1226 (254)

Table 6.1 Behavioural results for the participants who met inclusion criteria in both the single item face recognition task and the source memory task. Table shows mean hit and false alarm rates in percentages, mean discrimination accuracy, mean decision bias, and mean response times for hit and CR responses in milliseconds. Standard deviations for each measure are given in brackets.

6.3.2.2 ERP results

Single-item recognition for faces (Hits vs CRs):

Figure 6.3 shows grand-average ERPs for hit and CR responses, from the single-item recognition memory for faces task. The largest difference between conditions appears to be over left central electrodes between approximately 400-800ms, with hits more positive than CRs. The distribution of the old/new difference for the 300-500ms and 500-800ms time-window can be seen with the topographic maps presented in Figure 6.4. The old/new difference between 300-500ms appears to be minimal, but between 500-800ms there is a left hemispherically distributed old/new effect.

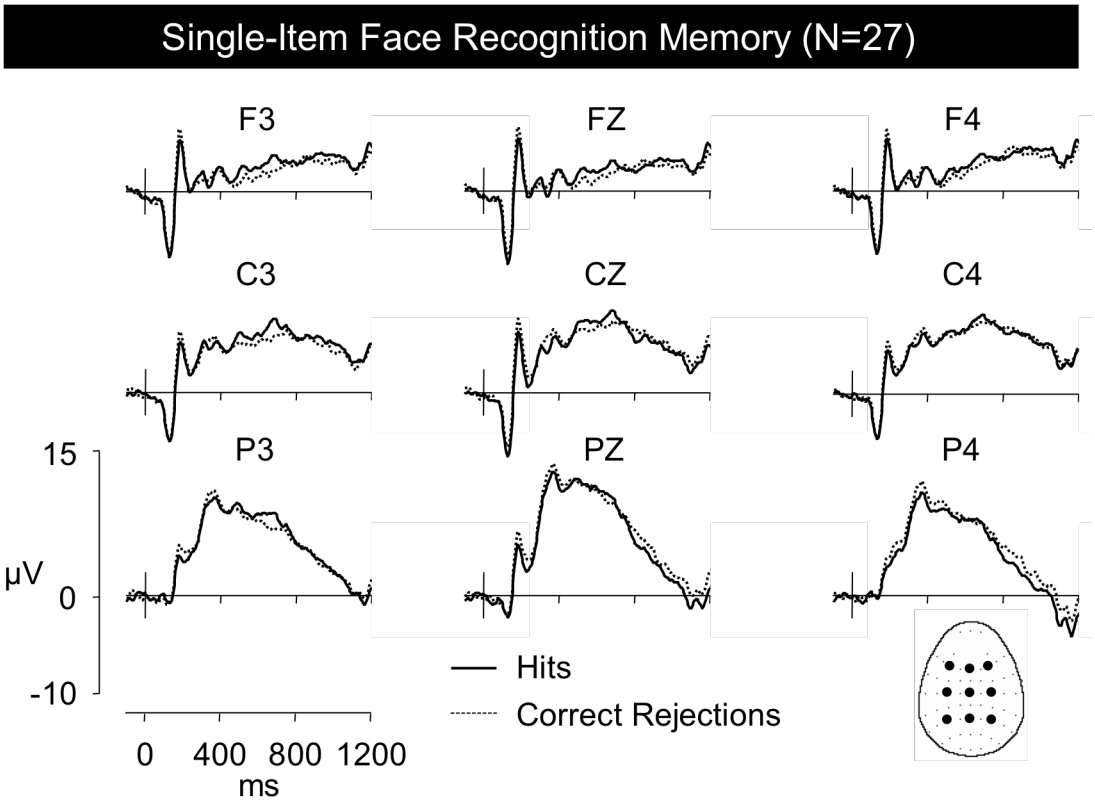


Figure 6.3 The grand average ERP waveforms for the single-item recognition memory for faces task. Waveforms are generated from a subset of participants who are also included in the source memory task analysis (n=27). Data as shown in Figure 6.1.

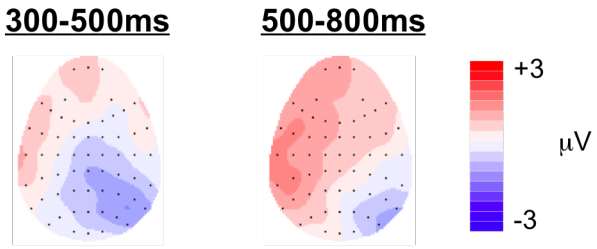


Figure 6.4 Topographic maps showing the distribution of the old/new difference for the face recognition task. Data shown as in Figure 6.2.

Analysis from 300-500 & 500-800ms:

Consistent with the initial single-item recognition memory for faces analysis presented in Chapter 5, no significant difference between conditions was found in the 300-500ms time-window. By contrast, between 500-800ms there was a significant condition by hemisphere [F(1,26)=4.62, p=0.041] interaction, indicating that hits were more positive than CRs, a difference largest over the left hemisphere. There was also a significant

condition by location by hemisphere by site [F(3,75)=3.3, p=0.027] interaction. Subsidiary analysis to break down the four-way interaction (consisting of ANOVA performed on factors of condition, hemisphere and site at each location) found no significant differences at frontal, frontocentral or central locations. However, significant condition by hemisphere, and condition by hemisphere by site interactions were found at centroparietal [F(1,26)=7.18, p=0.013; F(1,29)=6.62, p=0.013] and parietal [F(1,26)=9.7, p=0.004; F(1,30)=10.91, p=0.002] locations. These interactions indicate that over left centroparietal and parietal electrodes a positive going old/new effect is present, which is largest at more lateral electrodes. Visual inspection of the data showed that the difference between conditions was largest at electrode CP5, however a paired samples t-test revealed that this difference was not significant [t(26)=1.99, p=0.08]. Statistically, therefore, findings are consistent with the full sample results presented in Chapter 5, indicating a left-parietal old/new effect for successful single-item face recognition memory.

Source memory recognition for faces (Hits vs CRs):

Hit and CR ERPs for the old/new recognition judgment of the source memory task are shown in Figure 6.5. The waveforms show a clear divergence between conditions, with hits more positive going than CR from approximately 400ms until approximately 700ms over most electrodes, and maintained until approximately 800ms over left-parietal electrodes. The distribution of the old/new difference can be seen in the topographic maps shown in Figure 6.6. Between 300-500ms the old/new difference appears to be maximally distributed at posterior midline electrodes, a distribution that becomes more left lateralised in the 500-800ms time-window. In addition there appears

to be an anteriorly distributed old/new difference across both time-windows, over frontopolar electrodes, although this difference appears to be small.

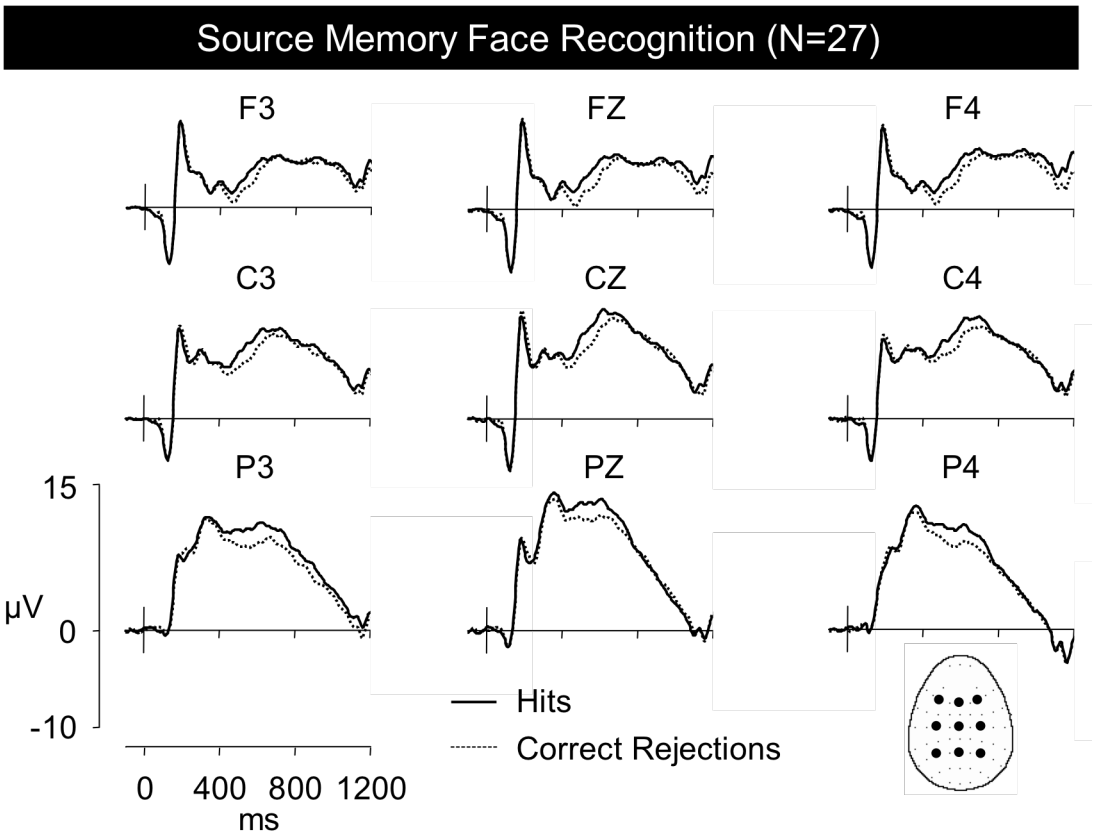


Figure 6.5 The grand average ERP waveforms for the source memory task. Waveforms are generated from a subset of participants who are also included in the single-item face recognition memory task analysis (n=27). Data as shown in Figure 6.1.

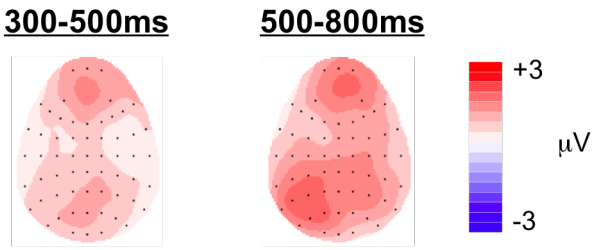


Figure 6.6 Topographic maps showing the distribution of the old/new difference for the source memory task. Data shown as in Figure 6.2.

Analysis from 300-500 & 500-800ms:

No significant differences between hit and CR responses were found from 300-500ms. By contrast, from 500-800ms a significant main effect of condition [F(1,26)=5.21, p=

0.031], and a significant interaction between condition, location, hemisphere and site [F(3,75)=3.82, p=0.014] were found. Subsidiary analysis showed no significant differences at frontal, frontocentral or central locations, but revealed a significant main effect of condition at centroparietal [F(1,26)=7.13, p=0.013] and parietal locations [F(1,26)=10.12, p=0.004], indicating that hit responses were more positive going than CRs at these locations. A marginally non-significant interaction between condition, hemisphere and site was also found at the parietal location [F(1,30)=3.79, p=0.056], indicating that although not significant, the old/new difference was largest over left lateral electrodes. These findings indicate that the old/new difference between 500-800ms is largest over parietal electrodes and exhibit a left hemispheric bias. Consistent with these findings, visual inspection of the data showed the old/new difference to be greatest at electrode P5, a difference that was significant [t(26)=3.61, p=0.001].

Comparison of single-item and source memory ERP effects:

Significant parietal old/new ERP effects were found for both tasks between 500-800ms, with neither task exhibiting significant differences in the earlier time-window. The old/new effect for the single-item task appears to be slightly more left lateralised than in the source memory task, and visual comparison of the topographic maps for the two tasks (Figure 6.4 and Figure 6.6) suggest that the difference in the single-item task may be larger over left frontal electrodes.

Analysis from 500-800ms:

Statistical comparison of the two tasks was conducted on rescaled data, to take into account overall amplitude differences between the two tasks (McCarthy & Wood, 1985), using ANOVA with factors of task (single-item faces/source memory), location (frontal/frontocentral/central/centroparietal/parietal), hemisphere (left/right) and site

(inferior/medial/superior). A significant task by location [F(1,35)=3.92, p=0.004] interaction was found, indicating that over anterior locations the old/new effect was larger in the single-item task than the source memory task, and in contrast, over parietal locations the source memory task exhibited the larger effect. This change in effect magnitude across locations can clearly be seen in Figure 6.7a. In addition a significant task by hemisphere [F(1,26)=4.8, p=0.038] interaction was found, indicating that the distribution of the old/new difference for the single-item task was more left lateralised across the entire scalp than in the source memory task, where the overall difference between hemispheres was minimal (Figure 6.7b).

6.3.2.3 Discussion

There are many possible reasons why old/new recognition performance (as index by *Pr*) was better in the source memory task than in the single-item task, many of which can't be directly examined in the current data. For example, variation in block sizes may contribute to performance differences, with larger blocks in the single-item task requiring participants to remember more items per block than in the source task. Equated block sizes in the two tasks may bring about similar levels of performance. The differences in behavioural performance may also be the result of practice effects, with participants completing the single-item task first. However, it seems unlikely that the better performance in the source memory task can be explained solely by the differences in task order, particularly because post hoc analysis reveals that performance in the first half of the source memory task (*Pr* = 0.38, s.d. 0.11) was not significantly better than performance in the second half (*Pr* = 0.36, s.d. 0.11) [F(1,26)=1.05, p=0.315].

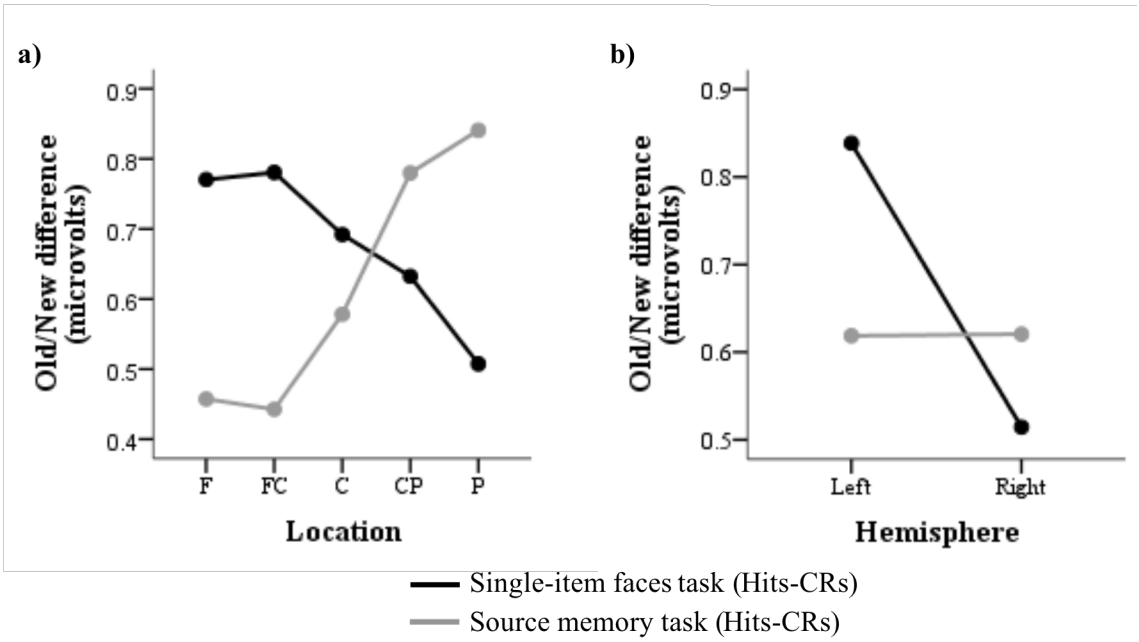


Figure 6.7 Plots showing average old/new effect magnitude (data rescaled to control for overall magnitude differences) between 500-800ms for both the single item recognition memory for faces task and the source memory task across a) locations (frontal, frontocentral, central, centroparietal and parietal), and b) hemispheres (left, right). Significant task by location, and task by hemisphere interactions were found in the 500-800ms time-window indicating distributional differences in the old/new effect across tasks.

One other factor that may have contributed to this performance difference is the additional associated information in the source task that was not available in the single-item task. A close look at the break down of responses indicates that the proportion of false alarms was consistent across the two tasks, with the key difference in performance relating to the increased number of hits in the source memory task. One hypothesis is that in the source memory task the associated phrase information may have provided more opportunity for recollection-based decisions to be made, leading to more hit responses. Participants exhibited an overall neutral decision bias in both tasks, however, indicating an equal likelihood of responding 'old' as 'new' if unsure, suggesting a similar response strategy was used in both tasks. Nonetheless, overall response times were longer in the source memory task, a difference that may reflect additional evaluation of knowledge concerning the associated information.

Statistical analysis of the ERP data found no significant difference between hits and CRs in the 300-500ms time-window in either task. Whilst this finding is consistent with the results from the full sample single-item recognition memory for faces analysis (Chapter 5), a significant widespread midline old/new effect was found between 300-500ms in the full sample analysis of the source memory task. The absence of a statistically significant old/new difference between 300-500ms in the source memory task may be caused by the reduction in the number of participants analysed, and hence a decrease in the statistical power of the analysis. Alternatively, whilst no significant differences between hit response type were found in the source memory task, as discussed in Section 6.3.1.3 , the point of maximal old/new difference suggests that the pattern of activity in the early time-window may be subtly different between hit response types in relation to CRs. The distribution of the old/new effect appears more anterior in the recollection contrast than in the familiarity contrast, which exhibits a more central distribution. Although very small, if these distributional differences between hit response types are real but statistically weak, collapsing across hit responses may mask possible effects by reducing the overall amplitude of activity associated with hit responses and consequently the size of the old/new difference, explaining the absence of statistically significant differences in the earlier time-window in both tasks.

Between 500-800ms both tasks showed a clear posterior old/new effect, with a clear left hemispheric laterality in the single-item task, and a left hemispheric bias in the source memory task, suggesting that asking participants to remember specific associated information does not in itself change the ERP recognition memory effects. However, whilst a left-parietal old/new effect is evident in both tasks, the magnitude of the old/new difference is larger in the source memory task, and comparison of the old/new

effect distribution, correcting for these magnitude differences, suggests that the overall distribution of activity is not the same. Comparisons indicated a clear hemispheric difference between 500-800ms, with the old/new effect in the single item task exhibiting an unmistakable left hemispheric laterality, whereas overall there was minimal hemispheric difference between conditions in the source memory task. Furthermore, disparity in the distribution of the old/new effect across locations was evident, with a more anterior old/new effect apparent in the single-item task, and a more posterior old/new effect in the source memory task; a pattern of activity this is highly reminiscent of the difference in activity seen between word and picture stimuli presented in the previous chapter (see Figure 5.16).

More broadly, in theoretical terms, the distributional differences evident between word and picture stimuli have been hypothesised to relate to the reinstatement of encoding activity, with greater perceptual processing required for pictorial than verbal stimuli, reflected in more anterior old/new effects (Galli & Otten, 2011). In the current study the same face stimuli were used in both the single-item and source memory tasks, with both stimulus sets made to the same specifications; however the key difference between the tasks was the introduction of a verbal phrase accompanying the face at study in the source memory task. Whilst the perceptual processing of the face stimuli is likely to have been consistent across the two tasks, the additional verbal information in the source task may be responsible for the more posterior distribution, as can be seen for words. However, although the distributional differences between the two face tasks follow a similar pattern to the differences evident between word and picture stimuli, it is not possible to ascertain in the current study whether these variations have a common basis or if they are indeed the same.

A key aim in the comparison of the ERP effects from the two tasks was to see if the anterior old/new difference between 500-800ms that overlaps with the more typical left-parietal old/new effect was specific to source memory tasks, or if the difference was participant specific. Analysis of the data found no significant right frontal old/new effects in either task, suggesting that the absence of the 500-800ms anterior old/new effect in the original single-item analysis may not be a function of task. The reduction in the number of participants included in the subsidiary analysis, and hence the reduction in statistical power, coupled with the fact that the effect in the full sample source memory task analysis was small, does not allow strong conclusions concerning this anterior effect to be made. It is therefore not possible to conclude that the effect was completely absent in this sub-sample of participants, simply that statistical analysis of the old/new difference did not reveal significant differences over right-frontal electrodes in either task.

6.3.3 Participant specific old/new ERP effects for faces?

Comparison of effects across two tasks with the same participants did not reveal significant differences over right-frontal electrodes, leading back to the question of whether or not the anterior old/new effect between 500-800ms is participant specific. Having looked at old/new differences in the sub-group of participants who were also included in the single-item analysis, and not finding significant anterior effects in the 500-800ms time-window, analysis of the remaining 27 participants was conducted to see if these participants are driving the pattern of effects evident in the full-sample analysis.

6.3.3.1 Behavioural results

Table 6.2 shows the behavioural data for the two source memory sub-groups, restating the results for the participants who were included in both the single item and source memory analysis described above (Both Tasks group), and presenting those from the remaining 27 participants who met the inclusion criteria on the source memory task, but did not meet the criteria on the single-item task (Source Memory Only group). Figure 6.8 illustrates the relationship between performance on the single-item and source memory tasks across groups. Memory performance (as indexed by *Pr*) was better for the participants included in both analyses than the source memory only group [$t(52)=4.51$, $p<0.001$], a difference caused by variations in hit rate, with participants included in both tasks making significantly more hit responses [$t(52)=4.22$, $p<0.001$]. The false alarm rate was consistent across groups. Whilst, overall, participants in the Both Tasks group were slower at hit and CR responses compared to participants in the Source Memory Only group, this difference was only significant for hit responses [$t(52)=2.18$, $p=0.034$], possibly reflecting the better performance.

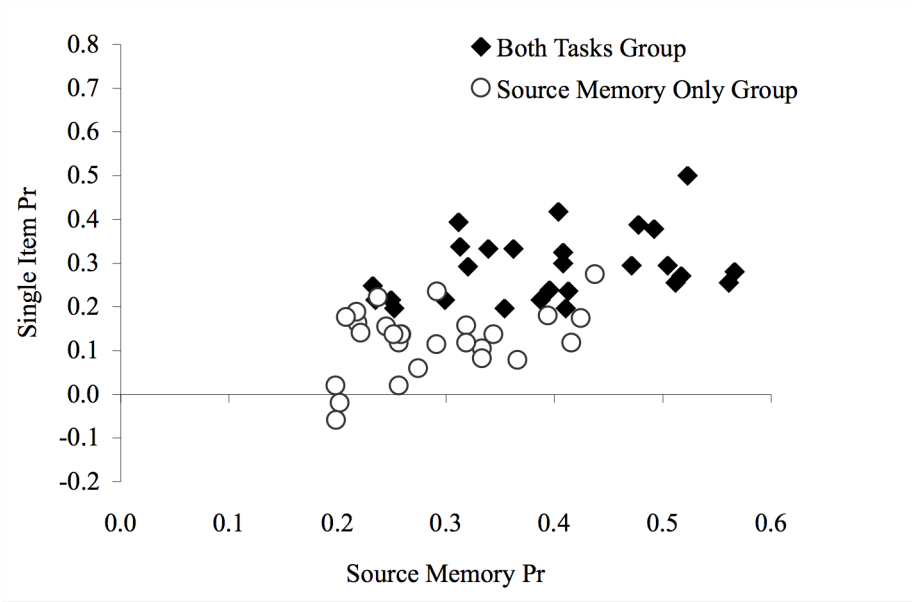


Figure 6.8 Scatterplot depicting the relationship between memory performance (Pr) on the single item and source memory tasks for the Both Tasks and Source Memory Only groups.

Overall, participants included in both tasks exhibited a neutral responses bias, whereas the Source Memory Only group were significantly more conservative in their bias [t(52)=2.03, p=0.047], although in comparison to the picture and word tasks presented in the previous chapter both groups show a fairly neutral response bias. Performance on the source judgment task was consistent across the two groups, however, with participants included in both task analyses scoring an average of 59% (s.d. 7%) correct, and the additional participants scoring an average of 57% (s.d. 4%). Participants in both groups were above chance level (50%) [t(26)=7.21, p<0.001; t(26)=9.05, p<0.001].

Source memory subgroups	Hit rate (%)	False Alarm rate (%)	Pr	Br	Hit RT (ms)	CR RT (ms)
Both Tasks group	70 (9)	30 (11)	0.40 (0.10)	0.49 (0.13)	1274 (282)	1226 (254)
Source Memory Only group	58 (11)	29 (12)	0.29 (0.07)	0.41 (0.16)	1107 (282)	1140 (314)

Table 6.2 Behavioural results for participants who met inclusion criteria in both face recognition tasks, and those who were only included in the source memory task analysis. Data shown as in Table 6.1.

6.3.3.2 ERP results

The Source Memory Only group (Hits vs CRs):

Hit and CR waveforms for the Source Memory Only group are shown in Figure 6.9. There is a clear divergence between conditions, starting at approximately 400ms, in which hits are more positive going than CRs, a difference lasting until approximately 800ms over parietal electrodes, and evident until approximately 1100ms over frontal electrodes. The distribution of the old/new difference can be seen in the topographic maps presented in Figure 6.10, which shows the old/new difference is widespread along midline electrodes between 300-500ms, becoming more right-frontal in distribution between 500-800ms.

Analysis from 300-500 & 500-800ms:

Interactions between condition and site were found between 300-500ms [F(1,29)=9.65, p=0.003), and between 500-800ms [F(1,28)=4.52, p=0.040], indicating a widespread bilateral effect in which hits were more positive going than CRs, a difference greatest at superior sites in both time-windows. A main effect of condition was also found between 500-800ms [F(1,26)=11.81, p=0.002]. Visual inspection of the data showed the old/new difference was largest at electrode CPZ between 300-500ms and FC2 between 500-800ms, the difference between conditions at both these electrodes was found to be statistically significant [t(26)=2.73, p=0.011; t(26)=3.89, p=0.001].

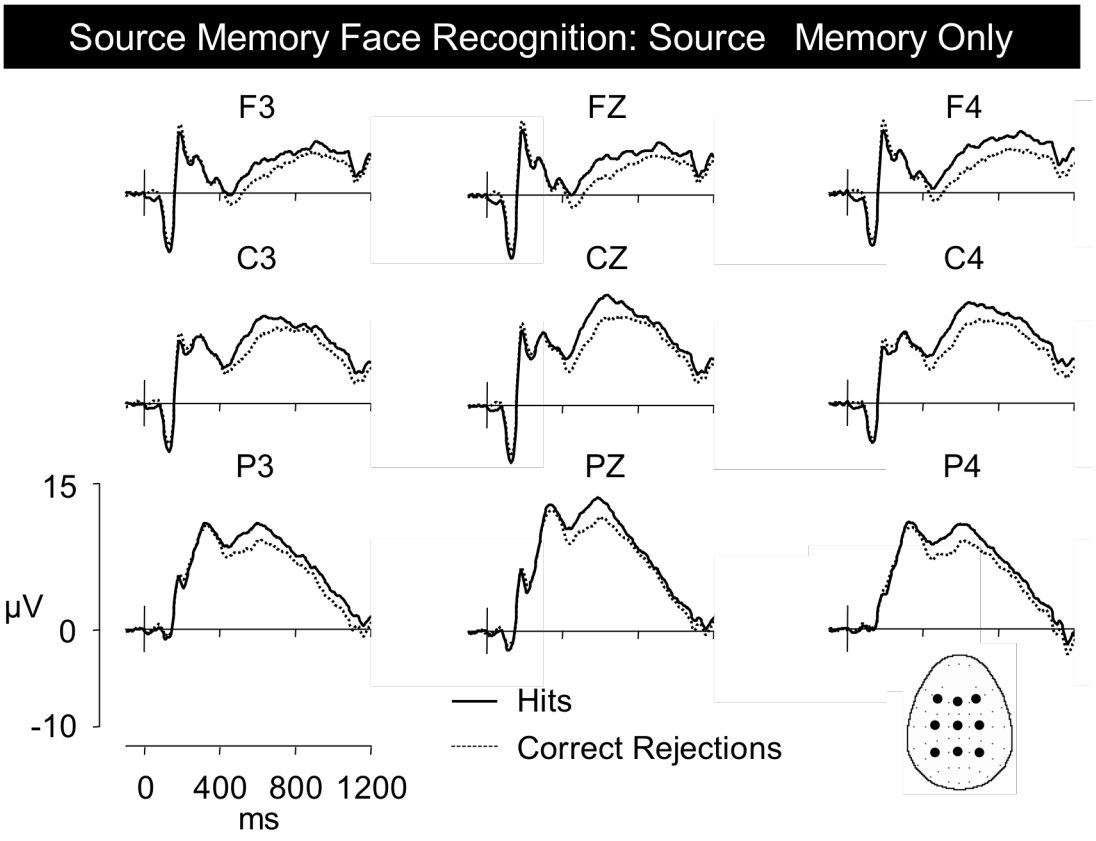


Figure 6.9 ERPs for the source memory task. Waveforms are generated from the subset of participants only included in the source memory task analysis (n=27). Shown as in Figure 6.1.

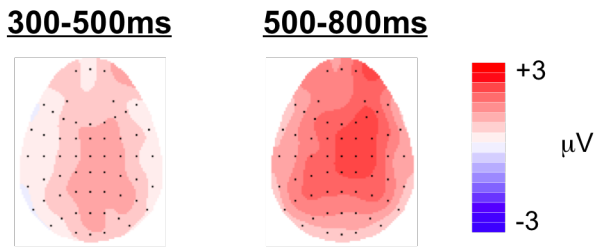


Figure 6.10 Topographic maps showing the source memory old/new difference distribution. Data is taken from participants who were only included in the source memory task analysis, and is shown as in Figure 6.2.

Comparison of ERP effects across the two source memory groups:

Analysis from 500-800ms:

Statistical comparison of the two source memory groups was conducted on rescaled data, using ANOVA with the between-subjects factor of group (Both Tasks group/Source Memory Only group), and within-subject factors of location (frontal/frontocentral/central/centroparietal/parietal), hemisphere (left/right) and site (inferior/medial/superior). No significant interactions with group were found, indicating that the apparent differences seen when comparing topographic maps from the two groups (Figure 6.6 & Figure 6.10) were statistically weak. However, whilst these differences in effect distribution may not be strong enough to reach statistical significance, the variations between subgroups that can be seen when comparing Figure 6.6 and Figure 6.10 remain interesting given their correspondence with the discrepancies seen in the literature.

6.3.3.3 Discussion

In comparison to the Both Tasks group, the performance (as indexed by *Pr*) of the Source Memory Only group was poor. This result is perhaps not surprising since participants included in the analysis of both tasks could reasonably be assumed to have a better memory for faces than the additional participants, who did not meet the

inclusion criteria on the single-item task. Interestingly, however, the performance difference between the two groups appears to be in relation to the proportion of hit responses made, with the number of false alarms consistent between groups. A smaller number of hit responses for the additional participants suggest a more conservative approach, in which 'old' responses were made only when confident in the decision, a hypothesis supported by the lower response bias (*Br*) score. Whilst performance on the old/new recognition task differed between groups, performance on the source task did not, suggesting an equivalent proportion of recollection-based trials in each group.

The topographic maps suggest that there are distributional differences between the two source memory groups in the 500-800ms time-window, with one group showing a left-parietal effect consistent with the typical recognition memory effects seen for words, and the other showing a more right lateralised central old/new effect resembling the effect reported by MacKenzie and Donaldson (2007). As the comparison of effects in Figure 6.11 illustrates, the distributions of Mackenzie and Donaldson (2007) and the Source Memory Only group are remarkably similar, and appear to differ in distribution from the Both Tasks group effect. Despite appearances, analysis revealed that the differences between the Both Tasks group and the Source Memory Only group in the current study were not statistically robust. However, examining the location of maximal old/new effect in each group highlights the differences that can be seen in the topographic maps, with the effect maximal at a left parietal electrode (P5) for participants in the Both Tasks group, whereas the maximal difference was at a right frontocentral electrode (FC2) in the Source Memory Only group. Therefore whilst direct comparison of the old/new effects from the two groups did not show statistically significant distributional differences, it is none the less worth noting the disparity in location of maximal old/new effect and the pattern of activity shown in the topographic

maps, which clearly map onto the competing arguments in the literature. Whilst it is not possible to draw strong conclusions from this data, it does suggest that a more systematic analysis of individual differences within face recognition memory is needed to assess the contribution of such variations to the competing theories.

Aside from the discussion of the 500-800ms anterior old/new effect, one of the most interesting results from the analysis of the Source Memory Only group is the presence of a widespread bilateral old/new effect between 300-500ms. No significant differences were found between 300-500ms in the initial sub-group for either the single-item or source memory tasks. The presence of an early effect is consistent with the findings from the full sample analysis; in particular the location of maximal old/new difference matches the location from the HI contrast, suggesting that participants in the Source Memory Only group were driving the early effect. As outlined above, taking into account the centroparietal maxima, this early old/new effect resembles the more centrally distributed 'familiarity' effect outlined by MacKenzie and Donaldson (2007). Given the old/new performance differences between the two source memory groups, and the fact that the participants also in the single-item analysis can be considered more skilled at remembering faces, it is not unreasonable to assume that the additional participants were more reliant on familiarity processes. It is therefore perhaps not surprising that there is a stronger effect, which resembles that of familiarity, for this group.

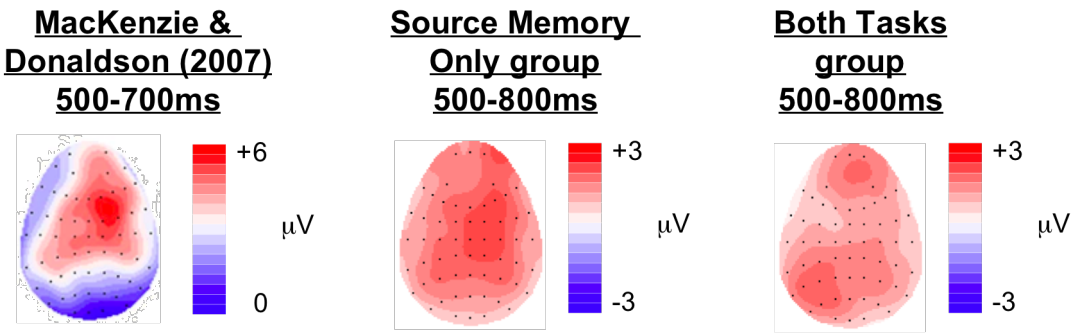


Figure 6.11 Topographic maps showing the distribution of old/new differences for faces from MacKenzie and Donaldson (2009) and the current study. The left map shows the distribution of recollection (correctly recognised 'old' items classified by participants as 'remembered') old/new effects for faces from MacKenzie and Donaldson (2007, figure adapted from MacKenzie and Donaldson, 2007). The centre map shows old/new effect distribution for the Source Memory Only group from the current study (as presented in Figure 6.10), and the right map shows old/new effect distribution for the Both Tasks group from the current study (as presented in Figure 6.6).

6.4 General Discussion

Successful old/new recognition of faces in the source memory task revealed an early bilateral old/new effect widely distributed across midline electrodes between 300-500ms and a later left-parietal old/new effect with overlapping frontal/central activity between 500-800ms. Whilst the principle aim of the additional source memory task was to gain estimates of familiarity and recollection to better understand the old/new ERP effects (through comparisons of hit responses with and without correct source retrieval), no statistically significant differences were found between the two types of hit response. The absence of ERP modulations by HC and HI responses that are apparent in the literature (Yovel & Paller, 2004; Curran & Hancock, 2007; MacKenzie & Donaldson, 2007 & 2009) may reflect the difficulty of the source task, with participants using factors other than the associated verbal phrase to make recollection-based decisions.

