RECOVERY OF NEUROPSYCHOLOGICAL FUNCTIONING

AFTER SUBARACHNOID HEMORRHAGE

by

SHELLEY PEERY

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4/22/04 ______ Joan C. Borod ______

Date Chair of Examining Committee

4/23/04 ______ ______

Date Executive Officer

Alan Kluger, Ph.D.______

Stephan Mayer, M.D.______

Yaakov Stern, Ph.D.______

Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

Abstract

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Adviser: Professor Joan C. Borod

Background: This study examined the effect of demographic and clinical variables on recovery of neuropsychological functioning after subarachnoid hemorrhage (SAH). Methods: Patients admitted from July 1996 to March 2000 to the Neurosciences Intensive Care Unit at Columbia Presbyterian Medical Center with spontaneous SAH were consecutively enrolled into the study. Exclusion criteria included SAH from arteriovenous malformation, SAH more than 14 days prior to admission to the hospital, and age less than 18 years. During this period, 339 patients met criteria. The average age of the patients in the study group was 51.0 ± 13.3 years, with a range from 19 to 87 years old. Informed consent was obtained at the time of study enrollment from all patients or a surrogate if the patient was incapacitated as determined by a study neurologist. Interviews with patients and/or their families were completed to obtain background

information. Medical condition and hospital course, including disease severity and complications, were recorded prospectively. Demographics including age, sex, race/ethnicity, primary language, handedness, and years of education were obtained during the initial interview with the patient and/or family members. These variables were also verified in each follow-up interview. Three months and 12 months after the date of the SAH, subjects were invited to complete a comprehensive neuropsychological battery in the patient's preferred language, either English or Spanish, administered by a trained psychometrician. Seven cognitive domains and a measure of overall cognition were assessed including attention/concentration, psychomotor speed, visuospatial skills, language skills, verbal memory, visual memory, executive functions, and. The results indicated that psychomotor speed and attention recovered over time. Global mental status measured at 3 months after SAH showed the strongest relationship with neuropsychological functioning after SAH. Factors that contributed to greater cognitive impairment after SAH included older age, anterior aneurysm location, amount and location of blood, infarctions, cerebral edema, worse clinical grade, male sex, and not speaking English, but not vasospasm alone. Multiple variables contributed to the role of aneurysm location in cognition after SAH. Findings are discussed in relation to current literature.

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CHAPTER ONE

I. INTRODUCTION

A. Research Question

Subarachnoid hemorrhage (SAH) can be a catastrophic event with a high initial mortality rate. SAH results in lasting cognitive deficits even for patients with good outcome on the Glasgow Outcome Scale (GOS = I). However, few investigators have examined the duration of cognitive deficits following subarachnoid hemorrhage or the factors that influence recovery patterns. Knowledge of the patterns of recovery after SAH and SAH-related complications has direct implications for acute treatment. This knowledge not only carries a prognostic value that is important to patients and their families but also informs the cognitive remediation treatment plan.

From the literature, it appears that brain damage most frequent after SAH is a diffuse process and that modest gains can be expected over the latter part of the first year after SAH. However, Maurice-Williams, Willison, and Hatfield (1991) and Stabell and Magnaes (1997) identified bimodal distributions of patient outcomes with the majority of complications affecting a small portion of patients and the remainder showing relatively minor subsequent impairments overall. This reflects the heterogeneous nature of SAH, with the majority of patients suffering the diffuse effects of bleeding, but some suffering additional complications that have strong effects on their recovery.

The current study proposes to investigate patterns of cognitive recovery after SAH and to identify factors that affect recovery of neuropsychological functioning.

B. Literature Review

1. Description of the disease

Annually, aneurysmal SAH in the United States occurs in 6 – 25 people per 100,000, or about 27,000 people each year (Schievink, 1997), and accounts for 5% to 10% of all strokes (Becker, 1998). Aneurysms are abnormal localized dilations of any vessel resulting from a weakening in the vessel wall, and they are found most frequently in cerebral arteries and occur in 1 – 6% of the general population (Schievink, 1997; Vega, Kwoon, & Lavine, 2002). The mean age of onset of SAH is 50 years. Current studies have shown that age over 50, female sex, smoking, and cocaine use are risk factors for intracranial aneurysms (Nanda, Vannemreddy, Polin, & Willis, 2000; Vega, Kwoon, & Lavine, 2002; Weibers International Study of Unruptured Intracranial Aneurysms Investigators, 1996). Mortality after aneurysm rupture is estimated to be 10-15% before reaching a hospital, with a mortality rate as high as 40% in the first week. Recovery after SAH is related to mortality and morbidity, which are associated with the severity of the hemorrhage and delayed complications (Dowling & Dacey, 1996). Among hospitalized patients, subarachnoid hemorrhage can be fatal in up to 26% of cases (Kassell, Torner, Haley, Jane, Adams, & Kongable, 1990).

2. Neuropsychological deficits after Subarachnoid Hemorrhage

The fact that SAH results in neuropsychological deficits is well documented, even among good grade patients (Hunt Hess Grade = I [Hadjivassiliou et al., 2001]). Cognitive impairments among SAH patients have been documented in the areas of visuospatial functioning, visual memory, psychomotor speed, verbal memory, executive functioning, and other areas (Ogden, Mee, & Henning, 1993; Hutter & Gilsbach, 1993; Hadjivassiliou et al., 2001).

3. Recovery of Neuropsychological Deficits after SAH

Eight prospective studies have previously examined SAH recovery using repeated neuropsychological testing (Bjeljac, Keller, Regard, & Yonekawa, 2002; Hillis, Anderson, Sampath, & Rigamonti, 2000; Maurice-Williams et al., 1991; McKenna, Willison, Phil, Lowe, & Neil-Dwyer, 1989; Mohanty, Das, Mukundan, & Jamuna, 1993; Ogden et al., 1993; Richardson, 1991; Stabell & Magnaes, 1997). The specific tests administered, as part of the repeated neuropsychological evaluations in these eight studies, and which tests showed significantly improved performance over the recovery period, are indicated in Table 1. Overall, this table shows that improvement has been observed on at least some of the neuropsychological tests administered after SAH in seven out of eight studies. Among these, performance improved on 15%-55% of the tests. The tests that most consistently captured neuropsychological improvements across the studies were the Grooved Pegboard test and the Digit Symbol Substitution test in the domain of *Reaction Time*; the Rey Auditory Verbal Learning Test and the Recognition

Memory Test for Words in the *Verbal Memory* domain; and Recognition Memory for Faces in the *Visual Memory* domain.

Overall, the literature to date on recovery after SAH is inconsistent. Although there is a considerable literature on SAH-related factors that result in cognitive deficits, these studies do not employ a repeated-measures design nor do their results point consistently to any single factor or group of factors that results in cognitive deficits after subarachnoid hemorrhage. Nevertheless, the identification of acute neurological factors that affect long-term recovery of cognitive abilities after subarachnoid hemorrhage has direct treatment implications. After the patient's mortal condition is stable, physicians treating patients in the acute stage of the disease may treat disease factors affecting morbidity and cognitive outcome. Rehabilitation professionals treating longer lasting cognitive dysfunction may target more quickly resolving cognitive impairments, with a strategy for restoration of the cognitive function and more long-lasting deficits with compensatory strategies.

McKenna, Willison, Phil, Lowe, and Neil-Dwyer (1989) reported on 83 patients who were between the ages of 20 and 65 who suffered from SAH in England. They compared SAH patients to 34 patients who suffered myocardial infarctions (MI). SAH patients underwent a neuropsychological test battery at 3 months and 12 months post SAH, and MI patients underwent the same battery upon discharge and one year post-MI. See Table 1 for the neuropsychological battery used. Comparisons were made to normative data and no effect of gender was found. In order to capture individual's deficits that fell within normal limits compared to normative data, the investigators recorded the standardized performance to magnify impairments such that scores above the 50^{th} percentile were coded as 0, from the 25^{th} to the 50^{th} percentile as 1, from the 10^{th} to the 25^{th} percentile as 2, and below the 10^{th} percentile as 3. Furthermore, they evaluated SAH patients with (N=13) and without (N=70) abnormal neurological exams separately. After one year, the MI group significantly outperformed the SAH group without neurological impairments on Performance IQ, who in turn significantly outperformed the MI group on the Nelson modification of the WCST. No other between-group differences were identified, although performance means for the SAH group with abnormal neurologic exams were lower than either the SAH group without neurological impairments or the MI group. At one year, there were no significant differences between the mean performance of the SAH group without neurological impairments relative to normative data. Within the SAH group without neurological impairments, significant differences over time consisted solely of an improvement of actual IQ relative to estimated premorbid IQ, which was in the average range. This pattern of performance is consistent with improvement suggesting subclinical impairments in overall intellectual functioning. Forty percent of the SAH patients demonstrated cognitive impairment evidenced by scoring below the 10^{th} percentile on at least one test, and 14% demonstrated cognitive impairment on two or more tests. Which cognitive domains these impairments fell in was not discussed by the authors nor was a repeated-measures analysis conducted to evaluate recovery of any scores except Full Scale IQ. The authors concluded that the number of test scores found to be impaired was within the expected limits for the number of tests given, thereby attributing their positive findings to Type I error. Furthermore, they concluded that no appreciable neuropsychological deficits persist over the year following SAH if the patient's neurological exam is normal. This suggests a bimodal distribution of patient outcome in which the majority of patients escape cognitive impairments and a few SAH patients who suffer complications experience neuropsychological deficits. The authors attribute their negative findings for cognitive deficits after SAH without neurological impairments in part to the use of a recognition memory test instead of one that required retrieval, and therefore more effort.

Richardson (1989, 1991) reported on 32 patients who underwent repeated neuropsychological testing at 6 weeks and 6 months after discharge from the hospital from a series of 76 patients who suffered spontaneous SAH secondary to a ruptured intracranial aneurysm in England. Scores were standardized using normative data, and age and sex were not found to relate to overall performance. At the initial evaluation, SAH patients were impaired relative to an orthopedic control group on Information, Mill Hill Synonyms, semantic verbal fluency, object naming response time, and delayed verbal recall relative, and older patients were impaired on facial recognition. At the final evaluation, these patients' performance was significantly worse than the performance of the orthopedic control group on a test of semantic verbal fluency. Although younger patients (<45 years) out-performed older patients on three tests (Object Naming, Face Recognition, and Information), Richardson (1991) argued that the lack of such a finding on the other tests administered "confirms the impression… that… age is not an important predictor of functional recovery after ruptured intracranial aneurysm." Although the pattern of performance over time on several tests was consistent with improvement being that they were significantly impaired on the initial evaluation but not on the final evaluation, significant improvement was observed between the two assessments on only three of the eight tests administered: Information and Vocabulary from the WAIS, and Cube Analysis. These results would have been more easily interpreted if the author had used a repeated-measures multifactorial design for the statistical analysis. However, he was restricted to individual t-tests because of unequal Ns. Nevertheless, several patterns are observed within these results. Semantic verbal fluency and object naming response time were impaired at both assessments, which is consistent with a pattern of long-lasting impairment. Performance on Mill Hill Synonyms test, facial recognition, and delayed free recall of verbal material was impaired initially and not impaired at 6 months, but not significantly improved either. The interpretation of this pattern is unclear and may or may not be consistent with improvement of impaired functioning. Information scores were impaired initially but significantly improved over time and were no longer significantly impaired after 6 months, which is consistent with improvement of impaired functioning. Although Cube Analysis was not significantly impaired initially or ultimately, performance on this test showed significant improvement over time suggesting improvement from what may have been a subclinical impairment. Vocabulary also improved significantly over time, although it is unclear from the article whether there was any initial clinical impairment. Taken together, these results seem to suggest that SAH patients suffer impairments of psychomotor speed and verbal and visual memory, and that recovery from memory impairments is faster than recovery from psychomotor slowing. Age affected the results such that recovery was poorer on some of the neuropsychological tests. Unrelated to cognitive test performance were aneurysm location, timing of surgery (before or after 72 hours post SAH), or treatment (clipping or wrapping). However, post-operative vasospasm was found to predict poorer neuropsychological performance.

Maurice-Williams, Willison, and Hatfield (1991) reported on 27 good-grade SAH patients (Hunt Hess I or II) who underwent repeated neuropsychological testing prior to surgery, upon discharge from the hospital, and one year later in England. Tests were selected for ease of bedside administration. See Table 1 for battery. There were no significant differences between the pre-operative testing performance and performance on testing upon discharge. After a year, digit span and verbal fluency mean scores were significantly improved relative to the pre-operative performance. However, it is unclear from the way the data were reported whether the pre-operative performance was significantly impaired relative to normative groups. Similarly, a trend was observed for the improvement of performance on the recognition memory tests for words and faces after one year. Evaluation of changes in the neuropsychological performance of individuals revealed a bimodal distribution such that five of the 27 patients showed deterioration from pre- to post-operative testing on at least two of the eight tests, which, in four cases, the authors attributed to an identifiable complication. Three patients showed deterioration on only one test, which the authors feel is too few to be confident that it reflects actual deterioration and thus disregard. The others did not show deterioration on any tests. After a year, four of the five patients who had deteriorated post-surgically had improved to the point of their pre-operative baseline performance. The results of additional neuropsychological tests administered only at the one-year testing are provided for only two of four tests, but performance on these is within normal limits relative to normative groups. The investigators concluded that there were no neuropsychological deficits relative to pre-surgical testing among patients who had not suffered complications while in the hospital. The results of this study are difficult to interpret because comparisons to the pre-surgical testing are emphasized over comparisons to normative data. Thus, while it may be true that most patients recovered from the effect of the surgery, as demonstrated by return to pre-surgical performance levels, the neuropsychological damage secondary to the SAH remains unclear, and recovery patterns cannot be derived from this article. However, consistent with the conclusions drawn by McKenna et al. (1989), these authors also found a bimodal distribution of patient outcomes such that those patients with poorer cognitive outcomes had suffered neurological complications whereas those who were free of complications escaped neuropsychological impairment. The complications identified for the small group of five SAH patients with impairments were different for each patient and included delayed cerebral ischemia, occlusion of the right anterior choroidal artery resulting in a small area of capsular ischemia, prolonged intra-operative retraction of the dominant hemisphere resulting in trauma to perforating vessels and severe contralateral hemiparesis, late onset hydrocephalus requiring multiple shunt revisions, and unknown cause. Although six patients who had relatively normal neuropsychological outcomes had suffered from hydrocephalus, it was successfully treated. One patient experienced occlusion of the left ophthalmic artery with no subsequent neurological deficit. In five patients who had relatively normal neuropsychological outcomes, the aneurysm bled intra-operatively without any apparent long-lasting ill effects. Three patients who had relatively normal neuropsychological outcomes had suffered from seizures without any apparent long-lasting ill effects. The effect of clinical severity was not evaluated since the study was restricted to patients who were classified as "good grade" (Hunt-Hess Grades I and II). Cerebral edema and treatment (clipping or wrapping) were not evaluated for effect on neuropsychological outcomes as no patients suffered from cerebral edema according to the authors, and all but one patient under went clipping of their aneurysm. Taken together, the results of this study seem to indicate that only untreated hydrocephalus and cerebral ischemia resulting in infarctions lead to long-lasting cognitive impairments after SAH. However, certain other factors that were not evaluated in this study may also contribute to patient outcomes.

Ogden, Mee, and Henning (1993) prospectively studied 66 good-grade (Hunt Hess I and II) SAH patients administering neuropsychological batteries upon discharge from the hospital, and at 10 weeks and 12 months post SAH in Australia. See Table 1 for the battery. These authors found that older patients recovered less over the 12-month period than did younger patients. Although it is well known that older age is associated with slower recovery, this finding in neuropsychological testing is often altered by age-stratified normative data. However, it is important to note here that recovery over time was affected even after standardized scores were corrected for age. No differences were found for sex. Unlike other investigators, Ogden et al. (1993) analyzed the proportion of patients with no, moderate, or severe impairment on each test. Normalized test scores were categorized into “unimpaired” (better than two standard deviations [SD] below the mean), “severely impaired” (worse than three SDs below the mean), and “moderately impaired” (the remainder). Significant improvement was derived from normative standardized scores, and three patterns of improvement were seen among tests showing significant differences. Performance on the Rey Complex Figure Test on both copy and recall was impaired at both 10 weeks and 12 months but showed significant improvement suggesting visuospatial functioning was significantly impaired in this cohort and remained impaired over the recovery period despite showing some improvement. Performance on the Recognition Memory Tests for both words and faces, and on the long-term store score of the Oral Selective Reminding Test were impaired at 10 weeks, showed significant improvement over the recovery period, and were unimpaired at 12 months, suggesting that verbal memory and visual recognition memory for faces was impaired initially but recovered completely by one year. The remainder of the tests that showed significant improvement (Digit Span Forward and Backward, VIQ, PIQ, Similarities, Picture Completion, Picture Arrangement, and Block Design) were unimpaired at both 10 weeks and 12 months, suggesting improvement from subclinical impairments. Although these researchers identify a subgroup of patients who continue to demonstrate neuropsychological impairment on testing at 12 months, it is unclear whether these are the same patients who showed impairments at 10 weeks or whether only these patients suffered from complications. Thus, this study cannot be compared to McKenna et al. (1989) or Maurice-Williams et al. (1991) to evaluate whether there is a bimodal distribution of patient outcomes such that the majority of patients is unimpaired by SAH but a small group who suffer complications experiences cognitive deficits.

Ogden et al. (1993) went on to analyze the disease-related factors that influenced recovery patterns. They found that worse neuropsychological performance 12 months after SAH was significantly associated with poorer admission grade, poorer discharge grade (RCFT-copy and recall, Trails, Digit Symbol Test), hydrocephalus, location of blood (DS forward, recognition memory test for words), and infarction (memory scores). Aneurysm location, hydrocephalus, infarction, and vasospasm were not significantly associated with poor neuropsychological performance after 12 months. The authors concluded that visuospatial memory deficits were more frequent and longer lasting than verbal memory problems.

Mohanty, Das, Mukundun, and Jamuna (1993) evaluated the neuropsychological functioning of 13 aneurysm patients at discharge, 6 months and 12 months following aneurysm rupture in India. See Table 1 for battery. Comparisons were made to Indian normal controls. No effects of age or sex were reported. Repeated-measures analyses (t-tests) between discharge and 12 months post SAH revealed significant improvement to the point of normal functioning on all tests except Visual Learning. This finding is consistent with the results of Ogden et al. (1993) who also found that visual learning was the domain with the longest lasting impairments. Furthermore, by the first follow-up at 6 months post SAH, significant improvement was observed in verbal learning. However, patient mean performance at discharge was below 2 SDs below the mean of the normal control group only on the performance quotient, a combination of Koh's block design and Alexander's Passalong test. Thus, the inference is that the pattern of performance is consistent with subclinical impairment improving significantly over the recovery period for most tests. For Koh's block design and Alexander's Passalong test, the pattern of performance was impairment, which recovered significantly over the recovery period. For visual learning, the pattern of recovery observed is consistent with subclinical impairment, which persisted over time. Since many studies reported a bimodal distribution of patient outcomes, it is likely that reporting on mean performance in this study obscured impairments suffered by some but not all patients in this cohort.

Stabell and Magnaes (1997) described the results of 41 SAH patients in Norway who had surgery for ruptured aneurysms of the anterior communicating artery (ACoA), internal carotid artery (ICA), or middle cerebral artery (MCA). Although this group included patients of all grades (Hunt Hess I – V), their inclusion criteria were more restricted by aneurysm location than in other studies. Whereas other studies included patients of all aneurysm locations, Stabell and Magnaes included only those patients who had aneurysms of the ACoA, ICA, or MCA. The patients were assessed 4 months and 1 year after their SAH. Scores were standardized using age- and, when possible, education-stratified Scandinavian normative data. See Table 1 for neuropsychological battery used. Change scores were calculated to identify clinically significant improvement among individual patients, defined as either an increase by two SDs on at least one test score or an increase by one SD on at least five test scores. A year after the SAH, significant improvement was noted in areas of abstract reasoning (Similarities, Dissimilarities), language abilities (vocabulary, verbal fluency), verbal memory (AVLT learning, AVLT immediate recall), visuospatial perception (Picture Completion, Picture Arrangement), visual memory (Gestalt learning, Gestalt delayed), and motor coordination (Pegboard but not Finger Tapping). The overall gains from 4 months to 12 months for the study group as a whole were relatively modest, though significant. Aneurysm location had a significant effect on the change score for verbal learning such that the group who had suffered left-sided ICA/MCA aneurysms improved the most over the recovery period, which was traced to poorer performance of these patients on tests of verbal abilities upon initial evaluation (i.e., Similarities and Token Test). Although the mean performance of the group was within one SD of the normative population by the first assessment at 4 months, 44% had three or more test results falling two SDs below the normative mean. However, 39% made clinically important gains with a trend toward improvement noted by the authors in the domains of verbal memory and psychomotor speed. This suggests a bimodal distribution of patient outcomes as was observed by other authors, such that patients who suffered complications show impairments for longer and recover more slowly, while patients with an uncomplicated hospital course demonstrate fewer cognitive impairments and recover more quickly. Also consistent with the results of others' studies, Stabell and Magnaes (1997) found that raw scores for all tests improved over the recovery period with the notable exception of retention for visual gestalts, a test of visual memory.

Hillis et al. (2000) reported on the neuropsychological performance of 27 patients with ruptured aneurysms in the United States three months post SAH and on a subset of six of these patients 12 months post SAH. See Table 1 for the neuropsychological battery used. Performance was compared to normative data. At the 3-month follow-up, significant impairments were found in the group performance on nearly all tests. However, the authors reported that the severely impaired performance of only a few patients accounted for group differences relative to normative data on several tests. They also found that the majority of patients with severely impaired performance had required shunts for hydrocephalus, which is consistent with other authors' conclusions that the patients who suffer complications experience the majority of neuropsychological impairments. By the time of the one-year follow-up, the investigators found significant improvement on only one of the 16 neuropsychological tests (i.e., Boston Naming Test), which they do not distinguish from chance although they note their low power with only six subjects.

Bjeljac and colleagues reported on the neuropsychological performance of 82 patients with ruptured aneurysms in Switzerland 3 and 12 months post SAH (Bjeljac et al., 2002). See Table 1 for the neuropsychological battery used. All patients reportedly improved on executive functions from admission to 3 and 12 months post SAH. At three months post SAH, almost three quarters of patients showed improvement on at least one of eight tests administered. By 12 months after the SAH, all patients showed improvement on at least one neuropsychological test, but 70% remained impaired on at least one test. These investigators reported on two variables that were predictive of neuropsychological outcome: aneurysm location and age. They found that people who had anterior communicating artery aneurysms performed better than people with aneurysms in other locations, which is contrary to much of the literature. On the other hand, they found that older people (>60 years) performed worse than younger people on measures of attention/concentration, short-term memory, and information processing capacity, which is consistent with other literature. These authors did not include a description of the statistical procedures used, making it difficult to evaluate their findings.

A clear picture of neuropsychological recovery after SAH is difficult to ascertain from the literature. The available research studies vary in terms of their inclusion criteria (e.g., admission grade, aneurysm location, and presence of an aneurysm), time period examined (e.g., from 6 weeks to 6 months, or from 10 – 18 weeks to 12 months), and the factors examined for effects on recovery (e.g., aneurysm location, vasospasm, amount and location of blood, and presence of infarction). These differences may be responsible for inconsistent conclusions. Whereas McKenna et al. (1989), Richardson (1991) and, Stabell and Magnaes (1997) found recovery on no or fewer than half the tests administered, the remainder of studies reported significant improvements on at least half the neuropsychological tests administered. (See Table 1). Furthermore, the cognitive domains in which recovery of function was observed varied across each of these studies.

4. Factors that affect recovery

SAH severity is most commonly measured by Hunt Hess grade (Hunt & Hess, 1968; a scale measuring clinical severity of SAH with five levels: I. Asymptomatic, II. Headache, II. Lethargic, IV. Stuporous, and V. Coma) and the Glasgow Coma Scale (GCS). The most devastating complications after SAH are rebleeding of the aneurysm, delayed cerebral ischemia resulting from vasospasm, and hydrocephalus. Intracerebral hemorrhage, intraventricular hemorrhage, cerebral edema, increased intracranial pressure, and herniation also are SAH-related complications that are associated with poor outcome (Dowling & Dacey, 1974). Seizure can cause deterioration after SAH as well (Butzkeuven et al., 2000; Claassen et al., 2003). Whether aneurysm location has an effect is questionable, as several studies have found evidence to support and to refute this claim (e.g., Kassell et al., 1990; Ogden et al., 1993; Richardson, 1991; Richardson, 1989; Stabell & Magnaes, 1997). Thick clots have been identified as contributing to risk for vasospasm (Claassen et al., 2001; Fisher, Kistler, & Davis, 1980; Qureshi et al., 2000) and cognitive impairments (Saveland, Sonesson, Ljunggren, Ryman, & Brandt, 1988; Sonesson, Saveland, Ljunggren, & Brandt, 1989). Location of ruptured aneurysm and initial GCS have also been identified as factors contributing to vasospasm, but ICH does not (Qureshi et al., 2000).

a. Rebleeding. The highest risk of rebleeding is during the first 48 hours after a subarachnoid hemorrhage, which can result in an additional mortality of up to 50% (Heros & Morcos, 2000). Depending on the amount and location of blood, rebleeding may also result in a cascade of secondary complications that also have deleterious effects including ICH, IVH, and increased intracranial pressure. Any blood in the subarachnoid space may result in cellular depolarization and therefore compromise higher cognitive functions (Sonesson et al., 1989). Butzkeuven et al. (2000) also found that rebleeding is a risk factor for late onset seizure disorders after SAH.

b. Vasospasm and cerebral ischemia. Vasospasm, defined as velocity in any vessel exceeding 120 cm/s (Charpentier et al., 1999), occurs secondary to the breakdown of blood products that are exposed to smooth muscles of vessel walls perivascularly for at least 72 hours (Mayberg, 1998). This theoretically results in selective neuronal necrosis in the case of reversible ischemia (Saveland et al., 1988) and infarcts in 50% of patients with vasospasm (Mayberg, 1998). Symptoms typically occur between 5 and 12 days after SAH and include worsening of headache or stiff neck, low-grade fever, and onset or worsening of confusion or disorientation or of a focal deficit (Qureshi et al., 2000). Symptomatic vasospasm is detected in 50% to 70% of patients and can cause delayed cerebral ischemia (DCI) (Hijdra, van Gijn, Nagelkerke, Vermeulen, & van Crevel, 1988; Kassell, Peerless, Durward, Beck, Drake, & Adams, 1982; Mayberg, 1998; Qureshi, Sung, Razumovsky, Lane, Straw, & Ulatowski, 2000). DCI occurs in 17% to 40% of patients (Charpentier et al., 1999). Vasospasm has been associated with an overall death rate of 30%, permanent deficits in 34%, and poor outcome in 64% of patients who experience vasospasm (Qureshi, Suarez, Bhardwaj, Yahia, Tamargo, & Ulatowski, 2000). Vasospasm also results in neurological sequelae six months post SAH twice as often than in patients without vasospasm (Charpentier et al., 1999) and is the leading predictor of mortality and morbidity after SAH (Kassell et al., 1990) as well as a consistent predictor of long-term cognitive deficits after SAH (Stenhouse, Knight, Longmore, & Bishara, 1991).

c. Hydrocephalus. The incidence of SAH-associated hydrocephalus reportedly ranges from 6 to 67% and can be acute, subacute, or chronic (Sheehan, Polin, & Sheehan, 1999). Left untreated, it can result in increased intracranial pressure. Treatment of hydrocephalus includes external ventricular drain placement or ventricular-peritoneal shunt, which can lead to improvements in 70% of patients. 'Over-drainage' can cause subdural hematomas, postural headaches (similar to 'spinal' headaches), hypovolemia of cerebrospinal fluid, and shunt malfunction as a result of the collapse of the cerebral ventricles (Sheehan et al., 1999).

d. Seizures. Seizures at the onset of subarachnoid hemorrhage (SAH) occur in 4% to 16% of patients. Late seizures (24 hours to 6 weeks after SAH onset) have been reported in 7% to 14% of patients. Administration of anti-epileptic drugs still varies.

However, one study reported that patients with a large amount of blood on initial CT scan are at increased risk of both early and late seizures (Butzkueven et al., 2000).

e. Edema. Cerebral edema is currently estimated to occur in 6% of patients. Although its etiology is poorly understood, it appears to play a significant role in acute deterioration of patients. On CT scan, there is a global brain hypodensity. It may reflect diffuse ischemic injury due to transient ictal cerebral circulatory arrest, diffuse inflammatory or neurotoxic effects of blood and its degradation products on brain tissue, or abnormal autoregulation due to microvascular damage or dysfunction of vasomotor centers in the brain stem. (Claassen, Carhuapoma, Kreiter, Du, Connolly, & Mayer, 2002). Left untreated, cerebral edema may result in increased intracranial pressure and herniation.

5. Theories of neuropsychological recovery

Flourens (as cited in Kertesz, 1993) was one of the earliest investigators to conclude that recovery of function occurs after cerebral damage. Kertesz (1993) describes two stages of recovery, acute and chronic. Underlying the acute stage of recovery as it applies to SAH are the metabolic effects of the hemorrhage on the ionic balance across cell membranes. The neurotoxicity of the hemorrhage stems from the presence of extracellular excitatory amino acids and intracellular calcium, which disrupts mitochondrial function and proliferates further cell damage. Thus, nimodipine, a calcium channel blocker, is commonly used in treatment during the acute stage of the SAH.

Behavioral deficits after stroke, such as reduced level of consciousness, likely reflect depression of the catecholamine system.

Theoretical mechanisms underlying cognitive recovery of function during the chronic phase, although not well understood, include cortical reorganization and regeneration. Regrowth of axons, dendritic sprouting, and neural development have been found to occur in the context of brain injury in the animal literature. However, in the case of severe injuries to the brain that cause neuropsychological impairment, a more likely mechanism for recovery of function is the compensation of intact structures that subsume the damaged structure's function (Kertesz, 1993). Ipsilateral structures surrounding the region of injury, contralateral structures homologous to the damaged areas, and subservient systems with afferents to the damaged region all may contribute to recovery of function.

That several brain regions may compensate for infarcted areas lends support to the theory of equipotentiality. First proposed by Lashley (as cited in Kertesz, 1993), the theory of equipotentiality suggests that association cortex has the potential to carry out all functions attributed to association cortex, and the extent of the lesion area correlates to the extent of dysfunction. On the other hand, multiple brain regions subsuming impaired functions may also lend support to redundancy vicarious functioning. First proposed by Fritz and Hitzig (as cited in Kertesz, 1993), redundancy vicarious functioning suggests that there are redundant structures so that in the case of injury, a structure not previously associated with a function can take over the function of the injured structure. Fritz and

Hitzig (as cited in Kertesz, 1993) also proposed hemispheric substitution, when brain regions contralateral to the injury subserve recovered functions. Hierarchical representation of function at multiple levels, proposed by Jackson (as cited in Kertesz, 1993), permits compensation when higher levels are injured thereby disinhibiting lower levels to functionally compensate for the injury. That injury leads to denervation of immediately surrounding areas resulting in impairment of those areas as well is known as diaschesis, a term coined by von Monakow (as cited in Kertesz, 1993). Reinervation from other regions alleviates diaschesis, and this process underlies recovery of function as well. Finally, in contrast to biological mechanisms for recovery of function, cognitive retraining, proposed by Luria (as cited in Kertesz, 1993), relies on a behavioral change in cognitive processes that depend on finding alternative solutions to solving problems using structures that remain intact. While the current study cannot test these theories directly, if any of them are operative, then recovery is expected.

6. Theories of neuropsychological impairments following SAH

Ogden et al. (1993) suggest that the effect that SAH has on the brain is diffuse and widespread cortical damage rather than focal. This suggests that neuropsychological damage would be seen on a wide range of neuropsychological tests and that recovery would be better predicted by factors that capture the global effects of disease severity, such as the Hunt Hess Grade.

C. Inclusion Of Minority Groups For Study

Literature that addresses long term recovery of neuropsychological functioning after SAH mostly comes from countries other than the Unites States: Australia (Ogden et al., 1993), Sweden (Stabell & Magnaes, 1997), Switzerland (Bjeljac et al., 2002), England (Hillis et al., 2000; Maurice-Williams et al., 1991; Richardson, 1989), and India (Mohanty et al., 1993). Race or ethnicity and language were not considered factors in any of the studies. However, in the United States, the heterogeneous population necessitates either examination of these factors or exclusion of substantial segments of the population. Furthermore, Becker (1998) reports that some minority groups have a higher incidence of SAH than white Caucasians from twice as great for blacks in the U.S. to four times as great for Eskimos in Denmark. Exclusion of minorities in outcome studies is an unethical distribution of research resources, and it limits the generalizability of results. In order to be able to ascertain the effects of minority status on recovery of neuropsychological functioning after SAH, the current study will assess the preferred language of the participant for the purpose of neuropsychological evaluation and, when possible, test them in their preferred language.

D. The Purpose of the Current Study

The purpose of the current study is to examine the recovery of neuropsychological functioning after subarachnoid hemorrhage from 3 to 12 months after the SAH, and to identify factors that influence the degree of recovery in various cognitive domains. In this naturalistic observation study, recovery of neuropsychological functioning from 3 months post SAH to 12 months post SAH was chosen because these are the most frequent time points after SAH that have been examined in the literature (Table 2; Bjeljac et al., 2002; Hillis et al., 2000; Maurice-Williams et al., 1991; McKenna, Willison, Phil, Lowe, & Neil-Dwyer, 1989; Mohanty et al., 1993; Ogden et al., 1993; Richardson, 1991; Stabell & Magnaes, 1997). Although four of the eight studies published to date included an evaluation upon discharge from the acute hospitalization, these were necessarily limited in scope due to the severity of impairments persistent upon discharge and did not include the entire battery used at later evaluations in any of the studies. Seven of the eight studies published to date included an evaluation at some point in time between discharge and 12 months post SAH. One study each followed patients at 6 weeks, 10 weeks, 4 months, and 6 months post SAH and four studies followed patients at 3 months post SAH. Because the 3 month follow-up was in the middle of the follow-up dates and more often used as a follow-up date in the literature, and because by 3 months after SAH most of the severely ill patients have recovered sufficiently to be testable, this was chosen as the first time point to complete a full neuropsychological battery. Because seven of the eight studies published to date examined neuropsychological functioning at 12 months, this was selected as the second follow-up time for a full neuropsychological battery.

