COGNITION, EMOTION AND QUALITY OF LIFE AFTER SUBARACHNOID HEMORRHAGE

by

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Abstract

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Cognitive dysfunction and depression are commonly reported sequelae of subarachnoid hemorrhage (SAH) and have been attributed to specific disease factors that reflect both focal (e.g., ischemic infarction) and diffuse (e.g., global hypoxia) injuries. We sought to comprehensively evaluate: 1) the impact of focal and diffuse disease factors on 3-month cognitive and emotional outcome, and 2) the association between cognitive/emotional disturbances and quality of life (QoL).

We prospectively evaluated 3-month outcomes in 68 of 150 consecutively admitted, non-traumatic SAH patients, with a comprehensive neuropsychological evaluation, including assessments of cognition (i.e., attention, verbal memory, language, etc.) and emotion (i.e., depression) and quality of life (QoL). Demographic and disease-specific variables were initially screened for univariate associations with cognitive and emotional outcomes in a series of analysis of variance (ANOVA) models. Disease factors with significant univariate associations were then entered into a series of forward stepwise multiple regression models, while controlling for relevant demographic factors. In separate analyses, indices of cognitive and emotional dysfunction that demonstrated significant univariate associations with Sickness Impact Profile scores were used as predictor variables in multiple linear regression models of QoL.

The proportion of subjects who scored in the impaired range (>2 SD below the normative mean) on each neuropsychological test ranged from 3 to 45 percent. Admission Hunt-Hess grade greater than 2, thick SAH in the anterior interhemispheric fissure, infarction from vasospasm, and left-sided aneurysm location were consistently associated with cognitive dysfunction in the univariate analysis. In the multivariate analysis, the presence of cerebral edema, infarction, and anterior circulation aneurysms were independent predictors of cognitive dysfunction after SAH. After controlling for demographics and premorbid cigarette use, depression was not associated with any disease factor. QoL scores were significantly associated with depression, motor performance, and verbal memory.

Cognitive dysfunction is predicted by both diffuse and focal pathology, and, along with depression, contributes to lower quality of life in patients with SAH . While treatment strategies aimed at reducing neurologic injury related to generalized brain swelling, infarction, and clot-related hemotoxicity hold the best promise for improving cognitive outcomes after SAH, aggressive treatment of depression may result in improved QoL after SAH.

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INTRODUCTION

Although early micro-neurosurgical treatment and aggressive post-operative management have been effective in reducing the overall mortality of subarachnoid hemorrhage (SAH) from over 50% to around 30% (Hop, Rinkel, Algra, & van Gijn, 1997), residual cognitive and emotional morbidity have consistently been documented in studies that evaluate these outcomes (for review, see Hutter et al., 1999). Clinically significant cognitive impairment in this population has been found in verbal memory (Barborotta, et al., 1989; Berry, Jones, West & Brown, 1997; Hadjivassiliou et al., 2001; Hillis, Anderson, Sampath, & Rigamonti, 2000; Hutter, Kreitschmann-Andermahr, & Gilsbach, 1998; Laiacona, et al., 1989; Larsson, et al., 1994; Larsson, et al., 1989; Ogden, Mee, & Henning, 1993; Richardson, 1989; Richardson, 1991; Stabell & Magnaes, 1997; Tidswell, Dias, Sagar, Mayes, & Battersby 1995), nonverbal memory (Berry, et al., 1997; Hadjivassiliou et al., 2001; Hillis, Anderson, Sampath, & Rigamonti, 2000; Hutter, et al., 1998; Ogden, Mee, & Henning, 1993; Sonesson, Saveland, Ljunggren, & Brandt, 1989), psychomotor speed (Hadjivassiliou, et al., 2001; Hillis, et al., 2000; Hutter, et al., 1998), executive function (Hadjivassiliou, et al., 2001; Hillis, et al., 2000; Hutter, et al., 1998; Hutter & Gilsbach, 1993; Ogden, et al., 1993; Tidswell, et al., 1995), visual-spatial function (Hadjivassiliou, et al., 2001; Hutter & Gilsbach, 1992; Laiacona, et al., 1989), and other cognitive domains (Hadjivassiliou, et al., 2001; Hutter, et al., 1999). In addition to these cognitive deficits, symptoms of depression and anxiety have also been reported after SAH in over a third of survivors (Hacket & Anderson, 2000). The pattern of emotional dysfunction seen after SAH fulfills DSM-IV criteria for Post Traumatic

Stress Disorder (PTSD) in over 30% of survivors that are referred for out-patient neuropsychological evaluation (Berry, 1998).

The fact that these deficits have been demonstrated in up to 50% of patients rated as having a 'good recovery' on the Glasgow Outcome Scale (Laiacona, et al., 1989; Ljunggren, Sonesson, Saveland, & Brandt, 1985; Ogden, Levin, & Mee, 1990, Ogden, et al., 1993; Richardson, 1991; Ropper & Zervas, 1984; Saveland, et al., 1986; Stenhouse, Knight, Longmore, & Bishara, 1991) and that 50% of patients who were previously employed do not return to the same level of work attests to the devastating nature of these deficits (Buchanan, Elias, & Goplen, 2000; Kreiter et al., 2001). Because of the relatively young age of this population (mean age ~ 55), even subtle residual deficits can have a significant impact on social and occupational role functioning.

One of the main ongoing debates regarding cognitive outcome after SAH involves the interpretation of test findings and whether they are more representative of a diffuse mechanism of injury, a focal pathology, or a combination of these. Although relationships between the side of infarction (Vilkki, Holst, Ohman, Servo, & Heiskanen, 1989) or site of aneurysm (Bornstein, Weir, Petruk, & Disney, 1987) and type of cognitive deficit have been reported, others argue that the neuropathology and pattern of deficits in SAH reflect damage of a more diffuse nature (Ogden, et al., 1993; Richardson, 1991; Smith, 1963; Tidswell, et al., 1995). Currently, it is not clear which factors best predict these disabling deficits, although a number of candidates have been proposed, including ictal intracranial circulatory arrest (Grote & Hassler, 1988; Ogden, et al., 1993), vessel ligation (Gade, 1982), exposure of the brain to subarachnoid blood (Hutter et al., 1999), intracerebral and intraventricular hemorrhage (Hutter, Kreitschmann-Andermahr,

& Gilsbach, 1998; Ogden, et al., 1993), hydrocephalus (Ogden, et al., 1993), delayed cerebral ischemia (DCI) or infarction (Ogden, et al., 1993; Richardson, 1991; Vilkki, Holst, Ohman, Servo & Heiskanen, 1990), and aneurysm location (Richardson, 1991; Stabell & Magnaes, 1997). Controversy still exists, however, as to which specific features and complications of SAH have the greatest impact on cognitive functioning and emotional status. Moreover, few published series of SAH patients have investigated the impact of acute disease factors on the subsequent development of depressive symptoms in a comprehensive manner (Irle, Wowra, Kunert, Hampl & Kunze, 1992). Finally, although the impact of SAH on QOL has been investigated (Hop, Rinkel, Algra & van Gijn, 2001; Hop, Rinkel, Algra & van Gijn, 1998b; Madureira, Canhao, Guerreiro & Ferro, 2000), the relative contributions of cognitive and emotional deficits to quality of life and return to work have not been previously reported. We sought to test the hypotheses that specific 'focal' and 'diffuse' SAH-related factors are predictive of cognitive and emotional outcome 3 months post-SAH and that emotional status, more so than cognitive impairment is related to survivors' quality of life (QoL).

Significance

Identifying the disease factors that lead to specific cognitive and emotional dysfunction is important not only for guiding the acute management of individual patients, but also in planning for rehabilitation and skilled nursing care needs, and issues related to long term recovery, including, return to work, resumption of driving and participation in social and recreational activities. A thorough understanding of relevant disease factors may prompt more aggressive management strategies designed to minimize

the deleterious effects of debilitating complications. Knowledge of these potentially modifiable disease factors may facilitate development of new, targeted treatment strategies. These results should aid in the selection of appropriately calibrated cognitive and behavioral assessments for tracking the recovery of individual patients and evaluating the efficacy of newly developed interventions and treatments.

BACKGROUND

Classic localization theory has provided a robust framework for explaining the origin of behavioral deficits seen after ischemic stroke and focal cortical damage. A wealth of converging evidence from lesion and imaging data suggests that cognition and emotion rely on networks of interconnected brain regions. Moreover, the organization of language and other cognitive abilities follows a similar pattern across individuals, such that damage to certain locations in the brain leads to predictable patterns of cognitive or emotional dysfunction.

Cognitive dysfunction after SAH – previous work

The long-term neurologic, cognitive, and emotional outcome in subarachnoid hemorrhage (SAH) has been reported since the late sixties (see Logue, Durward, Pratt , Piercy, & Nixon, 1968). Since then, many investigators have attempted to correlate acute clinical events with subsequent recovery using a variety of outcome measures, including global neurologic outcome scales, functional outcome scales, cognitive tests, psychological rating scales and structured interviews of social functioning, occupational functioning, and quality of life.

Because of the difficulty in selecting appropriate comparison groups, some have questioned whether SAH produces cognitive dysfunction. For example, McKenna, Willison, Phil, Lowe, & Neil-Dwyer (1989) prospectively studied the cognitive outcome of 100 SAH patients and 50 control subjects (myocardial infarction) one year after the initial illness onset and concluded that patients with no residual neurological deficits ('uncomplicated' cases, GOS = 1) "should expect no permanent disruption to their cognitive or emotional life". This conclusion was based on non-significant differences in test scores between uncomplicated SAH patients and control subjects. However, 40 percent of the 'uncomplicated' cases and 100 percent of the 'complicated' cases were impaired on one or more measure of cognitive functioning. In the study by Tidswell, et al. (1995), 65 percent of patients with aneurysms of the internal carotid artery system showed evidence for impairment in one or more cognitive domains, a finding in accordance with previously reported studies which indicate some degree of cognitive impairment in approximately 60 to 80 percent of SAH patients (Ljunggren, Sonesson, Saveland, & Brandt, 1985; Ogden, et al., 1990; Sonesson, Ljunggren, Saveland, & Brandt, 1987; Stenhouse, et al., 1991). Recent reviews have provided persuasive evidence that cognitive deficits do occur after SAH and are related to specific disease factors (Hutter, et al., 1999; Stabell & Magnaes, 1997). The following sections provide a review of the literature concerning the overall incidence of cognitive disturbances in this population. These sections will be followed by an examination of specific disease factors that occur in the setting of subarachnoid hemorrhage, and mechanisms by which they are thought to affect cognitive and emotional outcomes.

Measures of Intellectual Functioning

A fairly consistent finding after SAH is the apparent insensitivity of measures of intelligence (WAIS-R) to detect the effects of SAH (Hutter & Gilsbach, 1993; Ljunggren, Sonesson, Saveland & Brandt, 1985; Logue, et al., 1968; Sonesson, Ljunggren, Saveland & Brandt, 1987). However, when longitudinal assessment of WAIS-R scores has been reported, significant improvement occurs for at least one year after the bleed, suggesting that some subtle intellectual deficits may exist and can improve over time (Ogden, et al., 1993; Ogden, et al., 1990; Richardson, 1991).

Development of focal cortical syndromes, such as aphasia or apraxia, is uncommon (Irle, et al., 1992; Laiacona, et al., 1989; Teissier du Cros & Lhermitte, 1984;). In contrast, Hutter and Gilsbach (1993) did find evidence of an aphasic disturbance in 10 percent of patients experiencing a good recovery (GOS = 1). Deficits in immediate auditory attention span, measured by a digit span task, are often intact for forward span, but may be disrupted in reverse span tasks (Hutter & Gilsbach, 1992; Larsson, et al., 1989; Ogden, et al., 1993; Ogden, et al., 1990; Richardson, 1991; Vilkki, Holst, Ohman, Servo & Heiskanen, 1989).

Memory

The most consistently replicated neuropsychological deficit observed after SAH appears to be the impairment of explicit memory, visuo-spatial more so than verbal (Hutter & Gilsbach, 1993; Ljunggren, et al., 1985; Ogden, et al., 1993; Ogden, et al., 1990; Sonesson, et al., 1987). Most investigations of memory performance in SAH have focused on explicit memory in visual and verbal modalities (free recall, cued recall, and

recognition) and have found either visual or verbal memory deficits (or both) in up to 90 percent of study subjects (Romner, et al., 1989).

Larsson et al. (1989) retrospectively examined a "convenience" sample of 219 patients with SAH (follow-up 2-14 yrs) and fou nd short- and long-term verbal memory disturbances in 52 percent of their sample in a free recall task. In a prospective analysis of verbal free recall at 6 weeks (n=57) and 6 months (n=29; both sessions n=22), Richardson (1989) concluded that although deficits in free recall were frequent, only one could be regarded as "clinically amnestic."

In a prospective study (n=89), Ogden et al. (1993) found that verbal memory deficits improved over a 12-month period in 80 percent of patients but nonverbal memory (Rey Osterreith Complex figure test- ROCFT) remained moderately to severely impaired in 47 percent of the sample at 12 months. They conclude that the residual deficits in nonverbal memory reflect a more general visuo-spatial deficit, supported by the subject's continued poor performance on the copy trial. In an earlier study by the same author, (Ogden et al., 1990) visual memory impairment on the ROCFT was found in 100 percent of their 16 subjects at 5 years post-surgery. When compared to orthopedic controls, SAH patients score significantly lower on tests of facial recognition, immediate free recall of prose passages, and free recall of words (Tidswell, et al., 1995). The widespread replication of these results by a variety of investigators using analogous tests demonstrate that memory functioning is often affected by the effects of subarachnoid hemorrhage.

Psychomotor Speed

Although not widely investigated in SAH, reaction time tasks and tests of psychomotor speed have been shown to be sensitive to the effects of brain damage (Benton, 1994). Hutter & Gilsbach (1993) found that approximately 60 percent of SAH patients with a GOS=1 (n=31) were impaired in a choice reaction time for both RT and percent correct response. No differences in choice reaction time task were observed between aneurysmal and non-aneurysmal SAH subjects (Hutter, Gilsbach & Kreitschmann, 1994). When other timed tasks are evaluated (e.g., Trails A & B), approximately 50 to 75 percent of SAH patients exhibit impairment, with no significant improvement across testing sessions (Ogden, et al., 1993). Similar rates of impairment on the Trail Making Test (approximately 50 percent) have been found with even longer follow-up intervals (Romner, et al., 1989). Richardson (1991) reported significant differences between SAH patients (n=39) and laminectomy controls (n=16) on three timed tasks at a 6-month follow-up (object naming RT, and two fluency tasks). Curiously, in this study, the object naming RT 'deficit' was not significant at the 6-week testing. Indeed, on many if not most timed tasks, a large percentage of SAH patients consistently show evidence of cognitive slowing.

Executive Functioning

Because of their sensitivity to traditional frontal signs, including perseveration and decreased initiation, verbal fluency tasks (1st-letter cue or semantic cue) and the Wisconsin Card Sorting Task (WCST) or a modified version of it (Nelson, 1976) have often been used to investigate executive dysfunction. However, these tests are not

specific for frontal lobe dysfunction, and poor scores may result from non-frontal lesions (Ahola, Vilkki & Servo 1996; Lezak 1995).

The two primary response measures reported for the WCST are number of categories achieved and percent perseverative responses. Overall, indications of impairment on the WCST have ranged from 15 percent (Ogden, et al., 1993; Ogden, et al., 1990; Sonesson, et al., 1987) to 50 percent (Ljunggren, et al., 1985; Romner, et al., 1989) in SAH patients. When compared to controls and /or normative data, SAH patients obtain significantly fewer categories (Sonesson, et al., 1989; Stenhouse, et al., 1991) and commit significantly more perseverative errors (Tidswell, et al., 1995). Although, overall, the WCST appears to be sensitive to the effects of SAH (especially perseverative error scores), differences in the prevalence of dysfunction may be at least partially attributable to the use of slightly different forms (i.e., modified administration procedures that decrease the difficulty of the task, as in the 1993 study by Ogden, et al.). Comparison of anterior vs. non-anterior aneurysmal groups suffering from SAH revealed executive dysfunction as an isolated deficit in 19 percent of the patient group as a whole, however, differences between aneurysm location subgroups were not significant (Tidswell, et al., 1995). Despite the variation in methodologies, evidence for a "dysexecutive syndrome" after SAH has been acknowledged, especially in earlier case-series of patients with anterior communicating artery aneurysms (DeLuca & Diamond, 1995).

Visuo-Spatial Functioning

Visuo-spatial functioning after SAH has been evaluated by a variety of measures such as the Block Design subtest of the Wechsler Adult Intelligence Scale (WAIS-BD), the copy portion of the Rey Osterreith Complex Figure Test (ROCFT-copy), Raven's Colored Progressive Matrices (RCPM), Judgment of Line Orientation (JLO), Binet Cube Analysis, and the Line Bisection Test, with most studies finding basic perceptual abilities intact.

Studies reporting WAIS-R Block Design scores have revealed mixed results. In some series, patients are average or significantly above the normative mean, however, these patients also score above the mean on an estimate of pre-morbid verbal IQ (Nelson Adult Reading Test-NART) (Teissier du Cros & Lhermitte, 1984; Tidswell, et al., 1995). Other authors (Ogden, et al., 1993) have detected moderate to severe deficits on the WAIS-BD in 20 percent of the patients at 10 weeks post-surgery with significant improvement found at a 12-month assessment (only 10 percent moderately to severely impaired at 12 months post-SAH). Overall, they found that up to 39 percent of patients scored in the impaired range on tests of visuospatial function at 10 weeks. Other investigators have obtained similar rates of impairment on the block design subtest (approximately 20 percent), with evidence that more severely impaired subjects are more likely to show a more generalized visuo-spatial deficit (Romner et al., 1989; Sonesson, et al., 1989; Sonesson, et al., 1987).

The copy portion of the Rey Osterreith Complex Figure Task (ROCFT-copy) assesses visuo-spatial skills by requiring subjects to reproduce a complex geometric design in a paper-and-pen format. The subject's copy is rated for the accuracy and

relative positioning of the components of the original drawing. The ROCFT-copy has been assessed longitudinally in this population, and although performance can improve between discharge and 10 weeks post-SAH, approximately 40 percent of SAH patients will continue to be moderately to severely impaired 1 year after the hemorrhage (Ogden, et al., 1993; Ogden, et al., 1990). In a study of the effects of 'diffuse injury' (ventricular enlargement) and focal lesions as determined by CT, SAH patients with right lateral lesions and 'diffuse injury' but not right lateral lesion alone, were significantly impaired on the ROCFT-copy when compared to other lesion groups and a control group (Vilkki, et al., 1989). Interestingly, subjects with right lateral lesions only (no evidence of 'diffuse' damage) performed normally on WAIS-BD, JLO, and ROCFT-copy and delayed recall, tests that are usually sensitive to visuo-spatial functions and presumably mediated to some degree by the right hemisphere. In summary, the most consistent findings of visuospatial impairment in this population are seen on tasks requiring manipulation and organization of spatial material rather than a focal sensory deficit.

Psychological Outcome

Assessment of psychological status in SAH survivors has been limited. Prior studies looking at post-SAH depression have administered the Minnesota Multiphasic Personality Inventory (MMPI), the Hamilton Depression Rating Scale, and the Medical Outcomes Study Short Form-36, but most investigations have relied on semi-structured interviews and unvalidated questionnaires. Despite this shortcoming in the methodologies, depression and anxiety are commonly reported after SAH. Rates of

depression range from approximately 15 to 40 percent of SAH patients (Hackett & Anderson, 2000; Ogden, et al., 1993; Tidswell, et al., 1995).

To our knowledge, few studies have reported significant associations between acute SAH related disease factors and the development of depressive symptoms. Irle and her colleagues found that depressive symptoms were more common in patients with striatal lesions, independent of laterality (Irle, et al., 1992). A much larger literature exists describing the development of depression following ischemic stroke (i.e., 'post-stroke depression'). Reported associations between left-sided infarction and depressive symptoms (Morris, Robinson, Raphael & Hopwood, 1996; Shimoda & Robinson, 1999; Starkstein, Robinson & Price, 1987) have not been replicated by others, and many authors have failed to find associations between lesion laterality and the development of depression (Chemerinski & Robinson, 2000).

