COGNITION AND APATHY IN NORMAL PRESSURE HYDROCEPHALUS

Katie Ann Peterson

Lucy Cavendish College
Department of Psychiatry
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This dissertation is submitted for the degree of Doctor of Philosophy
To Granny and Grandad
Abstract

Normal pressure hydrocephalus (NPH) is characterised by a build-up of cerebrospinal fluid (CSF) in the brain despite apparently normal CSF pressure at lumbar puncture. In addition to movement and urinary symptoms, patients commonly display cognitive decline and apathy. NPH is recognised as an important cause of cognitive decline as it is thought be reversible with surgical CSF diversion (e.g. shunt surgery). However, this remains controversial and the neuropsychology of NPH is relatively poorly understood. Further, despite being the most commonly reported neuropsychiatric symptom in NPH, the significance of the symptom of apathy has not yet been elucidated. This thesis aims to expand on the neuropsychological and neuropsychiatric research in NPH, with the main objectives being to investigate neuropsychological outcome, and the significance of the symptom of apathy in NPH.

In order to investigate neuropsychological outcome following shunt surgery in NPH, a systematic review and meta-analysis was conducted (Chapter 2). The findings from studies which used a battery of neuropsychological tests to assess cognitive outcome in NPH were combined. Meta-analyses were conducted on pre-operative and difference scores for the most commonly used neuropsychological tests. These were seven tests which spanned global cognitive function, learning and memory, executive function and psychomotor speed. Results for all tests were significant in the direction of improvement. However, the significance of the results for two measures of executive function were deemed not to be robust. This is discussed in line with previous research which suggests that executive function may be less likely to improve following shunt surgery than other neuropsychological domains.

Next, the thesis focuses on the symptom of apathy. Chapter 3 investigated whether apathy in NPH relates to cognitive outcome and to a measure of ventricular enlargement. A reduction in apathetic symptoms following treatment was associated with better performance in a measure of global cognitive function. Further, larger ventricles (which may indicate greater disease severity/brain damage) was associated with more severe apathy. A structural MRI study was then conducted to expand on these findings and to define brain structural correlates of apathy in NPH (Chapter 4). Results from this study suggested a potential role of the caudate nuclei in apathetic symptoms in NPH.

Finally, consideration is given to the assessment of apathy in NPH. Since apathy is rarely investigated in patients with NPH it is unclear which assessment method is most appropriate for this patient group. Chapter 5 presents findings from a feasibility study of a novel
reward learning task to determine whether it might be useful as an objective measure of motivation and apathy in NPH.
Declaration

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as specified below, in the Acknowledgements, and in the text. It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. It does not exceed the prescribed word limit for the relevant Degree Committee.

Chapter 2: I conducted the literature review and extracted the raw data. The statistical analyses were conducted with help from Dan Jackson.

Chapters 3 and 4: The analyses in chapters 3 and 4 were conducted using previously collected data. The neuropsychological and imaging data were collected by previous PhD students Elise DeVito, Charlotte Housden, and Nicole Keong. I was responsible for the conception and design of the analyses, statistical and imaging analyses and interpretation of results. The bicaudate ratios for Chapter 3 were calculated by myself and Prof John D. Pickard since Prof Pickard has considerable expertise in calculating bicaudate ratios.

Chapter 5: Charlotte Housden programmed the simple Salience Attribution Task and recruited and tested the older adult participant group. I recruited and tested the younger adult participant group, conducted the statistical analysis (for both groups), and interpreted the results.
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Original Papers

The following publications have arisen from work contained in this thesis (see Appendix D for full texts):


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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
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<tr>
<td>AES</td>
<td>Apathy Evaluation Scale</td>
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<tr>
<td>AES-C</td>
<td>Clinician-rated Apathy Evaluation Scale</td>
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<tr>
<td>AES-I</td>
<td>Informant-rated Apathy Evaluation Scale</td>
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<tr>
<td>AES-S</td>
<td>Self-rated Apathy Evaluation Scale</td>
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<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
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<td>ANOVA</td>
<td>Analysis of variance</td>
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<tr>
<td>BCR</td>
<td>Bicaudate ratio</td>
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<tr>
<td>CANTAB</td>
<td>Cambridge neuropsychological test automated battery</td>
</tr>
<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<td>CSF-TT</td>
<td>Cerebrospinal fluid tap test</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>ELD</td>
<td>Continuous external lumbar CSF drainage</td>
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<tr>
<td>ETV</td>
<td>Endoscopic third ventriculostomy</td>
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<td>GDS-15</td>
<td>Geriatric Depression Scale short form</td>
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<tr>
<td>GM</td>
<td>Grey matter</td>
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<tr>
<td>HVLT</td>
<td>Hopkins Verbal Learning Test</td>
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<tr>
<td>IA</td>
<td>The Apathy Inventory</td>
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<tr>
<td>ICP</td>
<td>Intracranial pressure</td>
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<tr>
<td>iNPH</td>
<td>Idiopathic normal pressure hydrocephalus</td>
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<tr>
<td>LARS</td>
<td>The Lille Apathy Rating Scale</td>
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<tr>
<td>LP</td>
<td>Lumboperitoneal</td>
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<tr>
<td>MMSE</td>
<td>Mini-Mental State Examination</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NART</td>
<td>National Adult Reading Test</td>
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<td>NPH</td>
<td>Normal pressure hydrocephalus</td>
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<tr>
<td>NPI</td>
<td>Neuropsychiatric Inventory</td>
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<td>RAVLT</td>
<td>Rey Auditory Verbal Learning Test</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>R_{out}</td>
<td>Resistance to CSF outflow</td>
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<tr>
<td>RT</td>
<td>Response time</td>
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<td>SDGM</td>
<td>Subcortical deep grey matter</td>
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<td>sNPH</td>
<td>Secondary normal pressure hydrocephalus</td>
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<td>sSAT</td>
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<tr>
<td>TMT-A</td>
<td>Trail making test A</td>
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<tr>
<td>TMT-B</td>
<td>Trail making test B</td>
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<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
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<tr>
<td>VP</td>
<td>Ventriculoperitoneal</td>
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<td>WM</td>
<td>White matter</td>
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Chapter 1

Introduction

1.1. General introduction

The term “normal pressure hydrocephalus” (NPH) was first introduced by Hakim and Adams in 1965 following their observation of the symptomatic triad of gait apraxia, cognitive decline, and urinary incontinence in the presence of ventricular enlargement and normal cerebrospinal fluid (CSF) pressure in adult patients. Importantly, neurosurgical treatment using the then recently developed ventriculoperitoneal or ventriculoatrial CSF shunt resulted in marked improvement in functioning in these patients (Hakim & Adams, 1965). Today, the diagnosis and management of patients with NPH remains a challenge to clinicians. The pathological processes underlying the disorder are not completely understood, the heterogeneity of the disorder complicates differential diagnosis, and outcome following treatment can be difficult to predict.

The symptoms of NPH develop insidiously, usually over a period of years. There have been very few longitudinal studies, and therefore it is not known when the ventriculomegaly develops. NPH can occur secondary to head injury, brain haemorrhage, or infection (secondary NPH; sNPH). However, in many cases, NPH occurs without any obvious cause (idiopathic NPH; iNPH). While sNPH can occur at any age, iNPH typically affects older adults.

NPH is recognised as an important cause of cognitive decline as it is thought to be reversible with surgical CSF diversion. While improvement following shunting is most commonly observed in gait, the cognitive symptoms are also thought to show improvement in a number of patients and therefore NPH has been described as a reversible dementia. However, this is somewhat controversial likely due to the fact that there are no standardised clinical guidelines for assessing cognitive function in this patient group meaning that assessment methods often vary between centres, complicating interpretation of cognitive outcome.

In recent years, there has been greater emphasis on quantifying cognitive outcome following treatment for NPH through the use of detailed neuropsychological assessments.
although this is still an emerging aspect of NPH research and the neuropsychology of NPH is currently relatively poorly understood. A better understanding of the neuropsychology of NPH may be useful for diagnosis, and prediction and quantification of outcome following shunt treatment.

In addition to the cognitive symptoms, neuropsychiatric symptoms such as apathy (a loss of motivation, or impaired goal-directed behaviour) are frequently reported in NPH patients (Adams, Fisher, Hakim, Ojemann, & Sweet, 1965; Caltagirone, Gainotti, Masullo, & Villa, 1982; De Mol, 1986; Kanemoto et al., 2016; Kito et al., 2009). However, apathy has received little attention in NPH research. Apathy has been shown to be associated with severity of cognitive and functional impairment in patients with dementia (Boyle et al., 2003; Starkstein, Jorge, Mizrahi, & Robinson, 2006b) and may relate to dysfunction in the frontal or subcortical regions of the brain (Kanemoto et al., 2016; Levy & Dubois, 2006). Further, the symptoms of apathy may be misdiagnosed as depression which is more commonly assessed in NPH patients. Distinguishing apathy from depression is particularly important when considering treatment options. Therefore, there is clearly a need to assess the significance of the symptom of apathy in NPH patients.

This thesis provides:

- a meta-analysis of neuropsychological outcome following shunt surgery to determine from the literature whether there is a consensus as to which aspects of neuropsychological functioning improve following shunt surgery,

- an investigation of the significance of the symptom of apathy in NPH and, specifically, whether apathy in NPH is related to cognitive function and to a measure of ventricular enlargement,

- a structural magnetic resonance imaging (MRI) study to investigate structural correlates of cognitive dysfunction and apathy in NPH, and

- a feasibility study of a novel reward learning task to determine whether it might be useful as an objective measure of motivation and apathy for use with patients with dementia/ cognitive decline (including patients with NPH).

Chapter 1 begins with an introduction to NPH and includes an overview of the pathophysiological mechanisms underlying the disorder, the clinical features, diagnostic criteria, treatment methods, and criteria for classifying outcome following treatment. The
neuropsychology of NPH is then discussed. First, the typical pattern of neuropsychological impairment in NPH is described; and secondly, a summary of the research examining the effect of shunt surgery on neuropsychological performance is provided. The rationale for investigating apathy in NPH is then developed further, with a focus on possible neural mechanisms underlying this symptom in NPH. Current tools for assessing apathy are then reviewed. Chapter 1 concludes with a summary of the aims of the thesis.
1.2. Normal pressure hydrocephalus

Normal pressure hydrocephalus (NPH) is characterised by a build-up of cerebrospinal fluid (CSF) in the brain which causes enlargement of the cerebral ventricles over time (ventriculomegaly; Figure 1.1) despite a mean CSF opening pressure within the normal range (<18 cmH₂O or 13 mmHg; Hurley, Bradley, Latifi, & Taber, 1999). The ventricular enlargement is out of proportion to cortical atrophy. Impairments in gait and balance develop gradually, and may be accompanied by urinary incontinence and progressive cognitive decline. CSF diversion (e.g. with shunt surgery) results in clinical improvement for the majority of patients (Klinge, Hellström, Tans, & Wikkelsø, 2012; Malm, Kristensen, Stegmayr, Fagerlund, & Koskinen, 2000; Toma, Papadopoulos, Stapleton, Kitchen, & Watkins, 2013). However, for some patients, CSF diversion may only slow symptom progression rather than lead to improvements in functioning.

This section provides an overview of NPH, beginning with a description of the possible pathophysiological mechanisms underlying the disorder.

1.2.1. CSF flow

A disturbance of CSF dynamics is a primary feature of NPH. CSF has several functions including protection of the brain and spinal cord through buoyancy, removal of toxins and byproducts of brain metabolism, circulation of nutrients, and facilitation of molecular communication (Del Bigio, 2014; Kosztowski, Filippidis, Rory Goodwin, Elder, & Rigamonti, 2014). CSF is primarily produced in the choroid plexi within the cerebral ventricles. It is also produced via diffusion of the interstitial fluid from the parenchyma of the brain and spinal cord through the ependymal lining of the ventricles (Battal et al., 2011). CSF flows via net bulk flow through the ventricular system and enters the subarachnoid space from the fourth ventricle (Kosztowski et al., 2014). It is then reabsorbed via the arachnoid granulations and arachnoid villi and, at least in rodents, via lymphatic channels (Del Bigio, 2014). It has also been suggested that absorption occurs via the brain capillaries (Greitz, 2004; Weerakkody et al., 2011).
There is a pulsatile flow of CSF through the ventricles (Kosztowski et al., 2014). According to the Monro-Kellie hypothesis, a volume increase in one of the four main intracranial components (the brain, CSF, arterial and venous blood) causes a corresponding decrease in volume in the other components (once the fontanelle has closed in childhood). Thus, the total volume of intracranial compartments remains constant (Greitz, 2004; Greitz et al., 1992). During systole, expansion of the intracranial arteries is balanced by CSF expulsion through the foramen magnum and expulsion of blood from the veins into the dural venous sinuses (Greitz, 2004). Arterial compliance (expansion) dampens the arterial pulse wave, allowing constant capillary flow via the “windkessel” mechanism (Greitz, 2004). The dampened pulse wave in the artery is transmitted to the brain capillaries, causing a slight systolic volume increase in the brain. This expansion of the brain occurs inwards, compressing the ventricles, and causing pulsatile outflow of CSF through the aqueduct and the remaining ventricular system (Bradley, 2015). Respiration-induced changes in venous pressure also facilitate CSF flow.

An obstruction to CSF flow inside the ventricular system causes obstructive, or non-communicating hydrocephalus, while an obstruction to CSF flow outside of the ventricular system causes communicating hydrocephalus (Greitz, 2004). Further, NPH with a known cause (such as subarachnoid haemorrhage, meningitis, trauma, or neurosurgery; secondary NPH) has been distinguished from idiopathic NPH in which there is no known cause (Del Bigio, 2014; Vanneste, 1994). While baseline ICP is normal in NPH, intermittent elevations of pressure (B-waves) have been detected (Crockard, Hanlon, Duda, & Mullan, 1977; Pickard et al., 1980). Consequently, “adult hydrocephalus syndrome” or “adult symptomatic hydrocephalus” have been suggested to be more appropriate terms than “normal pressure hydrocephalus” (Vanneste, 2000) but these terms have not found general favour.