While it is difficult to draw firm conclusions about the contributions of familiarity and recollection to ERP effects for faces, it is interesting to note that in comparison to the old/new ERP effects found for the single-item faces task (Chapter 5), the early widespread bilateral effect and the later anterior effect were specific to the source

memory task. There were several key differences between the single-item and source memory tasks that might account for the discrepancies evident in the timing and distribution of the ERP effects. The reduced block sizes may have led to the increase in old/new recognition memory performance in the source task, resulting in more prominent ERP effects than observed in the single-item task. Equally, the introduction of the associated information may have provided more opportunity for participants to make recollection-based memory decisions, increasing the likelihood of statistically significant recollection ERP effects. Finally, and perhaps most importantly, another important difference between the two tasks was the participants contributing to the analysis. One possible explanation for the variations in ERP effects between the two tasks is that recognition memory ERP effects are not the same for all participants, and/or that participants are using different processes to complete the task.

Analysis of the data from participants who contributed to both tasks indicated that this group did not exhibit an early bilateral old/new effect in either task, nor was there strong evidence of the later anterior effect seen in the source memory task. These findings suggest that, for face recognition, the widespread 300-500ms bilateral old/new effect and the 500-800ms anterior effect found in the source memory task are participant specific.

Follow-up analysis of the additional 27 participants who contributed to the initial full sample source memory task analysis did show a widespread bilateral old/new effect between 300-500ms, suggesting that the absence of this effect in the group of participants analysed in both tasks was not simply caused by a reduction in power (i.e. resulting from fewer participants). Furthermore, visual inspection of the ERP effects between 500-800ms for the Source Memory Only group showed a clear right

frontocentral old/new effect, consistent with the recollection effect found by MacKenzie and Donaldson (2007). Statistical analysis characterises this difference as a more widespread bilateral old/new effect; however, this effect was not statistically different from the Both Tasks group effect, which had a left-parietal distribution.

In sum, whilst the ERP effects between 500-800ms were not significantly different between the two source memory groups, the variation in distributions evident in the topographic maps, and the effect differences found in the 300-500ms time-window, strongly suggest that there were participant differences in the ERP effects associated with successful recognition memory of faces. Furthermore, the data presented above suggest that the discrepancies seen in the face recognition memory literature (Yovel & Paller, 2004; Curren & Hancock, 2007; MacKenzie & Donaldson, 2007 & 2009; Donaldson & Curran, 2007) may relate to differences in individual participants, rather than to differences in task procedure or stimuli. One possibility is that the distributional differences evident between participants reflect strategic differences in the way participants completed the task. However, no manipulation of task strategy was included in the experiments, suggesting that the observed variations in ERP effect distribution are driven by inherent participant differences resulting in differing strategy use, or alternatively that the neural correlates of the same strategy differ across participants.

Chapter 7
Performance Analysis: Words and Pictures

The previous two chapters discussed the ERP correlates of episodic memory, looking at single item recognition and the retrieval of source information. In these analyses important disparities in performance were evident, with differences apparent between stimuli, tasks, and participants, which constrained the conclusions that could be drawn about differences in effect distribution evident between tasks.

Variation in task performance is not in itself unexpected of course, nor is it necessarily undesirable; indeed it can act as a comparatively simple indicator of changes in cognitive functioning. Equally, whilst variations in performance between individuals are normal, such differences can be potentially informative in terms of the conclusions that can be drawn about the processes involved in memory retrieval (and the associated neural correlates), particularly if behavioural performance differs across studies, groups or tasks that are being compared. Furthermore given the significance of memory in everyday functioning it is important to understand the reasons why healthy participants score differently from each other when completing the same task, and the potential consequences of differing strategies (such as a more liberal or conservative response bias). In particular, one key issue is whether differences in behavioural performance modulate the traditional retrieval effects or generate topographically distinct effects. In essence the question is whether individuals are engaging the same processes when they complete these tasks, and if so what is causing the variation in task performance.

As a result of the large variation in performance scores evident in the single-item recognition memory for words and pictures, these tasks will be the focus of

investigations into the impact of performance differences in the current chapter. By contrast, due to the comparatively poor performance and limited range of performance scores, data from the source memory task will not be included in the performance analysis. This chapter will first look at the ERP effects exhibited by groups of high and low performers on the word task, before examining the relationship between ERP effect magnitude and behavioural performance for both words and pictures. Finally, behavioural data from groups of participants exhibiting distinct ERP effects on the word task will be analysed to investigate the hypothesis that ERP correlates may be used as biomarkers of cognitive performance.

7.1 Introduction

The overall results for the word and picture recognition memory tasks were presented in Chapter 5, showing an early 300-500ms widespread bilateral old/new effect and a later 500-800ms left-parietal old/new effect, with the effects for pictures more anterior in distribution than words. As discussed in Chapter 5 these results are broadly consistent with previous literature, revealing putative correlates of familiarity and recollection. To reiterate, as discussed in Chapter 1, familiarity is a general sense that an item has been previously encountered, whereas recollection involves the recovery of details relating to a previous encounter. These two processes are considered to be independent from each other and are believed by dual process theorists to be the core processes that contribute to successful memory retrieval.

One important route toward understanding differences in performance across task, individuals and stimuli is to first clarify the relationship between the ERP correlates of retrieval and task performance. Here we focus on the most widely studied effect – the left-parietal effect, which is widely believed to provide an index of recollection. The

magnitude of the left-parietal effect has been shown to modulate with the amount of information recollected (Vilberg, Moosavi, & Rugg, 2006; Vilberg & Rugg, 2009), the number of correct source judgments made (Wilding & Rugg, 1996; Wilding, 2000), and the number of repeated study-test blocks (Johnson Jr, Kreiter, Russo & Zhu, 1998). Taken together, these data appear to be consistent with the idea that increases in recollection directly reflect (i.e. correlate with) increases in the magnitude of the left-parietal effect.

Not all published studies support this view however, for example, using a recognition task with 'old', 'new' and recombined word pairs Van Petten, Luka, Rubin and Ryan (2002) showed that ERP amplitude over posterior electrodes between 300-600ms was graded simply by the degree of stimulus 'oldness', with 'old' word pairs more positive than recombined pairs, which in turn were more positive than 'new'pairs. Importantly Van Petten and colleagues found that, across participants, the posterior effect was not sensitive to performance differences in distinguishing recombined pairs from 'new'pairs. In particular, no significant difference was found in the magnitude of old/recombined effects between good and bad recombined pair identifiers, or between recombined/new effects. By contrast, a bilateral prefrontal old/new difference between 700-1000ms was modulated by accuracy on recombined trials.

In contrast to the findings of Van Petten et al. (2002), however, other authors have claimed a direct link between performance differences across participants and the size of the left-parietal effect. For example, Curran and Cleary (2003) found that the size of the left-parietal old/new effect seen for pictures was modulated by recollection, but only when participants were good at distinguishing 'old' from similar lures. Good performers showed a significant studied/new ERP difference, but no significant difference between

similar and new conditions. Poor performers, by contrast, showed no significant ERP differences between studied and similar items, but significant differences when comparing either studied or similar conditions to new items. Overall therefore, Curran and Cleary (2003) found no performance differences in the studied/new ERP comparison, consistent with the fact that both performance groups were equally good at distinguishing studied images from new images. More importantly, they did find differences in the studied/similar ERP comparison consistent with the key behavioural difference between groups – differences in the discrimination of studied and similar images, a task thought to require recollection processes for completion.

Overall, therefore, these studies provide some degree of support for the claim that the left-parietal old/new effect is modulated by the amount of information retrieved about each episode (i.e. the degree of engagement of recollection processes). Following on from this there is a general assumption that recognition performance is positively correlated with recollection (Johnson Jr et al., 1998), in that the more an individual engages recollection processes the better they will perform on a recognition task. In support of this hypothesis Olichney, Van Petten, Paller, Salmon, Iragui and Kutas (2000) found a significant correlation between the amplitude of the posterior late positive component (LPC) repetition effect (in which previously presented items show more positive going activity than items presented on fewer occasions, an effect which exhibits a left hemispheric distribution) with word recall accuracy in subsequent memory tests for both an amnesic patient group and a control group. Collapsing across these groups also resulted in a positive correlation with recognition memory performance. Similarly Finnigan, Humphreys, Dennis and Geffen (2002) showed that the LPC is sensitive to recognition decision accuracy, with mean amplitude at electrode P3 between 500-800ms larger for correct responses (Hits and CRs) than incorrect

responses (Misses and false alarms), but not to memory strength (i.e. words presented once versus words presented three times). The LPC repetition effect has been linked to the successful recollection of previously presented stimuli (Finnigan et al., 2002), and closely resembles the left-parietal old/new effect discussed above.

In sum, given the general characterisation of the left-parietal effect, and the evidence described above, the literature makes clear predictions about the pattern of ERP effect that should occur when variability in performance is examined. First, we expect that the magnitude of the left-parietal old/new effect will be modulated by a participant's performance on the task, with good performers showing a larger effect than poor performers. Second, we expect that there will be a positive correlation between old/new effect magnitude at left-parietal electrodes and performance. Importantly, because of the number of participants in the initial study, here we are able to examine the predictions with considerably greater power than has ever been possible. Furthermore, the large database of participants also allows comparisons to be made whilst controlling for other variables (such as differences in response bias) that could potentially have influenced the outcome of previous small group comparisons.

7.2 Methods

The main focus of the performance analysis is the single item recognition memory for words task, and all 122 participants who met the inclusion criteria for the word task (Chapter 5) were included. Initial analysis considers a subset of the sample, selecting groups of high and low performers on the basis of discrimination accuracy (*Pr*) scores. Participants with $Pr \geq 0.65$ were assigned to the high performing group and those with $Pr \leq 0.55$ (but greater than $Pr = 0.2$) to the low performing group; participants scoring outwith these parameters were not included in the group analysis. The performance

groups were then matched for mean and standard deviation decision bias (Br) scores, as well as keeping mean hit and CR response times as consistent as possible, selecting 24 high and 24 low performers. All other aspects of the methods are as described in the General Methods (Chapter 4), with details of any additional analysis given alongside the relevant results section.

7.3 Results

7.3.1 High versus low performance groups: Words

7.3.1.1 Behavioural Results

The behavioural results for the high and low performing groups are presented in Table 7.1. As expected the two groups were significantly different in discrimination accuracy [$t(46)=-15.31$, $p<0.001$], but did not differ in decision bias (with both groups showing a conservative bias) nor in response times for either hits or CRs.

Performance Group	Hit rate (%)	False alarm rate (%)	Pr	Br	Hit RT (ms)	CR RT (ms)
High (n=24)	42 (4)	3 (2)	0.79 (0.09)	0.36 (0.15)	822 (176)	895 (181)
Low (n=24)	30 (5)	10 (5)	0.40 (0.09)	0.36 (0.14)	853 (174)	916 (194)

Table 7.1 Behavioural results for the high performance and low performance groups. Table shows mean hit and false alarm rates in percentages, mean discrimination accuracy, mean decision bias, and mean response times for hit and CR responses in milliseconds. Standard deviations for each measure are given in brackets.

7.3.1.2 ERP Results

High performers:

Figure 7.1 shows grand average ERPs for hit and CR responses at representative frontal, central and parietal locations for the high performers group. A divergence between conditions is evident across all electrodes, with hits more positive going than CRs, from

approximately 400ms until 700ms over parietal electrodes and continuing until approximately 1000ms over frontal electrodes. Whilst evident across all electrodes, the difference between conditions appears maximal over left hemisphere electrodes. The distribution of this old/new difference is evident from the topographic maps shown in Figure 7.2, which clearly show the left hemispheric distribution of the effect in both the 300-500ms and 500-800ms time-windows.

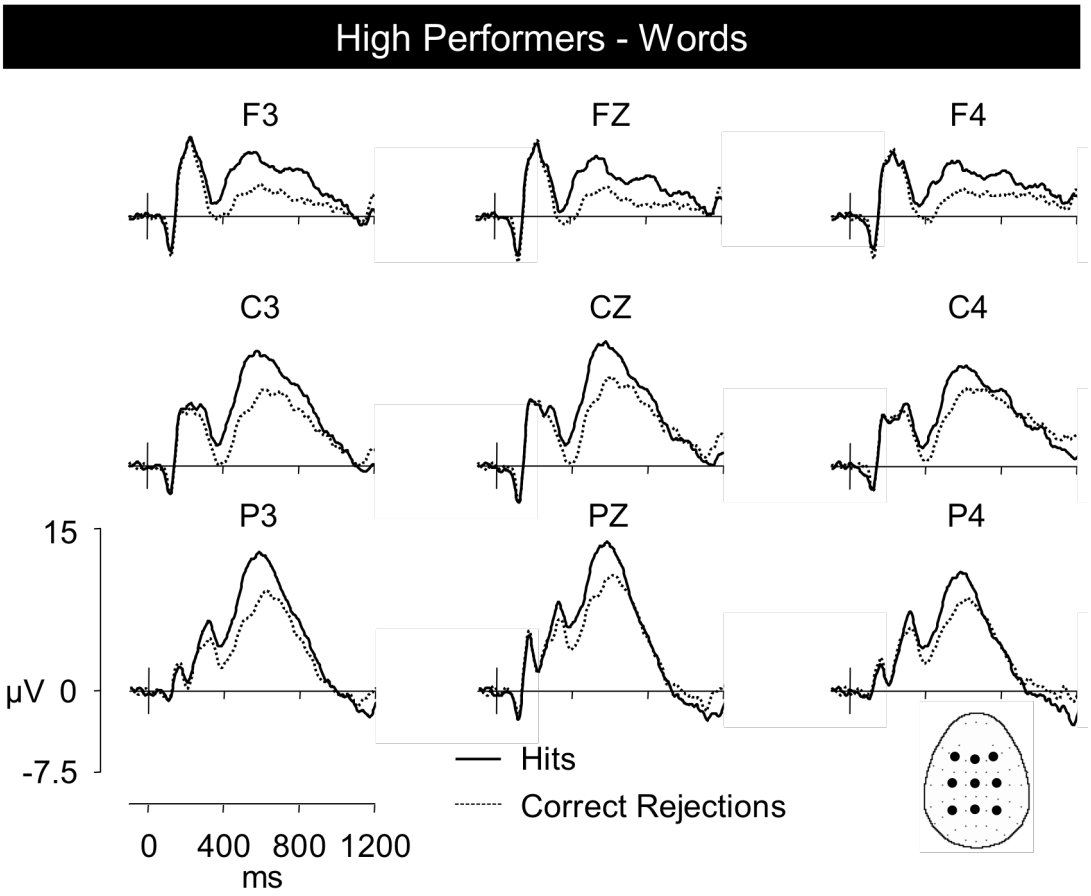


Figure 7.1 Grand average ERP waveforms for high performers on the recognition memory for words task, at representative frontal, central and parietal electrode sites (n=24). The vertical scale indicates electrode amplitude, measured in microvolts, whilst the horizontal scale indicates change in time, measured in milliseconds.

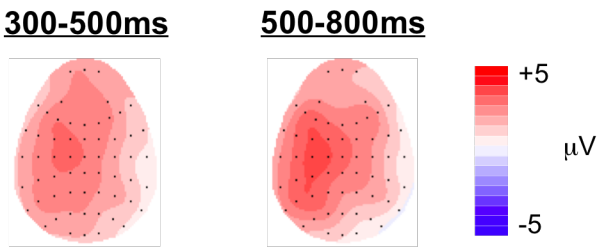


Figure 7.2 Topographic maps showing the distribution of the old/new differences for high performers. Two latency regions are shown, 300-500ms and 500-800ms, along with scale bars to show the size of the old/new difference. Maps show the subtraction of the grand average ERP for CRs from the grand average ERP for hits.

Analysis from 300-500ms:

Analysis of the ERP data was conducted using ANOVA, with factors of condition (Hits/CRs), location (frontal/frontocentral/central/centroparietal/parietal), hemisphere (left/right), and electrode site (inferior/medial/superior) as outlined in Chapter 4. Analysis of the 300-500ms time-window revealed a significant main effect of condition [$F(1,23)=18.67$, $p<0.001$], along with significant condition by hemisphere, condition by site, and condition by location by hemisphere interactions [$F(1,23)=5.66$, $p=0.026$; $F(1,24)= 15.24$, $p=0.001$; $F(2,43)=3.75$, $p=0.034$]. As Figure 7.2 shows, the old/new difference was largest over the left hemisphere showing a uniform spread across locations, whereas in the right hemisphere the old/new difference was larger at the frontal location. Visual inspection of the data revealed that the old/new difference was greatest at electrode C1 between 300-500ms; a t-test confirmed that the difference between conditions was significant at this electrode [$t(23)=4.52$, $p<0.001$].

Analysis from 500-800ms:

A significant main effect of condition [$F(1,23)=20.13$, $p<0.001$], and significant interactions between condition and hemisphere [$F(1,23)=8.22$, $p=0.009$]; condition and

site [F(1,24)=6.4, p=0.018]; condition, location and site [F(3,62)=3.41, p=0.027]; and condition, hemisphere and site [F(1,25)=8.88, p=0.032], were found in the 500-800ms time-window. These results indicate that overall hits were more positive than CRs, with a greater difference over left hemisphere electrodes. The left hemisphere old/new effect was evenly distributed across sites, with superior electrodes showing the greatest difference over the right hemisphere. At superior and medial sites the difference was greatest at central and centroparietal locations, with a more uniform distribution across locations at inferior sites. Visual inspection of the data indicated that the difference was maximal at electrode C3, and a paired-samples t-test found this difference to be significant [t(23)=5.33, p<0.001].

In contrast to the analysis of all participants presented in Chapter 5, comparison of the old/new effects across time windows for the high performers revealed no significant difference, suggesting that the old/new effects seen in the 300-500ms and 500-800ms time-windows do not differ.

Low performers:

Hit and CR ERPs for low performers on the word recognition task are shown in Figure 7.3. As for the high performers, there is a clear difference between hits and CRs across all electrodes between approximately 400-800ms. The topographic maps shown in Figure 7.4 reveal that the effect has a widespread distribution, and indicate that the old/new difference is largest in the 500-800ms time-window. The maximal old/new difference for low performers appears to be over midline and superior electrodes at the frontocentral location in both time-windows.

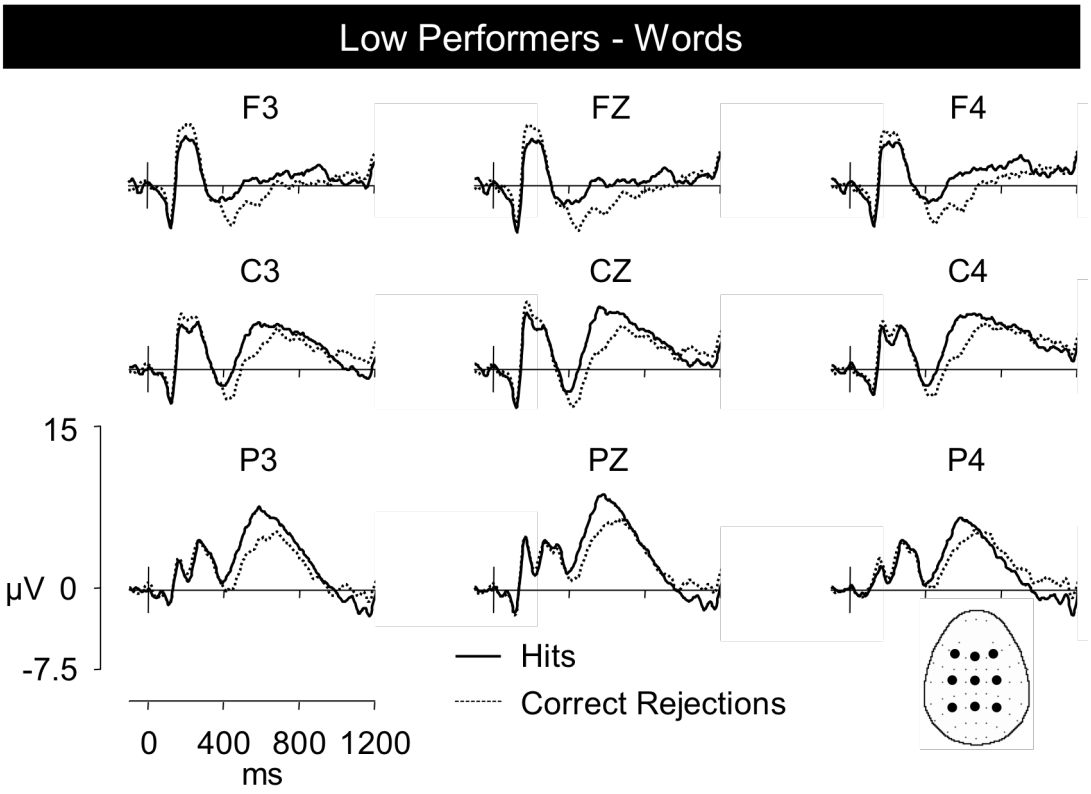


Figure 7.3 Grand average ERP waveforms for low performers on the recognition memory for words task (n=24). Data shown as in Figure 7.1.

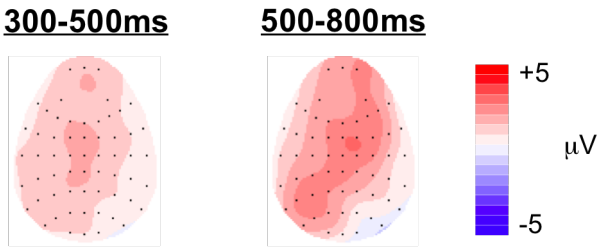


Figure 7.4 Topographic maps showing the distribution of the old/new difference for the low performers. Data shown as in Figure 7.2.

Analysis from 300-500ms and 500-800ms:

No significant differences between hit and CRs responses were found in the 300-500ms time-window for low performers. By contrast in the 500-800ms time-window a significant main effect of condition [F(1,23)=6.12, p=0.021] was found, along with significant interactions between condition, location and hemisphere [F(1,26)=9.13, p=0.004], and condition, location, hemisphere and site [F(3,59)=6.43, p=0.001]. Taken

together these results indicate that hits were more positive than CRs, a difference greatest over posterior locations across the left hemisphere and anterior locations in the right. Across frontocentral and central locations the old/new difference was larger at superior than inferior sites for both hemispheres. However, at centroparietal and parietal locations the distribution differed between hemispheres, appearing more uniform across sites in the left hemisphere and larger at superior than inferior sites in the right. Visual inspection of the data revealed the old/new difference to be maximal at electrode FC2 in the 500-800ms, a difference that was significant [$t(23)=2.69$, $p=0.013$].

Comparison of performance groups:

Figure 7.5 shows the ERP *difference waveforms* for the high and low performers, revealing a clear divergence between performance groups over left hemisphere electrodes that is not present over right hemisphere electrodes, with the high performers showing a larger old/new difference than low performers. The divergence between groups appears to onset as early as approximately 200ms and last until approximately 900ms, and is particularly evident over electrode C3. The difference in old/new effect distribution between groups is shown in the topographic maps presented in Figure 7.6, showing a left-central distribution in the 300-500ms time-window followed by a slightly more anterior frontocentral distribution in the 500-800ms window. As indicated by the *difference waveforms* this left-frontocentral distribution difference between groups is not confined to the typical 300-500ms and 500-800ms old/new effect time-windows, but is present between approximately 200-900ms.

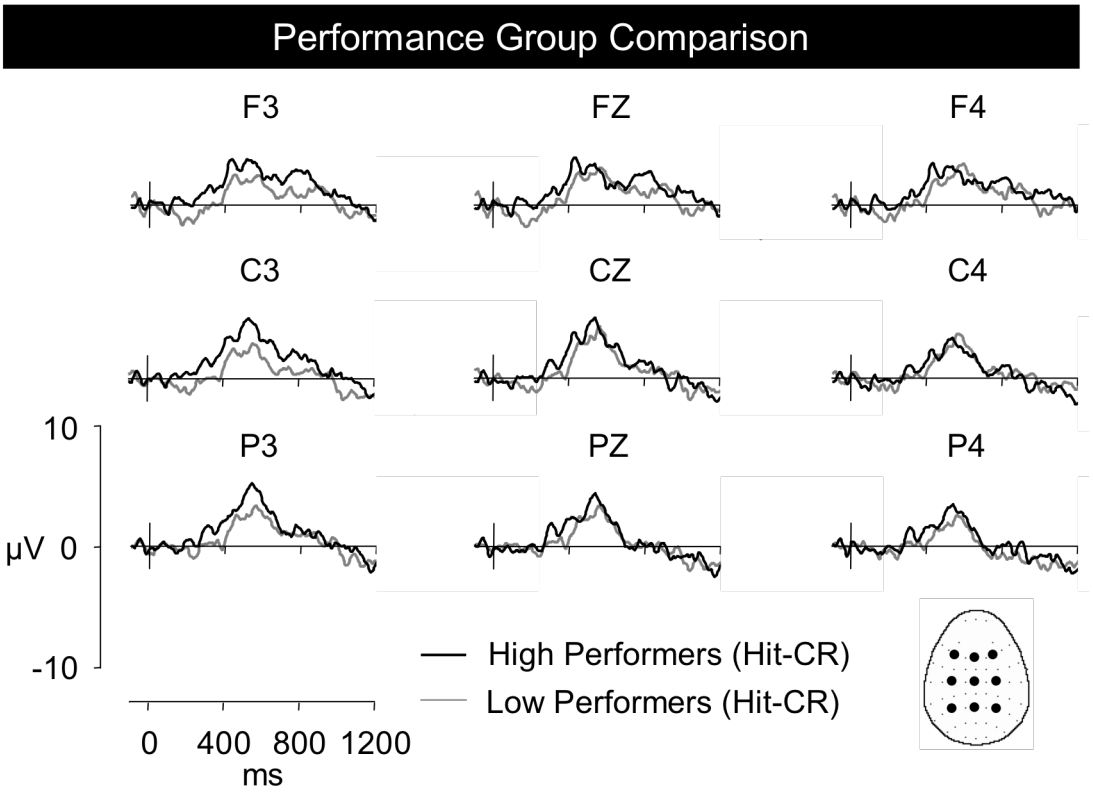


Figure 7.5 Grand average ERP difference waveforms (Hits-CRs) at representative frontal, central and parietal electrode sites, for high and low performers during word recognition.

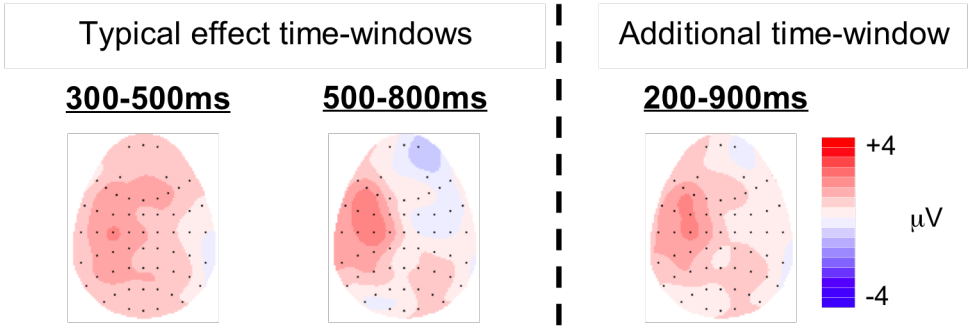


Figure 7.6 Topographic maps showing the difference in old/new effect distribution between high and low performers on the word recognition task. Maps were generated by the subtraction of the low performers difference waveform from the high performers difference waveform. Three latency regions are shown, 300-500ms, 500-800ms and 200-900ms, along with a scale bar to show the size of the difference.

Analysis from 300-500ms and 500-800ms:

In the analysis described above high performers exhibited an early, 300-500ms old/new effect that was widespread across the left hemisphere. In the same time-window no significant difference between conditions was found for low performers. Both groups

showed a significant old/new difference over left-parietal electrodes between 500-800ms, consistent with the 'all participants' analysis presented in Chapter 5. Given the absence of a significant old/new difference in the 300-500ms time-window for the low performers, statistical analysis comparing the two groups focused on the 500-800ms time-window. Analysis was conducted using ANOVA with between subjects factor of group (high *Pr* /low *Pr*), and within-subject factors of location (frontal/frontocentral/central/centroparietal/parietal), hemisphere (left/right) and site (inferior/medial/superior). Analysis revealed no significant interactions between performance group and factors of location, hemisphere or site, suggesting that the magnitude of the old/new effects did not differ across groups. Furthermore analysis on data rescaled in line with McCarthy and Wood, (1985), also revealed no significant interactions with performance group suggesting that the 500-800ms old/new effects in the two groups did not differ in distribution, suggesting that the neural generators in each group where the same.

Analysis from 200-900ms:

Analysis of the high performance group showed no significant differences between 300-500ms and 500-800ms indicating that the ERP effects exhibited by the high performers may be the same in both time-windows. The sustained nature of the effect is also evident in the group comparison topographic maps (Figure 7.6) which show a left-frontocentral difference across both 300-500ms and 500-800ms time-windows, a difference that the ERPs show as lasting from 200-900ms. However, statistical analysis of the 200-900ms time-window revealed no significant interactions with performance group suggesting that the magnitude of the effect did not differ between groups. Furthermore analysis with rescaled data also showed no significant difference between

groups for this extended time-window, suggesting that the effects between 200-900ms did not differ in distribution. A marginally non-significant interaction [$F(1,57)=3.39$, $p=0.062$] between hemisphere, location and performance group was however evident, indicating that the difference in the 200-900ms time-window may be real but that between the two selected groups the difference was not reliable enough to reach statistical significance. A more targeted analysis following the same hemisphere and site structure as used previously, but confining the comparison of location to frontocentral and parietal electrodes, again failed to reach significance [$F(1,46)=3.79$, $p=0.058$], although the result was also marginally non-significant highlighting the 200-900ms time-window as a potentially important time-window and one to include in further performance investigations.

7.3.1.3 Discussion of performance groups

The high and low performing groups were composed of participants that differed in performance (*Pr*), but were matched for response bias and response times for both hits and CRs. The high performers exhibited a widespread left hemisphere old/new difference, with hits more positive than CRs, which did not differ across the two time-windows. The low performers showed no significant effects in the 300-500ms time-window, but exhibited a typical left-parietal old/new effect in the 500-800ms time-window, alongside an additional right frontal old/new effect. This right frontal activity could reflect an early on-setting 'late right frontal effect' that is thought to reflect post-retrieval processes (Wilding & Rugg, 1996). Most importantly, statistical comparison of the effects for the high and low performers did not find any significant differences between the two groups in the 500-800ms time-window. Visual inspection of the data did indicate a left frontocentral difference between groups, a sustained effect present

between 200-900ms, however this difference also failed to reach statistical significance. Whilst the left frontocentral difference was not statistically robust, marginally non-significant interactions between performance group, location and hemisphere on rescaled data highlight this area and time-window as potential areas of interest for further investigation.

Overall there were two striking outcomes from the group analysis, firstly the lack of significant differences by group in the 500-800ms time-window, and secondly the absence of a topographically distinct early old/new effect for high performers and complete absence of an early effect for low performers. It was expected that differences in *Pr* would be reflected by differences in the magnitude of the left-parietal effect; a hypothesis based on the assumption that the left-parietal effect indexes recollection and has been shown to modulate with the amount of information retrieved. On this basis it was therefore anticipated that better recognition performance would be associated with recollection of more information[17], and consequently with a larger magnitude of the left-parietal effect. The absence of significant differences between the performance groups suggests that these assumptions may be incorrect.

The absence of topographic differences across time-windows in the high *Pr* group that had been previously noted in the all participant analysis (Chapter 5), and the absence of an early old/new difference for the low performers, indicates possible individual differences in the ERPs for the word task that may relate to performance. The absence of the early effect for the low performers is particularly puzzling as one hypothesis would be that low performers are more reliant on the process of familiarity, and

[17] Analysis of two supplementary behavioural studies looking at R/K/G responses and source accuracy in relation to recognition performance, suggests that the assumption that recognition performance would positively correlate with recollection was not unfounded. Section 7.3.2.4 will discuss these results in more detail.

therefore old/new effects relating to 'familiarity' would be expected, in contrast to high performers who would be expected to be more successful at utilising the process of recollection. The absence of the early effect in the low performers is therefore important in ruling out this possibility. The absence of a relationship between performance and the left-parietal effect cannot therefore be explained away with recourse to differential reliance on familiarity in the low performers.

The results of these analyses were clearly unexpected; the failure to find statistically significant differences between performance groups in the 500-800ms time-window is particularly surprising. Additional analysis looking at the full sample of participants was therefore conducted to see if the expected differences were in someway masked by the grouping process, and to further investigate potential individual differences in the ERP correlates of recognition memory that may be related to performance.

7.3.2 Full sample correlation analysis

With the apparent differences in ERP effects between the all participants, high performing and low performing groups in mind, further analyses were conducted to examine effect magnitude and performance in all participants who met the inclusion criteria. Comparisons were made of performance and old/new effect magnitude for the early 300-500ms bilateral effect and the typical 500-800ms left-parietal effect evident in Chapter 5. It was hypothesised that the magnitude of the left-parietal effect would correlate with performance - again, based on the assumption that the left-parietal effect reflects the process of recollection and should therefore modulate with the amount of information retrieved. However, given that the analysis of high and low performing groups presented above showed no evidence that the left-parietal effect differed according to group, but did point towards a 200-900ms effect over left frontocentral

electrodes, comparisons of performance and old/new effect magnitude over left frontocentral electrodes in the 200-900ms time-window were also conducted. In addition data from both the word and picture tasks were analysed to see if the relationship between ERP effects and performance were task dependent.

7.3.2.1 Word ERP effects and performance

Behavioural Results:

The behavioural results for the 122 participants who met the inclusion criteria for the word task are as presented in Chapter 5, in Table 5.2. Overall participants had a mean *Pr* of 0.54 (s.d. 0.17), and exhibited a conservative response bias (*Br* = 0.39, s.d. 0.16). The average response times for hit responses were 823ms (s.d. 138ms) and 898ms (s.d. 157ms) for CRs.

Performance and ERP effect correlations:

Correlations were performed on discrimination accuracy (*Pr*) scores and a) the magnitude of the bilateral-frontal effect, as indexed by the old/new difference between 300-500ms averaged across electrodes F1, FZ and F2 (Figure 7.7a); b) the left-parietal effect, indexed by the old/new difference between 500-800ms averaged across electrodes P5, P3 and P1 (Figure 7.7b); and c) the old/new difference between 200-900ms over left frontocentral electrodes (old/new difference averaged across electrodes FC5, FC3 and FC1) identified in the performance group analysis as a region and time-window of interest (Figure 7.7c). Data was averaged across electrodes to improve signal-to-noise ratio, with 3 electrodes selected in each case to ensure equivalent power in all comparisons.