A more likely reason why many patients develop depressive symptoms may stem from the change in life-style and functional disability following a serious medical illness such as SAH (McKenna, et al., 1989). A review of the literature indicates that the most consistent associations with depression after ischemic stroke have been with concurrent measures of functional disability, cognitive impairment, and neurologic deficits (Astrom, Asplund, & Astrom, 1992; Carod-Artal, Egido, Gonzalez, & Varela de Seijas, 2000; Kauhanen, et al., 1999) suggesting that this type of depression may be better viewed as an adjustment disorder rather than as a direct result of cortical injury (Andersen, Vestergaard, Ingemann-Nielsen & Lauritzen, 1995; Gainotti, Azzoni & Marra, 1999).

Clinical Pathology of SAH

The challenge of understanding the impact of hemorrhagic stroke on brain-behavior relationships arises from the complexity of the disease itself. Neurologic function can be impaired by global, diffuse pathological processes (e.g., hypoxia from intracranial circulatory arrest) as well as from more focal factors (e.g., cerebral infarction from vasospasm). To add to this complexity, some of these complications can occur acutely, in conjunction with the hemorrhagic event (intraventricular blood), while other risk factors exhibit a delayed onset (e.g., cerebral vasospasm).

As was shown in the previous sections, large retrospective series (n>100) documenting poor cognitive outcome in this population (Desantis, et al., 1998; Desantis, et al., 1989; Larsson, et al., 1989; Storey, 1967) have been validated, for the most part, by more recent, better-controlled prospective studies. These prospective studies have attempted to identify a number of 'focal' and 'diffuse' SAH disease factors that are predictive of cognitive dysfunction after SAH. The following section will provide a description of these disease factors, etiological mechanisms of action, methods quantification of these factors, their observed frequency in this population, their impact on mortality and gross morbidity, and their impact on cognitive and emotional outcomes.

GLOBAL / DIFFUSE FACTORS

Total amount of cisternal blood

SAH is characterized by the presence of blood in the subarachnoid space and is usually caused by the rupture of an intracranial aneurysm, however, 10% of cases will never have a focal vascular lesion identified. CT scanning is the preferred assay for detecting subarachnoid blood, but xanthrochromic CSF from a spinal tap can also be used

to make a definitive diagnosis. A number of rating scales have been developed to quantify the amount and location of subarachnoid blood. The scales quantify the amount and location of blood that has leaked into the subarachnoid space. The two most commonly used are the Fisher grading scale (Fisher, Kistler & Davis, 1980) and the method of Hijdra et al. (Hijdra, van Gijn, Nagelkerke, Vermeulen, & van Crevel, 1988).

The rupture of a cerebral aneurysm introduces varying amounts of arterial blood into the subarachnoid space, which has predictable effects on mortality and severe disability; higher volumes of SAH result in higher rates of death and disability (Hijdra, et al., 1988; Ogilvy & Carter 1998, Saveland & Brandt,1994). Surprisingly, associations between total amount of subarachnoid blood and cognitive deficits have been non-significant in most studies (Ogden, et al., 1993; Romner, et al., 1989; Satzger, Niedermeier, Schonberger, Engel & Beck, 1995; Tidswell, et al., 1995), but there are exceptions (Hutter & Gilsbach, 1993; Larsson, et al., 1994). The most consistent relationships between the total amount of subarachnoid blood and cognitive dysfunction have been found for memory and executive function, but only when patients are tested in the acute stage (Hutter, et al., 1998). To our knowledge, no studies to date have investigated the relationship between amount and location of SAH and the development of depression.

Initial severity of bleed

Subarachnoid hemorrhage (SAH) often presents with severe headache, nausea and/or vomiting and in some cases, loss of consciousness, presumably from the initial impact of the bleed. Evidence from a small series of patients who rebled while undergoing Transcranial Doppler Sonography (TCD) observation indicates that post-

hemorrhagic, intracerebral circulatory arrest can ensue as homeostatic mechanisms are initiated following the rupture of cerebral aneurysms (Grote & Hassler, 1988). These data suggest that as autonomic responses and homeostatic mechanisms are initiated to assist in clotting the ruptured aneurysm, there is a transient interruption of cerebral blood flow. This temporary reduction in cerebral blood flow results in varying degrees of global cerebral hypoxia and is reflected in the duration of loss of consciousness (LOC) at ictus. Studies have shown that LOC and coma at ictus are related to larger amounts of extravasated blood (Hunt & Hess, 1968).

Because of the inherent difficulty of quantifying the degree of hypoxia during the acute hemorrhagic event, clinical scales have been developed as surrogate measures of initial bleed severity. The two most widely used scales for rating the initial severity of the hemorrhage are the Hunt Hess scale (HH - Hunt & Hess, 1968; Appendix 1) and the Glasgow Coma Scale (GCS - Teasdale & Jennet, 1974; Appendix 2), both of which rate level of consciousness and the presence/absence of neurologic signs.

The Hunt Hess grade is a 6-point scale of neurologic status ranging from 0 (unruptured aneurysm) to 5 (deep coma; decerebrate posturing). The Glasgow Coma score (GCS) evaluates level of consciousness within 3 domains: motor function, eye opening, and verbal responses. Scores range from 3 (No motor response, no eye opening, and no verbal responses) to 15 (obeys commands, eyes open spontaneously, and oriented x3).

Preoperatively, approximately 40-55 percent of all SAH patients will have a Hunt and Hess grade of I or II (asymptomatic, headache only), 15 percent will be rated as grade III (stuporous), 30 percent will fall into grades IV and V (focal neurological signs),

and of those 30%, as many as half will be dead on admission (Navalitloha, Taechoran, & O'Chareon, 2000; Saveland, et al., 1986). The relationship between worse HH grade and higher rates of mortality and severe disability has been widely documented (Hernesniemi, et al., 1993) and linked to deficits in visual memory, verbal memory, and executive functioning (Berry, Jones, West, & Brown, 1997; Hutter, et al., 1998; De Santis, et al., 1998; Ogden et al., 1993). Because of the sensitivity of hippocampal neurons to hypoxic damage, we would expect memory functioning to be sensitive to the effect of reduced cerebral blood flow and predicted by the admission Hunt Hess grade.

Cerebral Edema

Although not previously reported in studies examining cognitive outcome after SAH, cerebral edema is a fairly common complication of SAH and occurs in approximately 6% - 20% of all SAH patients (Claassen, et al., 2002; Kassell, et al., 1990). Evidence from feline models of hemorrhagic stroke indicates that cerebral edema after SAH results from the combination of global cerebral ischemia followed by the subsequent recovery of circulation, suggesting a breakdown of the blood-brain barrier (Shigeno, et al., 1982). Experimental cerebral edema can also be modulated by impaired auto-regulation of vascular reactivity, rebound hypertension and impaired capillary perfusion (Johshita, Kassell, Sasaki, & Ogawa, 1990). Other SAH disease factors that have been shown to contribute to the development of cerebral edema include loss of consciousness at ictus, worse clinical grade, larger aneurysm size, and larger amounts of SAH (Claassen, et al., 2002).

In the neurologic intensive care setting, the standard of care for the prevention of delayed cerebral ischemia (DCI) due to vasospasm is the administration of 'HH therapy', which combines induced hypertension and hypervolemia (administration of IV fluids to increase intravascular volume) to maintain adequate cerebral perfusion pressure (Lennihan, et al., 2000). Claassen and his colleagues (2002) demonstrated an independent contribution of induced hypertension in the development of cerebral edema in a cohort of 374 patients with SAH. Subarachnoid hematomas and infarction have also been shown to aggravate the swelling of brain tissue with deleterious effects on outcome (Niikawa, Kitajima, Ohe, Miwa, & Ohkuma, 1998).

There are reports of increased mortality rates when edema follows closed head injury (Eker, Asgeirsson, Grande, Schalen, & Nordstrom, 1998), ischemic stroke (Kassner, et al., 2001) and SAH (Claassen, et al., 2002). A complete understanding of the mechanism by which edema is thought to affect mortality and morbidity is not clear at present, however, it is likely that its deleterious effect is due to both the increased intracranial pressure as well as the pathophysiology underlying the development of edema, including global ischemia, hemato-toxicity from blood breakdown products of oxyhemoglobin and thrombin (Figueroa, Keep, Betz, & Hoff, 1998), an exaggerated inflammatory response (Gong, Hoff, & Keep, 2000), and vasopressin release (Laszlo, Varga, & Nakamura, 1999). These mechanisms have all been postulated to contribute to the long-term neurologic consequences commonly associated with the development of cerebral edema (Avrahhami, Katz, Rabin, & Friedman, 1998; Niikawa, et al., 1998). This hypothesis is supported by the findings of Eker and colleagues, who report a reduction of cerebral edema and improved outcomes after closed head injury (CHI) by reducing

arterial pressure, inducing large vessel and capillary vasoconstriction, and maintaining normovolemia, the opposite strategy as that found for treatment of vasospasm after SAH (Eker, et al., 1998). Because of its reported associations with mortality, cerebral edema qualifies as a potential contributor to the global/diffuse pattern of deficits commonly reported in studies evaluating cognitive outcomes after SAH.

Intraventricular hemorrhage (IVH)

Another potential feature of aneurysm rupture is intraventricular hemorrhage (IVH). If the ruptured dome of an aneurysm is oriented properly, the hemorrhage may be introduced into the ventricular system. IVH occurs in up to 36% of patients with aneurysmal SAH (Rosenorn, et al., 1987) and is a potent risk factor for mortality and functional morbidity (Mori, Mori, Kurisaka, & Morimoto, 1997). Hutter and colleagues (1998) reported a significantly higher rate of reaction time and executive deficits in patients with IVH at 2 weeks post-hemorrhage. Of the two studies of long-term cognitive outcome, only one reported an association between IVH and cognitive dysfunction (verbal memory) (Ogden, et al., 1993). No studies were found that evaluated the effect of IVH on post-SAH depression. Though not often reported, and poorly understood, IVH may have a deleterious effect on some aspects of cognitive outcome, through an as yet, undefined mechanism.

Hydrocephalus

Hydrocephalus is defined by a buildup of CSF within the cranial cavity. There are at least two mechanisms by which hydrocephalus can develop after subarachnoid

hemorrhage. First, large amounts of intraventricular blood can collect at the ventricular foramina, blocking the normal flow of cerebrospinal fluid (CSF) through the ventricular system, resulting in communicating hydrocephalus. Secondly, the circulation of diffuse subarachnoid blood can block the re-absorption of CSF by interfering with the arachnoid granulations, leading to a build-up of intra-cranial CSF. Either of these scenarios can result in clinically significant hydrocephalus and can be detected several ways.

Because CSF flow abnormalities can result in clinical deterioration, serial neurological exams can detect changes in mental status and/or the onset of new neurologic signs. These are often some of the first indicators that hydrocephalus is present. Because the build-up of CSF results in dilated ventricles, hydrocephalus can be quantified by examining the size of the ventricles with CT scanning. Finally, the build-up of CSF can raise intracranial pressure (ICP), detected with special probes placed into the ventricular system.

Acute hydrocephalus develops in approximately 10-20% of patients with SAH (Saveland, et al., 1992; Schutz, et al., 1993). Hydrocephalus and increased intracranial pressure are life-threatening complications, primarily due to the risk of brainstem herniation. In addition to higher rates of functional disability at follow-up (Schutz, et al., 1993), hydrocephalus has also been implicated in the development of acute transient amnesia in patients with SAH (Hop, Brilstra, & Rinkle, 1998a). Studies with cognitive testing at longer follow-up intervals have also reported decreased performance on tests of visual and verbal memory in SAH patients (Larsson, et al., 1994; Ogden, et al., 1993). Thus, from both a theoretical and empirical point of view, hydrocephalus has the potential of predicting memory functioning after SAH.

FOCAL FACTORS

Location of subarachnoid blood

It is possible that the *amount* of blood is less important than the *location* of blood for contributing to cognitive dysfunction after SAH. Studies looking at focal subarachnoid clots find stronger relationships with ischemia than with total amount of blood (Claassen, et al., 2001). Blood and blood breakdown products from the ruptured aneurysm may pool near tissue surrounding the aneurysm, causing local inflammation and destructive biochemical cascades (Unterberg, Sakowitz, Sarrafzadeh, Benndorf, & Lanksch, 2001). Conflicting evidence suggests that the deleterious effect of subarachnoid blood may be global or focal in nature (or both), and its ability to impact cognitive outcome may rely at least partially on its direct contact with cortical sulci and gyri.

There are some data to suggest that local irritation of cortical brain tissue may be mediated by its direct contact with blood and its breakdown products (Claassen, et al., 2001). The only study to examine the effect of focal subarachnoid blood found that digit span performance was inversely related to amount of blood in the left sylvian fissure, but only at 12 months post-SAH (Ogden, et al., 1993). In that study, there were no significant associations between location of subarachnoid blood at the 10-week post-SAH visit. Finally, in a study investigating the inflammatory cascade associated with the collection of blood in the subarachnoid space, intracellular adhesion molecule levels (ICAM-2) measured within 14 days of the hemorrhage were significantly associated with quality of life scores 3 months after the hemorrhage (Mack, et al., 2002).

Focal cerebral ischemia

Although most patients initially show improvement in their overall condition in the first few days after the hemorrhage, a substantial number of patients will exhibit evidence of delayed focal cerebral ischemia (DCI), most commonly caused by delayed narrowing of the cerebral arteries (vasospasm). Typically, the highest rates of large vessels spasm are observed within 6 to 21 days after the initial bleed (Claassen, et al., 2001; Quereshi, et al., 2000) and are most clearly identified by cerebral angiography. This modality identifies arterial narrowing in the large vessels in over 50% of all SAH patients during this time period. It is important to keep in mind that because angiography is unable to detect microvascular changes, vasospasm identified by this modality is sensitive, but not specific for detecting risk of ischemia (Weir, Grace, Hansen, & Rothberg, 1978). In some, but not all patients with large-vessel vasaspasm, ischemia can result in a deterioration in clinical condition and the development of acute hypodensities on CT scans (delayed cerebral ischemia). Evidence of frank infarction due to cerebral vasospasm can be documented in only 20 – 40% of patients with evidence (angiographic or clinical) of delayed cerebral ischemia (Charpentier, et al., 1999; Claassen, et al., 2001; Hijdra, van Gijn, Nagelkerke, Vermeulen, & van Crevel, 1988; Hop, Rinkel, Algra, & van Gijn, 1999; Murayama, et al., 1997; Quereshi, et al., 2000;).

It is widely believed that blood-related hemotoxicity, primarily from oxyhemoglobin, can contribute to vessel spasm, potentially decreasing blood flow to surrounding brain tissue and resulting in varying degrees of ischemia (MacDonald, et al., 1991; Mayberg, 1998). Inflammatory responses following SAH may contribute to vessel

spasm and the development of delayed cerebral ischemia (DCI), as is suggested by the finding that pro-inflammatory markers obtained from serum are related to worse functional outcome (Mack, et al., 2002). Data regarding the importance of eicosanoids, nitric oxide, and potassium channel dysfunction for the development of vasospasm and DCI are still controversial (Barbosa, et al., 2001; Sobey, 2001).

Highlighting the impact of cerebral vasospasm, several early studies have found that after controlling for hemorrhage severity, delayed cerebral ischemia (DCI) from vasospasm was one of the "leading causes" of SAH-related mortality and morbidity (Artiola i Fortuny, & Prieto-Valiente, 1981; Kassell, et al., 1982; Kassell, Sasaki, Colohan, & Nazar, 1985), and subsequent series continue to report strong associations between delayed cerebral ischemia (DCI) and death and/or disability (Mayberg, 1998). Recent reports, however, indicate that advances in the management of vasospasm may be preventing the development of clinically relevant ischemia, resulting in improved outcomes for these patients (Claassen, et al., 2001). Even with large differences in definitions and criteria, vasospasm and delayed cerebral ischemia (DCI) have been consistently predictive of cognitive outcomes for global mental status (Stenhouse, et al., 1991), verbal memory (Larsson, et al., 1989; Richardson 1989, 1991; Tidswell, et al., 1995), executive function (Tidswell, et al., 1995), and language (Richardson, 1991). When strict criteria are employed, such as hypo-densities on CT, associations remain with verbal memory (Ogden, et al., 1993; Vilkki, et al., 1989) but not with other domains (Desantis, et al., 1998; Dombovy, Drew-Cates, & Serdans, 1998; Romner, et al., 1989). Thus, we expect that delayed cerebral ischemia (DCI), but not cerebral vasospasm alone,

will have significant associations with neuropsychological test scores and that the pattern of deficits will follow predictions based on classic localization theory.

Intracerebral hemorrhage (ICH)

ICH describes a focal clot within the brain parenchyma. Intracerebral hematomas are commonly formed when the orientation of the aneurysm allows the escaping blood to enter the intercellular space. These lesions are clearly visualized on CT scanning. Collection of blood in the brain parenchyma can lead to tissue ischemia, cell necrosis, infarction, and focal edema (Holtmannspotter, Schoch, Baethmann, Reulen, & Uhl, 2000).

ICH occurs in approximately 42% of patients with primary SAH and is correlated with higher rates of mortality and long-term disability (Hauerberg, Eskesen, & Rosenorn, 1994). Of all stroke subtypes, the fatality rates for primary ICH (28-day fatality rate = 45%) are exceeded only by SAH (28-day fatality rate = 50%) (Thrift, Dewey, Macdonell, McNeil, & Donnan, 2001). In terms of impact on cognitive outcomes, three out of four studies of ICH in primary SAH have found significant associations between ICH and verbal memory (Larsson, et al., 1994; Ogden, et al., 1993), reaction time, executive function, and language function (Hutter, et al., 1998). The impact of ICH on the development of depression has not previously been reported. We expect that the effects of ICH will mimic the effects of ischemic infarction, resulting in focal cognitive deficits based on lesion location.

Aneurysm Location

Cerebral aneurysms often develop at bifurcations of major cerebral arteries. In a 30-year autopsy series of 1230 patients, the most common locations for aneurysm development were middle cerebral (31.5%), anterior communicating (30.1%), anterior cerebral (15.1%), vertebro-basilar (12.3%), and internal carotid (11%) (Iwamoto, et al., 1999). Prospective epidemiological data corroborate these frequencies: MCA (27%), ACoA (36%), ICA (26%), VB (8%), and other (3%) (Rosenorn, et al., 1987). In approximately 20 percent of patients presenting with SAH, the source of the bleed is never determined (Hawkins, Sims, & Hanka, 1989; Schutz, et al., 1993).

Little is known about the pathophysiology of aneurysmal growth except that it appears to result from a focal congenital defect of the internal elastic lamina, which over time, develops into dilations of the vessel wall, some growing to over 2 centimeters (Krex, Schackert, & Schackert, 2001; Mizutani & Kojima, 2000). Careful screening demonstrates that approximately 10% of aneurysm cases have at least one other affected family member, and individuals with autosomal dominant polycystic kidney disease (PKD) have higher rates of aneurysm ruptures than the general population (Belz, et al., 2001). Preventable risk factors for aneurysm rupture include hypertension, cigarette smoking, and cocaine use (Krex, et al., 2001).

For many years, cerebral angiography has been the diagnostic tool of choice for imaging the location of aneurysm but advances in magnetic resonance angiography (MRA) may soon allow for a non-invasive method of imaging the cerebral vasculature (Bernstein, Huston, & Lin, 2001). Currently, inadequate resolution (~5 mm) precludes

diagnostic certainty, as aneurysms smaller than 5 mm can frequently rupture (Weir, Disney, & Karrison, 2002).

Larger size and posterior location of aneurysms are consistently associated with increased risk of death and severe disability (Ogilvy & Carter, 1998; Rosenorn, et al., 1987). The impact of aneurysm location on cognitive test performance, however, has been conflicting, and to our knowledge, no investigation to date has evaluated the effect of aneurysm location on the development of depressive symptoms.