1.2.2. Pathophysiology

Although the precise pathophysiological mechanisms underlying NPH are not completely understood, a number of theories have been proposed and it is likely that NPH is caused by several underlying pathologic processes (Krauss et al., 1996). An overview of the main theoretical explanations for the development of NPH are outlined below.
CSF hydrodynamic factors

According to an early theory of hydrocephalus, the bulk flow theory (Dandy & Blackfan, 1914), a hydrostatic pressure gradient (from a slightly higher pressure at the production sites to a slightly lower pressure at absorption sites) drives the flow of CSF through the ventricular system from production to reabsorption at the arachnoid villi (Battal et al., 2011). The theory states that ICP is dependent on a balance between CSF production and absorption, and that an imbalance between the two (or specifically, impaired reabsorption of CSF at the arachnoid villi) causes hydrocephalus. However, the bulk flow theory has been shown to be incompatible with communicating NPH as an absorption deficit across the arachnoid villi would not cause ventricular enlargement. That is, there would not be a pressure gradient between the ventricles and the subarachnoid space meaning that it would be the subarachnoid space which would dilate (Greitz, 2004; Vanneste, 2000).

More recent theories suggest that absorption of CSF occurs in the capillaries of the central nervous system (Greitz, 2004) and that, in addition to bulk flow of CSF from the ventricles to the subarachnoid space, intraventricular pulsations related to the cardiac cycle contribute to CSF flow (Battal et al., 2011; Qvarlander, Lundkvist, Koskinen, Malm, & Eklund, 2013). Increased CSF pulse pressure has been suggested to contribute to the development of NPH (Di Rocco, Pettorossi, Caldarelli, Mancinelli, & Velardi, 1977; Greitz, 2004) and may be related to vascular pathophysiology (Bateman, 2004). Decreased arterial compliance leads to a breakdown of the windkessel mechanism and a subsequent increase in intracerebral capillary pulsations (Greitz, 2004). This has been suggested to result in a “water hammer” effect, causing ventricular enlargement through shear stresses without an accompanying increase in ICP (Bateman, 2000; Di Rocco et al., 1977; Greitz, 2004; Stivaros & Jackson, 2007; Vanneste, 2000).

A CSF absorption deficit can be examined by measuring resistance to CSF outflow ($R_{\text{out}}$). $R_{\text{out}}$ provides an indication of the ease of CSF absorption that occurs over all CSF outflow pathways (Malm, Jacobsson, Birgander, & Eklund, 2011), and a higher $R_{\text{out}}$ has been associated with hydrocephalus (Boon, Tans, Delwel, Egeler-Peerdeman, Hanlo, Wurzer, Avezaat, et al., 1997). $R_{\text{out}}$ is suggested to affect ICP, pulsatility, CSF absorption, and craniospinal compliance (Malm et al., 2011). However, while some studies have found a relationship between $R_{\text{out}}$ and ICP (Børgesen & Gjerris, 1987), others have not (Eide, Fremming, & Sorteberg, 2003), and its predictive validity remains uncertain (Vanneste, 2000).
Cerebrovascular risk factors

The prevalence of cerebrovascular risk factors, including hypertension, cardiac disease, diabetes mellitus, and white matter lesions, has been shown to be high among patients with NPH (Boon et al., 1999; Casmiro et al., 1989; Graff-Radford & Godersky, 1987; Jaraj et al., 2016; Krauss et al., 1996), although the causal direction is unclear (Boon et al., 1999; Momjian et al., 2004). It has been suggested that periventricular white matter lesions may lead to reduced elasticity of the periventricular tissue, and subsequent ventricular enlargement (Bradley, Whittemore, Watanabe, et al., 1991; Earnest, Fahn, Karp, & Rowland, 1974; Koto, Rosenberg, Zingesser, Horoupian, & Katzman, 1977). However, it has also been postulated that NPH may, in fact, cause periventricular changes (Fisher, 1982; George, 1991).

Cerebral blood flow (CBF) may play an important role in the symptomology of NPH. Pre-operative reductions in CBF have been observed in the periventricular white matter regions, the cerebral cortex, and deep grey matter regions (Momjian et al., 2004; Owler et al., 2004; Owler & Pickard, 2001; Ziegelitz et al., 2014, 2015b). Frontal regions may be preferentially affected (Owler & Pickard, 2001). Further, CBF has been linked to clinical symptoms (Ziegelitz et al., 2015b) and post-shunt outcome (Klinge et al., 2008; Murakami, Hirata, & Kuratsu, 2007; Ziegelitz et al., 2015a). Reduced CBF may be caused by neuronal loss or hypometabolism (Bateman, 2008) or by “hydrocephalic compression and stretching of the periventricular arterioles and venules” (Vanneste, 1994). Vanneste (1994) suggested that reduced periventricular blood flow may result in axonal dysfunction without loss of cellular integrity, while prolonged periventricular ischaemia may cause myelin disintegration and irreversible axonal loss and that this may explain why some patients do not improve following treatment.

Venous hypotheses

Bateman (2008) proposed a venous hemodynamic theory of NPH which centres on a positive feedback loop. He suggested that reduced craniospinal compliance leads to elevated venous pressure, which in turn causes the cortical veins to stiffen, further reducing craniospinal compliance. The reduced craniospinal compliance would limit arterial expansion in the subarachnoid space, propagating pulse waves into the brain parenchyma and capillaries (Bateman, 2008). As a result, hyperdynamic pulsations directed centrally may lead to ventricular enlargement due to disruption of glial tissue in the subependymal white matter, and reduced elastic recoil of this region.
CSF metabolism

It has been suggested that changes to the choroid plexus associated with hydrocephalus, or downregulation of CSF production in response to acute hydrocephalus could underlie observed reductions in CSF production (Silverberg, Mayo, Saul, Rubenstein, & McGuire, 2003). A resultant reduction in CSF turnover would lead to reduced clearance of neurotoxins such as β-amyloid, tau-protein, and pro-inflammatory cytokines (Kondziella, Sonnewald, Tullberg, & Wikkelso, 2008; Silverberg et al., 2003). This theory could explain the high rates of Alzheimer’s disease pathology in the cortex of NPH patients (Kondziella et al., 2008).

Overall, altered CSF dynamics leading to reduced cerebral perfusion and subsequent hypoxia and ischaemia appear to be important pathophysiological mechanisms in NPH. Reduced periventricular blood flow likely underlies the symptomology in NPH (Vanneste, 2000). Ageing may make the brain susceptible to intermittent spikes of B waves, and increased CSF outflow resistance, leading to progressive ventriculomegaly and the development of NPH (Albeck et al., 1998). Indeed, it has been suggested that age-related changes in CSF production and turnover (that is, the observed reduction in CSF production and the increased $R_{out}$ that occurs during ageing) may underlie a common pathological pathway leading to the development of Alzheimer’s disease (AD) or NPH, with a predominant reduction in CSF production leading to AD and a predominant increase in $R_{out}$ leading to NPH (Silverberg et al., 2003).

1.2.3. Epidemiology

The reported incidence of NPH ranges from 1.8 to 5.5 cases per million per year (Brean & Eide, 2008b; Krauss & Halve, 2004; Vanneste, Augustijn, Dirven, Tan, & Goedhart, 1992). The prevalence of NPH in individuals older than 65 years was reported to be 0.41% by Trenkwaler et al. (1995), and 2.9% (iNPH) by Hiraoka, Meguro, and Mori (2008). It is estimated that NPH accounts for around 5% of dementia cases (Beck, Benson, Scheibel, Spar, & Rubenstein, 1982; Clarfield, 1988; Vanneste, 2000).
1.2.4. Clinical features

While sNPH can present at any age, iNPH usually occurs in later life (Hebb & Cusimano, 2001) and with insidious onset of symptoms. Gait disturbance has been shown to be the most frequent symptom in NPH (Hebb & Cusimano, 2001) and is usually the first presenting symptom (Vanneste, 2000). Small steps, reduced foot to floor clearance, wide base, and disequilibrium are the principle features of NPH gait (Boon, Tans, Delwel, Egeler-Peerdeman, Hanlo, Wurzer, & Hermans, 1997; Bugalho & Guimarães, 2007; Stolze et al., 2000). The hypokinetic features may be indicative of subcortical dysfunction (specifically, damage to the basal ganglia), while disequilibrium may reflect frontal dysfunction (Bugalho & Guimarães, 2007).

While the cognitive impairment in NPH is often characterised as “dementia”, this may be misleading. The term suggests an advanced stage of cognitive decline which many NPH patients do not reach and some patients have no, or only mild, evidence of dementia (Boon, Tans, Delwel, Egeler-Peerdeman, Hanlo, Wurzer, & Hermans, 1997; Iddon et al., 1999). The pattern of cognitive decline is of the “subcortical” type (DeVito et al., 2005), with measurable deficits in memory, speed of information processing, and visuospatial abilities, as well as increased inertia and apathy. NPH has been further characterised as a “fronto-subcortical dementia” due to commonly observed executive dysfunction in patients (DeVito et al., 2005).

In comparison with AD, the pattern of cognitive decline in NPH is characterised by greater severity of impairments in executive function, attention, and visuospatial abilities (Ogino et al., 2006; Saito et al., 2011), with an absence of cortical dysfunction (Vanneste, 1994) and comparable or less severe memory impairment (Iddon et al., 1999; Ogino et al., 2006; Saito et al., 2011). This pattern of cognitive decline has been suggested to reflect less severe medial temporal lobe damage but more prominent frontal or fronto-subcortical changes in NPH compared to AD (Ogino et al., 2006). It has been suggested that in cases where cognitive decline is the most prominent symptom, or when dementia is severe, AD may be the most likely diagnosis (Vanneste, 2000).

Increased urinary urgency and frequency are common features of NPH, however urinary incontinence generally only occurs in the later stages of disease progression (Ahlberg, Norlén, Blomstrand, & Wikkelso, 1988; Iddon et al., 1999). The prevalence of urinary symptoms is reported to be 45-90% (Damasceno, Carelli, Honorato, & Facure, 1997; Hebb & Cusimano, 2001). While it has been suggested that frontal dysfunction may underlie bladder disturbance in NPH, urinary incontinence has been shown to be present in the absence of severe cognitive impairment (Ahlberg et al., 1988). Ahlberg et al (1988) concluded that it is more likely that
bladder symptoms in NPH are due to impaired function in regions of the brain associated with micturition, while severe cognitive decline associated with frontal damage may increase the risk of urinary incontinence in NPH.

1.2.5. Diagnosis

Diagnosis of NPH is based on clinical history, examination, and neuroimaging findings. The classic clinical triad of gait disturbance, cognitive decline, and urinary incontinence with ventriculomegaly on computed tomography (CT) is suggestive of NPH (Vanneste, 2000), although many patients do not present with the complete symptom triad. Supplementary tests may assist in diagnosis or prediction of outcome.

Brain imaging

Brain imaging (e.g. CT or MRI) is used to assess ventricular size and to rule out other conditions which may mimic NPH. On CT, NPH patients show ventriculomegaly which is disproportionate to cerebral atrophy. Ventricular enlargement is assessed using a measure of the ratio of ventricular size to cranial diameter, such as the Evans’ index (Evans, 1942). The Evans’ index is the ratio of the maximal width of the frontal horns to the maximal biparietal diameter (Figure 1.2). An Evans’ index of 0.30 or greater indicates ventriculomegaly (Relkin, Marmarou, Klinge, Bergsneider, & Black, 2005).

It should be noted that, while a high Evans’ index is often required for diagnosis, it may be present in patients with other causes of dementia and the Evans’ index does not significantly correlate with clinical improvement (Hebb & Cusimano, 2001). Furthermore, for some patients with minimal ventricular enlargement, such techniques may be insensitive.

MRI is more useful for evaluating NPH patients as it has greater sensitivity for alternative diagnoses and allows evaluation of comorbid conditions such as cerebrovascular disease (Hebb & Cusimano, 2001; Vanneste, 2000). Additionally, MRI allows the identification of CSF flow effects which may be related to clinical outcome (Bradley, Whittemore, Kortman, et al., 1991; Egeler-Peerdeman, Barkhof, Walchenbach, & Valk, 1998).

Other imaging markers which have shown to be predictors of a positive outcome following shunting include a small callosal angle (Virhammar, Laurell, Cesarini, & Larsson, 2014b), wide temporal horns (Virhammar, Laurell, Cesarini, & Larsson, 2014a), and the
features of so-called ‘disproportionately enlarged subarachnoid space hydrocephalus’, i.e. tight high-convexity and medial subarachnoid spaces and enlarged Sylvian fissures (Hashimoto, Ishikawa, Mori, & Kuwana, 2010; Virhammar et al., 2014a).

Figure 1.2: Measurement of Evans’ index on CT scan (from N. C. Keong, Czosnyka, Czosnyka, & Pickard, 2011)

CSF removal

Removal of around 40-50 ml CSF with lumbar puncture (CSF tap test [CSF-TT]) is presumed to mimic shunt placement and has shown to result in clinical improvement in patients with NPH (Wikkelsø, Andersson, Blomstrand, & Lindqvist, 1982). The CSF-TT has variable predictive prognostic accuracy, however both false-positive and false-negative rates are high (Damasceno et al., 1997; Malm et al., 1995).

To reduce false-negatives, continuous external lumbar CSF drainage (ELD) has been used to drain around 100-200 ml CSF daily for around five days (Chen, Huang, Liu, & Chen, 1994; Haan & Thomeer, 1988). ELD has shown to be a good predictor of post-shunt outcome (Marmarou, Bergsneider, Klinge, Relkin, & Black, 2005).
**CSF dynamics**

Continuous intracranial pressure monitoring frequently shows intermittent rises in ICP (B-waves), although the significance of these is unclear as they are also demonstrated in healthy individuals (Mautner-Huppert et al., 1989; Vanneste, 2000). However, frequent occurrence of B-waves (>50% of ICP recording time) has been associated with good outcome following treatment, while infrequent B-waves has shown to predict poor outcome (Pickard et al., 1980; Vanneste, 2000).

