INFORMATION PROCESSING SPEED IMPAIRMENT AFTER STROKE, A DESCRIPTIVE STUDY

Susan Alderman

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INFORMATION PROCESSING SPEED IMPAIRMENT
AFTER STROKE, A DESCRIPTIVE STUDY

A DISSERTATION
SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF SCIENCE IN NURSING

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT HOUSTON
SCHOOL OF NURSING

BY
SUSAN ALDERMAN MSN RN

MAY, 2016
To the Dean for the School of Nursing:

I am submitting a dissertation written by Susan Alderman and entitled "Information Processing Speed Impairment after Stroke, A Descriptive Study." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Nursing.

We have read this dissertation and recommend its acceptance:

Dr. Terri Armstrong, Committee Chair

Accepted

Dean for the School of Nursing
Acknowledgements

Support for the research done during this program was generously given by the Speros Martel Endowment for the Aging, the William Randolph Hearst Endowed Nursing Scholarship, and the Joseph C. and Selenia E. Valley Memorial Scholarship in Geriatric Nursing. Support for the pursuit of scholarship and research through completion of the PhD program was generously provided by the Partners Scholarship at the University of Texas, School of Nursing.

I would like to acknowledge and thank God for His consistent and strong support. My deepest thanks to my father, LA Alderman, for being the first person to believe in me, and to my mother, Charlene Alderman, for her strength and wisdom after losing him during the first semester of the program. I thank my friends, specifically, Elena Dargan for her faithful encouragement and amazing editorial skills and my colleagues and peers Julie Walker and Maaidah Algamdi for their insight and professionalism.

I would like to acknowledge Dr. Sean Savitz for his vision, support, and encouragement. He is an exemplary, caring healer and a rigorous researcher; he is someone I strive to emulate. My thanks to Dr. Terri Armstrong for her knowledge, encouragement, and ability to rein me in without squelching my enthusiasm. Thanks are due to Dr. Nancy Bergstrom, Dr. Josh Breier, and Dr. Geri Wood for their guidance on this project. They are superior educators and the sacrifice of their time and effort is greatly appreciated. I would like to express gratitude to Dr. Nikhil Padhye for his patience and skill in teaching biostatistics and to Liz Vera Bolanos for her help in the data analysis on this project.
Abstract

Susan Alderman, MSN, RN

Information Processing Speed Impairment after Stroke,
A descriptive study (IPS)

May, 2016

Cognitive impairment is any impairment of mental abilities and processes related to knowing, specifically capacities for attending, remembering, and reasoning. Currently, there is not a universally accepted model of cognitive recovery. An elemental cognitive function, information processing speed (IPS) is defined as the time needed to complete a cognitive task or the amount of cognitive work that can be done within a finite amount of time. While there is agreement IPS is an essential function, there is no universally agreement on how IPS interacts with other cognitive functions, how frequently IPS becomes impaired, or the speed or magnitude of recovery. The aim of this study is to describe the natural history, frequency, and severity of IPS impairment in patients with recent mild to moderate stroke. A review of cognitive and self-care literature led to a conceptual synthesis that defined patient-centered cognitive recovery in stroke (PCRS) as a transitional state in which a person’s cognitive capacities can be modified by their personal capabilities and resources to approach or achieve their pre-injury level of cognitive health. As an essential cognitive function, the trajectory of spontaneous recovery of IPS was observed to more fully understand IPS impairment. Pilot work indicated IPS impairment in 97% of patients with acute stroke. Further, it indicated early cognitive research could be performed within 72 hours of acute stroke and subjects were able to complete the cognitive battery. In this exploratory study, cognitive measurements for IPS and quality of life (QOL) questionnaires explored association between IPS
impairment, stroke severity and QOL. Longitudinal data was obtained from 30 subjects with mild or moderate stroke, at three time points. Analysis indicated frequency and severity of IPS impairment was not associated of stroke severity and IPS impairment persisted to the 90-day endpoint in 79% of subjects. A linear mixed model regression indicated a relationship between IPS impairment and Applied Cognition Executive Function QOL scores. Persistent IPS impairment, regardless of stroke severity, is associated with poor QOL, demonstrating the need for a program of research to better understand this essential cognitive function and its impact on cognitive recovery. An exploratory evaluation of the adult short form Neuro-QOL as a unified scale was performed; total score was the sum of the 13 short form domain scores. Independent samples t-tests indicated the Neuro-QOL total score did not distinguishing between subjects based on stroke severity but less severe IPS impairment was associated with better QOL total scores. This preliminary evaluation encourages further research on a totaled Neuro-QOL in this population.
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Summary of Study

This dissertation consists of two sections: the dissertation proposal in NIH format with appendixes; and a manuscript entitled “Information Processing Speed after Stroke (IPS), A Descriptive Study”. The manuscript presents findings from original research approved by the Institutional Review Board on the University of Texas Health Science Center at Houston.

The overall objective was to describe the natural history of IPS impairment, namely its frequency, severity, and impact on quality of life (QOL) in acute to subacute stroke, by stroke severity. The specific aims of the longitudinal research were to determine the frequency and severity of IPS impairment in mild stroke and to evaluate the association between severity of IPS impairment and QOL in survivors with mild stroke compared to moderate stroke at 3 months.

The Patient-centered Cognitive Recovery in patients with Stroke (PCRS) model, developed during a concept synthesis on cognitive recovery, guided this research. The PCRS model defines cognitive recovery as a transitional state in which a person’s cognitive capacities can be modified by personal capabilities and environments to approach or achieve the person’s pre-injury level of cognitive health. An elemental cognitive function, information processing speed, has been identified as hindering performance of other cognitive functions such as memory, attention and executive function. Therefore, a better understanding of IPS impairment presentation and spontaneous recovery was needed; before an intervention to improve IPS function can be instituted. This study observed changes in IPS and memory during the acute and subacute phase of cognitive recovery and evaluated the impact of IPS impairment on QOL.
The initial pilot work on this study involved 10 subjects and focused on the feasibility of performing cognitive research in the acute setting. The dearth of acute phase cognitive research required performance of a pilot study to verify adequate availability of subjects with mild or moderate stroke, a significant amount of subjects could complete the cognitive testing, and subjects would not be negatively impacted by the burden of cognitive testing during their acute recovery phase. This phase of research indicated the protocol was adequate to provide sufficient data to answer the research questions and the study was continued.

The next phase of the research involved repeating cognitive testing in up to 30 subjects at two additional time points, three weeks and twelve weeks after stroke. A total of 42 subjects were enrolled and completed the baseline or in hospital visit. However, 12 subjects did not complete the three study visits and their data was not included in analysis.

Hospital patient census for the UT stroke service were screened daily for eligible patients. Based on medical records and discussions with healthcare providers, eligible patients were approached for a consent discussion. Prior to enrollment, a proxy, either family member or friend, verified an absence of pre-existing cognitive impairment and the potential subject was administered the Symbol Digit Modalities Test (SDMT). If the subject failed the SDMT, they were invited to participate. Multiple settings were used to perform the study. The initial visit was performed while the subject was admitted for acute stroke at the Memorial Hermann-TMC hospital. The two follow up visits were performed at testing centers, inpatient units, or at the subject’s residence. Strict safety procedures were followed to ensure safety of the investigator when testing was performed.
in subjects’ residences; including pre and post telephone calls to a monitor and use of a safety phrase at completion of each visit.

Collected data was transcribed to a case report form and tabulated onto an excel spread sheet. Once collected, 100% of the data was evaluated for quality of transcribed and tabulated data. Data analysis was performed by a statistician under the supervision of the investigator. Descriptive statistics were used to describe the sample. Independent t-tests indicated changes in frequency and severity of IPS impairment. Linear mixed method regression was used to determine lack of relationship between IPS impairment and stroke severity. Mixed methods did indicate a relationship between IPS impairment and poor QOL in relationship to executive function. These results are described in the manuscript, “Information Processing Speed Impairment after Stroke, A Descriptive Study”. This study is a preliminary step in a program of research to understand cognitive recovery after stroke. The planned research program will focus on factors that impede cognitive recovery and the testing of interventions to speed cognitive recovery.
INFORMATION PROCESSING SPEED IMPAIRMENT AFTER STROKE,
A DESCRIPTIVE STUDY

(IPS)

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MAY, 2015
Introduction

In 2010, there were seven million survivors of stroke in the USA (Center for Disease Control, 2013) with 65% developing cognitive impairments after stroke. With the current 3% prevalence of stroke there will be 13 million survivors of stroke in 2030 and 8.5 million of them will develop cognitive impairments (CI) (Rogers et al., 2011). For newly impaired survivors, 70% suffer from information processing speed (IPS) impairment; a particular cognitive impairment that will likely persist regardless of routine rehabilitation care (Lesniak, Bak, Czepiel, Seniow & Czlonkowska, 2008). IPS impairment slows the ability to process information, impacting instrumental activities of daily living (IADL), such as the ability to make decisions, understand conversations, pay bills, cook, or drive a car (Winkens, 2009). IPS impairment becomes most apparent after the discharge home, when patients frequently expect to function at a pre-stroke level. The seminal work by Salthouse (1996) indicated the impairment would be most noticeable during activities which are new to the patient or have an element of time pressure with a need for continuous and conscious processing of information. A clearer understanding of IPS impairment in acute stroke is required to identify treatment and improve quality of life. Little research has been done regarding IPS impairment after stroke and none related to IPS impairment progression in acute to sub-acute stroke, specifically the period up to three months after a stroke. Specific measurements for cognitive assessment are not routinely performed on the acute stroke population. Survivors of mild stroke, in particular, are discharged with limited rehabilitation, on the assumption that the stroke will have minimal residual effect.
The purpose of this observational study is to describe the natural history, frequency, and severity of IPS impairment in patients with recent mild to moderate stroke. The primary hypothesis of the study is that people with new mild strokes will experience IPS impairment at an equal or greater rate than those identified by Lesnik et al. (2008), in the overall stroke population. Additionally, IPS impairment will affect quality of life regardless of routine rehabilitation care. The results of this study will help in better understanding the feasibility of early IPS testing after stroke, if IPS impairment is associated with stroke severity and whether impaired IPS immediately after an ischemic stroke improves with routine acute and rehabilitation care. Determining the severity of IPS impairment in mild as well as moderate stroke will impact a significant amount of undertreated people. A well-supported understanding of how it presents is necessary before we can begin to formulate effective treatments.

Specific Aims

**Specific Aim 1:** To determine the frequency and severity of IPS impairment, as evidenced by abnormal Symbol Digit Modalities Test (SDMT) values, in mild stroke (NIHSS \( \leq 5 \)) compared to moderate stroke (NIHSS >5) at three time points.

**Hypothesis:** The rate of frequency and severity of IPS impairment will be similar in mild and moderate stroke at each time point, < 72 hours, 3 weeks and 12 weeks post stroke, as demonstrated by a medium effect size. Abnormal SDMT scores are: male a written score less than 51 (oral: < 61) and female a written score less than 54 (oral: < 62).

**Specific Aim 2:** To evaluate the association between severity of IPS impairment and quality of life in mild stroke (NIHSS \( \leq 5 \)) compared to moderate stroke (NIHSS >5) survivors at 3 months.
**Hypothesis:** There will be a significant correlation between severity of IPS impairment and quality of life indicators, independent of stroke-severity group membership.

**Specific Aim 3:** To evaluate the correlation between IPS impairment and four subsections of the Neuro-QOL compared to the overall Neuro-QOL score in mild survivors of stroke at 3 months.

**Hypothesis:** There will be a significant correlation between IPS impairment in mild stroke and subsections of the Neuro-QOL (Depression, Applied Cognition-general concerns, Applied Cognition-Executive Function and Positive Affect & Well-Being) when compared to the overall Neuro-QOL score.

**Background and Significance**

The proposed project is significant in that several knowledge gaps will be addressed:

- Patients with mild to moderate strokes can be impacted by unrecognized IPS impairment.
  - The frequency of IPS impairment is unknown in acute to sub-acute stroke.
  - It is unknown if patients with moderate stroke experience more severe IPS impairment than patients with mild stroke.
- Untreated IPS impairment in patients with mild to moderate strokes can seriously impact IADLs and quality of life (QOL).
  - It is unknown if patients with mild stroke experience a significant reduction in QOL in association with IPS impairment.
The overall score of common post-stroke QOL measurement, Neuro-QOL, may not accurately reflect quality of life in patients with mild stroke.

- An understanding of the natural history of IPS impairment in acute to sub-acute stroke is necessary before research in QOL measurements or IPS treatment can be initiated.
- An understanding of IPS impairment severity in patients with mild stroke may stimulate research into defining criteria for acute medical treatment and rehabilitation.

**Specific Aim 1 Knowledge Gap: IPS impairment and stroke severity**

If processing speed is a fundamental component of the architecture of cognition as Kail and Salthouse (1994) suggest then it is important to evaluate IPS impairment in stroke based on three factors: IPS impairment theory, IPS and stroke severity, and recovery time. Little research has been completed on IPS impairment after mild acute stroke. Typically, research endpoints for cognitive impairment after mild stroke start at between 3-12 months’ post stroke (Makin, Turpin, Dennis & Wardlaw, 2013). In Lesniak et al. (2008) IPS impairment was identified in 70% of patients at the first study contact, three months’ post stroke. But preliminary work on the current study indicates IPS impairment after acute stroke may be 100% (see Preliminary Study: Summary of results).

**IPS impairment theory.**

Most information on IPS changes comes from research on aging and degenerative diseases such as multiple sclerosis (Chiaravalloti & DeLuca, 2008; Rebok et al., 2014). Treating IPS impairment in stroke must begin with defining it and understanding the mechanism of impairment. Martin & Bush (2008) defined IPS as the time required to
execute a cognitive task or the amount of work that can be completed within a finite period of time. It may be a mediating agent between working memory and executive function (Jobe et al., 2001), increasing the efficiency of our ability to perform critical specialized and common activities of daily living. Salthouse (1996) determined two mechanisms can affect processing speed, the Limited Time and Simultaneity mechanisms.

In the first mechanism, Limited Time, the injured brain takes longer to perform multi-step or complex tasks because the time needed to perform later-step operations continues to be used in the execution of early-step operations. This problem is most noticeable when there are external time pressures and the patient executes information processing too slowly to complete a task in given amount of time (Winkens, 2009). For example, a person does not apply the brakes on a car before running a stop sign because of extended time required to process information (sign recognition). This leads to failure to recognize a stop sign and take action within the necessary time limit.

In the second mechanism, Simultaneity, “information decreases in availability over time as a function of decay or displacement…the products of early processing may be lost or may have become inaccurate before later processing is ready to use it” (Winkens, 2009). Processing impairment becomes apparent when slow IPS results in displaced (lost) or inaccurate low-level information affecting higher-order cognitive processes. For example, extended processing time is used to understand lower-order information such as sign identification and the distance to the stop sign. By the time the patient has moved onto a higher order processing step, e.g. calculating how much braking
pressure to apply to ensure appropriate stopping, the distance information has decayed or been lost from short term memory.

**Stroke severity and IPS impairment.**

Stroke severity is defined by severity of impairment, as indicated by a range of 0-42 points, on the National Institute of Health Stroke Scale (NIHSS). A mild stroke has a NIHSS of \( \leq 5 \) (Smith et al., 2005) and moderate stroke score is 6-12. Typically, patients with stroke are not treated with thrombolytic unless their National Institute of Health Stroke Scale (NIHSS) is moderately elevated (>5), even if the patient presents early enough for treatment (Smith et al., 2005). Survivors of moderate stroke frequently have severe motor impairment including hemiplegia, aphasia, visual impairment or neglect. Mild survivors of stroke usually have no or minimal motor dysfunction, such as numbness, minor arm weakness, mild facial drooping or dysarthria.

Lacking obviously debilitating physical impairments, patients with mild stroke (NIHSS \( \leq 5 \)) may be experiencing inequity in healthcare. Mild survivors of stroke are often sent home after a short admission without significant rehabilitation or social adjustments because, per NIHSS criterion, they appear to be minimally effected by their stroke. However, the NIHSS, used to determine medical treatment, is not designed to measure cognition (Balucani & Levine, 2011).

Few survivors of stroke receive IPS assessment in the acute or sub-acute recovery phase. It has been assumed that a mild stroke leaves less residual cognitive impairments but research indicates that may not be accurate. Edwards et al. (2006) indicated 62% of patients with mild strokes were unable to return to work or previous other activities despite returning to full physical independence. IPS impairment affects every aspect of
our daily life including the ability to think clearly, make decisions, understand conversations, or driving a car. Early detection and treatment of impairment can slow or halt brain degeneration and improve outcomes (Al-Qazzaz et al., 2014).

**Recovery time.**

Another factor to be considered in IPS evaluation is recovery time. Neuroplasticity is a brain recovery process with a relatively flexible 1 to 4-week time window; certain conditions such as physical therapy (PT) may keep it open longer (Murphy & Corbett, 2009). Their animal studies indicate the optimal neuroplasticity window might expand for the injured brain, even as far out as 8 weeks. Neuroplasticity changes occur in respect to increased demands made on the brain during challenging physical or cognitive activities. Further, these studies indicate brain remodeling begins within days of brain injury, with a neuronal hyper-excitability period encouraging axonal growth occurring 1-3 days after stroke (Murphy & Corbett, 2009). Additional animal studies indicate the ideal period to begin to relearn lost skills is within 5 days after a stroke, when the brain is remodeling its neural circuitry, encoding new experiences, and enabling behavioral and functional changes (Biernaskie, Chernenko & Corbett, 2004: Kleim & Jones, 2008).

Some patients with mild to moderate strokes receive PT while others return home, without rehabilitation, and attempt to resume their previous lifestyle. Specific assessments for cognitive function are not routinely performed in acute stroke (Gottesman & Hillis, 2010) with little research beginning earlier than one-month post stroke. If a simple quick IPS assessment can be performed in the acute stage, then clinical treatment can be instituted for cognitive or functional impairment.
Specific Aim 2 Knowledge Gap: impact of stroke severity and IPS impairment on quality of life

Despite minimal motor impairment in mild strokes, complaints of poor quality of life may persist long after the stroke event. Carlsson, Moller & Blomstrand (2009) noted that few people with mild strokes were able to return to full time employment and 60% rated their quality of life as not good. Patients, with mild stroke, report persistent symptoms at three months including poor outcomes on disability scales (29%) (Edwards et al, 2006), decreased ability in employment activities (62%), decreased social activity (36%), and are less able to drive (18%) compared to before their stroke (Nedeltchev et al, 2007; Smith et al, 2011). For this study it is hypothesized that cognitive impairment, rather than physical consequences, results in the radical changes in the lives of mild stroke survivors.

Specific Aim 3 Knowledge Gap: correlation of IPS impairment to quality of life (QOL) sub-scales

Information gained from any trial depends on the quality of instruments measuring the data. The Stroke Specific Quality of Life scale (SS-QOL) and Neuro-QOL scale have undergone sufficient analysis to indicate that they are acceptable instruments to measure QOL in the general stroke population (Lai, Studenski, Duncan, & Perera, 2002; Perez et al., 2007). But both instruments dedicate significant weight to motor function items, which may not be impacted in mild stroke survivors. In general, these scales may not accurately measure QOL in patients with stroke with predominately-cognitive impairments. To assess QOL specifically in this population, those Neuro-QOL subsections most impacted by cognitive impairment will be compared to the overall
Neuro-QOL score. The pertinent Neuro-QOL subsections include Depression, Applied Cognition-general concerns, Applied Cognition-Executive Function and Positive Affect & Well-Being. The additional subsections include Anxiety, Fatigue, Sleep Disturbance, Participation in social roles, Satisfaction in social roles, Stigma, Upper and Lower body function.

**Preliminary Study**

**Purpose.**

A preliminary study was done to determine the feasibility of IPS testing after acute stroke and to determine if there were indications of an association between IPS impairment and stroke severity. The preliminary study also identified logistical and clinical challenges of cognitive testing within 72 hours of stroke.

**Summary of Results.**

Patients admitted to the Stroke Service (N=163) at a tertiary hospital were screened from 10/8/14 to 11/21/14. Ten subjects (6%) were qualified, enrolled, and assessed (see Table 1). Four preliminary study subjects (40%) had moderate strokes (NIHSS > 6). Five criteria accounted for 83% of exclusion criteria and included: brain hemorrhage (n= 39), Age > 80 (n=29), NIHSS > 12 (n=27), not a stroke (n=24), stroke onset > 72 hours (n=16). The intent of the study is to assess IPS impairment in patients with mild and moderate acute stroke therefore enrollment was limited to subjects with acute ischemic strokes with a NIHSS ≤ 12. Treatment, complications and recovery for patients with hemorrhagic stroke or severe ischemic stroke can be different than in mild to moderate ischemic stroke; adding variables to the study which may confound comparisons between mild and moderate stroke. The age limit excludes patients older
than 80 years to avoid natural slowing with age confounding results. A stroke onset of greater than 72 hours was excluded in order to capture IPS status before brain structure changes occurred, according to neuroplasticity theory (Murphy & Corbett, 2009).

| Table 1 |
| Sample Description |

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ranges</th>
<th>Total Sample Mean ± SD</th>
<th>Mild stroke Mean ± SD</th>
<th>Moderate stroke Mean ± SD</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>33-77</td>
<td>58 ± 10.5</td>
<td>58 ± 6.6</td>
<td>57 ± 14.4</td>
<td>0.83</td>
</tr>
<tr>
<td>Education in years</td>
<td>8-16</td>
<td>12 ± 2.1</td>
<td>11 ± 1.6</td>
<td>12 ± 1.0</td>
<td>0.08</td>
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<td>NIHSS</td>
<td>0-7</td>
<td>4.1 ± 2.3</td>
<td>2.5 ± 1.5</td>
<td>6.5 ± 0.5</td>
<td>0.00008</td>
</tr>
<tr>
<td>Race (raw data) **</td>
<td>AA cauc, Hispanic</td>
<td>5 5 2</td>
<td>2 4 2</td>
<td>3 1 0</td>
<td>N/A</td>
</tr>
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</table>

Note. **Ethnicity is listed by total number by count for total number, number of patients with mild or moderate stroke.

All ten subjects in the feasibility study failed the SDMT, indicating IPS impairment. Therefore, there are a sufficient percentage of patients with IPS impairment to warrant continued study. Compared to the SDMT normative score table, the averaged Standard Deviation (SD) of less than 2 SD falls into the very low score category (Smith, 2013). The hypothesis that moderate stroke would be more likely to fail the SDMT was rejected. (p= 0.99).