A large body of research has accumulated on the effects of aneurysms of the anterior communicating artery (Alexander & Freedman, 1984; Hutter & Gilsbach, 1992; Irle, et al., 1992; Laiacona, et al., 1989; Parkin, Leng, Stanhope, & Smith, 1988; Stenhouse, et al., 1991; Teissier du Cros & Lhermitte, 1984; Volpe & Hurst, 1983). Gade (1982) prospectively examined the differential effects of two surgery techniques on memory tasks (ligation of neck or trapping of aneurysm) and presented a persuasive argument that areas supplied by the perforating branches of the anterior communicating artery (ACoA) play a significant role in memory functioning. This was supported by the observations of Irle et al. (1992) who suggest that combined basal forebrain and striatum lesions (areas supplied by the ACoA branches) may lead to significant and permanent amnesia. Older surgical techniques were limited to trap ligation of parent vessels and were notorious for eliminating the blood supply to regions of the brain supplied by those vessels, resulting in complete infarction of those territories.

A number of more recent studies, however, have been unable to demonstrate a clear relationship when comparing different aneurysm sites with performance on tasks of memory and cognition (Ogden, et al., 1993; Richardson, 1989; Tidswell, et al., 1995).

Neither have aneurysms of the anterior communicating artery been associated with increased rates of depression (Hutter, et al., 1998) or decreased quality of life (Hutter, Kreitschmann-Andermahr, & Gilsbach 2001). Patients in these recent studies were treated with micro-neurosurgical techniques that typically spared the perforating arteries arising from the anterior communicating artery, the major source of blood supply to the basal forebrain, areas important for memory and executive functioning. The best evidence suggests that infarction in these territories is required for the "ACoA syndrome" to manifest. Readers are directed to DeLuca and Diamond's thorough review of the ACoA 'syndrome' literature (Deluca & Diamond, 1995). It can be concluded that the case study approach provides the best evidence for a specific ACoA 'syndrome' ('Korsakoff's-like' amnesia, confabulation and personality changes), reflecting the impact of cerebral ischemia to corresponding vascular territories.

Relationship between Cognitive / Emotional deficits and Quality of life

It has become increasingly clear that many hemorrhage survivors rated as having a 'good' recovery on the Glasgow Outcome Scale (GOS) may still suffer from cognitive deficits and impairments in quality of life (QoL) (Beristain, et al., 1996; Hutter & Gilsbach 1993; Ogden, et al., 1990). Although there are reports of impaired quality of life and reduced functional ability after SAH, no published studies have simultaneously investigated the relative impact of both cognitive disability and emotional dysfunction on quality of life (Hop, et al., 1998b).

Relationships between cognitive impairment and disability in activities of daily living have been reported after epilepsy surgery (Perrine, et al., 1995) and hemorrhagic

stroke (Fertl, et al., 1999; Lindberg, Fogelsjoeoe, Aengguist, & Larsson, 1996). Evidence from SAH patients without neurologic deficits suggests that even in patients without measurable brain damage, reductions in functional ability and quality of life can be demonstrated. For example, several studies have evaluated activities of daily living and quality of life in subjects with peri-mesencephalic subarachnoid hemorrhage, a more benign variant of SAH, with few, if any complications and neurologic sequelae. Despite the rapid and complete neurologic recovery in these patients, they consistently experience increased rates of depression and subtle neuropsychological impairments (Hutter & Gilsbach, 1993; Hutter, et al., 1994). Several authors have suggested that these results raise the possibility that an underlying adjustment disorder contributes to the high rates of anxiety, depression, functional disability, and quality of life (Madureira, et al., 2000; McKenna, et al., 1989). This study, however, will be the first to directly evaluate the relative impact of specific cognitive and emotional deficits on a number of different measures of health-related QOL and functional disability.

Hypotheses

Demographics

Based on a wealth of normative data, we know that demographic factors such as age and education have profound effects on cognitive test performance. We predict that the pre-morbid characteristics, age and education, will be strongly and consistently associated with cognitive and emotional function.

Although no data exist concerning the demographic predictors of depression in this patient population, epidemiological studies have evaluated the rate of depression

across the lifespan and found mixed results. A recent review found that out of 14 epidemiological studies of depression across the lifespan, 5 found an increase in depression in older adults, 3 showed a decrease, and 4 studies did not detect any age-related changes. The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) notes that "major depressive disorder is twice as common in adolescent and adult females," "highest in the 25- to 44-year-old age group" and "...lower for both men and women over age 65 years" (APA, 1994, p. 341). Because of the negative impact of SAH (hospitalization and convalescence) on occupational role functioning, we expect that these age effects will be magnified. Finally, because years of formal education often serves as a surrogate marker of socio-economic status, we expect that higher education may attenuate depressive symptoms after SAH due to increased social support and access to mental health services.

We hypothesize that younger age and higher education will be associated with better cognitive outcomes. We also predict that younger age, lower education and female gender will be predictive of higher rates of post-SAH depression.

Global / Diffuse factors

The evidence supporting the prognostic value of the volume of subarachnoid blood on cognitive outcome is limited. The lack of significant associations in recent large-scale, prospective series indicates that this factor is not a major determinant of cognitive dysfunction after SAH, despite the use of detailed radiological rating scales for recording the total amount of subarachnoid blood. To our knowledge, there have not been any published reports evaluating the effect of either the total amount or location of

subarachnoid blood on the development of post-SAH depression. *We hypothesize that total amount of SAH will not be associated with cognitive dysfunction or depression.*

Acute neurological status (admission Hunt Hess grade) has been the most consistent predictor of mortality and morbidity after SAH, as it reflects the combination of all pathophysiologic processes associated with the initial hemorrhage, including the severity of the acute, global hypoxic event. Poor Hunt Hess grade, thus serves as a marker of neurologic damage, with increasing rates of morbidity and functional disability that require a greater adaptive response from the patient during recovery. *We predict that poor Hunt Hess grade on admission will be associated with dysfunction in all cognitive domains, especially memory and with higher rates of post-SAH depression.*

Cerebral edema has been shown to predict poor outcome in traumatic brain injury and ischemic stroke, and although this factor has not been investigated in past studies of outcome after SAH, we expect similar relationships to hold true for patients with SAH. Because of the co-morbidity associated with cerebral edema, patients with this complication often must recovery from other debilitating complications of SAH. *We predict that cerebral edema will be associated with global declines in performance across all cognitive domains and increased rates of depression resulting from adjustment to chronic disability.*

Two acute disease factors that have been conceptualized as 'global' in nature are expected to result in deficits limited to specific cognitive domains. Based on previously reported associations (Hutter, et al., 1998), *we hypothesize that intraventricular hemorrhage (IVH) will be related to poor cognitive performance in reaction time and executive function, while hydrocephalus will be associated with impairment in memory*

and motor performance. We do not expect these factors to exhibit relationships with the development of depression.

Focal factors

In addition to the potential toxic effects of direct contact of blood on cortical structures, the presence of subarachnoid blood has been consistently associated with the development of cerebral vasospasm and risk of ischemia. Although studies investigating the impact of the location of subarachnoid blood on cognitive performance have been limited (Larsson, et al., 1994, Ogden, et al., 1993), we hypothesize that the presence of blood in the subarachnoid space may result in deficits that could be predicted by classic localization theory through a direct toxic/inflammatory effect as well as a secondary ischemia caused by localized vasospasm. The only significant association between location of subarachnoid blood and cognitive outcome reported to date has been with the presence of blood in the left hemisphere and worse performance on a digit span task, a test of attention and working memory. Although reports of left sided ischemic infarction and development of depression are somewhat conflicting, they suggest that factors associated with the development of ischemia in the left anterior hemisphere might result in higher rates of depression. *We therefore hypothesize that thick SAH in the left sylvian fissure will result in deficits of language function and verbal memory, while thick SAH in the right sylvian fissure will predict non-verbal memory performance and visuo-spatial functioning. SAH in the anterior interhemispheric fissure is expected to result in higher rates of impairment on tasks of executive function.*

Delayed cerebral ischemia is present in approximately 10 to 20% of SAH survivors. Previous research suggests that long-term cognitive outcome is most often influenced when ischemia is detected by CT or MRI imaging, rather than from acute, temporary deterioration in neurologic status. For depression, there is some evidence from ischemic stroke literature that left sided infarction sometimes leads to higher rates of depression. *Therefore, following the predictions based on classical neuro-anatomical models, we hypothesize that left-sided infarction will result in deficits of verbal memory and language functioning and in increased rates of depression, while right-sided infarction will result in deficits on tests involving non-verbal and visuo-spatial material.*

Evidence for the prognostic significance on aneurysm location has been virtually non-existent with most studies demonstrating no effect (Hutter, et al., 1999). Rather, other factors associated with aneurysm location, and capable of damaging cortical structures, such as side of surgical approach, may have a higher likelihood of producing specific patterns of neuropsychological performance. Because of the technical considerations involved in repairing aneurysms of the anterior communicating artery, such as temporary vessel occlusion, aspiration of basal frontal cortex (gyrus rectus resection), and disruption of perforating arteries of the basal forebrain during aneurysm dissection/clipping, it is possible that this location might be more frequently associated with long-term cognitive impairment. *We hypothesize that aneurysm of the anterior communicating artery will result in greater impairment in memory performance for both verbal and non-verbal material, and that aneurysms located in either the left or right hemisphere will not be associated with specific patterns of cognitive deficits.*

METHODS

Patient Population

Three hundred and twenty-two SAH patients admitted consecutively to the Neurological Intensive Care Unit (NICU) of Columbia-Presbyterian Medical Center between July 1996 and March 2000 were prospectively enrolled in the Columbia University SAH Outcomes Project. The study was approved by the hospital Institutional Review Board, and in all cases, written informed consent was obtained from the patient or a surrogate.

The diagnosis of SAH was established on the basis of the clinical presentation and the admission computed tomography (CT scan) or by xanthochromia of the cerebrospinal fluid if the CT scan was negative. Exclusion criteria included SAH from trauma or rupture of an arteriovenous malformation, admission >14 days after onset, age <18 years, left-handedness, history of serious neurologic disease, and non-fluency in English. Patients with spontaneous, non-aneurysmal SAH were included in the study.

Clinical Management

Ruptured aneurysms were treated with surgical clipping or coil embolization as soon as possible, with the exception of some Hunt-Hess grade V patients whose extremely poor condition precluded immediate treatment. All patients received oral nimodipine. While in the NICU, transcranial Doppler (TCD) sonography was performed daily or every other day. All patients with signs of elevated intracranial pressure and hydrocephalus were treated with external ventricular drainage (EVD). Patients were given 0.9% saline and supplemental 5% albumin solution to maintain central venous

pressure >8 mm Hg, and those with clinical deterioration from delayed cerebral ischemia (DCI) were treated with hypertensive hypervolemic therapy (HHT) using vasopressors to maintain systolic blood pressure >200 mm Hg. When significant clinical symptoms persisted despite HHT, angiography with balloon angioplasty of vasospastic vessels was performed, if feasible.

Clinical and Radiologic Assessment

Basic demographic data (age, gender, race/ethnicity, fluency in English, education level), social and past medical history, and clinical features at onset were obtained by reviewing the medical record and interviewing the patient and family shortly after admission. Cognitive status on day 14 (or at discharge if before day 14) was evaluated with the Telephone Interview of Cognitive Status (TICS; Brandt, Spencer, & Folstein, 1988). A complete review of the entire hospital course was conducted at the time of discharge by a study neurologist to document important procedures, events and complications.

Each patient's admission and discharge CT scan, as well as those CT scans with significant interval changes during hospitalization were independently evaluated by a study neurologist for: the amount and location of SAH, IVH, and ICH; the severity of hydrocephalus; and the presence of acute infarction or cerebral edema. The amount of SAH in 10 individual cisterns or fissures on the admission CT scan (and after an episode of rebleeding) was quantified according to the method of Hijdra, et al. (1988). Hydrocephalus was evaluated using the bicaudate index (considered present when it exceeded the upper limit of normal per decile of age) and the mean temporal horn

diameter (van Gijn, Hijdra, Wijdicks, Vermuelen, & van Crevel, 1985). "Treated hydrocephalus" was defined by treatment with lumbar puncture or drainage, EVD, or ventriculoperitoneal (VP) shunting. Global edema was diagnosed when effacement of the hemispheric sulci or basal cisterns was present, in combination with disruption of the hemispheric gray-white matter junction either due to blurring or diffuse "finger-like" extension of the normal demarcation between gray and white matter and was classified as global or focal, with focal edema classified as being related to infarction, hemorrhage, retraction injury, EVD placement, or other.

DCI will be defined as otherwise unexplained (1) clinical deterioration (i.e., a new focal deficit, decrease in level of consciousness, or both), and/or (2) a new infarct on CT that was not visible on the admission or immediate post-operative scan. Other potential causes of clinical deterioration, such as hydrocephalus, rebleeding, or seizures, will be rigorously excluded. Patients were classified as having TCD evidence of vasospasm if the mean velocity of any vessel exceeded 140 cm/sec. (Quereshi, et al., 2000).

Predictor Variables

Clinical and radiologic predictor variables were grouped into six categories, as follows: (1) *Clinical condition:* admission and worst Hunt-Hess scale score (Hunt & Hess, 1968); (2) *Hemorrhage:* admission Hijdra SAH sum score (Hijdra, et al., 1988), complete filling of any of 10 cisterns and fissures, and any IVH; (3) *Hydrocephalus:* bicaudate index (van Gijn, et al., 1985), mean temporal horn diameter, and treated hydrocephalus; (4) *Ischemia:* right-sided, left-sided, or any acute infarction, and DCI; (5) *Edema:* global, focal, or any cerebral edema; (6) *Aneurysm location:* anterior

communicating, left-sided or right-sided anterior circulation, anterior circulation, or non-aneurysmal.

Three-Month Follow-Up Assessment

Three months after the onset of SAH, each subject and their nearest relative or spouse were asked to complete a 45-minute in-person or telephone basic outcomes assessment. This evaluation included a structured interview assessing interim medical and social history, medications, rehabilitation, and work status.

Neuropsychological battery (Appendix 3)

Test selection

In addition to the basic outcomes assessment, subjects were asked to complete a 3-hour battery of neuropsychological tests whenever possible. In order to facilitate comparisons with the results of other studies, we chose tests that have previously been used in this population and shown to be sensitive to the effects of SAH. Tests were also selected based on the availability of normative data to facilitate the analysis of clinically significant levels of impairment. Finally, the test battery was constructed so as to comprehensively assess the functional geography of both cerebral hemispheres, as focal damage different cortical areas can produce isolated cognitive deficits. Because of the potential for cortical injury in any part of the brain, it was important to select tests that were sensitive to cerebral injury, no matter where in the brain the injury may have occurred. The following sections describe the neuropsychological tests used in constructing the cognitive domain scores.

Global mental status

Because one of the goals of this study was to evaluate the impact of global versus focal pathology on cognitive functioning, we wanted to include a general measure of overall mental status that would be sensitive to global/diffuse declines in cognitive ability. Although rarely employed in studies of outcome after SAH, mental status testing offers a brief assessment of a variety of cognitive domains, with a single summary score. In addition, we preferred a test that has been validated for administration over the telephone as it would have additional benefits for use in clinical trials and would increase the chance of assessing patients who may be too ill to travel to complete an in-person evaluation. The **Telephone Interview of Cognitive Status** is a 51-point mental status exam, based on Folstein's Mini Mental State Exam, which was developed specifically for administration over the telephone (Brandt, et al., 1988). Items assess orientation (12 points), counting backwards from 20 to 1 (2 points), verbal learning (10 points), serial 7's (5 points), naming (6 points), repetition (2 points), motor function (2 points), antonyms (2 points), and verbal memory (10 points). It demonstrates good inter-rater and test-retest reliability, sensitivity and specificity, and validity; has been used in hemorrhage populations (Dumbovy, et al., 1998b); and can be completed in less than 10 minutes. A wide range of item difficulty ensures minimal floor and ceiling effects. We also chose a similar test of global mental status, the **Short Blessed Test**, (Katzman, et al., 1983) to enhance comparisons with other studies and stroke populations. Combined, these tests assess a variety of cognitive domains, including orientation, memory, praxis, and

language functioning, and provide a single summary score to gauge impairment, helping to minimize the number of statistical comparisons.

Attention

Previous studies evaluating cognitive functioning after SAH have consistently identified cognitive slowing and attentional deficits in these patients. Using these findings as a guide, we evaluated a number of tests of attention according to several criteria. Because of the widespread acceptance of digit span tasks as valid and reliable measures of attentional capacity, and their frequent inclusion in studies of cognitive outcomes after SAH, we chose the **digit span** subtest from the WAIS-R (WAIS-R; Wechsler, 1981) as one of our indices of attention. We supplemented this digit span task with a test of sustained attention and verbal sequencing, the **Verbal Series Attention Test** (VSAT; Mahurin & Cooke, 1996). This test assesses the speed (time in seconds) and accuracy (number of errors) for the repetition of over-learned sequences such as reciting the alphabet, counting backwards, serial subtractions and days of the week forward and reversed. It also includes a verbal analogue of the Trailmaking Test, part B which requires the subjects to alternate between saying numbers and letters in sequence, and a vigilance task requiring the subject to tap on the desk when they hear the target letter "A" read among a series of distracter letters. This test has not been previously reported in the SAH population, but due to the item content, was chosen for its sampling of a variety of sequences. The test exhibits sound psychometric characteristics and can be completed by moderately to severely impaired subjects without a ceiling effect in high functioning patients. Further, because it is a timed test, the VSAT is well suited for

documenting change across time, a secondary aim of our study. Finally, we chose the **Trail Making Test – Part A** (Lezak, 1995; Spreen & Strauss, 1998) as a test of attention with a motor component. The Trail Making Test has been widely used in this population and has been shown to be sensitive to the effects of subarachnoid hemorrhage. The psychometric properties of this test have been well established; it can be completed by subjects with a wide range of cognitive impairments; because of the timed component, lacks a ceiling effect in high functioning patients; and is well suited to longitudinal assessment of change.

Visual Memory

Visual memory has consistently been reported as a cognitive sequela of SAH. The vast majority of studies have employed either the Benton Visual Retention Test or the Rey Osterreith Complex Figure Test (RCFT). We chose the **Rey Complex Figure** test (Rey, 1941; Spreen & Strauss, 1998) as one of our measures of non-verbal memory to facilitate comparisons with previous studies. In addition, this test allows for evaluation of more basic visuo-construction skills and organizational strategies. Because of the relative difficulty of the RCFT, we also wanted to include a similar but less challenging test of non-verbal memory. We selected the **Visual Reproduction subtest of the Wechsler Memory Scale-Revised** (Wechsler, 1987), primarily due to its widespread use and acceptance as a valid assessment of visual memory and recall. Both tests have an abundance of representative normative data, can be administered in a relatively short period of time, and together, can be assessed in patients with a wide range of cognitive disability. Finally, we included an **immediate recall portion for the digit-symbol**

subtest from the WAIS-R (Wechsler, 1981). This is a visual analogue of a paired associate task that was intended to measure non-verbal associative memory, a function not assessed by either of the other 2 visual memory tasks.

Verbal learning/Memory

Because verbal memory has also been consistently reported as impaired in this population, we sought to include a test that provided an index of acquisition as well as retrieval, in both a free-recall as well as recognition format. The **California Verbal Learning Test** (CVLT – Delis, Kramer, Kaplan, & Ober, 1987) is a 5-trial list learning task with both free and cued recall components as well as a recognition trial. The psychometric characteristics have been well established and validate its use in brain-damaged populations. Its widespread use facilitates comparison with other studies and patient populations. In addition, computerized scoring procedures allow for quick and accurate calculation of a number of clinically relevant parameters of memory function with norm based scores from a large, sample of individuals with similar demographic characteristics as our cohort.

Reaction Time

Reaction time tasks have been reported by previous authors to be consistently impaired in patients after SAH. We chose to assess Reaction Time with the first 3 RT scores of the **California Computerized Assessment Program,** simple RT, choice RT and sequence 1 (Miller & Satz, 1987). The CalCAP is a series of 4 tasks, assessing simple RT and 3 additional choice RT tasks of increasing difficulty. Because it is

administered and scored entirely via a computer, test-retest and inter-rater reliability are high. The scoring software calculates a number of indices, including RT, hits, and false positives; determines population-based z-scores from a large normative sample; and ensures accurate and reliable values due to its automated administration and scoring procedures. The large number of calculated values allows for a comprehensive assessment of a number of different components of RT performance.

