Objective Measures of Response to Tap Test in Patients with Normal Pressure Hydrocephalus

by

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Abstract

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Tap Test (TT) response in Normal Pressure Hydrocephalus (NPH) was investigated with neuropsychological measures. Forty-two (30 men, 12 women) older adult patients (age range 66 – 93 years) suspected of idiopathic NPH participated in the study. Gait and neuropsychological assessments were performed within 1 week pre-TT and approximately 3 hours post-TT. Patients were divided into 2 groups, Responders (Rs: N = 26) and Non-Responders (NRs: N = 16) based on clinical assessment of gait post-TT. Rs also improved on psychomotor precision, as measured by Line Tracing, more than NRs ($p < .05$), and in preliminary data (n = 7), this change was correlated with post-shunt response. Groups did not differ on measures of higher order cognitive processing post-TT. Upper extremity psychomotor functioning can be used as an objective measure of motor functioning for the assessment of TT response.

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General Introduction and Background Information

Normal Pressure Hydrocephalus (NPH) is a distinct neurologic disorder that was first described by Hakim and Adams in 1965 and is characterized by excess cerebrospinal fluid in the brain. Although NPH generally occurs during the sixth and seventh decades of life (Black, Ojemann, & Tzouras, 1985), it can also occur in children and young adults (Torkelson, Leibrock, Gustavson, & Sundell, 1985). NPH remains a diagnostic and therapeutic challenge because it cannot be diagnosed on the basis of its clinical symptoms alone (Masters & O'Grady, 1992; Vanneste, 2000). NPH is characterized by enlargement of the cerebral ventricles as seen on neuroimaging, such as computed tomography (CT) or magnetic resonance imaging (MRI), and normal pressure of the cerebrospinal fluid (CSF) at lumbar puncture (Adams, Fisher, Hakim, Ojemann, & Sweet, 1965). When clinical findings and neuroradiologic investigations indicate greater than expected degree of ventriculomegaly as compared to the degree of brain atrophy, NPH is suspected (Fishman & Dillon, 2001). Only a small percentage of patients ultimately receive NPH as their primary diagnosis (Bech-Azeddine, Waldemar, Knudsen, Hogh, Bruhn, Wildschiodtz, et al., 2001).

There are two types of hydrocephalus, communicating and obstructive. Obstructive hydrocephalus is caused by the restriction of cerebrospinal fluid (CSF) flow within the ventricular system (Chahlavi, El-Babaa, & Luciano, 2001). Communicating hydrocephalus is when the flow of CSF is normal, and CSF in the ventricles continues to communicate with that in the subarachnoid space. NPH, a form of communicating hydrocephalus, has been divided into secondary and idiopathic forms (Casmiro,

D'Alessandro, Cacciatore, Daidone, Calbucci, & Lugaresi, 1989). Secondary NPH is usually associated with head trauma, meningitis, or subarachnoid hemorrhage. Although several hypotheses have been proposed, the etiology and pathogenesis of idiopathic NPH remains uncertain. Bret, Guyotat, & Chazal (2002) argue that NPH is a misnomer because the CSF pressure is not entirely normal in these patients, and propose the term "chronic hydrocephalus." Graff-Radford (1997) prefers the term "symptomatic hydrocephalus" because the increased pressure may be pathogenetic in these patients. About 10 percent of older adults presenting with signs and symptoms of hydrocephalus may have congenital hydrocephalus that has become symptomatic due to increasing age (Graff-Radford & Godersky, 1989). These particular patients are differentiated by the fact that their head circumference is above the 98th percentile. Also, suggestive of a chronic process, there is little or no periventricular increased signal on T2-weighted imaging associated with enlarged ventricles. Nevertheless, both of these proposed terms may be more appropriate from the pathophysiological point of view. A consensus about what term should be used for idiopathic NPH has not been established.

The three primary clinical symptoms of NPH are gait disturbance, urinary incontinence, and cognitive impairment, although all of these symptoms do not need to be present for the diagnosis (Adams, et al., 1965). The cognitive impairment in NPH patients is characterized by sub-cortical type deficits, such as slowing of information processing, and memory and executive function abnormalities, without the presence of focal cortical deficits (Merten, 1999). Due to the presentation of this type of clinical syndrome, NPH is considered a frontal systems / sub-cortical dementia (Cummings,

1990). Patients presenting with both dementia and enlarged ventricles are not necessarily referred for treatment, especially if they lack other clinical findings suggestive of hydrocephalus, such as gait abnormalities (Mulrow, Feussner, Williams, & Vokaty, 1987).

Patients in the early stage and late stage of the disorder may present with different symptoms and their prognoses may also be different. NPH is often progressive, and it can be present for months or years before patients seek medical help. Progressive symptoms usually leave patients in a severe state of impairment and dependency. Cases of NPH can vary in terms of initial manifestations, rate of progression, and treatment response. Provided that a correct diagnosis has been made and symptoms are properly treated, NPH is potentially reversible by shunt treatment. However, established objective measures for the assessment of responsiveness to shunt and diagnostic procedures are lacking.

Clinical Manifestations of NPH

Gait and Movement Disorders is a Prominent Symptom in NPH

The most pronounced symptom of NPH, and typically the first to become apparent is gait disturbance (Fisher, 1982; Meier, Zeilinger, & Kintzel, 1999; Ojemann, Fisher, Adams, Sweet, & New, 1969). The gait pattern in NPH is usually described as "magnetic," "short-stepped," "glue-footed," and "bradykinetic" (Relkin, Marmarou, Klinge, Bergsneider, & Black, 2005). The lower extremities of NPH patients are rigid, and patients walk slowly with small steps as though their feet are stuck on the floor. Stolze, Kuhtz-Buschbeck, Drucke, John, Diercks, & Palmie, et al. (2000), found a triad of decreased stride length, decreased foot-to-floor clearance, and a broad based gait to be the typical features of the gait abnormality in NPH.

Gait difficulties are typical in patients with NPH. However, the term gait apraxia is inappropriate in describing the NPH gait because patients can execute correct walking movements without difficulty when minimally supported or lying down (Vanneste, 2000). In patients with mild NPH, the gait may be ataxic and wide-based. At first, patients typically notice difficulties in climbing stairs and walking at the expected pace (Relkin, et al., 2005). NPH patients may have difficulties with rising from a chair, and fatigue upon ambulation, and in more advanced cases, postural instability and frequent falls are observed (Haan, Jansen, Oostrom, & Roos, 1987). Turning in place becomes troublesome at this stage, and it typically requires multiple steps (Relkin, et al.).

In addition to a gait disorder, NPH patients also have postural difficulties and motor symptoms that are common in other movement disorders. Symptoms commonly observed in patients with Parkinson's disease (PD) may also be present in NPH patients. Such symptoms include tremor, rigidity, with or without cogwheeling, decreased arm swing, festination, retropulsion, masked facies, and difficulty initiating movements (Relkin, et al., 2005). Bradykinesia affecting the upper extremities has been reported in as many as half of NPH cases (Krauss, Regel, Droste, Orszagh, Borremans, & Vach, 1997). NPH patients may be more forward-leaning, show a wider sway than normal controls, and have increased postural instability that may be exacerbated when their eyes are closed (Blomsterwall, Svantesson, Carlsson, Tullberg, & Wikkelso, 2000). Neurological symptoms in NPH patients are typically bilateral, although a few patients may exhibit unilateral symptoms (Relkin, et al.). Symptoms of PD in patients with NPH are not always levodopa responsive, and may or may not respond to NPH treatment. Such symptoms in NPH may reflect dysfunctional nigrostriatal dopaminergic pathways (Relkin, et al.).

Urinary Urgency and Frequency is Common in NPH

Urinary incontinence is an inconsistent and typically a late symptom of NPH. However, increased frequency and urgency is almost always present, and may be observed in the early stages of the disorder (Fisher, 1982; Masters & O'Grady, 1992; Relkin, et al., 2005). As NPH progresses, patients experience urinary incontinence. Fecal incontinence is not typically a presenting symptom; however, it may develop as the

disease progresses, especially if NPH is left untreated. During the later stages, the patient is typically indifferent about the incontinence, suggesting that the incontinence is related to frontal systems/executive dysfunction (Relkin, et al.). In patients with retained insight, the gait disturbance may physically restrict successful toileting, which results in functional incontinence. Urinary dysfunction in NPH may be related to the enlarged ventricles stretching the periventricular nerve fibers, in particular in the frontal horns of the lateral ventricles, and subsequent partial loss of inhibition of bladder contractions.

NPH Patients Exhibit Frontal Systems Dysfunction on Cognitive Testing

The cognitive profile of NPH patients is categorized as a subcortical or frontal systems dementia (Cummings, 1990; Cummings & Benson, 1984). The dichotomy of dementia as cortical or subcortical has been controversial, as subcortical dementias have pathological changes that extend to the cerebral cortex (Cummings, 1990). Although subcortical dementia produces symptoms that can be produced exclusively by subcortical pathology and the syndrome typically is different than disorders that involve mainly the cerebral cortex, the term subcortical dementia does not mean that the pathology is confined to subcortical structures. As there are extensive connections between subcortical structures and the frontal lobes, the frontal cortex is mostly involved in subcortical dementia. Hence, the terms frontal systems dementia or frontal-subcortical dementia are also used to describe the syndrome of subcortical dementia (Cummings, 1990).

Subcortical dementia patients do not exhibit higher cortical deficits such as aphasia, apraxia, agnosia, and alexia, as do patients with cortical dementia. Patients with subcortical dementia exhibit mainly slowed information processing, and memory and executive dysfunction. Albert (1978) proposed that patients with subcortical dementia have deficits in fundamental functions, including attention, rate of information processing, and manipulation of acquired information, as these functions are mediated by subcortical structures. In contrast, instrumental functions, such as praxis, perception, and communication, are disturbed in cortical dementias, as these functions are mediated by the cerebral cortex. Patients with a subcortical disease process may not initially present with severe deficits and may perform normally on simple screening measures. Their deficits are typically mild initially, and can only be demonstrated when specific functional domains are assessed (Cummings, 1990).

NPH contributes to approximately 1 - 6 % of all dementia in older adults (Casmiro, et al., 1989; Trenkwalder, Schwarz, Gebhard, Ruland, Trenkwalder, Hense, et al., 1995; Vanneste, 2000). The severity of the cognitive symptoms varies between NPH patients. The degree of impairment depends on the amount of brain damage that has already taken place, and the amount of comorbid hypertensive cerebrovascular disease (Iddon, Pickard, Cross, Griffiths, Czosnyka, & Sahakian, 1999). Early in the course of NPH, patients may present with only mild frontal subcortical type deficits. Although they may exhibit only mild dysfunction, executive impairment may have implications in their daily life and social functioning. When patients present with moderate to severe dementia, it typically suggests a progression of NPH. If NPH is left untreated and

progresses, the cognitive deficits become more severe and global. The progression of NPH, as observed in the deterioration of cognitive functioning, is also observed in the other symptoms of the triad, such as in the progression of gait and urinary disturbances.

NPH is not a degenerative disorder in the traditional sense, since the majority of the symptoms can be reversed if treated early. The reversibility of symptoms and the presentation of mild cognitive symptoms are useful in differentiating this group of patients from other conditions (Vanneste, 1994). Although some patients may present with dementia, especially if the NPH has been left untreated, patients do not typically present with global intellectual deterioration. When patients present with severe cognitive loss, other diagnoses such as Alzheimer's disease, should be considered. This is especially the case when cognitive impairment is the preceding or predominant clinical symptom (Bret, Guyotat, & Chazal, 2002; Helkala, Laulumaa, Soininen, & Riekkinen, 1988). Furthermore, when the principal clinical symptom is not gait disturbance, NPH is unlikely (Boon, Tans, Delwel, Egeler-Peerdeman, Hanlo, Wurzer, et al., 1997).

Global measures of cognition, such as the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), have been used to assess the cognitive functioning of NPH patients. However, the MMSE is not a sensitive test for subcortical and frontal type deficits, and therefore it is an inadequate tool for assessing the initial mild cognitive impairment that is typically observed in NPH patients (Nelson, Fogel, & Faust, 1986). Nevertheless, studies frequently use such global measures of cognition in diagnosing NPH and in post-shunt follow-up, and as a result, they conclude that

neuropsychological tests are of little value in the diagnostic process and in predicting treatment outcome (Savolainen, Hurskainen, Paljarvi, Alafuzoff, & Vapalahti, 2002).

Although there is limited research that includes comprehensive neuropsychological testing on patients with NPH, the pattern of deficits that has been observed is most consistent with frontal systems dysfunction. Cognitive deficits include memory dysfunction, bradyphrenia, executive dysfunction, visuospatial deficits, and mood changes. The typical pattern of memory impairment observed in NPH patients is a deficit in recall, but not in recognition memory (Boon et al., 1997; Vanneste & Human, 1987). Recall deficits are due to inefficient information processing and retrieval difficulties, as well as slowed information processing. Relatively normal performance on recognition tasks shows that NPH patients can retain newly learned information. Hence, memory storage takes place, but active retrieval of the material is disturbed. This pattern of memory impairment differs from that observed in patients with Alzheimer's disease (AD) and other cortical encephalopathies (Helkala, et al., 1988; Thomsen, Borgesen, Bruhn, & Gjerris, 1986).

Typically observed frontal systems deficits include inertia, mental slowness, slowed reaction time, decreased speed of complex information processing, impaired ability to manipulate acquired knowledge, and attention, and executive difficulties (Boon, et al., 1997; Caltagirone, Gainotti, Masullo, & Villa, 1982; Merten, 1999). The verbal fluency task (Spreen & Benton, 1969) is a sensitive tool for evaluating deficits in NPH patients. Generation of words to phonemic cues, phonemic fluency, has been shown to be sensitive to frontal systems dysfunction. Word generation to semantic cues, category

fluency, has been shown to be sensitive to temporoparietal lobe damage, such as in patients with Alzheimer's disease. NPH patients perform poorly on phonemic fluency, and AD patients are more impaired on semantic fluency (Iddon, et al., 1999; Miyoshi, Kazui, Ogino, Ishikawa, Miyake, Tokunaga, et al., 2005). Verbal fluency tasks may thus be useful in differential diagnosis.

Frontal systems deficits are observed even in those NPH patients with very subtle cognitive difficulties. Compared to normal controls, non-demented NPH patients, falling within normal limits on the MMSE, produced significantly fewer words to a phonemic category, but they were not significantly different on semantic fluency (Iddon, et al., 1999). Deficits on phonemic fluency persisted post-operatively. When compared to patients with mild Alzheimer's disease, non-demented NPH patients were impaired on tasks sensitive to frontal systems functioning, spatial recognition memory, and attentional set-shifting, but not to temporal lobe damage. NPH patients performed poorly during the same stage of the attentional set-shifting task as patients with frontal lobe excision and patients with frontal subcortical dementias, such as Parkinson's disease (Iddon, et al.). This finding is thought to reflect a cognitive flexibility deficit due to perseveration (Iddon, et al.; Robbins, James, Owen, et al., 1994). These deficits were also shown to persist post-shunt treatment. In comparison, patients with mild Alzheimer's disease were unimpaired on the attention set-shifting task. Impaired performance specifically on tasks sensitive to frontal lobe, but not to temporal lobe damage, further demonstrates that NPH is a frontal systems dementia.