Resistance to CSF outflow is measured using lumbar CSF infusion tests in which CSF pressure is monitored during lumbar or ventricular infusion of artificial CSF (Katzman & Hussey, 1970). The capacity to absorb the additional fluid is reduced in patients with NPH, meaning ICP during infusion is increased. A steady state pressure plateau is calculated, which is the level at which absorption balances infusion. From this, \( R_{out} \) can then be calculated (Boon, Tans, Delwel, Egeler-Peerdeman, Hanlo, Wurzer, Avezaat, et al., 1997). \( R_{out} \) values of 18 mmHg/ml per minute or higher are associated with good clinical outcome, however the predictive validity of lower values is limited and negative predictive power is low (Boon, Tans, Delwel, Egeler-Peerdeman, Hanlo, Wurzer, Avezaat, et al., 1997; Czosnyka & Pickard, 2004; Vanneste, 2000). Brean and Eide have found that CSF pressure pulsatility (quantified during infusion) and pulsatile ICP (assessed during over-night monitoring) may be more useful for predicting outcome (Brean & Eide, 2008a; Eide & Brean, 2010).

**Neuropsychological assessment**

While many of the early studies tended to rely on functional grading scales only (such as those presented in Table 1.1) for assessing cognitive function, more recent studies have emphasised the need for detailed neuropsychological assessment of patients with NPH. Neuropsychological assessment allows for more detailed quantification of cognitive symptoms, as well as their progression or response to treatment. Generalised screening measures, such as the Mini-Mental State Examination (MMSE; Cockrell & Folstein, 1988), are often used to assess cognitive decline in patients with NPH. The advantage of such tools are that they are both easy to use and quick to administer. However, for high functioning patients, these tests are insensitive to decline in specific aspects of higher order cognitive functions which may be early symptoms of a neurological problem. Accordingly, it is recommended that a battery of neuropsychological tests be administered in addition to the more generalised screening measures (DeVito et al., 2005; Iddon et al., 1999). Tests of psychomotor speed or executive function may detect subtle
or early cognitive decline (Hebb & Cusimano, 2001; Iddon et al., 1999). Additionally, neuropsychological testing can detect the subcortical profile of dementia which is characteristic of NPH (Vanneste, 2000).

Further, evidence-based guidelines for the clinical diagnosis of idiopathic NPH were developed by Relkin and colleagues (2005) who recommend that iNPH be classified as ‘probable’, ‘possible’, or ‘unlikely’ based on clinical, historical, brain imaging, physical, and physiological criteria.

1.2.6. Treatment

Currently, the only method of treatment for NPH is surgical CSF diversion, with shunt surgery being the most commonly used procedure. Shunt surgery involves the surgical insertion of a tube to redirect excess CSF from the brain to another part of the body where it can be reabsorbed into the blood. Both cerebral and lumbar shunts are used to treat NPH. Cerebral shunts divert excess CSF from a specified ventricle within the brain, whereas lumbar shunts divert from the lumbar subarachnoid space. Common types of shunts used are listed below:

**Cerebral shunts**

- Ventriculoperitoneal (VP) shunt
- Ventriculocisternal shunt
- Ventriculovenous shunt

**Lumbar shunts**

- Lumboperitoneal (LP) shunt
- Lumbar subcutaneous shunt

To date, there have been no randomised controlled trials (RCTs) investigating the efficacy of shunt surgery versus no treatment (Esmonde & Cooke, 2002), and studies assessing the natural progression of NPH are limited. A recent study, however, attempted to investigate the natural
progression of symptoms of iNPH in a set of patients for whom shunt surgery had been delayed due to uncontrollable circumstances (Andrén, Wikkelsø, Tisell, & Hellström, 2013). Thirty-three patients had a median waiting time of 13.2 months for shunt surgery. During this period, the group deteriorated 23% on the total iNPH scale score (see Table 1.1 for a description of the iNPH scale) and showed worsening in gait, balance, and cognitive abilities. The researchers also compared outcome following shunt surgery in this group (iNPH\textsubscript{Delayed}) to that of a second group of patients who had a normal waiting time for surgery (iNPH\textsubscript{Early}; median waiting time = 6 days). The iNPH\textsubscript{Delayed} group had a significantly poorer outcome at post-shunt compared to the iNPH\textsubscript{Early} group, highlighting the importance of early treatment. Despite the lack of RCTs, improvement rates as high as 80-90% have been documented following shunt surgery (Andrén et al., 2013; Eide & Sorteberg, 2010; Klinge et al., 2012). The improvement rates, combined with the evidence for decline in unshunted patients (Andrén et al., 2013; Toma, Stapleton, Papadopoulos, Kitchen, & Watkins, 2011), support the use of shunt surgery as a treatment option for NPH.

Possible complications associated with shunt surgery include subdural haemorrhage due to over-drainage, subdural effusion, or infection (Borgbjerg, Gjerris, Albeck, & Børgeresen, 1995; Hebb & Cusimano, 2001). Shunt revision surgeries may also be required in instances of shunt malfunction.

An alternative treatment to shunt surgery is endoscopic third ventriculostomy (ETV) in which a perforation is made in the floor of the third ventricle using an endoscope. CSF is therefore diverted from the ventricle into the basal cisterns. Although ETV has been shown to be an effective treatment option for obstructive hydrocephalus (Dusick, McArthur, & Bergsneider, 2008; Feng et al., 2004), the reported success rate of ETV for iNPH compared to shunting is variable (Fleck, Baldauf, & Schroeder, 2014). It has been suggested that ETV may be an effective treatment for a subset of patients with iNPH. Specifically, shorter duration of symptoms, prevalence of gait disturbance, slight mental impairment, and younger age have been associated with favourable outcome following ETV (Gangemi, Maiuri, Buonamassa, Colella, & de Divitiis, 2004; Hailong et al., 2008).

1.2.7. Outcome

There is no standard for assessing outcome following treatment for NPH, and methodological differences across studies complicate interpretation of outcome (Klinge, Marmarou,
Bergsneider, Relkin, & Black, 2005). For example, there is no consensus regarding the postoperative assessment period, or which assessment measures should be used. Various scales have been developed for assessing severity of NPH and/or outcome. Such scales typically grade functioning or activities of daily living (e.g. Stein & Langfitt, 1974), or rate the clinical symptoms of gait, incontinence, and dementia (e.g. Eide, 2006; Kiefer, Eymann, & Meier, 2002). Further scales have incorporated neuropsychological tests into the assessment protocol (Boon, Tans, Delwel, Egeler-Peerdeeman, Hanlo, Wurzer, & Hermans, 1997; Hellström, Klinge, Tans, & Wikkelsø, 2012a). Examples of the types of scales used are presented in Table 1.1. Varying rates of improvement following treatment have been documented, often depending on which assessment scale is used (Klinge et al., 2005).
Table 1.1: Examples of assessment scales for grading of severity of NPH and outcome

<table>
<thead>
<tr>
<th>Scale</th>
<th>Assessment criteria</th>
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<tr>
<td>Stein &amp; Langfitt Scale (1974)</td>
<td><strong>Grade 0</strong>&lt;br&gt;No neurological deficit, able to work&lt;br&gt;<strong>Grade 1</strong>&lt;br&gt;Minimal deficit, able to function independently at home&lt;br&gt;<strong>Grade 2</strong>&lt;br&gt;Some supervision required at home&lt;br&gt;<strong>Grade 3</strong>&lt;br&gt;Custodial care required despite considerable independent function&lt;br&gt;<strong>Grade 4</strong>&lt;br&gt;No practical capacity for independent function</td>
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<td>Black Scale (1980)</td>
<td><strong>Excellent</strong>&lt;br&gt;Resumed pre-illness activity without deficit&lt;br&gt;<strong>Good</strong>&lt;br&gt;Resumed pre-illness activity with moderate deficit&lt;br&gt;<strong>Fair</strong>&lt;br&gt;Improved, but no return to previous work&lt;br&gt;<strong>Transient</strong>&lt;br&gt;Temporary major improvement&lt;br&gt;<strong>Poor</strong>&lt;br&gt;No change or worse&lt;br&gt;<strong>Dead</strong>&lt;br&gt;Deceased within 6 weeks of surgery or as a result of surgery</td>
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<td>Kiefer Index (2002)</td>
<td><strong>Mental State</strong>&lt;br&gt;0 = No apparent deficit&lt;br&gt;1 = Forgetful, impaired concentration&lt;br&gt;4 = Apathy, or only partly oriented&lt;br&gt;6 = Totally disoriented&lt;br&gt;<strong>Gait disorders</strong>&lt;br&gt;0 = Not or only in special tests handicapped&lt;br&gt;2 = Wide legged but per se safe gait&lt;br&gt;4 = Troublesome gait, only with crutches possible&lt;br&gt;5 = Only a few steps with the aid of one person possible&lt;br&gt;6 = Unable to walk&lt;br&gt;<strong>Incontinence</strong>&lt;br&gt;0 = None&lt;br&gt;1 = Urge-incontinence&lt;br&gt;3 = Intermittent bladder incontinence&lt;br&gt;4 = Permanent bladder incontinence&lt;br&gt;6 = Bladder and bowel incontinence&lt;br&gt;<strong>Dizziness</strong>&lt;br&gt;0 = None&lt;br&gt;1 = Intermittent spontaneous dizziness&lt;br&gt;2 = Permanent dizziness</td>
</tr>
<tr>
<td>NPH Grading Scale, (Eide, 2006)</td>
<td><strong>Gait disturbance</strong>&lt;br&gt;5 = Normal gait&lt;br&gt;4 = Gait is abnormal, but walking is possible without support. Imbalance when turning with short steps. Widened base and occasional falling&lt;br&gt;3 = A cane is needed. Independent walking is possible but is unstable or the patient falls&lt;br&gt;2 = Support from another person is needed. Ambulation is possible with help&lt;br&gt;1 = Patient is bedridden or not able to ambulate&lt;br&gt;<strong>Urinary incontinence</strong>&lt;br&gt;5 = No subjective or objective incontinence&lt;br&gt;4 = Urinary urgency. Rare incontinence&lt;br&gt;3 = Occasional urinary incontinence</td>
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<tr>
<td></td>
<td>Dementia</td>
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<td>---------------------------------------------------------------------------</td>
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<tr>
<td></td>
<td>2 = Continuous urinary incontinence</td>
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<td></td>
<td>1 = Both urinary and faecal incontinence</td>
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<td></td>
<td>5 = Normal</td>
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<td></td>
<td>4 = Memory problems exist that are reported by patient or family</td>
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<td></td>
<td>3 = Important memory problems with more or less severe behaviour disturbances</td>
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<tr>
<td></td>
<td>2 = Severe dementia</td>
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<td></td>
<td>1 = Vegetative</td>
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<tr>
<th>iNPH Grading Scale</th>
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<tr>
<td>(Kubo et al., 2008)</td>
<td>0 = Normal</td>
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<td></td>
<td>1 = Complaints of amnesia or inattention but no objective memory and attentional impairment</td>
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<td></td>
<td>2 = Existence of amnesia or inattention but no disorientation of time and place</td>
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<td>3 = Existence of disorientation of time and place but conversation is possible</td>
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<td>4 = Disorientation for the situation or meaningful conversation impossible</td>
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<th>Gait disturbance</th>
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<td>0 = Normal</td>
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<td></td>
<td>1 = Complaints of dizziness of drift and dysbasia but no objective gait disturbance</td>
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<td></td>
<td>2 = Unstable but independent gait</td>
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<td></td>
<td>3 = Walking with any support</td>
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<td>4 = Walking not possible</td>
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<td>0 = Normal</td>
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<td></td>
<td>1 = Pollakiuria or urinary urgency</td>
</tr>
<tr>
<td></td>
<td>2 = Occasional urinary incontinence</td>
</tr>
<tr>
<td></td>
<td>3 = Continuous urinary incontinence</td>
</tr>
<tr>
<td></td>
<td>4 = Bladder function is almost or completely deficient</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>iNPH Scale, (Hellström et al., 2012a)</th>
<th>Gait</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The gait domain is evaluated by measurement of the number of steps and seconds needed to walk 10 m at free pace, and using the following ordinal rating of the gait:</td>
</tr>
<tr>
<td></td>
<td>1 = Normal</td>
</tr>
<tr>
<td></td>
<td>2 = Slight disturbance of tandem walk and turning</td>
</tr>
<tr>
<td></td>
<td>3 = Wide-based gait with sway, without foot corrections</td>
</tr>
<tr>
<td></td>
<td>4 = Tendency to fall, with foot corrections</td>
</tr>
<tr>
<td></td>
<td>5 = Walking with cane</td>
</tr>
<tr>
<td></td>
<td>6 = Bi-manual support needed</td>
</tr>
<tr>
<td></td>
<td>7 = Aided</td>
</tr>
<tr>
<td></td>
<td>8 = Wheelchair bound</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neuro-psychology</th>
<th>The neuropsychology domain includes four variables derived from three neuropsychological tests:</th>
</tr>
</thead>
</table>
| Balance | The Grooved pegboard  
The Rey Auditory Verbal Learning Test  
The Swedish Stroop Test |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The balance domain is represented by an ordinal rating scale based on observations of the patients’ efforts to stand up straight on one or both legs:</td>
</tr>
</tbody>
</table>
|         | 1 = Able to stand independently for more than 30 s on either lower extremity alone  
|         | 2 = Able to stand independently for <30 s on either lower extremity alone  
|         | 3 = Able to stand independently with the feet together (at the heels) for more than 30 s  
|         | 4 = Able to stand independently with the feet together for <30 s  
|         | 5 = Able to stand independently with the feet apart (one foot length) for more than 30 s  
|         | 6 = Able to stand independently with the feet apart for <30 s  
|         | 7 = Unable to stand without assistance |

| Continence | Normal  
|------------|----------------------------------|
|            | Urgency without incontinence  
|            | Infrequent incontinence without napkin  
|            | Frequent incontinence with napkin  
|            | Bladder incontinence  
|            | Bladder and bowel incontinence |

The iNPH scale features instructions for converting each rating scale score into an overall domain score.

