Long-term Neuropsychological Outcome following Subarachnoid Haemorrhage or Traumatic Brain Injury

Relationship with clinical indices & Apolipoprotein E genotype

Thesis submitted in fulfilment of requirements for the degree of

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Abstract

Purpose: The principal aim of this project was to investigate the influence of clinical indices of injury severity and polymorphism of the apolipoprotein E gene upon the long-term physical, cognitive and emotional sequelae of traumatic brain injury and spontaneous subarachnoid haemorrhage. It was also intended to determine the extent to which changes occur in these sequelae beyond the initial six months post injury.

Method: Sixty-two brain injury patients who had previously taken part in a neuropsychological assessment at six months post injury were traced and participated in a follow-up assessment some 6-9 years subsequent to their injury. Separately, a group of 70 subarachnoid patients drawn from a consecutive series of neurosurgical admissions participated in a neuropsychological assessment at 14 months subsequent to their haemorrhage. In both studies, the assessment comprised a semi-structured interview and a battery of cognitive measures focusing principally upon memory and executive function tasks. A questionnaire including a range of standardised measures of anxiety, depression and quality of life was left with patients to be returned by post.

Results: The ApoE ε4 allele did not appear to influence recovery amongst these brain injury survivors, though there are suggestions that it may have an influence upon subgroups of patients. Amongst traumatic brain injury survivors, post-traumatic amnesia was a better predictor of functional or emotional outcome than consciousness based measures. However, consciousness based measures were more predictive of cognitive sequelae and low admission Glasgow Coma Scale was associated with continued improvement on information processing tasks. Other than on these tasks, there was little evidence of change between 6 months and 6-9 years post injury. Amongst the subarachnoid haemorrhage patients, Fisher Grade was found to be more predictive of subsequent Glasgow Outcome Scale and cognitive function than WFNS Grade or other clinical indices. Surviving aneurysmal patients had comparable levels of recovery to patients who had a negative angiogram. In both studies emotional sequelae, in particular anxiety-related difficulties, were found to be a principal factor in the functional outcome of some 40% of patients.

Conclusions: Greater emphasis should be placed upon measures of post-traumatic amnesia as predictors of functional recovery in surviving patients. The use of an amnesia measure may also be warranted in studies of outcome following subarachnoid haemorrhage or other stroke. The ApoE ε4 allele does not appear to have a strong influence upon functional recovery after brain injury across all patients, though it is possible that it interacts with other factors to influence recovery in subgroups. Greater emphasis should be placed upon the prevention and / or detection and treatment of mood disorders following brain injury. In the absence of intensive rehabilitative interventions, survivors of serious brain injury are more likely to deteriorate than to continue to recover beyond six months post injury.

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Both studies were undertaken in collaboration with the research teams based in the Departments of Neurosurgery and Neuropathology at the Southern General Hospital in Glasgow. This included the support of Professor Graham Teasdale for the head injury study, Laurence Dunn for the subarachnoid haemorrhage study and Dr James Nicoll who arranged all of the APOE genotyping.

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Chapter 1 Subarachnoid Haemorrhage

Introduction & Overview

Subarachnoid haemorrhage is a form of haemorrhagic stroke that occurs when a blood vessel ruptures or leaks such that blood accumulates in the subarachnoid space. The haemorrhages are usually separated into those of traumatic origin, an occasional consequence of traumatic head injury, and those that occur spontaneously. The majority of spontaneous subarachnoid haemorrhages (SAH) are aneurysmal in origin with the source of the bleed identified as a cerebral aneurysm, usually at the bifurcation of the arteries at the base of the brain. These aneurysmal SAH account for approximately 85% of SAH, with a further 10% due to non-aneurysmal perimesencephalic haemorrhage and the remainder due to rare conditions.

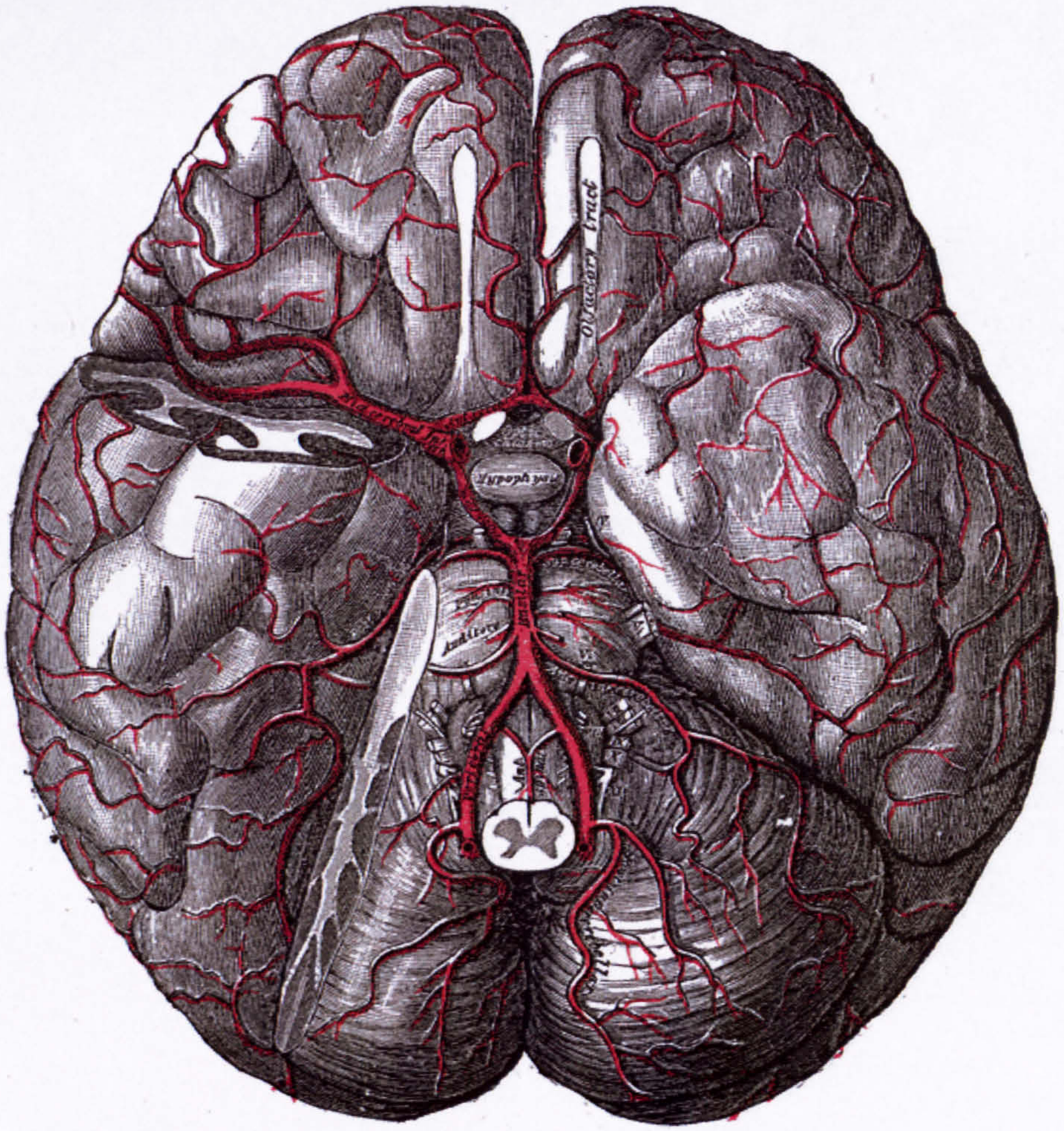
Although the incidence of SAH is fairly low, perhaps as few as 6 cases per 100,000 population each year, the consequences of aneurysmal haemorrhage are often dire, with approximately half of those affected dying within the first few days and many survivors left with considerable physical and / or psychological impairments. For the approximately 85% of patients who reach hospital alive, diagnosis is increasingly confirmed by CT and, where surgery is indicated, the aneurysm site is generally identified by cerebral angiography. Improvements to neurosurgical technology and techniques have enabled a greater proportion of ruptured aneurysms to be successfully clipped or otherwise treated in the days immediately following haemorrhage and this has improved survival rates and prognosis amongst those who reach neurosurgical units.

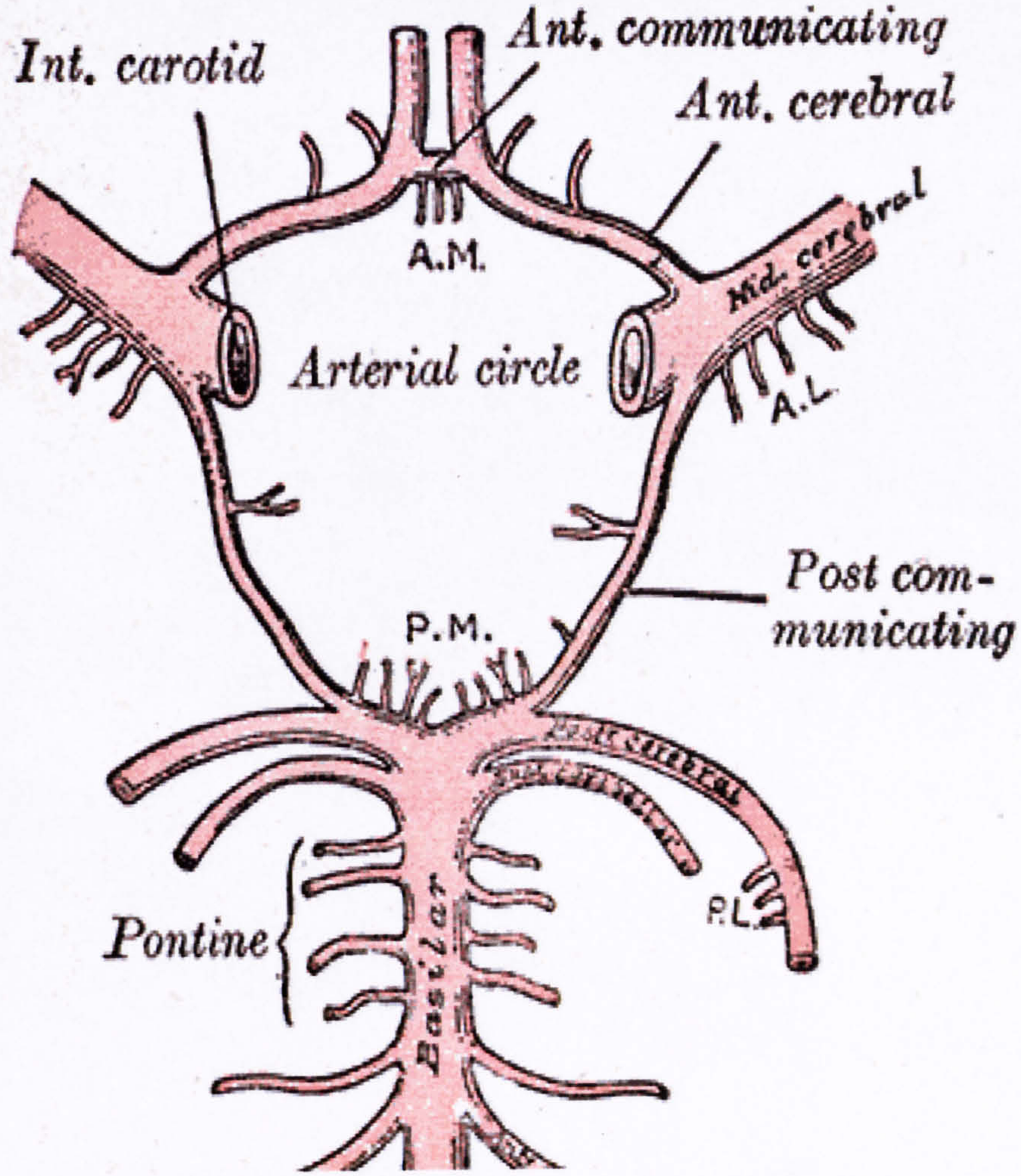
Types of Subarachnoid Haemorrhage

Aneurysmal Subarachnoid Haemorrhage

The most frequently encountered SAH, comprising some 85% of spontaneous cases, is the aneurysmal form caused by the rupture of an intracranial saccular aneurysm located at the base of the brain. These aneurysms form at the branch points of the major arteries around the circle of Willis (Figure 1-1) (Gray 1918) and are estimated by autopsy and angiography studies to be present in 2-6% of the population, with this figure rising with age such that they are very rare before the age of 20 and found in around 6% of those aged 60 or over (Ujiie, Sato et al. 1993). Approximately 85-90% of these aneurysms are found in the anterior circulation, with the most frequent sites including the branch point of the anterior cerebral arteries with the anterior communicating artery (ACoA), branch points on the left and right middle cerebral artery (MCA) and the branch point of the internal carotid artery (ICA) with the posterior communicating artery. Most aneurysms of the posterior circulation are at the tip of the basilar artery (BA). The relative frequencies of aneurysms found in a series of 326 consecutive patients and divided into four groups (Vermeulen, Lindsay et al. 1984) are shown in Table 1-1.

Figure 1-1 The Circle of Willis





Diagrams adapted from Gray's Anatomy of the Human Body (1918)

Table 1-1: Site of Ruptured Aneurysm

Site of Aneurysm	Number	Percent
Anterior Communicating Artery Complex	134	41
Internal Carotid Artery / Posterior Communicating	101	31
Middle Cerebral Artery	60	18
Posterior Circulation	31	10

(From Vermeulen et al 1984)

It was once assumed that aneurysms were congenital defects due to weakness in the vessel wall caused by interruptions of the tunica media. However this is no longer thought to be the case as such interruptions occur equally frequently in patients without aneurysms. Additionally, aneurysms are virtually never present in the brains of neonates, are very rarely encountered in children and appear to increase in frequency with age. It has subsequently been suggested that aneurysms are induced by haemodynamic stress, which causes disruption to the internal elastic lamina (Stehbens 1989). The sites at the arterial bifurcations are subject to the greatest haemodynamic stress and thickening of the internal elastic layer occurs here forming pads both distal and proximal to the bifurcation. This disruption to the elastic lamina increases the likelihood of aneurysm formation. Hypertension or connective tissue disease may facilitate this process, but are not necessary for the formation of the intracranial aneurysm.

Perimesencephalic Haemorrhage

This is a non-aneurysmal cause of SAH comprising some 10% of cases and which is relatively benign in contrast to the often devastating consequences of aneurysmal SAH. Approximately two-thirds of SAH cases in which the angiogram is negative are thought to be due to perimesencephalic haemorrhage (Ferbert, Hubo et al. 1992). The centre of these haemorrhages appears to be anterior to the midbrain and the blood gathers in the cisterns around the midbrain (Rinkel, Wijdicks et al. 1991c). The onset of headache is often gradual and loss of consciousness is rare. Patients with this form of SAH are usually apparently well except for the presence of headache (Rinkel, Wijdicks et al. 1991b) and have been reported to make a full recovery after a brief period of convalescence (Rinkel, Wijdicks et al. 1990; Rinkel, Wijdicks et al. 1991a). Re-haemorrhage in these patients is rare but has been documented (Marquardt, Niebauer et al. 2000). The precise aetiology of perimesencephalic haemorrhage is uncertain, in part due to the excellent prognosis corresponding with a poverty of post-mortem studies, though it is possible that the haemorrhage may be due to the rupture of a vein or venous malformation in the prepontine or interpenduncular cistern.

Cerebral Arteriovenous Malformations

These vascular abnormalities were previously thought to be responsible for a considerable proportion of observed SAH. However, the increased usage of CT scanning has demonstrated that the majority of arteriovenous malformations (AVMs) haemorrhage into parenchyma or ventricles rather than the subarachnoid space, though some have secondary extension into the subarachnoid space (Aoki 1991). Consequently AVM haemorrhage is a fairly rare cause of primary spontaneous subarachnoid haemorrhage.

Other Rare Causes of Subarachnoid Haemorrhage

Many unknown aetiology SAH cases are likely to be undiagnosed cases caused by the above reasons. Other rare causes of SAH include cerebral artery dissection, tumours, coagulation disorders, cocaine usage, pituitary apoplexy, and sickle cell disease. These rare causes combined account for a very small percentage of spontaneous subarachnoid haemorrhage cases.

Incidence

The incidence of SAH is fairly low, accounting for only approximately 5% of all strokes, though there appears to be considerable variation across populations. A recent World Health Organisation (WHO) epidemiological study using uniform methodology found a ten-fold variation, ranging from an annual incidence of 2.0 per 100,000 in China-Beijing to 22.5 per 100,000 in Finland (Ingall, Asplund et al. 2000). It is likely that some of the lower figures are under-estimates due to differences in post-mortem and 'sudden death' management procedures which lead to many early fatalities never being identified as due to SAH. A meta-analysis of 18 studies found a combined annual incidence of 7.8 per 100,000 in 15 non-Finnish studies (Linn, Rinkel et al. 1996). They estimated that this figure would be nearer 6 per 100,000 if CT had been used to confirm SAH in all cases. In contrast, the pooled incidence for the three Finnish studies was 21.4 per 100,000, with this enhanced incidence remaining over double that of the other studies after adjusting for year of study and use of CT.

This finding of considerably enhanced risk in Finland is fairly robust and may reflect as yet unidentified genetic risk factors amongst this population or possibly higher prevalence of hypertension. Other cardiovascular diseases also occur with higher frequency in Finland (Thorvaldsen, Asplund et al. 1995) indicating an increased susceptibility which is not specific to aneurysmal SAH. Linn et al (1996) suggest that apparent declines in the incidence of SAH over the past three decades can be explained entirely by the increased use of CT scanning, which increases the accuracy of diagnosis.

Risk Factors

A host of factors have been associated with SAH, but in many cases the studies had combined SAH with the more frequently encountered intracerebral haemorrhage (ICH) to form a haemorrhagic stroke group (Klatsky, Armstrong et al. 1989; Shinton and Beevers 1989). A recent study emphasises that the risk factors differ somewhat between these haemorrhagic strokes and thus that they ought to be considered separately (Juvela 1996). In studies that have done so, often reported risk factors have included hypertension, smoking, alcohol abuse, female gender and a family member with previous SAH, each of which shall be considered in turn below. Other risk factors which apply to a smaller percentage of the population and which predispose to haemorrhagic stroke in general include the use of anticoagulants, aspirin or cocaine.

Hypertension

Hypertension has been identified as a risk factor for SAH by a number of studies, both longitudinal (Knekt, Reunanen et al. 1991) and case control (Bonita 1986). A review of studies found that hypertension increased the risk of haemorrhage almost three-fold (Teunissen, Rinkel et al. 1996). However, whilst interventions aimed at reducing hypertension have succeeded in reducing the incidence of stroke in general, no such decline has been observed in the incidence of SAH (Sytkowski, Kannel et al. 1990; Vartiainen, Sarti et al. 1995). Teunissen et al (1996) suggest that this is an artefact of the relatively low incidence of SAH, such that it would be more difficult to detect a change. However there is evidence that hypertension may be a less significant risk factor for SAH than it is for ICH (Juvela 1996) and other studies also suggest a lesser influence of hypertension upon SAH relative to other stroke types (Longstreth, Nelson et al. 1992).

Smoking

Smoking is one of the most consistently reported risk factors for SAH. In contrast to many of the other risk factors, smoking is reported to be a greater risk factor for SAH than for ICH (Juvela 1996). Several studies have noted an increased risk of SAH for smokers (Shinton and Beevers 1989; Longstreth, Nelson et al. 1992; Juvela, Hillbom et al. 1993). A review of 7 case-control studies found elevated risk of current smoking with an odds ratio of 3.5 (Teunissen, Rinkel et al. 1996). It has been suggested that smoking may increase the likelihood of aneurysm formation via the release of proteolytic enzymes which damage the arterial walls (Juvela, Hillbom et al. 1993). Alternatively, or additionally, transient acute increases in blood pressure induced by smoking may increase the likelihood of aneurysmal rupture.

Alcohol Abuse

The Teunissen review (1996) found a 4.7 relative risk for those who drank in excess of 150g per week based on two longitudinal studies. However, the relative risk based on three case control studies was only 1.5, and after the three Finnish studies were excluded from the analysis, alcohol intake was no longer a risk factor. Other studies have reported conflicting findings, with some indicating no increased SAH risk with alcohol (Klatsky, Armstrong et al. 1989), whereas an increased risk of ICH is indicated (Juvela, Hillbom et al. 1995). It is possible that the mixed findings with respect to alcohol may in part be a consequence of the strong correlation between alcohol use and smoking, such that alcohol use may be serving as an indirect flag for smoking behaviour rather than having an aetiological role in itself.

Gender

A frequent finding is of higher incidence of SAH amongst women, despite the greater occurrence of other risk factors such as smoking, hypertension and alcohol use amongst men. The Linn et al (1996) meta-analysis found only six studies which separated gender, but from these studies women were found to have an incidence 1.6 times greater than that of men. It has been speculated that these differences are due to hormonal changes. However, the WHO study (Ingall, Asplund et al. 2000) reports considerable variation in the relative risk by gender across populations, with age adjusted rates approximately equivalent across gender in East Germany, Italy, Sweden and Beijing, but 40% higher in females in Warsaw and Denmark and in contrast 80% higher in males in Finland and Moscow. A review of the prevalence and risk of rupture of intracranial aneurysms found that women had only a slightly higher prevalence of aneurysms, but that they had over twice the risk of aneurysmal rupture (Rinkel, Djibuti et al. 1998).

Familial Subarachnoid Haemorrhage

Estimates of the percentage of cases with a familial association have been revised upwards in recent years. It is currently thought that at least 10% of those with aneurysmal SAH have a positive family history (Nakagawa and Hashi 1994; Ronkainen, Hernesniemi et al. 1997), though this has been defined by having at least two first degree family members with known intracranial aneurysms and is thus influenced by factors such as family size and the fact that family members may harbour unknown currently asymptomatic aneurysms. Thus it seems likely that this 10% figure is an underestimate. The occurrence of familial cases of SAH is of interest both because of the possibility of identifying genetic risk factors for SAH and because the higher risk of SAH amongst other family members increases the justification for screening and, where appropriate, the preventative elective treatment of unruptured aneurysms.

Case-Fatality Rates

The consequences of SAH are often devastating, with case fatality rates in a recent review varying between 32 and 67% (Hop, Rinkel et al. 1997). The fatality rates in some studies are artificially lowered due to the failure to identify all of those who died before medical help was available or sought or due to the studies adopting age cut-offs such that more elderly patients, who are less likely to survive, are simply not included in the study. There may also be an element of bias with neurosurgical units not wishing to publicise high mortality rates. The Hop (1997) study did however find that mortality rates following SAH have been declining over the past three decades, reflecting considerable improvements in diagnostic and therapeutic tools.

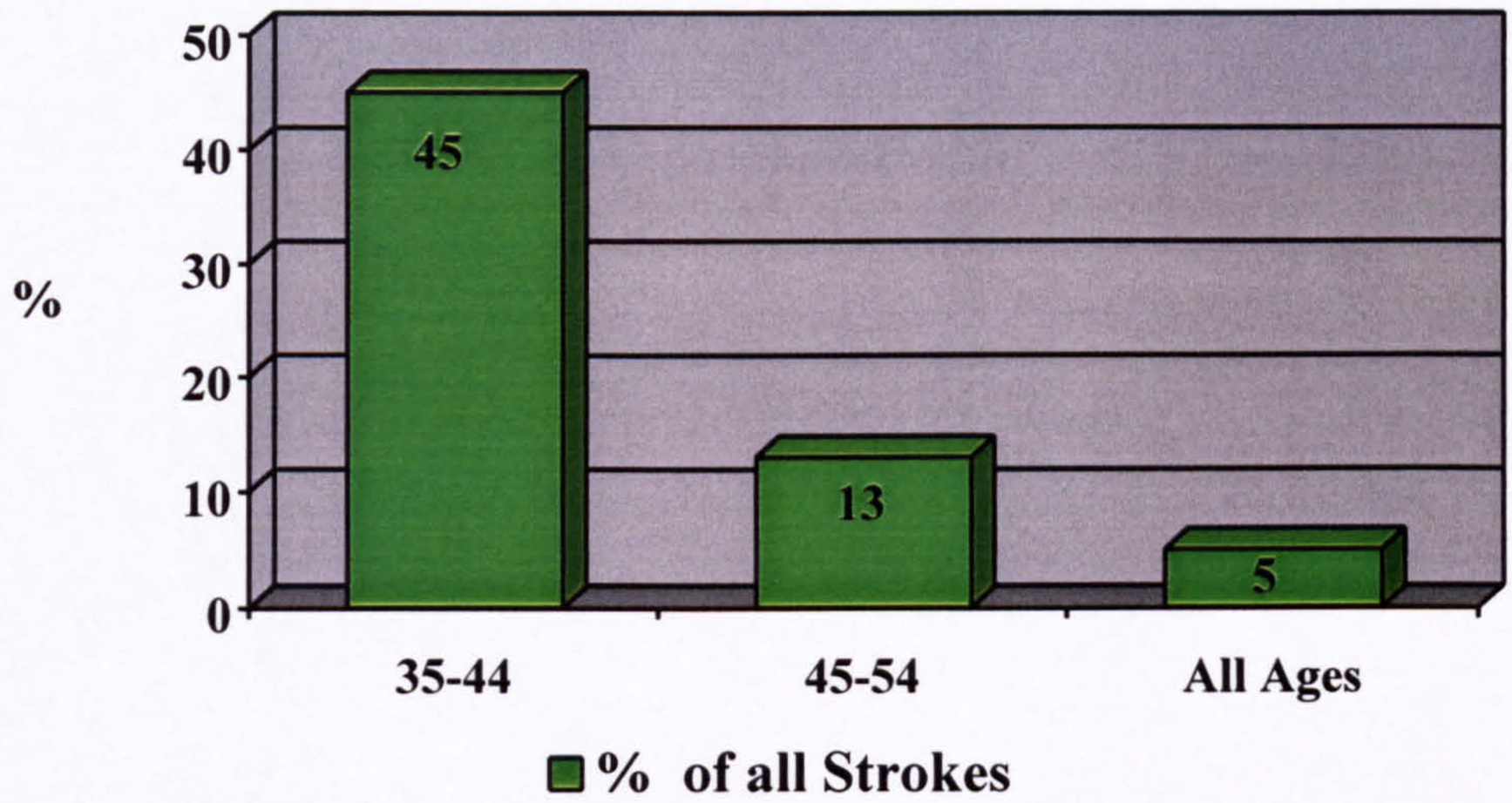
This suggests an increasing number of survivors amongst those who reach a neurosurgical unit. However, approximately 15% of patients die before admission to any hospital and further deaths occur before the patients can be transferred to specialist neurosurgical units for surgical interventions.

Atypical Age Distribution of Subarachnoid Haemorrhage

Although the risk of subarachnoid haemorrhage increases with age, it has been shown to have a linear relationship with age rather than the more exponential relationship typical of other more prevalent strokes. Consequently individuals who suffer a subarachnoid haemorrhage tend to be younger than is typically the case with other types of stroke. Thus although SAH accounts for only 5% of strokes overall, this figure increases dramatically with younger age (Figure 1-2), such that between the ages of 45-54 years 13% of strokes are due to SAH with this rising to 45% in those aged between 35 and 44 years (Bamford, Sandercock et al. 1990).

Therefore many SAH sufferers are in the middle of their lives, often with partners and young children, and the number of productive life years affected by the consequences of the haemorrhage is higher both for the patients and their partners. The atypical age distribution is even more pronounced amongst survivors of SAH, as older patients are significantly more likely to die as a consequence of the haemorrhage.

Figure 1-2: Association between SAH and Younger Stroke Patients



Clinical Signs and Symptoms

In the majority of cases there are no predictive symptoms prior to the haemorrhage and in most cases the first symptoms are the sudden onset of a particularly severe headache. This headache is often described as like a sudden explosion, excruciating, unbearable, the worst headache in their life or feeling as though their head had burst. In many patients the headache is accompanied by vomiting. Loss of consciousness occurs in at least 50%, though this figure does not include the approximately 15% of patients who die before reaching hospital. The loss of consciousness is a consequence of increased intracranial pressure subsequent to the haemorrhage such that it approaches mean arterial pressure and thus cerebral perfusion is reduced. In around 10% of cases the haemorrhage may be severe enough to cause loss of consciousness for several days.

'Sentinel' Headaches & Misdiagnosis

There is some controversy as to whether 'sentinel' or 'warning' headaches, perhaps corresponding to seepage of blood into the subarachnoid space, occur in a proportion of patients prior to the presenting SAH. Certainly many patients do report the occurrence of headaches prior to the main haemorrhage. It is uncertain whether these represent less severe undiagnosed aneurysmal haemorrhages or are merely an artefact of recall bias. In many cases the initial haemorrhage is less severe and the patient may simply retire to bed and not seek medical help until a later stage, perhaps following a repeat haemorrhage.

Even when medical help is sought there are a fairly considerable number, 23% in one study (Adams, Jergenson et al. 1980), who initially receive a wrong diagnosis, such as migraine or gastro-enteritis and may be sent home again. This misdiagnosis has to be put into the context of the low incidence, such that it is estimated that the average GP would only see one case of SAH in every six years of practice. Additionally many 'thunderclap headaches', which mimic the symptomatology of SAH, do not correspond to haemorrhage. However SAH should always be excluded by CT &/or lumbar puncture (Wijdicks, Kerkhoff et al. 1988; Markus 1991) as the consequences of misdiagnosis or failure to seek medical help are often severe due to the considerable likelihood of another haemorrhage with high mortality and morbidity rates.

Hospital Diagnosis

The presenting symptoms mentioned above are suggestive of SAH and may be accompanied by neck stiffness. Motor deficits occur in approximately 15% and are particularly associated with middle cerebral aneurysms. Around a further 15% present with aphasia, which may correspond to an intracerebral haematoma in the dominant hemisphere secondary to ACoA or MCA aneurysm rupture. Third nerve palsy may indicate a posterior communicating artery aneurysm. Ocular haemorrhages occur in a considerable proportion (20-40%) of patients, particularly in those with a more severe haemorrhage. These ocular haemorrhages may be a consequence of the sudden increase in intracerebral pressure causing compression of the central retinal vein (Tsementzis and Williams 1984; Garfinkle, Danys et al. 1992; Pfausler, Belcl et al. 1996).

Computerised Tomography Scanning

Computerised tomography (CT) scanning is recognised by most centres as essential in the accurate diagnosis of SAH and in indicating the extent and localisation of blood. In addition to facilitating diagnosis, the identification of intracerebral haematomas or certain patterns of aneurysmal haemorrhage also indicate the likely location of the ruptured aneurysm, though the aneurysm itself is usually not directly detectable on unenhanced CT scans. Perimesencephalic haemorrhages have a distinct pattern, with blood present mainly or exclusively in the perimesencephalic cisterns. In aneurysmal haemorrhages, the extent and distribution of blood has also been used as a measure of severity of haemorrhage and predictor of subsequent vasospasm. One such measure is the Fisher Grading Scale, shown in Table 1-2 (Fisher, Kistler et al. 1980), which has been used by some studies as a predictor of outcome. CT also enables the detection of hydrocephalus via the assessment of ventricular size.

A negative CT scan does not in itself rule out SAH, particularly if there was a notable delay between ictus and the scan, as blood confined to the subarachnoid space may become undetectable within 24 hours and after an interval of a week blood is undetectable in about 50% of cases (van Gijn and van Dongen 1982). In most cases where there is any uncertainty, lumbar puncture would be performed whereby xanthochromic spinal fluid or red blood cells are indicative of haemorrhage.

Table 1-2. Fisher Grading Scale

Fisher Grade	Description
Grade 0	No scan available
Grade 1	No blood detected
Grade 2	Diffuse deposition or thin layer. All vertical layers of blood <1mm thick
Grade 3	Localised clots and/or vertical layers of blood >1mm thick
Grade 4	Intraventricular or Intra parenchymal blood present

(Fisher, Kistler et al. 1980),

Cerebral Angiography

If diagnosis of aneurysmal SAH is confirmed and if the patient is deemed to be a suitable candidate for surgery, then cerebral four-vessel angiography is generally performed to identify or confirm the location of the aneurysm(s) and indicate their size. Angiography can also demonstrate the presence of cerebral vasospasm. However the procedure itself carries a risk, with one study finding a 1% risk of permanent stroke in patients with recent SAH (Dion, Gates et al. 1987). Thus angiography is not undertaken with all patients, particularly those for whom clinical condition or previous medical history contraindicates surgical interventions.

A negative angiogram may serve as confirmation of a perimesencephalic haemorrhage or may indicate one of several rare causes of SAH. However, it is also possible that a ruptured aneurysm exists but simply was not detected due to its being obscured by other vessels or as a consequence of vasospasm. Thus a repeat angiogram is often arranged before aneurysmal rupture is ruled out due to the risks inherent in the re-rupture of a missed aneurysm.

Complications

Re-haemorrhage

The greatest risk, particularly in the early stages, is of re-haemorrhage due to re-rupture of the aneurysm and corresponding sudden severe headache and likely loss of consciousness. The risk of re-haemorrhage from the unrepaired ruptured aneurysm is approximately 4% during the first 24 hours, then a further 1.5% for each of the next 13 days. Without surgical repair, around 50% are likely to suffer a re-haemorrhage within six months (Winn, Richardson et al. 1977). Repeat CT would be required to confirm the presence of fresh blood and it is likely that some instances of re-haemorrhage are not recorded. A recent study found that despite aims to prevent re-haemorrhage by early surgery, re-haemorrhage occurred in 16% of those patients who were admitted to hospital (Roos, de Haan et al. 2000). This risk is increased by the high blood pressure present in some 50% of patients on admission (Fortuny, Adams et al. 1980). In most cases this hypertension is a physiological response to the rise in intracranial pressure due to the haemorrhage and serves to facilitate cerebral perfusion.

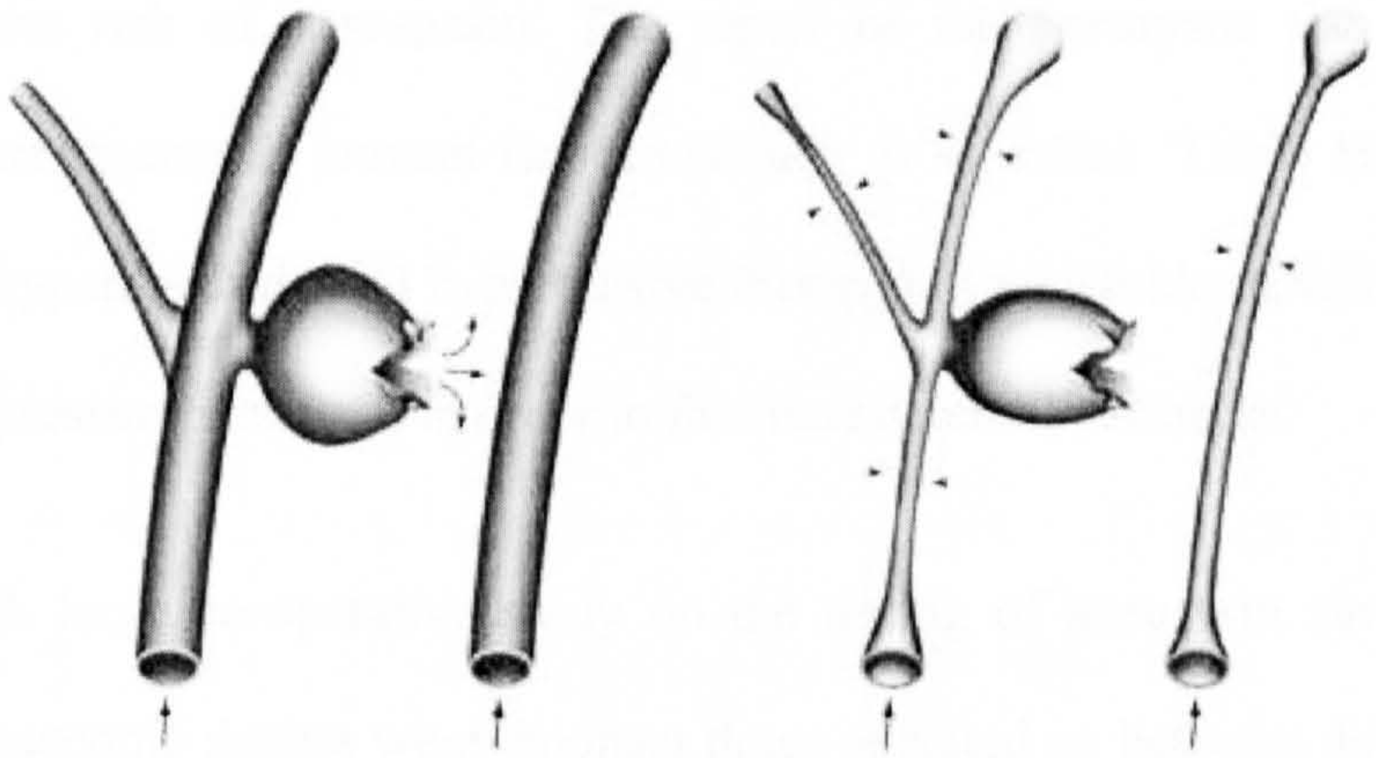
Thus, although the elevated blood pressure increases the risk of re-haemorrhage, the use of antihypertensive therapy substantially increases the likelihood of cerebral ischaemia (Wijdicks, Vermeulen et al. 1990) such that on the balance of risks it is now generally considered that antihypertensives are likely to cause more harm than good.

However, if re-haemorrhage does occur the prognosis is quite poor, with some 70% of those whose aneurysm re-ruptures dying as a consequence. That re-haemorrhage remains the major cause of poor outcome was confirmed by recent studies (Roos, Beenen et al. 1997; Roos, de Haan et al. 2000) in which re-haemorrhage caused almost twice as many cases of poor outcome as any other complication. A large American multicentre study suggests a comparable proportion of deaths are due to re-haemorrhage (22%) and vasospasm (23%) (Solenski, Haley et al. 1995). However this study does not present data for severe disability and has a low reported occurrence of re-haemorrhage (7%), which may indicate that many instances of re-haemorrhage were not detected. In the Roos (2000) study, 78% of those who had a re-haemorrhage had a poor outcome, defined as death, vegetative state or severe disability. Even if the patient survives the first six months, the risk of re-rupture from an unrepaired aneurysm remains at approximately 3.5% per year (Jane, Winn et al. 1977). Risk of re-haemorrhage is almost exclusively associated with aneurysmal SAH, risk of re-haemorrhage in patients with unknown aetiology SAH is considerably lower at less than 1% per year, with many of these cases being due to a previously undetected aneurysm.

Cerebral Vasospasm

Another serious complication is cerebral vasospasm in which the arteries at the base of the brain become abnormally constricted, as shown in Figure 1-3. The occurrence of vasospasm may be demonstrated by cerebral angiography or indicated by transcranial Doppler. The onset of vasospasm is virtually never before day 3, peaks at around day 6-8 and is common until around day 12 (Weir, Grace et al. 1978). It is caused by the presence of arterial blood in contact with the exterior of vessels at the base of the brain, though the mechanism of action is uncertain. It has been speculated that the blood metabolite oxyhaemoglobin induces vasoconstriction via a mechanism that may involve free radical generation and lipid peroxidation (Smith, Scherch et al. 1996). Vasospasm may occur without causing ischaemia and subsequent clinical deficit (radiological vasospasm), though the vasoconstriction does result in cerebral ischaemia and infarction in many cases (symptomatic or clinical vasospasm).

Figure 1-3: Cerebral Vasospasm



Vasospasm: Constriction of arteries due to presence of subarachnoid blood.

As the vasospasm is induced by the presence of blood metabolites, it follows that the severity and location of vasospasm can be predicted from the extent and location of clotted blood detected by CT scanning. Cerebral vasospasm is the most frequently encountered complication, with the large Solenski et al (1995) study reporting 46% symptomatic vasospasm in their sample. Others however report substantially lower occurrences of ischaemia (Roos, de Haan et al. 2000), reflecting differences in definitions and methods of assessing cerebral vasospasm.

Vasospasm or Re-haemorrhage the Greater Danger

There is some controversy as to whether vasospasm or re-haemorrhage is the more pathological complication, an important distinction as interventions to reduce the risk of re-haemorrhage, such as antihypertensive or antifibrinolytic therapy, may increase the risk of ischaemia and vice-versa. However, the likelihood or severity of *both* complications may be reduced by early surgery, whereby the aneurysm is clipped or otherwise obliterated to prevent further haemorrhage and any blood removed to reduce the risk of vasospasm. The repair of the aneurysm also enables more aggressive treatments to prevent ischaemia such as so-called 'Triple H Therapy' (hypervolaemic, hyperdynamic and hypertensive therapy) in which blood volume is expanded and blood pressure increased in order to facilitate cerebral perfusion.

A large co-operative study on the timing of aneurysm surgery found that the worst outcome figures were amongst those operated on between days 7 and 10, corresponding to the peak time period for cerebral vasospasm and corresponding ischaemia (Kassell, Torner et al. 1990a; Kassell, Torner et al. 1990b). Thus it is generally deemed advisable to undertake early surgery within the first three days wherever possible.

Hydrocephalus

Hydrocephalus may occur at differing stages subsequent to SAH and can be divided into acute, subacute and delayed hydrocephalus with differing symptomatology and management. It occurred in 28% of a large series of SAH patients (Solenski, Haley et al. 1995), but is considerably less frequently a cause of poor neurological outcome relative to re-haemorrhage or vasospasm. It has however been associated with cognitive or other functional deficits (Ogden, Mee et al. 1993; Dombovy, Drew-Cates et al. 1998; Hutter, Kreitschmann-Andermahr et al. 1998). The hydrocephalus is usually treated via means of ventricular drainage.

Non-neurological complications

In the Solenski (1995) report on medical complications, in which 457 patients were considered, the most frequent non-neurological complications were anaemia (37%), hypertension (36%), cardiac arrhythmia (35%), fever (29%), electrolyte imbalance (28%), hepatic dysfunction (24%), pulmonary oedema (23%) and pulmonary pneumonia (22%). The majority of patients had at least one such complication, with 40% suffering at least one life-threatening medical complication. These medical complications combined accounted for 23% of deaths, with pulmonary complications responsible for half of these deaths and other causes of death including gastrointestinal complications, sepsis, CNS infection and cardiac arrest.

Neurosurgical Management

As surgical technology and techniques have improved, surgical interventions have become viable for a greater number of patients. The principal aim of most surgical interventions is to obliterate the ruptured intracranial aneurysm so as to prevent it from causing a re-haemorrhage. When other 'incidental' aneurysms are present, these may also be treated during the surgical procedure. The most frequent procedure involves craniotomy and the application of an aneurysm clip. Blood pressure control and the temporary clipping of parent blood vessels may also be employed to reduce the possibility of the aneurysm rupturing intraoperatively. If the aneurysm cannot be clipped successfully, then it may be wrapped with muslin.

More recently endovascular techniques have been employed with some patients, particularly in those for whom traditional clipping might not be viable due to aneurysm location or previous medical history. In these procedures balloons or metallic coils are guided through the circulation and inserted into the aneurysm. A large multicentre study is currently gathering data in order to compare the merits of such endovascular techniques relative to clipping in cases where either method could have been employed.

The calcium antagonist nimodipine is used in the treatment of many patients after studies indicated that it was able to reduce the incidence of cerebral infarction and consequent poor outcome by about a third via the prevention of cerebral ischaemia. (Pickard, Murray et al. 1989; Pickard, Murray et al. 1990). Current evidence seems to suggest that nimodipine has its beneficial effects by serving as a neuroprotectant rather than by reducing vasospasm (Barker and Ogilvy 1996).

Other treatments for the prevention of ischaemia have been advanced, including 21-aminosteriods such as tirilazad mesylate. Studies with this free radical scavenger have demonstrated reduced symptomatic vasospasm and improved outcome in males, though higher doses may be required for females as they metabolise the drug 3 to 4 times faster (Kassell, Haley et al. 1996). Angioplasty and / or intra-arterial pavaverine may also be employed to avoid ischaemia by inducing vasodilatation, though both procedures carry risks (Newell, Eskridge et al. 1989; McAuliffe, Townsend et al. 1995; Miller, Cross et al. 1995). Some authors suggest that further improvements in the treatment of ischaemia will only lead to modest improvements in outcome as the majority of cases of poor outcome are due to the initial haemorrhage or subsequent re-haemorrhage (Roos, de Haan et al. 2000).

Early Versus Late Surgery

Early surgery where possible has become the stated aim for many centres in order to reduce the occurrence of re-haemorrhage and vasospasm. One study reporting decreasing mortality over a period of years describes a corresponding decrease in median time between initial haemorrhage and surgery from 12 days to 2 days (Ingall, Whisnant et al. 1989). The comparison of early and late operative mortality figures alone can be misleading because these do not account for the reduced risks of death from re-haemorrhage or ischaemia in those who undertake early operation. A large international study on the timing of surgery involving 3521 patients found no difference in management mortality between early and delayed surgery (Kassell, Torner et al. 1990a; Kassell, Torner et al. 1990b).

This study did however find dramatic variation in management mortality between centres, ranging from 4 to 60%, indicating that considerable improvements in overall mortality could be made if the centres with the worst results followed the practice of the more successful centres.

Unruptured Aneurysms & Elective Surgery

Screening and preventative treatment of aneurysms is rather controversial because although the mortality rate for preventative surgical repair of unruptured aneurysms is considerably lower than that of emergency repair for ruptured aneurysms (approximately 2% and 15-20% respectively), this has to be weighed against the risks of the unruptured and asymptomatic aneurysm ever rupturing during the individual's natural life-span (Heiskanen 1986; King, Berlin et al. 1994).

A review of 23 studies on the prevalence of intracranial aneurysms concluded that for adults without specific risk factors there is a 2.3% likelihood of an intracranial aneurysm being present (Rinkel, Djibuti et al. 1998). Those with a familial predisposition were four times more likely to have an aneurysm, and were also more likely to have multiple aneurysms and thus a risk of rupture for each of these. The likelihood of an aneurysm being present increased with age in all groups.

However, the annual risk of rupture for aneurysms which were less than 10mm in size was determined by Rinkel et al (1998) to be only 0.7%, though the risk was higher for posterior circulation aneurysms and increased to 4% for those over 10mm in size. Consequently even if an asymptomatic aneurysm is identified via a screening process, the balance of risks may indicate that surgery is not justified. In those with greater risk though, for example the 7.3% with aneurysms exceeding 10mm or the 10% with posterior circulation aneurysms, or even those of younger age for whom the accumulative annual risk is considerable, preventative surgery probably is justified on balance of risks alone.

Many survivors of SAH who have had a ruptured aneurysm clipped in emergency neurosurgery opt to have any existing incidental unruptured aneurysms electively clipped at a later stage if this was not done at the time of the original surgery. This decision to have the asymptomatic, unruptured and generally small aneurysm clipped or otherwise obliterated is often taken more-so for peace of mind rather than deduced on the logical balance of probabilities. Many survivors of SAH are understandably concerned about any indications or signs, such as headaches, which they associate with the possibility of another haemorrhage. Thus elective clipping of unruptured aneurysms or the screening of concerned family members may be justified on the grounds of preventing anxiety, particularly as it is conceivable that such anxiety could in itself increase the likelihood of rupture.

Grading Scales for Subarachnoid Haemorrhage

Hunt & Hess Grades

Level of consciousness has been the cornerstone of assorted grading systems for SAH and has implications for management and likely outcome. One of the more widely used scales was first described by Hunt & Hess, who demonstrated that admission grade corresponded strongly with mortality rates (Table 1-3) (Hunt and Hess 1968). Although this scale is still often used, studies found that there was considerable variation between neurosurgeons when grading the same patients, with as many as four grades being suggested for the same individual (Lindsay, Teasdale et al. 1982; Lindsay, Teasdale et al. 1983). This considerable inter-rater variation was due to difficulty in gauging severity of headache and interpretation of terms used to describe level of consciousness.

Table 1-3. Hunt and Hess Grading System

Grade	Description
I	Asymptomatic or minimal headache and slight nuchal rigidity
II	Moderate to severe headache, nuchal rigidity, no neurological deficit (except cranial nerve palsy)
III	Drowsiness, confusion or mild focal deficit
IV	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances
V	Deep coma, decerebrate rigidity, moribund

* Serious systemic disease such as hypertension, diabetes, severe arteriosclerosis, chronic pulmonary disease, and vasospasm on angiography result in placement in next less favourable category

Based upon (Hunt and Hess 1968).

World Federation of Neurological Surgeons Grades

Due to the apparent low inter-rater reliability of the Hunt & Hess Scale, the World Federation of Neurological Surgeons (WFNS) proposed a new scale using data collected for the International Timing of Aneurysm Study. It was decided to evaluate consciousness using the Glasgow Coma Scale (GCS) (Teasdale and Jennett 1974; Teasdale and Jennett 1976), which was originally designed for the assessment of coma after head injury and is described in more detail in Chapter 2. A five point WFNS scale (Table 1-4) was devised using GCS scales and the presence or absence of motor deficit (Drake 1988; Teasdale, Drake et al. 1988).

Table 1-4. WFNS Grading Scale

WFNS Grade	Glasgow Coma Scale Score	Motor Deficit
I	15	Absent
II	14-13	Absent
III	14-13	Present
IV	12-7	Present or absent
V	6-3	Present or absent

(Drake 1988; Teasdale, Drake et al. 1988).

Outcome after Subarachnoid Haemorrhage

Perhaps naturally in light of the high mortality rates associated with SAH, many earlier studies focused upon survival rates and management or operation mortality figures. A consideration of these case-fatality rates and how they correspond with timing of surgery and medical complications is given in the sections above. In other earlier studies, some consideration as to the relative functional status of survivors is given, often in terms of factors such as physical independence, neurological recovery and return to work. As neurosurgical techniques and management for SAH has improved considerably over the past few decades, the number of patients surviving SAH has correspondingly increased and greater emphasis has been put on the functional status of survivors and how this corresponds to various medical and surgical factors.

Glasgow Outcome Scale

An often-used index of outcome following SAH is the Glasgow Outcome Scale (GOS), which was originally developed as an index of neurological outcome after traumatic head injury (Jennett and Bond 1975) and correspondingly is outlined in greater detail in Chapter 2. It has also been used to assess outcome after a range of other neurological conditions and its use with SAH is justified as the pattern of brain injury and subsequent deficits following SAH are more akin to those of head injury than they are to most other types of stroke. More recently an extended 8-point version of the scale has been published (Table 1-5) but has not yet been used in published studies of outcome after SAH (Pettigrew, Wilson et al. 1998; Pettigrew 1998; Teasdale, Pettigrew et al. 1998; Wilson, Pettigrew et al. 1998).

Limitations of Glasgow Outcome Scale

Several studies report a good recovery based on the GOS for most patients who survive SAH, with 70-80% of survivors having a favourable neurological outcome (Kassell, Torner et al. 1990b; Hutchinson, Seeley et al. 1996). However, in more recent years it has become apparent that many patients demonstrate notable cognitive and emotional impairments which affect them in their daily lives and which may not be reflected by the GOS. One study found that 54% of GOS rated 'good recovery' patients had notable cognitive deficits (Hutter and Gilsbach 1993). Another study restricted to those with good or moderate grade GOS found that 50% of these patients reported significant quality of life impairments, with 30% suffering from clinical depression (Hutter, Gilsbach et al. 1995). Thus although the GOS remains a good broad measure of outcome, it is not sufficiently sensitive to detect many of the cognitive and psychological deficits which occur in many survivors of SAH and outcome studies based exclusively upon the GOS are likely to underestimate the deleterious consequence of SAH.

Neuropsychological Outcome after SAH

In recent years an increasing number of outcome studies have included some neuropsychological tests. The results from these studies have been varied, but the most frequent cognitive findings are difficulties with memory (Hutter and Gilsbach 1993; Ogden, Mee et al. 1993; Larsson, Forssell et al. 1994; Hutter, Gilsbach et al. 1995; Hutter and Gilsbach 1996; Berry, Jones et al. 1997; Ogden, Utley et al. 1997) and with concentration (Hutter and Gilsbach 1996; Hutter, Kreitschmann-Andermahr et al. 1998).