It has been suggested that NPH patients also exhibit visuospatial difficulties (Kaye, Grady, Haxby, Moore, & Friedland, 1990; Thomsen, et al., 1986). Boon, et al. (1997) found that the difference between NPH patients and controls for the Trail Making Test was large. The authors suggested that this underlined diminished visuospatial functioning. However, poor performance on a task such as the Trail Making Test may be due to frontal/executive deficits. Slowed information processing, psychomotor slowing, as well as an impaired ability to successfully and quickly switch cognitive sets may also explain such poor performance. NPH patients may perform poorly on visuospatial tasks, but it is possible that their poor performance may reflect impairment in organization and planning, essentially a frontal systems impairment.

Beyond their impairment in gross motor functioning and gait, NPH patients also have deficits in upper extremity motor and psychomotor speed, further providing evidence that NPH is a frontal systems dysfunction (Blomsterwall, Bilting, Stephensen, et al., 1999; Iddon, et al., 1999; Klinge, Ruckert, Schuhmann, Dorner, Brinker, & Sammi, 2002). NPH patients produce significantly fewer fingers taps as compared to controls (Boon, et al., 1997). Tests that are sensitive to "frontal" functioning such as attention tasks, the Trail Making Tests (Reitan & Wolfson, 1985), the Symbol Digit Memory Test (Smith, 1973), the Stroop Test (Stroop, 1935), and motor tasks such as Finger Tapping and Grooved Pegboard tests (Reitan & Wolfson, 1985) are more sensitive to the neuropsychological deficits in NPH patients.

Klinge, et al. (2002) developed simple upper extremity psychomotor tasks (Serial Dotting and Line Tracing) that are easy to use with the NPH patient population. Klinge,

et al. found that Serial Dotting and Line Tracing sufficiently and quickly assess psychomotor speed, and were reliable outcome assessment measures in follow-up of NPH patients after treatment. Serial Dotting assesses psychomotor speed, as patients place a dot in the center of circles on a page as quickly as possible, and time to completion is recorded. Line Tracing assesses psychomotor precision, as patients trace on the inside of maze-like parallel lines as quickly as possible without crossing or touching the lines, and without lifting the pencil or turning the paper, and errors and time to completion is recorded. The Line Tracing task was shown to differentiate NPH patients who respond to shunt treatment (Klinge, Ruckert, Brinker, Dorner, Samii, 2004). Assessment with the Line Tracing task was more powerful in demonstrating a response early in the recovery period post-shunt than the standard assessment of gait and balance. Clinical responders had less variation in their test performance early, one-week post treatment, and this change persisted at seven months post shunt treatment. Such tasks provide an additional measure of fine motor disturbances in the upper extremity of NPH patients (Klinge, et al., 2002). These tasks are practical for bedside testing and do not require complicated instructions. As a result, even the more cognitively impaired patients can complete them, although speed may be compromised. Furthermore, severely impaired gait frequently impedes proper or complete evaluation of gait for many NPH patients during the pre-treatment diagnostic phase, and evaluation of change post-treatment is compromised. Tasks assessing upper extremity motor and psychomotor functioning may offer a reliable and alternate measure of responsiveness in NPH patients.

Although the pattern of cognitive deficits that is most associated with NPH is a frontal systems dysfunction, heterogeneity of cognitive deficits is found in NPH patients. The heterogeneity of cognitive deficits in NPH may be related to the degree of severity. NPH patients with mild cognitive symptoms may differ from those presenting with dementia. Another explanation may be the selection criteria used in NPH studies. Some studies include both patients with idiopathic NPH and those with secondary NPH. Inclusion criteria also differ across studies such that some studies use intracranial pressure monitoring and CSF outflow resistance measurements and others use clinical symptoms with radiological findings. Furthermore, heterogeneity of cognitive deficits may be a result of the tasks used to assess functioning. Studies continue to use global measures of cognition as an assessment method or use tests that are inappropriate for NPH-specific deficits. Neuropsychological tests that assess specific functional domains associated with frontal systems impairment and that are also sensitive to mild cognitive dysfunction expected in early NPH may be more appropriate for this patient population.

NPH Patients May Also Exhibit Behavioral and Psychiatric Symptoms

Although not a hallmark symptom, abnormal behavior and other psychiatric signs may be observed in some patients with NPH as the presenting clinical symptom. However, a causal relationship between NPH and severe psychiatric disorders has not been supported. NPH patients may present with major depression, mania, and psychosis (Merten, 1999). Patients may present with apathy, emotional indifference, and bradyphrenia, which sometimes may resemble depression. Behavioral symptoms such as

hostility, aggression, and obsessive-compulsive disorder have also been described in association with NPH (Kwentus & Hart, 1987; Pinner, Johnson, Bouman, & Isaacs, 1997). The behavioral and psychiatric symptoms in NPH may be associated with the impairment of frontal executive functioning observed even in the early stages. McIntyre & Emsley (1990) reported a case where shoplifting, an indication of impairment of social judgment, was the prevalent feature of the clinical picture of NPH. Neuropsychiatric symptoms such as apathy, disinhibition, and mania can result from frontal executive impairment (Mega & Cummings, 1994). The association between frontal executive impairment and neuropsychiatric symptoms is consistent with a frontal systems disorder in NPH.

Pathophysiology of NPH Remains Uncertain

The enlargement of the ventricles has been hypothesized to be the cause of the gait disorder associated with NPH. It has been suggested that the enlarged ventricles lead to compression of the upper motor neuron fibers. The fibers of the corticospinal tract that supply motor function to the legs pass very close to the lateral ventricles in the medial portion of the corona radiata. Its close proximity to the lateral ventricles explains why the gait disorder in NPH is the earliest presenting clinical symptom as well as the first to improve post treatment (Graff-Radford & Godersky, 1986). However, the cause of the ventricular enlargement in NPH is not completely understood. Current theories suggest that a number of pathophysiological factors may result in NPH such as abnormal CSF absorption and cerebrovascular damage.

One of the Oldest Theories of NPH Pathophysiology is an Underlying Absorption Defect

A CSF absorption defect causes excessive accumulation of CSF, which leads to enlargement of the cerebral ventricles (Anderson, 1986). The CSF pressure is mostly regulated by the absorption of CSF into the subarachnoid villi, and this may be the site of the defect. During the early stages of NPH, there is an obstruction of CSF pathways which leads to an increase in resistance to CSF outflow and increased ICP, leading to ventricular enlargement (McCormick, Yamada, Rekate, & Miyake, 1992). This initial raised ICP normalizes, but the ventricles continue to enlarge. Hence, normal pressure observed in patients can be a sign of progression and later stages of NPH (Black, 1982).

Suggested mechanisms of how the absorption defect leads to the NPH syndrome include reduction of blood flow and metabolism (Waldemar, Schmidt, Delecluse, Andersen, Gjerris, & Paulson, 1993), increased transmantle pressure (difference in pressure between the ventricles and the subarachnoid space) (Conner, Foley, & Black, 1984), and stretching of the periventricular white matter (Fisher, 1982). Stephensen, Tisell, & Wikkelso (2002) demonstrated that in fact there is no transmantle pressure gradient in NPH, and that for the most part, the ICP is within normal limits. It is suggested that NPH symptoms, including behavioral changes, result from the expansion of the anterior horns of the lateral ventricles. As the frontal horns expand, fiber tracts from the frontal cortex are stretched and become dysfunctional. This underlying physiological dysfunction is associated with the frontal subcortical type cognitive deficits observed in NPH patients.

Decrease in CSF absorption and production has been shown in both NPH and normal aging (Albeck, Skak, Nielsen, Olsen, Borgesen, & Gjerris, 1998; Silverberg, Huhn, Jaffe, Chang, Saul, Heit, et al., 2002). Another suggested mechanism of how CSF absorption defect leads to NPH symptoms is that decreased CSF absorption leads to decreased CSF turnover, which ultimately leads to decreased clearance of amyloid β-peptides and tau protein (Silverberg, Mayo, Saul, Rubenstein, & McGuire, 2003; Tullberg, Hutlin, Ekholm, Mansson, Fredman, & Wikkelso, 2002). An accumulation of these products can be harmful to neuronal function, which can lead to dementia. The accumulation of amyloid β-peptides and tau protein has been implicated in NPH (Silverberg, et al., 2003). A higher than expected Alzheimer's disease (AD) pathology

has been found in the cortical biopsies from NPH patients taken during shunt surgery. A defect in CSF dynamics, including production and absorption, has been hypothesized as a unifying underlying pathophysiology for AD and NPH (Chakravarty, 2004; Silverberg, et al., 2003). It has been estimated that 30-50% of NPH patients will exhibit plaques and tangles, and 75% of severely demented NPH patients will show Alzheimer's disease pathology (Savolainen, Paljarvi, & Vapalahti, 1999; Silverberg, et al., 2003). Hence, a defect in absorption of CSF may lead to NPH symptoms directly through decreased CSF turnover and accumulation of harmful molecules. Another hypothesis is that CSF absorption may lead to NPH symptoms secondarily by vasoconstriction due to cerebrovascular changes.

Cerebrovascular Changes May Also Lead to NPH

Deep white matter ischemia and cerebrovascular disease have been associated with NPH (Casmiro, et al.,1989; Koto, Rosenberg, Zingesser, Horoupian, & Katzman, 1977; Tullberg, Mansson, Fredman, Lekman, Blennow, Ekman, et al., 2000). A reduction of cerebral blood flow (CBF) is pronounced in the frontal region and predominately in the white matter (Owler & Pickard, 2001). A significantly higher incidence of deep white matter ischemia was found in NPH patients than in age-matched controls (Bradley, Whittemore, Watanabe, Davis, Teresi, & Homyak, 1991). Reductions of regional cerebral blood flow (rCBF) in the subcortical white matter, and a widespread rCBF hypoperfusion pattern, especially in fronto-temporal cortical regions have also been

observed in NPH (Kristensen, Malm, Fagerland, Hietala, Johansson, Ekstedt, et al., 1996).

Although it has not been demonstrated whether the CBF changes observed in NPH patients are a cause or an effect, the relationship between reduced CBF and NPH has been furthered by recent studies. Momjian, Owler, Czosnyka, Czosnyka, Pena, & Pickard (2004) found that the distribution of the white matter CBF is different in NPH patients than in normal controls, and that there was more pronounced CBF reduction adjacent to the lateral ventricles and it normalized with distance moving laterally from the ventricles. Klinge, Samii, Muhlendyck, Visnyei, Meyer, Walter, et al. (2003) found a similar reduction in white matter blood flow in experimental chronic hydrocephalus in the rat along with immunohistochemical changes suggestive of ischemic neuronal damage. Silverberg (2004) suggested that chronic ischemic changes may be related to NPH symptoms. Ischemic changes may lead to structural axonal damage of the frontal fibers associated with bladder function and executive motor function. Ischemic changes, with associated damage to cortical and hippocampal neurons, may also play a role in NPH related cognitive deficits.

Since both NPH and Parkinson's disease (PD) patients have a gait disorder, they are investigated and compared in order to determine possible differences in pathophysiology. When patients with NPH are instructed to increase their stride length by stepping on stripes on the floor (visual cues) and walking to the beat of a metronome, their gait velocity only mildly improves (Stolze, et al., 2000). External cues are not helpful in improving the gait in NPH patients, but they are in PD patients. This has

raised the hypothesis that a lack of internal cues from the basal ganglia to drive the supplementary motor area and motor cortex, via the ventrolateral thalamus, may play a minor role in NPH. The interruption of the frontostriatal pathways that explain the cognitive deficits observed in PD may also explain the frontal type deficits observed in NPH. Hence, by demonstrating reduced CBF in the basal ganglia and the thalamus, but not in the white matter regions, Owler, Momjian, Czosnyka, Czosnyka, Pena, Harris, et al. (2004) implicated the basal ganglia and thalamus in NPH further than previously thought. Reduced CBF in the basal ganglia and thalamus are thought to contribute not only to the gait disorder of NPH, but also to the cognitive deficits observed in these patients (Owler, et al., 2004).

As hypertension has been associated with cerebrovascular disease, a relationship between systemic hypertension and NPH has also been supported (Casmiro, et al., 1989; Mysiw & Jackson, 1990). Postmortem studies have demonstrated hypertensive cerebrovascular changes in NPH (Earnest, Fahn, Karp, & Rowland, 1974; Koto, et al., 1977). Graff-Radford, Torner, Adams, & Kassell (1989) found that hypertension in patients with subarachnoid hemorrhage was related to the development of hydrocephalus. Animal studies have also substantiated the relationship between hypertension and hydrocephalus (Klinge, et al., 2003; Portnoy, Chopp, & Branch, 1983; Ritter & Dinh, 1986). Hypertension causes arteriosclerosis, and most commonly affected vessels are the lenticulostriate vessels that supply the basal ganglia and associated corona radiata (Owler & Pickard, 2001). Cerebrovascular disease in these areas of the brain further provides evidence that NPH is a subcortical dementia.

NPH is Likely Caused by Both Cerebrovascular Changes and Altered CSF Dynamics

Bradley (2001) proposed that patients with NPH have decreased CSF resorption with enlarged ventricles, but the degree is not sufficient to cause NPH related symptoms. However, with advancing age, deep white matter ischemia perhaps pushes these particular patients over the threshold. Due to arteriosclerosis, draining veins and capillaries, along with the deep white matter arterioles, close down as regional CBF decreases. This decreases the pathway for CSF resorption, which leads to enlargement of the ventricles due to the accumulation of CSF, and to the triad of NPH symptoms.

Both reduced CBF and altered CSF resorption are likely involved in NPH pathophysiology (Iencean, 2003). Bateman (2000) proposed that cortical venous compression is due to changes in vascular compliance, which is the amount of blood flow pulsation depending on the arterial and CSF pressure pulse and resistance of cranial vessels to compression (Bateman, 2004). Reduced venous compliance in the superior sagittal sinus (SSS) leads to vascular compression and ischemia. Bateman (2003) investigated the blood flow pulsatility of NPH with the theory that if cortical vein compression indeed causes NPH, then treatment for NPH should reverse this and produce cortical vein compliance. After surgical treatment, the reduced cortical vein pulsatility was reversed, as was the reduced CSF absorption. Bateman suggested that increasing vein pressure, which reverses the normal CSF absorption pathway, explains the pathophysiology of NPH.