In a review of diagnosis and outcome in idiopathic NPH, Hebb and Cusimano (2001) reported an overall improvement rate of 59% (range, 24-100%), and prolonged or significant improvement in 29% (range, 10-100%) of patients. However, assessment measures and criteria for improvement varied across studies. They also found high rates of complications. They reported a complication rate of 38%, with 22% of patients requiring additional surgery and 6% of patients experiencing permanent neurological deficit or death. Regarding the symptom triad in NPH, gait has been shown to be the most likely symptom to show improvement (Klinge et al., 2005; Malm, Kristensen, Stegmayr, Fagerlund, & Koskinen, 2000; Malm et al., 1995; Petersen, Mokri, & Laws Jr., 1985; Weiner, Constantini, Cohen, & Wisoff, 1995), while dementia has been reported to be the least likely symptom to show improvement (Duinkerke, Williams, Rigamonti, & Hillis, 2004; Petersen et al., 1985; Raftopoulos et al., 1994).
Guidelines for the assessment of outcome following shunt surgery have been developed (Klinge et al., 2005). Klinge et al. recommend that assessment of outcome be conducted at three, six, and 12 months following shunt surgery in order to differentiate short- and long-term response to treatment. Additionally, they highlight the importance of using objective scales to grade improvement of symptoms, in addition to functional scales, with psychometric evaluation noted to offer utility for assessment of the cognitive domain.

An important goal of NPH research is the identification of factors which predict good outcome following treatment. Vanneste (2000) outlined factors which have been associated with good and bad surgical outcome (Table 1.2).

Table 1.2: Factors predictive of good and bad surgical outcome (from Vanneste, 2000)

<table>
<thead>
<tr>
<th>Factors predictive of good surgical outcome</th>
<th>Factors predictive of bad surgical results</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Gait disturbance preceding mental impairment</td>
<td></td>
</tr>
<tr>
<td>• A short history of mental deterioration</td>
<td></td>
</tr>
<tr>
<td>• Only slight or moderate mental impairment</td>
<td></td>
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<tr>
<td>• A known cause of communicating or non-communicating hydrocephalus</td>
<td></td>
</tr>
<tr>
<td>• A pattern of hydrodynamic hydrocephalus and absence of substantial white matter lesions on MRI</td>
<td></td>
</tr>
<tr>
<td>• Substantial clinical improvement after one or several lumbar CSF taps or after ELD</td>
<td></td>
</tr>
<tr>
<td>• Occurrence of B-waves during 50% or more of the recording time during continuous ICP monitoring</td>
<td></td>
</tr>
<tr>
<td>• Resistance to CSF outflow of 18 mmHg/ml per minute or higher during continuous lumbar CSF infusion test</td>
<td></td>
</tr>
<tr>
<td>• Predominance of severe dementia</td>
<td></td>
</tr>
<tr>
<td>• Dementia as the first neurological sign</td>
<td></td>
</tr>
<tr>
<td>• MRI showing marked cerebral atrophy, widespread white matter involvement, or both</td>
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</tbody>
</table>
1.3. The neuropsychology of normal pressure hydrocephalus

1.3.1. Background

Clinical neuropsychology is the applied science of brain-behaviour relationships, which includes the study of the effects of abnormal brain function on cognition and behaviour. Neuropsychological impairment is a common feature of neurological conditions, reducing patients’ quality of life and independence. Despite increasing interest in the area, there remains a lack of neuropsychological research in the field of NPH. Cognition in NPH is often assessed using grading scales (such as those presented in section 1.2.7.) and therefore, rely on clinician-rated evaluation of symptoms. Screening measures, such as the MMSE (Cockrell & Folstein, 1988), are also frequently administered to give a general indication of cognitive functioning or degree of dementia. The MMSE is a brief examination assessing orientation to time and space, attention, recall, language, and drawing. However, the MMSE is prone to ceiling effects, and it is insensitive to subtle neuropsychological changes in areas such as memory and executive function (Iddon et al., 1999). Recent investigations have emphasised the need for detailed neuropsychological evaluation when assessing patients with NPH (e.g. Behrens et al., 2014; de la Calzada et al., 2010; DeVito et al., 2005; Duinkerke et al., 2004; Gleichgerrcht et al., 2009; Hellström et al., 2008; Hellström, Klinge, Tans, & Wikkelso, 2012b; Katzen et al., 2011; Solana, Sahuquillo, Junqué, Quintana, & Poca, 2012). In such studies, general cognitive assessment measures are supplemented with a battery of neuropsychological tests typically covering memory, executive function, attention, language, visuospatial abilities, psychomotor speed, as well as behavioural measures.

Neuropsychological investigations have helped to establish a cognitive profile for NPH which could aid diagnosis, clinical management, rehabilitation, and interpretation of outcome following treatment (DeVito et al., 2005), as well as providing an insight into the effect of shunt treatment on neuropsychological performance. Furthermore, neuropsychological testing may be more sensitive to early cognitive decline in patients with NPH than global screening measures (Iddon et al., 1999; Relkin & Katzen, 2014). However, currently there is no consensus about which neuropsychological tests are most appropriate for use in NPH research.

In this section, findings from neuropsychological investigations of NPH are reviewed. First, the pattern of neuropsychological impairment associated with NPH is presented, followed by a review of neuropsychological outcome following treatment.
1.3.2. Neuropsychological impairment in NPH

Studies investigating the neuropsychology of NPH have shown that patients typically present with impairments in a range of cognitive domains including in executive function, memory, psychomotor speed, and visuospatial abilities (DeVito et al., 2005; Duinkerke et al., 2004; Gleichgerrcht et al., 2009; Iddon et al., 1999; Katzen et al., 2011; Mataró et al., 2003; Saito et al., 2011; Solana, Sahuquillo, Junqué, Quintana, & Poca, 2012a). NPH has been described as a ‘subcortical dementia’ (DeVito et al., 2005; Solana et al., 2012a; Vanneste & van Acker, 1990), meaning the pattern of cognitive decline is consistent with dysfunction of the subcortical structures. However, frontal functions (such as executive functions) may also be compromised as a result of damage to subcortical structures and/or fronto-subcortical connectivity and so NPH has been further classified as a ‘fronto-subcortical dementia’ (DeVito et al., 2005; Hellström et al., 2008; Iddon et al., 1999; Thomas et al., 2005).

Impairment in tasks of executive function is a common feature of NPH (Iddon et al., 1999; Solana et al., 2012a). Executive functions are higher order cognitive functions, such as decision making, planning, and problem-solving, which are associated with frontal lobe function. Patients with NPH have shown more severe executive dysfunction than patients with AD (Ogino et al., 2006; Saito et al., 2011). Ogino and colleagues (2006) postulated that the cognitive impairment in NPH may be due to damage to frontal regions, or to secondary frontal dysfunction resulting from reduced white matter cerebral blood flow in subcortical regions of the brain which connect with the frontal cortex.

The memory deficit in NPH primarily presents as impaired immediate and delayed recall but intact or only mildly impaired recognition (Duinkerke et al., 2004; Hellström et al., 2008; Vanneste, 2000; Walchenbach, Geiger, Thomeer, & Vanneste, 2002). Again, it has been suggested that the pattern of memory impairment is suggestive of frontal pathology (Iddon et al., 1999). Iddon and colleagues (1999) examined cognitive performance in a group of high functioning NPH patients (preshunt MMSE score = 24 or above; n = 6) using tests from the Cambridge neuropsychological test automated battery (CANTAB; Robbins et al., 1994). Patients were impaired on the CANTAB spatial recognition task, a measure of spatial recognition memory sensitive to frontal lobe damage, compared to healthy controls; however, they were unimpaired on the pattern recognition task, a measure of visual recognition memory which has shown to be sensitive to temporal lobe damage (Iddon et al., 1999). These findings give further support to the suggestion that frontal lobe pathology and/or fronto-subcortical
changes underlie the cognitive decline in NPH (DeVito et al., 2005; Iddon et al., 1999; Ogino et al., 2006; Saito et al., 2011).

Pathological changes of the corpus callosum have also been reported in NPH and linked to neuropsychological performance (Mataró et al., 2007). Stretching, uniform and focal thinning, and upward elevation of the corpus callosum have been reported (Hofmann et al., 1995; Jinkins, 1991; Mataró et al., 2007; Röricht, Meyer, Woiciechowsky, & Lehmann, 1998). Mataró et al. (2007) found that smaller corpus callosum size was related to poorer neuropsychological performance. Specifically, the genu of the corpus callosum was related to psychomotor speed, while the rostral body and the splenium were associated with performance in tests of frontal function. The researchers concluded that atrophy in areas of the corpus callosum which contain projections from frontal cortical areas were most related to neuropsychological impairment.

Patients with NPH have shown greater severity of impairment in visuospatial and visuoconstructional abilities than controls and patients with AD (Saito et al., 2011). Relkin and Katzen (2014) note impairment in performing clock drawing which, they suggest, indicates both visuospatial disturbances (related to dysfunction of posterior brain regions) and frontal dysfunction (i.e. disrupted planning, and self-monitoring). Indeed, reduced rCBF has been observed in the parietal regions in patients with NPH and may explain the observed impairments in visuospatial abilities (Relkin & Katzen, 2014; Saito et al., 2011).

Impaired motor skills is one of the most consistent findings in patients with NPH. Patients display impairments in tests of psychomotor speed, manual dexterity, and manual coordination (Hellström et al., 2012b; Saito et al., 2011; Solana et al., 2012b). Dysfunction of the basal ganglia, or white matter projections to supplementary motor and frontal areas likely underlies impaired motor skills in NPH (Relkin & Katzen, 2014).

1.3.3. Neuropsychological outcome following CSF diversion

Reports of cognitive improvement following treatment for NPH led to its classification as a reversible dementia (DeVito et al., 2005; Thomsen, Børgeesen, Bruhn, & Gjerris, 1986). Cognitive improvement has been observed following CSF diversion with both lumbar puncture and shunt surgery (Duinkerke et al., 2004; Foss, Eide, & Finset, 2007; Gleichgerrcht et al., 2009; Hellström et al., 2008, 2012b; Iddon et al., 1999; Raftopoulos et al., 1994; Solana et al., 2012a; Stambrook et al., 1988; Thomas et al., 2005; Wikkelsø et al., 1982). However,
classification of NPH as a reversible form of dementia remains controversial (Duinkerke et al., 2004; Raftopoulos et al., 1994; Vanneste, 1994). While CSF drainage is generally considered to relieve problems with gait and incontinence, cognitive impairment is reported to be the least likely symptom to improve (Duinkerke et al., 2004; Petersen et al., 1985; Raftopoulos et al., 1994). Reports of post-operative cognitive improvement vary, with as few as 0 to as many as 80% of patients demonstrating some form of significant cognitive improvement (Duinkerke et al., 2004; Hellström et al., 2008; Poca et al., 2005; Raftopoulos et al., 1994; Thomas et al., 2005). However, as there are no standardised guidelines for assessing cognitive outcome in NPH, cognitive assessment measures vary between centres (Toma et al., 2013) and many studies have used general screening measures which may not be sensitive to subtle changes in cognition. Studies that have focused on neuropsychological test performance generally show a beneficial effect of shunt surgery on cognitive function, however the pattern of neuropsychological change varies widely between studies. The findings to date are reviewed below.

A number of studies have found the greatest improvement following shunt surgery to be on tests of memory. Duinkerke et al. (2004) investigated cognitive change following shunt surgery in 10 patients with iNPH, selected on the basis of positive response in any symptom to ELD. Post-operative assessments took place between six and 12 months post-shunt (mean = 8.2 months). They defined improvement as a score increase of at least 1 standard deviation compared with the baseline score, or improvement by at least 20 percentile points in timed motor tests. The greatest improvement was observed in tests of memory with 80% of patients showing significant improvement in verbal memory and retention, and 50% in delayed verbal recall. About 50% of patients improved on tests of psychomotor speed and 50-60% improved in tests of executive function. Only 13% of patients improved in the Controlled Oral Word Association Test, a test of word fluency.

Thomas et al. (2005) investigated cognitive change between three and nine months post shunt surgery (mean = 3.9 months) in 42 patients with iNPH. They found significant improvement in tests of verbal memory, delayed verbal recall, and psychomotor speed. However, there was no significant improvement on the Stroop Colour-Word test, a measure of executive function, or on the Rey-Osterrieth Complex Figure test, a measure of visuoconstructional skills. They concluded that executive function may not improve due to irreversible fronto-striatal dysfunction. Similarly, Solana et al. (2012) observed improvement six months following shunt surgery in tests of psychomotor speed and verbal memory.
However, the proportions of patients who significantly improved in tests of executive function was low.

Iddon et al. (1999) analysed cognitive outcome in a group of 11 patients with iNPH, split according to pre-operative MMSE score. Group 1 consisted of five patients who scored in the dementing range of the MMSE (a score below 24) at baseline. Group 2 were six patients who scored in the non-dementing range of the MMSE. Follow-up assessments were conducted at six months post-shunt. Group 1 showed significant improvement in the MMSE, with all patients scoring within the normal range at post-shunt. There was no significant difference in MMSE score for Group 2 at post-shunt. Group 2, however, completed a number of additional tests of executive function. Results showed no significant improvement in any of the tests of executive function. The researchers concluded that frontal executive impairment in NPH is not reversible.

While the above studies find greatest evidence for improvement in tests of memory and psychomotor speed with little evidence for improvement in executive functions, other studies have observed a different pattern of neuropsychological change. Hellström et al. (2008) investigated cognitive outcome in 47 iNPH patients 3 months after shunt surgery. The battery of tests used covered reaction time, psychomotor speed, verbal learning and memory, executive function, and working memory. Statistically significant improvement was observed for all tests from baseline to follow-up except in two tests of short-term or working memory and a simple reaction time task. Greatest improvement was observed in the Stroop test, a measure of executive function and attention (82-91% of patients), and in the Grooved Pegboard test, measuring dexterity (86-90% of patients). In a later study, Hellström et al. (2012b) again demonstrated significant improvement in the Grooved Pegboard test and the Stroop test as well as in the Rey Auditory Verbal Learning Test (RAVLT), which measures verbal learning and memory. They concluded that these tests (particularly the Grooved Pegboard and the Stroop tests) are highly sensitive to treatment effects in NPH, and therefore the researchers recommended these tests for evaluation of cognitive change following shunt surgery.

