Deficits of Language and Speech in Idiopathic Normal Pressure Hydrocephalus

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Abstract

**Title: Deficits of Language and Speech in Idiopathic Normal Pressure Hydrocephalus**

Esther H. Chung, BA, Thu-Trang Hickman, MPH, Mary-Ellen Meadows, PhD and Mark D. Johnson, MD, PhD

**Purpose:** Idiopathic normal pressure hydrocephalus (iNPH) is a disorder of unknown etiology characterized by gait instability, incontinence and dementia. Symptoms can be ameliorated by shunt placement for cerebrospinal fluid drainage. Although language and speech impairments have not traditionally been associated with iNPH, anecdotal reports commonly indicate otherwise. This study’s objective was to determine the prevalence and nature of language and speech difficulties in iNPH, and whether these deficits improve after shunt placement.

**Methods:** We analyzed the medical records of 529 patients who underwent shunt placement for iNPH at our institution between July 2001 and March 2015 for deficits in language or speech at initial presentation. A subset of 71 patients underwent formal pre-operative neurocognitive assessments, and thirteen of these patients also underwent post-operative testing at least 6 months after shunt insertion. Improvement was assessed using the Reliable Change Index.

**Results:** In the retrospective study of 529 patients, language deficits were identified in 23.1%, speech deficits in 12.9% and writing deficits in 4% of patients. Analysis of 71 prospectively collected pre-operative neurocognitive evaluations revealed semantic verbal fluency and fine motor impairments in more than two-thirds of patients. Of the 13 patients who underwent both pre- and post-operative testing, 84.6% experienced significant improvements in language and executive function.

**Conclusions:** We demonstrate that 70.4% and 67.6% of patients with shunt-responsive iNPH originally present with language and fine motor difficulties respectively. Improvement in these symptoms after shunting indicates that deficits in language are an integral component of iNPH pathology and should be considered during the diagnosis and management of this disorder.
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**Glossary of Abbreviations**

iNPH idiopathic normal pressure hydrocephalus

CSF cerebrospinal fluid

TT tap test

AD Alzheimer’s disease

WTAR Wechsler Test of Adult Reading

MMSE mini-mental state examination

WAIS-III Wechsler Adult Intelligence Scale-III

HVLT-R Hopkins Verbal Learning Test-Revised

PHQ-9 Patient Health Questionnaire-9

IQ Intelligence Quotient
**Section 1: Introduction**

Idiopathic Normal Pressure Hydrocephalus (iNPH) is a neurological disorder of unknown etiology that is characterized by gait instability, incontinence and dementia.\(^1\,^2\) Imaging findings include enlarged cerebral ventricles, deep white matter or periventricular white matter abnormalities and alterations in the size of the subarachnoid spaces.\(^3\) It has been estimated that about 1.4% of patients over the age of 65 and up to 14% of patients in nursing homes have iNPH, most of whom are undiagnosed.\(^4\,^6\) Given that the triad of symptoms in iNPH can be ameliorated by shunt placement for cerebrospinal fluid (CSF) drainage, this disorder has been classified as one of the reversible dementias with improvements seen in up to 80% of patients after CSF drainage.\(^7\,^9\,^10\)

Although most patients undergo lumbar CSF drainage trials to predict outcomes after shunt placement, the prediction of shunt success has been inconsistent.\(^11\) Evidence-based literature reviews have established that several diagnostic tests used to identify the syndrome, including a positive CSF tap test (TT), are insufficient for the accurate diagnosis of iNPH.\(^12\,^13\) The low sensitivity and negative predictive value of tests used to identify “shunt-responders” calls for continued investigation of predictors of disease and shunt response. The Adult Hydrocephalus Database offers one of the largest cohorts of iNPH patients published to date, from which we can better assess the clinical picture of this enigmatic syndrome.