The relationship between cerebrovascular changes and a defect in CSF dynamics in NPH continues to be investigated. A unifying theory for the pathophysiology of NPH,

vascular dementia, and AD has been proposed (Chakravarty, 2004; Silverber, et al., 2003). An underlying CSF dynamics deficit, which may lead to an accumulation of potentially toxic molecules, related to ischemic changes has been suggested as a unifying theory for the pathophysiology of NPH, AD, and vascular dementia (Silverberg, et al., 2003; Silverberg, 2004; Momjian, et al., 2004). Chakravarty has proposed that there is a relationship between the underlying pathophysiology of NPH and vascular dementia, specifically the subcortical white matter ischemic type (Binswanger's disease), which may explain why there is co-occurrence between these disorders. It has been proposed that decreased blood flow may affect venous circulation, which may cause periventricular venous changes. Such changes including thickening of venous channels may in turn affect CSF absorption and ultimately lead to the accumulation of CSF and NPH.

Diagnosis of NPH is Challenging

Neuroimaging Techniques are Used in the Diagnosis of NPH

Neuroimaging studies such as CT reveal moderate or severe ventricular enlargement that is out of proportion to cerebral atrophy (Huckman, 1981; George, Holodny, Golomb, & de Leon, 1995). Results of CT scans include enlarged frontal and temporal horns. MRI however is considered the best neuroimaging technique for confirming the diagnosis of NPH (Graff-Radford, 1997; Jack, Mokri, Laws, Houser, Baker, & Petersen, 1987). MRI is used for differential diagnosis because it has the advantage of visualizing structures in the posterior fossa such as the cerebral aqueduct that may be implicated in NPH. In addition, MRI can obtain volumetric measures of medial temporal lobe structures that may differentiate NPH from other dementias such as Alzheimer's disease (AD), which are associated with hippocampal volume loss (Graff-Radford, 1997). In NPH, if there is reduction of the hippocampus, it is due to dilatation of the temporal horn. However, in AD, the reduction of the hippocampus is due to atrophy. White matter changes appear as periventricular lesions that are most pronounced around the frontal horns (Krauss, Droste, Vach, Regel, Orszagh, Borremans, et al., 1996). The differential diagnosis is often difficult in older adults because enlarged ventricles, periventricular white matter (PVWM) signal anomalies, and vascular changes, in particular small vessel disease may be present in both NPH and AD.

Another important advantage of using MRI for diagnosis is that it allows for T2-weighted images which can show a CSF flow voiding sign (CSFVS), which manifests as

decreased MRI signal in the aqueduct, which is correlated with the velocity of pulsatile CSF flow (Bradley, Kortman, & Burgoyne, 1986; Bradley, Whittemore, Kortman, Watanabe, Homyak, Teresi, et al., 1991). Quantification diffusion tensor imaging (QDTI) via MRI measures water diffusion in brain tissue, as well as water mobility, content, and fiber microstructure, and it has been useful in identifying NPH (Ulug, Moore, Bojko, & Zimmerman, 1999). Ulug et al. propose that patients with enlarged ventricles due to atrophy have normal diffusion values, and patients with enlarged ventricles due to NPH have abnormal or high diffusion values. Chun, Filippi, Relkin, et al. (2000) demonstrated that although QDTI remains experimental for NPH, it may be useful in diagnosis and monitoring shunt response.

Functional neuroimaging, such as Positron Emission Tomography (PET) studies, have shown decreased CBF and metabolism in NPH patients (Jagust, Friedland, & Budinger, 1985; Tedeschi, Hasselbalch, Waldemar, Juhler, Hogh, Holm, et al., 1995). The most obvious changes have been observed in the frontal and periventricular areas (Vanneste, 2000). Kristensen, et al. (1996) found abnormal CSF hydrodynamic state that was associated with a widespread reduction in regional cerebral blood flow (rCBF) and preference for subcortical white matter and fronto-temporal cortical regions. However, the predictive value of CBF measurements is variable (Kristensen, et al., 1996; Waldemar, et al., 1993).

CSF Drainage is Used to Confirm NPH Diagnosis and Predict Treatment Response

CSF removal by lumbar puncture, commonly referred to as a Tap Test (TT), is the most widely used technique for confirming the diagnosis of NPH, predicting shunt response, and assessing CSF hydrodynamics. Typically, approximately 30-50 mL of CSF is removed via lumbar puncture at the level of L4-L5. Clinical improvement post-TT, a positive TT response, is highly suggestive of NPH and successful at predicting a good treatment response (Damasceno, Carelli, Honorato, & Facure, 1997; Wikkelso, Andersson, Blomstrand, & Lindqvist, 1982). Temporary as well as prolonged improvement post tap test has been demonstrated. However, there is a high false negative rate, and a negative CSF TT response has low predictive accuracy (Malm, Kristensen, Karlsson, Fagerlund, Elfverson, & Eksterdt, 1995). Several studies included imaging pre and post-TT in attempting to improve the accuracy of the TT. Improvement in gait post-TT was associated with rCBF increase in the bilateral dorsolateral frontal and left mesiotemporal cortex in SPECT (Dumarey, Massager, Laureys, & Goldman, 2005). Walter, Hertel, Naumann, & Morsdorf (2005) in an MRI study found that improved brain perfusion was shown in 33% of patients, whereas the clinical examination, including a walking test and neurological examination, was inconclusive post-TT.

Standard clinical practice for determining TT response is currently assessed by assessment of the patients' gait. When improvement in gait has been determined post-TT, a positive TT response, diagnosis of NPH is clinically confirmed, and a positive post-shunt response is predicted. However, post-TT gait changes can often be equivocal, due to the nature of the clinical assessment. Historically, the gait response to TT is based on

a neurologist's clinical impression; hence, it is subjective, and mostly based on the treating neurologist's expertise. Attempts at quantifying gait have been made (Boon, et al., 1997); although ultimately, a clinical judgment of motor impairment remains the gold standard.

As TT response can be equivocal and subjective, additional objective measures are needed to determine responsiveness. Recently, measures of upper extremity motor and psychomotor functioning detected post-shunt changes early in the recovery period, and were also associated with long-term functional outcome supporting their use as additional measures of motor functioning (Klinge, et al., 2004). The use of additional and objective measures of motor functioning early in the clinical process of NPH patients is crucial for diagnosis, making treatment decisions, and prediction of outcome, and yet it is lacking. NPH patients may present with severe lower extremity motor impairment, and in these cases, the evaluation of upper extremity motor functioning as an additional and objective measure of motor functioning and TT response becomes further important.

As gait may sometimes be difficult to assess, determining TT response by objective changes in other NPH symptoms, such as cognition, may also be useful. Systematic neuropsychological assessment pre- and post-TT is lacking. The use of objective neuropsychological measures sensitive to NPH deficits in conjunction with routine clinical assessment of gait pre- and post-TT may add quantifiable and objective evidence to support and substantiate conclusions of clinical gait assessment. Neuropsychological data may hence improve the predictive value of TT response, as

changes in cognitive and upper extremity motor functioning may be objectively documented and used for comparison in treatment follow-up.

In following patients with different pressure shunts, Boon, Tans, Delwel, et al. (1998) found that using neuropsychological tests may improve diagnosis and follow-up of NPH patients. Farace & Shaffrey (2005) found that including additional information based on neuropsychological assessment conducted pre- and post-TT raised the positive predictive value of the TT to 0.91 from 0.72, when it was based solely on the evaluation of symptoms by a neurosurgeon. Nevertheless, the inclusion of neuropsychological tests in the routine clinical care of NPH patients, including diagnosis and follow-up, has not been established (Klinge, et al., 2004). Previously included cognitive testing pre and post-TT involved global measures of functioning insensitive to these patients' deficits. As per Farace & Shaffrey (2005) and Marmarou, Young, Aygok, Sawauchi, Tsuji, Yamamoto, & Dunbar (2005), practical neuropsychological tests to evaluate the cognitive deficits and executive dysfunction specific to NPH patients, and that can detect responsiveness early in the diagnosis and treatment phase are limited.

Continuous or prolonged external lumbar CSF drainage (ELD) is also used as part of the evaluation for diagnosis and evaluation for shunt candidacy. If patients have a negative or an equivocal CSF TT response, an ELD is performed in order to determine if prolonged CSF drainage will result in improvement (Chen, Huang, Liu, & Chen, 1994). During an ELD, approximately 100-200 mL are removed daily via a catheter for approximately 3-5 days. Clinical improvement is typically judged on the last day of drainage. Removal of larger volumes of CSF has been shown to be a good predictor of

shunt response (Chen, et al., 1994; DiLauro, Mearini, & Bollati, 1986; Vanneste, 2000; Walchenbach, Geiger, Thomeer, & Vanneste, 2002). Williams, Razumovsky, & Hanley (1998) demonstrated that the sensitivity of the ELD is 97%, its specificity is 60%, and its positive predictive value is 84%. Marmarou, et al. (2005) concluded that gait improvement after ELD is the best predictor of a positive shunt response, and that a positive shunt response is independent of age, even if the patient is in his 9th decade. Balamurali, Golash, Starkey, & Bhatti, (2004) found that gait, and performance on verbal fluency and clock drawing improved following lumbar drain, although no single test was useful in determining suitability for shunt treatment. Although ELD has improved diagnostic accuracy, it also carries high risk complications such as meningitis and subdural hematomas (Wikkelso, et al., 1982).

Pressure Monitoring and Hydrodynamic Studies are Used in Diagnosis of NPH

Traditionally, NPH has been associated with enlargement of the cerebral ventricles without an increase in CSF pressure (Adams, et al., 1965). Normal CSF pressure is 100mm of water. In fact, the CSF pressure of NPH patients may be slightly increased, but not expected to be above 180-220 mm of water (Conner, Foley, & Black, 1984). Monitoring continuous intracranial pressure (ICP) is used in the diagnosis of NPH and predicting treatment outcome. B-waves, CSF pressure oscillations with a frequency of 0.5 – 2 per minute, indicating a general trend of high ICP levels, are a physiological phenomenon that occurs in healthy people (Borgesen & Gjerris, 1982; Mautner-Huppert, Haberl, Dirnagl, Villringer, Schmiedek, & Einhaupl, 1989). During prolonged CSF

pressure recordings, frequent occurrence of B-waves has been demonstrated in patients with NPH. A frequent occurrence of B-waves for more than 50% of the ICP recording time is a good prognostic sign for NPH patients (Borgesen & Gjerris, 1982; Graff-Radford & Godersky, 1989).

Cerebrospinal infusion tests have been used for determining the pressure volume index (PVI) and resistance to CSF outflow (R_{out}) (Meier & Miethke, 2003; Marmarou, Foda, Bondoh, Yoshihara, Yamamoto, Tsuji, et al., 1996). PVI refers to the fluid volume that is required to increase the CSF pressure by 10 mL of water. Albeck, et al. (1998) found that there is an increase in R_{out} with increased age. In patients with NPH, this value ranges from normal to low (Marmarou, et al., 1996). Measuring the CSF ICP and R_{out} is an important part of the analysis of the pathological process of cerebrospinal hydrodynamics (Meier & Miethke, 2003). This procedure is performed during a spinal tap, and it measures the decrease in pressure after the administration of a bolus of saline into the CSF space. It essentially measures the resistance of the re-absorption of CSF. An elevated R_{out} indicates abnormal circulation of CSF and it is suggestive of NPH. A variant of the infusion test is the constant rate infusion test where the pressure can be measured over an extended period of time.

Isotope cisternography assesses CSF circulation, and it has been used in the evaluation of NPH. It demonstrates disturbed CSF circulation with a reversed CSF flow into the ventricles (Bateman, 2003; Gado, Coleman, Lee, Mikhael, Alderson, & Archer, 1976). A radiolabeled pharmaceutical is injected via lumbar puncture. Its flow is then followed by taking sequential pictures over a period of hours and days. It has been

suggested that cisternography is not a reliable predictive test (Larsson, Arlig, Bergh, Bilting, Jacobsson, Stephensen, et al., 1994). Nevertheless, the best method to view CSF flow is by using nuclear cisternography (Bateman, 2003).

Differential Diagnosis of NPH

The executive / frontal systems dysfunction observed in NPH is also present in other neurological disorders such as AD, PD, Progressive Supranuclear Palsy (PSP), Lewy-body dementia, Frontal Temporal Dementia (FTD) and Corticobasal Ganglionic Degeneration (CBGD). However, in terms of differential diagnosis, it is of importance to distinguish NPH as a non-degenerative and a subcortical type dementia. If the predominant clinical symptom is not a gait disturbance, and patients present only with enlarged ventricles and cognitive impairment, differential diagnosis should include other neurological conditions. The triad of major clinical symptoms observed in NPH is common in older adults and may have multiple causes (Graff-Radford, 1997). Gait disturbances have multiple etiologies and occur in older adults (Sudarsky & Ronthal, 1983). Incontinence also occurs in 15 percent of women and 10 percent of men over the age of 70 (Yarnell & St Leger, 1979). The cerebral ventricles also enlarge with age (Barron, Jacobs, & Kinkel, 1976). Differential diagnosis then should include cortical, subcortical, as well as several mixed dementias.

AD Differs from NPH Frontal Systems Dementia

Enlarged ventricles are common in patients with cortical dementia such as AD, which complicates differential diagnosis (Damasio, Eslinger, Damasio, Rizzo, Huang, & Demeter, 1983). The presence of significant hippocampal atrophy on MRI has been reported as a distinguishing feature between AD and NPH (Holodny, Waxman, George,

Rusinek, Kalnin, & de Leon, 1998). The hippocampi are generally spared in NPH patients, relative to AD patients, and patients with NPH have significantly larger hippocampal volumes (Savolainen, Laakso, Paljarvi, Alafuzoff, Hurskainen, Partanen, et al., 2000). Enlarged ventricles may be present in AD due to a reduction in the integrity of the brain, which would lead to ex vacuo dilation (Bateman, 2003). Furthermore, PET studies have shown that NPH patients have predominantly decreased rCBF in the frontal areas, whereas AD patients have decreased rCBF predominantly in the temperoparietal areas (Jagust, Friedland, & Budinger, 1985).

AD is a cortical and degenerative dementia, and hence its clinical symptoms vary significantly from NPH. When dementia is the predominant symptom in NPH, the differential diagnosis should include AD or a co-morbid neurodegenerative disease should be suspected (Graff-Radford & Godersky, 1986). AD is a common co-morbid disorder in NPH and it may contribute significantly to the dementia of many NPH patients (Golomb, de Leon, George, Kluger, Convit, Rusinek, et al., 1994; Golomb, Wisoff, Miller, Boksay, Kluger, Weiner, et al., 2000). NPH patients differ from patients with AD in that they do not exhibit the "aphasia-apraxia-agnosia syndrome," which is observed in cortical dementia (Bret, Gyotat, & Chazal, 2002). In NPH, there is a discrepancy between a severely impaired delayed recall and less affected or sometimes normal delayed recognition (Helkala, et al., 1988). Patients with NPH have a retrieval deficit but intact recognition, whereas patients with AD have encoding deficits, rapid forgetting, and associated impairment in recognition.