Theoretically, four specific recovery patterns may be operative: a) improvement completed by 3 months (fast recovery), b) improvement spanning 12 months (slow recovery), c) no improvement secondary to lasting deficits (no recovery), and d) neuropsychological decline (worsening). In the current study, a fast recovery would be evidenced by unimpaired neuropsychological performance at the 3-month evaluation and no subsequent change by the 12-month evaluation; slow recovery would be evidenced by impaired neuropsychological performance at the 3-month evaluation and significantly improved performance by the 12-month evaluation; no recovery would be evidenced by sustained neuropsychological impairments at both the 3- and 12-month evaluation with no significant changes over the recovery period; and worsening would be evidenced by a significant decline in neuropsychological functioning. Improvement, either slow or fast, over the period from 3- to 12-months is the most likely of these as the literature reflects this pattern. However, lack of recovery due to ceiling or floor effects may be obscured in the context of group data as was noted by several authors who found a bimodal distribution of patient outcomes. Thus, another purpose of the current study will be to identify predictors of a speedy recovery such that neuropsychological recovery is completed by 3 months as well as an impaired recovery when an individual is too impaired to achieve any recovery at all in the 3 to 12 month time period. Finally, if any group of subjects shows a neuropsychological decline, the potential reasons of worsening will be explored. However, this is unlikely, as it was not found in any of the previous studies.

In addition, the current study will attempt to clarify the unique contribution made to neuropsychological recovery of function by demographic variables and disease-related variables. Past studies have been limited by their focus on a small number of variables (see Table 3). SAH is a complicated disease because the way in which the brain is injured is very diverse, with different complications in each patient. Thus, the results of the current study will generalize to all SAH patients as the study group will be quite heterogeneous, including nonaneurysmal patients as well as patients with ruptured aneurysms in various locations, and patients of all clinical grades.

E. Hypotheses

1. Age

Ogden et al. (1993) and Bjeljac et al. (2002) found that the recovery observed was modified by age with older patients recovering less by 12 months than younger patients, which is consistent with the well-documented effects of age on recovery from SAH specifically (Lanzino et al., 1996) and any brain injury in general (Saveland, Uski, Sjoholm, Sonesson, & Brandt, 1996). Thus, the same is expected in the current study. While there will be recovery, it will be modified by age such that younger patients recover more by 12 months.

2. Etiology

Ogden et al. (1993) found no difference in the recovery patterns of aneurysmal vs. nonaneurysmal SAH patients. Since the blood released in SAH is diffusely distributed regardless of source (aneurysmal or non-aneurysmal), presence of an aneurysm is not expected to make a unique contribution to recovery.

3. Aneurysm location

Neither Ogden et al. (1993) nor Richardson (1991) found an effect of aneurysm location. However, Stabell and Magnaes (1997) found that aneurysms of the left MCA or ICA resulted in worse verbal performance. Despite a large literature suggesting the deleterious effects of anterior communicating artery (ACoA) aneurysm surgery, Bjeljac et al. (2002) reported better neuropsychological outcome after ACoA aneurysm surgery relative to other locations, and Hutter (1999) found that aneurysm location does not appear to influence recovery when all aneurysm sites are evaluated. Furthermore, SAH patients do not usually present with focal neurological signs, but rather increasingly worse levels of consciousness (Hunt & Hess, 1968). Thus, in the present study, aneurysm location is not expected to have an effect. Locations of aneurysms that will be considered include anterior (anterior communicating artery), right-hemisphere (right anterior cerebral artery, right medial cerebral artery, right posterior cerebral artery, right posterior communicating artery, and right intracarotid artery), left-hemisphere (left anterior cerebral artery, left medial cerebral artery, left posterior cerebral artery, left posterior communicating artery, and left intracarotid artery), and posterior (vertebrobasilar artery, posterior inferior cerebellar artery [PICA], and basilar artery).

4. Lesion location: infarctions and thick clots

Location and amount of blood on CT has been found to be influential (Ogden et al., 1993) and will be examined in the current study, as well. This factor is hypothesized to be more salient than aneurysm location since blood spreads diffusely across the brain.

Another predictor of diffuse damage is overall amount of SAH blood as measured by Hijdra score. The more SAH blood, the slower the recovery expected. A tendency for subarachnoid blood to remain close to the source of bleeding may result in the influence of aneurysm location on outcome. The hypothesis that thick blood will be associated with location-specific neuropsychological deficits will be tested since it is more likely to cause irritation to the cortical surface yet this may be too diffuse to result in infarcts clearly visible on CT. In a similar vein, SAH location is also expected to result in damage correlating with specific neuropsychological deficits. Right-sided damage is expected to result in visuospatial deficits, left-sided damage is expected to lead to impairment of verbal memory, and frontal involvement is expected to cause deficits of executive function. Similarly, infarcts are expected to produce location-specific deficits, with anterior infarcts causing executive dysfunction, left sided infarcts resulting in verbal deficits, right sided infarcts impairing visuospatial abilities, and posterior infarcts affecting vision and motor coordination. Both infarcts and clots are expected to result in more persistent deficits than the diffuse effects of thin blood.

5. Vasospasm

In studies that have not evaluated the effects of infarction, vasospasm has been found to be a significant factor (e.g., Richardson, 1991). However, as vasospasm may cause infarction, this finding is likely to result from the influence of infarction being ascribed to vasospasm alone. Thus, vasospasm alone is not expected to result in poor recovery.

6. Clinical grade

The most important predictor of neurological outcome after SAH is clinical grade on admission (Vega, Kwoon, & Lavine, 2002). The Hunt Hess grade is a clinical measure that captures the global effects of the amount of blood released and early complications due to the SAH. Hunt Hess grade has been found to be a significant predictor of neuropsychological recovery after SAH (Bjeljac et al., 2002; Ogden et al., 1993; Richardson, 1991). Since the Hunt Hess grade worsens in the context of complications, the better the Hunt Hess grade, the better recovery is expected to be. In those patients without specific complications, diffuse damage will affect recovery.

7. Cerebral Edema

Due to the fact that cerebral edema has been found to result in mortality and morbidity after SAH (Dowling & Dacey, 1996), and that Kreiter et al. (2002) found cerebral edema to have a negative impact on cognition after SAH, cerebral edema is predicted to slow neuropsychological recovery in the current study.

8. Demographics

Demographics such as sex and primary language (English or Spanish) are not expected to have a significant impact on recovery patterns. Education is expected to have a significant impact on neuropsychological scores and will be used for covariation.

To summarize, the findings of the current study are expected to result from both focal and diffuse damage. Focal damage can take the form of infarcts and may result from the presence of thick clots or DCI. However, focal damage is not expected to correlate with aneurysm location or the occurrence of vasospasm without the development of an infarction. Focal damage is expected to result in impairments of specific neuropsychological abilities that have been localized to the areas damaged (i.e., right-sided damage is expected to result in visuospatial deficits, left-sided damage is expected to lead to impairment of verbal memory, and frontal involvement is expected to cause deficits of executive function). Diffuse damage is expected to correlate well with worst Hunt Hess grade and overall amount of blood, and to result in slower recovery. Age is expected to slow recovery from either diffuse or focal damage.

CHAPTER TWO

II. METHODS

A. Participants

Patients admitted from July 1996 to March 2000 to the Neurosciences Intensive Care Unit at Columbia Presbyterian Medical Center with spontaneous SAH were consecutively enrolled into the study. Exclusion criteria included SAH from arteriovenous malformation, SAH more than 14 days prior to admission to the hospital, and age less than 18 years. During this period 339 patients met criteria.

B. Study Group Demographics

The average age of the patients in the study group was 51.0 ± 13.3 years, with a range from 19 to 87 years old (Table 4). Years of education averaged 11.6 ± 4.6, with a range from 0 to 20 years of education (Table 4). Consistent with the literature, 69.5% of the sample were women (Vega, Kwoon, & Lavine, 2002), and 91.5% were right-handed (Lezak, 1995) (Table 5). There were 25 Spanish-speakers (30.5%) who were tested in their native language (Table 5). Hispanics comprised 45% of the sample, Whites 39%, Blacks 13.5%, and Asians 2.5% (Table 5).

C. Procedure

Informed consent was obtained at the time of study enrollment from all patients or a surrogate if the patient was incapacitated as determined by a study neurologist. Interviews with patients and/or their families were completed to obtain background information. Medical condition and hospital course, including disease severity and complications, were recorded prospectively. Treatment has been described in Kreiter et al. (2002). At 14 days post SAH, or discharge, a brief evaluation of patient handicap level was completed using the modified Rankin scale, a 7-point scale that ranges from 0 to 6, with 6 being "death" and 0 being "no disability," which has been found to have substantial interobserver agreement (Kappa = .56; van Swieten, Koudstaal, Visser, Schouten, & van Gijn, 1988). A comprehensive neuropsychological battery was conducted at 3 months and 12 months post SAH.

D. Data Collection

Demographics including age, sex, race/ethnicity, primary language, handedness, and years of education were obtained during the initial interview with the patient and/or family members. These variables were also verified in each follow-up interview at 3- and 12-months post SAH. Disease severity was measured by Hunt Hess grade (from I to V) and Glasgow Coma Scale (from 3 – 15), which were obtained upon admission by a study neurologist. Fisher grade (from I to IV), which is a predictor of vasospasm (Fisher, Kistler, & Davis, 1980), Hijdra score, which measures the amount of subarachnoid blood in 10 cisterns and fissures, and amount and location of intracerebral and intraventricular blood were documented from the admission CT by a study neurologist for all four cerebral ventricles. Aneurysm presence and location were obtained from the medical record of the angiogram. Complications including rebleeding of the aneurysm, delayed cerebral ischemia (infarction) resulting from vasospasm, hydrocephalus, cerebral edema, increased intracranial pressure, and herniation were obtained from the medical record of the hospital course and coded dichotomously.

E. Neuropsychological Battery

Three months and twelve months after the date of the SAH, subjects were invited to complete a comprehensive neuropsychological battery in the patients preferred language, either English or Spanish, administered by a trained psychometrician. The battery of tests (see Table 6) was selected based on several criteria. First, the tests are commonly used in clinical research settings and are known to be reasonably reliable and valid measures of the cognitive domain that they are designed to measure. Secondly, they can be administered to Spanish-speakers or they have equivalent forms available in Spanish. Third, normative data have been published for each of the tests, allowing a comparison to normal performance. The battery for the Spanish-speakers was the same as that for the English-speakers with the exception of some language based tests (i.e., the Word Accentuation Test was substituted for the National Adult Reading Test and the Auditory Verbal Learning Test was substituted for the California Verbal Learning Test).

1. Global mental status

   a) Telephone Interview for Cognitive Status (TICS; Brandt, Spencer, & Folstein, 1988)

Correlated highly with the Mini-Mental State examination, this is a brief test that can be conducted over the telephone. The 51-item version samples multiple domains of cognitive functioning including orientation, mental tracking, immediate and delayed verbal recall of a ten-word list, information, repetition, and motor inhibition (Lezak, 1995).

2. Attention/concentration

a) Digit Span

The Digit Span subtest of the WAIS-R (Wechsler, 1981) consists of two components: Digit Span Forward and Digit Span Backward. These components assess basic attention span and mental tracking ability. Beginning with 3 digits, subjects are presented with a series of digit sequences that increase in length by one digit every other trial, up to 9 digits, for a maximum possible score of 16 points per subtest.

b) Digit Symbol

The Digit Symbol subtest of the WAIS-R (Wechsler, 1981) consists of nine pairs of digits and symbols. Participants are requested to draw symbols corresponding to 93 digits as quickly as they can in 90 seconds. Their score is the number of symbols they correctly placed within the time limit. This test assesses attention/concentration and psychomotor speed.

c) Verbal Serial Attention Task (Mahurin & Cook, 1996)

This test is comprised of eight items that assess mental control for over-learned material and processing speed. The participant is requested to say a series (e.g., days of the week or months of the year) forward and/or backward. Time and errors are recorded with a maximum possible of 480 seconds, as timing is discontinued after 60 seconds per item.

d) California Computerized Assessment Package (Cal CAP; Miller, 1999)

This test is comprised of four subtests. In the *Simple* subtest, the subject is presented single digit numbers in the center of a computer screen and asked to press the space bar each time they see a number as quickly as possible. Measures provided by the program include reaction time in milliseconds, hit rate, false positives, and misses. In the *Choice* subtest, similar stimuli are presented, and the subject is asked to press the space bar each time they see the number "7" as quickly as possible. On the *Sequence 1* subtest, the subject is asked to press the space bar each time they see the same digit presented twice in a row. On the *Sequence 2* subtest, the subject is asked to press the space bar each time they see two consecutive numbers that are in numeric order (e.g., a 1 followed by a 2, or a 4 followed by a 5). The *Sequence 1* subtest measures attention and concentration.

3. Visuospatial skills

a) Block Design

The Block Design subtest of the WAIS-R (Wechsler, 1981) evaluates visuospatial function, praxis, construction, problem-solving, and psychomotor speed by asking subjects to construct up to nine designs from a picture with a possible maximum score of 51.

b) Visual Reproduction (VR) Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987)

On this test, subjects are asked to draw four images after a 10-second exposure to each, testing immediate visual recall. Twenty minutes later, subjects are asked to reproduce the images from memory, assessing delayed visual recall. Finally, they are presented the images again and asked to copy them, measuring visuospatial constructional skill. The copy score, with a maximum possible of 41 points, will be used as a measure of visuospatial skill.

c) Rey Complex Figure (Lezak, 1995)

On this test, subjects are asked to copy a complex figure, assessing visuospatial perception and construction. Eighteen elements of the drawing are scored from 0 – 2 points for a maximum possible of 36 points.

4. Psychomotor speed

a) Cal CAP (Miller, 1999)

The *Simple* reaction time measures the psychomotor speed of detecting the stimulus on the screen and responding by pressing a button.

b) Trailmaking Test (Lezak, 1995)

This test is composed of Part A and B. Part A assesses complex visual scanning, motor speed and agility. Twenty-five numbers are presented on a page and subjects are asked to connect them in order by drawing a line from one number to the next. The number of seconds to complete Part A is taken as a measure of psychomotor speed.

5. Language skills

a) Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983)

This test assesses confrontation naming of 60 pictured objects. Translations into Spanish were used for judging the word-finding abilities of the Spanish-speakers. The maximum possible score is 60 points.

b) Token Test (Spreen & Strauss, 1998)

This 36-item version of the Token Test assesses verbal comprehension of increasingly complex commands and was included to assess basic language abilities. It was translated to Spanish for use with the Spanish-speakers.

6. Verbal memory

a) California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1983)

The CVLT was used for English-speakers. This test assesses verbal memory via immediate and delayed recall with and without cues, and via recognition. The examiner reads the subject a shopping list of 16 items composed of four semantic categories with four exemplars per category in random-blocked order. The list is read five times, and after each time, the examiner asks the subject to recall as many of the shopping items as possible, for a maximum possible score of 80 points. After the fifth trial, the examiner presents the subject a different shopping list to remember, which is similarly constructed with four semantic categories and four examples per category. This interference trial is followed by an evaluation of the subject's free recall of the original list without any cueing. Subsequently, the examiner solicits only the words contained within each of the four categories, one by one. After a 20-minute delay, during which time other tests are administered that do not evaluate verbal memory, free recall is re-evaluated, followed by another evaluation of cued recall. Finally, 48 words, 16 from the shopping list and 32 foils, are read to the subject who must identify by recognition the words that were from the shopping list.

This test was selected because its structure includes both repetition and recognition testing paradigms, which were both observed to improve in previous studies (See Table 1). Scores used for the present study are total raw score, long delay free recall raw score, and recognition hits. The total raw score is the sum of the number of words the subject recalled on the first five presentations of the 16-item list. The range of possible scores is 0 to 80. The long delay free recall raw score is the number of words recalled without any cues after the 20-minute delay out of the maximum possible of 16. Recognition hits is the number of words correctly identified as belonging to the shopping list of 16 words; no adjustment to this score was made for false-positive responses.

b) Spanish Auditory Verbal Learning Test (Artiola, Hermosillo Romo, Heaton, & Pardee, 2000).

This test is similar in construction to the CVLT and was used to test verbal memory in Spanish-speakers.

7. Visual memory

a) WMS-R VRII (Wechsler, 1987).

This subtest in which the subject is asked to reproduce a drawing 20-minutes after having seen it was administered to measure memory visual for simple designs.

b) Rey Complex Figure (Lezak, 1995).

On this subtest, subjects are asked to draw a complex figure 30 minutes after seeing it. This test measures memory for complex visual material. Eighteen elements of the drawing are scored from 0 – 2 points, for a maximum possible score of 36 points.

8. Executive function

a) Modified Card Sorting Test (MCST; Nelson, 1976).

This is a modification of the Wisconsin Card Sorting Test (WCST; Lezak, 1995) in which only unambiguous stimuli are presented and no card shares more than one attribute with the key target cards; thus, only 48 cards are used instead of 128 as on the WCST, for a maximum possible score of 48. To complete a category, only six consecutive correct responses are required as opposed to 10 as in the WCST, and the subject is explicitly told the rule has changed. As on the WCST, the subject is asked to sort the cards into one of four groups and is provided feedback regarding the correctness of each choice. Perseverative responses are also tabulated as a proportion of total errors for a maximum possible of 100% of errors being perseverative.

b) Trailmaking Test (Lezak, 1995)

Part B of this test measures visual scanning, psychomotor speed, and cognitive set switching. On this test, the numbers one through 13 and the letters "A" through "L" are presented scattered across a page in pseudorandom format, and subjects are asked to draw a line to connect them in order alternating from number to letter to number to letter and so on, as quickly as they can without making errors. Errors are identified by the examiner during the test and the subject is asked to correct the error before continuing with the remainder of the task. The score is the number of seconds the subject takes to complete the task.

F. Data Analysis

1. Follow-up Bias Analyses

To ascertain whether the current cohort is a representative sample of all of the participants that qualified and were recruited for the study, mortality and drop out rates will be appraised, and follow-up bias will be examined. Four comparisons will be conducted using T-tests and chi-square tests to examine follow-up bias with respect to demographics, disease variables, and the 14-day Rankin score. First, among the subjects who are alive at 12 months, those who completed a neuropsychological evaluation at both 3 and 12 months post SAH will be compared to those who did not. Second, among subjects who are alive at 3 months, those who were followed at 3 months will be compared to those who were not. Third, among patients who alive at three months, those who were followed will be compared to those who were not followed. Finally, among all subjects, those who completed a neuropsychological evaluation at both 3 and 12 months post SAH will be compared to those who completed the neuropsychological evaluation only at 3 months post-SAH.

2. Data Reduction

In order to compare recovery patterns across different cognitive domains, the difference in patients' performance from 3 months to 12 months will be examined using standardized scores (Z scores). To develop standardized scores, means and SDs for the sample will be calculated from the performance of subjects who complete the 3-month follow-up assessment by subtracting the sample mean and dividing by the sample standard deviation. This procedure was adopted because 1) normative data for some tests correct for the effects of age, education and/or sex on scores but this is not consistent across all tests, and 2) normative groups are demographically dissimilar among tests and with respect to the current patient population.

Because of the large number of scores and the relatively small sample size, tests will be divided on an *a priori* basis into seven domains based on the cognitive domains they are purported to represent in the literature (Lezak, 1995; Spreen & Strauss, 1998). (See Table 6.) Tests that theoretically represent similar cognitive constructs will be standardized and the average standardized score of the subtests within a cognitive domain will be calculated for each of the seven *a priori* cognitive domains (Kreiter et al., 2002). This procedure serves to reduce the number of dependent measures and to increase the validity of the measures as it permits sampling from a broader array of subtests. An average of the seven domain scores will be taken as an overall cognitive index score, analogous to an IQ. Cognitive domain scores will be treated as dependent variables in subsequent analyses.

In order to evaluate the construct validity of the combinations of neuropsychological tests grouped into cognitive domains for this population, test scores among subjects who completed the assessment at 3 months post SAH will be subjected to a factor analysis. A principal components analysis will be conducted to reduce the tasks that comprise the test battery into the smallest number of factors, and the number of factors in the solution will be determined by the number of eigenvalues greater than 1.0 that result from the factor analysis. For missing cases, the PCA will be conducted twice, using casewise deletion, and again using pairwise deletion to increase power. Unrotated and varimax rotated solutions will be examined for overall maximal eigenvalues and best solution (Tabachnick & Fidell, 1996).

3. Repeated-Measures Multivariate Analyses of Covariance (MANCOVAs)

In order to examine the extent of recovery in each cognitive domain, two repeated-measures 2 x 2 multivariate analyses of covariance (MANCOVAs) will be completed. Education will be used as a covariate. The within-subjects variable will be Time (2: performance at 3 months and performance at 12 months). Because some subjects may not show very much recovery, and because this may be due to different reasons (e.g., intact subjects may recover little because they suffered little brain damage to begin with and impaired subjects may show a similar pattern because they suffered too much brain damage and have few cognitive resources to facilitate their recovery), the TICS will be used as an overall measure of global mental status to control for this potential confound between severity of injury and extent of recovery. Patients will be divided into two groups based on performance on the TICS at 3 months, with "high" performance being a score at or above the median performance of the group, and "low" performance being below the median. The between-subjects independent variable will be Group (2: high performance on the TICS, low performance on the TICS [<33]). In the first analysis, the seven cognitive domain scores will be used as the dependent variables. In the second analysis, the cognitive index score resulting from the mean of the cognitive domain scores will be used as the dependent variable.

To test each hypothesis, two mixed factorial repeated-measures MANCOVAs will be carried out. Because of the strong effects that education has been shown to have on neuropsychological test performance (e.g., Lezak, 1995), the number of years of school attended will be used as a covariate in the analyses of variance. For each MANCOVA, Group (2: High and Low performance on the TICS) will be a between-subjects variable, and the within-subjects variable will be Time (2: 3months, 12 months).

a) Age

To test the effect of Age on recovery, two Group (2) x Age (2) x Time (2) mixed factorial repeated-measures MANCOVA will be completed with Age (2: younger than the median, older than the median of the all the subjects [>51 years old]) entered as a between-subjects variable and education as a covariate (See Table 7). In the first analysis, the seven cognitive domain scores will be used as the dependent variables. In the second analysis, the cognitive index score resulting from the mean of the cognitive domain scores will be used as the dependent variable.

b) Etiology

To test the effect of etiology on recovery, two Group (2) x Etiology (2) x Time (2) mixed factorial repeated-measures MANCOVAs will be completed with Etiology (2: aneurysmal and non-aneurysmal) entered as a between-subjects variable, education, and as a covariate, and the seven cognitive domain scores as the dependent variables in the first analysis, and the cognitive index score as the dependent variable in the second analysis. See Table 7.

c) Aneurysm Location

To test the effect of aneurysm location on recovery, two Group (2) x Aneurysm location (4) x Time (2) mixed factorial repeated-measures MANCOVAs will be completed with Aneurysm location (4: anterior [anterior communicating artery], right-hemisphere [right anterior cerebral artery, right medial cerebral artery, right posterior cerebral artery, right posterior communicating artery, and right intracarotid artery], left-hemisphere [left anterior cerebral artery, left medial cerebral artery, left posterior cerebral artery, left posterior communicating artery, and left intracarotid artery], and posterior [vertebrobasilar artery, PICA, and basilar artery]) entered as a between-subjects variable and education as a covariate (See Table 7). Dependent variables will be the seven cognitive domain scores in one analysis and the cognitive index score in the second analysis. Significant findings will be followed up with univariate ANOVAs.

d) Lesion location: infarctions and thick clots

1. SAH amount. To test the effect of the amount of blood in the subarachnoid space on recovery, two Group (2) x SAH amount (2) x Time (2) mixed factorial repeated-measures MANCOVAs will be completed. SAH amount will be measured using the Hijdra score, which results from the quantification of the amount of subarachnoid blood as "no blood," "small SAH," "moderate SAH," and "completely filled with SAH" in 10 cerebral cisterns and fissures (i.e., the frontal interhemispheric fissure, bilateral lateral Sylvian fissures, bilateral basal Sylvian fissures, bilateral supracellar cisterns, bilateral ambient cisterns, and the quadrigeminal cistern; Hijdra et al., 1988) resulting in a maximum possible score of 30. Hijdra score (2: greater than the median Hijdra score, less than the median Hijdra score) entered as a between-subjects variable and education as a covariate (See Table 7). Dependent variables will be the seven cognitive domain scores in one analysis and the cognitive index score in a separate analysis.

2. *SAH location.* To examine the effect of SAH location on recovery, SAH location will be categorized into ten locations: anterior interhemispheric fissure, right lateral Sylvian fissure, right basal Sylvian fissure, right supracellar cistern, right ambient cistern, left lateral Sylvian fissure, left basal Sylvian fissure, left supracellar cistern, left ambient cistern, and quadrigeminal cistern. The amount of SAH in each

location will be classified as either "none," "small amount," "moderate amount," or the area was considered "completely full." These variables will be dichotomized into less SAH, including "none" and "small amount," and more SAH, including "moderate amount" and "completely filled," in order to maximize the effect of SAH location for these variables. Then, ten Group (2) x SAH Amount (2) x Time (2) repeated-measures MANCOVAs will be conducted in two sets of analyses with education as a covariate. (See Table 8). The domain scores were the dependent variables in the first analysis, and the cognitive index scores were the dependent measures in the second analysis.

3. *Infarction presence.* To test the effect of the presence of any infarction on recovery, two Group (2) x Infarction (2) x Time (2) mixed factorial repeated-measures MANCOVAs will be completed with Infarct (2: present, absent) entered as a between-subjects variable and education as a covariate (See Table 7). In order to address the question of whether infarct has an independent effect from vasospasm, the infarcts from admission, presumably before the period of potential vasospasm is in effect, will be examined. Dependent variables will be the seven cognitive domain scores in one analysis and the cognitive index score in a separate analysis.

4. *Infarction location.* To test the effect of location of cerebral infarctions on recovery, three Group (2) x Infarct (2) x Time (2) mixed factorial repeated-measures MANCOVAs will be completed with Infarct (2: absent, present) entered as a within-subjects variable and Education as a covariates (See Table 7) for each location:

anterior (bilateral ACA and ACA/MCA watershed), right-hemisphere (right MCA, MCA/PCA, PCA, anterior lenticulostriates, thalamic perforators, and cerebellum), and left-hemisphere (left MCA, MCA/PCA, PCA, anterior lenticulostriates, thalamic perforators, and cerebellum). Dependent variables will be the seven cognitive domain scores in one set of analyses and the cognitive index scores in a separate set of analyses. Significant multivariate findings will be followed with univariate ANOVAs.

e) Vasospasm

To test the effect of vasospasm on recovery, two Group (2) x Vasospasm (2) x Time (2) mixed factorial repeated-measures MANCOVAs will be completed with Vasospasm (2: present, absent) entered as a between-subjects variable and education as a covariate (See Table 7). Dependent variables will be the seven cognitive domain scores in one analysis and the cognitive index score in a separate analysis. To answer the question of whether Vasospasm had an effect independent of Infarction, patients with infarcts due to vasospasm will be removed from this analysis.

f) Clinical Grade

To test the effect of clinical grade upon admission on recovery, two Group (2) x Clinical Grade (2) x Time (2) mixed factorial repeated-measures MANCOVAs will be completed with Clinical grade on admission (2: Hunt Hess grades I and II, Hunt Hess grades III – V) entered as a between-subjects variable and education as a covariate (See Table 7). Dependent variables will be the seven cognitive domain scores in one analysis and the cognitive index score in a separate analysis.

g) <u>Cerebral Edema</u>

To test the effect of cerebral edema on recovery, two Group (2) x cerebral edema (2) x Time (2) mixed factorial repeated-measures MANCOVAs will be completed. Cerebral edema (2: present, absent) entered as a between-subjects variable and education as a covariate (See Table 7). Dependent variables will be the seven cognitive domain scores in one analysis and the cognitive index score in a separate analysis.

h) <u>Demographics</u>

1. *Sex.* To examine the effect of sex on recovery, two Group (2) x Sex (2) x Time (2) mixed factorial repeated-measures MANCOVAs will be completed with Sex (2: men, women) entered as a between-subjects variable and education as a covariate (See Table 7). Dependent variables will be the seven cognitive domain scores in one analysis and the cognitive index score in a separate analysis.

2. *Language.* To examine the effect of primary language on recovery, two Group (2) x Language (2) x Time (2) mixed factorial repeated-measures MANCOVAs will be completed with Language (2: English, Spanish) entered as a between-subjects variable and education as a covariate (See Table 7). Dependent variables will be the seven cognitive domain scores in one analysis and the cognitive index score in a separate analysis.

Significance levels will be set at p-value of 0.05.

CHAPTER THREE

III. RESULTS

All analyses were completed using a common commercially available computer software package for statistics: Statistical Package for the Social Sciences (SPSS), Version 9.0 (1998).

A. Follow-up bias.

1. Descriptive Characteristics of the Study Cohort

Figure 1 is a flow chart depicting the follow-up rates for all 339 patients that were enrolled in the study from July 1996 to March 2000. The study group, consisting of those patients who were tested at both time points (3 and 12 months post SAH), totaled 82. Demographics of the study group (age, education, sex, handedness, and race/ethnicity) are presented in Table 4 and Table 5. Disease characteristics (Admission Hunt Hess grade, aneurysm presence, treatment, frequency of complications [intraventricular hemorrhage, infarction, cerebral edema, hydrocephalus, intracerebral hemorrhage, and rebleed], and Fisher grades are presented in Table 9. Aneurysm locations, infarctions, amount and location of intraventricular hemorrhage and subarachnoid hemorrhage, length of hospital stay, day of SAH treatment, IVH score, and Hijdra score are presented in Table 10 through Table 14.

2. Generalizability of Results

a) Comparison 1: Is the study group representative of all the patients that qualified for the study?

To examine the data for follow-up bias, all subjects who were alive at 12 months were examined comparing those who completed both neuropsychological evaluations at 3 and 12 months, and those who did not. This analysis was performed to evaluate generalizability of the results of the current study to the remainder of the sample as well as to other SAH survivors. Demographic and disease variables were compared between groups using independent sample T-tests to compare eight continuous variables (see Table 15) and chi-square tests to examine 14 discrete variables (see Table 16). There were three significant differences between the study group and the members of the cohort who were not in the study group: treatment day, treatment type, and race/ethnicity. Those who were in the study group were treated significantly earlier than those who were not in the study group (M [study group] = 2.79 days after SAH ± 3.45 days, M [non-study group] = 4.15 days after SAH ± 4.66 days, $T_{194.458} = -2.438$, $p = 0.016$). They were also significantly more likely to have had surgery (Study group: 83% had surgery and 9% were embolized vs. the non-study group: 67% had surgery and 17% were embolized, $\chi^2_2 = 7.335$, $p = 0.025$). Those who were in the study group were significantly more likely to be Hispanic and significantly less likely to be White (Study group: 45% Hispanic and 39% White vs. the non-study group: 26% Hispanic and 61% White, $\chi^2_2 = 18.782$, $p < 0.001$). However, the two groups did not differ significantly in terms of age, years of education, length of hospital stay, independent functioning two weeks after SAH as determined by the modified Rankin scale, or the amount of SAH, IVH, or ICH upon admission ($p>0.05$). Nor did they differ significantly with regard to the percent who were women, were right-handed, had a poor grade on admission as identified by Hunt Hess Grade, ever had a poor grade throughout their hospitalization as identified by worst Hunt Hess, had an aneurysm, or suffered a complication such as a cerebral infarct, hydrocephalus, cerebral edema, rebleeding, or ICH ($p > 0.05$). Since 22 variables were examined, at least one variable would be expected to be found significant at the .05 alpha level, despite no real difference between the groups. Thus, the study group is closely representative of all of the SAH patients.

b) Comparison 2: Is the reference group representative of all the patients that qualified for the study?

Another analysis of follow-up bias included taking the 263 subjects who were alive at 3 months post-SAH and dividing them into two groups: those who completed neuropsychological testing at 3 months (N=117) and those who did not (N=146). This analysis was performed because of the need to ensure that those subjects who were followed up at three months were representative of the entire sample since their performance will be used as a reference at both time points of the study. Demographic and disease variables were compared between groups using T-tests to compare eight continuous variables (see Table 17) and chi-square tests to examine 14 discrete variables (see Table 18). Patients who underwent neuropsychological testing at 3 months were significantly younger (Reference group = 49.6 years ± 12.5 years vs. non-reference group = 54.1 years ± 15.0 years, $T_{261} = -2.572$, $p = 0.011$), had a significantly shorter hospital stay (Reference group = 17.1 days ± 10.96 days vs. non-reference group = 22.5 days ± 22.0 days, $T_{222.187} = -2.598$, $p = 0.010$), were treated significantly sooner than those who were alive but not tested at 3 months post-SAH (Reference group = 3.0 days ± 3.5 days vs. non-reference group = 4.6 days ± 5.7 days, $T_{206.852} = -2.473$, $p = 0.014$), and were significantly more likely to be Hispanic and less likely to be White (Reference group: 44% Hispanic and 41% White vs. the non-study group: 20% Hispanic and 58% White, $\chi^2_2 = 18.496$, $p < 0.001$). However, the two groups did not differ significantly in terms of age, years of education, independent functioning two weeks after SAH as determined by the modified Rankin scale, or the amount of SAH, IVH, or ICH upon admission ($p>0.05$). Nor did they differ significantly with regard to the percent who were women, right-handed, poor grade on admission as identified by Hunt Hess Grade, poor grade ever throughout their hospitalization as identified by worst Hunt Hess, aneurysmal vs. non-aneurysmal, or treated with surgery ($p > 0.05$). Thus, the reference group may actually be representative of younger, more Hispanic SAH patients, but the disease characteristics and the impact of the SAH as measures functionally by the modified Rankin scale were not significantly different from the entire sample. Therefore, this suggests that the performance of those patients who completed neuropsychological testing at 3 months is a reasonable estimate of the neuropsychological status of the larger group as a whole.

c) Comparison 3: Were the participants who were followed representative of all the patients that qualified for the study?