The causes of iNPH are not known, but clinical studies of iNPH patients and analyses of CSF biomarker profiles are beginning to guide etiological hypotheses and clinical management. To identify patients with iNPH and to better assess candidacy for shunt placement, in-depth neurocognitive testing serves as an important adjunct to the assessment of gait impairment. The literature has primarily associated acquired language disorders with the “cortical dementia” seen in neurodegenerative diseases such as Alzheimer’s Disease (AD) and frontotemporal dementia.\(^14\,^16\) Cortical deficits can encompass language, visuospatial abilities and executive function, depending on the presentation. On the other hand, the dementia of iNPH has been traditionally characterized as “subcortical,” consistent with changes in general cognitive processes (i.e. decreased processing speed, attention deficits, severe motor abnormalities), which can then impact memory and overall cognitive function.\(^16\)

A recent study in a relatively small sample of 32 iNPH and 32 AD patients noted that deficits in executive function and visuospatial abilities were more profound in iNPH than in AD, while deficits in language were only noted in the latter.\(^15\) This lends overall support to the notion that iNPH may actually present with a more mixed cortical and subcortical cognitive...
profile; yet the study still leaves language out of the profile. On the other hand, numerous anecdotal reports from healthcare providers, patients and their families suggest that the presence of difficulties with language and speech should not exclude iNPH from the differential diagnoses. To date, the prevalence and character of language difficulties in iNPH are not well understood. Very little is known about the progressive impairment in word-finding and other aspects of expressive and receptive language in patients with dementia and/or ventriculomegaly.(14) If these specific deficits can be rapidly reversed after shunt placement, this would not only suggest that iNPH involves more widespread cortical and subcortical dysfunction, but it would also be useful in more accurately identifying candidates for a trial of CSF drainage.

Section 2: Student Role

I completed the entire project, with help and advice on the statistical analysis and interpretation of the results from Dr. Johnson, Dr. Meadows and Ms. Hickman.

Section 3: Methods

Retrospective Study Design and Data Collection

This study was conducted under the auspices of a human subjects research protocol approved by the Partners IRB Committee. We retrospectively reviewed the medical records of patients diagnosed with disorders of CSF flow at Brigham and Women’s Hospital between July 2001 and May 2015 to identify patients who underwent evaluation for iNPH. Patients were selected for evaluation of possible iNPH if they had communicating hydrocephalus on cranial images, gait disturbance, urinary urgency/incontinence, cognitive impairment, and no clearly identifiable cause of their symptoms. At the time of the first clinic visit, clinical and demographic data were collected using a patient questionnaire. We combined this prospectively collected data with additional notes documented by all care providers in the electronic medical record. After an evaluation that included a thorough medical history, neurological examination, CT/MR imaging, and lumbar CSF drainage trials, 529 patients (267 men and 262 women) were identified to have probable iNPH and subsequently underwent ventriculoperitoneal shunt placement. The median and mean duration of symptoms prior to evaluation for iNPH were 24
months and 29.6 ± 20.9 months (mean ± SD), respectively. About two-thirds of patients presented with the classic triad of gait difficulty, urinary incontinence, and cognitive impairment.

Patients were then coded into three stratified categories: language, motor-related speech or motor-related writing deficits. Language difficulties were further divided into subcategories of receptive language, expressive language, and other (i.e. difficulties reading, non-motor writing, and/or other combinations). Receptive language deficits were defined as difficulty understanding simple or complex statements or commands during the patient’s neurological examination. Expressive language deficits were defined as difficulty translating thoughts into sensible words and sentences expressed in grammatically correct syntax. Expressive language was further subdivided into difficulties with word-finding or overall verbal fluency. To be explicit in defining our stratifications, speech difficulties were strictly defined as motor-related speech disorders arising from deficits in the motoric mechanics of oral communication. As opposed to expressive language, which refers to the ability to communicate information, speech deficits were defined by dysfunction in neuromuscular activity. This latter category was further subdivided into dysarthria (slurred speech), stuttering, overall slowness of speech, and combined and/or uncharacterized presentations. The categorizations of this retrospective study are represented in Figure 1.