In one of the more comprehensive neuropsychological follow-up studies (Ogden, Mee et al. 1993), impairments at 12 months, defined as scores at least 2 standard deviations below the age mean, were most notable in Rey complex figure recall (47%) and copy (43%); digit symbol (27%), Trail-Making A (76%) and B (43%) and modified Wisconsin perseverative errors (18%).

Anterior Communicating Artery Aneurysms and Memory Deficits

An early observation was that ruptured ACoA aneurysms frequently resulted in memory deficits similar to those in Korsakoff's amnesia. In a study of 85 post-operative ACoA patients, 66% had postoperative amnesia, with these memory deficits still present in 16% at long-term follow-up (Okawa, Maeda et al. 1980). These patients also displayed marked personality changes. A later study found memory deficits in 30% of operated ACoA patients (Gade 1982). ACoA aneurysms have also been associated with poor outcome (Bornstein, Weir et al. 1987) and emotional disturbances (Sengupta, Chiu et al. 1975). More recently, the majority of studies that have reported analysis of cognitive assessment according to aneurysm sites have reported no significant differences between ACoA patients and those with aneurysms at other sites (Ogden, Mee et al. 1993; Hutter and Gilsbach 1995; Tidswell, Dias et al. 1995; Hutter and Gilsbach 1996; De Santis, Laiacona et al. 1998).

It has been suggested that these apparent changes in the functional consequences of ACoA aneurysmal rupture are due to improvements in management which may prevent or reduce damage which was previously incurred as a consequence of ACoA rupture and consequent surgical clipping (Hutter and Gilsbach 1992). Perforators from the ACoA have been found to supply the basal nucleus of Meynert, a structure thought to be of importance in memory processing, and thus it may be damage to these small perforating arteries which were responsible for the observed memory deficits (Camuscu, Dujovny et al. 1997).

Although a recent series of studies indicate no effect of aneurysm site, where these studies provide a breakdown of scores by aneurysm site it is sometimes apparent that there were consistently lower scores amongst the ACoA patients, but that these differences did not reach statistical significance (e.g. Tidswell 95). Larsson (1994) found differences in memory deficits according to aneurysm site, with ACA aneurysms most frequently associated with long-term and short-term memory deficits. Thus it is possible that aneurysm site may still influence the presence and severity of temporal or frontal deficits in patients, but that these deficits in individuals may be masked when patients with differing focal injuries are merged into groups. Additionally, several published studies have been with relatively small groups of patients and thus may have had insufficient sample sizes to detect less pronounced memory differences.

Presence & Severity of Subarachnoid Blood

Several studies have reported associations between outcome and the amount of blood present on CT scans (Larsson, Forssell et al. 1994; Hutter and Gilsbach 1996; Fukuda, Hasue et al. 1998). The study by Fukuda et al (1998) involving 114 aneurysmal SAH cases used a grading system derived from Hounsfield units present in the cisterns to categorise patients according to the amount of subarachnoid blood and related this to GOS. As is shown in the Table 1-5, the extent of blood present in the cisterns was strongly predictive of subsequent outcome, with none of the patients in the lowest blood group being left with severe disability.

Table 1-5. Subarachnoid Blood Present on CT Predictive of Outcome

	Good Recovery or Moderate Disability	Severe Disability or Vegetative	Dead
CT Type 1	92.8%	0%	7.2%
CT Type 2	80.0%	7.5%	12.5%
CT Type 3	56.9%	7.8%	35.3%

Data derived from Fukuda et al (1998)

Ogden et al (1993) found that digit span and recognition memory for words were significantly affected by the amount and presence of blood. Hutter (1998) found correlations between Fisher Grade and a range of cognitive measures including verbal long-term memory, figural short-term memory and concentration speed. Larsson (1994) also found that the presence of blood on CT was significantly associated with poor word recall and other memory deficits. The authors suggested that the presence of blood increases vasospasm and that subsequent ischaemia resulted in the memory deficits observed.

It remains uncertain whether the negative consequences of the subarachnoid blood are a consequence of direct neurotoxic effects of the blood or its metabolites, such as the inducement of vasospasm, or whether the presence of blood merely serves as a marker for the severity of the initial haemorrhage. A recent study endeavoured to answer this by following up a group of patients with SAH of unknown origin in whom no surgical evacuation of subarachnoid blood had occurred (Germano, Caruso et al. 1998). These patients were found to have normal cognitive and emotional functioning, indicating that the presence of subarachnoid blood did not have a deleterious effect in these individuals. However only relatively benign Fisher Grade I or II patients were included and a number of exclusion criteria increased the likelihood of remaining patients having a positive outcome.

Aneurysmal Versus Non Aneurysmal Haemorrhage

A potentially confounding issue in the investigation of outcome after SAH is that patients with angiographically confirmed aneurysmal haemorrhage are usually banded together with patients whose angiogram was negative or who didn't undergo angiography. This angiogram-negative group is fairly heterogeneous, though is likely to comprise a considerable proportion of perimesencephalic haemorrhage cases as well as rarer causes of SAH and undetected cases of aneurysmal haemorrhage. There remains some controversy as to the relative functional outcome of aneurysmal SAH and SAH of unknown origin patients. A number of studies have demonstrated a considerably better outcome amongst angiogram-negative patients, particularly when survival rates are considered (Gomez, Lobato et al. 1989; Noterman, Dewitte et al. 1991; Goergen, Barrie et al. 1993; Congia, Carta et al. 1994).

In one such study, 95% of 65 unknown origin patients had a favourable outcome relative to 63% of aneurysmal haemorrhage control patients (Cioffi, Pasqualin et al. 1989). Another study found a similarly high 92% favourable outcome in a series of 50 unknown origin patients (Kawamura and Yasui 1990). These findings in part reflect the lower incidence of serious complications such as re-haemorrhage or vasospasm amongst unknown origin patients and also the generally lower admission grade.

However, when one only considers survivors of the haemorrhage, the difference between aneurysmal SAH and unknown origin SAH is not always as distinct. A study of 127 unknown origin patients found that although 80% had returned back to a fully active lifestyle, 22% of these active individuals still experienced some problems such as headaches, vertigo and increased fatigue (Brismar and Sundbarg 1985). Other studies report the presence of cognitive slowing and persistent headaches in over 50% of unknown aetiology SAH patients (Eskesen, Sorensen et al. 1984; Spallone, Ferrante et al. 1986). Another study considering only good neurological outcome patients (GOS=1) found no differences between those of aneurysmal and non-aneurysmal aetiology (Sonesson, Saveland et al. 1989) and a later study also found comparable cognitive deficits between the two groups (Hutter, Gilsbach et al. 1994).

This latter study found that amongst poorer clinical grade patients, aneurysmal SAH patients were more likely to have deficits in areas associated with focal injury, such as memory and word finding, whereas unknown aetiology patients had deficits in tasks related to attention which is more characteristic of diffuse injury. This may suggest that the damage in the unknown aetiology patients was mediated via neurotoxic effects of the blood itself.

Outcome after Non-aneurysmal Perimesencephalic Haemorrhage

In 1985, a distinctive pattern of haemorrhage confined to the perimesencephalic cisterns was first identified which was associated with a very good prognosis (van Gijn, van Dongen et al. 1985). This perimesencephalic haemorrhage is found in approximately 10% of SAH cases and probably accounts for around 50-75% of angiogram negative SAH (Schwartz and Solomon 1996). Several studies have suggested that the outcome after perimesencephalic non-aneurysmal subarachnoid haemorrhage is very positive with the vast majority of patients making a full recovery (Rinkel, Wijdicks et al. 1990; Rinkel, Wijdicks et al. 1991b; Goergen, Barrie et al. 1993; Van Calenbergh, Plets et al. 1993; Schwartz and Solomon 1996). Although residual problems typical of SAH may occur in some of these patients, with a recent study reporting that 62% of twenty-one perimesencephalic patients suffered from symptoms such as headaches, irritability, tiredness, depression or forgetfulness (Marquardt, Niebauer et al. 2000), these symptoms were less severe or frequent than is generally reported following aneurysmal SAH.

Thus it would appear that some of the variation in outcome following SAH might be a consequence of the heterogeneity of the angiogram-negative groups where these are included. Studies that have included patients with SAH of uncertain origin might have better overall outcome results than those that have focused exclusively upon angiographically proven aneurysmal SAH, as many of the uncertain origin patients will have had perimesencephalic haemorrhage. In contrast, studies without 100% CT scanning may have included some intracerebral haemorrhage patients amongst their uncertain aetiology group, which would have served to bias the results as ICH survivors would be expected to have a worse outcome than unknown aetiology SAH patients.

Additionally, as a negative angiogram does not exclude the possibility of an aneurysmal cause of haemorrhage, there is a likelihood that some aneurysmal SAH patients were present amongst the unknown aetiology groups, particularly in studies in which repeat angiogram was not performed. Consequently some of variation in the outcome of unknown aetiology SAH groups may be due to the inclusion of undetected intracerebral haemorrhage or aneurysmal patients.

Surgical Variables and Functional Outcome

As might be expected, initial WFNS or Hunt and Hess grade on admission and age are the most consistent predictors of outcome. The occurrence of complications such as re-haemorrhage, symptomatic vasospasm and hydrocephalus are also associated with poorer outcome (Lanzino, Kassell et al. 1996; Hutter, Kreitschmann-Andermahr et al. 1999). The controversy over the relative outcome between aneurysmal and unknown aetiology extends to discussion of the potential adverse effects of surgical procedures, as aneurysmal patients are generally the only patients to undergo surgery. Thus studies that find similar outcome between the two groups have been used to suggest that the surgical procedure itself does not cause impairments (Hutter, Gilsbach et al. 1994). The use of temporary clipping during the surgical procedure has however been associated with significantly worse performance on selective attention and short-term memory tasks in the days following surgery (Hutter and Gilsbach 1996). Another study found that clipping of the anterior cerebral artery was associated with higher impairment as rated by relatives (Tidswell, Dias et al. 1995).

Emotional Sequelae of SAH

Depression following SAH

Although several earlier studies briefly mentioned factors such as increased irritability, apathy, social difficulties and personality change, most paid relatively little attention to measures of functional outcome. More recently some studies have reported incidences of depressive illness after SAH (Stegen and Freckmann 1991; Hutter, Gilsbach et al. 1995; Berry, Jones et al. 1997; Mavaddat, Sahakian et al. 1999). Hutter (1995) found that 30% of their patients suffered from clinical depression (Beck Depression Score > 10), though Ogden (1993) reports lower incidence of depression (17% mild-moderate, 3% severe) in their larger follow-up study at 12 months. However, as with many of the other studies, a considerable number of patients either declined to participate or dropped out of the Ogden study, such that only 66 of the 111 patients who met criteria were assessed at 12 months. It is reasonable to assume that depressed individuals will be disproportionately represented amongst those who decline to participate and thus studies may underestimate the prevalence of depression and other psychological or emotional phenomenon.

A study determining functional outcome one year after aneurysmal SAH found that reduced work capacity was due mostly to emotional / psychological difficulties rather than physical problems (Ropper and Zervas 1984). This study found that 17% of their 112 patients were still dependent upon others after one year, with a further 25% independent but with emotional or psychological problems. The study only included patients with no neurological deficit on admission and it is likely that if all surviving patients had been included the prevalence of both physical and psychological problems would have been notably higher.

Distress in Partners and Relatives of SAH Patients

The considerable impact of the haemorrhage upon the partners or carers of SAH patients has been given very little attention. Recently though, both patients and their relatives were found to have significantly higher GHQ-28 scores than controls, indicating that psychological disturbance is also present in the immediate relatives or partner of the patient (Berry, Jones et al. 1997). In another study, the quality of life of partners of the SAH patients was found to be reduced in proportion to the patient's Rankin score (Hop, Rinkel et al. 1998). Many SAH sufferers are in long-term relationships which, in contrast to head injury survivors, do not break down as a consequence of their injury in the vast majority of cases. A considerable extent of the stress and burden of care is however placed upon the partners, who in many cases have to make major changes to their own lifestyle and work in order to be able to look after the patient and / or take over roles that the patient is unable to undertake.

Anxiety Difficulties following SAH

The earlier outcome studies tended not to have included any measures of anxiety related problems. In one of the earliest studies to point towards the presence of increased anxiety in SAH patients, psychological problems were found to be a greater factor in outcome than were physical or cognitive impairments (Stegen and Freckmann 1991). In this study, anxiety problems were more frequently associated with MCA aneurysms and personality changes most frequent with ACA aneurysms.

Ogden (1997) reports that 15% of their sample reported increased anxiety in telephone interviews. In contrast, another study reports only mild anxiety that was related to future work capacity, though this study was based on a substantially smaller sample group (N=20) and had extensive exclusion criterion as the study deliberately sought only patients with characteristics which were predictive of a favourable outcome (Germano, Tisano et al. 1997).

Berry (1997) reports levels of state anxiety that were significantly higher than a matched control group (Berry, Jones et al. 1997). A recent study reports lower levels amongst 22 patients at 12-month follow-up, with anxiety in 13% and depression in 9% as measured by the Hospital Anxiety and Depression Scale (Hellawell, Taylor et al. 1999a). They point out that these levels are similar to those reported in general practice (Goldberg 1995). The study does however also report proxy information from relatives who thought that anxiety was worse in the patient since the haemorrhage in 36% of cases and that depression was worse in 18% of cases. A short report by Berry (1998) draws attention to the presence of post traumatic stress disorder in 32% of SAH patients referred to their behavioural clinic. These patients reported recurrent intrusive thoughts, nightmares and flashbacks relating to the event. Anxiety was found to be the main presenting problem in a further 18% of cases (Berry 1998).

Chapter 2 Traumatic Brain Injury

Introduction

The term 'head injury' encompasses a range of severities of injury, with some studies including any injuries in which swelling, abrasion, or contusion to the scalp has occurred (Jennett and MacMillan 1981; Brookes, MacMillan et al. 1990) whilst others restrict their definition to include only cases where there are indicators of damage to the brain such as diminished consciousness level, or skull fracture (Jagger, Levine et al. 1984) or documented damage to the brain verified by brain scans. As this study relates only to adult patients in whom documented injury to the brain has occurred as a consequence of trauma, the review is largely focused upon studies of adults in whom traumatic injury to the head has occurred which has resulted either in symptoms which are indicative of brain injury or radiographically documented brain injury.

Epidemiology of Traumatic Brain Injury

Information on the epidemiology of head injuries in the U.K. for the year 1974 found that hospital admission rates following head injury were 270 per 100,000 in England and Wales, rising to 313 per 100,000 in Scotland (Jennett and MacMillan 1981). More recently, admission rates for traumatic brain injury of 341 per 100,000 have been reported for a large population based Scottish sample (Brookes, MacMillan et al. 1990). Though the majority of these injuries would be at the milder end of the brain injury severity spectrum, the numbers of severe injuries are reflected by the fact that traumatic brain injuries accounted for around 9-10 deaths per 100,000 UK population each year in the 1970s (Field 1976; Jennett and MacMillan 1981).

This UK fatality rate is two to three times lower than that in several other developed countries, including France, Spain, Australia and the United States, and has been falling since 1968 with an estimated figure of 7 per 100,000 in 1994 (Jennett 1996). Although young head injury patients are significantly more likely to survive their injury than older patients, head injuries cause a disproportionate proportion of overall mortality and morbidity in younger age groups. Around 15% of all deaths in the age range from 15 to 24 years are due to traumatic head injury.

In almost all studies of head injury, males considerably outnumber females, generally by a margin of at least two to one. This in part reflects the behavioural aspects inherent in the cause of many head injuries, with males generally more likely to be involved in high-risk activities. This factor is particularly apparent when one considers the relative numbers with head injury due to assault. As shown in Table 2-1, based on a large retrospective study involving case records from 23 Scottish accident and emergency departments, males are over six times as likely as females to suffer brain injury from an assault (Brookes, MacMillan et al. 1990). A recent Scottish study involving 35,377 cases of hospitalised head injury amongst patients aged 15-34 found comparable results, with males over four times as likely to suffer head injury of any kind and assaults accounting for 43% of male injuries in this age-range relative to 28% of female head injuries (MacCallum, Morrison et al. 2000).

Table 2-1. Gender Differences in Causes of Traumatic Brain Injury

	Annual Rates per 100,000		
	Males	Females	All Patients
Falls	168	73	118
Assaults	171	26	147
RTAs	77	39	70
All causes	537	163	166

Data adapted from Brookes et al (1990) based on those patients with evidence of brain damage

Causes of Head Injury

The number and cause of head injuries varies substantially between countries, due in part to differences in legislation and cultural norms of behaviour. For example, deaths from road traffic accidents (RTAs) have generally declined in developed countries over the past two decades, largely due to preventative measures such as improved car design, speed restrictions and enforcement of laws on seat belt / motorcycle helmet usage and alcohol limits. In contrast, the numbers of road deaths and injuries per head of population in developing countries are generally very much higher.

Road Traffic Accidents

Even in developed countries, RTAs still generally account for the majority of severe head injuries and head injury related deaths. In Scotland, RTAs account for approximately half of all severe head injuries, though only for about 13% of A&E attendees (Table 2-2) reflecting the greater severity of RTA injuries relative to those from falls etc (Jennett 1996). In Britain, around 40% of RTA head injury related fatalities are pedestrians. Motorcyclists and cyclists also constitute a disproportionate percentage of RTA related brain injuries.

Table 2-2. Main Causes of Head Injury by Severity

	A&E Attendees (S)	NSU Transfers (S)	NSU Severe (S)	Deaths (E / W)
Year	1985	1985	1984-6	1985
N	5242	572	391	4100
Falls (%)	41	37	27	25
Assaults (%)	20	15	12	2
RTAs (%)	13	32	50	58

Severe = coma > 6 hours; (S): Scotland; (E / W): England & Wales; NSU: Neurosurgical Unit
(Adapted from Jennet 1996)

Falls

Amongst adults, falls are generally associated with either older age or alcohol intoxication. The majority of these falls are from body height, though the grouping 'falls' also included individuals who may have fallen from a greater height such as from ladders or roofs. These individuals typically suffer greater severity of injury, such that falls from above one's own height might be best considered separately. It has previously been suggested that a fall needs to be from greater than one's own height in order for diffuse axonal injury to occur (Adams, Doyle et al. 1984). However a more recent neuropathological study involving 16 fatal falls found no statistical difference in terms of axonal injury between cases where the fall was from own height or from a greater height (Abou-Hamden, Blumbergs et al. 1997). Such neuropathological studies naturally have the bias of only including fatalities and falls from one's own height are less likely to prove fatal than falls from a considerable height (Steedman 1989). Thus the 'own height' fatalities available to neuropathological studies may be less representative of their group than are the 'greater height' fatalities. The grouping of 'falls' also overlaps with other causative groups such as injuries due to assaults, sports, or being knocked off bicycles, as these injuries generally involve a fall.

Assault

The relative number of brain injuries due to assault varies substantially from region to region, generally being notably higher in economically deprived urban regions. In the United States, the percentage of head injury admissions following assault varies from 4% in Olmsted County, Minnesota to around 40% amongst black citizens of Chicago (Annegers, Grabow et al. 1980; Whitman, Coonley-Hoganson et al. 1984). The United States differs from most other nations which report head injury data in that a substantial proportion of its head injury deaths are due to gunshot wounds. In some regions firearms account for up to 40% of all head injury related deaths, though an overall figure of 14% was reported by a national study. In Scotland, rates of head injury due to assault per capita tend to be higher than in England or Wales, with assaults responsible for some 20% of A&E attendees and 12% of severe brain injuries (Table 2-2). A recent Scottish based study reported that assaults are responsible for 40% of 35,377 recorded hospitalised head injuries in the age-range 15-34 years, with assaults significantly more likely to be the cause of injury amongst men. (MacCallum, Morrison et al. 2000)

Sport and Recreation

Sport has been attributed as the cause of some 12% of head injury attendees at emergency departments, though the vast majority of these are relatively mild head injuries. Sports most frequently associated with injury are horse riding and boxing, though in Scotland hill walking / mountaineering may be added to this category.

Alcohol

Alcohol is a well-documented cause of RTAs, with a review of US data finding that alcohol concentrations in excess of 100 mg/dl were present in 24.9% of drivers killed in two-vehicle crashes and 54.7% of drivers killed in single vehicle crashes (Evans 1991). As the authors point out, the former figure underestimates the role of alcohol as drunk drivers are often responsible for the deaths of sober drivers. Alcohol consumption is also frequently associated with head injuries due to falls or assaults and may also delay subsequent treatment of the injury, as passers-by or even relatives may consider concussion or other symptoms as due to intoxication rather than due to injury. Admissions data for Scotland found that alcohol was involved in four times as many injuries due to falls or assaults than in RTAs (Galbraith, Murray et al. 1976), though these RTAs would constitute a disproportionate number of the more severe brain injuries.

Neuropathology

Injury to the brain following trauma may be divided into primary and secondary damage. The primary damage occurs at the time of impact and results from mechanical injury to neuronal or glial cells or to the vasculature, which may cause a diffuse, focal or multifocal pattern of injury. Secondary damage occurs as a consequence of the primary damage and includes ischaemic or hypoxic damage, cerebral swelling, hydrocephalus and infection. The primary aim of neurosurgical management is to prevent or treat these mechanisms of secondary damage.

A second distinction between types of injury is between diffuse patterns of injury and focal injuries as shown in Table 2-3. Focal injuries would usually be identified by admission CT scan, whereas such scans often would not detect the smaller lesions characteristic of diffuse axonal injury. Prolonged diminished consciousness level in the acute stage is generally caused by diffuse axonal injury.

Table 2-3. Common Diffuse & Focal Patterns of Brain Damage

	Focal Injury	Diffuse Injury
Primary Damage	Contusion	Diffuse Axonal Injury (DAI)
	Laceration	Diffuse Vascular Injury (DVI)
	Haematoma	
	Intracerebral (ICH)	
	Subdural (SDH)	
	Extradural (EDH)	
Secondary Damage	Focal hypoxia-ischaemia	Diffuse hypoxia-ischaemia
	Focal brain swelling	Diffuse brain swelling

Based upon Teasdale (1995) & Blumbergs (1997)

Diffuse Axonal Injury and Diffuse Vascular Injury

Diffuse injuries involve damage across a large region of the brain and have been divided into the four categories shown in Table 2-3. Diffuse axonal injury (DAI) and diffuse vascular injury (DVI) are a direct consequence of the initial mechanical injury. DVI comprises of multiple small haemorrhages and is often found in patients who die very soon after the injury. In these very severe injuries, typically high speed RTAs, primary axotomy often occurs alongside vasculature disruption resulting in death usually prior to hospital admission.

In less severe cases some of the axons are damaged, causing disruption to the axoplasmic transport system and the flow of electrical communication along these nerves. These damaged axons sections may also separate during the hours following injury, forming the axonal retraction balls characteristic of severed axons, in a potentially preventable but little understood degenerative process which has been termed secondary axotomy (Povlishock 1992; Maxwell, Watt et al. 1993). Consequently brain damage in axonal injury, though once thought to be entirely primary irreversible damage incurred at the moment of injury, also involves potentially preventable secondary damage as axons continue to be disrupted and damaged.

Diffuse axonal injury is characteristically associated with the presence of identifiable lesions in the corpus callosum, internal capsule and superior cerebellar peduncles (Ng, Mahaliyana et al. 1994). DAI is present is around 30% of head injury fatalities who survive long enough to reach hospital and is probably the single most important form of brain injury (Adams, Doyle et al. 1989). It has become recognised that there is a spectrum of DAI injuries, with those described by pathological studies naturally representing the more severe extreme. DAI is thought to be responsible for much of observed impairment of consciousness in the acute stage, as this injury often involves damage in pathways connecting the cerebral hemispheres with the reticular activating system in the brain stem (Teasdale 1995; Blumbergs 1997). It typically occurs as a result of the deceleration or acceleration forces that occur in many RTAs and are akin to the mechanical injuries known to result in DAI in animal models of axonal injury (Adams, Graham et al. 1982; Gennarelli, Thibault et al. 1982).

However DAI has also been found to occur following falls or following assaults (Adams, Doyle et al. 1984; Graham, Clark et al. 1992; Imajo and Kazee 1992; Abou-Hamden, Blumbergs et al. 1997). DAI has also been identified in patients with co-existing skull fractures and focal lesions and it is likely that some DAI is present in many patients who are diagnosed with focal injury.

Hypoxic-Ischaemic Damage & Free Radical Damage

Diminished perfusion resulting in ischaemic hypoxia is the most frequent form of hypoxic-ischaemic brain damage following head injury. About a third of severely head-injured patients suffer from ischaemia in the hours following traumatic injury (Bouma and Muizelaar 1992; Bouma, Muizelaar et al. 1992) and ischaemic brain damage is present in over 80% of fatal injuries despite neurosurgical interventions aimed at minimising such secondary damage (Graham, Ford et al. 1989).

In addition to damage or infarction caused by cerebral ischaemia, it has been suggested that free radical generation could be enhanced in circumstances of post-ischaemic reperfusion (Siesjo 1992). Unbound iron is also often present in the brain within hours following traumatic injury as a consequence of the metabolism of haemoglobin from extravascular red blood cells. This free iron serves as a catalyst in the hydroxyl radical producing Haber-Weiss reaction. These very highly reactive free radicals would then cause secondary damage via oxidative reactions with various cellular structures, particularly if the enzymes which normally serve to protect against them, such as super-oxide dismutase, are relatively inactivated as a consequence of the ischaemia.

Although animal studies models have demonstrated increased free radical generation and subsequent oxidative damage following induced trauma and ischaemia (Shohami, Beit-Yannai et al. 1997), there are as yet no techniques for documenting free radical generation in the human brain following such injuries.

Cerebral Swelling

Cerebral swelling may be due to increased intra- or extra- cellular fluid within the brain (cerebral oedema) or increased intravascular blood volume (congestive brain swelling). Incidence of diffuse brain swelling varies from 5-40%, occurring more frequently in children than in adults. However, when it occurs in adults it is more likely to be predictive of poor outcome (Lang, Teasdale et al. 1994).

Cerebral Contusions & Lacerations

Contusions are focal injuries that result from mechanical damage to parenchymal tissue and associated vasculature. They most frequently occur on the inferior frontal lobes and the inferolateral temporal lobes and poles, largely due to contact of these regions against the irregular bony surfaces of the anterior and middle cranial fossae at the time of impact (Adams, Graham et al. 1980; Adams, Scott et al. 1980). Damage to blood vessels may lead to haemorrhages and localised infarction which, together with other secondary damage, may lead to further increases in size of the contusions during the hours or days following initial injury (Blumbergs 1997). Lacerations involve a greater severity of tissue injury, involving tearing of the pia-glial membrane and underlying parenchymal disruption which may extend into the deep white matter.

Haematomas

These are collections of blood occurring as a result of vascular injury and classified primarily according to the region of the collection. These haematomas often continue to increase in size during the days following injury (Bullock and Teasdale 1990). Large haematomas serve as space occupying lesions which may lead to increased intracranial pressure (ICP) and herniation. This raised ICP and hemisphere compression may result in ischaemic brain damage in the region of the haematoma, particularly in the case of subdural haematomas. As these consequences are often the cause of rapid deterioration in neurological condition, neurosurgical management usually involves the evacuation of any sizeable haematomas where this is possible.

Traumatic intracerebral haemorrhages (ICH) are haematomas greater than 2cm in size which are completely within the parenchyma (i.e. not in contact with the surface of the brain) (Adams 1992). Extradural haematomas, which form between the skull and the dura mater, are more frequently encountered in temporo-parietal regions and are often associated with skull fracture. Subdural haematomas, which as the name implies form beneath the dura mater, are often associated with adjacent contusions or lacerations. In more severe cases the SDH and lacerated tissue is continuous with an ICH and this complex of profound tissue damage is referred to as a 'burst lobe'. Mortality rates of 30-90% have been reported for traumatic SDH, though early surgical intervention has been associated with the reversal of ischaemia and improved outcome (Schroder, Muizelaar et al. 1994). Other areas where blood frequently collects following injury include the ventricles and the subarachnoid space. In the latter case, this traumatic subarachnoid haemorrhage may gather in the basal cisterns in a manner akin to spontaneous or aneurysmal subarachnoid haemorrhage.

Indices of Injury Severity

Concussion

Concussion may be described as an alteration of consciousness as an immediate consequence of trauma and is likely to occur in all but the mildest of head injuries. This may range from momentary confusion and / or disorientation to classical cerebral concussion in which full loss of consciousness occurs and thus the extent of concussion can be graded. Although in the vast majority of cases this concussion still corresponds with mild head injury, there is evidence that some residual damage may occur in individuals following concussion even in the absence of any other indications of injury (Gronwall and Wrightson 1975).

Post-Traumatic Amnesia

Memory disturbances for a period around the time of the injury are frequent sequelae of traumatic head injury. Forgetting of events occurring before the injury is termed retrograde amnesia whereas loss of memory for events following the injury is termed post-traumatic amnesia (PTA). The duration of PTA has long been used as an index of the severity of brain damage following injury and may be divided into levels of severity based on a logarithmic scale (Teasdale and Brookes 1985). PTA duration has been found to relate to lesions in both central and hemispheric structures, whereas consciousness-related severity indices related only to central structures (Wilson, Teasdale et al. 1994). Thus particularly with focal injuries, PTA may indicate severity of injury in the relative absence of changes in level of consciousness.

Glasgow Coma Scale

Level of consciousness and duration of loss of consciousness are obvious indexes of injury severity in the acute stage. Consciousness level changes can also serve to indicate clinical complications such as elevated ICP, enlargement of haematoma or brain swelling. The Glasgow Coma Scale is the most frequently employed measure of consciousness, comprising separate hierarchical levels of response in the domains of eye opening, verbal response and motor response as shown in Table 2-4. These scores can be used individually, though are often reported as summed scores with GCS scores of 7 or below on either scale corresponding to coma. On the now more frequently employed 15 point scale, in which the motor domain of flexion has been adapted to distinguish between flexor withdrawal and abnormal flexion, just over half (53%) of patients with a score of 8 were judged to be in coma (Teasdale and Jennett 1974; Teasdale and Jennett 1976). Consequently a GCS of 8 or below is often used by studies as the criteria for coma.

Table 2-4. Glasgow Coma Scale

	14-Point Scale		15-Point Scale	
Eye Opening	Spontaneous	4	Spontaneous	4
	To Sound	3	To Sound	3
	To Pain	2	To Pain	2
	None	1	None	1
Best Verbal Response	Orientated	5	Orientated	5
	Confused	4	Confused	4
	Inappropriate	3	Inappropriate	3
	Incomprehensible	2	Incomprehensible	2
	None	1	None	1
Best Motor Response	Obeying	5	Obeying	6
	Localising	4	Localising	5
	Flexing	3	Flexion withdrawal	4
	Extending	2	Flexion - abnormal	3
	None	1	Extending	2
			None	1

(Teasdale and Jennett 1974; Teasdale and Jennett 1976)

The summed GCS scores on the 15-point scale are often used as the primary gauge of severity of injury. Severe head injury is generally defined as the occurrence of a GCS score of 8 or less, with moderate head injury scores from 9 - 12 and mild head injuries as scores from 13 - 15. It has been suggested that this latter category should be subdivided as indicated in Table 2-5, as the vast majority (95%) of head injuries have an admission GCS of 15 and these patients have a far lower risk of complications and considerably better prognosis than those with GCS scores of 13 or 14 (Teasdale 1995).

Table 2-5. Severity Classification based on Glasgow Coma Scale

	Glasgow Coma Scale	% of Head Injury Attendees	% who Die from Injury
Minor	15	95	< 1
Mild	13 / 14	4 *	3 - 5
Moderate	9-12		9
Severe	3-8	1	35 - 40

* Mild and moderate head injuries combined constitute around 4% of attendees

(Based on Teasdale 1995)

Outcome after Traumatic Head Injury

Glasgow Outcome Scale

The Glasgow Outcome Scale (GOS) is one of the most frequently employed measures of outcome following head injury (Jennett and Bond 1975), largely because this measure is easily administered and has been demonstrated to correspond with other measures of functional outcome (Tate, Broe et al. 1989; Tate, Lulham et al. 1989; Clifton, Kreutzer et al. 1993). The first three categories have often been banded together as representing a 'poor outcome' group. However, the groupings on the scale are very broad, with the vast majority of survivors divided into one of three groups and inter-rater disagreements frequently occurring between the good and moderate recovery groupings. Additionally, the reliability of the original GOS varies with the method of data collection and inter-rater agreement can be as low as 50% (Anderson, Housley et al. 1993).

Table 2-6. Original and Extended Glasgow Outcome Scales

Original 5-Point GOS	Extended 8-Point GOS
Dead	Dead
Vegetative	Vegetative
Severely Disabled	Lower Severe Disability
	Upper Severe Disability
Moderately Disabled	Lower Moderate Disability
	Upper Moderate Disability
Good Recovery	Lower Good Recovery
	Upper Good Recovery

(Jennett and Bond 1975); (Pettigrew, Wilson et al. 1998; Pettigrew 1998)

The more recently developed extended 8-point GOS endeavours to increase inter-rater reliability by using a structured questionnaire format, which also increases the number of survivor groupings as shown in Table 2-6 (Pettigrew, Wilson et al. 1998; Pettigrew 1998; Teasdale, Pettigrew et al. 1998; Wilson, Pettigrew et al. 1998). The GOS may underestimate the impact of emotional or social deficits following brain injury, as is indicated by a study in which over half of the GOS good recovery patients still had substantial limitations on a measure of psychosocial reintegration six years following their injury (Tate, Lulham et al. 1989).

Assessment of outcome by GOS at six months has been recommended as the most appropriate time for the acute stage of injury, as several studies have found that the greatest amount of recovery occurs over this time-period (Clifton, Hayes et al. 1992). However, a large study of GOS measured recovery over time found that although a combined 'favourable outcome' grouping began to level out beyond six months, the proportion of patients with good recovery continued to increase in a linear fashion until at least 12 months post injury (Choi, Barnes et al. 1994).

Factors Associated with Fatality

As is indicated in Table 2-5, severity of injury as measured by level of consciousness on the GCS is predictive of subsequent survival, with patients who enter a coma naturally being far more likely to die as a consequence of their injury. The presence of subdural haematoma is frequently reported as being associated with high mortality rates, particularly where this is not evacuated in the acute stage (Gennarelli, Spielman et al. 1982).

Age at injury is also a strong predictor of outcome, particularly beyond the age of around 30-40, with older patients generally having a less favourable outcome for any given severity of injury (Tennant, Macdermott et al. 1995; Gomez, Lobato et al. 2000).

Duration of Coma

This measure is generally used as an indicator of severity of diffuse axonal injury where the patient has been in coma since the injury. However, patients with focal mass lesions may deteriorate and slip into a coma as a consequence of secondary damage caused by increased intracranial pressure or ischaemia. A number of studies report an association between longer duration of coma and worse performance on a range of neuropsychological tasks (Dikmen, Machamer et al. 1990; Ross, Temkin et al. 1994). However, some studies appear to have considered any loss of consciousness as constituting coma, whereas others may regard these same patients as merely having suffered concussion. Thus Ross et al (1994) include in their 'coma < 24 hrs' group patients who may have lost consciousness at the time of injury but had a mean GCS score of 13 soon after the injury. They subsequently report that patients in this group performed better than those who were in coma for longer than 24hrs on a range of tasks at one year post injury.

However some might consider the former group as including patients who, although having loss of consciousness, did not have 'true' verified coma and thus the results as reflecting differing severity of injury rather than differing duration of coma. That loss of consciousness should be considered separately from medically verified coma is supported by evidence from mild head injury cases that patients who suffer loss of consciousness do not differ in neuropsychological or vocational outcome from those who do not lose consciousness (Hanlon, Demery et al. 1999).

A study of 89 severely head injured patients found no statistically significant influence of coma duration on a range of cognitive tasks within two years of their injury (Brooks, Aughton et al. 1980). However, this study did report that those with coma duration of one day or less tended to have higher scores on most of the tasks. As shown in Table 2-7, large data sets from four British neurosurgical units demonstrate high levels of poor outcome for those who had clinically verified coma, but only moderate differences according to coma duration (Murray, Teasdale et al. 1993).

Table 2-7. Outcome at 6 months after severe head injury

Glasgow Outcome Scale	Coma > 6hrs (N=1067)	Coma < 6hrs (N=1353)
Good Recovery (%)	15	23
Moderate Disability (%)	18	18
Severe Disability (%)	20	18
Vegetative State (%)	2	1
Dead (%)	45	37

Based on data presented in Murray et al (1993)

Severity of Injury

The association between GCS and outcome is less strong when only survivors are considered, though the severity groupings of the GCS remain reasonable indicators of likely functional outcome. Around a third of those who survive from a severe head injury remain severely disabled at 6 months post injury (Table 2-7). All severe disability and most moderate disability patients are likely to have pronounced cognitive and emotional deficits, which may be a greater factor in their disability than any physical deficits (Levin, Grossman et al. 1979; Lezak 1995).

By contrast, the majority of patients with moderate or mild injury are usually at worst moderately disabled, with many continuing to recover to make a good recovery. However, some mild injury patients suffer long-term disability as a consequence of their injury, as shown by a recent 5 year outcome study in which 4 of 35 mild head injury patients were still found to be severely disabled with a further 7 moderately disabled (Dunn, Patterson et al. 2000). However, this study observed that much of the disability was due to musculoskeletal injury incurred at the time of the co-existing head injury, which is a factor rarely taken into account by other studies. Another study also found that milder head injuries can have long-term consequences, with 23 of 134 (23%) mild or minor GCS severity patients scoring in the psychiatric case range on screening instruments administered one year after their injury (Deb, Lyons et al. 1998).

A neuropsychological follow-up of 26 severely injured (GCS 3-8) and 24 moderately injured (GCS 9-12) patients at six months post injury found significant differences between these two groups on about a third of the tasks employed (Hellawell, Taylor et al. 1999b). These differences, particularly pronounced on the Boston naming task, delayed story recall and block design, remained present across subsequent assessments at 12 and 24 months.

PTA Duration and Outcome

Duration of PTA has been found by some studies to be a better predictor of outcome amongst survivors than duration of coma, though the two measures are usually strongly related. In a study involving 243 patients admitted to a rehabilitation unit, PTA duration was found to be more strongly predictive of subsequent GOS outcome at 6 and 12 months post injury than either GCS score or duration of coma (Katz and Alexander 1994). The majority of patients in this study had diffuse axonal injury, though a weaker relationship between PTA duration and GOS was also noted in a group of 21 patients with focal contusions. GCS based measures of severity did not predict outcome in these focal injury patients. This might be expected as coma since time of injury is generally an index of severity of diffuse rather than focal injury, whereas PTA is affected by both focal and diffuse injury (Wilson, Teasdale et al. 1994).

In separate studies, PTA duration was found to be significantly associated with GOS outcome at 6, 12 and 24 months in a group of consecutively admitted moderate- severe injury patients (Hellawell, Taylor et al. 1999b) and at 6 months in a study involving 314 severe injury patients (Ellenberg, Levin et al. 1996). The association with outcome also holds with less severe injury, as a study of mild-moderate injury patients found that GOS outcome at 12 months was significantly correlated with PTA duration, but not with admission GCS (van der Naalt, van Zomeren et al. 1999). Neuropsychological outcome has reflected this trend, with PTA duration significantly associated with six of fourteen tasks in a study that found no such relationship with coma duration (Brooks, Aughton et al. 1980).

Type of Lesion: Diffuse versus Local

As mentioned above, focal injuries are usually identified by admission or subsequent CT scans whereas diffuse injuries are generally inferred from presence of coma from injury, which may or may not correspond with small lesions on CT scan. As it is likely that diffuse injuries are present across a range of injury severities and often co-exist with focal injuries, it is likely that many head injuries involve some extent of diffuse injury even though they may be described in terms of lesions evident on CT. In some studies of head injury, other forms of imaging such as MRI, SPECT or PET have been utilised which give a more accurate picture of the type, region and severity of injury (Wilson 1992; Mitchener, Wyper et al. 1997), but these forms of imaging are not generally employed in day-to-day neurosurgical management.

A frequent finding in cognitive assessment following even relatively mild head injury is that speed of information processing or other measures of attention and vigilance are impaired. In most cases these information-processing deficits are a consequence of patterns of diffuse injury (McMillan and Glucksman 1987; Leininger, Gramling et al. 1990). In one such study, patients with brain stem and callosal injuries identified by MRI were found to be particularly impaired on a visual search task and the WAIS Digit-symbol task relative to patients with fronto-temporal lesions or orthopaedic controls (Wilson, Hadley et al. 1995).

Late ventricular enlargement has been suggested to serve as an index of severity of diffuse brain damage and correspondingly is correlated with duration of coma (Levin, Meyers et al. 1981), whereas early ventricular enlargement has been suggested to be primarily a consequence of hydrocephalus. Late ventricular enlargement, particularly of the third ventricle, has recently been demonstrated as the MRI measure which corresponds best with GOS measured outcome (Henry-Feugeas, Azouvi et al. 2000) and has also been associated with poorer performance on a number of neuropsychological tasks (Meyers, Levin et al. 1983; Cullum and Bigler 1986; Wilson, Wiedmann et al. 1988). These latter studies found that neuropsychological outcome could be predicted by late stage brain imaging but not from scans taken in the acute stage, demonstrating the importance of diffuse injuries and secondary damage in determining subsequent impairments.

Location of Lesion

The consequences of focal brain injury are naturally to some extent dependant upon the location in which the injury occurs. In general, damage involving the left hemisphere tends to be associated with more pronounced cognitive deficits. In part this reflects the lateralisation of language in the left hemisphere and the dominance in many neuropsychological batteries of verbal tasks or tasks with a significant verbal component. Focal lesions are found considerably more frequently in the frontal and temporal lobes than the occipital or parietal regions (Adams, Scott et al. 1980; Gentry, Godersky et al. 1988; Kesler, Adams et al. 2000).

Frontal lesions have been associated with characteristic patterns of cognitive and behavioural deficits, including impairments in developing strategies to solve novel problems, difficulties with response inhibition or in maintaining attention and inappropriate social behaviour (Mattson and Levin 1990; Malloy and Aloia 1998). Several of these deficits are particularly associated with diminished functioning of the pre-frontal areas of the brain. However, impairments that are present in one individual with frontal injury may not be present in others and lesions in other regions that have efferent pathways to the frontal lobes may also cause frontal deficits. Consequently the term 'dysexecutive syndrome' has been employed which emphasises the cognitive processes that are impaired rather than the region of brain in which the causative damage occurred (Baddeley and Wilson 1988).

Temporal lobe lesions are associated with disturbances of auditory sensation and perception due to damage to the auditory association cortex and surrounding region. Damage to the left temporal lobe may cause the disturbances of word recognition and fluent though confused speech characteristic of Wernicke's aphasia. Difficulties in verbal memory, such as word lists or short stories, or in word finding for nouns are also a frequent consequence of left temporal damage. Right temporal lesions may impair musical perception and cause deficits in visual perception and non-verbal memory, which may include impairments in the recognition and recall of faces (Lezak 1995).

However, in traumatic closed head injury focal lesions are frequently found in more than one region, for example in injuries involving coup and contra-coup lesions. A study of 30 patients with severe head injury found that bilateral lesions were present on CT in 17 of them with only 10 having unilateral lesions (Rao, Jellinek et al. 1984). The bilaterally injured patients tended to have poorer subsequent outcome, though it is difficult to determine whether this was due to the involvement of more than one region or simply because the bilateral lesions involved damage to a greater total brain area. Additionally CT may not detect all focal lesions present, as demonstrated by an imaging study of 17 patients in which the more sensitive MRI found 44 more lesions than were demonstrated by CT alone, indicating that head injuries tend to be multi-focal (Levin, Amparo et al. 1987).

Several studies have reported an association between the depth of the lesion within the brain and performance on neuropsychological tasks (Levin, Grossman et al. 1979; Levin, Williams et al. 1988; Wilson, Wiedmann et al. 1988; Wilson 1992). It is however uncertain whether this is due to specific effects of these deep lesions or simply that the depth of lesion serves as an index of severity of overall brain damage (Wilson 1990).

Anxiety & Depression following Traumatic Brain Injury

In more recent years, an increasing number of studies have documented emotional sequelae of traumatic brain injury. Whilst it is virtually impossible to separate direct organic causes for emotional disorders from indirect causation due to changes in social and economic circumstances, these emotional sequelae are often at least as responsible for restricting recovery from head injury as the more documented physical and cognitive consequences.

High levels of anxiety and depression have been reported to be a frequent and enduring consequence of head injury (Morton and Wehman 1995; Deb, Lyons et al. 1999; Hellawell, Taylor et al. 1999b; Kesler, Adams et al. 2000), with emotional and behavioural difficulties the most emphasised complaints by patients and their relatives (Brooks 1991; Kaitaro, Koskinen et al. 1995). One study of 99 head injury patients of various severity found that 38% suffered from mood disorders at 6 months post-injury (Bowen, Neumann et al. 1998). The occurrence of mood disorders could not be predicted from indicators of injury severity and did not change between 6 month and 12 month assessments in 75% of patients. Where change in emotional state did occur, it was just as likely to be in a negative as a positive direction, such that the percentage of patients with mood disorder remained essentially unchanged (Bowen, Chamberlain et al. 1999).

Other studies have suggested that emotional disorders such as anxiety and depression may increase with time since injury (Fordyce, Roueche et al. 1983). One such study at 2 years post injury found that nearly half of depressed patients and their family members considered that the depression did not start until at least 6 months after the injury (Varney, Martzke et al. 1987). This may reflect social changes occurring in the months following injury, such as the disruption or break up of intimate relationships and friendships and the assumption of a more permanently dependent role.

It has been suggested that emotional and behavioural issues may contribute more to disability following head injury than do cognitive or physical impairments (Lezak 1987). Supportive of this are findings that emotional difficulties are not associated with cognitive impairments (Franulic, Horta et al. 2000; Skell, Johnstone et al. 2000), but are related to GOS measured functional status (Satz, Forney et al. 1998; Satz, Zaucha et al. 1998; Wilson, Pettigrew et al. 2000). Satz et al found a trend towards increasing depressive symptomatology as a function of GOS severity, with a significant majority of depressed patients at 6 months in the severe or moderate disability groups. The same group report lower rates of depression at 12 months, which were no longer associated with GOS outcome (McCleary, Satz et al. 1998). However, as with several other studies, notably fewer patients participated at the later 12-month follow-up (66 versus 105 at 6 months), such that their findings may simply be an artefact of depressed patients being less likely to continue to participate in studies. Wilson et al (2000) studied a wider range of injury severity patients and found that measures of depression and other emotional disturbance were significantly correlated with both the original and extended GOS.

Chapter 3 Apolipoprotein E

Introduction and Overview

Apolipoprotein E (ApoE) is a member of a family of lipophilic plasma proteins that are involved in the transportation of cholesterol and lipids between the liver and other tissues in the periphery. It is a 299 amino acid protein that is secreted in a glycosylated and sialylated form. Although it is principally synthesised by the liver, it is also produced by a number of other tissues. In the brain glial cells, particularly astrocytes, express the mRNA for ApoE. Within the central nervous system ApoE is the major lipoprotein involved in neuronal lipid transportation and metabolism. It has a role in the mobilisation and redistribution of cholesterol in the maintenance of myelin and neuronal membranes both during development and subsequent to injury.

The ApoE protein is present in differing forms due to polymorphism of the APOE gene, with the most commonly expressed versions corresponding with the alleles ε2, ε3 and ε4. These alleles have frequencies of approximately 10%, 74% and 16% respectively, with the combinations of these alleles represented in the population as six APOE genotypes (Saunders, Schmader et al. 1993; Saunders, Strittmatter et al. 1993). The frequency of alleles and thus genotypes varies across races, though ε3/ε3 and ε3/ε4 are the most frequent genotypes. It is thought that ε3 is the ancestral gene, with cysteine present at position 112 and arginine at residue 158. In contrast, the ε4 allele has arginine at both sites and the ε2 allele has cysteine at both sites (Poirier, Davignon et al. 1993).

These mutations of the original ancestral form result in changes to the three-dimensional 'tertiary' structure of the protein, which in turn has implications for the interactions of the protein with other agents. Indeed it is the observation of genotype specific variations in a variety of disorders which have stimulated interest in the actions of apolipoprotein E. Whilst the polymorphism of APOE also has implications for the aetiology of disorders in peripheral lipid metabolism and pathologies of the cardiovascular system, this review will focus upon its apparent involvement in neurodegenerative pathologies. To date there have been associations between APOE polymorphism and heterogeneity of outcome in a variety of fields including Alzheimer's Disease (AD), traumatic head injury, and both ischaemic and haemorrhagic stroke.

This review firstly considers APOE polymorphism in the context of research into AD as much of this research has implications for possible influences of ApoE upon outcome after head injury. The research and literature on the associations with the development and progression of Alzheimer's Disease constitutes the bulk of the work undertaken on ApoE by a considerable margin. Much of this work is relevant to the potential role of ApoE upon head injury outcome as common mechanisms of action may be involved in the influence of ApoE polymorphism upon both head injury outcome and AD. It remains uncertain how ApoE exerts its influences, though some such possible common mechanisms of action of ApoE are outlined in Table 3-1. Evidence in support of these possible mechanisms will be outlined in the following sections.

Table 3-1: Possible Common Mechanisms of Action of Apolipoprotein E

1. Increased βA cytotoxicity in ε4 brains due to either less efficient removal of βA or accumulation of βA by ApoE4
2. Greater oxidative damage in ε4 patients mediated by ApoE isoform specific antioxidant properties
3. Reduced capacity for compensatory neuronal plasticity in ε4 brains – possible particular impact upon phospholipid dependant cholinergic system

The established epidemiological associations between head injury and increased risk of AD also emphasises the potential for common mechanisms and suggests that head injury may have long-term implications in addition to the immediate consequences of injury. These epidemiological associations between head injury and AD are considered later in the review and studies which suggest an interaction between head injury and ApoE in determining risk of AD are mentioned. The review finally covers the more recent research into the influence of ApoE polymorphism upon outcome after head injury and considers some expectations that might be formed based on the theoretical explanations of ApoE's mechanism(s) of action within the brain.

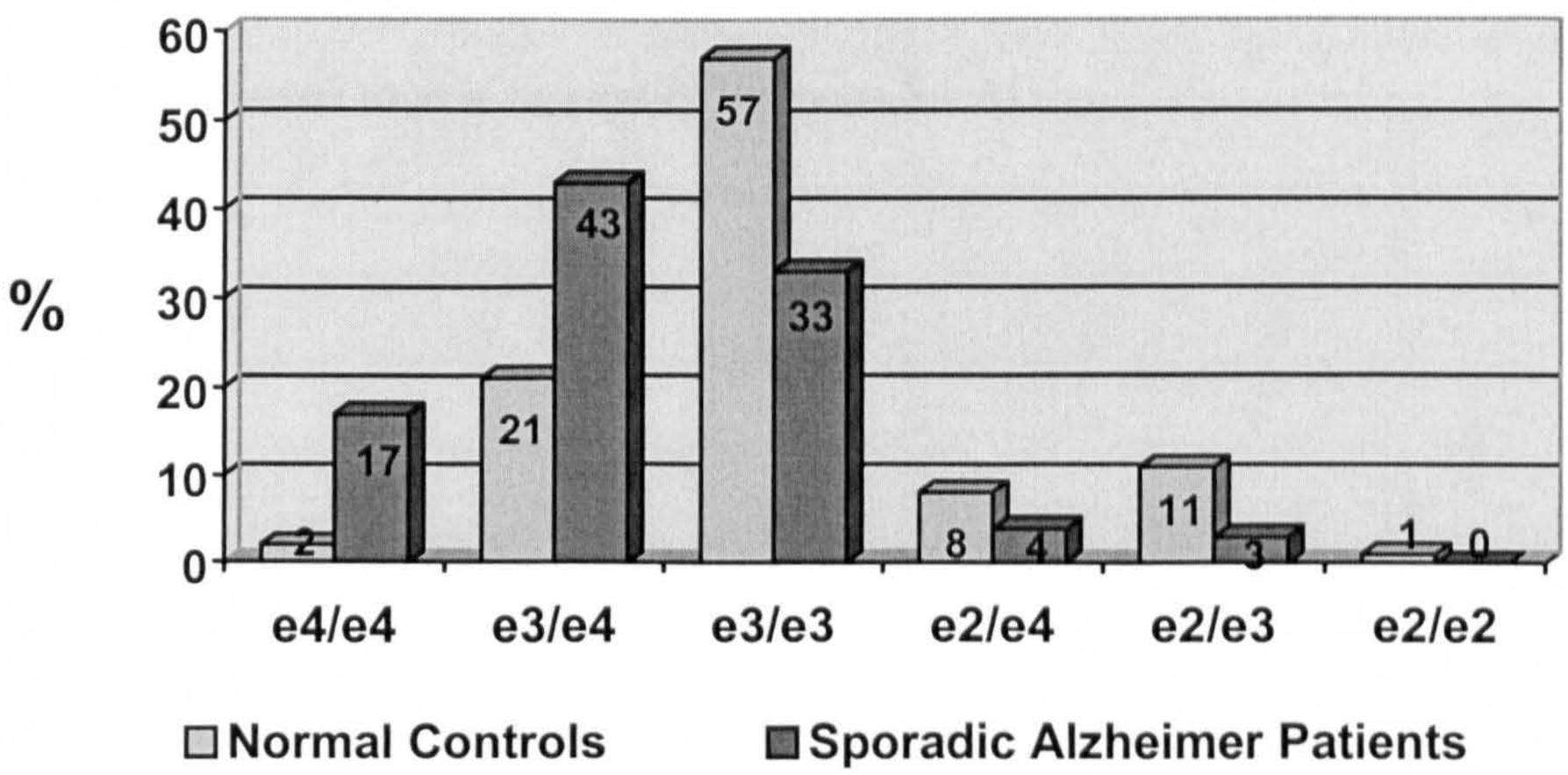
APOE Polymorphism and Alzheimer's Disease.