Saito and colleagues (2011) investigated cognitive outcome one year after shunt surgery in 32 patients with iNPH. They assessed memory, attention, language, executive function, psychomotor speed, and visuoperceptual and visuospatial skills. Significant group improvement from baseline to follow-up was found for a measure of psychomotor speed and a measure of executive function (the Frontal Assessment Battery, a bedside screening measure to
assess frontal lobe functions; Dubois, Slachevsky, Litvan, & Pillon, 2000). However, no other tests showed significant improvement. Gleichgerrcht et al. (2009) specifically sought to investigate changes in executive function following shunt surgery. They assessed language, attention, and executive function in a group of 10 patients with NPH who showed a positive response to ELD. Follow-up assessments were conducted between six and eight months following shunt surgery. There were significant group improvements in three out of the four tests of executive function. One of the three measures of language function also showed significant improvement. Performance on two tests of attention was not significantly improved.

Lastly, Savolainen and colleagues (Savolainen, Hurskainen, Paljärvi, Alafuzoff, & Vapalahti, 2002) investigated cognitive outcome in patients with iNPH between three and 12 months post-shunt. Twenty patients completed follow-up assessments after shunt surgery. The neuropsychological test battery covered learning and memory, visuoconstructional skills, verbal ability, attention and executive function. There were no significant differences in performance in any of the tests at outcome.

Interpretation of cognitive outcome in NPH is complicated by methodological differences across studies to date. There is a lack of consensus for defining improvement (Hellström et al., 2008; Solana et al., 2012b), patient selection criteria differ across the studies, and varying outcome intervals were used which can affect the results (Solana et al., 2012b). Furthermore, a number of the studies had small sample sizes. Overall, the results to date appear to support the notion that cognitive function is improved following shunt surgery. However, a clear pattern of neuropsychological change is yet to be elucidated. Determining a pattern of improvement may be useful for differential diagnosis. It may also provide insight into the neural mechanisms underlying the symptoms of NPH, and whether or not impairments in functioning are reversible.

Chapter 2 investigates the pattern of neuropsychological outcome in patients with NPH by using meta-analytic techniques, thus overcoming the sample size issue, with the aim being to establish a clearer profile of post-shunt neuropsychological change. Chapter 2 also investigates whether moderator variables (age, sex, or time between shunt and reassessment) predict cognitive outcome. Since it is unclear whether ceiling effects might underlie the absence of significant improvement in some neuropsychological tests, Chapter 2 also attempts to investigate this issue.
1.4. Motivation and apathy in normal pressure hydrocephalus

1.4.1. Definitions and background

Neuropsychiatric (behavioural or affective) symptoms, such as apathy or depression, are common in patients with dementia. These symptoms can lead to impairment in activities of daily living, cognitive decline, poorer quality of life, and greater caregiver burden (Lyketsos et al., 2002). Apathy in particular is associated with cognitive and functional impairment in patients with dementia (Boyle et al., 2003; Landes, Sperry, & Strauss, 2005; Starkstein et al., 2006b), including in patients with iNPH (Kito et al., 2009), and in cognitively normal older individuals (Onyike et al., 2007); as well as increased caregiver burden (Kaufer et al., 1998). Therefore, apathy is an important symptom for investigation in NPH.

Marin (1990) defined apathy as an absence or lack of motivation that is not attributable to cognitive impairment, emotional distress, or diminished level of consciousness. Apathy can be further defined as a reduction in the behavioural (lack of effort, dependency on others to structure activity), cognitive (lack of interest, lack of concern about one’s personal problems), and emotional (attenuated emotional responses to events) aspects of goal-directed behaviour (Marin, Biedrzycki, & Firinciogullari, 1991; Starkstein, Petracca, Chemerinski, & Kremer, 2001).

This section begins with a discussion on the prevalence of apathetic symptoms in NPH. Possible neural bases for apathy in NPH are then presented followed by an overview of the most commonly used apathy assessment measures.

1.4.2. The prevalence of apathy in NPH

Patients with NPH are frequently reported to display apathetic symptoms. Early investigations of NPH cited inertia, lack of spontaneity or initiative, and “apathy to the point of akinetic mutism” as the most notable behavioural symptoms in patients (Adams et al., 1965; Caltagirone et al., 1982; De Mol, 1986). However, despite this, few studies have objectively measured apathetic symptoms in patients with NPH and so the prevalence and severity of this symptom is not well established. Only two studies have provided information about the prevalence of apathy in NPH (Kanemoto et al., 2016; Kito et al., 2009). Kanemoto et al. and Kito et al. investigated neuropsychiatric symptoms in patients with iNPH using the Neuropsychiatric Inventory (NPI; see section 1.4.4 for a description). Apathy was found to be the most frequent
neuropsychiatric symptom in both studies (present in 70% of 64 patients in the study by Kito et al. and present in 86% of 22 patients in the study by Kanemoto et al.). Kito et al. further provided information about the severity of neuropsychiatric symptoms in their patients. Degree of apathy was found not to be severe despite the high prevalence.

Symptoms of depression are more commonly assessed in patients with NPH. Apathy may be misdiagnosed as depression due overlapping symptoms (such as diminished interest, psychomotor slowing, fatigue/hypersomnia, and lack of insight), however, research suggests that apathy is distinct from depression (Landes, Sperry, Strauss, & Geldmacher, 2001). Symptoms which distinguish apathy from depression include blunted emotional response, indifference, low social engagement, poor persistence and diminished initiation, while symptoms of dysphoria, suicidal ideation, self-criticism, guilt, pessimism, and hopelessness are indicative of depression (Landes et al., 2001). It is important to distinguish apathy from depression as the two syndromes respond to different treatments. For example, apathy has been shown to respond to administration of the psychostimulant drug methylphenidate. (Herrmann et al., 2008; Keenan, Mavaddat, Iddon, Pickard, & Sahakian, 2005; Padala et al., 2010; Rosenberg et al., 2013).

Israelsson, Allard, Eklund, and Malm (2016) investigated the prevalence of depression in a group of 165 iNPH patients. Depressive symptoms were present in 56% of patients pre-operatively and 46% of patients following shunt treatment. However, apathy was not assessed in this study. In contrast, Kito et al. (2009) and Kanemoto et al. (2016) reported much lower prevalence rates for depression (14% and 36%, respectively). Therefore, apathy could be misattributed to depression when assessing depression alone in patients with NPH. It is important for future studies to assess both apathetic and depressive symptoms, separately, in patients with NPH in order to delineate the two.

Chapter 3 investigates the prevalence of apathy and depression in patients with NPH at pre- and post-shunt.

1.4.3. Neural correlates of apathy in NPH

Due to lack of research, the neural underpinnings of apathy in NPH have not been elucidated. However, it has been suggested that frontal or subcortical pathology may underlie this symptom.
Kito and colleagues (2009) found evidence for an association between apathy and cognitive impairment, measured using the iNPH Grading Scale (Kubo et al., 2008; see Table 1.1 for a description) in patients with iNPH. The researchers suggested that apathy in NPH may be caused by damage to subcortical areas which project to the frontal lobes. More recently, Kanemoto and colleagues (2016) assessed change in neuropsychiatric symptoms three months following LP shunt surgery. A reduction in apathy post-shunt was associated with improved performance in the Frontal Assessment Battery, a measure of frontal lobe functioning, thus providing support to the notion that frontal lobe pathology may underlie apathy in NPH.

Further evidence for fronto-subcortical pathology underlying apathy in NPH has come from imaging studies (DeVito, Salmond, Owler, Sahakian, & Pickard, 2007; Kanemoto et al., 2015). DeVito et al. (2007) observed reduced caudate volumes in 11 patients with iNPH compared to healthy controls. Although volumes were not correlated with clinical measures, they hypothesised that the reduced caudate volumes may be important for the clinical symptoms of cognitive impairment and apathy. Recently, however, evidence has been found for an association between improvement in apathy following shunt surgery with improved rCBF in the anterior cingulate cortices and the right caudate nucleus (Kanemoto et al., 2015). Kanemoto et al. concluded that damage to the caudate could lead to frontal dysfunction and subsequent apathetic symptoms.

The caudate nucleus forms part of the striatum, together with the putamen and nucleus accumbens. The striatum in turn is one component of the basal ganglia, a collection of structures which play important roles in movement, cognition, learning, and motivation or goal-directed behaviour (Belin, Jonkman, Dickinson, Robbins, & Everitt, 2009; Middleton & Strick, 2000; Redgrave et al., 2010; Robbins & Everitt, 1996; Schultz, 1999). The striatum is linked to the frontal cortex via parallel frontal-subcortical circuits, lesions to which can cause executive dysfunction, personality changes, and impaired motivation or apathy (Mega & Cohenour, 1997; Tekin & Cummings, 2002). Further, focal lesions of the basal ganglia can cause apathy (Levy & Czernecki, 2006; Tekin & Cummings, 2002), including lesions located in the caudate nucleus (Bhatia & Marsden, 1994; Caplan et al., 1990; Mendez, Adams, & Lewandowski, 1989; Trillet, Croisile, Tourniaire, & Schott, 1990; Wang, 1991).

Overall, the findings from the above studies combined with evidence for reduced rCBF in periventricular and frontal regions in NPH (Momjian et al., 2004; Owler et al., 2004; Owler & Pickard, 2001; Ziegelitz et al., 2014, 2015b) suggest that fronto-subcortical changes in NPH
may give rise to apathy. Therefore, apathy and cognitive dysfunction in NPH may have common pathophysiological underpinnings.

Chapters 3 and 4 investigate neural correlates of apathy (and cognitive impairment) in patients with NPH. Chapter 3 investigates whether degree of ventricular enlargement is related to apathy and depression. Chapter 4 extends the findings from Chapter 3 by conducting a structural MRI study to investigate whether patients’ symptoms are related to volumetric changes of the whole brain or of the subcortical structures.

1.4.4. Apathy scales

Apathy is typically measured using self- (patient), informant-, or clinician-rated scales. The most commonly used apathy scales are The Apathy Evaluation Scale, The Lille Apathy Rating Scale, and The Neuropsychiatric Inventory. Below is a brief description of each:

*The Apathy Evaluation Scale (AES; Marin, Biedrzycki, & Firinciogullari, 1991)*

Clinician-, informant-, and self-rated versions of the AES are available (AES-C, AES-I, and AES-S, respectively). The AES is an 18-item scale. There are three types of items, tapping behavioural, cognitive, or emotional aspects of goal-directed behaviour. Responses to items are recorded using a 4-point Likert-type scale with the categories: Not at All Characteristic; Slightly Characteristic; Somewhat Characteristic; and Very Characteristic. Higher scores indicate more severe levels of apathy.

*The Lille Apathy Rating Scale (LARS; Sockeel et al., 2006)*

The Lille Apathy Rating Scale consists of 33 items, covering nine domains of apathy: reduced everyday productivity, lack of interest, lack of initiative, lack of novelty seeking/ motivation, emotional blunting, lack of concern, poor social life, and extinction of self-awareness. The LARS utilises a structured interview format between the clinician and the patient. There is also a caregiver-based version (Dujardin, Sockeel, Delliaux, Destée, & Defebvre, 2008).
The Neuropsychiatric Inventory (NPI; Cummings et al., 1994)

The Neuropsychiatric Inventory is an informant-based questionnaire which assesses a range of neuropsychiatric symptoms. The NPI assesses ten behavioural symptoms: delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, and aberrant motor behaviour. The questionnaire contains screening questions for each behaviour. For example, the screening questions for assessing the presence of apathy are as follows: *Has the patient lost interest in the world around him/her? Has he/she lost interest in doing things or a lack of motivation for starting new activities? Is he/she more difficult to engage in conversation or in doing chores? Is the patient apathetic or indifferent?* If, based on the response to the screening questions, a behaviour is indicated to be present, a number of additional questions are asked followed by determination of the frequency and severity of that behaviour. For each behavioural domain there are four scores: frequency, severity, total (frequency x severity), and caregiver distress. Further, a total NPI score can be calculated by combining the scores for the individual domains.

In addition, a number of apathy scales have been developed by modifying the above scales. The State Apathy Evaluation scale conceived by researchers at the University of Cambridge (Blackwell, Paterson, Barker, Robbins, & Sahakian, 2008) is a slightly modified version of the Apathy Evaluation Scale. It contains the same 18-item scale used in the AES but with slightly altered wording which allows the assessment of *state* rather than *trait* apathy (see Appendix A). It is scored in the same way as the AES. Starkstein et al. (Starkstein et al., 1992) developed The Apathy Scale, also based on the AES. Rather than using a self-rated format as in the AES, The Apathy Scale features a number of questions which should be read to the patient by the examiner and patients are provided with four possible answers as in the AES. The Apathy Inventory (IA; Robert et al., 2002) assesses three domains of apathy: emotional blunting, lack of initiative, and lack of interest. The IA (including administration and scoring) is based on the Neuropsychiatric Inventory and includes both patient- and caregiver-based versions.

In the studies contained in this thesis, apathy was measured using the Cambridge State Apathy Evaluation scale (Blackwell et al., 2008) in order to more accurately measure state-related changes in apathy between pre- and post-shunt assessment visits. The abbreviations AES, AES-C, AES-I, and AES-S are used in relation to the State Apathy Evaluation scale in the same way as for the Apathy Evaluation Scale, as described in Section 1.4.4.
Chapter 5 develops the rationale for developing an objective measure of apathy since apathy is currently measured using rating scales which are inherently subjective. Although every measure is taken to ensure the information obtained from self-rated scales is as accurate as possible at the CSF disorders clinic at Addenbrooke’s Hospital, an objective measure would clearly be hugely beneficial, particularly for use with patients with cognitive decline. In Chapter 5, the feasibility of a novel reward learning task as an objective measure of motivation or apathy is evaluated.