**Prospective Study Design and Data Collection**

Formal pre-operative neurocognitive evaluations of patients awaiting shunt placement (n=71) were conducted by a clinical neuropsychologist. The pre-surgical battery for iNPH included the following cognitive tests: Wechsler Test of Adult Reading (WTAR) for premorbid estimate of IQ,(17) the mini-mental state examination (MMSE) as a basic cognitive screen of attention (WORLD reversal, Serial 7 Subtraction tests),(18) Digit Span subtest from the Wechsler Adult Intelligence Scale-III (WAIS-III), Phonemic (FAS) and semantic (Animals) for verbal fluency,(19) Trails Making Test A for processing speed and Test B for executive function,(20) Grooved Pegboard Test for fine motor skills,(21) Hopkins Verbal Learning Test-Revised (HVLT-R) for verbal learning and verbal memory,(22) clock drawing for visuospatial function, and Patient Health Questionnaire-9 (PHQ-9) for emotional function. Specifically regarding the verbal fluency assessments, the FAS test evaluates phonemic fluency, whereas the Animals test evaluates semantic fluency. Each category of verbal fluency has distinct neural correlates with a relative importance of the left inferior temporal cortex in semantic versus phonemic, and of the pre-supplementary motor area and head of caudate bilaterally in phonemic versus semantic.(23) Additionally, the Grooved Pegboard test for upper extremity
Dexterity was used to assess fine motor skills that may reflect deficits in writing ability and speech. (24,25)

Each evaluation takes approximately 2 hours to complete. Post-operative neurocognitive evaluations (n=13) using the same battery with alternate forms for memory and phonemic and semantic fluency were completed during patient follow-up at least 6-18 months after shunt placement.

The Z scores for each subtest score for every patient were calculated and assessed using normative data from published reports or test manuals, taking into account age, gender and education. Impairment was defined as a Z score > -1.5 standard deviations (SD) below the mean. (26,27) Subsequently, improvement after shunt placement was assessed using the Reliable Change Index for each neurocognitive variable. (28) This measures whether the change (increased or decreased) in the individual’s score is statistically significant (P<0.05). Additionally, we identified a significant change in scores by defining “improvement” as an absolute change greater than 1 SD. (29)

**Ventriculoperitoneal Shunt Surgery**

Patients for whom a trial of CSF drainage supported a diagnosis of probable iNPH underwent surgical implantation of a ventriculoperitoneal shunt as treatment for their symptoms. The shunts generally contained programmable valves (Codman, Inc.) programmed initially to a setting of 120 mm of water. Valve settings were adjusted post-operatively as needed to maximize symptom improvement and minimize signs or symptoms of overdrainage such as positional headaches or subdural hematomas.

**Statistical Analysis**

The SAS statistical software program (SAS Inc, NC, version 9.3) and Microsoft Excel 2011 (Microsoft Office, version 14.0.0) was used for all database analyses. The Reliable Change Index for each neurocognitive test score was calculated using pre-programmed score change calculators on Microsoft Excel spreadsheets. Statistical significance was set at the P<0.05 level. All statistical analyses were performed by T.H., E.C., and M.M.

**Outcomes Assessment**

Patients were evaluated by a group of board certified neurosurgeons and/or neurologists before and after CSF drainage trials and shunt placement. Patients who showed signs of improvement in gait, incontinence or cognition after a trial of CSF drainage were offered
ventriculoperitoneal shunt placement. Patients were evaluated post-operatively at 2 weeks and at 6 weeks, and were then followed with periodic monthly or annual clinic visits as needed for a period of up to 11 years. Changes in gait were based upon assessments of Timed Up and Go test times, gait speed, step height, cadence, balance, the need for gait assistive devices and the number of falls. Changes in urinary/fecal incontinence or urgency were assessed in collaboration with nursing staff, caregivers and patients. Changes in cognitive function were assessed using neurological examinations, formal neurocognitive evaluations, statements by caregivers and patient self-reports. These criteria were collectively used to categorize the overall degree of improvement as improved or not improved.

For the retrospective cohort of 529 patients, the mean duration of follow up after shunt placement was 32.3 ± 30.8 months, with a range of 1 to 132 months. The median duration of follow up was 22 months. Based on the aforementioned criteria, the overall rate of positive shunt-response was found to be 79%. Approximately 78% of patients who presented with the classic iNPH triad improved after shunt placement.

Section 4: Results

Retrospective study on language, speech, and writing deficits in iNPH

Prevalence and characterization of deficits in iNPH

Of the 529 patients who underwent shunt placement for iNPH at the Brigham and Women’s Hospital between July 2001 and March 2015, 23.1% presented with language difficulties, 12.9% presented with motor-related speech difficulties, and 4% presented with motor-related writing deficits (Figure 2A).