The association between the apolipoprotein E ε4 allele and late-onset Alzheimer's disease was originally reported in 1993 (Saunders, Schmader et al. 1993; Saunders, Strittmatter et al. 1993). A number of subsequent studies have supported observations that ε4 was notably over-represented in those individuals who developed AD relative to control populations (Mayeux, Stern et al. 1993; Poirier, Davignon et al. 1993; Brousseau, Legrain et al. 1994; van Duijn, de Knijff et al. 1994).

Studies indicated an apparent 'dose response' relationship, with the inheritance of each ε4 allele associated with higher risk of AD and a disposition towards earlier age of onset, whilst each ε2 allele was associated with lower relative risk and later age of onset (Corder, Saunders et al. 1994). The effect is such that there appears to be over twenty years difference between the mean age of onset of ε4 / ε4 homozygotes (less than 70 years) and that of the ε2 / ε3 heterozygotes (over 90 years) (Roses 1997). Most studies have not reported results for ε2 / ε2 homozygotes due to the low percentage of the population with this genotype and the consequent poverty of such individuals in the study samples. However, the indications are that the ε2 allele is relatively benign with respect to AD and that ε2 homozygotes are consequently in a low risk group. The APOE genotype and allele frequencies for AD and controls based upon data from the study by Saunders (1993) are shown in Figure 3-1.

Although a number of studies have replicated the association between ApoE genotype and risk of AD, some more recent studies have indicated differences in the relative risk between ethnic groups. Thus in a prospective population based study, possession of the ε4 allele significantly increased the relative risk of AD relative to ε3 homozygotes amongst Caucasians (2.5), but not amongst Hispanics (1.1) or African Americans (1.0) (Tang, Stern et al. 1998). Although ε4 / ε4 homozygotes were at increased risk in all three groups, the relative risk was considerably greater for Caucasians (7.3) than for Hispanics (2.5) or African Americans (3.0) (Tang, Maestre et al. 1996). The latter ethnic groups appeared to have other non-ApoE dependant risk factors for AD, as the cumulative risk of AD by the age of 90 was broadly similar in all three groups. A recent smaller case-control study found greater similarity between Caucasian and Hispanic groups, with presence of the ε4 allele increasing the risk approximately threefold (Harwood, Barker et al. 1999).

Figure 3-1: APOE Genotype in Sporadic AD & Controls.



Based on data from Saunders (1993)

APOE & Other AD Genetic Loci

There are at least two key differences between this APOE genetic locus on chromosome 19 and previously identified causative mutations in relation to their influence on the development of Alzheimer's disease. Firstly, the known mutations at the PS1 or PS2 'presenilin' loci or within the APP gene are only associated with earlier onset 'familial' AD, whereas the APOE locus is also associated with the very considerably more prevalent (though later onset) sporadic forms of the disease.

Secondly, mutations in the three known early onset familial genes appear to act deterministically, such that the presence of the mutation leads *inevitably* to the development of the disease. In contrast the presence of one or more APOE ε4 alleles appears to serve only as a risk factor for the disease, such that although ε4 homozygotes are considerably more likely to develop AD, many of them continue to advanced years without undue cognitive deterioration. Likewise, absence of the e4 allele or presence of the ε2 allele reduces, but does not eliminate, the risk of AD. Consequently the APOE gene is often referred to as a *susceptibility* locus for AD.

Neuropathology of Alzheimer's Disease

Hyperphosphorylation of Microtubule Associated Tau Protein

The neuropathology of Alzheimer's disease is characterised by the presence of neuritic plaques with amyloid and neurofibrillary tangles, as first described by Alois Alzheimer in 1907. The neurofibrillary tangles are accumulations of fibrous proteins within the cell bodies of neurones and are found particularly in the cerebral cortex, hippocampus and brain stem. In distal dendrites they are found as neurophil threads and are also present in the abnormal neurites found in some of the larger amyloid plaques (Goedert 1993). The majority of the fibres found in these abnormal structures are paired helical filaments (PHFs), which are comprised of abnormally self-assembled microtubule associated protein tau in a hyperphosphorylated state (Lee, Balin et al. 1991). Tau is normally a regulator of microtubule assembly within the cell, but it is unable to fulfil this role in its abnormally phosphorylated state, resulting in destabilisation of the neural cytoskeleton. This in turn results in disruption to the essential axoplasmic transport mechanism and eventually neuronal death.

The β-amyloid Hypothesis

The neuritic plaques contain abnormally aggregated fibres of β-amyloid protein (βA), which is a metabolic product of Amyloid Precursor Protein (APP). A number of mutations on the APP gene on chromosome 21 were found to be responsible for separate cases of familial AD (Goate, Chartier-Harlin et al. 1991; Hardy 1997). These mutations are thought to interfere with normal enzymatic cleavage of APP, resulting in increased levels of βA. Age of onset in these cases is early, varying from 45 to 60 years in an ApoE isoform dependant manner, with presence of the ε4 allele associated with earlier onset (Houlden and et al. 1993).

The association between chromosome 21 and AD is also suggested by the high incidence of AD amongst Down's syndrome (trisomy 21) patients.

More recently, mutations on the presenilin 1 (PS1) gene on chromosome 14 (Sherrington, Rogaev et al. 1995) and the presenilin 2 (PS2) gene on chromosome 1 (Levy-Lahad, Wasco et al. 1995; Levy-Lahad, Wijsman et al. 1995) have also been found to lead to familial AD, with these mutations causing subtle alterations of APP processing which also result in greater levels of βA (Scheuner, Eckman et al. 1996). The apparent convergence of all of the known deterministic genes for familial AD with the β-amyloid hypothesis and the observations of β-amyloid in the brains of sporadic AD patients has naturally led to a prodigious amount of research endeavouring to associate the presence of β-amyloid with tau hyperphosphorylation or other possible mechanisms of AD neuropathology.

Despite the vast amount of research conducted, evidence for a causative role of β-amyloid in sporadic (as opposed to familial) AD is still rather weak. None-the-less, the β-amyloid hypothesis remains the dominant theoretical perspective in the aetiology of AD. There is much circumstantial evidence for a role of β-amyloid in sporadic AD, including its apparent involvement in familial AD, the presence of amyloid deposits in AD brains and its *in vitro* cytotoxicity. However there is also evidence that mitigates against a causative role. For example, some neuropathological studies have found that the extent of βA deposition does not correlate well with the degree of dementia observed during life (Roses 1994), though the reverse has also been reported (Naslund, Haroutunian et al. 2000).

Demonstrable neuropathology has been observed to occur prior to amyloid deposition (Braak and Braak 1994), though some research has suggested that the toxic forms of βA are relatively soluble dimers which could have cytotoxic effects in the absence of βA deposition (Roher, Chaney et al. 1996). Thus although βA remains a prime suspect in the aetiology of neuropathological processes in AD, there is sufficient doubt in the β-amyloid hypothesis to justify greater consideration of alternative theories.

Possible Involvement of APOE in Neuropathology of Alzheimer's Disease

As mentioned above, the association of the APOE gene with AD differs from other known genetic associations in that although it influences the risk of developing AD, it does not act deterministically. Additionally, unlike the other known familial genetic loci, the APOE gene also influences the far more prevalent sporadic form(s) of AD.

APOE & β-amyloid

The frequently replicated observation of an influence of APOE polymorphism upon risk of Alzheimer's led to much research which endeavoured to link ApoE in with the 'amyloid hypothesis'. Presence of the ε4 allele has been significantly associated with increased β-amyloid deposition in post-mortem studies of the brains of Alzheimer's patients (Schmechel, Saunders et al. 1993). Animal models of AD have also found substantially greater βA deposition in ε4 expressing mice relative to those expressing ε3 (Holtzman, Bales et al. 2000).

A number of studies using animal models have found ApoE isoform-specific affinities for β-amyloid, with E4 less efficient than E3 at forming complexes with β-amyloid (Zhou, Smith et al. 1996) and associated with slower uptake of βA (Yang, Small et al. 1999). Previous *in vitro* studies had found the reverse order of binding (i.e. ε4 > ε3) at certain pH levels (Strittmatter, Weisgraber et al. 1993). It has been speculated that apolipoprotein E may play a protective role in the removal of potentially toxic extracellular amyloid peptides via a receptor mediated mechanism, with the isoform-specific binding affinities mediating the efficiency of this role (Beffert, Aumont et al. 1999).

APOE & Microtubule Associated Tau Protein

The isoform-specific affinities of apolipoprotein E with the microtubule associated protein tau have also been of interest due to the apparent involvement of tau hyperphosphorylation as a precursor to the microtubule disruption observed in AD. This results in the paired helical filaments noted in neuropathological studies. ApoE3 and apoE2 bind avidly to tau *in vitro*, whereas apoE4 binds to tau either with less affinity or not at all (Strittmatter, Saunders et al. 1994). It has been speculated that the apoE2 and apoE3 isoforms may serve to provide greater protection against tau phosphorylation by binding to tau protein (Strittmatter, Weisgraber et al. 1994). This would be consistent with the finding of greater presence of unbound tau protein in the cerebral spinal fluid of living AD apoE4 patients relative to patients with apoE3 or apoE2 (Golombowski, Muller-Spahn et al. 1997).

There have been similar differential binding interactions with MAP2 (Huang, Goedert et al. 1994), a microtubule associated protein which functions in a similar manner to tau protein, lending further weight to suggestions that ApoE exerts its isoform-specific effects via influences upon microtubule stability or repair (Roses 1997). A study looking at isoform dependant rates of neurite outgrowth found that cells treated with apoE4 had fewer microtubules and greater depolymerisation of tubulin than did cells treated with apoE3 (Nathan, Chang et al. 1995), again suggesting a destabilising effect of E4 relative to E3.

ApoE, Neuronal Plasticity and Synaptogenesis

In the peripheral nervous system, apolipoprotein E has been demonstrated to be involved in the mobilisation and redistribution of cholesterol for the repair of myelin and neuronal membranes after injury. ApoE is synthesised and released by macrophages in response to neuronal injury and serves to scavenge cholesterol from cellular and myelin debris. This cholesterol is subsequently stored within the macrophages where it is available for later axonal regeneration (Rawlins, Villegas et al. 1972) and remyelination (Boyles, Zoellner et al. 1989). It has been speculated that ApoE is also involved in scavenging cholesterol following neuronal damage in the central nervous system (CNS) and in subsequently making this cholesterol available to neurones to be used in the genesis of new synapses and dendrites (Poirier 1994).

It has been shown that astrocytes engulf pre-synaptic terminals and associated axonal tissue during neuronal degeneration, resulting in increased intracellular cholesterol in the astrocytes (Lee, Stanford et al. 1977). This causes the synthesis of ApoE by the astrocytes and the release of a cholesterol-ApoE complex (Chiba, Mitamura et al. 1991), which may subsequently be internalised by neurones via LDL-receptor binding and the cholesterol made available for synaptogenesis (Poirier 1994). LDL-receptor activity has been shown to increase in hippocampal cells during the reinnervation process (Poirier, Baccichet et al. 1993).

ApoE and Compensatory Plasticity

Support for the involvement of ApoE in neuronal plasticity in the central nervous system comes from the observation of poor hippocampal compensatory synaptogenesis in ApoE deficient knockout mice (Masliah, Mallory et al. 1995). Additionally, an *in vitro* study using chicken neuronal cells found that the presence of apoE3 served to enhance neurite outgrowth whereas apoE4 reduced outgrowth relative to controls (Nathan, Bellosta et al. 1994). A later study by the same author demonstrated that the inhibited neurite outgrowth with apoE4 was associated with lower concentrations of apoE in both the cell bodies and neurites relative to apoE3 (Nathan, Chang et al. 1995).

If ApoE were involved in CNS compensatory synaptogenesis, then this could have a particular effect upon the cholinergic system as these neurones are more dependant upon intact phospholipid metabolism (Wurtman 1992). The cholinergic system, which is thought to have a role in memory and attention via projections to the hippocampus and neocortex respectively, is particularly impaired in AD. This is demonstrable in living AD patients via the observation of diminished choline acetyl transferase (ChAT) immunoreactivity relative to control subjects (Ransmayr, Cervera et al. 1989). More recently this reduction in ChAT activity has been found to be influenced by ApoE isoforms, with presence of the ε4 allele associated with reductions in ChAT activity in the frontal lobes (Soininen, Kosunen et al. 1995) and both the hippocampal formation and temporal cortex of AD brains (Poirier, Delisle et al. 1995). In contrast, AD patients without the ε4 allele had ChAT activity within normal levels.

This greater influence of the ε4 allele upon the cholinergic system may explain findings of particularly pronounced verbal memory disruption in AD ε4/ε4 patients relative to AD ε3/ε3 patients (Lehtovirta, Laakso et al. 1995) and reduced learning ability in non-demented elderly who carried at least one ε4 allele relative to those with ε2/ε2 or ε2/ε3 (Soininen and Riekkinen 1996).

A study of the influence of apolipoprotein polymorphism upon plastic neuronal remodelling in 64 AD brains found notable isoform-specific differences in dendritic plasticity in subcortical neurones (Arendt, Schindler et al. 1997). In APOE ε3/ε3 brains these dendritic changes were more pronounced and were of a higher order as they were more distally localised. In contrast, the growth processes were less notable in ε3/ε4 or ε4 / ε4 brains, being distributed approximately equally between distal and proximal branches of the dendritic tree in ε3/e4 brains and mostly proximally localised (i.e. of lowest order) in the brains of ε4/ε4 patients. Additionally, whilst the extent of dendritic growth was significantly related to neuronal loss in the ε3 / ε3 brains, this relationship was marginal in ε3/ε4 brains and not apparent in ε4/ε4 brains.

Using this relationship between dendritic growth and neuronal loss as an index of reparative capacity, it was estimated that the capacity for regeneration was reduced by up to 68% and 85% in ε3/ε4 and ε4/ε4 brains respectively relative to the brains in which ε4 was not present (Arendt, Schindler et al. 1997). These isoform specific effects were also observable in axons and indicate that the brain's capacity for compensatory neuronal plasticity is compromised in the presence of the ε4 allele in a gene dose dependant manner. This evidence of reduced capacity for compensatory mechanisms in the presence of ApoE4 may serve to account for the observations of earlier age of onset of disease in patients with ε4/ε4 (Corder, Saunders et al. 1993; Soininen, Kosunen et al. 1995) and the more rapid disease progression in these patients (Bennett, Crawford et al. 1995).

APOE and Oxidative Stress

Another theory on the influence of apolipoprotein E polymorphism upon Alzheimer's disease has related to its isoform specific antioxidant properties. Oxidative damage by free radicals to proteins and DNA, particularly mitochondrial DNA, has become an increasingly important area of ageing research (Shigenaga, Hagen et al. 1994; Sohal and Weindruch 1996; Yu, Kang et al. 1998). Free radicals are generally oxygen derivatives that have an unpaired electron and are consequently highly reactive. A major source of these oxidative species is as a by-product of the electron transport chain, which enables the production of adenosine triphosphate (ATP). The production of this energy-carrying molecule is essential to drive many of the cell's metabolic processes via its conversion to adenosine diphosphate (ADP). The high metabolic activity of neurones requires greater production of ATP and consequently increased levels of these damaging free radicals. As mitochondria provide approximately 90 percent of the cell's energy, they are also the focal point for the production of these free radicals and are also consequently most affected by consequent oxidative damage and mutations.

Neurones are post-mitotic by adulthood and are consequently particularly vulnerable to disruption by accumulative DNA mutations. Thus mutations of mitochondrial DNA due to oxidative damage are found as a function of age and have been associated with Alzheimer's disease (Mecocci, MacGarvey et al. 1994; Davis, Miller et al. 1997; Meier-Ruge and Bertoni-Freddari 1999; Trimmer, Swerdlow et al. 2000) and other neurodegenerative disorders (Beal 1995). The brains of AD patients have also been found to have evidence of damage which is characteristic of attack by free radicals, such as protein oxidation, DNA mutations and lipid peroxidation (Christen 2000) and APOE ε4 has been recently associated with higher levels of oxidative insults in AD brains (Ramassamy, Averill et al. 2000).

A series of studies found isoform specific differences in ApoE antioxidant properties in vitro, with ApoE protecting cells against damage from hydrogen peroxide in the order ε2 > ε3 > ε4 (Miyata and Smith 1996). Thus it is possible that ApoE could be involved in protecting against free radical damage and that ApoE4 is less efficient in this role than ApoE3 or ApoE2. Some support for the involvement of ApoE in protecting against oxidative damage comes from studies of LDL oxidation in animal models of atherosclerosis. Plasma LDL in ApoE-deficient (-/-) mice demonstrates an increased susceptibility to oxidation relative to plasma LDL in normal mice, which is not normally oxidised (Palinski, Ord et al. 1994; Maor, Hayek et al. 1997). However, supplementation with nutritional antioxidants appeared to partially compensate for the absence of ApoE in these mice by reducing the susceptibility of LDL to oxidation (Aviram 1996).

The ApoE isoforms can themselves be oxidised, with this oxidation decreasing their ability to be incorporated into phospholipid discs by approximately 50%. A recent study found that the susceptibility of ApoE to oxidation is differential, with apoE4 more readily oxidised than apoE3, which in turn is more susceptible than apoE2 (Jolivalt, Leininger-Muller et al. 2000). This suggests the possibility of oxidative alterations reducing, in an isoform dependant manner, the efficiency of ApoE's role of recycling lipids.

β-amyloid and Oxidative Damage

A number of studies have suggested that beta-amyloid peptide's (βA) cytotoxic properties may be mediated via a pathway involving oxidative damage (Davis 1996; Behl 1997; Behl 1999a; Pappolla, Chyan et al. 1999), either by directly stimulating radical production (Goodman and Mattson 1994; Hensley, Carney et al. 1994), possibly in concert with redox metal ions (Varadarajan, Yatin et al. 2000a; Varadarajan, Yatin et al. 2000b) or by inhibiting the cell's ability to remove free radicals. Vitamin E and other lipophilic antioxidants have been found to protect nerve cells from the cytotoxic effects of βA (Behl, Davis et al. 1992; Varadarajan, Yatin et al. 2000b) and in a placebo controlled trial appeared to slow the progression of AD (Sano, Ernesto et al. 1997; Behl 1999b).

Thus if βA is involved in the aetiology of AD, ApoE could be involved in preventing or reducing βA induced oxidative damage in an isoform dependant manner. A recent study supporting an interaction between ApoE and βA mediated oxidative damage found that, in the absence of βA, ApoE-deficient (-/-) mice had levels of oxidative stress and mitochondrial function which were comparable to control wild-type mice. The subsequent application of βA to these ApoE-deficient (-/-) mice resulted in increased levels of oxidative stress and mitochondrial dysfunction (Keller, Lauderback et al. 2000).

APOE, Head Injury & Alzheimer's Disease

Association between head injury and β-amyloid

Head injury, particularly when associated with loss of consciousness, has been identified by a number of studies as an epidemiological risk factor for Alzheimer's disease (Mortimer, French et al. 1985; Graves, White et al. 1990; Mayeux, Ottman et al. 1993; Rasmusson, Brandt et al. 1995; Salib and Hillier 1997; Schofield, Tang et al. 1997). Early neuropathological evidence for an association between repeated head injury and AD came from post-mortem studies of dementia pugilistica, the 'punch-drunk' syndrome associated with boxing, in which neurofibrillary tangles similar to those described in AD brains were reported (Corsellis, Bruton et al. 1973). More recently βA protein plaques, the other characteristic neuropathological consequence of AD, have also been found in dementia pugilistica brains (Roberts, Allsop et al. 1990) and have been suggested to be indicative of brain injury induced neurodegeneration which is akin to Alzheimer's (Clinton, Ambler et al. 1991).

Further evidence for an association between cerebral trauma and βA plaques came from evidence of the presence of βA deposition in six of sixteen patients (38%) who died within days of their single head injury (Roberts, Gentleman et al. 1991), indicating that βA deposition can occur within days of a single injury rather than solely as a consequence of the repeated injuries which precede dementia pugilistica. A larger study confirmed the presence of βA deposition in one or more cortical areas of 152 head injury fatalities (Roberts, Gentleman et al. 1994).

APOE mediates β-amyloid deposition after head injury

Subsequently an interaction between βA deposition following fatal head injury and APOE genotype was reported, with the presence of the ε4 allele strongly associated with βA deposition as indicated in Table 3-2 (Nicoll, Roberts et al. 1995). In this study all six of the ε4 homozygotes were amongst the 26% of patients who had βA deposition and there was a significant gene dose effect ($p < .001$). There was also a negative association between ε2 and βA, with ε2 patients least likely to have βA deposition. This corresponds with the lower incidence of AD in individuals carrying the ε2 allele and may reflect a protective role for this allele. It was suggested by the authors that head injury might serve as a trigger for the deposition of βA in ε4 patients. The alternative possibility that the βA deposits pre-date head injury in ε4 patients has also been suggested (Roses and Saunders 1995). However a recent neuropathological study mitigates against the importance of βA in head injury induced dementia as it found neurofibrillary tangles and neuropil threads, but no βA immunoreactivity, in the brains of five young men who had suffered from dementia pugilistica (Geddes, Vowles et al. 1999).

Table 3-2: ApoE & β-Amyloid deposition following Fatal Head Injury

APOE Genotype	Proportion with βA Deposition	
	Ratio	Percentage
2 / 2	0 / 2	0
2 / 3	0 / 7	0
3 / 3	5 / 41	12
2 / 4	1 / 4	25
3 / 4	11 / 30	37
4 / 4	6 / 6	100

(Based on data reported in Nicoll et al 1995)

Possible Interaction between APOE Genotype, Head Injury and Risk of AD

A retrospective study of 113 AD patients and 123 elderly controls found an apparently synergistic effect between head injury and APOE genotype on risk for AD (Mayeux, Ottman et al. 1995). Relative to those with neither a history of head injury or an ε4 allele, those with both of these risk factors were over ten times as likely to have developed AD. In contrast the presence of ε4 alone only doubled the risk of AD and head injury in the absence of ε4 did not increase the risk of AD. This would suggest that head injury was only a risk factor for AD in the presence of ε4, though some caution in interpreting the results is due as the interaction was not statistically significant and only 13 of the AD patients had a history of head injury.

A later study with a substantially larger genotyped sample size (230 AD and 309 controls) was more cautious (O'Meara, Kukull et al. 1997). This study found stronger main effects, with head injury alone doubling the risk of AD and ε4 alone conferring over four times the risk relative to those without either risk factor. Although the risk for those with both head injury and ε4, at OR = 11.7, was greater than the multiplicative risk of these main effects, the interaction still did not reach significance because of the low numbers of head injuries reported amongst control subjects. The authors suggested that the effects of ε4 and head injury might be additive rather than synergistic. This suggestion seems to be supported by a recent study which reports data from a considerably larger sample of genotyped individuals (942 AD and 327 controls) in which although both head injury and ε4 increased the risk of AD, the additional risk due to head injury was actually lower amongst those with the ε4 allele (Guo, Cupples et al. 2000).

APOE & Outcome after Head Injury or Stroke

In recent years a number of studies have suggested that ApoE may influence recovery from head injury or stroke in the short-medium term in addition to the possible longer-term influences upon risk of Alzheimer-type dementia. Some possible mechanisms via which ApoE polymorphism may influence outcome following brain injury are outlined in Table 3-3. Evidence for these possible mechanisms, which are neither exhaustive nor mutually exclusive, is presented in the following sections.

Table 3-3: Possible Mechanisms of Action of Apolipoprotein E upon Brain Injury

Increased Secondary Damage	1. Reduced protective response to injury in ε4 brains – possibly mediated by ApoE isoform specific antioxidant properties 2. Increased βA cytotoxicity in ε4 brains due greater prior deposition in vessels and subsequent release in haemorrhage 3. Increased βA cytotoxicity & deposition in response to injury due to either less efficient removal of βA or accumulation of βA by ApoE4 4. Pre-existing greater oxidative damage to mitochondrial DNA etc in ε4 patients restricts brain's capacity to deal with trauma
Diminished Capacity for Repair	5. Reduced capacity for compensatory neuronal plasticity in ε4 brains – possible particular impact upon phospholipid dependant cholinergic system

APOE and Outcome following Stroke

An interest in the role of apolipoprotein polymorphism in cerebrovascular disease originally stems from findings that this polymorphism appears to influence risk of coronary heart disease (Cumming and Robertson 1984) with later studies suggesting that the ε4 allele substantially increases the risk, whereas the presence of the ε2 allele slightly reduces the risk (Wilson, Schaefer et al. 1996). In one of the first studies to consider the influence of APOE polymorphism upon risk of ischaemic cerebrovascular disease, the ε4 allele was found to be more prevalent amongst 100 male patients than amongst controls, leading the authors to speculate that the ε4 allele could be a predisposing genetic marker for ischaemic stroke (Pedro-Botet, Senti et al. 1992).

Subsequent results have been conflicting, with some retrospective studies also reporting significant associations between presence of the ε4 allele and ischaemic stroke (Margaglione, Seripa et al. 1998; Peng, Zhao et al. 1999) whereas two much larger (N > 1000) prospective studies found no influence of ε4 upon risk of stroke (Kuusisto, Mykkanen et al. 1995; Ferrucci, Guralnik et al. 1997). The latter of these prospective studies does however report a protective effect of the ε2 allele upon risk of ischaemic stroke amongst those aged less than 80 which is not present in those of more advanced years. However the results of these prospective studies conflict with the findings of a recent meta-analysis, based upon nine retrospective case-control studies, which concludes that the ε4 allele is a risk factor for ischaemic stroke and that the ε2 allele is not protective (McCarron, Delong et al. 1999).

Another large-scale study found that risk of stroke was not influenced by APOE genotype (Basun, Corder et al. 1996). However, this study did find a lower than expected frequency of ε4 individuals amongst those who survived a stroke, indicating that this allele could be associated with greater mortality after stroke. Additionally, the risk of haemorrhagic stroke tended to be higher in the presence of ε4 and lower in those who expressed ε2, indicating that APOE polymorphism may influence the risk of haemorrhagic strokes, such as ICH or SAH, even if it does not influence the risk of ischaemic strokes.

APOE, Intracerebral Haemorrhage & Cerebral Amyloid Angiopathy

As outlined in Chapter 1, intracerebral haemorrhage (ICH) can be a consequence of trauma (traumatic ICH) or may be spontaneous in origin. This latter group can be divided into those that are associated with hypertension (hypertensive ICH) or those associated with cerebral amyloid angiopathy (CAA), referred to as CAA associated intracerebral haemorrhage (CAAH). Cerebral amyloid angiopathy is characterised by the presence of βA protein in leptomeningeal and cortical blood vessels and is often comorbid with Alzheimer's disease and / or Down's syndrome (McCarron, Nicoll et al. 1998).

The first study to find an association between APOE polymorphism and ICH reported significantly worse outcome, as measured by Barthel score, in those with the ε4 allele ($p < .001$) (Alberts, Graffagnino et al. 1995). Those with the ε4 allele in this study were three times as likely to die as a consequence of their ICH as non-ε4 patients. Additionally, there was a significantly higher frequency of the ε4 allele amongst the ICH patients than amongst controls, indicating that ε4 may predispose to ICH. The association between the ε4 allele and higher mortality rates following ICH was also found in a larger series of patients (McCarron, Hoffmann et al. 1999), even though haematoma size and oedema volume were not associated with ε4 in this study after controlling for other factors. This could potentially indicate a disposition amongst ε4 carriers towards a more deleterious consequence in response to a given level of injury, perhaps mediated via greater secondary damage. There was also a trend towards poorer outcome amongst survivors of ICH who carried the ε4 allele (McCarron, Muir et al. 1998).

A number of studies have reported an increased frequency of the generally relatively rare ε2 allele in patients with CAAH (Nicoll, Burnett et al. 1997; Greenberg, Vonsattel et al. 1998; McCarron and Nicoll 1998b). The ε4 allele has also been associated with both CAA and CAAH. In a neuropathological study of 93 cases, presence of the ε4 allele increased the odds ratio of moderate to severe CAA by nearly threefold, whereas ε4 homozygotes had over thirteen times the risk of moderate to severe CAA relative to non-ε4 cases (Greenberg, Rebeck et al. 1995).

However, another study involving 101 ICH cases found no influence of ε4 upon the severity of CAA (Itoh and Yamada 1997). The ε4 allele was also associated with CAAH in the Greenberg study and in a later study with a greater number of ICH patients (Greenberg, Briggs et al. 1996). In this later study, the association between ε4 and ICH was only true with CAAH patients and not with hypertensive deep ICH patients whose haemorrhage was not associated with CAA. The ε2 allele was later found to be significantly associated with vasculopathic changes (Greenberg, Vonsattel et al. 1998) leading to the suggestion that ε4 enhances the risk of CAA via increased βA deposition, whereas ε2 increases the risk of vasculopathic changes and rupture in the amyloid laden blood vessels.

This is supported by findings that ε2 or ε4 carriers are at higher risk of recurrent lobar ICH relative to ε3 / ε3 homozygotes, with half of those experiencing recurrent ICH having the uncommon ε2 / ε4 genotype (O'Donnell, Rosand et al. 2000). The assertion that ε2 only increases the risk of vasculopathy in the presence of amyloid laden blood vessels is supported by the finding that ε2 is significantly over-represented in CAAH, but not in subarachnoid haemorrhage or deep intracerebral haemorrhage (McCarron and Nicoll 1998a). Subsequent findings that anticoagulant medication, hypertension or minor head injury were significantly more likely to precede CAAH in those with the ε2 allele indicate ApoE isoform specific implications for the management of these patients (McCarron, Nicoll et al. 1999).

Animal Models of APOE Suggesting an Antioxidant Role following Brain Injury

In rodent models of brain injury, ApoE has been found to localise to the region of injury. Thus following induced transient cerebral ischaemia ApoE localised specifically to the damaged neurones (Horsburgh and Nicoll 1996). Similarly, subsequent to acute subdural haematoma ApoE was rapidly redistributed and levels of ApoE were significantly elevated in the cortex underlying the haematoma (Horsburgh, Fitzpatrick et al. 1997). This rapid cellular redistribution of ApoE following neurological insult suggests an involvement of ApoE in the brain's protective response to injury.

A study using ApoE deficient (-/-) mice found that these mice had more severe motor and behavioural deficits following closed head injury than injured controls. They also were markedly impaired in the Morris maze spatial memory task relative to the injured control rats, with this corresponding to subsequent findings of bilateral hippocampal atrophy in these (-/-) mice (Chen, Lomnitski et al. 1997). Another study which induced focal ischaemia in both ApoE (-/-) and control mice also found a greater impact of the neurological insult upon ApoE (-/-) mice, with significantly larger subsequent infarcts and substantially greater likelihood of mortality (Laskowitz, Sheng et al. 1997). A recent study in which ApoE (-/-) and control mice were subjected to closed head injury reported that whilst the region of damage had reduced by day 7 in control mice, no such recovery was observed in ApoE (-/-) mice up to at least 14 days post injury (Lomnitski, Nyska et al. 2000). These studies suggest that the deleterious effects of head injury are more pronounced in the absence of ApoE and thus that ApoE may play some protective role subsequent to brain injury.

This notion receives support from a recent study in which global ischaemia was induced in ApoE (-/-) and normal mice (Horsburgh, McCulloch et al. 2000). An intraventricular infusion of ApoE reduced neuronal damage in the caudate nucleus and CA2 hippocampal cells in the (-/-) mice by approximately 50% relative to a control vehicle infusion. A similar effect was found with the normal mice, but the protective effect of the infused ApoE was less pronounced as these mice already expressed their own ApoE. These studies are strongly suggestive of a neuroprotective role for ApoE in the immediate stages following neurological insult.

A possible mechanism for this neuroprotective role is ApoE's ability to counteract oxidative damage, which may otherwise contribute considerably to the secondary damage subsequent to the initial insult. A study on the role of ApoE upon antioxidants following closed head injury found that antioxidant levels were markedly less responsive to the injury in ApoE (-/-) mice (Lomnitski, Kohen et al. 1997). In normal control mice the response was biphasic, with an initial reduction in antioxidant levels that presumably corresponded to their consumption whilst neutralising oxidative species, followed by a marked increase to more than twice their original level, presumably reflecting increased recruitment or production of antioxidants. In contrast, the initial decrease of antioxidants in the ApoE (-/-) mice was less marked and they subsequently only increased to their original levels, thus half that of the injured control mice. This suggests a pronounced impairment of the brain's capacity to counteract injury induced oxidative damage in the absence of ApoE.

A potential role for redox metal irons is suggested by the finding that the greater damage in ApoE (-/-) mice following head injury corresponds with higher levels of intracellular iron, suggesting that ApoE deficient mice may suffer greater oxidative stress due to impairments of antioxidative iron chelating mechanisms (Lomnitski, Nyska et al. 2000). Other studies have also reported alterations in antioxidative metabolism in the brains of ApoE deficient mice (Matthews and Beal 1996; Lomnitski, Chapman et al. 1999), which appear to mirror the reduced ability of these mice to counteract oxidative damage in the periphery observed in animal models of atherosclerosis.

APOE and Outcome Following Traumatic Head Injury

The evidence from these animal studies that the APOE gene may also have a more direct impact upon recovery after head injury, in addition to its apparent role as a susceptibility locus for AD, is supported by recent patient studies. In the Nicoll (1995) study, which found a gene dose relationship between the ε4 allele and βA deposition, there was a notably higher frequency of the ε4 allele amongst those head injury patients who died within a relatively short time after their injuries than would be expected amongst the general population. Assuming that ε4 carriers are no more likely to suffer serious head injury than non-ε4 carriers, it could be inferred that the presence of ε4 increased the likelihood of death after serious head injury.

A subsequent study reported a higher frequency (0.42) of the APOE ε4 allele amongst six patients who had not recovered consciousness from post-traumatic coma, relative to that amongst ten patients who recovered consciousness within one year (0.15) (Sorbi, Nacmias et al. 1995). The presence or absence of the ε4 allele was found to be a better predictor of eventual outcome than admission Glasgow Coma Scale (GCS) or age.

The hypothesis of an influence of the APOE ε4 allele upon recovery from brain injury was supported by a study of thirty professional boxers who were assessed on a 10-point rating chronic brain injury (CBS) scale devised to assess the severity of boxing induced traumatic encephalopathy (Jordan, Relkin et al. 1997). Predictably those with higher exposure to boxing had higher CBS scores than those with low exposure. However, those high exposure boxers with an ε4 allele had significantly greater evidence of encephalopathy than those without ε4 ($p < .001$) and all of the boxers with severe impairment had at least one ε4 allele.

In the first prospective clinical study to determine the influence of APOE polymorphism upon outcome after head injury (Teasdale, Nicoll et al. 1997), the ε4 allele was again significantly associated with poor outcome ($p < .006$). This study determined outcome by use of the Glasgow Outcome Scale (GOS) in 89 patients and found that those with ε4 were more than twice as likely to have a poor outcome after head injury than those without ε4. All four of the ε4 / ε4 homozygotes were still severely disabled 6 months after injury.

This strong association of the ε4 allele with poor outcome was despite a relatively younger age in this group (mean 34.3 years vs 41.0 years), which would normally be associated with greater capacity for recovery. However recent evidence has suggested that there may be an interaction between ε4 and age, with ApoE polymorphism having a greater influence upon recovery in younger patients (Teasdale unpublished data). The ε4 group did however also have notably lower admission Glasgow Coma Scale scores, which would be indicative of greater severity of injury. Lower GCS scores and correspondingly poorer outcome were also present in ε4 patients in a recent study involving 69 head injury survivors (Friedman, Froom et al. 1999).

This tendency for lower GCS scores is of interest as it suggests that either these ε4 sufferers are behaviourally more likely to be involved in circumstances which result in greater severity of head injury or that they are more biologically disposed to be severely affected by head injury. The behavioural differences explanation is plausible due to the younger age of the ε4 patients in both studies, with younger adults more likely to have injuries due to assaults or RTAs, both of which are usually associated with greater severity of injury. However isoform-specific differences in biological response to injury are also a possible explanation. The animal studies mentioned above suggest that cellular redistribution of apolipoprotein E occurs rapidly following neurological insult, such that any isoform-specific effects may already be significantly influencing the brain's response to injury by the time the patient reaches a neurosurgical unit. Thus isoform-dependant differences in response in the hours after initial trauma could potentially result in the lower GCS scores observed in the ε4 allele group.

Expectations based on possible Mechanisms of Action of Apolipoprotein E

If the ε4 allele were consistently found to be associated with greater injury severity on admission, then this would be supportive of theories that suggest a mechanism of action that is influential in the very early stages after neurological insult. This would include the proposal of an isoform-dependant role for ApoE as a protective agent against oxidative damage as discussed above. As mentioned in Chapter 2, there is evidence to suggest an increased presence of free radicals in the brain following brain injury and any mechanism which had a differential impact upon the extent of oxidative damage caused by these radicals could have a considerable influence upon secondary damage occurring within a short period of the initial injury.

Thus if differential effects of ApoE are mediated via its isoform-dependant antioxidant properties, differences in head injury patients might be expected from relatively early stages due to greater secondary oxidative damage. This may correspond with lower GCS scores in ε4 patients due to less efficient neuroprotective mechanisms resulting in greater neurological damage. Thus any differences in outcome would reflect greater incidence of secondary damage and would be expected to be apparent from a relatively early stage.

Additionally, if ApoE were involved as an antioxidant protecting against free-radical mediated secondary damage, it is *possible* that its influence would be more apparent amongst those in whom there had been a haemorrhage of some form. If this were found to be the case, it could be due to greater production of free radicals in the brain as a consequence of the catalytic properties of free iron released as a breakdown product of haemoglobin.

Alternatively, a particular influence of ApoE upon haemorrhages could be due to greater release of accumulated oxidative βA from the vessels of ε4 carrying patients. Some support for a particular effect of ApoE in the presence of extravascular blood comes from a large recent prospective study by Teasdale et al (unpublished data) in which ε4 was more likely to be associated with unfavourable outcome amongst those with a mass lesion.

If ApoE's role were restricted to isoform-specific effects upon neuronal plasticity and the capacity for synaptogenesis, then this alone would not be expected to have an influence upon secondary damage or severity of injury in the very early stages following neurological insult. This well grounded theory for ApoE mediated differential recovery would be more likely to result in differences in recovery over a longer time frame, corresponding to isoform-dependant abilities for compensatory neuronal plasticity. Thus for patients with relatively equivalent severity of injury, this 'plasticity' hypothesis might be expected to result in greater recovery in those without ε4 and potentially recovery in these non-ε4 patients could occur over a longer time-period. If the cholinergic neurones are particularly dependant upon intact phospholipid mechanisms, as has been suggested in relation to AD, then one might expect APOE polymorphism to have a particular influence upon memory functions amongst survivors after head injury. Some preliminary evidence of an effect upon memory was provided by a pilot study (Wilson 1999) in which a verbal memory task (logical memory) was found to be significantly lower amongst those with the ε4 allele.

Chapter 4 Methods

Patient Recruitment for Subarachnoid Haemorrhage study

The SAH patients were drawn from a group of 100 patients who had participated in a brief telephone based outcome study of their functional status at six months. This earlier study had screened 125 consecutive patients with a suspected diagnosis of subarachnoid haemorrhage admitted to the Institute of Neurological Sciences in Glasgow between January and August 1998 (Dunn, Stewart et al. 2001). Of the 25 screened patients who did not take part in the earlier telephone study, 7 died before consent for the study could be obtained, 8 had negative CT and negative lumbar puncture and thus probably had not suffered SAH, 1 had a previously clipped aneurysm and 9 declined consent. A further four patients did not have their diagnosis of SAH confirmed by CT or lumbar puncture, leaving a potential study group of 96 patients.

Acute stage data for these patients was collected by a research nurse during the patient's hospital admission. This data included basic demographic information such as age, marital status and gender. Clinical variables recorded included whether the haemorrhage was angiographically confirmed as aneurysmal in origin, the aneurysmal site(s), WFNS grade at admission and pre-operatively where relevant, Fisher Grade based on CT scans, and the occurrence of haematoma, infarction or acute hydrocephalus. APOE genotypes were determined by PCR using buccal smears obtained from patients during their hospital admission. Medical records were requested and reviewed where available around 16 months subsequent to the haemorrhage to verify details and update data to account for later medical events.

A research nurse had contacted patients by telephone at around six months as part of the earlier study to determine their Glasgow Outcome Scale using the extended 8-point version. The follow-up interview was mentioned briefly to most of the patients during this telephone conversation. The patients were then contacted by letter at around 14 months subsequent to their haemorrhage to outline the follow-up study and ask whether they would be willing to participate.

Patient Recruitment for the Head Injury Study

The patients for this study were drawn from a group of 94 traumatic head injury patients who had been treated at the Southern General Hospital some 6 to 8 years earlier and participated in a neuropsychological assessment at around 6 months subsequent to the injury. In order to reduce the likelihood of inappropriately contacting deceased patients, attempts were made to contact the registered General Practitioners (GPs) for these patients prior to any attempt to contact the patients themselves. The current registered GPs were found where possible using hospital records or via the regional health boards. Attempts were then made to contact these GPs by letter to explain the intended study and to ask if there were any reasons why the patient would not be suitable for follow-up. If the GP replied and did not indicate any reasons to the contrary, then attempts were made to contact the patient by letter using the address held by the GP where available and /or previous addresses known for the patient.

For both SAH and head injury studies, all patients were offered either an appointment in their own homes or at the Southern General depending on which was most convenient for them. They were also offered times and dates of appointment which were most suitable to them, including weekends and evenings. Patients could indicate their preferences on a reply sheet to be returned in the enclosed stamped addressed envelope. Patients were then contacted by phone to answer any questions which they had regarding the study and to arrange a suitable appointment.

Reasons for Absence of Control Group

It was decided not to recruit control patients for comparison purposes in these studies for a variety of reasons. First and foremost, the main comparisons were intended to be between brain injury patient groups such that the differential influences of indices of injury severity and apolipoprotein E genotype could be compared amongst brain injury survivors. Secondly, the majority of tasks and measures employed had good normative data with which to compare performance such that, arguably, there was less need for a control group.

Very few outcome studies after head injury or stroke include any control groups and, even amongst those that do, the matching of patients is often far from ideal due to various practicalities. A control group comprising medical staff or students is unlikely to serve as a true comparison due to educational and social class differences, in addition to the failure to control for a sudden traumatic event. Orthopaedic control groups have been utilised on occasion in head injury studies, but there are considerable difficulties inherent in endeavouring to trace and recruit such patients, which would have been compounded in the case of the current study in that ideally such patients would also have been 6-9 years post injury.

In the case of the SAH patients, orthopaedic patients would probably not be suitable controls due to differences in typical age, educational status and social class between the groups and the differences between a spontaneous versus a traumatic event. Heart attack patients may have controlled for demographic variables and the occurrence of a sudden life-threatening event more closely, however such heart attack patients usually remain at risk of further heart attacks whereas SAH patients whose aneurysm, if present, has been successfully obliterated are usually not at any notable risk of further haemorrhage. Additionally, evidence suggests that the occurrence of heart attack causes ischaemic damage to the brain such that these patients cannot serve as true controls for the effects of brain injury. Even if suitable patient controls could be identified, the recruitment and assessment of such patients would have necessitated considerable reductions in the numbers of brain injury patients recruited to the studies which would have notably curtailed the ability of the study to determine influences of clinical indices or genotype upon outcome.

APOE Genotyping

All APOE genotypes were determined from buccal smears by the Department of Neuropathology at the Southern General Hospital using Polymerase Chain Reaction (Wenham, Price et al. 1991). Buccal smears were collected during assessments for the head injury study and had previously been collected during hospital admission for the SAH study. All assessments and corresponding data scoring and coding were completed without knowledge of the APOE genotype of patients

The head injury and SAH studies were separately submitted to and approved by the medical ethics committee of the Southern General NHS Trust.

Semi-Structured Interview

The assessment started with a semi-structured interview that was intended to elicit information relevant to the patient's recovery that might otherwise be missed and to facilitate some rapport with the patient before administering the neuropsychological tasks. The duration of this part of the assessment was largely dependant upon the patient, starting with very open questions asking the patient to mention difficulties which they had experienced since the haemorrhage or head injury before moving on to more directed questions relating to areas which the patient hadn't mentioned but which are known to affect individuals following subarachnoid haemorrhage or head injury.

The measures used in the SAH and head injury studies are outlined, along with differences in versions employed, in Table 4-1 on the following page. In several instances the selection of tasks for the head injury study was determined by the battery of tasks which had previously been used with these patients at the six month assessment some years earlier so that direct comparisons could be made of change over time. This battery of measures was then revised for the SAH study.

Table 4-1: Overview of Outcome Measures Employed

	Head Injury	Subarachnoid Haemorrhage
Global Outcome Measures		
Extended Glasgow Outcome Scale	Yes †	Yes †
Short Form-36 Health Survey	Yes	Yes
Cognitive Tasks		
Digit Span	WAIS version * †	WAIS-R version *
Comprehension	WAIS version * †	WAIS-R version *
Block Design	WAIS version * †	WAIS-R version *
Digit-Symbol	WAIS version * †	WAIS-R version *
Incidental Learning Task	Yes	Yes
Paced Auditory Serial Addition 4 second	Yes †	Yes
Paced Auditory Serial Addition 2 second	Yes * †	Yes *
National Adult Reading Test	Yes	Yes
Cambridge Contextual Reading Test	Yes	No
McKenna Graded Naming Test	Yes *	Yes *
Logical Memory	WMS version * †	WMS-R version *
Delayed Logical Memory	WMS version	WMS-R version *
Verbal Paired Associates	WMS version * †	WMS-R version *
Delayed Verbal Paired Associates	WMS version	WMS-R version *
Figural Memory WMS-R	No	Yes
Brixton Spatial Anticipation Test	No	Yes
Verbal Fluency	Animals 'S' 'J' †	'F' 'A' 'S'
Rey-Osterreith Complex Figure	Yes	Yes
Trail Making A & B	Yes	Yes
Stroop: Word	Yes *	Yes *
Stroop: Colour-Word	Yes *	Yes *
Stroop: Interference	Yes	Yes
Emotional Outcome Measures		
Hospital Anxiety and Depression Scale	Yes	Yes
State Trait Anxiety Inventory	Form X †	Form Y
Beck Depression Inventory	Yes †	Yes
General Health Questionnaire	Yes †	Yes
Adapted Relative's Questionnaire	Yes	Yes

*: Tasks with age-stratified normative data used for consideration of likely impairments
†: Measures with comparable data for most patients available from 6 months assessment

Extended Glasgow Outcome Scale

The Glasgow Outcome Scale (GOS) was completed towards the end of the semi-structured interview. As mentioned in chapters 1 & 2, the GOS is a frequently used measure of outcome that was originally developed as an index of neurological outcome after traumatic head injury (Jennett and Bond 1975), but has been used to assess outcome after a range of other neurological conditions. This study utilised the extended 8-point version of the scale (Pettigrew, Wilson et al. 1998; Wilson, Pettigrew et al. 1998).

Neuropsychological Assessment Battery

The battery of neuropsychological tasks used was partially determined by those tasks used in the earlier head injury study so that comparisons could be made between the patients' performance at 6 months and at the 6-8 year follow-up. The earlier study had included a particularly large battery of tasks and it was deemed necessary to reduce the number of tasks such that the assessment could be undertaken in less than two hours. Tasks were more likely to be retained if they were sensitive to differences in the earlier study, had good normative data and had been used in other studies of head injury.

This battery of tasks was then adapted for use with the subarachnoid haemorrhage study. The tasks are representative of the cognitive domains measured by previous SAH outcome studies, though many of these studies have not been conducted in the English language and thus the actual measures differ.

Whereas for the head injury study it was necessary to retain the original WAIS and WMS tasks used in the original study, for the SAH study these were updated to the corresponding WAIS-R and WMS-R tasks. Some tasks were used only in the head injury or the SAH study and where this is the case it is mentioned explicitly below and outlined in Table 4-1 above. However, for the majority of tasks the same or updated versions of the task were used in both the head injury and SAH studies, reflecting the similarities in cognitive deficits typically reported following these separate events. Tasks were presented in the order in which they are shown in Table 4-1 and described below. Tasks were not administered if the patient had physical or language difficulties that would have impaired performance upon the task or if the patient was unable to understand the instructions for the task despite reasonable re-explanation and / or demonstration.

Mini-Mental State Examination (MMSE)

This brief measure of cognitive status with norms based on age and education is often used as a screen for dementia or as a basic measure of severity of dementia where present (Folstein, Folstein et al. 1975). It was included initially for the head injury study but not found to be of particular utility and therefore not included in the SAH battery of tests.

Wechsler Adult Intelligence Scales (WAIS, WAIS-R)

The first four tasks were drawn from the Wechsler Adult Intelligence Scales, the revised versions of these tasks (WAIS-R) being used in the SAH study. Normative data stratified by age for these tasks is published in the corresponding manuals (Wechsler 1955; Wechsler 1981).

WAIS(-R) Digit Span

This is a subtest from the verbal intelligence scale of the WAIS which comprises two separate parts, digits forwards and digits backwards. For digits forwards a series of digits are presented at the rate of one per second, starting with a sequence of three digits. The patient is requested to repeat the sequence and if they do so successfully a new sequence is presented which is longer by one digit, up to a maximum of eight digits in the WAIS version and nine digits in the WAIS-R. Digits backwards is similar, though the patient is requested to repeat the digits in reverse order and the task starts with two digits progressing up to a maximum of eight digits. If the first attempt is unsuccessful a second trial using the same number of digits is administered. In both digits forwards and digits backwards the task is discontinued if both trials are unsuccessful.

The scoring is slightly different between the WAIS and WAIS-R versions. In the WAIS the score is the longest sequence repeated without error regardless of whether second attempts were required, thus yielding a maximum score of eight for each component which is summed to give a raw score for Digit Span. The WAIS-R scoring accounts for attempts taken and allocates a corresponding score of either 2, 1 or zero with a maximum score of fourteen for both of the subcomponents which is summed to give a raw score for Digit Span.

Digit Span is generally considered as a measure of immediate memory, though it also serves as a measure of attention, loading highly on a third 'attention / concentration' factor of the WAIS (Crawford 1992). This in part reflects the combination of the separate forwards and backwards components which themselves have differing though related neuropsychological properties (Banken 1985) and it is therefore suggested that the components be considered separately (Lezak 1995). The forwards component is probably primarily a measure of attention with the backwards component more truly measuring immediate memory. Digit span has been found to be more sensitive to left hemisphere lesions than to those of the right hemisphere or diffuse lesions (Black 1986).