Those patients who were followed (N=222) were compared to those who were alive at three months but not followed up (N=41) to examine whether there was bias, not only in who was followed with neuropsychological testing, but rather in who was followed at all. Demographic and disease variables were compared between groups using T-tests to compare eight continuous variables (see Table 19) and chi-square tests to examine 14 discrete variables (see Table 20). Patients who were followed at 3 months were significantly more likely to be White (53% vs. 34%, $\chi^2_1 = 7.681$, $p = 0.021$), were treated significantly earlier (2.23 days post SAH ± 2.80 days vs. 4.10 days ± 5.10 days, $T_{66.222} = -3.027$, $p = 0.004$), and were significantly more functionally impaired on the modified Rankin scale two weeks after their SAH than those who were alive but not followed at 3 months post-SAH (2.35 ± 1.81 vs. 2.98 ± 1.66, $T_{258} = -2.172$, $p = 0.031$). Thus, the results of the current study probably do not apply to the sickest 18% of SAH patients.

d) Comparison 4: Is the Study Group representative of the Reference Group?

Another analysis of follow-up bias analysis included taking the 117 subjects who completed neuropsychological testing at 3 months post-SAH (Reference Group) and dividing them into two groups: those who completed neuropsychological testing at 12 months (Study Group; N=82) and those who did not (N=35). This was done to evaluate the equivalence of the Study Group and Reference Group so that, if not significantly different, the neuropsychological performance of the entire Reference Group would be justified, thereby providing more powerful and more reliable data for developing standardized scores. Demographic and disease variables were compared between groups using T-tests to compare continuous variables (see Table 21) and chi-square tests to examine discrete variables (see Table 22). There were no significant differences between the groups at the 0.05 level. Thus, the study group is representative of the reference group, and the neuropsychological performance of the Reference Group was used to calculate standardized scores.

B. Data Reduction

1. Raw Data

Means and standard deviations of the study group's performance on all test scores at 3 and 12-month evaluations are presented in Table 23. This table, when compared to the maximal test score values shown in Table 6, shows that a ceiling effect was not operative at either time point.

2. Cognitive Domains

In order to compare recovery patterns across different tests and different cognitive domains, patients' performance at 3 and 12 months post SAH was examined using standardized scores based on the mean and standard deviation of the performance of all of the subjects who completed the three-month evaluation. Because more participants completed the three-month evaluation (N = 117), independent samples t-tests were conducted comparing the performance on each neuropsychological test score to determine whether there were any differences between those patients who completed neuropsychological testing at both follow-up periods (N=82) vs. those who completed it only at 3 months (N=35; see Table 24). On 22 neuropsychological test scores from 14 different-tests, only one score (Trailmaking Test Part B) was significantly worse in the group that was tested both times (129.06 seconds ± 81.27 seconds vs. 95.78 seconds ± 60.74 seconds, $T_{92} = 2.17$, $p = 0.034$). There were no significant differences between the two groups on any of the other test scores. Since one finding is not more than would occur by chance at the .05 level, the test scores for all subjects who were evaluated at the 3-month follow-up were used to standardize scores for comparison across all seven domains (Attention, Language, Verbal Memory, Visuospatial Skills, Visual Memory, Psychomotor Speed, and Executive Functions). See Table 25.

Individuals' performance on each test or subtest was standardized by subtracting the sample mean and dividing by the sample standard deviation. In cases where raw scores represented time or errors, the individual performance was subtracted from the sample mean so that standardized scores were all on the same scale with good performance being higher than poor performance. The mean of the tests comprising each domain was then calculated for the 82 people who underwent repeat testing to obtain the seven domain scores for performance at 3 and 12 months post SAH. See Table 26. The mean of the seven cognitive domain scores was taken as the Cognitive Index Score. See Table 27.

As the purpose of developing domain scores was to reduce the number of variables to be submitted to a multivariate analysis of covariance (MANCOVA), the assumption of normal distribution of the domain scores was examined using a Kolmogorov-Smirnov test. All domain scores were normally distributed except those for Processing Speed ($p = 0.002$). Since MANCOVAs are considered robust to violations of assumptions of normality of the distribution (Tabachnick & Fidell, 1996), all of the domain scores were considered useable for the multivariate analyses.

3. Principal Components Analysis

To evaluate the validity of the *a priori* groupings of tests into eight domains, a principal components analysis (PCA) was considered. The assumptions for valid results of a PCA include a minimal number of subjects of 300 and normal distributions for variables that are entered into the analysis (Tabachnick & Fidell, 1996). While the procedure may be conducted using variables that are not normally distributed, this degrades the solution. Thus, the distributions of each of the neuropsychological variables were examined for significant differences for normality using the Kolmogorov-Smirnov test. Those with distributions that were significantly different from normal were subjected to mathematical transformations. See Table 28.

Transformations were conducted according to guidelines set forth in Tabachnick & Fidell (1996). Which transformation was performed on each variable to normalize its distribution depended on the direction and the degree to which the variable was skewed. The square root was taken for variables moderately skewed to the left ($\sqrt{x}$ or $x^{1/2}$).

Substantially skewed variables called for the logarithm ($\log_{10}x$). Severely skewed variables required the inverse (1/x) in order to be normalized. Distributions skewed to the right were reflected by subtracting values from one greater than the maximum value ([1 + max] – x) before subsequently applying one of the above transformations depending on how skewed the reflected distribution is. See Table 28 for the particular transformations used in each case.

This process resulted in all but three neuropsychological variables being normally distributed: CVLT recognition hits, RCFT copy, and MCST total correct. Thus, these variables and the normally distributed variables were entered into the PCA. The criterion for factor extraction was that the eigenvalues be greater than one. Missing variables were deleted, both pair-wise and list-wise, to evaluate whether the pattern of missing variables had an impact. To maximize factor differentiation, a varimax rotation was selected. See Table 29 and Table 30. Rotated eigenvalues were all greater than 1.00. See Table 31 and Table 32. Both PCAs yielded four factors: Visual Skills, Auditory Attention, Verbal Memory, and Psychomotor Speed. Using list-wise deletion, the more conservative method, yielded 53 participants with all 20 neuropsychology test scores. In the first PCA, the Visual Skills factor was comprised of all three test scores assigned to the Visual skills domain *a priori*, both of the test scores in the Visual Memory domain, two of the test scores in the Executive Function domain, and one test score each in the domains of Attention and Psychomotor Speed. The Auditory Attention factor was comprised of three of the test scores in the Attention domain, both of the test scores in the Language domain, and one of the test scores from the Executive Function domain. The Verbal Memory Factor was comprised of all three test scores from the Verbal Memory domain and one test score from the Language domain. The Speed factor was comprised of one test score each from Psychomotor Speed and Attention. Using pair-wise deletion yielded from 79 to 117 participants with the 20 neuropsychology test scores. In this second PCA, the Visual Skills factor was comprised of all three test scores assigned to the Visual skills domain *a priori*, both of the test scores in the Visual Memory domain, all three of the test scores in the Executive Function domain, and one test score each in the domains of Attention and Psychomotor Speed. The Auditory Attention factor was comprised of three of the test scores in the Attention domain, and both of the test scores in the Language domain. The Verbal Memory Factor was comprised of all three test scores from the Verbal Memory domain. The Speed factor was comprised of one test score each from Psychomotor Speed and Attention.

Because the Visual Skills factor, the first factor of the rotated solutions described above, was loaded with several tests from different domains that have been purported in the literature to represent distinct cognitive functions (Lezak, 1995; Spreen & Strauss, 1998) such as visuospatial skills (especially construction), visual memory, psychomotor speed, and executive functions, additional PCAs were run using only those test score variables that loaded on the first factor: Trails A and B, WMS-R VR II and VR copy, RCFT copy and delayed recall, MCST total correct and percent perseverative errors, Digit Symbol, and Block Design. Since four factors were expected, the criterion for extraction was set to four factors. Two separate PCAs were conducted using pair-wise deletion for missing variables for one PCA, resulting in an N of 80, and list-wise deletion for missing variables for the second follow up PCA, resulting in an N ranging from 94 to 112. Using varimax rotation to maximize the variability and increase the likelihood of separating out the expected factors, the resulting rotated eigenvalues were all greater than one (see Table 33 and Table 34). The four factors that resulted were the same for both follow up PCAs. The Visual Construction factor included three of three neuropsychological test scores from the *a priori* domain of Visual Skills. The Visual Memory factor included both of the neuropsychological test scores from the *a priori* domain of Visual Memory. The Executive Functions factor included two of the three neuropsychological test scores from the *a priori* domain of Executive Functions. Finally, the Attention factor included the remaining neuropsychological test scores, one from each of the following *a priori* domains: Attention, Psychomotor Speed, and Executive Functions. See Table 35 and Table 36. Thus, the factor structure that resulted from the PCA largely supports the construct validity of the groups of neuropsychological test scores assigned to different cognitive domains.

C. Repeated-measures MANCOVAs

In order to examine the impact of each of the variables hypothesized to impact recovery, separate repeated-measures MANCOVAs were conducted for each of the variables. To control for the fact that the degree of cognitive impairment may interact with the degree of recovery, subjects were divided into two groups based on their performance on the TICS at three months, divided at the median. Thus, Group was a between-subjects variable. Time was a within-subjects variable. The dependent variables were the *a priori* cognitive domain scores in an initial analysis for each variable of interest. Thus, the seven domain scores used as dependent variables were Attention/Concentration, Visuospatial Skills, Language, Verbal Memory, Visual Memory, Psychomotor Speed, and Executive Functioning. See Table 37. Education level in years was used as a covariate. A secondary analysis was also completed using the cognitive index scores as the dependent variable. See Table 27. Each independent variable of interest (i.e., Age, Etiology, Aneurysm Location, SAH Amount, SAH Location, Infarction, Vasospasm, Clinical Grade, Cerebral Edema, Sex, and Language) was evaluated in separate MANCOVAs as described above, and significant multivariate findings will be followed up with an evaluation of the univariate findings. The basic MANCOVA model was used to determine the impact of the variables of Time and Group. Therefore, the results for these variables were not explored with univariate analysis in any other MANCOVA that includes the other variables of interest.

1. <u>Time and Group MANCOVA:</u>

In order to examine the effect of severity of cognitive impairment on recovery over time, the first MANCOVA included Time (2: 3 months, 12 months) as the within-subjects variable, Group [2: high performance on TICS (>33), low performance on TICS (<34)] as the between-subjects variable, and Education in years as the covariate. The seven cognitive domain scores were used as the dependent variables.

For the first analysis, significant multivariate findings (df=7, 56) included Group ($F = 5.864$, $p<.001$), Time ($F = 2.772$, $p = .015$), and Time X Group ($F = 3.076$, $p = .008$). See Table 38 for the univariate findings. The main effect of Time was significant such that performance at 12 months was significantly better than performance at 3 months on measures of Attention/ Concentration ($M_3 = 0.0505 \pm 0.4477$, $M_{12} = 0.2090 \pm 0.6539$, $F_{1,62} = 4.754$, $p = .033$) and Psychomotor Speed ($M_3 = 0.0101 \pm 0.9043$, $M_{12} = 0.2530 \pm 0.4886$, $F_{1,62} = 6.413$, $p = .014$). See Figure 2. This supports the basic premise of the study, though not specifically hypothesized, that recovery of cognitive functions would be observed.

The main effect of Group was significant for all domains such that those who did well on the TICS also significantly outperformed those who did not do well on the TICS in all of the other domains as well. See Figure 3. The interaction effect between Time and Group was significant for Psychomotor Speed ($F_{1,62} = 6.818$, $p = 0.011$, see Figure 4) and Verbal Memory ($F_{1,62} = 5.621$, $p = 0.021$, see Figure 5) such that the significant improvement in scores seen from 3 to 12 months post-SAH was significantly greater for the people in the Low Group than for the people in the High Group (See Table 39, Figure 6, and Figure 7). This is consistent with the premise of the design of the study.

In order to evaluate overall cognitive functioning, a Group (2) x Time (2) repeated-measures MANCOVA was conducted, with education as a covariate and the cognitive index scores as the dependent variables. See Table 40. Group was significant such that people in the High Group significantly outperformed those in the Low Group. See Figure 8. This finding is consistent with the expectations for the study.

2. Age:

To examine the effect of Age on recovery, Age was divided at the median, 51 years, and two Group (2) x Age (2) x Time (2) repeated-measures MANCOVAs were conducted, with education as a covariate. The domain scores were the dependent variables in the first analysis, and the cognitive index scores were the dependent measures in the second analysis. See Table 7. For the first analysis, significant multivariate findings (df = 7, 54) included: Group ($F = 5.242$, $P<.001$), Time (2.282, $p = .041$), and Time X Group ($F = 3.021$, $p = .009$). Age ($F = 1.273$, $p = .281$), Time X Age ($F = .595$, $p = .757$), Age X Group ($F = .708$, $p = .666$), and Age X Group X Time ($F = 1.414$, $p = .219$) were not significant. There was no significant main effect of Age nor were any interaction effects with Age significant. Significant univariate results are parallel to those found in the original MANCOVA model described above. See Table 41.

In the second analysis for the cognitive index scores, there was a significant main effect of Age ($F_{1, 75} = 4.085$, $p = .047$) such that younger participants ($M = .3038 \pm .5873$) significantly outperformed older participants ($M = -.2096 \pm .7142$). However, no significant interactions were found (Age x Group $F_{1,75} = .021$, $p = .886$, Age x Time $F_{1,75} = 3.534$, $p = .064$). These findings reveal that cognition after SAH is worse among older individuals. However, the fact that there was not a significant interaction between Age and Time indicates that the hypothesis that Age would negatively impact recovery of cognition was not supported.

3. Etiology:

To examine the effect of Etiology on recovery, subjects were divided into two groups: those with a ruptured aneurysm (Aneurysmal) and those without (Non-Aneurysmal). Then, two Group (2) x Etiology (2) x Time (2) repeated-measures MANCOVAs were conducted, with education as a covariate. The domain scores were the dependent variables in the first analysis, and the cognitive index scores were the dependent measures in the second analysis. See Table 7. For the first analysis, the only significant multivariate finding was for Group ($F_{7,54} = 2.413$, $p = .032$). Time, Etiology, Time X Etiology, Time X Group, Etiology X Group, and Etiology X Group X Time were not significant. See Table 42. There was no significant main effect of etiology, but the small number of subjects limited power. There was no significant main effect of Time in this analysis. There was a significant main effect of Group such that those who did well on the TICS did significantly better than those who performed poorly on the TICS, which is consistent with the findings from the basic MANCOVA model.

In the second analysis for the cognitive index scores, there was no significant main effect of Etiology, nor did Etiology significantly interact with any other variable. The fact that there were no significant effects of Etiology is consistent with the hypothesis for Etiology.

4. Aneurysm Location:

To examine the effect of Aneurysm Location on recovery, subjects were divided into four groups based on the location of their ruptured aneurysms. As each patient had only one ruptured aneurysm, this was a between-subjects variable: anterior (N = 11), left (N = 15), right (N = 21), and posterior (N = 13). Then, two Group (2) x Aneurysm Location (4) x Time (2) repeated-measures MANCOVAs were conducted, with education as a covariate. The domain scores were the dependent variables in the first analysis, and the cognitive index scores were the dependent measures in the second analysis. See Table 7. For the first analysis, significant multivariate findings included Group and Group x Aneurysm Location. See Table 43. The interaction effect between Group and Aneurysm Location was significant only for executive functions ($F_{3,51} = 4.134$, $p = .011$; see Table 44) such that the extent to which the High Group significantly outperformed the Low Group was significantly greater for those with ruptured aneurysms in the left, right, and posterior areas than the frontal circulation. See Table 45. Thus, it would appear that the extent to the High Group performed better on executive functions was significantly less for patients with anterior circulation aneurysms than for patients with aneurysms located anywhere else. See Figure 9. Post-hoc testing, using independent sample T-tests comparing the High Group to the Low Group on Executive Functions, confirmed this interpretation. See Table 46. One-way ANOVAs comparing Aneurysm Locations on Executive Functions were not significant (High Group $F_{3,33} = 2.569$, p =

.066; Low Group $F_{3,33} = 2.639$, p .072). As Aneurysm Location was predicted not to have an impact on recovery over time, these findings support the hypothesis.

In the second analysis for the cognitive index scores, there was no significant main effect of Aneurysm Location, nor did Aneurysm Location significantly interact with any other variable. This finding is consistent with the hypothesis for Aneurysm Location.

5. Lesion Location and Amount:

a. SAH Amount. Overall amount of blood visualized on the admission CT scan was calculated using the Hijdra scale (maximum score = 30). To examine the effect of SAH Amount on recovery, subjects were divided into two groups: those with a Hijdra score less than 14 and those with a Hijdra score of 14 or more. Then, two Group (2) x SAH Amount (2) x Time (2) repeated-measures MANCOVAs were conducted, with education as a covariate. The domain scores were the dependent variables in the first analysis, and the cognitive index scores were the dependent measures in the second analysis. See Table 7. For the first analysis, significant multivariate findings (df= 7, 52) included Group, Time, and Time x Group. See Table 47. There was no significant main effect of SAH Amount, nor any significant interaction effect with SAH Amount. In the second analysis for the cognitive index scores, there was a significant effect of SAH Amount with Group ($F_{1,71} = 5.091$, $p = .027$) such that the extent to which participants with less SAH outperformed those with more SAH was significantly greater among participants in the Low Group than in the High Group. See Figure 10. This finding is consistent with the literature. However, since there was no significant interaction between SAH Amount and Time, the hypothesis that greater SAH Amount would slow recovery was not supported.

b. *SAH location.* To examine the effect of SAH location on recovery, SAH location was categorized into ten locations: anterior interhemispheric fissure, right lateral Sylvian fissure, right basal Sylvian fissure, right supracellar cistern, right ambient cistern, left lateral Sylvian fissure, left basal Sylvian fissure, left supracellar cistern, left ambient cistern, and quadrigeminal cistern. See Table 8. The amount of SAH in each location was classified as either "none," "small amount," "moderate amount," or the area was considered "completely full." These variables were dichotomized into less SAH, which included "none" and "small amount," and more SAH, which included "moderate amount" and "completely filled," in order to maximize the effect of SAH location for these variables. Then, ten Group (2) x SAH Amount (2) x Time (2) repeated-measures MANCOVAs were conducted in two sets of analyses with education as a covariate. The domain scores were the dependent variables in the first analysis, and the cognitive index scores were the dependent measures in the second analysis.

The effect of SAH in the anterior interhemispheric fissure on the domain scores was not significant, nor did it significantly interact with any other variable. See Table 48. The same was true for the right lateral Sylvian fissure (see Table 49), the left lateral Sylvian fissure (see Table 50), right basal Sylvian fissure (see Table 51), left basal Sylvian fissure (see Table 52), the right supracellar cistern (see Table 53), the left supracellar cistern (see Table 54), the right ambient cistern (see Table 55), and the left ambient cistern (see Table 56).

The effect of SAH in the quadrigeminal cistern was significant as was the three-way interaction between Time x Group x Quadrigeminal Cistern SAH (see Table 57). The two-way interactions between SAH in the Quadrigeminal Cistern and both Time and Group separately were not significant. The univariate results for the main effect of SAH in the Quadrigeminal Cistern and for the three-way interaction are in Table 58. Those who had less SAH in the quadrigeminal cistern performed significantly better on the domain of attention (M = .1991 ± .1516) than those who had more SAH in the quadrigeminal cistern (M = -.1187 ± 4724; $F_{1, 58}$ = 13.190, p = .001). The three-way interaction had a significant effect on both Psychomotor Speed ($F_{1, 58}$ = 6.230, p = .015; see Figure 11) and Language Skills ($F_{1, 58}$ = 10.150, p = .002; see Figure 12).

On a post-hoc basis, a repeated-measures MANCOVA was conducted separately for each Group, with Time as a within-subjects variable, SAH in the Quadrigeminal Cistern as the between-subjects variable, Education as the covariate, and Psychomotor Speed and Language Skills as the dependent variables. These analyses revealed that, for the Low Group, who performed less well on the TICS at three months, there was a significant effect of Time ($F_{2,25}$= 5.240, p = .013) such that there was significant improvement from 3 to 12 months for Psychomotor Speed ($F_{1,26}$= 10.896, p = .003), but not for Language ($F_{1,26}$= .021, p = .886), and there was no significant effect of SAH in the Quadrigeminal Cistern ($F_{2,25}$= 1.348, p = .278), nor was there a significant Time x

Quadrigeminal Cistern SAH interaction ($F_{2,25}$= 3.394, p = .05). On the other hand, for the High Group, the pattern was reversed so that the significant effect of Time interacted with amount of blood in the Quadrigeminal Cistern ($F_{2,31}$= 4.292, p =.023) for Language ($F_{1,32}$= 7.212, p = .011) such that the extent to which improvement from 3 to 12 months was observed was significantly greater for those with more SAH in the Quadrigeminal Cistern, but not for Psychomotor Speed ($F_{1,32}$= 1.481, p = .233), and there were no significant main effects for Time ($F_{2,31}$= .362, p = .699) or Quadrigeminal Cistern SAH ($F_{2,31}$= .032, p = .968).

For the second set of analyses with the cognitive domain scores, there were four SAH locations with significant effects for cognitive index scores: the right lateral Sylvian fissure, the right basal Sylvian fissure, the left supracellar cistern, and the right ambient cistern. There were significant main effects of SAH in the right lateral Sylvian fissure ($F_{1,73}$ = 4.438, p = .039) and in the Left Supracellar Cistern ($F_{1,73}$ = 6.081, p = .016) such that participants with less SAH in these areas significantly outperformed those with more SAH on the Cognitive Index. See Figure 13. There were significant interaction effects between Group and SAH in the right basal Sylvian fissure ($F_{1,73}$ = 5.725, p = .019, see Figure 14) and in the right ambient cistern ($F_{1,73}$ = 4.824, p = .031, see Figure 15) such that the extent to which participants with less SAH in these two cisterns outperformed participants with more SAH was significantly greater for those in the Low Group than for people in the High Group.

SAH Location was predicted to have a significant effect on recovery of cognition, which was supported as clots in several cisterns and fissures resulted in impaired cognition even at 12 months post onset. However, the prediction that clots would have location-specific effects on cognition was not supported as only one location of 10 had a significant negative impact on any specific cognitive domain.

c. Infarction presence. To examine the effect of cerebral infarction on recovery, subjects were divided into two groups: those with a cerebral infarction resulting from the SAH, and those without infarctions. Then, two Group (2) x Infarction (2) x Time (2) repeated-measures MANCOVAs were conducted, with education as a covariate. The domain scores were the dependent variables in the first analysis, and the cognitive index scores were the dependent measures in the second analysis. See Table 7. For the first analysis, significant multivariate findings (df=7, 54) included Group, Time, Time x Group, and Group x Infarct. See Table 59 and Table 60. Presence of an infarction by itself was not a significant predictor of neuropsychological performance ($p = .251$), but there was a significant interaction effect of Infarct with Group ($F_{7, 54} = 3.405$, $p = .004$) for Attention / Concentration ($F_{1, 60} = 10.389$, $p = .002$, see Figure 16) and for Visuospatial Skills ($F_{1, 60} = 12.637$, $p = .001$, see Figure 17) such that the extent to which the participants in the High Group outperformed those in the Low Group was significantly greater for people without an infarct. Thus, among people in the High Group, those with Infarcts performed worse, but among people in the Low Group, those with Infarcts performed better. In the second analysis for the cognitive index scores, there was no significant main effect of Infarct, nor did Infarct significantly interact with any other variable. As infarctions were predicted to result in persistent cognitive deficits, this hypothesis was not supported.

d. Infarction location. To test the effect of location of cerebral infarctions on recovery, three Group (2) x Infarct (2) x Time (2) mixed factorial repeated-measures MANCOVAs were completed with Infarct (2: absent, present) entered as a within-subjects variable and Education as a covariates (See Table 7) for each location: anterior, right-hemisphere and left-hemisphere.

For the first multivariate analysis using the seven cognitive domain scores as dependent variable, there was no significant main effect of frontal infarction ($F_{7,32}$= 0.690, p = .678) nor were there any significant interactions between frontal infarct and Time ($F_{7,32}$= 1.883, p = .105), Group ($F_{7,32}$= 0.573, p = .773), or the three-way (Time x Group x Frontal Infarct $F_{7,32}$= 1.956, p = .093). When the Cognitive Index scores were the dependent variables, there was no significant main effect of frontal infarction ($F_{1,45}$= 0.049, p = .825) nor were there any significant interactions between frontal infarct and Time ($F_{1,45}$= 1.798, p = .187), Group ($F_{1,45}$= 0.004, p = .951), or the three-way (Time x Group x Frontal Infarct $F_{1,45}$= 0.064, p = .802).

For left-sided infarctions, the multivariate analysis using the seven cognitive domains as dependent variables revealed a similar pattern, with no significant main or interaction effects with left sided infarcts (Left Infarct $F_{7,32}$= 1.329, p = .269; Left Infarct x Time $F_{7,32}$= 1.146, p = .360; Left Infarct x Group $F_{7,32}$= 0.526, p = .808; Left Infarct x

Time x Group $F_{7,32}$= .979, p = .463). Similarly, no significant effects were found on the Cognitive Index scores, either (Left Infarct $F_{1,45}$= .218, p = .643; Left Infarct x Time $F_{1,45}$= 1.241, p = .271; Left Infarct x Group $F_{1,45}$= 0.169, p = .683; Left Infarct x Time x Group $F_{1,45}$= 1.991, p = .165).

For right-sided infarctions, the multivariate analysis using the seven cognitive domains as dependent variables yielded the same pattern of results, with no significant main or interaction effects (Right Infarct $F_{7,32}$= 1.529, p = .193; Right Infarct x Time $F_{7,32}$= .767, p = .618; Right Infarct x Group $F_{7,32}$= 1.279, p = .292; Right Infarct x Time x Group $F_{7,32}$= .795, p = .597), nor were there any significant findings for the Cognitive Index scores (Right Infarct $F_{1,45}$= .324, p = .572; Right Infarct x Time $F_{1,45}$= 2.441, p = .125; Right Infarct x Group $F_{1,45}$= .701, p = .407; Right Infarct x Time x Group $F_{1,45}$= .173, p = .679).

As there were no relationships between infarct location and deficits in specific domains, the hypothesis was not supported.

6. Vasospasm:

To examine the effect of Vasospasm on recovery, subjects were divided into two groups: those with and those without clinical deterioration due vasospasm. Then, two Group (2) x Vasospasm (2) x Time (2) repeated-measures MANCOVAs were conducted, with education as a covariate. The domain scores were the dependent variables in the first analysis, and the cognitive index scores were the dependent measures in the second analysis. Patients with infarcts due to vasospasm were removed from this analysis so that the effect of vasospasm alone could be examined. See Table 7. For the first analysis, significant multivariate findings (df = 7, 49) included Group and Time. See Table 61. There were no significant effects of Vasospasm or any significant interactions with Vasospasm. In the second analysis for the cognitive index scores, there was no significant main effect of Vasospasm, nor did Vasospasm significantly interact with any other variable. See Table 62. Thus, the hypothesis that vasospasm alone, without infarction, would not impair cognition was supported.

7. Clinical Grade:

To examine the effect of Clinical Grade on recovery, subjects were divided into two groups: those with Good clinical grades (Hunt Hess Grades I & II) and those with Poor Clinical Grades (Hunt Hess Grades III, IV, & V). Then, two Group (2) x Clinical Grade (2) x Time (2) repeated-measures MANCOVAs were conducted, with education as a covariate. The domain scores were the dependent variables in the first analysis, and the cognitive index scores were the dependent measures in the second analysis. See Table 7. For the first analysis, significant multivariate findings (df = 7, 54) included Group, Time, and Time x Group (p = .001). See Table 63. Clinical Grade was not a significant predictor of neuropsychological performance, nor did it significantly interact with any other variable. In the second analysis for the cognitive index scores, there was a significant main effect of Clinical Grade ($F_{1, 75} = 1.403$, p = .027) such that those with a Good Grade (Hunt Hess Grades I or II, M = .1910 ± .6128) significantly outperformed those with a Poor Grade (Hunt Hess Grades III, IV, or V, M = -.1287 ± .7658). Thus, the hypothesis that worse Clinical Grade would negatively impact overall Cognition in a diffuse manner was supported.

8. Cerebral Edema:

To examine the effect of Cerebral Edema on recovery, subjects were divided into two groups: those with and without cerebral edema. Then, two Group (2) x Cerebral Edema (2) x Time (2) repeated-measures MANCOVAs were conducted, with education as a covariate. The domain scores were the dependent variables in the first analysis, and the cognitive index scores were the dependent measures in the second analysis. See Table 7. For the first analysis, significant multivariate findings (df = 7, 54) included Group, Time, Time X Group, and Time x Cerebral Edema. See Table 64. Cerebral Edema by itself was not a significant predictor of neuropsychological performance. However, it did interact significantly with Time for Visuospatial Skills ($F_{1,60} = 13.049$, $p = .001$) and Visual Memory ($F_{1,60} = 6.237$, $p = .015$). See Table 65. For Visuospatial Skills, the extent to which people with edema performed worse than those without edema became significantly greater with time (see Figure 18), while for Visual Memory, the extent to which people with edema performed worse than those without edema became significantly less with time (see Figure 19). For the second analysis, with cognitive index scores, there was a significant interaction effect between Edema and Time ($F_{1,75} = 5.847$, $p = .018$) such that the extent to which participants with Cerebral Edema improve over time is significantly greater than for those without edema. See Figure 20. Thus, the hypothesis that Cerebral Edema would slow recovery was supported, both diffusely, as well as specifically for Visuospatial Skills and Visual Memory.

9. Demographics.

a. *Sex.* To examine the effect of Sex, two Group (2) x Sex (2) x Time (2) repeated-measures MANCOVAs were conducted, with education as a covariate. The domain scores were the dependent variables in the first analysis, and the cognitive index scores were the dependent measures in the second analysis. See Table 7. For the first analysis, significant multivariate findings (df = 7, 54) included Group, Sex, and Time, with no significant interactions. See Table 66. For the univariate results (see Table 67), there was a significant main effect of Sex for Verbal Memory ($F_{1, 60} = 16.243$, $p < .001$) and for Visual Memory ($F_{1, 60} = 4.517$, $p = 0.38$) such that women significantly outperformed men on tests of verbal memory and visual memory (see Figure 25). There were no significant effects of Sex nor any significant interactions with Sex affecting the Cognitive Index scores. The fact that Sex had a significant main effect on memory scores was not expected, and therefore the hypothesis that Sex would not have an impact on cognition after SAH was not supported.

b. *Language.* To examine the effect of primary language (English vs. Spanish) on recovery, two Group (2) x Language (2) x Time (2) repeated-measures MANCOVAs were conducted, with education as a covariate. The domain scores were the dependent variables in the first analysis, and the cognitive index scores were the dependent measures in the second analysis. See Table 7. For the first analysis, significant multivariate findings (df = 7, 54) included Group, Language, and Time X Group. See Table 68. There was a significant main effect of Language for Visuospatial Skills ($F_{1, 60} = 4.551$, $p = .037$, Table 69) such that English-speakers significantly outperformed Spanish-speakers. See Figure 22. There were no significant effects of Language on the Cognitive Index Scores. The fact that Language had a significant main effect on Visuospatial Skills was not expected, and therefore the hypothesis that Language would not have an impact on cognition after SAH was not supported.

10. <u>Summary of MANCOVA findings.</u>

There were several significant findings as a result of the MANCOVA series (see Table 70).

Time and Group. Attention/Concentration and Psychomotor Speed improved significantly over Time. Performance for the High Group, determined by the score on the TICS at three months, was significantly better than for the Low Group across all seven cognitive domains as well as on the Cognitive Index. Psychomotor Speed and Verbal Memory significantly improved over Time for the Low Group to a significantly greater extent than for the High Group.

Age. The overall Cognitive Index was significantly worse for older patients than younger patients, but recovery over Time was not impacted by Age.

Etiology. As predicted, whether the source of SAH was aneurysmal was not a significant predictor of performance or recovery.

Aneurysm Location. As predicted, location of the ruptured aneurysm did not significantly affect recovery. However, patients in the High Group significantly outperformed those in the Low Group on Executive Functions for every Aneurysm Location except those in the Anterior circulation, suggesting that Aneurysm Location does have a significant impact on cognition after SAH, but only in the case of Executive Functions.

Amount of Blood. Greater SAH Amount resulted in significantly worse overall cognition in the Low Group, but this did not slow recovery as hypothesized.

Location of Blood. The hypothesis that more blood in specific locations would result in persistent cognitive deficits was supported, but the hypothesis that clots would have location-specific effects consistent with localization theory was not. Psychomotor Speed and Language Skills were each significantly affected by a three-way interaction between blood in the Quadrigeminal Cistern, Group, and Time. Among patients in the Low Group with more blood in the Quadrigeminal Cistern, significant improvement was observed in Psychomotor Speed. Among members of the High Group, improvement observed from 3 to 12 months in Language Skills was significantly greater for those with more blood in the Quadrigeminal Cistern. Overall Cognition was significantly negatively impacted by more blood in the Right Lateral Sylvian Fissures and the Left Supracellar Cistern. Overall Cognition was significantly more negatively impacted by more blood in the Right Ambient Cistern and the Right Basal Sylvian Fissure for the Low Group than the High Group. Attention was significantly negatively impacted overall by more blood in the Quadrigeminal Cistern.

Infarctions. The hypothesis that cerebral infarctions would result in persistent cognitive impairments was not supported. Among the less cognitive impaired group only, infarctions resulted in worse Attention / Concentration and Visuospatial Skills, with no effects on the Cognition Index. However, there were no significant findings for any specific infarct location.

Vasospasm. As there were no significant effects of Vasospasm, the hypothesis that Vasospasm alone, without Infarct, would not result in cognitive impairment was supported.

Clinical Grade. The hypothesis that worse Clinical Grade would result in impaired cognition was supported by the fact that the Cognitive Index was significantly impaired by worse Clinical Grade. The hypothesis that the effect of Clinical Grade would be diffuse was supported by the fact that there were no significant effects of Clinical Grade on any specific cognitive domains.