Of those patients who presented with deficits in language (Figure 2B), 75.4% specifically demonstrated deficits in expressive language, while 10.7% exhibited difficulties in receptive language. An additional 10.7% presented with difficulties in both expressive and receptive language, while 3.3% displayed difficulties with reading and writing complete, grammatically correct sentences. Among the subset of patients who presented with expressive language deficits, word-finding difficulties were notably prevalent at 43.9%. Word-finding difficulty was commonly self-reported by patients and their families during history taking, as well as noted by healthcare providers during their respective examinations. Deficits in overall verbal fluency were also prevalent, affecting 29.0% of the subgroup of patients with expressive language difficulties.
Here, verbal fluency was defined as difficulty in accessing proper grammar structure, sound forms and/or vocabulary in order to communicate with ease.

Among patients who presented with deficits in motor-related speech (Figure 2C), the most common difficulties included dysarthria (25.0%), overall slowness of speech (27.9%), and stuttering/shakiness (10.3%).

**Prospective study of neurocognitive dysfunctions in iNPH**

Quantitative characterization of neurocognitive dysfunctions in iNPH

Prior to shunt placement for iNPH, 71 patients underwent formal pre-operative neurocognitive evaluations. The pre-surgical battery for iNPH included a variety of cognitive tests as detailed above in the Methods section.

We defined impairment as a Z score $\geq -1.5$ SD below the mean, standardized for patient age, sex, and level of education. Data analysis revealed that at least half of the iNPH patient population demonstrated impairments across the selected neurocognitive evaluations (Figure 3). Baseline testing of premorbid intelligence (IQ) of this patient pool was tested using the WTAR, which assess abilities usually unaffected by cognitive decline associated with neurological damage. Nearly three-quarters of patients tested above average on this measure (Z score $> 0$). In contrast, patient scores were skewed toward below average in the MMSE and Trails A test, which account for overall cognitive deficits and attention/processing speed, respectively. Additionally, the distributions of Z scores on the FAS and Animals verbal fluency tests, and on the Grooved Pegboard fine motor skill test, were spread predominantly below the quantitative level of impairment. Approximately two-thirds of patients scored below average on the MMSE and Trails A tests, which primarily test subcortical functions, while more than 75% ranged below average on the Animals, Trails B and Grooved Pegboard tests, which primarily assess cortical functions. Prospectively collected formal pre-operative neurocognitive evaluations indicate that cortical dementia (i.e. declines in language ability, fine motor skills and executive function) is indeed characteristic of the neurocognitive profile of patients with iNPH.

Prevalence of neurocognitive dysfunctions in iNPH

Analysis of the 71 prospectively performed pre-operative neurocognitive evaluations revealed the presence of a variety of language deficits (Figure 4). Assessment of cortical functions indicated that semantic verbal fluency was impaired in 67.6% of iNPH patients, and phonemic verbal fluency was impaired in 53.5% of these patients. When upper extremity
dexterity associated with writing and left cortex-controlled motor speech functions were examined, fine motor coordination on the Grooved Pegboard test was found to be impaired in 67.6% of patients. Executive function, as determined by set switching in the Trails B test, was impaired in 69.0% of patients. Looking next at “subcortical” functions, 42.2% of patients demonstrated impaired cognitive processing speed, as measured by the Trails A test, and 35.2% of patients had impaired attention in the context of overall cognitive status as assessed in the MMSE. Overall, cortical dysfunction, specifically in semantic verbal fluency, executive function and fine motor skills, was more prevalent among the iNPH population than subcortical dysfunction.

Focused analysis of pre- and post-operative cognitive evaluations

Analysis of 13 iNPH patients who received neurocognitive evaluations before and after shunt placement revealed that 12 out of 13 experienced overall improvements in gait, urinary incontinence and/or cognition. To identify post-operative changes in cognitive function, significant improvement or decline (P<0.05) after shunt placement was assessed using the Reliable Change Index for each neurocognitive subtest.

On the FAS and Animals test, 31.0% demonstrated significant improvement in semantic or phonemic verbal fluency, while 7.7% declined. On the Trails A test, 23.1% demonstrated significant improvement in processing speed, while 15.0% declined. Notably, in the Trails B set switching test, 38.5% improved in executive function, while 23.1% declined. On the Grooved Pegboard test of the dominant hand, 30.8% demonstrated significant improvement in fine motor dexterity, while 7.7% declined. In HVLT-R Total Recall, 23.1% of patients showed significant improvement in verbal learning, while 7.7% declined. In HVLT-R Delayed Recall, 38.5% of patients demonstrated significant improvement in verbal retrieval and verbal memory, while 7.7% declined.