Motor Function

Another area of cognitive functioning that has been consistently reported as impaired after SAH has been psychomotor speed. Motor functioning was assessed with the **Grooved Pegboard Test** (Klove, 1963) for both dominant and non-dominant hands and with **Luria's Unimanual Motor Programming** test (finger sequencing task) (Christensen, 1979) in which performance for each hand is summed and averaged. We chose these tests because of their widespread use and reported sensitivity to the adverse effects of SAH. These tests demonstrate good reliability and validity. Further, because of the timed component, they are sensitive to the cognitive slowing seen after SAH, sensitive to change across time, and resistant to floor and ceiling effects.

Executive Function

Although considerable controversy exists regarding the classification of certain tests as involving executive functions and the cause of poor performance, card-sorting tests have been widely used to assess this function. Because of the wide range of impairment seen after SAH, we chose a modified version of the **Wisconsin Card Sorting**

Test (Berg, 1948; Nelson, 1976) that could be completed by more severely impaired patients. We used normative data from the study by Lineweaver (Lineweaver, Bond, Thomas, & Salmon, 1999). This version differs from the traditional administration procedure in that ambiguous cards are removed and patients are told when the category shifts occur.

Visuo-spatial Function

Although basic perceptual functions are not commonly impaired following subarachnoid hemorrhage, many authors have reported deficits in visuo-spatial reasoning and analysis. Nearly all studies we reviewed have utilized the **Block Design subtest from the WAIS-R** (Wechsler, 1981) for evaluating visuo-spatial reasoning and have demonstrated that a significant number of patients experience difficulty on this task. We further chose to include the Block Design subtest as it has been shown to be sensitive to the effect of hemorrhagic stroke, has good psychometric properties, involves a timed component which minimizes ceiling and floor effects, and allows for assessment of longitudinal change. Also, this task is widely used in studies of cognitive outcome, facilitating comparison with previous studies and other patient populations. For efficiency sake, we also utilized the **copy portions of the RCFT** (Rey, 1941, Spreen & Strauss 1998) and **Visual Reproduction subtest of the Wechsler Memory Scale-Revised** (Wechsler, 1987) as measures of visuo-spatial function, since those tests were already routinely given as part of the visual memory assessment.

Language Function

Although aphasia is rarely seen after SAH, we included tests of language function to screen for left hemispheric damage. We chose widely used tests of confrontation naming, **Boston Naming Test** (Kaplan, Goodglass, & Weintraub 1983) and comprehension, the **Token Test** (Boller & Vignolo, 1966) to facilitate comparison of test results across studies and patient populations. These tests have been shown to be sensitive to left-sided lesions and can be assessed across a wide range of impairment levels.

Emotional Status

Common sequelae of SAH include fatigue, mental slowness, irritability, and related vegetative symptoms, which may result from prolonged hospitalization, bed rest, and inactivity. Therefore, we tried to avoid scales that defined depression primarily through vegetative symptoms. We chose to evaluate depression with the Center for Epidemiological Studies-Depression scale (CES-D, Radloff, 1977). The CES-D was chosen because it is heavily weighted towards non-somatic symptoms of depression and has been shown to exhibit a high degree of specificity and sensitivity with DSM-IIIR diagnosis of major depression in stroke populations, using a cutoff score of greater than 15 (Parikh, Eden, Price & Robinson, 1988).

Quality of Life (QoL)

Health-related quality of life was assessed with the Sickness Impact Profile (SIP), an objective, behaviorally-based assessment of quality of life that has previously been validated in stroke populations (Hop, et al., 1998b). The SIP provides a comprehensive

assessment of multiple domains of QoL and can be reduced to three dimension scores; physical, psychosocial, and total (Damiano, 1996).

Construction of cognitive domain scores

We selected three primary scores (2 for global mental status) for each cognitive domain to create a summary score for that cognitive function (Table 2). All raw scores were evaluated for non-normal distributions by calculating the skewness of the distribution of raw scores, then transforming the scores when the assumption of normality was not met. Data transformation of this type improves the ability of parametric statistical tests to identify trends, while maintaining relative relationships between scores (Fleiss, 1998). To accomplish this, we divided the skew statistic by the standard deviation of the skew statistic, and when the result exceeded ±1.96, we used a square root transformation and re-evaluated the distribution for normality. If the skew statistic remained greater than ±1.96, a log transformation was performed. Following this normalization procedure, the sample mean and standard deviation of our study cohort was calculated for each raw test score. These individual raw test scores were normalized into sample z-scores by subtracting the raw test scores from the sample mean, then dividing by the sample standard deviation. Using these data, summary scores for eight cognitive domains were created for each patient by averaging the three primary scores (normalized raw scores) from related neuropsychological tests. The tests selected to be included within each domain are listed in Table 2. Tests that were judged to tap similar cognitive functions on the basis of face validity were chosen for inclusion into each domain score (Table 2). The Kolmogorov-Smirnov test was used to confirm normality

of all domain scores (Fleiss, 1998). Emotional status was simply the raw total CES-D score.

For example, we evaluated the distribution of 3 raw test scores from the CVLT that were to be included in the verbal memory domain score (trial 1-5 total, short delay free recall, and long delay free recall). For each of the three raw test scores, we calculated the distribution statistics and then divided the skew statistic by the standard deviation of the skew statistic for the entire distribution of scores. If the result exceeded ±1.96, we replaced each subject's raw score with its square root and recalculated the sample distribution statistics (skew, standard deviation of the skew). If the skew statistic continued to exceed 1.96, we applied a log transformation to the original raw score and concluded the normalization procedure.

In the next step, the sample mean and standard deviation were calculated for each of the three normalized, raw test scores, and sample z-scores were created by subtracting the sample mean from a subject's test score and dividing by the sample standard deviation to create a new sample z-score for each subject for each of the three primary test scores (trial 1-5 total, short delay free recall, and long delay free recall). This procedure ensured that all individual test scores would share the same metric, allowing direct comparisons of performance between tests and between domains. The three sample z-scores were summed and then averaged to create a summary score representing the subject's performance on tasks of verbal memory relative to the scores of other subject's in the study. The normality of the final domain score was evaluated by calculating the Kolmogorov-Smirnov statistic for the final verbal memory domain score.

Statistical Analyses

All data analyses were performed with commercially available statistical software (SPSS version 9.0, SPSS Inc., Chicago, Illinois). Student's one-sample t-test was used to test normative Z scores of cognitive performance for significant deviations from zero (Fleiss, 1998).

Cohort descriptives

For descriptive purposes only, we converted raw test scores to population based Z-scores based on published normative data. We then calculated the proportion of subjects whose score fell in the clinically impaired range on each test (2 SD below the normative sample mean). It is important to note that for the actual statistical analyses we used sample rather than normative Z-scores, because in most cases, significant associations with demographic factors persisted, even after correction using published normative data (unpublished pilot data).

Using the verbal memory scores as an example, for descriptive purposes only, we evaluated the population-based z-scores for each of the three memory scores (trial 1-5 total, short delay free recall, and long delay free recall) and calculated the percent of subjects whose norm-adjusted test scores fell 2 or more standard deviations below age- and education-matched controls to give an overall rate of impairment for each of the tests comprising the domain score.

Follow-up Bias

We evaluated follow-up bias among subjects alive at 3 months by comparing selected demographic, clinical, and radiographic variables between patients who had neuropsychological testing and those who did not. One-way analysis of variance (ANOVA) was used to compare continuous variables, and the chi-square test was used for categorical variables (Fleiss, 1998).

Using the admission neurologic grade (Hunt Hess score) and age as examples, we sought to determine if there were systematic differences in the demographic characteristics of patients coded as a Hunt Hess grade of 1 or 2 versus those coded as a Hunt Hess grade of greater than 2. To do this, we first assigned a score of "0" for every patient with a Hunt Hess grade of 1 or 2. Patients with a Hunt Hess grade of 3, 4, or 5 were assigned a score of "1". We then calculated the mean age of subjects coded as 0 versus 1, and tested for significant group differences in age with a one-way ANOVA model. If the F-test was less than or equal to .05, we concluded that the mean age of subjects with a Hunt Hess of 1 or 2 was significantly different than the mean age of subjects with a Hunt Hess grade of 3, 4, or 5, and that a significant demographic bias existed for Hunt Hess scores. We felt that screening for this type of demographic bias was important because demographic factors are notorious for influencing cognitive test performance. For example, we know that younger subjects perform better than older subjects on tests of psychomotor speed. If we found a significant association between Hunt Hess grade and motor function, we might be tempted to conclude that Hunt Hess grade is a predictor of motor performance. However, if Hunt Hess grade was also strongly influenced by age, then we might want to control for the effects of age when evaluating the association between Hunt Hess scores and motor performance because it

could be that the one reason why Hunt Hess grade is significantly associated with motor performance is because it is also associated with increasing age, a factor we already know can lead to lower performance on motor tasks. This type of result may only indicate that age affects motor performance, which was not a primary aim of the study. Thus, we evaluated all acute disease factors for significant associations with demographic factors that can affect cognitive test performance. When a specific demographic factor was found to be significantly associated with both an acute factor (Hunt Hess grade) and a dependent measure (motor function), steps were taken to control for this confound in the univariate models (e.g., through the use of analysis of covariance [ANCOVA] models to control for the particular demographic factor).

Univariate predictors of cognitive function, emotional status, and quality of life

After dichotomizing continuous variables at the median, all demographic, clinical, and radiographic variables were tested for univariate associations with cognitive domain scores and total CES-D scores using ANOVA models (Tables 3 & 5). To evaluate the effect of aneurysm location, we compared subjects within each anatomic category to all other patients.

ANCOVA models were used to control for demographic bias in situations where a specific demographic variable was significantly associated with both a clinical or radiographic variable and a particular dependent variable. We used Levene's test to verify that the ANOVA assumption of equal variance was satisfied for both levels of the dichotomized independent variables (i.e., risk factor present versus absent) (Neter, Kutner, Nachtsheim, & Wasserman, 1996). When this assumption was not satisfied,

univariate associations were tested with t-tests without assuming equal variance (Fleiss, 1998).

For example, we compared the group mean motor function domain score in patients with a Hunt Hess grade of 1 or 2 to the group mean motor function domain score in patients with a Hunt Hess grade of greater than 2 using ANCOVA models, controlling for any demographic factor (e.g., age) that had previously been shown to be significantly associated with both the independent variable (Hunt Hess grade) and dependent variable (motor function domain score). A significant main effect of Hunt Hess grade indicated that Hunt Hess grade was a significant predictor of motor functioning.

Cognitive and emotional outcomes were initially evaluated for significant relationships with quality of life scores using a series of ANCOVA models, controlling for age and education effects. CES-D scores were dichotomized using a clinical cut-point of 16 (Parikh, et al., 1988). Cognitive domain scores (z-scores derived from the sample population) were dichotomized at the median. Significant group mean differences in QoL scores between depressed/non-depressed and high/low cognitive functioning were interpreted as significant contributors to SIP scores and included as criterion variables in the multivariate QoL regression models.

Using verbal memory domain scores as an example, we sought to evaluate the group mean quality of life scores (SIP scores) between subjects who performed in the upper 50% of the sample on tests of verbal memory to the group mean quality of life scores (SIP) for the subjects who performed in the lower 50% of the sample. Subjects in the upper 50^{th} percentile for verbal memory domain scores were coded as "1" whereas subjects falling in the lower 50^{th} percentile were coded as "0". We used ANCOVA

models (age and education as covariates) with cognitive performance as the factor (upper 50^{th} %ile vs. lower 50^{th} %ile) and the SIP score as the dependent variable.

Multivariate models of cognitive and emotional outcome

To identify independent predictors of cognitive and emotional outcome, we used a series of forward stepwise multiple linear regression models (list-wise deletion) with cognitive domain scores and total CES-D scores as the dependent variables (Fleiss, 1998). Regression models were constructed in two steps. Demographic variables that exhibit univariate associations were forced in on step one; candidate clinical and radiographic variables with significant univariate associations were then entered in a forward stepwise fashion in step two. For pathophysiologic categories exhibiting more than one significant univariate association, the most significant variable was selected. Significance was judged at $p<.05$ for all analyses.

Multivariate models of Quality of Life

We evaluated relationships between 3-month cognitive and emotional status and quality of life ratings with a series of forward stepwise multiple linear regression models (Fleiss, 1998). For each model, the quality of life score (SIP physical, SIP psychosocial, and SIP Total) was the criterion variable, and the cognitive domain and CES-D scores were the predictor variables. Regression models were constructed in two steps. Demographic factors (age and education) were forced into the model on step one. Cognitive domain scores and depression scores that exhibited significant univariate associations with QoL scores were entered in a forward stepwise procedure in step two.

Significance levels

Statistical significance was set at $p<.05$ for the analysis of follow-up bias, univariate models, and for the multiple linear regression models.

RESULTS

Study Population

The 68 patients who underwent neuropsychological testing ranged in age from 19 to 86 years (Table 2) with 2 to 19 years of formal education. A ruptured aneurysm was identified in 65 cases; 56 were treated with surgical clipping, 9 with coil embolization, and in three patients, an aneurysm was not detected or repaired. The proportion of subjects with each disease factor is listed in Table 3.

Follow-Up Bias (Table 1)

Figure 1 shows the follow-up status of the 322 patients enrolled in the study. Of 150 patients (76%) meeting inclusion criteria and known to be alive at 3 months, 68 (45%) underwent neuropsychological testing. The most common reasons for failure to undergo neuropsychological testing were patient refusal (N = 56) and severe cognitive impairment (N = 14). Table 1 summarizes the results of the follow-up bias analysis. Patients who underwent neuropsychological testing were significantly younger (p=.007) and more likely to have a ruptured aneurysm identified as the source of the hemorrhage (p=.015) than those who did not. The two groups were similar with regard to clinical disease severity, complication rates, and 14-day cognitive status (i.e., Telephone Interview for Cognitive Status scores).

Neuropsychological Performance (Table 2)

The proportion of subjects who scored in the impaired range (>2 SD below the normative mean) on each test ranged from 3 to 45 percent. The highest frequency of impairment was on tests of verbal memory and motor functioning (all >40%), and the lowest on tests of visual-spatial functioning (all <10%).

Emotional outcome

Forty percent of the subjects exceeded the cut-point of 16 for probable depression on the CES-D at the 3-month visit (mean=14.6, S.D.=12.3, range=0-50).

UNIVARIATE PREDICTORS OF COGNITIVE DOMAIN SCORES (Table 3)

Demographics

Patient age and education had consistent and robust associations with every cognitive domain score evaluated. Patients over 49 years of age scored significantly lower than younger patients on tests of global mental status (t=2.6, p=.014), visual memory (F=5.6 , p=.021) and motor function (t=2.9 , p=.006). Subjects with less than a high school diploma scored significantly lower than those with at least a high school education on tests of global mental status (F=4.1, p=.046), attention (F=7.5, p=.008),verbal memory (F=4.6, p=.035), reaction time (F=6.0, p=.018), and visuo-spatial function (F=15.1, p=.000). Test scores of subjects of non-white ethnicity were significantly decreased relative to whites for global mental status (t=3.6, p=.001), attention (t=4.3, p=.000), verbal memory (F=6.1, p=.016), reaction time (F=4.5, p=.037), visuo-spatial function (t=3.6, p=.001), and language functioning (t=4.8, p=.000). Only

one cognitive domain was influenced by gender; male subjects scored below female subjects only on tests of verbal memory (F=9.8, p=.003).

GLOBAL/DIFFUSE FACTORS

Admission Hunt Hess grade

As hypothesized, a higher (worse) Hunt Hess grade on admission was highly correlated with other parameters of acute disease severity; increased amounts of cisternal blood (Pearson's r^2 = +0.255, p<.042), IVH (Pearson's r^2 = +0.277, p<.027), more ICH (Spearman's r^2 = +0.284, p<.019), more hydrocephalus (Spearman's r^2= +0.509, p<.000), and increased frequency of edema (Spearman's r^2 = +0.458, p<.000). Associations with frequency of infarction and DCI did not reach significance.

Poor clinical grade (Hunt Hess > 2) was significantly associated with only 4 out of 7 cognitive domain scores; global mental status (t=3.0, p=0.005), attention (F=5.3, p=0.025), verbal memory (F=5.4, p=0.023), and motor functioning (F=6.5, p=0.013).

Edema

Compared to the other acute factors studied, cerebral edema was the only variable that predicted the majority of domain scores (67%). Global, generalized edema was associated with decreased performance in attention (F=4.9, p=.030), executive functioning (F=7.5, p=.008) and visuo-spatial functioning (F=4.1, p=.047). Focal edema was associated with worse motor functioning (F=8.7, p=.004). The presence of any cerebral edema (global or focal) was significantly related to poorer scores on tests of

attention (F=5.7, p=.020), verbal memory (F=4.4, p=.040), motor functioning (F=10.5, p=.002), reaction time (F=5.2, p=.026), and visuo-spatial function (F=4.3, p=.041).

Intraventricular blood and Hydrocephalus

No indices of early cognitive outcome were found to correlate with the presence or severity of intraventricular hemorrhage or hydrocephalus.

FOCAL FACTORS

Aneurysm Location

Overall, aneurysm location was related to cognitive outcome in four out of eight (50%) of the domains. Left-sided aneurysms predicted worse scores on tests of global mental status (F=5.0, p=.029), attention (F=5.7, p=.020) and verbal memory (F=4.9, p=.031). Aneurysms in the anterior circulation were predictive of lower verbal memory scores (F=7.0, p=.011). Aneurysms of the anterior communicating artery were associated with lower performance on language tasks (t=2.4, p=.017).

Cisternal blood

None of the cognitive domains appeared to be sensitive to the overall amount of SAH, however, focal clot/thick SAH in the anterior interhemispheric fissure was associated with relatively poorer performance on tests of global mental status (F=5.7, p=.020) and verbal memory (F=4.6, p=.035).

Intracerebral blood

No indices of early cognitive outcome were found to correlate with the presence or severity of intracerebral hemorrhage.

Cerebral Ischemia/Infarction

Not surprisingly, among all the disease factors investigated, the most robust associations were found between presence of infarction on CT scans and cognitive outcome. Infarctions in the left hemisphere were associated with relatively decreased performance on tests tapping global mental status (F=7.1, p=.010), visual memory (F=13.4, p=.000), and verbal memory (F=14.5, p=.000). Infarction attributed specifically to cerebral vasospasm predicted relatively poorer scores on tests of global mental status (t=2.8, p=.019), attention (F=6.1, p=.016). visual memory (F=5.5, p=.022), and verbal memory (F=10.0, p=.002). Any infarction, regardless of location or etiology, was significantly associated with decreased performance on tests of visual memory (F=6.0, p=.017) and visuo-spatial functioning (F=4.1, p=.048).

MULTIVARIATE MODELS OF COGNITIVE OUTCOME (Table 4)

Global Mental Status (GMS)

After controlling for the deleterious effects of higher age (B= -0.297, p=.004), and lower education (B=0.168, p=.136), only left-sided infarction remained as an independent predictor of global mental status (B= -0.279, p=.007) (Adjusted R^2 = .366).

Attention/concentration

After correcting for the influence of education (B=0.344, p=.001), cerebral edema (B= -0.237, p=.015) and infarction from vasospasm (B= -0.206, p=.037) exhibited significant associations with tests of attention (adjusted R^2 =.399).

Visual Memory

Independent predictors of visual memory performance were lower age (B= -0.230, p=.042) and left sided infarction (B= -0.387, p=.001) (adjusted R^2 =.199).

Verbal Memory

Of the three demographic factors exhibiting significant univariate associations with verbal memory performance, only gender remained as an independent predictor (B= +0.331, p=.002). After controlling for the influence of education and gender, two acute factors remained as independent predictors of lower verbal memory scores: infarcts in the left hemisphere (B= -0.354, p=.001) and aneurysms of the anterior circulation (B= -0.268, p=.015) (adjusted R^2 =.423).