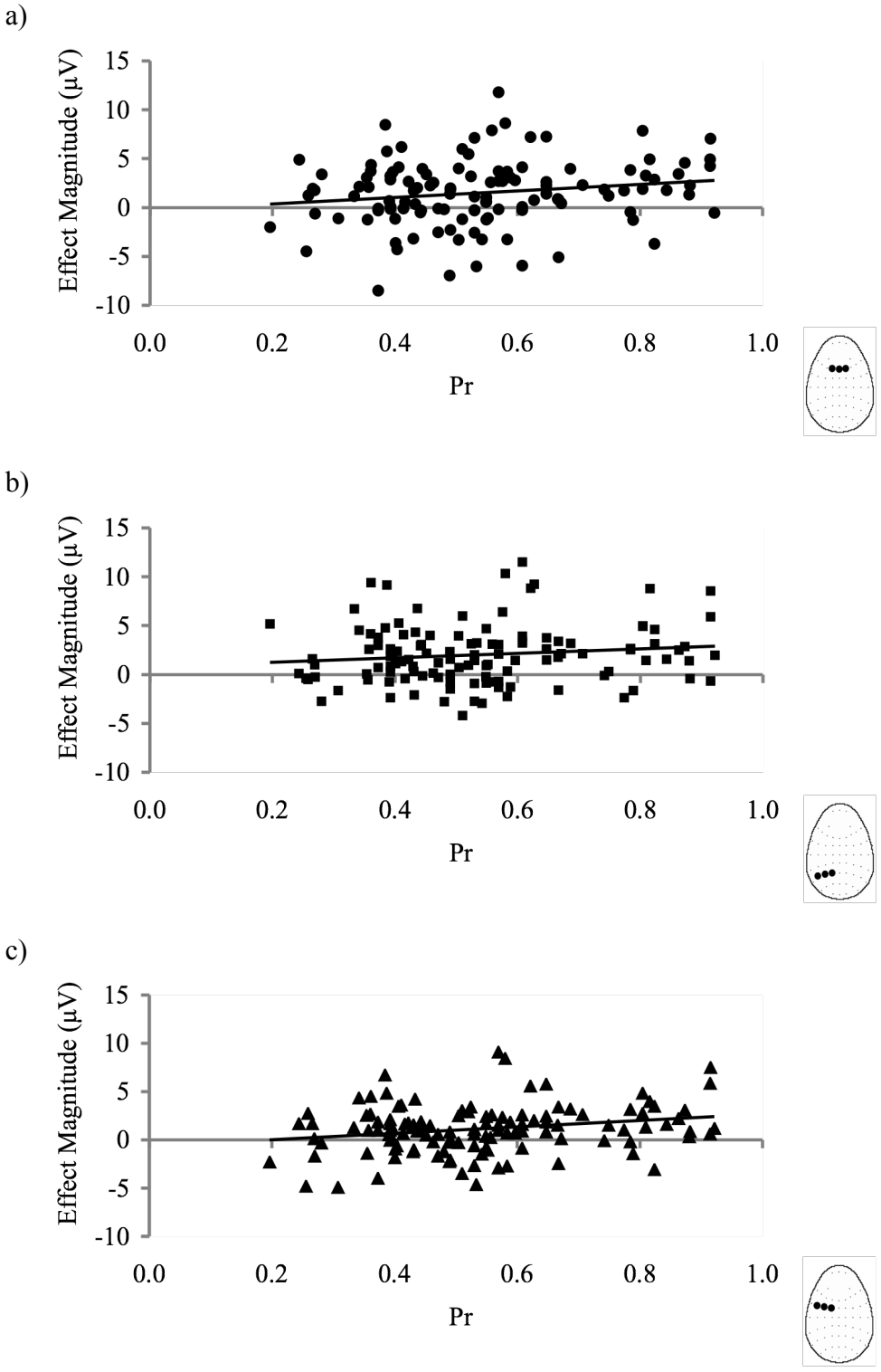


Figure 7.7 Scatterplots depicting the relationship between Pr and ERP old/new effect magnitude for a) the 300-500ms bilateral-frontal putative correlate of familiairty, b) the 500-800ms left-parietal putative recollection correlate, and c) the 200-900ms left frontocentral performance effect, evident in the performance group analysis. Correlations were performed on Hit-CR data, measured in microvolts, collapsed across electrodes a) F1, FZ, F2, b) P5, P3, P1, and c) FC5, FC3, FC1. A significant correlation was only found for the 200-900ms left frontocentral effect.

The correlations between *Pr* and the magnitude of the 300-500ms bilateral-frontal effect, and with the magnitude of the 500-800ms left-parietal effect were not significant. However, a significant correlation was found between *Pr* and the 200-900ms left frontocentral old/new effect identified in the performance group analysis [r=0.228, p=0.012]. Whilst the ERPs (Figure 7.5) indicate that this left frontocentral performance difference is a relatively long lasting effect between 200-900ms, this difference appears maximal between 500-800ms (Figure 7.6) and a stronger correlation [r=0.234, p=0.010] between *Pr* and old/new effect magnitude over left frontocentral electrodes is evident between 500-800ms (Figure 7.8) than in the 200-900ms time-window.

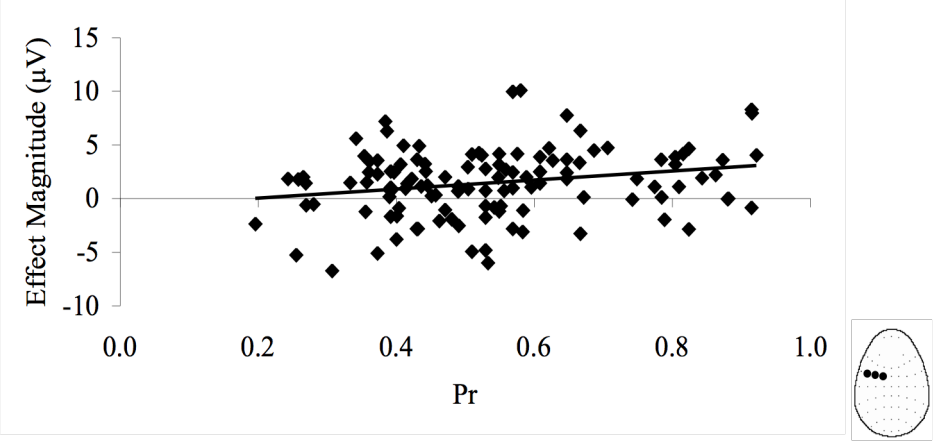


Figure 7.8 Scatterplot depicting the relationship between Pr and ERP old/new effect magnitude over left frontocentral electrodes (FC5, FC3, FC1), between 500-800ms.

7.3.2.2 Picture ERP effects and performance

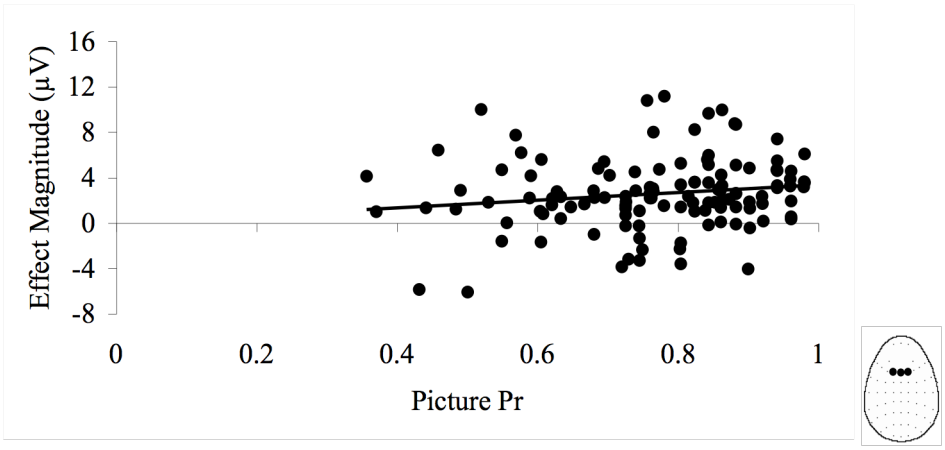
Behavioural Results:

The behavioural data for the 122 participants who met the inclusion on both the picture and word tasks are presented in Chapter 5, in Table 5.2. Participants had a mean discrimination accuracy (*Pr*) of 0.77 (s.d. 0.15), and exhibited an overall conservative decision bias (*Br* = 0.26, s.d. 0.18). Average response time for hits was 800ms (s.d. 137ms), and 850ms (s.d. 145ms) for CRs.

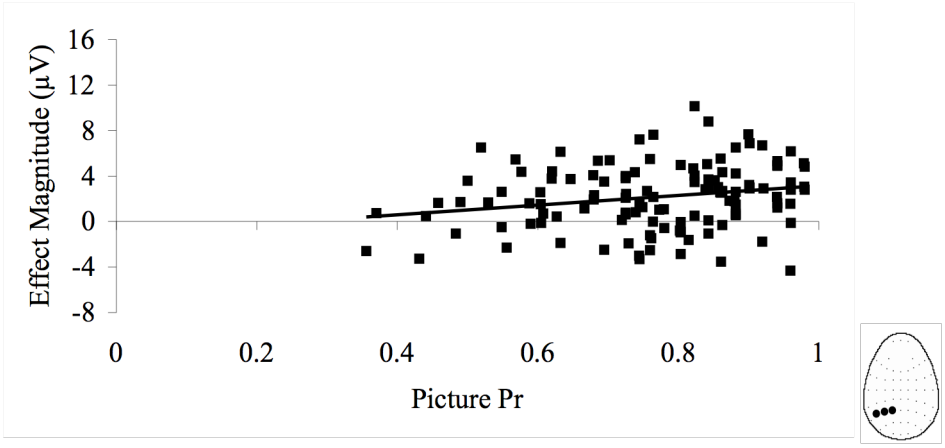
Performance and ERP effect correlations:

Correlations examining the relationship between picture old/new effect magnitude and *Pr* were performed as per the word data, looking at a) the 300-500ms bilateral-frontal effect (Figure 7.9a), b) 500-800ms left-parietal effect (Figure 7.9b), c) the 200-900ms left frontocentral effect (Figure 7.9c), and d) the 500-800ms left frontocentral effect (Figure 7.10). There was no significant correlation between *Pr* and the 300-500ms bilateral-frontal effect, however significant correlations were found between *Pr* and the 500-800ms left-parietal effect [$r=0.216$, $p=0.017$] and the 200-900ms left frontocentral effect [$r=0.215$, $p=0.017$]. As for the word task the strongest correlation was between *Pr* and old/new effect magnitude over left frontocentral electrodes between 500-800ms [$r=0.312$, $p<0.001$].

a)



b)



c)

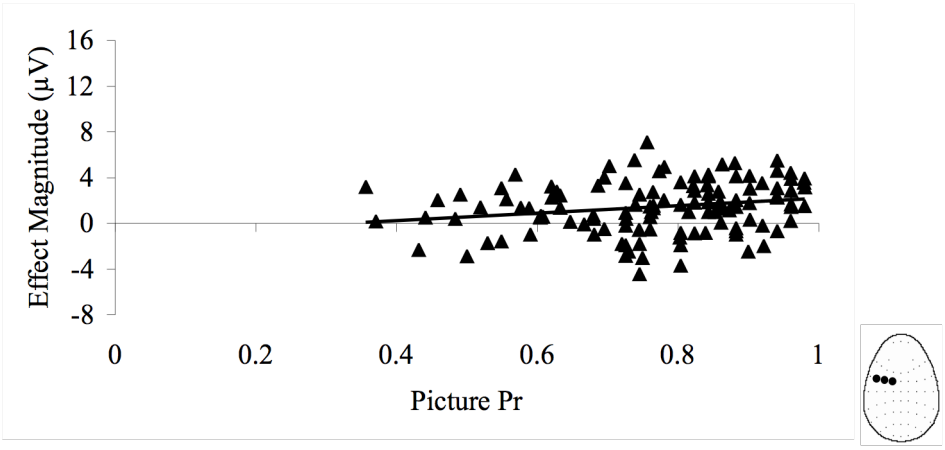


Figure 7.9 Scatterplots depicting the relationship between picture Pr and picture ERP old/new effect magnitude for a) the 300-500ms bilateral-frontal effect, b) the 500-800ms left-parietal effect, and c) the 200-900ms left frontocentral performance effect. Correlations were performed as per the word task (Figure 7.7).

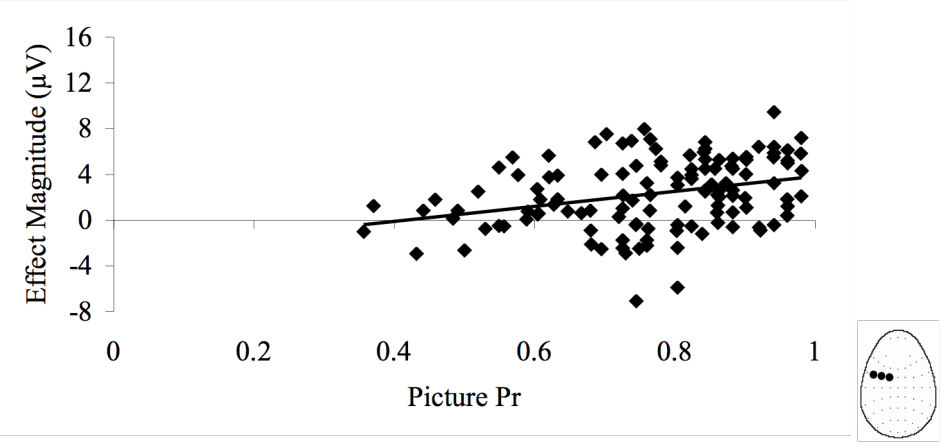


Figure 7.10 Scatterplot depicting the relationship between picture Pr and picture ERP old/new effect magnitude over left frontocentral electrodes (FC5, FC3, FC1), between 500-800ms.

7.3.2.3 Comparison of words and pictures

Across participant comparisons can be problematic, for example differences in the neural generator depth across participants may affect the magnitude of the ERP effect and therefore suppress potential correlations between effect magnitude and performance. An analysis directly comparing magnitude of the left-parietal old/new effect for words with the left-parietal effect for pictures was therefore conducted to see if effect magnitude correlated across tasks. Whilst analysis in Chapter 5 suggests that there are different ERP effects for words and pictures, a left-parietal old/new effect was present for both stimuli. A comparison of behavioural performance on both tasks was therefore conducted to see if performance on one task was indicative of performance on the other task.

No significant correlation was found when comparing the magnitude of the 500-800ms left-parietal old/new effect in the word task with the magnitude of the 500-800ms left-parietal old/new effect in the picture task (Figure 7.11). By contrast, however, comparison of behavioural performance (*Pr)* on the two tasks did reveal a significant correlation [$r=0.337$, $p<0.001$] (Figure 7.12).

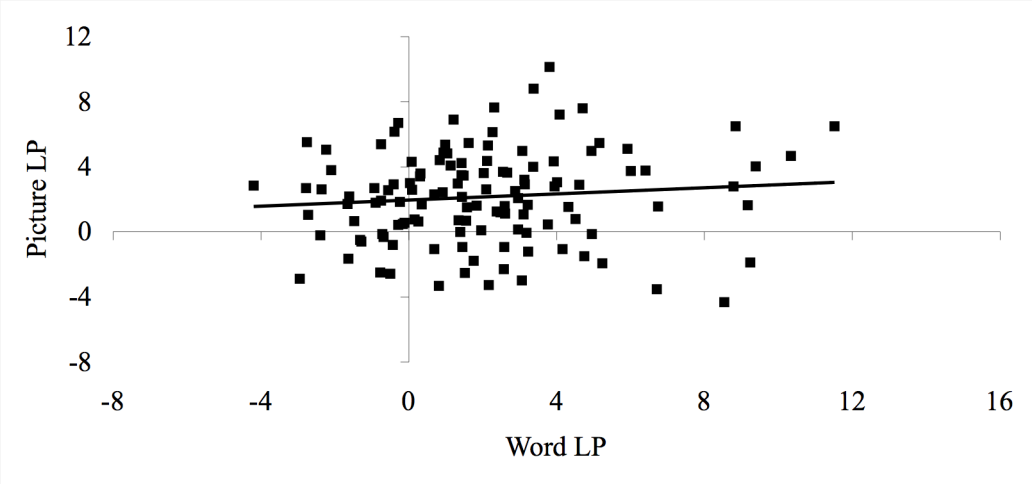


Figure 7.11 Scatterplot depicting the relationship between the magnitude of the 500-800ms left-parietal old/new effect generated in the word task, to that generated by the picture task. A correlation was performed on Hit-CR data, measured in microvolts, collapsed across electrodes P5, P3 and P1. No significant correlation was found.

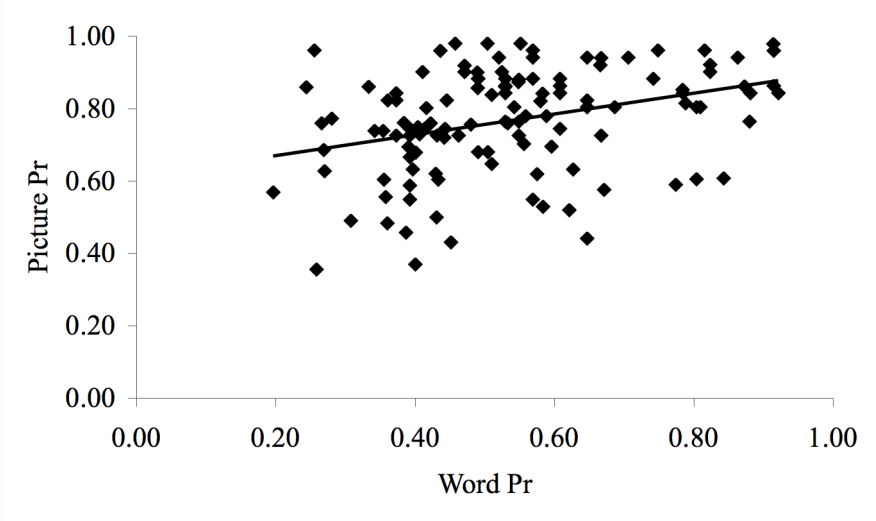


Figure 7.12 Scatterplot depicting the relationship between performance (as indexed by Pr) on the word task and performance on the picture task. A significant positive correlation was found, indicating that in general participants who performed well on one task also performed well on the other.

7.3.2.4 Discussion of correlation analysis

'Typical' recognition effects and performance:

Correlational analysis performed on the word data replicated the findings from the performance group analysis, showing no significant correlation between *Pr* and the magnitude of the 300-500ms bilateral-frontal or 500-800ms left-parietal effect. There

was, however, a significant positive correlation between *Pr* and the 200-900ms left frontocentral old/new effect, with the strongest correlation over left frontocentral electrodes in the 500-800ms time-window. Analysis of the picture data also showed no significant correlation between *Pr* and the early bilateral-frontal effect, but in contrast to the word analysis a significant positive correlation with the left-parietal effect was found. The strength of the correlation for the left-parietal effect and the 200-900ms left frontocentral effect was equal in the picture task, but as per the word task, the strongest correlation was over left-frontocentral electrodes between 500-800ms.

The absence of a significant correlation between behavioural task performance and the typical old/new recognition effects mirror those found in the group performance analysis, and suggest that behavioural performance cannot be inferred from the magnitude of these typical recognition effects on a between participant basis. It was hypothesised that performance would correlate with the putative neural correlate of recollection, on the assumption that recollection is positively correlated with recognition. Given this assumption one possible explanation for the absence of a significant correlation between performance and the left-parietal effect is that, in the current task, changes in overall recognition performance were not reflected by changes in recollection. If the proportion of trials in which recollection occurs is consistent across participants, irrespective of overall task performance, then no significant correlation with left-parietal effect magnitude would be expected.

Whilst no independent estimates of recollection were taken in the current study an additional follow-up behavioural experiment was conducted, with a new cohort of 59 participants. The procedure involved the same recognition word task as in the ERP study, but with the inclusion of a remember/know/guess response at the end of each

trial. The results indicated that participants were able to complete the task with a *Pr* of 0.51 (s.d. 0.03), and revealed a significant positive correlation between the proportion of 'remember' responses and recognition performance [r=0.436, p=0.001]. Furthermore, the data indicated that on average participants predominately engaged recollection processes to complete the task, with participants on average giving 'remember' responses on 58% of trials, responding 'know' on 32% of trials and 'Guess' on 10% of trials. In addition, a second follow-up behavioural experiment was carried out in which 65 participants were asked to remember words and the colour they were presented in. This experiment revealed a significant positive correlation between accuracy of source judgment and old/new recognition performance [r=0.688, p<0.001][18]. Taken together therefore these results strongly suggest that the assumption that recognition is positively correlated with recollection is not in itself inaccurate, and indicates that participants in the current ERP study are likely to be utilising recollection to perform the task.

The presence of significant correlations between performance and old/new effect size in other locations suggests that the lack of correlation with the typical ERP effects cannot be explained by poor statistical power. Indeed, one notable feature of the data is that both performance and ERP measures exhibited a good degree of variability across participants. On this basis alone, the data would appear to be well able to reveal a correlation if one were present. Furthermore the fact that there was a significant correlation in the picture task, albeit overshadowed by a stronger correlation at another location in the same time-window, makes it very difficult to argue that the sample size was insufficient to reveal a significant correlation between these two factors.

[18] Average decision accuracy scores on the word source task were 0.70 (s.d. 0.02), with an average proportion of 0.67 (s.d. 0.01) correct source judgments made.

Whilst it was hypothesised that performance differences would be reflected in the ERP effects, previous studies have shown that this is not necessarily the case. For example, using data from 24 participants, Yick and Wilding (2008) correlated the magnitude of a frontal old/new recognition ERP effect for faces with discrimination accuracy and failed to find a significant correlation. Furthermore, as discussed in the introduction, Van Petten et al. (2002) found that the posterior ERP effects between 300-600ms for the old/recombined contrast and for the recombined/new contrast were not modulated by an individual's ability to identify recombined word pairs, but by the degree of oldness of the stimuli.

Further evidence against a link between the left-parietal magnitude and performance comes from a study by Curran, Schacter, Johnson and Spinks (2001). They compared participants who were good at discriminating 'old' words from semantically related new 'lure' words, with those who were poor at this discrimination, under conditions in which both groups were equally able to distinguish 'lure' words from semantically unrelated 'new' words. Analysis of parietal old/new effects between 400-800ms showed a significant difference between correctly identified 'old' and falsely recognised lure conditions over posterior/superior electrodes, with ERPs to 'old' words more positive going than those to lure words. Although there was no significant interaction with performance group, analysis of the two groups separately indicated that the posterior/superior old/lure effect was only statistically significant for the poor performers. Good performers, by contrast, exhibited a late right frontal effect between 1000-1500ms that was not present for poor performers. To account for the unexpected pattern of effects the authors argued that good performers use evaluative processes to facilitate recognition of 'old' items where the retrieved information is relatively low quality, and therefore show a smaller average parietal old/lure effect than poor

performers who only respond to items with high quality information, and consequently show a large old/lure effect. The standard parietal old/new effect was evident for both groups, although no comparison of effect by group was reported.

In a similar study to Curran et al. (2001), Curran and Cleary (2003) looked at performance differences in discriminating 'old' pictures from mirror-reversed 'similar' pictures. No significant interactions were found between group and the parietal Hit/CR effect (measured between 400-800ms), however a significant interaction between group and the magnitude of the hits/'similar false alarms' difference over parietal electrodes was found, with a significant effect for good but not for poor performers. In this study, however, poor performers did show a significant false alarm (similar)/CR (new) difference that was not evident for good performers. As should be clear, these findings are in direct contrast to the findings from Curran et al's. (2001) study of word recognition.

Left frontocentral effect and performance:

Returning to the current ERP findings, the left frontocentral old/new effect is in itself a surprising result. The importance of activity across these electrodes in relation to recognition performance was first highlighted in the performance group analysis, and this effect was then shown to significantly correlate with performance in the full sample analysis. Although the ERPs from the group analysis indicated that a sustained old/new effect was present over left frontocentral electrodes between 200-900ms, the strongest correlation was found between 500-800ms, the typical left-parietal effect time window. The stronger left frontocentral correlation in the 500-800ms time-window suggests that the lack of correlation with the left-parietal effect is not a direction function of the time-window (e.g. the number of available data points). Furthermore the overlap in timing

between the left frontocentral performance effect and the left-parietal recollection effect suggests that old/new activity over left frontocentral electrodes may have been previously overlooked as a by-product of activity that is maximal at left-parietal electrodes. Activity over left frontocentral electrodes is not typically considered an ERP correlate of successful recognition memory, however there is evidence of a left-frontal retrieval effect when comparing 'new' items from retrieval sets with differing task demands, which are broadly interpreted as reflecting differences in "retrieval effort" (see Chapter 2).

As discussed in Chapter 2, Ranganath and Paller (1999) showed that between 500-1200ms 'new' items from a specific retrieval block (in which participants had to discriminate identical 'old' items from similar 'old' and 'new' items) were more positive over left-frontal electrodes than 'new' items from a more general retrieval block (where participants discriminated identical and similar items from 'new' items). Similarly, Rugg, Allan and Birch (2000) found that between 200-1400ms 'new' items from a shallowly encoded test block were more positive than a deeply encoded test block - again over left-frontal electrodes. Ranganath and Paller (1999) suggest that this frontal activity reflects the differential engagement of strategic retrieval processes in the two test conditions, with the specific retrieval condition requiring greater engagement of working memory than the general condition. Rugg et al. (2000), by contrast, suggest that the left-frontal effect reflects differences in response criteria, as evident by differences in decision bias scores (*Br)* in the two retrieval conditions.

Whilst both these studies report this left-frontal effect as a difference across 'new' items, this is not to say that the difference is restricted to 'new' items. Retrieval success effects may mask such pre-retrieval processing effects and, as discussed in Chapter 2,

comparisons of 'new' items are recommended to reduce the risk of retrieval success confounds (Rugg & Wilding, 2000). Both Ranganath and Paller (1999) and Rugg et al. (2000) show a more positive going effect in the more difficult of the two tasks. In the current study high performers show a larger old/new effect than poor performers over left-frontocentral electrodes, a difference that appears to onset as early as 200ms and is sustained until 900ms. The onset of this difference is consistent with the effect onset reported by Rugg et al. (2000), although the current effect appears to be shorter in duration. In broad terms, therefore, if the left-frontocentral old/new effect in the current study reflects activity of the same generators as those active for 'new' items by Ranganath and Paller (1999) and Rugg et al. (2000), then the current data suggest that the differences in performance reflect differences in 'retrieval effort'.

More specifically, however, the present findings are difficult to reconcile with the detailed explanations provided by Ranganath and Paller (1999) and Rugg et al. (2000). First, in the current study the decision bias scores between high and low performers were not significantly different, and a partial correlation controlling for *Br* did not change the relationship between *Pr* and the magnitude of the old/new effect over left-frontocentral electrodes between 200-900ms [r=0.232, p=0.010]. These results suggest that the left-frontocentral performance difference in the current study cannot be accounted for in terms of differences in decision bias, as suggested by Rugg et al. (2000). Second, in relation to the suggestion from Ranganath and Paller (1999) that the effect reflects differences in working memory demands, correlations between scores (strategy, number of total errors, and number of between errors) on the Spatial Working Memory task from the CANTAB with *Pr* and effect magnitude over Left frontocentral electrodes between 200-900ms on the word recognition task, all failed to reach significance. These results suggest that the left-frontocentral effect for words in the

current study is not significantly related to overall working memory performance, as index by measures from a Spatial Working Memory task. However, whilst this finding suggests that the left-frontocentral effect on the word task is not significantly related to an individual's general working memory ability, it does not provide any direct insight into the engagement of working memory by individuals when completing the word recognition task.

Word and picture task consistency:

In addition to the comparisons of behavioural performance and ERP effect magnitude, analyses comparing individual behavioural performance on the word and picture tasks were conducted. These data revealed a significant positive correlation, showing that participants scoring highly on one task also scored highly on the other. However, whilst behavioural performance correlated, there was no significant correlation between left-parietal effect magnitude in the two tasks. The absence of a correlation in the size of effect for word and picture tasks is important because it demonstrates that the magnitude of ERP old/new effects is not particularly dependent on inherent individual differences per se. To be clear, the absence of a correlation across task (within participant) rules out the possibility that differences in the size of the left-parietal effect reflect nothing more than anatomical differences across participants. For example, if the generators of the effect were deeper in one participant than another, this could have introduced variability in the size of the left-parietal effect that would have masked any variability related to memory performance. Overall, therefore, data from the current experiment suggests that the size of the left-parietal effect does vary as a function of task related processes.

How then might task related differences be exhibited? As noted above behavioural performance on average was different for the two stimuli, however, the significant correlation in performance scores across the two tasks suggests that the absence of a significant ERP effect correlation cannot simply be explained by the overall performance differences in the two tasks. Another possibility is that participants are relying on different recognition processes when completing the task with words compared to pictures. If the degree to which recollection processes are engaged modulates the magnitude of the left-parietal effect, inconsistency in the engagement of recollection in these tasks across participants would give a null result when comparing effect magnitudes.

As discussed previously no independent measure of recollection and familiarity was taken with these tasks, however a supplementary behavioural study was conducted which employed the same tasks with an additional R/K/G judgement after each 'old' response. This study compared word, picture and face recognition in 27 participants, revealing significant differences in *Pr* scores across the three tasks [$F(2,51)=136.81$, $p<0.001$], consistent with the results presented in Chapter 5, but no significant differences in the proportion of 'Remember' responses made across tasks [$F(1,38)=2.37$, $p=0.1$]. Furthermore, direct comparison of word and picture data from this supplementary study revealed significant positive correlations between *Pr* on both tasks [$r=0.396$, $p=0.041$], and between the proportions of 'Remember' responses made on both tasks [$r=0.581$, $p=0.001$]. Overall these results suggest that the level of engagement of recollection processes across the picture and word tasks did not significantly differ, and that the proportion of 'Remember' responses on one task was related to the proportion on the other. These results therefore suggest that the absence of a significant correlation between the magnitude of the left-parietal effect on the word

and picture tasks are not the result of differential engagement of recollection across tasks, nor inconsistency in the way participants engaged recollection in the two tasks. However, the relationship between the magnitude of ERP old/new effects and behavioural performance needs to be examined in tasks that directly measure familiarity and recollection, to fully understand this relationship and the influence of the different memory processes.

In sum, the data from the current study and subsidiary behavioural studies show that an individual's behaviour on one recognition task is related to their behaviour on other recognition tasks. Nonetheless, despite the behavioural correlations, the magnitude of the left-parietal old/new ERP effect across tasks was not significantly correlated. Taken at face value therefore, the findings from these within participant comparisons indicate that the left-parietal old/new ERP effect cannot safely be used as a global indicator of memory performance. In the following section this conclusion is investigated further using a stronger, more stringent, test.

7.3.3 Left-parietal effect polarity and performance

Contrary to expectations the performance group analysis of data from the word recognition task and the correlation analysis of the word data, and to some extent the picture data, suggest that left-parietal effect magnitude is not modulated by behavioural performance, as indexed by discrimination accuracy (*Pr*). As outlined above this outcome is surprising given the assumption that the left-parietal effect is a neural correlate of recollection, and that the number of trials in which recollection occurs increases with higher recognition performance. To further test the findings from the current chapter two groups of participants were selected, based on both the magnitude

and polarity of the left-parietal old/new effect in the word task, and analysis of behavioural performance in these two groups was then conducted.

In the foregoing analysis a virtual left-parietal electrode was created by averaging mean amplitude, between 500-800ms, at electrodes P5, P3 and P1. Looking at the data from all 122 participants who met the inclusion criteria on the word task, 32 participants exhibited a 'negative going' old/new effect at this left-parietal electrode, in which CR responses were more positive going than hits; the reverse of that considered to be a typical left-parietal effect. A second group of 32 participants were selected who exhibited a more typical 'positive effect', in which hit responses are more positive going than CRs, matching for the size of the old/new difference.

7.3.3.1 Positive versus negative left-parietal effect groups: Words

ERP Results:

The mean amplitude of the left-parietal effect for the 'positive effect' group was 1.42μV (s.d. 0.97μV), with a mean amplitude of -1.32μV (s.d. 1.03μV) for the 'negative group' (Figure 7.13). As would be expected, the ERPs for the positive group (Figure 7.14) resemble the pattern of activity seen in the whole sample analysis (Chapter 5), with hits becoming more positive going than CRs over parietal sites from approximately 400-800ms. Topographic maps (Figure 7.15) show that the distribution of this old/new difference is fairly widespread between 300-500ms, becoming more focused between 500-800ms with a clear left hemispheric distribution over parietal locations and a more right hemispheric distribution over frontal locations.

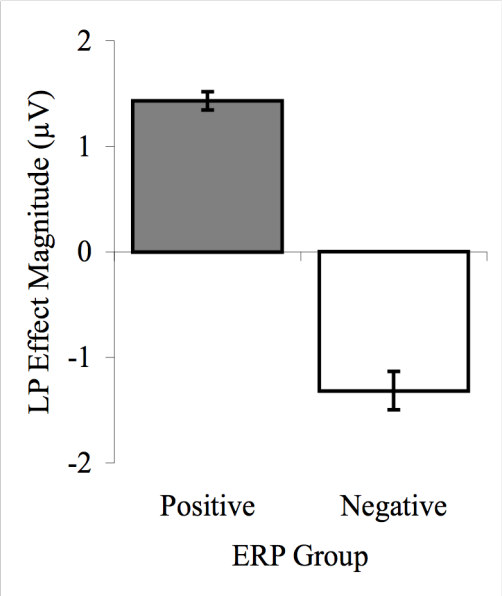


Figure 7.13 Plot showing the average magnitude of the left-parietal effect (as indexed by the Hit-CR difference between 500-800ms averaged over electrode P5, P3, & P1) for the 'matched positive' group and the 'negative effect' group.

Also as expected, the ERPs for the negative group (Figure 7.16) are markedly different from both the positive group and the whole sample analysis. For this group minimal differences can be seen between conditions until approximately 600ms when CRs become more positive going than hits, a difference that is sustained until the end of the epoch over parietal sites, and until approximately 900ms over frontal electrodes. The absence of an old/new difference in the early time-window can be clearly seen from the topographic maps presented in (Figure 7.17). Nonetheless, the topographic map clearly shows a parietal distribution of the negative going old/new difference in the 500-800ms time-window.

Interestingly the difference between the positive and negative group over left-parietal electrodes appears to be limited to a time-window between 400-1100ms (Figure 7.18), showing a comparable pattern of hit and CR activity outwith this time-window.

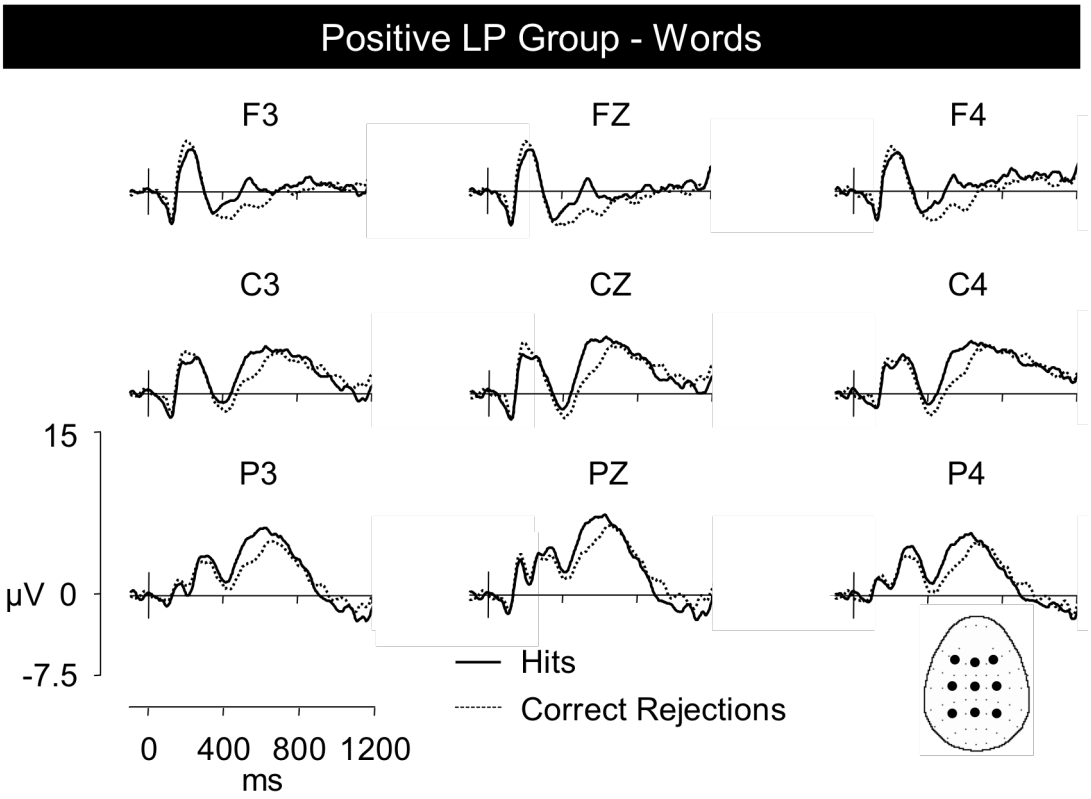


Figure 7.14 Grand average ERP waveforms for the 'positive LP' group, in which hits are more positive going than CRs over left-parietal electrodes on the recognition memory for words task (n=32). Data shown as in Figure 7.1.