Cerebral Edema. The hypothesis that Cerebral Edema would slow recovery was born out by a significant Time x Cerebral Edema interaction for Visual Memory, Visuospatial Skills, and the Cognitive Index.

Sex. An unexpected finding revealed that women significantly outperformed men on Verbal and Visual Memory.

Language. An unexpected finding revealed that English speakers significantly outperformed Spanish speakers on Visuospatial Skills.

CHAPTER FOUR

IV. DISCUSSION

The current study examined the recovery of neuropsychological functioning from 3 to 12 months after subarachnoid hemorrhage and factors that influence the degree of recovery in various cognitive domains. Seven cognitive domains were examined, including Attention/Concentration, Language, Verbal Memory, Visuospatial Skills, Visual Memory, Psychomotor Speed, and Executive Functions. A combination of all of these domains, comprising an overall Cognitive Index, was also evaluated. Recovery over time was evaluated as a function of severity of cognitive impact of SAH by evaluating several factors which included demographic influences such as age, sex, and primary language, as well as disease-related factors, such as etiology, aneurysm location, infarction, amount and location of SAH, vasospasm, clinical grade, and cerebral edema. While older age, more hemorrhagic blood, localized clots, infarctions, poor clinical grade on admission, and cerebral edema were hypothesized to slow recovery, presence of an aneurysm, aneurysm location, vasospasm, sex, and primary language were predicted to have no impact on recovery of neuropsychological functions after SAH.

A. Generalizability of the Results

The pool of participants was evaluated for any follow-up bias since this was a longitudinal study and because any systematic pattern of dropout from the study had the potential to skew the results toward reflecting the characteristics of only the remaining participants. When 22 disease-related and demographic variables were examined, those participants who were followed in the study group were found to have been treated earlier, more often surgically, and more often Hispanic than the rest of the study patients who were alive at 12 months post SAH. After Bonferroni corrections, only ethnicity remained a significant factor. Thus, regarding disease characteristics, age, and sex, the study group is comprised of a typical sample of the patients who qualified for participation. As such, the results of the current study may be considered generalizable to several other patient populations.

Nevertheless, there also exists the possibility that these findings reflect actual differences between the groups. The group that was followed with neuropsychological testing was treated significantly sooner after SAH onset than the group that was not followed with neuropsychological testing. This may be due to the distance between the hospital and the patients' homes. If people live nearby, they are more likely to be treated sooner as well as to be followed, whereas when people are transferred from a distant hospital close to their home, they are more likely to be treated later after the SAH onset and less likely to be followed. The group that was followed was also significantly more likely to be Hispanic and less likely to be White than the group that was not followed. Considering the demographics of the neighborhood immediately surrounding the hospital where these data were collected, it is likely that this finding reflects the composition of the local community. Finally, the group that was followed was significantly more likely to have been treated surgically. Surgical patients may have a tendency to return to the hospital more frequently for follow-up visits with the surgeon than embolization patients or patients who are observed only without an aneurysm. Therefore, surgical patients were more likely to be followed for the purposes of the current study as well. Since most patients are, in fact, typically treated surgically and since the recommendation is to treat SAH early, generalization of the results from the current study to other SAH populations is valid.

The comparison between the reference group and the patients who were not followed at 3 months revealed that the reference group was younger, with shorter hospital stays, treated earlier, and more likely to be Hispanic. These factors may all be interrelated and also influenced by the hospital's catchment area, located in a Hispanic community. Living nearby, it was more convenient to return to the hospital for follow-up as well as more likely that soon after the SAH, local Hispanics were taken directly to Columbia as opposed to being transferred there later on from another hospital. Having arrived for treatment sooner may have contributed to being released sooner. Being younger may have also contributed to a shorter hospital stay. As there were no differences between the reference group and the study group, who was examined both at 3 and 12 months, these differences are likely to reflect the study group as well. While the recovery patterns observed in the current study may more accurately be generalized to a younger contingent of patients, the generalization of results to other SAH populations remains valid to the extent that the differences between the study group and the rest of the sample were due to proximity of the hospital to their homes.

The fact that those who were followed, whether tested or not, were more likely to be White is consistent with the psychological literature that generally participants in voluntary research protocols are more often White, female, and college-educated (Whitley, 1995). Indeed, the current follow-up bias analysis also revealed that the people who were followed were, in fact, more often female, but this did not reach statistical significance, possibly due to low power since 84% of the sample were followed, and therefore, the group that was not followed was relatively small. Additionally, those people who were not followed at three months had significantly longer hospital stays and were significantly more functionally impaired two weeks after their hemorrhage. Therefore, it is likely these individuals' impairments continued to impede their functioning by three months post SAH, and this may have made them less likely to be able to participate in the follow-up interviews even by phone. Thus, the results of the current study probably do not reflect what may be expected for the portion of SAH patients too sick for follow-up. However, this does not limit the comparability of the results of the current study to those of other studies, since some investigators reported a similar pattern for follow-up (Mohanty et al., 1993).

No differences were found between the study group and the reference group. Thus, the study group was considered representative of the reference group suggesting that the patterns of recovery found for those who completed both evaluations may be generalized to all those who were tested at the three-month follow-up.

B. Validity of Methodology.

As a group, patients' performance was considerably below that of published normative data (see Kreiter et al., 2002), which is consistent with the findings of other investigations (e.g., Hillis et al., 2000; Romner et al., 1989). In combination with visual inspection of the date, it also indicates that a ceiling effect was not operative for the group for any of the test measures.

Construct validity of the groups of scores comprising each cognitive domain was evaluated with factor analysis using both pairwise and listwise deletion of missing variables. Both principal components analyses (PCA) resulted in very similar solutions, which indicates that the pairwise deletion is a valid reflection of the data, despite missing data. As it also has the added power of additional participants and data, this supports the factor structure yielded in the first PCA with listwise deletion. However, this procedure resulted in only four factors (i.e., Visual Skills, Auditory Attention, Verbal Memory, and Psychomotor Speed), which, compared to the seven cognitive domains examined in the study, was relatively few. Since several tests aligned with the first factor, an additional follow up PCA was conducted using only those variables. Once this was done, four factors were identified (i.e., Visual Construction, Speed, Visual Memory, and Executive Functions).

Taken together, the factor structures yielded from the two principal components analyses were similar to the composition of the *a priori* domains. See Table 71. Most of the test scores correlated with factors in a similar organization to the cognitive domains.

The cognitive domains of Attention and Language both correlated with the factor labeled Auditory Attention. This may be due to the variability within the Language performance being a function of attention, since SAH does not typically result in deficits of language skills.

While most of the test scores in the cognitive domain of Attention correlated with the factor of Attention, two did not: Digit Symbol and Cal CAP Attention. These both correlated with the factor of Psychomotor Speed. Both of the test scores in the cognitive domain of Psychomotor Speed correlated with the factor of Psychomotor Speed, but one (Trails A time) did so only after being further analyzed within Visual Skills, and one score from the Executive Functions domain also correlated best with the factor of Psychomotor Speed. Within the factor analysis for Visual Skills, all three of the test scores for Visual Construction correlated with a factor for Visual Construction, both of the test scores from the Visual Memory domain correlated with that factor, and two of the three scores from the Executive Function domain correlated with a factor for Executive functions. Thus, overall, the construct validity of the organization of the *a priori* cognitive domains was supported by the factor analyses.

Nevertheless, the results of the factor analysis were not identical to the domain composition. The fact that more test scores than originally anticipated correlated with the factors of Psychomotor Speed and Visual Skills may indicate that the degree to which these abilities were affected in this patient population was greater than the effect of the impairment of other cognitive domains. As no neuropsychological test is truly pure, the results of the factor analyses highlight the differential impact of SAH on cognitive domains that are components of the abilities required to perform well on any single neuropsychological task. For example, Trails B performance relies on an individual's ability to scan the visual field, sequence familiar information, switch sets, and do all of this quickly (Lezak, 1998). Thus, performance on this test theoretically reflects attention, visuospatial skills, working memory, executive functions, and psychomotor speed. The fact that in this study, using a patient population, performance on Trails B correlated most with Visual Skills and Psychomotor Speed suggests that variability within these domains, probably due to impairments, was what was driving the performance on this test. A similar argument can be made for the other two test scores, Digit Symbol and Cal CAP Attention. Although performance on these tests among unimpaired individuals may rely more on attention skills than visual skills or psychomotor speed, in a SAH patient population, these are the cognitive domains that introduce variability into group performance. Thus, some differences between the organization of the cognitive domains and the factor structure must be expected when conducting a factor analysis with an impaired group. A future study may take this into consideration to the development of factor scores for evaluation with impaired populations. Another limitation of the factor analysis in the current study was due to the number of participants being insufficient to draw statistical inference. Nevertheless, the resulting factor structure is largely supportive of the composition of the cognitive domains.

C. Factors Affecting Recovery

1. <u>Time</u>

Time is the most relevant variable to the current study as interactions with Time reflect each variable's impact on the recovery process after SAH. Thus, higher order interactions with Time will be addressed with the discussion of the results for each independent variable.

Recovery over Time was expected to be observed, and the results supported this assumption for Attention/Concentration and Psychomotor Speed, regardless of severity of impact of SAH as reflected by global mental status. However, it is interesting to note that Time was not found significant for more of the cognitive domains and that the measure of overall cognition did not improve over time when education was controlled. In the literature on repeated measures of cognition over time after SAH, the range of proportion of tests that improve is from none (McKenna et al., 1989) to 55% (six of 11, Mohanty et al., 1993) with a median of 50% (four of eight, Maurice-Williams et al., 1991; eight of 16, Ogden et al., 1993). Thus, two of seven domains (28%) falls within the range and is consistent with the proportion of improvement seen in the literature.

The two domains found to improve over time in the current study, Attention/Concentration and Psychomotor Speed, are considered very sensitive to any change in mental status as they are diffusely represented in the brain. This pattern is consistent with recovery from penetrating injuries: "Many of the general effects of brain damage, such as distractibility and slowing, tend to improve but may never return to the premorbid level of efficiency," (Lezak, 1998). The fact that most of the mean scores were impaired at the 3-month evaluation indicates that these domains were among the first to show improvements. Regarding Attention/Concentration, this finding is consistent with the theory of cognitive performance proposed by Sohlberg and Mateer (1989). These authors proposed that all other cognitive functions rely on Attention, and if attention is impaired, performance within all other domains will be impaired. Therefore, one cannot expect to see improvements in any of the cognitive domains until Attention recovers. Further evaluation of this hypothesis would require longer follow-up periods. Alternatively, the fact that deficits of attention are among the most common symptoms of acute brain damage (Lezak, 1998) may have also resulted in increased power to detect relatively small changes in attentional capacity. The finding that there was significant improvement in Psychomotor Speed may be a function of the degree of impairment observed at the 3-month evaluation on this domain. Regression to the mean could explain part of the improvement observed on such a severely impaired group of scores. Psychomotor slowing is a sign of a diffuse process (Lezak, 1998; Ogden et al., 1993). This means that changes in psychomotor speed are a sensitive indicator of cerebral changes. Thus, the finding that Attention/Concentration and Psychomotor Speed, as opposed to the other cognitive domains, showed the most recovery over time is consistent with these theories.

Mohanty et al. (1993) found recovery of verbal memory, kinetic melody, and digit symbol substitution. Due to lack of overlap of specific test measures with the current study, the meaning of this information is difficult to infer. Nevertheless, the possibility exists that these findings are consistent, at least in part, with those of the current study. Kinetic melody likely relies on psychomotor performance. Digit symbol substitution was used in the current study as a measure of attention, and therefore this result is consistent across these two studies. In the current study, verbal memory was found to improve among more cognitively impaired patients. Given the reported global impairments in the patient group examined by Mohanty et al. (1993), and the fact that global mental status was not separately evaluated by their group, these results may also be consistent. Stabell and Magnaes also reported improvement of Psychomotor Speed (1997).

2. Global Mental Status

The purpose of dividing patients into two Groups, based on the global mental status as a function of the TICS score, was to control for the severity of the SAH. Thus, worse cognitive impairment was expected to negatively impact the cognitive recovery process. This was clearly borne out by the results as all domains, and the Cognitive Index, were worse among those with poorer global mental status and this effect had the greatest magnitude of all findings in the current study. This confirms previous findings with this cohort (Mayer et al., 2002) and is also consistent with the literature on the importance of severity of brain damage as "… by far the most important variable in determining the patient's ultimate level of improvement," (Lezak, 1998).

Worse global mental status delayed the recovery processes for verbal memory and psychomotor speed such that patients who were more severely cognitively impaired at the

3-month evaluation made more gains from 3 to 12 months, and did not significantly differ in their performance from the less severely impaired patients by the 12-month evaluation. These findings are consistent with the results provided by Ogden et al. (1993) and Stabell and Magnaes (1997), who both reported improvements over time for verbal memory measures. The fact that Verbal Memory improved more over time among those with worse global mental status, but it did not improve over time across both mental status groups suggests that for some people, verbal memory was not impaired at the 3-month evaluation. This highlights the need for future studies on recovery of cognitive functions to control for different courses of recovery as a function of severity of brain damage and the fact that, for some people, all of their recovery process is completed relatively early on. Otherwise, a lack of recovery in these individuals may be misinterpreted as permanent impairment.

Overall cognition was also influenced by severity of cognitive impairment. As global mental status was measured by the TICS, which is comprised of a small number of items from several different domains, this finding supports the validity of the TICS as a measure of global mental status.

3. Age

Older age was hypothesized to slow recovery. However, no effects of Age were significant. Although older individuals were found to have significantly worse cognitive function overall on the Cognitive Index, this did not slow their recovery per se. Therefore, this hypothesis was not supported. However, the fact that older individuals were worse cognitively than younger individuals at both time points is consistent with the other researchers' findings for cognition (Bjeljac et al., 2002; Ogden et al., 1993; Richardson, 1991). These groups identified differences at a single time point suggesting slowed recovery for their older groups. Bjeljac et al., found that "older patients (>60 years) were at follow-up significantly more disturbed in concentration, short-term memory and information processing capacity..." compared to younger patients (2002). Ogden et al. (1993) found that older patients performed more poorly than younger patients on measures of psychomotor speed, visuospatial skills, and frontal lobe functions at the 12-month evaluation only, suggesting a possibly permanent deficit in these areas. Richardson (1991), however, found mixed results, with some tests being negatively affected by older age at one or both time points, and others unaffected.

While older people in the current study did not recover more slowly per se, they were more severely impaired at the beginning of the study and therefore remained more severely impaired by the end of the year. This is also consistent with general neuropsychological findings for age since cognitive performance tends to decline with age (Lezak, 1998) and with neurological findings that older individuals have poorer clinical outcomes after SAH (Lanzino et al., 1996; Satzger, Niedermeier, Schonberger, Engel, & Beck, 1995). Lanzino et al. (1996) found that older age correlated with worse clinical grade on admission, which was found to result in worse cognitive performance in the current study, and with thick clots, which were found to result in worse cognitive performance in several locations, their group also found the impact of age to be greatest after the age of 60. In the current study, the cutoff of age 50 was used as it was the median and it corresponded to the average age of SAH survivors in the literature. However, this may have prevented detection of a significant impact of age in the current study.

Nevertheless, it appears that the disadvantage for recovery of cognitive functioning due to older age seems to be conferred to individuals before the SAH. Future investigation may reveal that, among people who enjoyed a relatively high level of cognitive function premorbidly, age will not appear to have the negative impact currently attributed to it in clinical settings. Indeed, Maurice-Williams et al. (1991) did not find any relationship between frequency of cognitive impairments and age of their patients, and Elliot and LeRoux (1998) reviewed a substantial literature suggesting that people in the same clinical condition, regardless of age, have similar outcomes.

4. Etiology

Whether the cause of the SAH was an aneurysm or not was predicted to have no impact on recovery. Although this hypothesis was supported, there were only 7 patients with non-aneurysmal SAH. Relative to 75 ruptured aneurysm patients, there was not enough power to definitively answer the question whether having an aneurysm affects recovery. Nevertheless, for the current study, whether SAH was caused by an aneurysm or the cause was unknown did not have a bearing on patterns of recovery in neuropsychological functioning. This suggests that the etiology of the SAH does not influence recovery of cognition as the cause of cognitive damage is the result of the hemorrhage, per se, and complications stemming from intracerebral hemorrhage. Hutter, Gilsbach, and Kreitschmann (1994) found that both aneurysmal and non-aneurysmal patients showed cognitive impairments despite less severe SAH among the non-aneurysmal group. However, others have identified a cognitive advantage for patients with non-aneurysmal SAH (Sonesson et al., 1989) with less impairment but no difference between groups. If there is less cognitive impairment among non-aneurysmal SAH patients, this may suggest that bleeding from an aneurysm may permit a greater volume of blood to leave the vasculature than from unidentified sources, which presumably are smaller, consistent with Hutter et al. (1994). However, Hutter et al. (1994) found a pattern of diffuse cognitive impairments among patients with SAH of unknown origin versus focal impairments among aneurysmal SAH patients, an important distinction that was not addressed by Sonesson et al. (1989). Despite not having enough power to detect such a relationship in the current study, the number of aneurysmal and non-aneurysmal patients falling into the more and less cognitively impaired groups differed by only one in each case (see Table 7), casting doubt on any independent effect of etiology in the current cohort. A future study designed to definitively answer this question would have to make a greater effort to specifically recruit participants with SAH of unknown etiology and to evaluate the relative volume of SAH from aneurysmal and non-aneurysmal sources.

5. Aneurysm Location

Much controversy surrounds the question of whether aneurysm location impacts recovery from SAH. While some investigators have not found a relationship between aneurysm location and neuropsychological impairments (Hillis et al., 2000; Maurice-Williams et al., 1991; Ogden et al., 1993; Richardson, 1989; Romner et al., 1989; Satzger et al., 1995; Stabell & Magnaes, 1997), those who have found a relationship report complex findings (Logue, Durward, Pratt, Piercy, & Nixon, 1968). Bjeljac et al. (2002) found that anterior aneurysm location was protective against cognitive deficits, whereas others report more severe cognitive deficits when a ruptured aneurysm is in the anterior communicating artery (for review, see Richardson, 1989). Saveland et al. (1996) reported an association between aneurysm location and neuropsychological deficits but minimized it by pointing out that neuropsychological functions are conducted by "widespread neuronal integration, on which different focal lesions may have a minor impact." This same group found no relationship between cognition and aneurysm in another study cohort, but then identified "a further decrease in tempo and perceptual vigilance" in anterior communicating aneurysm patients (Sonesson, Ljunggren, Saveland, & Brandt, 1987). Stenhouse et al. (1991) reported on a series of anterior communicating artery aneurysm patients who revealed two patterns of executive dysfunction: one portion performed poorly on executive functions and the other portion showed global impairments. However, this group only examined anterior communicating artery aneurysm patients, a common limitation to properly evaluating this problem. Larsson et al. (1994) reported short-term memory problems among patients with a variety of ruptured aneurysm locations, and that patients with ACA and ICA aneurysms were more impaired. Barbarotto et al. (1989) reported a relationship between aneurysm location and cognition, with a tendency for left-sided aneurysms to impair language functions and right-sided aneurysms to impair visuospatial skills, but they only evaluated patients with aneurysms of the middle cerebral arteries and posterior communicating arteries. In the current study, aneurysms along all cerebral arteries were evaluated together in the hope of meaningfully contributing to this debate.

As patients with ruptured aneurysms present with increasingly worse levels of consciousness, as opposed to focal neurological signs, aneurysm location was predicted not to influence recovery patterns. This hypothesis was supported. The theoretical mechanism for aneurysm location to influence cognitive functioning and recovery is that SAH blood causes damage and that it remains close to the site of the rupture (Mayberg, 1998). However, the blood in the subarachnoid space may be distributed mechanically, thereby reducing the correlation between aneurysm location and SAH location and consequently minimizing the localizing effect of the ruptured aneurysm on cognition.

Aneurysm location did, however, have an influence on Executive Functions when global mental status was considered. In particular, among patients with aneurysms located anywhere other than in the anterior circulation (i.e., left, right, and posterior), those who had an overall good global mental status performed better than the rest of the patients on tests of executive functioning. Patients with aneurysm rupture in the anterior circulation performed about the same on tests of executive functions regardless of their global mental status. This suggests that ruptured aneurysm of the anterior circulation negatively impacts executive functioning among less cognitively impaired patients.

Possibly, in the case of those with worse cognitive functioning, this relationship is masked by global cognitive impairments. Although this finding is somewhat consistent with studies that find a deleterious effect of anterior aneurysms on cognition, those refer to memory problems as opposed to executive dysfunction (Vilkki, 1985; Volpe & Hirsch, 1983). While some of the symptoms described by Vilkki (1985) could be considered executive dysfunction (e.g., confabulation, uncritical guessing, impaired initiation), their patients were not given tests of abstract reasoning, hypothesis testing, or set shifting as in the current study. Bjeljac's group used a measure of verbal fluency, whereas Trails B and the Nelson modified Cart Sorting Test were used in the current study to evaluate the executive functions of set-switching and hypothesis-testing. Thus, the multifactorial nature of executive functions, as well as their influence on encoding processes of memory (Lezak, 1998), may contribute to the continuing controversy on the question of the effect of aneurysm location on neuropsychological outcome after SAH. Furthermore, personality measures were not administered in the current study and may differ according to aneurysm location as well (Stenhouse et al., 1991).

None of the studies on recovery of cognitive functions after SAH published to date have controlled for the impact of severity of brain damage on recovery as done in the current study. The addition of a measure of global mental status revealed that, depending on how severely brain damaged the SAH cohort is, Aneurysm Location may or may not have any impact, with the less brain-damaged cohort showing this relationship. Further, much of the literature on the impact of aneurysm location addresses only anterior circulation aneurysms. This is consistent with the findings of the current study, but only for executive functions, which is consistent with localization theory that suggests that executive functions are coordinated in the frontal lobes of the cerebral cortex.

Future studies designed to answer the question regarding the impact of aneurysm location on neuropsychological functioning should include measures of overall severity of cognitive impairments, a wide variety of aneurysm locations, and multiple measures of distinct executive and memory functions in addition to other cognitive functions. Furthermore, SAH location and infarct location should simultaneously be evaluated as these have been identified as contributing to cerebral damage (Vilkki, Holst, Ohman, Servo, & Heiskanen, 1989) and their close but imperfect relationship with aneurysm location may also contribute to ongoing confusion. Maurice-Williams et al. (1991) also point out that the type of aneurysm operation may differentially lead to cognitive deficits. For example, there is more likely to be damage if the artery is occluded than if the neck of the aneurysm can be occluded. Thus, this variable too should be considered although its effect may be captured if infarcts are also addressed.

6. SAH Amount

The amount of blood released into the subarachnoid space was hypothesized to predict recovery, and this hypothesis was not supported. However, among those with poor mental status, more blood did result in worse overall cognition, with no effect on any specific cognitive domain detected. This finding was not modified by the effect of time. This suggests that, in patients who experience a relatively poor global mental status at 3 months, amount of blood is a significant predictor of severity of cognitive impairment. On the other hand, among those who do relatively well cognitively, amount of blood does not predict neuropsychological functioning. This pattern suggests that amount of SAH is a measure of diffuse cerebral damage and is consistent with a pattern previously reported in the literature in which diffuse damage magnifies the negative impact of a complication (Hutter et al., 1994; Vilkki et al., 1989). In fact, Vilkki et al. (1989) only identified poor visuospatial skills in the context of right-hemisphere infarct when patients had diffuse damage. The findings of the current study are also consistent with those of Larsson et al. (1994) who found a correlation between the amount of blood and severity of subsequent verbal memory problems, the only cognitive domain they reported evaluating. On the other hand, Romner et al. (1989) found no relationship between cognitive outcome and amount of SAH, but the vast majority of their patient cohort (13 of 18) had the same score on the Fisher scale (i.e., 3 on an integer scale of 1 to 4), thus limiting variability necessary to detect a relationship. Although the current study's findings point to a diffuse effect of SAH, the analysis did not rule out the possibility that the relationship between vasospasm and amount of SAH could be responsible for the impairments of overall cognition.

7. SAH Location

More blood collecting in single locations (i.e., a clot) was predicted to result in more permanent deficits of neuropsychological functions, which was supported. However, the hypothesis that clots would have location-specific effects, consistent with the findings of Vilkki et al. (1989), was not supported. Only one SAH location, the quadrigeminal cistern, significantly affected specific cognitive domains. For patients with more blood in the quadrigeminal cistern, recovery over time was delayed for Psychomotor Speed among the more cognitively impaired patients and Language Skills among the less cognitively impaired patients. Attention was also significantly impaired for those with more blood in the quadrigeminal cistern. For more cognitively impaired patients with more blood in the right ambient cistern or the right basal Sylvian fissure, overall cognition was significantly negatively impacted, but no specific areas of cognition were particularly worse than any other. Overall cognition was also significantly impaired for patients with more blood in the right lateral Sylvian fissure and for those with more blood in the left supracellar cistern.

The quadrigeminal cistern is surrounded by the quadrigeminal plate, the splenium, and the cerebellar vermis (Parent, 1996). The quadrigeminal plate is in the mesencephalon which includes the inferior and superior colliculi, known to play roles in mediating auditory and visual signals, respectively. The splenium serves as interhemispheric communication for posterior regions of the brain. The cerebellum is involved with coordination of a variety of cognitive functions, especially motor functions, and more recently, a role has also been speculated for language functions in the cerebellum (Kandel, Schwartz, & Jessell, 1995). Irritation to the brain tissue surrounding the quadrigeminal cistern, therefore, may contribute to disturbances of these cognitive functions, especially since Attention and Psychomotor speed are particularly sensitive to any reduced efficacy in cerebral processing.

Blood in the right hemisphere seemed to impair overall cognition without specific effects. This may be consistent with the findings of the factor analysis that several domains correlated with Visual Skills, commonly attributed to the right hemisphere. On the other hand, the fact that the overall cognitive index was affected may also point to diffuse damage.

These findings were not consistent with those of Ogden et al. (1993) who reported decreases in attention due to more blood in the left Sylvian fissure. They also reported decreases in verbal memory due to blood intracerebrally and intraventricularly, areas that were not examined in the current study. However, they also reported prolonged deficits of visuospatial skills, and these findings may reflect a similar disability.

8. <u>Infarcts</u>

Patients with cerebral infarctions performed worse in the domains of Attention/Concentration and Visuospatial Skills if they were less cognitively impaired. At first, this finding appears paradoxical, as one would expect to see worse performance among patients with infarctions if they were more cognitively impaired. However, this may indicate that infarctions are not the worst complication from an SAH one can experience and that it takes a more severe complication to cause so much brain damage as to result in a low TICS score (<34). Second, infarctions, as hypothesized, do have specific cognitive effects as opposed to affecting global mental status, and these are persistent, which is consistent with other researchers' findings. Hillis et al. (2000) reported infarcts were a significant predictor of cognitive impairment when they occurred in the basal ganglia or frontal lobes. These findings also are consistent with those of Ogden et al. (1993), who found infarcts to be predictive of cognitive impairments. However, this group found a relationship only for verbal memory. However, in the current study, no specific infarct location had an impact on either specific cognitive domains or the overall cognitive index, which stands in contrast to the findings of Vilkki et al. (1989). Vilkki et al. (1989) do not mention covarying for education nor did they account for severity, which was done for all analyses in the current study and may, therefore, account for this disparity. Results of the current study may be obscured by presence of infarcts undetected by CT as MRI has been shown to be more sensitive to infarcts after SAH (Romner et al., 1989) or they may be consistent with the view put forth by Saveland et al. (1996) that infarcts do not have much impact on higher mental functions mediated by diffuse integrated neuronal circuits.

9. Vasospasm

The hypothesis that vasospasm alone does not cause cognitive impairment was supported. This finding is consistent with the results reported by Hillis et al. (2000) and Ogden et al. (1993). Given that these researchers also reported impairments due to infarctions, this suggests that, unless vasospasm causes an infarction, the clinical deterioration caused by vasospasm is reversible (Kassell et al., 1982; Mayberg, 1998; Qureshi et al., 2000). On the other hand, Richardson (1989, 1991) reported a significant effect of arterial vasospasm, but did not report on infarctions; other authors as well have suggested the cause of cognitive impairments often seen after SAH is vasospasm (Saveland et al., 1988). As untreated symptomatic vasospasm results in infarctions in approximately 50% of cases (Mayberg, 1998), this relationship is confounded. Therefore, this has important, and well-known, implications for clinical management of patients to continue to aggressively monitor for signs of and treat vasospasm and its predictors (e.g., Charpentier et al., 1999; Qureshi et al., 2000; Vilkki et al., 1989), as well as for future research to target ways to prevent and halt vasospasm when it occurs. Nevertheless, the possibility remains that no significant effect of vasospasm occurred in the current study because of the inclusion of patients with all grades, as clinical deterioration due to vasospasm is difficult to detect in patients with worse clinical grades (Charpentier et al., 1999).

10. Clinical Grade

Worse clinical presentation was hypothesized to predict worse overall cognition, which was supported by the results. As patients present with progressively worse states of consciousness as opposed to focal neurological signs, Clinical Grade captures the effect of diffuse cognitive damage done by SAH. This finding contrasts with those of other studies in which clinical severity was not a significant predictor of neuropsychological impairment (Hillis et al., 2000; Satzger et al., 1995). However, Satzger et al. (1995) only evaluated good grade patients. Richardson (1991) found an effect of clinical severity and suggested this controversy may result from preoperative medication affecting the clinical presentation.

Another possible explanation might lie in the variability in amount of time before the patient is admitted. In the current study, the clinical grade on admission was evaluated on admission to the study site, Columbia Presbyterian Medical Center. However, 70% of the patients in the current study were transferred from another hospital where they were initially evaluated. Nevertheless, there was no difference between those who were admitted directly to the study site and those who were transferred from another facility on either number of days since the SAH or Admission Hunt Hess Grade. Therefore, the clinical grade can be assumed to be a reliable measure.

A neuropsychological explanation for the contrary findings resulting from clinical grade may be that the diffuse nature of cerebral damage from SAH captured by clinical grade is not identified on some tests designed to detect localized impairments. This interpretation is supported by the fact that worse clinical grade negatively impacted overall cognition but not any of the individual domains. Hillis et al. (2000) did not include a global measure of cognition, and therefore, their study was not designed to capture this distinction. As SAH generally causes diffuse cerebral damage (Richardson, 1991), with complications less often causing localized impairments, future studies on the neuropsychological outcome of SAH should be certain to include measures to detect both types of damage.

11. Cerebral Edema

The hypothesis that cerebral edema would slow recovery was supported. Overall cognition was slower to recover over time, appearing to be delayed with greater cognitive impairment at 3 months but more recovery by 12 months. The effect of cerebral edema on visual memory showed a similar pattern, with worse performance at 3 months, but faster recovery by 12 months resulting in less difference between those with and without cerebral edema by one year. On the other hand, the results for Visuospatial Skills revealed more persistent deficits and an apparent disadvantage for the recovery of visual skills as patients with cerebral edema not only showed greater visuospatial impairments at 3 months, but by 12 months, the disparity had grown, with people who had not had cerebral edema recovering more of their visuospatial skills in the first year after SAH than those with cerebral edema.

Very few studies have evaluated the cognitive impact of cerebral edema following SAH (Kreiter et al., 2002). However, these results highlight the need for future studies to consider this variable in long-term outcome studies. The mechanism thought to underlie edema involves hypometabolism of cerebral tissue following alterations in cerebral perfusion pressure (Skirboll & Newell, 1998). Thus, this would seem to apply globally to differing extents even if it is only observed on CT in certain regions, which is consistent with the finding here that edema affected overall cognition.

12. Sex

Verbal and visual memory scores were significantly better among women versus men, which was not expected. Thus, the hypothesis that Sex would not have an impact on cognition after SAH was not supported. This finding contrasts with the results of McKenna et al. (1989) and Ogden et al. (1993) who found no differences as a result of gender.

On an exploratory post-hoc basis, a one-way ANOVA was conducted evaluating the effect of Sex on Global Mental Status (TICS scores at 3 months post SAH) since this was the best predictor in this study of cognitive functioning. Results revealed a significant effect of Sex ($F_{1,79}$= 5.413, p = .023) with women (M = 34.05 ± 6.79) significantly outperforming men (M = 29.92 ± 8.43). Although this may contribute to the observation that women were not as cognitively impaired as men, thereby explaining their advantage on memory testing, it does not offer an explanation for this finding.

Becker (1998) reported that anterior communicating artery aneurysms are more frequent in men (46%) than in women (27%). To evaluate whether this might be playing a role here, an exploratory post-hoc Chi-square analysis was performed. Indeed, results were significant (X^2 = 12.239, p = .007) with 50% of all of men's aneurysms being in the ACA or ACoA versus the women's 13% (see Table 72). Another interesting result of this comparison was the fact that 86% of posterior aneurysms were in women. Given that vital functions are fed by the posterior circulation, this finding may shed light on why women have often been thought to fare worse than men after SAH (Becker, 1998).

Although many researchers have found a relationship between anterior communicating artery aneurysms and amnesia, as reviewed previously, the current study identified a relationship between executive functions, severity of cognitive impairment, and anterior communicating artery aneurysms. These data reflect the complexity of this question by suggesting a multifactorial solution underlying the controversy of aneurysm location's role in cognition that appears to also be modified by severity of cognitive impairment and sex, and, possibly, the interrelationship between memory and executive functioning.

13. Language

Primary language, English or Spanish, was not expected to have an impact on cognition since the tests were all conducted in the patients' preferred language. However, English-speakers significantly outperformed Spanish-speakers on tests of Visuospatial Skills, despite the fact that test instructions were translated for these non-verbal tests. Nevertheless, non-verbal tests have been found to be biased culturally (Jacobs et al., 1997; Nell, 2000). Thus, this finding is consistent with that literature, which suggests the effects of culture may reflect differences in educational background, cultural value systems, and/or test-wiseness (i.e., familiarity with a test situation and presumed examiner demands). Although one would expect an advantage based on language ability to affect Language Skills and Verbal Memory, this did not occur despite the measures comprising the Language domain being direct translations. The test scores comprising the Verbal Memory domain included a test developed for Spanish speakers, as opposed to a direct translation, which may have removed cultural, linguistic, or educational bias.