Reaction Time

In the univariate analyses, significant associations with reaction time scores were found for years of education and non-white ethnicity, however, when both demographic characteristics were forced into the multivariate model, neither factor remained as an independent predictor of RT performance. After adjusting for these demographic

characteristics, the presence of cerebral edema (B= -0.265, p=.033) was the only significant independent predictor of reaction time performance (adjusted R^2 =.108).

Motor Functioning

Independent predictors of better motor functioning with lower age (B= -0.439, p=.000) and the absence of any cerebral edema (B= -0.366, p=.001) (adjusted R^2 =.311).

Executive Functioning

After controlling for the effects of age (B= +0.130, p=.307), global cerebral edema (B= -0.274, p=.021) emerged as the only multivariate predictor of executive functioning (adjusted R^2 =.168).

Visuo-spatial Functioning

After controlling for the significant influence of education (B= +0.464, p=.000), cerebral edema (B= -.220, p .027) was the only acute disease factor that was independently predictive of performance on measures of visuospatial function (adjusted R^2 =.384).

Language Functioning

No acute variables were included in the multivariate model for the prediction of language functioning.

UNIVARIATE PREDICTORS OF DEPRESSION (Table 5)

Patient Demographics

Increased depressive symptoms were seen in patients with less than 12 years of formal education for total CES-D scores (F= 7.9, p=.007), CES-D somatic item scores (F= 6.9, p=.011), and CES-D non-somatic scores (F= 7.5, p=.012).

Social History

A number of premorbid psychosocial factors were significantly related to increased depression scores 3-months post-SAH. Part-time occupational status prior to the SAH predicted CES-D non-somatic scores (F= 4.3, p=.043). Premorbid household income of less than $30,000 was predictive of increased depression scores for CES-D total (F= 7.4, p=.009), CES-D somatic scores (F= 6.8, p=.012), and CES-D non-somatic scores (F= 5.9, p=.019). Finally, subjects who were smoking cigarettes prior to the SAH, endorsed more items on the CES-D total (F= 9.0, p=.004), CES-D somatic scores (F= 4.2, p=.046), and CES-D non-somatic scores (F= 10.0, p=.003). History of prior treatment for depression was not predictive of 3-month CES-D scores.

Medical History

A history of hypertension was predictive of increased somatic symptoms at the 3-month visit (F=4.1. p=.048), but otherwise, no other pre-existing medical conditions were found to predict depression after SAH.

SAH Related Factors

Right-sided aneurysms were found to predict both CES-D total score (F=6.2, p=.016), and CES-D non-somatic score (F=7.8, p=.007), whereas experiencing an acute rebleed resulted in more somatic complaints at 3-months SAH (F=5.4, p=.023).

MULTIVARIATE MODELS OF EMOTIONAL OUTCOME (Table 6)

After controlling for the effects of education (B=-0.264, p=.083), only premorbid smoking status (B=-0.338, p=.017) was found to predict total CES-D scores (adjusted r^2 = .325). A similar pattern was found for the non-somatic score total, such that, after controlling for the effect of education (B=-0.245, p=.110), premorbid smoking status (B=-0.359, p=.012) was found to predict total CES-D non-somatic scores (adjusted r^2 = .317). None of the factors we investigated demonstrated an independent effect on the somatic scores (adjusted r^2=.114).

UNIVARIATE ASSOCIATIONS WITH QUALITY OF LIFE (Table 7)

After controlling for the effects of age and education, SIP physical scores were significantly associated with depression (F=7.71, p=.007), attention (F=5.31, p=.025), and motor functioning (F=9.08, p=.004). SIP psychosocial scores were significantly associated with depression (F=38.7, p=.000), attention (F=5.23, p=.026), visual memory (F=5.79, p=.019), and verbal memory (F=4.70, p=.034). SIP total scores were significantly related to depression (F=33.1, p=.000), attention (F=6.05, p=.017), visual memory (F=5.77, p=.019), verbal memory (F=4.7, p=.034), and motor functioning (F=5.95, p=.018). Global mental status, reaction time, executive functioning, visuo-

spatial functioning, and language functioning were not related to any aspect of quality of life as measured by the SIP.

MULTIVARIATE MODELS OF QUALITY OF LIFE

Table 8 shows the explanatory value of cognitive and emotional impairment, for predicting SIP dimension scores after adjustment for demographics (age and education) and emotional health (CES-D scores). The overall proportion of variance of these outcome measures explained by these models was lowest for the SIP physical dimension score (total adjusted R^2 =.512), moderate for the SIP total dimension (total adjusted R^2 =.702), and highest for the SIP psychosocial dimension (total adjusted R^2 =.711). Compared to cognitive and emotional status, demographic characteristics contributed only modestly to SIP dimension scores. For the SIP physical dimension scores, the proportion of explained variance was 10% for age and education, 64% for cognitive performance (motor function), and 16% for depression scores. The proportion of explained variance of SIP psychosocial dimension scores was 18% for age and education, 7% for cognitive function (verbal memory), and 75% for depression scores. For the SIP total scores, the proportion of explained variance was 16% for the effects of age and education, 72% for depression scores, and 12% for cognitive status (motor function and verbal memory).

Discussion

This study prospectively evaluated the impact of acute SAH disease factors on cognitive and emotional outcome in a multi-ethnic cohort of 68 subjects. After controlling for the strong influence demographic characteristics had on test performance, both focal (left-sided infarction) and global/diffuse (cerebral edema) factors remained as significant independent predictors of cognitive outcome following SAH. Only two other acute disease factors (1 focal, 1 diffuse) demonstrated significant and independent associations with cognitive domain scores: admission Hunt Hess grade with motor function and rupture of an anterior circulation aneurysm with verbal memory.

Only one acute disease factor (right-sided aneurysm location) was significantly associated with the development of depression; however, in the multivariate analysis, only premorbid cigarette use exhibited an independent effect on emotional outcome. These results indicate that depression following SAH may be less related to disease-specific factors and more dependent upon premorbid psychosocial factors and concurrent level of disability.

Depression scores were consistently related to quality of life scores, as was performance in a number of specific cognitive domains (attention, memory, and motor function) whereas demographic factors (age and education) were only modestly related. Depression status explained much of the SIP psychosocial and total scores while cognitive performance was a more important factor for SIP physical scores.

Demographics

As predicted, demographic characteristics were highly predictive of cognitive performance in this cohort. Higher age was strongly associated with poorer performance on tests of global mental status and motor function. There was a less pronounced, but still significant effect of increasing age and worse visual memory performance, while the domains of attention, verbal memory, reaction time, executive functioning, visuo-spatial function, and language function appeared to be resistant to the adverse effects of increasing age. Normative studies have consistently found age-related declines across a wide range of psychometric tests, with the most precipitous declines seen on tasks of frontal lobe function, motor performance, and memory after age 60 (Lezak, 1995). Cerebrovascular pathology has been suggested as a potential mechanism for frontal/subcortical age dysfunction (Pugh & Lipsitz, 2002), while glucocorticoid toxicity has been forwarded as a mechanism for hippocampal damage and memory loss (Nichols, Zeiba, & Bye, 2001). Given the relatively young age of this population (mean age = 50 years), it is not surprising that some age-related declines are less apparent; however, patients with SAH do exhibit higher rates of hypertension and smoking, which are known risk factors for cerbrovascular pathology, a factor linked to age-related frontal/subcortical dysfunction.

Contrary to our hypothesis, younger age was *not* associated with increased rates of depression in this cohort. Although cross-sectional, epidemiological data suggest that depression is more common in younger (25-44 years) adults (APA, 1994, p. 341), this was not observed in this patient population or in a similar cohort of good outcome SAH patients reported previously (Carter, Buckley, Ferraro, Rordorf, & Ogilvy, 2000). We expected that younger patients might experience increased rates of depression due to the

fact that the hemorrhage might be more disruptive to occupational activities (and financial repercussions), compared to older patients who are more likely to be retired. It does not appear that age-related factors in isolation are sufficient to precipitate post-SAH depression.

Evidence has been reported, both for implicating (Hutter, Kreitschmann-Andermahr, & Gilsbach, 2001) and excluding (Carter, et al., 2000) the influence of older age on quality of life scales. In our study, we found that age and education combined had only modest explanatory value for quality of life ratings, and more importantly, when the individual effect of age was examined, it was insignificant. The relative resistance of SIP dimension scores to demographic biases makes them desirable outcome instruments for use in this population.

Formal education has been established as a potent determinant of performance on cognitive testing, and in accord with this understanding, we found that fewer years of formal education was a significant predictor of poor cognitive function in six out of nine cognitive domains, the most robust and consistent demographic predictor of cognitive outcomes. The most pronounced effects of education were in the domains of visuo-spatial function (p=.000), executive function (p=.002), attention (p=.008), and reaction time (p=.018). The three cognitive domains that were resistant to the effects of educational bias were visual memory, motor function, and language function.

In the current study, both depressive symptoms and quality of life scores were related to fewer years of education. These findings have not been previously reported after subarachnoid hemorrhage. Given the correlation between educational attainment and other measures of socio-economic status (income, access to mental health resources,

and other social support mechanisms), it is possible that low education is simply a marker of other psychosocial stress factors (financial uncertainties, sub-optimal coping strategies, etc.). The increased psychosocial stressors and fewer education-mediated attenuating factors (e.g., financial) could lead to higher rates of dysphoria, although this is purely speculative.

The neuropsychological tests employed in this study were selected based on previously reported associations with SAH factors, to facilitate direct comparisons with previous studies. Tests were also chosen from the clinical literature, where normative data were available for assessment of impairment rates. However, when correlations between demographic factors and norm-adjusted z-scores were evaluated, significant associations remained, indicating that population-based demographic corrections were not completely removing the influence of demographic characteristics from the test scores. Because of this, demographic biases were removed from the test scores statistically, before evaluating the impact of acute disease factors on cognitive outcome. Although the influence of demographic characteristics on cognitive test performance has been well established, this study is the first in the SAH literature to systematically control for their influence with statistical methods (ANCOVA models).

These findings are important for clinical trials investigating cognitive outcomes because outcome measures used in these studies should ideally be sensitive to the effects of the disease and treatment, rather than patient specific factors such as age and educational level. Selection of cognitive tests that are resistant to demographic biases should increase the signal-to-noise ratio, increasing the power of the design, lowering subject numbers, and reducing the costs of conducting the study. Based on the results of

this study, language tests were the only cognitive domain that did not exhibit age and education effects.

Global/Diffuse Factors

Total amount of subarachnoid blood

In this cohort, we found that the total amount of SAH was unrelated to cognitive outcome. Consistent with previous studies (Ogden, et al., 1993; Satzger, Niedermeier, Schonberger, Engel, & Beck, 1995; Tidswell, et al., 1995), none of our measures of cognitive functioning were predicted by the total amount of SAH seen on admission CT scanning, despite our use of a rating scale that evaluated the total amount of blood in 10 different locations. One study by Hutter and colleagues (1998) demonstrated an association between Fisher grade (total amount of subarachnoid blood) and memory and executive function, however, testing was performed acutely, while patients were still in the hospital recovering from the initial SAH (< 2 weeks post SAH), a very different cohort of subjects, and not directly comparable with the current results.

Only two previous studies have reported an association between total SAH and cognition. In a retrospective study of 90 patients at a follow-up interval of 24-48 months, Larsson, et al. (1994) reported a significant association between total SAH as measured by the Hijdra scale and performance on a list-learning task. Hutter & Gilsbach (1993) published a series of 31 patients with a follow-up interval of 1 to 5 years and found that Fisher grade predicted performance on the Stroop task, but not on other tests. At the present time, the deleterious effects of total SAH on cognitive outcome appear to have only temporary or inconsistent effects on cognitive outcome. The lack of associations

between total amount of subarachnoid blood in the current study bring into question the significance of this variable as an important predictor of cognitive outcome after SAH.

Hunt Hess Grade

As hypothesized, in the univariate analyses, admission HH grade was associated with poor cognitive outcome in multiple domains. The univariate associations with global mental status, attention, memory, and motor functioning support the hypothesis that the initial pathology resulting from SAH as measured by clinical grade is diffuse and widespread (Ogden, et al., 1993). Motor function was the only cognitive domain that was independently predicted by initial SAH grade. The lack of independent effects in the other multivariate models suggests that secondary complications may play a more significant role in the development of cognitive dysfunction after SAH than previously acknowledged.

Cerebral Edema

Cerebral edema had its strongest influence on tests of attention/concentration, motor function, and executive function, domains relying on relatively diverse brain regions, consistent with the diffuse nature of this complication. The finding of cerebral edema as an independent predictor of cognitive outcome after SAH is novel and has not been investigated in previous reports of cognitive outcome after SAH. Moreover, comparison studies investigating the effect of cerebral edema on cognitive outcome after ischemic stroke and closed head injury are conspicuously absent.

Unfortunately, it is impossible from these data to determine the underlying patho-physiological mechanism of action leading to reduced cognitive abilities in patients who develop cerebral edema. The relatively low frequency of occurrence and strong associations with cognitive outcome in our cohort may be explained by its strong association with mortality and known deleterious effects on acute brain function (Claassen, et al., 2001, Shimoda, Oda, Tsugane, & Sato, 1993). At present, we interpret the association between cerebral edema and poor cognitive outcome as reflecting the impact of the initial bleed and subsequent development of global ischemia. Because of its strong association with ischemia, edema may best be viewed as a surrogate marker for the total burden of ischemia caused by both the initial hemorrhage as well as the secondary events, including vasospasm and temporary occlusion during surgical treatment.

IVH

Contrary to our hypothesis, none of our indices of verbal memory or RT were associated with IVH, in contrast to the results of Ogden, et al. (1993) and Larsson, et al. (1994) who identified IVH as a predictor of poor verbal memory performance and the study by Hutter, et al., (1998) that documented reduced RT scores in patients with IVH. Because of the known dissociations between different aspects of verbal memory (encoding, retrieval, discriminability, percent retention, etc.) it is possible that these discrepancies partially reflect differences in task requirements as well as differences in treatment and management strategies, as our patients with IVH are treated aggressively with external ventricular drains and V-P shunts, potentially minimizing the negative

effects of IVH in our cohort. We also did not find differences in RT performance among participants with and without IVH, possibly due to differences in follow-up intervals, as the study by Hutter, et al. conducted the neuropsychological evaluation less than a week after the SAH, whereas the current follow-up interval was closer to 90 days post-SAH.

Hydrocephalus

None of the measures of hydrocephalus were related to specific patterns of cognitive outcome in our cohort. Both prospective studies that have evaluated hydrocephalus and cognitive outcomes have reported significant associations with memory scores. In the study by Hutter, et al. (1998), hydrocephalus was associated with decreased memory performance during hospitalization, however, because the testing was performed less than 2 weeks after the onset of the SAH, these results are not directly comparable to the current findings. In a more comparable prospective study by Ogden, et al. (1993), CT evidence of acute (during hospitalization) hydrocephalus was associated with visual and verbal memory performance at 10 weeks after SAH, but not at 12 months post-SAH, suggesting that hydrocephalus may hamper memory processing, but only at relatively short follow-up periods.

Only one retrospective study investigating hydrocephalus has found significant associations with cognitive scores. Larsson and colleagues (1994) reported a significant association between a measure of hydrocephalus and verbal memory performance, however, their operational definition of hydrocephalus included "peri-ventricular edema". In our study, cerebral edema also showed a univariate association with verbal memory performance. Taken together, it appears that the impact of hydrocephalus on poor

cognitive outcome is greatest at shorter follow-up intervals, on tests of memory, and only when involving significant edema.

Focal Factors

Location of subarachnoid blood

In contrast to total amount of SAH, presence of thick blood in certain locations did demonstrate associations with 3-month cognitive outcome in the univariate analyses for global mental status and verbal memory. The fact that this predictor did not remain in the multivariate models when evaluated with CT infarction suggests that the effect of thick SAH on cognitive outcome may be mediated by (and dependent on) the development of ischemia. Only one other study to date has evaluated the effect of focal subarachnoid clots on cognitive outcome. They found that focal clots in the left sylvian fissure were predictive of poor digit span scores (Ogden, et al., 1993). These data, in combination with studies demonstrating the prognostic value of focal SAH for predicting the development of clinically significant vasospasm (Claassen, et al., 2001), indicate that the location and thickness of SAH has the potential to impact long-term cognitive outcome through an ischemic process.

Cerebral infarction-Ischemia

Not surprisingly, we found consistent and robust univariate associations between radiological markers of cerebral ischemia and six cognitive domain scores: global mental status, attention/concentration, visual memory verbal memory, visuospatial function, and language function. However, only left-sided infarction remained as an independent

predictor of 3 domains: global mental status and both memory scores. The large number of associations with a majority of the test scores indicates that focal ischemia is a large contributor to post-SAH cognitive morbidity.

The association between indices of ischemia and infarction are common in the SAH literature, however, the interpretation of these results is complicated by the qualitative and discrepant nature of the various definitions, sometimes defined radiologically (infarction on CT, angiographic evidence of vessel stenosis, and increased Transcranial Doppler velocities indicative of accelerated blood flow caused by vessel narrowing) and at other times, by clinical criteria (neurological deterioration). For example, retrospective reports have identified ischemia in mostly clinical terms, such as the new onset of "neurological events" (Tidswell, et al., 1995).

Even when imaging data were available, definitions of ischemia eluded rigorous quantification, such as angiographic evidence of vessel narrowing (Larsson, et al., 1989) and "hypodensities" and "mass effect" on CT scanning (DeSantis, et al., 1998; Dombovy, Drew-Cates, & Serdans, 1998a; Dombovy, et al., 1998b; Larsson, et al., 1989). Of the seven retrospective studies that have evaluated ischemia (DeSantis, et al., Dombovy, et al., 1998a; 1998; Hutter 1993; Larsson, et al., 1989; Romner, et al., 1989; Stenhouse, et al., 1991; Tidswell, et al., 1995), three reported significant associations with tests of global mental status (Stenhouse, et al., 1991), verbal memory (Larsson, et al., 1989; Tidswell 1995), and executive functioning (Tidswell, et al., 1995).

More recent prospective studies have corroborated the finding of delayed cerebral ischemia as a predictor of cognitive outcome, despite the qualitative definitions (i.e., angiographic narrowing of large vessels, hypodensities on CT, increased Transcranial

doppler flow velocities, and new onset of focal neurological signs) (McKenna, et al., 1989; Ogden, et al., 1993; Vilkki, et al., 1989). To date, six prospective studies have specifically evaluated the impact of ischemia (as defined above) on delayed cognitive outcome. Of these 6 studies, half reported significant associations with verbal memory (Ogden, et al., 1993; Richardson, 1989; Richardson, 1991) and/or language tasks (Richardson 1991). Differences in definitions of ischemia, wide variations in surgical morbidity, and small sample sizes may help to explain why more associations were not found.

Since the very recent introduction of non-ferromagnetic surgical clips, one recent report was able to define ischemia by the identification of infarction on MRI (Hadjisoulou, et al., 2001); however, direct comparisons were not reported for the effect of infarction on cognitive test scores. Nevertheless, the absence of carefully quantified radiological indices of ischemia after SAH in the literature is conspicuous, and our results serve to confirm the importance of infarction (seen on CT scanning) as a major determinant of cognitive outcome after SAH.

We were unable to replicate the previously reported association between left sided infarction and depressive symptoms (Morris, Robinson, Raphael, & Hopwood, 1996; Shimoda, et al., 1999; Starkstein, Robinson, & Price, 1987). On the contrary, in the univariate analysis, *right-sided* aneurysm location was associated with more depressive symptoms, however, this association did not remain significant in the multivariate model for prediction of CES-D scores. These patterns of results are consistent with previous reports that concluded that depression following stroke is mediated more by psychological than neurological factors (Anderson, Vestergaard, Ingemann-Nielsen, &

Lauritzen 1995; Gainotti, Azzoni, & Marra, 1999). Factors indicative of lifestyle changes are consistently associated with measures of depression, including functional disability and physical handicap.