WAIS(-R) Comprehension

This is another subtest from the WAIS(-R) verbal intelligence scale which comprises a series of verbal reasoning questions which assess common-sense judgement and practical reasoning and two questions requesting the meaning of proverbs (Lezak 1995). The answers to each of these questions is allocated a score between zero and two depending on the appropriateness of the response. Comprehension is not affected much by age differences, but is significantly affected by education reflecting its utility as an indicator of pre-morbid ability amongst those without verbal deficits. The considerable verbal demands of the task make it sensitive to left hemisphere lesions (Crosson, Greene et al. 1990).

WAIS(-R) Block Design

A subtest from the performance scales of the WAIS(-R) in which the patient is requested to replicate designs using a number of identical cube-shaped blocks. Four blocks are used for the earlier designs increasing to nine blocks for the final four designs. Each of the blocks has two white sides, two red sides and two sides that are half red and half white, with the colours separated at the diagonal.

For the first two designs the patient is requested to replicate a design arranged in separate blocks by the assessor, with the later designs presented using a booklet. The time taken to complete the design is recorded, with a time limit of 60 seconds for each of the four block designs and 120 seconds for the nine block designs. Additional points are allocated according to time taken, particularly in the WAIS-R scoring. The WAIS-R omits the third design used in the WAIS, but otherwise the designs used are identical.

Scores on the block design task are lower in the presence of brain injury, particularly parietal lesions and right hemisphere lesions (Warrington 1986). Individuals with visuospatial deficits due to right hemisphere lesions have particular difficulties with the designs that use the diagonally shaped blocks to form bands of colour (i.e. blocks 2, 3, 5, 7, 8 & 9 of the WAIS-R version) (Walsh 1985). A recent study found that this task was the most consistently impaired in a group of 27 patients following aneurysmal SAH (Hillis, Anderson et al. 2000), with the mean score of these patients more than 2 standard deviations below normative data. An earlier study also reports frequent dysfunction in block design following SAH (Ljunggren, Sonesson et al. 1985).

WAIS(-R) Digit-Symbol

This task comprises four rows of 25 boxes, each of which is immediately below a corresponding number ranging from 1 to 9. Above these boxes the numbers from 1 - 9 are printed in order and each is shown to correspond to a particular symbol. The task involves matching each number in the rows of boxes with its corresponding symbol after a brief demonstration and practice. The measure taken is the number of consecutive symbols correctly completed within 90 seconds.

The task is primarily a test of psychomotor speed which is relatively unaffected by education or memory. Sustained attention, motor speed and visuo-motor coordination have all been reported as playing important roles in the performance of the task (Schear and Sato 1989). The test is particularly sensitive to brain injury with scores in such patients typically reduced even where the severity of the lesion is relatively mild. The task has been reported to be significantly impaired in patients following surgical repair of both ruptured and unruptured aneurysms (Hillis, Anderson et al. 2000).

Incidental Learning Task

This task uses the symbols from the WAIS(-R) Digit Symbol task. After completing the Digit Symbol task, the patient is presented with a sheet in which the numbers from 1 to 9 are printed above empty boxes and is asked to complete as many of the previously encountered symbols as possible. They are not given any indication that they will be required to recall the symbols from the earlier task and thus this serves as a measure of incidental learning.

Paced Auditory Serial Addition Task (PASAT)

This is a sensitive measure of information processing and sustained attention which requires the patient to attend to a tape presented series of 61 numbers ranging from 1 to 9 and to add each new number to the preceding number (Gronwall 1977). The difficulty of the task is varied by altering the speed of presentation of the numbers, with presentation speeds of 2.4, 2.0, 1.6 and 1.2 often being used. The task's primary measure is the number of correct responses, with incorrect responses and omissions separately recorded. This measure has been found to be sensitive to head injury (Leininger, Gramling et al. 1990), particularly to individuals with diffuse damage (Roman, Edwall et al. 1991). It has been suggested that this task may be used to determine whether a patient should be able to return to a normal level of social and occupational activity (Gronwall 1977).

The task is however particularly demanding and stressful for patients and may elicit floor performances amongst head injury patients at the faster presentation rates. For this reason the current study retained a slower 4-second presentation rate used by the earlier head injury study and by some other studies of head injury (McMillan and Glucksman 1987). This was supplemented by the 2-second presentation rate in those patients who were capable of the slower 4-second presentation. Normative data stratified by age was only available for the 2-second presentation rate (Stuss, Stethem et al. 1988).

National Adult Reading Test (NART)

This is a widely used measure of pre-morbid intelligence which assesses the pronunciation of 50 irregularly spelt words and is based upon the observation that reading ability is relatively well preserved in dementing individuals (Nelson and McKenna 1975; Nelson 1982). A revised manual was produced to update the measure in relation to the WAIS-R (Nelson and Willison 1991). Although originally devised for use with dementia patients, the measure has rightly or wrongly become the most frequently employed standard of pre-morbid estimation across a range of conditions (O'Carroll 1995). Its use as a valid premorbid measure following closed head injury has been supported by previous studies (Crawford, Parker et al. 1988; Moss and Dowd 1991; Watt and O'Carroll 1999).

Cambridge Contextual Reading Test (CCRT)

The Cambridge Contextual Reading Task (CCRT) was devised by Beardsall and Huppert (1994). They reasoned that the failure to correctly pronounce NART words may sometimes be an artefact of the unnatural presentation of the words in list form rather than due to unfamiliarity with the word (Beardsall and Huppert 1994). The CCRT places the NART words into sentences such that they are presented in a meaningful context rather than in isolation. It is suggested that the provision of contextual cues should facilitate correct word recognition if a lexical entry is present for the word and thus enable greater accuracy of premorbid estimation (Beardsall 1998).

Some supportive evidence for the use of the CCRT in estimating the premorbid ability of head injured patients comes from a study involving 25 head injury patients and 20 orthopaedic controls. This study found that the CCRT was more resistant to the effects of brain injury and that head injury patients benefited more from the context provided by the CCRT than did controls (Watt and O'Carroll 1999).

McKenna Graded Naming Test

This confrontation naming task presents a series of 30 line drawings of increasing difficulty to the patient who is requested to name the drawings (McKenna and Warrington 1983). As such it has similarities to the longer Boston Naming Test, but lacks the American cultural biases and as such is more suited to a UK population. It is used as an index of difficulties in word retrieval.

Wechsler Memory Scales (WMS, WMS-R)

The original WMS versions of tasks were used in the head injury study to enable comparisons with the previously obtained six month data available for this group. The revised versions were used in the SAH study. Normative data for these tasks is provided by their corresponding manuals (Wechsler 1973; Wechsler 1987).

WMS(-R) Logical Memory

This task comprises two story recall tasks (A & B). The stories are read separately to the patient who has been asked to listen carefully to each story in order to be able to recall as much as the story as possible immediately afterwards. For the head injury study, the same WMS stories were used as used in the earlier studies, though a 30 minute delayed recall of these stories was added. For the SAH study, the WMS-R stories were amended slightly to increase their validity for a Scottish population (e.g. Anna Thompson from East Kilbride rather than from South Boston) and both immediate and delayed recall tasks were administered and scored according to the manual.

The logical memory task has high face validity amongst patients who report that it corresponds with the 'real-world' memory difficulties that they face such as recalling messages from telephone or other conversations. The task has been reported to differentiate even between mild head injury patients with ostensibly 'good' recovery and control individuals (Stuss, Ely et al. 1985) and between head injury patients and controls at two years subsequent to the injury (Dikmen, Machamer et al. 1990). A study of 37 SAH patients found that these patients scored significantly lower than controls on logical memory immediate recall (Tidswell, Dias et al. 1995)

WMS(-R) Verbal Paired Associates

The WMS version of this task consists of ten pairs of words, six 'easy' (e.g. fruit - apple) and four 'hard' (e.g. crush - dark), which are read slowly to the patient. The patient is then asked to recall the partner for each word when prompted with the first word of each pair. The task is repeated three times and the number of easy and hard word pairs correctly recalled recorded for each trial. The WMS-R version dispenses with two of the easiest associations leaving four of each level of difficulty. In both cases a delayed recall of these verbal paired associates was assessed approximately 30 minutes later. This verbal memory task has been found to discriminate between lateralised lesions, with significantly lower scores in patients with left hemisphere lesions (Vakil, Hoofien et al. 1992). A Swedish verbal associates task was found to be impaired in 17 of 38 late surgery aneurysmal SAH patients (Sonesson, Saveland et al. 1989).

Brixton Spatial Anticipation Test

The Brixton spatial anticipation test (Burgess and Shallice 1997) was designed to detect dysexecutive impairments in a similar manner to the Wisconsin Card Sorting Test (WCST). It consists of a series of pages in a booklet which each have the same basic design involving ten circles in two rows of five, one of which is coloured blue. The patient's task is to detect patterns in the sequence of blue circles such that they will be able to accurately predict in which position the blue circle will be on subsequent pages. They are informed that the pattern will change from time to time and that they will then have to pick up on the new pattern. The measure taken is the number of incorrect guesses for the position of the blue circle across 56 pages of the booklet.

The Brixton test is relatively new and consequently has not as yet been used in many published studies of brain injury. However, the WCST is well established as being sensitive to certain frontal lobe lesions (Stuss, Eskes et al. 1992) and the Brixton test endeavours to assess much the same processes of rule attainment and perseverative errors in a manner which is less frustrating or time consuming for patients. The task has been reported to differentiate between patients with frontal lobe lesions and either controls or patients with posterior lesions (Burgess and Shallice 1996).

Verbal Fluency Task

Verbal fluency measures were included as measures of word generation difficulties and possible dysphasic symptoms. Impaired verbal fluency is associated with frontal lobe lesions, particularly lesions affecting the region around Broca's area in the left frontal lobe (Janowsky, Shimamura et al. 1989). However, Positron Emission Tomography (PET) scans indicate that verbal fluency tasks activate temporal and frontal lobes bilaterally such that reduced performance may be expected in response to injury in any of these areas (Parks, Loewenstein et al. 1988). The extent of verbal fluency impairment has also been correlated with measures of severity of brain injury such as PTA duration, Glasgow Coma Scale and early lesions on CT scans (Vilkki, Holst et al. 1992). Patients have been found to be significantly impaired on the 'FAS' version of the task after surgery for both ruptured and unruptured aneurysms (Hillis, Anderson et al. 2000) and in another study 74.5% of ACoA patients were found to be impaired on this measure (Mavaddat, Sahakian et al. 1999).

Both head injury and SAH patients were first asked to recall as many animals as possible within one minute, thus giving a structured verbal fluency category for comparison. The initial letter fluency tests differed slightly, with head injury patients asked to recall words beginning with the high frequency letter 'S' & low frequency letter 'J', which were the letters chosen for the earlier study, whilst the more frequently utilised 'FAS' letters were used for the SAH patients. Normative data stratified by age is available for the 'FAS' task (Yeudall, Fromm et al. 1986; Read 1987). In each case the number of words recalled within 60 seconds was recorded, as were any repetitions or rule breaks.

Rey-Osterreith Complex Figure Test

This is a frequently used measure of visuospatial constructional ability and visual memory in which patients are initially requested to copy a complex figure. Once they have completed this to the best of their ability, the figure is removed and they are requested to draw the figure from memory without prior warning (Rey 1941; Osterrieth 1944). The copy and recall of the figure were scored according to the placement and accuracy of 18 separate details with a maximum score of 36 in accordance with Taylor's Scoring criteria for the Rey Complex Figure.

Brain injured patients are more likely to utilise a piece-meal approach to the copy of the figure which subsequently hinders them when endeavouring to recall the figure from memory. Left hemisphere lesioned patients have been shown to recall fewer details of the figure but to keep the overall structure preserved, whereas right hemisphere lesioned patients are more likely to have difficulty copying the figure and have considerable recall difficulties (Binder 1982). Recall of the Rey Figure was found to be severely impaired, defined as 3 standard deviations or more below the mean, in 29.7% of a group of 89 SAH patients and moderately impaired in a further 17.2% (Ogden, Mee et al. 1993). This level of impairment was notably higher than that reported for several other neuropsychological measures in the same study.

Trail-Making A&B

These related tasks are measures of visuomotor tracking and attention, with Trails B involving an element of response inhibition. Trails A simply requires the joining of a series of consecutively numbered circles from 1 to 25. Trails B is more demanding, requiring the patient to alternate between consecutive numbers and letters. The Trail-making tasks are very sensitive to brain injury, with slower performances associated with greater severity of damage (Leininger, Gramling et al. 1990) and impairments on these tasks have been found to be indicative of general marked cognitive disturbances amongst SAH patients (Ljunggren, Sonesson et al. 1985; Sonesson, Saveland et al. 1989; Seeger, Mueck et al. 1998). The trail-making tasks have also been found to be predictive of subsequent levels of independence in head injury patients (Acker and Davis 1989).

Stroop Test

Stroop tests are based on the observation that it takes more time to read a colour word when it is presented in an incongruent colour. The version of the Stroop task used involved three trials, one reading the names of three colours printed in black, one naming colours printed as 'XXXX' and the latter the colour-word 'interference' presentation (Golden 1978). Normative data from separate studies is assimilated by the manual's author to enable scores to be corrected for age and converted into t-scores (Stroop 1935; Jensen 1965; Jensen and Rohwer 1966; Golden 1978).

The Stroop measure has been reported to be sensitive to head injury (Stuss, Ely et al. 1985), with poor performance across all conditions attributed to attention or information processing deficits (Ponsford and Kinsella 1992). Particular impairments on the colour-word interference trials have often been associated with deficits affecting the frontal lobes (Perret 1974; Holst and Vilkki 1988). A recent study reports impaired Stroop interference scores following surgical repair of both ruptured and unruptured aneurysms (Hillis, Anderson et al. 2000).

'Low Score' Range and Impairments on Tasks

It is likely that following brain injury some individuals will suffer notable cognitive impairments in particular domains, such as memory tasks, whilst others are unaffected by memory deficits but may have other cognitive difficulties. Whilst statistical analyses such as ANOVA are likely to detect even relatively small differences if these occur uniformly across a group, they are less likely to detect even notable cognitive impairments within a group if these occur in some individuals and not others. However, particular cognitive deficits rarely occur uniformly across a group and a single notable cognitive impairment is likely to have a greater impact on a patient's quality of life than a range of mild impairments. Additionally, as no control group data is available for this study, it is useful to be able to compare scores with matched normative data where possible to identify probable impairments of cognitive functioning.

For these purposes, amongst those cognitive tasks with age stratified normative data (indicated by asterisks in Table 4-1), a record was kept of patients who scored one standard deviation or more below the normative mean. As only 16% of the normal population would be expected to score below this point, groups of patients amongst whom *substantially more* than 16% score below this point are likely to include individuals whose injury has resulted in impairment upon the task. For the purpose of reference, these scores more than one standard deviation (SD) below the normative mean are referred to as being in the 'low score' range rather than as 'impairments', as 16% of a normal population would be expected to score within this range.

Other studies have used a more conservative cut-off of more than two standard deviations below the mean, however this would identify only very substantial impairments amongst individuals whose premorbid functioning was at or above the normative mean and would thus be likely to miss many or most individuals whose cognitive impairment was sufficient to have had a notable influence upon quality of life. It was deemed more appropriate to use a cut-off of 1 SD and recognise that around 16% of these low scores do not represent true impairments (i.e. Type I errors) than to use a more conservative cut-off with fewer Type I errors but which failed to identify a larger number of true impairments.

Patients were also considered to be in the 'low score' range if they were unable to complete a task due to cognitive difficulties incurred as a consequence of the head injury. In practice, this related largely to the PASAT task, where several patients were unable to complete or attempt the 2 second version due to poor concentration. To ignore data from such patients would have resulted in considerable underestimation of the proportion of patients with information-processing difficulties.

Feedback to Patients

It was made clear to patients that they could ask questions at any time during or after the interview / neuropsychological assessment and the assessments always went at the pace of the patient. Thus although the majority of interviews took place over a duration of 2-3 hours, including breaks for tea etc, some took notably longer due to questions from the patient and / or relatives. Separate 'jargon-free' reports to patients of the key findings from the SAH and head injury studies have been prepared and sent to all of the participating patients.

Questionnaires & Emotional Outcome

The questionnaires to be completed by the patient and those to be completed by the relative were bound separately and had clear 'title' pages to reduce any potential for confusion. These questionnaires were shown and explained to patients at the end of the neuropsychological assessment. Reply paid envelopes were included with the questionnaires. The questionnaires included a number of emotional outcome measures as this aspect of outcome had been suggested to be of importance in the few outcome studies to have included measures of anxiety or depression.

Patient Questionnaire

Short-Form 36 Health survey (SF-36)

This is a very widely used and well-validated measure of health that has been recommended for the evaluation of patients following SAH [Deane, 1996 #264] and has been used in previous studies of head injury outcome (Wilson, Pettigrew et al. 2000). The SF-36 is a 36-item quality of life measure that is divided into eight separate domains as listed in Table 4.1. An SPSS syntax programme was created to facilitate the coding and scoring of the employed UK version of this health survey (Morris 2000). Normative data based on a UK population are available for the measure (Jenkinson, Layte et al. 1996).

Table 4-2: Short Form Health Survey

Health Domain	Measures
Physical Functioning (10)	Physical Ability
Social Functioning (4)	Social Activities
Role limitation due to physical problems (3)	Affects Daily Activities
Role limitation due to emotional problems (2)	Affects Daily Activities
Mental Health (5)	Anxiety / Depression
Energy (4)	Energetic / Fatigue
Pain (2)	Physical pain
General Health Perception (5)	Own Health beliefs

Number in parentheses indicates number of questions for corresponding domain

Hospital Anxiety and Depression Scale (HADS)

This is a brief 14-item scale divided equally into questions relating to anxiety or depression and yielding separate scores for these two domains. The measure avoids items which are likely to be reflective of physical illness rather than truly reflecting adverse emotional states (Zigmond and Snaith 1983; Snaith and Zigmond 1994). The HADS has previously been used in outcome studies of SAH (Hellawell, Taylor et al. 1999a), other forms of stroke (Dennis, O'Rourke et al. 2000) and traumatic head injury (Hellawell, Taylor et al. 1999b; King, Crawford et al. 1999).

State Trait Anxiety Inventory (STAI)

The State Trait Anxiety Inventory measures state and trait anxiety separately, with trait anxiety referring to relatively stable differences in anxiety-proneness, whereas state anxiety refers to levels of anxiety present at a given time. Both the state and trait anxiety scales comprise 20 questions. The earlier 'Form X' version was used in the head injury study as this had been used in the assessment of these patients at six months post injury and it was intended to compare scores to determine whether change occurred over time (Spielberger, Gorsuch et al. 1970). The later improved 'Form Y' version, which was designed to be a purer measure of anxiety by replacing items which were more closely related to depression than to anxiety, was used in the SAH study (Spielberger 1983). The STAI scales were used in one of the first SAH studies to include a measure of anxiety and were found to be significantly elevated in these patients (Stegen and Freckmann 1991).

Beck Depression Inventory (BDI)

This is a frequently employed 21-item measure designed to assess severity of depressive illness in adolescents and adults (Beck and Steer 1987). Each item is rated on a scale ranging from 0 to 3 with a maximum score of 63. Thresholds for separate depression groupings are available based on clinical ratings. The BDI has been used to document depressive illness amongst patients by a number of studies of outcome following SAH (Ogden, Mee et al. 1993; Hutter, Gilsbach et al. 1995; Berry, Jones et al. 1997; Mavaddat, Sahakian et al. 1999) and head injury (Wilson, Pettigrew et al. 2000).

General Health Questionnaire 30 (GHQ-30)

This 30-item version of the General Health Questionnaire is the most frequently used version in health outcome studies. It was derived from the 60 item version by excluding items which corresponded to physical health and then selecting those items which loaded most heavily on the 'severity of illness' factor (Goldberg and Williams 1991). Each question has four possible responses, indicating whether a particular aspect of functioning has improved, not changed, worsened or considerably worsened.

There are at least two recognised scoring procedures for the measure, both of which were employed by this study. The first is the 'GHQ' method in which responses are dichotomised, thus using a scoring system of 0-0-1-1. This method is required in order to compare scores with published thresholds for psychological morbidity. A threshold of 3 / 4 is often suggested using this method, though a study focusing upon outcome following stroke has suggested that a threshold of 8 / 9 is more appropriate with this population (O'Rourke, MacHale et al. 1998) and thus both thresholds have been considered in relation to the SAH study. The other method of scoring is the likert method, with a scoring system of 0-1-2-3, which is more sensitive to the extent to which symptoms differ and is reported to correspond with a more normally distributed range of scores.

Relative's Questionnaire

An adapted version of Brooks and McKinlay's Relative's Questionnaire was used to obtain proxy information regarding consequences of the injury or haemorrhage that affect everyday life in patients (Brooks and McKinlay 1983; Brooks, Campsie et al. 1986). Relatives are also asked to rate the level of strain that they themselves have been under as a consequence of the head injury or haemorrhage. The questionnaire was originally developed as the basis of a semi-structure interview with relatives of head injury patients, though it has previously been used as a postal questionnaire and with relatives of SAH patients (Hellawell, Taylor et al. 1999a).

Analyses

The principle independent variable of interest in both studies was the apolipoprotein E gene and the influence of the ε4 allele upon recovery from brain injury. The other variables were frequently employed clinical indices of injury severity. These indices differ between head injury and subarachnoid haemorrhage and have been described in earlier chapters.

Differences between dichotomised clinical variables upon performance on the neuropsychological tasks were analysed using univariate analysis of variance, with age at assessment and an index of pre-morbid ability included as co-variates. Although results are reported for all tasks, in relation to some variables there is particular interest in specific cognitive functions. For example, the primary cognitive interest in relation to anterior communicating aneurysms is a possible influence upon memory tasks as this has often been previously reported. Similarly, with severity indices indicative of diffuse injury there is reason for particular interest in measures of information processing, though differences in the other tasks are also reported.

The number of patients involved in analyses varies slightly according to the variable of interest. Thus for example only those who underwent an operation are involved in the pre-operative WFNS variable and only those patients with angiographically confirmed aneurysm are involved in the consideration of ACoA aneurysmal site. Some patients are excluded from particular analyses due to missing data.

The number of analyses necessitates a conservative consideration of probability values due to the greater likelihood of chance results. However, to report only findings which exceed a particular 'probability' threshold would be likely to overlook genuine effects present in the patterns of results. Thus results are presented for all tasks and consideration is given not only to the statistical probability of individual task differences, but also to how these relate to findings upon related tasks and prior expectations. For example, the presence of a difference significant at $p = .01$ upon each of three separate memory tasks is more likely to represent a genuine effect than the presence of a difference significant at $p = .001$ upon only one of these tasks. It is also more likely to represent a genuine effect where there was particular prior reason to expect such a finding, such as in relation to ACoA aneurysms, than where no such expectation were present.

Some ordinal variables, particularly head injury severity indices such as GCS score or PTA duration, are analysed using spearman correlations. One-tailed analyses are used where differences would only be expected to occur in one direction. Non-parametric statistics are also used in analyses involving 'emotional outcome' questionnaire data, cognitive 'low scores' and Glasgow Outcome Scale.

Chapter 5 Subarachnoid Haemorrhage Results

Patient Selection and Participation

The patients were drawn from a group of 100 patients who had participated in a brief telephone based outcome study of their functional status at six months. This earlier study had screened 125 consecutive patients with a suspected diagnosis of subarachnoid haemorrhage admitted to the Institute of Neurological Sciences in Glasgow between January and August 1998 (Dunn, Stewart et al. 2001). Of the 25 screened patients who did not take part in the earlier telephone study, 7 died before consent for the study could be obtained, 8 had negative CT and negative lumbar puncture and thus probably had not suffered SAH, 1 had a previously clipped aneurysm and 9 declined consent.

In four of the 100 available cases, the diagnosis of SAH was not confirmed and thus these patients were deleted from the study leaving a study population of 96 patients. Of these 96 patients, a further twelve died as a direct consequence of their haemorrhage. Seventy of the remaining 84 patients were followed up with the semi-structured interview and neuropsychological tests. Fourteen patients did not participate in the follow-up for reasons given in Table 5-1, though questionnaire information was returned by one of these non-participants.

Table 5-1 Reasons for Non-Participation

Reason for Non-Participation	Number
No Reply	4
New Address Unknown to study	3
Non-attendance at Appointments	3
Declined to Participate	3
Distance (resident on Isle of Lewis)	1
Total Non-participants	14

As can be seen from Tables 5-2 and 5-4 below, the non-participants did not differ substantially from participants on any of the clinical variables, including admission WFNS Grade, Fisher Grade, angiographically proven aneurysmal origin, occurrence of clinical deterioration, surgical intervention, APOE genotype, age at admission, or gender. Chi-square testing confirms that there is no significant difference between participants and non-participants on any of these variables.

Of those who participated in the neuropsychological assessment (N = 70, 43 females) the mean age was 45.2 years (SD 15.2) with a range from 25 to 74 years. Mean years of education were 12.21 (SD 2.1) ranging from 9 to 19 years. The social class percentage distribution based upon current or past occupation was: Class I (professional) 2.9%, Class II (managerial / technical) 18.6%, Class III (skilled) 34.3%, Class IV (semi-skilled) 32.9%, and Class V (unskilled) 11.4%. The mean time between initial admission to the neurosurgical unit and neuropsychological assessment was 16.3 months (SD 2.1) with a range from 14 to 23 months. The majority (79.5%) of patients were married or in a stable cohabiting relationship.

Table 5-2 Clinical Variables

	Died	Participants	Non-Participants
Fisher Grade 0	1 (8.3)	1 (1.4)	0
Fisher Grade I	0	6 (8.6)	2 (14.3)
Fisher Grade II	1 (8.3)	6 (8.6)	0
Fisher Grade III	1 (8.3)	37 (52.9)	6 (42.9)
Fisher Grade IV	9 (75.0)	20 (28.5)	6 (42.9)
WFNS Grade I	4 (33.3)	48 (68.6)	10 (71.4)
WFNS Grade II	3 (25.0)	11 (15.7)	2 (14.3)
WFNS Grade III	1 (8.3)	2 (2.9)	0
WFNS Grade IV	3 (25.0)	3 (4.3)	0
WFNS Grade V	1 (8.3)	6 (8.6)	2 (14.3)
No Deterioration	1 (8.3)	50 (71.4)	10 (71.4)
Deteriorated Once	4 (33.3)	7 (10.0)	2 (14.3)
More than Once	7 (58.3)	13 (18.6)	2 (14.3)
Haematoma Present †	5 (45.5)	10 (14.3)	2 (14.3)
No Haematoma	6 (54.5)	58 (82.9)	12 (85.7)
Surgical Intervention	4 (33.3)	54 (77.1)	12 (85.7)
No Surgery	8 (66.7)	16 (22.9)	2 (14.3)

(Percentage for variable by column given in parentheses)

† : Presence or absence of haematoma unknown for one of the deceased patients and for 2 participants

Table 5-3: Dichotomised Clinical Variables

Variable	Group 1	Group 2	Variable	Group 1	Group 2
Fisher Grade	I - III	IV	***WFNS Grade***	I	II - IV
Haematoma	Absent	Present	***APOE ε4 allele***	Absent	Present

APOE: Apolipoprotein E

Table 5-4: APOE Genotype & Gender

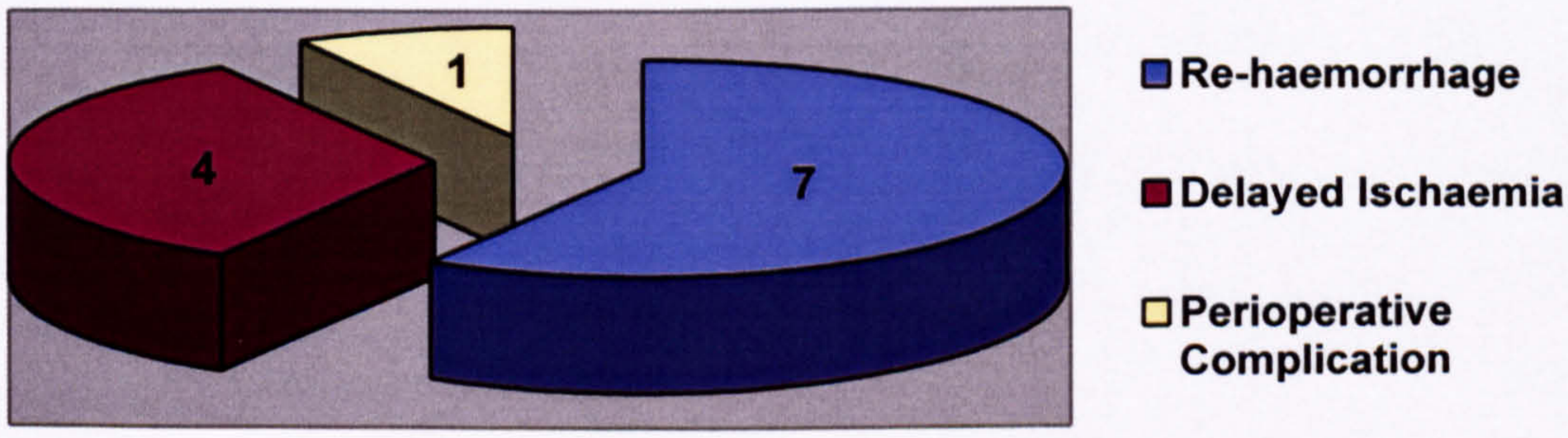
	Died	Participants	Non-Participants
Male	5 (41.7)	27 (38.6)	6 (42.9)
Female	7 (58.3)	43 (61.4)	8 (57.1)
APOE ε2 / ε3	1 (8.3)	4 (5.7)	1 (7.1)
APOE ε3 / ε3	9 (75.0)	50 (71.4)	11 (78.6)
APOE ε3 / ε4	2 (16.7)	16 (22.9)	2 (14.3)

(Percentage for variable by column given in parentheses)

Case-Fatalities and Clinical Variables

The 12 patients included in the study population who died are likely to under-estimate mortality following SAH for the overall population. The deaths of the 7 patients screened for the original study for whom no consent could be obtained are not included here and it is likely that at least 15% of those who suffered SAH died before reaching neurosurgery. The cause of deaths for the 12 patients entered into the study are shown in Figure 5-1 below, where it can be seen that re-haemorrhage accounts for the majority (58.3%) of fatalities.

Figure 5-1 Cause of Death



Case Fatality & Clinical Complications

Clinical complications had been classified as either none, probable or definite. For the purposes of analysis, the probable and definite complication groupings were merged such that patients are categorised as either having or not having suffered re-haemorrhage, infarction or hydrocephalus.

The relationship between clinical variables and case-fatality was analysed using chi-square testing based on the 96 patients for whom survival data was available. The more conservative Fisher's Exact Test was employed where expected frequencies for any cell was below five. The most significant predictor of mortality was the occurrence of re-haemorrhage, which occurred in 7 (58%) of those who died relative to only 4 (4.8%) of survivors ($\chi^2 = 29.70$, $p < .001$). Thus the occurrence of a re-haemorrhage was associated with subsequent fatality in 64% of cases and is likely to have been a principal cause of death amongst those who died in the early stages and were not entered into the study. This contrasts with the lower fatality rates associated with the other documented complications, with 4 (29%) deaths amongst the 14 patients who suffered probable or proven infarction and 3 (21%) deaths amongst the 14 patients with identified hydrocephalus. Neither infarction nor hydrocephalus was significantly more likely to have occurred in those who died.

A Fisher Grade of 4, indicating the presence of intraventricular or intraparenchymal blood was also significantly associated with fatality, being present in 9 (75%) of those who died relative to 26 (31%) of survivors (χ^2 =10.60, p = .002). An admission WFNS grade greater than I was also significantly associated with mortality (χ^2 = 6.86, p =.013) being present in 8 (67%) of fatalities relative to 26 (31%) of survivors. A fatal outcome was also significantly more likely amongst those with a haematoma, with 29.4% of those with identified haematoma dying relative to 7.7% of those without haematoma (χ^2 =6.43, p = .024). There was no significant association between fatality and APOE genotype in this study group.

None of the patients who died had a negative angiogram, though seven had no cerebral angiography undertaken due to their poor clinical condition. Of these seven patients, six subsequently died from a re-haemorrhage such that it is highly likely that their subarachnoid haemorrhage was also aneurysmal in origin. The patients who died were also significantly older than those who survived the haemorrhage as shown in Table 5-5, with the mean age of the case-fatalities over 11 years greater than that of the survivors (t = 2.68, p (one tailed) = .0045).

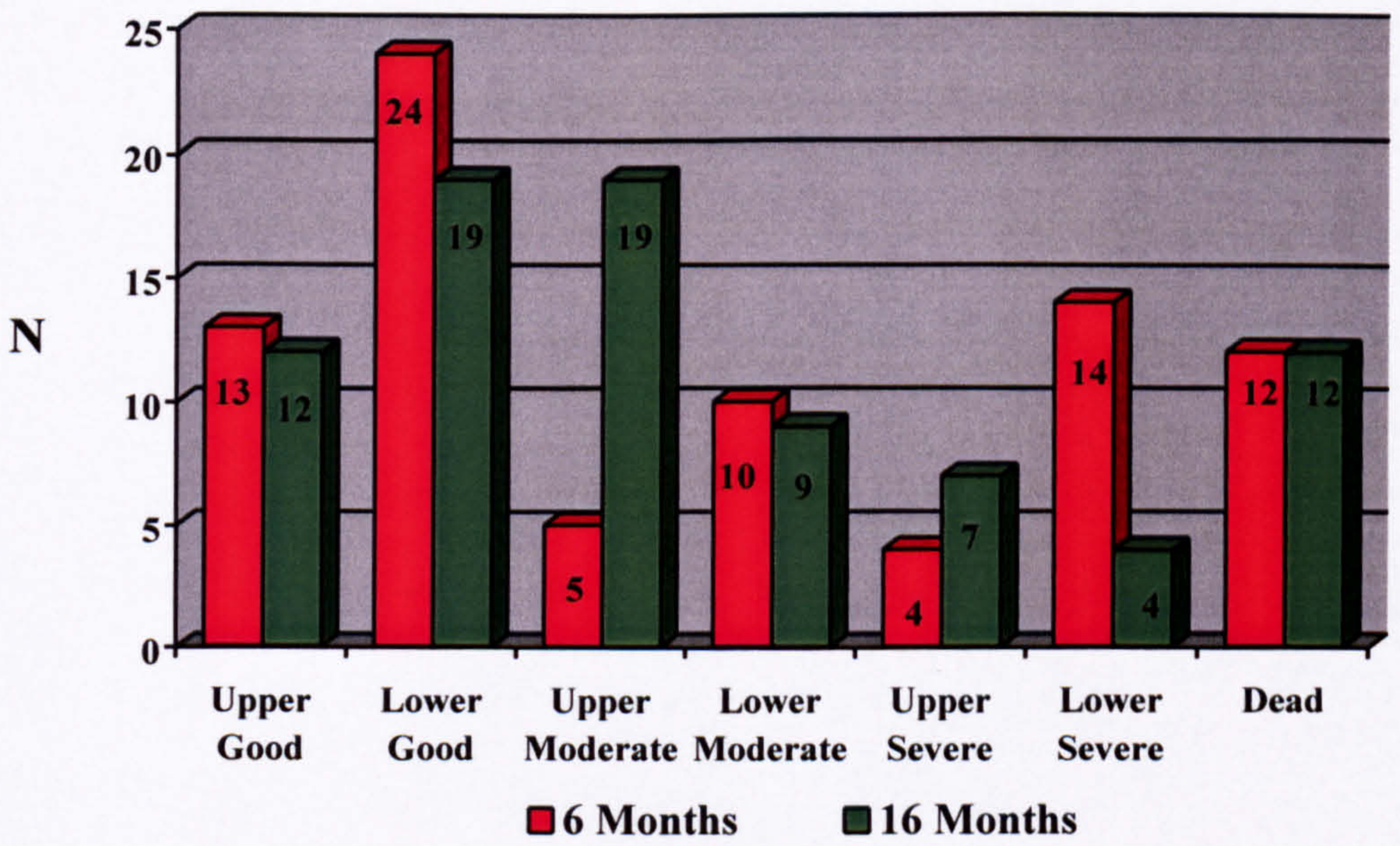
Table 5-5 Age on Admission to Institute

	Died	Survivors	Participants	Non-Participants
Mean Age in Years	56.8	45.4	45.2	46.6
(SD)	(10.1)	(14.2)	(15.2)	(8.3)

Extended Glasgow Outcome Scale

Glasgow Outcome Scale scores are shown in Figure 5-2 below for the 82 patients for whom GOS data is available at both 6 months and 16 months. As shown in the graph, there were no further deaths during this period. The number of patients with severe disability had reduced by 39% from eighteen to eleven by the 16-month follow-up, with a particularly notable drop in the number of patients with lower severe disability. Of the 14 patients with lower severe disability at six months, 5 (36%) improved considerably to at least lower moderate disability with a further 5 improving slightly to upper severe disability. There was however an increase in the number of patients with upper moderate disability, indicating notable residual difficulties in this cohort of patients despite a general trend towards continued functional improvement.

Figure 5-2: Glasgow Outcome Scale at 6 and 16 Months



The upper moderate disability (UMD) group appeared to have more in common with the lower good recovery group (LGR) in terms of functional difficulties than with the lower moderate disability (LMD) Group. Ten patients who had been classified LGR by the telephone study at six months were deemed to be UMD during the later semi-structured interview indicating the greater permeability at this boundary.

Clinical Variables and Glasgow Outcome Scale

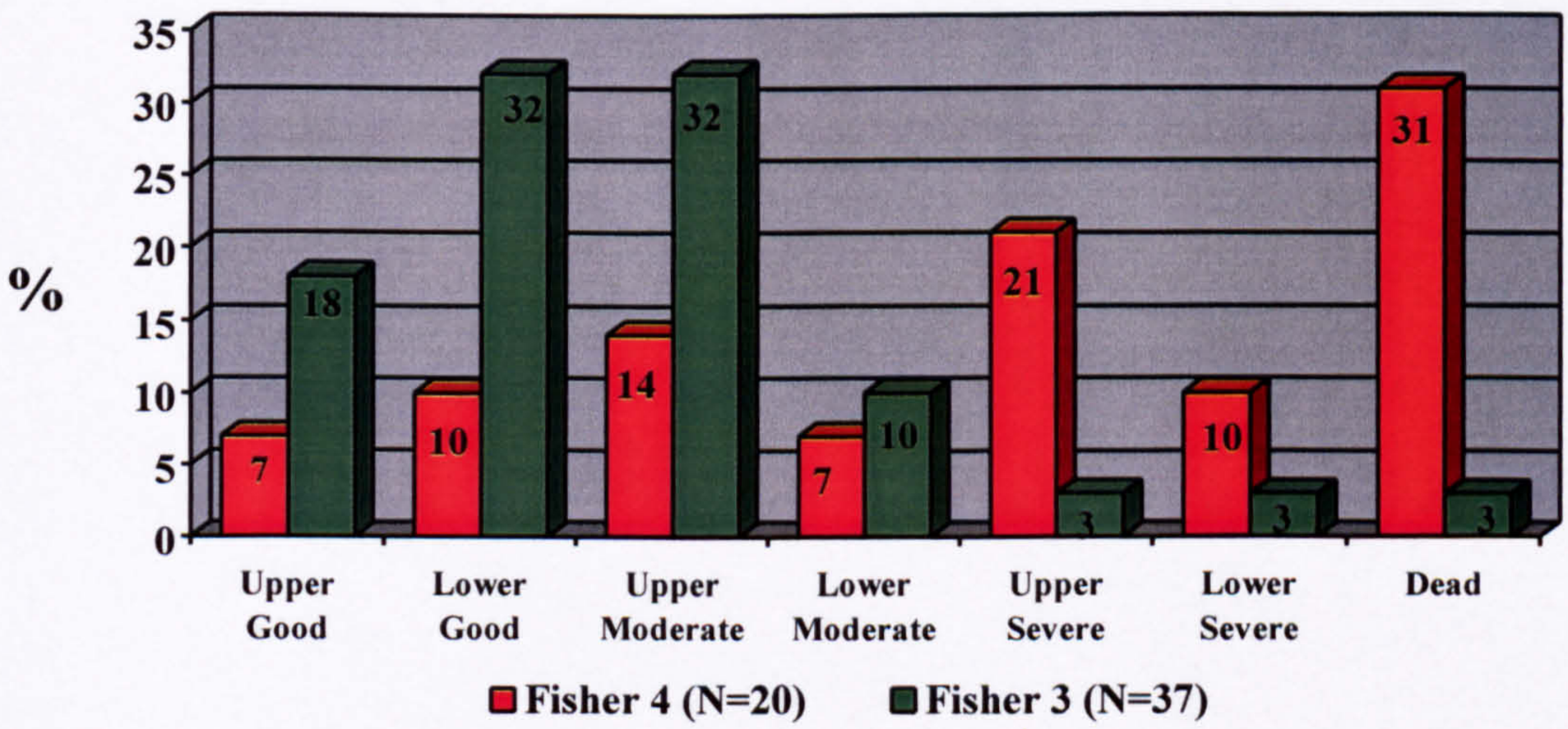
In subsequent analyses in which the GOS groups have been dichotomised, moderate disability and good recovery patients have been combined to form a relatively 'favourable' outcome group and the severe disability and death groups are merged to form an 'unfavourable outcome' group. However, as the focus of this study was upon survivors and as factors that influence survival may differ from those that influence functional status amongst survivors, separate analyses were also conducted between GOS survival groups (i.e. excluding dead patients) and clinical grades.

In chi-square 2x2 testing, re-haemorrhage was significantly more likely to have occurred in those with unfavourable outcome. Nine (82%) of the 11 documented cases of re-haemorrhage had an unfavourable outcome, with 7 of these patients dying as a direct result of the re-haemorrhage. In contrast only 20% of those without re-haemorrhage had an unfavourable outcome at 16 months (χ^2 =18.20, $p < .001$). The occurrence of infarct was also significantly associated with poor outcome, with 6 (55%) of 11 patients with infarct having an unfavourable outcome relative to 16 (23%) of the 70 patients without identified infarct (χ^2 =4.03, $p = .038$).

Fisher Grade and Glasgow Outcome Scale

A Fisher Grade of 4 was significantly more likely in patients who subsequently had an unfavourable outcome, with 18 (62%) of 29 Fisher Grade 4 patients having an unfavourable outcome relative to only 4 (8%) of 51 Fisher Grade 1-3 patients (χ^2 = 27.27, $p < .001$). Part of this relationship with unfavourable outcome is due to high mortality rates, with nine of the twelve deaths being patients with Grade 4. However, the relationship remains highly significant even if fatalities are excluded, with 9 of the 20 surviving Fisher 4 patients having a severe disability relative to only 2 of the 49 Fisher 1-3 patients (χ^2 = 17.75, $p < .001$). There were only six patients each in Fisher Grades 1 and 2, none of whom had a severe disability. The comparison between the two main Fisher grades (4 and 3) is shown in Figure 5-3 below. Fisher Grade and Glasgow Outcome Scale were significantly correlated, both when including patients who died (rs = .387. $p < .001$) and when only considering survivors (rs = .327, p = .003).

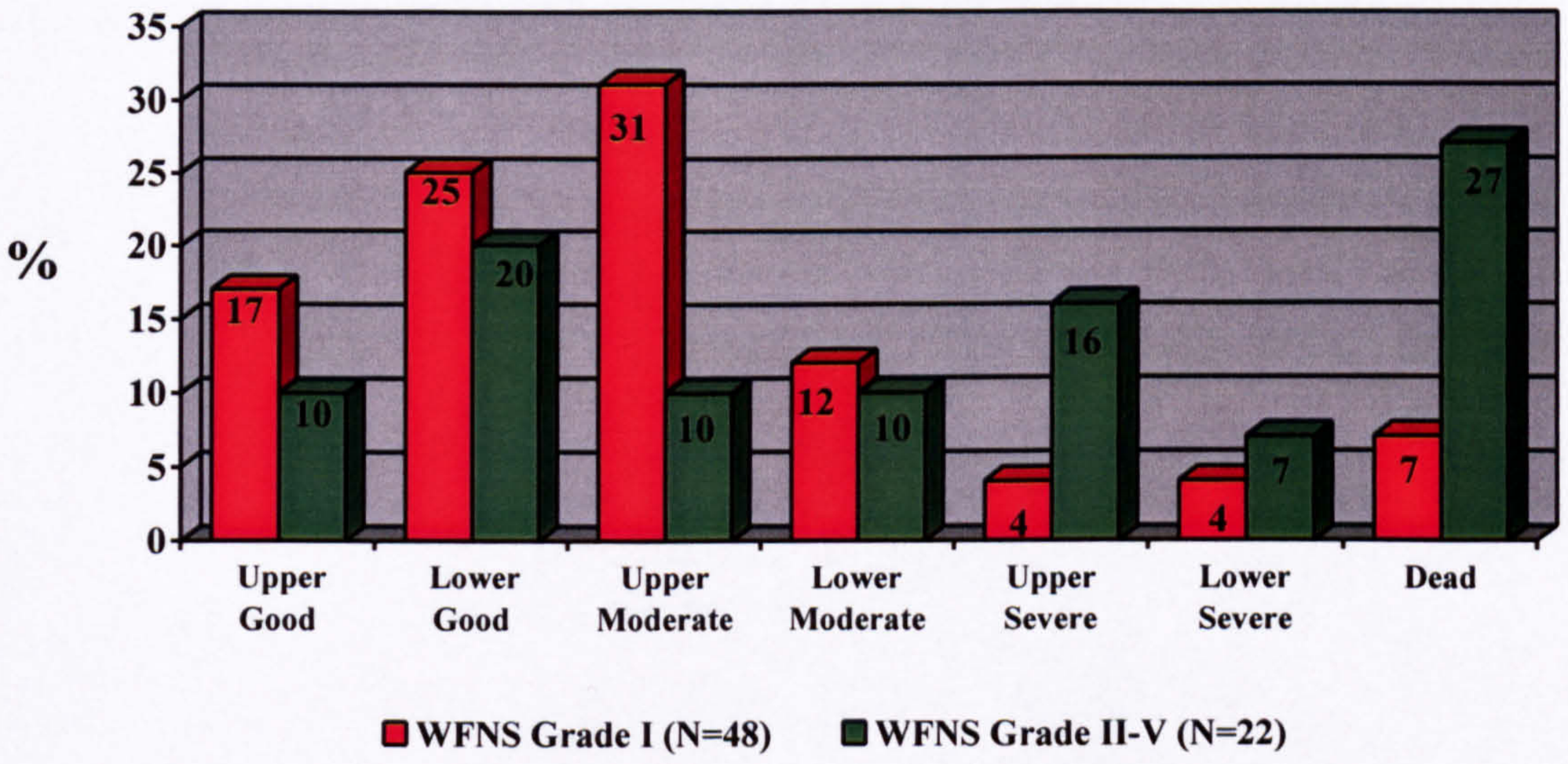
Figure 5-3: Fisher Grade and Glasgow Outcome Scale



WFNS Grade and Glasgow Outcome Scale

WFNS Grade I patients were significantly more likely to have a favourable outcome than those with higher grades. A shown in Figure 5-4, WFNS Grade I patients had a favourable outcome in 44 (85%) of 52 cases, relative to only half of the 30 Grade II-V patients ($\chi^2 = 11.30$, $p < .001$). WFNS Grade and GOS were also significantly correlated both when including patients who died (rs = .349. p = .001) and when only considering survivors (rs = .271, p = .012).

Figure 5-4: WFNS Grade and Glasgow Outcome Scale

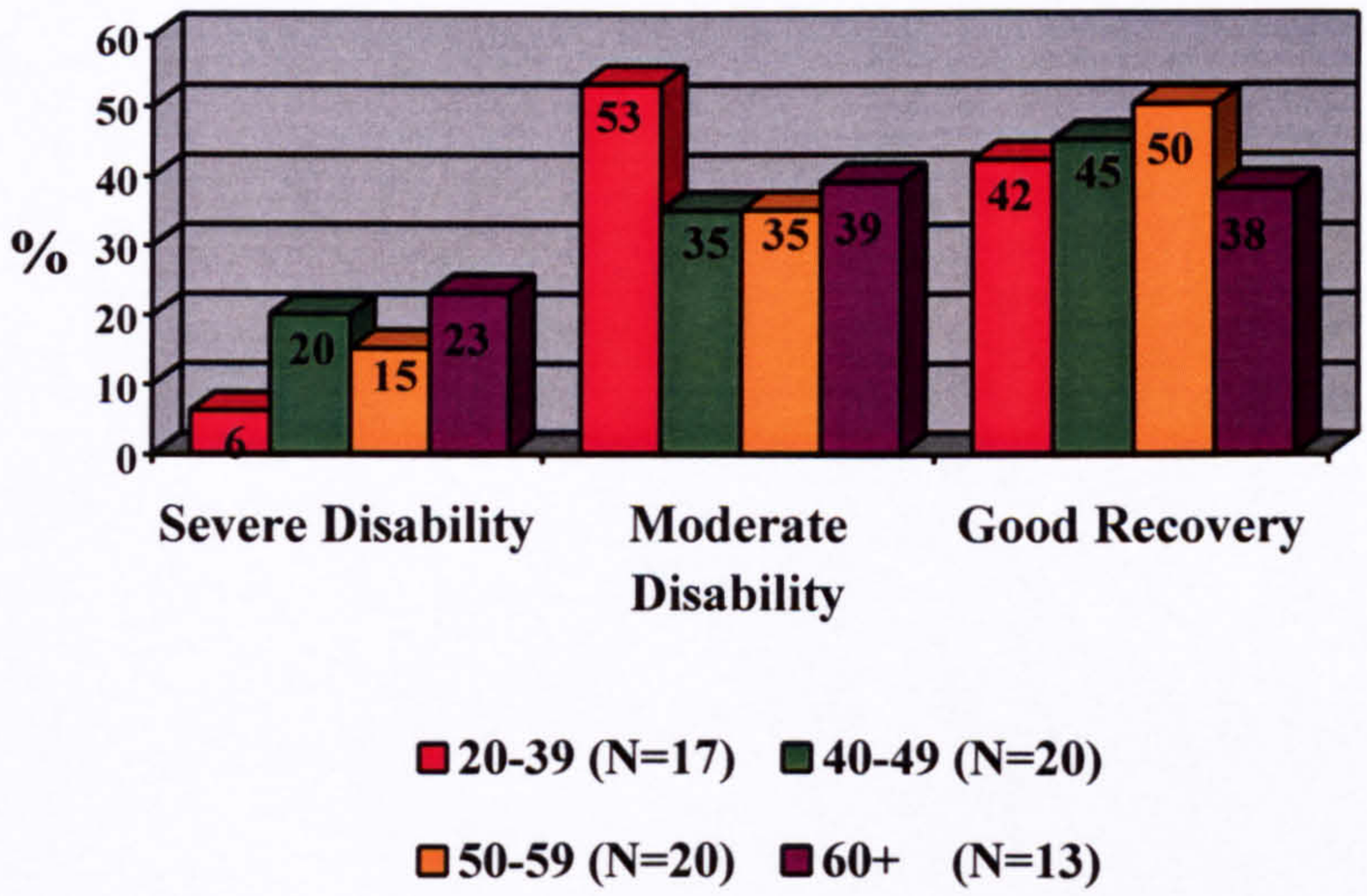


Age and Glasgow Outcome Scale

Those with unfavourable outcome were significantly older at the time of the bleed, with a mean age of 54.8 years (SD 10.8), whereas those with a favourable outcome had a mean age eight years younger at 46.8 (SD 11.9) ($t = 2.90$, $p = .006$). However this difference was considerably affected by the significantly higher age of those who died. When only survivors were considered there were relatively few effects of age at injury upon outcome, as shown in Figure 5-5 where the only apparent effect is for the youngest age group to be less likely to have a severe disability. Although the mean age at injury of severe disability patients (52.5 years, SD 11.6) was greater than that of moderate disability or good recovery patients (46.8 years, SD 11.9), this difference did not reach statistical significance ($t = 1.49$, $p = .159$).