Considering significant improvements in language and executive function together, 84.6% of these patients (11 out of 13) improved in overall cortical function, with significant improvements seen in language and executive function. Of these patients whose cortical dementia improved (n=11), nearly two-thirds (63.6%) improved specifically in language-related functions, including verbal fluency, verbal learning, and/or verbal memory. Looking at language-related functions in isolation, 53.8% (7 out of 13) of patients improved. There was also improvement seen in subcortical functioning, as assessed by increased processing speed in 23.1% (3 out of 13) of patients. Fine motor coordination skills were improved as well in 30.8% of patients (4 out of 13). Two patients, one of whom did not show overall improvement in
symptoms post-operatively, were reported to be co-morbid for Alzheimer’s disease. However, both patients’ gait and subsequent quality of life were documented to have improved over time.

**Section 5: Discussion**

In this study, we present data both from a retrospective medical record review of 529 iNPH patients as well as prospectively performed pre-operative neurocognitive evaluations of 71 iNPH patients that reveal the prevalence and nature of speech and language difficulties in iNPH. Whereas the retrospective analysis suggested a prevalence of 23.1% (122 out of 529), the more rigorous prospective analysis using formal neurocognitive battery measures revealed a prevalence of language-related deficits of 70.4% (50 out of 71) among patients with shunt-responsive iNPH. Our study is the first to demonstrate language difficulties in a majority of shunt-responsive iNPH patients. Analysis of the 71 neurocognitive evaluations completed prior to shunt placement revealed impairments specifically in verbal fluency, supporting our findings from a retrospective analysis of a larger iNPH cohort (n=529) that language and speech deficits occur commonly in this disorder. We also prospectively identified fine motor deficits in approximately 71.0% of patients with iNPH, indicating that such deficits are not limited to lower extremity function.

Contrary to the current dogma, we find that the presence of language or speech difficulties is not a negative predictor of iNPH. A comparison of data from our retrospective and prospective studies suggests that the estimate of 23.1% of iNPH patients who reported “language difficulty” in the retrospective study is an underestimate of the true prevalence of deficits in language in iNPH. Difficulties with speech and writing may also be more prevalent than were noted in hospital records. Formal assessment of impairments in speech and language are needed to more consistently identify deficits in these areas in patients with possible iNPH. While the symptoms of gait disturbance and urinary incontinence are easier to identify and are more commonly reported by patients and caregivers, the third symptom of “subcortical dementia” is neither well-defined nor comprehensive. Along with accurate gait analyses, patients with potential iNPH would benefit from careful neurological assessments of cognition and language both before and after shunt placement surgery.

Current research recommends supplemental tests, including prolonged CSF drainage, to increase diagnostic accuracy in iNPH.(13) However, tailored neuropsychological assessments may also help to differentiate iNPH from other diseases that can mimic this disorder. For example, our study demonstrates that patients with iNPH do not display the baseline decline in
premorbid IQ or intellectual function seen in patients with progressing AD.(31) In support of the notion that iNPH is primarily characterized by a decline in subcortical functions of the brain, past studies have focused on significant differences between iNPH patients and age-, sex- and MMSE-matched probable AD patients in terms of their performance on various tests of attention and psychomotor speed.(15,16,31) In contrast, our study has revealed that patients with iNPH demonstrate significant cortical impairment, including deficits in language, fine motor skills, and executive function. These findings indicate that patients with iNPH may present with more of a “mixed dementia” characterized by declining subcortical and cortical function.

Until now, there has been no general agreement concerning which cognitive functions are more likely to be restored after shunt placement.(10) In this study, pre- and post-operative neurocognitive evaluations revealed that 84.6% of iNPH patients (11 out of 13) experienced improvement in one or more areas of cortical function after shunt surgery, with two-thirds demonstrating significant improvement in language functions. Overall, more than half of patients scored significantly higher on tests of language-related functions after shunt placement. Improvement was also seen in subcortical functions and fine motor skills. These post-shunt improvements not only affirm the profile of a mixed cortical and subcortical dementia in this disease, but they also reveal the existence of pathophysiological mechanisms underlying language processing and production that can be reversed by CSF drainage in iNPH patients. Pathologic changes in iNPH are widespread and include cortical thinning of white matter in most areas of the brain, including inferior and posterior regions.(15,32,33) Previous studies on cognitive dysfunction in iNPH have delved focally into frontal lobe functions of attention, executive function and memory,(34–36) but our findings indicate that a more comprehensive characterization of iNPH dementia is warranted.