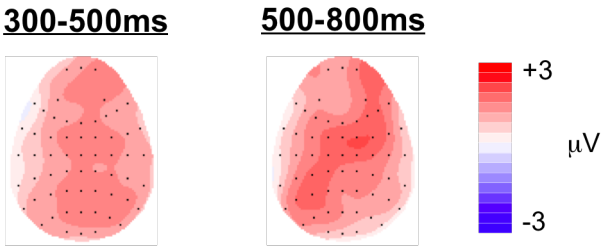


Figure 7.15 Topographic maps showing the distribution of the old/new difference for the 'positive LP' group. Data shown as in Figure 7.2.

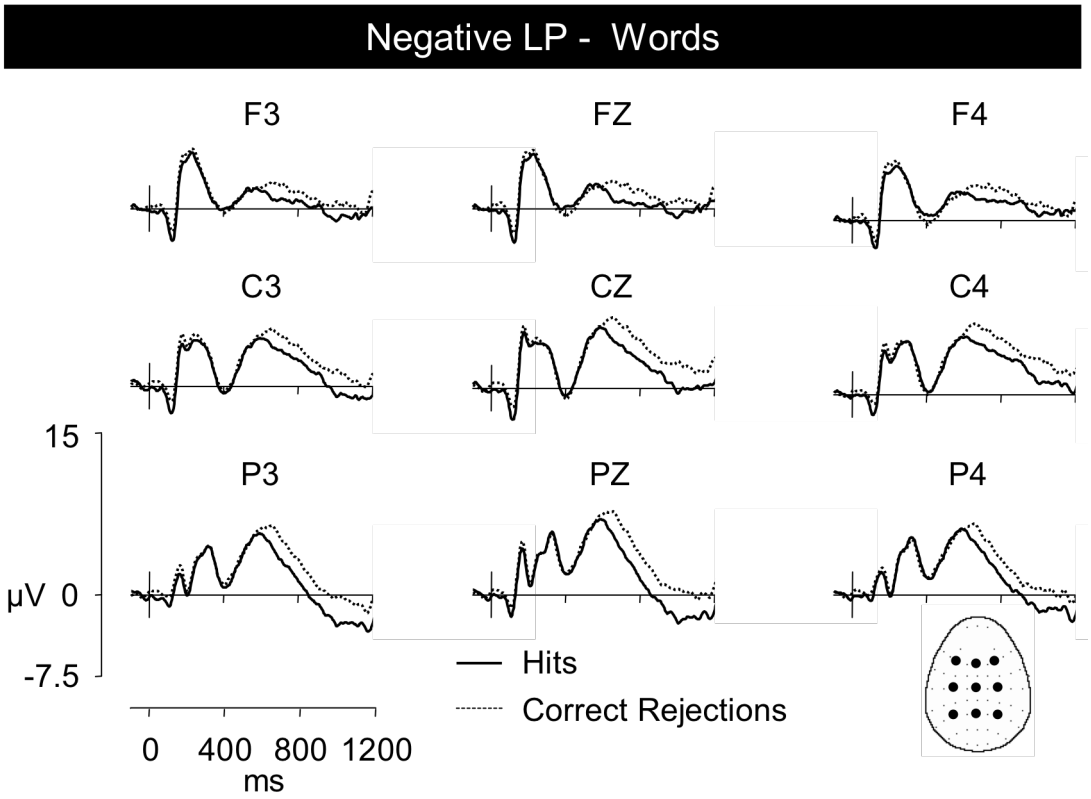


Figure 7.16 Grand average ERP waveforms for the 'negative LP' group, in which CRs are more positive going than hits over left-parietal electrodes on the recognition memory for words task (n=32). Data shown as in Figure 7.1.

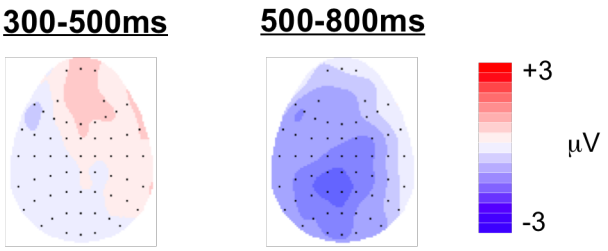


Figure 7.17 Topographic maps showing the distribution of the old/new difference for the 'negative LP' group. Data shown as in Figure 7.2.

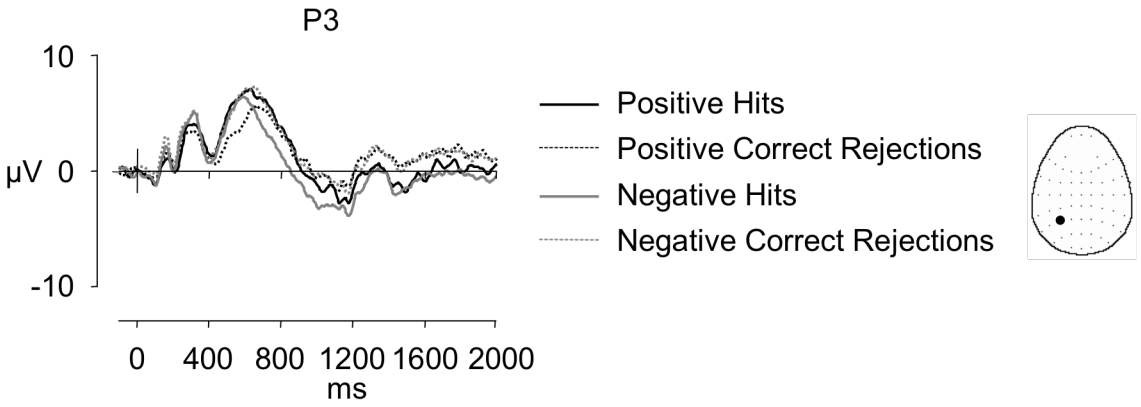


Figure 7.18 Grand average ERP waveforms at electrode P3 showing the overlap between 'positive' and 'negative' groups for hit and CR responses. The ERPs for hits and CRs appear consistent across positive and negative groups at the beginning of the epoch and at the end, with the key difference between the two groups evident from approximately 400ms until approximately 1200ms. The vertical scale indicates electrode amplitude, measured in microvolts, whilst the horizontal scale indicates change in time, measured in milliseconds.

Analysis from 300-500ms:

Statistical analysis of the ERP data for the 'positive group' only revealed a significant main effect of condition [$F(1,31)=7.92$, $p=0.008$], indicating that hits were more positive going than CRs. No significant differences between conditions were found between 300-500ms for the 'negative group'.

Analysis from 500-800ms:

Analysis of the ERP data between 500-800ms for the 'positive group' revealed a significant main effect of condition [$F(1,31)=19.69$, $p<0.001$], and significant interactions between condition, location and hemisphere [$F(4,39)=3.97$, $p=0.045$], and condition, location, hemisphere and site [$F(3,96)=3.53$, $p=0.017$]. These results indicate that, overall, hits were more positive going than CRs, but that this difference was greater over parietal electrodes in the left hemisphere and frontal electrodes in the right hemisphere. A breakdown of the 4-way interaction revealed main effects of condition at all locations (frontal, frontocentral, central, centroparietal and parietal), significant condition by site interactions at frontocentral [$F(1,35)=7.77$, $p=0.007$] and central

[F(1,36)=6.62, p=0.011] locations, showing that the old/new difference was greatest at superior sites. No significant interactions with hemisphere were found in the subsidiary ANOVA.

Analysis of the 'negative group' also revealed a significant main effect of condition [F(1,31)=11.58, p=0.002], showing in this case that CRs were more positive going than hits. A significant condition by site interaction [F(1,34)=4.35, p=0.042] indicates that the old/new difference was largest at superior sites, however a significant condition by hemisphere by site interaction [F(2,48)=4.65, p=0.021] indicates a more uniform effect distribution across sites in the left than right hemisphere. Analysis of the negative group did not reveal an anterior/posterior difference, despite the impression provided by Figure 7.17.

Given the statistical differences in the pattern of effects found for positive and negative groups an additional comparison was made across groups. This topographic analysis was designed to show if there was any evidence that the effects reflect underlying differences in the generators of the activity. Direct comparison of the old/new effects between the two groups (using data rescaled in line with the max/min method of McCarthy and Wood, 1985), only revealed a significant group by site interaction [F(1,67)=7.84, p=0.006]. This effect simply reflects the differences in polarity between the two groups, with the magnitude of the old/new difference for the Positive group becoming larger from inferior to superior electrodes and the negative group becoming smaller (Figure 7.19). The absence of interactions involving hemisphere and/or location indicates that there is no significant difference in the underlying distribution of the positive and negative going effects.

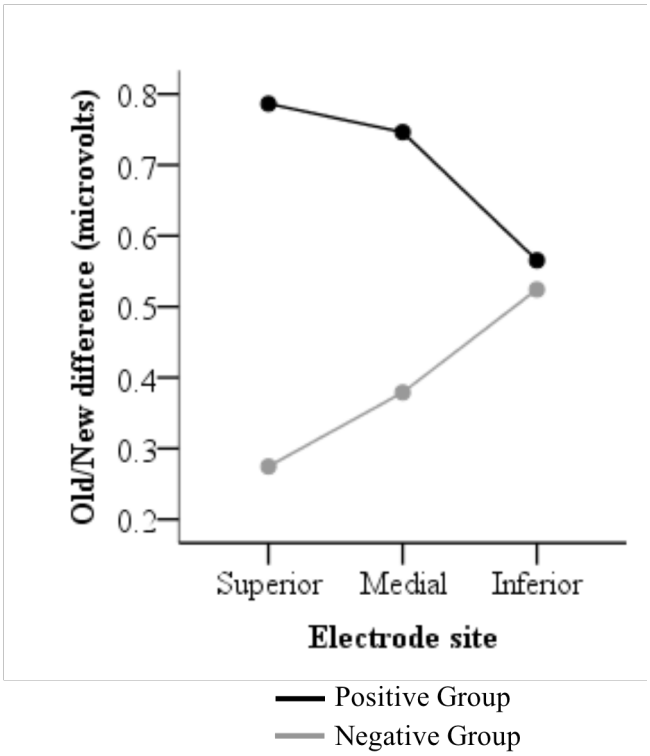


Figure 7.19 Plot showing average old/new effect magnitude (data rescaled inline with McCarthy & Wood, 1985) for the positive and negative left-parietal effect groups across electrode site (superior, medial and inferior sites) for the 500-800ms time-window. A significant group by site interaction was found reflecting the polarity difference of the two groups at superior sites.

Behavioural Results:

The behavioural results for the positive and negative effect groups are presented in Table 7.2. Statistical comparison of the behavioural scores revealed no significant differences between groups on hit rate, false alarm rate, *Pr, Br*, hit response time nor CR response time. Statistically, the behavioural results for the two groups are the same.

ERP Group	Hit rate (%)	False alarm rate (%)	Pr	Br	Hit RT (ms)	CR RT (ms)
Positive (n=32)	70 (12)	21 (11)	0.50 (0.17)	0.38 (0.18)	843 (129)	914 (146)
Negative (n=32)	71 (11)	19 (11)	0.52 (0.17)	0.38 (0.13)	828 (158)	894 (181)

Table 7.2 Behavioural results for participants with a 'positive going' left-parietal effect (Hits>CRs), and those with a 'negative going' left-parietal effect (CRs > Hits). Data as shown in Table 7.1.

7.3.3.2 Typical 'positive' left-parietal effect participants

In addition to the left-parietal old/new effect, for the magnitude matched positive group the analysis above revealed an additional right-frontal old/new effect in the 500-800ms time-window, which may reflect an early on-setting late right frontal effect (thought to reflect post-retrieval processing, see Wilding & Rugg, 1996). There was no evidence of a 500-800ms right-frontal old/new effect in the full sample analysis presented in Chapter 5, so an additional analysis of the remaining 58 participants from the full sample analysis, (who also show a typical positive going left-parietal effect) was conducted to compare the behavioural results of the three groups: the Negative left-parietal effect group, the 'Matched' Positive left-parietal effect group, and the 'Typical' left-parietal group.

ERP Results:

The ERPs for the 'typical' Positive group (Figure 7.20) reflect the left-parietal old/new effect shown in Chapter 5, with hits more positive than CRs over parietal electrodes. In contrast to the Matched Positive group, the topographic maps (Figure 7.21) indicate that the old/new difference is maximal over left-parietal electrodes, and with no indication of an additional right-frontal effect in the 500-800ms time-window.

Analysis from 300-500ms:

Statistical analysis of the 'typical' Positive group in the 300-500ms time-window revealed a significant main effect of condition [$F(1,57)=54.56$, $p<0.001$], and a significant condition by site interaction [$F(1,61)=62.28$, $p<0.001$]. These results indicate that hits were significantly more positive going than CRs and that this difference was greatest at superior electrodes.

Analysis from 500-800ms:

Analysis of the 500-800ms time-window revealed a significant main effect of condition [F(1,57)=102.16, p<0.001], as well as a number of significant interactions: condition by location [F(1,66)=5.74, p=0.015], condition by hemisphere [F(1,57)=8.65, p=.0.005], condition by location by hemisphere [F(1,73)=6.32, p=0.009], condition by site [F(1,61)=48.25, p<0.001], condition by location by site [F(2,119)=8.12, p<0.001], condition by hemisphere by site [F(1,67)=6.37, p=0.010], and condition by location by hemisphere by site [F(3,172)=7.49, p<0.001]. These interactions show that hits were more positive going than CRs, a difference that was greatest over left-parietal electrodes, where the difference between conditions was uniform across electrode sites, compared to a superior site bias in the right hemisphere.

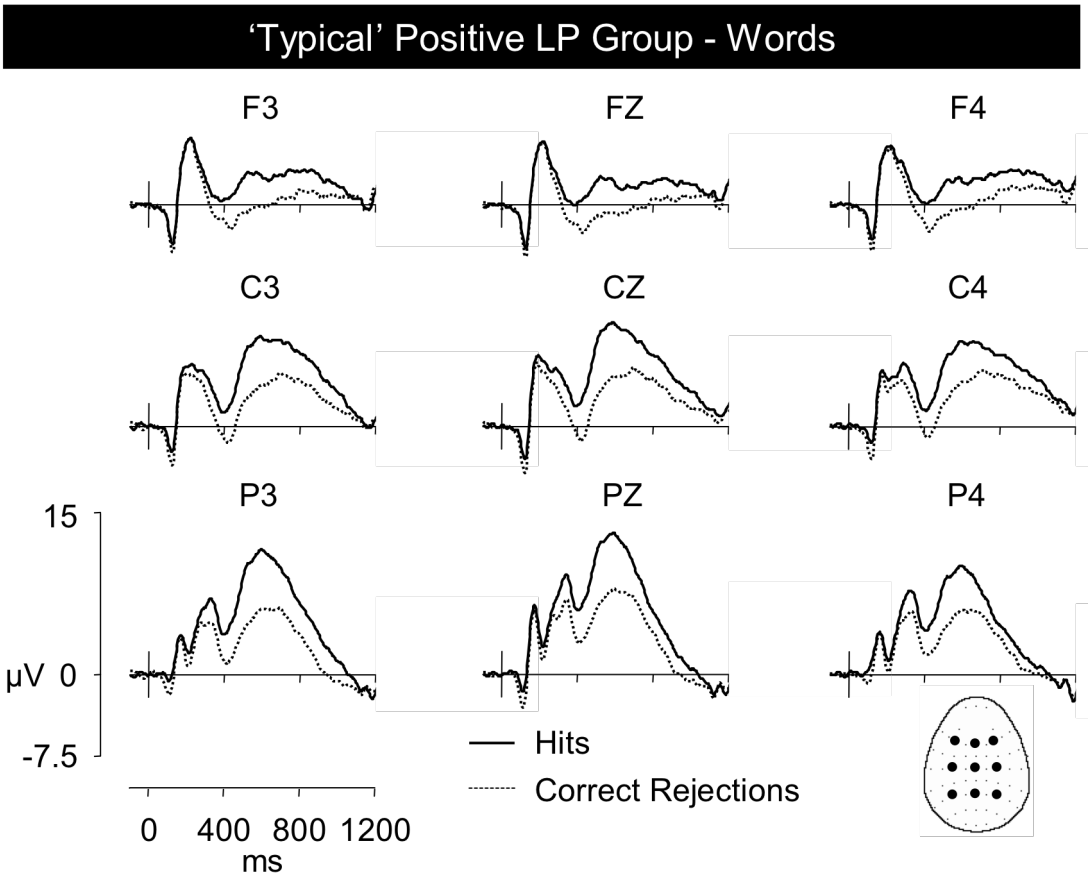


Figure 7.20 Grand average ERP waveforms for the 'Typical' Positive LP group, in which hits are more positive going than CRs over left-parietal electrodes on the recognition memory for words task (n=58). Data shown as in Figure 7.1.

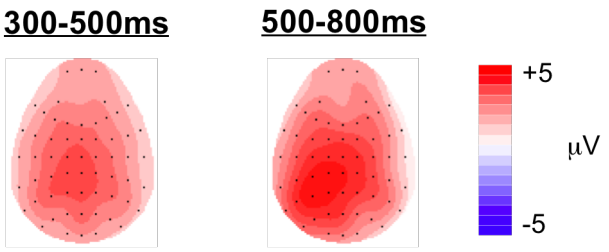


Figure 7.21 Topographic maps showing the distribution of the old/new difference for the 'Typical' Positive LP group. Data shown as in Figure 7.2.

Behavioural Results:

The behavioural results for the typical Positive participants are presented in Table 7.3, along with the behavioural data for the Matched Positive and Negative groups, as presented in Table 7.2. A one-way ANOVA comparing the behavioural scores between groups revealed no significant differences in hit rate, false alarm rate, *Pr*, *Br*, hit response time nor CR response time, indicating that there is no statistical difference in performance between groups.

ERP Group	Hit rate (%)	False alarm rate (%)	Pr	Br	Hit RT (ms)	CR RT (ms)
'Typical' Positive (n=58)	75 (12)	17 (11)	0.57 (0.17)	0.39 (0.17)	820 (133)	890 (151)
'Matched' Positive (n=32)	70 (12)	21 (11)	0.50 (0.17)	0.38 (0.18)	843 (129)	914 (146)
Negative (n=32)	71 (11)	19 (11)	0.52 (0.17)	0.38 (0.13)	828 (158)	894 (181)

Table 7.3 Behavioural results for the remaining participants alongside those for the amplitude mirrored 'positive' group, and the 'negative' group. Data as shown in Table 7.1.

7.3.3.3 Effect polarity across tasks

As discussed in section 7.3.2.3 there was no significant correlation between the magnitude of the left-parietal old/new effect in the word task and in the picture task. One possible explanation for the absence of a correlation is that the old/new effects for words and pictures differ, as indicated in Chapter 5. However, whilst there is no

evidence that the magnitude of the ERP effects correlate across tasks, it could be hypothesised that the polarity of these effects would be consistent, based on the working assumption that those participants showing a 'negative effect' are inherently different from those with the more common 'positive effect'. By this account participants who show a 'positive effect' will always show a 'positive effect', and those exhibiting a 'negative effect' always exhibit a 'negative effect'.

Close examination of the ERP data provides little support for this account however. As is illustrated in Figure 7.22, the data showed that overall 42% of participants (i.e. of the 122 usable in both the word and picture tasks) exhibited a 'negative' effect (CR>Hits) in at least one of these tasks, with only 8% of the full sample exhibiting a 'negative' effect in both tasks. Moreover the data clearly shows that participants who exhibit a 'negative' left-parietal effect in the word task do not necessarily exhibit a 'negative' effect in the picture task (and vice versa), suggesting that participants with 'negative' going effects are not inherently different. Nonetheless, the data do show that approximately one quarter of the sample in the word task exhibited a 'negative' effect, with a similar number in the picture task (26% for the word task, and 24% for the picture task), indicating that the occurrence of such anomalous effects are perhaps more common than would be expected given the assumptions about the left-parietal old/new effect in the literature.

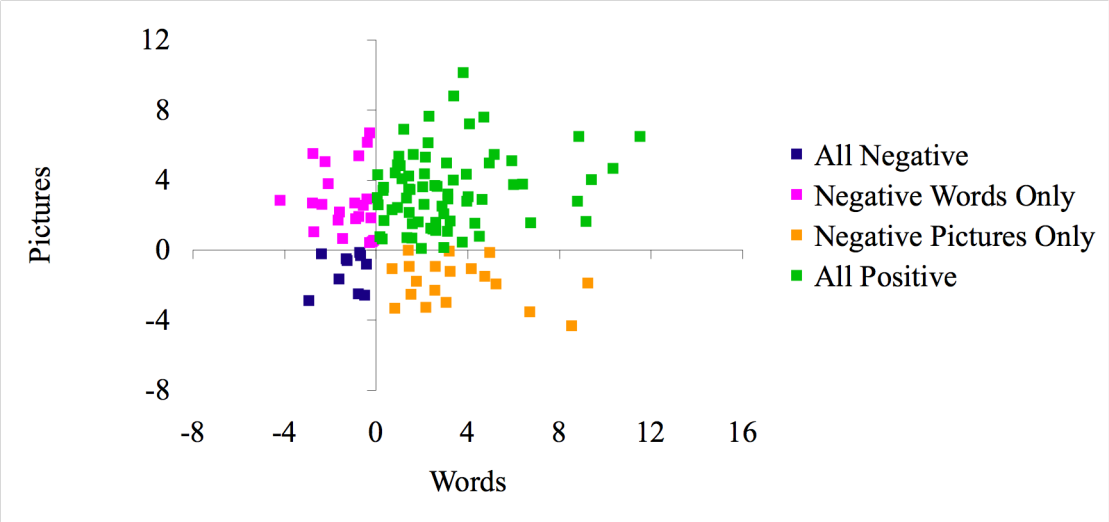


Figure 7.22 Scatterplot depicting the relationship between the magnitude of the 500-800ms left-parietal old/new effect in the word and picture tasks, as presented in Figure 7.11. It is clear from the scatterplot that not all participants exhibit a 'positive going' old/new effect, in which activity for hits is greater than activity for CRs (as depicted in green). Approximately 42% of participants show a 'negative going' left-parietal effect in either the word or picture task. Furthermore exhibiting a 'negative effect' in one task does not necessarily mean that individuals will exhibit a 'negative effect' in the other (depicted by the pink and orange points); only 8% of all participants exhibit a 'negative effect' in both tasks (shown in navy).

7.3.3.4 Discussion of effect polarity and performance

Dividing the data into groups based on the magnitude and polarity of the 'left-parietal effect', and comparing those exhibiting a 'negative' effect, a magnitude mirrored 'positive' effect and a 'typical' effect, revealed no significant differences in behavioural measures of performance accuracy, decision bias or response time in the word recognition task. Furthermore, inspection of data from both the word and picture tasks revealed that a larger proportion of participants than would have been expected exhibited a 'negative left-parietal effect' in at least one of the two tasks, but only a small proportion of participants exhibited a 'negative' effect in both tasks.

The finding that directionality of the old/new difference over left-parietal electrodes between 500-800ms is not reflected in decision accuracy scores (or any of the other behavioural measures taken) is in stark contrast to the expectations that were outlined at the beginning of the chapter. Nonetheless, the findings are consistent with the picture

that has developed throughout the current chapter. These analyses suggest that whilst the magnitude of the left-parietal effect may provide an index of recollection, across participants it is not a good predictor of overall memory performance, with equivalent behavioural outcomes appearing to reflect the engagement of different underlying neural systems and strategies. Furthermore the lack of a significant correlation between left-parietal effect magnitude in the word and picture tasks, and the evidence indicating that there is not a consistent pattern of old/new directionality across tasks, suggests that individual participants may engage different strategies when trying to remember different stimuli.

7.4 General Discussion

Initial analysis compared the ERP effects of two groups of participants selected to represent high and low performers, an analysis of performance and old/new effect magnitude was then conducted on the whole sample, and finally an analysis of behaviour between three groups selected for left-parietal old/new effect magnitude and distribution was conducted. There were three main outcomes from these investigations: firstly, the magnitude of the left-parietal old/new effect was not modulated by behavioural performance; secondly, performance did modulate activity over left frontocentral electrodes between 200-900ms; and thirdly, left-parietal effect magnitude did not correlate across tasks. Supplementary experiments confirm that estimates of recollection and performance accuracy do correlate, on both a source memory and an R/K/G task, suggesting that the lack of left-parietal effect modulation was not caused by limited variation in the level of engagement of recollection.

A summary of the current understanding of the relationship between these ERP effects and performance is presented in Figure 7.23, which includes a significant correlation in

the magnitude of the 200-900ms left frontocentral old/new effect and the 500-800ms left-parietal old/new effect for both words [$r=0.559$, $p<0.001$] and pictures [$r=0.292$, $p=0.001$]. A significant correlation between effect magnitudes within a task is perhaps to be expected given that current analytical methods do not allow specific effects to be spatially isolated. That is, the signal generated by one population of neurons will not only be recorded by one cluster of electrodes but will be recorded by all electrodes, allbeit differing in signal strength. Therefore activity generated by several populations of neurons will overlap in terms of the signal recorded at each electrode, making it difficult to identify spatially distinct effects that occur in the same time-window. Given the properties of the ERP data, the signal recorded at one electrode will be intrinsically proportional to the signal recorded at another electrode.

The variation in performance scores evident across participants suggests that people are doing something different from each other when completing the same task. It is not clear whether these differences are principally manifested at the encoding stage or retrieval stage of the task, nor whether they reflect differences in strategy, attention, or engagement of recognition processes. The absence of a significant modulation of the 500-800ms left-parietal effect by performance suggests that this difference may be unrelated to the processes of recollection; furthermore the absence of a significant 300-500ms bilateral-frontal difference also suggests that the performance differences are not related to variation in the engagement of familiarity. Variation in the magnitude of the 200-900ms left frontocentral effect suggests that perhaps differences in 'retrieval effort' processes may relate to performance differences. However, the limited influence of decision bias (in both the group and the individual analysis) suggests that the left frontocentral effect is not related to differences in response criterion (as suggested by Rugg et al., 2000). Nor does the difference appear to relate to differences in working

memory ability, as measured by the Spatial Working Memory test from the CANTAB (as suggested by Ranganath and Paller, 1999).

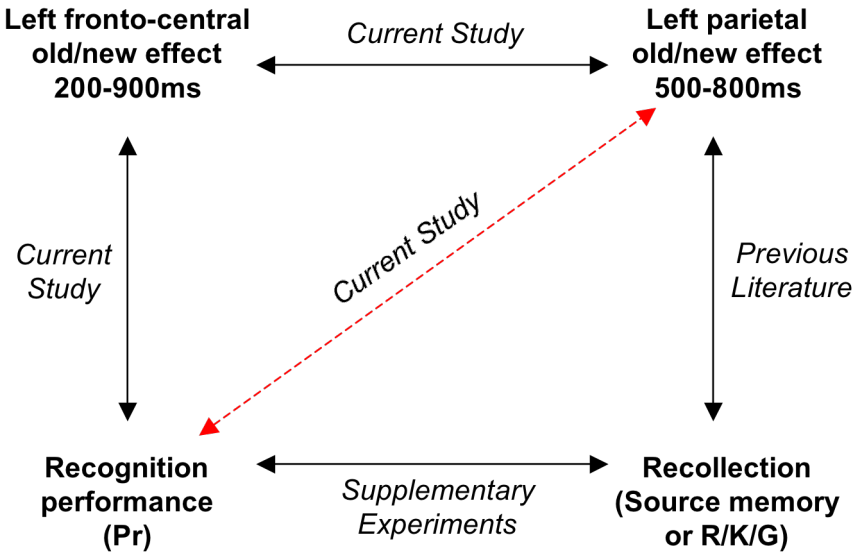


Figure 7.23 Summary of current findings and understanding of the relationship between the left-parietal old/new effect, the sustained left frontocentral effect, behavioural recognition performance and estimates of recollection. Black arrows represent putative significant relationships, with the red arrow representing an unsubstantiated relationship. The source of each element of information is given in italics.

Finally the lack of significant behavioural differences (in relation to performance accuracy, decision bias, proportion of hits and false alarms, and response times for hits and CRs) in groups of participants with distinct ERP effects (in terms of polarity and distribution) leads to the disconcerting conclusion that perhaps ERP effects cannot be used to infer recognition performance across individuals. Furthermore, the lack of a significant correlation between left-parietal effect magnitude in the word and picture tasks, when a significant correlation for performance on the two tasks was found, suggests that ERP effect magnitude (at least for the left-parietal effect and left frontocentral effect[19]), cannot even be used to infer recognition performance across tasks for the same individual. Therefore whilst these ERP effects may provide a good

[19] Comparison of the magnitude of the left frontocentral old/new effect between 200-900ms in the word and picture task did not result in a significant correlation [r=0.094, p=0.302].

indicator of memory processes such as recollection and familiarity, as clearly demonstrated in the literature, the data presented here strongly suggests that ERP old/new effects cannot be used as a biomarker of memory performance either across individuals or within an individual across tasks.

Chapter 8
Genetic Analysis: Words and Pictures

The previous chapter discussed the relationship between recognition memory performance and ERP old/new effects, finding that the magnitude of the typical left-parietal old/new effect did not correlate with recognition memory performance. Furthermore analysis of three groups showing different topographic distributions in the word task were found to have the same behavioural scores in relation to performance accuracy, decision bias and response times. These findings raise the question of what is driving these distributional differences, given that the distributional differences do not relate directly to behaviour?

It is widely accepted that individual differences influence electrophysiological measures, with ERP research typically controlling the study population to make the sample as homogenous as possible. For example, it is common practice to only include right-handed individuals in the study (to reduce confounds of brain laterality) and to report both the number of males and females in the study and the age of participants (to make the composition of the sample clear). The contribution of individual differences to neural activity are therefore acknowledged in ERP research, although there are many individual differences that are yet to be understood.

ERPs are essentially a measure of a biological response to a set of stimuli, and as outlined in Chapter 3 biological variations such as sex have been found to contribute to ERP measures of episodic memory. Furthermore, there is strong evidence to suggest that genetic makeup can influence both behavioural outcome and brain activity in relation to memory, although there do not appear to be any studies looking at genetic

polymorphisms and ERP correlates of episodic memory[20]. Having examined the neural correlates of recognition memory from a behavioural angle in the previous chapter, the current chapter will examine these neural correlates, and behavioural measures, from a biological angle, focusing on a number of Single Nucleotide Polymorphisms (SNPs) that have been shown to influence memory retrieval (Chapter 3).

A summary of the main literature findings presented in Chapter 3, in relation to APOE, BDNF, COMT and KIBRA, will firstly be given, as well as a discussion of the findings expected in the current study. Three additional SNPs (ADCY8, PRKACG and PRKCA) will then be introduced, and the expected outcomes discussed. The results from the analysis of these genetic polymorphisms will be presented for both the word and picture recognition tasks, concluding with a discussion of the findings: what the findings suggest, how previous findings may be interpreted in light of the current results, and the implications for future investigations of the ERP neural correlates of recognition memory.

8.1 Introduction

Chapter 3 outlined the literature on APOE, BDNF, KIBRA and COMT genetic polymorphisms, in relation to both healthy memory and memory disorders. A study by de Quervain and Papassotiropoulos (2006) also identified additional genes as being highly associated with episodic memory and MTL activation, including ADYC8, PRKACG and PRKCA. These seven genes will be the focus of the current chapter,

[20] Whilst there don't appear to be any studies looking at genetic polymorphisms and ERP correlates of recognition memory, a number of studies have shown associations between ERP effects and genes, particularly in relation to the P300/P3 component relating to rare target identification or novelty detection. These include the DRD2 SNP (Noble, Berman, Ozkargoz & Ritchie, 1994; Hill et al., 1998), the CNRI polymorphisms (Johnson et al., 1997), and ABCB1 (rs1128503), ABCB1 (rs1045642), ADRA2A (rs1800545), ADRA2A (rs521674), APOE (rs7412), APOE (rs429358), MDH1 (rs2278718), PIK3C3 (rs3813065), PRK3C3 (rs4121817), TH (rs6578993), TH (rs3842726) polymorphisms (Liu et al., 2009).

investigating the relationship between the different polymorphisms and the ERP effects identified in Chapter 5. Details of the specific polymorphisms relating to SNP reference numbers, assay identifiers, and SNP locations are presented in Table 8.1. As with the performance analysis chapter (Chapter 7) the focus of the genetic analysis will be on the word and picture recognition tasks, due to the large number of participants successfully able to complete the task and the wide range of performance scores. Below each of the candidate SNPs is introduced, briefly highlighting their potential role in memory, and predictions that can be formed on the basis of current findings.

As discussed in Chapter 3 polymorphisms of the APOE gene have been strongly linked to Alzheimer's Disease, with carriers of the ε4 allele more predisposed to the disease than ε3 and ε2 carriers. There is also evidence suggesting that the ε2 allele may act as a protective factor against episodic memory decline and Alzheimer's Disease. In relation to cognitively healthy participants the literature provides contradictory evidence in terms of the effect of the APOE ε4 allele on brain activity, as measured using fMRI. Some studies find increases in activity for ε4 carriers compared to non-ε4 carriers, whilst others show no difference and some a decrease in activity. In addition to the directionality of the change in activity across ε4 carriers and non-carriers, the location of these activity changes also vary across studies (see Trachtenberg, Filippini & Mackay, in press, for a review). Furthermore, few studies compare ε2 and ε3 carriers with the majority of studies restricting analysis to ε4 carriers and non-ε4 carriers, making it difficult to formulate solid predictions regarding the differences in the pattern of ERP activity for APOE genotypes, particularly for ε2 carriers. However, previous research does clearly suggest that in young adults APOE ε4 carriers will perform better on memory tasks than ε2 or ε3 carriers, and consequently it is expected that there will be evidence of some ERP differences between genotypes. One hypothesis being that

old/new effect magnitude over left frontocentral electrodes will be greater for ε4 carriers to reflect performance differences, as indicated in Chapter 7.

The second gene discussed in Chapter 3 relates to a polymorphism of the BDNF gene, which affects the precursor peptide of the BDNF protein. BDNF is important in the modulation of synaptic changes and is involved in hippocampal long-term potentiation. As discussed in Chapter 3, the BDNF polymorphism has been shown to affect episodic memory and hippocampal functioning with met or 'A' allele carriers having poorer memory performance, diminished hippocampal engagement, and reduced hippocampal formation volume compared to val or 'G' allele carriers. It is therefore expected that in the current study task performance will be poorer for A allele carriers than G carriers, as evident in previous literature. In addition, due to the involvement of the hippocampus in recollection, it is also hypothesised that the magnitude of the left-parietal old/new effect will be reduced for A allele carriers compared to G allele carriers, on the assumption that the magnitude of the left-parietal effect reflects engagement of recollection, a process believed to be dependent on the hippocampus (for a discussion of the role of MTL structures in recognition memory see Voss & Paller, 2010).