In order to determine whether this relative absence of an effect of age upon survivors was simply an artefact of lesser haemorrhage severities amongst surviving elderly patients, partial correlations were conducted between age at injury and GOS, controlling for Fisher and WFNS Grades. These confirmed that age was only significantly correlated with GOS when those who died were included ($r = .275$ (df 78), $p = .007$) but not if only survivors were considered ($r = .122$ (df 66), $p = .161$).

Figure 5-5: Age at Ictus and GOS amongst survivors



Glasgow Outcome Scale and Cognitive 'Low scores'

The extended GOS groups were significantly correlated with the number of cognitive tasks in which patients scored 1 SD or more below the normative mean (low score range). As shown in Table 5-6, nine (82%) of eleven patients with severe disability scored in the 'low score' range on at least five of the twelve cognitive tasks, relative to only three (10%) of thirty-one good recovery patients. This contrasts with the good recovery patients, the vast majority of whom scored below 1 s.d. on 3 or less tasks, which might be considered to be within normal limits. However, the majority (68%) of lower good recovery patients scored in the low score range on at least 3 tasks, such that only the upper good recovery patients were relatively free of cognitive impairments. The GOS was strongly correlated with the number of tasks in which patients scored more than 1 SD below the normative mean, with the extended scores (i.e. upper and lower) more predictive of such low scores than the collapsed scores (Table 5-7).

Table 5-6 Number of 'Low Score' Tasks by GOS Classification

	Lower SD	Upper SD	Lower MD	Upper MD	Lower GR	Upper GR	Total
0 - 2	1 (25)	0	0	9 (47)	6 (32)	10 (84)	26 (37)
3 - 4	1 (25)	0	5 (56)	6 (32)	11 (58)	1 (8)	24 (34)
5+	2 (50)	7 (100)	4 (44)	4 (21)	2 (10)	1 (8)	20 (29)
Mean Tasks In Low Score Range [SD]	5.3 [3.5]	9.4 [2.1]	5.3 [2.8]	3.4 [2.9]	2.7 [1.8]	1.3 [2.2]	3.8 [3.3]

(Percentage of corresponding GOS classification in parentheses)

Table 5-7. Correlations Between GOS and Cognitive 'Low Scores'

		16 Month GOS Extended	16 Month GOS Collapsed	6 Month Extended GOS
No of Tasks in Low Score Range	r	.598	.539	.552
	p (2-tailed)	< .001	< .001	< .001

N = 70; Spearman correlations

Reported Symptoms

Symptoms reported by patients in the semi-structured interview are presented in Table 5-8 in decreasing order of prevalence.

Table 5-8 Reported Symptoms

	Worse		Worse
Finding Words	50 (72.5%)	Dizzy Spells	22 (31.4%)
Memory	49 (70.0%)	Hearing	20 (28.6%)
Fatigue	47 (67.1%)	Physical (eg arm, leg)	19 (27.1%)
Concentration	41 (58.6%)	Sense of Taste	16 (22.9%)
Irritability	36 (51.4%)	Blank Spells	14 (20.3%)
Dissociating Voices	22 (48.9%)	Sense of Smell	11 (15.7%)
Depression	34 (48.6%)	Violence	6 (8.6%)
Anxiety	33 (47.1%)	Epilepsy	4 (5.7%)
Vision	27 (38.6%)		

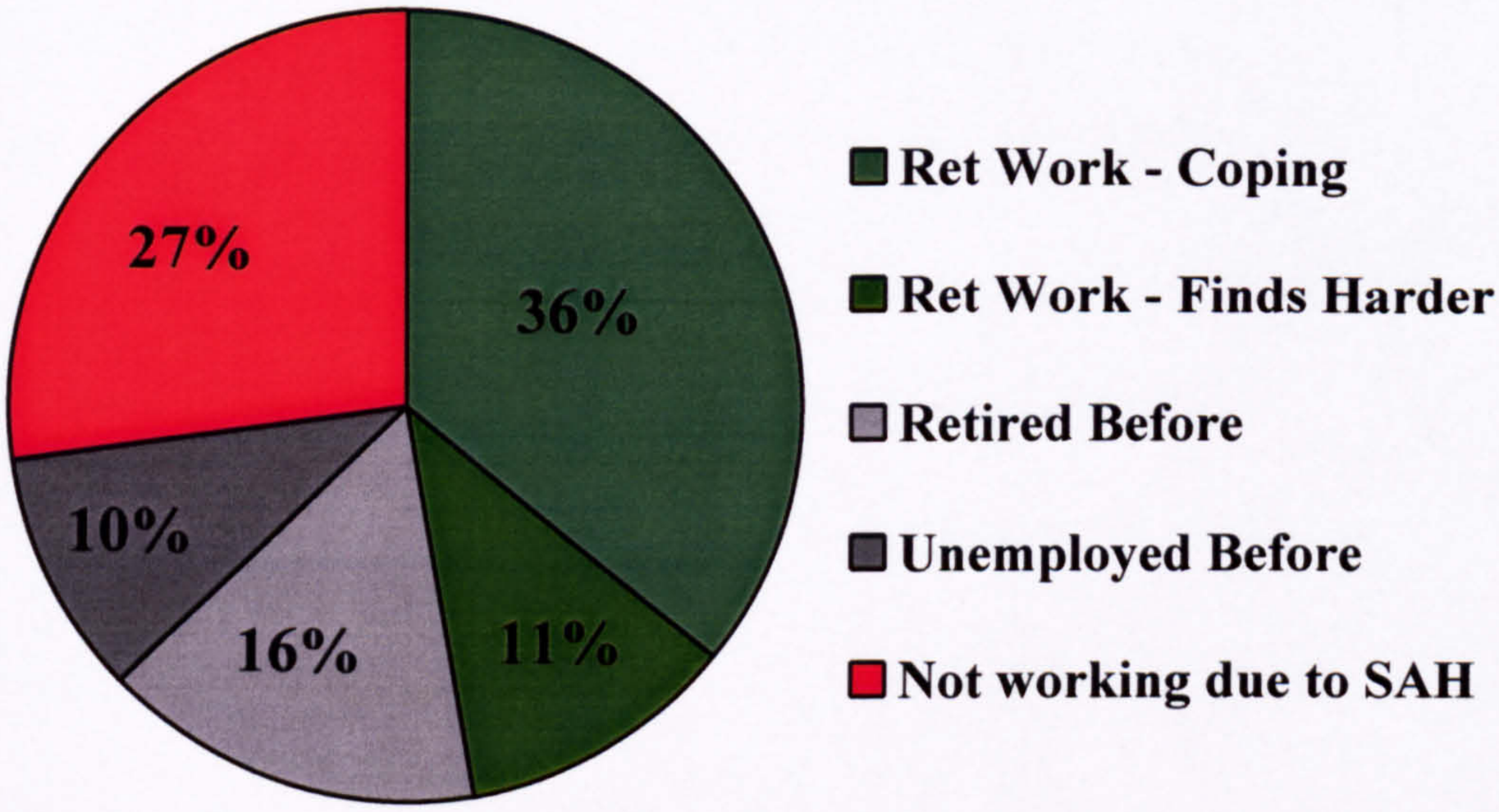
(Percentages given as proportion of patients who answered corresponding question)

Return to Work

Return to work data for the 70 patients who participated in interviews at 16 months after their haemorrhage is summarised in Figure 5-6. By the time of the interview, 33 of the 70 patients (47.1%) had returned to work, of whom all but two had returned to the same job and the majority (25) deemed themselves to be coping as well now as before the haemorrhage. Many of these patients reported feeling better once they had returned to work even though several of them found it harder than usual to start with and were often more fatigued than before following a day at work.

A further 18 (25.7%) had not been working before the haemorrhage due to previous retirement in 11 cases and unemployment in a further 7 cases. This left 19 patients (27.1%) who had not returned to work since the haemorrhage, most of whom did not anticipate a return to work in the near future. In some of these cases the patients had decided to retire earlier as a consequence of their haemorrhage, though the mean age of this group was actually lower than that of those who had returned to work (44 versus 46 years) demonstrating that many were not of a normal retiring age and might have been expected to work for several more years.

Figure 5-6: Employment Status 16 months Post Ictus



Neuropsychological Outcome Related to Clinical Variables

NART as Measure of Pre-morbid Intelligence

The NART was included in the assessment battery as it is normally assumed that performance on the NART is relatively unaffected by injury or cognitive decline and that it can thus be used as an index of pre-morbid verbal intelligence (Crawford, Parker et al. 1988). The study had intended to use NART error scores as a covariate in univariate analyses of the influence of clinical variables upon cognitive performance in order to minimise the effect of differences in pre-morbid intelligence.

However, exploratory data analysis indicated that NART scores were significantly influenced by clinical measures indicative of the severity of the haemorrhage. For example, the mean number of NART errors for patients with a haematoma was notably significantly higher than that for patients without a haematoma ($t = 2.87$, $p = .006$). The mean NART errors for patients with a Fisher Grade of 4 was also significantly higher than for those with lower Fisher Grades ($t = 2.56$, $p = .013$) and NART error scores for patients with a WFNS Grade of V were also significantly higher than those of less severe grades ($t = 3.07$, $p = .036$).

These differences in part reflected differences in years of education in the Fisher Grade and WFNS Grade groups, with those patients with a higher education level tending to be in the less severe grade groups. However, differences in education did not account for all of the NART differences, particularly the very pronounced differences in those with or without a haematoma. A regression equation using years of education, social class, age and gender was used to obtain predicted NART error scores (Crawford 1990) and these were compared with obtained NART error scores. As can be seen in Table 5-9, the predicted NART error scores were notably lower than obtained NART error scores for patients with a haematoma. Discrepancies between predicted and obtained NART were more often in the direction of a greater than expected number of NART errors in patients with greater injury severity.

Table 5-9 Mean Predicted & Obtained NART Errors

	Mean Predicted NART Errors	Mean Obtained NART Errors
Fisher Grade 1-3	21.13	21.20
Fisher Grade 4	23.81	27.44
Admission WFNS Grade I	21.24	22.31
Admission WFNS Grade II - V	23.19	24.69
Haematoma Present	23.17	30.30
No Haematoma	21.47	21.72
All Patients	21.78	22.89

As the predicted NART accounts for years of education, social class (based on occupation prior to haemorrhage), age and gender, it is reasonable to infer that in at least some patients the higher than predicted obtained NART error scores are a consequence of the NART itself being affected by the haemorrhage and consequently not providing a valid index of pre-morbid intelligence. Thus to have included the obtained NART as a covariate in analysis would have served to underestimate the true cognitive consequences of the haemorrhage in patients in whom the NART score was impaired. However, to exclude a premorbid measure when there were evident differences in education and other predictors of intelligence between some clinical variables would have resulted in a strong bias in the result reflective of premorbid intelligence differences. Consequently it was decided to use the predicted NART, based on the regression equation including years of education, age, social class and gender, as this could not have been affected by the haemorrhage and as such was the best available index of pre-morbid intelligence.

Thus the influence of each clinical variable was determined using univariate General Linear Model analysis with predicted NART error score and age at assessment as covariates. Additionally, a 'low score' comparison of the number of patients scoring below one standard deviation below the normative mean was undertaken as outlined in chapter 4.

Aneurysmal Origin vs Unknown Aetiology Haemorrhage

Fifty-six of the 70 patients who underwent neuropsychological assessment had an angiographically confirmed origin for their haemorrhage, which was comparable to the percentage of non-participants as shown in Table 5-10. Twelve patients had a negative angiogram but SAH confirmed by CT or lumbar puncture and the remaining two patients had no angiogram performed due to advanced age and contraindicating previous medical history.

Although all of those who died from their haemorrhage are likely to have had an aneurysmal origin, there were no significant differences in GOS outcome *amongst survivors* between those cases with or without proven aneurysmal origin.

Table 5-10 Angiographically proven Aneurysmal Origin

	Died	Participants	Non-Participants
Yes	5 (41.7%)	56 (80.0%)	12 (85.7%)
No (Negative Angio)	0	12 (17.1%)	2 (14.3%)
Unknown (No Angio)	7 (58.3%)*	2 (2.9%)	0

* It is likely that all of these patients, whose condition excluded angiogram and subsequently died from either re-haemorrhage or ischaemia, suffered an aneurysmal SAH.

The aneurysmal origin patients were significantly younger than those of unknown origin (47.2 versus 54.8 years; t = -2.1, p = .039) and had lower mean predicted NART error scores (21.32 versus 24.23) such that they might be expected to perform better on neuropsychological tasks. Thus although aneurysmal patients appeared to perform better on comparison of mean scores, when age and predicted premorbid intelligence differences were accounted for none of the differences were statistically significant. There was however a tendency for aneurysmal SAH patients to have higher scores on measures of psychological distress and the direct carers of aneurysmal SAH patients rated themselves as being under significantly greater strain as a result of the injury than did carers of unknown aetiology patients.

Site of Aneurysm

The angiographically confirmed sites of both participants and non-participants are shown in Table 5-11 below. This table relates to the aneurysms which ruptured leading to the haemorrhage and does not include unruptured incidental aneurysms which were present in several patients. It can be seen that the majority of ruptured aneurysms were either on the Anterior Communicating Artery (ACoA), Middle Cerebral Artery (MCA) or the Posterior Communicating Artery (PCA).

Table 5-11 Aneurysm Site

	Participants	%	Non-participants	%
Anterior Communicating Artery	19	33.9	3	25.0
Pericallosal Artery	5	8.9		
Other Anterior Cerebral			1	8.3
Middle Cerebral Artery	14	25.0	3	25.0
Posterior Communicating Artery	10	17.9	2	16.7
Carotid Bifurcation	1	1.8		
Ophthalmic Artery	1	1.8		
Other Internal Carotid	1	1.8	1	8.3
Basilar Artery	2	3.6	1	8.3
Posterior Inferior Cerebellar Artery	3	5.4	1	8.3

Memory and ACoA Aneurysms

Memory tasks are of particular interest in relation to aneurysm site because previous studies have indicated a link between ACoA aneurysmal rupture and an amnesic syndrome. After controlling for age and predicted NART, neither patients with ruptured Anterior Communicating Artery aneurysms or Middle Cerebral Artery aneurysms had significantly different cognitive or functional outcome scores than patients with ruptured aneurysms at other sites. The only exception was the logical memory 'passage recall' task in which patients with ACoA aneurysms performed worse, particularly on the delayed recall of passage A, with a mean score of 8.58 (SD 4.90) relative to 11.71 (SD 4.58) for other aneurysmal sites ($F(1, 49) = 4.97$, $p = .030$).

On further analysis, it was found that performance on this passage recall task was accounted for substantially better if a group of anterior aneurysm sites, comprising the ACoA, MCA, pericallosal and ophthalmic aneurysm patients, was considered relative to those with ruptured aneurysms at other sites. This anterior aneurysm group performed significantly worse on both versions of the immediate recall task ($F(1, 51) = 9.48$, $p = .003$) and on both versions of the delayed recall task ($F(1, 49) = 8.07$, $p = .007$). There were no other significant differences between this anterior aneurysm group and those with aneurysms at other sites.

That the relationship between aneurysm site and poorer logical memory performance was not restricted to the ACoA site but also extended to other anterior aneurysms is also demonstrated by consideration of the patients who score in the 'low score' range on this passage recall task (Table 5-12). It can be seen that the Anterior group of aneurysms account for virtually all of those scoring less than one SD below the normative mean on this task, with this only partially accounted for by ACoA aneurysms.

Table 5-12 Anterior Aneurysms and 'Low Scores' on Logical Memory

	ACoA (19)	Other Aneurysmal (36)		
	Below 1 SD (%)	Below 1 SD (%)	χ^2	p
Logical Memory T	31.6	16.7	1.62	NS
Delayed LogMem T	31.6	11.8	3.13	.077
	Anterior Group (38)	Other Aneurysmal (17)		
	Below 1 SD (%)	Below 1 SD (%)	χ^2	p
Logical Memory T	28.9	5.9	3.67	.056
Delayed LogMem T	27.0	0	5.33	.023

Number of patients in parentheses

Below 1 SD = Proportion of patients scoring less than 1 sd below normative mean

Fisher Grade

Fisher Grade was consistently associated with cognitive outcome, with Fisher Grade 4 patients performing significantly worse than Grade 1-3 patients across a range of tasks. Grade 3 patients had consistently lower cognitive scores than those with Grades 1-2, but the differences between these lower grade patients was generally slight, such that Grades 1-3 were merged for the purpose of univariate analysis. The differences in cognitive performance by Fisher Grade can be seen in Table 5-13 below.

Table 5-13 Fisher Grade and Cognitive Performance

	Fisher Grade 1-3		Fisher Grade 4			
	Mean	SD	Mean	SD	F	p
Digit Span	15.98	4.41	13.84	3.72	1.57 (1,64)	.214
Comprehension	19.59	5.45	15.84	5.65	3.32 (1,64)	.073
Block Design	24.49	9.41	17.50	8.46	8.54 (1,65)	.005 **
Digit Symbol	46.26	12.44	38.16	11.50	5.44 (1,62)	.023 *
ILDS	4.88	2.45	3.47	2.44	3.27 (1,63)	.075
PASAT4	48.25	12.65	42.64	17.57	1.86 (1,54)	.179
PASAT2	31.51	11.43	33.89	12.11	0.81 (1,46)	.373
GNT	21.04	5.09	17.11	5.94	4.71 (1,65)	.034 *
Logical Memory T	24.81	7.94	19.58	7.80	4.15 (1,64)	.046 *
Delayed LogMem T	20.30	8.70	13.79	9.25	5.94 (1,62)	.018 *
Paired Associates	16.87	4.53	13.63	4.92	5.30 (1,60)	.025 *
Delayed Associates	6.56	1.80	5.00	2.25	9.18 (1,57)	.004 **
Figural Memory	7.00	1.65	5.71	1.65	6.06 (1,59)	.017 *
Brixton Spatial †	19.16	7.72	23.11	9.10	1.98 (1,59)	.165
Verbal Fluency FAS	34.25	13.77	29.00	16.57	0.63 (1,63)	.431
Rey Copy	30.07	5.35	26.39	5.65	4.92 (1,61)	.030 *
Rey Immed Recall	15.30	8.26	10.19	6.37	6.32 (1,60)	.015 *
Trailmaking A †	41.64	18.06	53.85	31.89	3.15 (1,63)	.081
Trailmaking B †	85.89	35.48	101.00	40.07	1.99 (1,57)	.164
Stroop Interference	0.64	6.26	-2.58	6.81	2.62 (1,55)	.111

† Denotes task in which higher score represents worse performance

* $p < .05$, ** $p < .01$

The Fisher Grade 4 patients were also significantly more likely to fall within the 'low score' range of many of the neuropsychological tasks as shown in Tables 5-14 & 5-15. The majority (55%) of Fisher Grade 4 patients scored in the low score range in at least 7 of the 12 measures, relative to only 18% of those with lower Fisher Grades ($\chi^2 = 13.64$, $p < .001$).

Table 5-14 Cognitive 'Low Scores' by Fisher Grade

	Fisher Grade 1-3	Fisher Grade 4		
	% Below 1 SD	% Below 1 SD	χ^2	p
Digit Span	8.2	31.6	6.00	.023 *
Comprehension	16.3	47.4	7.04	.008 **
Block Design	20.4	65.0	12.71	<.001 **
Digit Symbol	21.3	47.4	4.49	.034 *
PASAT2	51.0	68.4	1.68	.195
GNT	20.4	52.6	6.85	.009 **
Logical Memory T	20.4	42.1	3.31	.069
Delayed LogMem T	22.4	47.4	4.10	.043 *
Paired Associates	33.3	68.4	6.68	.010 **
Delayed Associates	31.8	68.4	7.26	.007 **
Stroop Word	26.2	64.7	7.68	.006 **
Stroop Colour Word	23.8	58.8	6.62	.010

* $p < .05$, ** $p < .01$

Below 1 SD = Proportion of patients scoring less than 1 sd below normative mean

Table 5-15 Number of 'Low Score' Tasks by Fisher Grade

	Grade 1	Grade 2	Grade 3	Grade 4
0 - 3	1 (16.7)	3 (50.0)	18 (48.6)	4 (20.0)
4 - 6	5 (83.3)	2 (33.3)	11 (29.7)	5 (25.0)
7+	0	1 (16.7)	8 (21.6)	11 (55.0)

Percentage of corresponding Grade in parentheses

Admission WFNS Grade and Cognitive Performance

Participants and non-participants had a similar spread of WFNS Grades and in both groups the majority of patients had an admission Grade of I (Table 5-2). For the purposes of analysis, the patients were divided into those with Grade I and those with Grades II - V. There was a mild association between WFNS Grade I and higher cognitive performance on all of the tasks administered (Table 5-16). This effect appears more notable in some of the verbal memory tasks such as logical memory, which represent the only significant differences after adjustments for age and predicted premorbid intelligence. The Trail-making B findings were not reflected in a 'Trails B minus Trails A' variable, which is sometimes used to separate out the motor and rule change components of Trails B, and thus may in part be due to differences in motor speed.

The lower verbal memory scores in those with Grade II-V are reflected by chi-square analysis of those in the 'low score' range. Only 18% of Grade I patients scored one standard deviation or more below the normative mean on the logical memory task, which is close to the 16% of the population who would normally be expected to fall in this range. In contrast, over 47% of the Grade II-V patients fall below this point ($\chi^2 = 6.16$, $p = .013$). A similar pattern was present for the delayed recall of this task with 22% of Grade I patients scoring in the 'low score' range relative to 47% of those with higher grades ($\chi^2 = 4.30$, $p = .038$).

Table 5-16 Admission WFNS Grade & Cognitive Performance

	WFNS Grade I		WFNS Grade II-V			
	Mean	SD	Mean	SD	F	p
Digit Span	15.94	4.36	14.00	3.84	2.02 (1,63)	.160
Comprehension	19.24	5.60	16.89	5.73	1.66 (1,65)	.202
Block Design	22.94	9.45	21.15	9.96	0.04 (1,66)	.853
Digit Symbol	45.67	12.66	39.95	11.72	0.51 (1,65)	.476
ILDS	4.63	2.41	4.05	2.70	0.10 (1,64)	.750
PASAT4	48.24	13.23	42.86	15.78	0.54 (1,55)	.466
PASAT2	33.18	11.28	27.25	11.07	0.99 (1,47)	.325
GNT	20.52	5.34	18.16	5.96	1.57 (1,65)	.215
Logical Memory T	25.16	7.93	18.84	7.24	6.86 (1,65)	.011 *
Delayed LogMem T	20.63	8.73	13.26	8.60	6.27 (1,63)	.015 *
Paired Associates	16.88	4.02	13.00	5.80	6.78 (1,61)	.012 *
Delayed Associates	6.43	1.79	5.13	2.50	1.97 (1,58)	.165
Figural Memory	6.77	1.78	6.31	1.54	0.04 (1,60)	.843
Brixton Spatial †	18.81	6.61	24.19	11.25	3.08 (1,60)	.084
Verbal Fluency FAS	34.67	14.80	28.53	13.70	0.83 (1,64)	.365
Rey Copy	29.57	5.17	27.42	6.54	0.59 (1,62)	.446
Rey Immed Recall	15.10	8.00	10.11	7.39	2.65 (1,61)	.109
Trailmaking A †	41.27	18.49	54.20	30.94	2.07 (1,64)	.155
Trailmaking B †	81.16	30.01	110.53	45.74	4.69 (1,58)	.034 *
Stroop Interference	0.24	5.88	-2.06	7.99	1.00 (1,56)	.323

† Denotes task in which higher score represents worse performance

* $p < .05$, ** $p < .01$

On comparing the neuropsychological scores by WFNS Grade, it was apparent that there was a general association between worse WFNS Grade and lower cognitive performance. The breakdown of mean scores for those tasks which were more strongly correlated with admission WFNS grade ($r > .240$) is shown in Table 5-17. The numbers of patients with Grades III & IV who completed the tasks was very low, with only between one to three patients for each condition, and are thus not included in the table.

Table 5-17 Mean Scores & Age-controlled Correlations with WFNS Grade

	Grade I	Grade II	Grade V	r	p
Logical Memory T	25.17	19.81	17.80	-.260	.016
Delayed LogMem T	20.49	14.20	13.00	-.245	.024
Paired Associates	16.76	14.63	13.00	-.269	.016
Rey Immed Recall	14.96	12.81	6.25	-.304	.007
Brixton Spatial †	19.02	17.00	33.00	.404	.001
Trailmaking B †	81.14	88.25	129.80	.400	.001

† Denotes task in which higher score represents worse performance

Age controlled 1-tailed partial correlations

It can be seen from the table above that a difference in mean scores is apparent between Grades I and II, with Grade V patients unsurprisingly performing consistently worse. This difference between Grades I and II was also present in several other neuropsychological measures and justifies the consideration of Grade I patients separately from all other Grades. The very notably lower performance in Grade V patients in Rey Recall and the Brixton Spatial task may reflect impaired visuospatial ability in these patients. These Grade V patients also performed notably lower than other Grades on the Rey Copy.

Pre-operative WFNS Grade

As can be seen in Table 5-18 below, a pre-operative WFNS Grade of I was associated with better cognitive outcome across a range of cognitive tasks, including verbal memory as might be expected given the association with admission WFNS. The power for these analyses was lower as this variable naturally only includes the 54 patients who underwent some form of neurosurgical procedure (usually craniotomy and clipping of the ruptured aneurysm).

Table 5-18 Pre-operative WFNS Grade & Cognitive Performance

	Pre-op WFNS Grade I		Pre-op WFNS Grade II-V			
	Mean	SD	Mean	SD	F	p
Digit Span	16.33	4.37	15.00	3.77	0.65 (1, 49)	.423
Comprehension	19.90	5.38	15.91	6.53	4.43 (1, 49)	.041 *
Block Design	23.43	8.76	22.50	12.52	0.01 (1, 50)	.936
Digit Symbol	46.88	9.91	41.82	16.87	1.17 (1, 47)	.285
ILDS	4.73	24.2	3.91	2.74	0.65 (1, 48)	.426
PASAT4	48.89	13.10	42.63	19.13	1.35 (1, 42)	.252
PASAT2	33.10	10.75	31.14	11.64	0.12 (1, 36)	.734
GNT	21.29	4.32	16.55	7.03	8.00 (1, 49)	.007 **
Logical Memory T	25.37	8.23	19.64	5.55	4.78 (1, 49)	.034 *
Delayed LogMem T	21.03	8.75	15.73	7.96	2.64 (1, 47)	.111
Paired Associates	16.97	4.22	13.27	6.74	4.63 (1, 46)	.037 *
Delayed Associates	6.45	1.62	5.80	2.20	0.84 (1, 44)	.364
Figural Memory	6.93	1.70	6.33	1.80	0.57 (1, 45)	.456
Brixton Spatial †	17.46	5.71	22.30	11.78	3.23 (1, 45)	.079
Verbal Fluency FAS	37.44	14.19	27.27	17.28	3.71 (1, 48)	.060
Rey Copy	30.24	4.29	27.77	7.66	1.67 (1, 47)	.203
Rey Immed Recall	15.89	8.26	9.45	7.71	5.40 (1, 47)	.025 *
Trailmaking A †	37.00	10.55	55.50	40.64	6.27 (1, 48)	.016 *
Trailmaking B †	76.64	19.70	97.10	44.16	5.35 (1, 45)	.025 *
Stroop Interference	0.77	-5.86	-1.98	8.66	1.38 (1, 43)	.246

† Denotes task in which higher score represents worse performance; * $p < .05$, ** $p < .01$

The statistical significance of these differences is low, particularly given the number of comparisons. However, the consistency of direction suggests that it reflects a genuine if modest difference between pre-operative grades. Forty-two (78%) of these patients had pre-operative WFNS grade I, a further eight (15%) having a pre-op Grade of II, leaving only one patient in each of grades III and IV and two with grade V.

Presence of Haematoma

Only ten of the 70 patients who undertook neuropsychological investigation had an identified haematoma. In two patients information could not be found as to whether or not a haematoma was present and thus they were excluded from analysis.

Overall the haematoma group performed worse on cognitive testing, though as would be expected their performance reflected the region of the haematoma, such that the deficits are to some extent masked by mean scores and univariate analysis. As a group, significantly worse performance is evident in visuospatial tasks such as Rey complex figure copy, block design and figural memory, as demonstrated in Table 5-19. The impact of the haematoma upon functioning can be gauged by consideration of the percentages of those with haematoma scoring in the 'low score' range on a number of the neuropsychological tasks as shown in Table 5-20. The differences are apparent though they generally do not reach statistical significance due to the low numbers in the haematoma group and the differing regions of haematoma affecting differing cognitive functions. Five of the ten haematoma patients scored in the 'low score' range on at least 7 of the 12 tasks, relative to 18.2% of those without haematoma, demonstrating the greater prevalence of probable cognitive deficits in this group.

Table 5-19 Presence of Haematoma & Cognitive Performance

	Haematoma Present		No Haematoma			
	Mean	SD	Mean	SD	F	p
Digit Span	14.30	4.32	15.82	4.11	0.38 (1,63)	.541
Comprehension	14.60	6.24	19.35	5.44	4.92 (1,63)	.030 *
Block Design	17.80	7.21	23.17	9.87	5.78 (1,64)	.019 *
Digit Symbol	43.30	16.85	43.96	12.02	0.59 (1,61)	.445
ILDS	3.40	3.27	4.61	2.33	2.51 (1,62)	.118
PASAT4	46.71	20.78	47.20	12.85	0.22 (1,53)	.639
PASAT2	41.60	16.52	30.53	10.46	4.69 (1,46)	.036 *
GNT	17.10	5.55	20.09	5.35	1.52 (1,63)	.222
Logical Memory T	20.30	8.35	24.02	8.26	1.91 (1,63)	.172
Delayed LogMem T	15.50	9.78	19.18	9.28	2.31 (1,61)	.133
Paired Associates	15.22	6.02	15.93	4.74	0.45 (1,59)	.507
Delayed Associates	6.38	1.85	6.08	1.97	0.21 (1,56)	.885
Figural Memory	5.56	2.13	6.79	1.56	6.80 (1,58)	.012 *
Brixton Spatial †	22.38	12.94	19.67	7.57	1.37 (1,58)	.246
Verbal Fluency FAS	27.70	15.07	33.77	14.77	1.88 (1,62)	.175
Rey Copy	25.83	8.26	29.42	5.01	5.18 (1,61)	.026 *
Rey Immed Recall	11.63	8.01	13.72	7.91	2.23 (1,60)	.140
Trailmaking A †	48.40	24.85	44.46	23.70	0.85 (1,62)	.361
Trailmaking B †	96.44	47.00	87.69	36.05	2.25 (1,56)	.140
Stroop Interference	-2.03	8.37	-0.27	6.09	0.51 (1,55)	.477

† Denotes task in which higher score represents worse performance

* $p < .05$, ** $p < .01$

Table 5-20 Presence of Haematoma and Cognitive 'Low Scores'

	Haematoma	No Haematoma		
	% Below 1SD	% Below 1SD	χ^2	p
Comprehension	60.0	18.6	7.88	.005 **
Block Design	60.0	30.0	3.42	.064
Graded Naming	60.0	25.4	4.83	.023 *
Logical Memory	50.0	22.0	3.47	.063

* $p < .05$, ** $p < .01$

% Below 1 SD = Proportion of patients scoring less than 1 sd below normative mean

Clinical Complications

The relatively small numbers with individual complications resulting in clinical deterioration restrict the ability to infer the presence or otherwise of cognitive deficits due to these clinical complications. For example, only 4 of the 11 patients who suffered a re-haemorrhage survived. Of the 70 patients who underwent neuropsychological investigation, 8 had an identified infarct and 11 had identified hydrocephalus during the acute stage.

Amongst the patients with hydrocephalus there was a pattern of reduced verbal memory performance, with lower scores on the logical memory task and on verbal paired associates as shown in Table 5-21. The difference in the logical memory task was more pronounced in version A, such that the effect is slightly muted when both versions are combined. The suggestion of an influence upon verbal memory is also supported by the observation of more repetitions by those with previous hydrocephalus on the verbal fluency task.

These differences are reflected by the percentage differences in those performing in the 'low score' range on the verbal paired associates task, with 70% of those with a history of hydrocephalus scoring 1SD or more below the normative mean relative to 37% of those without hydrocephalus ($\chi^2 = 3.75$, p = .053). There were no significant effects of hydrocephalus upon non-memory cognitive tasks.

Table 5-21 Hydrocephalus & Verbal Memory Performance

	Hydrocephalus		No Hydrocephalus			
	Mean	SD	Mean	SD	F	p
Logical Memory A	9.82	4.85	12.95	4.57	4.46 (1, 65)	.039 *
Logical Memory T	19.36	9.63	24.19	7.76	3.76 (1, 65)	.057 *
Delayed LogMem A	6.36	4.39	10.25	5.14	6.33 (1, 63)	.014 *
Delayed LogMem T	13.45	9.07	19.54	9.03	4.92 (1, 63)	.030 *
Paired Associates	12.40	7.07	16.49	4.07	7.94 (1, 61)	.007 **

* p < .05, ** p < .01

The presence of infarct was associated with significantly lower Digit Span, with a mean of 12.88 (sd 6.58) relative to 15.74 (sd 3.85) in those without infarct (F (1, 65) = 5.29, p =.025). Four of the eight patients with infarct were in the 'low score' range on this task. There were no other cognitive associations with the presence of infarct, perhaps reflecting the low numbers in this group. Infarct did however appear to impact upon psychological and other health measures, with mean scores on HADS depression more than double those of non-infarct patients (10.83 (sd 6.85) relative to 5.29 (sd 4.35), F (1, 47) =11.03, p = .002), though this apparently higher depression rate was not reflected by the Beck Depression Inventory. These indications of worse functional outcome amongst those with an infarct are reflected by significantly higher levels of strain reported by their carers, with mean strain ratings of 7.57 (sd 2.43) relative to 4.89 (sd 3.27) by the carers of other patients (F (1, 43) =4.24, p = .046).

Apolipoprotein E Genotype

As outlined in Table 5-4, the apolipoprotein E ε4 allele was present in 16 (23%) of the 70 patients who participated in assessments at 14 months. There were only slight differences between ε4 and non-ε4 patients in terms of aneurysmal origin (ε4 88% vs non ε4 81%), admission WFNS grade (Grade I: ε4 63% vs. non-ε4 70%) or mean age at ictus (ε4 50.6 years (sd 12.4) vs. non-ε4 46.9 years (sd 11.9).

However, a Fisher Grade of 4 was more likely amongst ε4 patients, with six (38%) of sixteen ε4 patients having a Fisher Grade 4 relative to fourteen (26%) of fifty-four non-ε4 patients, though this difference did not reach statistical significance due to the small numbers involved. This difference is however perhaps particularly notable as none of the sixteen ε4 patients had a haematoma present whereas haematomas were present in ten of the non-ε4 patients. Thus the greater prevalence of Fisher Grade 4 amongst ε4 patients is likely to be due to a notably greater presence of intraventricular rather than intraparenchymal blood.

Table 5-22: Apolipoprotein E ε4 allele & Cognitive Performance

	ε4 allele present		No ε4 allele			
	Mean	SD	Mean	SD	F	p
Digit Span	15.47	3.85	15.39	4.43	0.64 (1,65)	.429
Comprehension	19.93	3.94	18.22	6.07	4.68 (1,65)	.034 *
Block Design	22.00	9.74	22.56	9.59	0.98 (1,66)	.326
Digit Symbol	40.20	11.43	45.15	12.78	0.01 (1,63)	.946
ILDS	3.80	2.78	4.66	2.39	0.28 (1,64)	.598
PASAT4	47.54	14.32	46.80	13.97	0.69 (1,55)	.411
PASAT2	30.08	9.78	32.31	11.93	0.01 (1,47)	.940
GNT	20.07	5.66	19.81	5.60	0.94 (1,65)	.337
Logical Memory T	22.93	7.71	23.56	8.40	0.31 (1,65)	.579
Delayed LogMem T	17.43	11.03	18.83	8.82	0.11 (1,63)	.741
Paired Associates	15.36	5.21	16.00	4.75	0.04 (1,61)	.845
Delayed Associates	5.43	2.77	6.38	1.58	1.02 (1,58)	.318
Figural Memory	6.54	1.94	6.69	1.68	0.65 (1,60)	.424
Brixton Spatial †	22.36	6.42	19.54	8.66	0.22 (1,60)	.642
Verbal Fluency FAS	31.53	13.58	33.36	15.05	0.38 (1,64)	.542
Rey Copy	27.72	6.19	29.39	5.41	0.02 (1,62)	.893
Rey Immed Recall	11.47	9.62	14.45	7.49	0.12 (1,61)	.727
Trailmaking A †	54.93	33.31	42.28	19.22	1.39 (1,64)	.242
Trailmaking B †	95.31	30.24	87.59	38.77	0.14 (1,58)	.709
Stroop Interference	0.97	6.51	-0.74	6.54	1.14 (1,56)	.291

† Denotes task in which higher score represents worse performance

* $p < .05$

There were no notable effects relating to the presence of the ε4 allele upon any of the neuropsychological measures employed (Table 5-22). The WAIS comprehension task was the only difference to be 'significant' at $p<.05$, with this difference in the opposite direction to that expected and likely to be a chance finding given the number of comparisons. The ε4 allele also had no notable effects upon the presence of anxiety or depression amongst patients and there were no differences in terms of GOS measured outcome. There were also no marked APOE related differences in terms of change in GOS between assessments at 6 & 16 months. An improvement in GOS occurred in 5 (31%) of 16 ε4 patients relative to 20 (37%) of 54 non-ε4, whereas deterioration occurred in 4 (25%) of the ε4 patients relative to 13 (24%) of non-ε4 patients.

There was however some suggestion of an interaction between the ε4 allele and Fisher Grade, though this did not reach statistical significance. Only one (17%) of the six ε4 Fisher 4 patients improved on GOS, relative to 6 (43%) of 14 non-ε4 Fisher 4 patients. Consequently, by 16 month assessment four (67%) of the six ε4 Fisher 4 patients remained severely disabled relative to five (36%) of fourteen non-ε4 Fisher 4 patients. By contrast amongst those with Fisher Grades 1-3, none of the ten ε4, and only two of the forty non-ε4 patients were severely disabled at 16 months. The ε4 Fisher 4 patients also performed notably worse than non-ε4 Fisher 4 patients on verbal memory tasks such as logical memory and verbal paired associates (Table 5-23), though statistical significance was largely precluded by the small numbers of patients involved.

Table 5-23: Mean Verbal Memory Performance in Fisher 4 Patients by ε4 allele

	Logical Memory	Delayed Logical Memory	Verbal Paired Associates	Delayed Verbal Paired Associates
ε4 (n=6)	15.8 (5.9)	6.0 (6.7)	9.3 (3.3)	2.0 (1.2)
Non-ε4 (n=14)	20.8 (8.6)	16.2 (9.1)	14.9 (4.8)	6.1 (1.5)

(Standard deviation in parentheses)

Functional / Psychological Outcome

Short Form 36 Health Survey

The calculated domain scores from the Short Form 36 Health Survey (SF36) were compared with normative data matched individually for age, social class and gender (Jenkinson, Layte et al. 1996). The SAH patients scored significantly lower on each of the domains measured by the SF36 than their expected levels based on these matched norms. These differences were all significant at the $p < .001$ level on Wilcoxon related samples testing, with the exception of the pain dimension where the difference was significant at $p < .05$.

These reduced scores, reflecting differing impairments in functional status, were not present in all patients and were affected by certain clinical categories, such as Fisher Grade, Anterior Communicating Artery Aneurysm and to a lesser extent WFNS Admission Grade. Other clinical groupings, such as presence of haematoma and clinical complications such as hydrocephalus or infarct were not analysed statistically due to low numbers in individual groupings amongst those who returned accurately completed questionnaires.

SF-36 and Severity Indices

The relationship of Fisher Grade and SF36 health dimensions is shown in Figure 5-7 where it can be seen that Fisher Grade 4 was associated with poorer functional health status across all domains. The difference between Grade 4 and other grades was most pronounced in relation to general health perception scores ($\mu = 120$, $p = .032$). None of the Fisher Grade 4 patients regarded their health as 'very good' and over half of these patients viewed their health as no better than fair or poor (Table 5-24).

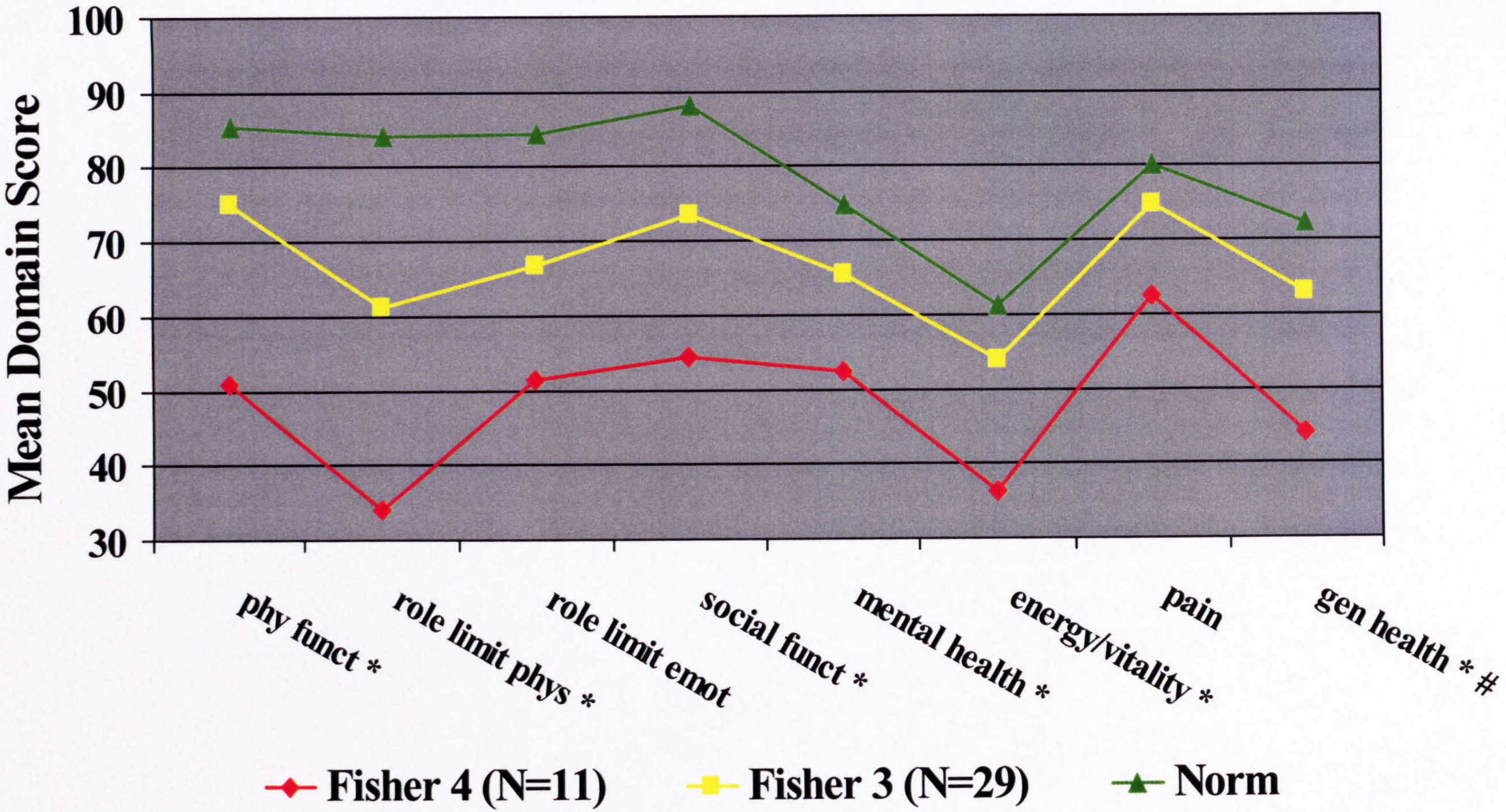
Table 5-24 View of Own Health by Fisher Grade

	Fisher 1-3	Fisher 4	Total
Very Good	10 (25.0)	0	10 (19.6)
Good	16 (40.0)	5 (45.5)	21 (41.2)
Fair	11 (27.5)	4 (36.4)	15 (29.4)
Poor	3 (7.5)	2 (18.2)	5 (9.8)

(Percentage of column in parentheses)

Admission WFNS Grade had a weaker association with the SF36 dimension scores as shown in Figure 5-8, with WFNS Grade I patients scoring much the same as other grade patients on the mental health and energy / vitality dimensions, though generally better on other dimensions. This difference was most notable in the Pain dimension, in which Grade I patients' mean scores were akin to matched normative data, whereas lower grade patients were more frequently troubled affected by pain which invariably manifested as headaches. Half of those with Grades II-V reported having experienced moderate to severe pain within the last 4 weeks relative to just over a quarter of those with an admission Grade I. Additionally, pain was reported to have interfered at least moderately with normal activities or work in 58.3% of those with Grades II-V relative to 23.7% of those with Grade I.

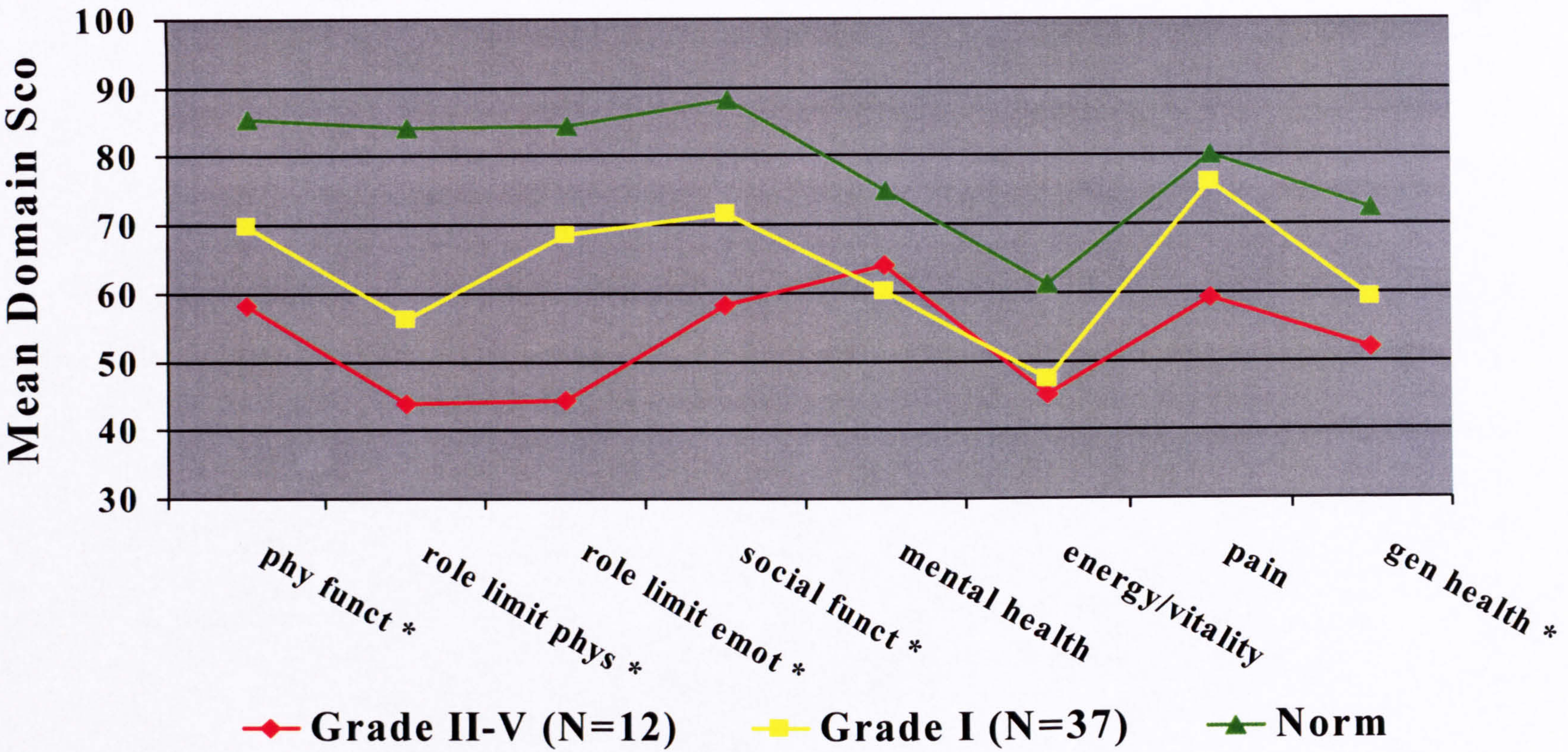
Figure 5-7: Fisher Grade and SF-36 Health Survey



* p > .05 (Wilcoxan related samples: Fisher 4 vs matched normative data)

p = .032 (Mann Whitney independent samples: Fisher 4 vs Fisher 3)

Figure 5-8: Admission WFNS Grade & SF-36 Health Survey



* p > .05 (Wilcoxan related samples: WFNS II-V vs matched normative data)

Figure 5-9: Aneurysmal Origin & SF-36 Health Survey

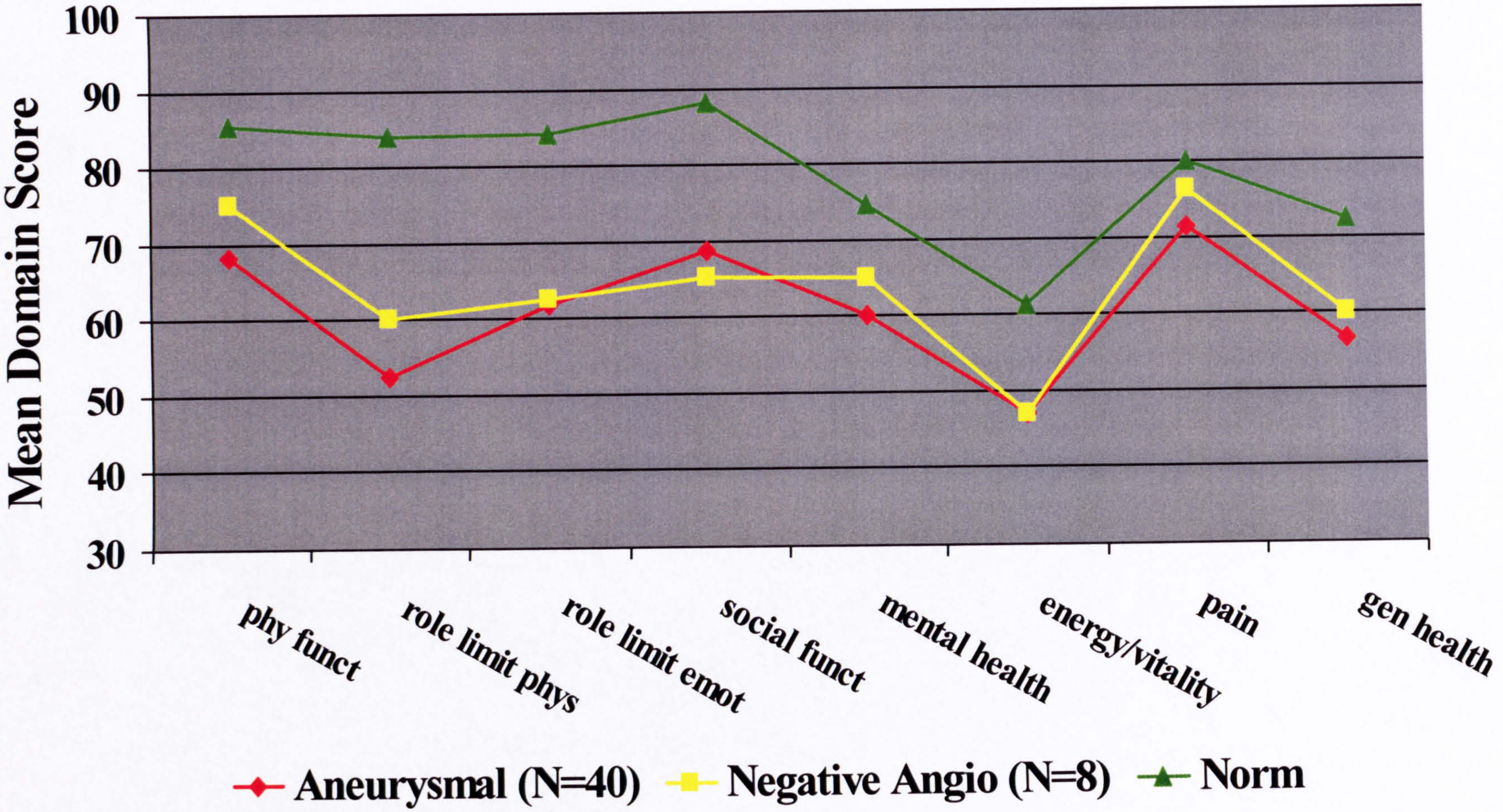
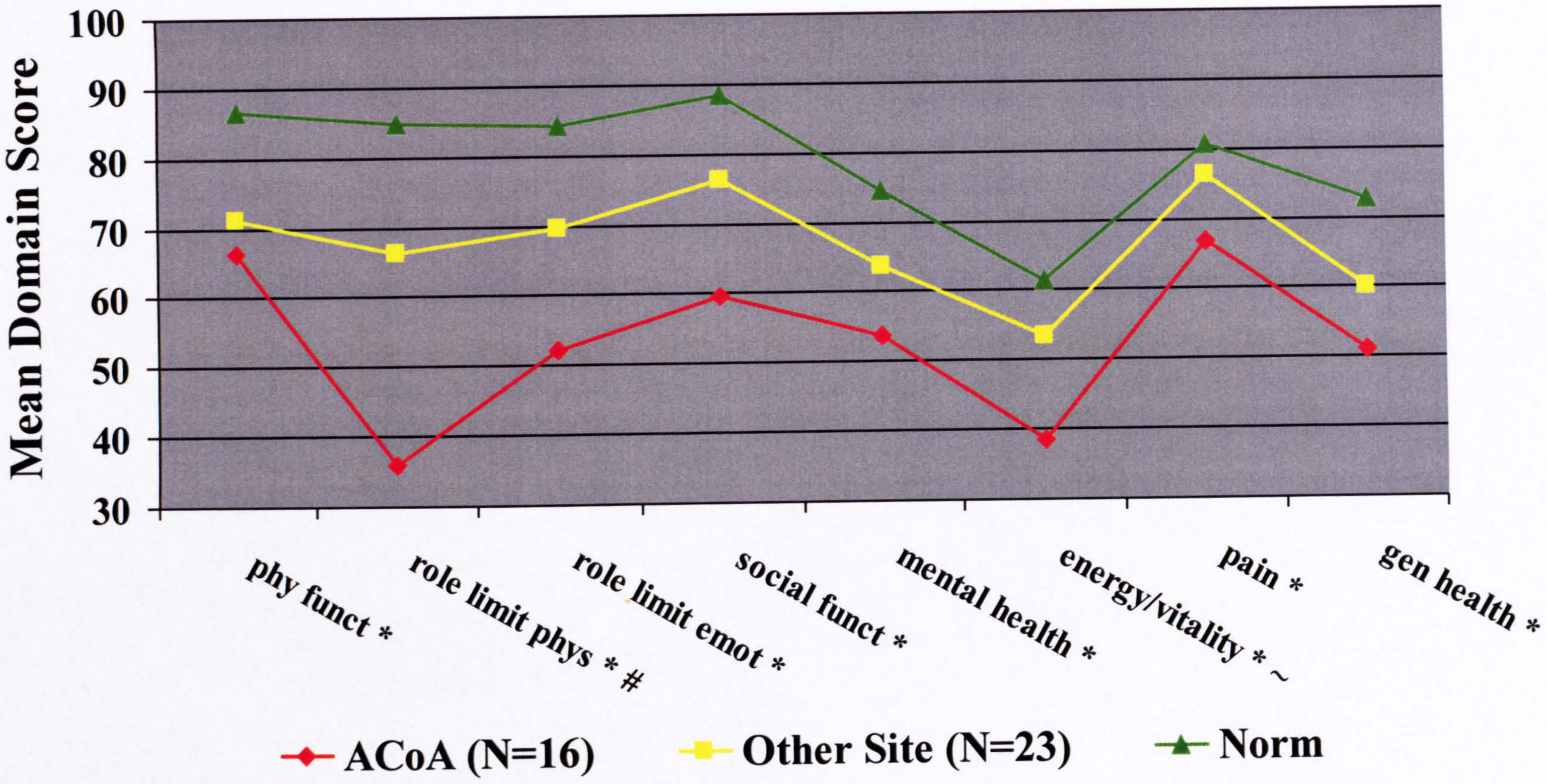


Figure 5-10: ACoA Aneurysm and SF-36 Health Survey



* p > .05 (Wilcoxan related samples: ACoA vs matched normative data)

p = .031; ~ p = .059 (Mann Whitney independent samples: ACoA vs Other Site)

Reflecting the findings in relation to GOS and cognitive outcome, SF36 domain scores did not differ notably between patients with angiographically proven aneurysmal origin and the unknown aetiology patients (Figure 5-9). There were however some effects of aneurysm site amongst the aneurysmal patients, with Anterior Communicating Artery aneurysm patients tending to have lower SF36 health scores as shown in Figure 5-10. These differences reached were most notable on the physical role limitation ($\mu = 111$, $p = .031$) and energy / vitality ($\mu = 118$, $p = .059$) dimensions.