D. Possible Limitations of the Current Study

1. Practice effects

The design of the current study called for repeated administration of a neuropsychological battery of tests nine months apart. This presents the possibility that practice effects may explain any improvement observed. However, there are number of reasons practice effects likely do not explain the current findings. First, Stabell and Magnaes (1997) argue that practice effects are not likely to introduce significant variability in a sample for whom memory is impaired, as was true in the current study. Second, if practice effects were operational, one might expect to see improvement across all domains over time and especially for the overall Cognitive Index and the Visual and Verbal Memory domains (Wilson, Watson, Baddeley, Emslie, & Evans, 2000), which was not observed.

Some authors argue that practice does not have a significant effect beyond two months after the initial testing (Spreen & Strauss, 1991), but clinicians typically wait six months before retesting patients (Watson et al., 2000). Dikmen, Heaton, Grant, and Temkin (1999) found that there was a significant drop in the effects of practice when the test-retest interval was greater than 3 months. Due to the evaluation of patients of all clinical grades, it may be possible that practice effects were only operative among less cognitively impaired patients (Dikmen et al., 1999). However, this was not observed either since the interaction between Global Mental Status Group and Time for Verbal Memory actually occurred for the more cognitively impaired group. Therefore, instead of attributing change to practice effects, this finding is more consistent with the interpretation that people with worse neuropsychological functioning are likely to demonstrate greater improvements because they have more potential for improvement. Dikmen et al. (1999) also found practice effects to vary with age, so younger people might have been expected to show more improvement than older people, but no significant effect of age was observed over time in the current study. These investigators also found that practice effects vary with the type of test. In evaluating a variety of neuropsychological tests for practice effects over 20 trials in a month among both brain injured and non-brain-injured participants, Watson et al. (2000) found that tests of reaction time, Digits Forward, and Digits Backward showed the least effect of practice. Dikmen et al. (1999) also found little effects of practice on measures of attention and motor skill. These findings support the interpretation that the improvements observed over time in the domains of Psychomotor Speed and Attention/Concentration are real.

The majority of the findings in the current study came from comparing across two subgroups within the study group. One can assume that the differences observed between groups separated by presence and absence of various complications are attributable to the complications as practice should have affected both groups equally. However, there remains the possibility that practice could differentially affect one of the two groups more than the other.

The use of parallel forms of neuropsychological tests is an alternative future studies may adopt to control for possible practice effects. However, Stabell and Magnaes (1997) argue that this is not always possible due to lack of equivalence among parallel forms. Indeed, they reported a decline in scores on a test of visuospatial skills from one evaluation to the next, which they attributed to this problem (i.e., the parallel form given at the time of the second administration was actually more difficult). Although a counterbalanced administration may have mitigated the problem of unequal parallel forms, this approach does not resolve the problem entirely in the case of SAH due to the complexity of interactions among multiple variables as was seen, for example, in the relationship between sex and aneurysm location and the current findings.

2. Cognitive Remediation

A portion of the patients in the current study reported that they underwent cognitive remediation, which may have confounded the effects of the variables examined in the current study. However, it was not possible to control for the effects of cognitive remediation for a number of reasons. First, information about whether patients received any cognitive remediation was gathered from the patient or a surrogate in a follow-up interview. As no definitions were offered, patients are not trained in the distinctive therapies offered in a rehabilitation setting, answers were not confirmed with therapists, and different therapies overlap (e.g., speech therapists and occupational therapists sometimes conduct cognitive remediation), this variable was not considered reliable. Second, as the study was not designed to measure the effects of cognitive remediation, the quality and quantity of the cognitive remediation was not recorded. Third, the decision to prescribe cognitive remediation may have been dependent on a number of variables varying from a patient's insurance policy, proximity of a rehabilitation facility to a patient's home, and the treating physiatrist's prediction regarding whether the patient would benefit from cognitive remediation, which may or may not be related to the severity of the patient's cognitive status. In the current study, it appears that those who received cognitive remediation were more cognitively impaired at the 3-month follow-up.

Despite not controlling for the effects cognitive remediation may have had in the current study, it is important to examine the results of the interview question to evaluate the potential role cognitive remediation may have played in the current study. Thus, on a post-hoc basis, the Cognitive Index was examined in a repeated-measures ANCOVA with Time as the within-subjects variable, Cognitive Remediation as the between-subjects variable, and Education as the covariate. (See Table 73.) Only 14 of the 82 patients who completed neuropsychological testing at both 3 and 12 months reported having received any cognitive remediation by 12 months post SAH. There were no significant effects involving cognitive remediation (Cognitive Remediation $F_{1,75}= 1.20$, $p = .277$; Cognitive Remediation x Time $F_{1,75}= 3.60$, $p = .062$; Cognitive Remediation x Group $F_{1,75}= 0.07$, $p = .788$; Cognitive Remediation x Time x Group $F_{1,75}= 1.36$, $p = .247$). This is consistent with a report by Dombovy, Drew-Cates, and Serdans (1998) who found that SAH patients who underwent inpatient rehabilitation continued to evidence impairment on the TICS 28 months after their SAH.

When an additional repeated-measures MANCOVA was conducted, with Time as the within-subjects variable, Cognitive Remediation as the between-subjects variable, Education as the covariate, and the seven cognitive domains as dependent variables, there was a significant interaction effect between Group and Cognitive Remediation ($F_{7, 54}$= 2.517, p = .021). See Table 74. Univariate analyses revealed significant effects for Visuospatial Skills ($F_{1,60}$= 6.785, p = .012), such that the extent to which performance was better for the High Group was significantly less among those who received cognitive remediation (see Figure 23), and for Verbal Memory ($F_{1,60}$= 5.890, p = .018), such that the extent to which performance was better for the those who were less cognitively impaired was significantly more among those who received cognitive remediation (see Figure 24). The contrary relationship of these two univariate results suggests the low power for this analysis may be resulting in inconclusive findings.

Even though Dombovy et al. (1998) reported negative findings for cognitive rehabilitation, they evaluated SAH survivors who had undergone inpatient rehabilitation, whereas most cognitive remediation is carried out on an outpatient basis. Future studies specifically designed to evaluate the effects of cognitive remediation should recruit more subjects for a planned cognitive remediation condition as well as control for the potential confounds described above.

Every conceivable variable was not controlled, and one that may have had some unmeasured effect is dependent on whether patients were taking antiepileptic drugs that also may have slowed their motor performance or processing speed, thereby affecting their performance on timed tasks.

3. Individual variability

Several studies previously reported individual data. This was not done in the current study due to methodological difficulties of defining a clinically meaningful change in neuropsychological test performance. In exploring the data, the individual data yielded quite a different picture than the group data as well as among different cut points used to define improvement and worsening. There were several instances of worsening observed among individuals that were not at all captured in the group data. However, Vilkki et al. (1989) warn that exploring individual data may result in overestimation of deficits. A more comprehensive study may include both methods as group data are clearly valuable as evidenced by the current results. Although decline in cognitive functioning has not been identified in group data, there are several possible explanations that were not addressed in this study including depression, seizures, and medications.

E. Conclusions

The current study attempted to bridge some of the gaps in the literature on recovery of cognitive functioning after SAH by addressing a number of inconsistencies. Methodological differences among the studies that have, in the past, addressed this topic may contribute to differences in results. One of these is clinical grade, which was not addressed in several studies but may have limited the generalizability of the results of those studies. Maurice-Williams et al. (1991) and Ogden et al. (1993) followed only "good grade" patients (Hunt Hess I & II), and Stabell and Magnaes (1997) were the only investigators prior to the current study to address all clinical grades. This may be the reason for the consistency observed in domains showing improvement over time was best with Stabell and Magnaes (1997). Nevertheless, these investigators did not include patients with all aneurysm locations, thereby limiting the generalizability of their study results as well. The current study is the only one to date to comprehensively include all aneurysm locations and patients of all clinical grades. Furthermore, the widest range of clinical variables were included, which permitted the simultaneous evaluation of several possible sources of neuropsychological dysfunction. Although an exhaustive battery is not very feasible, some lack of comparability among study results remains because of the lack of standardization of test batteries and the multifactorial nature of individual tests.

On the question of whether aneurysm location plays a role in cognitive outcome after SAH, the results of the current study paint a complex picture. A relationship was detected between anterior aneurysm and cognition, but it was for executive functions instead of memory as is commonly reported. However, the syndrome as described in the literature includes evidence of executive dysfunction such as confabulation and perseveration. Furthermore, sex was unexpectedly linked with memory impairments. Closer inspection of the data revealed a complex relationship between sex, severity of cognitive impairments, and aneurysm location. Men were more likely to have anterior aneurysms that resulted in more severe cognitive impairments, and this in turn, seems to be why they evidenced greater memory impairment than women. Elliot and LeRoux

(1998) also described evidence for a role of estrogen in cognition after SAH, suggested by interactions between age of SAH onset, sex, and estrogen levels. Furthermore, anterior SAH location (i.e., in the left supracellar cistern) resulted in worse overall cognition. Thus, future studies wishing to address the controversy of the effect of aneurysm location on cognitive functioning should evaluate all of these variables together.

Inclusion of minorities in the current study proved to be valuable, as there was an unexpected relationship between language spoken and visuospatial skills. Although this has been documented in the literature previously, this finding emphasizes the need to evaluate members of all groups to identify differences due to demographics and maximize the generalizability of results.

Future studies intended to answer questions about Etiology or Cognitive Remediation should specifically recruit patients for those purposes, as a naturalistic observation study design does not tend to result in sufficiently equal numbers of participants in each condition for valid statistical evaluation of these questions.

F. Clinical Implications

There are several possible clinical implications for the information emanating from the current study. Most importantly, it is clear that cognitive functions continue to recover throughout the first year after SAH. There may be additional recovery after the first year that future studies should measure. Indeed, Satzger et al. (1995) reported that the cognitive functioning of their patient group, studied 3 years post SAH, fell in the normal range, and Saveland et al. (1988) found no cognitive deficits in a group of SAH survivors 2 years after their bleeds. Global mental status as measured by the TICS was found in the current study to be a strong predictor of overall cognition and of every cognitive domain examined in this study. Furthermore, the impact of several factors was magnified in the more cognitively impaired group, which is consistent with other investigators' findings that deficits are pronounced in the context of diffuse damage (Hutter et al., 1994; Vilkki et al., 1989). As the TICS is a brief instrument, it may be advisable to screen all SAH patients with such an instrument to assess the need for cognitive rehabilitation and for problems affecting daily living skills that result from cognitive impairments (e.g., managing one's finances).

Regarding immutable variables, the results of the current study may be used to plan appropriate rehabilitation treatments. Older people are more likely to be more cognitively impaired than younger people. Thus, special attention should be paid to evaluating this group so that issues including safety and responsibilities, such as managing finances or a complex schedule for medications, are addressed. The same may be said of people who have more SAH (Hijdra scores greater than 14), worse clinical grades (Hunt Hess III or more), anterior circulation aneurysms, infarcts, and cerebral edema.

Some of the results have implications for acute treatment. As cerebral edema was found to have particularly negative consequences for cognition, treatment should continue to target reducing edema. It should also continue to target vasospasm as the results of the current study revealed that infarctions resulted in more permanent cognitive deficits but that vasospasm that did not cause infarctions were not associated with any long-lasting cognitive effects.

V. TABLES & FIGURES

Figure 1: Follow-up rates of mortality and drop out.

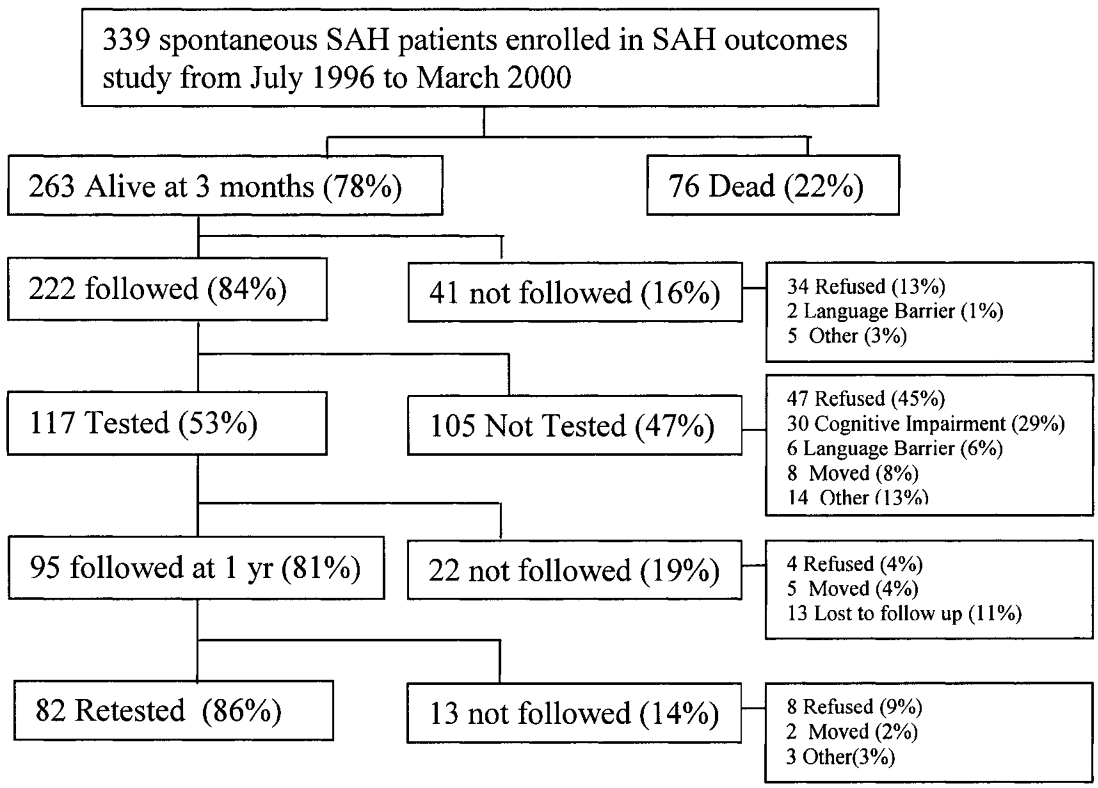


Table 1: Neuropsychological Tests Used To Evaluate Recovery After SAH In The Literature

Study	Bjeljac et al., 2002	Mohanty et al., 1993	Stabell & Magnaes 1997	Ogden, Mee, & Henning 1993	Hillis et al., 2000	Richardson 1991	McKenna et al., 1989	Maurice-Williams et al., 1990
Number of subjects	82	7	41	66	6	32	83	27
Age range (years)	Not given	M = 43.4	17-65	19-68	20- 65	20-67	21-66	30-77
Percent female	Not given	54%	63%	66%	56%	53%	54%	74%
Times of evaluations in months (m) after SAH (D/C = discharge from hospital)	3m, 12m	6 m, 12 m	4 m, 12 m	2.5 m, 12 m	3 m, 12 m	1.5 (2) m, 6 (10) m	3 m, 12 m	D/C, 12 m
Number of tests showing improvement*	Not given	6	5	12	8	3	0	4
Number of tests examined	8	11	18	24	15	20	20	8
Percent of tests showing improvement*	Not given	55%	28%	50%	53%	15%	0%	50%
Fund Of Knowledge								
NART				Same			Same	
Schonal Graded Reading Test							Same	
WAIS Information						Better		
WAIS R Comprehension				Same				
WAIS R VIQ				Better				

Language Skills								
Boston Naming Test					Better			
Comprehension of Descriptions of Objects								Same
Fragmented Letters Perception Test							Same	Same
Graded Naming Test				Same			Same	
Mill Hill Synonyms						Same		
Minnesota Test for the Differential Diagnosis of Aphasia				Same				
Object Naming						Same		Same
Semantic Verbal Fluency			Same			Same		Better
Token Test	**		Same	Same				
WAIS Vocabulary			Same			Better	Same	
WAIS-R Vocabulary				Same				
Visuospatial Skills								
Alexander's Pass Along Test		Better						
Binet Cube Counting						Better		Same
Corsi Blocks						Same		
Koh's Block Design		Better						
Hooper Test (modified)	**							
Raven's			Same				Same	

Advanced Progressive Matrices								
Rey Complex Figure Copy				Better				
Visual Gestalt			Better					
Visual Neglect Test				Same				
Visual Scanning Test		Same						
WAIS Block Design			Same	Better	Same	Same	Same	
WAIS Picture Arrangement			Same	Better			Same	
WAIS Picture Completion			Same	Better			Same	
WAIS R PIQ				Better				
Visual Memory								
Benton VRT			Same					
Recognition Memory For Faces-50				Better	Better		Same	Better
Rey Complex Figure Recall	**			Better	Same			
Visual Learning & Memory Function Test		Better						
WMS-VR					Same	Same		
Verbal Memory								
Delayed Response Ability Test		Better						
Newcomb Story Recall						Same		
Oral Selective Reminding Test				Better				

Recognition Memory For Words-25				Better	Better		Same	Better
Rey Auditory Verbal Learning Test	**		Better		Better			
Richardson Multitrial Free Recall						Same		
Richardson Single Trial Free Recall						Same		
Verbal Learning & Memory Function Test		Better						
WMS Information						Same		
WMS Orientation						Same		
WMS Paired Associates			Same	Same	Same	Same		
WMS-R Logical Memory				Same	Same	Same		
Executive Functions								
COWAT: FAS			Same		Better			
COWAT: verbs	**							
D2 Test	**							
Dissimilarities			Same					
Ruff Figural Fluency	**							
Stroop	**				Better			
Trailmaking Test			Better	Same			Same	
WAIS Arithmetic						Same	Same	

WAIS Similarities			Same	Better		Same	Same	
WAIS-R Digit Span				Better	Same	Same	Same	Better
MCST				Same			Same	
WMS-Mental Control					Same	Same		
Reaction Time								
Digit Symbol Substitution Test		Better	Better	Same	Better			
Fist And Outstretched Finger Test		Same						
Fist And Ring Test		Same						
Grooved Pegboard			Better		Better			
Kinetic Melody Test		Same						
Manual Speed							Same	
Oral Speed							Same	
Tapping Test		Same	Same					

NART = National Adult Reading Test; WAIS = Wechsler Adult Intelligence Scales; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; VRT = Visual Retention Test; WMS = Wechsler Memory Scales; VR = Visual Reproduction; COWAT = Controlled Oral Word Association Test; WCST = Wisconsin Card Sorting Test, *=p<0.05, **= tests given by Bjeljac et al., but change in performance not published.

Table 2: Follow-Up Dates After SAH Used To Evaluate Recovery In The Literature To Date

Study	Discharge[1]	Early[2]	Late[3]
Bjeljac et al.	No	3 months	12 months
Mohanty et al.	Yes	6 months	12 months
Stabell & Magnaes	No	4 months	12 months
Ogden, Mee, & Henning	Yes	10 weeks	12 months
Hillis et al.	No	3 months	12 months
Richardson	No	6 weeks	6 months
McKenna et al.	Yes	3 months	12 months
Maurice-Williams et al.	Yes	None	12 months

1. On the last day of the acute hospitalization
2. The earliest follow-up after discharge from the hospital
3. The final follow-up

Table 3: Effects Of Complications And Demographics On Neuropsychological Recovery After SAH from Literature

Study*	Bjeljac et al., 2002	Stabell & Magnaes 1997	Ogden, Mee, & Henning 1993	Richardson 1989, 1991	McKenna et al., 1989	Maurice-Williams et al., 1991
Hunt Hess Grade	correlated		Predictive of executive functions, psychomotor speed	correlated		
Aneurysm Location	ACoA best, PCA 2nd best	Left MCA/ICA = worse verbal ability	No relationship	No relationship		
Location of Blood			ICH, IVH = worse verbal memory; Left Sylvian fissure = worse attention			
Amount of Blood			More blood = worse test scores			
Ischemia			Verbal memory worse			Poorer performance
Hydrocephalus			Visual memory worse; Verbal memory worse			Poorer performance
Vasospasm			No relationship	Poorer performance		
Premorbid IQ			Verbal abilities; Visual abilities		No relationship	
Age			Older = poorer performance	No relationship		
Sex			No relationship		No relationship	
Education			No relationship			

*Mohanty et al., 1993 and Hillis et al., 2000 did not remark on variables affecting recovery. ACoA = anterior communicating artery; PCA = posterior communicating artery; ICA = internal carotid artery; MCA = middle cerebral arty; ICH = intracerebral aneurysm; IVH = intraventricular aneurysm

Table 4: Age and Education Of Study Group

	N	Minimum	Maximum	Mean	Std. Deviation
Age (y)	82	19	87	51.01	13.29
Education (y)	82	0	20	11.63	4.55

Table 5: Sex, Handedness, Language, And Race/Ethnicity Of Study Group

Variable	Levels	N	%
Sex	Male	25	30.5%
	Female	57	69.5%
Handedness	Right	75	91.5%
	Left	6	7.3%
	Ambidextrous	1	1.2%
Primary Language	English	57	69.5%
	Spanish	25	30.5%
Ethnicity	White	32	39.0%
	Black	11	13.5%
	Asian	2	2.5%
	Hispanic	37	45.0%

Table 6: Neuropsychological Battery By *A Priori* Cognitive Domains

<table>
<tr><th>Cognitive Domain</th><th>Neuropsychological Test</th><th>Scoring</th><th>Authors</th></tr>
<tr><td>Global Mental Status</td><td>TICS raw score</td><td>Accuracy (0-51)</td><td>Brandt, Spencer, & Folstein, 1988</td></tr>
<tr><td rowspan="5">Attention / Concentration</td><td>Digit Span Forward</td><td>Accuracy (0-16)</td><td>Wechsler, 1981</td></tr>
<tr><td>Digit Span Backward</td><td>Accuracy (0-16)</td><td>Wechsler, 1981</td></tr>
<tr><td>Digit Symbol Total</td><td>Accuracy (0-93)</td><td>Wechsler, 1981</td></tr>
<tr><td>Verbal Serial Attention Task time</td><td>Time (0"- 240")</td><td>Mahurin & Cook, 1996</td></tr>
<tr><td>Cal CAP (Sequence 1 RT ÷ Simple RT)</td><td>Time</td><td>Miller, 1999</td></tr>
<tr><td rowspan="3">Visuospatial Skills</td><td>Block Design raw score</td><td>Accuracy (0-51)</td><td>Wechsler, 1981</td></tr>
<tr><td>WMS-R VR Copy</td><td>Accuracy (0-41)</td><td>Wechsler, 1987</td></tr>
<tr><td>Rey Complex Figure Copy</td><td>Accuracy (0-36)</td><td>Lezak, 1995</td></tr>
<tr><td rowspan="2">Psychomotor Speed</td><td>Cal CAP Simple RT</td><td>Time</td><td>Miller, 1999</td></tr>
<tr><td>Trails A</td><td>Time</td><td>Lezak, 1995</td></tr>
<tr><td rowspan="3">Verbal Memory</td><td>CVLT/AVLT total raw score (trials1 thru 5)</td><td>Accuracy (0-80)</td><td rowspan="3">Delis, Kramer, Kaplan, & Ober, 1983 (CVLT) / Artiola et al., 2000 (AVLT)</td></tr>
<tr><td>CVLT/AVLT long delay free recall raw scores</td><td>Accuracy (0-16)</td></tr>
<tr><td>CVLT/AVLT recognition hits</td><td>Accuracy (0-16)</td></tr>
<tr><td rowspan="2">Language Skills</td><td>Boston Naming Test raw score</td><td>Accuracy (0-60)</td><td>Kaplan, Goodglass, & Weintraub, 1983</td></tr>
<tr><td>Token Test</td><td>Accuracy (0-36)</td><td>Spreen & Strauss, 1998</td></tr>
<tr><td rowspan="2">Visual Memory</td><td>WMS-R VRII raw score</td><td>Accuracy (0-41)</td><td>Wechsler, 1987</td></tr>
<tr><td>Rey Complex Figure delayed recall raw score</td><td>Accuracy (0-36)</td><td>Lezak, 1995</td></tr>
<tr><td rowspan="3">Executive Functions</td><td>MCST total correct raw score</td><td>Accuracy (0-48)</td><td>Nelson, 1976</td></tr>
<tr><td>MCST average percent perseverative errors</td><td>Accuracy (0-100)</td><td>Nelson, 1976</td></tr>
<tr><td>Trails B time</td><td>Time</td><td>Lezak, 1995</td></tr>
</table>

TICS = Telephone Interview for Cognitive Skills, Cal CAP = California Computerized Assessment Package, RT = reaction time, CVLT = California Verbal Learning Test, AVLT = Auditory Verbal Learning Test, WMS-R= Wechsler Memory Scale-revised, VR = Visual Reproduction, MCST = Modified Card Sorting Test.

Table 7: Group X Between-Subject Variables Cross Tabulations (Number Of Participants)

Between-Subjects Variable	Levels	Low performance on TICS	High performance on TICS
Age	Young (<52)	15	26
	Old	26	15
Etiology	Aneurysmal	38	37
	Non-Aneurysmal	3	4
Aneurysm Location	Anterior	12	6
	Right	12	12
	Left	12	7
	Posterior	3	4
Hijdra Score	High (>14)	20	19
	Low	19	20
Infarction upon admission	Yes	15	12
	No	26	29
Infarct Location by discharge	Anterior	6	3
	Right	6	7
	Left	7	2
Vasospasm that did not cause Infarct	Yes	2	5
	No	22	30
Hunt Hess Grade	I & II	20	25
	III, IV, & V	21	16
Cerebral Edema	Yes	9	9
	No	28	19
Sex	Male	18	7
	Female	23	34
Primary Language	English	20	37
	Spanish	21	4

Table 8: Frequency of Participants with SAH in each of Ten Cerebral Cisterns and Fissures.

Between-Subjects Variable		Levels	Low performance on TICS	High performance on TICS
SAH Location	Anterior Interhemispheric Fissure	None or A Little	17	23
		Moderately or Completely Filled	11	13
	Right Lateral Sylvian Fissure	None or A Little	19	18
		Moderately or Completely Filled	9	18
	Left Lateral Sylvian Fissure	None or A Little	16	21
		Moderately or Completely Filled	12	15
	Right Basal Sylvian Fissure	None or A Little	19	17
		Moderately or Completely Filled	9	19
	Left Basal Sylvian Fissure	None or A Little	15	20
		Moderately or Completely Filled	13	16
	Right Supracellar Fissure	None or A Little	17	12
		Moderately or Completely Filled	11	24
	Left Supracellar Fissure	None or A Little	13	11
		Moderately or Completely Filled	15	25
	Right Ambient Cistern	None or A Little	17	17
		Moderately or Completely Filled	11	19
	Left Ambient Cistern	None or A Little	13	20
		Moderately or Completely Filled	15	16
	Quadrigeminal Cistern	None or A Little	21	26
		Moderately or Completely Filled	7	9

Table 9: Frequency of Disease Characteristics in Study Group

		N	%
Admission Hunt Hess Grades	I	22	26.8
	II	23	28.0
	III	27	32.9
	IV	9	11.0
	V	1	1.2
Aneurysm Presence	No	7	8.5
	Yes	75	91.5
Types of Treatment	None	7	8.5
	Surgical	68	82.9
	Embolization	7	8.5
Complications	Intraventricular Hemorrhage	33	42.0
	Infarction	27	32.9
	Cerebral Edema	22	26.8
	Hydrocephalus	18	22.0
	Intracerebral Hemorrhage	14	17.1
	Rebleed	8	9.8
	Global Edema	7	8.5
Fisher Grades (Amount of Blood on CT)	None	17	20.7
	Diffuse	30	36.6
	Thick clot	21	25.6
	Focal ICH IVH	12	14.6

Table 10: Aneurysm Location in Study Group

Territory	Location	N	%
Anterior	Anterior Communicating Artery	9	11.0
	Left Anterior Communicating Artery	5	6.1
	Right Anterior Communicating Artery	4	4.9
	Subtotal	18	22
Left	Left Anterior Cerebral Artery	1	1.2
	Left Internal Carotid Communicating Artery	7	8.5
	Left Middle Cerebral Artery	3	3.7
	Left Posterior Communicating Artery	8	9.8
	Subtotal	19	23
Right	Right Anterior Cerebral Artery	4	4.9
	Right Internal Carotid Communicating Artery	5	6.1
	Right Middle Cerebral Artery	4	4.9
	Right Posterior Communicating Artery	11	13.4
	Subtotal	24	29
Posterior	Basilar Artery-Apex	3	3.7
	Basilar Artery-Other	3	3.7
	Left Vertebral Artery/ Posterior Inferior Cerebellar Artery	6	7.3
	Right Vertebral Artery/ Posterior Inferior Cerebellar Artery	2	2.4
	Subtotal	14	17

Table 11: Frequency Of Infarctions In Study Group

	N	%
Infarction	26	33
No Infarction	54	67

Table 12: Amount And Location Of Intraventricular Hemorrhage In Study Group

	Right		Left		Third		Fourth	
	N	%	N	%	N	%	N	%
none	66	80.5	64	78.0	62	75.6	46	56.1
sedimentation	11	13.4	11	13.4	9	11.0	11	13.4
partial	1	1.2	2	2.4	4	4.9	18	22.0
complete	1	1.2	2	2.4	4	4.9	4	4.9
Total	79	96.3	79	96.3	79	96.3	79	96.3

Table 13: Mean and Standard Deviation of Study group Length of Stay, Treatment Day, IVH Score, and Hijdra Score

	N	Minimum	Maximum	Mean	Std. Deviation
length of stay	82	5	76	17.07	11.09
Treatment SAH day	76	0	19	2.79	3.45
IVH score	79	0	11	1.58	2.42
Hijdra score	78	0	28	13.85	8.68

IVH = intraventricular hemorrhage; SAH = subarachnoid hemorrhage

Table 14: Amount And Location Of SAH In Study Group

SAH site		None	Small	Moderate	Complete	Total
Anterior Interhemi-spheric fissure	N	17	28	26	9	80
	%	20.7	34.1	31.7	11	97.6
Right Lateral Sylvian fissure	N	22	21	24	13	80
	%	26.8	25.6	29.3	15.9	97.6
Right Basal Sylvian fissure	N	21	24	23	12	80
	%	25.6	29.3	28	14.6	97.6
Right Supra-cellar cistern	N	17	17	20	26	80
	%	20.7	20.7	24.4	31.7	97.6
Right Ambient cistern	N	21	22	21	16	80
	%	25.6	26.8	25.6	19.5	97.6
Quadrigeminal cistern	N	38	21	15	5	79
	%	46.3	25.6	18.3	6.1	96.3
Left Lateral Sylvian fissure	N	24	21	23	11	79
	%	29.3	25.6	28	13.4	96.3
Left Basal Sylvian fissure	N	18	25	21	16	80
	%	22	30.5	25.6	19.5	97.6
Left Supra-cellar cistern	N	17	12	22	29	80
	%	20.7	14.6	26.8	35.4	97.6
Left Ambient cistern	N	25	18	19	18	80
	%	30.5	22	23.2	22	97.6

Table 15: Follow-Up Bias Between The Study Group And Those People Alive At 12 Months On Continuous Variables.

	Study group (evaluations at both 3 and 12 months) (N = 82)		Alive at 12 months but not in Study Group (N=136)		T test	P value
	Mean	SD	Mean	SD		
Age	50.72	13.22	52.19	15.03	-0.732	0.465
Education (yrs)	11.63	4.59	12.32	3.71	-1.138	0.257
Length of stay (days)	17.07	11.09	19.78	16.15	-1.464	0.145
Treatment day	2.79	3.45	4.21	4.45	-2.503	0.013
14 day modified Rankin score	2.90	1.47	2.84	1.77	0.298	0.766
Hijdra score (Amount of SAH)	13.85	8.68	12.82	7.69	0.875	0.382
Amount of IVH	1.58	2.42	1.75	2.54	-0.478	0.633
Amount of ICH	1.27	4.90	1.71	5.98	-0.552	0.581

SAH = subarachnoid hemorrhage; IVH = intraventricular hemorrhage; ICH = intracerebral hemorrhage.

Table 16: Follow-Up Bias Among People Alive At 12 Months On Discrete Variables.

		Study group (N = 82)	Not Study Group (N=164)	(χ^2)	P value
Sex	Female	69.5%	58.5%	2.801	0.094
	Male	30.5%	41.5%		
Race	White	39.0%	56.1%	9.828	0.007
	Hispanic	45.1%	25.6%		
	Other	15.9%	18.3%		
Handedness	Right handed	87.8%	88.4%	1.421	0.491
	Left handed	9.8%	5.5%		
	Ambidextrous	2.4%	1.8%		
Admission Hunt Hess Grade	1,2	54.9%	48.8%	0.813	0.367
	3-5	45.1%	51.2%		
Worst Hunt Hess Grade	1,2	36.6%	34.1%	0.143	0.705
	3-5	63.4%	65.9%		
Aneurysm	Present	91.5%	84.8%	2.173	0.140
	Absent	8.5%	15.2%		
Aneurysm location	Anterior	22.0%	25.0%	7.335	0.119
	Right	29.3%	18.3%		
	Left	23.2%	17.7%		
	Posterior	17.1%	22.6%		
	Non-aneurysmal	8.5%	16.5%		
Treatment	None	8.5%	16.5%	7.345	0.025
	Surgery	82.9%	66.5%		
	Embolization	8.5%	17.1%		
Infarction	Yes	32.9%	30.5%	0.151	0.697
	no	67.1%	69.5%		
Hydrocephalus	Yes	22.0%	27.4%	0.819	0.365
	No	76.8%	72.0%		
Cerebral Edema	Yes	26.8%	26.2%	0.010	0.919
	No	73.2%	73.8%		
Rebleed	Yes	9.8%	7.3%	0.435	0.509
	No	90.2%	92.7%		
Intracerebral Hemorrhage	Yes	17.1%	15.2%	0.137	0.711
	No	82.9%	84.8%		
Fisher Grade	No Blood	20.7%	18.9%	0.825	0.843
	Diffuse Blood	36.6%	29.9%		
	Thick Clot	25.6%	25.6%		
	Focal Blood	14.6%	17.1%		

Table 17: Follow-Up Bias On Continuous Variables Between Subjects Who Completed Neuropsychological Testing At Three Months (Reference Group) Vs. Those Who Were Alive At Three Months But Who Did Not Complete Neuropsychological Testing.