NPH Differs from Other Subcortical Dementias

Unlike NPH, PD is a degenerative disorder. In addition, although NPH patients may sometimes present with Parkinsonian symptoms, the presentation of these symptoms as the predominant symptom is very rare in NPH (Miodrag, Das, & Shepherd, 1987). However, like NPH, PD exhibits a subcortical type dementia. Cognitive symptoms resembling the dementia seen in PD patients have also been described in NPH (Relkin, et al., 2005). PD patients, like NPH patients, have a memory retrieval deficit, executive dysfunction, and cognitive slowing (Kaufer & Cummings, 1997). Co-morbid Parkinsonian symptoms in NPH patients such as bradykinesia, retropulsion, postural instability, and tremor can occur, likely reflecting compromised nigrostriatal dopaminergic pathways resulting from abnormal pulsatile CSF flow impacting on the substantia nigra and/or striatum (Relkin, et al., 2005). Clinical signs that differ in the two disorders include ventriculomegaly and distinct gait abnormalities such as a wide based gait in NPH (Stolze, Kuhtz-Buschbeck, Drucke, John, illert, & Deuschl, 2001). In addition, PD is diagnosed if the presenting neurological symptoms have a unilateral accentuation, whereas in NPH, neurological symptoms are bilateral.

Other subcortical dementias that may resemble NPH include PSP, infectious dementias such as dementia of Human Immunodeficiency Virus (HIV), and vascular dementias, including a subcortical white matter ischemic disease, Binswanger's disease (Kaufer & Cummings, 1997). Patients with subcortical dementias, such as PSP, exhibit executive deficits, gait imbalance, and reductions in frontal lobe metabolism or blood flow (Foster, Gilman, Berent, Morin, Brown, & Koeppe, 1988; Sawada, Udaka,

Kameyama, Seriu, Nishinaka, Shindou, et al., 1992). However, PSP patients exhibit pseudobulbar palsy and supranuclear vertical gaze palsy not typically observed in NPH patients (Collins, Ahlskog, Parisi, & Maraganore, 1995). Patients with HIV also present with subcortical dysfunction such as psychomotor slowing, and memory and concentration difficulties because of the invasion of the virus into the central nervous system (Navia, Jordan, & Price, 1986). In addition they may also present with gait and motor disturbances due to myelopathy. As HIV patients may also present with enlarged ventricles, testing for HIV is part of the differential diagnosis in possible NPH patients.

Patients with vascular dementias also exhibit memory retrieval deficits and executive dysfunction on neuropsychological assessment (Kaufer & Cummings, 1997) as well as similar features on imaging as NPH (Bradley, et al., 1991). Vascular dementia is often characterized by small-vessel ischemic disease that is affecting the periventricular white matter or basal ganglia and thalamic nuclei, and can present with ventriculomegaly and subcortical type deficits similar to NPH (Tullberg, et al., 2000). Periventricular and deep white matter hyperintensities on MRI makes it difficult to distinguish between NPH and vascular dementia except that the periventricular intensity profile in NPH patients is typically higher in the white matter near the frontal horns (Tullberg, et al., 2002).

Some patients with vascular dementia also improve after shunt treatment, and some propose that the two diseases have a similar underlying dementia pathophysiology (Bateman, 2004; George, 1991; Momjian, et al., 2004; Roman, 1991; Silverberg, et al., 2003). In the differential diagnosis process, it has been shown that patients with vascular dementia and NPH, have similar biochemical markers, but to a different extent. CSF

sulfatide, a biochemical marker of demyelination, is increased in patients with vascular dementia, but is normal in NPH patients (Tullberg, et al., 2000). Neurofilament triplet protein (NFL), a CSF marker of axonal degeneration, was also increased in NPH patients, which was associated with disturbed, but reversible axonal transmission. CSF sulfatide and NFL are important diagnostic markers between vascular dementia and NPH.

Depression may be associated with cognitive decline, and in severe cases, can present with dementia (Kaufer & Cummings, 1997). Geriatric depression also presents with increased vascular changes and enlarged lateral ventricles (Alexopoulos, Meyers, Young, et al., 1997; Simpson, Baldwin, Burns, & Jackson, 2001). Differential diagnosis between NPH and depression may be difficult since both conditions may have a similar profile on neuropsychological assessment. The cognitive impairment or dementia observed with depression is often reversible, except when depression is a prodrome to dementia, and it is commonly seen in older adults with a history of severe or psychotic depression (Rosen & Swigar, 1976). The neuropsychological symptoms of depression are typically of the subcortical type, with impaired attention and concentration, forgetfulness, psychomotor slowing, and decreased motivation (Caine, 1981). Impaired retrieval memory and executive dysfunction may also be observed. Patients with NPH may present with neurovegetative symptoms as the primary sign of the disorder, making differential diagnosis difficult between depression and NPH on the basis of these symptoms alone (Relkin, et al., 2005). In NPH patients, depression may also be secondary to the physical and mental disabilities that are associated with the disorder.

Nevertheless, the psychiatric symptoms of NPH should be recognized as they can potentially confound clinical diagnosis, and are important for treatment and prognosis.

Dementias such as Lewy-body dementia, FTD, Pick's disease, and CBGD also present with symptoms of the subcortical type, which may confound the diagnosis of NPH. Lewy-body dementia presents with overlapping features of AD and PD. A typical profile for Lewy-body dementia includes cognitive impairment, fluctuations in mental status, visual hallucinations, and gait and balance difficulties (Hansen, Salmon, Galasko, Masliah, Katzman, De Teresa, et al., 1990). However, the gait of patients with Lewy-body dementia is not wide based as is in those with NPH. FTD presents with personality changes and primarily neuropsychiatric features such as irritability and mood changes, disinhibition, distractibility, and perseverative behaviors (Lund, 1994). Although in some FTD patients, there is a history of urinary incontinence and motor symptoms such as apraxia and Parkinsonism, the disinhibition observed in FTD is not common in NPH. The frontal lobe cortical areas, limbic temporal cortex, and subcortical basal ganglia structures such as the striatum are particularly involved in the pathology. In addition, NPH patients lack the presence of Pick bodies. FTD patients typically show frontotemporal atrophy on CT or MRI, which is not typical in NPH (Knopmann, Christensen, Schut, Harbaugh, Reeder, Ngo, et al., 1989). CBGD is a rare disorder, and patients with CBGD present with motor symptoms such as rigidity and postural instability (Riley, Lang, Lewis, Resch, Ashby, Hornykiewicz, et al., 1990). However, unlike NPH patients, patients with CBGD can present with asymmetric "alien-limb"

phenomena, severe apraxia, supranuclear gaze palsy, and cortical sensory loss. Unlike NPH patients, CBGD patients typically have asymmetric motor symptoms.

Treatment of NPH Consists of Shunt Placement

Controlled drainage of CSF from the cerebral ventricles via a mechanical device (shunt) is the neurosurgical intervention and treatment for the symptoms of NPH. A shunt allows for the drainage of ventricular excess CSF into another location such as the peritoneal space of the abdomen, hence a ventriculoperitoneal shunt. Most shunts contain a fixed pressure valve with a low, medium, or high-pressure setting, and CSF drains out of the ventricles when the pressure exceeds the set pressure of the valve. Currently, adjustable shunts are available such as the Codman-Medos Hakim programmable shunt. These shunts have a magnetically adjustable valve that can be reset within a few minutes by pressing a small probe against the scalp. This procedure can be carried out at the doctor's office without the need for additional surgery. Shunt complications occur in approximately 30-40 percent of patients, of which 20 percent are severe, and 6-8 percent result in death or severe morbidity (Peterson, Mokri, & Laws, 1985; Vanneste, Augustijn, Dirven, Tan, & Goedhart, 1992). Complications from placement of the ventricular catheter include intracranial hemorrhage, and although rare, intra-abdominal injury, infection, subdural hematomas, and CSF hypotensive headaches. Other complications include shunt occlusion or catheter breakage.

Treatment Response Depends on Initial Symptom Presentation, Duration, and Severity

Prognosis for Gait, Urinary Symptoms, and Psychiatric Symptoms

As the gait disorder is typically the most prominent feature of NPH, the evaluation of change in gait post treatment is well established in the clinical care of NPH patients. Gait continues to be primarily judged qualitatively by the treating physician and determination of change is frequently depended on patient and caregiver reports. Quantitative judgment with clinical gait scales has been more widely used recently (Boon, et al., 1998). Post-shunt response is most common in patients who initially present with gait abnormality alone or simultaneously with cognitive impairment (Graff-Radford & Godersky, 1986). In patients that respond positively to shunt treatment, it is usually gait and balance difficulties, and urinary symptoms that improve (Blomsterwall, et al., 2000; Graff-Radford & Godersky, 1989; Graff-Radford & Godersky, 1986; Meyer, Kitagawa, Tanahashi, Tachibana, Kandula, Cech, et al., 1985). Although affective symptoms are not characteristic of NPH, affective symptoms have also shown to be responsive to treatment (Price & Tucker, 1977).

Prognosis for Cognitive Impairment

NPH became popular as a diagnosis when it was first established as a distinct disorder because it represented a form of "reversible dementia." However, using the term "reversible dementia" should be used with caution, since significant improvement in cognitive functioning is not always observed and is less frequent than improvement in gait (Esmonde & Cooke, 2002; Freter, Bergman, Gold, Chertkow, & Clarfield, 1998;

Graff-Radford & Godersky, 1986; Malm, et al., 1995). Substantial improvement post-shunt treatment occurs in approximately 30-50 percent of NPH patients (Vanneste, 2000). Meyer, et al. (1985) found that cognition was the last factor to improve, following improvements in gait, urinary incontinence, and activities of daily living. Reversibility of symptoms also depends on the type of NPH the patients have, idiopathic vs. secondary. Studies examining treatment response have not always discriminated between idiopathic NPH versus patients with secondary NPH, who are more likely to respond positively to treatment. In addition, varying time intervals have been used for post-shunt assessment, varying between days to one-year post-treatment. The expected time course of recovery of cognitive functions post-shunt treatment has not been established. Hence, differing results in terms of cognitive response have been reported in the literature.

Co-morbidity reduces the likelihood of a positive treatment response. When patients exhibit cognitive deficits reflective of cortical systems involvement, prognosis is not as favorable, and the likelihood of a co-morbid neurodegenerative disorder such as AD increases (De Mol, 1986). The prevalence of AD in patients with NPH is relatively high, and follow-up studies show poor treatment outcome (Savolainen, Paljarvi, & Vapalahti, 1999). Parkinsonian symptoms in patients with NPH are not always responsive to treatment (Relkin, et al., 2005). Additional factors, such as cerebrovascular disease, moderate or extensive cortical atrophy, and diffuse ischemic white matter changes, typically predict an unfavorable response to shunt treatment (Boon, Tans, Delwel, Egeler-Peerdeman, Hanlo, Wurzer, et al., 1999; Peterson, Mokri, & Laws, 1985; Tans & Boon, 2002; Wikkelso, Andersson, Blomstrand, Matousek, & Svendsen, 1989).

Nevertheless, imaging studies have shown evidence of outcome predictors and changes post-shunt treatment. Reduced CBF in the frontobasal cortex has been associated with a positive treatment response (Klinge, Berding, Brinker, Weckesser, Knapp, & Samii, 2002), and furthermore, a relative increase in rCBF in the frontal lobes has been found post-shunt treatment (Mataro, Poca, Salgado-Pineda, Castell-Conesa, Sahuquillo, Diez-Castro, et al., 2003). Overall, failure to control for co-morbid disorders has been a common methodological limitation in studies of NPH. However, due to the high co-morbidity in this aged population, controlling for these factors is especially challenging.

It has been suggested that the length of clinical history should be regarded as a crucial factor in predicting response to shunt treatment. The desirability of early shunt treatment has been suggested by research in experimentally induced models of animal hydrocephalus showing that only partial recovery of neuronal response occurred after late shunting (Klinge, Gerkmann, Samii, & Brinker, 2004). Similarly, patients with NPH in the advanced stage generally have poor prognosis (Caruso, Cervoni, Vitale, & Salvati, 1997; Meier, Knoig, & Miethke, 2004). If cognitive impairment was the first presenting symptom, a poor treatment response is predicted (Graff-Radford & Godersky, 1986). Furthermore, the evidence of aphasia (e.g., anomia) was shown to predict poor treatment response (Graff-Radford & Godersky, 1989). Early stage NPH, a short course of less than one year and minimal cerebral atrophy, is thought to be a good predictor of positive improvement. Although patients with a slight or moderate cognitive deficit typically show a positive response (Graff-Radford & Godersky, 1986), Iddon et al. (1999) showed that frontal / executive type deficits observed in non-demented patients pre-shunt

persisted postoperatively. These conflicting findings lend support to the complex nature of this disorder and reflect that measurement of cognitive dysfunction and response has not been consistent across studies.

Studies have shown that even patients with significant cognitive impairment may have a positive response to shunt treatment (Bekkelund, Marthinsen, & Harr, 1999; Golomb, et al., 2000). Iddon, et al. (1999) demonstrated that NPH patients who were classified as demented pre-shunt showed improvement in global cognitive function, falling within normal range on MMSE postoperatively. Although the response rate is less likely for patients with cerebral atrophy (Tsunoda, Mitsuoka, Bandai, Endo, Arai, & Sato, 2002), those in the late stage with cerebral atrophy may show improvement post treatment if they are not also severely demented (Caruso, et al., 1997; Meier, Knoig, & Miethke, 2004). Overall, failure to control for the duration and the severity of symptoms has been a common methodological limitation in studies of NPH.

Improvement in specific cognitive domains has been demonstrated after shunt. Improvement in attention, concentration, verbal and nonverbal memory, constructional skills, and language have been described. Thomas, McGirt, Woodworth, Heidler, Rigamonti, Hillis, & Williams (2005) found that patients with higher baseline verbal memory scores showed improvement in verbal memory, psychomotor speed, as well as overall cognitive improvement post-shunt. Improvements in reaction time and visuospatial functions have also been observed in patients who responded positively to treatment, and visuospatial functions were found to improve earlier than attention and memory (Gustafson & Hagberg, 1978; Kaye, et al., 1990; Thomsen, et al., 1986).

Duinkerke, Williams, Rigamonti, & Hillis (2004) found that patients who showed improvement in any clinical symptom post-TT were more likely to show significant long-term improvement in memory post-shunt. Although the study had a small sample size and post-shunt cognitive assessment varied from 6 months to 12 months, Duinkerke, et al. found that about 50% of patients improved on tests of psychomotor speed, and 80% improved in total learning on a word list.