ACoA patients were far more likely than other aneurysmal patients to report having cut down the amount of time spent on work or other activities as a consequence of their physical health (62.5% versus 17.4%, $\chi^2 = 8.34$, $p = .004$) and were also more than twice as likely to deem themselves restricted in the kinds of activities they could undertake (62.5% versus 30.4%, $\chi^2 = 3.95$, $p = .047$). The energy / vitality difference reflects greater reported tiredness and fatigue amongst ACoA patients, with over a third reporting feeling worn out most of the time.

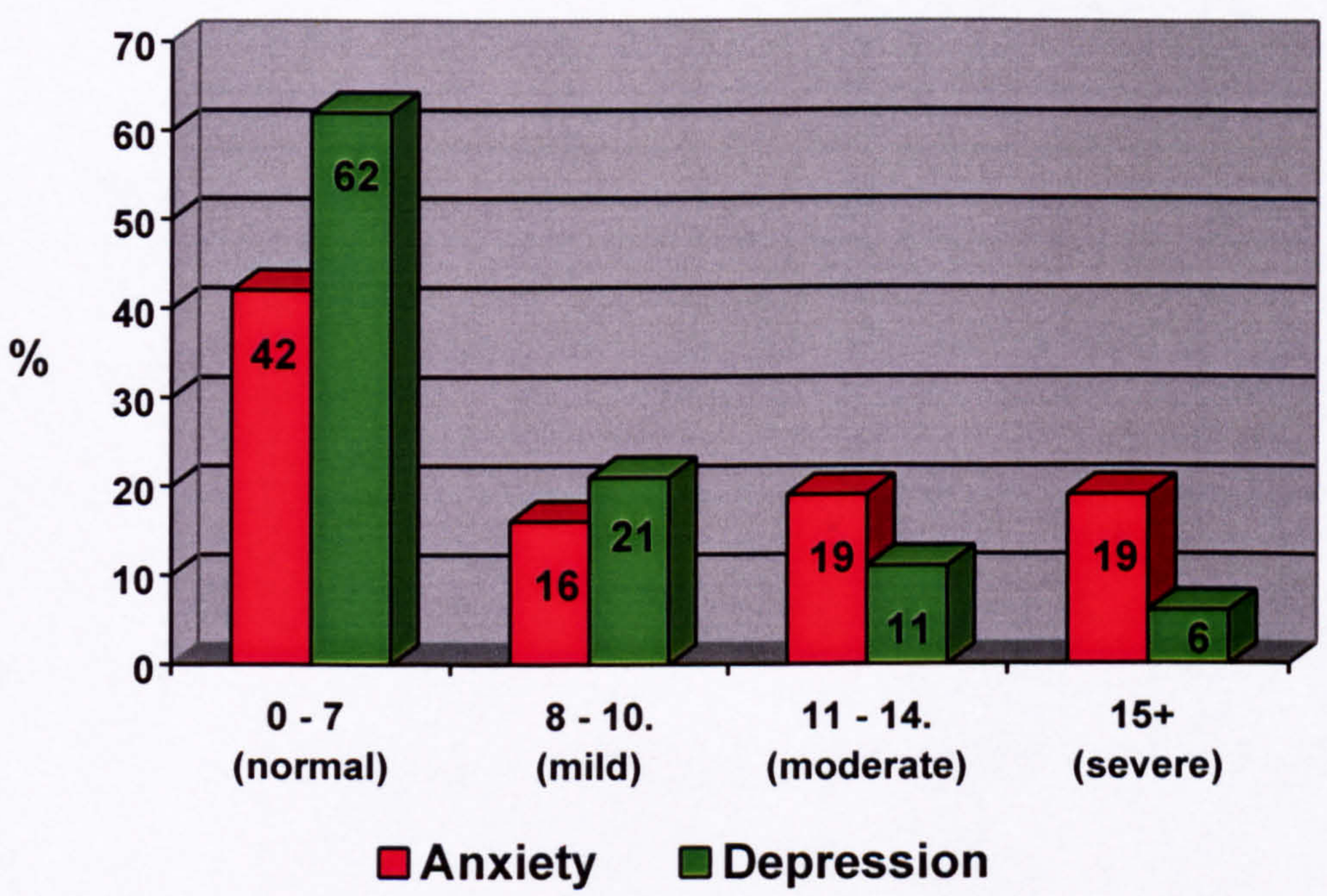
Anxiety Related Disorders

It became apparent during the course of the semi-structured interviews that anxiety related disorders were a significant problem in the day-to-day lives of a substantial proportion of the patients, with a considerable number of them reporting symptoms of panic disorder and agoraphobia. In many cases these anxiety related difficulties were considerably more disabling to the patient than any existing physical or neuropsychological deficits. Several were afraid to leave the house on their own and thus were unable to go shopping or travel locally, despite the absence of any physical disability. Others were apprehensive about being in the house on their own and thus required the presence of their partner or other carer although they were otherwise physically independent. In some cases their partners had either given up or reduced their own employment because of these anxiety related problems.

Fifty-two of these patients returned a patient questionnaire which included the Hospital Anxiety & Depression Scale (HADS), a scale which focuses upon questions which are not influenced by physical health problems. From this scale, 38% of the SAH survivors were found to suffer from moderate or severe levels of anxiety, as indicated by scores greater than 10 in Figure 5-11. Virtually all of these moderate or severe anxiety patients reported feelings of panic either quite often or very often. Scores on the Depression Scale of the HADS were notably lower, with only 17% scoring in the moderate or severe depression range and a further 21% scoring in the mild depression range. These levels of depression are consistent with levels of depression noted after other forms of stroke.

Beck Depression Inventory scores were slightly higher with 14 (28%) of patients scoring in the mild-moderate depression range (10-18) and a further 11 (22%) scoring in the moderate - severe depression range (19+). Measures that give a general index of psychological well-being, such as the GHQ and Mental Health domain of the SF36, were more strongly correlated with measures of anxiety than with measures of depression. This is consistent with the balance of findings suggesting that whilst depression is present in a notable proportion of patients, anxiety is more frequently the primary cause of psychological morbidity in this cohort of patients.

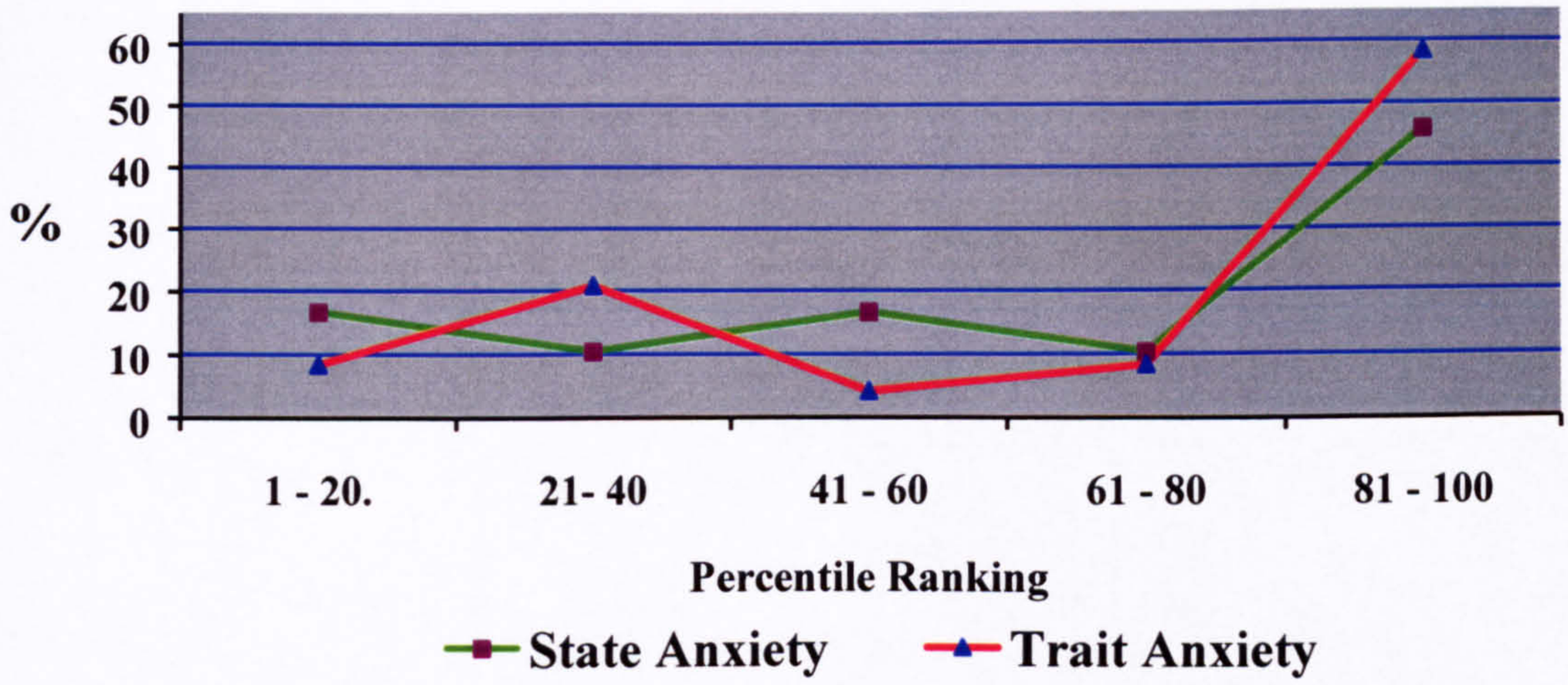
Figure 5-11: Hospital Anxiety and Depression Scale



The distribution of anxiety scores was fairly bimodal, reflecting observations made from the interviews that anxiety tended to either be present and cause difficulties in day to day living or not to be present at all in individual patients. Scores on the more comprehensive State-Trait Anxiety Inventory also reflect this tendency for anxiety to affect some individuals particularly severely whilst not troubling others (Figure 5-12). There is a marked change in the distribution of scores from around the 70th percentile, with a considerable proportion of patients having higher state and trait anxiety levels than would be expected in individuals of their age and gender.

These individuals above the 70th percentile on the State-Trait or in the clinical anxiety range on the HADS did not differ significantly from those with lower anxiety scores in terms of gender, Fisher Grade, WFNS grade, aneurysm site or other clinical variables. There were no significant correlations between either Fisher Grade or WFNS Grade and any of the measures of anxiety or depression. Of the four patients with infarct who returned questionnaires, 3 of them scored above the 90th percentile on Trait anxiety, though the small numbers preclude meaningful statistical analysis. There was a non-significant tendency for older patients to be less affected by anxiety, though the variance in anxiety scores could not be adequately accounted for by any of the demographic or clinical variables.

Figure 5-12: State Trait Anxiety Inventory



General Health Questionnaire

The GHQ 30 was scored using both the likert and 'GHQ' scoring methods to facilitate comparisons with other studies. From the latter 0-0-1-1 method, which is often employed as a screen for psychiatric disturbance, the more conservative threshold of above 5 was used to identify patients with such possible psychiatric disorder. Eighteen (39%) of 46 patients who returned the fully completed GHQ30 scored above this threshold for possible psychiatric disturbance, with 14 of these scoring ten or above indicating high levels of psychiatric disturbance. Chi-square analysis found no relationships between any clinical or demographic variables and above threshold scores. Similarly, Mann Whitney independent samples tests using total GHQ scores from the likert method, which accounts for severity of symptoms, also found no significant differences due to any of the clinical or demographic variables.

Consideration was given to the individual items which patients reported greater difficulties with in order to determine which areas of lower functioning are reflected by the scores indicative of psychiatric disturbance. The areas covered by the GHQ30 with the corresponding percentage of patients who reported greater difficulties in that particular domain are shown in Table 5-25 in decreasing order of morbidity. Several of the most frequently reported areas of reduced functioning, such as not enjoying normal activities, feeling unhappy and feeling life a struggle would be consistent with depression. Other areas indicative of more severe depression, such as feeling hopeless, viewing self as worthless or that life was not worth living were however considerably less frequently reported. A number of areas which are indicative of anxiety are also frequently reported, including getting scared or panicky or nervous / highly strung.

Table 5-25 GHQ Reported Symptoms

	% Worse		% Worse
Enjoy normal activities	42.0	Generally doing well	27.1
Feel unhappy and depressed	38.5	Generally satisfied	27.1
Lost confidence	38.5	Felt reasonably happy	25.5
Felt life a struggle	38.0	Restless nights	25.0
Concentration	37.5	Taking things hard	24.0
Getting out of house	37.5	Managing to keep occupied	22.9
Felt playing useful part	37.0	Think of self as worthless	17.3
Decision making	36.0	Felt life hopeless	15.4
Felt under strain	34.0	Sleep	14.6
Everything getting on top	32.7	Getting on with others	13.0
Get scared or panicky	32.0	Managing as well as others	12.5
Felt hopeful about future	31.4	Able to feel warmth / affection	10.9
Felt nervous / highly strung	28.8	Can't do things due to nerves	9.6
Unable to face up to problems	28.0	Spend time chatting	6.5
Felt can't overcome difficulties	28.0	Felt life not worth living	5.8

Relatives Questionnaire

Relative's questionnaires were returned for fifty-two patients. In the majority of cases (72%), the questionnaire was completed by the patient's partner, who had been their main carer since discharge from hospital. In the remaining 14 cases the questionnaire was completed by another relative, usually a sibling or child of the patient.

Most of the questions in the relatives questionnaire are answered with either 'no change', 'rather worse' or 'much worse'. Thus the questionnaire can be scored in either a Likert manner or a change - no change fashion akin to the scoring methods for the GHQ. The latter approach demonstrates the overall percentage of patients deemed to be worse in each domain by their relative, as shown in decreasing order of frequency in Table 5-26. In many instances these reported symptoms by proxy are comparable with those reported by the patients themselves either in the interview or questionnaires such as the GHQ. As might be expected, the relatives are more likely to report temper outbursts or violence, though increased irritability is reported in just over 50% by both patients and their relatives. Depression is reported in just under half of cases by both patients and relatives, though anxiety is more often reported to have worsened since the haemorrhage by relatives (60.8%) than by patients (47.1%). This may reflect slight differences in the question, as the Relative's questionnaire refers to 'tension or anxiety' rather than anxiety alone. The most frequently reported memory difficulties were forgetting verbal information and mislaying things.

Table 5-26 Proxy Rating of Patient & Correlation with Strain in Relatives

Symptom	% Worse	r_s	Symptom	% Worse	r_s
Tiredness	72.5	.387 **	Balance	35.3	.146
Tension or Anxiety	60.8	.460 ***	Behaviour	34.7	.223
Headaches	58.8	.110	Decision Making	32.6	.204
Passivity - less drive	56.9	.166	Social Life	32.0	.449 ***
Memory	56.9	.087	Vision	31.4	.319 *
Impatience	54.9	.299 *	Requires Supervision	29.4	.324 *
Irritability	54.9	.394 **	Mobility	28.0	.213
Distressed by Noise	49.0	.212	Tact	27.1	.312 *
Depression	48.0	.272 *	Participation in Household tasks	26.6	.420 **
Sudden Mood Changes	45.1	.450 ***	Sense of Taste	26.0	.440 **
Personality Changes	45.1	.135	Able to discuss problems with patient	24.4	.420 **
Difficulty Finding Words	45.1	.242 *	Sense of Smell	23.5	.283 *
Slowness	43.1	.352 **	Affectionate	22.5	.273 *
Sociable	42.8	.382 **	Difficulty Speaking	21.6	.275 *
Temper Outbursts	41.2	.341 **	Self Care	21.6	.287 *
Concentration	41.2	.346 **	Violent Outbursts	20.4	.243
Dizzy Spells	39.2	.206	Able to talk about everyday things	20.4	.300 *

* $p < .05$, ** $p < .01$, *** $p < .001$, Spearman 1-tailed correlations, N = 48

It was noted in the interviews that the main carers of the patient, invariably their partners, were themselves very much affected by the haemorrhage. They had often needed to make considerable changes to their own lives in order to care for their partner and / or take over roles previously performed by the partner, such as looking after children. These observations were supported by the self-reported levels of strain which relatives considered themselves to have been under since the haemorrhage. On a likert scale where '0' represented no strain and '10' severe strain, twenty (40%) of the relatives reported their level of strain to be 7 or above.

This percentage was higher (50%) amongst partners of the patient, who were more likely to have been the main carer. This perceived strain was higher in relatives of patients with a confirmed aneurysmal aetiology ($t = 2.62$, $p = .023$) or in whom an infarct had been identified ($t = 2.67$, $p = .023$). The level of reported strain in relatives was also correlated with measures of psychological distress in patients, including the Beck Depression ($r_s = .362$, $p = .007$), HADS Depression ($r_s = .292$, $p = .023$), HADS Anxiety ($r_s = .301$ $p = .020$) and State Anxiety ($r_s = .306$, $p = .023$), indicating that it reflected emotional disturbance in the patient.

In order to determine which reported symptoms were related to the strain in relatives, Spearman correlations were performed between the reported strain and the relative's reported proxy ratings of the patient's functioning. The areas of proxy rated functioning that were significantly correlated with relative strain are shown in Table 5-26, as these are the areas which presumably cause the greatest difficulty for the functioning of the family unit. It can be seen that some frequently reported symptoms, such as headaches and memory difficulties, are not correlated with relative strain whereas some less frequent symptoms are highly predictive of such strain. Worse tension or anxiety in the patient was the most significantly correlated symptom with strain in relatives, with other proxy rated symptoms most predictive of carer strain including sudden mood changes, reduced social life, reduced participation in household tasks and being unable to discuss problems with their partner.

Chapter 6 Head Injury Results

Patient Participation

The last known GP of each of the 94 patients who participated in a 6 month outcome study some 6-9 years previously was contacted to establish whether it was appropriate to contact the patients and to attain their most recently known contact address. In eight cases the current registered GP could not be established, with at least four of these patients known to have moved from Scotland. In a further two cases there was no reply from the Health Board confirmed GP despite repeated attempts at contact. Two patients were confirmed as having died since the previous study by their regional health board, though it could not be confirmed whether this was as a direct result of the head injury. A further two patients were deemed by their GP to be too ill to participate in the study. In one case this was due to advanced stage cancer and thus apparently unrelated to the head injury.

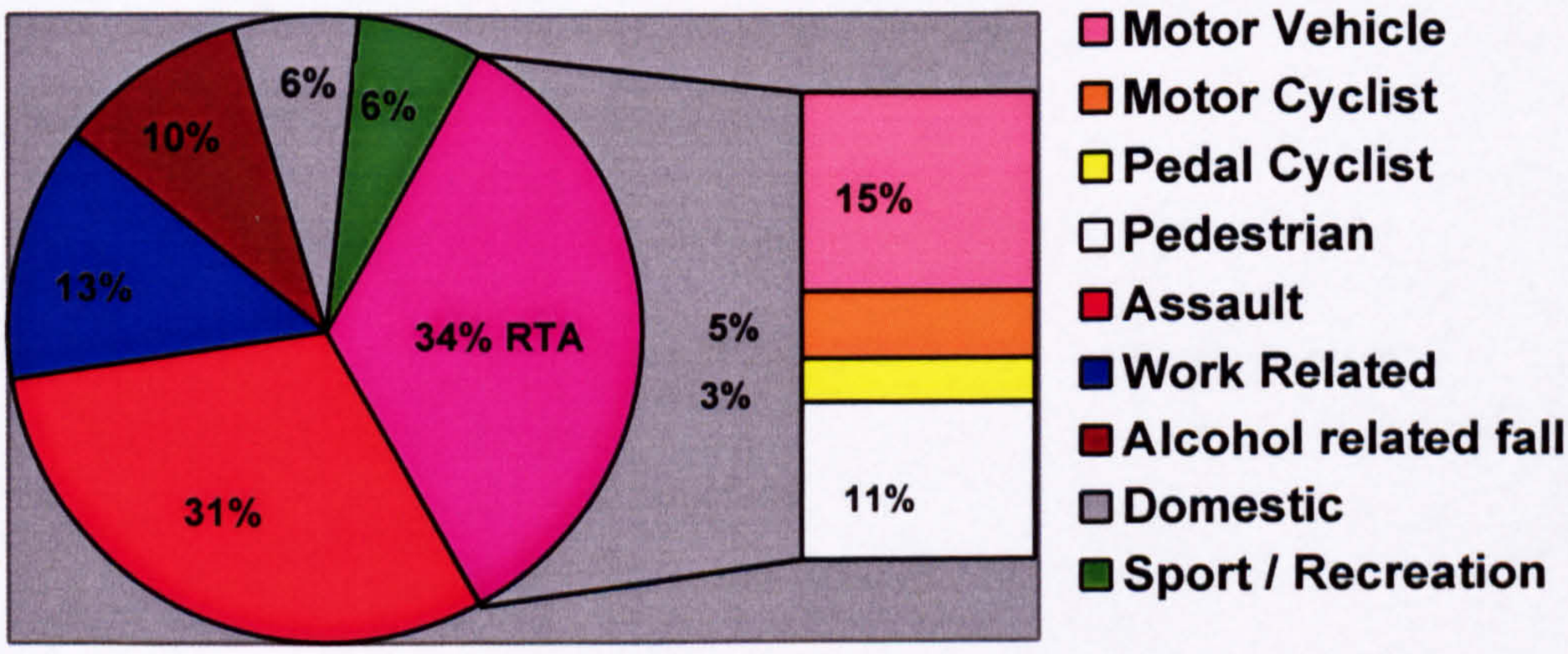
Table 6-1. Reasons for Non-Participation

Reason for Non-Participation	Number
Death since previous assessment	2
Serious Illness	2
Unable to contact current GP	10
Patient Declined to Participate	3
No reply from last known Patient address	15
Total Non-participants	32

Attempts were made to contact the remaining 80 patients by letter using the last known address from their GP where this was available. Three of these patients replied to indicate that they did not wish to participate in the study and a further 15 patients did not reply. In at least 5 of these 15 patients the last known contact details given by the GP were no longer valid and in several of the remaining cases no contact telephone number was available for the patient (Table 6-1).

The remaining 62 patients participated in the long-term neuropsychological assessment, with a mean duration from injury to assessment of 7.3 years (SD 0.8) and a range from 5.7 to 8.9 years. The mean age of participants at assessment was 37.4 years (SD 11.4, range 24-68), with a mean age at injury of 29.8 years (SD 10.9, range 17-60). The considerable majority (n=56) were male and the causes of their injuries are shown in Figure 6-1.

Figure 6-1: Cause of Injury in Participants



Clinical Indices of Injury Severity

Glasgow Coma scale was recorded for these patients at three stages, namely at arrival at first hospital, first admission to neurosurgery and the worst GCS score over the first 24 hour period as shown in Table 6-2. The first hospital was usually at a regional accident and emergency department before referral to the neurosurgical department at the Southern General. Some patients, particularly those with more severe injuries, were intubated and ventilated for transfer and thus no initial neurosurgery GCS score is available for these patients. Consequently initial neurosurgical GCS scores may under-represent the number of patients with severe injury. Worst 24 hour GCS includes a number of patients whose condition deteriorated as a secondary consequence of focal lesions.

Table 6-2. Injury Severity According to Glasgow Coma Scale

	Glasgow Coma Scale Severity Grouping (Number of Patients)			
	3-8 (severe)	9-12 (moderate)	13-14 (mild)	15 (minor)
Initial A&E	22 (35.4)	12 (19.4)	16 (25.8)	12 (19.4)
Initial Neurosurgery †	22 (41.5)	8 (15.1)	17 (32.1)	6 (11.3)
Worst during first 24 hours	36 (58.1)	11 (17.7)	14 (22.6)	1 (1.6)

† : Not available for 9 patients due to sedation, intubation & ventilation

(percentages for row in parentheses)

Table 6-4 on the next page details other clinical indices of injury severity or classification and the APOE genotypes of the patients. Different measures of injury severity are outlined, as whilst duration of loss of consciousness or initial GCS may indicate severity of initial diffuse injury, later GCS or PTA duration may be more indicative of focal injury severity. It can be seen from these various indices of injury severity that the majority of patients had suffered a moderate or severe head injury. For the purposes of some analyses clinical variables were collapsed to form the dichotomised clinical variables shown in Table 6-3.

Table 6-3: Dichotomised Clinical Variables

Variable	Group 1	Group 2	Variable	Group 1	Group 2
Post Traumatic Amnesia	Less than 1 week	Greater than 1 week	***TCDB Classification***	Diffuse	Focal
Significant haematoma	Absent	Present	***Significant ICH***	Absent	Present
Loss of Consciousness	None or less than 5 min	Greater than 5 min	***APOE ε4 allele***	Absent	Present
Coma at First Admission	Absent	Present	***Coma at any stage***	Absent	Present

TCBD: Traumatic Coma Data Bank; ICH: Intracerebral haematoma; APOE: Apolipoprotein E

Table 6-4. Other Clinical and Demographic Variables

APOE Genotype †	N	%	Estimated Duration of loss of Consciousness *	N	%
ε2 / ε3	9	14.8	None	10	16.4
ε3 / ε3	38	62.3	< 5min	13	21.3
ε3 / ε4	13	21.3	5 - 10 min	4	6.6
ε4 / ε4	1	1.6	10 - 60 min	8	13.1
			1 - 6 hours	7	11.5
ε4 allele present	14	23.0	6 - 24 hours	8	13.1
ε2 allele present	9	14.8	> 24 hours	10	16.4
TCDB Classification			**Coma**		
Diffuse I Normal CT	8	12.9	Coma > 24hrs	9	14.5
Diffuse II Abnormal CT	32	51.6	Coma 6-24 hrs	13	21.0
Diffuse III Swelling	1	1.6	Coma < 6hrs	9	14.5
Evacuated Mass	17	27.4	Never in coma	28	45.2
Non Evacuated Mass >25cc	4	6.5	Unknown Duration	3	4.8
Significant Haematoma			**Age Group at Injury**		
Any location	35	56.5	16 - 19	10	16.1
Subdural	6	9.7	20 - 29	26	41.9
Extradural	11	17.7	30 - 39	15	24.2
Intracerebral	27	43.5	40 - 49	7	11.3
			50+	4	6.5
Skull Fracture			**Duration of PTA**		
No Fracture	16	25.8	< 5 min	4	6.5
Vault	22	35.5	5 - 60 min	4	6.5
Base	11	17.7	1 - 24 hours	5	8.1
Both	11	17.7	1 - 7 days	24	38.7
Unknown	2	3.2	1 - 4 weeks	16	25.8
			over 4 weeks	9	14.5

Percentages given as proportion of all participating patients

APOE = Apolipoprotein E; TCBD = Traumatic Coma Data Bank; PTA = Post Traumatic Amnesia

†: No genotype obtained for one patient; * Duration of Loss of consciousness unknown for 2 patients

Reported Symptoms

Symptoms reported by patients in the semi-structured interview at 6-9 years post injury are presented in Table 6-5 in decreasing order of prevalence.

Table 6-5 Symptoms Reported by Patients in Interviews

	Patients at 6 months (N=49) †	Same Patients at 6-9 years †	All patients at 6-9 years (N=62)
Irritable	33 (67%)	39 (80%)	49 (79%)
Fatigue	33 (67%)	31 (63%)	41 (66%)
Memory Problems	29 (59%)	29 (59%)	39 (63%)
Difficulty finding words	29 (59%)	32 (65%)	38 (61%)
Depression	23 (47%)	31 (63%)	38 (61%)
Concentration Problems	30 (61%)	32 (65%)	37 (60%)
Anxiety	25 (51%)	27 (55%)	33 (53%)
Physical Problems	24 (49%)	19 (39%)	23 (37%)
Visual Problems	18 (37%)	13 (27%)	18 (29%)
Violence	11 (22%)	5 (10%)	5 (8%)

†: 49 patients were asked these questions at both assessments

Percentages given as proportion of patients who responded to individual questions

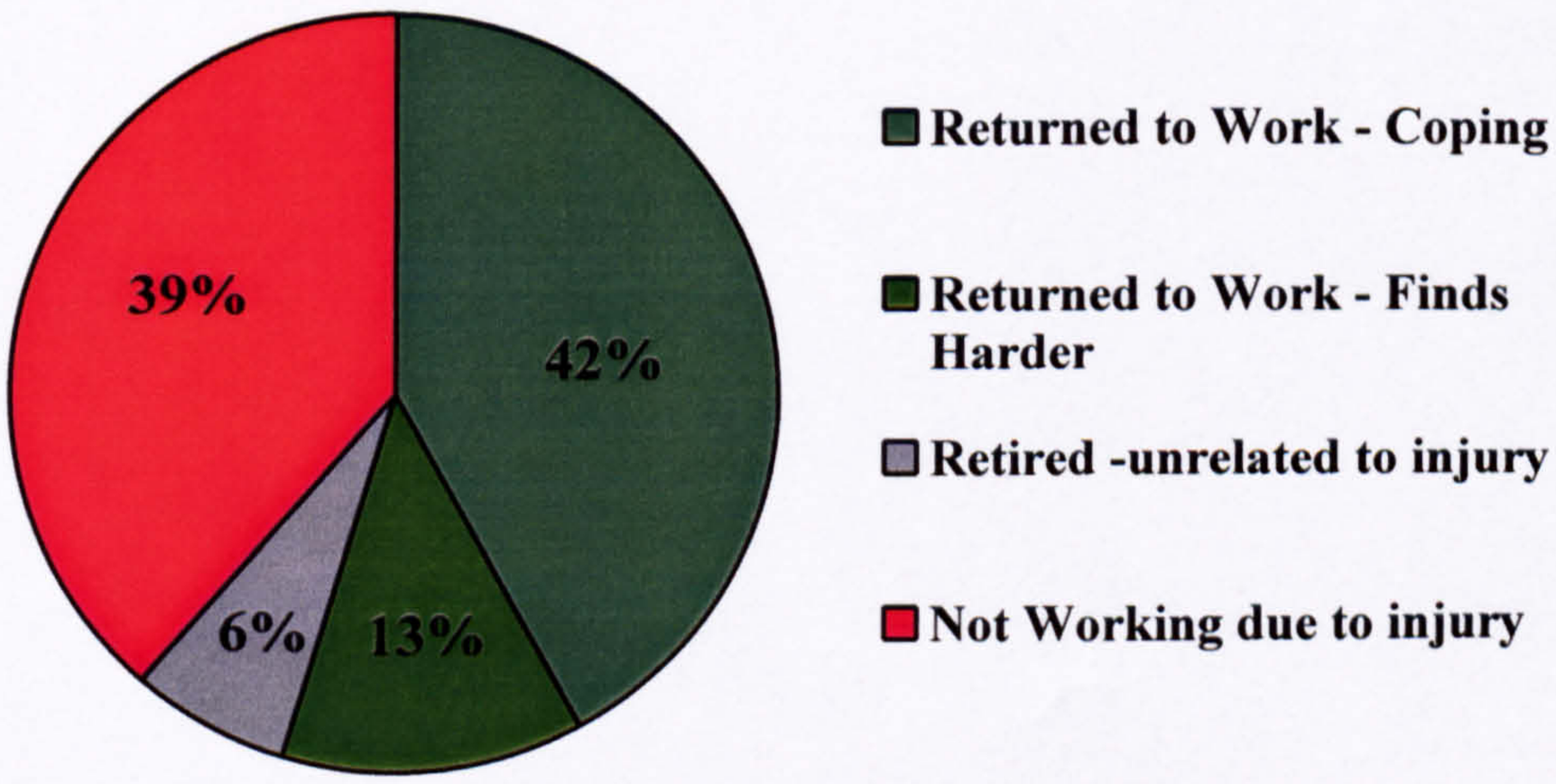
Forty-nine patients answered these questions as part of a semi-structured interview at *both* six month and 6 - 9 year assessments. A comparison of the reported symptoms for these 49 patients across both assessments found that most of the symptoms remained virtually unchanged over time. There were reductions in the number of patients reporting physical disabilities, such as weakness in arms or legs, and visual deficits. Despite this, there was a trend towards greater depression, with over 63% reporting feelings of depression at 6-9 years relative to fewer than 47% at six months. These differences were not statistically significant.

Return to Work

Data regarding return to work was available at *both* assessments for forty-four of the patients who had not retired for reasons unrelated to the injury. At the six month assessment, only 14 (32%) of these patients had returned to work, whereas by the time of the 6 - 9 year assessment this figure had risen to 22 (50%).

Return to work data for all 62 patients assessed at 6-9 years post injury is summarised in Figure 6-2. Only two had been unavailable for work due to retirement or disability at the time of the injury, though by the time of the 6 - 9 year assessment, a further two patients had retired for reasons unrelated to the injury. Thirty-four (55%) of patients had returned to work, of whom 19 had returned to the same employment and felt that they were coping as well as before, with a further 7 employed in new jobs which were at least as demanding as their pre-injury positions. Four patients had returned to the same employment but felt that they were still coping less well since the injury and a further four had taken less demanding jobs as a consequence of the injury. Only two of the 24 (39%) unemployed / medically retired patients felt that it was likely that they would return to work.

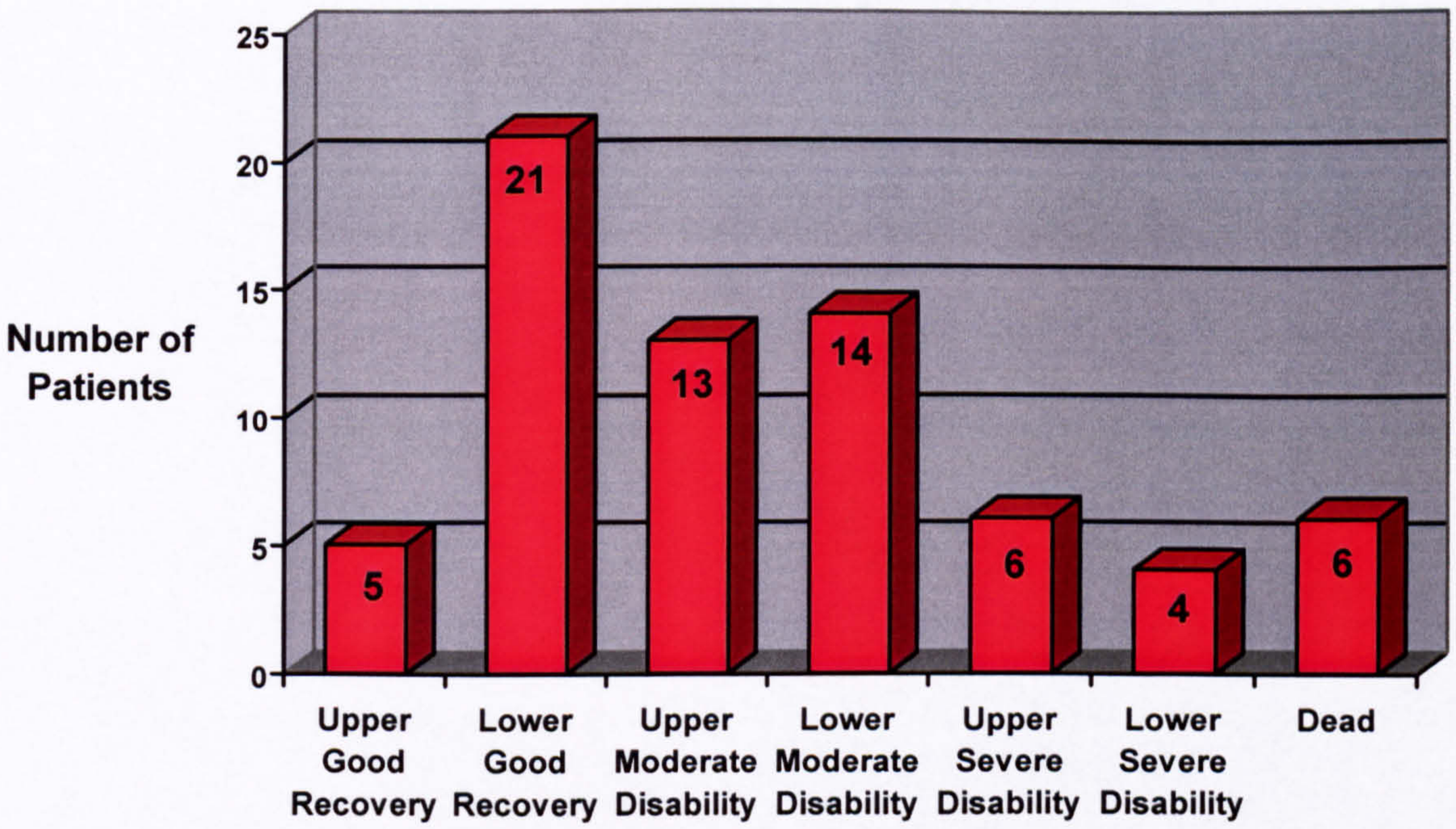
Figure 6-2: Employment Status at 6-9 Years Post Injury



Glasgow Outcome Scale

Glasgow Outcome Scale was obtained for 69 patients, including 6 patients who had died since their head injury and one patient who was deemed too ill to participate in the neuropsychological assessment. GOS outcome at 6-9 year follow-up using the extended structured interview 8-point scale is shown in Figure 6-3. No patient was in a vegetative state at the time of assessment and thus this grouping is not included.

Figure 6-3. Glasgow Outcome Scale at 6-9 Year Assessment



One tailed Spearman correlations revealed significant associations between 6-9 year GOS and indices of injury severity such as GCS and duration of PTA and coma as shown in Table 6-6 below. However, the strength of associations between these indices of injury severity and the 5-point GOS at 6-9 years were generally weaker than they had been amongst the same patients at 6 months.

Table 6-6: Indices of Injury Severity and Glasgow Outcome Scale

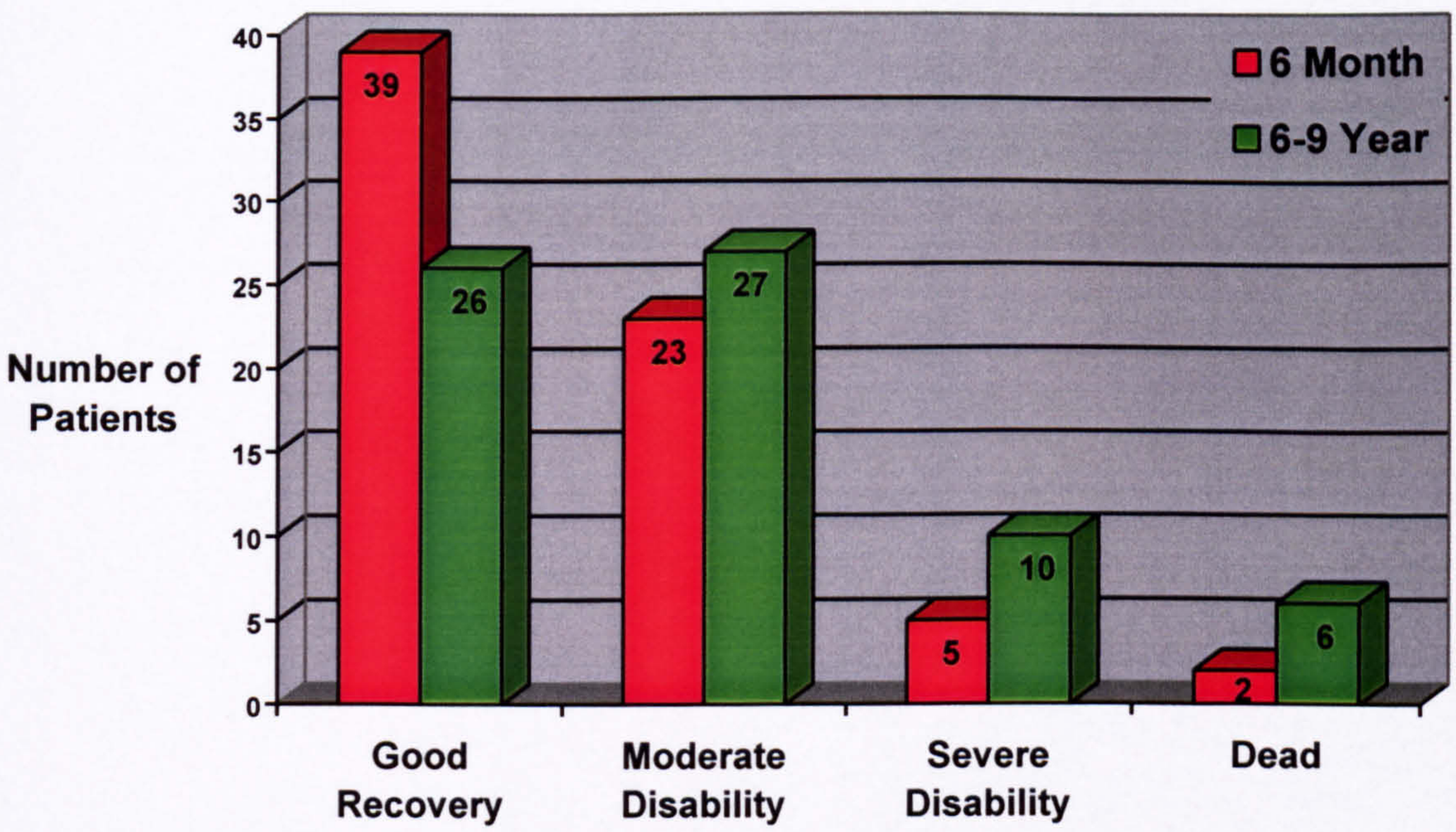
	N	6-9 year Extended 8 point GOS	6-9 year Collapsed 5-point GOS	6 Month 5- point GOS
GCS (A&E)	62	$r_s = .185$	$r_s = .216$ *	$r_s = .251$ *
GCS (NSU)	40	$r_s = .302$ *	$r_s = .366$ *	$r_s = .218$
GCS (24 hour worst)	44	$r_s = .245$	$r_s = .290$ *	$r_s = .436$ **
PTA duration (est days)	67	$r_s = .306$ **	$r_s = .254$ *	$r_s = .479$ **
PTA severity group	67	$r_s = .290$ **	$r_s = .262$ *	$r_s = .466$ **
Duration of LOC	54	$r_s = .160$	$r_s = .154$	$r_s = .202$ *
Coma Duration	65	$r_s = .295$ **	$r_s = .316$ **	$r_s = .377$ **

* $p < .05$, ** $p < .01$; (Spearman 1-tailed correlations)

Age at injury was significantly associated with both extended 8-point (rs = .371, p=.001) and collapsed 5 point scales (rs = .325, p = .003), reflecting a similar relationship in the same patients at the 6 month GOS assessment (rs = .282, p = .009). However, this relationship between age and outcome was considerably weaker if only survivors were considered (extended rs = .241, p=.029; collapsed rs = .179, p=.082). The 8-point GOS was dichotomised into a relatively favourable outcome group comprising the 39 patients above the median point and a less favourable outcome group comprising the 30 remaining patients. Chi-square analysis between these groups and the dichotomised clinical variables demonstrated that PTA of a week or more was significantly associated with a less favourable outcome ($\chi^2 = 4.70$, p = .030).

Patients who had been in a coma of any duration were also more likely to have a less favourable outcome ($\chi^2 = 3.66$, $p = .056$). These relationships were stronger if the two patients who had died from unknown cause since the earlier assessment were removed from consideration. Both of these patients had benign clinical indicators and had made a good recovery by 6 months suggesting that their deaths may have been unrelated to the head injury.

Figure 6-4. Change in Glasgow Outcome Scale



The extended 8-point scale was not available at the time of the original assessment and thus the extended scale has been collapsed to enable comparisons between 5-point GOS at 6 month and 6 - 9 year assessments.

As can be seen from Figure 6-4, the GOS measured outcome for these 69 patients was generally worse at 6-9 years than it had been at 6 months post injury, with this difference significant on Wilcoxon matched pairs testing ($W = 37.5$, $p < .001$). The number of patients with a 'good recovery' had fallen by a third over this time whilst the number of 'severe disability' patients had doubled. Overall, in terms of GOS, 23 patients deteriorated, 39 remained in the same classification and only four improved. Chi-square testing revealed no association between any of the dichotomised clinical variables and a deterioration vs no change / improvement grouping and there were no significant differences in age between these two groups.

The GOS groupings were significantly associated with the number of tasks in which patients scored less than 1 SD below the normative mean (Table 6-7). Over 77% of the severe disability patients were in the 'low score' range on at least 3 of the 10 cognitive tasks for which scores were considered in relation to normative data (Figure 6-5). In contrast, the vast majority of good recovery patients (84.6%) scored below the 1 SD point on only two or fewer tasks, which might be considered within normal limits. The mean number of 'low scores' for good recovery patients was 1.71, relative to 3.52 for moderate disability and 5.67 for severe disability patients.

Figure 6-5: Glasgow Outcome Scale and Cognitive 'Low Scores'

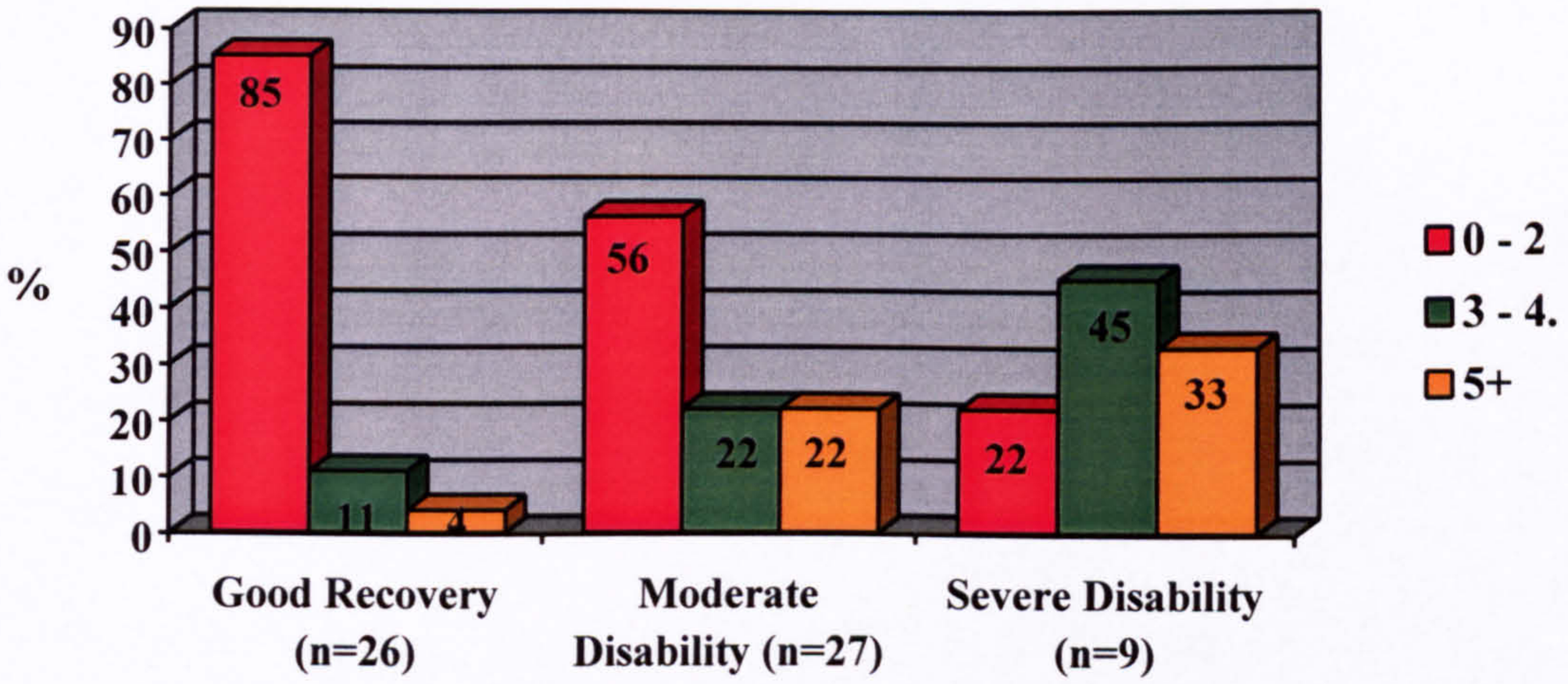


Table 6-7: Correlations Between GOS and Cognitive Low Scores

		6-9 Year Extended GOS	6-9 Year 5 point GOS	6 Month 5 point GOS
No of Tasks in Low	r	.434	.447	.520
Score Range	p	< .001	< .001	< .001

N = 62; Two-tailed Spearman correlations

Cognitive Outcome at 6-9 Years Post Injury

Premorbid Intelligence Measures

In the Subarachnoid Haemorrhage study it was observed that the NART measure of premorbid intelligence appeared to be affected by some indices of severity of injury, particularly the presence of haematoma, such that it appeared not to be validly indicating premorbid intelligence functioning in these patients. Analyses with the head injury study data also suggest that the NART is not resilient to cognitive changes following injury, with NART error scores significantly associated with admission GCS ($rs = -.327$, $p = .015$). NART error scores were also notably higher amongst patients who had a history of significant intracerebral haematoma (mean 27.42 (SD 10.84)) relative to those without (mean 23.32 (SD 7.92)).