	Reference Group (N = 117)		No 3 month evaluation (N = 146)				
	Mean	SD	Mean	SD	T test	df	P value
Age (years)	49.58	12.54	54.08	15.04	-2.572	261	0.011
Education (number of years)	11.72	4.40	12.12	3.64	-0.794	253	0.428
Length of stay (number of days)	17.09	10.96	22.49	21.97	-2.598	222.187	0.010
Treatment day	3.03	3.54	4.56	5.73	-2.473	206.852	0.014
14 day modified Rankin score	2.74	1.54	2.99	1.81	-1.184	258	0.238
Hijdra score (Amount of SAH)	12.97	8.51	12.88	7.71	0.091	226.218	0.928
Amount of IVH	1.58	2.57	1.71	2.34	-0.392	241	0.695
Amount of ICH	1.64	5.95	1.67	5.17	-0.035	241	0.972

SAH = subarachnoid hemorrhage; IVH = intraventricular hemorrhage; ICH = intracerebral hemorrhage.

Table 18: Follow-Up Bias On Discrete Variables Between Subjects Who Completed Neuropsychological Testing At Three Months (Reference Group) Vs. Those Who Were Alive At Three Months But Who Did Not Complete Neuropsychological Testing.

Variable	Levels	Reference Group (N = 117)	Alive at 3 months, not in Reference Group (N=146)	Chi-square (χ^2)	DF	P value
Sex	Female	69.2%	58.2%	3.383	1	0.066
	Male	30.8%	41.8%			
Race	White	41.0%	57.5%	18.496	2	0.000
	Hispanic	44.4%	19.9%			
	Other	14.5%	22.6%			
Handedness	Right handed	88.9%	86.3%	0.200	2	0.905
	Left handed	7.7%	6.2%			
	Ambidextrous	2.6%	2.1%			
Admission Hunt Hess Grade	1,2	56.4%	45.2%	3.262	1	0.071
	3-5	43.6%	54.8%			
Worst Hunt Hess Grade	1,2	36.8%	32.9%	0.431	2	0.511
	3-5	63.2%	67.1%			
Aneurysm	present	88.9%	84.2%	2.328	1	0.127
	absent	11.1%	15.8%			
Aneurysm location	Anterior	23.9%	24.0%	5.917	4	0.205
	Right	26.5%	19.2%			
	Left	22.2%	16.4%			
	Posterior	16.2%	24.7%			
	No aneurysm	11.1%	15.8%			
Treatment	None	9.4%	17.8%	5.269	2	0.072
	Surgery	78.6%	66.4%			
	Embolization	12.0%	15.8%			
Infarction	Yes	30.8%	32.9%	0.133	1	0.716
	No	69.2%	67.1%			
Hydrocephalus	Yes	22.2%	28.8%	0.436	1	0.231
	No	76.9%	70.5%			
Cerebral Edema	Yes	24.8%	30.1%	0.927	1	0.336
	No	75.2%	69.9%			
Rebleed	Yes	6.8%	11.0%	1.330	1	0.249
	No	93.2%	89.0%			

Intracerebral Hemorrhage	Yes	16.2%	17.1%	0.036	1	0.849
	No	83.8%	82.9%			
Fisher Grade	No Blood	22.2%	16.4%	2.960	3	0.398
	Diffuse Blood	35.0%	29.5%			
	Thick Clot	26.5%	24.0%			
	Focal Blood	13.7%	19.9%			

Table 19: Follow-Up Bias On Continuous Variables Between Subjects Who Were Followed Up At Three Months Vs. Those Who Were Alive At Three Months But Who Were Not Followed.

	Followed Group (N = 222)		Not Followed At 3 months (N = 41)				
	Mean	SD	Mean	SD	T test	DF	P value
Age (years)	49.78	14.10	52.50	14.27	-1.125	261	0.262
Education (number of years)	12.45	3.53	11.84	4.08	.889	253	0.375
Length of stay (number of days)	16.54	14.19	20.74	18.69	-1.370	261	0.172
Treatment day	2.23	2.80	4.10	5.10	-3.027	66.222	0.004
14 day modified Rankin score	2.35	1.81	2.98	1.66	-2.172	258	0.031
Hijdra score (Amount of SAH)	10.78	7.36	13.29	8.15	-1.734	241	0.084
Amount of IVH	1.39	2.52	1.70	2.44	-.694	241	0.488
Amount of ICH	2.4996	7.0336	1.5061	5.2410	.994	241	0.321

SAH = subarachnoid hemorrhage; IVH = intraventricular hemorrhage; ICH = intracerebral hemorrhage.

Table 20: Follow-Up Bias On Discrete Variables Between Subjects Who Were Followed Up At Three Months Vs. Those Who Were Alive At Three Months But Who Were Not Followed.

Variable (df)		Followed up at 3 months (N = 222)	Alive at 3 months not followed-up (N=41)	Chi-square	P value
Sex (1)	Female	63.5%	36.4%	0.096	0.757
	Male	36.5%	56.8%		
Race (2)	White	52.7%	34.1%	7.681	0.021
	Hispanic	31.1%	27.3%		
	Other	16.2%	31.8%		
Handedness (2)	Right handed	87.4%	81.8%	0.017	0.992
	Left handed	6.8%	6.8%		
	Ambidextrous	2.3%	2.3%		
Admission Hunt Hess Grade (1)	1,2	49.5%	50.0%	0.234	0.629
	3-5	50.5%	43.2%		
Worst Hunt Hess Grade (1)	1,2	32.9%	40.9%	1.857	0.173
	3-5	67.1%	52.3%		
Aneurysm (1)	Present	87.8%	72.7%	2.807	0.094
	Absent	12.2%	20.5%		
Aneurysm location (4)	Anterior	25.2%	15.9%	3.815	0.432
	Right	22.1%	22.7%		
	Left	18.9%	18.2%		
	Posterior	21.6%	15.9%		
	No aneurysm	12.2%	20.5%		
Treatment (2)	None	12.2%	22.7%	4.282	0.118
	Surgery	73.4%	59.1%		
	Embolization	14.4%	11.4%		
Infarction (1)	Yes	33.8%	20.5%	2.229	0.135
	No	66.2%	72.7%		
Hydrocephalus (1)	Yes	27.9%	13.6%	3.292	0.070
	No	71.2%	79.5%		
Cerebral Edema (1)	Yes	27.0%	29.5%	0.378	0.539
	No	73.0%	63.6%		
Rebleed (1)	Yes	9.5%	6.8%	0.192	0.662
	No	90.5%	86.4%		

Intracerebral Hemorrhage (1)	Yes	17.6%	11.4%	0.717	0.397
	No	82.4%	81.8%		
Fisher Grade (3)	No Blood	18.9%	18.2%	0.234	0.972
	Diffuse Blood	32.0%	29.5%		
	Thick Clot	25.7%	20.5%		
	Focal Blood	17.6%	13.6%		

Table 21: Follow-Up Bias Between Groups With One Vs. Two Follow-Ups On Continuous Variables.

	3 month evaluation only (N = 35)		Study group (evaluations at both 3 and 12 months) (N = 82)				
	Mean	SD	Mean	SD	T test	DF	P value
Age	46.91	11.65	50.72	13.22	1.476	115	0.143
Education (number of years)	11.91	3.97	11.63	4.59	-0.319	114	0.750
Length of stay (number of days)	17.11	10.79	17.07	11.09	-0.019	115	0.985
Treatment day	3.61	3.77	2.79	3.45	-1.091	105	0.278
14 day modified Rankin score	2.37	1.65	2.90	1.47	1.725	115	0.087
Hijdra score (Amount of SAH)	10.97	7.87	13.85	8.68	1.657	110	0.100
Amount of IVH	1.59	2.92	1.58	2.42	-0.011	111	0.991
Amount of ICH	2.51	7.92	1.27	4.90	-0.849	44.110	0.400

SAH = subarachnoid hemorrhage; IVH = intraventricular hemorrhage; ICH = intracerebral hemorrhage.

Table 22: Follow-Up Bias Among Groups With One Vs. Two Follow-Ups On Discrete Variables.

Variable (df)		3 month evaluation only (N = 35)	Study group (evaluations at both 3 and 12 months) (N = 82)	Chi-square (χ^2)	P value
Sex (1)	Female	68.6%	69.5%	1.00	0.542
	Male	31.4%	30.5%		
Race (2)	White	45.7%	39.0%	0.626	0.731
	Hispanic	42.9%	45.1%		
	Other	11.4%	15.9%		
Handedness (2)	Right handed	91.4%	87.8%	1.569	0.456
	Left handed	2.9%	9.8%		
	Ambidextrous	2.9%	2.4%		
Admission Hunt Hess Grade (1)	1,2	60.0%	54.9%	0.262	0.609
	3-5	40.0%	45.1%		
Worst Hunt Hess Grade (1)	1,2	37.1%	36.6%	0.003	0.954
	3-5	62.9%	63.4%		
Aneurysm (1)	present	82.9%	91.5%	1.840	0.175
	absent	17.1%	8.5%		
Aneurysm location (4)	Anterior	28.6%	22.0%	3.108	0.540
	Right	20.0%	29.3%		
	Left	20.0%	23.2%		
	Posterior	14.3%	17.1%		
	No aneurysm	17.1%	8.5%		
Treatment (2)	None	11.4%	8.5%	3.555	0.169
	Surgery	68.6%	82.9%		
	Embolization	20.0%	8.5%		
Infarction (1)	Yes	25.7%	32.9%	0.599	0.439
	no	74.3%	67.1%		
Hydrocephalus (1)	Yes	22.9%	22.0%	0.006	0.940
	No	77.1%	76.8%		
Cerebral Edema (1)	Yes	20.0%	26.8%	0.614	0.433
	No	80.0%	73.2%		
Rebleed (1)	Yes	0.0%	9.8%	3.665	0.056
	No	100.0%	90.2%		
Intracerebral Hemorrhage (1)	Yes	14.3%	17.1%	0.140	0.708
	No	85.7%	82.9%		

Fisher Grade (3)	No Blood	25.7%	20.7%	0.727	0.867
	Diffuse Blood	31.4%	36.6%		
	Thick Clot	28.6%	25.6%		
	Focal Blood	11.4%	14.6%		

Table 23: Neuropsychological Test Raw Scores for Study Group.

Domain	Test	3-Months		12-Months	
		Mean	Std. Deviation	Mean	Std. Deviation
Attention	Digits forward	5.46	1.38	5.83	1.719
	Digits reversed	3.98	1.39	4.20	1.42
	Digit symbol	37.81	18.94	39.90	18.88
	VSAT time	148.71	85.05	140.63	83.69
	Cal CAP Attention	1.74	0.48	1.75	.43
Language	BNT correct	43.78	14.67	44.45	15.16
	Token Test	42.76	32.71	55.32	34.33
Visual Skills	WMSR VR Copy	34.78	5.77	34.85	6.05
	RCFT Copy	29.46	7.22	29.48	7.50
	Block design raw	17.38	11.82	19.68	11.91
Verbal Memory	CVLT total	43.13	14.57	47.59	15.74
	CVLT long delay free recall	8.11	4.54	9.36	4.26
	CVLT recognition hits	12.78	3.28	13.48	2.92
Visual Memory	WMSR VR II	19.36	12.00	22.03	12.12
	RCFT Delayed recall	14.48	7.32	16.80	8.14
Psychomotor Speed	Simple RT mean (sec)	422.23	194.22	392.79	198.13
	Trails A time	63.95	50.84	51.45	31.10
Executive Functions	MCST Total Correct	24.14	10.75	26.74	10.05
	MCST Total Perseverative errors	7.68	9.55	4.79	5.66
	Trails B time	119.16	72.93	107.25	59.31
Global Mental Status	TICS	32.83	7.50	34.56	6.49

VSAT = Verbal Serial Attention Test, Cal CAP = California Computerized Assessment Package, BNT = Boston Naming Test

Table 24: Neuropsychological Test Raw Scores At Three-month Follow-Up.

Domain	Test	Repeated testing		Testing at 3 months only		T	DF	p
		Mean	Std. Deviation	Mean	Std. Deviation			
Attention	Digits forward	5.39	1.5	5.51	1.82	-0.384	115	0.702
	Digits reversed	3.98	1.39	4.2	1.55	-0.773	114	0.441
	Digit symbol raw	37.65	18.87	43.5	20.53	-1.443	109	0.152
	VSAT time	150.67	86.32	145.85	86.59	0.273	113	0.786
	Cal CAP Attention	1.7583	0.4804	1.58	0.4465	1.66	99	0.1
Language	BNT correct	43.32	14.68	41.61	14.52	0.547	103	0.586
	Token Test	41.5424	31.9257	39.4	37.1758	0.249	77	0.804
Visual Skills	WMSR VR Copy	34.74	5.68	35.48	4.25	-0.639	104	0.524
	RCFT Copy	29.4375	7.1734	31.2188	6.4719	-1.22	110	0.225
	Block design raw	17.57	11.88	20.84	12.5	-1.302	112	0.196
Verbal Memory	CVLT total	43.13	14.57	44.19	12.4	-0.357	105	0.721
	CVLT long delay free recall	8.11	4.54	8.75	3.85	-0.698	104	0.487
	CVLT recognition hits	12.78	3.28	13.56	2.05	-1.241	104	0.217
Visual Memory	WMSR VR II	19.22	11.99	20.97	12.57	-0.681	108	0.498
	RCFT Delayed recall	14.2314	7.4268	14.9844	7.1069	-0.491	110	0.625
Psychomotor Speed	Simple RT mean (sec)	416.13	185.34	395.96	149.89	0.508	100	0.612
	Trails A time	50.13	50.93	65.76	37.01	1.577	110	0.118
Executive Functions	MCST Total Correct	25.29	10.77	24.23	11.64	-0.435	104	0.664
	MCST Total % Perseverative errors	31.3671	29.2649	31.7038	28.9083	0.052	104	0.958
	Trails B time	129.06	81.27	95.78	60.74	2.17	92	0.034

Global Mental Status	TICS	32.83	8.99	32.29	8.99	0.336	114	0.738

VSAT = Verbal Serial Attention Test, Cal CAP = California Computerized Assessment Package, BNT = Boston Naming Test, WMS-R= Wechsler Memory Scale – Revised, VR = Visual Reproduction, RCFT = Rey Complex Figure Test, CVLT = California Verbal Learning Test, RT = reaction time, MCST = Modified Card Sorting Test, TICS = Telephone Interview for Cognitive Skills

Table 25: Means And Standard Deviations Of Test Performance For All Subjects Followed At 3 Months Post-SAH.

Domain	Test	N	Mean	Std. Deviation
Attention	Digits forward	117	5.43	1.59
	Digits reversed	116	4.04	1.43
	Digit symbol raw	111	39.33	19.45
	VSAT time	115	149.24	86.05
	Cal CAP Attention	101	1.7124	.4762
Language	BNT correct	105	42.82	14.59
	Token Test	79	41.0000	33.0974
Visual Skills	WMSR VR Copy	106	34.94	5.32
	RCFT Copy	112	29.9464	6.9982
	Block design raw	114	18.49	12.09
Verbal Memory	CVLT total	107	43.45	13.91
	CVLT long delay free recall	106	8.30	4.33
	CVLT recognition hits	106	13.02	2.97
Visual Memory	WMSR VR II	110	19.71	12.12
	RCFT Delayed recall	112	14.4465	7.3129
Psychomotor Speed	Simple RT mean (sec)	102	410.79	176.16
	Trails A time	112	61.29	47.74
Executive Functions	MCST Total Correct	106	24.51	10.96
	MCST Total % Perseverative errors	106	31.6149	29.0339
	Trails B time	94	119.50	77.12
Global Mental Status	TICS	116	32.66	7.95

VSAT = Verbal Serial Attention Test, Cal CAP = California Computerized Assessment Package, BNT = Boston Naming Test, WMS-R= Wechsler Memory Scale – Revised, VR = Visual Reproduction, RCFT = Rey Complex Figure Test, CVLT = California Verbal Learning Test, RT = reaction time, MCST = Modified Card Sorting Test, TICS = Telephone Interview for Cognitive Skills

Table 26: Mean ± SD Of Domain Scores For Study Group (N = 82).

Cognitive Domain	Neuropsychological Test	3 months	12 months
Attention / Concentration	Digit Span Forward Digit Span Backward Digit Symbol Total Verbal Serial Attention Task time Cal CAP (Sequence 1 RT ÷ Simple RT)	-0.0302±0.5174	0.0718±0.7439
Visuospatial Skills	Block Design raw score WMS-R VR Copy Rey Complex Figure Copy	-0.0706±0.9097	-0.0055±0.9317
Psychomotor Speed	Cal CAP Simple RT Trails A	-0.0837±0.9679	.0262±1.0995
Verbal Memory	CVLT/AVLT total raw score (trials1 thru 5) CVLT/AVLT long delay free recall raw scores CVLT/AVLT recognition hits	-0.0613±0.9697	0.1861±0.9529
Language Skills	Boston Naming Test raw score Token Test	-0.0429±0.9449	0.1240±1.0240
Visual Memory	WMS-R VRII raw score Rey Complex Figure delayed recall raw score	-0.0435±0.9444	0.2402±0.9999
Executive Functions	MCST total correct raw score MCST average percent perseverative errors Trails B time	-0.0873±0.8429	0.0843±0.6986

VSAT = Verbal Serial Attention Test, Cal CAP = California Computerized Assessment Package, BNT = Boston Naming Test, WMS-R= Wechsler Memory Scale – Revised, VR = Visual Reproduction, RCFT = Rey Complex Figure Test, CVLT = California Verbal Learning Test, AVLT = Auditory Verbal Learning Test, RT = reaction time, MCST = Modified Card Sorting Test, TICS = Telephone Interview for Cognitive Skills

Table 27: Cognitive Index Scores

	N	Minimum	Maximum	Mean	SD	Skewness		Kurtosis	
						Statistic	Std. Error	Statistic	Std. Error
Cognitive Index Score For 3m	82	-2.09	1.20	-.0717	.7123	-.534	.266	.000	.526
Cognitive Index Score For 12m	82	-2.27	1.33	.0879	.7707	-.845	.266	.742	.526

Table 28: Results Of Kolmogorov-Smirnov Tests

Domain (P value)	Test	Z	P values	Transformation
Attention (NS)	Digit Span Forward	1.929	.001	Log
	Digit Span Reversed	2.265	.000	Reflect and Log
	Digit Symbol	.894	.401	NA
	VSAT time	1.846	.002	Log
	Cal CAP Attention	.440	.990	NA
Visuospatial (NS)	Block Design	1.078	.195	NA
	WMS-R VR copy	2.083	.000	Reflect and Invert
	RCFT copy	2.145	.000	Invert
Psychomotor Speed (.002)	Cal CAP Simple RT	1.850	.002	Reflect and Invert
	Trails A time	2.077	.000	Reflect and Invert
Verbal Memory (NS)	CVLT total	.846	.427	NA
	CVLT LDFR	1.041	.228	NA
	CVLT recognition	1.917	.001	Log
Language (NS)	Boston Naming Test	1.534	.018	Reflect and Invert
	Token Test	1.241	.092	NA
Visual Memory (NS)	WMS-R VRII	.937	.343	NA
	RCFT delay	.515	.954	NA
Executive Functions (NS)	MCST total	1.981	.001	Invert
	MCST % PE	1.422	.035	Invert
	Trails B time	1.750	.004	Reflect and Log
Global Mental Status (NS)	TICS	1.152	.140	NA

NS = not significant, NA = not applicable, VSAT = Verbal Serial Attention Test, Cal CAP = California Computerized Assessment Package, WMS-R= Wechsler Memory Scale – Revised, VR = Visual Reproduction, RCFT = Rey Complex Figure Test, RT = reaction time, CVLT = California Verbal Learning Test, BNT = Boston Naming Test, MCST = Modified Card Sorting Test, PE = perseverative errors, TICS = Telephone Interview for Cognitive Skills

Table 29: Varimax Rotated Solution For PCA Using List-wise Deletion Of Missing Variables. (N=53).

A Priori Domains	Neuropsychological Test Scores	Visual Skills	Auditory Attention	Verbal Memory	Psychomotor Speed
Attention	Digit Span Forwards Transformed	-.125	-.765	0.0	0.0
	Digit Span Backwards Transformed	-.374	-.742	0.0	0.0
	Digit Symbol	.600	.460	.341	.231
	VSAT Time Transformed	-.363	-.600	-.354	-.285
	Cal Cap Attention	0.0	0.0	0.0	.918
Visuospatial Skills	Block Design	.763	.289	.157	0.0
	WMSR VR Copy Transformed	.693	.296	0.0	.150
	RCFT Copy Transformed	.779	.178	0.0	0.0
Psychomotor Speed	Cal CAP Simple RT Transformed	.284	.141	.143	.863
	Trails A Time Transformed	.654	.197	.198	.287
Verbal Memory	CVLT Total	.378	.318	.793	0.0
	CVLT Long Delay Free Recall	.330	.213	.839	.113
	CVLT Recognition Hits Transformed	-.109	0.0	-.818	-.129
Language	BNT Transformed	.279	.688	0.0	0.0
	Token Test	0.0	.646	.550	0.0
Visual Memory	WMSR VR II	.605	.358	.450	.117
	RCFT Delayed Recall	.711	0.0	.420	0.0
Executive Functions	MCST Total Correct Transformed	.476	.434	.147	.261
	MCST % PE Transformed	-.210	-.485	0.0	-.258
	Trails B Time Transformed	-.638	-.458	-.344	-.164

VSAT = Verbal Serial Attention Test, Cal CAP = California Computerized Assessment Package, WMS-R= Wechsler Memory Scale – Revised, VR = Visual Reproduction, RCFT = Rey Complex Figure Test, RT = reaction time, CVLT = California Verbal Learning Test, BNT = Boston Naming Test, MCST = Modified Card Sorting Test, PE = perseverative errors

Table 30: Varimax Rotated Solution For PCA With Pair-wise Deletion (N=79-117).

A Priori Domains	Neuropsychological Test Scores	Visual skills	Auditory Attention	Verbal Memory	Psychomotor Speed
Attention	Digit Span Forwards Transformed	-.104	-.830	-.177	-.127
	Digit Span Backwards Transformed	-.362	-.725	-.122	-.134
	Digit Symbol	.633	.494	.376	.194
	VSAT Time Transformed	-.478	-.625	-.330	-.314
	Cal Cap Attention	0.0	0.0	0.0	.926
Visuospatial Skills	Block Design	.757	.391	0.0	.145
	WMSR VR Copy Transformed	.657	.409	0.0	0.0
	RCFT Copy Transformed	.757	.335	0.0	.122
Psychomotor Speed	Cal CAP Simple RT Transformed	.272	.224	.158	.855
	Trails A Time Transformed	.683	.295	.283	.312
Verbal memory	CVLT Total	.494	.275	.751	0.0
	CVLT Long Delay Free Recall	.440	.151	.800	0.0
	CVLT Recognition Hits Transformed	0.0	-.146	-.838	0.0
Language	BNT Transformed	.452	.722	0.0	0.0
	Token Test	.367	.599	.389	0.0
Visual Memory	WMSR VR II	.674	.300	.393	.135
	RCFT Delayed Recall	.717	0.0	.382	0.0
Executive Functions	MCST Total Correct Transformed	.658	.263	.136	.272
	MCST % PE Transformed	-.533	-.106	-.163	0.0
	Trails B Time Transformed	-.545	-.309	-.491	-.254

VSAT = Verbal Serial Attention Test, Cal CAP = California Computerized Assessment Package, WMS-R= Wechsler Memory Scale – Revised, VR = Visual Reproduction, RCFT = Rey Complex Figure Test, RT = reaction time, CVLT = California Verbal Learning Test, BNT = Boston Naming Test, MCST = Modified Card Sorting Test, PE = perseverative errors

Table 31: Eigenvalues and Percent of Variance Explained for PCA using Listwise Deletion of Missing Variables.

	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	9.159	45.793	45.793	9.159	45.793	45.793	4.716	23.581	23.581
2	1.718	8.591	54.384	1.718	8.591	54.384	3.770	18.852	42.434
3	1.534	7.671	62.055	1.534	7.671	62.055	3.191	15.954	58.387
4	1.325	6.626	68.681	1.325	6.626	68.681	2.059	10.293	68.681

Table 32: Eigenvalues And Percent Of Variance Explained For PCA Using Listwise Deletion.

Component	Initial Eigen values			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	10.366	51.828	51.828	10.366	51.828	51.828	5.645	28.224	28.224
2	1.737	8.683	60.511	1.737	8.683	60.511	3.689	18.445	46.670
3	1.315	6.576	67.087	1.315	6.576	67.087	3.076	15.379	62.048
4	1.065	5.327	72.414	1.065	5.327	72.414	2.073	10.366	72.414

Table 33: Eigenvalues And Percent Of Variance Explained For Follow Up PCA Using Pairwise Deletion

	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	6.206	62.058	62.058	6.206	62.058	62.058	2.500	25.002	25.002
2	.910	9.105	71.163	.910	9.105	71.163	2.487	24.867	49.869
3	.642	6.423	77.586	.642	6.423	77.586	1.916	19.163	69.031
4	.587	5.867	83.453	.587	5.867	83.453	1.442	14.421	83.453

Table 34: Eigenvalues And Percent Of Variance Explained For Follow Up PCA Using Listwise Deletion.

	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	5.454	54.543	54.543	5.454	54.543	54.543	2.546	25.457	25.457
2	.995	9.946	64.489	.995	9.946	64.489	2.304	23.043	48.500
3	.849	8.488	72.978	.849	8.488	72.978	1.678	16.784	65.284
4	.676	6.764	79.742	.676	6.764	79.742	1.446	14.457	79.742

Table 35: Rotated Factor Loadings For Follow Up PCA Using Pairwise Deletion Of Missing Variables. (N = [94, 112]).

A Priori Domain	Neuropsychological Test Score	Visual Construction	Visual Attention	Visual Memory	Executive Functions
Visuospatial Skills	Block Design Raw	.740	.372	.293	.217
	RCFT Copy Transformed	.673	.239	.472	.180
	WMSR VR Copy Transformed	.802	.300	.188	.039
Visual Memory	RCFT Delayed Recall	.291	.216	.888	.118
	WMSR VR II	.297	.490	.684	.162
Psychomotor Speed	Digit Symbol Raw	.401	.695	.393	.232
	Trails A Time Transformed	.405	.795	.258	.149
Executive Functions	Trails B Time Transformed	-.230	-.834	-.201	-.301
	MCST % PE Transformed	-.075	-.225	-.102	-.906
	MCST Total Correct Transformed	.547	.230	.209	.577

PCA = Principal Components Analysis, RCFT = Rey Complex Figure Test, WMS-R= Wechsler Memory Scale – Revised, VR = Visual Reproduction, MCST = Modified Card Sorting Test, PE = perseverative errors

Table 36: Rotated Factor Loadings For Follow Up PCA Using Listwise Deletion Of Missing Variables. (N = 80).

A Priori Domain	Neuropsychological Test Score	Attention	Visual Construction	Visual Memory	Executive Functions
Visuospatial Skills	Block Design Raw	.254	.779	.276	.201
	RCFT Copy Transformed	.220	.670	.413	.113
	WMSR VR Copy Transformed	.340	.774	-.031	.022
Visual Memory	RCFT Delayed Recall	.213	.209	.902	.053
	WMSR VR II	.607	.158	.602	.112
Attention	Digit Symbol Raw	.746	.286	.318	.267
Psychomotor Speed	Trails A Time Transformed	.831	.314	.118	.158
Executive Functions	Trails B Time Transformed	-.745	-.360	-.228	-.301
	MCST % PE Transformed	-.257	-.042	.006	-.902
	MCST Total Correct Transformed	.185	.518	.297	.613

PCA = Principal Components Analysis, RCFT = Rey Complex Figure Test, WMS-R= Wechsler Memory Scale – Revised, VR = Visual Reproduction, MCST = Modified Card Sorting Test, PE = perseverative errors

Table 37: Standardized Scores (Mean ± Standard Deviation).

Cognitive Domain	Neuropsychological Test	3 Months	12 Months
Global Mental Status	TICS	0.0206 ± 0.9444	0.2384 ± 0.8162
Attention / Concentration	Digit Span Forward	-0.0233 ± 0.9393	0.2498 ± 1.0747
	Digit Span Backward	-0.0472 ± 0.9668	0.1102 ± 0.9916
	Digit Symbol Total	-0.0868 ± 0.9701	-0.0087 ± 0.9823
	VSAT time	0.0165 ± 1.0031	0.1000 ± 0.9726
	Cal CAP (Sequence 1 RT ÷ Simple RT)	0.0964 ± 1.0088	0.0653 ± 0.9613
Visuospatial Skills	Block Design raw score	-0.0759 ± 0.9823	0.0984 ± 0.9849
	WMS-R VR Copy	-0.0382 ± 1.0682	-0.0268 ± 1.1211
	Rey Complex Figure Copy	-0.0727 ± 1.0250	-0.0576 ± 1.0594
Psychomotor Speed	Cal CAP Simple RT	-0.0305 ± 1.0521	-0.0577 ± 1.4006
	Trails A	-0.0937 ± 1.0668	0.1366 ± 0.8915
Verbal Memory	CVLT/AVLT total raw score (trials1 thru 5)	-0.0227 ± 1.0477	0.2401 ± 1.1488
	CVLT/AVLT long delay free recall raw scores	-0.0447 ± 1.0470	0.2044 ± 0.9961
	CVLT/AVLT recognition hits	-0.0791 ± 1.1027	0.1138 ± 0.9850
Language Skills	BNT raw score	0.0346 ± 1.0067	-0.0409 ± 1.1204
	Token Test	0.0164 ± 0.9646	0.3599 ± 0.9884
Visual Memory	WMS-R VR II raw score	-0.0407 ± 0.9890	0.1665 ± 1.0055
	RCFT delayed recall raw score	-0.0294 ± 1.0156	0.3329 ± 1.1025
Executive Functions	MCST total correct raw score	-0.0254 ± 0.9827	0.1371 ± 0.9473
	MCST average percent perseverative errors	-0.0031 ± 1.0080	0.1588 ± 0.7450
	Trails B time	-0.1240 ± 1.0538	0.0893 ± 0.8206

VSAT = Verbal Serial Attention Test, Cal CAP = California Computerized Assessment Package, RT = reaction time, WMS-R= Wechsler Memory Scale – Revised, VR = Visual Reproduction, RCFT = Rey Complex Figure Test, CVLT = California Verbal Learning Test, AVLT = Auditory Verbal Learning Test, BNT = Boston Naming Test, MCST = Modified Card Sorting Test

Table 38: Univariate Results (DF=1,62) Of The Basic MANCOVA Model (F Statistics And P Values).