To determine if an assessment can be completed within the required time span, the time from symptom onset was compared to time of testing. All subjects were able to undergo study testing within 72 hours of stroke symptom onset (Mean 47.5 hours, SD 0.31, time range 31-65 hours). All subjects completed testing within approximately 30 minutes. Sufficient information from the feasibility study indicates that it is possible to perform cognitive research during the acute phase after stroke.
A sample of 10 subjects is likely too small to make a truly valid determination regarding accepting or rejecting a hypothesis. However, it may give indications that are of interest to an investigator. The NIHSS’ were statistically significantly different between the mild and moderate stroke subjects in this sample \((p=0.0008)\). But none of the cognitive assessments indicated a significant difference based on stroke severity (see Table 2), indicating both mild and moderate survivors of stroke may suffer from similar IPS impairments.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Sample Mean +/- SD</th>
<th>Mild stroke Mean +/- SD</th>
<th>Moderate stroke Mean +/- SD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVLT II immediate recall</td>
<td>-0.7 ± 1.2</td>
<td>-0.4 ± 1.1</td>
<td>-1.1 ± 1.1</td>
<td>0.42</td>
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<tr>
<td>CVLT short delay</td>
<td>-1.0 ± 1.0</td>
<td>-0.8 ± 1.3</td>
<td>-1.2 ± 0.9</td>
<td>0.57</td>
</tr>
<tr>
<td>CVLT long delay</td>
<td>-0.35 ± 1.0</td>
<td>0.8 ± 1.0</td>
<td>-1.0 ± 0.6</td>
<td>0.09</td>
</tr>
<tr>
<td>Digit Span</td>
<td>-0.8 ± 0.9</td>
<td>-0.9 ± 0.9</td>
<td>-0.9 ± 0.6</td>
<td>0.64</td>
</tr>
<tr>
<td>SDMT</td>
<td>-2.5 ± 8</td>
<td>-2.5 ± 1.4</td>
<td>-2.7 ± 2.0</td>
<td>0.99</td>
</tr>
<tr>
<td>SDMT memory</td>
<td>3:30 ± 0.05</td>
<td>3:47 ± 0.02</td>
<td>3:10 ± 0.05</td>
<td>0.60</td>
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<td>DSC</td>
<td>-2.4 ± 0.7</td>
<td>-2.5 ± 0.5</td>
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<td>-2.0 ± 1.4</td>
<td>-2.3 ± 0.7</td>
<td>0.70</td>
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<td>MoCA</td>
<td>-3.3 ± 2.9</td>
<td>-3.4 ± 3.1</td>
<td>0.96</td>
<td></td>
</tr>
</tbody>
</table>

*Note: *DSC added to battery after study initiation; calculations included only five subjects. **the MoCA measures six other domains, in addition to IPS and memory.

This lack of significant difference may indicate that cognitive impairment is not based on stroke severity; contradicting the assumption that patients with mild stroke are not significantly impacted by their stroke. If so, patients with a low NIHSS but undiagnosed cognitive impairments are being under treated in the acute setting. Patients with mild stroke may benefit from t-PA administration, even though they have only minor motor dysfunction. Additionally, there was no significant difference in time of
symptom onset to assessment between the mild and moderate stroke groups (p=0.99).
This indicates that the moderate stroke subjects did not require additional resting time before assessment.

**Innovation**

There has been no research on IPS impairment frequency or severity in survivors of acute stroke, if stroke severity impacts IPS severity or if IPS stabilizes or worsens over the first few months’ post stroke. The innovative study objectives include:

- The study design uses SDMT and PSI to categorize IPS impairment severity in acute and sub-acute mild & moderate stroke, filling a current gap in knowledge.
- Specifically identifying IPS impairment in mild compared to moderate stroke can encourage a change in stroke treatment for mild strokes by indicating that they are currently an undertreated population.
- Success in this project will identify IPS impairment as a reason for poor quality of life in patients with mild stroke.
- This project will provide much needed information on two common QOL instruments and their adequacy for assessment in patients with mild stroke. This will lay a foundation for further research and creation of a QOL instrument specifically for patients with mild stroke or TIA.
- Applying neuroplasticity time-window principles, the study’s post stroke time points of <72 hours, 3 weeks and 12 weeks correlate the IPS recovery period to the timing of neuroplasticity changes, leading to future research on early neurocognitive assessment and on IPS impairment interventions.
Approach Section

Overview

This is a prospective, longitudinal observational study of 30 subjects in two groups (mild and moderate acute ischemic stroke). The purpose of the study is to describe the natural history, frequency and severity of IPS impairment in the acute and sub-acute periods after recent mild or moderate stroke. Subjects with strokes will be assigned to the mild or the moderate group, with approximately 50% of subjects as mild (NIHSS ≤5) (n=15) and 50% (n=15) moderate (NIHSS > 5). A number count will be kept for the duration of the study so that prevalence calculations can be performed on all persons approached for the study.

A pilot study was performed focusing on feasibility and prevalence of IPS impairment in mild to moderate stroke. A convenience sample of 10 patients, admitted with stroke and meeting inclusion/exclusion criteria (except SDMT as a screening score), participated in the study. Subjects in the pilot study did not have the SDMT assessment until after enrollment to protect against bias related to prevalence calculations. At the completion of the preliminary study it was noted that all 10 subjects had IPS impairment and were eligible to complete all three study visit time points. Therefore, all pilot study subjects have dual participation in the overall dissertation study. Their presence in the pilot study will relate to study feasibility and prevalence of IPS impairment and their participation in the larger study will be as IPS impaired subjects in the natural history study.
Study Design and Methods

Study Population.

To participate, subjects must meet the following inclusion criteria: have a diagnosis of acute ischemic stroke identified by clinical exam, CT or MRI done as standard of care, Age ≥ 18 and < 80 years old, NIHSS ≤ 12 for left hemispheric stroke and ≤ 10 for right hemispheric stroke, and abnormal screening SDMT scores. Subjects will be not be enrolled if any of the following exclusion criteria are identified: if they have any prior neurological, psychiatric or physical disorder which might confound testing, such as brain cancer, neurodegenerative disorders, blindness, severe depression or schizophrenia; if the NIHSS 1a (level of consciousness) is > 0; unable to complete follow up visits; or are unable to converse in English language with ease (dysarthria and mild aphasia allowed i.e. NIHSS 9 and 10 scores ≤ 1). A database will be updated daily, indicating exclusion criteria, and will be used to inform future study design and possible enrollment bias.

Recruitment and Retention

Study subjects will be enrolled and undergo the baseline visit at a Comprehensive Stroke Center located in Houston, Texas and the two follow up visits will be done at a quiet place the subject selects or at the University of Texas Nursing School Center for Nursing Research. Approximately 100 patients with ischemic and hemorrhagic stroke are admitted monthly at this hospital. The study PI has full access to the study population through a relationship with the treating neurology group.

Potential subjects will be approached at any time within 72 hours of the stroke symptom onset. This time period was selected because it matches the acute stroke
treatment phase. The nearer to the time of onset is preferred but testing must not interfere with acute treatment. With the subject’s permission, the consent process will include discussions with available family, at the subject’s bedside or by phone as necessary. Family involvement is a key to retention in stroke research (Hadidi, Buckwalter, Lindquist, & Rangen, 2012). Subject retention will be facilitated by periodic phone calls, reminder post cards and by creating an environment of cooperation and buy-in from the subject and family at the baseline visit. The investigator’s contact information is given to the subject and available family and they are encouraged to have friends or family call with any questions. Retention strategies also included payment of a $40.00 subject stipend, to cover subject travel expenses and presenting subjects and families with multiple options for follow up visit locations, including the investigator traveling to the subject’s home. Lost to follow up rate of retention for the pilot study was 12%.

**Research Subject Risk and Protection**

The protocol and proposed consent was approved by the University of Texas-Houston Committee for the Protection of Human Subjects (CPHS) and the Memorial Hermann Hospital Research Office. The protocol includes strict inclusion and exclusion criteria which will not exclude subjects based on race or gender but will limit age due to increased likelihood of cognitive effects of normal brain aging. The consent form will be reviewed to ensure that language is at the fifth grade reading level. After a thorough explanation of the risks and benefits by a member of the research team, consent will be obtained from the subject or LAR. Adequate time to read and ask questions will be given to the subject. Additionally, if the subject becomes fatigued during testing a short break will occur and length of break will be noted on the source documents. There are no
known risks for cognitive testing and an explanation of cognitive impairments, IPS impairment in particular, is given to the subject and available family. Subject and family are encouraged to discuss concerns about the subject’s cognitive status and possible recovery trajectories. The subject and family are made aware that the results of testing will be discussed after the week 12 evaluation and further suggestions will be given to the subject, including the suggestion to contact the neurologists for additional evaluation and possible referral to a neuropsychologist. All data will be protected to the full extent of the law by use of a de-identifying code; password protected computers and double locked cabinets.

**Data Plan**

**Measurements:**

Six paper and pencil cognitive instruments are completed by the subject within a 30 minutes’ time-period; the instruments are three measuring IPS (SDMT, DSC, and Symbol Search), two measuring memory (CVLT II SF and Digit Span), and the MoCA which measure multiple cognitive domains. The instruments administered in sequential order are the CVLT (immediate and short delay trials), SDMT, DSC, Symbol Search, Digit Span, CVLT long-delay trial, and MoCA.

A break between tests can be taken without interfering with testing, with the exception of the CVLT long-delay. A 15-25 minutes’ interval between the short and long delay trials is acceptable (Delis, 2000). If the break time extends beyond 25 minutes, then the alternate CVLT form will be used when testing recommences. The order of tests enables the IPS tests to be done relatively early in the testing period, before potential fatigue occurs.
To decrease likelihood of practice effect there are three weeks between the baseline testing and Week 3 visit and nine weeks between the Week 3 and the Week 12 visit. Practice effect on cognitive instruments is noted on high frequency testing but not on low frequency testing (Falleti, Maruff, Collie, & Darby, 2006). High frequency testing is repeatedly administering the testing battery several times at 10-minute intervals. Low frequency testing would include a weeks or months long time intervals between a single administering of the battery. No significant practice effect was noted on the SDMT (Smith, 2013) or the MoCA (Costa et al., 2012) at any time interval. No significant practice effect was noted on the DSC, Symbol Search, or the Digit Span at the four-week intervals (Strauss, Sherman and Spreen, 2006). The CVLT-II short form has a negligible practice effect at a four-week time intervals between testing (Woods, Delis, Scott, Kramer, & Holdnack, 2006).

Two quality of life instruments are completed by the subject at the 12 Week visit. As part of subject history, the IQCODE will be completed by a proxy who has known the subject for five years prior to baseline visit. A description of each instrument is included below.

- **California Verbal Learning test– 2nd Ed. Short form (CVLT-II SF):** The subject is asked to learn and remember a short list of words (9-words) with four immediate and two delayed recalls (5 and 10 minutes apart). For the immediate recall trials, the subject is read the word list and asked to repeat the words immediately after each of 4 list readings. Then a short delay (about 5 min) occurs while the other cognitive tests are performed. After the short delay the subject is asked to recall the list, i.e. the short delay test. Afterward additional activities
(other cognitive tests) are performed and 10 minutes later the subject is asked to recall the list again, i.e. the long delay test. Delis et al. (2000) evaluated the CVLT II for split-half and word category reliability and show Cronbach’s alpha of 0.96 and 0.83 respectively with adequate test-retest reliability for a median time interval of 3 weeks. Evidence of validity was indicated for the CVLT II by factor analysis showing the same six factor analysis as occurred with the original CVLT. Scoring and interpretation information was obtained from Delis, Kramer, Kaplan, & Ober (2000).

- **Scoring:** 1 point for each correctly recalled word from the word list.
  Scoring performed on CVLT licensed software, comparing subject raw score results to normative data and converted to z-score.

- **Interpretation:** In Trial 4, Short, and Long Delay Trials: z score of zero is average with (+/-) 0.3 to 1 score reflects the above/below average recall or retention rate. Trial 4 indicates the level of recall; the Short and Long delay trials test durability of memory. Both Short and Long z-scores should be similar indicating no variable attention problem. In subcortical stroke there may be a deficit in level of recall but a more normal retention rate.

- **Digit Span:** The Digit Span is a WAIS III subtest indicating working memory impairment. It tests immediate recall, reversibility, ability to shift thought patterns, concentration and attention. For Digit Span Forward, the subject is read a series of numbers and recalls the numbers in the same order. For Digit Span
Backward, the subject is read a series of numbers and recalls the numbers in reverse order.

- Scoring: 1 point for each set of digits properly recalled. Testing stops after two failures of the same digit length. Maximum score is 30 points.

Scoring follows Wechsler Classification range: The normative table converts the raw score to a standard score. If the standard score is 10 then the z-score is 0. For each increase or decrease of 1 point in standard score, z-score goes up or down by 0.33. For example, standard score of 13 = z-score of 1.0. (Wechsler, 1997).

- Interpretation: Wechsler’s Classification Range (standard score):
  
  Extremely Low (1-4), Unusually low (5-6), Low Average (7), Average (8-12), High Average (13), Superior (14-15), Very Superior (16-19) (Brooks, Sherman, Iverson, Slick, & Strauss, 2011).

- **Digit Symbol – Coding (DSC):** The DSC involves a simple substitution task using a reference key. The subject has 120 seconds to pair specific geometric figures with given numbers, drawing the figures in the box of the matching number (Tulsky, Saklofske, & Zhu, 2003). The DSC specifically informs on perception and graphomotor speed therefore poor performance, when compared to the SDMT and the Symbol Search, may inform on motor as well as cognitive impairment (Strauss et al., 2006).
  
  - Scoring: 1 point for each figure properly drawn. Maximum score is 133 points. Follows Wechsler Classification range scoring (Wechsler, 1997).
- Interpretation: Follows Wechsler’s Classification Range (standard score) (Brooks et al., 2011).

- **Informant Questionnaire on Cognitive Decline – Short Form** (IQCODE-SF) is completed by a proxy who has known the subject for five years prior to the stroke. It will indicate if the subject has had a cognitive decline prior to the stroke. The 16 item IQCODE-SF has a 0.98 correlation with the full 26 item form, Cronbach’s alpha 0.97, a sensitivity of 73% for vascular dementia and has been found to predict dementia in patients with stroke at 3 years’ post-stroke (Jorm, 2004).
  - Scoring: scored on a Likert scale of 1-5 ranging from Much Improved (1) to Much Worse (5). All item scores should be three or below.
  - Interpretation: A score of 4-5 indicates dementia, signifying the subject has a history of cognitive impairment over the five years prior to the stroke.

- **MoCA**: The Montreal Cognitive Assessment assesses cognitive domains of attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. Nasreddine et al. (2005) examined the internal consistency of the MoCA and reported a Cronbach's alpha (alpha = 0.83). The test-retest reliability correlation between the two evaluations was r = 0.92. Nasreddine et al. (2005) the MoCA indicate concurrent validity by correlation between the MoCA and the MMSE (r = 0.87).
- **Scoring:** Each of the ten items can score 1-6 points. Maximum score of 30. The average score for all ages is 27.4 with a standard deviation of 2.2. Add a point to the subject’s raw score if they have ≤ 12 years of education and then subtract the average score (27.4) from the raw score. Divide that difference by 2.2 and the result is the z-score.

- **Interpretation:** Add one point for subjects with 12 or less years of education. A final score of 26 or above is considered normal. A final score of less than 26 indicates cognitive impairment (Canadian Partnership for Stroke Recovery, 2015).

- **Neuro-QOL:** Neuro-QOL is a set of self-report measures that assesses the health-related quality of life (HRQOL) of adults and children with neurological disorders. Neuro-QOL is comprised of item banks and scales that evaluate symptoms, concerns, and issues that are relevant across disorders (generic measures) and can be given as a fixed-length short form. The Neuro-QOL instruments enable within-disease as well as cross-disease comparisons and are intended for use in both neurology clinical trials and clinical practice. Scoring and interpretation was obtained from National Institute of Neurological Disorders and Stroke (NINDS) website (2010) and the Neuro-QOL Assessment Center (2015).

  - **Scoring:** Sum total responses from 13 sections (domains) 5-point Likert scale, responses range from a very positive to a very negative. Maximum score of 525.

  - **Interpretation:** Using the NINDS manual conversion table, the raw scores are converted to t-scores. No standardized or normative values available.
for comparison; high score indicates either worse (undesirable) or better (desirable) QOL, depending on domain of interest, with a high overall score indicating a better (desirable) QOL.

- **SDMT:** Both a screening tool to determine eligibility and is a primary outcome variable. The SDMT involves a simple substitution task using a reference key. The subject has 60 seconds to pair a number with a given specific geometric figure, writing the numbers in the box of the matching figure. The SDMT involves a simple substitution task designed to assess attention, visual scanning, and motor and psychomotor speed. Because subjects can give written or spoken responses, the test can be used in motor disabilities or speech disorders (Sheridan et al., 2006). Reliability for three alternate forms demonstrated at $r > .80$. There is a high correlation for validity (0.88) in patients with head injury. Because SDMT involves only geometric figures and numbers, it is relatively culture bias free. It shows high correlation for processing speed and is extremely sensitive in brain insult (Strauss, Sherman, E. & Spreen, 2006). Felmingham, Baguley, and Green et al., (2004) indicates it is particularly sensitive to the cognitive effects of diffuse axonal injury in traumatic brain injury (TBI). The SDMT is considered a “purer” measurement of IPS than other processing speed tests (Martin & Bush, 2008) and is the single best indicator of information processing impairment in patients with TBI (Ponsford & Kinsella, 1992). The SDMT has been used to evaluate IPS in TBI, Alzheimer’s and multiple sclerosis. This study is novel in the use of the SDMT to evaluate IPS impairment in patients with stroke. Scoring and interpretation was obtained from the SDMT manual (Smith, 2013)
○ Scoring: 1 point for each number correctly matched to presented figures. Maximum score is 110. The raw score is converted to a z-score using the SDMT Manual (Table 3) based on education level (≤ 12 years or ≥ 13 years).

○ Interpretation: Scores are ranged by SD for a particular age group at a particular education level; one SD can range from 7.98- 13.54 points, depending on age. Low scores are approximately 1 SD (7.98- 13.54) below mean, Moderately Low scores are approximately 1.5 SD below mean, Very Low scores are approximately 2 SD below mean.

- **SS-QOL:** The Stroke Specific Quality Of Life scale (SS-QOL) is a patient-centered outcome measure intended to provide an assessment of health-related quality of life specific to patients with stroke. It measures stroke specific changes in quality of life for individuals who have had a stroke. This evaluation consists of 49 items that focus on 12 areas of health-related quality of life. The areas include the following: energy, family roles, language, mobility, mood, personality, self-care, social roles, thinking, vision, upper-extremity function and work productivity.

○ Scoring: Scale contains 49 items in 12 domains on a 5-point Likert scale, responses range from a very positive to a very negative. Maximum score of 245.

○ Interpretation: No standardized or normative values available for comparison; higher score indicates better function in both domain and overall summary score.
Symbol Search: The Symbol Search is a WAIS III subtest indicating information processing speed. It tests speed of visual search, speed of processing information, planning, encoding information in preparation for further processing, visuo-motor coordination and learning ability. The subject has 120 seconds, using the Symbol search booklet, to scan several rows of symbols and on each row indicates whether one of the symbols in the small target group matches a symbol in a larger search group.

- Scoring: 1 point for each correct answer per row. Subtract the total number of incorrect responses from the total number of correct responses. Maximum score is 60 points. Follows Wechsler Classification range scoring (Wechsler, 1997).
- Interpretation: Follows Wechsler’s Classification Range (standard score) (Brooks et al., 2011).

Data Collection

Data will be collected by the primary investigator (PI) beginning immediately after study enrollment. The baseline NIHSS will be performed by the treating neurologists. The PI will perform all cognitive assessments as well as all follow up visit activities. The PI has training and two years of experience in assessments for the study.

There are three measurement time points: baseline (within 72 hours after stroke), Week 3 and Week 12 after stroke. The cognitive assessments take approximately 30 minutes to complete and the SDMT may be completed using either the written or the oral test format. The Week 3-time point was selected because most acute inpatient rehabilitation for patients with mild or moderate stroke has been completed and they will
be transitioning home. Therefore, it will be of interest to evaluate changes between this time-point and the Week 12 assessment. It is anticipated that by the Week 12 time point the subject has resumed residence at home and is adjusting to new life conditions after stroke. At Week 12 patients with stroke are entering the chronic stroke recovery phase and assessment of their IPS compared to baseline should answer the hypothesis of IPS impairment based on stroke severity.

At the baseline visit, standard of care information will be abstracted from the medical records, including a pre & post stroke mRS and NIHSS performed by the treatment team. The medical records will also be reviewed for demographic information and evidence of rehabilitation therapies (PT/OT/ST).

At each of the three visits, the following assessments will be collected by the PI: The Barthel Index (BI), NIHSS, the SDMT, the WAIS III Processing Speed Index (PSI): Symbol Search and Digit Symbol – Coding, the CVLT-2II SF, Digit Span, and the MoCA. The NIHSS indicates stroke severity and the SDMT and the PSI indicate IPS impairment. The CVLT III and Digit Span will be used to indicate impairment of working memory which can confound the IPS assessments, namely the Symbol Search results. The MoCA assesses multiple cognitive domains including IPS and working memory.

Quality of life (QOL) data will be collected by the PI at the Week 12 visit using two QOL instruments, the Stroke Specific Quality of Life scale (SS-QOL) and the Quality of Life in Neurological Disorders (Neuro-QOL). The QOL indicators will not be collected at the Week 3 visit because the subject may still be undergoing rehabilitation or just beginning adjustment to their new post stroke status. It is unlikely that the subject is
fully cognizant of how much their lives have changed, holding out hope that they will recover quickly. In the CASTLe study, the QOL results were not consistent between these two measurements (Bursaw, submitted for publication). Additional research may indicate a lack of sensitivity of the Neuro-QOL in mild stroke subjects.

**Data Analysis Plan**

**Sample Size/Power Considerations**

The power analysis for the sample size of $n = 34$ was completed using GLIMMPSE, an online tool for calculating sample size and power in general linear multivariate models (GLMM) (Kreidler et al., 2013; Muller & Glueck, 2012). With this sample size, a repeated measures analysis with three time points will have 80% power to detect as significant an effect size of $f = .27$, calculated by G3 power software (G* Power, 2014). Effect size is based on Lunsford & Lunsford (1995) determination that a medium effect size (epsilon = .50 or $f^2$ of .15) implies that a trained observer may be able to note an observable difference but testing is necessary to verify the differences. The hypothesis is that, between the groups, the differences will be too small to be observed by the average healthcare provider and testing is necessary. This is significant because it may indicate that patients with mild stroke experience an IPS impairment as severe as the patients with moderate stroke but, historically, they do not receive similar levels of medical and rehabilitation care.

Based on the selected effect size and an anticipated 20% lost to follow up, a minimum of 33 subjects will need to be consented to obtain the necessary completed follow up visits (N=30 subjects). Due to experiences with high lost to follow up reported in other cognitive studies, it was decided that an additional 12 subjects will be enrolled to
ensure adequate sample size at the end of the study. Therefore, a minimum of 46 subjects will be enrolled in the study, with data analysis completed on at least 30 subjects.

The Digit Symbol-Coding (DSC) further characterizing IPS impairment, was added after the fifth subject was enrolled. Because the intent of this descriptive study is to more fully characterize IPS impairment after stroke, the PI continued to consider how best to achieve that goal. Additional reading of stroke and non-stroke related material produced information on the Processing Speed Index (PSI) being used in clinical settings. The lack of baseline DSC will be considered during data analysis as it will effect four subjects, with Subject 001 having expired prior to Week 3. Mixed-effects regression models will be used for the study; a model tolerant of missing data, if it is missing completely at random (MCAR). Data qualifies as MCAR when it is missing because of either an instrument fails or is not completed, or when the probability of a subject dropping out depends only on covariates included in the model (Gueorguieva & Krystal, 2004). Two reasons noted for missing data at this point in the study include DCS not administered at baseline for four subjects and two subjects out of town for the Week 3 visit.