Unfortunately information on social class, occupational status and years of education were not available for sufficient numbers of the head injury patients to use these as alternative pre-morbid indices. The CCRT had however been administered to all patients and there is evidence to suggest that this measure is more resilient to cognitive impairment than the NART. Correspondingly, although the CCRT also appeared to be affected by GCS and the presence of significant haematoma, these effects were less pronounced than with the NART, such that CCRT error score was used as the *best available* measure of premorbid intelligence. It was deemed preferable to accept some bias in terms of the CCRT being affected by cognitive impairment than to incur the considerable biases inherent in not utilising any measure of premorbid functioning.

Influence of Clinical Indices of Injury Severity upon Cognitive Outcome

Spearman correlations were performed between each of the Glasgow Coma Scale measures and the neuropsychological test scores at the 6 - 9 year follow-up assessment. As can be seen in Table 6-8, only the initial GCS assessment generally taken at regional accident and emergency departments consistently correlated with neuropsychological performance. The GCS grouping (severe, moderate, mild, minor) was at least as predictive of subsequent cognitive performance as the actual GCS scores.

Table 6-8. Acute Stage Glasgow Coma Scale and Cognitive Outcome

	A&E GCS Group		A&E GCS Scores		NSU GCS Group		24hr Worst GCS Group	
	r_s	p	r_s	p	r_s	p	r_s	p
Digit Span	.246 *	.028	.208	.054	.011	.469	.148	.127
Comprehension	.337 **	.004	.293 *	.012	.183	.102	.098	.231
Block Design	.193	.072	.161	.111	.076	.298	.006	.482
Digit Symbol	.236 *	.036	.215	.051	.038	.395	.026	.423
ILDS	.024	.427	-.007	.480	-.065	.325	-.202	.062
PASAT4	.319 **	.009	.303 *	.013	-.003	.491	.122	.190
PASAT2	.287 *	.022	.310 *	.014	.091	.284	.055	.352
GNT	.399 **	.001	.323 **	.006	.170	.117	.122	.177
Logical Memory T	.184	.078	.189	.072	.188	.091	.058	.328
Delayed LogMem T	.250 *	.026	.248 *	.027	.271 *	.026	.193	.068
Paired Associates	-.101	.224	-.130	.162	-.036	.402	-.102	.222
Delayed Associates	-.161	.111	-.168	.101	-.106	.232	-.163	.109
Verbal Fluency Animals	.114	.193	.103	.217	-.034	.406	-.006	.482
Verbal Fluency 'J'	.139	.145	.122	.176	.100	.242	.109	.203
Rey Copy	.137	.151	.109	.205	.035	.404	-.002	.495
Rey Immed Recall	.122	.179	.110	.203	-.041	.388	-.086	.259
Trailmaking A †	-.152	.123	-.175	.090	-.098	.248	-.136	.150
Trailmaking B †	-.278 *	.017	-.226 *	.044	-.174	.115	-.187	.080
Stroop Interference	.246 *	.041	.269 *	.028	.096	.271	.118	.205

† Denotes task in which higher score represents worse performance

* $p < .05$, ** $p < .01$; (Spearman 1-tailed correlations)

Spearman correlations were also performed between neuropsychological task scores and the three 'duration' indices of severity, namely coma duration, PTA duration and duration of loss of consciousness (Table 6-9). Virtually all of the correlations are in the anticipated direction, with longer duration associated with lower cognitive task scores. However, these one-tailed correlations were not significant for duration of loss of consciousness and were only significant at the .05 level for coma and PTA duration in 5 of the 19 neuropsychological measures taken. There were no significant associations between any of these duration indices and the number of tasks in the low score range.

Table 6-9: Duration Severity Indices with Cognitive Outcome

	Duration of Coma	p	Duration of PTA	p	Duration of LOC	p
Digit Span	-.090	.252	-.048	.357	-.137	.175
Comprehension	-.226 *	.047	-.063	.317	-.152	.153
Block Design	-.026	.424	-.052	.347	-.129	.194
Digit Symbol	-.228 *	.045	-.220 *	.047	-.210	.079
ILDS	.060	.331	.010	.470	-.017	.455
PASAT4	-.161	.129	-.135	.165	-.130	.205
PASAT2	-.041	.391	-.021	.443	-.103	.267
GNT	-.271 *	.021	-.022	.434	-.125	.198
Logical Memory T	-.267 *	.021	-.313 **	.007	-.199	.086
Delayed LogMem T	-.355 **	.003	-.360 **	.002	-.239 *	.049
Paired Associates	.024	.430	-.061	.322	.140	.173
Delayed Associates	.077	.287	-.093	.242	.059	.346
Verbal Fluency Animals	-.161	.116	-.142	.139	-.072	.313
Verbal Fluency 'J'	-.128	.170	-.059	.326	.030	.420
Rey Copy	-.019	.445	.000	.499	-.089	.277
Rey Immed Recall	.047	.366	-.062	.319	-.091	.272
Trailmaking A †	.205	.063	.366 **	.002	.153	.150
Trailmaking B †	.204	.068	.309 **	.009	.198	.094
Stroop Interference	-.024	.436	-.101	.241	-.135	.200

† Denotes task in which higher score represents worse performance
* $p < .05$, ** $p < .01$ (Spearman 1-tailed correlations)

Dichotomised Clinical Variables & 6-9 Year Neuropsychological Assessment

Univariate analyses of variance were conducted between the dichotomised clinical variables (Table 6-4) and the 19 core neuropsychological measures, using age at assessment and CCRT errors as covariates. There were no significant effects of loss of consciousness (comparison 5 min or less vs 5min+), presence of significant haematoma (present or absent), or of APOE ε4 (present or absent) on any of these measures. Diffuse injury was associated with worse performance when copying the Rey Figure, with a mean score for diffuse injuries of 29.19 (SD 3.48) vs 31.50 (SD 2.46) for focal injuries ($F(1,50) = 6.59$, $p = .013$). However this may be a chance finding given the overall number of comparisons. Patients with PTA of greater than one week scored significantly worse on both the immediate (means 11.72 (SD 3.68) vs 13.90 (SD 3.02)) ($F(1,52) = 4.30$, $p = .043$) and delayed (means 10.03 (SD 3.58) vs 12.36 (SD 3.40)) ($F(1,52) = 5.08$, $p = .029$) presentations of the logical memory task, reflecting differences observed in the non-parametric correlations.

Coma & Neuropsychological Performance

The occurrence of coma was only significantly associated with lower performance on the logical memory and trail-making tasks. However mean performances scores were worse for those patients who had suffered coma in nearly all tasks despite the younger age of the coma patients (Table 6-10). Thus it seems that the differences may reflect genuinely worse performance amongst those who had suffered coma, though the possibility of chance findings remains due to the number of comparisons.

Table 6-10. Occurrence of Coma & Cognitive Performance

	Coma		Never in Coma			
	Mean	SD	Mean	SD	F	p
Digit Span	11.37	2.24	11.88	2.39	(1,48) 0.05	.832
Comprehension	16.78	4.37	18.71	3.61	(1,47) 0.18	.674
Block Design	34.31	9.27	36.20	8.51	(1,47) 0.03	.856
Digit Symbol	43.11	14.75	50.64	15.04	(1,48) 1.12	.296
ILDS	5.56	2.33	5.48	2.04	(1,48) 0.30	.589
PASAT4	48.20	12.45	52.21	10.06	(1,45) 0.25	.620
PASAT2	32.05	11.37	35.22	15.35	(1,41) 0.13	.726
GNT	18.30	4.54	20.04	4.22	(1,48) 0.01	.965
Logical Memory T	11.34	3.44	13.64	2.92	(1,49) 4.22	.045 *
Delayed LogMem T	9.52	2.99	12.36	3.91	(1,49) 7.82	.007 **
Paired Associates	14.48	2.79	14.10	4.18	(1,47) 0.75	.392
Delayed Associates	8.39	1.62	8.16	2.17	(1,47) 1.42	.239
Verbal Fluency Animals	18.64	5.96	19.84	5.68	(1,49) 0.01	.947
Verbal Fluency J	5.50	2.69	5.92	2.69	(1,49) 0.01	.925
Rey Copy	30.02	3.80	30.02	3.05	(1,47) 0.43	.513
Rey Immed Recall	19.81	7.39	18.08	8.31	(1,47) 3.24	.078
Trailmaking A †	50.59	26.90	37.52	10.39	(1,48) 3.86	.055
Trailmaking B †	106.60	57.47	76.84	31.33	(1,46) 5.24	.027 *
Stroop Interference	-0.52	7.38	1.05	7.96	(1,43) 0.55	.463

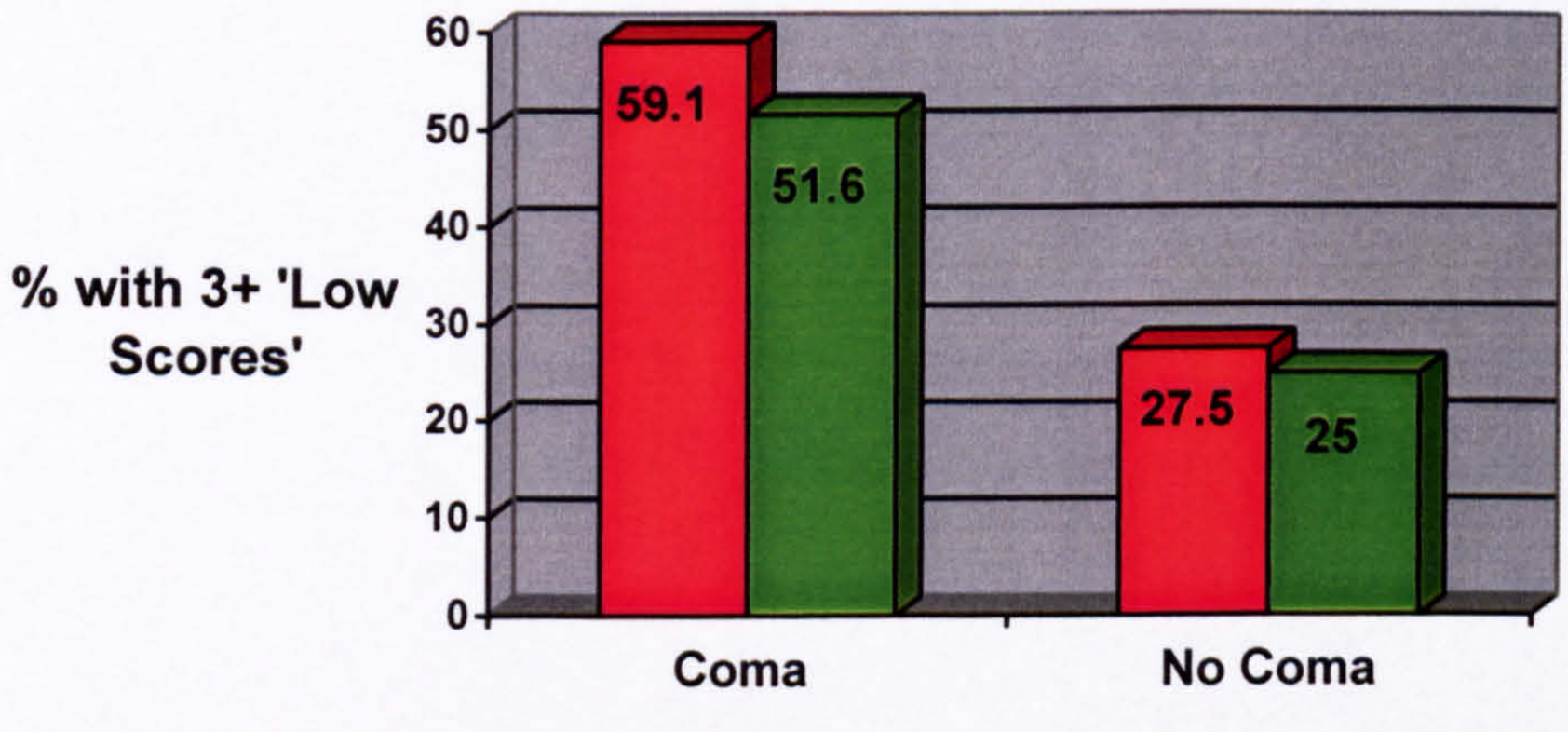
† Denotes task in which higher score represents worse performance

* $p < .05$, ** $p < .01$

The influence of GCS grades and coma upon subsequent cognitive performance may be more accurately gauged by consideration of the number of tasks in which individuals scored in the 'low score' range, as diffuse injuries typical of coma patients are less likely to uniformly affect individual tasks which are sensitive to particular focal deficits.

Those patients who suffered coma were over twice as likely to have scored in the 'low score' range on 3 or more tasks than those who were never in coma (52% vs 25%; $\chi^2 = 4.38$, $p = .036$). As shown in Figure 6-6, this association between coma and cognitive performance in the 'low score' range is stronger if only those who were in coma from first admission are considered (59% vs 27%) ($\chi^2 = 5.97$, $p = .015$). These patients are more likely to have DAI induced coma, whereas the other patients may have deteriorated into coma due to secondary damage following primary focal injuries. The mean number of 'low scores' for those in coma from first admission was 3.68 (sd 2.40), relative to 3.16 (sd 2.40) for those in coma at any stage and 1.89 (sd 1.59) for those never in coma.

Figure 6-6: Coma and Cognitive 'Low Scores'



These associations between coma and cognitive low scores are also reflected in significant Spearman correlations between the number of cognitive 'low scores' and Glasgow Coma Scale (Table 6-11).

Table 6-11. Spearman Correlations Between GCS and Cognitive 'Low Scores'

		Initial (A&E) GCS	Neurosurgical admission GCS†	Worst 24 hr GCS †
No of Tasks in the	r	-.416	-.363	-.487
Low Score Range	Sig (2-tailed)	< .001	.021	< .001
	N	62	40	44

† GCS unavailable for some patients due to intubation, ventilation and / or sedation

Cognitive Changes from 6 Months to 6-9 Years

Paired t-tests were calculated for each of the ten repeated neuropsychological measures. The only task to improve significantly across all patients over time was the PASAT, whereas mean performance scores had deteriorated slightly over time for 7 of the measures as can be seen in Table 6-12.

Table 6-12. Repeated Neuropsychological Tasks

	Mean 6 Months	Mean 6 - 9 Years	t	p (2 - tailed)
Comprehension	18.1 (4.7)	17.9 (4.0)	0.490	.626
Digit Span	11.6 (2.5)	11.5 (2.3)	0.281	.780
Block Design	35.8 (7.9)	34.9 (8.8)	1.301	.198
Digit Symbol	48.0 (13.3)	47.1 (15.3)	0.937	.353
PASAT (4 sec)	47.8 (11.7)	51.0 (9.5)	-2.592	.012 *
PASAT (2 sec)	30.4 (12.1)	33.7 (13.4)	-2.668	.010 **
Paired Associates	14.2 (3.7)	14.3 (3.6)	-0.177	.860
Logical Memory	13.1 (3.2)	12.6 (3.6)	1.292	.201
Verbal Fluency Animals	20.1 (4.8)	19.4 (5.8)	1.208	.232
Verbal Fluency J	6.4 (3.1)	5.9 (2.7)	1.014	.315

(Standard deviation in parentheses) * $p < .05$; ** $p < .01$

Age and Cognitive Deterioration

Difference scores (DS) were calculated for each of the repeated neuropsychological measures by subtracting the 6-month assessment score from that obtained at the 6 - 9 year assessment. As shown in Table 6-13, several of these difference scores were significantly correlated with both age at injury and age at assessments, with increasing age associated with either less improvement or greater deterioration in cognitive performance. There were no associations between these difference scores and either of the premorbid measures (NART or CCRT).

Table 6-13. Age and Neuropsychological Task Difference Scores

	N		Age at Injury	Age at 6 month assessment	Age at 6 - 9 Year Assessment
Digit Symbol DS	57	r	-.386	-.392	-.384
		p	.003	.003	.003
Associate Learning DS	59	r	-.254	-.259	-.270
		p	.052	.048	.039
PASAT	53	r	-.303	-.309	-.302
4 second DS		p	.027	.024	.028
PASAT	49	r	-.256	-.281	-.263
2 second DS		p	.075	.050	.068
Verbal Fluency	59	r	-.317	-.299	-.324
Animal DS		p	.014	.021	.012
Verbal Fluency	59	r	-269	-.271	-.277
'J' DS		p	.040	.038	.033

Pearson 2-tailed correlations; DS: Difference Score

These differences in change over time were particularly apparent in those patients over the age of 35 at the time of the injury (mean 47.1 years; sd 7.7). As is shown in Table 6-14, there was a tendency for these patients to have deteriorated over time whilst those under the age of 35 at injury (mean 25.2 years; sd 5.7) either stayed the same or made moderate improvements in cognitive function.

Table 6-14. Deterioration in those Aged 35+ at Injury

	Age at Injury	6 Month Assessment		6 - 9 Year Assessment			
		Mean	SE	Mean	SE	F	p
Digit Symbol	35+	44.62	3.7	38.69	4.1	(1,55) 8.94	.004
	<35	49.05	2.0	49.61	2.2		
Block Design	35+	35.23	2.2	32.15	2.4	(1,57) 3.25	.076
	<35	35.94	1.17	35.70	1.29		
Paired Associates	35+	14.65	1.04	12.54	0.96	(1,57) 5.32	.025
	<35	14.08	0.56	14.79	0.51		
PASAT4	35+	53.33	3.83	49.56	3.20	(1,51) 7.26	.010
	<35	46.64	1.73	51.30	1.45		
Verbal Fluency	35+	20.46	1.34	16.92	1.57	(1,57) 5.57	.022
Animals	<35	20.04	0.71	20.04	0.84		

Clinical Indices of Injury Severity & Cognitive Change

Spearman correlations between the duration indices of severity and neuropsychological task difference scores were only significant for the PASAT and Digit Symbol tasks (Table 6-15), with greater duration associated with greater improvement on these tasks. This relationship was strongest for duration of coma, followed by duration of loss of consciousness and relatively weak associations with PTA duration. The associations between coma and cognitive improvement on these tasks are also reflected by significant correlations with GCS scores (Table 6-16). Again greater severity of injury is associated with greater improvement between assessments.

Table 6-15. Difference Scores and Durations based Severity Indices

	Duration of Coma	Duration of Loss of Consciousness	Duration of PTA (groupings)
Digit Symbol DS	r_s = .387 (54) **	r_s = .346 (46)**	r_s = -.086 (57)
PASAT 4 second DS	r_s = .331 (50) **	r_s = .463 (41) **	r_s = .111 (53)
PASAT 2 second DS	r_s = .515 (46) ***	r_s = .401 (39) **	r_s = .254 (49) *
PASAT Total DS	r_s = .548 (46) ***	r_s = .542 (39) ***	r_s = .307 (49) *

Table 6-16. Difference Scores correlated with Glasgow Coma Scale Scores

	GCS (A&E)	GCS (NSU)	GCS (worst 24hr)
Digit Symbol DS	r_s = -.276 (57) *	r_s = -.163 (37)	r_s = -.304 (41) *
PASAT 4 second DS	r_s = -.384 (53) **	r_s = -.293 (33) *	r_s = -.450 (36) **
PASAT 2 second DS	r_s = -.304 (49) *	r_s = -.347 (30) *	r_s = -.468 (33) **
PASAT Total DS	r_s = -.376 (49) **	r_s = -.386 (30) *	r_s = -.550 (33) ***

* $p < .05$; ** $p < .01$; *** $p < .001$ (One-tailed Spearman correlations)

N in parentheses; DS = Difference Score (6-9 year score minus 6 month score)

As patient age appears to have significantly influenced change in cognitive status between the two assessments, age at injury was entered into subsequent repeated measures ANOVAS as a co-variate. Each of the dichotomised clinical variables were then entered into these repeated measures ANOVAs to determine any influence of these variables upon cognitive change between assessments. These analyses found no significant effects of PTA (greater vs less than one week) or APOE ε4 allele (present vs absent) or TCDB classification (diffuse vs focal).

Although patients who had been in coma continued to have lower scores on information processing tasks, these coma patients were consistently more likely to have improved on these tasks relative to the six month assessment, whereas other patients either remained unchanged or had deteriorated slightly (Table 6-17).

Table 6-17. Improved Information Processing in Patients who suffered Coma

	Coma	6 Month Assessment		6 - 9 Year Assessment			
		Mean	SE	Mean	SE	F	p
Digit Symbol	Y	41.4	2.3	42.8	2.7	(1,51) 6.03	.018
	N	53.4	2.3	50.4	2.7		
PASAT4	Y	44.1	2.2	50.0	1.9	(1,47) 4.40	.041
	N	51.7	2.2	52.5	1.9		
PASAT2	Y	25.8	2.3	31.9	2.9	(1,43) 6.31	.016
	N	35.0	2.2	35.2	2.8		
PASAT Total	Y	70.1	3.9	83.4	4.2	(1,43) 15.93	>.001
	N	87.5	3.7	88.0	4.1		

Y = Coma; N = Never in coma

Those with a history of immediate loss of consciousness were more likely to have improved on the PASAT tasks at both 4 second ($F(1,49) = 3.24$, $p = .078$) and 2 second presentations ($F(1,45) = 7.23$, $p = .010$) giving a highly significant improvement in overall PASAT scores ($F(1,45) = 10.29$, $p = .002$). These findings remained when the comparison was between those with immediate loss of consciousness lasting longer than 5 minutes and those with either no loss of consciousness or of duration less than 5 minutes (PASAT4 ($F(1,47) = 6.39$, $p = .015$), PASAT2 ($F(1,43) = 6.35$ $p = .016$), PASAT total ($F(1,43) = 11.09$, $p = .002$)). The PASAT2 and PASAT total findings remained significant even when occurrence of coma was added as a covariate, indicating that the findings in relation to immediate loss of consciousness were not simply an artefact of the inclusion of patients with coma.

Patients whose head injury resulted in a significant haematoma were significantly more likely to improve on the PASAT2 task, with mean scores rising from 28.24 (sd 2.42) to 34.76 (sd 2.83), whilst those without significant haematoma remained virtually unchanged with mean scores of 32.37 (sd 2.28) and 32.75 (sd 2.67) respectively ($F(1,46) = 7.55$, $p = .009$). There were no other significant changes related to the presence of haematoma.

Apolipoprotein E Overview

Apolipoprotein E genotypes were available for 61 of the 62 patients who participated in the follow-up assessments at 6-9 years. A buccal smear could not be obtained for the remaining patient. Of these 61 patients, 14 (23%) had an ε4 allele as outlined in Table 6-3. There were no significant differences between patients with or without the ε4 allele in terms of age at injury (ε4 27.1 years (sd 7.7) vs non-ε4 30.8 years (sd 11.6); t = 1.4, p = .171) or PTA duration (ε4 9.3 days (sd 17.3) vs non-ε4 13.5 days (sd 18.9); t = 0.79, p = .454).

There were also no significant differences in terms of first admission GCS, neurosurgical admission GCS, worst 24 hour GCS, duration of coma or loss of consciousness. Mean A&E GCS for *both* groups was 10.8, despite the apparently slightly higher GCS scores amongst ε4 patients shown in Table 6-18, reflecting a trend towards a polarisation of consciousness based severity scores amongst the ε4 patients relative to non-ε4 patients. Thus, whilst at the upper extreme of the GCS (mild and minor injuries) ε4 patients were more likely than non-e4 patients to have a higher GCS, conversely at the lower end of the spectrum, severe injury ε4 patients were more likely to have a lower GCS as shown in Tables 6-18 and 6-19.

Table 6-18: Relationship between Admission GCS and the ε4 allele

GCS A&E	N	3-8	9 - 12	13 - 14	15
ε4	14	36%	14%	21%	29%
Non-ε4	47	34%	21%	28%	17%

Table 6-19: Lower GCS Scores amongst Severe Injury ε4 patients

GCS Score	3	4	5	6	7	8
ε4 (n=5)	20%	0%	20%	20%	20%	20%
Non-ε4 (n=16)	6%	13%	13%	13%	31%	25%

There were no differences according to APOE genotype in terms of the presence of a significant haematoma in any location (ε4 57%, non-ε4 55%) or a significant intracerebral haematoma (ε4 43%, non-ε4 43%). There were essentially no significant or notable influences of the Apolipoprotein E ε4 allele upon any of the physical, cognitive and emotional outcome measures employed. In fact, there was a tendency for ε4 patients to have slightly higher mean cognitive scores (Table 6-20), though this may reflect their slightly younger age. The analyses were controlled for age and the negative findings remained essentially unchanged if analyses were also controlled for the slight differences in PTA duration. The APOE ε4 patients were no better or worse than non-ε4 patients at 6-9 year assessment and were no more likely to have improved or deteriorated between assessments.

Table 6-20: Apolipoprotein E and Cognitive Performance

	ε4 present		No ε4 allele			
	Mean	SD	Mean	SD	F	p
Digit Span	12.23	2.74	11.43	2.17	(1,51) 0.56	.456
Comprehension	18.38	4.21	17.37	4.02	(1,50) 0.74	.395
Block Design	36.46	9.70	34.39	8.48	(1,50) 0.02	.899
Digit Symbol	53.62	18.29	45.31	13.60	(1,51) 1.64	.206
ILDS	5.46	2.26	5.67	2.17	(1,51) 0.61	.438
PASAT4	54.75	3.64	48.58	12.57	(1,48) 1.49	.229
PASAT2	36.25	12.56	32.92	13.93	(1,44) 0.30	.587
GNT	19.00	4.76	19.26	4.29	(1,51) 0.46	.500
Logical Memory T	12.81	1.84	12.71	3.93	(1,52) 0.20	.659
Delayed LogMem T	11.54	2.73	11.05	3.94	(1,52) 0.01	.941
Paired Associates	15.50	3.84	14.01	3.35	(1,50) 0.68	.413
Delayed Associates	9.25	1.42	8.24	1.96	(1,50) 1.91	.173
Verbal Fluency Animals	20.85	5.60	18.74	5.84	(1,52) 0.51	.478
Verbal Fluency J	5.38	1.71	5.88	2.90	(1,52) 1.32	.257
Rey Copy	31.33	2.27	29.57	3.51	(1,50) 1.61	.211
Rey Immed Recall	20.29	7.13	18.54	7.86	(1,50) 0.01	.937
Trailmaking A †	39.46	15.18	45.21	22.50	(1,51) 0.33	.567
Trailmaking B †	71.67	19.75	96.63	51.74	(1,49) 1.42	.240
Stroop Interference	2.67	7.26	-0.73	7.93	(1,46) 1.76	.192

† Denotes task in which higher score represents worse performance

No statistically significant differences

Short Form 36 Health Survey

Calculated scores for each of the eight domains of the SF-36 were compared with age matched normative data. Wilcoxon matched pairs tests demonstrated that patient scores were significantly lower for each of the domains with the exception of the energy / vitality domain (Table 6-21). These differences can be seen in Figure 6-7, which illustrates the differences between mean patient scores and aged matched normative data.

Table 6-21. Mean SF-36 Domain Scores Relative to Age-Matched Normative Data

	Patient Mean	Norm Mean	W	p
Physical Function	72.16	90.18	174	.007
Role Limitation (physical)	56.75	86.66	138	<.001
Role Limitation (emotional)	59.45	83.32	179	.009
Social Functioning	63.96	88.42	148	.002
Mental Health	57.19	73.74	89	<.001
Energy / Vitality	54.32	60.97	251	.129
Pain	66.67	82.55	171	.011
General Health Perception	62.73	74.90	183	.011

Wilcoxon non-parametric matched pairs tests

Clinical Indices of Injury Severity and Short Form-36 Health Domain Scores

Spearman correlations revealed consistently significant associations between PTA duration and virtually all domains measured by the SF-36 as shown in Table 6-22. Duration of loss of consciousness or of coma were associated with fewer SF-36 domain scores. For all of the duration measures the strongest correlations were with the Energy / Vitality and General Health Perception domains.

Table 6-22. SF-36 and Duration of PTA, Loss of Consciousness & Coma

	Duration of PTA (estimated days)	Duration of PTA (groupings)	Duration of Loss of Consciousness	Duration of Coma
Physical Function	r_s = -.387 **	r_s = -.381 **	r_s = -.202	r_s = -.338 (34) *
Role Limitation (physical)	r_s = -.344 *	r_s = -.365 *	r_s = -.041	r_s = -.165 (34)
Role Limitation (emotional)	r_s = -.225	r_s = -.269	r_s = -.024	r_s = -.181 (34)
Social Functioning	r_s = -.290 *	r_s = -.312 *	r_s = -.130	r_s = -.222 (34)
Mental Health	r_s = -.263	r_s = -.310 *	r_s = -.314 *	r_s = -.270 (34)
Energy / Vitality	r_s = -.410 **	r_s = -.435 **	r_s = -.394 *	r_s = -.396 (34) **
Pain	r_s = -.312 *	r_s = -.229	r_s = -.096	r_s = -.037 (33)
General Health Perception	r_s = -.641 ***	r_s = -.565 ***	r_s = -.423 **	r_s = -.566 (34) ***

N = 37 for all domains except for pain where N = 36 and for Duration of coma where N is in parentheses

* $p < .05$; ** $p < .01$ (One-tailed Spearman correlations)

Glasgow Coma Scale scores were in contrast considerably less predictive of SF-36 domain scores, with only General Health Perception consistently associated with GCS (Table 6-23). General Health Perception was the only domain to remain significantly correlated at the .05 level if GCS groupings were used in place of actual GCS scores. Worst 24 hr GCS was more frequently associated with SF-36 domain scores, particularly in those domains related to physical disability, than either A&E GCS or neurosurgical admission GCS.

Patients who suffered coma at any stage tended to have lower domain scores as shown in Figure 6-8, with these differences reaching statistical significance for physical function ($\mu = 91.0$, $p = .064$) and general health perception ($\mu = 65.5$, $p = .007$). These differences were less pronounced if only those in coma at first admission were considered. There were no significant influences of ε4 allele, presence of haematoma or TCDB classification upon SF-36 domain scores.

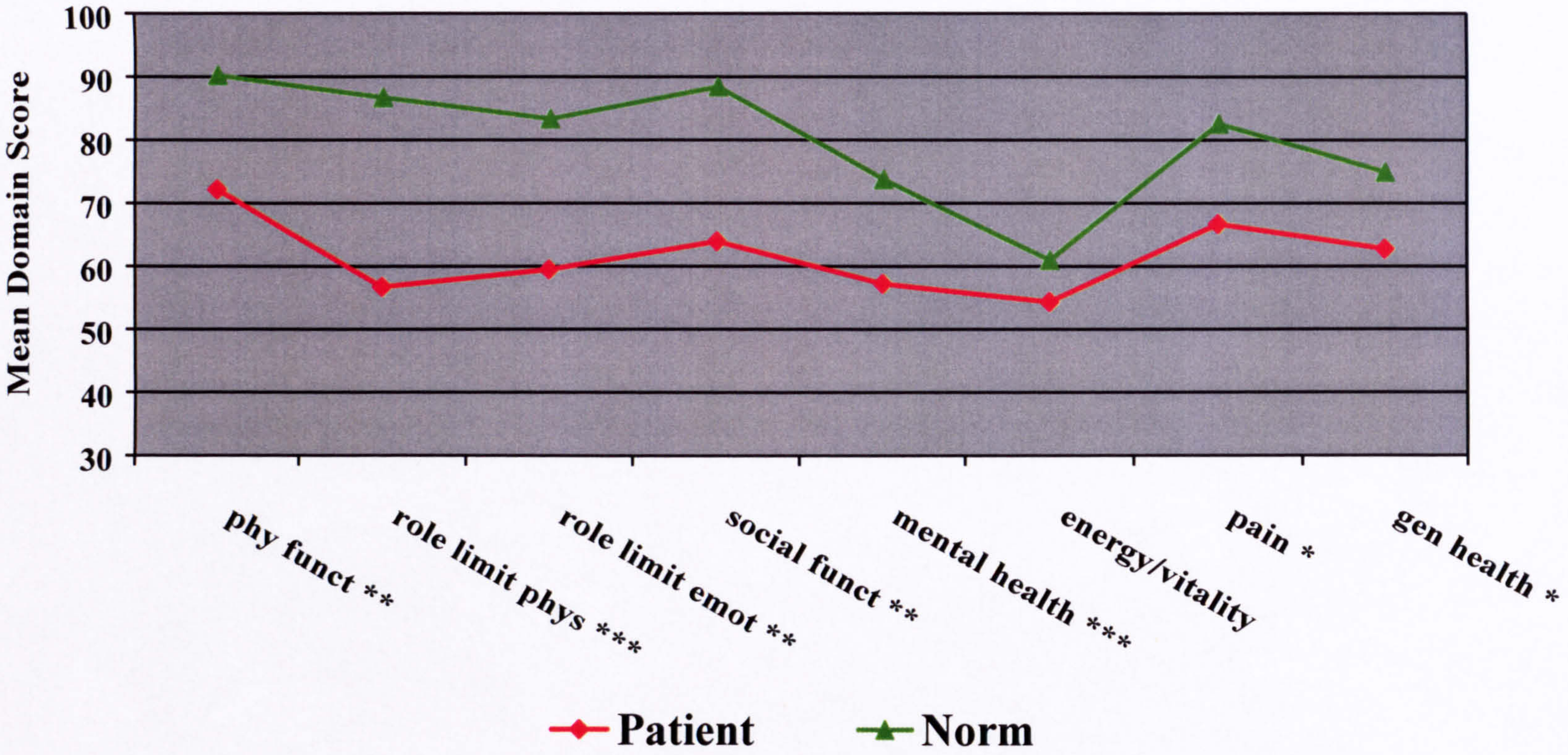
Table 6-23. SF-36 Domain Scores correlated with Glasgow Coma Scale Scores

	GCS (A&E)	GCS (NSU)	GCS (worst 24hr)
Physical Function	$r_s = .094$ (37)	$r_s = .195$ (25)	$r_s = .396$ (26) *
Role Limitation (physical)	$r_s = .053$ (37)	$r_s = .281$ (25)	$r_s = .328$ (26) *
Role Limitation (emotional)	$r_s = .179$ (37)	$r_s = .349$ (25) *	$r_s = .262$ (26)
Social Functioning	$r_s = .177$ (37)	$r_s = .336$ (25) *	$r_s = .283$ (26)
Mental Health	$r_s = .270$ (37)	$r_s = .196$ (25)	$r_s = .221$ (26)
Energy / Vitality	$r_s = .043$ (37)	$r_s = .259$ (25)	$r_s = .337$ (26) *
Pain	$r_s = -.185$ (36)	$r_s = .147$ (24)	$r_s = .002$ (25)
General Health Perception	$r_s = .282$ (37) *	$r_s = .439$ (25) *	$r_s = .501$ (26) **

Number of patients involved in each correlation in parentheses

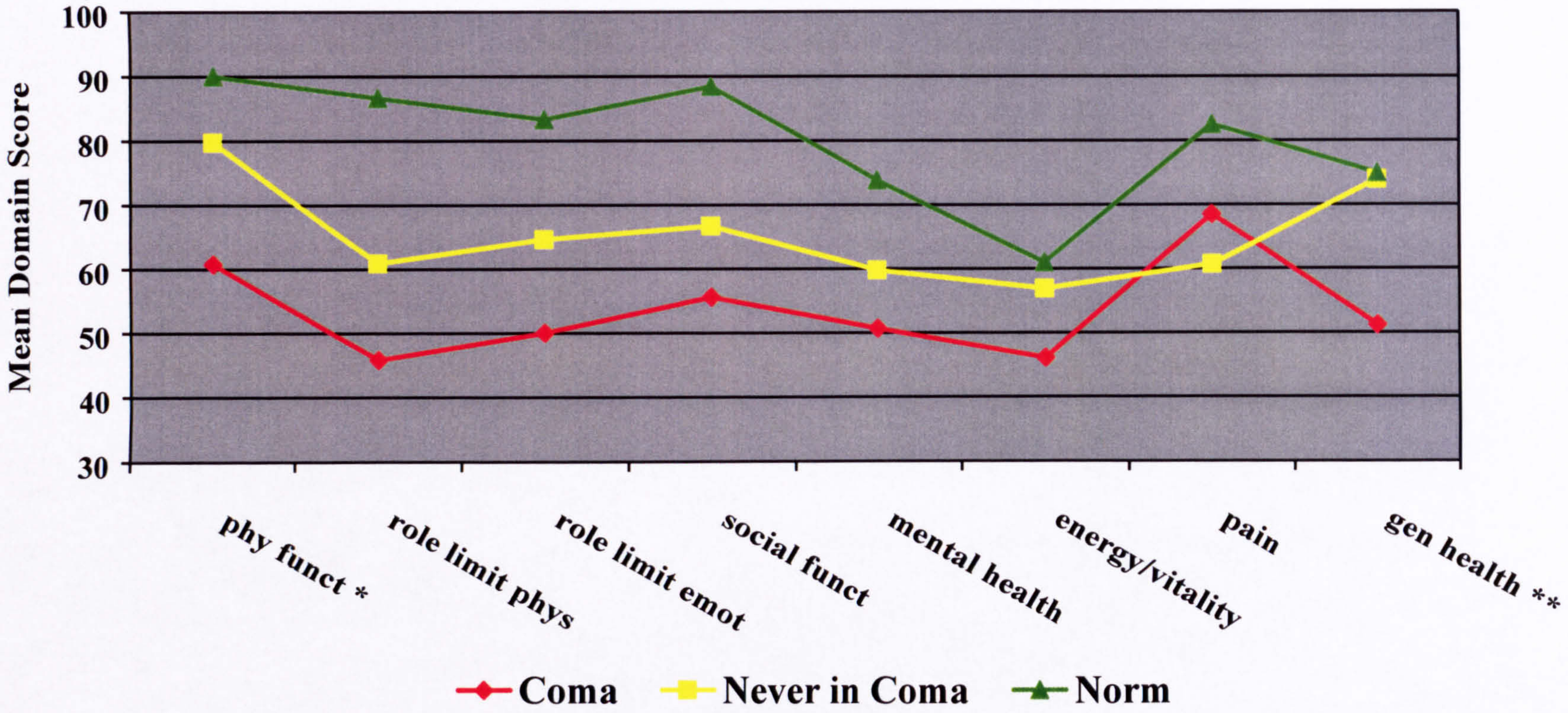
*$p < .05$; ** $p < .01$ (One-tailed Spearman correlations)

Figure 6-7. SF-36 Domain Scores relative to Age-Matched Normative Data



* p < .05; **p < .01, *** p < .001 (Wilcoxan matched pairs tests)

Figure 6-8. Influence of Coma upon SF-36 Domain Scores



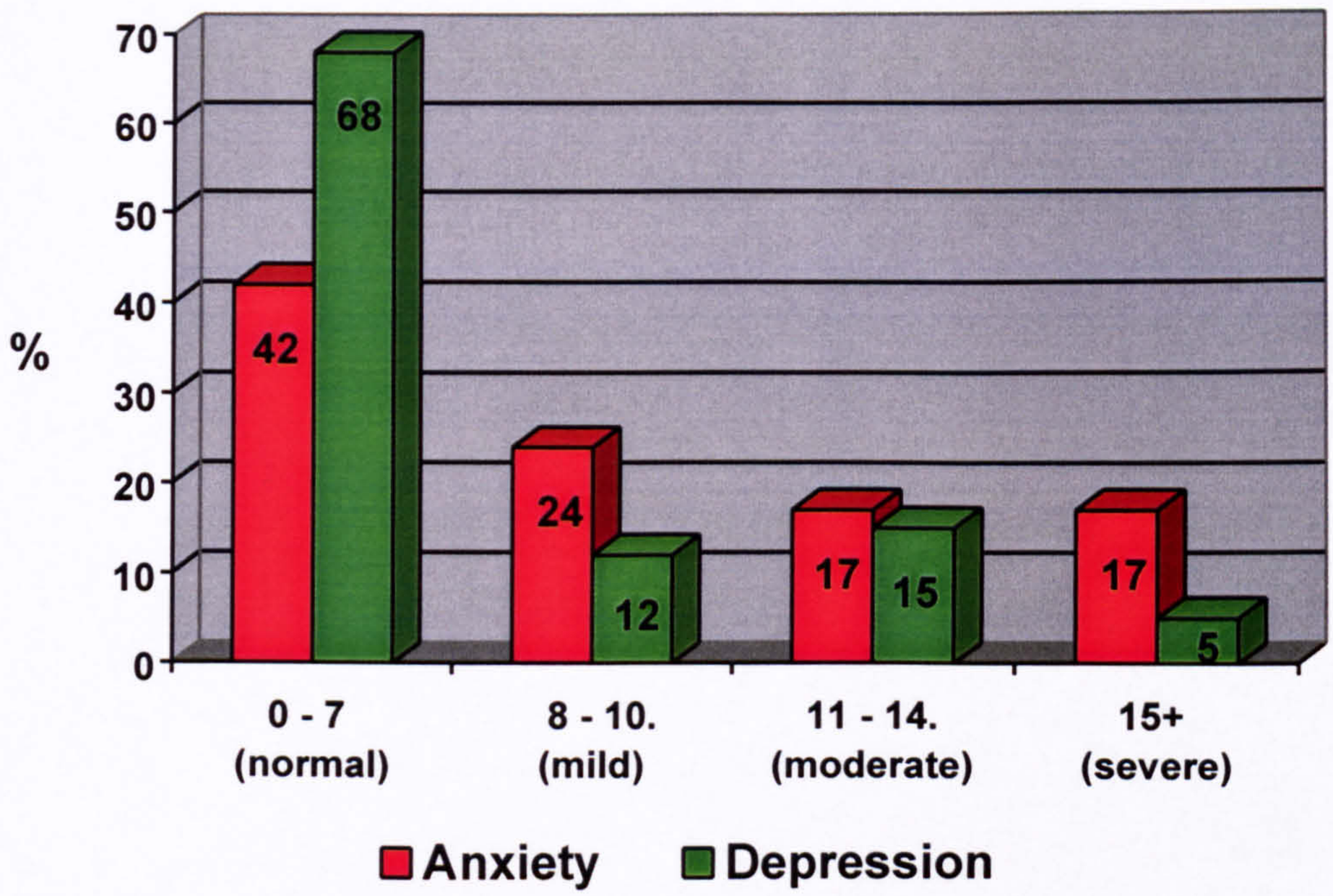
* p = .064; ** p = .007 (Mann Whitney independent pairs: coma vs no coma)

Anxiety & Depression 6-9 Years Post Injury

Forty-one patients returned questionnaires, which included the Hospital Anxiety and Depression Scale (HADS). Based on this scale, 7 patients (17%) were suffering from severe anxiety (scores over 15), with a further 7 (17%) suffering moderate anxiety (scores 11-14) and 10 (24%) with mild anxiety. As shown in Figure 6-9, anxiety scores were generally notably higher than depression scores. The majority of patients (68%) scored in the normal range on the HADS depression scale, with a further 12% with mild depression, leaving only 2 patients (5%) suffering severe depression and a further 6 (15%) with moderate depression.

The Beck Depression Inventory suggested higher levels of depression with 15 (41%) within the normal range, 13 (35%) with mild-moderate depression, 7 (19%) with moderate to severe depression and 2 with extremely severe depression. Eighteen (46%) of the 39 patients who returned the fully completed GHQ 30 scored above the threshold of 5 frequently used to screen for psychiatric disorder. Fifteen of these patients scored above 10 using this GHQ scoring method, indicating high levels of psychiatric disturbance. Chi-square analysis found no relationship between any of the dichotomised clinical measures and above threshold scores.

Figure 6-9: Hospital Anxiety and Depression Scale



Spearman correlations were conducted between these measures of anxiety and depression and indices of injury severity. As shown in Table 6-24, there are consistent significant correlations between virtually all of these measures and both PTA duration and loss of consciousness. However coma duration was less strongly associated with these emotional outcome measures. Reflecting this, correlations with GCS scores did not reach significance for the HADS, GHQ or Trait anxiety. There were however significant correlations between A&E GCS and both Beck Depression (r_s = -.317, p = .028) and State anxiety (r_s = -.335, p = .021)

Table 6-24. Anxiety & Depression correlated with PTA and Loss of Consciousness

	Duration of PTA (estimated days)	Duration of PTA (groupings)	Duration of Loss of Consciousness	Duration of Coma
HADS Anxiety	r_s = .299 (41) *	r_s = .282 (41) *	r_s = .305 (34) *	r_s = .260 (38)
HADS Depression	r_s = .484 (41) ***	r_s = .417 (41) **	r_s = .322 (34) *	r_s = .234 (38)
Beck Depression	r_s = .371 (37) *	r_s = .358 (37) *	r_s = .331 (31) *	r_s = .227 (34)
GHQ (0 or 1)	r_s = .351 (39) *	r_s = .294 (39) *	r_s = .417 (32) **	r_s = .119 (36)
GHQ (likert)	r_s = .322 (39) *	r_s = .275 (39) *	r_s = .380 (32) *	r_s = .127 (36)
State Anxiety	r_s = .229 (37)	r_s = .268 (37)	r_s = .378 (30) *	r_s = .331 (34) *
Trait Anxiety	r_s = .291 (37) *	r_s = .272 (37) *	r_s = .343 (30) *	r_s = .201 (34)

Number of patients involved in each correlation in parentheses

* $p < .05$; ** $p < .01$ (One-tailed Spearman correlations)

Assault and Emotional Outcome

There were consistent relationships between cause of injury and subsequent scores on these measures of anxiety and depression at 6-9 years post injury. Those patients whose injury was caused by assault had significantly higher scores upon non-parametric independent samples Mann-Whitney tests on all of the emotional outcome measures employed as indicated in Table 6-25.

Table 6-25: Assault as Cause of Injury and Emotional Outcome Measures

	Mean Rank			
	Assault	Non-Assault	Mann-Whitney U	p
HADS Anxiety	26.3 (14)	18.3 (27)	115.5	.042
HADS Depression	27.3 (14)	17.7 (27)	101.0	.015
Beck Depression	24.7 (12)	16.3 (25)	82.0	.027
GHQ (0 or 1)	25.5 (13)	17.3 (26)	98.0	.034
GHQ (likert)	26.2 (13)	16.9 (26)	89.0	.016
State Anxiety	24.2 (12)	16.5 (25)	87.5	.041
Trait Anxiety	25.8 (12)	15.7 (25)	68.0	.007

Number of patients involved in each group shown in parentheses

2-tailed independent samples Mann Whitney tests

In terms of injury severity, the assault patients were more likely to have been in coma at initial A&E assessment (47% vs. 30%), but non-assault patients were more likely to deteriorate such that in both groups approximately 50% of patients were in coma at some stage. The non-assault patients actually tended to have higher PTA measured levels of injury severity, with 85% of these patients having PTA lasting longer than a day relative to 68% of assault patients. As mentioned above, PTA measured indices of injury severity were found to be more predictive of anxiety and depression in the current study than indices based upon consciousness level. Thus it is particularly notable that these assault patients had significantly higher levels of anxiety and depression despite less severe PTA measured injury severity.

Emotional Outcome and Glasgow Outcome Scale

There were no significant changes on paired sample testing on Beck Depression, GHQ and the STAI for the 33 patients who completed these measures at both 6 month and 6-9 year assessments (Table 6-26). All of the measures of emotional outcome employed were strongly correlated with outcome as measured by the Glasgow Outcome Scale as shown in Table 6-27 below. The correlations for each measure were stronger with the extended 8-point GOS, in which the original groupings of good recovery, moderate disability and severe disability are dichotomised into upper and lower categories.

Table 6-26: No improvement in Repeated Emotional Outcome Measures

	N	Mean at 6 months	Mean at 6-9 years	W	p
Beck Depression	33	13.3	13.0	278	.964
General Health Questionnaire	37	37.1	36.8	287	.465
State Anxiety	35	45.5	44.5	239	.453
Trait Anxiety	35	44.3	47.2	225	.212

Mean scores and Wilcoxon non-parametric matched pairs tests

Table 6-27: Emotional outcome and Glasgow Outcome Scale

	N	Extended 8-point GOS	Collapsed 5-point GOS
HADS Anxiety	41	r_s = .563 ***	r_s = .476 **
HADS Depression	41	r_s = .756 ***	r_s = .669 ***
Beck Depression	37	r_s = .696 ***	r_s = .591 ***
GHQ (0 or 1)	39	r_s = .561 ***	r_s = .477 **
GHQ (likert)	39	r_s = .629 ***	r_s = .541 ***
State Anxiety	37	r_s = .570 ***	r_s = .496 **
Trait Anxiety	37	r_s = .629 ***	r_s = .531 ***

* $p < .05$; ** $p < .01$; *** $p < .001$ (One-tailed Spearman correlations)

Relatives' Questionnaire

The Relative's questionnaire was returned for 40 patients. It was completed by the patient's partner in 19 (48%) of cases, by a parent in 14 (35%) of cases, by a sibling in 6 (15%) and by a cousin for the remaining patient. The residual symptoms reported by proxy at 6 - 9 years are shown in decreasing order of prevalence in Table 6-28. These proxy reported residual symptoms were generally consistent with those self-reported by patients.

However, relatives were more likely to report that the patient was more anxious since the injury (78% vs 55%) and were far more likely to report that the patient was inclined towards violent outbursts than were the patients themselves (35% vs 8%). Several relatives had mentioned these episodes of violence during the semi-structured interviews and most reported that the violence was directed at objects rather than at individuals. This may account for why violent episodes were not significantly correlated with self-reported strain in relatives, whereas most other symptoms were more strongly associated with increased strain. Irritability, fatigue, anxiety and temper outbursts were the most frequently reported difficulties, with each of them considered to be worse since the injury by nearly 78% of relatives.