As indicated, responsivess of symptoms to diagnostic procedures and shunt treatment remains uncertain. While some studies find that deficits persist post-drainage performed for diagnostic purposes and post-operatively, others find improvement. Most measures used are either insensitive or inappropriate for deficits specific to NPH or use only tasks that are timed. Due to the upper extremity motor disturbances characterized by motor and psychomotor slowing in this patient population and overall inefficient information processing, it is unclear whether the outcome response is due primarily to improvement in motor symptoms or to a cognitive component. Future investigations are needed to elucidate the specific type of frontal systems deficits characteristic of NPH, and which deficits are likely to improve post-treatment. Furthermore, the assessment of neuropsychological deficits has not been established for NPH patients undergoing diagnostic or treatment procedures. As a result, comparative neuropsychological data is lacking for these patients. The establishment of neuropsychological measures as objective measures of motor functioning is essential, as responsiveness is currently based on subjective clinical assessment, and gait is sometimes so impaired that qualitative or quantitative measurement for diagnostic purposes and treatment follow-up is difficult.

Study Aims and Hypotheses

The general aim of the current study is to provide objective neuropsychological measures with which TT response may be systematically evaluated.

Primary Aim:

To provide objective measures of change in motor functioning post-TT.

Primary Hypothesis 1:

Patients who improve in gait after the TT (Responders) will also show post-TT improvement in upper extremity basic motor functioning.

Primary Hypothesis 2:

Responders will also show post-TT improvement in psychomotor functioning.

Secondary Aim:

To provide objective measures of change in cognitive functioning post- TT.

Secondary Hypothesis:

Responders (Rs) will improve in cognitive functioning post-TT.

Method

Participants

Forty-two (30 men, 12 women) consecutive older adult patients (age range 66 – 93 years) were evaluated in an outpatient NPH clinical service (The Cornell Memory Disorders Program in the Department of Neurology at The New York Presbyterian Hospital - Weill Cornell Medical Center) and recruited for participation. Patients were initially evaluated by the same treating neurologist. Diagnosis of idiopathic NPH was based on symptom history, including gait disturbance, cognitive dysfunction, and urinary symptoms, in the context of an enlarged ventricular system out of proportion to cerebral atrophy. Patients who were referred for a TT (removal of 30-50 cc of CSF), as part of their clinical work-up to confirm diagnosis and determine candidacy for shunt placement, were recruited for the study. Patients with secondary NPH were excluded from the study.

Assessment

Clinical Gait Assessment

Gait was clinically assessed by one neurologist pre- and post-TT, and gait was also quantified using the Boon Gait Scale (Boon, et al., 1997). The Boon Gait Scale Total score ranges from 2-40, with higher scores reflective of more significant gait dysfunction and a score of 2 of normal gait. The scale includes three scores (Walking, Step, and Time), which comprise the Total score. Eight gait characteristics, such as turning ability, tandem walking, wide based stride, and foot-floor clearance, are

quantified into a Walking score with 2 points given for each abnormal characteristic. The number of seconds (Time score) and steps (Step score) required for a 10-meter walk are also recorded and added to the Total score.

Neuropsychological Measures

All patients were evaluated with a neuropsychological battery that has been used routinely in the clinical care of NPH patients referred to the outpatient neuropsychology service in which the study was conducted. The battery assesses a broad range of cognitive domains, and has been clinically demonstrated to be of sufficient length and suitable difficulty level for this particular patient population. All patients were evaluated by the same examiner pre- and post-TT.

Patients were assessed for clinical purposes pre-TT (Baseline) with the following tasks, to assess a broad range of cognitive domains: Overall mental status assessment: Dementia Rating Scale (DRS) (Mattis, 1988), Psychological functioning: Geriatric Depression Scale (GDS) (Yesavage, Brink, & Rose, et. al., 1982), Attention and executive functioning: Digit Span subtest of the WAIS-III (Wechsler, 1997), Trail Making Tests A and B (Reitan, & Wolfson, 1985), and Controlled Oral Word Association Test (COWAT) (F, A, S, and Animals) (Spreen & Benton, 1969), Memory functioning: Hopkins Verbal Learning Test – Revised (HVLT-R) (Benedict, Schretlen, Groninger, & Brandt, 1998), Language functioning: Boston Naming Test (Goodglass & Kaplan, 1987), Visuoconstructional skills: Clock Drawing Test (Tuokko, Hadjistavropoulos, Miller, & Beattie, 1992), which was scored based on a 10-point

system with scores ranging from 0-10, Psychomotor and motor skills: Symbol-Digit Modalities Test (Smith, 1973), Grooved Pegboard Test (Reitan, & Wolfson, 1985), Finger Tapping Test (Reitan, & Wolfson, 1985), Serial Dotting (Klinge, et al., 2002), and Line Tracing (Klinge, et al., 2002).

The following measures were used in the experimental analyses, and were administered pre- and post-TT: Attention and executive functioning: Digit Span subtest of WAIS-III, alternate forms of Trail Making Tests A and B, and semantic clustering, as calculated based on delayed recall of HVLT-R, Memory functioning: alternate form of HVLT-R, Psychomotor and motor skills: alternate form of Symbol-Digit Modalities Test, Grooved Pegboard Test, Finger Tapping Test, alternate form of Line Tracing, and Serial Dotting.

Calculation of Semantic Clustering

Higher order processing can also be assessed by the use of efficient learning strategies, which has been linked with better test performance (Hill, Allen, & Gregory, 1990; Kramer, Delis, & Daniel, 1988; Paolo, Troster, & Ryan, 1997), as adults who use elaborative encoding strategies outperform those who do not, during delayed free-recall. An established effective learning strategy is semantic clustering, which refers to the recall of words from the same semantic category, and reflects the extent to which the subject has actively manipulated the newly acquired information and imposed structure or organization (Bousfield, 1953). An example of semantic clustering is if the words "horse" and "cow" are recalled in sequence, even though on the stimulus list the two

were not presented together. The use of this method to assess higher order cognitive processing during the diagnostic process and follow-up assessment of NPH patients was considered to be useful, as it does not involve a motor component. The use of efficient learning strategies was investigated by examining the patients' pre- and post-TT performance on delayed free recall of the HVLT-R. Semantic clustering was computed using the method described by Shuell (1969), with one point scored each time the patient consecutively recalled two words from the same semantic category.

Procedure

Patients were initially evaluated by the treating neurologist who determined their eligibility based on clinical criteria including history of symptoms (gait disturbance, cognitive dysfunction, and urinary dysfunction), and neurological findings, including degree of ventriculomegaly. As part of routine clinical care, the treating neurologist referred patients who met criteria for suspected NPH for neuropsychological assessment pre- and post-TT. Gait was assessed pre- and post-TT at the time of neuropsychological assessment. Informed consent for participation in the study was obtained according to an institutionally approved protocol.

Neuropsychological Assessment Pre- and Post-TT

Neuropsychological assessments were conducted in an outpatient clinical office. All tests were administered and scored according to the standard instructions provided in respective test manuals. Pre-TT (baseline) testing was conducted within one week prior

to TT and lasted approximately three hours, with breaks given as needed. The day of the TT, patients presented to an outpatient clinic within the hospital system where a medical team performed the TT procedure. After a recovery period of 2-3 hours, patients returned to the NPH outpatient clinical office for post-TT gait and neuropsychological assessment. Assessment three hours after the TT has been previously used as the time frame in which observable changes are most likely (Kahlon, Sundbarg, & Rehncrona, 2002; Wikkelso, et al. 1986; Wikkelso, et al. 1982). Neuropsychological assessment post-TT lasted approximately 1 ½ hour with breaks given as needed.

Post-Shunt Follow-up

Post-shunt data were available on 7 patients that had participated in the pre- and post-TT study. Patients were treated with a VP programmable shunt, and were judged by their treating neurologist as Rs or NRs based on gait changes post-shunt. Patients underwent neuropsychological assessment 6 months post-shunt with the same battery used during the current study's baseline evaluation. Exploratory analysis was conducted comparing post-shunt data with variables of interest from the TT study to determine hypotheses for future clinical research.

Design and Statistical Analysis

Participants were divided into two groups, Responders (Rs) and Non-Responders (NRs), according to the neurologist's clinical assessment of gait post-TT. A 2 x 2 mixed model repeated-measures analysis was conducted. Since a repeated-measures design was

performed, patients served as their own controls in pre and post-TT neuropsychological assessment. As the study design required repeated neuropsychological assessment, alternate forms of the tests, which have been shown to be comparable and can be used interchangeably, were used whenever possible in order to minimize practice effects in test performance.

For the statistical analysis, a 2 x 2 repeated measures mixed model ANOVA was performed to examine the relationship between neuropsychological measures and TT response; comparing neuropsychological performance of Rs and NRs. Scores from neuropsychological tests were converted to standardized z-scores based on age-adjusted normative data available for the various measures. Performance out of the clinically meaningful range (z-scores less than -3.00) was coded as the lowest clinically meaningful z score (-3.00). Where appropriate and clinically meaningful, variables were clustered conceptually to create broader cognitively functional domains and minimize the number of statistical analyses. Clustering of variables was computed using the z-scores of the selective measures of motor, and attention / executive functioning.

Where clinically and conceptually appropriate, individual tests were analyzed independently. Line Tracing and Serial Dotting were analyzed independently as experimental measures of psychomotor precision, as they have previously been used as objective measures of upper extremity motor functioning in NPH patients at post-shunt follow-up. In terms of attention / executive measures, Digit Span Forward and Digit Span Backward were analyzed independently, as they are clinically interpreted as measures of Auditory Attention and Working Memory, respectively. HVLT-R Delay

Recall and HVLT-R Recognition were also analyzed separately, as Recall and Recognition is clinically interpreted as qualitatively different. Performance on HVLT-R Total Trials 1 –3 was analyzed as a measure of Learning.

Post-TT data on COWAT CFL, Fruits and Vegetables, and Clock Drawing was available on a small subset of the patients (n = 13), and was used for assessment of Phonemic Fluency, Semantic Fluency, and visuoconstructional skills, respectively. Analyses were included to obtain preliminary data on these measures of frontal systems functioning and visuoconstructional skills post-TT.

Results

Demographic Characteristics of the Participants

Forty-two NPH patients (30 men, 12 women) with a mean age of 77.71 (SD = 5.0, range 66-93 years), participated in the study. The group was highly educated, with a mean education of 15.76 years (SD = 3.46). On assessment of global cognitive functioning, patients performed in the impaired range with a mean total DRS score of 122.26 (SD = 11.81). Patients were not significantly depressed; mean GDS score was 8.83 (SD = 6.16) during baseline evaluation. They had a mean duration of gait symptoms of approximately 3 years (M = 34.53 months, SD = 32.33, range 2 months - 11 years). All patients presented with impaired gait, cognitive deficits, and urinary urgency and/or frequency. Thirty-seven patients (88%) reported urinary incontinence. A paired samples t-test showed a significant overall improvement in gait (pre-TT Boon Gait Scale M = 14.89, SD = 6.76; post-TT M = 11.62, SD = 7.0; t (32) = 4.64, $p < .001$). Higher scores on the Boon Gait Scale indicate a greater degree of gait impairment.

The sample was divided into two groups, Responders (Rs) and Non-Responders (NRs), according to clinical judgment of gait improvement post-TT. Among the 42 patients, 26 were judged as Rs (20 men, 6 women) and 16 (10 men, 6 women) were judged as NRs. The groups did not differ in age, years of education, DRS, and GDS scores at baseline testing. Rs and NRs were also not significantly different at baseline in the severity of gait dysfunction (pre-TT Boon Gait Scale) or duration of symptoms.

Table 1 shows the mean and SD for Rs and NRs on each measure. Seventeen Rs (65%) and eight NRs (50%) reported urinary incontinence.

Clustering of Variables and Correlation Analyses of Functional Domains

Due to multiple measures of theoretical constructs, certain variables were clustered conceptually to create broad functional domains and minimize the number of analyses. The functional domains include *Basic Motor* functioning, *Fine Motor*, *Visual Motor Attention*, and *Semantic Fluency*. Correlation analyses were conducted for measures within each functional domain to assure that tests comprising that domain were associated. Performances of both dominant and non-dominant hands on Finger Tapping were combined into a measure of *Basic Motor* (pre-TT: $r = .759$, $p < .001$; post-TT: $r = .655$, $p < .001$). Pre-TT performances on Grooved Pegboard (of both dominant and non-dominant hands) and Symbol-Digit Modalities were combined for the domain of *Fine Motor* functioning (pre-TT: Cronbach's alpha = .748; post-TT: Cronbach's alpha = .689). Performances on Trail Making Tests A and B were clustered as *Visual Motor Attention* (pre-TT: $r = .621$, $p < .001$; post-TT: $r = .561$, $p < .001$).

Performances on Animal naming and DRS Supermarket items were clustered as pre-TT *Semantic Fluency* ($r = .675$, $p < .001$), and scores on Vegetables and Fruit were clustered conceptually as post-TT *Semantic Fluency*; however, the association between the two post-TT measures did not reach statistical significance ($r = .542$, $p = .08$). Table 2 shows the correlation analyses for measures clustered into functional domains.

TT Response and Performance on Gait and Neuropsychological Measures

A 2 x 2 mixed model repeated measures ANOVA was performed to identify an interaction between TT response and performance on neuropsychological measures. The Bonferroni adjustment for multiple comparisons was conducted for all repeated measures ANOVA, and the adjustment is represented in reported p values. The z-scores from neuropsychological measures were used in the analyses, with z-scores less than -3.00 coded as the lowest clinically meaningful z-score (-3.00). The z-scores were calculated using published age adjusted normative data. See Appendix A for raw data (mean and standard deviation) of all variables that were not clustered for analysis. See Appendix B for raw data (mean and standard deviation) of all variables that were clustered into functional domains for analysis.

Lower Extremity Motor Functioning

Boon Gait Scale scores revealed impaired gait at baseline for both Rs (M = 15.14, SD = 5.09) and NRs (M = 13.88, SD = 8.88), and persisting deficits post-TT (Rs: M = 10.10, SD = 4.53; NRs: M = 13.96, SD = 9.45). There was a significant main effect between pre- and post-TT gait, F (1, 31) = 24.84, $p < .001$ ($\eta^2 = .45$, power = .99) and a significant group interaction, F (1, 31) = 26.28, $p < .001$ ($\eta^2 = .46$, power = .99). The Rs significantly improved in gait post-TT ($p < .001$); whereas, NRs did not change (see Figure 1).