We have taken this approach of a small study because of the need to characterize level of IPS impairment found in the acute population, the persistence of symptoms, and any association of IPS impairment with stroke severity and decreased quality of life at Week 12; this information is not available in the literature. The predictor variable is the NIHSS score, with covariates of the SDMT, the PSI and the CVLT II. Possible confounders are age and level of education. Additional sample description variables will be BI, co-morbidities, race, and gender. A significance level of 0.05 will be used for all
tests to assess statistical difference. The statistical analysis will be performed using Statistical Analysis System (SAS, 2015) under the supervision of a biostatistician.

**Analysis by Aim**

**Specific Aim 1:** To determine the frequency and severity of IPS impairment, as evidenced by abnormal SDMT values, in mild stroke (NIHSS $\leq 5$) compared to moderate stroke (NIHSS $>5$) over time.

Descriptive statistics, including means with standard deviations, medians, or proportions will be used to initially characterize the sample. Baseline differences between those with mild and moderate stroke will be assessed using the t-test for independent samples, chi-square tests, Fisher’s exact test, or Mann-Whitney U test, wherever applicable.

**Specific Aim 2:** To evaluate the association between severity of IPS impairment & QOL in mild stroke (NIHSS $\leq 5$) compared to moderate stroke (NIHSS $>5$) survivors at 3 months.

A linear mixed model regression will be used to test for differences over time in SDMT & PSI scores between those with mild and moderate stroke. The effects to be tested will include group, time, time X group interaction and possible confounding terms of age and education level. A multivariable linear regression will be performed to determine association between stroke severity, SDMT & PSI scores and quality of life scales at Week 12.

**Specific Aim 3:** To evaluate the correlation between IPS impairment and four subsections of the Neuro-QOL compared to the overall Neuro-QOL score in mild survivors of stroke at 3 months.
A linear mixed model regression will be performed using two predictors, SDMT & PSI scores, and four covariates, the Neuro-QOL subsections (Depression, Applied Cognition-general concerns, Applied Cognition-Executive Function and Positive Affect & Well-Being) to determine if there is a stronger association with these three than with the overall Neuro-QOL score.

**Potential limitations and solutions**

The PI’s prior experience has indicated that there may be a larger than usual lost to follow up percentage (>20%) in cognitive studies. Increase efforts to retain contact with the subject and next of kin may assuage this concern. Effort to ensure compliance will be attempted by periodic contact by phone and mail. The PI has worked as study coordinator in other stroke studies and, in these prior studies, had an approximate 10% lost to follow up rate.

Subjects may not be able to complete the baseline assessments within 72 hours of stroke. If it is noted that a statistically significant amount of subjects are unable to complete cognitive testing at baseline then the baseline time point will not be used in data analysis, only the Week 3 and Week 12 time points. There is precedence for using a Week 4 as baseline in other cognitive studies. Nevertheless, all subjects in the IPS pilot study were enrolled and tested within 72 hours of stroke. In the CASTLe study, the study team was able to enroll and complete cognitive testing with 44 out of 45 subjects within 24 hours of stroke (Bursaw, submitted for publication). This IPS study’s PI completed 75% of the CASTLe study enrollment and testing.

Additionally, performance of cognitive testing within 72 hours of stroke can experience logistical and clinical challenges. One potential problem is the need to time
the testing period to avoid conflict with the patient’s standard of care activities. Careful coordination with the physician and nursing staff generates adequate study testing time. The key to performing a successful cognitive study is frequent and open communication between the study team and the subject, family members and the healthcare team.

**Timetable**

The study site admits approximately 60-80 patients with ischemic stroke in each month. It is anticipated that it will take 8-12 months to complete the project (see Table 3).

Manuscripts from the dissertation will be submitted to peer-reviewed journals for publication.

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<thead>
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<th>Table 3</th>
<th>Study activities time table from initial enrollment until planned publication submission</th>
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<td>Enrollment &amp; Baseline testing</td>
<td>0-39 subjects enrolled, Week 3 visits ongoing</td>
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<td>Week 3 and Week 12 testing</td>
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Information Processing Speed Impairment after Stroke,

A Descriptive Study

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Abstract

Background Information processing speed (IPS) is an elemental cognitive function impacting multiple functions including memory, attention, and executive function, and - arithmetic, reading and writing academic skills. However, little research has been conducted on IPS impairment in acute stroke. This article compares the frequency and severity of IPS impairment in mild and moderate acute stroke and its impact on quality of life.

Methods A longitudinal study of patients with mild stroke (NIHSS ≤5) and moderate stroke (NIHSS 6-12) tested IPS and working memory on five cognitive measurements, at three time points from 72 hours to 12 weeks after an acute ischemic stroke. A quality of life (QOL) scale (Neuro-QOL) was administered to assess the relationship of QOL to stroke severity and IPS impairment.

Results Similar frequency and severity of IPS and memory impairments were noted, regardless of stroke severity, in the sample of 30 patients (60% mild stroke). Statistically significant improvement of IPS (p=.005) occurred with percentages of 100% impaired (baseline), 97% (Week 3) and 79% (Week 12). Decreased quality of life associated with IPS impairment was significant in the AC Executive QOL domain (p=0.04) but no difference was noted based on stroke severity.

Conclusion There is evidence of minimal spontaneous IPS and memory recovery regardless of stroke severity at 12 weeks post stroke. IPS was equally impaired in mild and moderate stroke. Frequent and severe IPS impairment is clinically significantly during the acute and rehabilitation phase of stroke recovery, potentially impacting a
patient’s independence or ability to participate in his own care. The Neuro-QOL measurement indicated impaired IPS impacts quality of life but only in relation to executive function interference.

**Introduction**

A stroke occurs every 40 seconds in the US; that equates to almost 800,000 people experiencing a stroke annually (Mozaffarian et al., 2015). Currently, approximately seven million adults are living with the consequences of stroke, with 30% having been discharged from hospital to a skilled nursing home (Mozaffarian et al., 2015). The annual financial impact on society totals $34 billion; projected to be $96 billion in 2030 (CDC, 2013).

An ischemic stroke is an infarction of brain tissue attributable to focal ischemia resulting in permanent injury (Sacco et al., 2013), with severity indicated by scores on the National Institute of Health Stroke Scale (NIHSS). The NIHSS score for mild stroke is considered 0-4 (Fischer et al., 2010). In the literature, upper NIHSS range for mild stroke varies from three to six (Hassan, Hassanzadeh, Tohidi, & Kirmani, 2010; Smith et al., 2005) However, there may be minimal clinical differences in scores between 0-3, but significant differences between 0-6 (Fischer et al., 2010). NIHSS range for moderate stroke typically is 6-12; however, left hemisphere lesions can result in more profound language involvement (Corballis, Badzakova-Trajkov, & Häberling, 2012), confounding cognitive assessment. Thus, upper range NIHSS for moderate stroke is 12, except in left hemisphere lesions; then upper NIHSS should be 10 (S. Savitz MD, personal communications, April, 2014).
Regardless of stroke severity, at least 70% of survivors of stroke experience a subtle cognitive dysfunction, information processing speed (IPS) impairment (Lesniak, Bak, Czepiel, Seniow & Czlonkowska, 2008). Slowed IPS can persist up to five years in mild to moderate stroke (Barker-Collo, 2012) and be unimproved by routine care (Jokinen et al., 2015). Interaction between impaired IPS and attention can decrease patient’s ability to understand or participate in healthcare (Lustig, Hasher & Tonev, 2006). Interaction between impaired IPS and memory can diminish the ability to perform instrumental activities of daily living (IADL) (Winkens, 2006). IPS impairment is not typically assessed in the acute stroke period regardless of stroke severity nor is it typically assessed in mild stroke at any time period.

IPS is an elemental cognitive function, with a simple dimension (i.e. reaction time) and a complex dimension; the complex dimension is known to impact multiple other functions including memory, attention, reasoning, and executive function, and academic skills such as arithmetic, reading and writing (DeLuca, 2008). The pervasive nature of IPS impairment has been evaluated by extensive research in the areas of education, aging and quality of life (Ball & Vance, 2008). Salthouse (1996) first defined IPS as having two components known as Limited Time and Simultaneity mechanisms. The consequence of faulty mechanisms is either 1) limited time is available to complete the later steps of mental operations; available processing time having been consumed performing the earlier steps or 2) information from the earlier mental processing is too impoverished or degraded by the time other simultaneous information needs to be processed (DeLuca, 2008).
Almost immediately after a stroke brain plasticity aids the brain to adapt to environmental pressures, experiences and challenges at many levels, through molecular to cortical reorganization (Johansson, 2011). This active brain remodeling period lasts approximately four to eight weeks after a stroke (Murphy & Corbett, 2009). Spontaneous IPS recovery in humans occurs sooner in diffuse axonal injuries, such as mild traumatic brain injury, then in focal brain injuries (Kinsella, 2008) such as stroke. To capture variation over time due to neuroplastic changes, cognitive measurements need to be repeated throughout this time window. Inpatient acute and rehabilitation care are usually completed for patients with moderate strokes by three weeks after stroke, though the brain is still undergoing neuroplastic changes. Twelve weeks after stroke is a typical measurement time point in stroke research (Johansson, 2011) and can be viewed as a demarcation between subacute and chronic stroke recover. Week 12 is outside the window for neuroplastic changes (Murphy, & Corbett, 2009), however, cognitive recovery may continue at a markedly slower rate for up to 16-18 weeks (Christensen et al., 2008; Suzuki et al., 2013).

Most survivors of mild stroke are discharged from the hospital with limited rehabilitation, on the assumption there will be minimal residual effect (Edwards, Hahn, Baum, & Dromerick, 2006). However, as many as 30% of survivors of mild stroke are not discharged directly home and Romano et al. (2015) suspects this is due to cognitive impairments. Cognitive impairment interferes with rehabilitation, nonetheless, specific cognitive assessment and rehabilitation are neglected in early stroke (Johansson, 2011). Limited research has been conducted on IPS impairment in acute stroke, due to concerns that it does not represent a general cognitive profile (Lesniak et al, 2008). While this
concern maybe accurate in relation to chronic cognitive impairment, it limits identification and treatment of cognitive impairments in early stroke. In addition to the NIHSS, clinical assessment of stroke patients focuses on level of disability. Global disability scales, such as the Barthel Index (BI) and modified Rankin Scale (mRS), may indicate minimal residual effect but not accurately measure cognitive impairment. Furthermore, disability scales are not designed to measure the impact of cognitive impairment on life activities and on QOL (Edwards et al., 2006). Use of a QOL scale, responsive to cognitive impairments, may indicate that mild stroke is not as benign as previously believed and it may indicate poor QOL can be associated with IPS impairment rather than stroke severity.

The purpose of this longitudinal observational study was to describe the frequency and severity of IPS impairment, in acute to subacute stroke, by stroke severity and its relationship to QOL at 3 months. The primary hypothesis was patients, regardless of stroke severity, will experience similar IPS impairment and QOL at three months after stroke.

**Method**

This was a longitudinal observational study of 30 patients with acute ischemic stroke divided into two groups by stroke severity. IPS impairment and QOL were assessed in relationship to stroke severity, either mild or moderate stroke. A convenience sample was enrolled at a large comprehensive stroke center hospital and cognitive testing was completed at three time points: within 72 hours of stroke (baseline), post-stroke Week 3 (+/- 5-days) and post-stroke Week 12 (+/- 14-days). All participants were admitted under the care of a stroke neurology group and baseline cognitive assessments
were completed at the bedside by the investigator. Follow up visits were performed either at a testing center, the participants’ home or work. Demographic information was collected including age, gender, education level, medical history, MRI/CT findings, and concurrent medications. A control group was deemed unnecessary due to the availability of well-established, instrument-specific norm value tables used for diagnosis of cognitive impairments. The investigator, a registered nurse, was trained to administer the tests and research was performed as part of the author’s PhD dissertation program. The study was performed with supervision of a neurologist and a neuropsychologist, was approved by a university based institutional review board, and each participant signed an approved written consent.

Sample size calculation was obtained using online G-Power program and verified by a biostatistician during study design. The program determined significance can be obtained with 90 data points or three data points for each of the 30 participants. The statistical analysis for the study was performed by a biostatistician using SPSS (IBM SPSS Statistics, Version 23) under the supervision of the investigator.

Subjects were included based on IPS impairment, as indicated by an abnormal Symbol Digit Modalities Test (SDMT), stroke severity (NIHSS) at baseline, had ischemic stroke identified by clinical exam, CT or MRI, and were between 18-80 years old. Initial NIHSS inclusion criteria was based on stroke hemisphere (left: NIHSS less than 11; right: less than 13). Participants were assigned to either mild (NIHSS 0-5) or moderate groups (NIHSS 6-12) based on actual score; patients with mild dysarthria and mild aphasia were also included.
Patients were excluded if they had a severe prior neurological, psychiatric or physical disorder which might confound testing (e.g. brain tumor, brain surgery, traumatic or neurodegenerative brain disorders, dementia, schizophrenia, blind or mute, etc.), or experienced prior cognitive impairment, drug or alcohol abuse, were unable to stay awake for 30 minutes or unable to converse in English. Enrollment was age restricted to less than 81 years old due to increased likelihood of cognitive effects of normal brain aging.

The Informant Questionnaire on Cognitive Decline – Short Form (IQCODE), a 16-item questionnaire capable of indicating dementia in patients with stroke (Butt, 2015), was used as a screening tool to assess prior cognitive impairment and was completed by a proxy known to the patient for five years prior to enrollment. The IQCODE assesses cognitive function through informant observations, related to life changes, rather than direct assessment of a patient’s current cognitive status. The advantage of screening observed behavior is that it is not dependent on culture, language or level of intelligence (Jorm, 2004). IQCODE has a Cronbach’s alpha 0.97, a sensitivity of 73% for vascular dementia, and has been previously shown to be useful as a screening tool for dementia in patients with stroke (Butt, 2015; Jorm, 2004).

Five paper and pencil cognitive instruments were completed by participants, over 30 minutes at each visit, and were administered in a standardized sequential order (Table 1). A short rest break during testing was offered but declined by all participants. The cognitive instruments (Table 1) measured IPS (SDMT, Digit Symbol-Coding (DSC), and Symbol Search) and memory (California Verbal Learning test– 2nd Ed. Short form (CVLT-II) and Digit Span). Research on IPS function and interactions, related to
cognition, has produced term confusion in literature between IPS and working memory (DeLuca, 2008). Therefore, a combination of IPS and working memory (WM) instruments were included in this study. Working memory is a limited capacity system that supports mental operations; a workspace for brief storage and manipulation of information (Baddeley, Eysenck & Anderson, 2009). IPS and working memory (WM) can impact each other but not always consistently, as noted by DeLuca (2008) in the WM-PS model. Therefore, association between these constructs was evaluated in the current study.

The SDMT is considered a measurement least likely to suffer from construct contamination by memory function interference (DeLuca, 2008) and was selected to represent IPS impairment in this study. The other IPS tests combine to form the Processing Speed Index (PSI) used in the Wechsler Adult Intelligence Scale III (WAIS III), an instrument of frequently used in research and clinical settings (Strauss, Sherman and Spreen, 2006). The PSI findings were evaluated to give indication of SDMT measurement accuracy. Poor scores on both SDMT and PSI supported the determination of IPS impairment in a participant. Strauss et al. (2006) identified adequate reliability and validity (Table 1) and normative values for the IPS and memory instruments. To decrease likelihood of practice effect, a 3-week interval (mean=23 days) was scheduled between baseline and Week 3 visit. No significant practice effect at four-week testing intervals have been noted in the SDMT (Smith, 2013) or the DSC, Symbol Search, and the Digit Span (Strauss et al., 2006). The CVLT-II has a negligible practice effect at four-week intervals (Woods, Delis, Scott, Kramer, & Holdnack, 2006).
The Neuro-QOL, completed at Week12 visit, is a 13-section self-report domain measurement for within-disease as well as cross-disease health-related quality of life comparisons, used in neurology research and clinical practice (NINDS, 2010). Traditionally, an investigator selects a few pertinent domains or short forms from the static 13 domains form, based on an area of interest (Cella et al., 2012). Investigators select domains of interest, related to physical, social, emotional or cognitive QOL, and the selected short forms are completed by a participant. Likert scores (1-5) are tallied in each short form with both positively-keyed and negatively-keyed items within the instrument; limiting its ability to be used as a summarized measurement. Depending on the polarity of the domain (negative or positive) the score may be high or low and may be interpreted as much by extremity of polarity as by actual score (NINDS, 2010).

For this study, four domains were selected as the QOL domains most likely to be affected by IPS impairment in patients with mild or moderate stroke. They included Depression, Positive Affect & Well-Being (PAW), Applied Cognition General Concern (AC General), and Applied Cognition Executive Function (AC Executive). PAW and Depression were assessed because of potential impact of the psychological state on cognition (Sheline et al., 2006). The four short forms were scored and interpreted based on manual instructions (NINDS, 2010) and literature guidance (Salsman et al., 2013). Neuro-QOL raw scores were converted to T-scores (mean 50, SD 10) (NINDS, 2010). For this study, T score range of Fair (50 ≤ T-score < 60) was considered the median scores, with all other categories either good or poor in increments of 10 points. Therefore, Neuro-QOL scores were categorized as follows: Very good (T-score < 40), Good (40 ≤
T-score < 50), Fair (50 ≤ T-score < 60), Poor (60 ≤ T-score < 70), Very poor (T-score ≥ 70).

Patients with stroke are confronted with physical, cognitive, emotional, and social changes (Nichols-Larsen, Clark, Zeringue, Greenspan, & Blanton, 2005). In preparation for future research, the study explored an association between summary-scored Neuro-QOL, stroke severity, and IPS impairment at Week 12. QOL is a multidimensional construct and, at a minimum, several aspects of physical, emotional and social functioning should be evaluated to fully understand QOL (Fayers & Machin, 2013). This preliminary examination assessed any differences in a summarized overall score and the scores from the four selected cognitive/affect domains, in relation to stroke severity and IPS impairment. The exploration sought an alternate use for the form which may encourage its creators in further instrument evaluation. The Neuro-QOL does not have a uniform polarity. To calculate a summary score all items values needed to point in the same direction, e.g. a more negative reply resulting in a higher score (WFU, 2015). After all participants had completed the 13 Neuro-QOL short forms, the tabulated scores for seven of the short forms were changed from positively-keyed to negatively-keyed resulting in the direction of higher score equaling worse QOL. For example, response 1-always became response 5-never. The reverse-keying was performed on tabulated scores rather than by participants answering altered items. The reverse-keyed sections included Ability to Participate in Social Roles and Activities, Satisfaction with Social Roles and Activities, AC-General, AC-Executive, PAW, Upper Extremity Function -Fine Motor, ADL and Lower Extremity Function -Mobility. The remaining sections without reverse-
keying were Anxiety, Depression, Fatigue, Emotional & Behavioral Dyscontrol, Sleep Disturbance, and Stigma.

**Statistical methods**

Descriptive statistics (frequencies, mean, standard deviations) were used to described the sample, IPS impairment, and quality of life (QOL). The NIHSS score was selected as a predictor variable with the SDMT and Neuro-QOL scores as covariates to characterize IPS impairment in participants with acute mild or moderate stroke participants. Well-established normative value tables accounted for subject’s age and education level thus eliminating the need to treat these concepts as potentially confounding terms (Delis, Kaplan, & Ober, 2000; Smith, 2013; Wechsler, 1997).

Differences between mild & moderate stroke: t-test, Fisher’s exact test, or Spearman rho, wherever applicable. A Spearman’s rho indicated significant correlation (p=0.001) between SDMT and PSI scores for IPS impairment, therefore, to simplify analysis only SDMT scores were used. A significance level of p < 0.05 indicated statistical difference.

A linear mixed model regression was used to test differences in SDMT, rate of IPS impairment, and stroke severity over time. The effects tested included group, time, and time X group interaction. The mixed-effects regression model is tolerant of randomly missing data (Gueorguieva & Krystal, 2004). Differences in SDMT scores and Neuro-QOL scores, based on stroke severity or IPS impairment, were assessed using linear mixed model regression: using SDMT as a predictor to determine if there is an association with an overall Neuro-QOL score.
Results

Sample Description

This was a longitudinal observational study of 30 patients with acute ischemic stroke divided into two groups. Categorized by NIHSS score at baseline, 60% of participants had a mild stroke (n=18) and the remaining had a moderate stroke (n=12). Participants age range was between 45-79 years. Patients admitted to the hospital’s stroke neurology service were screened (N=1194) from 10/8/2014 until enrollment was completed on 9/15/15. Analysis was based on participants who completed the Week 3 visit. Demographic characteristics, NIHSS findings, Barthel Index (BI) and modified Rankin Scores (mRS) are presented in Table 2. Four risk factors for mild cognitive impairment (Gorelick et al., 2011) were present in sample: hypertension (n=25), cardiac disease (n=13), diabetes (n=11), and hyperlipidemia (n=9). Fisher’s Exact test showed no significant difference related to these risk factors between those with mild versus moderate stroke. One participant (baseline NIHSS=1) had a second stroke prior to Week 12 visit. No difference was found on t-test using SDMT scores between this participant and other participants with mild stroke, at baseline or Week 3. Therefore, he remained in the study. There was no difference in age or education between mild and moderate stroke participants (Table 2). Random missing data included DCS not administered in four participants at baseline and no data collected for the participant with a second stroke at Week 12.

The IQCODE questionnaire was used to exclude one patient for prior cognitive impairments; information which had not been noted in medical history or at initial family interview. Four patients with prior mild stroke were enrolled: three of the patients, aged
52-56 years, were actively employed and one, aged 73 years, was retired but active. Their IQCODE evaluations identified no prior cognitive impairments.

Exclusions

Of the 42 participants enrolled in the study, 12 did not complete the study (28%) and were excluded from analysis. One died; one moved due to persistent unemployment; five withdrew consent; five (13%) were lost to follow up after baseline testing. Participants with mild stroke accounted for 60% of withdrawn or lost to follow up. The participant who died and the one who moved had mild strokes. Reasons to withdrawal given as: lack of interest in research (n=3) and inconvenience of research (n=2). No difference was found on t-test between enrolled participants and non-completing participants for gender, NIHSS, education or all cognitive tests scores. There was a statistical, but not clinical, age difference between group means (t (37) =1.443, p<.05), with non-completing participants being younger than participants (mean=57, SD = 15 versus mean= 63, SD =9).