Table 6-28 Proxy Rating of Patient and Correlation with Strain in Relatives

Symptom	% Worse	r	Symptom	% Worse	r
Irritability	77.5	.596 ***	Slowness	50.0	.495 **
Fatigue	77.5	.553 ***	Decision Making	50.0	.488 **
Tension or Anxiety	77.5	.507 ***	Dizzy Spells	50.0	.362 *
Temper Outbursts	77.5	.479 **	Social Life	47.5	.467 **
Personality Changes	75.0	.470 **	Balance	47.5	.281 *
Behaviour	72.5	.643 ***	Affectionate	42.5	.578 ***
Memory	72.5	.614 ***	Able to talk about everyday things	40.0	.478 **
Impatience	72.5	.534 ***	Sense of Taste	37.5	.293 *
Sociable	65.0	.571 ***	Requires Supervision Outdoors	35.0	.306 *
Depression	65.0	.569 ***	Violent Outbursts	35.0	.257
Disturbed Sleep	60.0	.569 ***	Participation in Household tasks	32.5	.439 **
Headaches	60.0	.387 **	Hearing	30.0	.261
Passivity - less drive	60.0	.356 *	Sense of Smell	27.5	.218
Tact or Manners	57.5	.666 ***	Epilepsy	25.0	.178
Difficulty Finding Words	57.5	.615 ***	Self Care	22.5	.499 **
Concentration	57.5	.466 **	Vision	25.0	.218
Able to discuss problems	55.0	.521 ***	Mobility	22.5	.292 *

* $p < .05$, ** $p < .01$, *** $p < .001$, Spearman 1-tailed correlations, N = 40

Table 6-28 also shows the relationship between these symptoms and self-reported levels of strain in the relatives in the form of Spearman correlations. On a likert scale where '0' represented no strain and '10' severe strain, 19 (48%) of relatives reported the level of strain that they had been under as a consequence of the patients injury to be '7' or above, with 10 of these relatives indicating severe levels of strain. It can be seen that the symptoms most strongly associated with higher levels of strain in relatives are behavioural and memory problems, reduced tactfulness or manners, difficulty finding words, irritability and being less affectionate.

Chapter 7 Discussion

Introduction

These studies report outcome data for SAH and traumatic head injury using a more comprehensive range of physical, cognitive and emotional measures than have been employed in previous studies of a comparable size. The studies also recorded qualitative observations from interview, which were available for comparison with these more quantitative measures. In discussing the results, aspects for which the same discussion is relevant to both SAH and head injury are considered first. These include both the role of apolipoprotein E polymorphism and the use of premorbid intelligence measures. Other aspects which warrant more individual consideration are then discussed separately under subtitles for both SAH and head injury. Finally conclusions based upon the evidence from the current studies are summarised and directions suggested for future research.

Apolipoprotein E

The hypothesised role of apolipoprotein E gene polymorphism upon functional recovery following brain injury was not supported by this study. There were no apparent main effects of the ε4 allele upon recovery as gauged by any of the measures employed with either the head injury or subarachnoid haemorrhage patients. There were however some suggestions that ApoE may have a role amongst subgroups of patients. For example, ε4 patients were more likely than non-ε4 patients to have a Fisher Grade 4, which was invariably associated with the presence of intraventricular blood.

Additionally, amongst the twenty patients with a Fisher Grade 4, the ε4 patients tended to have a less positive outcome. There also appeared to be some polarisation of injury severity amongst head injury patients, with severe injury ε4 patients having lower GCS scores than their non-ε4 counterparts, whilst at the other end of the spectrum ε4 patients were more likely to have the more benign minor injury (GCS 15) than a mild injury (GCS 13-14). It is possible that ApoE may interact with other genetic polymorphism(s) such that the influence of the ε4 allele is more pronounced in individuals who co-express another genotype. Evidence already suggests a second susceptibility gene on chromosome 12 in relation to late-onset Alzheimer's disease (Pericak-Vance, Grubber et al. 2000; Scott, Grubber et al. 2000) and other such genes may serve to modify the role of ApoE.

ApoE and Recovery from Head Injury

The main ApoE related findings from the current study are that the ε4 allele does not appear to play a strong role in the functional recovery of survivors of brain injury. Although the association between the ε4 allele and increased risk of Alzheimer's type dementia is now well established, the association between ApoE and outcome following brain injury is less clear. Much of the evidence to date has come from animal studies, with a relative poverty of patient outcome studies. Most of these patient outcome studies have been based upon small numbers with limited outcome measures. For example, in outcome studies of head injury, one of the first papers to suggest an association with ε4 was based upon only 16 patients and used duration of post-traumatic unawareness as the sole measure (Sorbi, Nacmias et al. 1995).

Another study, which suggests an association between ε4 and chronic neurological deficits in boxers, involved thirty boxers but devised its own 10-point rating scale of traumatic encephalopathy as the sole measure (Jordan, Relkin et al. 1997).

The first prospective study of the role of ApoE polymorphism upon outcome after traumatic head injury followed up a more impressive 89 patients, but used GOS at six months as the sole outcome measure (Teasdale, Nicoll et al. 1997). Additionally, the ε4 patients in this study had substantially lower admission GCS scores. This bias was particularly notable amongst the severe injury patients, with 37% of the ε4 patients having an admission GCS of 3-8 relative to only 17% of the non-ε4 patients. Admission GCS, particularly a GCS of 3-8, has been found by the current study and earlier studies to be one of the strongest predictors of outcome. This association between severity of injury and GOS is likely to be particularly pronounced within the first few months following injury, with the current study suggesting that severe injury patients are more likely to continue to recover over a longer time period. The authors however suggested that the differences in injury severity were more than off-set by the younger age of ε4 patients, such that when these confounds were accounted for the effect of ε4 upon GOS measured outcome remained significant.

The age range of the Teasdale et al (1997) study differed substantially from that of the current study, with their study having an age at injury range of <1–82 years (mean 38) relative to 17-60 years (mean 30) in the current study. Thus it is possible that if an effect of ε4 is present, its influence may be more marked either in children or in those of more advanced years at the time of injury. Some recent evidence suggests that the influence of ε4 upon outcome following head injury is influenced by age at injury, with a more pronounced effect observed amongst children (Teasdale, unpublished data).

In contrast, some evidence suggests that older ε4 patients may be more likely to die from their injury. In the Teasdale et al (1997), Friedman (1999) and the current head injury study, ε4 patients tended to be younger than their non-ε4 counterparts, which leads to the possibility that older ε4 patients were less available for participation in studies due to death or disability. This latter possibility is also suggested by the authors of the boxing study in which high exposure boxers with the ε4 allele, who were most likely to exhibit signs of neurological deficit, were on average over ten years younger than the less impaired high exposure non ε4 boxers (Jordan, Relkin et al. 1997).

It is possible that expression of ApoE4 has a deleterious effect upon the brain such that the brain is less capable of responding to and recovering from injury. It has frequently been observed that individuals of more advanced years are both more likely to die from head injury and less likely to make a good recovery (Tennant, Macdermott et al. 1995; Gomez, Lobato et al. 2000). Part of the explanation for these age related differences might lie in the mutations and other oxidative damage that are present in all brains as a function of age. The older brain has accumulated a greater extent of such oxidative damage and thus may be less capable of responding to injury.

Several studies suggest a role for ApoE either directly or indirectly in serving as an antioxidant (Palinski, Ord et al. 1994; Aviram 1996; Lomnitski, Kohen et al. 1997; Maor, Hayek et al. 1997; Lomnitski, Chapman et al. 1999) with E4 apparently less effective in this role (Miyata and Smith 1996; Ramassamy, Averill et al. 2000). Thus the ε4 brain may accumulate oxidative damage at a greater rate than non-ε4 brains, such that patients with the ε4 allele are less capable of responding to brain injury. This would appear inconsistent with suggestions of a greater influence of ApoE upon younger patients, as accumulative differences would be expected to be more pronounced in older patients. However, it is plausible that most older patients are already less able to respond to injury, such that differences between ε4 and non-ε4 patients are more apparent amongst younger patients. These ε4 patients may also present with a greater severity of biological injury for a given mechanical injury due to differences in response to injury. In the earlier prospective study of 89 patients (Teasdale, Nicoll et al. 1997) the ε4 patients were notably more likely to have suffered a severe injury as measured by GCS and in the current study there was some tendency towards a polarisation of GCS scores amongst ε4 patients.

Other studies that have suggested a negative influence of the ε4 allele upon recovery from brain injury have been based upon patients who had participated in specialist rehabilitation programmes and have used a relatively restricted range of measures (Friedman, Froom et al. 1999; Lichtman, Seliger et al. 2000; Teasdale 2000). In the Lichtman et al study, which used a telephone administered functional independence measure as the sole index of outcome, the differences between 7 ε4 and 24 non-ε4 patients were only present after adjustment for a surprisingly greater coma duration amongst non-ε4 patients.

The Teasdale et al (2000) study involved a mixed brain injury group, including 19 with unspecified cerebrovascular accident and 18 with traumatic brain injury. This study found no APOE related differences on the European Brain Injury Questionnaire upon entry into the rehabilitation programme at a mean of over one and a half years post injury. However notable differences were apparent at follow-up, which was on average over a year following the programme, with significant genotype by time interactions resulting from apparent deterioration amongst ε4 patients and improvements upon non-ε4 patients (Teasdale 2000). It is of particular interest that these differences were not present at entry into the programme some duration after the injury, but apparently resulted as a consequence of the intensive rehabilitation programme.

A possible explanation for this and the other results based upon rehabilitation patients is that non-ε4 patients have a greater capacity than ε4 patients for any compensatory mechanisms potentially facilitated by these rehabilitative interventions. This would be consistent with suggestions of a role for ApoE in neuronal plasticity from animal models (Poirier 1994; Masliah, Mallory et al. 1995), with the ε4 allele associated with less pronounced capacity for plasticity (Nathan, Bellosta et al. 1994; Nathan, Chang et al. 1995; Arendt, Schindler et al. 1997).

The suggestions of a greater influence of the ε4 allele upon children are also consistent with such an isoform specific influence upon neuronal plasticity. However, the extent of rehabilitation services offered or available to head injury survivors varies substantially and many patients, including most of those involved in the current study, are not offered the benefits of intensive rehabilitation programmes. Many patients return home after their time in hospital and spend some months following injury 'recovering' at home in an environment which typically involves fewer social contacts and reduced stimulation, thus not being conducive to eliciting compensatory neuronal changes regardless of genotype.

ApoE and Recovery from Stroke

The possible role of ApoE polymorphism upon recovery from stroke is complicated by evidence that the alleles also serve as risk factors for the initial occurrence of stroke, with these isoform specific effects varying according to the type of stroke. Thus even when only considering haemorrhagic stroke, the ε2 allele has been associated with greater risk of CAAH but not SAH (Nicoll, Burnett et al. 1997; Greenberg, Vonsattel et al. 1998; McCarron and Nicoll 1998b), whereas the ε4 allele has been associated with greater risk of both ICH and SAH (Alberts, Graffagnino et al. 1995; Kokubo, Chowdhury et al. 2000).

Most of the studies to date comparing ApoE genotype with recovery from stroke have focused upon ischaemic stroke or ICH rather than SAH. These studies have only used basic measures of outcome, but have generally found poorer outcome amongst ε4 ICH patients (Alberts, Graffagnino et al. 1995; McCarron, Muir et al. 1998; McCarron, Hoffmann et al. 1999), but no effect of the ε4 allele upon outcome following ischaemic stroke (McCarron, Muir et al. 1998; Catto, McCormack et al. 2000; McCarron, Muir et al. 2000). Additionally, recent studies suggest that the ε4 allele has an independent rather than a synergistic influence upon the risk of cognitive decline or dementia following stroke (Barba, Martinez-Espinosa et al. 2000; Dik, Deeg et al. 2000; Zhu, Fratiglioni et al. 2000).

In the current study, the ε4 allele appeared to have no notable influence upon recovery amongst patients in whom the haemorrhage was confined to the subarachnoid space, however there were suggestions of an influence amongst the Fisher Grade 4 patients in whom the haemorrhage extended into the ventricles or parenchyma. These Fisher 4 patients may be viewed as having more in common with ICH patients than do the lower Fisher Grade patients and thus it might be expected that they would be more likely to demonstrate an effect of the ε4 allele. Two possible mechanisms for an interaction between ε4 and Fisher Grade are suggested. Firstly, it is possible that the ε4 patients were disposed towards greater severity of haemorrhage, which resulted in a greater proportion of them having a Fisher Grade 4 with blood extending into the ventricles. This would result in a greater primary injury amongst ε4 SAH patients and the expectation of a greater risk of re-haemorrhage amongst these patients. Indeed, evidence from the acute stage of treatment of the patient cohort on which this study is based suggests an increased risk of re-haemorrhage amongst ε4 patients (Dunn, Stewart et al. 2001). It was suggested in this paper that the ε4 patients, who are predisposed to atherosclerosis and amyloid angiopathy, may have stiffer blood vessels which are less susceptible to vasospasm but more susceptible to haemorrhage. This would be consistent with findings indicating an influence of ε4 upon recovery from ICH but not ischaemic stroke. The suggestions of greater initial haemorrhage and risk of re-haemorrhage amongst ε4 patients are also consistent with emerging evidence suggesting that ε4 individuals may have deficient blood clotting mechanisms and larger haematoma volumes (Nicoll 2001).

A second possible mechanism, which is not mutually exclusive with the first, is that greater secondary damage occurs amongst ε4 patients following haemorrhagic stroke, particularly when extravascular blood is present in the parenchyma or ventricles. The mechanism of this secondary damage is uncertain, though oxidative damage has been demonstrated following induced trauma in animal models (Shohami, Beit-Yannai et al. 1997) and the release of free iron as a breakdown product of haemaglobin is known to catalyse free radical generation. The presence of intracellular iron has recently been found to be higher in ApoE (-/-) mice than in controls following closed head injury and to be significantly correlated with the extent of subsequent damage (Lomnitski, Nyska et al. 2000).

Alternatively, previous studies have demonstrated that βA's cytotoxic effects may be mediated by oxidative damage (Davis 1996; Behl 1997; Behl 1999a; Pappolla, Chyan et al. 1999) in a manner which may interact with redox metal ions such as iron (Varadarajan, Yatin et al. 2000a), such that the greater βA depositions typically present in the vessels of ε4 patients may also increase oxidative damage following haemorrhage. ApoE has been suggested by several studies to have a direct or indirect role in antioxidative responses to brain injury (Chen, Lomnitski et al. 1997; Laskowitz, Sheng et al. 1997; Horsburgh, Kelly et al. 1999; Lomnitski, Chapman et al. 1999) with ε4 less effective in this antioxidative role than ε3 or ε2 (Miyata and Smith 1996). Thus ApoE polymorphism may influence outcome from haemorrhagic stroke via isoform-dependant antioxidative roles which affect the extent of secondary oxidative damage.

Premorbid Intelligence

This study found evidence to suggest that the National Adult Reading Test (NART) is not an appropriate measure of pre-morbid intelligence for patients following brain injury. Despite excluding patients with any signs of language deficits, in both studies NART error scores were found to be related to indices of injury severity such that it appeared that performance on the NART was itself affected by the brain injury in at least some patients.

In the subarachnoid haemorrhage study, sufficient information regarding prior education and employment was collected to enable a comparison between predicted NART using a regression equation based on demographics and obtained NART. This revealed notable discrepancies, with obtained NART error scores often higher than expected, particularly amongst those in whom a haematoma had been detected. Thus it seems likely that the NART is not resilient to brain injury in all patients and consequently that exclusive reliance on the NART may result in considerable underestimation of pre-morbid ability and thus underestimation of the deleterious cognitive effects of brain injury. Studies that have supported the use of the NART in traumatic head injury have often cited a case report in which the NART error score of a 20-year-old severe head injury patient is compared with results of a WISC-R assessment conducted some seven years prior to the injury (Moss and Dowd 1991). However, even if it is accepted that the NART score matches the WISC-R score (of which there is some doubt), there is little information about the region and type of brain injury involved.

Additionally, head injuries are far too heterogeneous to generalise with any confidence from an individual case. Whilst it may be the case that the NART is less likely to be affected by diffuse injuries or by right hemisphere lesions than by mass lesions or left hemisphere lesions, there is little to support the assumption that the NART is generally resilient to head injury. The NART is already unsuitable for a considerable proportion of brain injury patients due to acquired language deficits and many patients feel understandable discomfort in attempting to pronounce words which they do not recognise. Consequently it is perhaps more appropriate to utilise demographically derived equations of premorbid intelligence, at least to compare against NART derived estimates (Crawford, Stewart et al. 1989; Crawford, Allan et al. 1990).

Alternatively the Cambridge Contextual Reading Task, which places NART words into a meaningful context and appeared to be less affected by injury severity amongst head injury patients in this study, may be a more appropriate index of premorbid verbal ability (Beardsall and Huppert 1994; Beardsall and Huppert 1997; Beardsall 1998). In dementia patients, the CCRT has been found to be less affected by severity of cognitive impairment than the NART and thus may provide a more robust premorbid measure (Conway and O'Carroll 1997). This reflects findings which suggest that the reading of single irregular words in isolation is compromised in more cognitively impaired Alzheimer patients (Patterson, Graham et al. 1994), whereas contextual priming is relatively preserved (Nebes 1994; Nebes and Halligan 1996).

In addition to appearing to be more resilient to cognitive deficits, the CCRT was preferred by 69% of patients in the current study, with only 11% preferring the NART and the remaining 20% having no preference. The CCRT was more likely to be preferred by those with lower verbal ability, who were more inclined to essentially 'give up' on the later stages of the NART. Patients viewed the CCRT as more 'realistic' and less intimidating, reflecting observations that patients seemed less aware or concerned by errors of pronunciation whilst reading the words in the context of sentences. Supportive evidence for the use of the CCRT as an alternative to the NART in estimating the premorbid ability of head injured patients comes from a study in which the CCRT was found to be resistant to the effects of injury and head injury patients were found to derive a particular benefit of the context provided by the CCRT (Watt and O'Carroll 1999).

Subarachnoid Haemorrhage

As outlined in chapter 1, there have been few studies of functional outcome amongst survivors of SAH and those studies which do exist have generally employed only a restricted range of tasks or non-standardised measures and have generally been based upon smaller opportunity or rehabilitation samples which are not representative of all subarachnoid haemorrhage survivors. The current study involved the comprehensive assessment of physical, cognitive and emotional outcome in 70 survivors of SAH. These patients were drawn from a consecutive sample of neurosurgical admissions, from which over 75% of survivors who had suffered a confirmed SAH participated in the follow-up interview.

Comparisons of clinical grades and demographic variables found no differences between participants and non-participants, such that reasonable confidence can be expressed that the study group are representative of surviving patients who attend neurosurgical units for spontaneous subarachnoid haemorrhage. Seventy four percent of those who participated in the interview returned correctly completed emotional outcome questionnaires. The non-completion or incorrect completion of questionnaires by 18 patients is a potential source of bias, though again comparisons of completers and non-completers reveal no differences in terms of clinical, demographic or interview data.

Fisher and WFNS Grades

Both Fisher and WFNS Grades were found to be predictive of physical and cognitive outcome as measured by the GOS, neuropsychological tasks and SF-36, but were not predictive of emotional disturbance including anxiety and depression. Fisher Grade was consistently more strongly associated with outcome than WFNS Grade, with Fisher 4 patients significantly more impaired than other patients. In this study, Fisher Grade 4 was present in nine of the twelve deaths and in nine of the eleven patients who were severely disabled at 16 months. WFNS grade was only slightly less predictive of mortality, but was notably less predictive of functional outcome amongst survivors.

This would suggest that Fisher Grade should be accorded greater prominence in the consideration of haemorrhage severity and likely prognosis. Currently most texts focus upon measures of consciousness such as Hunt and Hess or WFNS Grade as the primary index of SAH severity and give relatively little mention of measures of the amount and region of collected blood. It also suggests that the region in which subarachnoid blood accumulates is of importance as well as the amount of such blood, as Fisher Grade 4 is defined by the presence of blood in the ventricles or parenchyma. Extravascular blood is thought to have a neurotoxic influence, possibly via the release of free iron during the process of metabolising haemoglobin. It is possible that extravascular blood in the ventricles or parenchyma has a greater neurotoxic influence and thus the importance of time from ictus to surgical evacuation of blood may differ according to region in which the blood has collected.

The Fisher Grading system was originally intended as a means of predicting risk of vasospasm, with Fisher grade 3 patients at notably greater risk. Consequently it was not intended as a hierarchical scale with Fisher grade 4 patients having the worst prognosis. Whilst this study suggests that there are considerable advantages of considering Fisher Grade in relation to prognosis, it is possible that measures which more accurately record the amount and region of collected blood may have greater predictive ability.

Aneurysmal versus Unknown Aetiology Subarachnoid Haemorrhage

The twelve patients with negative angiograms did not differ in terms of any of the measures of outcome from the angiographically confirmed aneurysmal patients. It is often assumed that aneurysmal patients will fare considerably worse, with negative angiogram patients having a relatively benign prognosis. This assumption is driven in part by the notably higher mortality amongst aneurysmal patients and their far greater risk of rehaemorrhage. These are naturally the primary concern of clinicians in the acute stage and their prevalence amongst aneurysmal patients and relative absence in negative angiogram patients leads to the assumption that only aneurysmal patients have a poor prognosis. Additionally, aneurysmal patients often undergo neurosurgery in order to clip or otherwise seal the aneurysm and the surgical procedure may also cause some damage to the brain. Angiogram negative patients generally do not undergo any form of neurosurgery.

Although the distinction between confirmed aneurysmal and angiogram negative patients is certainly warranted in terms of mortality and risk of re-haemorrhage, evidence from the current study suggests that there are few if any differences in outcome *amongst survivors*. This is consistent with previous studies which have found that when only survivors of SAH are considered there are only moderate differences between those of aneurysmal and non-aneurysmal aetiology (Sonesson, Saveland et al. 1989; Hutter, Gilsbach et al. 1994).

Many previous studies have not separated survivors from those who die from their haemorrhage and have then usually compared outcome measures, which incorporated mortality, with haemorrhage type and clinical grades. As aneurysmal patients are far more likely to die as a direct consequence of their haemorrhage, any such GOS measurement is certain to be strongly influenced by this factor. It is reasonable to suppose that factors that influence survival may in some respects differ from factors that influence functional recovery amongst survivors. Consequently there are worthwhile grounds for comparing survival GOS with clinical variables in order to ascertain more accurately factors which influence functional recovery amongst survivors.

Anterior Communicating Artery Aneurysms

As outlined in Chapter 1, several previous studies have reported a syndrome of consequences particular to ruptured aneurysms of the anterior communicating artery. These have included most notably memory deficits and personality change. However, more recent studies have generally not found significant differential effects according to aneurysmal site. It has been suggested that previously observed deficits were at least in part due to damage caused during the neurosurgical obliteration of ACoA and that advances in neurosurgical technology and practice have substantially reduced such perioperative damage.

In the current study there were no notable cognitive differences between patients according to aneurysm site on any tasks except the logical memory passage recall task. The nineteen ACoA patients were twice as likely to score less than 1 SD below the normative mean on both the immediate and delayed recalls of this task relative to patients with aneurysms at other sites. This is consistent with the greater tendency for verbal memory deficits in ACoA patients. However, performance in this passage recall task was accounted for more completely if ACoA, MCA and other frontal aneurysm patients were considered separately from posterior communicating and posterior circulation aneurysm patients.

ACoA patients tended to have lower scores on the SF-36 health survey, particularly on the physical role limitation domain. This is especially notable because these ACoA patients were rather *less* likely to have a Fisher Grade 4 and thus, given that Fisher Grade 1 to 3 patients tended to have a better outcome on the SF-36 and other measures, might have been expected to fare better than other patients. However, these ACoA patients scored consistently worse than the other aneurysmal patients on each of the eight domains measured by the questionnaire.

Taken together, these findings suggest that ACoA patients still tend to have a greater disposition towards memory deficits and poorer outcome than other aneurysmal patients. Due to neurosurgical advances, these differences may be considerably less pronounced than in series of patients reported nearly two decades ago. Consequently the differences may not have been detected by more recent studies or have not reached traditional levels of statistical significance due to the smaller effect size and / or the relatively small numbers of patients and measures involved in most previous outcome studies that have incorporated some form of neuropsychological assessment.

Anxiety and Depression following Subarachnoid Haemorrhage

This study finds that whilst mild depression is present in a considerable proportion of patients 16 months post haemorrhage, anxiety is probably more frequently the primary cause of psychological morbidity in this cohort of patients. Many patients reported that they went out far less frequently due to previous experience of severe anxiety or panic attacks whilst away from home. They were particularly less likely to go out socially and thus their anxiety often resulted in increasing social isolation and depression.

As with virtually all other such studies, no quantitative measures of pre-haemorrhage psychological functioning were available, restricting the ability to comment on how such factors may relate to or be predictive of subsequent emotional outcome. However the considerable majority of patients reported no previous psychological difficulties prior to the haemorrhage suggesting that in most part subsequent emotional disturbances are triggered by this event. A recent study of emotional outcome after stroke, which excluded subarachnoid haemorrhage, found that anxiety and depression were present in approximately equivalent proportions, with 16% and 12% scoring above 10 on the respective HADS subscales (Dennis, O'Rourke et al. 2000). The current study has found considerably higher anxiety levels and somewhat higher levels of depression, particularly mild depression, amongst survivors of subarachnoid haemorrhage.

Social isolation is recognised as being associated with depressive illness following brain injury (Morton and Wehman 1995) and is likely to either cause or exacerbate such depression. An interesting finding from the current study is the strong association between difficulty in dissociating voices and reduced social activity. Several patients reported being able to understand a single voice perfectly but having difficulty in separating one voice from amongst others. These patients comprised the vast majority of those who rarely if ever participated in social activities since the haemorrhage, with many of them reported avoiding social situations because their difficulty in dissociating voices led to embarrassment or feeling left out. It seems possible that such difficulty in dissociating voices is an important factor in predicting subsequent social isolation and depression. These patients may benefit from techniques, such as lip-reading, which may facilitate them in these social situations.

Anxiety difficulties were found to be an important factor in the functional outcome of a considerable percentage of SAH patients, with over double the percentage of SAH patients (38%) scoring over 10 on the HADS relative to that reported for other types of stroke. This figure of around 40% of SAH patients suffering from anxiety disorders is also demonstrated by interview and STAI data such that it is unlikely to be an artefact of the measure used. This difference between SAH and other strokes may be in part due to the younger age at which patients typically suffer SAH, with its occurrence invariably sudden and unexpected in individuals who are generally otherwise healthy.

Hellawell et al report lower reporting of anxiety difficulties by patients in their sample of SAH patients which was also drawn from consecutive admissions and with broadly similar age and admission grades (Hellawell, Taylor et al. 1999a). It is possible that this reflects some as yet unidentified difference either in patient population or after-care practices, though their data at 12 months is based upon only 22 of 42 potential patients whereas this study reports interview data at 16 months from 70 of 93 patients with questionnaire data from 52. The Hellawell study does however report that 36% of the relatives of SAH patients considered that anxiety / tension in the patient had increased since the haemorrhage.

Ogden et al found that 15.4 % of their sample of 123 patients reported increased anxiety when questioned, in most cases by brief telephone interview, at 4 to 7 years after their haemorrhage (Ogden, Utley et al. 1997). This may indicate that anxiety difficulties, if present, gradually resolve over time. However it is also possible that patients are less likely to mention emotional difficulties, such as anxiety and depression, during the course of a brief telephone interview than they are having met with and spent some time with someone during face-to-face interviews arranged at their convenience. Their study reports similar rates of difficulties of a more physical nature such as reduced memory and fatigue.

An earlier study by Ogden et al reports interview data from a 12 month follow-up of 66 patients in which 61% of those patients who had been working prior to SAH had returned to work, a figure which is very much akin to the 63% reported by this study (Ogden, Mee et al. 1993). Their study however found lower rates of depression as measured by the BDI at 12 months, with 17% scoring in the mild-moderate range relative to 28% in this study and only two of their patients scoring in the moderately severe range. The study included no measure of anxiety or other emotional outcome measures. Hutter et al reported that 30% of their SAH patients suffered from clinical depression (BDI >10) (Hutter, Gilsbach et al. 1995). Although their study also included no formal assessment of anxiety, 36% of their patients reported feeling strained and insecure socially with 48% reporting emotional lability. These numbers would be broadly consistent with the approximately 40% of patients reporting anxiety difficulties in this study.

A recent study based on cases referred to clinical psychologists found that in 50% of cases anxiety was the main presenting problem (Berry 1998). A further 36% had experienced anxiety and memory difficulties at the time of referral that had since resolved. Only 14% of cases presented with cognitive impairment as the primary problem. This is consistent with the balance of findings from this study that whilst probable cognitive impairments are present in a considerable proportion of patients following SAH, anxiety difficulties are often the primary cause of difficulties in returning to pre-haemorrhage levels of work and social activity.

It is notable from the SAH study that there were no consistent significant associations between reported emotional disturbance and any of the clinical variables measured. Although Fisher Grade 4 tended to be associated with worse emotional outcome, this effect was not significant on any of the standardised measures and did not account for the variance in anxiety scores. Thus it would appear that whilst factors such as WFNS Grade and Fisher Grade influence survival and physical / cognitive outcome, they are not predictive of emotional outcome. There were also no significant differences between patients with aneurysmal or non-aneurysmal haemorrhage, with 3 of the 9 non-aneurysmal patients suffering from moderate to severe anxiety. A previous study had tentatively suggested a correlation between a summed HADS score and admission WFNS Grade (Hellawell, Taylor et al. 1999a), but the same comparison here with a larger sample size found no association either with summed or individual HADS scores or with any of the other emotional outcome measures.

The distribution of anxiety in this sample tended towards being bimodal, with around 40% of patients notably affected whilst the remainder seemed untroubled by anxiety despite an equivalent severity of haemorrhage and comparable clinical grades. The high incidence of anxiety disorders after SAH and their very substantial effects upon the quality of life of both patients and their partners is of particular interest because, unlike physical or cognitive disabilities, many anxiety disorders can be successfully treated with cognitive behavioural therapy (Chambless and Gillis 1993; Harvey and Rapee 1995; Basco, Glickman et al. 2000; Stanley and Novy 2000). Thus the identification of these anxiety disorders and referral to a clinical psychologist or other suitably trained professional could substantially improve the functional outcome of these patients.

It is also of interest why these anxiety disorders develop in some individuals subsequent to SAH and not in others. It is known that individuals adopt differing coping styles in response to traumatic events and that some of these styles of coping are more consistent with a positive outcome than others. It is possible that the coping styles adopted by either the patient or the carer(s) in response to the SAH may influence their subsequent recovery and predisposition towards anxiety related disorders. In recent years, studies using the Ways of Coping Checklist have indicated that the use of particular coping styles are predictive of functional outcome after head injury, with problem focused coping associated with better outcome (Malia, Powell et al. 1995). In a more recent study of 44 head injury patients, problem focused coping strategies were found to be employed more frequently amongst good recovery patients whereas avoidance coping strategies were associated with higher levels of anxiety and depression (Pettigrew 1998).

The extent and format of information given to patients and their family may also be a factor in influencing emotional outcome. During the interviews at 16 months it was notable that many of the patients and their carers still had many unanswered questions relating to their haemorrhage and often commented that they would have appreciated more digestible information at the time of the haemorrhage. Several carers and patients mentioned that although health care professionals had talked to them about the haemorrhage and taken the time to answer questions, they had been unable to take it all in at the time. Thus verbal information given by health care professionals would probably be best supplemented by suitable written material as many patients and their relatives report not being able to understand or remember much of the information given to them in hospital.

Head Injury

This is one of very few studies of outcome after head injury to have followed up patients some years after their initial injury. It is fairly unique in having comprehensive medical information and indices of injury severity available from the acute stage and neuropsychological data available from six months with which to compare with long-term neuropsychological outcome taken at 6-9 years post injury.

Changes Between Assessments at 6 Months and 6-9 Years

The results from the current study indicate that some moderate changes do occur beyond six months post injury in at least some patients. The increase in numbers of patients who had returned to work from 32% at six months to 50% at 6-9 years and the reduced reporting of physical problems (from 49% to 39%) appears to indicate functional improvement beyond six months. However, comparison of GOS scores over the same period by contrast indicates a tendency towards lower functioning. It seems unlikely that these deteriorations in GOS were merely due to the greater age of patients at 6-9 year assessment as most patients were still young at the later assessment. Additionally, those functions that might reasonably be expected to deteriorate with age, such as physical ability and information processing, were actually amongst the few areas of functioning to have demonstrated improvement.

The apparent reduction in patients with a good recovery may indicate that the interview based GOS used at the 6-9 year assessment was more sensitive in identifying social or emotional difficulties than the original GOS had been. However, it is also possible that these social or emotional difficulties, which were often the reason for a moderate rather than a good recovery, tended to increase beyond six months. There is some evidence for this, with depression more frequently reported at 6-9 year assessment (63% vs. 47%) and more patients indicating that they no longer had the same circle of friends as before the injury. These social changes were often forced rather than chosen, with previous friends 'moving on' and disassociating with the head injured individual.

Other patients reported that whilst they had initially been optimistic about making a full recovery with family and friends rallying round, they had eventually become more resigned and despondent. Several patients seemed to have adopted a more dependant role, having moved either back in with parents or to a flat with family nearby. At the 6-9 year assessment, the GOS category percentages of surviving patients were good recovery (41%), moderate disability (43%) and severe disability (16%), which is highly consistent with recently reported long-term outcome data from a group of 91 patients with comparable injury severity which describes percentages of 44%, 39% and 13% respectively 5 years post injury (Dunn, Patterson et al. 2000).

Comparison of the repeated neuropsychological tasks revealed few changes between assessments, reflecting comparable reporting of concentration and memory difficulties by patients between interviews at 6 months and 6-9 years. Age at injury was associated with cognitive changes, with those over age 35 at injury tending to deteriorate on tasks over time, whereas younger patients had comparable or modest improvements across assessments. It is possible that the difference is simply an artefact of ageing, with disproportionately greater cognitive deterioration over time amongst older patients which is unrelated to brain injury. However, it is also possible that this reflects some differential effect of response to injury, with the brains of older patients less capable of compensating for the sequelae of brain injury. Other studies have also noted poorer outcome amongst older patients, even when only survivors are considered. One such study reported worse functional outcome as measured by GOS amongst survivors aged over 40 (Katz and Alexander 1994), whilst in another study age over 30 at injury was one of the key predictors of subsequent quality of life impairment (Tennant, Macdermott et al. 1995).

The only other cognitive changes of note were consistent improvements upon information processing tasks amongst patients who had impaired consciousness or coma in the acute stage following injury. Changes in performance on these information-processing tasks were significantly correlated with duration of coma and GCS scores at first A&E admission. Although the more severely injured patients who suffered coma still scored lower on these tasks than patients who had suffered less severe injuries, their performance notably improved whereas the performance of other patients remained consistent across assessments.

This is indicative of potential for improvements in information processing beyond six months amongst patients who suffer severe injury. It may be speculated that these patients have injuries consistent with diffuse axonal injury, which may have greater potential for continued recovery over a longer time period. These diffuse injuries are known to have a particular influence upon information processing (McMillan and Glucksman 1987; Leininger, Gramling et al. 1990), such that the gradual recovery of diffuse injury is most likely to be reflected by improvements upon tasks with a strong information-processing component.

Long-Term 6-9 Year Neuropsychological Outcome

Cognitive performance at 6-9 year assessment was most frequently associated with A&E GCS scores, with lower initial consciousness level predictive of lower performance, particularly upon tasks with an information-processing component such as PASAT, Digit Symbol and Trail-Making. It was notable that A&E GCS scores were more strongly associated with performance on these tasks than were later neurosurgical admission or 24 hour worst GCS scores. This may reflect the importance of diffuse axonal injury in determining subsequent performance on these tasks, as A&E GCS is particularly reflective of such diffuse injuries. The other GCS measures are less reflective of this injury pattern as some of the more severe diffuse axonal patients would have no available initial neurosurgical GCS due to intubation and ventilation, and 24 hour GCS would be influenced by patients whose consciousness level had deteriorated secondary to primary focal injury.

The importance of DAI in determining residual cognitive impairments is also illustrated by the highly significant correlations between patients' A&E GCS and the number of tasks in which scores were in the 'low score' range. Similarly, the presence of coma was consistently associated with lower cognitive performance and with the presence of a greater number of cognitive scores in the 'low score' range. The occurrence of coma is often a consequence of diffuse axonal damage, particularly when such coma was present from initial A&E admission. Correspondingly the association between coma and cognitive performance in the current study is strongest amongst those patients who had been in coma from initial A&E admission.

Previous studies have also reported worse cognitive performance amongst patients who had suffered coma (Hellawell, Taylor et al. 1999b; Novack, Alderson et al. 2000), though mixed findings have been reported in relation to coma duration. Some studies have found that longer coma duration corresponds with worse cognitive performance (Dikmen, Machamer et al. 1990; Ross, Temkin et al. 1994) whilst others found no such effect (Brooks, Aughton et al. 1980). The current study found that coma duration corresponded with worse performance in 15 of 19 tasks, but that in the majority of these tasks the effect was fairly modest. Thus on balance the presence of coma or the related GCS score at first admission, rather than duration of such coma, was the most predictive measure of subsequent cognitive outcome.

Haematoma and TDCB Classification

In contrast to the consciousness-based measures of injury severity, other clinical variables such as significant haematoma or TDCB classification were not predictive of cognitive outcome. The lack of any clear association between haematoma and cognitive performance may be a consequence of the heterogeneous nature of the haematoma group. Thus even when only significant intracerebral haematomas were concerned, the region(s) in which ICH was present varied and consequently the cognitive functions affected may have varied accordingly rather than being consistent across all ICH patients. Thus for example, individuals with haematomas in left temporal regions may have had memory deficits that were masked by being grouped with individuals with haematomas in other locations.

The relative absence of differences according to TDCB classification, despite other evidence suggestive of differential cognitive effects of diffuse injury, may reflect limitations of the TDCB classification system. For example, Diffuse I patients with a normal CT may include both patients with severe primary diffuse axonal injury and patients with minimal brain injury. Evacuated mass injury patients may have pronounced co-existing diffuse injury and conversely patients with multiple focal injuries may be classified as Diffuse II. These TCDB classifications of diffuse and focal injury were not found to be predictive of subsequent outcome. This study would suggest that presence of coma at first A&E admission is a more prognostic indicator of diffuse injury than these CT derived classifications.

Indices of Injury Severity

Both A&E GCS and PTA duration from the acute stage were still predictive of aspects of outcome 6-9 years following injury. Consciousness based indices of severity, such as A&E GCS, were generally more predictive of 6-9 year cognitive outcome and of cognitive change between assessments, whereas PTA duration was more predictive of physical and emotional outcome. Thus whereas A&E GCS was significantly correlated with nine of the nineteen core cognitive measures, durations of both PTA and of coma were only significantly correlated with five of these measures. GCS scores and duration of coma were notably more predictive of cognitive change across assessments, particularly on information processing tasks, reflecting perhaps their serving as an index of diffuse injury whereas PTA duration is more likely to be influenced by both diffuse and focal injury (Wilson, Teasdale et al. 1994). This difference, with PTA duration more reflective of focal injury, may explain the greater relationship between PTA duration and the physical functioning and physical role limitation domains of the SF-36. PTA duration was also notably more predictive of measures of emotional outcome than were either coma duration or GCS scores.

This is reflected by the observation that PTA duration was notably more predictive of global outcome, as measured by both the GOS and SF-36 health survey, at 6-9 years post injury. The consciousness based indices of injury severity, although more predictive of cognitive outcome, were notably less predictive of scores on these global functional outcome measures. A previous study has also reported PTA duration to be a better predictor of GOS measured outcome at 6 and 12 months post injury than consciousness based indices of injury severity such as GCS score or coma duration (Katz and Alexander 1994).

Absence of Control Group

Control groups were not used in these studies for reasons outlined in Chapter 4. In brief, this was primarily as the main comparisons were between brain injury patient groups, but also due to the considerable difficulties inherent in identifying and recruiting suitable controls. However the absence of suitable control groups does have implications for some of the results, in particular where patient scores are compared with normative data.

It is possible, or indeed likely, that patients may have differed from normative data even prior to their brain injury due to differences in educational and social background. This is perhaps more likely with regards to the head injury population, as lower educational achievement and socio-economic class appear to increase the risk of head injury. Premorbid differences are less likely to have been an issue in the subarachnoid haemorrhage population as there is no evidence to suggest differences in the occurrence of SAH between educational or socio-economic groups.

Thus, at least in the head injury study, some of the apparent 'deterioration' relative to normative data may reflect differences between the head injury and normal population. In order to account for such pre-injury differences it would have been preferable to compare scores either with matched controls or with normative data derived from a population with similar educational and socio-economic background. However, if the 'low scores' were primarily due to premorbid differences between head injury patients and the normal population, this would have been likely to result in fairly uniformly lower scores across all clinical groups and tasks. In contrast, these 'lower scores' were generally only evident in certain clinical groups on particular cognitive tasks, suggesting a greater likelihood that these reflected deterioration due to brain injury.

Anxiety and Depression following Head Injury

This study found that both anxiety and depression were frequent sequelae of head injury some 6-9 years post injury, with 34% of patients having moderate or severe anxiety difficulties and around 20% with moderate or severe depression as measured by the HADS. Patients were more likely to self-report depression in interviews, with depression one of the few symptoms to be reported more frequently at 6-9 year interview than at 6 months post injury. As mentioned earlier, this was reflected by comments of some patients suggesting that optimism of recovery in the early months had gradually been replaced by despondence and resignation. However there were few changes in Beck depression scores amongst the 33 patients who completed this measure at both assessments, with moderate-severe depression cases reducing from ten at 6 months to eight at 6-9 years whilst mild-moderate cases increased from six cases to eleven.

The increased reporting of depression is consistent with previous studies, which have suggested that the number of patients with emotional difficulties tends either to remain fairly constant over time or to increase some months after the initial injury (Fordyce, Roueche et al. 1983; Varney, Martzke et al. 1987; Bowen, Chamberlain et al. 1999). The current study extends these findings by comparison of emotional outcome measures across a longer time-period with scores on the Beck, GHQ and State Trait Anxiety Inventory remaining essentially unchanged in most patients across assessments. Where change did occur, it was just as likely to be deterioration as an improvement, suggesting that emotional difficulties remain one of the most important residual consequences of head injury several years following trauma.

In contrast with depression, head injury patients were generally less disposed to mention at interview anxiety difficulties, such as panic attacks or agoraphobia, than were their subarachnoid haemorrhage counterparts. In spite of this, questionnaire measures of anxiety were high in both groups indicating that actual prevalence of anxiety difficulties may be comparable between groups. The differences in reporting at interview may reflect various social differences between the groups. The head injury patients were more frequently young single males who may be more disinclined to discuss or seek help for difficulties with anxiety than on the whole are subarachnoid haemorrhage patients who tend to be middle-aged married females. Supportive of the suggestion that head injury patients are reluctant to report existing anxiety difficulties is the observation that the reporting of anxiety problems was one of the few discrepancies between patient and relative reports of patient symptoms, with relatives notably more likely to report increased patient anxiety.

Anxiety and depression have been frequently reported as enduring sequelae of traumatic head injury (Morton and Wehman 1995; Hellawell, Taylor et al. 1999b; Kesler, Adams et al. 2000). In the current study, these measures of anxiety and depression were generally not correlated with consciousness-based measures of injury severity such as GCS scores or coma duration. However PTA duration was consistently associated with these anxiety and depression measures. A previous study found no association between a brief measure of mood disorder and a scale of injury severity based upon both PTA and coma duration (Bowen, Chamberlain et al. 1999). The results from the current study would suggest that PTA duration is notably more predictive of subsequent emotional difficulties than consciousness based severity indices such as GCS score and coma duration.

Cause of injury was also of importance in relation to subsequent emotional scquelae, with patients whose injury was caused by an assault having significantly higher levels of anxiety and depression. Post Traumatic Stress Disorder (PTSD) has previously been demonstrated to be a frequent consequence of both sexual and non-sexual assault upon female victims (Dancu, Riggs et al. 1996; Valentiner, Foa et al. 1996; Feeny, Zoellner et al. 2000) and has been reported as a frequent consequence of traumatic brain injury (McMillan 1996; Ohry, Rattok et al. 1996; Hickling, Gillen et al. 1998; Bryant and Harvey 1999; Bryant, Marosszeky et al. 2000). The Oxford Head Injury Service have previously reported worse outcome at six months amongst patients who had been assaulted (Wenden, Crawford et al. 1998).

Further evidence to suggest a poorer outcome amongst victims of assault came from a recent unpublished study which suggested that anxiety and depression levels are higher amongst assaulted head injury patients than amongst non-assault patients, with assaulted patients also having higher scores on the PTSD checklist (Lawrie 2000). The current study supports the assertion that head injury patients who were victims of assault are significantly more likely to subsequently suffer from enduring emotional difficulties and suggests that the cause of the injury is of considerable prognostic value in predicting later emotional sequelae.

All of the measures of anxiety and depression were strongly correlated with outcome as measured by the GOS, with the correlations tending to be stronger for measures of depression than for measures of anxiety. These findings are consistent with previous reports of correspondence between the GOS and emotional difficulties (Satz, Forney et al. 1998; Satz, Zaucha et al. 1998). A recent study also reports strong correspondence between the extended GOS and emotional consequences of head injury, with modest benefits of the extended version over the original scale (Wilson, Pettigrew et al. 2000).

The current study, using a greater range of emotional outcome measures, found notably greater benefits of the extended scale, suggesting that this extended measure more accurately reflects emotional difficulties following head injury. This study did however complete the extended GOS towards the end of a patient-centred semi-structured interview in which the GOS was part of a fairly comprehensive assessment of outcome. Consequently the current study may have identified more disability due to emotional and social consequences of injury than may be elicited by means of a more-structured or telephone based interview conducted in isolation.

Conclusions and Summary

The apolipoprotein ε4 allele does not appear to have had any notable influence upon the recovery of the 62 head injury and 70 subarachnoid haemorrhage patients as a group. It is however possible that the ε4 allele may influence recovery in subgroups of patients. The current study did not include children and there is some evidence to suggest that younger patients may be more influenced by the presence of the ε4 allele. This may relate to observations of differential effects of ApoE isoforms upon neuronal plasticity and could explain findings of an effect of ApoE upon recovery in groups of patients who have participated in specialised rehabilitation programmes. There is also evidence to suggest that ApoE4 is less effective at preventing oxidative damage in the brain, such that patients with the ε4 allele may be less able to respond effectively to injury in a manner which could be age-dependant.

There was an association between the presence of ε4 and greater severity of haemorrhage amongst SAH patients. Patients with ε4 were more likely to have a Fisher Grade of 4, indicating intraventricular or intraparenchymal blood, and these ε4 Fisher 4 patients tended to have a poorer outcome than their non-ε4 counterparts. This is consistent with studies indicating an influence of ApoE upon outcome following intracerebral haemorrhage. These findings may relate either to a disposition towards a greater initial haemorrhage amongst ε4 patients due to deficiencies in blood clotting, or to greater secondary damage in ε4 patients which is possibly mediated via oxidative mechanisms.

Evidence from the current studies suggests that the NART may not be an appropriate measure of pre-morbid intelligence for use with survivors of head injury. The measure appeared to be influenced by severity of injury and there were discrepancies with demographically derived estimates of pre-morbid ability. Additionally, the NART is in any case inappropriate for those brain injury patients with acquired language deficits and is not a particularly patient friendly task. The study supports the use of the CCRT as an alternative measure to the NART, but suggests that any such measures should be considered in combination with demographically derived premorbid estimates.

The SAH study finds that Fisher Grades, based on the severity and extension of haemorrhage, are notably more predictive of subsequent outcome than the more frequently employed consciousness based WFNS Grade. The current consciousness based indices of SAH severity are restricted by the number of patients with GCS of 15 despite notable haemorrhage. The strong associations between GOS, SF-36 and cognitive outcome with Fisher Grade suggest that greater consideration should be placed upon the amount and region of haemorrhagic blood.

Contrary to assumptions amongst medial staff that aneurysmal patients always have a worse outcome than unknown aetiology patients, findings from this study support a growing body of evidence to suggest that there are no notable differences in functional outcome amongst *survivors* of aneurysmal SAH relative to unknown aetiology SAH. In part, this emphasises the importance of separate consideration of factors that influence functional recovery amongst survivors, as these factors are not necessarily the same as those that influence survival.

The study did find some moderate influences of site of aneurysm, with ACoA patients more likely than other aneurysmal patients to be in the 'low score' range on a passage recall task and tending to score more poorly on the various domains of the SF-36 health survey. These differences are substantially less pronounced than those reported in earlier studies that pre-dated the many recent advances in neurosurgical management. However they suggest that certain deficits remain more likely amongst ACoA patients and that recent studies that have reported no such differences may not have identified these differences due to their smaller sample sizes or more limited range of measurements.

Post traumatic amnesia (PTA) was found to be a better predictor of emotional and physical outcome than consciousness based indices of injury severity and was more predictive of 6-9 year Glasgow Outcome Scale than were GCS scores. Although GCS scores were more predictive of cognitive outcome, the apparently greater influence of emotional and physical consequences upon every-day functioning would suggest that PTA should at least be considered in combination with GCS when endeavouring to predict likely functional outcome. It is suggested that some measure of duration of disorientation or amnesia may also be of utility in predicting functional outcome from SAH.

Although there was some evidence of continued improvement beyond six months amongst SAH survivors as measured by extended Glasgow Outcome Scale, the balance of findings from the head injury study was that patients are at least as likely to deteriorate as to continue to improve in the longer term. Comparison of self-reported difficulties and ten repeated cognitive measures revealed few changes between assessments. There was some effect of age, with those aged over 35 deteriorating on cognitive tasks whilst the performance of younger patients remained largely unchanged.

Only patients who had been in coma demonstrated consistent improvements, with these improvements restricted to performance on information-processing tasks. This indicates that cognitive recovery from severe injuries continues beyond six months, which may reflect a greater recovery period following diffuse axonal injuries. Although more patients had returned to work by the time of the 6-9 year assessment, with a corresponding reduction in reported physical difficulties, there was a downward trend in GOS scores which seemed to reflect greater emotional and social difficulties. Depression was notably more frequently reported at the 6-9 year assessment and many patients indicated that initial optimism about recovery had gradually been replaced by resignation and greater social isolation.

The prevalence of clinical levels of anxiety and / or depression amongst around 40% of patients at least one year following brain injury is one of the key findings from these studies. The proportion of patients with moderate to severe anxiety was over twice as high in this SAH patient group than has previously been reported following other types of stroke. These differences may reflect in part the typically younger age of SAH patients relative to other strokes, with SAH patients suddenly suffering a life-threatening event which generally has no warning signs and prior to which they believed themselves to being healthy and not prone to such illness. Many patients had lost the confidence to go out on their own or even to be in the house without others in case anything happened again. This sense of loss of control over events is perhaps reflected by the findings amongst head injury patients that those whose injury was caused by an assault were more likely to suffer from anxiety and depression. Whereas the likelihood of a fall or a road traffic accident may be deemed to be to some extent influenced by an individual, this perception of control over events may be less true of assault victims.

With the exceptions of PTA and duration of loss of consciousness amongst head injury patients, most of the indices of injury severity were not predictive of subsequent levels of anxiety or depression. Thus although organic brain injury may directly lead to anxiety or depression in some cases (van Reekum, Cohen et al. 2000), it is reasonable to suppose that direct biological consequences are not necessarily the primary cause of all brain injury related cases of emotional disturbance.

Coping style has been suggested by some head injury studies to be predictive of subsequent emotional difficulties and it is possible that endeavouring to facilitate more adaptive coping styles may serve to improve functional outcome amongst some patients. Many patients, particularly those who had suffered SAH, felt that they would have benefited from further information about the haemorrhage or injury. It was often reported that although medical staff had been very helpful and had answered all questions, the patients had not really known what to ask or had been unable to understand or take in information provided at the time. Consequently it is possible that the supplementation of such information with tailored information booklets may serve to increase the sense of control that patients and their families feel in relation to the haemorrhage and potentially serve to reduce the incidence of subsequent anxiety disorders.

Even if such measures prove to be unable to reduce the incidence of anxiety or depression, the identification and treatment of such sequelae could substantially improve functional outcome in some 30-40% of patients. Whereas residual cognitive and physical difficulties are generally particularly resilient to therapeutic interventions, these emotional disorders can usually be successfully treated with interventions such as cognitive behavioural therapy and / or medication. Thus the use of some form of screening instrument, such as the HADS, may be useful in helping to identify those with or prone to these emotional disorders such that measures can be taken to reduce their impact upon functional outcome.

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