ICH

In contrast to the results of 4 previously published studies, we failed to show an association between IVH or ICH and cognitive outcome. Ogden, et al. (1993), in a study with the most comparable follow-up interval (10 weeks), identified ICH as a univariate predictor of verbal free recall performance and IVH as a univariate predictor of verbal recognition memory. Another study reported a significant effect of ICH on verbal memory performance in a retrospective study with a longer follow-up interval of 2-7 years (Larsson, et al., 1994). In the current study, although the presence of ICH exhibited consistent associations with individual indices of verbal memory performance, these associations did not remain significant when evaluated as a composite score.

Aneurysm location

In the univariate analyses, left-sided aneurysm location was associated with relatively reduced performance on tests of global mental status, attention/concentration, and verbal memory, however, only aneurysms of the anterior circulation remained as an independent predictor of verbal memory performance, consistent with previously published reports (Barbarotto, et al., 1989; Stabell & Magnaes, 1997). Aneurysm location was not associated with depression, nor did we did find a specific, independent effect of ACoA location on cognitive or emotional status, in contrast to case series

reported previously (Alexander & Freedman, 1984; Hutter & Gilsbach, 1992; Irle, et al., 1992; Laiacona, et al., 1989; Parkin, et al., 1988; Stenhouse, et al., 1991; Teissier du Cros & Lhermitte, 1984; Volpe & Hurst, 1983).

Gade (1982) prospectively examined the differential effects of two surgery techniques on memory tasks (ligation of neck or trapping of aneurysm) and presented a persuasive argument that areas supplied by the perforating branches of the anterior communicating artery (ACoA) play a significant role in memory functioning. When surgical procedures disrupted the thalamo-perforators of the ACoA, severe memory deficits resulted. This mechanism of action was supported by the observations of Irle et al. (1992) who found that combined basal forebrain and striatum lesions (areas supplied by the ACoA branches) lead to significant and permanent amnesia.

A number of other studies have been unable to demonstrate a clear relationship when comparing a number of different aneurysm sites with memory performance (Ogden, et al., 1993; Richardson, 1989; Tidswell, et al., 1995;), likely due to at least three reasons: the large variability introduced by different types of repair procedures, differing skill levels of the surgeons, and small sample sizes. It should be noted that in one of the few studies to simultaneously compare multiple aneurysm locations, Ogden, et al. (1993) did not find a significant effect for aneurysm location. The relatively small sample (n=89) and comparison between 8 different sites resulted in small group sizes, likely minimizing the chance of obtaining statistical significance.

Two exceptions to these largely negative findings are the studies by Richardson (1991) and Stabell & Magnaes (1997), who found an association between left-sided aneurysms and poor performance on tests of verbal memory and language function. The

authors of one study attributed this association to the increased frequency of ipsilateral infarctions in that group (Stabell & Magnaes, 1997). Possible reasons why our results and other studies have not found a consistent relationship between the pattern of cognitive deficits and aneurysm location include significant differences in subject selection, differences in operative morbidity, differences in post-operative management and complication rates, timing of follow-up evaluations, and the use of qualitatively diverse measures of memory (immediate free recall, recognition, delayed free recall, etc). Taken together, our results indicate that the observed associations between aneurysm location and cognitive or emotional dysfunction, when they do occur, are likely mediated by secondary complications that are indirectly related to aneurysm location such as iatrogenic injury and focal ischemia, rather than from focal mechanisms directly related to the location of the aneurysm rupture itself.

Summary of Global/Focal Dispute

Based on the results of the multivariate models, of all the global and focal disease factors investigated, cerebral edema (global factor) and infarction (focal factor) are the two main acute disease factors that contribute independent effects on short term cognitive outcome after SAH in 8/9 cognitive domains assessed. Perhaps the most novel finding of the current study was the observation that cerebral edema exhibited robust and widespread univariate associations with cognitive domain scores, and remained significant in three out of eight multivariate models of neuropsychological outcome. The association of cerebral edema with the domains of attention, motor function and reaction time suggests that a global/diffuse injury related to the hemorrhage likely contributes to a

variety of neuropsychological impairments commonly seen in this population. Further, because of the watershed effects of attention and motor function on other cognitive abilities, cerebral edema may also impact other cognitive skills in a more subtle fashion that was not detected in this sample. Taken together, the pathology underlying the development of cerebral edema appears to be diffuse in nature, and an important predictor of outcome in a variety of cognitive domains after SAH.

Although focal cerebral edema is commonly seen after ischemic infarction and could demonstrate strong associations with cognitive outcome solely due to it's strong correlation with infarction, we did not find evidence that this was true. For example, both cerebral edema and infarction remained in the multivariate models of attention, indicating that the effects of both infarction and cerebral edema were independent, at least in some cognitive domains.

In addition to cerebral edema, two focal factors (the presence of cerebral ischemia and location of aneurysm in the anterior circulation) were powerful predictors of neuropsychological impairment, especially in the areas of verbal and non-verbal memory. Consistent with the vast literature on cognitive outcomes after ischemic stroke, these results indicate that the focal pathology seen after cerebral ischemia can exert a strong, independent effect on memory functioning after SAH.

The fact that the deleterious effects of focal pathology were limited to domains with large memory components (verbal memory, visual memory, mental status) suggests that this type of injury produces more circumscribed deficits than the diffuse injury related to cerebral edema, which exerted its effects on more widespread functions (attention, motor functioning, reaction time). These results suggest that global/diffuse

pathology (i.e., cerebral edema) is more important than focal injuries (cerebral ischemia) in predicting the range and extent of neuropsychological impairment after SAH and that the impact of focal damage is most often limited to memory functioning.

The highest rates of impairments found in our cohort were in the areas of memory, psychomotor speed/dexterity, executive function and attentional capacity, while receptive language and visuospatial functioning were only rarely affected. This pattern of performance suggests the localization of dysfunction primarily to anterior cortical and medial temporal lobe structures. One possible explanation of this finding is that most ruptured aneurysms arise from branches of the internal carotid artery, and the homeostatic mechanisms that are invoked to aid in clot development severely reduce intracranial circulation in the affected vessels. This acute, post-hemorrhagic intracranial circulatory arrest results in varying levels of ischemia, which has its most significant impact on vascular borderzone/watershed areas and hippocampal (CA1) neurons, which have been shown to be uniquely sensitive to disruptions in blood supply. Thus, if cognitive deficits are primarily driven by the effects of ictal ischemia, cognitive functions mediated by these cortical areas should be the first to demonstrate disruptions in functioning. The finding of high levels of impairment on tasks of memory, motor, and executive function provides support for this hypothesis.

Although we chose to evaluate the independent effect of acute disease factors with regression models, alternate statistical methods could be employed to identify the associations between SAH risk factors and neuropsychological outcome. For example, a discriminant function analysis including both acute factors and cognitive test results could identify which acute disease factors are related to specific cognitive tests.

Typically, however, these types of statistical procedures require sample sizes that exceed the number of participants enrolled in the current study.

Correlates of Quality of Life

Depression, as defined by CES-D scores greater than 16, was highly associated with all three measures of quality of life and remained in all three multivariate models for the prediction of QOL, highlighting the strong relationship between emotional function and measures of quality of life. This result underscores the significant impact depressive symptoms have on these patients' recovery and highlights the importance of assessing mood in SAH survivors. Future studies evaluating the effect of anti-depressant therapy should include measures of quality of life to evaluate the full range of benefits accrued by these interventions.

Performance on tests of cognitive function was associated with quality of life for only four domains: attention, visual and verbal memory, and motor function. Only verbal memory and motor function remained in the final multivariate models of quality of life. Variability in SIP physical dimension scores was explained more by test of psychomotor speed and dexterity than by depressive symptoms, in accord with the physical functioning items that comprise the scale. Similarly, variability in psychosocial dimension scores were strongly predicted by depressive symptoms, although, verbal memory did contribute significantly to the model. Finally, we found that both cognitive and emotional status (depression, motor function, and verbal memory) were significantly associated with SIP total scores, indicating that both emotional as well as cognitive dysfunction are significant contributors to poor quality of life after subarachnoid hemorrhage.

One provocative interpretation of the pattern of cognitive deficits reported after SAH is that the neuropsychological profile of SAH survivors mimics that seen in depressive pseudodementia. We found that the highest rates of impairment were found in tests of memory and motor function, two cognitive domains which are also compromised in individuals with chronic depression (e.g., Lezak, 1995). This interpretation is supported by the high rate of depressive symptoms found in these subjects, and the strong associations between cognitive test performance and CES-D scores (unpublished observation). If this hypothesis is true, the implications for recovery are significant, and we would expect that aggressive treatment of depressive symptoms may have a mitigating effect on the cognitive deficits seen in this population.

Although the correlation between post-SAH depression and cognitive dysfunction has been previously reported (Kauhanen, et al., 1999; Madureira, et al., 2000), few investigators have simultaneously evaluated the impact of both emotional and cognitive dysfunction on quality of life measures. One study that evaluated depression and a measure of physical handicap (Barthel Index), found that both contributed to predicting quality of life with the Reintegration to Normal Living Scale (Carter et al., 2000). The current study is the first, to our knowledge, to demonstrate the robust association between cognition, depression, and quality of life measures. These results suggest that among SAH survivors who are able to complete a neuropsychological evaluation, the factors most likely to affect quality of life are depression, verbal memory dysfunction, and deficits in psychomotor speed and dexterity. The moderate to high adjusted R^2 values of the multiple regression models for SIP scores indicate that indices of cognitive and

emotional status meaningful in terms of quality of life and valid endpoints for assessing outcomes.

As part of a larger study, these subjects returned for repeat testing at 12-months post-hemorrhage. One very important question yet to be addressed is the impact of early depression (3-months post-SAH) on long-term cognitive outcome. Analyses have been planned to evaluate the temporal relationship between depression and cognitive function by comparing 1) the effect of early depression (3-month) on late cognitive outcome (12-month) to 2) the effect of ultra early cognitive function (day 14 post-SAH) on early depression (3-month). These two analyses will provide an opportunity to infer the temporal relationship between cognition and depression.

Although not evaluated in the current study, the relationship between domain-specific cognitive dysfunction and return to work may contribute to our understanding of why cognitive dysfunction is associated with disability. For example, SAH survivors who suffer memory loss may experience severe occupational disability if they were working pre-morbidly in a job with high demands on remembering job-specific details. This same level of memory impairment, however, may be only mildly disruptive or inconsequential to someone who is already retired, with reduced demands on memory functioning.

Conclusion

Overall, the highest and most consistent rates of cognitive impairment after SAH were found on tests of verbal memory (43-45%) and motor performance (42%). High, but more variable rates of impairment were found on tests of executive functioning (16-36%), attention (10-38%), visual memory (16-23%), global mental status (24-25%), and reaction time (10-24%). Visuospatial (3-9%) and language tests (3-35%) were only minimally and/or inconsistently impaired in this population. After controlling for demographic influences, cerebral edema and left-sided infarction emerged as the most consistent predictors of worse cognitive functioning 3 months after the hemorrhage.

Consistent with previous reports, depression was common and was identified in 40 percent of our participants. The strongest and most consistent univariate predictors of depression were demographic characteristics (lower education) and measures of premorbid psychosocial functioning, including income level, insurance status, and cigarette use. Univariate associations between depression scores and disease factors were weaker, less consistent, and limited to right-sided aneurysm location and aneurysm rebleeding. Only premorbid cigarette use remained as independent predictors of post-SAH depression.

Adjusted R^2 values for the multivariate models predicting depression scores indicated that the majority of variance in emotional outcome was left unexplained. We did not identify any acute disease factors that were independently associated with higher depression scores. Based on the inconsistent relationships found in the ischemic stroke literature, the lack of an association between location of infarction and depression is not

surprising, since many authors have failed to find associations between lesion laterality and development of depression after ischemic stroke (Chemerinski, et al., 2000).

A more likely reason why many patients develop depressive symptoms may stem from the change in lifestyle and the functional disability following a serious medical illness such as SAH (McKenna, et al., 1989). A review of the literature indicates that the most consistent associations with depression following ischemic stroke have been with concurrent measures of functional disability, cognitive impairment and neurologic deficits (Carod-Artal, et al., 2000; Kauhanen, et al., 1999). Unpublished data from our group indicate that depression is highly associated with a variety of outcomes; participants with depressed mood score significantly lower than non-depressed subjects on a wide range of cognitive tests, measures of functional disability, and assessments of quality of life. McKenna and colleagues (1989) have described a group of "uncomplicated" SAH survivors who seem to perform as well as control subjects, which led them to the conclusion that recovery after SAH may be mediated, to a large part, by motivational and personality factors rather than by the acute effects of the original hemorrhage. Further research is needed to evaluate the influence of pre-morbid personality characteristics on long-term recovery.

Our experience with this population also suggests that family members and spouses might also be influencing patient's perceptions of recovery via a similar mechanism. In the process of conducting this study, we acquired anecdotal evidence that recovery is, at least in some ways, influenced by coping strategies and the personalities of individuals with whom the patient lives. Many times an overprotective family member will discourage the patient from resuming pre-morbid activities due to the fear of re-bleeding.

Often, scores on assessments of functional disability will reflect this decrease in activity level, however, often there is ample evidence that patients are physically capable of performing these activities if it were not for the admonitions of an overprotective family member. These observations suggest that an evaluation of the personality characteristics of family members and the patient's spouse/significant other may also contribute to our understanding of recovery after SAH. Previous research into caregivers of Alzheimer's patients suggests that the personality traits of spouses and caregivers are robust predictors of the use of successful coping mechanisms. The use of these coping mechanisms in family members of SAH patients may have a direct impact on the *reported* level of functional disability, and should therefore be investigated more thoroughly in this population. We would hypothesize that family members with more flexible personality traits and those who are more extroverted might respond to the hemorrhage in a spouse or family member more adaptively than individuals with less flexible or introverted personality styles.

We did not find that a simple question about previous treatment for anxiety of depression was predictive of post-SAH depression, nor did we find that acute disease factors were predictive of 3-month depression. Nevertheless, a large percent of our subjects scored in the range of probable depression on the CES-D, which was strongly correlated with decreased functional outcome and quality of life. Information gleaned from personality inventories (e.g., Eysenck [Eysenck & Eysenck, 1975]) and the Structured Clinical Intervirew for the Diagnostic and Statistical Manual (SCID; First, Spitzer, Gibbon and William, 1996) may provide clinicians with a more accurate method of identifying premorbid traits and predicting which patients should be followed more

closely for depressive symptoms, as treatment of mood should have a significant impact on recovery. Similarly, an evaluation of the personality traits of family members and the corresponding group dynamics may assist clinicians in maximizing the chances for a maximal recovery and return to premorbid activities.

Finally, the inclusion of both cognitive and emotional factors in the multivariate models of quality of life validates the use of these instruments in assessing outcomes after SAH. Tests of verbal memory and motor function demonstrated significant relationships with acute disease factors as well as with concurrent measures of quality of life, validating their use in clinical trials as relevant to SAH-related pathology as well as meaningful in relation to quality of life.

Implications for Clinical Trials

These results indicate that therapeutic agents designed to target the pathophysiologic processes underlying cerebral edema and ischemia (global and focal) hold the most promise for improving cognitive outcomes in patients with SAH. Interventions aimed at reducing the deleterious effects of subarachnoid clots may also have beneficial effects on patient's cognitive recovery.

The current study identified several neuropsychological measures that appeared to be exceptionally sensitive to the effects of the hemorrhage, namely: tests of verbal and visual memory as well as tests of psychomotor speed and dexterity. Clinical trials evaluating efficacy of new treatments for acute SAH should included these assessments of memory and motor function to increase the likelihood of establishing clinical benefit. Although depression was not predicted by SAH-related disease factors, it was shown to

correlate with quality of life, and therefore should be routinely assessed in SAH survivors as part of a comprehensive recovery plan.

One of the primary aims of this study was to develop a cognitive battery that is both sensitive to the specific effects of subarachnoid hemorrhage and meaningful in terms of functional outcome and quality of life. Neuropsychological tests that exhibit robust associations with acute disease factors as well as measures of functional outcome and quality of life are likely to provide the most reliable indicators of efficacy in clinical trials evaluating new treatments for hemorrhagic stroke. Other factors to consider when constructing a neuropsychological test battery for use in clinical trials include: construct validity of the test, inter-rater reliability, test-retest reliability, brief administration and scoring time, availability of alternate forms, unambiguous scoring criteria, and flexible administration modalities (e.g., in-person, phone, and internet-based).

Our findings indicate that tests of verbal memory exhibited widespread and robust associations with acute SAH factors and remained significant in the multivariate models of quality of life. Verbal memory has been the most consistently reported cognitive impairment after SAH and was the most frequently impaired domain in our sample. Tests of attention and global mental status were associated with a number of acute disease factors in the univariate analyses, but were not included in the final multivariate models of quality of life. Tests of global mental status share many of the same associations with disease factors as verbal memory scores, which likely reflects the composition of the test items; up to 40% of the mental status test points are derived from memory items. The primary advantage to using these tests is that they are relatively brief (5 minutes) and can be administered over the phone, an important consideration when constructing a test

battery, as telephonic assessment of outcome can attenuate subject attrition at longer follow-up periods. Tests of motor speed/dexterity and visuo-spatial function were associated with SAH severity, cerebral edema, and focal ischemia, indicating that they were reflecting the deleterious effect of the SAH. Further, tests of psychomotor speed and dexterity were correlated with two out of three indices of quality of life, and remained significant in the multivariate models. Previous studies of cognitive outcomes after SAH have identified visuo-spatial processing and tests of psychomotor speed and dexterity as domains frequently impaired after SAH. One cognitive domain that has commonly been reported as impaired in SAH survivors has been visual memory. A likely reason why we were unable to replicate this finding may be due to our choice of non-verbal memory tasks. Because of the nature of the test stimuli utilized in the Rey Complex Figure Test and the WMS-VR, it is possible that subjects utilized verbal strategies to solve these tasks, attenuating the well-documented effects of right hemisphere injury on non-verbal processing (Lezak, 1995).

Based on these observations, we feel that the ideal cognitive battery for assessing SAH induced brain injury ought to include a list-learning task such as the California Verbal Learning Test. In addition to exhibiting strong relationships to SAH disease factors and short-term quality of life, the CVLT allows for the quantitative as well as the qualitative analysis of performance. Alternate tests of verbal learning and memory would include Bushcke's Selective Reminding task or the Rey Auditory Verbal Learning Test, which have the added benefit of alternate forms. A brief test of global mental status could be added to this test battery to allow for assessment of cognitive function in the event an in-person assessment was not possible. We would recommend including the

TICS, as it has been well validated in dementia and ischemic stroke populations, and is correlated with SAH disease factors. Tests of attention (e.g., digit span and the Verbal Series Attention Test) were also associated with SAH disease factors and short-term quality of life. These tests are brief, are reliably administered and scored, and can be assessed over the phone if necessary. Tests assessing motor speed and dexterity should be a necessary part of any comprehensive neuropsychological battery for use after stroke, ischemic or hemorrhagic. Based on the results of previous studies as well as our current findings, the Trailmaking Test, The Grooved Pegboard Test, and Finger Tapping should provide a comprehensive assessment of motor function. Finally, based on previous studies, the inclusion of non-verbal memory tests seems warranted. A facial recognition test, such as the one in the third edition of the Wechsler Memory Scale would satisfy many of the requirements for use in a clinical trial. Administration times are short, scoring techniques unambiguous, and construct validity established previously by functional imaging studies.

Limitations

Clearly, one of the most significant limitations of this study resulted from our reliance on secondary markers of brain injury, for example, using the Hunt Hess grade as a measure of acute disease severity. Evaluation of the adjusted R^2 values for the multivariate predictors of neuropsychological outcome scores reveals that the acute factors never explained more than 42% of the variance in the cognitive outcome scores. One potential explanation for this low proportion of explained variance may lie in the measurement of the acute disease factors and the relatively qualitative nature of our

measurements of brain injury. For example, we relied on a clinical rating scale (Hunt Hess grade) to infer the initial ischemic deficit caused by the SAH, which may not be dissociable from other ictal pathology. Our only method of directly assessing neuronal injury was serial CT scanning, which has been shown to be unreliable for detecting acute infarction. CT scanning is also unable to detect the sub-clinical effects on brain functioning that are common after SAH, including acute hypoxic injury, reduced cerebral perfusion and blood flow, disruptions in neurotransmitter function, and the effects of chemical meningitis from subarachnoid blood. Without reliable assays of brain damage, the etiology of long-term cognitive deficits will remain ambiguous.