Upper Extremity Motor Functioning

Baseline performance on measures of *Basic Motor*, *Fine Motor*, and Line Tracing and Serial Dotting, both measures of psychomotor precision, was not significantly different between Rs and NRs. Table 3 shows pre- and post-TT performance of upper extremity motor and psychomotor functioning of both Rs and NRs.

Both Rs and NRs improved on *Basic Motor* post-TT, F (1, 36) = 11.08, $p < .01$ ($\eta^2 = .24$, power = .90). The interaction effect between the groups did not reach statistical significance; however, exploratory analysis of pre- and post-TT change for each group separately suggested that Rs significantly improved on *Basic Motor* functioning post-TT ($p < .001$), whereas the change in NRs was not significant (see Figure 2). There were no significant findings on *Fine Motor* functioning, and performance was poor in both groups.

The data revealed group differences in psychomotor precision post-TT. Both Rs and NRs improved on Line Tracing, F (1, 39) = 19.41, $p < .001$ ($\eta^2 = .33$, power = .99), and there was a significant group interaction, F (1, 39) = 4.61, $p < .05$ ($\eta^2 = .11$, power = .55), with Rs improving more than the NRs. Comparison of pre- and post-TT mean difference within each group showed that Rs improved significantly on Line Tracing ($p < .001$); however, post-TT performance of NRs was not significantly different from pre-TT (see Figure 3). There were no significant differences on Serial Dotting, but there was a trend towards a group interaction, F (1, 39) = 3.16, N.S. ($p = .08$, $\eta^2 = .08$, power = .41), see Figure 4. Exploratory analysis for changes within the groups suggested that Rs improved significantly on Serial Dotting ($p < .01$), and NRs did not.

Memory Functioning

Both groups were impaired pre-TT and post-TT for all measures of memory. While Rs tended to have lower scores than NRs, these differences were not significant. There were no significant group interactions on memory functioning. However, performance declined for both Rs and NRs on Learning, $\underline{F}$ (1, 40) = 6.05, $\underline{p} < .01$ (η^2 = .13, power = .67) and Recall post-TT, $\underline{F}$ (1, 40) = 18.06, $\underline{p} < .001$ (η^2 = .31 and power = .99). Performance on Recognition Hits appeared to improve for both Rs and NRs, although this did not reach statistical significance, $\underline{F}$ (1, 39) = 2.94, N.S. ($\underline{p}$ = .09, η^2 = .07, power = .39). Exploratory analysis of post-TT change in each group separately suggested that Rs improved significantly in their Recognition performance ($\underline{p} < .01$), whereas the change in NRs was not significant (see Figure 5). Nevertheless, this improvement trend on Recognition Hits within Rs was negated, as performance of Rs and NRs significantly declined on false positive errors, $\underline{F}$ (1, 39) = 12.98, $\underline{p} < .001$ (η^2 = .25, power = .94) and Discriminability (hits - false positive errors), $\underline{F}$ (1, 39) = 4.23, $\underline{p} < .05$ (η^2 = .10, power = .52). Table 4 shows performances on memory functioning.

Attention / Executive Functioning

Baseline performance for both groups was within the average range on Auditory Attention (Digits Forward) and Working Memory (Digits Backward), and within the borderline impaired range on the functional domain of *Visual Motor Attention* (Trails A and B), as it has a motor component. Baseline differences on Auditory and *Visual Motor Attention* were not statistically significant. However, there was a significant group

interaction on Working Memory, $\underline{F}$ (1, 34) = 4.63, $\underline{p} < .05$ ($\eta^2 = .12$, power = .55), with Rs scoring significantly lower pre-TT than NRs ($\underline{p} < .05$). There were no significant group interactions post-TT.

A 2 x 2 mixed model repeated measures ANCOVA was conducted for the analysis of semantic clustering. Performance on delayed recall of HVLT-R was used as a covariate to account for effects of overall poor recall performance on clustering. There were no significant group differences at baseline or post-TT, and performance was poor for both groups. Performance on delayed recall was a significantly contributing covariate, $\underline{p} < .001$, suggesting that poor clustering was affected by impaired recall.

Preliminary Findings on Other Measures of Higher Order Cognitive Processing

Performance on Clock Drawing, Phonemic Fluency, and the clustered variable *Semantic Fluency*, was available on a subset of the sample (n = 13), and data are presented as preliminary findings. Both Rs and NRs were impaired pre-TT on these additional measures. Both groups appeared to improve post-TT on Phonemic Fluency, and both appeared to decline on *Semantic Fluency*. Clock Drawing performance of Rs appeared to improve (pre-TT: M = 6.63, SD = 2.26; post-TT: M = 7.88, SD = 2.95; see Figure 6); however, performance of NRs remained relatively unchanged (pre-TT: M = 5.25, SD = 2.99; post-TT: M = 5.25, SD = 3.59). Table 5 shows pre- and post-TT performance on measures of attention / executive functioning.

Post-Shunt Treatment Exploratory Analyses

Long-term data were available for 7 of the patients (4 men, 3 women) who participated in the pre- and post-TT study, and subsequently underwent shunt placement for the treatment of NPH. Exploratory analyses were conducted to investigate the relationship between variables of interest from the initial study and post-shunt response. All 7 of these patients were judged as Rs in gait post-TT, and were also judged by the same treating neurologist as Rs in gait post-shunt treatment. As compared to baseline, performance following shunt treatment appeared to have improved on Line Tracing (pre-TT: M = -0.90; post-TT: M = -0.07; post-shunt: M = -0.45), *Basic Motor* (pre-TT: M = -0.73; post-TT: M = -0.33; post-shunt: M = -0.63), and Serial Dotting (pre-TT: M = -2.41; post-TT: M = -1.64; post-shunt: M = -1.75). Performance on Recognition Hits (pre-TT: M = -2.46; post-TT: M = -1.86; post-shunt: M = -1.51) and Discriminability (pre-TT: M = -1.81; post-TT: M = -2.35; post-shunt: M = -1.89) appeared to improve post-shunt as compared to post-TT performance. Using pre- and post-TT performance on variables of interest, individual change scores (difference scores) were computed to assess the correlation between this observed post-TT change and post-shunt response. Only performance change on Line Tracing was significantly correlated with shunt response ($\underline{r} = -.750$, $\underline{p} < .05$), see Figure 7. Table 6 shows demographic characteristics of the post-shunt sample, and Figure 8 illustrates the directional change for performance on *Basic Motor*, Serial Dotting, and Recognition Hits.

Discussion

These findings reveal that individuals judged as responders based on clinical assessment of gait post-TT also improve on upper extremity motor functioning, in particular, in psychomotor functioning. The Line Tracing task, as a measure of psychomotor precision, was sensitive to changes in upper extremity motor functioning, supporting the hypothesis that responders in gait will also improve in psychomotor functioning. These results are clinically meaningful in that they provide an additional and most importantly an objective measure of motor functioning that can be used to reliably measure TT response. Preliminary data from this study suggest that post-TT improvement on Line Tracing is also correlated with shunt response.

The results of this study substantiate a previous report that upper extremity motor functioning, as measured by psychomotor precision, can be used as an additional measure of motor dysfunction in NPH patients (Klinge, et al., 2002). Klinge, et al. found that the Line Tracing task differentiates response to shunt, and the present findings show that it is also useful in identifying response to TT. In the Klinge, et al. study, the Line Tracing task was found to be the most sensitive measure to motor changes early in the recovery period post-shunt, and it was predictive of long-term functional outcome. These current findings are clinically meaningful in that they show the Line Tracing task to be sensitive to motor changes early in the diagnostic process, where confirming diagnosis and predicting treatment response are the issues, and where objective measures of motor functioning are lacking.

Line Tracing may have been a sensitive measure of change in psychomotor precision because it does not require complex hand movements and sequencing. In contrast, patients were more impaired on Serial Dotting, which requires lifting the hand repeatedly off the page in sequence. Although Trail Making Tests are similar to Line Tracing in this respect, Trail tests involve a higher order cognitive component, which according to the results of this study, may not benefit from subtle changes of this diagnostic procedure. Other measures of upper extremity motor functioning did not differentiate TT Rs from NRs; however, Finger Tapping, as a measure of basic motor functioning, and Serial Dotting detected changes in Rs that may be supported in future studies with a larger sample.

Data from memory measures did not support the secondary hypothesis that cognitive functioning will respond to TT, as Responders did not improve on Recall or Learning. This finding is similar to the findings of another study (Marmarou, et al., 2005) showing no improvement on Recall and Learning post-ELD and post-shunt. Further, both groups declined post-TT, which may suggest that fatigue from a medical procedure and hours of assessment in already impaired older adult patients may significantly affect tasks that require a lot of effort, such as recall. This study differs from others in the literature since memory was assessed with learning, recall, and recognition measures, whereas other studies tended to use measures of learning, recall, or global measures of cognitive functioning, but not recognition (Marmarou, et. al, 2005; Farace & Shaffrey, 2005). As the pattern of memory deficit in NPH patients is considered a recall deficit due to retrieval problems, patients are typically more intact on

recognition and observable changes on this measure may be more likely. Also, as recognition is a less effortful task, it may also be more likely to detect changes even if the patient is fatigued.

The memory measure used in this study, the HVLT-R, has been used routinely, as it is more suitable for evaluating older adult patients. The HVLT-R is composed of a shorter word list (less number of words to remember), and it includes a Recognition task. Responders to TT appeared to show improvement in Recognition Hits, but as their Discriminability was poor, post-TT findings were negated. However, Recognition Hits and Discriminability appeared improved in preliminary data of shunt responders. These findings suggest that the use of a recognition task may prove useful in larger NPH studies, and perhaps in a less impaired patient sample.

Other measures of cognitive processing also did not respond to TT, including measures of attention and executive functioning. The use of semantic clustering did not prove a useful measure of assessing higher-order cognitive functioning in this patient population, probably due to very impaired recall performance both pre- and post-TT. Preliminary findings on visuoconstructional skills appeared promising as a correlate to TT response, as Clock drawing improved only in Rs post-TT. These results are similar to the shunt study of Kaye, et al. (1990), which showed that visuospatial functions improved earlier post-shunt treatment than attention and memory functioning (Kaye, et al., 1990).

Overall, these data suggest that TT Rs also improve in psychomotor precision, as assessed by Line Tracing, and preliminary data suggest that this change post-TT is correlated with post-shunt response. Although cognitive improvement in response to TT

has not been supported, several areas appeared worthy of further investigation, including Recognition memory, Phonemic Fluency, and Clock Drawing. With the exception of significant baseline differences on working memory, pre-TT differences on neuropsychological measures were not significant between the groups. However, it is important to note that Rs had lower scores than NRs across most tasks and functional domains. Although baseline differences in gait severity were also not significant, Responders had higher scores on the Boon Gait Scale indicative of greater impairment than NRs. Thus, severity of cognitive and motor symptoms may impact TT response. Also of note is that 65% of Rs reported the complete clinical triad (gait, cognitive, and urinary symptoms), and although there was not a significant difference between the groups, it should be further investigated as a correlate to TT response since it appears consistent with previous findings showing that the best predictor of a positive shunt response is presentation of all three symptoms.

Limitations

Participants in the study were recruited from clinical practice, and, as a result, not all data points were available on all patients. Although this is one of the largest samples that systematically examined neuropsychological deficits in NPH patients pre- and post-TT, the sample size was relatively small. At times, testing was discontinued based on time constraints or patients' degree of impairment. Co-morbidity was not controlled for in this study; patients were not excluded due to co-morbid disorders such as depression and cerebrovascular disease. This was a significantly impaired NPH patient sample, both

in cognition and gait; patients had a relatively long history of gait symptoms and the majority of the patients reported the complete triad of symptoms. The current study's design was not a predictive model, and as such, the specificity of the measures was not formally investigated. An attempt was made nevertheless towards this goal by exploring pilot data 6 months post-shunt. However, as all shunted patients were judged as Responders and had also been judged as TT Rs, specificity could not be explored in any systematic way.

In the Klinge, et al. (2002) study, Line Tracing was scored in terms of time to completion and number of errors. In the current study, only the time score was used since the computation of the specific accuracy score is ambiguous, unreliable, and not clinically practical. However, there is a component of this timed test that requires accuracy and precision, which qualitatively cannot be parceled out, as patients sacrifice their time in order to be more accurate.

Contributions and Directions for Future Research

These findings substantiate that upper extremity motor functioning, as measured by psychomotor precision, can be used as an additional and objective measure of motor functioning following Tap Test. Current clinical practice continues to rely heavily on subjective measures of TT response, particularly on the clinician's assessment of gait changes. In comparison to this gold standard of clinical assessment, Line Tracing, as a measure of psychomotor precision, is an objective measure, which quantifies the level of motor impairment early in the diagnostic process. This approach can be especially useful

in patients with severe lower motor dysfunction, as post-TT comparisons can be difficult when assessment of response is based on gait alone. Even when using available measures of gait, such as the Boon Gait Scale, the walking score is somewhat based on the clinician's judgment, and it only allows for dichotomous scoring (impaired or not impaired). As a result, clinically meaningful changes can be missed, and negative results falsely interpreted. In comparison, Line Tracing is a continuous variable obtained from an objective measure of motor functioning, is sensitive to subtle changes post-TT, and correlates to shunt response.

Future studies with larger samples of NPH patients are needed to systematically address specificity and sensitivity of neuropsychological measures sensitive to TT and shunt response. Improving the clinical utility of objective factors associated with TT response is of importance, as it plays a crucial role in diagnosis and determination of whether an individual is treated. Furthermore, adding an easily administered measure of motor functioning as a determinant of responsiveness can be particularly helpful to patients who are treated with programmable shunts and rely on small symptom changes to determine shunt adjustments.

Table 1.

Demographic Characteristics of TT Responders and Non-Responders

	Responders		Non-Responders		
	Mean	**SD**	**Mean**	**SD**	**p**
Age	77.42	4.31	78.19	6.18	n.s.
Education	15.73	4.04	15.81	2.37	n.s.
DRS	121.18	12.32	124.25	11.05	n.s.
GDS	8.83	5.02	8.85	8.03	n.s.
Pre-TT Boon†	15.55*	5.09	13.88	8.88	n.s.
Post-TT Boon†	10.10*	4.53	13.96	9.45	n.s.
Gait Symptoms (*duration in months*)	41.96	36.91	23.13	19.77	n.s.

Note: SD = Standard Deviation; n.s. = not statistically significant;
DRS = Dementia Rating Scale; GDS = Geriatric Depression Scale;
† Pre-TT Boon and Post-TT Boon = higher scores indicate greater impairment;
* = significant difference between pre- and post-TT performance in Rs ($p < .001$).

Table 2.