The third polymorphism, COMT, results in changes in the level of COMT enzyme in the brain with val or 'G' allele carriers exhibiting greater COMT activity and subsequently catabolizing neurotransmitters such as dopamine faster than met or 'A' allele carriers. Genotypic performance differences have been found in relation to episodic recall, and in some studies recognition, with better performance for A allele carriers. However, other studies show no performance differences, but do show increased activation of the prefrontal cortex during encoding and retrieval for G allele carriers, and reduced hippocampal activity. Behavioural performance differences are

therefore also expected in the current study, with A carriers predicted to perform better than G carriers. In relation to the ERP effects, one hypothesis is that G allele carriers may show a reduction in the magnitude of the left-parietal effect, reflecting a reduction in hippocampal engagement, although the likely influence of genotype on ERP effects are unclear.

The final gene discussed in Chapter 3 is KIBRA, or WCCI. As with the other genes discussed, the literature on the KIBRA polymorphism is contradictory, with several studies reporting an association between the polymorphism and episodic memory, and others not able to replicate this finding. In general, studies in which an association has been found, show better memory performance for T allele carriers compared to C carriers. In addition an fMRI study found increased activation of the frontal cortex, medial frontal gyrus and parietal cortex for C/C carriers compared to T carriers with matched behavioural performance, indicating greater activation of these regions by C/C carriers to achieve the same level of performance (Papassotiropoulos et al., 2006). Therefore, behaviourally, it is hypothesised that in the current study T carriers will perform better than C/C carriers. The influence of KIBRA genotype on ERP activity is however unclear, as there are few neuroimaging studies looking at the influence of KIBRA on memory related activity. On the basis of the fMRI data available (Papassotiropoulos et al., 2006) it is not possible to infer how the ERP effects may change. However, since differences in brain activity were found in the study by Papassotiropoulos et al. (2006), it is hypothesised that the ERP effects will differ in some way.

Another SNP that may be important for memory is ADCY8 (de Quervain & Papassotiropoulos, 2006). Adenylate cyclase type 8 is an enzyme, coded for by the

ADCY8 gene, which is involved in the cyclic-adenosine monophosphate (cAMP) pathway. The ADCY enzyme catalyses cAMP from adenosine triphosphate (ATP), activating cAMP-dependent protein kinase A (PKA), an enzyme that enhances neurotransmitter release through the phosphorylation of potassium channels. Potassium channel phosphorylation decreases the potassium current, prolonging the action potential and increasing the influx of ions such as calcium, triggering the release of neurotransmitters, initiating a postsynaptic potential (Kandel, 2000). Calcium stimulated ADCY has been shown to be essential for late phase long-term potentiation (L-LTP) and long-term memory (LTM). ADCY types 1 and 8 are the only types of adenylate cyclases known to be stimulated by calcium (Wong et al., 1999), suggesting that ADCY8 genetic polymorphisms may be important for memory.

The exact affect of the ADCY8 SNP (rs263249) on ADCY8 is currently unclear, however a study by de Quervain and Papassotiropoulos (2006) identified seven SNPs (GRIN2A, GRIN2B, GRM3, ADCY8, PRKACG, CAMK2G and PRKCA) associated with episodic memory performance, including ADCY8 SNP rs263249, which showed the greatest contribution to the genetic cluster. An 'Individual Memory-Related Genetic Score' (IMAGS) was calculated based on the number of memory associated genetic variations each participant had, weighted by each SNPs effect size. A follow-up fMRI study with 32 new (performance matched) participants revealed a significant positive correlation between IMAGS and brain activation in the MTLs during learning of face-profession associations. This study suggests that the ADCY8 SNP may influence episodic memory performance and encoding brain activity, however the directionality of these differences in relation to individual ADCY8 genotypes is not reported. In contrast, a study by Jablensky et al. (2011) looking at normal memory in 172 control participants and memory impairment in 336 participants with schizophrenia, failed to

find significant differences in memory performance across ADCY8 genotype for either sample. It is therefore difficult to make predictions about the directionality of either behavioural or ERP effects across ADCY8 genotypes, on the basis of previous literature. Nonetheless, the study by de Quervain and Papassotiropoulos (2006) does clearly suggest potential variation in memory and brain activity as a function of the ADCY8 SNP.

In addition to the ADCY8 SNP, de Quervain and Papassotiropoulos (2006) also identified the PRKACG SNP (rs3730386) as being highly associated with memory performance. The PRKACG gene codes for the enzyme cAMP-dependent protein kinase catalytic subunit gamma, an isoform of catalytic PKA (cPKA). cPKA has been found to be expressed in the hippocampus (Liu, Tang, Liu & Tang, 2010), although specific information relating to expression of the gamma isoform in the brain is not currently available. As discussed above, PKA plays an important part in the cAMP pathway and L-LTP, and has also been associated with the regulation of beta amyloid secretion. Silencing of the PRKACG gene increases the levels of amyloid precursor protein, which degrades to beta amyloid - the main component of amyloid plaques (Adachi, Kano, Saido & Murate, 2009), suggesting a possible role in AD.

In relation to memory performance the PRKACG SNP has been associated with delayed (20 minutes) free recall in patients with schizophrenia who show cognitive deficits, with homozygous C carriers performing better than G allele carriers. No such association was found for controls (Jablensky et al., 2011). The study by de Quervain and Papassotiropoulos (2006) suggests that this SNP may play an important role in episodic memory in healthy populations, and whilst no effect of PRKACG genotype was found

for controls in the Jablensky et al. (2011) study, the findings from the patient group suggests that C allele carriers would perform better than G carriers[21].

The final SNP identified by de Quervain and Papassotiropoulos (2006) that will be included in the current study is PRKCA (rs8074995). Protein Kinase C alpha (PRKCA) is an enzyme involved in cell signalling that is activated by calcium. PKC is thought to be important in learning and memory through its role in synaptic plasticity (see Nogues, 1997, for a discussion of the role of PKC in memory). Jablensky et al. (2011) found significant associations between PRKCA genotype and immediate recall in controls and patients with schizophrenia who showed evidence of cognitive decline. Interestingly, however, the two groups showed opposite patterns of effect, with homozygous G carriers performing better than homozygous A carriers for controls, and the reverse for the patients group, with homozygous A carriers performing better than homozygous G carriers. Based on the data from the control participants in the Jablensky et al. (2011) study it is expected that in the current study G allele carriers will perform better than A carriers. With evidence associating ADCY8, PRKACG and PRKCA polymorphisms with memory performance, it is also hypothesised that there will be genotypic ERP differences, however the specific details of these ERP differences (in relation to direction and distribution) are not clear from previous literature.

In sum, comparisons of behavioural and ERP memory effects will be made for the words and picture tasks, across genetic polymorphisms of APOE, BDNF, COMT, KIBRA, ADCY8, PRKACG and PRKCA. Details relating to the genotyping process and the genetic composition of the study sample will be presented in the following

[21] The absence of a significant genotype effect for controls, and for immediate recall in patients with schizophrenia, may reflect the insensitivity of the task to identify genotypic differences in the control sample, with only the most difficult part of the task, in participants who show some cognitive deficit, revealing genotypic differences.

methods section. Analysis of the word and picture data will then be presented, and the chapter will conclude with a discussion of the results in relation to the current ERP memory literature.

8.2 Methods

8.2.1 Genotyping

As discussed in the General Methods (Chapter 4) DNA was collected in the form of saliva samples using Oragene OG-100 DNA collection vials (DNA Genotek Inc: www.dnagenotek.com), which were processed at the Welcome Trust Clinical Research Facility, Edinburgh (WTRCF Edinburgh: www.wtcrf.ed.ac.uk), genotyping eight SNPs, outlined in Table 8.1, with Applied Biosystems Taqman SNP assays. The overall success of the genotyping process is given in Table 8.2, showing a high call rate and low false call rate. The observed genotypic frequencies were as follows: ADCY8 A/G = 0.53, A/A = 0.12, G/G = 0.24, undetermined = 0.01; APOE_1 C/T = 0.26, C/C = 0.71, T/T = 0, undetermined = 0.02; APOE_2 C/T = 0.24, C/C = 0.04, T/T = 0.72, undetermined = 0; BDNF A/G = 0.33, A/A = 0.01, G/G = 0.66[22], undetermined = 0.01; COMT A/G = 0.50, A/A = 0.30, G/G = 0.20, undetermined = 0; PRKACG C/G = 0.34, C/C = 0.62, G/G = 0.03[22], undetermined = 0.01, PRKCA A/G = 0.26, A/A = 0.04, G/G = 0.67, undetermined = 0.02; KIBRA C/T = 0.45, C/C = 0.43, T/T = 0.08, undetermined = 0.05. The study sample reflected the genotype distributions expected in a normal population for ADCY8, APOE_2, COMT, PRKACG, PRKCA and KIBRA genotypes, however the distribution of the observed genotypes for APOE-1 and BDNF were not in

[22] Genotypes for BDNF and PRKACG are presented as reverse strands, with the remaining SNPs presented as forward strands, consistent with the format presented by NCBI (www.ncbi.nlm.nih.gov/projects/SNP).

Hardy-Weinberg equilibrium, suggesting that the genotype distribution in the current study differs from those expected in the normal population (Table 8.2).

In addition to looking at the individual SNPs outlined above, analysis of a combination of APOE_1 and APOE_2 will also be conducted. As discussed in Chapter 3, the APOE gene is polymorphic with three main alleles (ε2, ε3 and ε4), differing in composition by the combination of APOE_1 (rs7412) and APOE_2 (rs429358) alleles. The observed genotype frequencies for APOE were as follows: ε2/ε2 = 0, ε2/ε3 = 0.22, ε3/ε3 = 0.50, ε3/ε4 = 0.18, ε4/ε4 = 0.04, undetermined = 0.07. Due to the low numbers of homozygous ε4 carriers and absence of homozygous ε2 carriers it was decided to collapse the homozygous ε4 carriers into a group with the ε3/ε4 carriers, thereby focusing analysis on three main groups ε2 carriers (ε2/ε3), homozygous ε3 carriers (ε3/ε3), and ε4 carriers (ε3/ε4 + ε4/ε4) with a frequency of 0.22, 0.50 and 0.22 respectively.

Gene	ADCY8	APOE_1	APOE_2	BDNF	COMT	PRKACG	PRKCA	WWC1 (KIBRA)
dbSNP	rs263249	rs7412	rs429358	rs6265	rs4680	rs3730386	rs8074995	rs17070145
ABI Assay ID	C_1548078	C_904973	C_3084793	C_11592758	C_25746809	C_1463138	C_11612258	C_33286269
SNP location	8q24.22a	19q13.32a	19q13.32a	11p14.1d	22q11.21-q11.23	9q21.11a	17q24.2a	5q35.1a

Table 8.1 Candidate genes investigated in the current chapter. Abbreviated gene names are given along side dbSNP reference number (www.ncbi.nlm.nih.gov/projects/SNP), Applied Biosystems assay identifier (www.appliedbiosystems.com), and the location of each SNP.

Gene	ADCY8	APOE_1	APOE_2	BDNF	COMT	PRKACG	PRKCA	WWC1 (KIBRA)
Total number of samples	129	129	129	129	129	129	129	129
Call rate	99.2%	97.7%	100.0%	99.2%	100.0%	99.2%	97.7%	95.3%
Number of control samples	63	63	63	63	63	63	63	63
False call rate	1.6%	0.0%	0.0%	0.0%	0.0%	1.6%	0.0%	4.8%
Hardy-Weinberg equilibrium	χ^2=1.72, p=0.19	χ^2=3.06, p=0.08	χ^2=1.32, p=0.25	χ^2=2.98, p=0.08	χ^2=0, p=0.98	χ^2=0.49, p=0.48	χ^2=0.51, p=0.47	χ^2=0.97, p=0.32

Table 8.2 Results of the genotyping process for each gene. Table shows the number of samples tested, the success rate, the number of control samples tested, the false call rate, and the Hardy-Weinberg equilibrium for each gene.

8.2.2 Sample

The same inclusion criteria used in previous chapters was applied to the current analysis, including a performance criterion of $Pr \geq 0.2$ on both the word and picture tasks. In addition, as outlined in the General Methods chapter, participants identified as potentially being affected by any of the conditions included in the PDSQ, were also excluded from the analysis. Therefore, 84 participants met the inclusion criteria and were included in the genetic analysis. The number of participants with each genotype and the associated frequency is presented in Table 8.3, along with a breakdown of sex, ethnicity and familial history of Alzheimer's Disease (AD) for each genotype. Comparisons of sex and familial history of AD across genotypes included in the analysis was conducted to determine if the basic composition of each genotype group differed (Table 8.4). Due to the small sample sizes in some of the conditions Fisher's Exact probability is reported, indicating a relationship between sex and PRKACG genotype, with a larger proportion of the C/T sample constituting males than the homozygous C sample. Similarly a relationship between sex and PRKCA was also found with more males in the A/G group than the homozygous G group. No significant relationship between genotype and familial history of AD were found for any SNPs.

Descriptives	Genotype	No. of participants	No. of Males	Ethnicity: White	Ethnicity: Other	Familial history of AD.
ADCY8	A/G	40 (0.48)	12 (0.30)	39 (0.98)	White-Asian:1	5 (0.13)
	A/A	11 (0.13)	6 (0.55)	10 (0.91)	White-Asian:1	2 (0.18)
	G/G	32 (0.38)	11 (0.34)	31 (0.97)	White-Black African:1	6 (0.19)
APOE_1	C/T	23 (0.27)	6 (0.26)	21 (0.91)	White-Asian =1 White-Black African:1	2 (0.09)
	C/C	59 (0.70)	22 (0.37)	58 (0.98)	White-Asian: 1	10 (0.17)
	T/T	0 (0)	0 (0)	0 (0)	0	0 (0)
APOE_2	C/T	21 (0.25)	6 (0.29)	21 (1)	0	3 (0.14)
	C/C	3 (0.04)	2 (0.67)	3 (1)	0	1 (0.33)
	T/T	60 (0.71)	21 (0.35)	57 (0.95)	White-Asian: 2 White-Black African: 1	9 (0.15)
BDNF	A/G	28 (0.33)	9 (0.32)	25 (0.89)	White-Asian: 2 White-Black African: 1	4 (0.14)
	A/A	1 (0.01)	1 (1)	1 (1)	0	1 (1)
	G/G	55 (0.65)	19 (0.35)	55 (1)	0	8 (0.15)
COMT	A/G	42 (0.50)	16 (0.38)	41 (0.98)	White-Asian: 1	6 (0.14)
	A/A	23 (0.27)	6 (0.26)	22 (0.96)	White-Asian: 1	4 (0.17)
	G/G	19 (0.23)	7 (0.37)	18 (0.95)	White-Black African: 1	3 (0.16)
PRKACG	C/G	24 (0.29)	14 (0.58)	23 (0.96)	White-Asian: 1	3 (0.13)
	C/C	58 (0.69)	14 (0.24)	56 (0.97)	White-Asian: 1 White-Black African: 1	8 (0.14)
	G/G	2 (0.02)	1 (0.50)	2 (1)	0	2 (1)
PRKCA	A/G	20 (0.24)	11 (0.55)	19 (0.95)	White-Asian: 1	2 (0.10)
	A/A	4 (0.05)	1 (0.25)	3 (0.75)	White-Asian: 1	1 (0.25)
	G/G	58 (0.69)	15 (0.26)	57 (0.98)	White-Black African: 1	9 (0.16)
WWC1 (KIBRA)	C/T	38 (0.45)	14 (0.37)	35 (0.92)	White-Asian: 2 White-Black African: 1	8 (0.21)
	C/C	35 (0.42)	9 (0.26)	35 (1)	0	4 (0.11)
	T/T	7 (0.08)	3 (0.43)	7 (1)	0	0 (0)
APOE	ε2 carriers	19 (0.23)	5 (0.26)	17 (0.89)	White-Asian: 1 White-Black African: 1	2 (0.11)
	ε3/ε3	41 (0.49)	16 (0.39)	40 (0.98)	White-Asian: 1	7 (0.17)
	ε4 carriers	18 (0.21)	6 (0.33)	18 (0.33)	0	3 (0.17)

Table 8.3 Descriptive information of study sample. Table shows the number of participants with each genotype, and a breakdown by sex, ethnicity and familial history of Alzheimer's Disease (AD). Frequencies are presented in brackets.

Words	Genotype	Sex % Male	Familial history of AD % Yes
ADCY8	A/G v. G/G	30:34, p=0.801	13:19, p=0.522
APOE_1	C/T v. C/C	26:37, p=0.440	9:17, p=0.494
APOE_2	C/T v. T/T	29:35, p=0.789	14:15, p=1.000
BDNF	A/G v. G/G	32: 35, p=1.000	14:15, p=1.000
COMT	A/A v. A/G	26:38, p=0.416	17:14, p=0.733
	A/A v. G/G	26:37, p=0.516	17:16, p=1.000
	A/G v. G/G	38:37, p=1.000	14:16, p=1.000
PRKACG	C/G v. C/C	58:24, p=0.005	13:14, p=1.00
PRKCA	A/G v. G/G	55:26, p=0.027	10:16, p=0.719
WWC1 (KIBRA)	C/T v. C/C	37:26, p=0.327	21:11, p=0.350
APOE	ε2 carriers v. ε3/ε3	26:39, p=0.395	11:17, p=0.407
	ε2 carriers v. ε4 carriers	26:33, p=0.728	11:17, p=0.660
	ε3/ε3 v. ε4 carriers	39:33, p=0.775	17:17, p=1.000

Table 8.4 Genotypes analysed for each genetic polymorphism, and comparisons of the proportion of males and the proportion of participants with a familial history of Alzheimer's Disease across genotypes. Percentages are presented as phenotype ratios, and Fisher's Exact probability is reported for each polymorphism.

8.2.3 Analysis

Analysis of ADCY8, APOE_1, APOE_2, BDNF, PRKACG, PRKCA and KIBRA genetic polymorphisms were conducted on the two most common variants, with an insufficient number of participants exhibiting the rarest variants to be included in the analysis. All three polymorphisms for COMT were analysed, and as discussed above analysis of the APOE haplotype focused on three main groups, ε2 carriers, homozygous ε3 carriers, and ε4 carriers (analysed genotypes are listed in Table 8.4). The number of participants contributing to the different genotype groups ranged from 18-60, with an average of 36 participants (s.d. 15).

Comparisons of behavioural measures across genotypes were made using independent t-tests, looking at discrimination accuracy, response bias, percentage of hit and false

alarm responses, and hit and CR response times. ERP comparisons of old/new effects (Hits-CRs) across genotypes in the 300-500ms and 500-800ms time-windows were conducted using within participant factors of location (frontal/frontocentral/central/centroparietal/parietal), hemisphere (left/right), and electrode site (inferior/medial/superior), and a between participant factor of genotype (i.e. ADCY8 A/G v. ADCY8 G/G).

8.3 Results

8.3.1 Words

8.3.1.1 Behavioural Results

The behavioural results for each genotype are presented in Table 8.5. All groups performed above chance, as indexed by mean discrimination accuracy (*Pr*) scores (Table 8.6). Independent samples t-tests revealed no significant differences in discrimination accuracy scores between genotypes for most genes, with the exception of KIBRA [t(71)=-2.15, p=0.035], which showed significantly higher Pr for homozygous C allele carriers (*Pr* = 0.58) than C/T carriers (*Pr*=0.50). Similarly response bias scores generally did not differ between genotypes, with the exception of COMT where a one-way ANOVA revealed a significant difference between the three genotypes for response bias [F(2,81)=4.18, p=0.019]. Additional analysis of COMT genotypes revealed significant differences between homozygous A carriers and A/G carriers [t(63)=2.74, p=0.008], and between homozygous A and homozygous G carriers [t(40)=-2.22, p=0.032], reflecting the more conservative bias for the homozygous A carriers than either of the other genotypes. No significant response bias differences between A/G and G were found. Overall, all groups exhibited a conservative response bias.

Words	Genotype	Hit rate (%)	False alarm rate (%)	Pr	Br	Hit RT (ms)	CR RT (ms)
ADCY8	A/G	**76 (12)**	17 (13)	0.57 (0.19)	0.41 (0.18)	798 (121)	882 (151)
	G/G	**70 (9)**	18 (9)	0.52 (0.14)	0.37 (0.13)	833 (138)	893 (144)
APOE_1	C/T	73 (8)	21 (11)	0.51 (0.11)	0.43 (0.15)	811 (129)	885 (136)
	C/C	72 (13)	16 (11)	0.55 (0.18)	0.37 (0.17)	827 (141)	893 (153)
APOE_2	C/T	72 (14)	22 (11)	0.49 (0.19)	0.44 (0.14)	831 (170)	905 (194)
	T/T	73 (11)	16 (11)	0.55 (0.16)	0.37 (0.17)	822 (130)	890 (138)
BDNF	A/G	72 (13)	19 (12)	0.52 (0.17)	0.41 (0.17)	829 (126)	902 (122)
	G/G	73 (11)	17 (11)	0.54 (0.17)	0.38 (0.16)	824 (146)	899 (169)
COMT	A/G	**75 (11)**	20 (12)	0.54 (0.17)	**0.42 (0.17)**	821 (149)	901 (172)
	A/A	**67 (11)**	15 (9)	0.51 (0.15)	**0.31 (0.15)**	822 (112)	902 (140)
	G/G	**74 (13)**	17 (10)	0.56 (0.19)	**0.41 (0.14)**	838 (146)	887 (132)
PRKACG	C/G	74 (12)	17 (12)	0.55 (0.18)	0.39 (0.15)	805 (122)	858 (96)
	C/C	72 (11)	18 (11)	0.53 (0.16)	0.38 (0.17)	835 (146)	918 (171)
PRKCA	A/G	73 (11)	18 (13)	0.54 (0.18)	0.38 (0.17)	851 (202)	907 (203)
	G/G	72 (11)	18 (11)	0.53 (0.16)	0.38 (0.16)	811 (109)	891 (136)
WWC1 (KIBRA)	C/T	71 (11)	20 (11)	**0.50 (0.15)**	0.40 (0.16)	804 (141)	882 (162)
	C/C	74 (11)	15 (10)	**0.58 (0.15)**	0.36 (0.17)	819 (118)	888 (126)
APOE	ε2 carriers	72 (8)	**20 (11)**	0.51 (0.11)	0.41 (0.15)	823 (130)	891 (123)
	ε3/ε3	73 (12)	**15 (11)**	0.57 (0.17)	0.35 (0.17)	821 (132)	889 (146)
	ε4 carriers	72 (15)	**19 (12)**	0.52 (0.20)	0.39 (0.15)	839 (164)	903 (171)

Table 8.5 Behavioural results from the word recognition task for each genotype. Table shows mean hit and false alarm rates in percentages, mean discrimination accuracy, mean decision bias, and mean response times for hit and CR responses in milliseconds. Standard deviations for each measure are given in brackets. Significant differences between genotypes are highlighted in yellow.

Significant differences in hit rate were also observed between COMT homozygous A carriers and A/G carriers [t(63)=2.57, p=0.012], reflecting the higher hit rate for A/G carriers. Similarly a significant difference in hit rate was found for ADCY8 [t(70)=2.25, p=0.028] with A/G carriers obtaining a higher hit rate than homozygous G carriers. Finally, ANOVA revealed a significant difference in false alarm rate between APOE genotypes [F(3,80)=2.95, p=0.037], however examination of the differences between each genotypic group revealed no significant differences (ε2 v. ε3 [t(58)=1.65, p=0.104], ε2 v. ε4 [t(35)=0.381, p=0.705], ε3 v. ε4 [t(57)=-1.139, p=0.259]), suggesting

that the differences between each group were not great enough to reach significance at this level. No significant differences in reaction times for either hits or CRs were found for any genetic polymorphism.

Words	Genotype	Pr > 0
ADCY8	A/G	t(39)=19.11, p<0.001
	G/G	t(31)=20.47, p<0.001
APOE_1	C/T	t(22)=21.56, p<0.001
	C/C	t(58)=23.43, p<0.001
APOE_2	C/T	t(20)=11.97, p<0.001
	T/T	t(59)=27.21, p<0.001
BDNF	A/G	t(27)=16.05, p<0.001
	G/G	t(54)=24.22, p<0.001
COMT	A/G	t(41)=20.49, p<0.001
	A/A	t(22)=16.93, p<0.001
	G/G	t(18)=13.02, p<0.001
PRKACG	C/G	t(23)=15.04, p<0.001
	C/C	t(57)=24.46, p<0.001
PRKCA	A/G	t(19)=13.46, p<0.001
	G/G	t(57)=25.84, p<0.001
WWC1 (KIBRA)	C/T	t(37)=21.3, p<0.001
	C/C	t(34)=22.58, p<0.001
APOE	ε2 carriers	t(18)=20.69, p<0.001
	ε3/ε3	t(40)=20.97, p<0.001
	ε4 carriers	t(17)=11.05, p<0.001

Table 8.6 Analysis confirming that all groups had mean discrimination accuracy scores above chance for the word task.

8.3.1.2 ERP Results

Analysis from 300-500ms:

Statistical analysis comparing the ERP old/new difference in the 300-500ms time-window across genotypes revealed significant main effects of genotype for the APOE_1 SNP [F(1,80)=7.6, p=0.007] with the old/new effect for C/C carriers larger than C/T carriers; and for the combined APOE polymorphisms [F(2,75)=5.76, p=0.005] where the size of the old/new effect for ε2 carriers was smaller than both the homozygous ε3

carriers [F(1,58)=8.97, p=0.004], and the ε4 carriers [F(1,35)=11, p=0.002]. No significant interactions with location, hemisphere or site were found for APOE SNPs in the 300-500ms time-window, suggesting that whilst the magnitude of the old/effect differed by APOE genotype, the distribution did not (Figure 8.1 and Figure 8.2).

Significant genotype interactions in the 300-500ms time-window were found for COMT and for PRKACG. A significant genotype by hemisphere interaction [F(1,59)=4.08, p=0.048] was found for COMT when comparing A/G to homozygous G carriers, with the difference between the two genotypes greatest over the right hemisphere. This right hemispheric difference reflects the left hemispheric distribution of the old/new effect for homozygous G carriers, compared to the more bilateral distribution for A/G carriers (Figure 8.3). No significant differences were found when comparing COMT homozygous A carriers to either A/G or homozygous G carriers (Figure 8.4). A significant PRKACG genotype by location by site interaction was also found in the 300-500ms time-window [F(2,187)=3.27, p=0.033], reflecting the more posterior distribution for homozygous C carriers compared to C/G carriers, a difference greatest at superior electrode sites (Figure 8.5 and Figure 8.6). No significant genotypic ERP differences were found for SNPs ADCY8, PRKCA, APOE_2, BDNF, or KIBRA.

Follow-up topographic analysis of COMT and PRKACG genotypes was conducted on data rescaled in line with McCarthy and Wood (1985), using ANOVA with between subjects factor of genotype and within subject factors of location (frontal/frontocentral/central/centroparietal/parietal), hemisphere (left/right) and site (inferior/medial/superior). A significant genotype by hemisphere interaction was found for the COMT A/G v. G/G comparison [F(1,59)=4.18, p=0.045], and a significant genotype by location by site interaction was found for the PRKACG SNP

[F(2,190)=4.45, p=0.009], suggesting that the differences outlined above are not just magnitude differences, but differences in the distribution of the old/new effects, providing evidence of underlying differences in the neural systems supporting memory.

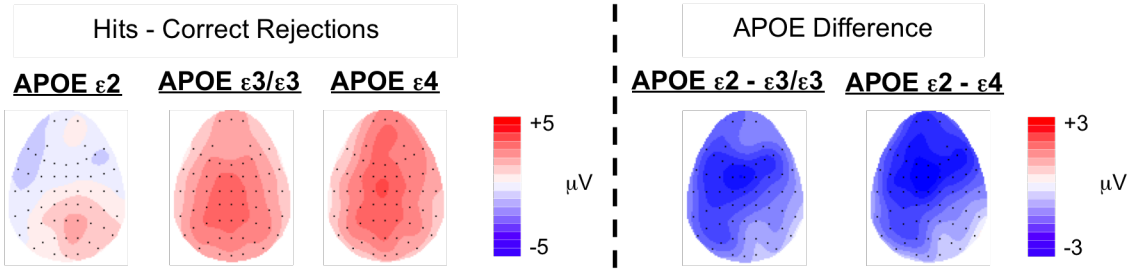


Figure 8.1 Topographic maps showing the distribution of the word old/new differences for APOE ε2, ε3/ε3 and ε4 carriers in the 300-500ms time-window, along with scale bars to show the size of the old/new difference. Maps show the subtraction of the grand average ERP for CRs from the grand average ERP for hits. Genotype difference maps are also given showing the difference in old/new effect distribution between APOE ε2 and ε3/ε3 genotypes, and between ε2 and ε4 genotypes.

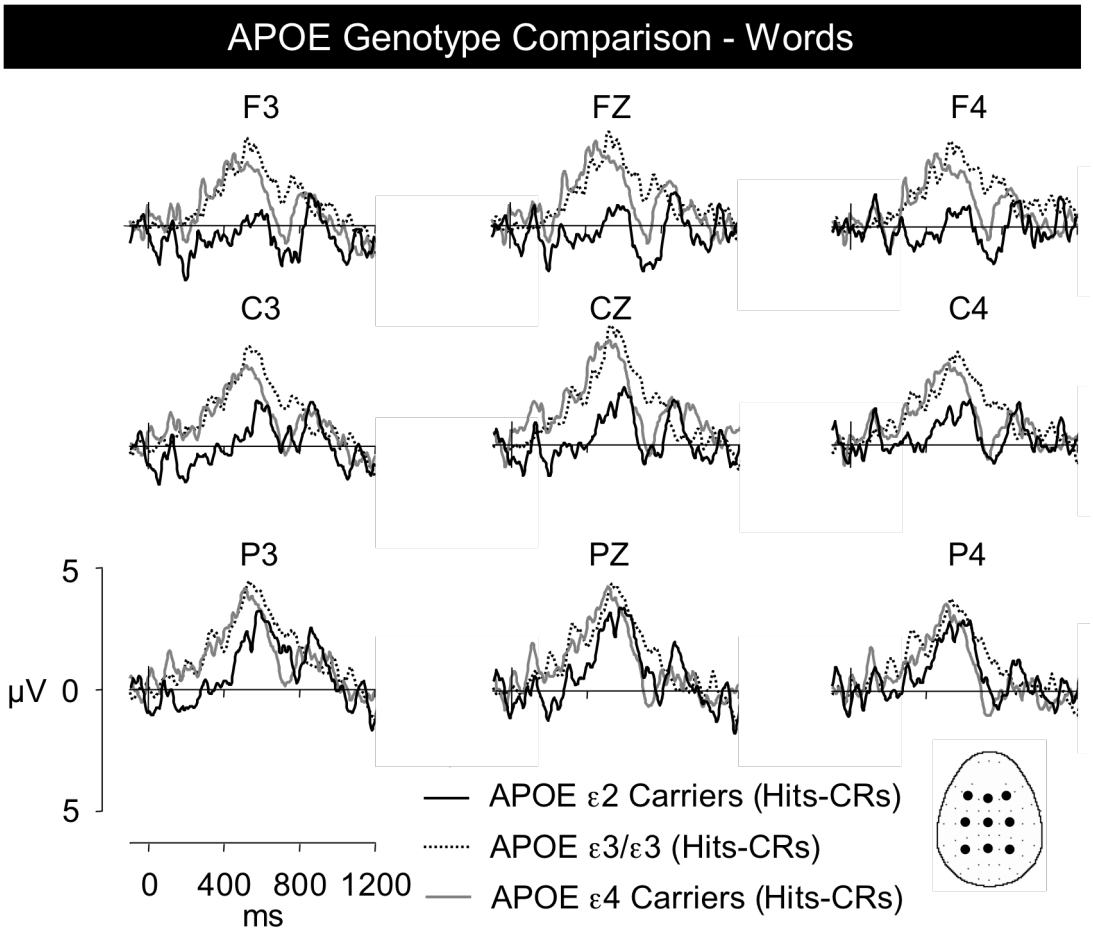


Figure 8.2 Grand average ERP word difference waveforms (Hits-CRs) for APOE ε2 (n=19), ε3/ε3 (n=41) and ε4 carriers (n=18), at representative frontal, central and parietal electrode sites. The vertical scale indicates electrode amplitude, measured in microvolts, whilst the horizontal scale indicates change in time, measured in milliseconds.

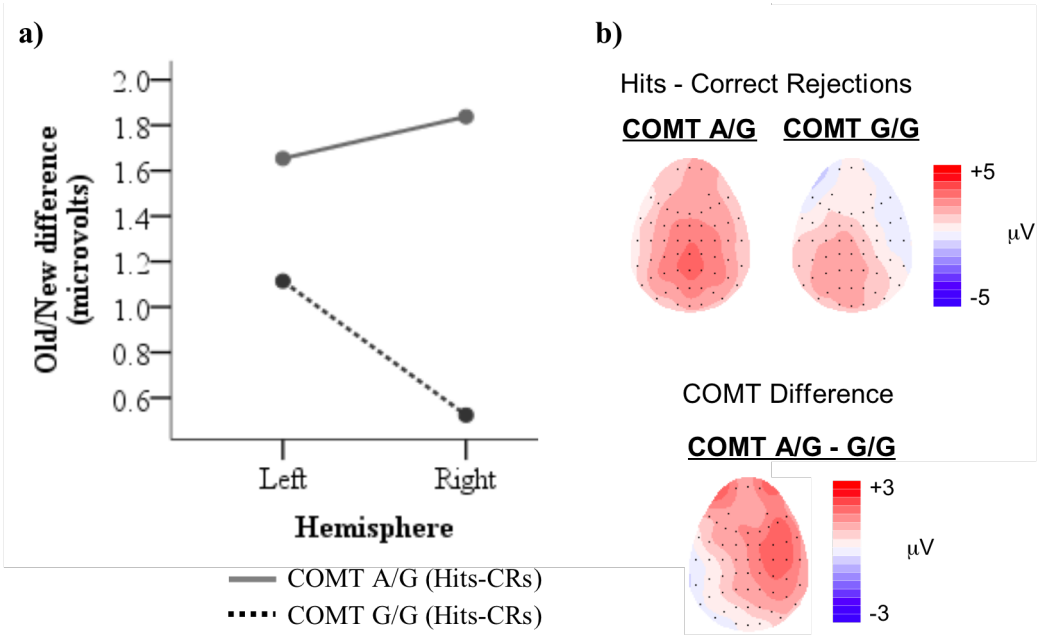


Figure 8.3 a) Plot showing average old/new effect magnitude for COMT A/G and G/G carriers across hemisphere for the 300-500ms time-window. b) Topographic maps showing the distribution of the word old/new differences for COMT A/G and G/G carriers in the 300-500ms time-window, and the difference between genotypes (COMT A/G old/new effect – COMT G/G old/new effect). Data as shown in Figure 8.1.