Five exclusion criteria (Table 3) accounted for the majority of screened patients (77%) being excluded: including hemorrhagic stroke, NIHSS criteria, age greater than 80, no stroke, and stroke onset greater than 72 hours prior to admission. Three patients with mild stroke were excluded due to normal SDMT scores at baseline; thus, of the patients with mild stroke who were tested (n=26), 12% did not have IPS impairment. There was no significant difference in their NIHSS means compared to means of enrolled participants with mild stroke.
IPS Impairment and stroke severity

Overall sample’s SDMT score frequency was abnormal for 100%, 97% and 79% of the participants, respectively at baseline, visit 2 and visit 3. Linear mixed modeling indicated IPS impairment change, either in frequency or severity, was not dependent on stroke severity; IPS impairment did improve over time (p=0.005), with similar improvement over time regardless of stroke severity; from 100% to 77% for mild stroke participants and to 83% for moderate stroke participants at Week 12 (Figure 1). Linear mixed modeling for the combined sample demonstrated IPS impairment severity also decreased by Week 12 regardless of stroke severity; participant SDMT mean points were 23, 28, and 33, respective of the three visit time points. Normal SDMT score range is 51-62. Effect size could not be calculated due to no difference in IPS impairment between mild and moderate stroke groups at any time point.

Of note, for the three visits, all CVLT-II scores were abnormal in 100% of participants, while Digit Span scores were abnormal for 83%, 70% and 66% of participants, respectively. However, there was no correlation between the SDMT scores and the two memory measurement scores at any of the three time points.

IPS Impairment and Quality of Life

At Week 12 there is evidence of minimal disability in the sample: modified Rankin scale (mRS) (mean 2, SD 1) and Barthel Index (BI) (mean 92, SD 20), and NIHSS (mean 1, SD 2). Independent sample t-tests indicated no difference in QOL by stroke severity at Week 12, i.e. QOL was similar in both mild and moderate stroke participants. Most participants characterized their QOL as fair (28%) to good (48%) with
20% as poor or very poor. Of note, there was no significant association between SDMT scores and the Depression short form QOL (p=0.52). Decreased quality of life was associated with presence of IPS impairment at Week 12, though significant only in AC Executive QOL (p=0.04). Better AC Executive QOL scores correlated with non-IPS impaired participants (mean 11.3, SD 2.7) rather than impaired participants (mean 16.1, SD 9.2) (Table 4). Finally, although not a significant difference, a similar trend was noted with better QOL scores in non-IPS impaired participants for Depression, AC-General and PAW: 11.3(5.0), 15.7(7.0), 14.2(8.5) than in IPS impaired participants: 13.4(8.8), 20.7(10.1), 17.9(10.4), respectively.

**Exploratory analysis**

As the Neuro-QOL total score has not yet been validated, its use and analysis in the current study were exploratory (Table 4). Participant totals by categories, from very good to very poor, were n=3, n=12, n=7, n=1, n=3, respectively. A Spearman’s rho indicated a correlation between Neuro-QOL summary score and SDMT scores (p=0.03). Higher SDMT scores were associated with better QOL. However, independent sample t-tests did not indicate a difference in Neuro-QOL summary scores between participants categorized as IPS impaired or unimpaired (i.e. abnormal or normal SDMT scores, respectively). An association among stroke severity, summary Neuro-QOL score and its four pre-selected domain or short form scores was not statistically evaluated due to the small sample size. However, over 70% of participants with mild stroke self-reported a good or very good summarized QOL with 18% of mild stroke participants and 16% of moderate stroke participants reported poor or very poor on the summarized Neuro-QOL.
Discussion

This study of 30 participants with acute ischemic stroke and IPS impairment presents three key findings. First, all participants experienced persistent impairment in IPS and working memory during the first 12 weeks, regardless of stroke severity. This is not unexpected with brain injury, however, there is limited studies exploring this during acute stroke, and in particularly those with mild stroke, with one previous study reporting…..previously patients with mild stroke were assumed to have minor deficits which recover spontaneously (Edwards et al., 2006). In the current study, frequency of IPS impairment was100% with a 21% reduction in 12 weeks. In an acute stroke study which included both mild and moderate??, Hurford, Charidimou, Fox, Cipolotti, & Werring (2013) linked speed and attention as one domain, indicated it was the most frequently impaired and had the most rapid recovery; 72% of patients were impaired with a 50% recovery rate at three months. However, the sample was not separated by stroke severity and two separate cognitive functions were measured together. While evaluating improvement over time, Barker-Collo et al. (2012) and Cumming, Marshall & Lazar, (2013) determined executive function and IPS remained the most impaired functions five years after stroke. Rasquin et al. (2004) noted mental speed improved after one-year but continued to have more impact on cognitive functioning than memory impairment.

The results of this study support that persistent and pervasive IPS impairment must be considered when interacting with patients with stroke, regardless of stroke severity during the acute stroke period. Patients with stroke have difficulty either comprehending or framing questions to ask, resulting in anxiety and feelings of inadequacy (Olofsson, Andersson, & Carlberg, 2005). IPS impairment related to
dysfunction in limited time and/or simultaneity mechanisms are likely a component of these difficulties. Patients with stroke may require more time to process information or may need information presented in smaller amounts for effective processing. Instead, they receive care in loud and frequently frenetic environments where they are expected to give consent before they can gain access to time sensitive stroke treatment. During the acute stay patients receive incalculable instructions, from initial encounter to discharge instructions, regardless of limited ability to understand. Additionally, Suzuki et al., (2013) suggests patients can be identified as non-compliant without providers determining if the patient actually understands the directions (Suzuki et al., 2013).

As noted earlier, in this study IPS impairment percentages at Week 12 (79%) exceeds similar findings noted in other studies. One explanation may be construct interference. Other studies have linked IPS and either attention or memory in a measurement. There is a conceptual relationship between abnormal IPS and memory, nevertheless, IPS can be impaired yet have little impact on memory and vice versa (DeLuca, 2008). The measurements in this study were specifically selected to limit construct interference (Strauss et al., 2006). However, in the current study there was no significant correlation between the SDMT and the two memory measurements (CVLT II and Digit Span) at any of the three time points.

The second key finding is the acknowledgement that other possible causes of poor QOL, such as disability and depression, must be evaluated in order to isolate the impact of cognitive impairment on QOL. Depression has been reported previously as being associated with poor QOL after stroke (Haacke et al., 2006). However, in this study, the
results for the Depression short form did not reach significance, indicating no relationship between depression and poor AC Executive QOL.

Healthcare providers in research and clinical care assess impairment after stroke using a variety of tools. Measurements in common use in the clinical setting, such as NIHSS, mRS, BI, and Neuro-QOL are not designed to adequately measure all aspects of stroke injury and recovery (Kasner, 2006), particularly cognitive impairment (Sangha et al., 2015). In this study, the NIHSS, mRS, and BI indicated minimal disability and only one QOL short form was significant at Week 12. Despite this data, the SDMT test indicated 79% of participants had IPS impairment. One reason could be IPS impairment does not impact QOL or instrumental ADLs, however, this is not supported in literature (Barker-Collo, 2006; Cumming, Brodtmann, Darby, & Bernhardt, 2014). A second reason is the NIHSS, mRS, and BI scales give more weight to physical impairment than cognitive impairment, thus producing a biased view of patient condition (Gottesman et al., 2009; Kasner, 2006). Up to 60% of patients defined as nondependent on these scales have been previous reported to have some degree of cognitive impairment (Pendlebury, Rothwell, Mariz, Mehta, & Baig, 2010).

The third key finding is Neuro-QOL does not adequately screen for certain cognitive impairments, like IPS impairment. Indeed, 18% of participants with mild stroke and IPS impairment in this study indicated poor QOL. These findings contradict another study (Sangha et al., 2015) of patients with mild stroke using Neuro-QOL to assess QOL. General cognitive impairment was associated with poor QOL in only 8-16% of participants with mild stroke and transient ischemic attack (TIA) (Sangha et al., 2015). One difference is in the previous reported study in the literature, the sample included
patients with TIA, which may present with a different cognitive profile compared to mild stroke.

Neuro-QOL was designed as an efficient, flexible and precise measurement of the physical, emotional, cognitive and social patient functions (Gershon et al., 2012). The cognitive sections were developed and validated as a measurement with a common language for use in multiple neurological populations (Gershon et al., 2012). However, a general instrument may not have the depth required to identify such a subtle dysfunction as IPS impairment (Ready & Ott, 2003). Careful consideration should be given to use of QOL instruments in stroke research or the clinical setting. Unless specifically designed to indicate how cognitive status impacts QOL, these instruments may not adequately assess patients with stroke. QOL measurements have three potential drawbacks: they may not be sufficiently relevant or sensitive to measure a particular population (Fayers & Machin, 2013) they must be self-reports and yet may be difficult to complete for elderly patients (Carlson et al., 2011) or those with IPS impairment.

Neuro-QOL, while one of the better self-report QOL instruments (NINDS, 2010), may be limited in measuring changes in QOL impacted by IPS impairment. In elderly patients with stroke many life activities with aspects of time pressures, like managing finances and appointments, have been assumed by spouses or adult children. Thus, patients may be guessing on 60% of the activities assessed by the AC-Executive; the one Neuro-QOL section indicated as statistically significant in the study. AC-General appears to focuses on memory and attention, with only one item addressing IPS. AC-Executive does not directly address IPS, nonetheless, it does present items impacted by time pressures. Time pressures can exacerbate faulty limited time and simultaneity
mechanisms, resulting in slow IPS (Salthouse, 1996). Additionally, there is concern with the reverse scoring on the Neuro-QOL Likert scale which occurs between and within domains. Reverse scoring relates to items in which the score indicates the opposite of the construct being assessed. For instance, in the Anxiety domain “1-Never” is a positive response, however, in AC General it is a negative response. Within the Satisfaction with Social Roles section “1-Not at all” response may be positive or negative, depending on the item presented. Reverse scored items are especially problematic for older participants (Carlson et al., 2011) and very likely for persons with IPS impairment, due to the need for complex reading comprehension (DeLuca, 2008).

Several limitations do exist in the current study. The a priori effect size was not calculated due to no statistically significant difference in SDMT scores by stroke severity. While this supports the hypothesis of no difference between the mild and moderate groups, there is concern that the sample was too small to identify a very small difference. In addition, the sample size limited analysis of the totaled Neuro-QOL score based on stroke severity or IPS impairment. However, the exploratory nature of this inquiry has laid the foundation for further research. Another limitation, in study reproducibility, relates to completion of follow up visits. The study was based at a metropolitan hospital using a rescue helicopter to transport patients hundreds of miles to receive stroke treatment. Therefore, to complete follow up visits some participants had to travel significant distances to a testing center. To decrease lost to follow up the investigator met participants at locations convenient to the participant. This required significant travel time for the investigator, averaging 85 minutes per visit, but did equate
to a relatively low lost to follow up percentage (13%). To perform a similar study an additional exclusion of distance to testing center may need to be imposed.

**Conclusion**

Findings from the current study have profound implications in clinical care and in research for patients with stroke. Consideration should be given for adopting the use of the SDMT in clinical settings. The SDMT, as a screening instrument, is brief, easily scored at the bedside, requires only a few minutes to administer, and uses either written or oral format (Sheridan et al., 2006). For patients with low NIHSS this may provide the physician with sufficient information regarding the need for emergency treatment. Further, precautions should be taken to avoid rushed explanations of care at the bedside or research consent forms of extended length and complexity. Patients with IPS impairment have slow thinking to a degree not previously appreciated, impacting their ability to understand and actively participate in their own care. Awareness of IPS impairment can assist nurses in formulating effective patient education and therapists in shaping rehabilitation goals and capabilities.

This study provides evidence of minimal spontaneous IPS and memory recovery in patients with mild and moderate stroke after 12 weeks. Cognitive impairment is not minor in patients with mild stroke; IPS impairment often becomes chronic. Therefore, neurocognitive assessment and initiation of treatment should be considered in the acute setting, while the brain is undergoing its most active neuroplastic changes. Future research should be done on the factors that promote or hinder cognitive recovery within the first 12 weeks. Additionally, research on QOL instruments is necessary, to investigate what actually causes poor QOL in patients with mild stroke. Discussion with
the Neuro-QOL creators may encourage further analysis of the scale in the stroke population or, possibly, addition of a domain specifically evaluating IPS. As a small observation study the information obtained was sufficient to encourage design of a larger randomized trial regarding instrument development, to further identify interactions between IPS and other cognitive functions.
References


Wake Forest University (WFU). *Negatively-keyed items and reverse-scoring, Getting SPSS to do it*. Retrieved from psych.wfu.edu/furr/716/Reverse-scoring.doc


Tables and Figure

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<tr>
<th>Table 1</th>
<th>Test Sequencing and Description</th>
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<tbody>
<tr>
<td>I. Cognitive Test Sequence</td>
<td>1. CVLT II SF (immediate recall)</td>
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<tr>
<td></td>
<td>2. Distractor (count backward)</td>
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<tr>
<td></td>
<td>3. CVLT II SF (short delay recall)</td>
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<tr>
<td>II. Test Description</td>
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<tr>
<td>Cognitive Test</td>
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<td>California Verbal Learning test–2nd Ed. Short form (CVLT II SF)</td>
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<tr>
<td>Digit Span</td>
<td>Working Memory</td>
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<td>Symbol Digit Modalities Test (SDMT)</td>
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<td>Digit Symbol-Coding (DSC)</td>
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<td>Symbol Search</td>
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Note. I. Cognitive Test Sequence section demonstrates the sequence of cognitive testing, specifically use of other tests to create distraction for CVLT II long delay recall. II. Test Description section briefly describes the test or participant activity followed by psychometric information related to reliability and validity. DSC and Symbol Search are the two components of the Processing Speed Index (PSI) from the WAIS III.
### Table 2
*Patient Characteristics*

<table>
<thead>
<tr>
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<th>All (N=30)</th>
<th>Mild Stroke (n=18, 60%)</th>
<th>Moderate Stroke (n=12, 40%)</th>
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<td>Mean (SD)</td>
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<td>--</td>
<td>12 (40)</td>
<td>8 (44)</td>
</tr>
</tbody>
</table>

*Note* Patient characteristics apportioned by stroke severity and time. Age and education not used as covariates, variance accounted for by norm values tables. Week 12 NIHSS, mRS and BI used to indicate general disability during QOL consideration at Week 12. Mean and SD values are rounded to whole numbers.
Table 3

*Most Common Reasons for Exclusion*

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain Hemorrhage</td>
<td>296 (25%)</td>
</tr>
<tr>
<td>NIHSS</td>
<td>179 (15%)</td>
</tr>
<tr>
<td>Age &gt; 80</td>
<td>179 (15%)</td>
</tr>
<tr>
<td>No stroke</td>
<td>147 (13%)</td>
</tr>
<tr>
<td>Stroke onset &gt; 72 hours</td>
<td>96 (9%)</td>
</tr>
</tbody>
</table>

*Note.* Five most common reasons for exclusion by total number of excluded patients & percentage of excluded to total number of patients screened (N=1194).
### Table 4
SDMT and QOL Tests at 3 months

<table>
<thead>
<tr>
<th></th>
<th>All (N=29)</th>
<th>Mild Stroke (n=17, 59%)</th>
<th>Moderate Stroke (n=12, 41%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Range</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>SDMT</td>
<td>33.0 (11.3)</td>
<td>9-51</td>
<td>34.3 (11.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>31.1 (11.6)</td>
</tr>
<tr>
<td>Neuro-QOL Total*</td>
<td>189.5 (66.9)</td>
<td>111-341</td>
<td>182.3 (71.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>199.8 (61.4)</td>
</tr>
<tr>
<td>Neuro-QOL Domains</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>13.5 (8.8)</td>
<td>8-37</td>
<td>13.1 (9.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13.9 (8.8)</td>
</tr>
<tr>
<td>App Cog Gen</td>
<td>20.7 (10.1)</td>
<td>8-40</td>
<td>18.8 (9.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23.3 (10.8)</td>
</tr>
<tr>
<td>App Cog Exec</td>
<td>15.1 (8.5)</td>
<td>8-36</td>
<td>14.2 (9.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16.3 (7.5)</td>
</tr>
<tr>
<td>Positive Affect</td>
<td>17.5 (10.4)</td>
<td>8-45</td>
<td>17.9 (11.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17 (8.6)</td>
</tr>
</tbody>
</table>

*Note. Values apportioned by stroke severity. *Neuro-QOL total score is exploratory and has not been validated through testing. Neuro-QOL total includes scores for all 13 domains in a static test. Neuro-QOL domains includes selected domains for this study, scored & interpreted per scoring manual (NINDS, 2010).*
Figure 1. SDMT score changes over time

Figure 1. Decline in SDMT scores over 3 study time points overall and by stroke severity
Appendix A

Patient-centered Cognitive Recovery in Stroke:

A Concept Synthesis

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University of Texas

Health Science Center at Houston

School of Nursing
Abstract

Purpose/Objectives: To provide a clearly constructed definition of Patient-centered Cognitive Recovery in patients with Stroke (PCRS)

Data Sources: Peer reviewed articles and book chapters.

Data Synthesis: Cognitive impairment affects patients with stroke and can lead to dementia. Recovery is unpredictable, prolonged, and is patient centered and patient controlled. Multiple models of cognitive recovery exist but are limited or discipline biased. These models are hampered by the user’s viewpoint or aims, use of loose or confusing terms, and the restrictiveness of the biomedical model. However, a collaborative patient-centered cognitive recovery model has not been previously explored.

Conclusions: PCRS is a transitional state in which a person’s cognitive capacities can be modified to approach or achieve pre-injury levels. Cognitive changes are promoted or hindered by the interaction between personal capacities and a person’s resources. Antecedents to the transitional state are stroke with cognitive impairment, some level of self-awareness, and absence of significant pre-existing cognitive disorder. Consequences include improved cognitive function and quality of life; and ability to function in the community.

Implications for Nursing: Cognitive recovery is not a one size fits all process. The PCRS model promotes collaboration, self-care, and provides a framework to guide all healthcare providers in identifying and addressing patient needs beginning in the acute care setting.
Introduction

Stroke can impair the individual mental attributes which allow a person to understand the world and to function within it. Mental abilities and processes are the cognitive capacities required for thinking and knowing. Cognitive impairments are experienced by 50-90% of survivors after stroke (Gottesman & Hillis, 2010). Approximately 17 different cognitive impairments can occur after stroke and, further, impairments can have a multiplicative impact (Donovan et al., 2008). The lateralized nature of cognitive impairments, along with the physical and emotional impact of stroke, requires treatment to be planned, organized, and comprehensive. Cognitive impairment and, therefore, cognitive recovery concerns several different health disciplines. Each discipline considers the recovery concept from the bias of their own medical, psychological or rehabilitation prospective (Davidson, Lawless, & Leary, 2005). This paper will present a concept synthesis for cognitive recovery and will display different aspects of patient-centered cognitive recovery for stroke patients within a multicomponent model.

The concept of health recovery is critical in health care but is difficult to define or even to identify precisely (Collier, 2010). Recovery is a transitional state from illness to wellness (Skärsäter & Willman, 2006). The understanding or interpretation of recovery depends on which discipline is viewing the illness or injury and even upon whose prospective: patient or healthcare provider. Multiple models of cognitive recovery exist but controversy remains on their adequacy, both within and without the particular discipline (Collier, 2010; Whitley & Drake, 2010; Wilson, 1998). Some rehabilitation and psychiatric models have begun to reach beyond traditional biomedical model format.
by adding psychosocial dimensions (Albert & Kesselring, 2012; Wilson, 2002b).

However, it remains remain essentially biomedical models with the goal of diagnosing and treating, i.e. the concept generally expressing or guiding provider activities. Patient centered care involves a collaboration between provider and patient (Stewart et al., 2000). Understanding how and why cognitive recovery is happening requires looking at how bio-psychosocial domains are interacting within the person and what may influence these interactions.

The complex nature of cognitive recovery in stroke requires a top down knowledge synthesis approach to more fully explore the changing state. A concept synthesis is a new way of grouping or ordering information when relevant information such as attributes are unclear or unknown (Walker & Avant, 2005). The synthesis will add new insights and may point to a foundational basis or connection between the various recovery models and suggest more comprehensive interventions.

The current concept synthesis examined sets of related concepts and is supported by aspects of two parent theories: Neuman System theory (Neuman & Fawcett, 2001) and Orem’s Self-care theory (Orem, 2001), specifically, the System Model’s environment constructs and the concepts of self-care and of self-care agency. This concept synthesis represents a clear definition of patient-centered cognitive recovery as it pertains to patients with stroke, identifiable antecedents, attributes and consequences of the concept, and a model case and related cases.
**Literature Review**

The study of cognition and cognitive recovery have been of scientific interest since 400 B.C.E. when Plato first determined the brain was the seat of all mental processes (Crivellato, 2006). Cognition is defined as the set of all mental abilities and processes related to knowing, specifically capacities for attending, remembering and reasoning, and activities such as problem solving, decision making, comprehension, language use, etc. (APA, 2015). Thus in stroke, cognitive impairment is an intrinsic deficit that alters these functions and capabilities. Jaillard et al. (2009) noted 92% of patients were impaired two weeks after stroke and between 38-92% are impaired at 12 weeks, depending on clinical factors (Brainin et al., 2015; Patel, Coshall, Rudd, & Wolfe, 2002). Spontaneous cognitive recovery by 12 weeks may account for some degree of improvement (Cramer, 2008). However, cognitive impairments have been noted in at least 80% patients with stroke for two years, with a 10-fold increase in dementia rates in this population (Rasquin, Lodder, & Verhey, 2005). Within five years of stroke, 30-50% patients with cognitive impairment advance to dementia (Alvarez-Sabin & Román, 2011; Leys, Hénon, Mackowiak-Cordoliani, & Pasquier, 2005) with a 3-fold increased risk of death (Desmond, Moroney, Sano, & Stern, 2002). Therefore, interventions to promote recovery continue to be of interest.

The terms cognitive rehabilitation and cognitive recovery are used interchangeably but are not well defined in literature (Bour et al., 2010; Das Nair & Lincoln, 2008; Green et al., 2008). Rehabilitation is defined as physical restoration by therapeutic measures and reeducation, from the 16th century Latin word habilitate meaning to make fit or capable (Merriam-Webster’s Collegiate Dictionary, 2015). The
American Congress of Rehabilitation Medicine (SCR, 2015) defines cognitive rehabilitation as a service intent on establishing new patterns of cognitive activity or compensatory mechanisms or reinforcing, strengthening, or reestablishing previously learned patterns of behavior.

Recovery, a more inclusive term from the 15th century, refers to changes in a state of being, as in regaining or returning toward a normal or healthy state (Merriam-Webster’s Collegiate Dictionary, 2015). The term encompasses the more holistic change in mode or condition of being rather than a response to treatment. In the self-care theory, changes in state require the human being to attend to and deal with impairments themselves (Denyes, Orem, & Bekel, 2001). Considering recovery as a state extends the concept of healing beyond biomedical models of rehabilitation. While cognitive recovery is not well defined, some recovery outcomes have been identified. A meta-analysis of cognitive rehabilitation research by Cicerone et al. (2011) reported multiple descriptive indicators of cognitive recovery including compensation without necessarily improving, improvement of overall cognitive function or of underlying neurocognitive system, effectiveness of interventions and cognitive remediation.