There are several strengths and limitations of the current study. The large number of iNPH patients included in this study (n = 529) allowed us to unambiguously document the presence of speech and language dysfunctions in iNPH, as well as other deficits (e.g. writing deficits) that occur less commonly in this disorder. As always, studies involving the retrospective review of medical records raises concerns of potential selection bias or recall bias that could lead to inaccurate estimates of incidence or prevalence. Indeed, our analysis of prospectively collected data from formal neurocognitive evaluations in a subset of 71 patients who were later proven to have shunt-responsive iNPH revealed a much higher prevalence language deficits among iNPH patients than was observed in the retrospective analysis. This analysis thus serves as a valuable addition to the larger retrospective analysis.
We obtained pre-operative and post-operative neurocognitive evaluations in a small group (n = 13) of iNPH patients. Our analysis demonstrated clear improvements in language and speech functions in a majority of affected iNPH patients. These data provide a rational basis for a similar study involving a larger group of iNPH patients to replicate these findings.

Given the high prevalence of deficits in language and speech in patients with iNPH, our findings endorse the integration of a standardized iNPH neurocognitive assessment battery into the clinical diagnosis and management of iNPH. Limiting factors include both the lengthy duration and inherently strenuous nature of multiple neurocognitive tests for iNPH patients, given their advanced age and the impairments associated with this disorder. However, future streamlining of the neurocognitive battery and strategic scheduling of post-operative appointments with both neurosurgery and neurology will facilitate the accrual of additional post-shunt placement data and allow us to more clearly define the cognitive deficits in iNPH.
Section 6: Acknowledgments

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Figure 1. Retrospective study design. Flow diagram depicting the stratification of deficits in language, speech and writing among iNPH patients.
Figure 2. Retrospective analysis of the prevalence and characterization of language and speech deficits in iNPH (n=529).  

A) Prevalence of language difficulties, motor-related speech difficulties and motor-related writing difficulties prior to shunt placement.  

B) Stratification of the 122 patients with language deficits into those demonstrating deficits in expressive versus receptive language, those who display both, and those with more complex manifestations of language function. Expressive language difficulties include symptoms of word-finding difficulty and verbal fluency in conversation. Receptive language difficulties include inability to comprehend simple and multistep statements or commands during hospital visits.  

C) Categorization of the 68 patients with motor-related speech deficits into those with dysarthria, overall slowness, stuttering and combinations/other.
Figure 3. Boxplots depicting the distribution of pre-operative neurocognitive battery Z scores of shunt-responsive iNPH patients (n=71). Raw data were obtained from prospective formal neurocognitive evaluations of 71 possible iNPH patients prior to lumbar CSF drainage trials and shunt placement for iNPH. Impairment on the various neuropsychiatric assessment tools was defined as a Z score greater than 1.5 SD below the mean (standardized for age, sex, and education level). Descriptions of the tests included in the iNPH battery can be found in the Methods section. A majority of patients demonstrated above average premorbid IQ, but nearly three-quarters of patients attained scores below average or at the level of impairment across a number of neurocognitive tests.
Figure 4. Analysis of prospectively collected data on the prevalence of language and speech dysfunction in 71 iNPH patients. Impairments in cortical functions (including language, fine motor, executive function) and subcortical functions (including processing speed and attention) were assessed using formal neurocognitive evaluations completed prior to shunt placement. Deficits in semantic verbal fluency and executive function, as well as fine motor skills, are prevalent among the iNPH population.
Figure 5. Focused analysis of pre- and post-operative cognitive evaluations reveal improved outcomes in various cognitive functions. Thirteen iNPH patients received neurocognitive evaluations before and after shunt placement. Significant improvement or decline ($P<0.05$) post-surgery was assessed using the Reliable Change Index for each neurocognitive subtest.