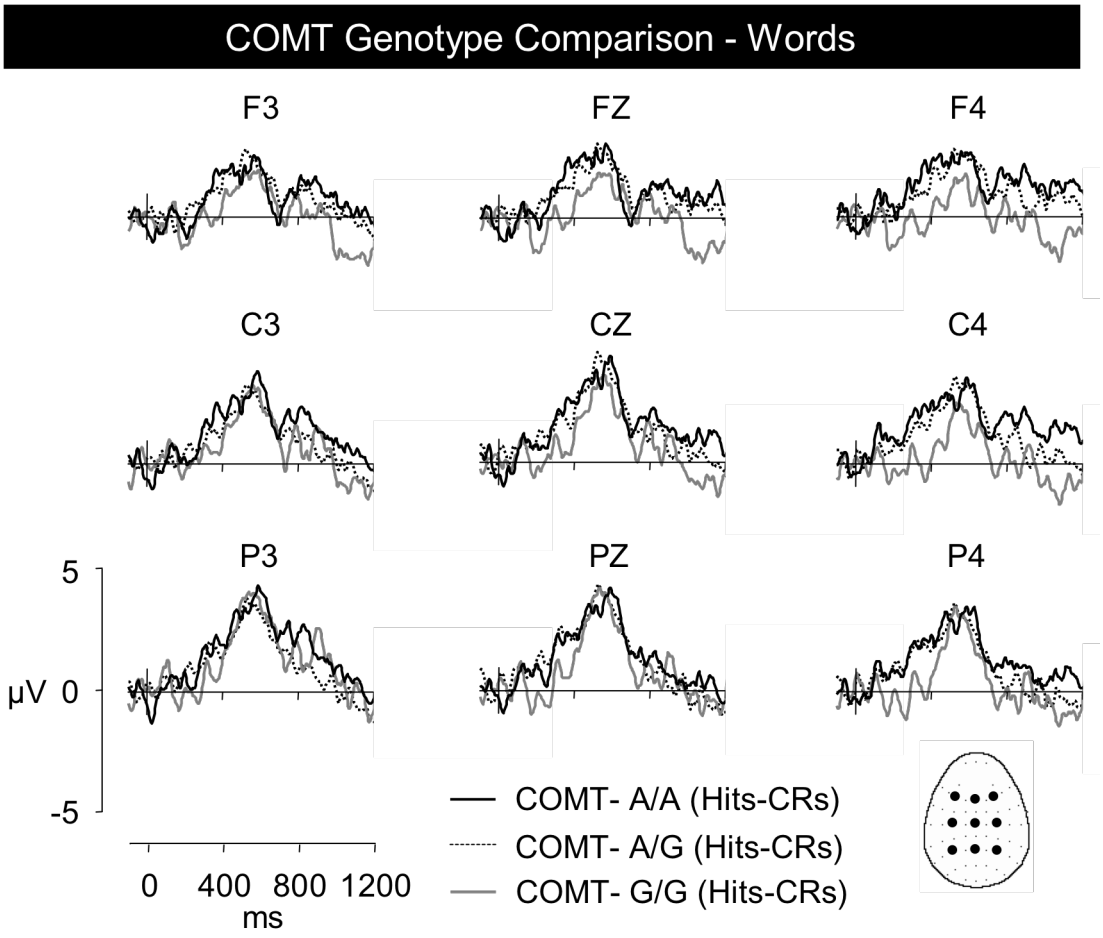


Figure 8.4 Grand average word difference waveforms (Hits-CRs) for COMT homozygous A carriers (n=23), A/G carriers (n=42) and homozygous G carriers (n=19). Data as shown in Figure 8.2.

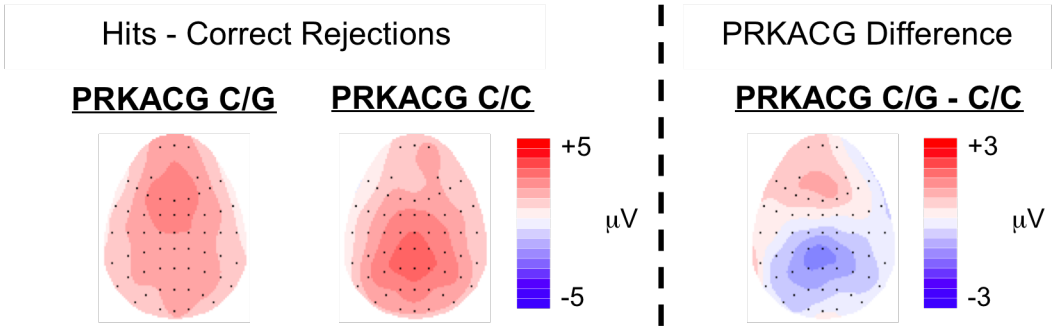


Figure 8.5 Topographic maps showing the distribution of the word old/new differences for PRKACG C/G and C/C carriers in the 300-500ms time-window. A genotype difference map is also given showing the difference in old/new effect distribution between PRKACG C/G and homozygous C genotypes. Data as shown in Figure 8.1.

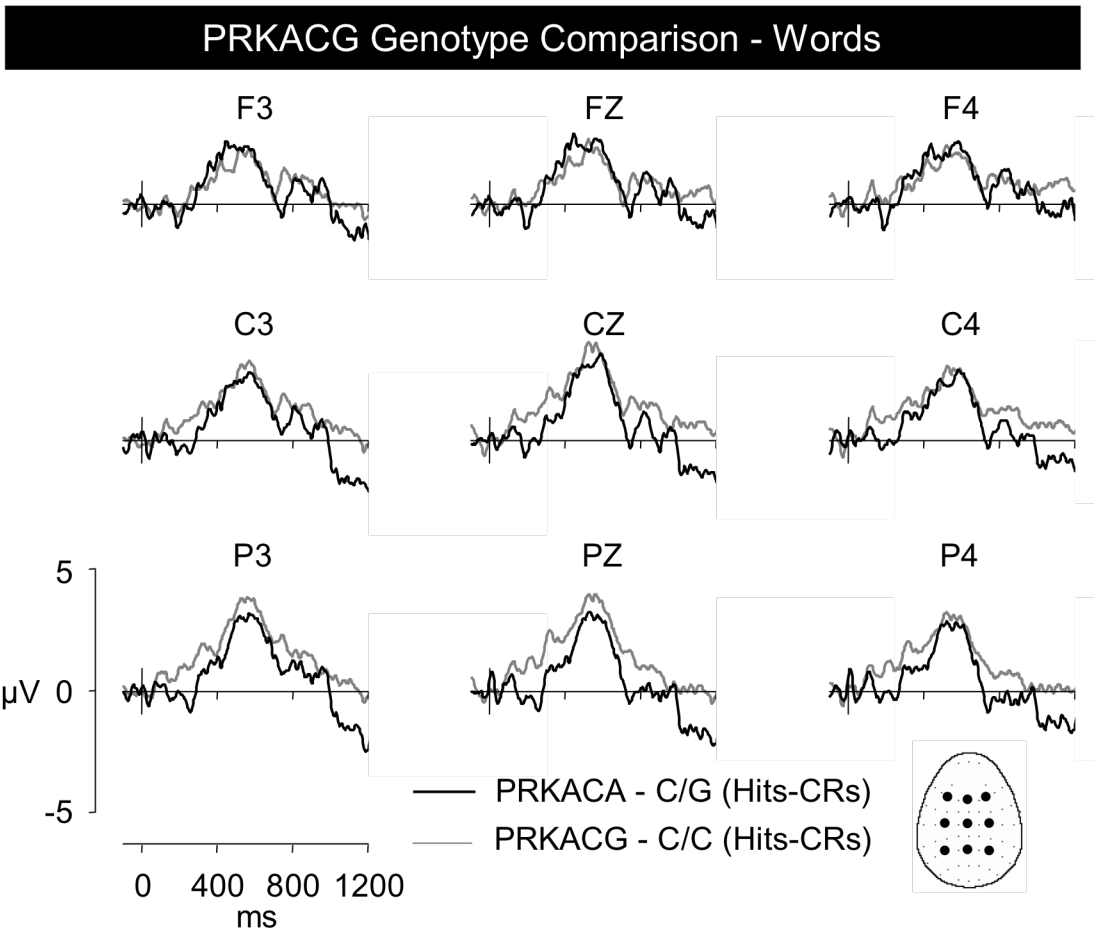


Figure 8.6 Grand average ERP word difference waveforms (Hits-CRs) for PRKACG C/G carriers (n=24) and homozygous C carriers (n=58). Data as shown in Figure 8.2.

Analysis from 500-800ms:

Statistical analysis of the 500-800ms time-window revealed a significant main effect of genotype for the APOE gene [(2,75)=3.7, p=0.029], with the magnitude of the old/new

effect significantly smaller for ε2 carriers compared to homozygous ε3 carriers [F(1,58)=6.68, p=0.011]. As with the 300-500ms time-window no significant interactions with location, hemisphere or site were found for the APOE polymorphisms, suggesting that genotype differences were limited to differences in magnitude and not distribution (Figure 8.7 and Figure 8.2). No main effects of genotype were found for the other SNPs.

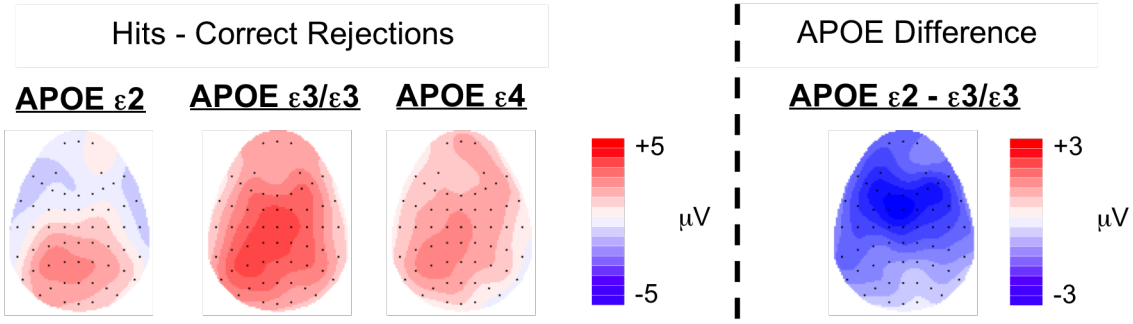


Figure 8.7 Topographic maps showing the distribution of the word old/new differences for APOE ε2, ε3/ε3 and ε4 carriers between 500-800ms. A genotype difference map showing the difference in old/new effect distribution between APOE ε2 and ε4 genotypes is also given. Data as shown in Figure 8.1. ERP waveforms are shown in Figure 8.2.

A significant interaction between PRKACG genotype, location and site was found in the 500-800ms time-window [F(2,192)=3.44, p=0.026], reflecting a greater old/new effect for homozygous C carriers over posterior electrodes than evident for C/G carriers, a difference greatest at superior electrodes (Figure 8.8). In addition, there was a significant interaction between PRKCA genotype and location [F(1,89)=6.10, p=0.012], with A/G carriers exhibiting a more anteriorly distributed old/new effect than homozygous G carriers (Figure 8.9 and Figure 8.10). No significant genotypic ERP differences were found for SNPs ADCY8, APOE_1, APOE_2, BDNF, KIBRA or COMT.

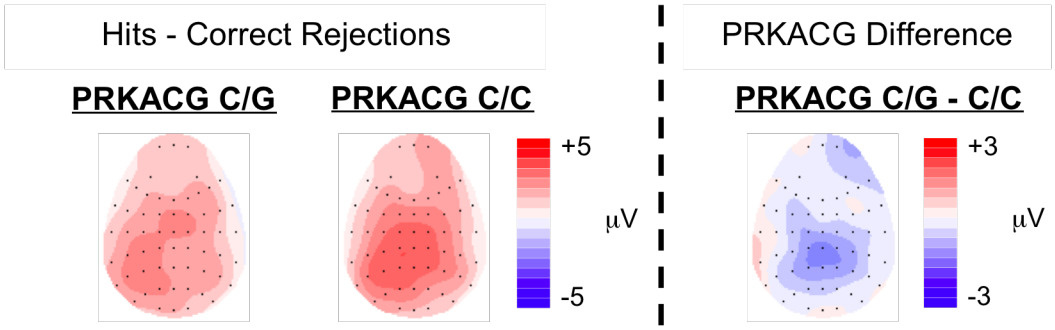


Figure 8.8 Topographic maps showing the distribution of the word old/new differences for PRKACG C/G and C/C carriers in the 500-800ms time-window. A genotype difference map is also given showing the difference in old/new effect distribution between PRKACG C/G and homozygous C genotypes. Data as shown in Figure 8.1. ERP waveforms are shown in Figure 8.6.

Follow-up genotype comparisons using rescaled data indicated that the topographically distinct effects seen for the different PRKACG genotypes and for the PRKCA genotypes do reflect distributional differences and are not simply magnitude differences, with a PRKACG genotype by location by site interaction [F(2,197)=3.8, p=0.017] and a PRKCA genotype by location interaction [F(1,89)=5.72, p=0.015].

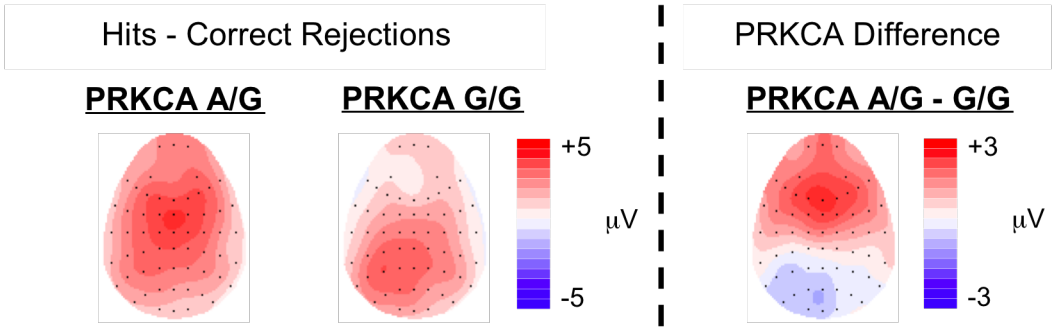


Figure 8.9 Topographic maps showing the distribution of the word old/new differences for PRKCA A/G and G/G carriers in the 500-800ms time-window. A genotype difference map is also given showing the difference in old/new effect distribution between PRKCA A/G and homozygous G genotypes. Data as shown in Figure 8.1.

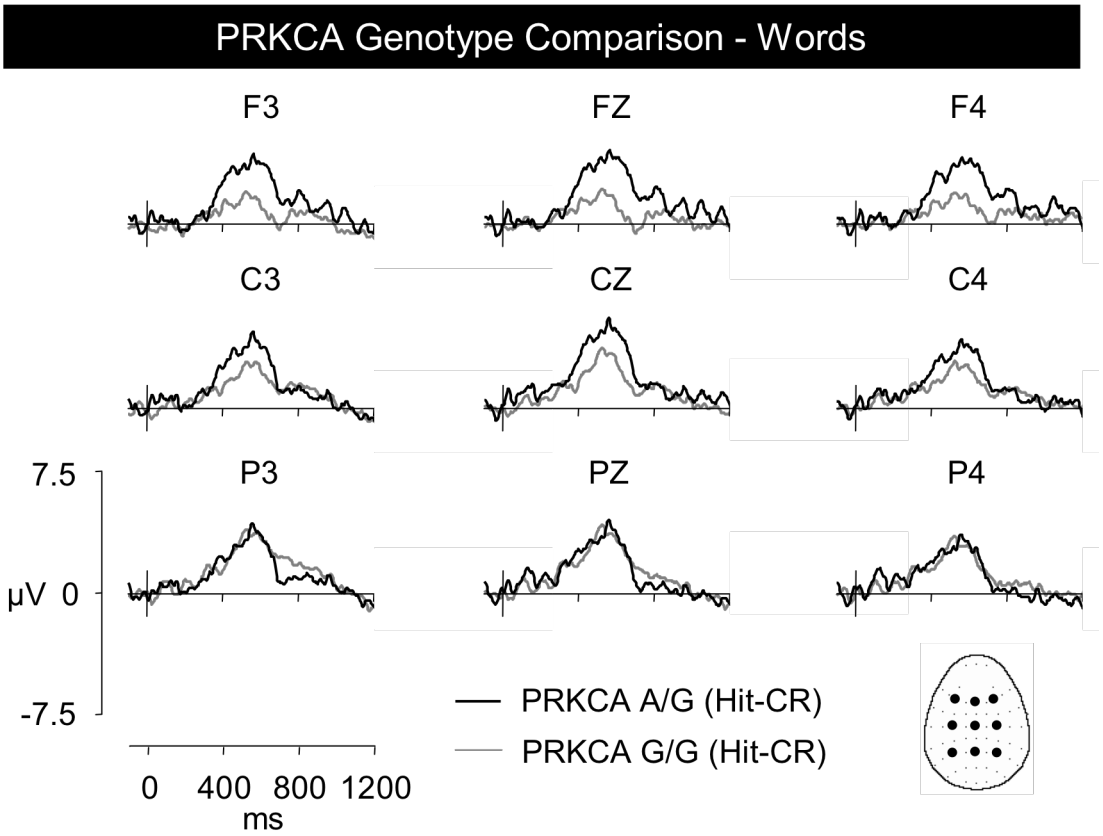


Figure 8.10 Grand average ERP word difference waveforms (Hits-CRs) for PRKCA A/G carriers (n=20) and homozygous G carriers (n=58). Data as shown in Figure 8.2.

8.3.1.3 Discussion of genetic differences on word recognition effects

Analysis of word old/new ERP recognition memory effects across genotype was conducted, looking at eight different SNPs, six located in separate genes (ADCY8, BDNF, COMT, PRKACG, PRKCA and KIBRA) and two located in the same gene (APOE_1 and APOE_2). APOE_1 and APOE_2 were also analysed as a haplotype (APOE). Significant behavioural and ERP differences across genotypes were found, with KIBRA genotype significantly influencing discrimination accuracy (*Pr*), where homozygous C carriers performed better than C/T carriers. The direction of this difference is in contrast to the findings from previous literature, presented in Chapter 3, and the hypothesis outlined in the introduction, in which T allele carriers were expected to perform better than C carriers.

The reason for this pattern reversal is unclear, but may be related to changes in specific task detail across studies, with the majority of studies finding episodic memory associations with KIBRA genotype using recall tasks. However, Schaper et al. (2008) did find that T carriers performed better than C carriers on tests of recognition. The variation across studies could also be related to population differences, although the participants in the current sample were largely Caucasian with European ancestry, as were the majority of participants in previous studies. Another important difference between the current study and those presented in Chapter 3 is sample size, with the current sample much smaller than those in the literature who report significant behavioural differences. Typically larger sample sizes are needed to see robust behavioural effects than ERP differences, and the absence of ERP modulations for KIBRA could be interpreted as evidence that the behavioural difference is a false positive.

Alternatively, a study by Papassotiropoulos et al. (2006) reported differences in fMRI bold signal between T carriers and non-carriers for matched behavioural performance, suggesting differing neural activation across genotypes. Whilst it is difficult to make inferences about the influence of genotype on ERP effects based on fMRI data, it can be hypothesised that differences in neural activity, inferred from changes in BOLD signal, will also be evident in the pattern of ERP activity. Therefore the absence of ERP modulations between the two genotypes may be indicative of changes in the typical pattern of discrimination accuracy scores, if studies in which T carriers perform better than non-carriers show differences in ERP old/new effect magnitude, or differing effect distributions.

Significant differences in hit rate were found for ADCY8 genotype with A/G carriers exhibiting a higher hit rate than homozygous G carriers. The overall performance accuracy, as indexed by *Pr*, did not differ, and no significant ERP differences were found. However, the differing hit rate between genotypes supports the findings of de Quervain and Papassotiropoulos (2006), who identified the SNP as being important for memory. The role of ADCY8 in the c-AMP pathway, suggests that the differences in hit rate may be related to differences in the catabolism of adenosine triphosphate and consequently neuronal signalling, although no ERP differences were found, and the functional effect of the ADCY8 SNP on ADCY8 is unclear. Nonetheless, the results from the current study do indicate a potential role of ADCY8 in episodic memory.

APOE genotype was found to influence the overall magnitude of the old/new effect with ε2 carriers exhibiting a smaller effect than both ε3/ε3 and ε4 carriers in the 300-500ms time-window[23] and smaller than ε3/ε3 carriers in the 500-800ms time-window. Although it was hypothesised that ε4 carriers would perform better than ε2 or homozygous ε3 carriers, no differences in behavioural scores as a function of APOE genotype were found. The different ERP effect magnitudes for ε2 carriers compared to ε3/ε3 and ε4 carriers may indicate that ε2 carriers have greater neural efficiency than ε3/ε3 and ε4 carriers, and therefore exhibit smaller old/new effects than the other genotypes. Mondadori et al. (2006) found that the ε4 isoform was more advantageous in young participants, and on the basis of fMRI data, suggest ε4 carriers show better neural efficiency. However, as discussed by Tractenberg et al. (in press), the literature on the effect of APOE genotype on memory related neural activity in young participants is inconsistent.

[23] A significant difference was also found for APOE_1 with homozygous C carriers exhibiting a larger old/new effect than C/T carriers. Typically, and as is the case in this study, carriers of a T allele at the APOE_1 SNP will typically have an APOE ε2 genotype, and the APOE_1 results will therefore not be considered separately, but will be discussed as APOE ε2 genotypes.

ERP differences were also found for PRKACG genotype, with homozygous C carriers exhibiting a greater old/new difference over posterior electrodes than C/G carriers, between 300-500ms and 500-800ms. Figure 8.5 suggests the distribution of the old/new effect in the 300-500ms time-window for homozygous C carriers is more posterior than the effect reported in Chapter 5, and that typically seen in the literature. The distribution of the effect for C/G carriers closely resembles the bilateral-frontal effect reported in the literature. The ERPs presented in Figure 8.6, however indicate that the difference over anterior electrodes between the two groups is minimal suggesting that the posterior maxima evident for homozygous C carriers reflects additional activity, not evident for C/G carriers. The larger parietal old/new effect for homozygous C carriers in the 500-800ms time-window further suggests that the additional posterior activity in the 300-500ms time-window may represent an earlier onsetting parietal old/new effect for homozygous C carriers than C/G carriers.

Whilst the ERP differences seen for PRKACG are statistically robust, suggesting a gene specific change in the neural basis of retrieval, it is important to consider a potential alternative source of the finding. Namely, that the more posterior activity for homozygous C carriers may be confounded by differences in the sex composition of the two genotype groups, with a significantly greater proportion of the C/G sample being male than the homozygous C group (Table 8.4). As discussed in Chapter 3 females have been shown to exhibit larger old/new effects than males over anterior electrodes during nonverbal memory tasks, and over posterior electrodes in verbal memory tasks, differences onsetting as early as 300ms (Taylor, Smith & Iron, 1990). With the proportion of female participants making up the homozygous C group greater than the C/G group, the posterior genotype differences seen in the current study may reflect the sex differences reported for verbal memory tasks in the literature.

Significant genotypic ERP differences were also found for PRKCA, with A/G carriers exhibiting more anterior old/new effects than homozygous G carriers between 500-800ms. The ERPs in Figure 8.10 indicate that the magnitude of the old/new effect at parietal electrodes was similar in both genotypes, suggesting that A/G carriers exhibit additional frontal activity not present for the homozygous G group. Akin to the PRKACG SNP, a significant relationship between sex and PRKCA genotype was found in the current study (Table 8.4), with the A/G group having a larger proportion of males then the homozygous G group. Whilst sex may be a confounding factor for PRKACG the evidence that sex differences are driving the distributional differences seen between PRKCA genotypes is less convincing. As discussed above, in verbal memory tasks sex differences appear to be greatest over posterior electrodes. By contrast, the genotypic differences evident in the current study appear to be over anterior electrodes with minimal difference between the two genotypes over posterior electrodes, suggesting that differences in sex composition are not causing the genotype ERP differences.

The enzyme PRKCA is thought to be in involved in cell signalling, but the functional effect of the A to G polymorphism is not currently clear, making interpretation of the distributional differences seen in the current study difficult. Additional anterior activity may reflect differences in retrieval monitoring strategies, with A allele carriers showing greater engagement of retrieval monitoring than homozygous G carriers. Whilst no difference in behavioural performance was found in the current study, a retrieval monitoring hypothesis would fit previous results shown in the literature, with healthy homozygous A carriers performing better than homozygous G carriers on recall tasks. Greater engagement of monitoring processes by homozygous A carriers would aid in the completion of memory tasks, and the absence of behavioural differences in the

current study may reflect the easier nature of recognition tasks compared to recall tasks, making recognition tasks less sensitive to potential group differences.

The final SNP exhibiting genotypic effects in the word recognition task was COMT. Old/new effect magnitude for COMT G/G carriers was smaller than for A/G carriers, and Figure 8.4 suggests that the amplitude of the old/new effect for G/G carriers was also smaller than for A/A carriers (although this difference was not significantly different). The smaller magnitude for G/G carriers may reflect the greater neurotransmitter catabolism of homozygous G carriers, with greater catabolism reducing the level of neurotransmitter in the DLPFC available to bind at the postsynaptic terminal, reducing the number of ion channels opening/closing. The fewer ion channels available the smaller the number of ions entering/exciting the cell, and consequently the size of the postsynaptic potential is reduced. A smaller postsynaptic potential reduces the likelihood that an action potential will be triggered resulting in a reduction in the number and frequency of neurons firing. Ultimately the reduction in the amount of available neurotransmitter, as a result of increased catabolism, may have reduced the voltage recorded at the scalp for homozygous G allele carriers.

The old/new effect for G/G carriers was largest over the left hemisphere between 300-500ms, whereas A/G carriers exhibited a right hemisphere bias, as illustrated in Figure 8.3a. The topographic map in Figure 8.3b showing the difference between the two genotypes clearly indicates the hemispheric differences, and further indicates that A/G carriers may have additional right-frontal lateral old/new differences not evident for G/G carriers. Catabolism differences have been indicated to occur in the DLPFC so it is not surprising that the ERP difference is present over frontal electrodes. The distribution of the difference between the two groups is reminiscent of the right-frontal old/new

effect associated with post-retrieval monitoring (Wilding and Rugg, 1996), which has been shown to onset as early as 400ms. It may be that A/G carriers are beginning to exhibit signs of post-retrieval monitoring that G/G carriers do not, because of the reduced levels of DLPFC neurotransmitter for G/G carriers. Furthermore, the behavioural difference between these two genotypes typically seen in the literature (in which A carriers perform better than G carriers) may reflect strategy differences related to retrieval monitoring processes.

Behaviourally response bias was affected by COMT genotype, with homozygous A carriers more conservative than either A/G or homozygous G carriers. These response bias differences may also reflect differences in dopamine availability, with G allele carriers catabolizing dopamine faster and therefore exhibiting less dopamine signalling than homozygous A carriers, in the DLPFC. During normal ageing the dopaminergic system shows evidence of decline, with a reduction in the number of D2 dopamine receptors in the brain (for a review see Li, Lindenberger & Sikström, 2001). Recognition memory response bias has also been shown to change with age, with older participants exhibiting a more liberal bias than younger participants, and in this older cohort, participants became more liberal with increasing age (Huh, Kramer, Gazzaley & Delis, 2006). In addition a study by Morcom et al. (2010) showed that both young and old participants given Sulpiride, a D2-like antagonist, exhibited a less conservative response bias in a recognition memory test for words, than participants given either a placebo, or Bromocriptine, a D2-like agonist. These studies therefore suggest that dopamine is an important factor in response bias, with a reduction in dopamine associated with a less conservative, or more liberal response bias. Furthermore, Miller, Handy, Cutler, Inati and Wolford (2001), showed that activity in the DLPFC was associated with changes in response criteria during a recognition memory task.

Therefore, the differences in response bias across COMT genotype, seen in the current study, may be caused by reduced dopamine signalling in the DLPFC in G allele carriers (Chen et al., 2004), resulting in a less conservative response bias compared to homozygous A carriers.

The findings from the word task clearly indicate that genetic polymorphisms can influence the ERP correlates of word recognition memory. Whilst it is not possible to fully explain all the ERP variations evident across genotypes, the different distributions evident in the topographic maps (across genes and genotypes) highlight the variability that exists in the ERP effects of word recognition memory. The next section will look at the influence of genotype on the picture old/new recognition memory effects.

8.3.2 Pictures

8.3.2.1 Behavioural Results

The behavioural results for the picture task, split by genotype, are presented in Table 8.7. As with the word task all groups had a mean discrimination accuracy score significantly above chance (Table 8.8), with no significant differences in *Pr* between genotypes for any gene. Overall mean response bias scores were conservative, and generally did not differ between genotypes. As per the word task, significant differences in response bias were evident for COMT [$F(2,81)=5.8$, $p=0.004$], with homozygous A carriers exhibiting a more conservative bias than both A/G carriers [$t(61),=-3.74$, $p<0.001$], and homozygous G carriers [$t(40)=-2.42$, $p=0.02$]. No significant difference in response bias was found between A/G and homozygous G carriers. Significant differences in false alarm rates were also found between COMT homozygous A carriers and A/G carriers [$t(55)=-3.93$, $p<0.001$], with a higher false alarm rate evident for A/G

carriers. No significant genotypic differences were found for hit rate, hit response times or CR response times across any of the genes.

Pictures	Genotype	Hit rate (%)	False alarm rate (%)	Pr	Br	Hit RT (ms)	CR RT (ms)
ADCY8	A/G	83 (14)	4 (6)	0.77 (0.16)	0.27 (0.19)	774 (122)	823 (124)
	G/G	87 (8)	3 (3)	0.82 (0.09)	0.23 (0.15)	795 (124)	832 (127)
APOE_1	C/T	85 (9)	3 (4)	0.80 (0.09)	0.24 (0.18)	780 (133)	818 (129)
	C/C	83 (13)	4 (6)	0.77 (0.16)	0.25 (0.17)	795 (119)	835 (123)
APOE_2	C/T	85 (10)	6 (7)	0.78 (0.15)	0.28 (0.16)	801 (127)	867 (127)
	T/T	83 (13)	3 (4)	0.78 (0.14)	0.23 (0.18)	789 (124)	821 (127)
BDNF	A/G	85 (12)	4 (5)	0.78 (0.14)	0.27 (0.18)	783 (100)	834 (98)
	G/G	83 (13)	3 (5)	0.78 (0.14)	0.23 (0.17)	800 (133)	836 (140)
COMT	A/G	84 (13)	**5 (6)**	0.77 (0.15)	**0.29 (0.19)**	789 (128)	851 (134)
	A/A	81 (11)	**1 (2)**	0.78 (0.10)	**0.15 (0.12)**	778 (98)	796 (92)
	G/G	86 (13)	**3 (6)**	0.81 (0.16)	**0.25 (0.15)**	818 (137)	846 (141)
PRKACG	C/G	86 (13)	3 (4)	0.81 (0.14)	0.25 (0.18)	786 (103)	813 (104)
	C/C	82 (12)	4 (5)	0.76 (0.14)	0.24 (0.17)	800 (130)	846 (136)
PRKCA	A/G	83 (11)	5 (7)	0.76 (0.16)	0.24 (0.16)	816 (162)	851 (143)
	G/G	84 (13)	3 (4)	0.79 (0.14)	0.24 (0.17)	785 (111)	828 (123)
WWC1 (KIBRA)	C/T	86 (9)	4 (6)	0.80 (0.12)	0.25 (0.17)	766 (101)	816 (107)
	C/C	82 (15)	4 (5)	0.76 (0.16)	0.25 (0.19)	802 (127)	831 (124)
APOE	ε2 carriers	85 (9)	3 (4)	0.80 (0.09)	0.22 (0.19)	790 (140)	810 (137)
	ε3/ε3	82 (14)	3 (4)	0.77 (0.16)	0.24 (0.18)	788 (118)	826 (124)
	ε4 carriers	85 (12)	5 (8)	0.78 (0.16)	0.27 (0.17)	810 (122)	855 (122)

Table 8.7 Behavioural results from the picture task for each genotype. Data as shown in Table 8.5.

Pictures	Genotype	Pr > 0
ADCY8	A/G	t(39)=31.1, p<0.001
	G/G	t(31)=52, p<0.001
APOE_1	C/T	t(22)=42.64, p<0.001
	C/C	t(58)=38.02, p<0.001
APOE_2	C/T	t(20)=24.26, p<0.001
	T/T	t(59)=43.9, p<0.001
BDNF	A/G	t(27)=29.58, p<0.001
	G/G	t(54)=41, p<0.001
COMT	A/G	t(41)=33.78, p<0.001
	A/A	t(22)=36.63, p<0.001
	G/G	t(18)=21.81, p<0.001
PRKACG	C/G	t(23)=29.22, p<0.001
	C/C	t(57)=41.37, p<0.001
PRKCA	A/G	t(19)=21.99, p<0.001
	G/G	t(57)=43.56, p<0.001
WWC1 (KIBRA)	C/T	t(37)=40.41, p<0.001
	C/C	t(34)=28.27, p<0.001
APOE	ε2 carriers	t(18)=40.2, p<0.001
	ε3/ε3	t(40)=31.69, p<0.001
	ε4 carriers	t(17)=20.44, p<0.001

Table 8.8 Results from analysis confirming that all groups had mean discrimination accuracy scores that were above chance for the picture task.

8.3.2.2 ERP Results

Analysis from 300-500ms:

Statistical analysis of the old/new effects for picture recognition in the 300-500ms time-window revealed a significant main effect of genotype for the COMT SNP [F(2,81)=3.35, p=0.04] with the old/new effect for A/G carriers larger than homozygous A carriers [F(1,63)=7.97, p=0.006]. No significant differences were found between homozygous G carriers and either homozygous A or A/G carriers (Figure 8.11 and Figure 8.12). A significant interaction between APOE genotype, location and site was

also found [F(2,61)= 3.46, p=0.043] with ε4 carriers exhibiting a larger old/new effect than ε2 carriers over frontal locations, a difference greatest at superior electrodes (Figure 8.13 and Figure 8.14).

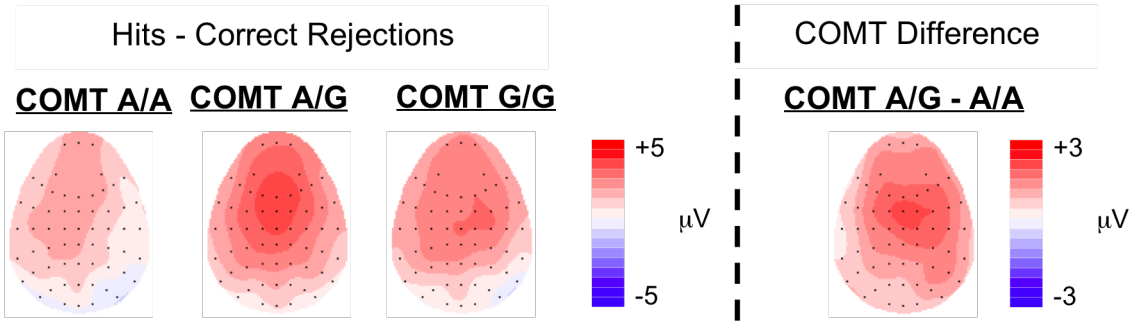


Figure 8.11 Topographic maps showing the distribution of the picture old/new differences for COMT A/A, A/G and G/G carriers in the 300-500ms time-window. A genotype difference map showing the difference in old/new effect distribution between COMT A/G and A/A genotypes is also given. Data as shown in Figure 8.1.