Correlation Analyses for Variables Clustered in Functional Domains

	Pre-TT	Post-TT
Functional Domain	**r**	**r**
Basic Motor		
Finger Tapping: both hands	.759*	.655*
Fine Motor		
Grooved Pegboard; Symbol Digit Modalities	.748[†]	.689[†]
Visual Motor Attention		
Trail Making Tests A and B	.621*	.561*
Semantic Fluency		
Animals and Supermarket items	.675*	.542[±]

Note: * $p < .001$; [†]Cronbach's α for performance of both hands on Grooved Pegboard and performance on Symbol Digit Modalities; [±] = post-TT *Semantic Fluency* consisted of scores on word list generation of Vegetables and Fruit and correlation was not statistically significant (n = 13 post-TT).

Table 3.

Upper Extremity Motor Functioning of Rs and NRs

	Responders		Non-Responders	
Variable	**Pre-TT**	**Post-TT**	**Pre-TT**	**Post-TT**
Basic Motor [±]	-1.77 (1.12)	-1.32 (1.19) [†]	-1.14 (1.22)	-0.98 (1.23) [†]
Fine Motor [±]	-1.77 (0.75)	-1.73 (0.71)	-1.81 (0.76)	-1.88 (0.69)
Line Tracing	-0.88 (1.55)	0.00 (1.40)*	-0.45 (1.59)	-0.14 (1.66)*
Serial Dotting	-2.27 (1.17)	-1.77 (1.40)	-2.11 (1.39)	-2.16 (1.06)

Note: Values enclosed in parentheses represent Standard Deviations;
[±] = variables in italics represent clustered variables;
[†] = both groups improved on *Basic Motor* post-TT (main effect, $p < .01$);
* = interaction between Rs and NRs on Line Tracing post-TT ($p < .05$), and post-TT improvement within Rs on Line Tracing ($p < .001$).

Table 4.

Memory Functioning of Rs and NRs

	Responders		Non-Responders	
Variable	**Pre-TT**	**Post-TT**	**Pre-TT**	**Post-TT**
Learning	-2.31 (0.70)	-2.41 (0.64)$^{\pm}$	-1.92 (1.02)	-2.26 (0.80)$^{\pm}$
Recall	-2.26 (0.75)	-2.67 (0.46)$^{\pm}$	-1.83 (1.10)	-2.33 (0.92)$^{\pm}$
Recognition	-2.09 (1.07)	-1.29 (1.50)	-1.56 (1.35)	-1.47 (1.37)
False Positives	-1.85 (1.09)	-2.34 (0.97)$^{\pm}$	-1.37 (0.98)	-2.01 (1.03)$^{\pm}$
Discriminability	-2.26 (0.98)	-2.43 (0.97)$^{\pm}$	-1.61 (1.31)	-2.12 (1.20)$^{\pm}$

Note: Values enclosed in parentheses represent Standard Deviations;
$^{\pm}$ = main effects for pre- and post-TT performance on Learning ($p < .01$), Recall ($p < .001$), False Positives ($p < .001$), and Discriminability ($p < .05$).

Table 5.

Attention and Higher Order Cognitive Functioning of Rs and NRs

	Responders		Non-Responders	
Variable	**Pre-TT**	**Post-TT**	**Pre-TT**	**Post-TT**
Auditory Attention	-0.35 (0.86)	-0.37 (0.93)	-0.22 (0.61)	0.00 (0.90)
Visual Motor Attention[±]	-1.51 (1.03)	-1.62 (1.06)	-1.49 (1.32)	-1.70 (1.39)
Working Memory	-0.96 (0.65)*	-0.75 (0.86)	-0.44 (0.79)*	-0.69 (0.70)
Phonemic Fluency†	-2.29 (0.79)	-1.99 (0.77)	-1.70 (1.32)	-0.91 (1.80)
Semantic Fluency[±]†	-2.14 (0.92)	-2.37 (0.70)	-1.91(0.81)	-2.54 (0.52)

Note: Values enclosed in parentheses represent Standard Deviations;
[±] = variables in italics represent clustered variables;
* = interaction effect between groups at baseline ($p < .05$);
† = preliminary data presented (n = 13 post-TT).

Table 6.

Demographic Characteristics of Shunt Responders*

	Mean	SD
Age	77.86	5.08
Education	14.68	4.45
Baseline DRS	129.43	7.46
Post-Shunt DRS	131.33	4.13
Baseline GDS	10.67	6.71
Post-Shunt GDS	10.83	6.71
Pre-TT Boon†	13.29	6.18
Post-TT Boon†	7.50	4.37
Post-Shunt Boon†	8.67	4.08
Gait Symptoms (*duration in months*)	52.29	51.93

Note: * 6 months post-shunt (n = 7);
SD = Standard Deviation;
DRS = Dementia Rating Scale;
GDS = Geriatric Depression Scale;
† Boon = higher scores indicate greater impairment.

Figure 1

The Boon Gait Scale shows a group interaction with significant improvement in gait of TT Rs (determined by clinical gait assessment), ($p < .001$). Higher scores indicate greater impairment.

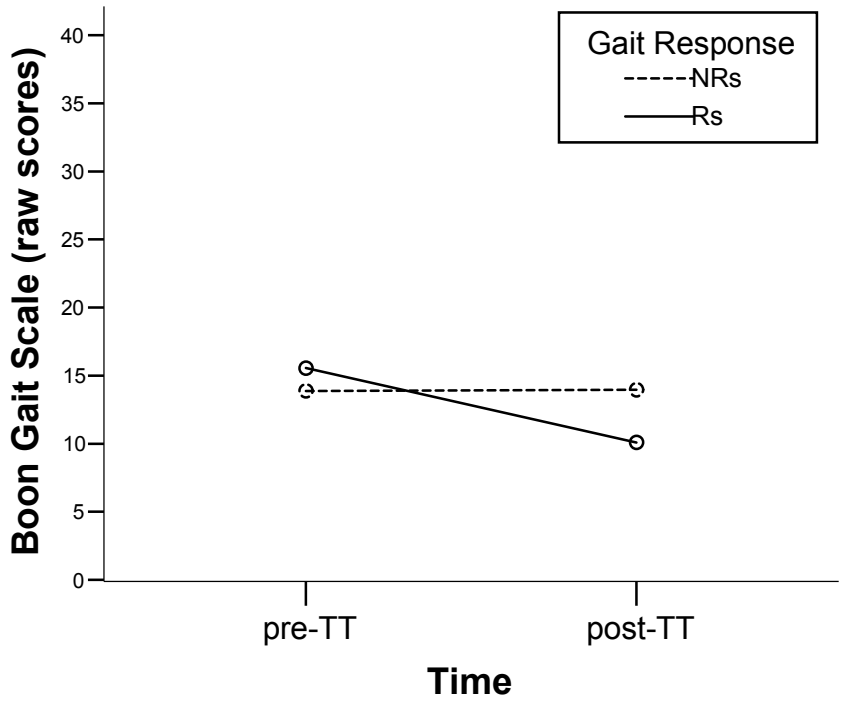
Gait Response
NRs
Rs
Boon Gait Scale (raw scores)
40
35
30
25
20
15
10
5
0
pre-TT
post-TT
Time

Figure 1

Figure 2

Both Rs and NRs improved post-TT on the clustered variable of *Basic Motor* functioning.

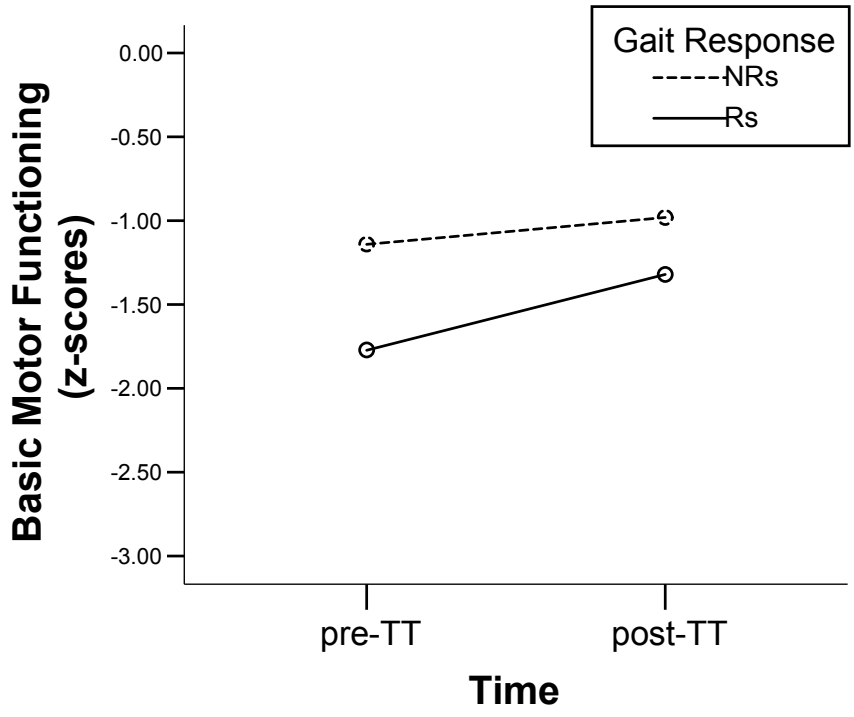
Gait Response
NRs
Rs
Basic Motor Functioning
(z-scores)
0.00
-0.50
-1.00
-1.50
-2.00
-2.50
-3.00
pre-TT
post-TT
Time

Figure 2

Figure 3

Rs improved on Line Tracing significantly more than NRs ($p < .05$), with significant post-TT improvement within Rs ($p < .001$), and non-significant change within NRs.

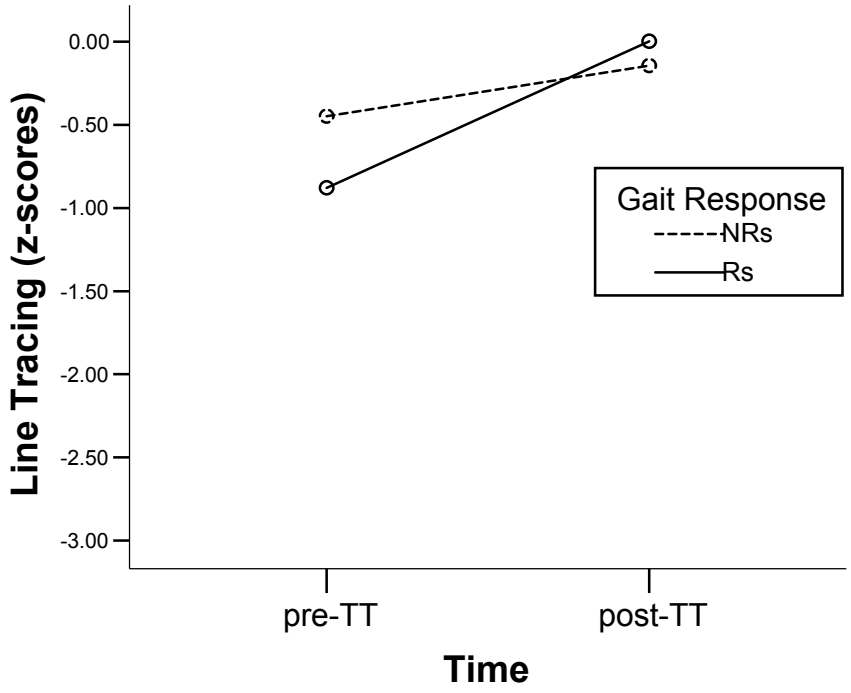
0.00
-0.50
-1.00
-1.50
-2.00
-2.50
-3.00
Line Tracing (z-scores)
pre-TT
post-TT
Time
Gait Response
NRs
Rs

Figure 3

Figure 4

A trend towards a group interaction on Serial Dotting suggested that Rs improved more than NRs post-TT; exploratory analysis showed significant improvement within Rs ($p < .01$), and non-significant change within NRs.

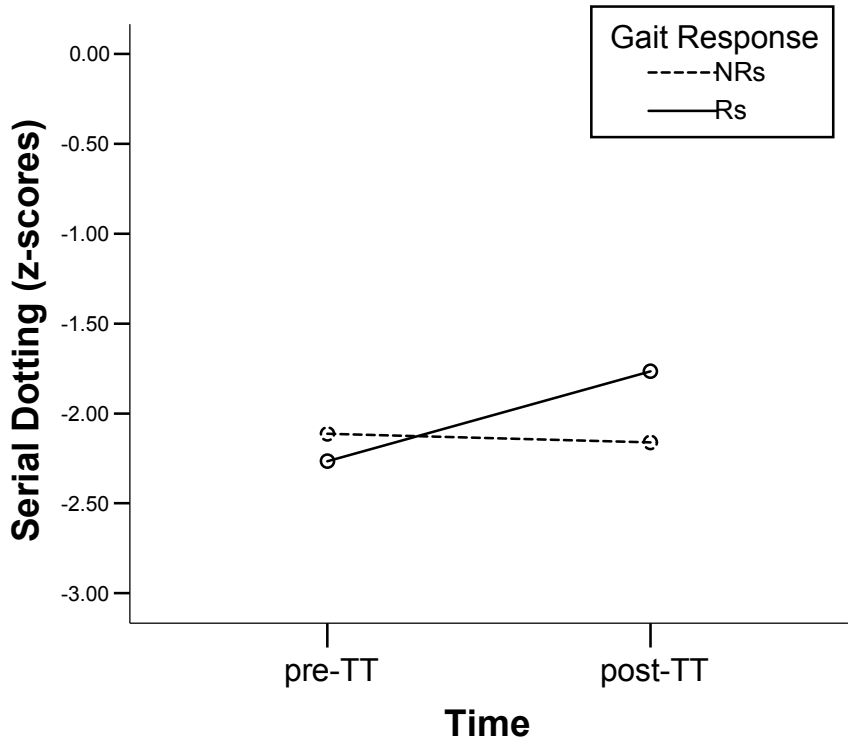
Gait Response
NRs
Rs
Serial Dotting (z-scores)
0.00
-0.50
-1.00
-1.50
-2.00
-2.50
-3.00
pre-TT
post-TT
Time

Figure 4

Figure 5

Rs appeared to improve on Recognition Hits, and exploratory analysis showed a significant change only within Rs ($p < .01$); however, Discriminability was impaired for both groups pre- and post-TT.