In addition to outcomes, certain antecedents have been identified, namely neuroplastic changes in the brain. Murphy and Corbett (2009) view cognitive recovery as varying degrees of behavioral compensation and spontaneous return of function or improved performance provided by the remaining and newly developed brain circuits. This implies that recovery is not dependent on rehabilitation, though logically recovery benefits from it. Physical rehabilitation takes advantage of brain neuroplasticity by beginning almost immediately after stroke (Duncan et al., 2005). This immediacy
addresses caveats to Murphy and Corbett (2009) view of cognitive recovery after stroke. Neuroplasticity is dependent on a critical time window opening shortly after injury, there is sufficient undamaged brain, and training-dependent effects. There are synaptic-based learning rules which require adequate synaptic input (stimuli) and early mechanisms to redistribute synaptic strength (neuroplasticity). However, cognitive rehabilitation research is typically performed months or years after brain injury (Beasley & Davies, 2013; Dawson et al., 2013; Kerhoff et al., 2014); an exception is aphasia research which frequently begins 2-4 weeks after stroke (Bakheit et al., 2007; Conklyn et al., 2012). Formal cognitive rehabilitation is typically dependent on physician referral 1-3 months after the hospital discharge.

Attempts to create a theoretical model expressing cognitive recovery or rehabilitation are hindered by three factors. First, there is a general lack of unity or agreement over key terms related to cognitive operations such as what constitutes impairment (Jokinen et al., 2006; Nys et al., 2007), impact of impairment (Edwards, Hahn, Baum & Dromerick, 2006; van Schouwen-van Kranen, 2014), treatment factors (Särkämö et al., 2008; Hachinski et al., 2006), how to measure recovery (Bour et al., 2010; Castellanos et al., 2010; Liman et al., 2011), or what other factors may impact recovery (Carlsson, Moller & Blomstrand, 2009; Greenop, Almeida, Hankey, van Bockxmeer, & Lautenschlager, 2009; Mayo, Fellows, Scott, Cameron & Wood-Dauphinee, 2009). Second, term imprecision in literature, i.e. the interchangeability of cognitive recovery and rehabilitation, support concerns that neuroscientists use terms in conflicting ways that vary from their original meanings (Figdor, 2012). This term looseness promotes a systematic lack of relationship between the original meanings of
mental terms and research findings, thus confusing research implications and the nature of cognitive operations.

The third factor hindering successful cognitive recovery model creation relate to model structure. Structurally, attempts to model cognitive recovery have depended on a biomedical model (Albert & Kesselring, 2012; Wilson, 2002b). The earliest treatise on cognitive rehabilitation, in the 1600s, discussed treatments for brain injury related impairments (Boake, 2003). Biomedical models focus on natural sciences and consist of practical applications of these sciences to illness and rehabilitation (Goldenberg, 2006). Natural science lacks the scientific nomenclature for the human experience crucial to the experience of illness and recovery. As a result, illness and recovery becomes a breakdown or repair of objectified body-machine (Goldenberg, 2006). Of course, people are more than just physical entities or disease exemplars and the goal of recovery is as much reintegration of the person as it is physical restoration.

To date, cognitive rehabilitation is considered a modality based process whereby health service professionals ameliorate or alleviate cognitive impairment (Wilson, 2002a). The model does not adequately incorporate psycho-social aspects of recovery or the mediators and moderators of health; the primary focus is not on the individual patient, who will ultimately control the progress of treatment. Cognitive recovery is the process whereby a patient’s cognitive capacities are regained and reach baseline performance (Linqvist, Schening, Granstrom, Bjorne, & Jakobsson, 2014); the patient is the actor and interventions are the tools.
In summary, the literature review demonstrates a lack of unity in term use or to
demonstrate a comprehensive recovery model, despite multiple attempts ongoing for
almost two decades. Cognitive rehabilitation models have taken into account physical
impairment, treatment modalities and, to a degree, the psychosocial aspects of stroke
treatment. However, the models fail to center recovery around the patient, who is most
impacted by, and most significantly impacts, recovery progress. This paper will explore
the concept of patient-centered cognitive recovery in stroke.

**Patient-centered Cognitive Recovery in Stroke**

The term recovery has been used several in diverse health disciplines, i.e. in
rehabilitation, physical and mental health. In mental health, recovery is a therapies-
induced reduction or control of symptoms and a return to baseline levels of functioning
(Whitley & Drake, 2010). Though it is the consumer of the mental health services who
identifies recovery, i.e. symptoms no longer overwhelm and incapacitate. Wilson (2002b)
created one of the most comprehensive biomedical models, the provisional model of
cognitive rehabilitation. However, she recognized the impossibility of addressing all the
complex problems of patients with cognitive impairment using the medical model.
Biomedical models are excellent at finding solutions to specific problems and measuring
response to interventions. But patients with stroke are more than their problems.
Therefore, a more fluid model is needed, one which focuses on the main actor in the
recovery process.

For the purpose of the current concept synthesis the model, patient-centered
cognitive recovery in patients with stroke (PCRS), is defined as a transitional state in
which a person’s cognitive capacities can be modified by personal capabilities and environments to approach or achieve the person’s pre-injury level of cognitive health (Figure 1).

Transitional state, a fundamental concept in nursing theory, occurs between two fairly stable states pertaining to illness and health (Chick & Meleis, 1986). Stable state refers to a relatively unchanging condition, not to medical stability. An acute stroke will not become an un-stroke and, therefore, will be followed by a transitional state which results in an outcome of cognitive improvement or subpar recovery. The PCRS model is applicable in stroke specifically because stroke follows an established injury and recovery pattern. Additionally, neuroplastic changes after stroke are the result of behavioral, sensory, and cognitive experiences (Kleim & Jones, 2008); if experiences are therapeutic or positive then the outcome is cognitive improvement. In PCRS model, transitional experiences are driven by patient needs and are supported by two cognitive treatment approaches: relearning and compensatory strategies (Miller et al., 2010).

The main component of the model is named cognitive accommodation (Figure 1) and is considered the workstation for the translational state. Accommodation, a Latin word circa 1600, is a state or process of adjustment or adaptation, as of differences or to new circumstances (Dictionary.com, 2015). Accommodation in learning theory is a radical conceptual change occurring when central concepts are replaced or reorganized (Posner, Strike, Hewson, & Gertzog, 1982). In cognitive accommodation, a patient’s cognitive capacities change in response to interactions between his personal capabilities and his environments. Personal capabilities (acceptance, agency and congruence) are internally oriented activities directed to the control of behavior that people need to
perform self-care (Orem, 2001). The environments (Figure 1) are a person’s resources or interactive forces which bind together to aid or hinder recovery (Neuman & Fawcett, 2001). The outcome of cognitive accommodation depends on the interactions that occurred in the workstation. If they are supportive and adequate than recovery will occur. If not, there will be no significant improvement of the cognitive impairments.

**Defining attributes**

Defining attributes are the cluster of characteristics most frequently associated with the concept and allow the broadest possible insight into a concept (Walker & Avant, 2005). Several disciplines use the cognitive recovery concept but each lack some aspect or key attribute. The closest recovery concept is seen in the mental health discipline but it does not account for the physical environment. Thus, key attributes for the current concept will include a synthesis of attributes from the other disciplines and the parent theories. In the PCRS model attributes are divided into environments, acting as the framework in which a person functions, and personal capabilities which are proactive abilities acting as drivers and guiders of behavior. These attributes are modified in some degree, either positively or negatively, during the translational state. The work of cognitive accommodation involves the supportive or deleterious interactions within and between the attributes. The interactions must be more supportive than deleterious for effective recovery and to produce self-care promoting decisions and actions.

**Environments**

The four environments (physical, internal, created and external) are forces or interactive influences within or without the patient, unique to each person based on past
life experiences and current physical or social conditions (Orem, 2001). In the PCRS model there are no dividing lines between the environments, indicating each one is able to impact the other three.

The physical environment is any purely physical human factor in stroke and health, including brain neuroplasticity (Murphy & Corbett, 2009), age (Green et al., 2008), co-morbidities (Kruyt et al., 2008; Patel, Coshall, Rudd, & Wolfe, 2003), decreased level of consciousness after stroke (León-Carrión et al., 2012), biological changes due to disrupted sleep state (Goel, Rao, Durmer & Dinges, 2009) and severity of physical impairments, size and location of lesion (Sachdev et al., 2006). Lesion location can sometimes indicate which cognitive functions will be most affected and, logically, larger lesions have higher neuroplastic repair requirements, and thus slow cognitive recovery. Also known to slow recovery, fragmented sleep induces a fatigue effect when cognitive tasks are extended or demanding (Goel et al., 2009). Overall the physical environment, not included in the Neuman system model, plays a significant role in cognitive recovery after stroke.

The internal environment is defined as all internal forces or interactive influences contained solely within the boundaries of the patient (Neuman & Fawcett, 2001). In stroke, they can include depression (Narushima, Chan, Kosier & Robinson, 2014), apathy (Mayo et al., 2009), anxiety, fear, delirium (Rijsbergen et al., 2011), personality (Carver & Connor-Smith, 2010), cognitive reserve (Sharp, Turkheimer, Bose, Scott & Wise, 2010), pre-stroke dementia or other psychiatric history. These are psychiatric factors that influence learning, perception and behavior.
The created environment is representative of an open system exchanging energy with the other environments (Neuman & Fawcett, 2001); similar to personal capabilities, this environment acts as background guiders of behavior. In the Neuman System model this environment is inherently purposeful and functions as a protective perceptive coping shield, unconsciously developed with a main goal of stimulating system health. In patients with stroke, the created environment includes belief systems, perceptions of life (McKenna, Liddle, Brown, Lee, & Gustafsson, 2009), self-esteem, attitude, self-efficacy (Aben, Busschbach, Ponds, & Ribbers, 2008), learned helplessness (Mayo et al., 2009), resilience, cognitive reserve (Stern, 2009), and reactions to uncertainty. Recovery is enhanced by attitude and self-efficacy, for instance, motivating patients to exceed health provider expectations (Medin, Barajas, & Ekberg, 2006) while defeatist beliefs can slow progress.

The external environment is defined as forces or interactive influences external to the patient (Neuman & Fawcett, 2001). They can include social support (Glymour, Weuve, Fay, Glass & Berkman, 2008), access to care, social interactions (Mukherjee, Levin, & Heller, 2006) and resources (Chumbler et al., 2004), cost (healthcare cost, financial loss, etc.) and holistic therapy (Cicerone et al., 2011). The forces of the external environment are contacts or conditions outside the patient which hinders or helps recovery. A simple combination of physical therapy and occupational therapy does not meet the needs of stroke patients (Cicerone et al., 2011; Nys et al., 2005).

Therapy is a mediator variable between cognitive accommodation and positive recovery indicators. A mediator variable explains the relationship between the two other variables (Baron & Kenny, 1986). In the PCRS model, holistic therapies are specifically
identified because these therapies address the multiple needs of the patient with stroke. Due to the brain’s limited neuroplasticity window after stroke and the need for high levels of stimulating input (Murphy & Corbett, 2009), effective recovery is dependent on comprehensive-holistic neuropsychological rehabilitation (Cicerone et al., 2011). Therapies can be cognitive, physical, behavioral, social or psychiatric in nature (Alvarez-Jimenez et al., 2013; Cicerone et al., 2011) and are initiated and conducted by trained providers.

The final pathway or visible expression of the accommodation workshop is through the external environment. In other words, the mediator explains how the external events (participation and response to therapies) take on internal psychosocial significance.

**Personal Capacities**

Personal capabilities, the proactive abilities acting as drivers and guiders of behavior, include self-care agency, congruence, and accommodative coping. In the current model (Figure 1), interactions are indicated by dotted lines between capabilities, environments, and cognition. Reciprocating arrows along these lines show active and continuous interactions, all are equally important but some may take precedence based on a person’s ever changing needs or self-care requisites. Self-care agency is necessary for development of positive self-care behaviors (Daryasari, Karkezloo, Mohammadnejad, Vosooghi, & Kagi, 2012; Shreck, Gonzalez, Cohen, & Walker, 2014).

According to Orem’s (2001) foundational work in the 1960s, self-care is a lifelong process contributing to life, health, and well-being. This process includes
characterizing and meeting self-care requisites, making decisions about what can and should be done, and deliberately performing chosen actions. Agency is the capabilities and power to perform self-care for survival (Welzel & Inglehart, 2010). The human ability for engaging in self-care is conditioned by such factors as age, developmental state, life experience, sociocultural orientation, health, and available resources; including self-care skills, the valuing of health, knowledge and energy for self-care (Gast et al., 1989). Further, to engage in deliberate actions a person must have essential powers that are activated through stimuli.

Accommodative coping is the mechanism or inward behavior of adapting or adjusting to the stress of insurmountable interference (as in cognitive and physical impairments) and includes acceptance, cognitive restructuring, and scaling back one’s goals in response to those impairments (Carver & Connor-Smith, 2010). Morling and Evered (2006) determined that it is a type of secondary control in which a person aligns one-self to circumstances in an effort to maintain the perception of control. The alignment is not resignation to new reality but to set new goals. Morling and Evered (2006) understood acceptance as enhancing motivation or the capacity to change. Greenglass and Fiksenbaum (2009) view it not as a reaction to stress but as proactive coping, involved in goal setting and having efficacious beliefs and associated with resources for self-improvement, including social support. During cognitive recovery the patient with stroke accepts their present condition while becoming determined to do what is necessary to regain lost function. Patients begin to identify practical problems and plan for possible solutions motivating them to participate more fully with rehabilitation
(Kirkevold, 2002). The act of adjusting self and accepting the new reality promotes fit (Morling & Evered, 2006).

Congruence relates to a fit-focused reality. The classical definition of congruence is an organizational philosophy regarding the consistency or fit between components in an organization (Nadler & Tushman, 1980). In this concept synthesis the organization is a person, therefore, congruence guides all decisions about how patient resources and inputs will be configured to meet demands, constraints, and opportunities within the context of the person’s reality and history. “Congruence involve(s) pursuing goals for self-determined reasons and being oriented toward goals that entail intrinsically satisfying activity (and) connect with organismic needs” (Sheldon & Kasser, 1995, p. 533). It is the aligning of all that is within the environments, through the power of personal capabilities and cognition, in the performance of life. Congruence occurs when patients with stroke experience personal strivings for genuinely chosen goals that are of intrinsically satisfying value. The strivings, combined with recognition of satisfying values, help the patient connect with a desired possible future.

**Antecedents**

Antecedents are events that must happen or exist prior to the occurrence of a concept. Four antecedents are identified relating to cognitive recovery. For the purposes of this synthesis, a person must have experienced an ischemic stroke resulting in cognitive impairments. It can be expected that a severe ischemic event would leave cognitive impairments but it has been noted that patients with minor strokes can experience multiplicative cognitive impairments (Li et al., 2010; Dong et al., 2012).
The third antecedent is some level of self-awareness after stroke. Self-awareness is the ability to perceive ourselves objectively while congruently aligning our behavior to a set of standards and values (Schmidt, Lannin, Fleming, & Ownsworth, 2011). Early research determined that cognitive therapies can be initiated shortly after stroke even if self-awareness is limited (Parente & Herrmann, 2003).

Cognitive recovery can occur in a mild pre-existing cognitive disorder because the goal of recovery is to approach or achieve their pre-injury level of cognitive health. However, in more severe disorders there may be disruption in self-awareness and ability to participate in cognitive assessment or therapy. Thus the final antecedent is absence of significant pre-existing cognitive disorder, i.e. incapacitating dementia, mental illness, or developmental impairment.

**Consequences**

The consequences of effective cognitive recovery are improved cognition and a productive life. A productive life is defined by the patient alone. However, indicators of successful cognitive recovery can include improved cognitive function (Cicerone et al., 2008), ability to function in the community (Stephens et al., 2005), and a good quality of life (QOL) (Edwards, Hahn, Baum, & Dromerick, A., 2006). There is a dearth of research specifically reflecting the patient-centered cognitive recovery or rehabilitation in stroke despite support from the American Heart Association (Miller et al., 2010).

Research in comprehensive holistic cognitive rehabilitation therapies (CRT) in traumatic brain injury offer insight to positive recovery results. Consequences of CRT include improved community functioning (Geurtsen, van Heugten, Martina, & Geurts,
2010; Sarajuuri et al., 2005), life satisfaction (Mateer, Sira, & O’Connell, 2005; Svendsen & Teasdale, 2006; Tiersky et al., 2005), self-efficacy and improvement of cognitive and emotional symptoms (Cicerone et al., 2008), and improved memory (Mateer et al., 2005). Research on the psychological aspects of patients with stroke supports use of various therapies for apathy (Kohno et al., 2010), depression, coping and self-efficacy to improved QOL (Aben et al., 2008), cognition (Narushima et al., 2014), and verbal memory and focused attention (Särkämö et al., 2008).

The alternative to effective cognitive recovery is continued cognitive impairment resulting in poor QOL, possibly dementia and an early death. Approximately 80% of all stroke survivors with mild cognitive impairment will develop Alzheimer’s disease within 6 years of stroke (Li et al., 2011). Further, patients have a decrease life expectancy if they develop dementia after stroke (Wiberg et al., 2012); 29-60% shorter than those without post-stroke cognitive impairments (Oksala et al., 2009).

Model Cases

Walker & Avant (2005) recommend presenting four types of cases (model, borderline, contrary, and related cases) to clarify a concept and its characteristics. A model case is a pure exemplar of the concept demonstrating its use while utilizing all of its defining attributes. The following is an example.

Model case

P.A. experienced a moderate ischemic stroke while at work as a medical transcriptionist. She was treated promptly but still had significant left hand weakness, difficulty reading, and slow thinking. She expressed concern over return to work, became anxious for the future, and stated “I don’t believe people ever get all better after a stroke”.

...
P.A. ’s care was performed by an interdisciplinary team consisting of a stroke neurologist, neuropsychologist, stroke specialty nurses, physical and occupational therapists, social worker, and the recovery case manager (RCM). Within 24 hours of admission P.A. met with the RCM who coordinated team activities and ensured services were delivered efficiently. The RCM was a neuroscience nurse practitioner employed by the hospital system to perform and coordinate care in hospital and as outpatient care provider through the first few months after the stroke.

At the initial meeting, the RCM identified physical and cognitive needs, namely impaired working memory and processing speed. P.A. and the RCM identified P.A. ’s limitations in her support system and in her health beliefs. P.A. admitted feeling fear, hopelessness, confusion, and overwhelming panic, making her reluctant to take part in rehabilitation activities or engage in conversation. Afterward, the RCM met with the care team, discussed the assessment and considered plan options. At subsequent meetings, P.A., her family, and the RCM formally identified P.A. ’s physical, psychosocial, and behavioral needs and goals to be achieved.

Also, the RCM counseled P.A. on personal empowerment, decision making and coping strategies. Plans were initiated during the hospital admission including physical and occupation therapy, the neuropsychologist assessed and initiated cognitive and behavioral therapies, and a social worker met with P.A. and her family to discuss restructuring family dynamics to facilitate recovery. The RCM completed follow up appointments with P.A and verified treatment by various care providers, including participation in stroke support group. Meeting with the RCM six weeks after the stroke, P.A. stated: “I would not have gotten through this without you all. I know I would not be
able to go back to work and my life would have been horrible. Now I think so much clearer and I feel like my old self again. I still have work to do getting better but now I know I can do whatever it takes.”

P.A. experienced a moderate stroke having both physical and cognitive aspects. Aspects of her internal, external and created environments as well as limitations in her agency and coping abilities had the potential to hinder her recovery. Her early cognitive recovery was dependent on a well-organized care process which started with the patient acknowledging and agreeing on a plan that fit needs, goals and interventions. Lack of a treatment plan would have resulted in diminished physical therapy, worsening of psychiatric and cognitive issues, and possible loss of employment.

**Borderline Cases**

A borderline model case contains most of the defining attributes but differs substantially in some aspect of them, such as by intensity or length of time (Walker & Avant, 2005). The following is an example: J.W. experienced a moderate stroke resulting in mild aphasia, dysarthria, and right hand and leg weakness. The RCM evaluated him but did not identify any psychosocial or behavioral needs to be addressed, found a strong agency and adequate coping skills. All stroke symptoms resolved four days after the stroke and J.W. was discharged with a routine follow up appointment with the stroke neurologist.

**Related Cases**

A related case are cases that are in some way related to the concept being studied but do not contain all of the defining attributes. The following is an example: W.K. has been diagnosed with schizophrenia and has persistent problems with executive function
impairment, learned helplessness and social communication skills. W.K.’s psychiatrist and psychiatric case worker perform psychosocial-behavioral therapies and training, allowing him to live a stable life in a group home.

**Contrary Cases**

Lastly, contrary cases are clear examples of cases not related to the concept being developed. The following is an example: J.J. experienced a severe stroke resulting in coma for 10 days. He remained disoriented, advancing to incapacitating dementia within two months. When medically stable, J.J. was transferred to a skilled nursing home for passive physical therapy.

**Conclusion**

Although multiple models of cognitive recovery or rehabilitation exist they are not adequate. The models are hampered by 1) the user’s viewpoint, i.e. the disciplines, the patient or the care provider, 2) use of loose or 3) confusing terms and 4) the restrictiveness of the medical model, focusing mainly on healthcare provider activities. A concept synthesis is inclusive, does not promote one view over the others and brings various pieces together synergistically. The current concept synthesis re-orders known information related to patients’ cognitive, psychosocial, behavioral, neurological, and rehabilitation status. This reordering involves interactions between environments driven or powered by the patient’s own capabilities resulting in transition to a more stable state. A patient-centered cognitive recovery model is flexible enough to subsume or support the other models.

Use of the PCRS model to identify the structure and interactions involved within cognitive accommodation can promote diverse research. It is anticipated this synthesized
model will change and grow as interactions between its components undergo empirical
testing. For instance, research is needed to evaluate the importance of each component
and measurement of component influence on recovery outcome. Further questions
include: does a hierarchy of needs effect the transitional state? Can recovery outcome be
consistently predicted? Are indirect indicators like the Neuro-QOL adequate to measure
overall cognitive recovery or is it preferable to measure recovery of each cognitive
impairment? Use of QOL measures present difficulties in regards to the PCRS model.
Neuro-QOL, for instance, measures some aspects of cognition, the physical, internal and
external environments and agency (NINDS, 2010). However, it is not readily apparent if
it measures created environment, acceptance or congruence.

Promoting cognitive recovery is critical in the promotion of health and well-
being. Despite significant interest and effort on behalf of several health disciplines, at
least 50% of patients continue to be cognitively impaired a decade after stroke (Brainin et
al., 2015). Currently, cognitive therapies focus on adaptation and, to a lesser degree, re-
learning. While both adaptation and learning are linked to promotion of wellbeing
(Shapira, Barak, & Gal, 2007; Welzel & Inglehart, 2010), it is likely learning would more
useful in attaining the goal of pre-injury level of cognitive health. Early intervention and
knowledge of component prioritization could be linked with interventions and promoting
early relearning.