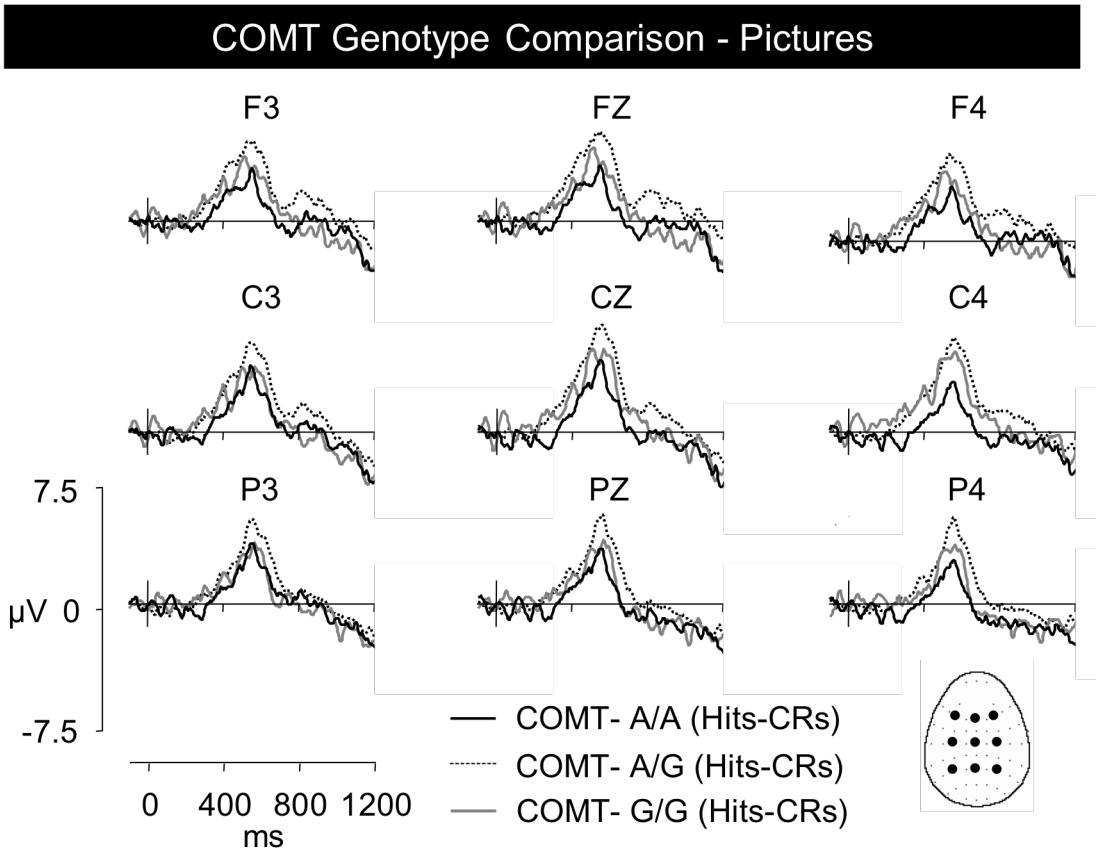


Figure 8.12 Grand average ERP picture difference waveforms (Hits-CRs) for COMT homozygous A carriers (n=23), A/G carriers (n=42) and homozygous G carriers (n=19). Data as shown in Figure 8.2.

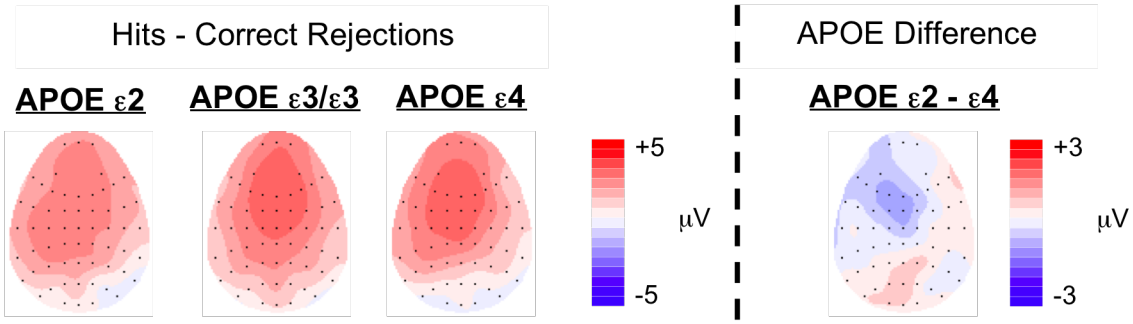


Figure 8.13 Topographic maps showing the distribution of the picture old/new differences for APOE ε2, ε3/ε3 and ε4 carriers between 300-500ms. A Genotype difference map showing the difference in old/new effect distribution between APOE ε2 and ε4 genotypes is also shown. Data as shown in Figure 8.1.

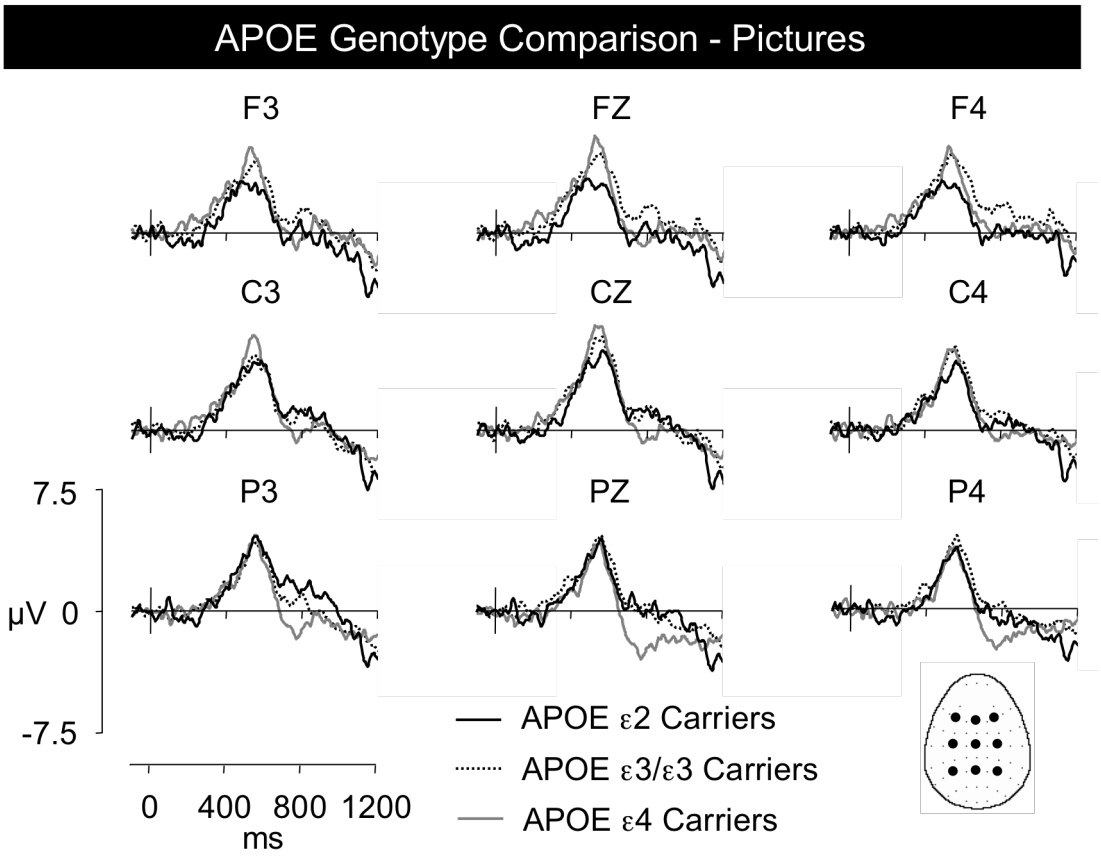


Figure 8.14 Grand average ERP picture difference waveforms (Hits-CRs) for APOE ε2 (n=19), ε3/ε3 (n=41) and ε4 carriers (n=18). Data as shown in Figure 8.2.

Significant genotype by hemisphere [F(1,70)=9.8, p=0.003], and genotype by hemisphere by site [F(1,87)=7.8, p=0.004], interactions were found for the ADCY8 SNP, with A/G carriers exhibiting a left hemisphere bias, and G/G carriers a right hemisphere bias (Figure 8.15 and Figure 8.16). A significant interaction between PRKCA genotype, location and site was also found [F(2,135)=3.25, p=0.047], in which homozygous G carriers exhibited a more posterior going effect than A/G carriers, a

difference maximal at superior electrodes (Figure 8.17 and Figure 8.18). No significant genotypic ERP differences were found for SNPs PRKACG, APOE_1, APOE_2, BDNF, or KIBRA.

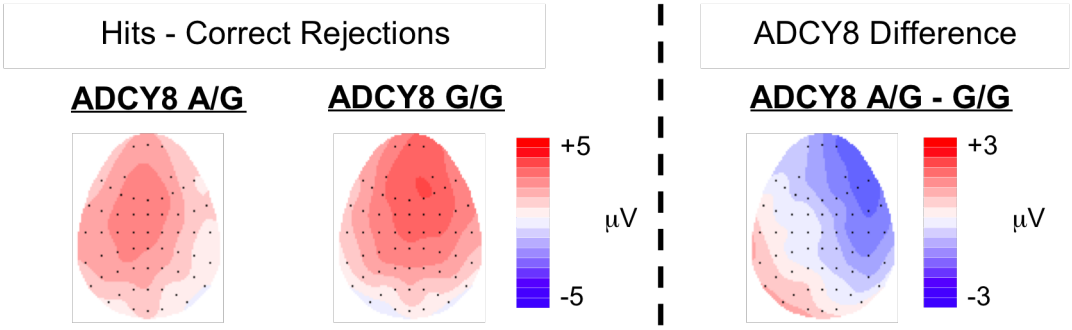


Figure 8.15 Topographic maps showing the distribution of the picture old/new differences for ADCY8 A/G and G/G carriers in the 300-500ms time-window. A genotype difference map is also presented showing the difference in old/new effect distribution between ADCY8 A/G and homozygous G genotypes. Data as shown in Figure 8.1.

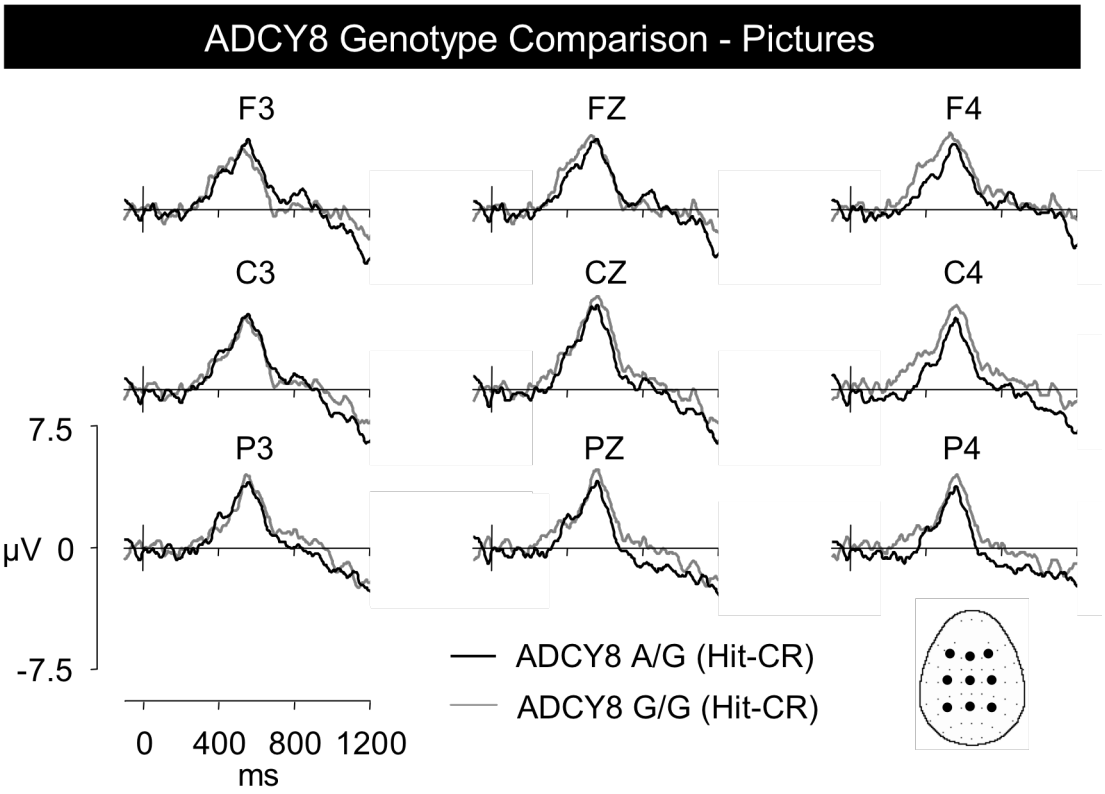


Figure 8.16 Grand average ERP picture difference waveforms (Hits-CRs) for ADCY8 A/G (n=40) and homozygous G carriers (n=32). Data as shown in Figure 8.2.

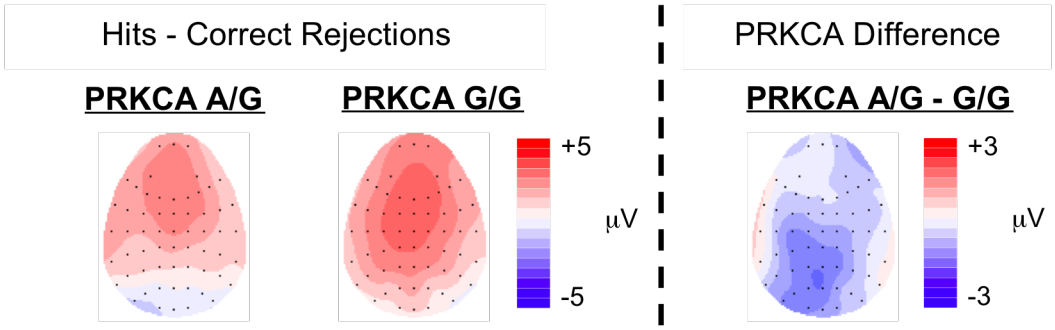


Figure 8.17 Topographic maps showing the distribution of the picture old/new differences for PRKCA A/G and G/G carriers in the 300-500ms time-window. A genotype difference map is also given showing the difference in old/new effect distribution between PRKCA A/G and homozygous G genotypes. Data as shown in Figure 8.1.

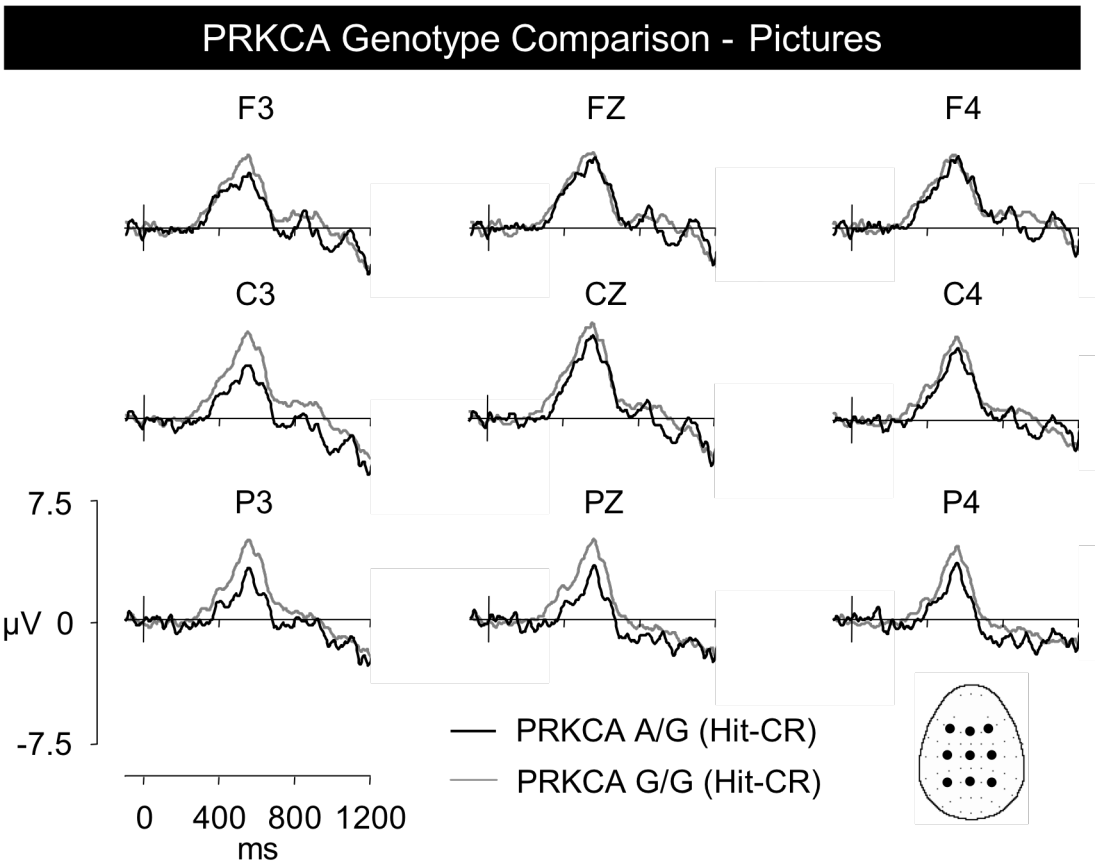


Figure 8.18 Grand average ERP picture difference waveforms (Hits-CRs) for PRKCA A/G carriers (n=20) and homozygous G carriers (n=58). Data as shown in Figure 8.2.

Follow-up topographic analysis using rescaled data revealed significant interactions between ADCY8 genotype and hemisphere [F(1,70)=9.29, p=0.003], and ADCY8 genotype, hemisphere and site [F(1,89)=3.38, p=0.005], suggesting the topographically distinct effects identified above, are a reflection of distribution rather than magnitude differences. However, analysis of APOE (ε2 v. ε4) and PRKCA (A/G v. G/G) genes all

revealed marginally non-significant genotypic effects when analysing rescaled data: a APOE genotype by location by site interaction [F(2,63)=3.08, p=0.059], and a PRKCA genotype by location by site interaction [F(2,135)=2.97, p=0.061]. The sample size of the rarer COMT genotype, both genotypes for the APOE gene, and the rarer genotype for PRKCA SNP were small (COMT A/A n=23, APOE ε2 n=19, APOE ε4 n=18, PRKCA A/G n=20), and the marginally non-significant topographic analyses suggest that these groups may not have the statistical power necessary for the distributional differences apparent in Figure 8.11, Figure 8.13 and Figure 8.17 to be statistically significant. Additional analysis with a larger sample is therefore needed to fully evaluate the topographic differences for these SNPs.

Analysis from 500-800ms:

Statistical analysis of the 500-800ms time-window also revealed a significant main effect of genotype for the COMT polymorphisms [F(2,81)=5.67, p=0.005], with the A/G carriers again exhibiting a larger old/new effect than homozygous A carriers [F(1,63)=11.97, p=0.001]. Significant COMT genotype (A/A v. A/G) and site [F(1,69)=4.33, p=0.038], and genotype, hemisphere and site [F(1,87)=3.66, p=0.045] interactions were also found, reflecting the larger old/new effect for A/G carriers, a difference greatest uniformly over the right hemisphere, and over superior electrodes in the left hemisphere. As per the 300-500ms time-window no significant differences between homozygous G and homozygous A carriers, or A/G carriers were found (Figure 8.19 and Figure 8.12).

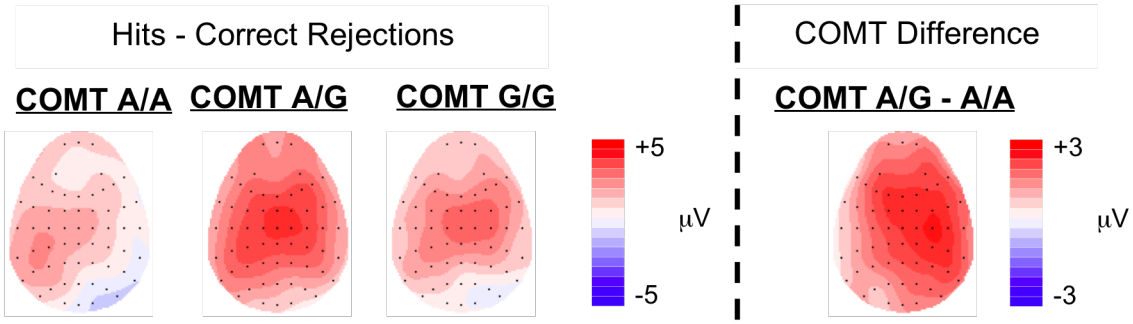


Figure 8.19 Topographic maps showing the distribution of the picture old/new differences for COMT A/A, A/G and G/G carriers in the 500-800ms time-window. A genotype difference map showing the difference in old/new effect distribution between COMT A/G and A/A genotypes is also given. Data as shown in Figure 8.1. ERP waveforms are shown in Figure 8.12.

There was a significant APOE genotype (ε2 v. ε4) by location interaction between 500-800ms [F(1,46)=3.95, p=0.042], with ε2 carriers exhibiting a more posterior old/new effect than ε4 carriers (Figure 8.20 and Figure 8.14). Significant interactions with ADCY8 genotype were also found, with genotype by hemisphere [F(1,70)=5.35, p=0.024], and genotype by hemisphere by site [F(1,94)=4.30, p=0.030] interactions, reflecting the left hemisphere distribution of the old/new effect for A/G carriers and the right hemisphere distribution for the homozygous G group. The differences in effect distribution were uniform across electrode sites in the right hemisphere, with homozygous G carriers exhibiting a larger old/new effect, but in the left hemisphere the greatest effect was at superior electrodes for homozygous G carriers, with a more widespread distribution for A/G carriers (Figure 8.21 and Figure 8.16).

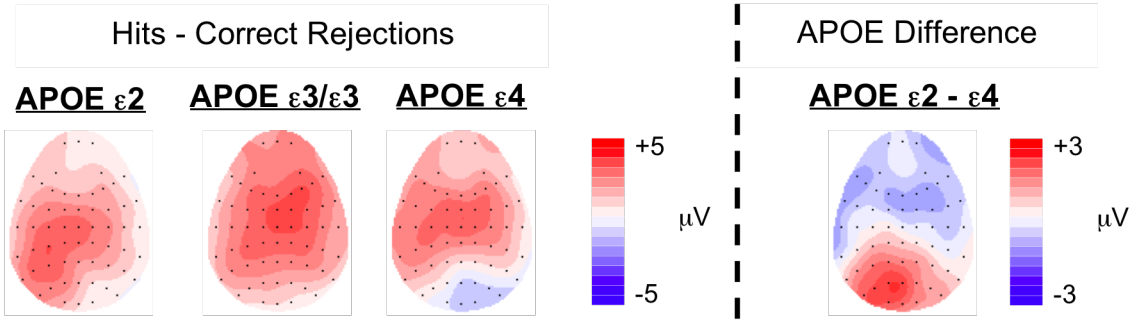


Figure 8.20 Topographic maps showing the distribution of the picture old/new differences for APOE ε2, ε3/ε3 and ε4 carriers between 500-800ms. A Genotype difference map showing the difference in old/new effect distribution between APOE ε2 and ε4 genotypes is also given. Data as shown in Figure 8.1. ERP waveforms are shown in Figure 8.14.

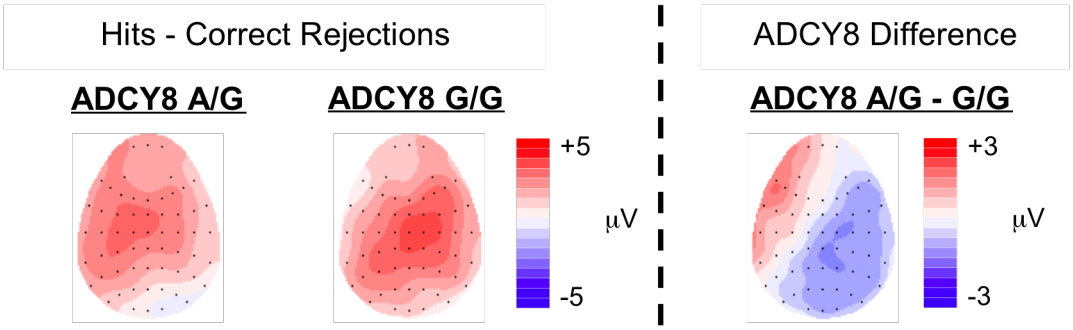


Figure 8.21 Topographic maps showing the distribution of the picture old/new differences for ADCY8 A/G and G/G carriers in the 500-800ms time-window. A genotype difference map is also given showing the difference in old/new effect distribution between ADCY8 A/G and homozygous G genotypes. Data as shown in Figure 8.1. ERP waveforms are shown in Figure 8.16.

Finally, a significant PRKCA genotype by location by site interaction was found [F(2,162)=3.92, p=0.020], in which homozygous G carriers exhibited a more posterior old/new effect that A/G carriers, a difference greatest at inferior electrodes at anterior locations, and superior electrodes at posterior locations (Figure 8.22 and Figure 8.18). No significant genotypic ERP differences were found for SNPs PRKACG, APOE_1, APOE_2, BDNF, or KIBRA.

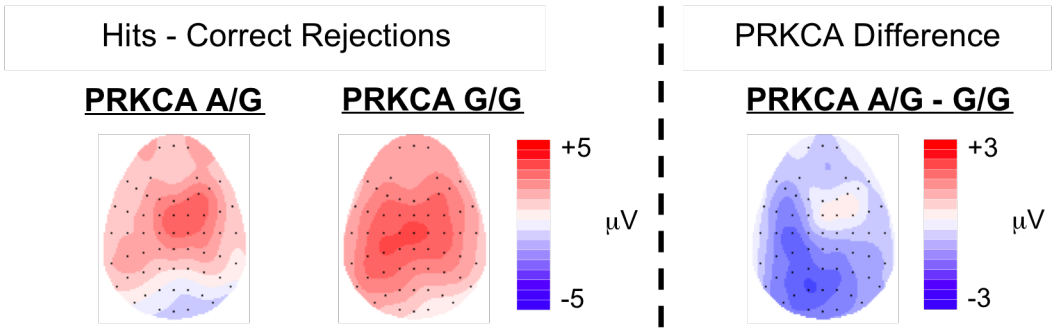


Figure 8.22 Topographic maps showing the distribution of the picture old/new differences for PRKCA A/G and G/G carriers in the 500-800ms time-window. A genotype difference map is also given showing the difference in old/new effect distribution between PRKCA A/G and homozygous G genotypes. Data as shown in Figure 8.1. ERP waveforms are shown in Figure 8.18.

Follow-up topographic analysis using rescaled data on SNPs COMT (A/A v. A/G), ADCY8 (A/G v. G/G), PRKCA (A/G v. G/G), and combined polymorphisms APOE (ε2 v. ε4) in the 500-800ms time-window were conducted. Significant genotype by hemisphere [F(1,70)=5.37, p=0.023] and genotype by hemisphere by site [F(1,94)=4.42,

p=0.027] interactions were found for SNP ADCY8, suggesting the hemispheric differences observed across the two genotypes are distributional, rather than reflecting magnitude differences. Furthermore, a significant COMT genotype by hemisphere by site interaction was found [F(1,87)=4.98, p=0.018], indicating that the hemispheric differences were unlikely to be caused by magnitude differences across the two groups.

As per the 300-500ms time-window, both the APOE genotype by location interaction [F(1,46)=3.67, p=0.051], and the PRKCA genotype by location by site interaction [F(2,163)=2.69, p=0.067], observed in the initial analysis were marginally non-significant when analysed with rescaled data. The sample sizes of these genotypes again suggest that analysis of these SNPs with larger sample sizes needs to be conducted to fully understand the topographic differences evident in Figure 8.20 and Figure 8.22.

8.3.2.3 Discussion of genetic differences on picture recognition effects

Analysis of the picture data revealed significant genotype effects for COMT, APOE, PRKCA and ADCY8. Consistent with the findings from the word task, a significant response bias difference across COMT genotype was found in the picture task, with homozygous A carriers more conservative than either A/G or homozygous G carriers, a difference that may reflect the level of dopamine signalling in the DLPFC, as discussed above. Significant COMT ERP differences were also found for the picture task, with A/G carriers exhibiting greater old/new effect magnitudes in both the 300-500ms and 500-800ms time-windows than homozygous A carriers, a difference greatest over the right hemisphere in the later time-window.

The right hemispheric distribution of the COMT difference between genotypes is consistent with the findings from the word task, however whereas the difference in the word task was between A/G and homozygous G carriers the difference in the picture

task is between A/G and homozygous A carriers. In both the word and picture tasks A/G carriers exhibited greater old/new effects than either homozygous A or G carriers, suggesting that the dopamine hypothesis may not be sufficient to explain the differences in ERP effect magnitude or distribution in either task. However, these results do suggest that A/G carriers exhibit additional right hemispheric old/new differences compared to both homozygous groups, a difference which may reflect differences in retrieval monitoring processes.

The ERP old/new effects for pictures were also modulated by APOE genotype, with ε4 carriers showing a greater old/new effect than ε2 carriers over frontal electrodes, in both the 300-500ms and 500-800ms time-windows, and ε2 carriers showing a larger old/new effect than ε4 carriers in the 500-800ms time-window over posterior electrodes, a difference the ERPs indicate onsets around 700ms. Topographic analysis using rescaled data resulted in marginally non-significant interactions, indicating distributional difference trends. The difference pattern over frontal electrodes is consistent with the pattern evident for words, with ε2 carriers exhibiting a smaller effect magnitude than ε4 carriers, a difference which the absence of behavioural differences suggests may be reflective of greater neural efficiency (as discussed above). The different pattern of activity over parietal electrodes, evident at electrode P3 in Figure 8.14 from approximately 700ms, appears to reflect differing durations of the left-parietal old/new effect, with ε2 carriers exhibiting a shorter left-parietal effect than ε4 carriers. The functional significance of these genotypic ERP differences is currently not clear.

It is however, interesting to note that the 500-800ms old/new effect in Figure 8.20 for ε4 carriers is a close resemblance to the picture old/new recognition effect reported in Chapter 5, which showed that pictures evoked more anteriorly distributed left-parietal

effects than words. In contrast, the 500-800ms old/new effect for the ε2 carriers is a closer resemblance to the left-parietal effect seen for word recognition. These individual differences may help to explain some of the discrepancies reported in the literature with regards to the distribution of ERP effects for pictorial stimuli (i.e. face stimuli, as discussed by Donaldson and Curran, 2007),with different study samples potentially being made up with different proportions of APOE genotypes.

Marginally non-significant rescaled interactions were also found for PRKCA, in which homozygous G carriers showed a trend towards more parietally distributed old/new effects than A/G carriers in both the 300-500ms and 500-800ms time-windows. Analysis of PRKCA differences identified for words showed additional frontal activity for A/G carriers, whilst effect magnitude over parietal electrodes did not differ. In contrast to the word task, the ERPs for the picture task in Figure 8.18 show limited differences in effect magnitude over frontal electrodes across genotype, but show homozygous G/G carriers exhibiting greater old/new effects than A/G carriers over parietal electrodes, suggesting an interaction between task and PRKCA genotype.

As discussed in relation to the word task, the proportion of males with an A/G genotype was significantly greater than the proportion with a homozygous G genotype. However, the literature discussed in Chapter 3 suggests that sex differences in nonverbal tasks are evident over anterior electrodes, rather than posterior electrodes as is the case for the PRKCA SNP, suggesting that the distributional differences observed are not caused by sex differences. However, sex differences for verbal tasks are evident over posterior electrodes, and the pictorial stimuli used in the current study were nameable pictures, and therefore may be reflective of the verbal tasks used by Taylor, Smith and Iron (1990) to investigate sex differences. Although the differences evident for the word task

don't appear to reflect sex differences, additional analysis of the picture data, matching the proportion of males and females in each genotype group, needs to be conducted before firm conclusions about the influence of PRKCA genotypes can be made.

Finally the ERP old/new effects for pictures were also modulated by ADCY8 genotype, with A/G carriers exhibiting old/new effects with a left hemispheric distribution, and homozygous G carriers a right hemispheric distribution in both the 300-500ms and 500-800ms time-windows. Inspection of the ERPs in Figure 8.16 indicates that the magnitude of the old/new effect in the left hemisphere doesn't differ across genotype, with the main difference being driven by a larger effect for homozygous G carriers in the right hemisphere. The differing distributions of the old/new effects across genotypes may reflect differing engagement of strategic processes, such as greater engagement of retrieval monitoring processes by homozygous G carriers, reflected in the additional right hemispheric activity.

8.4 General Discussion

A summary of the main chapter hypotheses and findings are presented in Table 8.9, finding significant differences in behavioural and ERP measures of word and picture recognition for several genes. Behavioural measures were included in the analysis, however, in comparison to the behavioural studies reported in the literature, the sample size in the current study is small. This small sample size leads to concerns regarding the statistical power of any behavioural analysis conducted with the current sample and the reliablility of any conclusions that are drawn from these data in relation to the replication of previous studies. Any conclusions about the impact of genotype on behavioural outcome in the current study are therefore made tentatively.

A more central aim of this chapter was to investigate the role of genetic differences on the ERP correlates of recognition memory identified in Chapter 5. This focus was driven by the findings from Chapter 7, in which performance was not found to significantly correlate with the magnitude of typical recognition memory old/new effects, and distributional differences were not mirrored by behavioural differences. Whilst previous literature has examined the consequences of differing genotypes on behavioural measures of cognition, relatively few studies have looked at the relationship between electrophysiological correlates and genotype. The sample sizes of each genotype group in the current study reflect those typically reported in the literature for ERP memory studies, as well as reflecting the sample sizes reported by the few studies looking at genetic polymorphisms and ERPs (Noble et al., 1994; Johnson et al., 1997; Hill et al., 1998; Liu et al., 2009), and those looking at individual differences and ERP correlates of memory (Taylor, Smith & Iron, 1990; Guillem & Mograss, 2005). The similarlities in the size of the samples used in the current study and in the previous literature suggest that the current sample is sufficient to provide adequate statistical power to detect significant differences in the ERP effects between genotype groups.

Gene	Hypotheses	Words	Pictures
APOE	- ε4 carriers perform better behaviourally than ε2 & ε3/ε3 carriers. - Greater old/new effect over left frontocentral electrodes for ε4 carriers.	- 300-500ms ε2 carriers reduced effect magnitude compared to ε3/3 and ε4. - 500-800ms ε2 carriers reduced effect magnitude compared to ε3/3 carriers.	- 300-500ms ε2 carriers reduced effect magnitude compared to ε4 carriers over frontal electrodes. - 500-800ms ε2 carriers more posterior distribution than ε4.
BDNF	- G/G carriers perform better behaviourally than A/G carriers. - A/G carriers would exhibit a smaller left-parietal effect than G/G.	- No differences in behavioural or ERP measures were found across genotypes.	- No differences in behavioural or ERP measures were found across genotypes.
COMT	- A carriers perform better behaviourally than G carriers. - G carriers would exhibit a smaller left-parietal effect than A carriers.	- A/A carriers more conservative response bias than A/G or G/G carriers. - 300-500ms G/G carriers more left hemispheric distribution, A/G more bilateral, leading to right hemispheric difference.	- A/A carriers more conservative response bias than A/G or G/G carriers. - 300-500ms A/G carriers show greater effect magnitude than A/A. - 500-800ms A/G greater than A/A carriers over right hemisphere.
KIBRA	- C/T carriers perform better behaviourally than C/C carriers. - ERP effects expected to differ, but detailed hypotheses were not made.	- C/C carriers performed better than C/T carriers. - No differences in ERP effects were found across genotypes.	- No differences in behavioural or ERP measures were found across genotypes.
ADCY8	- Differences in both behaviour and ERP effects were expected, but detailed hypotheses were not made.	- A/G carriers had a higher hit rate than G/G carriers. - No differences in ERP effects were found across genotypes.	- 300-500ms A/G carriers exhibited more left and G/G more right hemispheric distributions. - 500-800ms A/G carriers exhibited more left and G/G more right hemispheric distributions.
PRKACG	- C/C carriers were expected to be better than C/G carriers. - ERP effects expected to differ, but detailed hypotheses were not made.	- 300-500ms C/C carriers more posterior distribution than C/G carriers who show a more anterior distribution. - 500-800ms C/C carriers more posterior distribution than C/G carriers.	- No differences in behavioural or ERP measures were found across genotypes.
PRKCA	- G/G carriers were expected to be better than A/G carriers. - ERP effects expected to differ, but detailed hypotheses were not made.	-500-800ms A/G carriers more anterior distribution than G/G carriers.	-300-500ms G/G carriers more posterior distribution than A/G carriers. -500-800ms G/G carriers more posterior distribution than A/G.

Table 8.9 Summary of the main hypotheses, word and picture results for each gene.