	Time		Group		Time x Group	
	F	P	F	P	F	P
Attention/Concentration	4.754	.033	11.171	.001	2.715	.104
Visuospatial Skills	.629	.431	6.496	.013	3.823	.055
Psychomotor Speed	6.413	.014	9.287	.003	6.818	.011
Verbal Memory	.207	.650	30.060	.000	5.621	.021
Language Skills	.998	.322	10.326	.002	.024	.878
Visual Memory	.106	.746	22.217	.000	.133	.717
Executive Functions	2.757	.102	20.792	.000	3.465	.067

Figure 2: Main Effect of Time

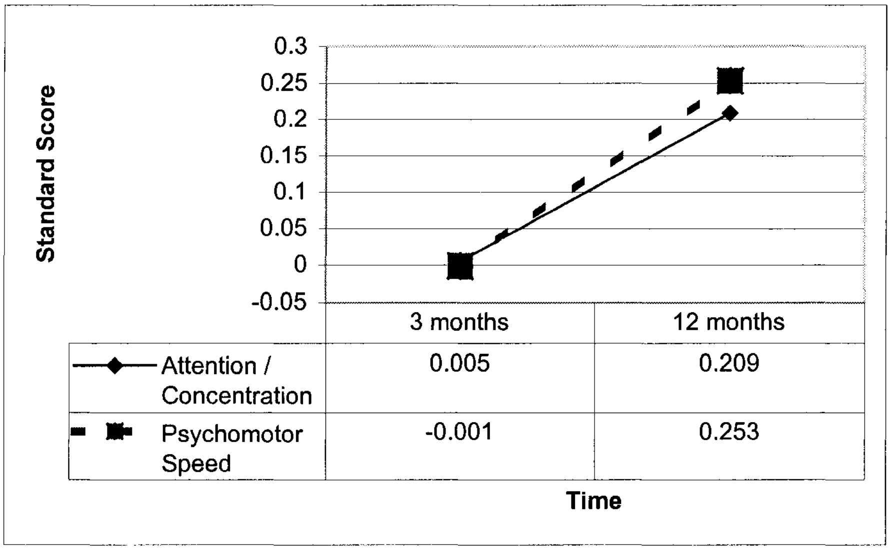


Figure 3: Main Effect of Group

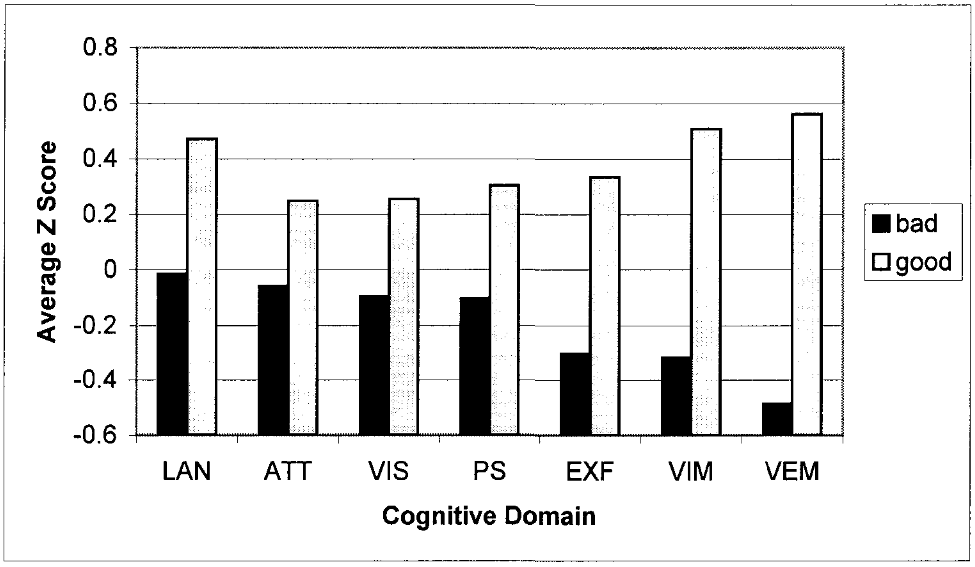


Figure 4: Time x Group on Psychomotor Speed

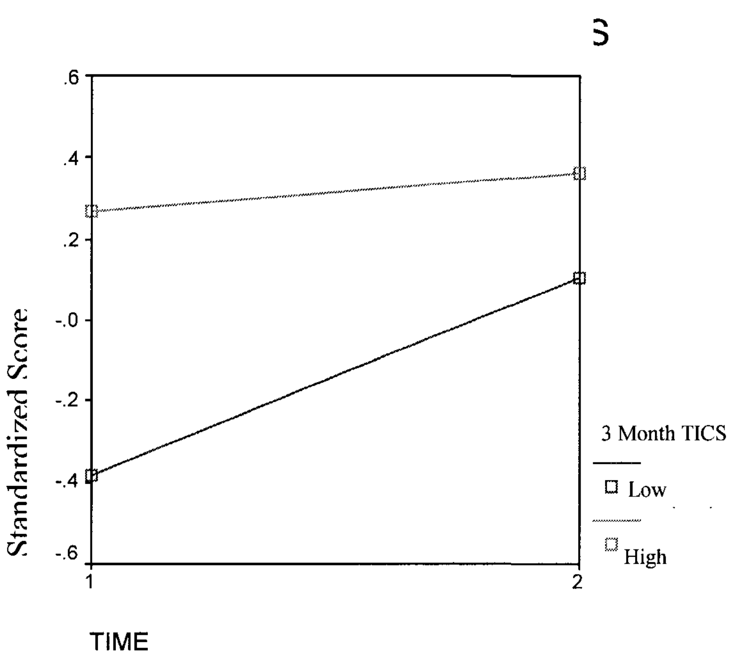


Figure 5: Time x Group on Verbal Memory

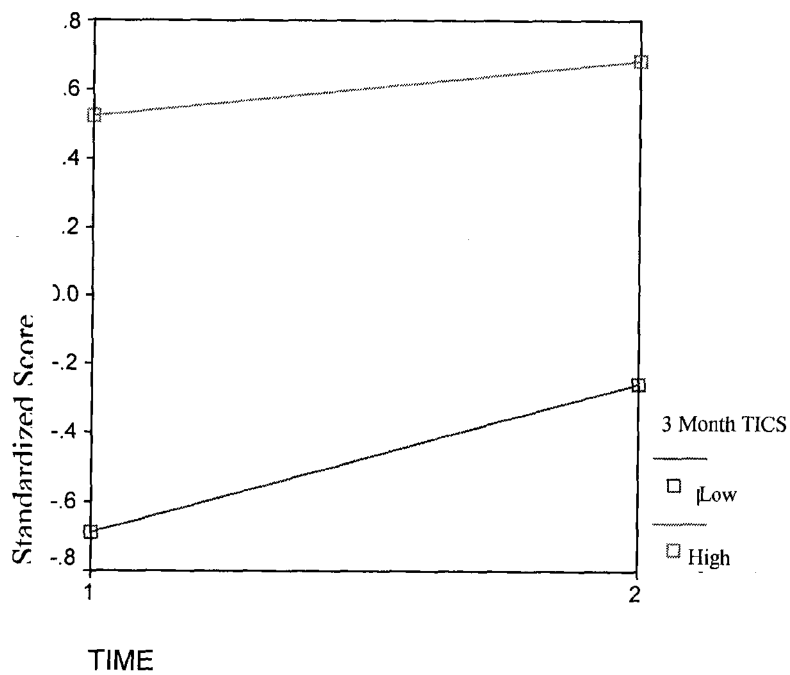


Table 39: Interaction Effect Between Group And Time For Psychomotor Speed And Verbal Memory.

Domain Score	Time	TICS	Mean	Std. Deviation	N
Psychomotor Speed	3 Months	Low	-.5427	1.1184	28
		High	.3930	.3577	37
		Total	-.0101	.9043	65
	12 Months	Low	-.0067	.5559	28
		High	.4496	.3171	37
		Total	.2530	.4886	65
Verbal Memory	3 Months	Low	-.7096	.8021	28
		High	.5429	.6661	37
		Total	.0034	.9548	65
	12 Months	Low	-.3544	.8672	28
		High	.7530	.6000	37
		Total	.2760	.9084	65

Figure 6: Recovery of Psychomotor Speed

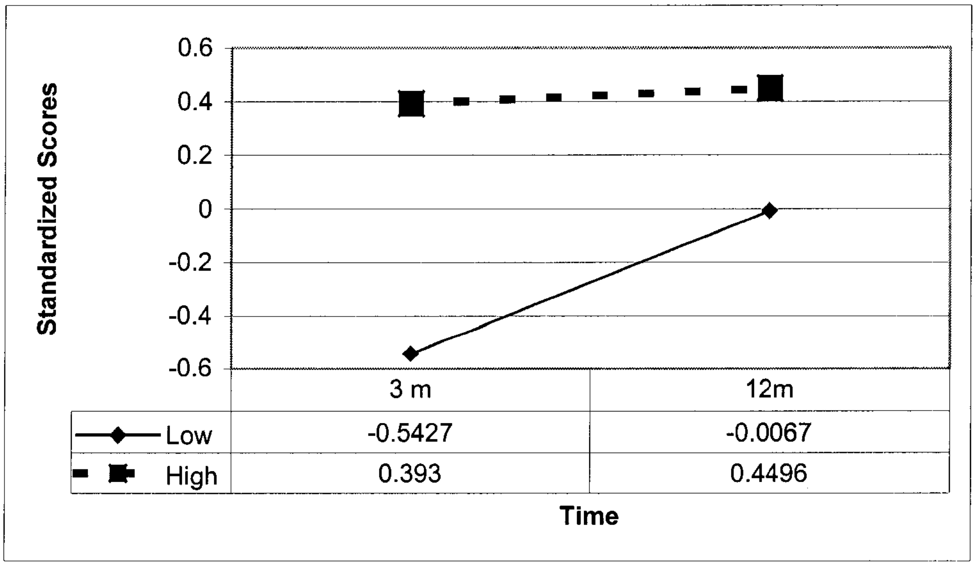


Figure 7: Recovery of Verbal Memory

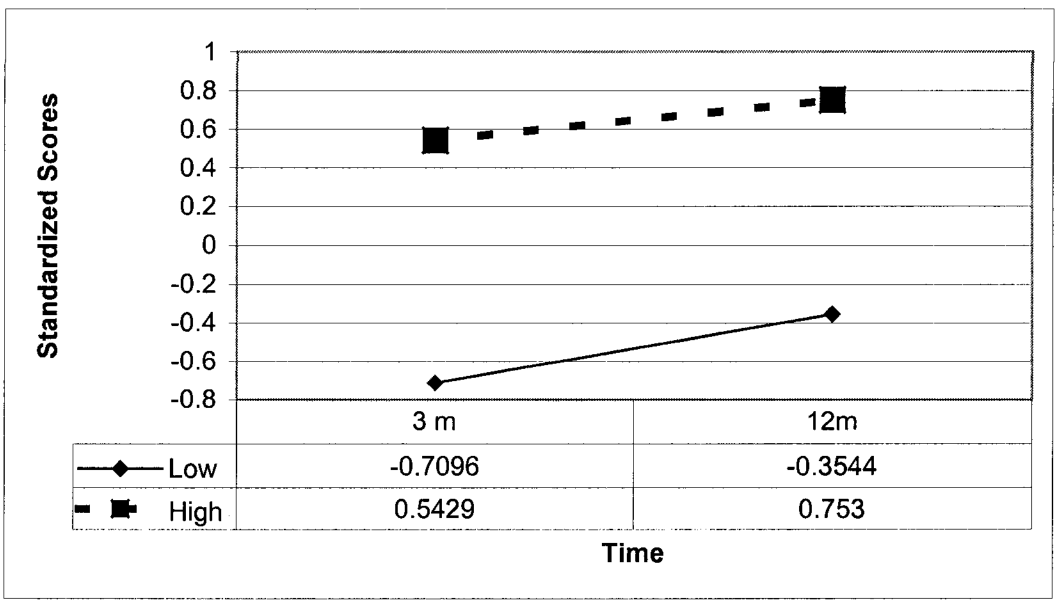


Table 40: Basic MANCOVA Results for Cognitive Index Score. (DF = 1, 77).

Effect	F	Sig.
Time	.205	.652
Time * Group	.394	.532
Group	40.554	.000

Figure 8: Cognitive Index Scores over Time for High and Low Groups

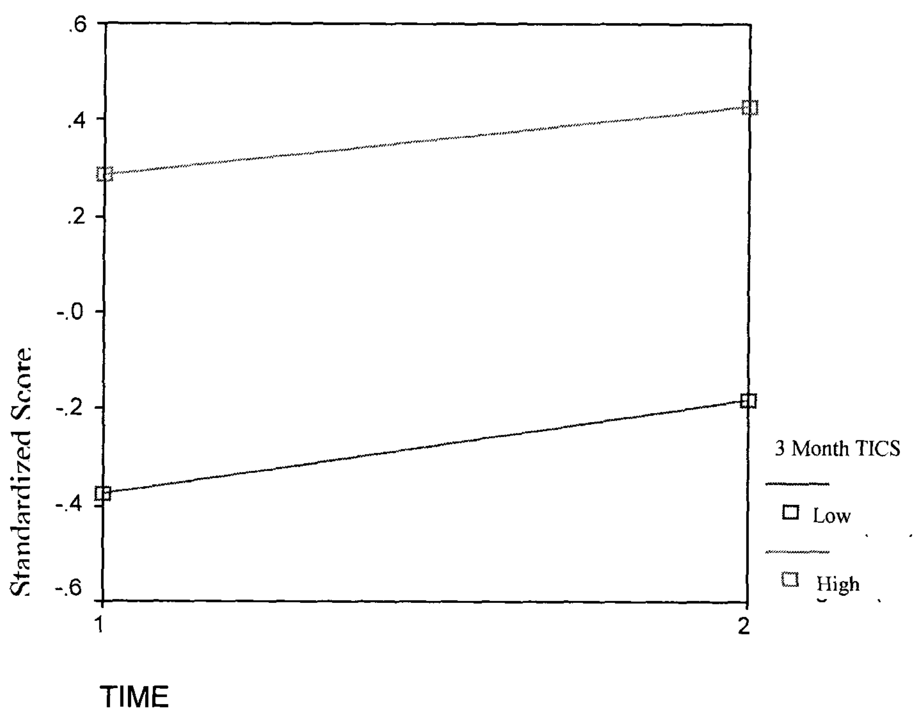


Table 41: Univariate Results Of The RM-MANCOVA For Age. (DF =1, 60).

	Time		Group		Time x Group	
	F	P	F	P	F	P
Attention/Concentration	5.765	.019	11.079	.001	3.214	.078
Visuospatial Skills	.467	.497	5.243	.026	3.800	.056
Psychomotor Speed	4.342	.041	7.087	.010	5.785	.019
Verbal Memory	.172	.680	27.135	.000	5.774	.019
Language Skills	.888	.350	10.633	.002	.226	.636
Visual Memory	.135	.714	18.116	.000	.219	.641
Executive Functions	1.526	.222	18.546	.000	2.986	.089

Table 42: Multivariate Results Of The RM-MANCOVA For Etiology (DF = 7, 54).

Effect		F	Sig.
Between Subjects	Group	2.413	.032
	Etiology	.907	.508
	Group * Etiology	.348	.928
Within Subjects	Time	1.234	.301
	Time * Group	1.500	.187
	Time * Etiology	1.193	.323
	Time * Group * Etiology	.573	.775

Table 43: Multivariate Results Of The RM-MANCOVA For Aneurysm Location.

Effect		F	Hypothesis df	Error df	P
Between Subjects	Group	3.051	7.000	45.000	.010
	Aneurysm Location	.830	21.000	131.000	.679
	Group * Aneurysm Location	1.721	21.000	131.000	.035
Within Subjects	Time	2.046	7.000	45.000	.070
	Time * Group	2.211	7.000	45.000	.051
	Time * Aneurysm Location	.348	21.000	131.000	.997
	Time * Group * Aneurysm Location	1.081	21.000	131.000	.376

Table 44: Univariate Results Of The RM-MANCOVA For Aneurysm Location X Group (DF = 3, 51).

	F	Sig.
Attention/Concentration	1.126	.347
Visuospatial Skills	.623	.603
Psychomotor Skills	.703	.554
Verbal Memory	.235	.872
Language Skills	.775	.513
Visual Memory	.166	.919
Executive Functions	4.134	.011

Table 45: Domain Scores For Interaction Effect Of Aneurysm Location By TICS Group On Executive Functions.

TICS Group	High Performance			Low Performance			Total		
Aneurysm Location	M	SD	N	M	SD	N	M	SD	N
Frontal	-0.20365	0.6858	5	-0.0095	0.66685	6	-0.09776	0.64945	11
Left	0.4944	0.47765	6	-0.58845	0.76035	9	-0.15533	0.84705	15
Right	0.3555	0.5403	11	-0.485	0.59815	10	-0.0447	0.7065	21
Posterior	0.71095	0.45115	12	-0.7637	.	1	0.59755	0.5949	13
Total	0.42325	0.58675	34	-0.4218	0.6835	26	0.057043	0.7558	60

Table 46: Post Hoc Analyses Comparing Group by Aneurysm Locations on Executive Functions Domain.

Aneurysm Location	Time	Mean ± SD of High Group	Mean ± SD of Low Group	T (df)	Sig.
Anterior	3 months	-.1395 ± .8798	-.2730 ± .5903	-.399 (16)	.695
	12 months	-.0861 ± .4745	-.2406 ± .5938	-.553 (16)	.588
Right	3 months	.3713 ±.5379	-.7473 ± .6419	-4.544 (21)	.000
	12 months	.4244 ± .5336	-.2937 ± .5670	-3.129 (21)	.005
Left	3 months	.3778 ± .5286	-.9863 ± .7545	-4.157 (16)	.001
	12 months	.4748 ± .4315	-.3849 ± .6882	-2.936 (16)	.010
Posterior	3 months	.6633 ± .4160	-1.0450 ± .4517	-5.337 (12)	.000
	12 months	.7586 ± .4863	-.7838 ± .0254	-4.337 (12)	.001

Figure 9: Interaction Effect of Aneurysm Location and Group on Executive Functions

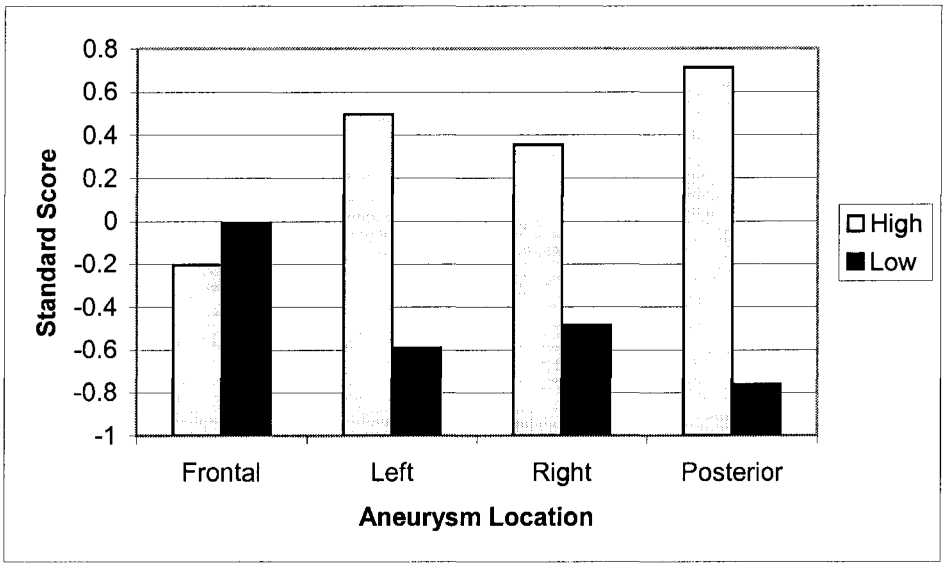
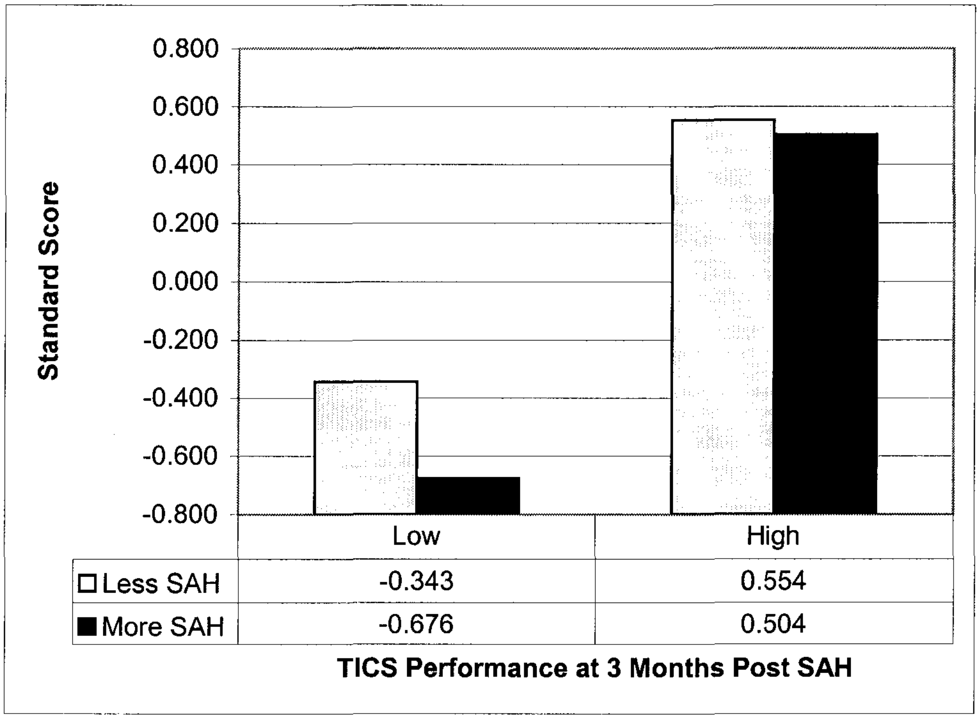


Table 47: Multivariate Results of MANCOVA for SAH Amount (DF = 7, 52).

Effect		F	Sig.
Between Subjects	Group	6.186	.000
	SAH Amount	.629	.729
	Group * SAH Amount	.525	.812
Within Subjects	Time	2.707	.018
	Time * Group	3.233	.006
	Time * SAH Amount	1.497	.189
	Time * Group * SAH Amount	1.326	.257

SAH = subarachnoid hemorrhage

Figure 10: Interaction Effect of SAH Amount x Group on Cognitive Index Scores



SAH = subarachnoid hemorrhage

Table 48: Anterior Interhemispheric Fissure SAH Multivariate Results. (DF = 7,53).

Effect		F	Sig.
Between Subjects	Group	6.770	.000
	Anterior Interhemispheric Fissure	1.769	.113
	Group * Anterior Interhemispheric Fissure	1.403	.224
Within Subjects	Time	2.656	.020
	Time * Group	3.049	.009
	Time * Anterior Interhemispheric Fissure	1.361	.241
	Time * Group * Anterior Interhemispheric Fissure	1.639	.145

SAH = subarachnoid hemorrhage

Table 49: Right Lateral Sylvian Fissure Multivariate Results. (DF = 7,53).

Effect		F	Sig.
Between Subjects	Group	6.465	.000
	Right Lateral Sylvian Fissure	1.247	.294
	Group * Right Lateral Sylvian Fissure	1.021	.428
Within Subjects	Time	3.016	.010
	Time * Group	3.103	.008
	Time * Right Lateral Sylvian Fissure	1.457	.203
	Time * Group * Right Lateral Sylvian Fissure	1.422	.216

Table 50: Left Lateral Sylvian Fissure Multivariate Results.

Effect		F	Sig.
Between Subjects	Group	6.897	.000
	Left Lateral Sylvian Fissure	.772	.613
	Group * Left Lateral Sylvian Fissure	.853	.549
Within Subjects	Time	2.711	.018
	Time * Group	3.018	.010
	Time * Left Lateral Sylvian Fissure	.671	.696
	Time * Group * Left Lateral Sylvian Fissure	.906	.509

Table 51: Right Basal Sylvian Fissure Multivariate Results. (DF = 7, 53).

Effect		F	Sig.
Between Subjects	Group	6.195	.000
	Right Basal Sylvian Fissure	1.467	.199
	Group * Right Basal Sylvian Fissure	1.108	.372
Within Subjects	Time	2.945	.011
	Time * Group	3.185	.007
	Time * Right Basal Sylvian Fissure	1.568	.165
	Time * Group * Right Basal Sylvian Fissure	1.360	.242

Table 52: Left Basal Sylvian Fissure Multivariate Results. (DF = 7, 53).

Effect		F	Sig.
Between Subjects	Group	6.331	.000
	Left Lateral Sylvian Fissure	.314	.945
	Group * Left Lateral Sylvian Fissure	.569	.778
Within Subjects	Time	3.083	.008
	Time * Group	3.006	.010
	Time * Left Lateral Sylvian Fissure	.631	.728
	Time * Group * Left Lateral Sylvian Fissure	.953	.475

Table 53: Right Supracellar Cistern Multivariate Results. (DF = 7, 53).

Effect		F	Sig.
Between Subjects	Group	6.338	.000
	Right Supracellar Cistern	1.307	.265
	Group * Right Supracellar Cistern	.335	.934
Within Subjects	Time	2.672	.019
	Time * Group	3.228	.006
	Time * Right Supracellar Cistern	.869	.537
	Time * Group * Right Supracellar Cistern	.582	.768

Table 54: Left Supracellar Cistern Multivariate Results. (DF = 7, 53).

Effect		F	Sig.
Between Subjects	Group	6.535	.000
	Left Supracellar Cistern	.550	.793
	Group * Left Supracellar Cistern	.331	.936
Within Subjects	Time	2.795	.015
	Time * Group	3.072	.009
	Time * Left Supracellar Cistern	.810	.583
	Time * Group * Left Supracellar Cistern	.694	.676

Table 55: Right Ambient Cistern Multivariate Results. (DF = 7, 53).

Effect		F	Sig.
Between Subjects	Group	6.274	.000
	Right Ambient Cistern	.928	.493
	Group * Right Ambient Cistern	.675	.692
Within Subjects	Time	2.667	.019
	Time * Group	3.410	.004
	Time * Right Ambient Cistern	.608	.747
	Time * Group * Right Ambient Cistern	1.629	.147

Table 56: Left Ambient Cistern Multivariate Results. (DF = 7, 53).

Effect		F	Sig.
Between Subjects	Group	6.249	.000
	Left Ambient Cistern	.450	.866
	Group * Left Ambient Cistern	.526	.811
Within Subjects	Time	2.870	.013
	Time * Group	2.967	.011
	Time * Left Ambient Cistern	.731	.647
	Time * Group * Left Ambient Cistern	.899	.514

Table 57: Quadrigeminal Cistern Multivariate Results. (DF = 7, 52).

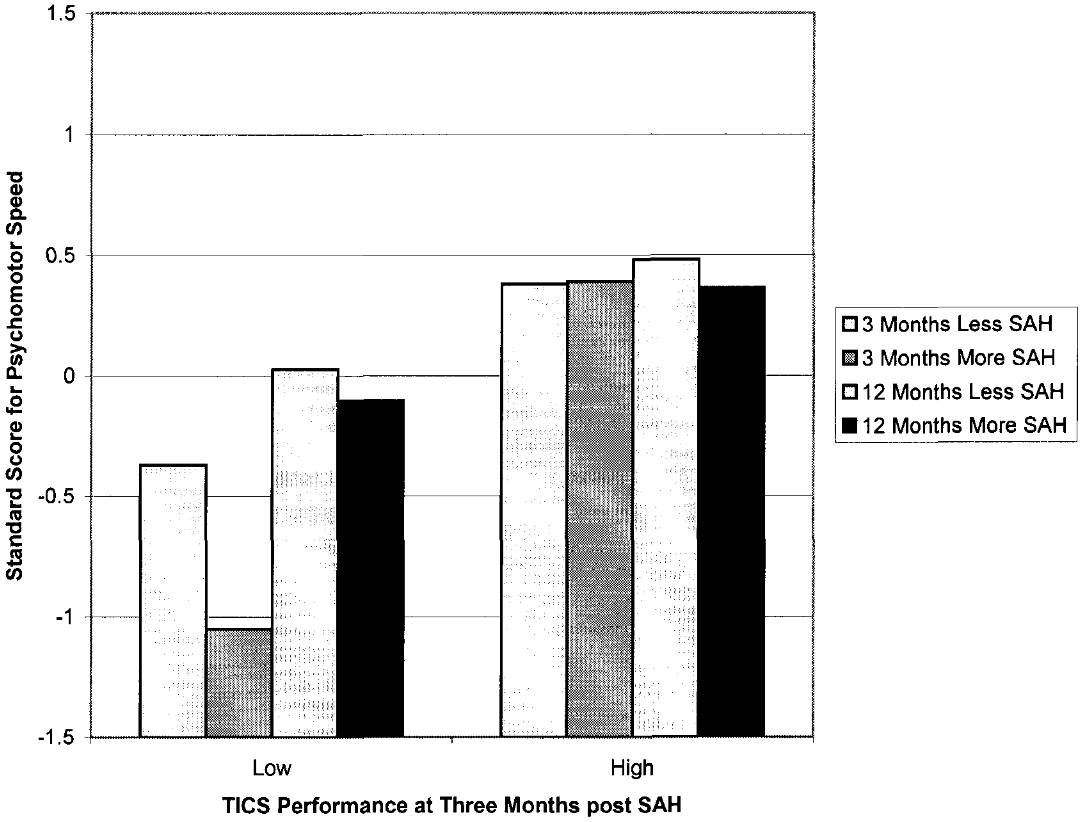
Effect		F	Sig.
Between Subjects	Group	5.638	.000
	Quadrigeminal Cistern	2.657	.020
	Group * Quadrigeminal Cistern	.906	.509
Within Subjects	Time	3.209	.007
	Time * Group	3.990	.001
	Time * Quadrigeminal Cistern	.823	.572
	Time * Group * Quadrigeminal Cistern	2.659	.020

Table 58: Univariate Results for the Effects of SAH in the Quadrigeminal Cistern. (DF = 1, 58).

	Main Effect of SAH in the Quadrigeminal Cistern		Three-way Interaction Effect Between Time x Group x SAH in the Quadrigeminal Cistern	
Measure	F	Sig.	F	Sig.
Attention / Concentration	13.190	.001	.868	.355
Visuospatial Skills	1.177	.282	1.338	.252
Psychomotor Speed	2.159	.147	6.230	.015
Verbal Memory	1.876	.176	.155	.695
Language	.003	.953	10.150	.002
Visual Memory	2.222	.141	.010	.923
Executive Functions	.113	.738	.244	.623

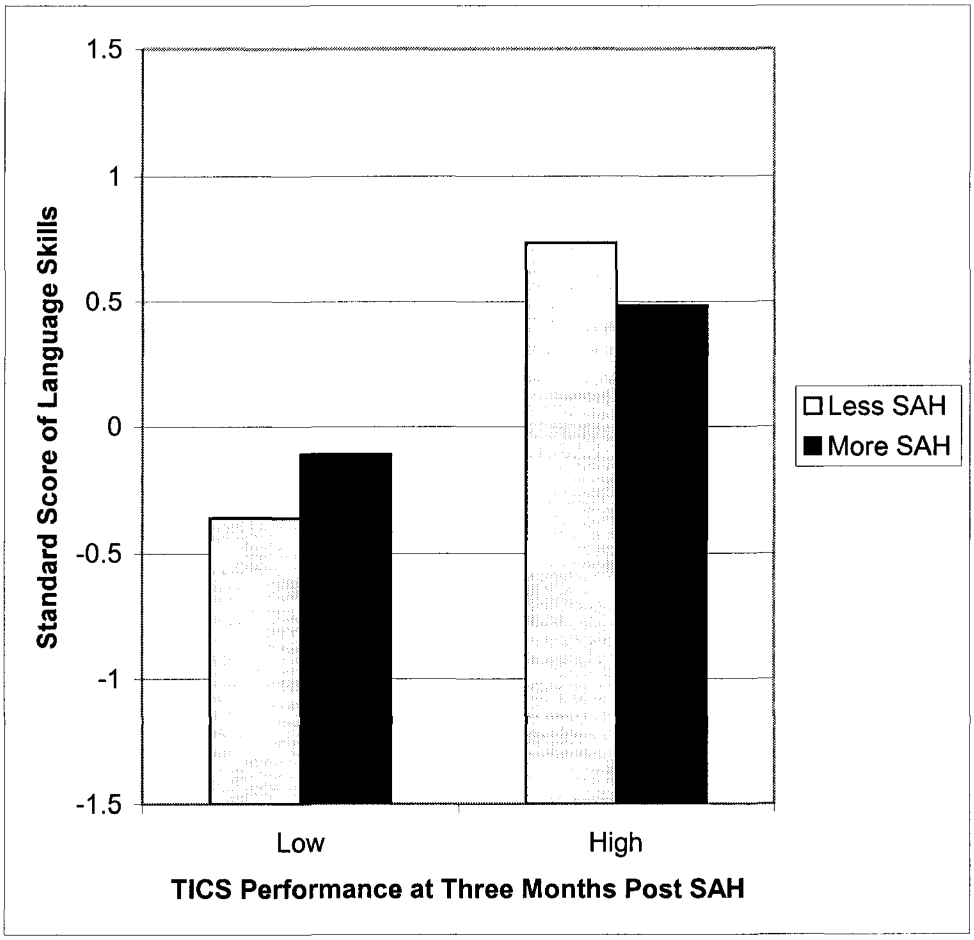
SAH = subarachnoid hemorrhage

Figure 11: Three Way Interaction Effect Between Time x Group x SAH in the Quadrigeminal Cistern on Psychomotor Speed



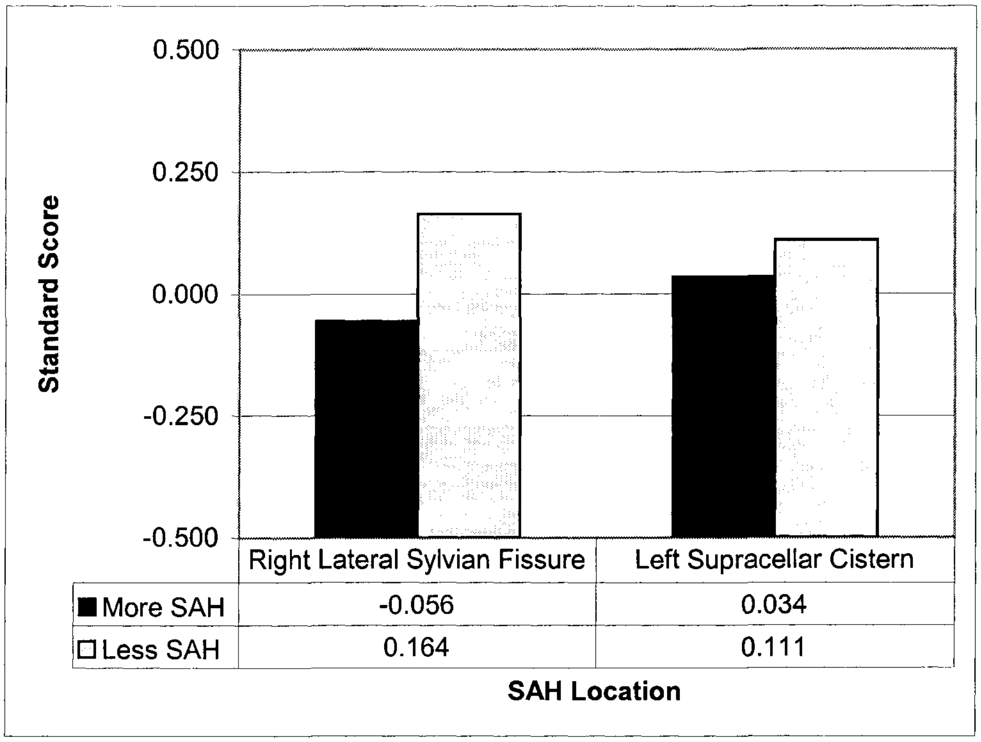
SAH = subarachnoid hemorrhage, TICS = Telephone Interview for Cognitive Status

Figure 12: Three Way Interaction Effect Between Time x Group x SAH in the Quadrigeminal Cistern on Language Skills



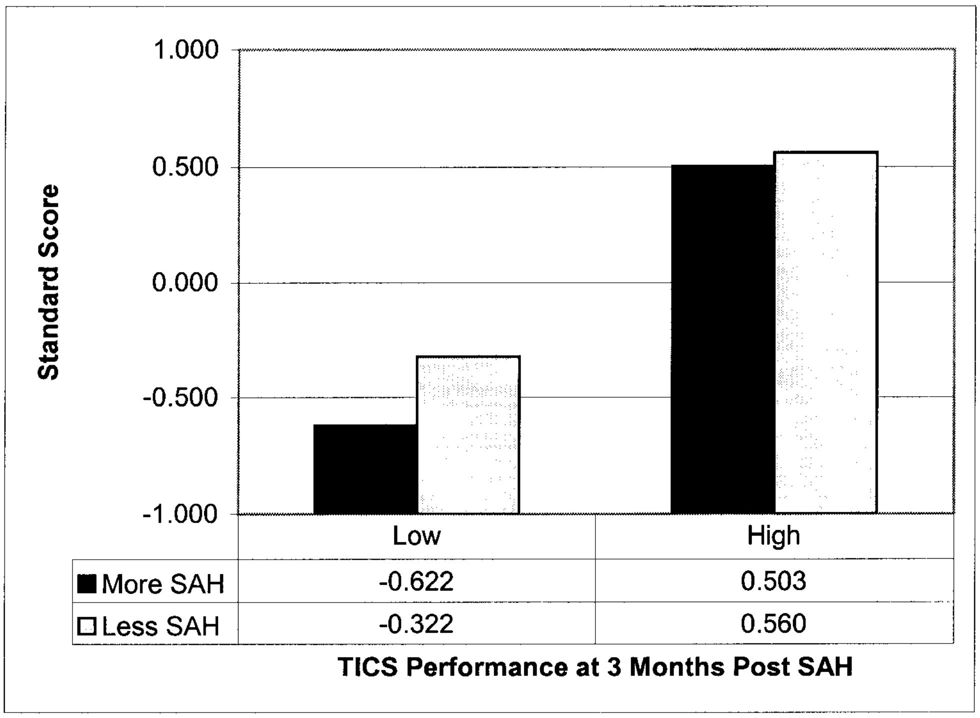
SAH = subarachnoid hemorrhage, TICS = Telephone Interview for Cognitive Status