1.5. Aims of the thesis

This thesis aimed to expand on the neuropsychological and neuropsychiatric research in NPH. Chapter 2 presents results from a meta-analysis of neuropsychological outcome following shunt surgery. The objective of this chapter was to combine the results from investigations of neuropsychological outcome in patients with NPH in order to try to determine which aspects of neuropsychological functioning improve following shunt surgery. Additionally, this study investigated whether moderator variables (age, sex, and time between shunt and reassessment) affected outcome on the MMSE. Chapter 3 investigated the significance of the symptom of apathy in NPH. Specifically, Chapter 3 investigated the prevalence of apathy in patients with NPH, and whether apathy in NPH is related to (i) ventricular enlargement; (ii) cognitive function; and (ii) cognitive outcome. Chapter 4 used structural imaging techniques, including automated measurement of total brain and subcortical segmentation; as well as manual tracing to investigate structural correlates of cognitive dysfunction and apathy in NPH. Chapter 5 presents results from a feasibility study of a novel reward learning task to determine whether it could be used as an objective measure of motivation and apathy for use in patients with dementia (including patients with NPH). Chapter 6, the General Discussion, summarises the findings of the thesis within the context of the wider literature.
Chapter 2

The effect of shunt surgery on neuropsychological performance in normal pressure hydrocephalus: a systematic review and meta-analysis

2.1. Introduction

The classic triad of symptoms in normal pressure hydrocephalus (NPH) are gait disturbance, urinary incontinence, and progressive dementia/cognitive decline (Hakim & Adams, 1965). Dementia-related symptoms are characterised by deficits in memory, visuospatial abilities, psychomotor speed and executive function (DeVito et al., 2005; Duinkerke et al., 2004; Gleichgerrcht et al., 2009; Iddon et al., 1999; Katzen et al., 2011; Mataró et al., 2003; Saito et al., 2011; Solana et al., 2012a). The effect of shunt treatment on cognitive performance in patients with NPH is controversial. While cerebrospinal fluid (CSF) drainage is generally considered to relieve problems with gait and incontinence, cognitive impairment is reported to be the least likely symptom to improve (Duinkerke et al., 2004). Rates of cognitive improvement range from 0 to 80% of patients in a given series (Duinkerke et al., 2004; Hellström et al., 2008; Poca et al., 2005; Raftopoulos et al., 1994; Thomas et al., 2005). However, methodological limitations have been identified which could explain the variability observed between studies. These include unclear patient selection criteria, inconsistent follow-up intervals and use of subjective measures of improvement (Klinge et al., 2005). Additionally, due to the lack of standardised clinical guidelines for assessing cognitive function in this patient group, assessment methods often vary between centres with functional grading scales, clinical rating scales, and neuropsychological testing being employed (Klinge et al., 2005). Studies that have focused on neuropsychological test performance generally show a beneficial effect of shunt surgery on cognitive function. However, again, the pattern of post-operative neuropsychological improvement varies widely between studies (e.g. Duinkerke et al., 2004; Gleichgerrcht et al., 2009; Hellström et al., 2008; Solana et al., 2012).

Investigations into the neuropsychology of NPH are plagued by the same limitations identified above, but further, many such studies have small sample sizes. This is the case for a number of reasons: NPH is a rare disorder (see section 1.2.3) and likely underdiagnosed due to the difficulty of diagnosis and the fact that the symptoms develop insidiously; most of the
patients with NPH are elderly and may have contraindications for shunt surgery; and in many cases, a high proportion of patients are lost to follow-up.

Understanding the neuropsychology of NPH may be useful for differential diagnosis as well as interpretation of outcome following treatment (Solana et al., 2012b). The present study combined data from the most frequently used neuropsychological tests in an attempt to determine the effect of shunt surgery on neuropsychological performance in patients with NPH. Studies using neuropsychological tests to assess cognition before and after shunt surgery were included. Meta-analyses were conducted on the pre- to post-operative difference scores for each test. In case there was a lack of improvement in any of the cognitive domains which might have been due to a ceiling effect (i.e. patients were not significantly impaired in the test at baseline and so a significant improvement would not be expected to occur), meta-analyses were also conducted on the average pre-operative score for each test. Finally, exploratory analyses investigated the effects of moderator variables (age, sex, and time between shunt and reassessment) on cognitive outcome. This could be useful for predicting outcome following treatment.

2.2. Methods

2.2.1. Search strategy

A systematic search of the electronic databases PubMed and Web of Science was conducted in October 2015 using the key words: ‘NPH’, ‘normal pressure hydrocephalus’, ‘cognition’, ‘shunt outcome’, ‘neuropsychological outcome’ and ‘neuropsychological assessment’ (separately and in combination) for studies published before October 2015. Due to the limited pool of papers recovered, Google Scholar was included in the search strategy. Reference lists of relevant studies were searched manually. The present review did not have a registered protocol but followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009).
2.2.2. Study selection

Selection of studies

Titles and abstracts of articles were scanned independently by two researchers (Katie Peterson and Clare Killikelly) to identify articles to retrieve in full. Disagreement was dealt with by discussion including a third person (George Savulich).

Inclusion criteria

Inclusion criteria were: (1) prospective investigations of cognitive outcome following shunt surgery; (2) patients were adults with a diagnosis of NPH; (3) within-subjects design; and (4) report of pre- and post-operative neuropsychological test scores.

Exclusion criteria

Exclusion criteria were: (1) case studies; (2) studies which did not use neuropsychological tests; (3) used neuropsychological tests which were not analysed based on insufficient data; (4) reported composite scores. One study (Poca et al., 2005) was excluded due to patient overlap with Poca et al. (2004). Three other papers were excluded due to likely patient overlap with other papers that involve larger patient numbers and were included in the review and the analyses that follow. These are detailed below:

- de la Calzada et al. (2010) due to likely overlap with Poca et al. (2004)
- Poca et al. (2001) due to likely overlap with Poca et al. (2004)
- Wada et al. (2013) due to likely overlap with Yamamoto et al. (2013)

2.2.3. Primary outcome measures

Meta-analyses were conducted on pre-operative and “difference” scores for seven neuropsychological tests: the Mini-Mental State Examination (MMSE); the Rey Auditory Verbal Learning Test (RAVLT) total verbal recall and delayed verbal recall subtests; backwards digit span; phonemic verbal fluency; trail making test A (TMT-A); and trail making test B (TMT-B). Section 2.2.4 contains a description of each test. These tests were selected as each had at least five studies providing supporting data. Follow-up intervals ranged from three to 12 months post-shunt (Table 2.1). One study reported outcome data from more than one post-
operative assessment (Hellström et al., 2012b). In this case, data from the earliest follow-up assessment (3 months) were included.

2.2.4. Neuropsychological tests

The Mini-Mental State Examination (MMSE; Cockrell & Folstein, 1988)

The MMSE is a widely used bedside measure for mental status evaluation. It is useful in detecting dementia and for assessing severity of dementia. The MMSE includes tests of memory, attention, personal orientation, reading, writing, and visuospatial ability. The maximum score is 30, and a score below the cut off of 24 is considered to indicate the presence of dementia.

The Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996)

The RAVLT assesses verbal learning and memory. A list of 15 unrelated words are read aloud to the participant by the examiner. The participant is asked to recall as many of the words as they can. This is repeated five times. Thus the total verbal recall score is the total number of words correctly recalled over five trials (maximum score = 75). After a delay of 30 minutes, participants are again asked to recall as many of the words as possible from the list. The number of words recalled is the delayed verbal recall score (maximum score = 15).

Backwards digit span (Wechsler, 1945)

The backwards digit span test assesses working memory. In this task, participants must repeat strings of digits backwards. The score is the number of digits in the longest completed series.

Phonemic verbal fluency (Benton & Hamsher, 1989)

The phonemic verbal fluency task assesses executive function. Patients are asked to generate as many words as they can beginning with the letters ‘F’, ‘A’, then ‘S’ (or culturally adapted variations of these) with a time limit of 60 seconds per letter. The score represents the total number of words generated for the three letters combined.
**Trail making test A (TMT-A; Reitan, 1958)**

The TMT-A assesses visual search scanning and psychomotor speed. The task involves connecting an array of 25 encircled numbers displayed on a sheet of paper. Participants must connect the numbers in sequential order without lifting the pen or pencil. The score is represented as the number of seconds taken to complete the task.

**Trail making test B (TMT-B; Reitan, 1958)**

The TMT-B is similar to the TMT-A, but the circles contain either a number (1-13) or a letter (A-L). Participants are instructed to connect the circles in sequential order but this time alternating between letters and numbers. Therefore, the TMT-B incorporates an executive component. As with the TMT-A, it is scored in seconds to complete.

**2.2.5. Statistical analysis**

Analyses were performed using Stata v13. Random-effects meta-analyses were performed using the average difference between pre-operative and post-operative scores (difference scores) as outcome data and the standard method of DerSimonian and Laird (DerSimonian & Laird, 1986). Average difference scores were provided by some studies, while for others these were calculated from average pre-operative and post-operative scores. In all meta-analyses, a positive difference indicates that the average post-operative score is more than the pre-operative score. Hence in some meta-analyses positive estimates indicate patient improvement and in others positive estimates indicate deterioration. However, pooled estimates from all seven meta-analyses lie in the direction where post-operative scores are better than the corresponding pre-operative score.

To include all studies providing relevant outcome data, medians were used as means where these were reported. Where interquartile ranges or ranges were reported instead of standard deviations, these were converted to standard deviations by assuming that their bounds correspond to appropriate quantiles from a normal distribution.

The within-study variances of the average differences were calculated using the reported standard deviations and the numbers of patients. For studies that did not give average difference scores directly, we calculated variances of the average pre-operative and post-operative scores in the same way and allowed for a correlation between these two scores when calculating
within-study variances of their difference; this is important because scores from the same patients will generally be positively correlated. We assumed a moderate correlation of 0.6 between the average pre-operative and post-operative scores. Our conclusions were robust when assuming alternative correlations of 0.4 and 0.8 (results shown in Appendix B).

Due to the small numbers of patients comprising the studies, the approximations that underlie the random-effects model are not especially precise. This is evident when, for example, studies’ statements about the statistical significance of their difference scores are not necessarily reflected in the forest plots. Therefore, whether the results are robust is carefully assessed below.

Random-effects meta-analyses were also performed using average pre-operative scores to investigate whether instances of lack of improvement were due to ceiling effects. Finally, three random-effects meta-regression models were fitted using the average difference in MMSE as outcome data to assess the evidence that three covariates may be useful predictors of cognitive change.

No statistical method was used to assess publication bias. Whilst recognising this as an important issue for meta-analyses, not all studies contribute outcome data to all meta-analyses. Hence the sample sizes are inadequate to assess this issue formally. Furthermore, it is plausible to assume an absence of publication bias in the present systematic review. This is because publication bias is usually thought to occur because studies indicating a treatment effect are more likely to be published but the studies included here do not compare treatment groups in this way.

2.3. Results

2.3.1. Search results

Seventy-one studies were identified following a systematic literature search. Forty-eight were excluded (Figure 2.1) and twenty-three met criteria for inclusion in meta-analyses (Table 2.1). A subset of these studies provide outcome data for each neuropsychological test. Nineteen studies provide outcome data for the MMSE; seven studies provide outcome data for RAVLT total and delayed recall subtests; six studies provide outcome data for backwards digit span; eight studies provide outcome data for phonemic verbal fluency; 13 studies provide outcome data for TMT-A; and nine studies provide outcome data for TMT-B (Table 2.2; section 2.3.6).
2.3.2. Average pre-operative scores

The estimated average pre-operative score for each test was as follows: MMSE = 23.10 points (95% CI 22.13 to 24.08); RAVLT total verbal recall = 22.73 words (95% CI 19.86 to 25.61); RAVLT delayed verbal recall = 1.90 words (95% CI 1.22 to 2.57); backwards digit span = 2.92 digits (95% CI 2.38 to 3.46); phonemic verbal fluency = 19.67 words (95% CI 13.60 to 25.74); TMT-B = 293.03 seconds (95% CI 221.09 to 364.97); and TMT-A = 132.48 seconds (95% CI 108.48 to 156.49) (Table 2.2).
Table 2.1: Characteristics of the studies included in meta-analyses

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient n</th>
<th>Patient Selection</th>
<th>Age of patients Mean (SD) years</th>
<th>Follow-up Interval</th>
<th>% males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrén et al. (2013)</td>
<td>69*</td>
<td>Patients with idiopathic NPH</td>
<td>70 (48-84)</td>
<td>3 months</td>
<td>54</td>
</tr>
<tr>
<td>Duinkerke et al. (2004)</td>
<td>10</td>
<td>Patients with idiopathic NPH who showed improvement in at least one clinical symptom with temporary lumbar drainage</td>
<td>70.9 (10.26)</td>
<td>6-12 months</td>
<td>40</td>
</tr>
<tr>
<td>Foss et al. (2007)</td>
<td>27</td>
<td>Patients with idiopathic NPH</td>
<td>72 (46-81)</td>
<td>6-9 months</td>
<td>29.6</td>
</tr>
<tr>
<td>Gleichgerrcht et al. (2009)</td>
<td>10</td>
<td>Patients with NPH who showed clinical response to continuous CSF drainage</td>
<td>69.4 (9.3)</td>
<td>6-8 months</td>
<td>70</td>
</tr>
<tr>
<td>Hellström et al. (2008)</td>
<td>47</td>
<td>Patients with idiopathic NPH</td>
<td>73 (24-84)</td>
<td>3 months</td>
<td>47</td>
</tr>
<tr>
<td>Hellström et al. (2012b)</td>
<td>142</td>
<td>Patients with idiopathic NPH</td>
<td>72.5 (30-87)</td>
<td>3 months</td>
<td>51</td>
</tr>
<tr>
<td>Hiraoka et al. (2015)</td>
<td>11</td>
<td>Patients with idiopathic NPH</td>
<td>77.9 (4.1)</td>
<td>3 months</td>
<td>40</td>
</tr>
<tr>
<td>Iddon et al. (1999)</td>
<td>11</td>
<td>Patients with idiopathic NPH</td>
<td>69.64 (6.14)</td>
<td>6 months</td>
<td>72.7</td>
</tr>
<tr>
<td>Katzen et al. (2011)</td>
<td>12</td>
<td>Patients with idiopathic NPH</td>
<td>74.92 (7.72)</td>
<td>6 months</td>
<td>33.3</td>
</tr>
<tr>
<td>Kazui et al. (2015)</td>
<td>49*</td>
<td>Patients with idiopathic NPH</td>
<td>76.4 (4.4)</td>
<td>3 months</td>
<td>41</td>
</tr>
<tr>
<td>Lundin et al. (2013)</td>
<td>35</td>
<td>Patients with idiopathic NPH</td>
<td>73 (49-81)</td>
<td>3 months</td>
<td>45.7</td>
</tr>
<tr>
<td>Mataró et al. (2003)</td>
<td>8</td>
<td>Patients with idiopathic NPH</td>
<td>73.4 (6.8)</td>
<td>6 months</td>
<td>50</td>
</tr>
<tr>
<td>Mataró et al. (2007)</td>
<td>18</td>
<td>Patients with idiopathic NPH</td>
<td>74.56 (7.06)</td>
<td>6 months</td>
<td>50</td>
</tr>
<tr>
<td>Moriya et al. (2015)</td>
<td>32</td>
<td>Patients with idiopathic NPH</td>
<td>73.7 (6.8)</td>
<td>12 months</td>
<td>71.9</td>
</tr>
<tr>
<td>Peterson et al. (2016)</td>
<td>22</td>
<td>Patients with NPH</td>
<td>68.3 (10.8)</td>
<td>3-9 months</td>
<td>63.6</td>
</tr>
<tr>
<td>Poca et al. (2004)</td>
<td>43</td>
<td>Patients with idiopathic NPH</td>
<td>71.1 (6.9)</td>
<td>6 months</td>
<td>69.8</td>
</tr>
<tr>
<td>Saito et al. (2011)</td>
<td>32</td>
<td>Patients with idiopathic NPH who showed ≥ 1 point reduction on the total iNPH Grading Scale following shunt surgery</td>
<td>75.7 (4.5)</td>
<td>12 months</td>
<td>50</td>
</tr>
<tr>
<td>Savolainen et al. (2002)</td>
<td>51</td>
<td>Patients with idiopathic NPH</td>
<td>67.5</td>
<td>3-12 months</td>
<td>52.9</td>
</tr>
<tr>
<td>Solana et al. (2012)</td>
<td>185</td>
<td>Patients with idiopathic NPH</td>
<td>73.96 (6.3)</td>
<td>6 months</td>
<td>60</td>
</tr>
<tr>
<td>Stambrook et al. (1988)</td>
<td>14</td>
<td>Patients with NPH</td>
<td>66.0 (14.16)</td>
<td>Mean = 23.73 weeks</td>
<td>64.3</td>
</tr>
<tr>
<td>Thomas et al. (2005)</td>
<td>42</td>
<td>Patients with idiopathic NPH</td>
<td>73 (10)</td>
<td>3-9 months</td>
<td>45.2</td>
</tr>
<tr>
<td>Virhammar et al. (2014b)</td>
<td>173</td>
<td>Patients with idiopathic NPH</td>
<td>74 (54-88)</td>
<td>12 months</td>
<td>53</td>
</tr>
<tr>
<td>Yamamoto et al. (2013)</td>
<td>16</td>
<td>Patients with idiopathic NPH</td>
<td>75.8 (4.9)</td>
<td>3 months</td>
<td>50</td>
</tr>
</tbody>
</table>