The results of the genetic analysis reveal several behavioural and ERP differences, that whilst in many cases are difficult to interpret functionally, clearly indicate the potential role that genetic polymorphisms play in relation to behavioural and ERP measures of episodic memory. Perhaps more importantly the results highlight the role of individual differences in memory, in terms of both behavioural outcome and the associated neural correlates. A quick glance at the ERP and topographic figures in this chapter show the level of variance that exists in the ERP effects generated by participants completing the same simple old/new recognition task. It is not possible to tell from the current study in what way the genotypic differences evident reflect differences in strategic retrieval processing, however it is clear that genotypic differences exist, and that ERPs are sensitive enough to detect neural activity differences at the genetic level.

The investigation of specific genetic polymorphisms in relation to cognition, neuroimaging, and particularly ERPs is in its infancy. There are many factors with regards to the understanding of specific genetic polymorphisms, which can make interpretation of the results difficult, and may cause inconsistency across studies. Firstly, whilst many of the target SNPs have been identified as potentially important for a particular cognitive process through genome wide association studies, it is often not clear if the specific SNP identified is the functional SNP, or if it is indirectly associated with the process. Target SNPs are often tag SNPs, which are representative SNPs that are highly associated (have a high linkage disequilibrium) with polymorphisms at other loci. Genetic SNPs that are positioned close together tend to be inherited together, and therefore people with the same variant at one SNP (the tag SNP) are also likely to have the same variants as each other at other SNPs. Therefore whilst initial analysis may indicate that a SNP is associated with differences in a particular cognitive process, the functional SNP which drives these cognitive differences may actually be at a different

location, where the variant is always the same for a given allele at the tag SNP. Furthermore, the functional SNP may be a polymorphism that is yet to be discovered.

A second factor that may cause inconsistencies between the findings from the current study and those in the literature, as well as producing inconsistencies within the literature, is gene-gene associations. Whilst studies may be investigating one specific SNP the proportion of participants with other genetic variants that are not being reported will vary across samples. It is highly unlikely that one SNP will be solely responsible for a particular cognitive process and it is likely that there will be an interaction between different SNPs[24]. There is evidence of this type of gene-gene interaction influencing memory, with Presuschhof et al. (2010) finding an interaction between KIBRA and CLSTN2, showing better memory performance for KIBRA T and CLSTRN2 C carriers compared to other genotypes including KIBRA T and CLSTRN2 T/T carriers. Therefore, whilst studies may be reporting the effects of one SNP, there may be other SNPs that differ across the study samples that are also influencing the process of interest, resulting in inconsistencies across studies.

A third factor that may lead to inconsistencies across studies is gene-environment interactions. As discussed in Chapter 3, McClearn et al. (1997) estimated heritability of memory performance to be 52%, however genes alone do not determine human behaviour, and they also estimated 38% of memory variability to be related to non-shared environment. Animal models of memory have also highlighted the importance of environment, with studies showing that enriched stimulating environments can enhance learning and memory function (for a review see Van Praag, Kempermann & Gage, 2000). Furthermore, environmental factors have been shown to influence proteins thought

[24] For example, process differences are observed across genotypes A and B of SNP1, a second SNP (SNP2) does not show a genotype difference on its own, but in combination with SNP1, shows genotypic effects, with genotype 1A/2A showing process differences from genotype 1A/2B.

to be modulated by specific SNPs. For example, Ickes et al. (2000) showed that rats in an enriched environment showed increased levels of BDNF (thought to be influenced by the BDNF val^{66}met SNP) in the cerebral cortex, hippocampal formation, basal forebrain and hindbrain compared to age matched rats in isolated conditions. Environmental factors therefore also play a key part in memory function and will differ not just between study samples, but the environmental variability within study samples will also differ across studies (i.e. a sample of university students will most likely be more homogenous than a sample composed of members of the public).

Literature discrepancies are not specific to genetic studies, and as discussed in Chapters 2 and 3 there are often inconsistencies in the literature with regards to the ERP effects observed for specific tasks or conditions. One such example is the material specificity debate discussed in Chapter 2, in which some studies report old/new effects for pictures resembling those seen for words, whilst others suggest additional overlapping frontal activity (there is currently also a similar debate for recognition memory for faces). The top row of Figure 8.23 shows some examples from the literature of picture recognition memory effects, each showing contrasts thought to reflect recollection processes. The topographic map from Vilberg and Rugg (2009) shows a typical left-parietal effect akin to those reported for words, Curran and Cleary (2003) show a more widespread parietal effect, and Durate et al. (2004) show a parietal effect with overlapping frontal activity.

The bottom row of Figure 8.23 shows the APOE old/new effects in the recollection time-window (500-800ms) presented in the current chapter. All participants contributing to these three different APOE maps completed the same task and the three groups did not differ behaviourally. However, these groups appear to show differing effect distributions, with statistical analysis showing significant differences between

APOE ε2 and ε4 carriers, and a marginally non-significant difference with rescaled data (p=0.051), indicating likely distributional differences across genotype. Comparisons of the top and bottom rows of Figure 8.23 suggest that the discrepancies evident in the ERP literature may not simply be a reflection of task differences, but may reflect individual differences in the study samples.

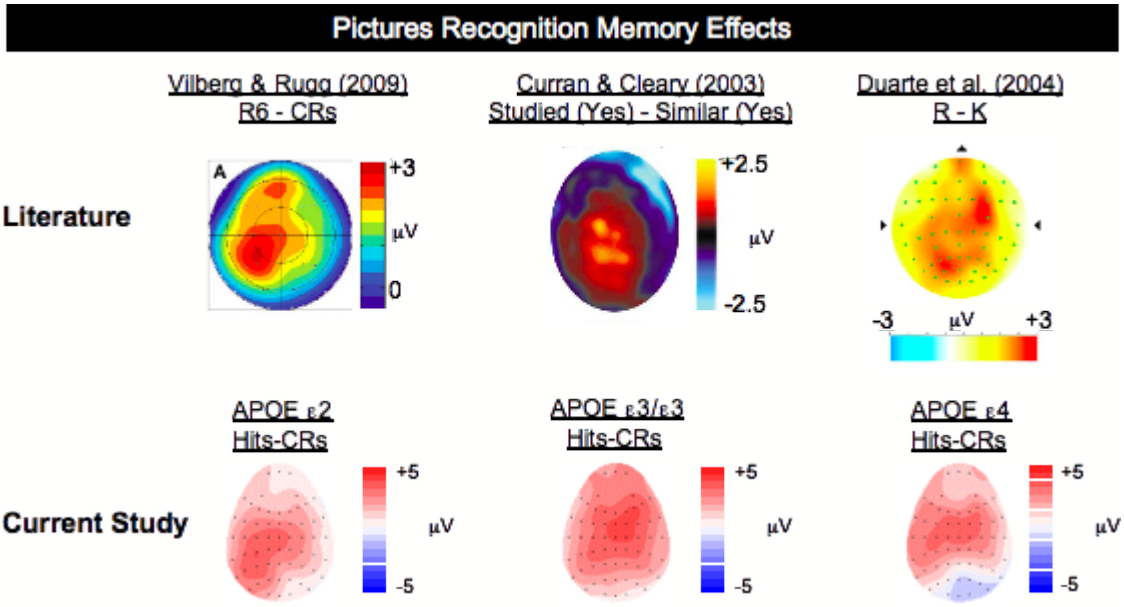


Figure 8.23 Topographic maps showing picture recognition memory effects from the literature and current study, highlighting the variation in effect distribution seen. Detailed discussion of the three literature studies is given in Chapter 2. The map from Vilberg & Rugg (2009) represents the difference between remembered hits seen for 6 seconds and CRs from 500-800ms; the map from Curran & Cleary (2003) represents activity between hits to studied items and false alarms to similar lures between 642-683ms; and the map from Durate et al. (2004) represents the difference between remembered hits and know hits between 600-800ms. Whilst each study differs slightly in the contrast and timing reported, each is thought reflect activity associated with recollection responses. The maps from the current study represent the old/new recognition effects for pictures between 500-800ms across different APOE genotypes, and are as presented in Figure 8.20.

The results from the genetic analysis reported in this chapter highlight not only the potential role of genetic differences in episodic memory and the ERP correlates of recognition memory, but also the role of individual differences more generally. In order to better understand the relationship between behavioural and ERP effects found in different studies it would be beneficial for future research to report the genotype composition of the study sample, in much the same way sex and age is currently reported. Whilst it is clearly unfeasible to report the full genotype of samples, there are

a few SNPs emerging that appear to be consistently associated with episodic memory and could be reported, such as those discussed in Chapter 3. Research into AD has already adopted this practice with a large proportion of studies now reporting the APOE genotype composition of the sample, because of the strong association between APOE ε4 genotype and AD. In addition, this chapter also highlights the need for greater understanding of the influence of individual differences on the ERP correlates of recognition memory, before these ERP correlates can be used as biomarkers of disease.

Chapter 9
General Discussion

The final chapter presents a brief overview of the main findings from this thesis, summarising the results from Chapters 5-8 and discussing these findings in relation to the research aims outlined in Section 3.4.1. The theoretical implications of these results will then be discussed in the context of the wider literature, focusing on the role of the parietal cortex in episodic memory and the role of individual differences. Finally, questions that have arisen as a result of the research in this thesis will be considered in relation to future research directions.

9.1 Summary of results

The aim of this thesis was to investigate individual differences in episodic memory, to gain a greater understanding of episodic memory, how it differs between people and why. The following sections summarise the key findings from the current study, considering the results in relation to the main research questions outlined in Chapter 3.

9.1.1 Do the neural correlates of episodic memory vary with stimulus material, and what drives material specificity effects?

Examination of single item old/new recognition ERP effects across different stimuli (Chapter 5) revealed an early (300-500ms) widespread bilateral effect for words that was more anteriorly distributed than the later (500-800ms) left lateralised posterior effect. A 300-500ms bilateral-frontal effect and a 500-800ms left-parietal effect were also found for pictures. Despite the similarity in the characterisation of the effects in the two tasks, direct comparison revealed topographically dissociable effects in both time-

windows, with pictures exhibiting a more anteriorly distributed effect than words. In contrast to the word and picture tasks, no significant old/new effect was found for faces between 300-500ms, however a left-parietal effect was found between 500-800ms. The final stimulus material examined in Chapter 5 was recognition memory for voices, revealing no sign of the ERP effects seen for the other classes of stimuli, despite examining participants with good memory for voices ($Pr \geq 0.2$). However, a late onsetting (1000-1800ms) old/new effect was found for voices over frontopolar electrodes.

The first key research question asked whether the neural correlates of recognition memory varied with stimulus material. The current findings as well as recent studies in the literature, clearly suggest that this is the case (Yick & Wilding, 2008; Galli & Otten, 2011). The current study included an additional stimulus material (voices) not included in previous studies, allowing a comparison of the neural correlates of stimuli differing in terms of modality: verbal (words and voices) and pictorial (pictures and faces); and homogeneity: heterogeneous (words and pictures) and homogenous (voices and faces). Whilst direct comparison of all four stimuli was not possible (due to the few participants who could successfully complete all four tasks) the results do suggest that the differences evident between stimuli are not simply a function of either stimulus modality (a) or stimulus homogeneity (b). In relation to stimulus modality, the ERP effects characterised for pictures and faces were different, as were the effects characterised for words and voices, suggesting that the differing distributions are not modality specific. Furthermore, faces and voices also showed dissociable effects, with faces exhibiting a parietally distributed effect, and voices a late onsetting frontopolar effect, suggesting that for faces and voices, the similarities in the level of homogeneity in these stimulus sets were not driving material specificity effects.

9.1.2 What factors cause face recognition effects to vary?

The literature presents conflicting results as to the ERP correlates of face recognition, particularly in terms of familiarity-based recognition (Curran & Hancock, 2007; MacKenzie & Donaldson, 2007; Yovel & Paller, 2004). Initial examination of ERP effects for faces was conducted in Chapter 5, however, the paradigm did not allow independent estimates of familiarity and recollection to be made. Chapter 6 further examined recognition memory for faces with a face-verbal phrase source task, allowing comparison of successful face recognition with and without successful recollection of the paired verbal phrase. In contrast to the single item recognition task, the source task revealed a significant widespread bilateral old/new effect in the 300-500ms time-window, followed by a left-parietal effect between 500-800ms, with evidence of additional overlapping frontocentral activity.

Comparisons of the ERP effects between trials with and without correct source retrieval revealed no significant differences, indicating that in the current task, successful source retrieval did not modulate the ERP correlates of face recognition (a). The distribution of the face old/new effects found in the single item and source tasks clearly differed. However, follow-up comparisons of the two tasks suggested that the differences might reflect individual differences in the two samples, rather than task related differences (b). Participants who successfully completed both the single item and source tasks showed the same 500-800ms parietal effect in the two tasks and the same absence of a significant effect between 300-500ms. Participants who were excluded from the single item task (for poor performance) and were only included in the source task, showed an early bilateral effect followed by a later parietal effect and exhibited a right-frontal maxima in the 500-800ms time-window. These results suggested that the differing

patterns of ERP activity evident in the literature might be participant specific, with those inherently poorer at face recognition exhibiting an early bilateral effect, not present for participants showing greater face recognition ability.

9.1.3 Are the bilateral-frontal and left-parietal old/new effects good predictors of memory ability?

Analysis of performance differences in Chapter 7, through both comparisons of high and low performers on the word task, and through correlations of the magnitude of the bilateral-frontal effect (a) and the left-parietal effect (b), revealed that neither effect was modulated by task performance. These results suggest that the different distributions for face recognition evident between groups in Chapter 6, are not simply caused by differences in task performance. A significant correlation between left-parietal effect magnitude and performance was found in the picture task, however a stronger correlation was found with old/new effect magnitude over left frontocentral electrodes between 500-800ms. The left-frontocentral correlation was also evident for the word task. The timing of the effect was not restricted to the 500-800ms time-window, but was sustained between 200-900ms. Chapter 7 also showed the surprising finding that whilst behavioural performance correlated across the picture and word tasks, the magnitude of the left-parietal effect did not, suggesting the magnitude of the left-parietal effect is not an individual inherent characteristic (although comparisons of effect magnitude across tasks employing the same type of stimuli are necessary to confirm this). Therefore, overall, the results from Chapter 7 suggest that the left-parietal old/new effect does not provide a reliable index of memory performance, either between individuals on the same task, or within individuals across tasks.

9.1.4 Is recognition memory sensitive to genetic variation?

The final data chapter, Chapter 8, examined the influence of genotype in the word and picture tasks, revealing a number of significant genotypic differences on both behavioural measures (a) and ERP recognition memory effects (b). Polymorphism of APOE, COMT, and PRKCA appear to be particularly influential on the pattern of ERP activity exhibited in both the picture and word tasks. Interestingly, analysis of two relatively high profile memory SNPs, BDNF and KIBRA, failed to find significant genotypic differences in either behavioural measures or ERP effects. These results show that genetic differences in neural activity are detectable with ERPs and highlight the potential use of ERPs as a tool to understand genetic differences in relation to cognition. Whilst any conclusions drawn about the role of the different SNPs on episodic memory are made tentatively, the findings highlight the degree of variation in old/new ERP recognition effects across participants and may explain some of the discrepancies in effect distribution that have been reported in the literature.

9.2 Theoretical implications

The literature reviewed in Chapters 2 and 3 suggests that the bilateral-frontal and left-parietal old/new ERP effects, typically associated with recognition memory processes, may only occur under specific conditions, relating to task and participant. The data presented in this thesis further highlights the conditional nature of the two recognition effects, showing distributional differences as a result of stimulus material (Chapter 5), and participant genotype (Chapter 8). Interestingly, contrary to expectations, neither the bilateral-frontal effect for words nor pictures, nor the left-parietal effect for words, were sensitive to variations in behavioural performance. However, activity over left-frontocentral electrodes between 200-900ms was found to be sensitive to behavioural

performance in both the word and picture tasks (Chapter 7). From these results, two key themes emerged: firstly, the results question the role of parietal activity in episodic memory retrieval, and secondly the results suggest that individual differences play an important role in the pattern of brain regions engaged during recognition memory. The next section will consider these themes in more detail, before discussing possible future research.

9.2.1 The role of parietal activity in episodic memory

One of the most interesting findings in this thesis was the failure to find a significant correlation between the magnitude of the left-parietal old/new effect and recognition performance (as indexed by *Pr*) in the word task, despite a comparatively large number of participants and large variability in performance scores. As discussed in Chapter 7 it was hypothesised that if the left-parietal effect is a correlate of recollection, as is suggested in the literature, then an increase in recognition performance, and presumably an increase in recollection, would be reflected by an increase in the magnitude of the left-parietal effect. Analysis of behavioural data from subsidiary experiments confirmed significant correlations between *Pr* and both source accuracy and proportion of 'remember' responses, suggesting that the assumption of a positive correlation between performance and recollection was not unfounded. Hence, if recollection increases with recognition accuracy but left-parietal effect magnitude does not, what do changes in left-parietal effect magnitude reflect? Furthermore, the absence of behavioural differences between participants with a typical (hits greater than CRs) left-parietal effect and those with a 'reverse' left-parietal effect (CRs greater than hits) raises questions regarding the functional role of parietal activity in episodic memory.

The parietal cortex has been implicated in episodic memory retrieval through a number of neuroimaging studies, with ERP studies showing that the left-parietal effect tracks the presence of recollection in R/K and source memory tasks (as discussed in Chapter 2). Event-related fMRI studies have also shown greater activation of the parietal cortex for correctly recognised 'old' items compared to 'new' items (for reviews see Wagner, Shannon, Kahn & Buckner, 2005; Cabeza, Ciaramelli, Olson & Moscovitch, 2008; Vilberg & Rugg, 2008). However, the late onsetting frontopolar old/new effects in the recognition for voices tasks (Chapter 5) suggests that successful retrieval can occur in healthy participants without either the bilateral-frontal or left-parietal effects typically associated with recognition memory and, more generally, without parietal activity.

In contrast to the findings of neuroimaging studies, patients with parietal lobe damage do not typically show amnesia and, studies have shown that recognition memory performance does not differ between controls and patients with left parietal lesions and patients with right parietal lesions (Simons, Peers, Hwang, Ally, Fletcher & Budson, 2008; Ally, Simons, McKeever, Peers & Budson, 2008), or patients with bilateral parietal lesions (Simons, Peers, Mazuz, Berryhill & Olson, 2010). Similarly, Rossi et al. (2006) found repetitive transcranial magnetic stimulation (rTMS) of the parietal cortex in healthy participants (at sites P3 and P4 from the 10-20 international EEG system), did not significantly disrupt episodic encoding or retrieval of visual scenes, suggesting that the parietal cortex is not directly involved in successful episodic memory retrieval (although see Vilberg & Rugg, 2008, for an alternative interpretation of the results from Rossi et al., 2006).

Berryhill, Phuong, Picasso, Cabeza and Olson (2007) suggest that whilst patients do not typically show signs of amnesia, more subtle episodic memory deficits may be

occurring. Berryhill and colleagues conducted detailed assessment of the autobiographical memories of two patients suffering bilateral parietal lobe damage, finding that patients performed as well as the control group when asked specific pointed questions, but showed impoverished memories during free recall that lacked the same level of detail shown by the control group. These results suggest that memory in patients with parietal lobe damage remains intact, but that they lack the internal retrieval cues necessary to produce rich, detailed memories during free recall. Similarly, Davidson et al. (2008) found reduced richness of autobiographical memories in patients with parietal cortex damage and, a reduced number of 'remember' responses in a paired definition-word memory task, compared to the control group. However, despite the reduction in the number of 'remember' responses made in this task, patients were conversely not impaired on source memory accuracy (whether the words were presented visually or auditorily). Finally, Simons et al. (2010) found that patients with bilateral parietal lobe damage showed reduced confidence in their ability to recollect source information, despite performing as well as matched control participants. These findings therefore suggest that whilst patients with parietal lobe damage do not suffer from amnesia they do show some evidence of episodic memory impairment, particularly in relation to subjective measures of memory phenomena.

In light of the evidence presented above, Simons et al. (2010) suggest that the involvement of the parietal lobe in episodic memory relates to the 'subjective' experience of episodic memory, rather than the 'objective' recollection of details. These studies of patients with parietal lobe damage show that memory impairment is not related to task performance, but show evidence of disruption in the 'richness' of the experience of retrieving. In addition, consistent with the idea that the parietal lobe contributes to the 'subjective' experience of episodic memory, Wheeler and Buckner

(2003) found increased activation of the left parietal cortex for 'new' items incorrectly characterised as 'old' (false alarms) compared to correctly identified 'new' items (CRs). The results of Wheeler and Buckner suggest that parietal activity is sensitive to the perceived 'oldness' of stimuli, rather than simply to genuinely 'old' stimuli, supporting the hypothesis that parietal activity reflects the 'subjective' experience of memory.

If the task performance data from Chapter 7 is reconsidered in terms of the 'subjective' experience account of parietal activity, then the lack of correlation between the left-parietal effect and task performance is no longer surprising, because task success does not provide information about the retrieval 'experience'. Similarly, from this perspective, the ERP differences between the typical left-parietal and the 'reverse' left-parietal groups could be interpreted as reflecting differences in the way the two groups 'experience' recollection.

In relation to the voice task the lack of parietal activity may indicate that participants did not 'experience' recollection, despite being able to successfully complete the task, in a way similar to the patients with parietal lobe damage. The reduced 'subjective experience' for voices may be the result of the homogeneity of the stimuli and task difficulty that reduced the opportunity to make each trial a unique distinguishable experience. Similarly, the face task could also be argued to be less conducive to a rich 'subjective' experience than the word task (in which each word represents a distinct object or place), reflected by the smaller left-parietal effect magnitude for faces. Therefore whilst it was initially concluded that the material specificity effects evident in the literature, and in Chapter 5, were not the result of stimulus homogeneity, if considered specifically in relation to the left-parietal effect (rather than to the global pattern of ERP activity), then stimulus homogeneity may play an important part in the

'subjective experience' of an event and consequently the magnitude of the left-parietal effect (particularly for voices, faces and words).

In relation to pictures, Chapter 5 clearly indicates a more anteriorly distributed effect compared to words, which may go against the 'subjective' experience argument, on the basis of stimuli richness. Whilst the picture stimuli are the richest stimuli presented in the current study, there are a number of possibilities that may explain the more anterior distribution of the old/new effect in the 500-800ms time-window. Firstly, the old/new effect for pictures between 500-800ms is a posterior effect with overlapping anterior activity. The anterior activity may reflect an additional process engaged during picture recognition not seen for words. It is not currently possible to dissociate different processes occurring at the same time using ERPs, making it difficult to gain an accurate estimate of the magnitude of the left-parietal effect in isolation. Secondly, whilst the pictures are visually rich, they may not stimulate internally rich memories of the event in which they were encountered, because the inherent richness of the stimuli themselves is sufficient to complete the recognition task. Therefore, whilst at first glance the results from the picture stimuli may argue against the hypothesis that the left-parietal effect reflects the 'subjective' experience of episodic recollection, further consideration of the stimuli in terms of the internal experience, does not sufficiently argue against it.

In addition to the 'subjective experience' account, two other prominent theories of parietal memory activity require consideration – the episodic buffer account (Vilberg & Rugg, 2008) and the attention to internal representations account (Wagner, 2005). Before discussing these two alternative accounts in more detail, it is first important to draw a distinction between two areas of the parietal cortex, which are divided by the intra-parietal sulcus (IPS) – the dorsal/superior parietal cortex (DPC) and the

ventral/inferior parietal cortex (VPC). In relation to dual-process models of recognition memory, the DPC has been associated with familiarity and the VPC with recollection (e.g., see Berryhill et al., 2007).

9.2.1.1 Episodic buffer model

The episodic buffer, described by Baddley (2000), acts as an interface between working memory and long-term memory that is controlled by the central executive, temporarily storing and integrating information from a variety of systems into an episodic representation. Vilberg and Rugg (2008) suggest that activation of the VPC reflects the involvement of the episodic buffer, which in combination with other regions, supports the episodic representation of information. In this respect, if the episodic buffer links working memory and long-term memory and, the left-parietal effect reflects recollection and consequently VPC activity, it could be argued that changes in the magnitude of the left-parietal effect would correlate with working memory capacity. That is to say that the ability to hold the content of episodic memory in mind, in the episodic buffer, would be reflected by VPC activity and consequently the magnitude of the left-parietal effect.

The data presented in this thesis provides little direct support for this view: analysis of the magnitude of the left-parietal effect with SWM scores from the CANTAB failed to find significant differences between left-parietal effect magnitude in the word tasks and SWM measures of strategy ($r=0.126$, $p=0.167$), total errors ($r=0.088$, $p=0.336$), and between stage errors ($r=0.085$, $p=0.355$). However, whilst this suggests that general working memory capacity does not correlate with left-parietal effect magnitude, this is not to say that differential engagement of working memory during task completion would not modulate the magnitude of the ERP effect. The lack of correlation between the size of the left-parietal effect across different recognition tasks (as presented in

Chapter 7), suggests that magnitude of the effect varies with the specific engagement of cognitive processes during the task, rather than reflecting cognitive abilities such as working memory in general. Therefore analysis of left-parietal effect magnitude and engagement of working memory would need to be conducted on the same task to fully evaluate the episodic buffer model.

9.2.1.2 Attention to memory model

The final model considered in this chapter is the attention to memory (AtoM) model, an extension of the attention to internal representations account – the suggestion that parietal regions are involved in the direction and maintenance of attention to internal mnemonic representations (Wagner et al., 2005). The AtoM model shares the same basic principles as the attention to internal representations account, but extends the account by drawing a distinction between the role of the DPC and VPC. According to the AtoM model the DPC is involved with the intentional allocation of attention relating to the internal goals of the individual – top-down attention, whereas the VPC is associated with reflexive attention, captured by retrieved information – bottom-up attention (Cabeza et al., 2008). Therefore, the DPC maintains the retrieval goals and modulates MTL activity, whereas the VPC signals a need for attention, detecting relevant information from the MTL. In relation to the patients with parietal damage presented by Berryhill et al. (2007), the AtoM model suggests that deficits in the free recall of detailed information are due to damage to the VPC, resulting in problems with the detection of information recovered from memory.

If the left-parietal effect is sensitive to changes in recollection and VPC activity reflects recollection, the AtoM model would suggest that the magnitude of the left-parietal old/new effect reflects variation in bottom-up attention. Participants exhibiting the

largest old/new effects would therefore attend to the contents of retrieval better than those with smaller effects. Whilst the AtoM model suggests the parietal regions essentially support episodic retrieval through the allocation of attentional resources, it is not clear how the model would account for participants who exhibit 'reverse' parietal effects in the word and picture tasks, nor the absence of parietal activity in the voices task.

One possibility is that participants showing reverse effects are allocating attention to the identification of 'new' items more than 'old' items, resulting in more positive going ERPs for CRs than hits over parietal electrodes. That is, perhaps variation in left-parietal effect magnitude reflects not only the degree to which an individual is attending to the contents of retrieval but also the degree to which attention is focused on deciding if the information is 'old', or deciding if the information 'new'. However, if the left-parietal effect did reflect such differences in decision criteria (i.e. differences in whether 'old' or 'new' items are considered the target), it would be expected that decision bias (*Br*) would correlate with effect magnitude. Analysis of the word and picture data from the current study showed that this was not the case for the word task ($r=0.032$, $p=0.725$), although a significant correlation between left-parietal effect magnitude and *Br* was found for the picture task ($r=0.214$, $p=0.018$). Furthermore, in an *f*MRI study Shannon and Buckner (2004) found that hit responses showed significantly greater activity than CRs over inferior parietal lobule complex and precuneus complex irrespective of whether participants made responses to both 'old' and 'new' items, 'old' items only, or 'new' items only. If parietal cortex activity reflected the allocation of attention to a specific category of items, it would be expected that CRs would elicit greater activity than hits when participants were instructed to only respond to 'new' items. The results from Shannon and Buckner therefore suggest that the 'reverse' left-

parietal effect in the current study does not reflect the allocation of attention to 'new' items instead of 'old' items.

In conclusion, the data presented in this thesis questions the role of the left-parietal effect in episodic memory and, by extension the parietal cortex, notwithstanding concerns about source localisation of ERP data. The results have been discussed in relation to a number of theories regarding the function of the parietal cortex in episodic memory, including theories of 'subjective' experience, episodic buffer and attention. The inherent problem of spatial resolution in ERPs makes it difficult to interpret the pattern of ERP activity in relation to patient models and anatomical models that separate the DPC and VPC. A number of assumptions regarding the overlap between ERPs and other neuroimaging methods (such as fMRI), and also the relationship between the left-parietal effect and recollection, have to be made to assess the current results in terms of these theories. The data from the current thesis cannot be fully explained through any of the three models discussed, leaving the question of the functional role of parietal activity in episodic memory open.

9.2.2 The role of individual differences in episodic memory

The second central theme in the thesis is the important role that individual differences play in episodic memory, particularly in terms of the ERP correlates of recognition memory. As discussed in Chapter 2, investigations of memory processes typically average together the data from many participants to reduce the contribution of noise to the ERP signal of interest. Whilst this is an essential step in the pursuit of greater understanding of the neural activity associated with particular cognitive processes, the averaging step may remove individual variations that could be informative in understanding how memory processes work and how they fail. Importantly, the data

presented in this thesis shows clear evidence of individual differences in the ERP activity associated with recognition memory.

Chapter 6 revealed distributional differences in two groups of participants in the face-verbal phrase source task, with participants who were in general poorer at face recognition showing an early 300-500ms old/new effect not present for participants who were better at face recognition (as indexed by successful completion of the single item for faces task). In the ERP old/new effect literature the 300-500ms time-window is typically associated with familiarity, however the findings in the literature relating to the ERP correlates of face recognition are inconsistent, especially with regards to the correlates associated with familiarity. Curran and Hancock (2007) report a bilateral-frontal effect, whereas Mackenzie and Donaldson (2007) report a posterior effect. The data from the current thesis indicates that not all participants exhibit an early old/new effect and, those that do show poorer performance. The results from the current study therefore suggest that the 300-500ms old/new affect for faces may be an additional support process, which is not necessary for successful retrieval but may be engaged to assist in recognition if ability is poor. Therefore, the data are not consistent with either side of the current face recognition debate, reflecting the complexity of the issue, but suggests that further examination of individual differences are necessary to understand these discrepancies.

Clear evidence of individual differences was also apparent in Chapter 8, in which genotype appeared to have a significant effect on a number of behavioural measures and revealed topographically distinct effects across genotypes. Whilst on average the pattern of ERP activity in the word and picture tasks are consistent with those reported in the literature (Chapter 5), dividing participants into groups based on different characterising

features (such as genotype) indicates that the 'typical' bilateral-frontal and left-parietal effects are not the definitive pattern of ERP recognition activity. These results confirm that potentially important individual variations are typically being overlooked and ignored.

In addition, dividing participants into groups based on characterising features of exhibited ERP effects, such as left-parietal effect magnitude (Chapter 7), revealed that distinct patterns of ERP activity in the word task did not reflect distinct patterns of behavioural scores. These results strongly suggest that participants may be engaging different processes in order to achieve the same outcome. In addition, the processes engaged by an individual may vary depending on the task being completed, as indicated by the lack of correlation between effect magnitude in the word and picture tasks. Taken together the findings from this thesis suggest that the specific processes engaged during retrieval (as indexed by variations in ERP activity) may depend on the specific requirements of the task, the type of stimuli being retrieved, the genetic makeup of the individual, as well other individual factors evident in the literature, but not directly addressed in this thesis (e.g., age and sex).

In conclusion, individual differences should not be overlooked and may provide valuable insight into memory processes. Looking at healthy 'outliers' can help to assess the validity of a theory and may be beneficial in identifying occasions where consistent results may actually reflect a moderating factor, rather than a modulation of the process of interest. That is, in much the same way that it is currently difficult to tell if a particular SNP is an active polymorphism (or if it is simply a co-varying SNP, or a SNP downstream from a functionally active polymorphism). Looking at outliers may provide

insight into whether a particular ERP effect is functionally associated with the cognitive process of interest, or it is a co-varying or down-stream effect.

9.2.3 Future directions

The research presented in this thesis suggests that individual differences influence the ERP activity associated with recognition memory. As discussed in Chapter 2 ERPs have the potential to be used as biomarkers to predict and monitor disease progression and treatment effectiveness. However, before ERPs can be implemented as disease biomarkers reliable effects that accurately reflect behaviour need to be found. ERP word repetition effects have already been proposed as biomarkers for memory disorders (Olichney et al., 2002; Olichney et al., 2006), however the data presented in this thesis suggests that memory related ERP effects are subject to variation based on individual differences such as genotype. In addition the left-parietal old/new effect does not reflect behavioural changes and appears inconsistent across tasks, making it currently unsuitable for use as a biomarker. In order for recognition memory ERP effects to be successfully used as biomarkers serious consideration needs to be undertaken of: a) the specific process the biomarker aims to track; b) the development of a series of standardised tasks that produce consistency both within individuals across several assessments and, between participants tracking behavioural measures; and c) modulating factors (i.e. genotype). Although these conditions may be met, Luck (2005) suggests that between participant variability in EEG may be largely influenced by individual differences in the folding pattern of the cortex, which questions the overall suitability of ERPs as biomarkers.

The results from this thesis also suggest that genotype may affect the pattern of recognition memory activity. Whilst replication of these results are needed, further

investigation of the significant SNPs should be undertaken to understand specifically what is driving the topographic differences – whether they reflect different strategic processes, or if they are different manifestations of the same process. The occurrence of topographically distinct effects for different genotypes suggests that future research investigating memory processes should report the genotypes of each research sample, on a number of SNPs (including APOE, COMT, PRKCA), in a similar manner to the way age and sex are currently routinely reported, to help understand discrepancies in the literature and assist replication.

Further investigations into participants exhibiting 'reverse' left-parietal effects should also be conducted to try to understand what causes these atypical patterns, and how these might relate to current theories of familiarity and recollection. These 'reverse' effects do not appear to be participant specific, as this pattern of activity was not consistent across tasks, suggesting that it may reflect strategic differences in the way the task is completed. In the current study effect comparisons were made across two procedurally identical tasks that differed in the stimuli used and were shown in Chapter 5 to exhibit overall different patterns of neural activity. Comparisons are therefore needed of effects from two tasks that use the same stimuli, to see if the inconsistency across the word and picture tasks relate to differences in stimuli, rather than participant specific differences. The same type of task (e.g., a simple old/new word recognition task), completed on more than one occasion, would indicate whether ERP effects are stable within individuals over time. Comparisons of differing tasks with the same stimulus material (e.g., a simple old/new word recognition task and a word-colour source memory task) would indicate whether ERP effects could be generalised across tasks; that is, if the effects from one type of task can be used to predict the effects on a second differing task.

Finally, the word and picture tasks used in the current study to investigate individual differences and episodic memory do not provide estimates of familiarity and recollection, and therefore limit the conclusions that can be drawn about the relationship between memory performance and the 'typical' ERP old/new effects. The results presented here demonstrate substantial differences in the magnitude of these old/new effects across participants, and additional research is needed to further examine the relationship between these effects, memory performance, and the contribution of familiarity and recollection to successful retrieval. More specifically, additional research is needed to understand the relationship between left-parietal effect magnitude and recollection; that is, to determine if effect magnitude variation reflects differences in the amount of information recollected or in the strength of recollection.

9.3 Conclusion

The aim of this thesis was to investigate individual differences and episodic memory to gain a greater understanding of how episodic memory differs as a function of stimulus material, performance and individual features such as genetic polymorphisms. Using a recognition memory task to investigate the ERP correlates of episodic memory, the findings from the current thesis question the function of parietal activity in episodic memory and the reliability of ERP effects as an index of recognition memory. In addition, this thesis highlights the importance of considering individual differences when investigating memory processes and suggests that the processes engaged during episodic retrieval (at least as indexed by ERP old/new effects) may differ as a function of stimuli, general recognition ability, and genetic makeup. In sum, individual differences matter.

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