Future studies of cognitive outcome after SAH will need to address these considerations by the use of more sensitive imaging protocols, including: T1/T2 weighted magnetic resonance imaging for precise identification, localization, and quantification of frank infarction and cerebral edema; diffusion/perfusion weighted MR imaging for detection of cerebral perfusion deficits; magnetic resonance spectroscopy for detection of disruptions in cerebral metabolism and energy use; and SPECT or PET studies with radio-labeled ligands for the evaluation of neurotransmitter function. Other assays of neuronal damage, such as biochemical markers of neuronal damage (S100-B), bio-chemical markers of cerebral inflammation (e-selectin, I-CAM 1), and evoked potential/event-related potential studies for the detection of subtle electrophysiological abnormalities might also contribute important information about the various types of acute injury, which in turn, could lead to the identification of etiological mechanisms and potential therapeutic interventions (Cunningham, Morrow, Johnston, & Buchanan, 1994; Hardemark, Almqvist, Johansson, Pahlman, & Persson, 1989; Mase, et al., 1999).

Another potential limitation to this study design involved the assessment of language function. The test battery used in the current study utilized four language tests to assess comprehension, repetition, syntax, and confrontation naming. Low rates of impairment on tests of comprehension, repetition, and syntax (Token Test) indicate that basic comprehension was intact for the most part, however, a significant proportion of subjects (35%) scored in the impaired range on a naming task, indicating some disruption of language functioning. Further testing with more sophisticated tests derived from psycholinguistic models may provide important clues regarding the origin of the naming deficit in this cohort.

Delayed cerebral ischemia was a strong predictor of cognitive outcome in this cohort, however, our criteria for identifying these events could be improved with the use of volumetric MRI measurements. It is widely recognized that MRI is superior to CT in detecting ischemic changes, and with the recent introduction of non-ferrous clips, MR imaging prior to discharge should allow for better identification, localization, and quantification of cerebral infarcts after SAH.

Cerebral edema, like infarction, was another consistent predictor of cognitive outcomes, but was limited due to the relatively crude nature of detection, i.e., qualitative judgment based on CT scanning. Again, the use of MR imaging (T2 signal) can provide a quantitative value of brain water content, which should reduce the variability in edema ratings by clinicians and better clarify the relationship between cerebral edema and cognitive outcome.

Neuropsychological tests developed for clinical use have several major disadvantages when used in the research setting. For example, the Wisconsin Card

Sorting Test, once thought to reflect frontal lobe dysfunction, is not specific for frontal lobe damage. An accumulating body of evidence suggests that poor performance on this test is not predictive of lesion location (Ahola, et al., 1996). Our failure to observe high rates of visuo-spatial memory deficits was somewhat surprising, given the large number of investigators who have previously reported this finding using identical measures (RCFT, WMS-R VR, and WAIS-R), however this unexpected finding may be related to the insensitivity of our non-verbal tasks to the effects of right hemispheric damage (i.e., right-sided infarction). One possible explanation for this negative result is that the participants utilized verbal strategies that rely heavily on structures in the left hemisphere. This hypothesis is supported by the significant associations between left-sided infarction and poor visual memory scores, perhaps reflecting the effect of damage to these areas that were recruited when verbal strategies were employed in an effort to enhance performance. Future work will need to consider assessing right hemispheric injury with other tasks that are resistant to verbal mediation.

All of the tests used in this study were developed for clinical use and, as such, do not measure discrete, functional areas of the brain. Thus, poor test scores may be reflecting decreased functioning in cognitive areas which are only secondarily related to the cognitive domains they are reported to reflect. For example, it is possible that for individual subjects, poor performance on the Trailmaking Test may be more related to difficulty with sequencing rather than to inattention or psychomotor retardation. A more reliable way of assessing specific cognitive functions may require the use of experimental tasks originally developed for functional imaging paradigms. Such methodology has allowed investigators to infer the specific cortical areas and functional networks activated

during task completion. As these tasks become more refined, researchers will begin to have confidence that cognitive tests measure what they purport. Future studies should consider employing experimental tasks that constrain the problem-solving strategies and using only tasks that have been wel! characterized in terms of anatomic activations in functional imaging experiments to ensure comprehensive assessment of functionally relevant anatomic regions.

Another way to evaluate the meaning of poor test scores involves a qualitative analysis of test performance. It is no longer sufficient to claim that subjects experience 'memory deficits'. Rather, a more interesting question is "what aspect of memory functioning seems to be impaired?" Previous research has shown that there are many components of "memory" that can be dissociated (e.g., Squire 1992). Different anatomic regions have been linked to different aspects of learning and recall, and poor memory scores can be caused by encoding or retrieval deficits or both. Understanding which components are affected can provide useful information regarding the etiology of the deficits, the responsiveness of the deficits to rehabilitation, and the potential for future recovery.

This study has identified both focal and diffuse mechanisms of injury that can impact cognitive outcome after SAH. The cognitive domains most often affected after SAH in this cohort were memory and motor functioning. This study also identified three potentially modifiable disease factors for therapeutic interventions: cerebral edema, focal subarachnoid clots, and ischemic infarction. These pathological processes should be a focus for the development of therapeutic agents and treatment strategies to improve outcome. These results further indicate that tests of verbal memory and motor function

are sensitive to the effects of SAH and meaningful in terms of quality of life. Clinical trials investigating the therapeutic effects of different treatments after SAH should utilize tests of verbal memory and motor function to assess the efficacy of these newly developed treatments and interventions.

Directions for future studies

Because of the strong associations between edema, infarction, and cognitive outcome, future studies should begin to investigate the etiological mechanisms behind the identified disease processes. In our study, infarctions were identified on follow-up CT scanning, indicating that they were precipitated either by vasospasm or repair procedure complications. A more careful evaluation of surgical methods (retraction force/time, duration of temporary clipping, resection of surrounding brain tissue, etc.) may begin to reveal the relative contribution of procedural complications to the development of infarction and other events that influence SAH-related cognitive and emotional morbidity.

Both human and animal models indicate that cerebral edema develops after ischemic insults to the brain. While global cerebral edema occurs in approximately 20% of all patients with SAH and is a major contributor to acute mortality in this population, very little is known about the exact mechanisms through which it develops. Cerebral edema is also a feature of traumatic brain injury, a condition that has been compared to subarachnoid hemorrhage because of its similar pattern of long-term neuropsychological deficits. There is evidence to suggest that the optimal treatment for cerebral edema is mannitol therapy, diruesis, and induced hypotension (Eker, et al., 1998). Curiously, this

strategy is in direct contrast with the standard of care following aneurysm repair where neuro-intensivists seek to increase cardiovascular volume and raise blood pressure to prevent ischemia resulting from cerebral vasospasm. Although delayed ischemia from vasospasm no longer appears to be the main determinant of neurologic morbidity after SAH, the use of vasospressors to prevent vasospasm has been shown to contribute to the development of cerebral edema and may indirectly have a detrimental effect on cognitive outcomes. The current results indicate that the presence of cerebral edema was an important contributor to SAH related morbidity, and as such, should be the focus of future research to specifically evaluate vasospasm treatment protocols for their contribution to the development of cerebral edema in these patients. The recent availability of parenchymal blood oxygen sensors should provide real-time feedback of cerebral oxygenation, allowing clinicians to maximize vasospasm prevention while minimizing cerebral edema.

Investigation of the inflammatory cascade following the introduction of blood into the subarachnoid space may provide insights into the apparent dissociation between patients with evidence of vessel narrowing and those who go on to develop ischemic injuries (Mack, et al., 2002). The identification of the necessary and sufficient conditions for the development of ischemia from vasospasm may yield important clues to the development of therapeutic agents.

An important, yet unresolved question in the field of SAH outcome research is the relative safety, efficacy, and durability of the two main methods of repairing aneurysms, that is, surgical clipping and endovascular embolization. While surgical clipping is widely believed to be superior to endovascular embolization in terms of efficacy and

durability, the iatrogenic injury resulting from each type of procedure has only recently been investigated (ISAT collaborative group, 2002). Unfortunately, until very recently, patients selected for clipping versus coiling were treated as a function of aneurysm size and location. As a result, patients selected for endovascular treatment differ from those receiving surgical treatment, introducing a systematic bias of aneurysm location on outcomes, as coiling is usually only performed when surgical approaches risk damage to areas vital for cardiopulmonary function (i.e., brainstem). In order to fully evaluate the relative benefit of one treatment over the other, treatment would have to be randomly assigned to patients with clinical equipoise.

The high rate of depression seen in this population does not appear to be related to the hemorrhage itself. In fact, nearly 70% of the variance in depression scores was unaccounted for by the multivariate regression model. It is not known whether the depression seen after SAH is accompanied by reductions in 5-HT levels in the brain, nor have any double-blind, placebo-controlled studies of selective serotonin re-uptake inhibitors been conducted to evaluate the effect of anti-depressant therapy on mood in this population. Imaging protocols should be employed in future studies to evaluate the predictive strength of acute 5-HT and DA function for predicting the development of cognitive dysfunction and depressive symptoms as well as gaging an individual's response to pharmacologic treatment. Although improvement in mood is the direct benefit of anti-depressant therapy, our data suggest that there is a potential for concomitant improvement in quality of life and functional outcome. Further, if an agent such as Wellbutrin is chosen, with its stimulant properties and proven efficacy in smoking cessation, the potential benefit is even greater, as debilitating fatigue and

resumption of cigarette use are common sequela of SAH, impeding recovery and contributing to the risk of rebleeding. The potential benefit of anti-depressant therapy following SAH cannot be understated, as it currently appears to be the most promising intervention for impacting recovery after SAH.

Table 1. COMPARISON OF PATIENT CHARACTERISTICS FOR SUBJECTS ENROLLED IN THE CURRENT STUDY AND THOSE LOST TO FOLLOW-UP.[a]

Variable	Study Cohort (n=68)	Lost to follow-up (n=82)	*P*
Demographics			
Age, years	**48.9 ± 13.4**	**55.4 ± 15.2**	***.007***
Education, years	13.5 ± 2.8	13.1 ± 3.1	*NS*
White	38/68 (56%)	56/82 (68%)	*NS*
Female	46/68 (68%)	48/82 (59%)	*NS*
Social History			
Premorbid Tx for Dep or Anx	12/68 (18%)	16/82 (20%)	*NS*
Acute Clinical			
Admission H-H grade			*NS*
1 or 2	39/68 (57%)	42/82 (51%)	
3	18/68 (26)	27 (33%)	
4	8/68 (12%)	11 (13%)	
5	3/68 (4%)	2 (2%)	
Hijdra Sum Score	14.1 ± 8.0	11.9 ± 7.5	*NS*
IVH	1.7 ± 2.4	1.4 ± 2.0	*NS*
Bicaud Index exceeding ULN	21/64 (33%)	29/69 (42%)	*NS*
Right sided aneurysm	18/63 (29%)	12/68 (18%)	*NS*
Left sided aneurysm	13/63 (21%)	15/68 (22%)	*NS*
Anterior circulation aneurysm	48/63 (76%)	46/68 (68)	*NS*
Anterior communicating aneurysm	17/68 (25%)	19/82 (23%)	*NS*
Non-aneurysmal	**3/68 (4%)**	**14/82 (17%)**	***.015***
Delayed Cerebral Ischemia (DCI)[b]	18/68 (26%)	15/82 (18%)	*NS*
Any infarction	23/68 (34%)	26/82 (32%)	*NS*
Global Edema	7/68 (10%)	7/82 (9%)	*NS*
14-day TICS score	28.7 ± 11.7	25.0 ± 14.0	*NS*

Table 1.

[a] Group differences on selected demographic and disease related factors between study cohort and subjects lost to follow-up. Except for age and bleed source, the two groups were comparable in terms of disease severity and complication rate.

Values are mean ± SD or n (%)

[b] Refer to methods for definition of DCI.

H-H = Hunt Hess; IVH = Intraventricular hemorrhage; NS = non-significant; SAH = subarachnoid hemorrhage; TICS = Telephone Interview of Cognitive Status; ULN = upper limit of normal for age

Table 2. TEST RANGE, SAMPLE RANGE AND DESCRIPTIVE STATISTICS FOR NEUROPSYCHOLOGICAL TEST PERFORMANCE OF STUDY COHORT [a]

Cognitive Domain	Tests	Test Range (poor-good)	Sample Range	Mean Raw Score	Mean Z-score [b]	Percent Impaired [c]	Kolmogorov-Smirnoff *p*
GLOBAL MENTAL STATUS	TICS (cut-point ≤30)	0-51	18-46	35.0 ± 6.9	--	24	.020
	Katzman OMC (cut-point ≥6)	28-0	19-0	3.5 ± 4.1	--	25	
ATTENTION	WAIS-R Digit Span	0-28	5-24	13.1 ± 4.4	-0.4 ± 1.01	10	.177
	VSAT – Time (sec)	480-0	349-40	120.1 ± 71.2	-0.8 ± 1.6	31	
	Trails A (sec)	300-0	240-14	47.2 ± 32.3	-1.3 ± 1.3	38	
VISUAL MEMORY	WMS-R Visual Reproduction II	0-41	0-39	22.1 ± 11.0	-0.51 ± 1.3	16	.470
	RCFT – delayed recall	0-36	0-31	15.4 ± 6.3	-1.2 ± 1.2	23	
	WAIS-R Digit Symbol recall	0-9	0-9	5.2 ± 2.6	---	---	
VERBAL MEMORY	CVLT Trials 1-5	0-80	10-65	44.3 ± 14.2	-1.4 ± 1.4	44	.670
	CVLT Short Delay Free Recall	0-16	0-15	8.0 ± 4.0	-1.6 ± 1.7	45	
	CVLT Long Delay Free Recall	0-16	0-16	8.4 ± 4.4	-1.6 ± 1.7	43	
REACTION TIME (RT)	Cal-CAP – Simple RT (ms)	5000-0	1131-242	382.2 ± 140.4	-0.2 ± 1.1	10	.311
	Cal-CAP – Choice RT (ms)	870-0	759-335	463.3 ± 101.3	-0.7 ± 1.5	24	
	Cal-CAP – Sequence 1 (ms)	870-0	856-401	627.8 ± 120.0	-0.8 ± 1.3	18	
MOTOR FUNCTIONING	GPT – dominant hand (sec)	300-0	300-55	95.4 ± 48.2	-1.4 ± 1.4	42	.287
	GPT – non-dominant hand (sec)	300-0	300-59	109.0 ± 50.1	-1.5 ± 1.3	42	
	Uni-manual programming	0-	3-22	12.7 ± 4.0	---	---	
EXECUTIVE FUNCTIONING	MWCST- # of categories	0-6	1-6	4.08 ± 1.88	-1.1 ± 1.3	36	.506
	MWCST - perseverative errors	47-0	0 - 42	7.67 ± 11.0	-0.72 ± 1.23	16	
	Trails B – time (sec)	300-0	180-31	111.9 ± 70.0	-1.0 ± 1.4	31	
VISUAL-SPATIAL FUNCTIONING	RCFT Copy	0-36	18-36	32.4 ± 4.1	0.2 ± 1.9	9	.751
	WAIS-R BD	0-51	1-46	22.2 ± 10.8	-0.3 ± 1.0	3	
	WMS-R VR Copy	0-41	27-41	36.7 ± 3.3	---	---	
LANGUAGE FUNCTIONING	Boston Naming Test	0-60	15-60	48.3 ± 11.0	-1.0 ± 1.6	35	.010
	Token Test	0-163	2-163	154.8 ± 24.7	0.2 ± 1.5	3	

Table 2.

[a] Descriptive statistics for the study cohort's performance on the neuropsychological tests used in the creation of cognitive domain scores. Ranges of possible scores for each test are listed under "test range". Ranges of scores observed in the study cohort are listed under the heading "sample range". Group mean scores for raw and normative population adjusted Z-scores for the study cohort are listed under the columns "mean raw score" and "mean Z-score", respectively. Values are mean ± S.D. The proportions of subjects scoring more than 2 standard deviations below the normative reference population for each of the cognitive tests are listed under "percent impaired". The distributions of cognitive domain scores were evaluated with the Kolmogorov-Smirnoff test, with the p-values listed under the heading "Kolmogorov-Smirnoff p". Domain scores with non-significant Kolmogorov-Smirnoff values ($p>.05$) were considered normally distributed. Refer to text for methods used to calculate domain summary scores.

[b] Based on published normative data; [c] Percent of subjects falling 2 standard deviations below the normative sample mean or cut point

CalCAP = California Computerized Assessment Package; CVLT = California Verbal Learning Test; GPT = Grooved Pegboard Test; mWCST = Modified Wisconsin Card Sorting Test (Nelson's version); OMC = Short Blessed Test of Orientation, Memory and Concentration; RCFT = Rey Osterrieth Complex Figure Test; TICS = Telephone Interview of Cognitive Status; Trails A = Trailmaking Test-Part A; Trails B = Trailmaking Test-Part B; WAIS-R BD = Wechsler Adult Intelligence Scale-Revised Block Design subtest ; WMS-R VR copy = Copy portion of the Wechsler Memory Scale-Revised Visual Reproduction subtest.

Table 3. UNIVARIATE ANALYSIS OF DEMOGRAPHIC, CLINICAL AND RADIOLOGIC VARIABLES ASSOCIATED WITH POOR COGNITIVE DOMAIN SCORES [a]

		Cognitive Domain									
		Mental Status		Attention		Visual Memory		Verbal Memory		Motor Functioning	
Risk Factor	%[b]	F	*p*	F	*p*	F	*p*	F	*P*	F	*p*
Demographic											
Age 50 years	44	**2.6**	***.014*** [c]	---	---	**5.6**	***.021***	---	---	**2.9**	***.006*** [c]
Education 12 years	16	4.1	*.046*	**7.5**	***.008***	---	---	4.6	*.035*	---	---
Non-white ethnicity	44	**3.6**	***.001*** [c]	**4.3**	***.000*** [c]	---	---	6.1	*.016*	---	---
Male gender	32	---	---	---	---	---	---	**9.8**	***.003***	---	---
Clinical Condition											
Admission Hunt-Hess >2	43	3.0	*.005* [c]	5.3	*.025*	---	---	5.4	*.023*	**6.5**	***.013***
NIHSS > 0 [d]	41	---	---	---	---	---	---	---	---	---	---
Focal SAH Clot											
Anterior Interhemispheric	14	5.7	*.020*	---	---	---	---	4.6	*.035*	---	---
Cerebral Edema											
Global Edema	10	---	---	4.9	*.030*	---	---	---	---	---	---
Focal Edema	19	---	---	---	---	---	---	---	---	8.7	*.004*
Any Edema	26	---	---	**5.7**	***.020***	---	---	4.4	*.040*	**10.5**	***.002***
Ischemia											
Left-sided infarction	16	**7.1**	***.010***	---	---	**13.4**	***.000***	**14.5**	***.000***	---	---
Infarction from vasospasm	13	2.8	*.019* [c]	**6.1**	***.016***	5.5	*.022*	*10.0*	*.002*	---	---
Any infarction	34	---	---	---	---	6.0	*.017*	---	---	---	---
Aneurysm Location											
Left sided	19	5.0	*.029*	5.7	*.020*	---	---	4.9	*.031*	---	---
Anterior circulation [e]	71	---	---	---	---	---	---	**7.0**	***.011***	---	---
Anterior communicating	25	---	---	---	---	---	---	---	---	---	---

Table 3.

[a] Impact of demographic and disease-specific factors on cognitive domain scores. Proportion of subjects with each risk factor is listed under "%". For each risk factor, significant F-tests ($p<.05$) indicate poorer performance in that cognitive domain for participants with that risk factor. Values in bold indicate significance in multivariate models; [a] Percent of the study population with the given risk factor; [b] Domain scores exhibiting unequal variance between risk factor levels. In these cases, differences were tested with a t-test, without assuming equal variance; [c] Adjustment for education level using ANCOVA model; [d] Adjustment for ethnicity using ANCOVA model

GCS = Glasgow Coma Score; NIHSS = National Institutes of Health Stroke Scale; SAH = subarachnoid hemorrhage.