Note: *Median (range); bMean (range); *treatment-as-normal group; CSF, cerebrospinal fluid; NPH, normal pressure hydrocephalus.
2.3.3. Average difference scores (pre- to post-shunt)

There was a statistically significant effect of shunt surgery on cognition (MMSE: pooled average difference = 2.20 points, 95% CI 1.45 to 2.95, \( p < 0.001; \ I^2 = 81.9\% \), Figure 2.2), memory (RAVLT total verbal recall: pooled average difference = 5.64 words, 95% CI 3.86 to 7.43; \( p < 0.001; \ I^2 = 57.2\% \), Figure 2.3; delayed verbal recall: pooled average difference = 1.43 words, 0.55 to 2.31; \( p = 0.001; \ I^2 = 89.3\% \), Figure 2.4), executive function (backwards digit span: pooled average difference = 0.36 digits, 0.04 to 0.67; \( p = 0.03; \ I^2 = 87.0\% \), Figure 2.5; phonemic verbal fluency: pooled average difference = 2.73 words, 95% CI 0.84 to 4.63, \( p = 0.005; \ I^2 = 33.6\% \), Figure 2.6; TMT-B: pooled average difference = -43.46 seconds, 95% CI -83.23 to -3.70, \( p = 0.03; \ I^2 = 77.7\% \), Figure 2.7), and psychomotor speed (TMT-A: pooled average difference = -25.90 seconds, 95% CI -36.11 to -15.69; \( p < 0.001; \ I^2 = 36.1\% \); Figure 2.8).

2.3.4. Interpretation of difference scores

All analyses show statistically significant estimated average differences in the direction of improvement following shunt surgery in the presence of moderate to high heterogeneity (Table 2.2). There is strong evidence for five of these average differences: MMSE (\( p < 0.001 \)), RAVLT total verbal recall (\( p < 0.001 \)), RAVLT delayed verbal recall (\( p = 0.001 \)), phonemic verbal fluency (\( p = 0.005 \)) and TMT-A (\( p < 0.001 \)). The remaining tests (backwards digit span, and TMT-B) show weaker significance levels (\( p = 0.03 \); 0.03; respectively). Given the problems associated with repeated testing, and because of the approximations made by the statistical methods used, we suggest that the statistical significance of these two tests be treated with caution and we do not view them as robust. The \( I^2 \) statistics range from 33-90%, indicating considerable between-study heterogeneity in all outcomes and meaning that the studies estimate substantially different effects. This means that any single study is susceptible to producing results that differ from the estimated average differences. The pooled estimates must therefore be interpreted as population average differences, and not study specific differences, in accordance with the random effects model for meta-analysis.

Visual analysis of the forest plots supports the above interpretations. For all forest plots, average scores across studies are in very good directional agreement with the estimated average difference scores, but this is less clear for backwards digit span and TMT-B.
Table 2.2: Meta-analyses results

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Test</th>
<th>n of Studies</th>
<th>Estimated average pre-shunt score*</th>
<th>95% CI</th>
<th>Estimated average difference*</th>
<th>95% CI</th>
<th>p</th>
<th>Cochran’s Q (d.f.; p)</th>
<th>I²</th>
<th>Estimated between-study variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global function</td>
<td>MMSE</td>
<td>19</td>
<td>23.10 points</td>
<td>22.13, 24.08</td>
<td>2.20 points</td>
<td>1.45, 2.95</td>
<td>&lt; 0.001</td>
<td>99.62 (18; &lt; 0.001)</td>
<td>81.9%</td>
<td>1.99</td>
</tr>
<tr>
<td>Learning and memory</td>
<td>RAVLT total</td>
<td>7</td>
<td>22.73 words</td>
<td>19.86, 25.61</td>
<td>5.64 words</td>
<td>3.86, 7.43</td>
<td>&lt; 0.001</td>
<td>14.02 (6; 0.03)</td>
<td>57.2%</td>
<td>2.68</td>
</tr>
<tr>
<td></td>
<td>RAVLT delayed</td>
<td>7</td>
<td>1.90 words</td>
<td>1.22, 2.57</td>
<td>1.43 words</td>
<td>0.55, 2.31</td>
<td>0.001</td>
<td>56.33 (6; &lt; 0.001)</td>
<td>89.3%</td>
<td>1.11</td>
</tr>
<tr>
<td></td>
<td>Backwards digit span</td>
<td>6</td>
<td>2.92 digits</td>
<td>2.38, 3.46</td>
<td>0.36 digits</td>
<td>0.04, 0.67</td>
<td>0.03</td>
<td>38.61 (5; &lt; 0.001)</td>
<td>87.0%</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Phonemic verbal fluency</td>
<td>8</td>
<td>19.67 words</td>
<td>13.60, 25.74</td>
<td>2.73 words</td>
<td>0.84, 4.63</td>
<td>0.005</td>
<td>10.55 (7; 0.16)</td>
<td>33.6%</td>
<td>2.32</td>
</tr>
<tr>
<td>Executive function</td>
<td>TMT-B</td>
<td>9</td>
<td>293.03 sec</td>
<td>221.09, 364.97</td>
<td>-43.46 sec</td>
<td>-83.23, -3.70</td>
<td>0.03</td>
<td>35.89 (8; &lt; 0.001)</td>
<td>77.7%</td>
<td>2494.80</td>
</tr>
<tr>
<td>Psychomotor speed</td>
<td>TMT-A</td>
<td>13</td>
<td>132.48 sec</td>
<td>108.48, 156.49</td>
<td>-25.90 sec</td>
<td>-36.11, -15.69</td>
<td>&lt; 0.001</td>
<td>18.78 (12; 0.09)</td>
<td>36.1%</td>
<td>104.03</td>
</tr>
</tbody>
</table>

Note: MMSE, Mini-mental state examination; RAVLT, Rey Auditory Verbal Learning Test; TMT, trail making test; *estimates of the underlying mean pre-shunt and the underlying mean difference scores, terminology used in line with Higgins, Thompson, and Spiegelhalter (2009) who note that the inference from a random-effects meta-analysis is an “estimate of the underlying mean effect μ”. Here, we substitute “effect” with “pre-shunt score” and “difference score” to more accurately represent the data.
2.3.5. Moderator variables

All nineteen studies included in the analysis of moderator variables provided information about average age, time-to-retest and % males. Random effects meta-regressions using average difference in MMSE as outcome data were all non-significant (Table 2.3). This study did not find evidence that average age, time-to-retest or sex predict improvement on the MMSE.

Table 2.3: Meta-regressions of average difference of MMSE on moderator variables

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-to-retest</td>
<td>0.01</td>
<td>0.13</td>
<td>0.96</td>
<td>-0.24, 0.25</td>
</tr>
<tr>
<td>(months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Av. age (years)</td>
<td>-0.15</td>
<td>0.15</td>
<td>0.29</td>
<td>-0.44, 0.13</td>
</tr>
<tr>
<td>% male</td>
<td>0.05</td>
<td>0.03</td>
<td>0.09</td>
<td>-0.01, 0.11</td>
</tr>
</tbody>
</table>

2.3.6. Forest plots

Figure 2.2: Forest plot for difference in MMSE

The pooled outcome was determined using a random-effects model. Average differences are shown with 95 per cent confidence intervals.
Figure 2.3: Forest plot for difference in RAVLT total verbal recall
The pooled outcome was determined using a random-effects model. Average differences are shown with 95 per cent confidence intervals.

Figure 2.4: Forest plot for difference in RAVLT delayed verbal recall
The pooled outcome was determined using a random-effects model. Average differences are shown with 95 per cent confidence intervals.
Figure 2.5: Forest plot for difference in backwards digit span score

The pooled outcome was determined using a random-effects model. Average differences are shown with 95 per cent confidence intervals.

Figure 2.6: Forest plot for difference in phonemic verbal fluency

The pooled outcome was determined using a random-effects model. Average differences are shown with 95 per cent confidence intervals.
Figure 2.7: Forest plot for difference in trail making test B (seconds to complete)
The pooled outcome was determined using a random-effects model. Average differences are shown with 95 per cent confidence intervals.

Figure 2.8: Forest plot for difference in trail making test A (seconds to complete)
The pooled outcome was determined using a random-effects model. Average differences are shown with 95 per cent confidence intervals.
2.4. Discussion

The aim of the current review was to determine the effect of shunt surgery on neuropsychological test performance in patients with NPH. Twenty-three studies (containing information for 1059 patients) were eligible for inclusion within one or more meta-analyses. Meta-analyses were conducted on average pre-operative and average “difference” scores for seven neuropsychological tests. Statistically significant estimated average difference scores were observed for all tests in the direction of improvement following shunt surgery. However, detailed examination of the results suggested robust evidence for improved MMSE, RAVLT total verbal recall, RAVLT delayed verbal recall, phonemic verbal fluency and TMT-A only. Meta-regressions revealed no significant effects of age, time-to-retest or sex on average MMSE difference score.

Memory

Post-shunt improvement in memory is frequently reported in patients with NPH. Significant improvement has been found for visual recall (Kahlon, Sundbärg, & Rehncrona, 2002; Larsson, Wikkelsø, Bilting, & Stephensen, 1991), spatial memory (Iddon et al., 1999), and in various subtests of the Wechsler Memory Scale (Chaudhry et al., 2007; Duinkerke et al., 2004; Solana et al., 2012a; Thomas et al., 2005). However, the Rey Auditory Verbal Learning test appears to be highly sensitive to cognitive improvement in NPH. The present study found robust evidence for improvement in the total and delayed verbal recall subtests and significant improvement has also been documented in RAVLT retention score (Chaudhry et al., 2007; Duinkerke et al., 2004).

Executive function

It is unclear from the literature whether executive function improves following shunt surgery. Indeed, only one of three tests of executive function showed robust evidence for improvement (phonemic verbal fluency) in the above meta-analyses. The remaining two (backwards digit span and TMT-B) had weaker significance levels, and supporting studies did not indicate agreement in the direction of improvement. Meta-analyses were performed using average pre-operative scores to investigate whether instances of lack of improvement were due to ceiling effects. The estimated average pre-operative score for backwards digit span was 2.92 digits. Median score in this test by 159 healthy controls in a study by Hellstrom et al. (2008) was 4
digits. Estimated average pre-operative score for TMT-B was 293.03 seconds. Normative data provided by Tombaugh (2004) suggests individuals aged 70 to 74 complete this test in 109.95 seconds (less time indicates better performance). Estimated average pre-operative scores for both tests indicated that, on average, patients were impaired in these tests compared to age-matched normative data. This suggests that ceiling effects cannot explain the lack of robust evidence for improvement in these tests following shunt. Nevertheless, robust evidence for improvement was observed for phonemic verbal fluency. However, phonemic verbal fluency is simplistic compared to executive tests with strategic or problem solving aspects. Therefore, improvement in this test likely reflects improved attentional capacity rather than higher level executive function.

Overall, given the tests that could be included in the analyses, the results of the present study do not provide strong evidence for improvement in executive function following shunt surgery, tentatively supporting the hypothesis that executive impairment in NPH may reflect irreversible damage to fronto-subcortical connectivity.

**Psychomotor speed**

There was good evidence for improvement in psychomotor speed, as measured by the TMT-A. Due to lack of data, other tests of psychomotor speed could not be included, although improvements have also been documented in the Grooved pegboard test (Hellström et al., 2012b), the Purdue pegboard test (Mataró et al., 2003), and the Line-tracing test (Thomas et al., 2005).