Cognitive recovery after stroke is a complex concept requiring an
interdisciplinary approach under the leadership of providers well versed in the areas of
treatment and wellbeing. For instance, neuroscience nurse practitioners, trained in both
medical and nursing philosophies, would be uniquely equipped to manage cognitive
recovery care. The PCRS is a cognitive recovery model flexible enough to subsume or support the other models facilitating diagnosis, treatment, and the promotion of health and well-being.
References


Figure 1. Patient-Centered Cognitive Recovery in Stroke (PCRS) Model. Central box denotes the patient’s cognition, surrounded by a perforated line triangle containing personal capabilities. Arrows indicate continuous interactions between cognitive and personal capabilities and the Environments or patient’s resources residing within the Cognitive Accommodation workstation. Lack of dividing lines between Environments indicates frequent interaction and interdependence. The highlighted aspect of External Environment, therapy, connotes the final pathway toward recovery outcomes; the expression of internal psychosocial change through behavior which generates neuroplastic changes altering cognitive capabilities.
Appendix B

Acquired Brain Injury:

Implications of Early versus Late Interventions for Motor and Cognitive Recovery

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Abstract

Purpose: To determine the significance and implications of timing in early versus late intervention on cognitive and motor function following acute brain injury (ABI)

Organizing Construct: Similarities exist between different areas of novel ABI research which informs on the process of research, as it relates to the significance of timing of interventions and recovery outcomes.

Methods: Literature pertaining to historic motor impairment research and current cognitive impairment research were reviewed and analyzed, comparing the process leading up to the, at that time, novel use of physical therapies after ABI to the ongoing process of cognitive impairment research.

Findings: Two common themes emerged between early motor and cognitive therapies. The first was both therapies were considered controversial, costly, possibly ineffective, and possibly unnecessary due to spontaneous recovery. The second theme was empirical evidence indicating improved motor and cognitive function when interventions were started within days of ABI.

Conclusions: Motor impairment physical therapies are now standard of care but only after investigators answered the questions of therapy timing, frequency, and duration. These same questions plague cognitive research today, therefore, future research should be intensely focused these questions, specifically on timing.
Introduction

Currently, ten million Americans live with the consequences of acquired brain injury (ABI), either from stroke (Go et al., 2014) or traumatic brain injury (Corrigan, Selassie, & Orman, 2010). In 1960 the U.S. Surgeon General (Burney, 1960) determined that physical therapy was not routinely or consistently used and called for methods to decrease physical impairment from ABI. Twenty-six years later, cumulative research had provided solid therapeutic recommendations for motor impairments, including selecting appropriate patients and best standards for intensity of therapies, setting and timing, i.e. beginning as soon as possible after injury (Dombovy, Sandok, & Basford, 1986). These were codified as treatment guidelines by the World Health Organization (WHO) (1989).

However, cognitive impairment after ABI is just as devastating as physical impairment, sharing a common result: persistently poor quality of life (Hawthorne, Gruen, & Kaye, 2009; Nys et al, 2006). Treatment guidelines are intended to improve quality of life, however, there are no universally accepted cognitive treatment recommendations in acute ABI (Bragge et al., 2014). The aim of this systematic review is to identify significant common themes between two research areas, historic motor and current cognitive studies, by comparing findings related to the timing of interventions, outcomes, and confounders affecting outcomes. This review seeks to determine the implications of time sensitive interventions and identify knowledge gaps, suggesting a direction for future cognitive research. The studies were reviewed based on type of impairment, motor or cognitive, and the results were then combined and examined in the discussion section.
Background

The historic motor studies cited in this review were considered novel and significant, by starting physical therapy relatively early after ABI and involving planned therapy or a formal Physical Medicine & Rehabilitation consultation (Tobias, Puri, & Sheridan, 1982). Before the WHO guidelines (1989) a typical treatment trajectory was as follows: medically stabilize the patient, transfer to a lower level of care or home while they recuperated and then attempt formal rehabilitation at one to two years post injury (Rusk, Block, & Lowman, 1969). There were real doubts as to the effectiveness of early motor rehabilitation in ABI. Brocklehurst, Andrews, Richards, & Laycock (1978) noted it was not cost effective because those least likely to recover were receiving the most long-term and intense therapy. In cognitive rehabilitation, timing rather than cost is more controversial. Currently, cognitive research frequently starts months or years after the injury (Lewald, Tegenthoff, Peters, Markus, 2012). Cicerone et al. (2011) noted cognitive therapy should begin no earlier than the subacute phase because there was not sufficient data (due to a paucity of study) indicating if recovery is spontaneous or resulting from interventions. The same lack of available evidence was noted in historic interventional motor research (MacKay et al., 1992).

Neuroplasticity was the framework used in this review to understand the changes related to motor and cognitive recovery. The experience-dependent neural plasticity (Kleim & Jones, 2008) supports the pattern of ABI physical and cognitive rehabilitation. Neuroplasticity is the adaptive capacity of the brain; identified by accelerated axon and dendrite growth, forging of new brain circuitry, and recruitment of compensatory brain tissue (Dancause et al., 2005; Murphy & Corbett, 2009). However, brain neural circuits, not stimulated by activity, will begin to degrade or cortical territory will be taken over by other more competitive brain processes.
(Kleim & Jones, 2008). The activity lasts approximately four weeks and may not be as robust in the elderly (Murphy & Corbett, 2009). However, it may be possible to extend the window in some forms of acute injury (Kleim & Jones, 2008), therefore time-to-intervention matters.

**Methods**

Two searches of the PubMed, OVID Medline, PsychInfo and SCOPUS databases were executed separately and the results of study selection are presented in Figure 1. One search comprised ABI motor impairment interventions and a second comprised ABI cognitive impairments interventions. The strategy for both searches included a series of core and topic specific search terms (Figure 2). The core terms related to ABI with limited exclusion terms. The motor impairment search included the core terms and motor therapy related search terms and the cognitive impairment search included the core terms and cognitive disorder related terms.

In the initial screening titles and abstracts were assessed for relevance. Any ABI study, involving physical or cognitive interventions, was initially considered. Cognitive studies were restricted to randomized clinical trials (RCT) as the highest level of evidence (Cicerone et al., 2000). Due to the paucity of motor RCTs prior to 1985, RCTs and crossover case-controlled trials (CCT) were allowed. Risk of bias for the individual studies was evaluated using internal and external study level assessment tools (Hafner, 2008). Information gained from bias assessment will help characterize study limitations, providing evidence which either strengthens or weakens conclusions regarding the efficacy of early rehabilitation.

This article will review status of research as it relates to similar therapies for ABI related motor and cognitive impairment in humans, therefore, studies unrelated to these themes were excluded. Excluded articles involved non-interventional research (e.g. descriptive studies,
concept analysis, systematic reviews), technological or pharmacological research, studies outside the selected time windows, research involving animals or children. Technology based device and pharmacological research were excluded as they are not yet generalizable to many non-medical center hospitals; examples include software programs (LoPresti, 2004), virtual reality simulations (Crosbie et al., 2007) and hyperbaric chamber interventions (Walker, Franke, Cifu, & Hart, 2014; Wolf, Cifu, Baugh, Carne, & Profenna., 2012).

Included in this review are adult human inpatient ABI interventional studies published in an English-language, peer-reviewed journal, for motor impairment from January 1, 1975, to January 1, 1996 and for cognitive impairment from January 1, 2000 to July 7, 2014. These time windows were selected to compare the initial research in motor interventions to recent research done in cognitive interventions. Comparing these different periods of research may produce common themes. The motor studies reflect the period of time when early physical intervention were controversial (Dombovy et al., 1986; Indredavik et al., 1991); a time before patients with acute ABI used stroke units or routine physical, occupational, or speech therapy. Therapies for the late interventional motor group were a hit or miss concept (Dombovy et al., 1986) with little (Dombovy, Basford, Whisnant, & Bergstralh, 1987; Garraway, Akhtar, Prescott, & Hockey, 1980; Indredavik et al., 1991; Strand et al., 1985) or no therapy while in hospital (Truscott et al., 1971; Wood-Dauphinee et al., 1984) or after discharge.

The time restriction for cognitive studies captures the beginning of a significant research proliferation. The older cognitive research (Carter et al., 1983; Hartman et al., 1987; Lincoln et al., 1984; Lincoln et al., 1985; Rossetti et al., 1998; Rossi, Kheyfets, & Reding,1990; Wiart et al., 1997) created the foundation for current innovations. Nine cognitive RCTs, between 1975 and 1999, involved interventions that have since become standards of care (Weinberg et al.,
1977; Ownsworth & McFarland, 1999) or have been expanded upon by later research, described in this review.

Results

Motor Studies Results

After initial screening, one hundred and seventy-nine motor articles were retrieved and ten studies (Table 1) met inclusion criteria. The publication dates ranged from 1971 to 1992 with the majority published in the 1980s (n=7). This reflects the upsurge in early stage rehabilitation research in the 1980s, with the creation of stroke units, and then decreasing as it became standard of care in the 1990s. Six motor studies were a retrospective design with a sample size ranging from 30 to 483 subjects. Three studies were stroke RCTs (Garraway et al., 1980; Indredavik et al., 1991; Wood-Dauphinee et al., 1984) and one was a prospective non-randomized control trial (Strand et al., 1985) with moderate sample sizes (N= 126 to 309); only Wood-Dauphinee et al. (1984) had less than 200 subjects. All of the TBI studies had small samples (N= 35-75). All the research articles except one (Dombovy et al., 1987) expressed the intent to identify benefits of early rehabilitation.

Differences in design hindered easy comparison between studies. Four motor studies (Cope & Hall, 1982; Hayes et al., 1986; MacKay et al., 1992; Tobis, Puri, & Sheridan, 1981) had small sample sizes (mean: 45 subjects) but enrolled over a four-year time period. It is concerning that investigators, with such a small catchment of ABI subjects, may not have the opportunity to perform this research adequately. The outcomes of two of these studies (MacKay et al., 1992; Tobias et al., 1981) far exceeded the results of all the other motor studies. Equally disturbing is the lack of adequate descriptions for the physical interventions. Six articles give a very brief
general description (Table 1) while the other four list the number of overall therapy units but not the duration or intensity making it impossible to duplicate the studies. A unique problem in the stroke sample involved subject selection. One article (Garraway et al., 1980) did not define stroke and two articles defined stroke as either ischemic or hemorrhagic (Dombovy et al., 1987; Wood-Dauphinee et al., 1984). The remaining studies allowed only ischemic stroke. Three studies specifically disallowed transient ischemic attacks (Garraway et al., 1980; Indredavik et al., 1991; Strand et al., 1985) to ensure that early spontaneous recovery would not confound findings.

The motor studies used descriptive statistics to describe their sample and identify patterns but were not able to supply evidence beyond their data sets or predict population level patterns. This unavoidable limitation changed when use of inferential statistics (Nunnally & Bernstein, 1994) became more common in the 1990’s. The descriptive statistics, namely the variables of length of stay (LOS) and functional independence, indicated early intervention was more effective than late (Table 1). In the early group subjects LOS was shorter by 50% (Cope & Hall, 1982; MacKay et al., 1992) to 72% (Tobias et al., 1981) and functional status was approximately 50% better in the early group than in the late, in all three TBI studies.

For this review motor studies with planned interventions beginning before 30 days are considered the early or experimental group and those without inconsistent therapy or therapy beginning after 30 days are considered the late or control group. Each study defined the early versus late group slightly differently. Cope & Hall (1982) differentiated their two study groups by the amount of time from injury to physical therapy (PT), early (mean of 21 days) and late (mean of 61 days) groups. This aligns with the first four weeks of intensive brain remodeling,
remaining aware that the longer the time between injury and brain stimulation the less the neuroplastic changes (Kleim & Jones, 2008).

On the other hand, a hospital based study (MacKay et al., 1992) identified the early group by participation within 48 hours of injury at one acute hospital’s formalized brain injury program. The study’s late group had a mean of only 21 days from injury to first PT. However, in the MacKay et al. (1992) study, PT was inconsistent, ordered at private physicians’ discretion, and done at ten different hospitals without formalized brain injury programs. As such, it does not meet the criteria for early and planned stimuli or interventions indicated by Kleim & Jones (2008). MacKay et al. (1992) reported the early group had decreased mortality and 50% less length of stay (LOS). Clinically, this was significant as it gives some evidence that organized PT is as important as timing of therapy. The third TBI study, Tobias et al. (1981) identified three TBI groups by injury to PT time: onset less than four weeks to PT start, 4-8 weeks, or greater than eight weeks. But in line with the neuroplasticity window, the review evaluated this as early (less than four weeks) or late (greater than four weeks).

The seven stroke trials (Dombovy et al., 1987; Garraway et al., 1980; Hayes et al., 1986; Indredavik et al., 1991; Strand et al., 1985; Truscott et al., 1971; Wood-Dauphinee et al., 1984) were all located in the acute hospital setting with the main inclusion criteria being time between symptom onset and therapy. Three studies started PT within 72 hours of stroke onset (Garraway et al., 1980; Hayes et al., 1986; Truscott et al., 1971) and the remaining studies started PT within seven days. Treated subjects in these trials received early rehabilitation and late or untreated subjects received standard of care. Routinely, as many as 41% of patients did not receive any PT in an acute hospital (Truscott, Kretschmann, Tooke, & Pajak, 1971). Unfortunately, after the research subjects left the acute setting, data related to any PT received was not presented.
Similar to the TBI studies, the stroke study results indicated early intervention was more effective than late. Outcome variables (Table 1) were LOS, mortality, and functional indicators including final discharge location, Rankin Scale (RS), & activities of daily living (ADLs). For studies using LOS and discharge location variables (Hayes et al., 1986; Indredavik et al., 1991; Strand et al., 1985) early group LOS was a statistically shorter and, of clinical significance, patients were 50% more likely to be discharged directly home. Dombovy et al. (1987) indicated early group RS was lower (better) at each follow up time point (up to five years post stroke) with early group rate of improvement at discharge twice that of the late group. However, the instruments used to measure ADL or RS were not defined and RS reliability and validity psychometrics where not presented.

**Motor Study Bias**

Multiple risks of bias in research exist (Pannucci & Wilkins, 2010). The risk of bias, related to study design, within these early studies must be addressed and two factors should also be taken into account. First, rehabilitation studies are complicated to design, even today. They can have multiple confounding variables such as severity of injury, patient age, the use of different sites for acute and rehabilitation care and the varied rehabilitation needs of the patients. Second, modern research methods (Bhatt, 2010; Moon, 2009) were relatively young and statistical methods (Nunnally & Bernstein, 1994), considered common place today, were still being tried out in the real world of bedside healthcare research.

Examples of risk of bias within the studies, found in each of the motor studies include no blinded assessments, validation for sample size, or psychometrics for any measurement tool, analysis limited to descriptive statistics, convenience sampling, retrospective design for six
studies, and no mention of potential investigator conflict of interest, despite many of the studies being done in the investigator’s hospital. The RCTs had minimal description of randomization schemes and two had no explanation of subject washout or high attrition (Strand et al., 1985; Wood-Dauphinee et al., 1984). Four studies did not indicate initial severity of study population making it difficult to judge the accuracy of improvement results presented in the articles (Dombovy et al., 1987; Hayes et al., 1986; Indredavik et al., 1991; Strand et al., 1985). One study included TIAs and an ill-defined CVD category in the subject population (Truscott et al., 1971) despite the fact TIAs rarely require inpatient rehabilitation and ill-defined CVD diagnosis are frequently stroke mimics. No risk of bias across studies was identified. There were fewer journals in existence at this time and these articles were published in four of them. No articles on negative results for early physical activity were found but that was not surprising as it is considered standard of care today.

**Cognitive Studies Results**

After screening, two hundred and twenty cognitive articles were retrieved, and nine cognitive articles (Table 2) met inclusion criteria. The publication dates range from 2000 to 2012. Three TBI trials (N= from 12 to 360) and six stroke trials (N= from 11 to 123) have been included. Two of the TBI trials are RCTs (Fasotti, Kovacs, Eling, & Brouwer, 2000; Vanderploeg et al., 2008) and one used a form of crossover design (Couillet et al., 2010). All the stroke trials are RCTs (Akinwuntan et al., 2010; Chen, Hartman, Galarza, & DeLuca, 2012; Godecke, Hird, Lalor, Rai, & Phillips, 2012; Laska et al., 2011; Nys et al., 2008; Tsang, Sze, & Fong, 2009). The names of ten cognitive impairments were included as MESH and key word terms but only five cognitive impairments resulted in appropriate studies: attention, memory, aphasia, neglect and information processing speed (IPS). Other cognitive impairments were
evaluated in studies that did not meet the review exclusions, related to study design or device and pharmacology interventions.

Multiple interventions were evaluated. Two studies for memory impairments used either a cognitive-didactic training model (Vanderploeg et al., 2008), allowing errors as part of the process to cognitive self-awareness through learning, or used cognitive task training, requiring errorless learning (Chen et al., 2012). Two studies evaluated aphasia; Godecke et al. (2012) addressed the concept of intervention dose by requiring daily aphasia therapy while Laska et al. (2011) specifically addressed the early versus late timing of interventions. Two studies (Nys et al., 2008; Tsang et al., 2009) evaluated neglect through the use of low-technology tools (experimental glasses), believing it can promote neuroplasticity and thus enhance attention. Akinwuntan et al., (2010) evaluated improve attention and information processing speed (IPS) via error versus errorless learning rehabilitation models. Fasotti et al. (2000) evaluated improving IPS impairment via adaptation as well as learning in the intervention, time pressure management (TPM) (Winkens, Van Heugten, Wade, & Fasotti, 2009).

Only two studies specifically intended to address early versus late cognitive rehabilitation (Laska et al., 2011; Tsang et al., 2009). Laska et al. (2011) had onset to intervention at a mean of three days and Tsang et al (2009) had mean of 22 days which is within the neuroplasticity model time window. Additionally, two other stroke trials, Nys et al. (2008) with mean of nine days and Godecke et al. (2012) with a median of three days will be considered early intervention studies for this review. The other studies included in this review have a time range up to 12 weeks. Of special note are the extended onset time window (at 24 weeks) of two of the TBI cognitive studies (Couillet et al., 2010; Vanderploeg et al., 2008). Frequently, TBI research time frames
begin after 24 weeks, based on the literature search. Unlike stroke research, it is not unusual for TBI studies to begin 5-20 years after injury.

**Cognitive Study Bias**

There were risks of bias in the cognitive studies, despite investigator efforts. Risk of bias was assessed on an internal and external study level. A risk does not necessarily mean that the conclusions of the study should be disregarded as it is nearly impossible to know how much a bias affected results (Higgins et al., 2011). Most of the articles readily identified the risks and discussed results in the light of efforts to avoid bias.

All studies used control groups formed by random assignment but the control groups were not always comparable. In Fasotti et al. (2000) the experimental group was post injury a mean of 9.8 months (control group mean of 5.3 months). The experimental group would be less likely to learn, following the concept of brain plasticity. The investigators reported success on managing time pressure problems (adapting) but not on preventing them, which would require the ability to learn and plan ahead. The control group in Godecke et al. (2012) was overall significantly more disabled (p= 0.008). In aphasia training this concern may not be readily apparent but more disable patients receive increased motor therapy and may experience more fatigue and depression than lesser disabled stroke survivors. The control group may not have been able to participate equally in the standard of care speech therapy offered to them. This may have accounted somewhat for the significant experimental group scores (p= 0.004).

Other risks of bias included unsuitable placebo (Akinwuntan et al., 2010), no blinded assessments (Akinwuntan et al., 2010; Couillet et al., 2012; Nys et al., 2008; Vanderploeg et al., 2008), limited psychometric evidence (Akinwuntan et al., 2010; Chen et al., 2012; Laska et al.,
2011), limited statistical analysis (Tsang et al., 2009; Vanderploeg et al., 2008), and inadequate sample exclusion criteria. For instance, in Akinwuntan et al. (2010) post hoc analysis, two-third of the subjects (82% of experimental & 50% of controls) had mild or no cognitive impairment. Four of the studies calculated effect size (Couillet et al.; 2012; Laska et al., 2011; Tsang et al., 2009; Vanderploeg et al., 2008) but Tsang et al. (2009) violated the aim of a moderate effect of 0.5 by enrolling 17 subject per group instead of the required 50 per group.

A final internal bias in the articles was a lack of conflict of interest discussion, funding sources or proprietary status on the therapies or glasses used in the studies. Regarding external validity for the studies, one study (Laska et al., 2011) did not place its conclusions in context of existing literature, instead only referred to two studies the investigators themselves had previously performed. Regarding risk of bias across the studies, it is apparent that there is no publication bias as both positive and negative study results are published in multiple journals. This will aid researchers in formulating new studies and extending knowledge.

**Discussion**

Current and historical research were compared in this review, to identify early and late group findings related to the timing of the intervention, resulting outcomes and potential confounders affecting study outcomes, with the intent to determine if interventions are time dependent. Study outcomes are categorized as early study outcomes versus late study outcomes, regardless of injury type (TBI or stroke) or impairment (motor or cognitive). In this review, classification criteria for early (interventional) and late (control) groups depends on neuroplasticity principles of a time window and intense neural stimuli, as occurs in physical or cognitive therapy. To qualify, the interventional group must have planned therapy started within
a time window of 4-12 weeks post injury. Murphy and Corbett, (2009) found the neuroplasticity window could be extended past four weeks under the condition of increased neural input, such as physical therapy. The control groups must not have an organized plan of therapy (retrospective motor studies) or not have therapy designed to affect the impairment (cognitive control groups). The interventions in all motor studies (Table 1) began within the four-week neuroplasticity window; most (80%) within seven days of injury, with 50% starting within 72 hours. In these retrospective studies, the control group were patients undergoing standard brain injury care in which motor rehabilitation, prior to 1985, it was inconsistent or absent.

There is a paucity of cognitive research in the acute period after brain injury. Therefore, for the purpose of this review, seven cognitive studies (Table 2) were considered as early or within the neuroplasticity window: four studies within four weeks and three within 12 weeks post injury. Two additional TBI studies, considered late studies, were highlighted in the review to evaluate possible exceptions to the neuroplasticity time window rule. At 24 weeks post injury, Couillet et al., (2010) evaluated an attention intervention and Vanderploeg et al. (2008) evaluated memory interventions. All nine cognitive studies had planned interventions and designated control groups, though one was a cross-over design (Couillet et al., 2010).

Therapeutic interventions in the cognitive studies were primarily designed as learning interventions. Adaptive training also occurred, in part, in the Fasotti et al. study (2000), an information processing speed intervention and possibly, to some degree, in the physical therapy interventions in the motor retrospective studies. Study outcomes provided evidence in support of early intervention, regardless of injury or impairment type. Early interventions resulted in improved ADLs (Garraway et al., 1980; Hayes et al., 1986) and improved impairments (Chen et al., 2012; Godecke et al., 2012; Nys et al., 2008; Tsang et al., 2009). Early group patients (54-
94%) were more likely to be discharged home rather than institutionalized (Indredavik et al., 1991; MacKay et al., 1992; Strand et al., 1985), have 50% more strength (Truscott et al., 1971) and less disability (Dombovy et al., 1987).