Table 4. UNIVARIATE ANALYSIS OF DEMOGRAPHIC, CLINICAL AND RADIOLOGIC VARIABLES ASSOCIATED WITH POOR COGNITIVE DOMAIN SCORES [a]

		Cognitive Domain							
		Reaction Time		Executive Functioning		Visuo-spatial Functioning		Language Functioning	
Risk Factor	%[b]	F	*p*	F	*p*	F	*p*	F	*p*
Demographic									
Age 50 years	44	---	---	---	---	---	---	---	---
Education 12 years	16	6.0	*.018*	10.6	*.002*	**15.1**	***.000***	---	---
Non-white ethnicity	44	4.5	*.037*	**7.5**	***.008***	**3.6**	***.001*** [c]	**4.8**	***.000*** [c]
Male gender	32	---	---	---	---	---	---	---	---
Clinical Condition									
Admission Hunt-Hess >2	43	---	---	---	---	---	---	---	---
NIHSS > 0 [d]	41	---	---	---	---	---	---	---	---
Focal SAH Clot									
Anterior Interhemispheric	14	---	---	---	---	---	---	---	---
Cerebral Edema									
Global Edema	10	---	---	**7.5**	***.008***	4.1	*.047*	---	---
Focal Edema	19	---	---	---	---	---	---	---	---
Any Edema	26	5.2	*.026*	---	---	4.3	*.041*	---	---
Ischemia									
Left-sided infarction	16	---	---	---	---	---	---	---	---
Infarction from vasospasm	13	---	---	---	---	---	---	4.4	*.041*
Any infarction	34	---	---	---	---	4.1	*.048*	---	---
Aneurysm Location									
Left sided	19	---	---	---	---	---	---	---	---
Anterior circulation [e]	71	---	---	---	---	---	---	---	---
Anterior communicating	25	---	---	---	---	---	---	2.4	*.017* [c]

Table 4.

[a] Impact of demographic and disease-specific factors on cognitive domain scores. For each risk factor, significant ($p<.05$) F-tests indicate poorer performance in that cognitive domain for participants with that risk factor. Values in bold indicate significance in multivariate models; [b] Percent of the study population with the given risk factor; [c] Domain scores exhibiting unequal variance between risk factor levels. In these cases, differences were tested with a t-test, without assuming equal variance; [d] Adjustment for education level using ANCOVA model; [e] Adjustment for ethnicity using ANCOVA model

GCS = Glasgow Coma Score; NIHSS = National Institutes of Health Stroke Scale; SAH = subarachnoid hemorrhage.

Table 5. MULTIVARIATE ANALYSIS OF DEMOGRAPHIC, CLINICAL AND RADIOLOGIC VARIABLES ASSOCIATED WITH POOR COGNITIVE DOMAIN SCORES [a]

	Cognitive Domains								
	Mental Status	Attention	Visual Memory	Verbal Memory	Motor Functioning	Reaction Time	Executive Functioning	Visual-spatial Functioning	Language Functioning
Risk Factor	B *p*	B *p*	B *p*	B *p*	B *p*	B *p*	B *p*	B *p*	B *p*
Demographic									
Higher Age (per year)	**-.300 *.005***	--- ---	**-.230 *.042***	--- ---	**-.439 *.000***	--- ---	**.130 *.307***	--- ---	--- ---
Lower Education (per year)	**.168 *.136***	**.344 *.001***	--- ---	**.199 *.071***	--- ---	**.114 *.392***	--- ---	**.464 *.000***	--- ---
Non-white ethnicity	**-.394 *.001***	**-.295 *.007***	--- ---	**-.136 *.237***	--- ---	**-.201 *.135***	**-.247 *.050***	**-.225 *.037***	**-.564 *.000***
Male gender	--- ---	--- ---	--- ---	**.331 *.002***	--- ---	--- ---	--- ---	--- ---	--- ---
Clinical / Radiographic									
Admission Hunt-Hess >2	-.113 .286	-.072 .530	--- ---	-.143 .175	-.205 .076	--- ---	--- ---	--- ---	--- ---
Thick SAH – Ant. Interhem.	-.194 .059	--- ---	--- ---	-.102 .334	--- ---	--- ---	--- ---	--- ---	--- ---
Global edema	--- ---	--- ---	--- ---	--- ---	--- ---	--- ---	**-.274 *.021***		
Any edema	--- ---	**-.237 *.015***	--- ---	-.125 *.219*	**-.366 *.001***	**-.265 *.033***	--- ---	**-.220 *.027***	--- ---
Anterior circ. aneurysm	--- ---	--- ---	--- ---	**-.268 .015**	--- ---	--- ---	--- ---	--- ---	--- ---
Left-sided infarction	**-.279 *.007***	--- ---	**-.387 *.001***	**-.354 *.001***	--- ---	--- ---	--- ---	--- ---	--- ---
Infarction from vasospasm	--- ---	**-.206 *.037***	--- ---	--- ---	--- ---	--- ---	--- ---	--- ---	-.161 *.132*
Any infarction	--- ---	--- ---	--- ---	--- ---	--- ---	--- ---	--- ---	-.145 .142	--- ---
Left sided aneurysm	-.118 *.262*	-.128 *.192*	--- ---	-.104 *.336*	--- ---	--- ---	--- ---	--- ---	--- ---
Anterior aneurysm	--- ---	--- ---	--- ---	--- ---	--- ---	--- ---	--- ---	--- ---	--- ---
ACoA	--- ---	--- ---	--- ---	--- ---	--- ---	--- ---	--- ---	--- ---	.141 *.182*
Adjusted R^2 for entire model	.366	.399	.199	423	.311	.108	.168	.384	.308

Table 5.

[a] Results of the multivariate models for the prediction of cognitive performance after subarachnoid hemorrhage. Bold indicates variables that remained in the final multiple linear regression models. Demographic variables that were related to each cognitive domain were forced into the model in step 1, and clinical/radiographic variables were added using a forward stepwise selection procedure in step 2. Beta values (B) represent average change in z-score units for performance in each cognitive domain for patients with the risk factor. Adjusted R^2 values indicate the proportion of variance in cognitive domain scores explained by all of the factors included in the final model.

ACoA = Anterior communicating artery

Table 6. UNIVARIATE PREDICTORS OF TOTAL DEPRESSION [a]

Risk Factor	%	CES-D Total Score: With Risk Factor	CES-D Total Score: W/O Risk Factor	*p*
Demographics				
Ed < 12 years	16	23.6 ± 13.7	12.8 ± 11.3	.007
Social History				
PT occup. Status	9	---	---	.105
Income <30k	56	18.6 ± 13.9	10.0 ± 8.2	.009
Current nicotine	57	**19.6 ± 13.5**	**10.2 ± 9.0**	**.004**
Medical History				
Hx of Hypertension	35	---	---	.254
Disease Factors				
Right sided aneurysm	26	20.5 ± 13.8	12.7 ± 11.4	.026
Rebleed	10	---	---	.105

Table 6.

[a] Impact of demographic and disease-specific factors on total CES-D scores. Proportion of subjects with each risk factor is listed under "%". Mean CES-D scores are given for subjects with and without each risk factor. For each risk factor, significant ($p<.05$) F-tests indicate higher CES-D scores for participants with that risk factor. Values in bold indicate risk factors that remained significant in the multivariate model.

Table 7. UNIVARIATE PREDICTORS OF SOMATIC DEPRESSION [a]

		CES-D Somatic Score		
Risk Factor	%	With Risk	W/O Risk Factor	*p*
Demographics				
Ed < 12 years	16	7.9 ± 4.2	4.5 ± 3.9	.011
Social History				
PT occup. Status	9	---	---	.702
Income <30k	56	6.7 ± 4.8	3.7 ± 3.3	.012
Current nicotine	57	6.0 ± 4.4	3.9 ± 3.1	.046
Medical History				
Hx of Hypertension	35	6.4 ± 4.8	4.3 ± 3.6	.048
Disease Factors				
Right sided aneurysm	26	---	---	.259
Rebleed	10	8.7 ± 1.2	4.7 ± 4.1	.023

Table 7.

[a] Impact of demographic and disease-specific factors on CES-D "somatic items" scores. Proportion of subjects with each risk factor is listed under "%". Mean CES-D "somatic item"scores are given for subjects with and without each risk factor. For each risk factor, significant ($p<.05$) F-tests indicate higher CES-D "somatic item"scores for participants with that risk factor. Values in bold indicate risk factors that remained significant in the multivariate model.

Table 8. UNIVARIATE PREDICTORS OF NON-SOMATIC DEPRESSION [a]

		CES-D Non-Somatic Score		
Risk Factor	%	With Risk	W/O Risk Factor	*p*
Demographics				
Ed < 12 years	16	15.7 ± 9.9	8.3 ± 8.5	.012
Social History				
PT occup. Status	9	16.7 ± 16.2	8.8 ± 8.0	.043
Income <30k	56	11.9 ± 10.4	6.3 ± 5.8	.019
Current nicotine	57	**13.5 ± 10.1**	**6.3 ± 6.3**	**.003**
Medical History				
Hx of Hypertension	35	---	---	.515
Disease Factors				
Right sided aneurysm	26	14.4 ± 10.0	8.0 ± 8.4	.012
Rebleed	10	---	---	.245

Table 8.

[a] Impact of demographic and disease-specific factors on CES-D "non-somatic items" scores. Proportion of subjects with each risk factor is listed under "%". Mean CES-D "non-somatic item"scores are given for subjects with and without each risk factor. For each risk factor, significant ($p<.05$) F-tests indicate higher CES-D "non-somatic item"scores for participants with that risk factor. Values in bold indicate risk factors that remained significant in the multivariate model.

TABLE 9. MULTIVARIATE ANALYSIS OF CES-D SCORES [a]

	CES-D Scores					
	Total		Somatic items		Non-somatic items	
Risk Factor	B	*p*	B	*p*	B	*p*
Demographic						
Lower Education (per year)	-.264	*.083*	-.257	*.122*	-.245	*.110*
Non-white ethnicity	.218	*.140*	.218	*.188*	.210	*.157*
Social / Med Hx						
Income < 30k						
Living alone						
Current nicotine use	**.338**	***.017***			**.359**	***.012***
Hypertension						
Clinical / Radiographic						
Right sided aneurysm						
Aneurysm rebleed						
Adjusted R^2 for entire model	.325		.114		.317	

Table 9.

[a] Results of the multivariate predictors of depression scores. Bold indicates variables that remained significant (P<.05) in the final multiple linear regression model. Demographic variables that were related to each depression score were forced into the model in step 1; risk factors with significant univariate associations were added using a forward stepwise selection procedure in step 2. Beta values (B) represent average change in CES-D score for patients with the risk factor. Adjusted R2 values represent the total ampount of variance in depression scores explained by factors included in the final regression model.

Table 10. ASSOCIATIONS BETWEEN DEPRESSION AND COGNITIVE PERFOMANCE AND THREE ASPECTS OF QUALITY OF LIFE [a]

	CES-D	Mental Status	Attention	Visual Memory	Verbal Memory
	F *P*	F *P*	F *P*	F *P*	F *P*
Quality of Life					
SIP-Physical	7.71 *.007*	1.73 *.193*	5.31 *.025*	3.67 *.060*	3.47 *.068*
SIP-Psychosocial	38.7 *.000*	0.67 *.417*	5.23 *.026*	5.79 *.019*	4.70 *.034*
SIP-Total	33.1 *.000*	1.04 *.311*	6.05 *.017*	5.77 *.019*	4.70 *.034*

[a] Impact of depression and cognitive dysfunction on quality of life (Sickness Impact Profile scores). Presence of depression (CES-D scores >15) and cognitive dysfunction (domain score > 2 standard deviations below normative mean) were used as factors in a series of ANOVA models. Significant F-tests ($p<.05$) indicate significantly reduced quality of life (SIP scores) for individuals with depression or cognitive dysfunction.

Table 11. ASSOCIATIONS BETWEEN COGNITIVE PERFOMANCE AND THREE ASPECTS OF QUALITY OF LIFE [a]

	Motor Functioning	Reaction Time	Executive Functioning	Visuo-spatial Functioning	Language Functioning
	F *P*	F *P*	F *P*	F *P*	F *P*
Quality of Life					
SIP-Physical	9.08 *.004*	2.02 *.161*	0.18 *.667*	2.34 *.131*	2.55 *.116*
SIP-Psychosocial	2.82 *.098*	2.46 *.123*	0.99 *.324*	2.55 *.116*	1.03 *.315*
SIP-Total	5.95 *.018*	2.35 *.131*	0.83 *.367*	2.07 *.155*	1.62 *.208*

Table 11.

[a] Impact of cognitive dysfunction on quality of life (Sickness Impact Profile scores). Presence of cognitive dysfunction (domain score > 2 standard deviations below normative mean) in each domain was used as factors in a series of ANOVA models. Significant F-tests ($p<.05$) indicate significantly reduced quality of life (SIP scores) for individuals with cognitive dysfunction in that domain.

Table 12. EXPLANATORY VALUE OF DEMOGRAPHICS, DEPRESSION, AND DOMAIN-SPECIFIC COGNITIVE DYSFUNCTION FOR PREDICTING QUALITY OF LIFE SCORES THREE MONTHS AFTER SAH [a]

	Components		Model Summary	
	B	*p*	Adjusted R^2	Sig. F change
SIP Physical Dimension				
Demographics			.049	.081
+ Motor Function	-0.530	.000	.378	.000
+ Depression	0.434	.000	.512	.000
SIP Psychosocial Dimension				
Demographics			.126	.007
+ Depression	0.775	.000	.658	.000
+ Verbal Memory	-0.250	.001	.711	.001
SIP Total Score				
Demographics			.109	.012
+ Depression	0.685	.000	.613	.000
+ Motor Function	-0.266	.004	.679	.001
+ Verbal Memory	-0.180	.021	.702	.021

[a] Summary of the independent effects of depression and cognitive dysfunction on quality of life scores. Stepwise multiple linear regression models were constructed to assess the relative variance in quality of life measures that could be explained by demographic variables (age and years of education), depression (CES-D score), and detailed neuropsychological testing (cognitive domain scores). Demographic factors were forced into each regression model in step one; CES-D and cognitive domain Z-scores were entered in stepwise fashion in step two if they contributed significantly to the model ($P < .05$). B = standardized Beta coefficient.

Figure 1.

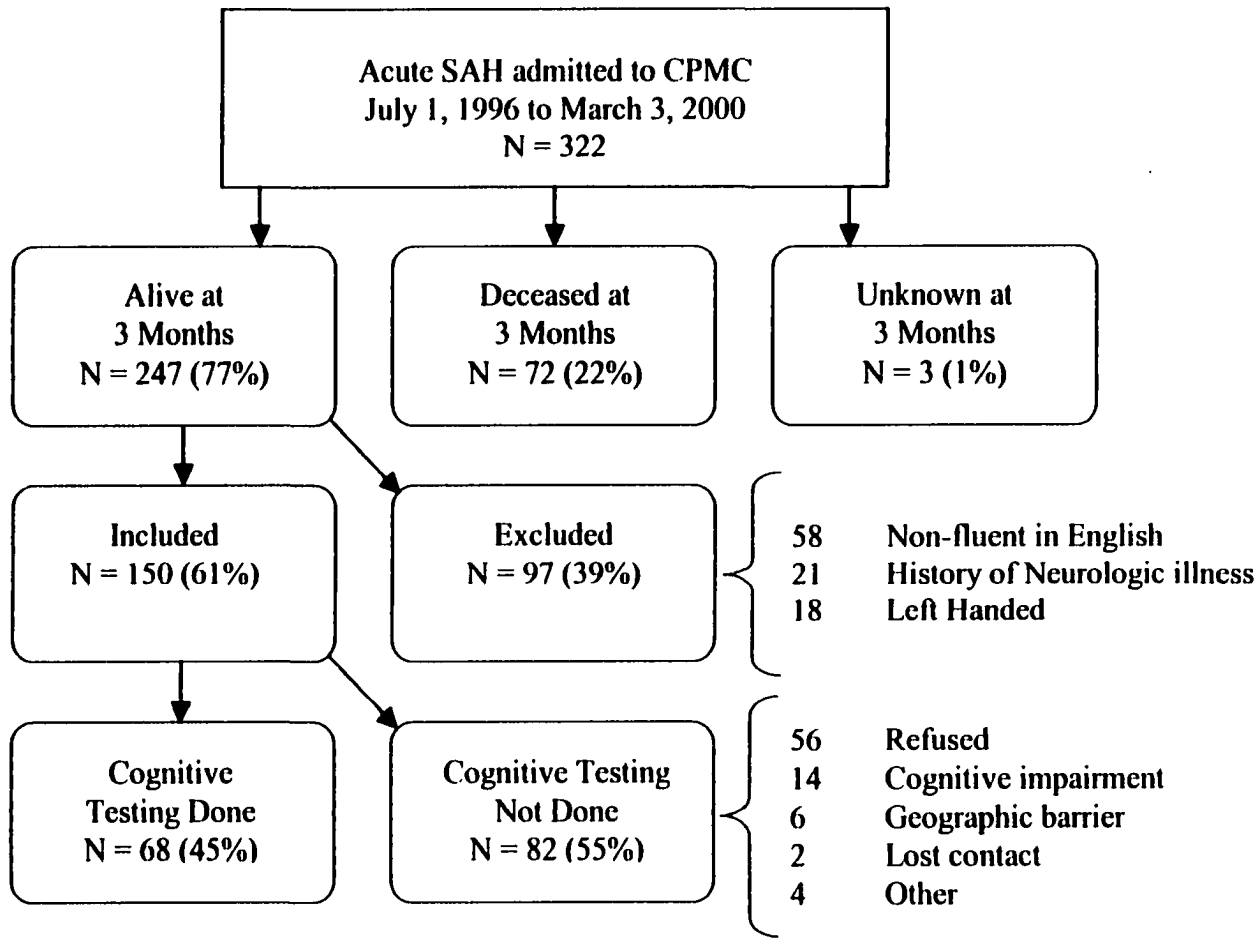

Figure 1. Flow diagram of study cohort enrollment and reasons why subjects were lost to follow-up.

Appendix 1. Hunt Hess Scale (Hunt & Hess, 1968)

Grade	Neurologic condition
0	Unruptured
1	Asymptomatic
2	Severe headache or meningismus; no neurological deficit
3	Drowsy; minimal neurological deficit
4	Stuporous; moderate to severe hemiparesis
5	Deep coma; decerebrate posturing

Appendix 2. Glasgow Coma Scale

Verbal Responses
- 1 = None (choose if intubated)
- 2 = Incomprehensible sounds
- 3 = Words
- 4 = Disoriented
- 5 = Oriented

Eye Opening
- 1 = No eye opening
- 2 = Eyes open to pain
- 3 = Eyes open to speech
- 4 = Eyes open spontaneously

Motor Response
- 1 = No motor response
- 2 = Extensor posturing
- 3 = Flexor posturing
- 4 = Withdrawal
- 5 = Localize
- 6 = Obeys

Glasgow Coma Score: (Sum of verbal, eye and motor) _____

Appendix 3. Neuropsychological battery

Global Mental Status
Telephone Interview of Cognitive Status
Short Blessed Test

Attention
Trail Making Test - Part A
WAIS-R Digit Span
Verbal Series Attention Test

Visual Memory
WMS-R Visual Reproduction I & II
WMS-R Visual Reproduction recognition
Rey Osterreith Complex Figure Test
WAIS-R Digit Symbol Recall

Verbal Memory
California Verbal Learning Test

Motor Function
Grooved Pegboard Test
Luria's Unimanual motor programming

Reaction Time
California Computerized Assessment Package

Executive Function
Modified Wisconsin Card Sorting Test

Visuo-Spatial Function
WAIS-R Block Design
Rey Osterreith Complex Figure Test Copy
WMS-R Visual Reproduction Copy

Language Function
Boston Naming Test
Token Test
Boston Diagnostic Aphasia Exam
    Comprehension
    Repetition

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