Figure 13: Main Effects of SAH Location on Cognition



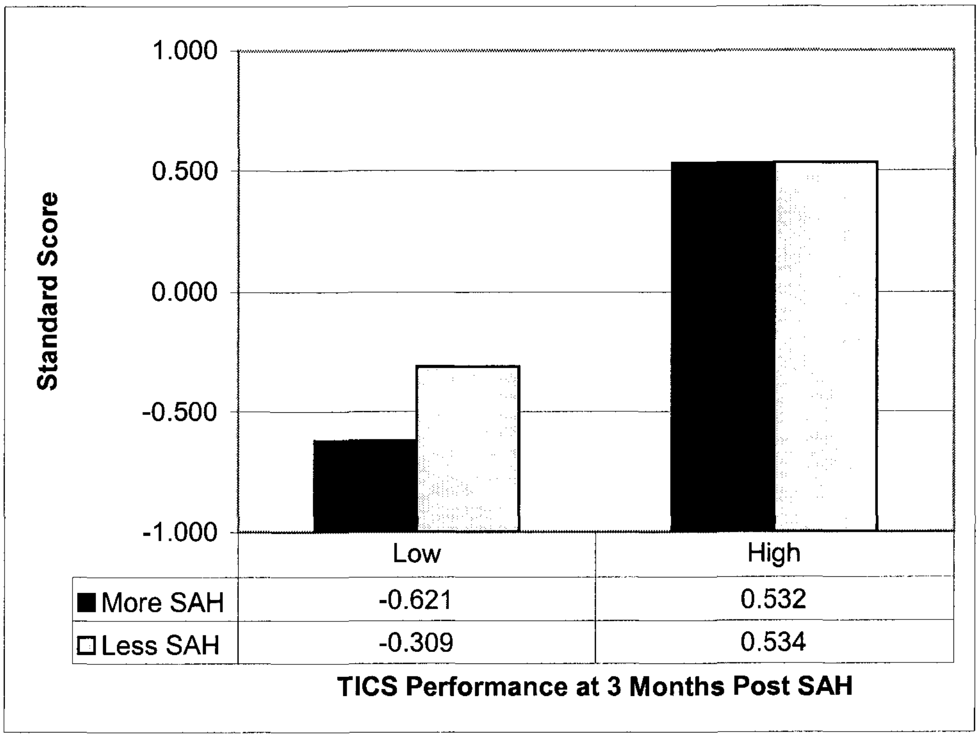
SAH = subarachnoid hemorrhage

Figure 14: Interaction Effect of Group x SAH in Right Basal Sylvian Cistern



SAH = subarachnoid hemorrhage, TICS = Telephone Interview for Cognitive Status

Figure 15: Interaction Effect of Group x SAH in Right Ambient Cistern



SAH = subarachnoid hemorrhage, TICS = Telephone Interview for Cognitive Status

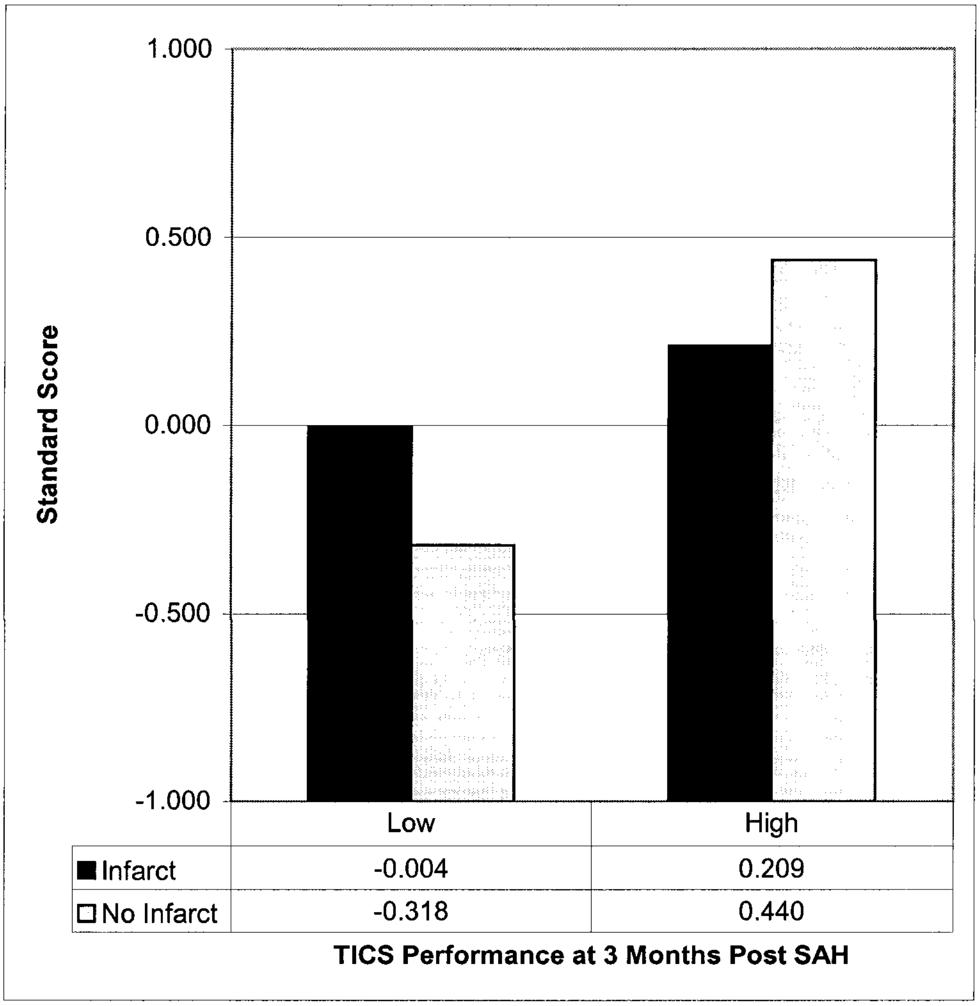
Table 59: Multivariate Results for Infarct Presence. (DF = 7, 54)

Effect		F	Sig.
Between Subjects	Group	8.540	.000
	Infarct	1.338	.251
	Group * Infarct	3.495	.004
Within Subjects	Time	2.606	.022
	Time * Group	2.254	.044
	Time * Infarct	1.518	.181
	Time * Group * Infarct	1.432	.212

Table 60: Univariate Results for Infarct Presence. (DF = 1, 60)

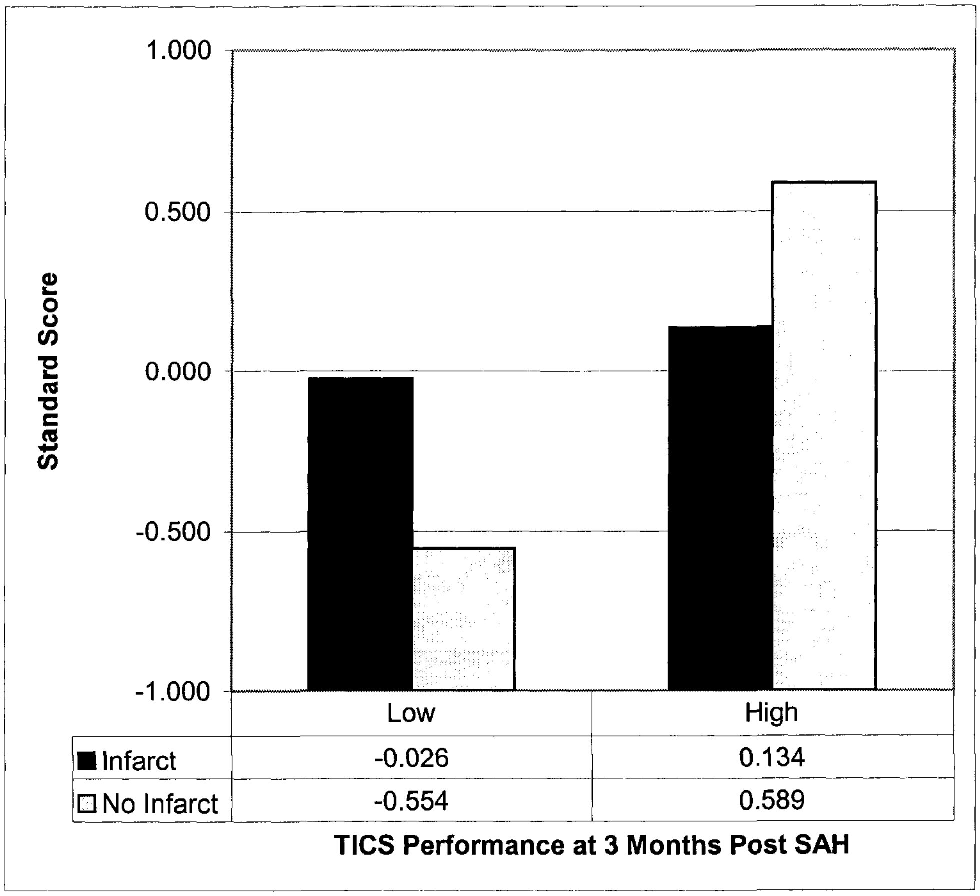
Measure	F	Sig.
Attention / Concentration	10.389	.002
Visuospatial Skills	12.637	.001
Psychomotor Speed	2.752	.102
Verbal Memory	.442	.509
Language	.039	.843
Visual Memory	2.976	.090
Executive Functions	1.624	.207

Figure 16: Group by Infarct Interaction Effect on Attention / Concentration



SAH = subarachnoid hemorrhage, TICS = Telephone Interview for Cognitive Status

Figure 17: Group by Infarct Interaction Effect on Visuospatial Skills



SAH = subarachnoid hemorrhage, TICS = Telephone Interview for Cognitive Status

Table 61: Multivariate Results for Vasospasm for Seven Cognitive Domains (DF = 7, 49).

Effect		F	Sig.
Between Subjects	Group	2.587	.024
	Vasospasm	.926	.495
	Group * Vasospasm	1.092	.383
Within Subjects	Time	5.843	.000
	Time * Group	1.244	.298
	Time * Vasospasm	.811	.583
	Time * Group * Vasospasm	.519	.816

Table 62: Multivariate Results for Vasospasm for Cognitive Index Score (DF = 1, 66).

	F	P
Vasospasm	.335	.565
Vasospasm x Group	.185	.669
Vasospasm x Time	.707	.403
Vasospasm x Group x Time	.015	.902

Table 63: Multivariate Results for Clinical Grade. (DF = 7, 54).

Effect		F	Sig.
Between Subjects	Group	5.742	.000
	Clinical Grade	1.073	.393
	Group * Clinical Grade	.823	.573
Within Subjects	Time	2.860	.013
	Time * Group	2.881	.012
	Time * Clinical Grade	.904	.511
	Time * Group * Clinical Grade	1.091	.382

Table 64: Multivariate Results for Cerebral Edema. (DF = 7, 54).

Effect		F	Sig.
Between Subjects	Group	5.090	.000
	Cerebral Edema	.667	.699
	Group * Cerebral Edema	.937	.486
Within Subjects	Time	3.118	.008
	Time * Group	3.001	.010
	Time * Cerebral Edema	4.896	.000
	Time * Group * Cerebral Edema	1.339	.250

Table 65: Univariate Results for the Interaction Effect of Cerebral Edema and Time. (DF = 1, 60).

Measure	F	Sig.
Attention / Concentration	.010	.920
Visuospatial Skills	13.049	.001
Psychomotor Speed	2.242	.140
Verbal Memory	.039	.844
Language	3.529	.065
Visual Memory	6.237	.015
Executive Functions	3.479	.067

Figure 18: Interaction Effect of Cerebral Edema and Time on Visuospatial Skills

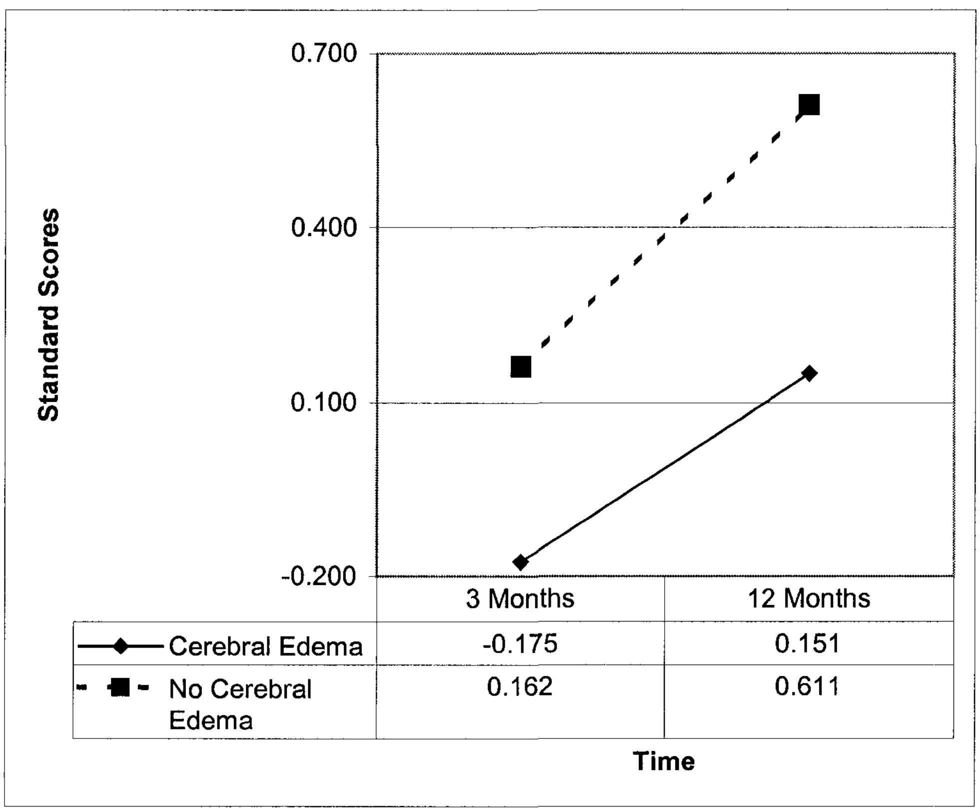


Figure 19: Interaction Effect of Cerebral Edema and Time on Visual Memory

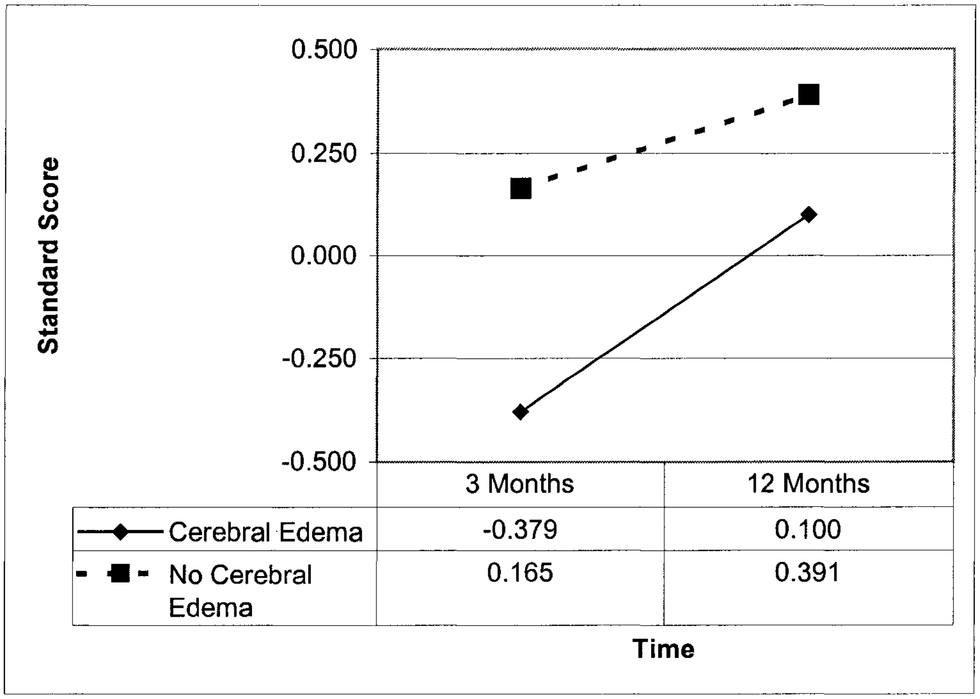


Figure 20: Recovery from Cerebral Edema

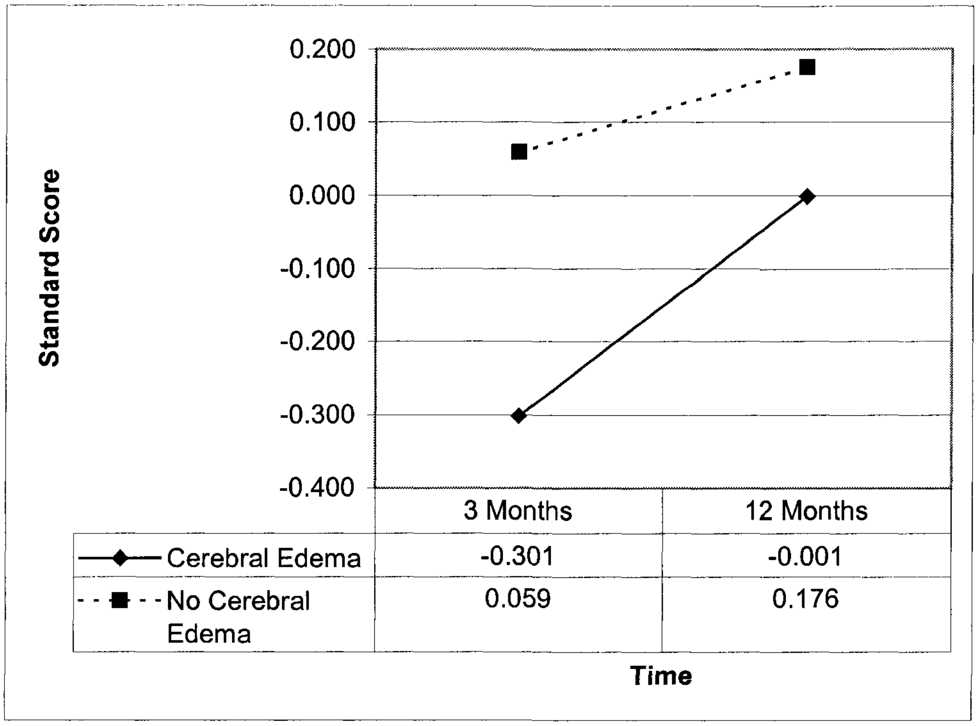


Table 66: Multivariate Results for Sex. (DF = 7, 54).

Effect		F	Sig.
Between Subjects	Group	4.992	.000
	Sex	2.679	.019
	Group * Sex	2.101	.059
Within Subjects	Time	3.160	.007
	Time * Group	2.131	.056
	Time * Sex	1.242	.297
	Time * Group * Sex	.446	.869

Table 67: Univariate Results for the Main Effect of Sex. (DF = 1, 60).

Measure	F	Sig.
Attention / Concentration	.353	.555
Visuospatial Skills	.856	.359
Psychomotor Speed	.129	.721
Verbal Memory	16.243	.000
Language	.001	.979
Visual Memory	4.517	.038
Executive Functions	.916	.342

Figure 21: Main Effect of Sex on Memory

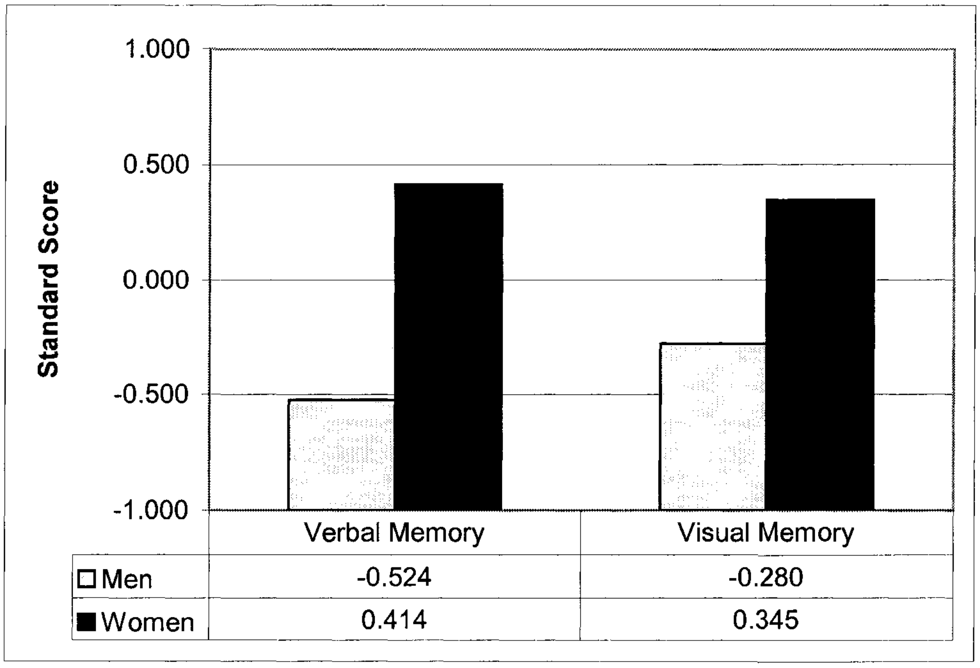


Table 68: Multivariate Results for Language. (DF = 7, 54).

Effect		F	Sig.
Between Subjects	Group	3.060	.009
	Language	3.445	.004
	Group * Language	1.252	.292
Within Subjects	Time	2.059	.064
	Time * Group	3.406	.004
	Time * Language	2.170	.051
	Time * Group * Language	1.105	.374

Table 69: Univariate Results for Language. (DF = 1, 60).

Measure	F	Sig.
Attention / Concentration	3.982	.051
Visuospatial Skills	4.551	.037
Psychomotor Speed	.856	.359
Verbal Memory	1.701	.197
Language	2.091	.153
Visual Memory	1.815	.183
Executive Functions	2.417	.125

Figure 22: Main Effect of Language on Visuospatial Skills

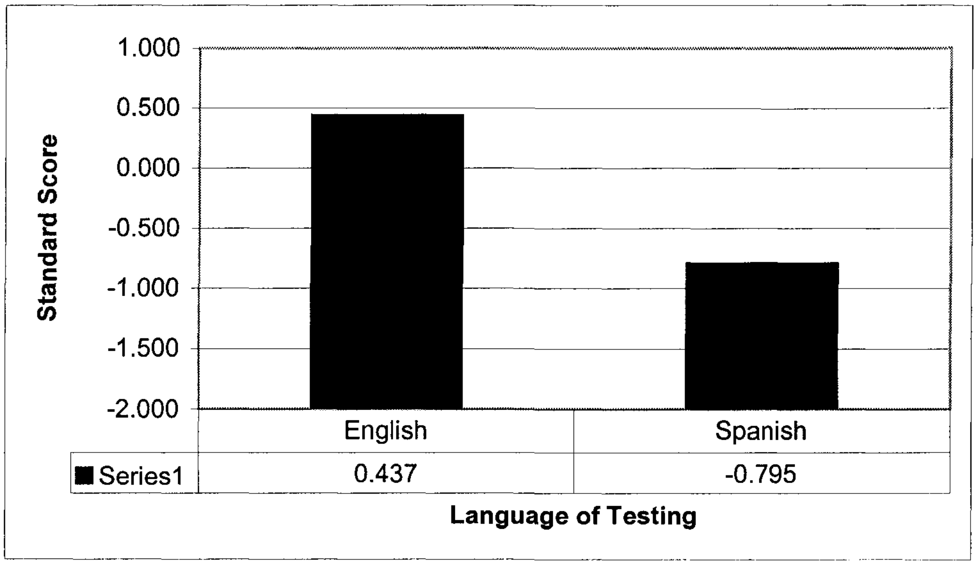


Table 70: Summary Table For Significant Results Of RM-MANCOVAs with Multivariate and Univariate F values.

Variable	Main Effect of Variable	Time x Variable	Group x Variable	Time x Group x Variable
Time (3 and 12 months)	2.77 Attention/ Concentration 4.75, Psychomotor Speed 6.41	NA	NA	NA
Group (High and Low TICS scores at 3 months)	5.86 All domains 6.50-30.06 and overall Cognitive Index 40.55	3.08 Psychomotor Speed 6.82, Verbal Memory 5.62	NA	NA
Age	4.09 Cognitive Index	NS	NS	NS
Sex	2.68 Verbal Memory 16.24; Visual Memory 4.52	NS	NS	NS
Language	3.45 Visuospatial Skills 4.55	NS	NS	NS
Etiology	NS	NS	NS	NS
Aneurysm Location	NS	NS	1.72 Executive Functions 4.13	NS
SAH Amount	NS	NS	5.09 Cognitive Index	NS
SAH Location	Attention / Concentration 13.19 (Quadrigeminal Cistern 2.66); Cognitive Index (Right Lateral Sylvian Fissure 4.44, Left Supracellar Cistern 6.08)	NS	Cognitive Index (Right Basal Sylvian Fissure 5.73, Right Ambient Cistern 4.82)	Psychomotor Speed 6.23 (Quadrigeminal Cistern 2.66); Language Skills 10.15 (Quadrigeminal Cistern 2.66)
Infarct Presence	NS	NS	3.50 Attention / Concentration 10.39; Visuospatial Skills 12.64	NS
Vasospasm	NS	NS	NS	NS

Clinical Grade	1.40 Cognitive Index	NS	NS	NS
Cerebral Edema	NS	4.90 Visuospatial Skills 13.05; Visual Memory 6.24; Cognitive Index 5.85	NS	NS

NA = Not applicable. NS = Not significant.

Table 71: Overall Factor Structure of Combined Factor Analyses

A Priori Domains	Neuro-psychological Test Scores	Atten-tion	Verbal Mem-ory	Speed	Visual Skills			
					Speed	Construc-tion	Visual Mem.	Executive Functions
Attention	Digit Span Forwards	*						
	Digit Span Backwards	*						
	Digit Symbol				*			
	VSAT Time	*						
	Cal Cap Attention			*				
Language	BNT	*						
	Token Test	*						
Verbal Memory	CVLT Total		*					
	CVLT Long Delay Free Recall		*					
	CVLT Recognition Hits		*					
Speed	Cal CAP Simple RT			*				
	Trails A Time				*			
Visual Skills	Block Design					*		
	WMSR VR Copy					*		
	RCFT Copy					*		

Visual Memory	WMSR VR II						*	
	RCFT Delayed Recall						*	
Executive Functions	MCST Total Correct							*
	MCST % PE							*
	Trails B Time				*			

VSAT = Verbal Serial Attention Test, Cal CAP = California Computerized Assessment Package, BNT = Boston Naming Test, CVLT = California Verbal Learning Test, RT = reaction time, WMS-R= Wechsler Memory Scale – Revised, VR = Visual Reproduction, RCFT = Rey Complex Figure Test, MCST = Modified Card Sorting Test, PE = perseverative errors

Table 72: Aneurysm Location by Sex Cross Tabulation

		Sex		Total
		Male	Female	
Frontal	Count	11	7	18
	Expected Count	5.3	12.7	18.0
	% Within Aneurysm Location 4	61.1%	38.9%	100.0%
	% Within Sex	50.0%	13.2%	24.0%
Right	Count	4	20	24
	Expected Count	7.0	17.0	24.0
	% Within Aneurysm Location 4	16.7%	83.3%	100.0%
	% Within Sex	18.2%	37.7%	32.0%
Left	Count	5	14	19
	Expected Count	5.6	13.4	19.0
	% Within Aneurysm Location 4	26.3%	73.7%	100.0%
	% Within Sex	22.7%	26.4%	25.3%
Posterior	Count	2	12	14
	Expected Count	4.1	9.9	14.0
	% Within Aneurysm Location 4	14.3%	85.7%	100.0%
	% Within Sex	9.1%	22.6%	18.7%
Total	Count	22	53	75
	Expected Count	22.0	53.0	75.0
	% Within Aneurysm Location 4	29.3%	70.7%	100.0%
	% Within Sex	100.0%	100.0%	100.0%

Table 73: Cognitive Index Scores as a Function of Cognitive Remediation

Time	Group (3 Month TICS Score)	Cognitive Remediation	Mean	Std. Deviation	N
3m Months	Low	No	-.4856	.5045	30
		Yes	-.6618	.6126	9
		Total	-.5263	.5281	39
	High	No	.4348	.4361	36
		Yes	.4089	.3607	5
		Total	.4316	.4236	41
	Total	No	.01639	.6551	66
		Yes	-.2794	.7446	14
		Total	-.0354	.6762	80
12 Months	Low	No	-.4081	.5854	30
		Yes	-.2846	.7337	9
		Total	-.3796	.6145	39
	High	No	.6037	.4264	36
		Yes	.6885	.4945	5
		Total	.6141	.4293	41
	Total	No	.1438	.7131	66
		Yes	.0629	.8004	14
		Total	.1296	.7244	80

Table 74: Multivariate Results for the Effects of Cognitive Remediation of Cognitive Domains (DF = 7, 54).

Effect		F	Sig.
Between Subjects	Group	4.573	.000
	Cognitive Remediation	1.089	.384
	Group * Cognitive Remediation	2.620	.021
Within Subjects	Time	2.517	.026
	Time * Group	1.863	.094
	Time * Cognitive Remediation	1.085	.386
	Time * Group * Cognitive Remediation	1.496	.188

Figure 23: Cognitive Remediation x Group on Visuospatial Skills

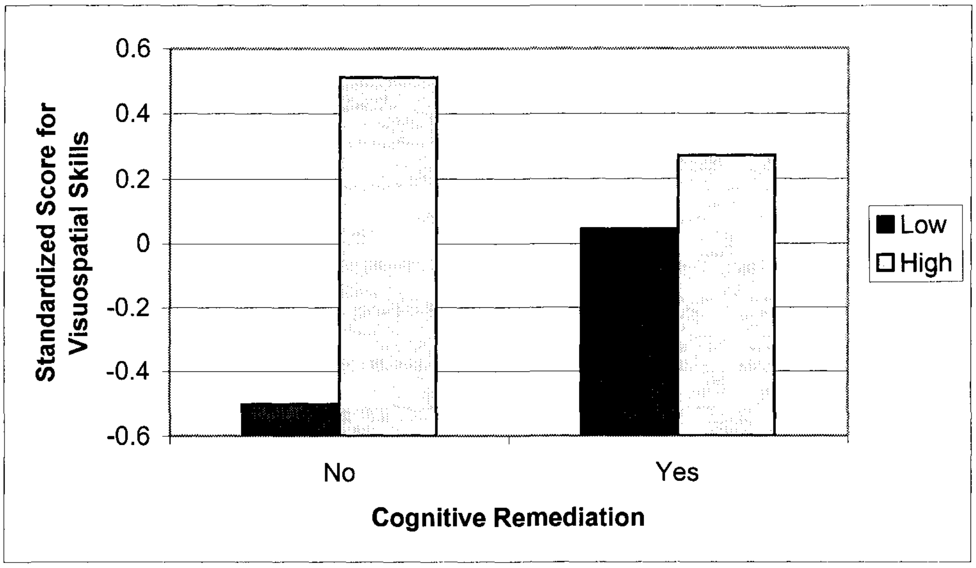
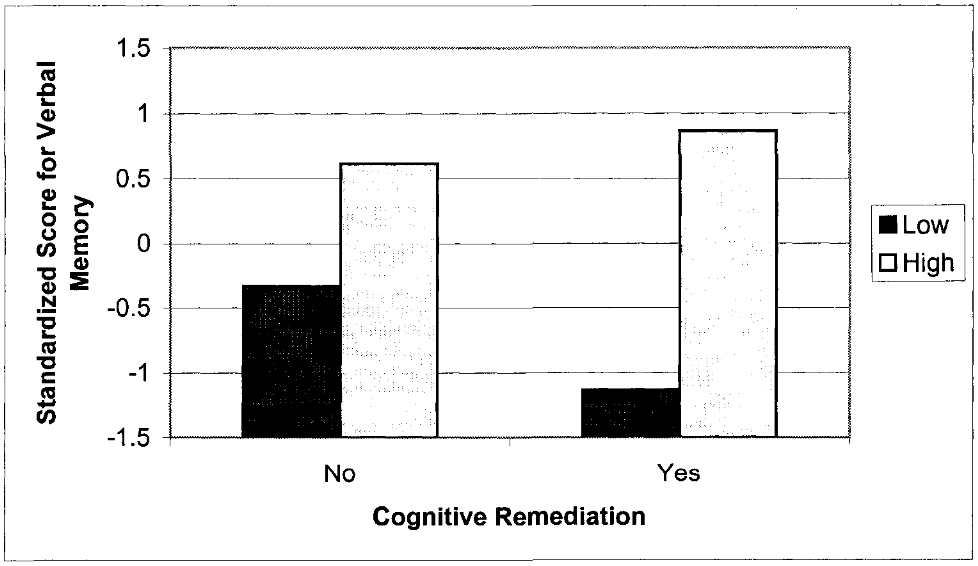


Figure 24: Cognitive Remediation x Group on Verbal Memory Skills



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