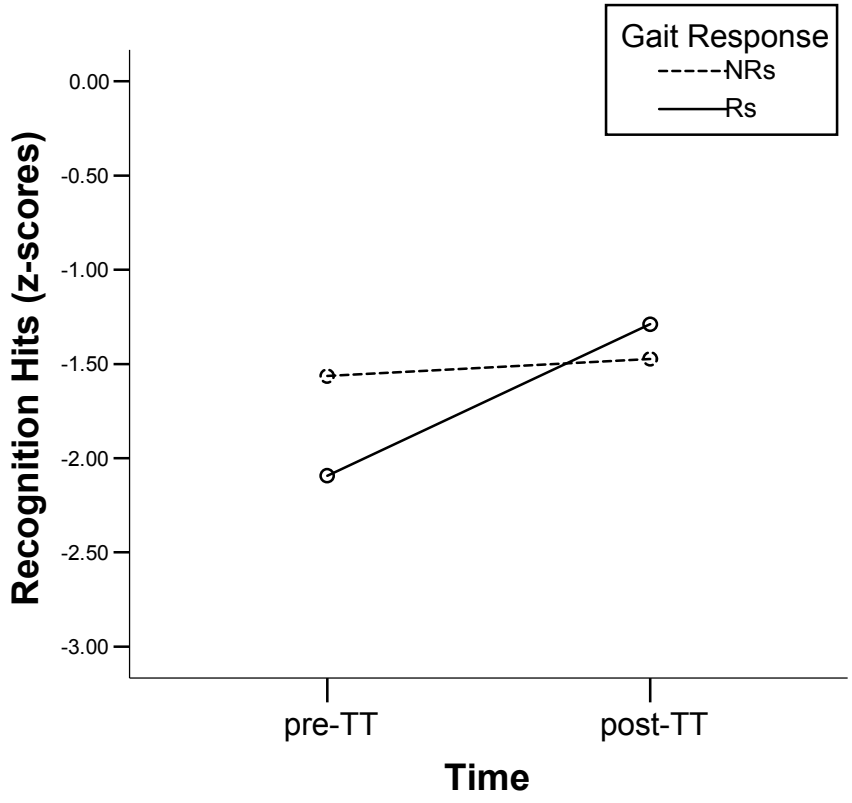
Gait Response
NRs
Rs
Recognition Hits (z-scores)
0.00
-0.50
-1.00
-1.50
-2.00
-2.50
-3.00
pre-TT
post-TT
Time

Figure 5

Figure 6

Preliminary findings on Clock Drawing showed a trend that post-TT performance of Rs improved, whereas performance of NRs did not change.

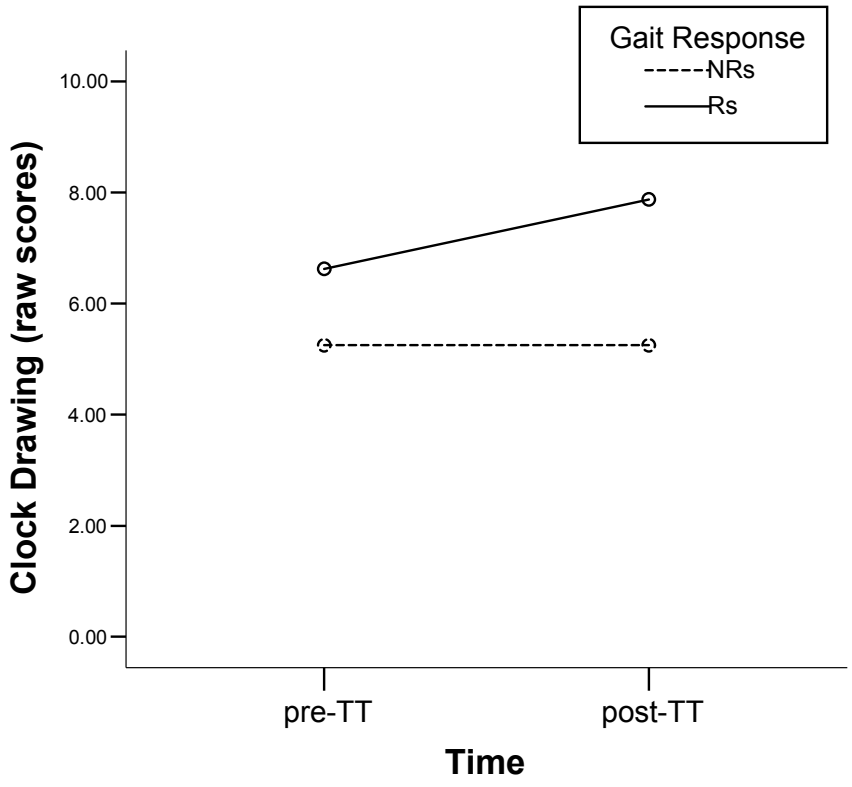
Gait Response
NRs
Rs
Clock Drawing (raw scores)
10.00
8.00
6.00
4.00
2.00
0.00
pre-TT
post-TT
Time

Figure 6

Figure 7

Post-shunt performance on Line Tracing improved in comparison to pre- TT performance, and post-TT change in performance was correlated with shunt response (preliminary data, n = 7).

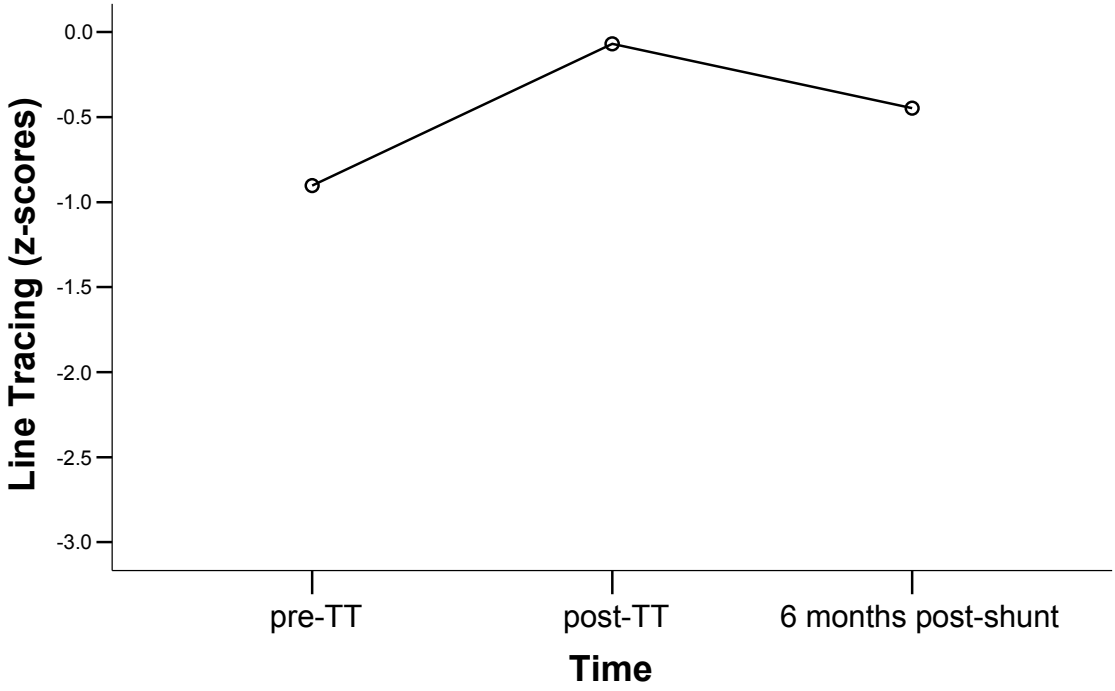
Line Tracing (z-scores)
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
pre-TT
post-TT
6 months post-shunt
Time

Figure 7

Figure 8

Post-shunt Serial Dotting and *Basic Motor* functioning remain stable or improve as compared to pre-TT, and improved post-TT performance on Recognition Hits persists post-shunt (preliminary data, n = 7).

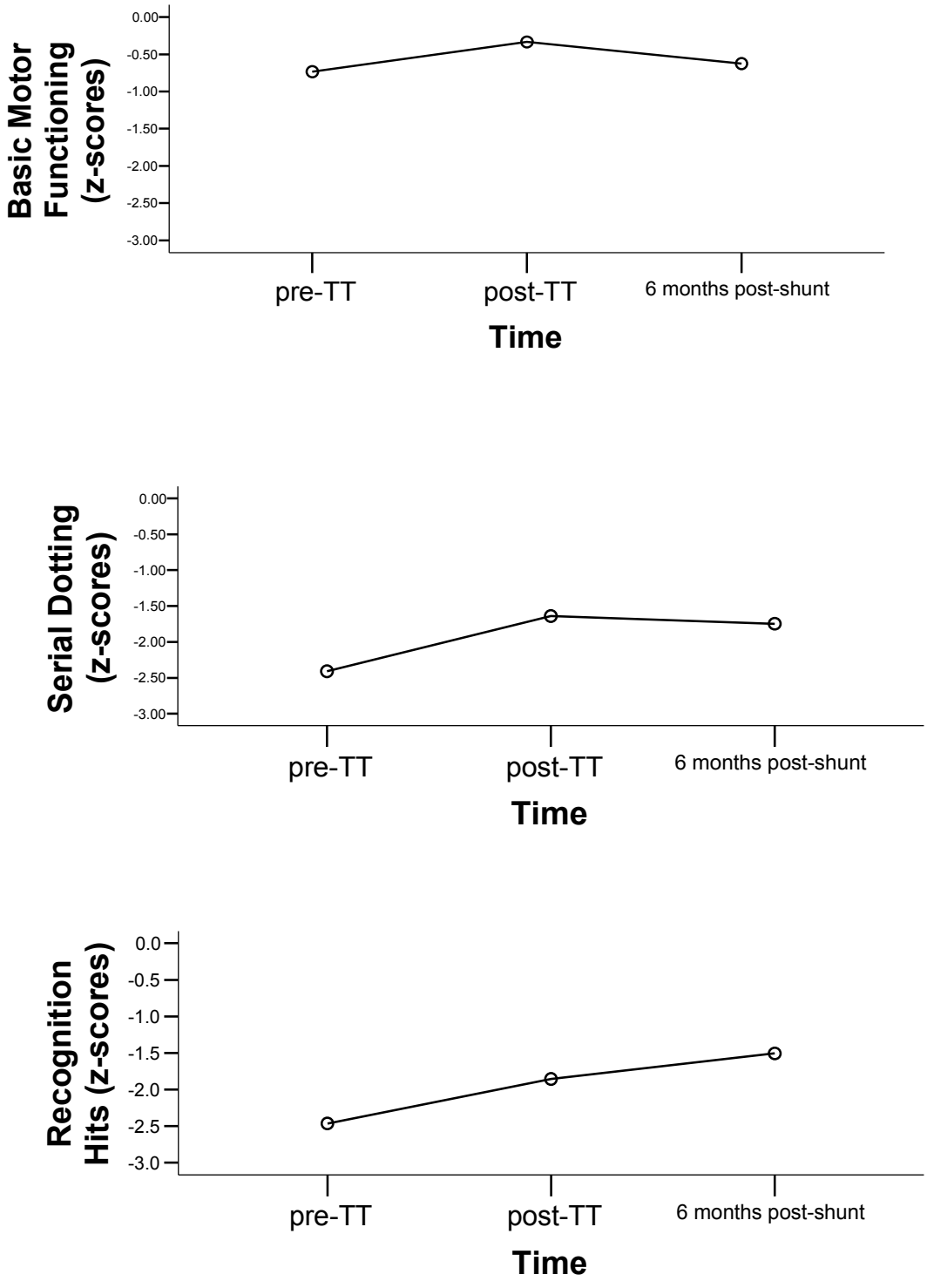
Basic Motor Functioning (z-scores)
0.00
-0.50
-1.00
-1.50
-2.00
-2.50
-3.00
pre-TT
post-TT
6 months post-shunt
Time
Serial Dotting (z-scores)
0.00
-0.50
-1.00
-1.50
-2.00
-2.50
-3.00
pre-TT
post-TT
6 months post-shunt
Time
Recognition Hits (z-scores)
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
pre-TT
post-TT
6 months post-shunt
Time

Figure 8

Appendix A

	Responders		Non-Responders	
	pre-TT	**post-TT**	**pre-TT**	**post-TT**
Non-Clustered Variables				
Line Tracing (*seconds*)	105.72 (54.14)	75.80 (34.38)	102.00 (66.14)	85.13 (58.69)
Serial Dotting (*seconds*)	90.80 (50.31)	82.64 (49.76)	87.19 (33.83)	79.00 (26.31)
Learning	11.88 (4.69)	11.92 (3.68)	14.50 (6.91)	12.56 (5.51)
Recall	2.31 (2.17)	1.04 (1.43)	3.38 (3.44)	2.13 (2.66)
Recognition Hits	8.73 (1.93)	9.81 (1.86)	9.60 (1.81)	9.80 (1.52)
Discrimination Index	5.92 (2.92)	5.50 (2.86)	7.60 (3.18)	6.53 (2.80)
False Positive Errors	2.81 (2.53)	4.31 (2.68)	2.00 (1.89)	3.27 (2.74)
Auditory Attention	5.64 (1.14)	5.64 (1.22)	5.71 (0.83)	6.00 (1.18)
Working Memory	3.23 (0.69)	3.45 (0.96)	3.79 (0.89)	3.50 (0.76)
Phonemic Fluency†	20.20 (8.54)	20.90 (6.76)	21.80 (12.60)	24.20 (15.75)
Clock Drawing†	6.63 (2.26)	7.89 (2.95)	5.25 (2.99)	5.25 (3.59)

Note: Raw data (Means and Standard Deviations) of non-clustered Variables; Values enclosed in parentheses represent Standard Deviations; † = preliminary data presented (n = 13 post-TT).

Appendix B

	Responders		Non-Responders	
	pre-TT	**post-TT**	**pre-TT**	**post-TT**
Clustered Variables				
Basic Motor				
Finger Tapping:				
Dominant	31.84	37.05	36.36	38.34
	(12.40)	(11.39)	(13.11)	(13.00)
Non-Dominant	29.22	31.84	31.92	34.61
	(10.21)	(11.44)	(12.34)	(10.37)
Fine Motor				
Grooved Pegboard (seconds):				
Dominant	159.35	143.30	154.85	171.08
	(59.33)	(52.64)	(43.66)	(66.80)
Non-Dominant	174.06	174.88	192.92	195.77
	(59.86)	(62.11)	(47.22)	(57.77)
Symbol Digits Modalities	17.13	17.09	18.92	19.69
	(9.50)	(7.98)	(8.07)	(9.71)
Visual Motor *(seconds)*				
Trail Making Test A	84.18	92.25	88.27	83.00
	(39.89)	(61.38)	(65.68)	(42.48)
Trail Making Test B	327.88	349.94	320.08	320.00
	(210.24)	(196.71)	(194.37)	(204.05)
Semantic Fluency†				
Animals	7.72	5.38*	9.81	6.75*
	(3.51)	(2.67)	(5.22)	(2.63)
Supermarket Items (DRS)	13.43	3.43♦	12.36	4.25♦
	(6.87)	(2.51)	(5.12)	(4.35)

Note: Raw data (Means and Standard Deviations) of clustered variables; Values enclosed in parentheses represent Standard Deviations; † = preliminary data presented (n = 13 post-TT); * and ♦ = post-TT *Semantic Fluency* consisted of scores on word list generation of Fruit* and Vegetables♦.

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