Clinical experience indicates improvement of impairments achieved after physical therapy is sustained, however, there was mixed evidence related to sustained improvement for the various cognitive impairments. Four studies assessed for sustained change, Godecke et al. (2012) and Tsang et al. (2009) noted the effect was sustained up to four weeks post intervention but Chen et al. (2012) and Nys et al. (2008) found no sustained change at 2-4 weeks. One reason for this observation may be intervention frequency and duration (Nys et al., 2008). The cognitive studies had a priori intervention parameters, unlike the motor interventions which based therapy on case-by-case patient requirements (Dombovy et al., 1987).

Unlike the motor studies, some cognitive studies tested for improvement of impairment and in function (Fasotti et al., 2000; Godecke et al., 2012; Tsang et al., 2009; Vanderploeg et al., 2008). Tsang et al. (2009) and Vanderploeg et al. (2008), a late study, showed no or limited functional improvement, respectively. Two early cognitive studies indicated no to little improvement; possibly due to randomization issues rather than study timing. The negative study results in Akinwuntan et al. (2010) can be explained by a post hoc analysis indicating more severe impairment in the control group than interventional group. Laska et al. (2011) had limited positive main variable improvement but only in one subgroup. A late cognitive study (Vanderploeg et al., 2008), initiated at 24 weeks after injury, compared two training methods with the intent to demonstrate improvement in memory as a function in life skills. The study did indicate that both arms improved life skills but did not supply results specifically demonstrating
changes in memory impairment scores. Therefore, other factors in this interdisciplinary inpatient rehabilitation program may have resulted in improved adaptation rather than neural changes.

A second late cognitive study (Couillet et al., 2010), also initiated 24 weeks after injury, showed improvement in divided attention due to specific divided attention training; outside of the neuroplasticity model time frame by at least 12 weeks. There are three possibilities for this unexpected result. The first and most likely possibility is that the sample size (N= 12) is too small, increasing the possibility of type I error, i.e. detecting a difference which does not exist. The second possible explanation is that the crossover study design itself is not suitable for cognitive studies. Investigators scrupulously attempted to find control procedures which would not impact the intervention assessment.

However, the brain’s cognitive capabilities and circuitry is still a “black box”. It cannot be known, for an absolute certainty, that the control tasks did not have some learning impact, a priming of the pump as is suspected regarding physical activity (Murphy & Corbett, 2009). Finally, TBI is a unique condition frequently accompanied by an episode of coma and extended, severe post trauma amnesia. It is not known if different types of injury impact cognitive recovery differently. It is unlikely that trauma related neuroplasticity is ongoing at that far stage but could the usual extensive physical rehabilitation be producing brain circuitry that is ripe for cognitive recover? Literature does support physical exercise’s positive influence on working memory (Ratey & Loehr, 2011).
Conclusion

Reducing cognitive impairment after acute ABI will improve the lives of billions of people worldwide. Nevertheless, early cognitive therapy is controversial today, similar to early physical therapy decades ago (Dombovy et al., 1986). A more important common theme between motor and cognitive studies is the empirical evidence showing early intervention results in more improvement than late intervention. Early motor therapy became standard of care because research indicated benefit to the patient and informed on therapy type, duration, and frequency. These few early cognitive studies give indication of patient benefit; perhaps even a glimpse of a synergistic relationship between motor and cognitive therapy, promoting cognitive recovery as far out as 24 weeks after injury.

Cognitive recovery is a complex multidimensional area of research. During the flexible ultra-active neuroplastic window brain changes occur as a result of stimuli, regardless of source, i.e. from motor or cognitive therapy. More research needs to be built on the framework of neuroplasticity and potentially other important considerations yet defined. It is critical that studies are designed carefully and outcomes should be translatable to everyday life situations. Knowledge gaps range from temporal to practical, including when to start cognitive therapy, what extends the neuroplastic window and how far can it go, can certain therapies affect multiple cognitive impairments and what is optimal duration and frequency, how long does cognitive improvement last and are booster treatments helpful? Almost three decades past from Dr. Burney’s (1960) call, to decrease in physical impairment, to the passage of the WHO guidelines (1989). Using their work as a guide, it is past time for an acceleration in early cognitive research.
References


Figure 1. PRISMA Diagram for study selection of motor & cognitive articles

Records identified through database searching:
- Motor (N=769)
- Cognitive (N=4015)

Additional records identified through other sources:
- Motor (N=1)
- Cognitive (N=9)

Records after duplicates or near duplicates removed:
- Motor (N=600)
- Cognitive (N=3030)

Motor Records excluded (n=421):
- Not ABI (n=368)
- Descriptive only (n=53)

Records screened:
- Motor (N=600)
- Cognitive (N=3030)

Cognitive Records excluded (n=2810):
- Not ABI (n=2274)
- Descriptive only (n=536)

Full-text Motor articles excluded (n=169):
- no physical therapy (n=96)
- Study timing (n=51)
- pediatric or animal (n=22)

Full-text articles assessed for eligibility:
- Motor (N=179)
- Cognitive (N=220)

Studies included in qualitative synthesis:
- Motor (N=10)
- Cognitive (N=9)

Figure 1. Combined motor and cognitive PRISMA Diagram indicating flow of study exclusion and selection.
Figure 2. MESH terms used in literature search divided into three sections: Core terms, motor and cognitive search terms. Two searches were completed: first search used Core terms and motor terms and second search used Core terms and cognitive terms.
### Table 1. Summary of ABI Motor Studies

<table>
<thead>
<tr>
<th>Author (year) &amp; Study Design</th>
<th>ABI type / Purpose (to evaluate...)</th>
<th>Sample / Inpatient Setting</th>
<th>Early Group and (Late Group) Initiation / End Point from start of intervention</th>
<th>Early Group Intervention</th>
<th>Outcomes: Early Group and (Late Group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cope &amp; Hall (1982) Retrospective</td>
<td>TBI / Identify benefit of early rehab.</td>
<td>N = 36 / TBI rehabilitation hospital</td>
<td>Mean = 21d (Mean = 61d) Endpoint: 2 years</td>
<td>PT / OT (102 hours) with psych. counseling &amp; academic remediation</td>
<td>Early group at 2 months: Shorter LOS by 50%, Less bowel &amp; bladder impairment by 50%</td>
</tr>
<tr>
<td>Domboy et al. (1987) Retrospective</td>
<td>Stroke (hemorrhagic or ischemic) / Determine rate &amp; use of rehab.</td>
<td>N = 281 / rehabilitation unit</td>
<td>Mean = 5d (no formal rehab.) Endpoint: 5 years</td>
<td>PT: 16 hours, OT: 8 hours &amp;/or ST: 24 hours</td>
<td>% Rate of improved Rankin score: Early group = 85% (48%)</td>
</tr>
<tr>
<td>Garraway et al. (1980) RCT</td>
<td>Stroke / Identify benefit of stroke unit / early rehab.</td>
<td>N = 309 / Stroke unit</td>
<td>Mean = 26 hours (no formal rehab.) Endpoint: 2 months</td>
<td>PT: mean 23 hours OT: mean 33 hours</td>
<td>% independent in ADLs at 2 months: Early group = 62% (45%), % Hospital mortality: Early group = 19% (28%)</td>
</tr>
<tr>
<td>Hayes et al. (1986) Retrospective</td>
<td>Stroke / Identify benefit of early rehab.</td>
<td>N = 30 / acute hospital</td>
<td>&lt;72 hours (4-15d) Endpoint: discharge usually within day 39</td>
<td>&quot;rehabilitation services&quot;</td>
<td>% independent in ADLs, p&lt;0.05: Early group = 60% (30%)</td>
</tr>
<tr>
<td>Indredavik et al. (1991) RCT</td>
<td>Stroke / Identify benefit of stroke unit / early rehab.</td>
<td>N = 206 / Stroke unit</td>
<td>&lt;36 hours (no formal rehab.) Endpoint: 1 year</td>
<td>&quot;systematic program for recovery of function&quot;</td>
<td>% Discharge home at 6 weeks: Early group = 60% (35%)</td>
</tr>
<tr>
<td>MaKay et al. (1992) Retrospective</td>
<td>TBI / Identify benefit of formal, early rehab.</td>
<td>N = 38 / Acute hospital</td>
<td>&lt;48 hours (Mean = 23d) Endpoint: 1 year</td>
<td>&quot;100% had PT / OT / ST&quot; with social / family support</td>
<td>% Discharge home: Early group = 94% (57%)</td>
</tr>
<tr>
<td>Strand et al. (1985) nonrandomized Controlled Trial</td>
<td>Stroke / Identify benefit of stroke unit / early rehab.</td>
<td>N = 293 / Stroke unit</td>
<td>&lt;7d (no formal rehabilitation) Endpoint: 1 year</td>
<td>&quot;very early &amp; determined rehab.&quot; with family education</td>
<td>% Discharge home, p&lt;0.05: Early group = 54% (39%)</td>
</tr>
<tr>
<td>Author (year) &amp; Study Design</td>
<td>ABI type/ Purpose: (to evaluate...)</td>
<td>Sample/ Inpatient Setting</td>
<td>Early Group and (Late Group) Initiation/ End Point from start of intervention¹</td>
<td>Early Group Intervention²</td>
<td>Outcomes: Early Group and (Late Group)³</td>
</tr>
<tr>
<td>-----------------------------</td>
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<td>-----------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Tobias et al. (1982) Retrospective</td>
<td>TBI/ Identify benefit of formal, early rehab.</td>
<td>N = 75/ hosp. &amp; rehabilitation unit</td>
<td>&lt;4 weeks (&gt; 4 weeks) Endpoint: Rehabilitation discharge</td>
<td>&quot;early rehabilitation intervention&quot;</td>
<td>% Early group improved more than Late group: feeding = 47%, walking = 63%, bowel/bladder = 43%, Early discharged home = 73%</td>
</tr>
<tr>
<td>Truscott et al. (1971) Retrospective</td>
<td>Stroke (allowed TLAs)/ Identify benefit of formal, early rehabilitation</td>
<td>N = 483/ acute hospital</td>
<td>&lt;48 hours (No rehabilitation) Endpoint: 3 months</td>
<td>&quot;ROM, positioning &amp; mobilization procedures&quot;</td>
<td>Early group: Less mortality = 50% Better motor strength = 50%</td>
</tr>
<tr>
<td>Wood-Dauphinee et al. (1984) RCT</td>
<td>Stroke (hemorrhagic or ischemic)/ Identify benefit of formal, early rehab.</td>
<td>N = 126/ rehabilitation unit</td>
<td>&lt;7 d (variable rehabilitation) Endpoint: 5 weeks</td>
<td>PT: 14 d, OT: 7 d, ST: 8 d</td>
<td>Early group compared to Late group in motor performance: Males had &quot;superior outcomes&quot; but not females</td>
</tr>
</tbody>
</table>

Note: Summarizes historic motor studies to identify common themes: 1. Study interventions identified by therapy start times in early and start time or intensity in (late) groups; Endpoint is time of last assessment. 2. Early group therapeutic dose defined or described by quote from article. 3. Main study outcomes identified by category, statistical results and by early or (late) group.
Table 2.  
Summary of Cognitive Studies

<table>
<thead>
<tr>
<th>Author (year) / ABI/Impairment</th>
<th>Design/ Purpose</th>
<th>Sample/ inpatient setting</th>
<th>Group: Early or Late Start (duration)</th>
<th>Intervention/ Intensity/ Power analysis, sample or effect size</th>
<th>Experimental (EXP) and Control Group Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akinwotun et al. (2010)</td>
<td>RCT</td>
<td>N = 69</td>
<td>Early group</td>
<td>Driving simulations or cognitive games = 15 hr.</td>
<td>Both groups improved: no significant difference</td>
</tr>
<tr>
<td>Stroke/ Attention</td>
<td>Benefit of two rehab models</td>
<td>Rehab unit</td>
<td>Mean = 53 days (5 weeks)</td>
<td>No sample or effect size reported</td>
<td>On pretest: only 6 EXP &amp; 20 Controls had mod. to severe impairment</td>
</tr>
<tr>
<td>Chen et al. (2012)</td>
<td>RCT</td>
<td>N = 11</td>
<td>Early group</td>
<td>Global-to-local encoding training = 1.5 hour</td>
<td>EXP group: improved (p&lt;0.001) one day after intervention</td>
</tr>
<tr>
<td>Stroke/ Memory</td>
<td>Benefit of GPT (task training)</td>
<td>Rehab unit</td>
<td>Mean = 48 days (1 session)</td>
<td>No sample or effect size reported</td>
<td>No significant difference at 2 weeks (p = 0.427)</td>
</tr>
<tr>
<td>Couillet et al. (2010)</td>
<td>Crossover</td>
<td>N = 12</td>
<td>Late group</td>
<td>Concurrent task training = 4 hours/wk.</td>
<td>EXP group: Significant Improvement (p&lt;0.0001)</td>
</tr>
<tr>
<td>TBI/ Attention</td>
<td>Benefit of training using hierarchal difficulty order</td>
<td>Rehab unit</td>
<td>6 months (6 weeks)</td>
<td>large effect-size (Cohen’s d &gt; 1.5), no sample size reported</td>
<td>Results sustained at 4 weeks</td>
</tr>
<tr>
<td>Fasotti et al. (2000)</td>
<td>RCT</td>
<td>N = 22</td>
<td>Early group</td>
<td>TPM training = 3 hours/week</td>
<td>Sign. Improvement (P &lt; .01) in management of Time pressures</td>
</tr>
<tr>
<td>TBI/ Processing Speed</td>
<td>Benefit of TPM training</td>
<td>Rehab unit</td>
<td>Mean = 3 months (3 weeks)</td>
<td>No sample or effect size reported</td>
<td>Significant Improvement (P &lt; .05) in non-targeted variables (memory/attention)</td>
</tr>
<tr>
<td>Godecke et al. (2012)</td>
<td>RCT</td>
<td>N = 59</td>
<td>Early group</td>
<td>Daily aphasia therapy = mean of 45 min./day</td>
<td>EXP group at 4 weeks: Improved AQ scores (P=0.010) &amp; FCP scores (P=0.004)</td>
</tr>
<tr>
<td>Stroke/ Aphasia</td>
<td>Benefit of daily training</td>
<td>Stroke unit</td>
<td>Median = 3 d (19 weeks).</td>
<td>No sample or effect size reported</td>
<td>No significant difference at 6 months: AQ(P=0.322) &amp; FCP (P=0.117).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Post Hoc: Control cohort had more severe disability (P=0.008)</td>
</tr>
<tr>
<td>Author (year)/ABI/Impairment</td>
<td>Design/Purpose</td>
<td>Sample/inpatient setting</td>
<td>Group: Early or Late/Start (duration)¹</td>
<td>Intervention/Intensity/Power analysis, sample or effect size²</td>
<td>Experimental (EXP) and Control Group Outcomes³</td>
</tr>
<tr>
<td>-----------------------------</td>
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</tr>
<tr>
<td>Laska et al. (2011)</td>
<td>RCT</td>
<td>N = 123</td>
<td>Early group</td>
<td>Enrichment Therapy (LET Model) = 45 min/d</td>
<td>No significant difference for EXP group except in more fluent subgroup (p=0.05)</td>
</tr>
<tr>
<td>Stroke/Aphasia</td>
<td>Benefit of early rehabilitation</td>
<td>Stroke unit</td>
<td>Mean = 3 day (15 weekdays)</td>
<td>Power analysis: 104 subjects = 90%</td>
<td>Delay to intervention had neg. effect on outcome (p&lt; 0.01)</td>
</tr>
<tr>
<td>Nys et al. (2008)</td>
<td>RCT</td>
<td>N = 16</td>
<td>Early group</td>
<td>Deviating prism glasses: (once/day sessions)</td>
<td>EXP group: Faster recovery (p = 0.035) but no significant difference at 4 weeks</td>
</tr>
<tr>
<td>Stroke/Neglect</td>
<td>Benefit of prism glasses adaptation</td>
<td>Stroke unit</td>
<td>Mean = 9 days (4 days)</td>
<td>No sample or effect size reported</td>
<td>Confounding variable: Both EXP &amp; Control used arm pointing</td>
</tr>
<tr>
<td>Tsang et al. (2009)</td>
<td>RCT</td>
<td>N = 34</td>
<td>Early group</td>
<td>modified right half-field eye-patching; with OT sessions</td>
<td>EXP group: improvement in BIT scales (p= 0.046)</td>
</tr>
<tr>
<td>Stroke/Neglect</td>
<td>Benefit of early eye patch glasses use</td>
<td>Rehab unit</td>
<td>Mean = 22 days (4 weeks)</td>
<td>Power analysis: 100 subject = 80% for mod. effect size of 0.5</td>
<td>No significant difference in functional activity (p=0.467)</td>
</tr>
<tr>
<td>Vanderploeg et al. (2008)</td>
<td>Randomized to training arm</td>
<td>N = 360</td>
<td>Late group</td>
<td>1.5 to 2.5 hours of Cognitive (CD) or Functional (FE) training/day</td>
<td>No significant differences based on group: Return to work (p=0.5) &amp; living independent (P=0.33)</td>
</tr>
<tr>
<td>TBU/ Memory</td>
<td>Benefit of two models (CD v. FE training)</td>
<td>Rehab unit</td>
<td>Late group</td>
<td>Power analyses: 364 subjects = 80% power</td>
<td>Cognitive FIM (P=0.01) improved in CD training group</td>
</tr>
</tbody>
</table>

Note: Summarizes cognitive studies to identify common themes: 1. Study identified as Early or Late group, i.e. intervention started < 4 weeks post injury or > 4 weeks post injury; duration is intervention period. 2. Intervention and frequency or length of treatment identified. 3. Main study outcomes and statistical results identified by experimental and/or control group.
APPENDIX C

IRB Approval Forms
NOTICE OF APPROVAL TO BEGIN RESEARCH

May 23, 2014

HSC-SN-14-0059 - Information Processing Speed Impairment after Stroke, A Descriptive Study

Number of Subjects Approved: Target: 30 / Screen: 40

PROVISIONS: This approval relates to the research to be conducted under the above referenced title and/or to any associated materials considered by the Committee for the Protection of Human Subjects, e.g. study documents, informed consent, etc.

APPROVED: By Expedited Review and Approval

REVIEW DATE: 05/23/2014

APPROVAL DATE: 05/23/2014

EXPIRATION DATE: 04/30/2015

CHAIRPERSON: John C. Ribble, MD

Subject to any provisions noted above, you may now begin this research.

CHANGES: The principal investigator (PI) must receive approval from the CPHS before initiating any changes, including those required by the sponsor, which would affect human subjects, e.g. changes in methods or procedures, numbers or kinds of human subjects, or revisions to the informed consent document or procedures. The addition of co-investigators must also receive approval from the CPHS. ALL PROTOCOL REVISIONS MUST BE SUBMITTED TO THE SPONSOR OF THE RESEARCH.

INFORMED CONSENT DETERMINATION:
Signed Informed Consent Required

INFORMED CONSENT: When Informed consent is required, it must be obtained by the PI or designee(s), using the format and procedures approved by the CPHS. The PI is responsible to instruct the designee in the methods approved by the CPHS for the consent process. The individual obtaining informed consent must also sign the consent document. Please note that only copies of the stamped approved informed consent form can be used when obtaining consent.

HEALTH INSURANCE PORTABILITY and ACCOUNTABILITY ACT (HIPAA):
HIPAA Authorization required:
HIPAA Authorization within consent form
Waiver for Screening and Recruitment granted:
  Information to be accessed:
    Name, address, city, zipcode, telephone number, treatment dates, admission date, discharge date
  Information to be retained:
    treatment dates, admission date, discharge date

UNANTICIPATED RISK OR HARM, OR ADVERSE DRUG REACTIONS: The PI will immediately inform the CPHS of any unanticipated problems involving risks to subjects or others, of any serious harm to subjects, and of any adverse drug reactions.

RECORDS: The PI will maintain adequate records, including signed consent and HIPAA documents if required, in a manner that ensures subject confidentiality.
Dr. Susan Alderman  
UT-H - MS - Neurology  

**NOTICE OF CONTINUING REVIEW APPROVAL**  
November 11, 2015  

HSC-SN-14-0059 - Information Processing Speed Impairment after Stroke, A Descriptive Study  

PI: Susan Alderman  

**PROVISOS:** Unless otherwise noted, this approval relates to the research to be conducted under the above referenced title and/or to any associated materials considered at this meeting, e.g. study documents, informed consents, etc.  

**NOTE:** If this study meets the federal registration requirements and this is an investigator-initiated study, or if the PI is the study sponsor or holds the IND/IDE applicable to this study, and no one else has registered this trial on the national registry, you are required to register this trial on the national registry at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) in order to publish results in any of the key peer-reviewed journals. For further information write to clinicaltrials@uth.tmc.edu or call 713-500-7909.  

**APPROVED:** By Expedited Review and Approval  

**REVIEW DATE:** November 10, 2015  

**APPROVAL DATE:** November 11, 2015  

**EXPIRATION DATE:** 10/31/2016  

**CHAIRPERSON:** John C. Ribble, M.D.  

Upon review, the CPHS finds that this research is being conducted in accord with its guidelines and with the methods agreed upon by the principal investigator (PI) and approved by the Committee. This approval, subject to any listed provisions and contingent upon compliance with the following stipulations, will expire as noted above:  

**CHANGES:** The PI must receive approval from the CPHS before initiating any changes, including those required by the sponsor, which would affect human subjects, e.g. changes in methods or procedures, numbers or kinds of human subjects, or revisions to the informed consent document or procedures. The addition of co-investigators must also receive approval from the CPHS. ALL PROTOCOL REVISIONS MUST BE SUBMITTED TO THE SPONSOR OF THE RESEARCH.  

**INFORMED CONSENT:** Informed consent must be obtained by the PI or designee(s), using the format and procedures approved by the CPHS. The PI is responsible to instruct the designee in the methods approved by the CPHS for the consent process. The individual obtaining informed consent must also sign the consent document.  

Please note that only copies of the...
appropriately dated, stamped approved informed consent form can be used when obtaining consent.

UNANTICIPATED RISK OR HARM, OR ADVERSE DRUG REACTIONS: The PI will immediately inform the CPHS of any unanticipated problems involving risks to subjects or others, of any serious harm to subjects, and of any adverse drug reactions.

RECORDS: The PI will maintain adequate records, including signed consent documents if required, in a manner which ensures subject confidentiality.
June 18, 2014

MEMORIAL HERMANN HEALTH SYSTEM

APPROVAL FOR

MEMORIAL HERMANN – TEXAS MEDICAL CENTER

Thank you for choosing Memorial Hermann as your service provider for this research study.

IRB ID: HSC-SN-14-0059
PRINCIPAL INVESTIGATOR: Susan Alderman, BSN, MSN
STUDY TITLE: Information Processing Speed Impairment after Stroke, a Descriptive Study
NUMBER OF SUBJECTS: 30

Approval is hereby granted by Memorial Hermann Health System to initiate this research study at the Memorial Hermann – Texas Medical Center location. This approval is subject to the Principal Investigator’s acceptance of the following stipulations:

STUDY-SPECIFIC STIPULATIONS

1. The Joint Commission requires that a copy of the signed consent form for hospital-based studies be in all subjects’ hospital medical records. In addition, the MHHS Authorization for Disclosure of Protected Health Information for Research (with IRB approval stamp) must be placed in all subjects’ hospital medical records. The informed consent and disclosure form must remain in the subjects’ charts.

2. All data security computer devices used in this study must be password protected and/or data encrypted.

3. Please remember to acknowledge the Memorial Hermann – Texas Medical Center in any publications resulting from this study, and provide a copy of the publication to the Executive Director of the Memorial Hermann Clinical Innovation & Research Institute (Cheryl.Chanaud@memorialhermann.org). The methods of acknowledgement may include:
   a. Memorial Hermann – Texas Medical Center as an author’s affiliation;
   b. mention in an “acknowledgement” section; or
   c. as a footnote.

Please sign and return a copy of this letter to the Memorial Hermann Clinical Innovation & Research Institute, c/o Memorial Hermann Hospital, Mailbox 90, via FAX (713) 704-5124, or scanned .pdf file to Cassandra.Varacalli@memorialhermann.org to indicate your acceptance of our terms and policies (guidelines attached).

This study may not be initiated until the letter is signed and returned to the Memorial Hermann Clinical Innovation & Research Institute.

If you have questions or need additional information, please contact the Memorial Hermann Clinical Innovation & Research Institute at (713) 704-4226.

APPROVED:

Cheryl M. Chanaud, PhD, CCRP
System Executive Director, Research
Memorial Hermann Healthcare System

Date 6/16/14

ACCEPTANCE:

Susan Alderman, BSN, MSN
Principal Investigator

Date 6/20/14

cc:
Sean Savitz, MD - Co-Investigator
Terri Armstrong, PhD - Faculty Advisor
Bela Patel, MD – Assistant Chief Medical Officer MH-TMC
Eneida Allen-McBride, MSN, RN – Director of NIMU and Stroke Unit

Attachments:
Memorial Hermann Clinical Innovation and Research Institute Guidelines
APPENDIX D

Informed Consent Form
INFORMED CONSENT TO JOIN A RESEARCH STUDY

INVITATION TO TAKE PART

You are invited to take part in a research project called Information Processing Speed Impairment after Stroke, a Descriptive Study (IPS), conducted by Susan Alderman, RN, PhD(c) of the University of Texas Health Science Center-Houston, School of Nursing. For this research project, she will be called the Principal Investigator or PI. For full disclosure, please know that the PI is performing this study as part of the PhD program requirement.

You have been invited to join this research study because you have experienced a mild or moderate acute ischemic stroke. Your decision to take part is voluntary and you may refuse to take part, or choose to stop from taking part, at any time. A decision not to take part or to stop being a part of the research project will not change the services available to you from your physician or Memorial Hermann Hospital Texas Medical Center. You may refuse to answer any questions asked or written on any forms. This research project has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston as HSCSN-14-0059.

DESCRIPTION OF RESEARCH:

PURPOSE:

The purpose of this study is to learn if people develop problems with thinking clearly because they have difficulty processing information after having a stroke. These problems may be caused by a decreased ability to think quickly, which is called our information processing speed. When there is a problem with
information processing speed we may not always understand how to do tasks, feel pressured or feel that “things are moving too fast”. We may lose the ability to quickly think through a task with several steps, like how to drive a car or we may have trouble following a conversation or watch a TV program. These problems may be mild or may greatly effects how we get along in life.

The results of this study will help in better understanding how often problems with information processing speed happen and if they last for several months. We will also compare the processing speed of people who have routine rehabilitation with those people who do not have rehabilitation ordered by their doctor. This will help us understand if rehabilitation for other stroke symptoms may also help with information processing speed. People who have a mild stroke and are otherwise qualified to have a MRI will be asked to take part in the MRI sub-study. Two MRIs will be done after you are discharged from the hospital. We watch for stroke lesion changes and to see how the changes compare to changes in your thinking skills.

This is a local study with one location in Houston, Texas. The study will enroll a total of fifty-six (56) people at this location. The Principal Investigator is paying for this study through a small research grant. The outpatient MRIs are paid for by the UT Medical School Department of Neurology.

**PROCEDURE:**

Six (6) thinking (cognitive) tests for this study will be completed by question and answer tests for this study, using pencil and paper. There will not be any blood work. On the last visit we will ask you to complete questionnaires about how you think your quality of life is at that time. A list of the thinking tests to be done during each visit can be given to you if you wish. The investigator can explain them in as much detail as you would like to know.

There will be three study visits; the visit while in hospital, another visit about 3 weeks later and a final visit about 12 weeks from the time you were enrolled in the study. All together people enrolled in the study will have a total of 3 visits.
over a 12-week time period. Each follow-up visit will last 40-50 minutes and we will call 1 week prior to verify our appointment with you. In addition to the test information we will ask about your general health, history of medical problems and medications, demographic information like race, gender, what was the last grade of school you attended, about the stroke and any changes you noticed between visits. You may refuse to answer any questions asked or written on any forms.

If you agree to take part in the MRI sub-study, a study MRI may will be done within the next 3 weeks at the UT MRI suite and a follow up MRI will be done at 3 months after the stroke; these MRIs are just like the one you had in the hospital. The follow up visits may take up to 2 hours; the sub-study MRIs may take up to 1 hour each and the thinking tests and questionnaires may take 50 minutes. The total time commitment to take part in the study is about 90 days.

SPECIAL CIRCUMSTANCE

One of the baseline cognitive tests, the SDMT, may be completed before the informed consent process is complete in this study to ensure all participants meet study criteria. All other study procedures will be performed after informed consent process has been completed.

TIME COMMITMENT:

The baseline or hospital visit will last about 30 minutes with the PI completing the study thinking tests. You will also be contacted for 2 follow up visits each lasting about 40-50 minutes. The participation time will be a total of 3 visits over three months, starting with the one today in the hospital. If you decide to take part in the MRI sub-study, we will ask you to return to the UT Medical School Building within 3 weeks of stroke and after 3 months to have the follow-up MRI.

BENEFITS:

You may receive no direct benefit from being in this study; however, your taking
part may help patients get better care in the future.

**RISKS AND/OR DISCOMFORTS:**

There are no known risks from completing these study tests. If you become tired during the testing sessions, please let the investigator know and a short rest break can be arranged. Some of your private health information is gathered for this study, and there is a risk of loss of confidentiality. Information gathered in the study will be kept strictly confidential to the full extent of the law.

The MRI scanner uses a large magnet and radio signals to take pictures of your brain. People who have implants/pacemakers or who are known to become afraid in small areas (claustrophobic) should not have an MRI. Claustrophobia (fear of being in small spaces) may occur during the procedure and the noise of the machine could be uncomfortable and awkward. We will provide earplugs for your comfort. The MRI machine may be stopped at any time at your request. There is no radiation exposure with MRI. There are no known potential long-term risks from frequent MRI. You cannot take part in the MRI sub-study if you are pregnant. If you get pregnant during the study you must tell the doctor immediately. You will not be able to continue in the MRI sub-study since elective MRIs are not approved for pregnant people.

**ALTERNATIVES:**

The only alternative is not to take part in this study. You can take part in the study but decline the MRI sub-study.

**STUDY WITHDRAWAL:**

Taking part in this study is voluntary. You may choose to stop taking part in the study at any time by notifying the PI, Susan Alderman, at 713-304-7355. Any data already collected prior to your withdrawal from the study will be included in the data analysis for the study. The PI may decide to withdraw you from the study without regard to your wishes. Reasons for this may be a worsening of your health which may confuse test results or an inability to maintain
appointments.

**IN CASE OF INJURY:**

It is unlikely that an injury may occur from the testing sessions or the MRI but please report any study related injury to the principal investigator (Susan Alderman, 713- 305-7355) and to the Committee for the Protection of Human Subjects at (713) 500- 7943.

If you suffer any injury as a result of taking part in this research study, please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, all needed facilities, emergency treatment and professional services will be available to you, just as they are to the community in general. You will not give up any of your legal rights by signing this consent form.

**COSTS, REIMBURSEMENT, AND COMPENSATION:**

All the study related tests done with the Primary Investigator will be provided at no charge. This does not include the standard of care treatment, such as the MRI done during your admission, which remains the responsibility of the patient. The MRIs done as part of the study at the 2 outpatient visits will be paid for by the study.

If you are selected to take part in the MRI sub-study at 3 weeks and at 3 months, you will be given $100.00 after the MRI; to cover the parking and travel expenses to the MRI facility.

If you received a bill that you believe is related to your taking part in this research study, please contact Susan Alderman at 713-304-7355 with questions.
CONFIDENTIALITY:

You will not be personally identified in any reports or publications that may result from this study. Any demographic and personal information about you that is gathered during this study will remain confidential to every extent of the law. A special number will be used to identify you in the study and only the investigator will know your name. If the investigator will be coming to your home a backup investigator will be made aware and will have access to your personal information in case of emergency. There is a separate section in this consent form that you will be asked to sign which details the use and disclosure of your protected health information. A signature on the receipt log will be signed for each follow up visit and kept in a secured area at the University of Texas for the life of the study and then will be destroyed.

NEW INFORMATION:

Significant new findings developed during the course of the research which might relate to your willingness to continue participation will be provided to you. During your Week 12 visit the PI will discuss the results of your participation in the study and, upon request, will notify you if any manuscripts are published after the study is completed.

QUESTIONS:

The PI will be glad to answer any further questions at any time. Please contact the PI to discuss problems, voice concerns, obtain information, and offer input in addition to asking questions about the research. Please call Susan Alderman during business hours at 713-304-7355. Include your name and a call-back phone number.
AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION FOR RESEARCH

Patient Name: ________________________________

Date of birth: ________________________________

Protocol Number and Title: HSC-SN-14-0059. Information Processing Speed Impairment after Stroke, A Descriptive Study (IPS)

Principal Investigator: Susan Alderman RN PhD(c)

If you sign this document, you give permission to The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System to use or disclose (release) your health information that identifies you for the research study named above.

The health information that we may use or disclose (release) for this research includes medication list, NIHSS results and the type of stroke you have experienced. The information disclosed will not contain any identifying information.

The health information listed above may be used by and/or disclosed (released) to researchers and their staff. The researchers may disclose information to employees at The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System for the purposes of verifying research records.

The researchers may also disclose information to the following entities: UT School of Nursing Faculty Advisor and other faculty members

The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System is required by law to protect your health information. By signing this document, you authorize The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your child's information with others without your permission, if permitted by laws governing them.

If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes. No publication or public presentation about the research described above will reveal your
identity without another authorization from you.

Please note that health information used and disclosed may include information relating to HIV infection; treatment for or history of drug or alcohol abuse; or mental or behavioral health or psychiatric care. In case of an adverse event related to or resulting from taking part in this study, you give permission to the researchers involved in this research to access test, treatment and outcome information related to the adverse event from the treating facility.

Please note that you do not have to sign this Authorization, but if you do not, you may not participate in this research study. University of Texas Health Science Center AND/OR Memorial Hermann Healthcare System may not withhold treatment or refuse treating you if you do not sign this Authorization.

You may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers may still use or disclose health information they already have obtained as necessary to maintain the integrity or reliability of the current research. To revoke this Authorization, you must call or write to:

Susan Alderman, RN
The University of Texas Health Science Center at Houston School of Nursing
713-304-7355

Privacy Officer
Memorial Hermann Healthcare System
909 Frostwood
Texas 77074
Fax: 713-338-4542

This Authorization will expire 6 years after the end of the study.
SIGNATURES

Sign below only if you understand the information given to you about the research and you choose to take part. Make sure that any questions have been answered and that you understand the study. If you have any questions or concerns about your rights as a research subject, call the Committee for the Protection of Human Subjects at (713) 500-7943. You may also call the Committee if you wish to discuss problems, concerns, and questions; obtain information about the research; and offer input about current or past participation in a research study. If you decide to take part in this research study, a copy of this signed consent form will be given to you.

For the MRI sub-study: please initial

☐ I agree to take part in the MRI sub-study.

Printed Name of Subject ____________________________ Signature of Subject ________________ Date and Time ____________________________

Printed Name of Legally Authorized Representative ____________________________ Signature of Legally Authorized Representative ________________ Date and Time ____________________________

Relationship to Subject ____________________________

Printed Name of Person Obtaining Consent ____________________________ Signature of Person Obtaining Consent ________________ Date and Time ____________________________

CPHS STATEMENT: This study (HSC-SN-14-0059) has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston. For any questions about research subject’s rights, to report a research-related injury, call the CPHS at (713) 500-7943.
APPENDIX E

Case Report Form
Information Processing Speed Impairment after Stroke, A Descriptive Study (IPS) HSC-SN-14-0059

Section 1 - BASELINE

Table of Contents

1. Demographics
2. Inclusion & Exclusion Criteria
3. Presentation Data
4. Medical History
5. NIHSS
6. BI
7. mRS
8. Cognitive Tests
   a. CVLT II
   b. DIGIT SPANSDMT
   c. DIGIT SYMBOL-CODING
   d. SYMBOL SEARCH
   e. MoCA
9. Vital signs
10. Concomitant Medications
Section 2 – WEEK 3

Table of Contents

1. Presentation Data
2. NIHSS
3. BI
4. mRS
5. Cognitive Tests
   a. CVLT II
   b. DIGIT SPANSDMT
   c. DIGIT SYMBOL-CODING
   d. SYMBOL SEARCH
   e. MoCA
6. Concomitant Medications
Information Processing Speed Impairment after Stroke,  
A Descriptive Study (IPS) HSC-SN-14-0059

**Section 3 – WEEK 12**

**Table of Contents**

1. Presentation Data  
2. NIHSS  
3. BI  
4. mRS  
5. Cognitive Tests  
   a. CVLT II  
   b. DIGIT SPAN SDMT  
   c. DIGIT SYMBOL-CODING  
   d. SYMBOL SEARCH  
   e. MoCA  
6. SS-QOL  
7. NEURO-QOL  
8. Concomitant Medications  
9. investigator’s SIGNATURE PAGE
Information Processing Speed Impairment after Stroke,  
A Descriptive Study (IPS) HSC-SN-14-0059

**Baseline Demographics**

1. Age | | | years  
2. Gender | Male | Female  
3. Years of education  
5. Race | Asian | Pacific Islander | Black | White | Native American  
6. Ethnicity | Hispanic | Not Hispanic

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<td>10. Week 3 Time (+/- 3 days)</td>
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<td>11. Week 12 Date (+/- 7 days)</td>
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Completed by:  
Date Completed: | | - | | - | |
Information Processing Speed Impairment after Stroke,
A Descriptive Study (IPS) HSC-SN-14-0059

Inclusion Criteria
Must be all YES to be eligible.

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Exclusion Criteria
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Completed by: ______________________________  Date Completed: __.__.____
# Information Processing Speed Impairment after Stroke,
A Descriptive Study (IPS) HSC-SN-14-0059

## Presentation Data

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3. Baseline MRI/CT results:

4. Diagnosis:

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4. PRESENTATION DATA

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Does Patient have any of the following medical history?

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If Other, please describe:

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**Completed by:**

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### NIH STROKE SCALE

1. Time point
   - [ ] Baseline
   - [ ] Week 3 Visit
   - [ ] Week 12 Visit

2. Date: | | | - | | | | (m-dd-yyyy)

3. Time: | | | - | | | |

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<tr>
<td>1b LOC Questions (0-2)</td>
<td>___</td>
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<tr>
<td>1c LOC Commands (0-2)</td>
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<td>2 Best Gaze (0-2)</td>
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<td>4 Facial Palsy (0-3)</td>
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<tr>
<td>5 &amp; 6 Motor Arm and Leg</td>
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<tr>
<td>5a Motor Left Arm (0-4 or UN)</td>
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<tr>
<td>5b Motor Right Arm (0-4 or UN)</td>
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<td>7 Limb Ataxia (0-2 or UN)</td>
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<td>8 Sensory (0-2)</td>
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</tr>
<tr>
<td>9 Best Language (0-3)</td>
<td>___</td>
</tr>
<tr>
<td>10 Dysarthria (0-2 or UN)</td>
<td>___</td>
</tr>
<tr>
<td>11 Extinction and Inattention (formerly Neglect) (0-2)</td>
<td>___</td>
</tr>
<tr>
<td>12 TOTAL SCORE</td>
<td>____</td>
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</table>

NAME OF PERSON ADMINISTERING SCALE:

______________________________

Completed by: | Date Completed: | | | | - | | | |
| | | ___ | | | | ___ | | |

STUDY ID: | | | |
Information Processing Speed Impairment after Stroke, A Descriptive Study (IPS) HSC-SN-14-0059

Cognitive Testing Scales
(NIHSS, CVLT II SF, Digit Span, SDMT, Digit Symbol-Coding, Symbol Search, BI, MoCA, mRS, SS-QOL, Neuro-QOL)

<table>
<thead>
<tr>
<th>Study Code #________</th>
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</thead>
</table>

Baseline: / / ___ Week 3: ___/ ___ Week 12: ___/ ___

1. **NIHSS**

<table>
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<tr>
<th>Visit:</th>
<th>Baseline</th>
<th>Week 3</th>
<th>Week 12</th>
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</thead>
<tbody>
<tr>
<td>Total</td>
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<tr>
<td><strong>Difference</strong></td>
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2. **California Verbal Learning Test:**

<table>
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<th>Visit:</th>
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<th>Week 3</th>
<th>Week 12</th>
</tr>
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<tbody>
<tr>
<td>4th Trail</td>
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<tr>
<td>z-score</td>
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<tr>
<td><strong>Difference</strong></td>
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<tr>
<td>Short-Delay</td>
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<td><strong>Difference</strong></td>
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<tr>
<td>Long-Delay</td>
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<td>z-score</td>
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<tr>
<td><strong>Difference</strong></td>
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</table>
3. **Digit Span:**

<table>
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<th>Visit:</th>
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<th>Week 3</th>
<th>Week 12</th>
</tr>
</thead>
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<tr>
<td>Total</td>
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<td>z-score</td>
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<tr>
<td>Difference</td>
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4. **Symbol digit modality test:**

<table>
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<th>Week 12</th>
</tr>
</thead>
<tbody>
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<tr>
<td>z-score</td>
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<td>Memory test</td>
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<tr>
<td>Difference</td>
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5. **Digit Symbol – Coding:**

<table>
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<th>Week 3</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
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<td>Total</td>
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<tr>
<td>z-score</td>
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<td></td>
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</tr>
<tr>
<td>Difference</td>
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</table>
6. **Symbol Search:**

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<th>Baseline</th>
<th>Week 3</th>
<th>Week 12</th>
</tr>
</thead>
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</tr>
<tr>
<td>Difference</td>
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7. **Barthel Index:**

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<th>Week 3</th>
<th>Week 12</th>
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</thead>
<tbody>
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</tr>
<tr>
<td>Difference</td>
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</table>

8. **Montreal Cognitive Assessment:**

<table>
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<th>Visit:</th>
<th>Baseline</th>
<th>Week 3</th>
<th>Week 12</th>
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</thead>
<tbody>
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<td>Total</td>
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<tr>
<td>Difference</td>
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</table>

9. **Modified Rankin Scale:**

<table>
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<th>Visit:</th>
<th>Baseline</th>
<th>Week 3</th>
<th>Week 12</th>
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<tbody>
<tr>
<td>Total</td>
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<tr>
<td>Difference</td>
<td>N/A</td>
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</table>
Week 12 Visit Only:

10. **SS-QOL**: **Total:** _______.

11. **Neuro-QOL**: **Total:** _______.
   - Applied Cognition-general concerns: **Sub-total:** _______.
   - Applied Cognition-Executive Function: **Sub-total:** _______.
   - Positive Affect & Well-Being: **Sub-total:** _______.

I have reviewed the information in the Case Report Form pertaining to the study *Information Processing Speed Impairment after Stroke, A Descriptive Study (IPS) HSC-SN-14-0059* and all source documents. I have verified that they accurately reflect this patient’s data, that the study was conducted according to the protocol and any amendments, the Declaration of Helsinki and Good Clinical Practices. The patient or the patient’s representative provided written informed consent prior to the patient’s participation in the study.

Principal Investigator’s Name
(Printed)

_________________________  __________
Principal Investigator’s Signature      Date
<table>
<thead>
<tr>
<th>#</th>
<th>Medication</th>
<th>Route</th>
<th>Indication</th>
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</table>

Completed by: __________________________

Date Completed: [__] [__] [__] - [__] [__] [__]

9. Concurrent MEDICATIONS
APPENDIX F

Curriculum Vitae
CURRICULUM VITAE
Susan Alderman, MSN, BSN RN

EDUCATION:

University of Texas Pursuing PhD in Nursing
Houston, Texas

Texas Women’s University 2012 MS Nursing Education
Houston, Texas

Texas Women’s University 2000 BSN Nursing
Houston, Texas

Lone Star College 1987 ADN Nursing
Houston, Texas

PROFESSIONAL POSITIONS:

University of Texas Health Science Center at Houston
School of Nursing
Houston Texas
Primary Investigator IPS Study 2014–current

University of Texas Health Science Center at Houston
McGovern Medical School, Department of Neurology
Houston Texas
Primary Investigator CASTLe Study 2013-2014

University of Texas Health Science Center at Houston
McGovern Medical School, Department of Neurology
Houston Texas
Senior Research Nurse Coordinator 2008–2015

Brazosport Regional Health-System Hospital
Emergency Center
Lake Jackson, Texas
Staff Nurse 2006-2008

Park Plaza Hospital
Emergency Center
Houston, Texas
Charge Nurse and Case Manager 2001-2006
PROFESSIONAL POSITIONS (Cont'd):

Aetna Healthcare  
Houston, Texas  
Utilization Management  
2000-2001

The Methodist Hospital  
Emergency Center & ICU  
Houston, Texas  
Staff/Charge nurse  
1988-1998

S.E. TX Medical Center  
Emergency Center  
Conroe Texas  
Staff Nurse  
1987-1988

US Air Force  
Medic, Rank: Sargent  
1984-1984

PROFESSIONAL MEMBERSHIPS:

Sigma Theta Tau International Honor Society  
Zeta Pi Chapter member  
2014-current

American Association of Neuroscience Nurses  
Educational Approval Committee member  
2012-current  
2013-current

American Stroke Association member  
2008-current

Phi Kappa Phi Honor Society  
1999 & 1987

PUBLICATIONS:


Savitz, S., Hicks, W., Misra, V., Alderman, S., & Vahidy, F. (2016). Recruiting stroke patients into cell therapy trials. Accepted for publication in JAMA Neurology.


Alderman, S., Bursaw, A., Karamchandani, R., Breier, J., Vahidy, F., Aden, J. & Savitz, S. Cognitive deficits are detectable within 24 hours of mild ischemic stroke or TIA. Submitted for publication.

PRESENTATIONS:

Paper


Poster session


**AWARDS AND RECOGNITIONS:**

2012-2015  Recipient, PARTNERS Scholarship, University of Texas-Houston School of Nursing ($22,000)

2014-2015  Recipient, Speros Martel Endowment for the Aging, University of Texas-Houston School of Nursing ($10,000)

2014      Joseph C. Valley, Sr. Memorial Trust Fund for Gerontological Nursing University of Texas-Houston School of Nursing ($3,000)

2014-2015  Recipient, William Randolph Hearst Foundation Scholarship, University of Texas-Houston School of Nursing ($2,000)