**Global cognitive functioning**

The present study found robust evidence for improved performance on the MMSE. This test is commonly used to assess cognitive function in NPH, although results vary with some studies finding significant improvements (Mataró et al., 2007; Thomas et al., 2005; Yamamoto et al., 2013), and others finding no change (Gleichgerrcht et al., 2009; Poca et al., 2004, 2005; Saito et al., 2011). A ceiling effect may explain why some studies find no change on the MMSE. High functioning patients can perform well on this test while specific cognitive deficits may be missed unless detailed neuropsychological testing is conducted (Relkin & Katzen, 2014). Indeed, in their study, Iddon et al. (1999) split patients according to their pre-operative MMSE scores. Patients who scored in the dementing range of the MMSE at baseline (<24 points)
improved to the normal range post-operatively. However, no significant difference was observed between baseline and outcome scores for patients who did not score in the dementing range at baseline. Therefore, it is important that cognitive assessments include a battery of neuropsychological tests in addition to the MMSE.

**Practice effects**

Studies with test-retest control groups provide evidence that improvements following shunt surgery are due to treatment effects rather than practice effects. Katzen and colleagues (2011) found greater improvement in measures of mental tracking speed and sustained attention in shunted idiopathic NPH patients than in healthy controls who had undergone repeated testing. Saito and colleagues (2011) found evidence for improvements in executive function following shunt which were not ascribable to practice effects. Furthermore, Solana and colleagues (2010) investigated the effect of testing-retesting in patients with NPH using a battery of neuropsychological tests administered over four consecutive days. No learning effect was observed for any of the tests and it was concluded that improvements following shunt reflect a true treatment effect.

In summary, the results suggest that, on average, shunt surgery has a beneficial effect on neuropsychological functioning, including in the domains of verbal learning and memory, psychomotor speed, and global cognitive functioning. This could be beneficial to patients in a range of ways related to their daily functioning. However, the present study did not find strong evidence for improvements in executive function. Executive functions include abilities such as planning and decision-making, abilities which are important for the successful completion of day-to-day activities.

As outlined in section 1.3.3, a number of studies have hypothesised that executive dysfunction in NPH may be irreversible. However, some studies did find improvements on tests of executive function. For example, Hellström and colleagues (2008, 2012b) found high rates of improvement using the Swedish version of the Stroop test (Hellström & Scharin, 2001). The Stroop test measures naming speed, response selection, and inhibition and consists of different subtasks i.e. naming the colours of various shapes; or naming the printed colour of incongruent colour words (e.g. the word “blue” printed in red). Therefore, the task provides different types of outcome data. The Stroop test could not be included in the present study due to an insufficient
number of supporting studies providing data for the various components of the test, and therefore, this data is missing from the analyses of executive function.

While the variability in outcome reported across studies may be due to test selection, evidence remains which suggests that this is not the sole explanation. For example, some studies report significant improvement in performance on the backwards digit span test following shunt (Gleichgerrcht et al., 2009; Hellström et al., 2008; Mataró et al., 2007; Solana et al., 2012a), whilst others report no change (de la Calzada et al., 2010; Mataró et al., 2003; Poca et al., 2004, 2005). Similarly, improvements in the Stroop test have been observed in some studies (Duinkerke et al., 2004; Hellström et al., 2008, 2012b), but not in others (Mataró et al., 2003, 2007; Savolainen et al., 2002; Thomas et al., 2005). While one study suggested that a ceiling effect could explain the absence of improved executive function following shunt (Chaudhry et al., 2007), other studies have found that performance in tests of executive function is disproportionately impaired in NPH patients at baseline (Iddon et al., 1999; Saito et al., 2011).

Therefore, the results to date suggest that outcome in the domain of executive function is variable in patients with NPH. This may indicate that, of the neuropsychological domains in which patients show impairments, executive function is the least likely to respond to shunting, perhaps only showing improvements in a subgroup of shunted patients. However, further investigation using more sensitive tests of executive function is needed to clarify the issues highlighted above.

2.4.1. Predicting improvement

Since shunt surgery is an invasive procedure and patients are often elderly, it is important to identify factors which predict positive outcome following treatment. Previously, Chang, Agarwal, Williams, Rigamonti, and Hillis (2006) found evidence for associations between age and sex with cognitive outcome following shunt. Specifically, they found that younger age predicted good outcome on tests of memory, and that women were more likely than men to exhibit improvements on non-memory tests.

In order to investigate predictors of positive cognitive outcome in the present study, age, sex, and time between shunt and reassessment were included as moderator variables in three random-effects meta-regression models to assess the evidence that they may be useful predictors of cognitive outcome. Results suggested no significant effects of age, sex, or time
between shunt and reassessment on outcome in the MMSE. However, this was an exploratory analysis and effects may be observed using other measures of cognitive or functional outcome.

2.4.2. Extent and duration of improvement

Although cognitive improvement has been observed in patients with NPH following shunt surgery, patients remain impaired in neuropsychological tests compared to age-matched controls. Shunted patients have shown to perform significantly poorer than healthy controls in tests of psychomotor speed, memory and executive function at both three and 12 months post-shunt (Hellström et al., 2008, 2012b). The present study investigated outcome between three and 12 months post-shunt, however, from the available data, outcome at longer durations could not be assessed. To determine the extent of cognitive recovery, longer-term monitoring of patients is required using multiple post-operative assessments as improvements have been documented as late five years post-shunt (Kahlon, Sjunnesson, & Rehncrona, 2007). Tracking post-shunt neuropsychological change is important for a number of reasons, such as providing information about subtle changes to functioning, and informing treatment options.

2.4.3. Limitations and methodological considerations

The present study did not attempt to formally assess the risk of bias because of small sample sizes and the difficult nature of determining what constitutes study quality in this area. Methodological differences across studies complicate interpretation of results. Variability within tests used meant that the analyses were limited to seven neuropsychological tests when others may show improvement following shunt surgery. Furthermore, higher level executive functions could not be assessed with the restricted set of tests used to date. Additionally, time between shunt and reassessment varied with three, six and 12 month delays being used. Consistency here is pertinent as different patterns of improvement may be seen at different intervals. Improvement may be observed more readily at shorter intervals due to immediate effect of the shunt, whereas initial improvement may be missed at longer intervals due to effects of comorbid disorders or increasing age (Solana et al., 2012b).
2.5. Conclusions

The present study found evidence for improved performance in global cognitive function, verbal learning and memory, and psychomotor speed following shunt surgery. However, the results did not provide strong evidence for improvement in tests of executive function based on the available data. In order to clarify these findings, there is a need to assess high-level executive functions in patients with NPH before and after shunt surgery. Additionally, longer-term monitoring of patients is required to determine the extent to which cognitive functions may improve. The Mini-Mental State Examination, the Rey Auditory Verbal Learning Test, phonemic verbal fluency and trail making test A may be useful for assessment of cognitive outcome following treatment for NPH.
Chapter 3

Apathy, ventriculomegaly and neurocognitive improvement following shunt surgery in normal pressure hydrocephalus

3.1. Introduction

Chapter 2 provided evidence for improved neuropsychological performance following shunt surgery in patients with NPH, particularly in global cognitive functioning, learning and memory, and psychomotor speed. Problematically however, apathy is often observed in NPH patients (DeVito et al., 2007; Keenan et al., 2005), yet the significance of this symptom for cognitive function and outcome has not been elucidated.

Only two studies have objectively assessed apathetic symptoms in patients with NPH (Kanemoto et al., 2016; Kito et al., 2009). Kanemoto et al. and Kito et al. investigated the prevalence of neuropsychiatric symptoms in patients with idiopathic NPH (iNPH) using the Neuropsychiatric Inventory (NPI; Cummings et al., 1994). Kanemoto et al. reported a prevalence of 86% in a group of 22 patients with iNPH and Kito et al. reported a prevalence of 70.3% in a group of 64 patients with iNPH. In both cases, apathy was found to be the most frequent neuropsychiatric symptom. Further, Kito et al. found an association between increased apathy with more severe cognitive impairment as measured by the iNPH Grading Scale (iNPHGS; see Table 1.1 for a description; Kubo et al., 2008). Meanwhile, Kanemoto et al. found that a reduction in apathy severity following lumboperitoneal shunt surgery was associated with improved performance in the Frontal Assessment Battery, a measure of frontal lobe functioning. These findings suggest that the symptom of apathy in NPH may be a significant obstacle for cognitive function and outcome.

Due to the lack of research into this symptom, the neural underpinnings of apathy in NPH have not been established. Kanemoto et al. (2016) hypothesised that frontal lobe pathology may underlie apathy in NPH, whereas Kito et al. hypothesised that apathy could arise due to impaired oxygen metabolism or cerebral perfusion in areas of the brain that form parts of the fronto-subcortical circuits.

A subcortical pathological basis for apathy was further hypothesised by DeVito et al., (2007) following their observation of diminished caudate volume in patients with NPH. The
caudate nucleus, a subcortical structure and part of the fronto-subcortical dopaminergic system, plays a role in reward processing and motivation (Haruno et al., 2004). Importantly, dysfunction of subcortical structures has been associated with apathy (Bhatia & Marsden, 1994; Caplan et al., 1990; David et al., 2008; Levy & Dubois, 2006; Mendez et al., 1989). Therefore, caudate atrophy and impairments of associated striatal circuitry may underlie the symptom of apathy in NPH.

It is not yet established whether caudate atrophy relates to degree of ventriculomegaly in NPH, however ventriculomegaly measured using the bicaudate ratio (BCR) has been shown to be associated with caudate atrophy in patients with Huntington’s disease (Aylward, Schwartz, Machlin, & Pearlson, 1991). The BCR is the width of the lateral ventricles at the level of the body of the caudate nuclei as a percentage of the width of brain across the same line (Figure 3.1). The BCR is a useful measure as it is easily obtainable without complex computerised techniques. The present study investigated whether BCR is related to apathy severity in patients with NPH. In addition, cognition and apathy were assessed before and after shunt surgery to explore the relationship between apathy and cognitive function and outcome, and to provide a clearer profile of the mechanisms driving post-shunt recovery. Apathy was assessed in the present study using the Cambridge State Apathy Evaluation scale (Blackwell et al., 2008; Appendix A), a modified version of the self-rated Apathy Evaluation Scale (AES-S; Marin et al., 1991), which was adapted specifically to measure state-related changes in apathy and is therefore more suitable for repeated assessment. Prevalence of apathy was also investigated using this measure. The prevalence of depression was assessed for comparison.

3.2. Methods

3.2.1. Patients

Participants were patients who were given a diagnosis of possible or probable NPH at the CSF disorders clinic, Addenbrooke’s Hospital. As part of an ongoing audit, a clinically representative sample of 22 patients with NPH were referred by a neurosurgeon (JDP) to be included in the present study. All were assessed using a brief neuropsychological test battery as part of their normal clinical pathway prior to shunt surgery and three to nine months post-shunt surgery ($M = 4.17$ months). Neuropsychological test data were collected at the CSF disorders clinic, Addenbrooke’s Hospital.
Figure 3.1: Measurement of bicaudate ratio on MRI axial flair

An illustration of BCR before (a.) and following (b.) shunt surgery. BCR is calculated as the width of the lateral ventricles at the level of the body of the caudate nuclei as a percentage of the width of brain across the same line. In this example, BCR = 0.32 at pre-shunt scan and reduces to 0.31 at 3 month post-shunt scan.

3.2.2. Imaging analysis

All patients were scanned using magnetic resonance imaging (MRI) or computed tomography (CT) prior to shunt surgery as part of the standard diagnostic procedure. MRI scans were used by a neurosurgeon to calculate BCRs. Where these were unavailable, CT scans were used (n = 5). Figure 3.1 provides an illustration of BCR measurement in a patient with NPH before and following shunt surgery.

3.2.3. Neuropsychological assessment

Patients completed the Mini-Mental State Examination (MMSE), the Hopkins Verbal Learning Test (HVLT), the Controlled Oral Word Association Test (COWAT), the Cambridge State Apathy Evaluation scale (self-rated; AES-S), and the short form of the Geriatric Depression Scale (GDS-15) pre- and post-operatively. IQ was assessed using the National Adult Reading Test (NART). The tests are described in detail below. To minimise practice effects, alternate
versions of the phonemic and semantic fluency categories and the HVLT word list were used during the follow-up assessment.

The Mini-Mental State Examination (MMSE; Cockrell & Folstein, 1988)

The MMSE is a widely used bedside measure of mental status evaluation. It includes tests of memory, attention, personal orientation, reading, writing, and visuospatial ability. The maximum score is 30, and scores of 23 and below are in the dementia range.

The Hopkins Verbal Learning Test (HVLT; Brandt, 1991)

The HVLT assesses verbal learning and memory and has been shown to be sensitive to hydrocephalus (Iddon, Morgan, Loveday, Sahakian, & Pickard, 2004). The experimenter reads aloud 12 nouns, four words from one of three semantic categories (e.g. animals, human dwellings, and precious stones). The patient is then asked to repeat back as many of the words as they can immediately after hearing the list. This gives an immediate recall score out of a maximum of 12. This procedure is then repeated a further two times to assess learning. The learning score is the total number of words recalled after trials 1, 2, and 3 with a maximum of 36. After a delay of 25-30 minutes the patient is asked to recall as many of the words from the list as they can giving a delayed recall score out of 12.

The Controlled Oral Word Association Test (COWAT; Benton & Hamsher, 1989)

Phonemic and semantic fluency tests from the COWAT were administered. Phonemic verbal fluency is assessed using the FAS version of the task. Patients are asked to generate as many words as they can beginning with the letters ‘F’, ‘A’, then ‘S’ with a time limit of 60 seconds per letter. The score represents total number of words generated for the three letters combined. For the semantic fluency task patients are asked to generate as many words as they can from a given category (e.g. animals) in 60 seconds. The score represents the number of words generated.

The Cambridge State Apathy Evaluation scale (Blackwell et al., 2008)

Apathy was assessed using the self-rated State Apathy Evaluation scale which is a modified version of the self-rated Apathy Evaluation Scale (AES-S; Marin et al., 1991). This scale was
chosen as it allows assessment of state-related changes in apathy between assessments. Scores range from 0 to 54. A score of 19-21 is defined as mild apathetic symptoms. A score of 22 or higher is defined as moderate apathetic symptoms. See Appendix A for items and instructions.

*The Geriatric Depression Scale 15 (GDS-15; Sheikh & Yesavage, 1986)*

Depression was assessed using the GDS-15 since depression has been shown to affect cognitive performance (Robbins, Elliott, & Sahakian, 1996). The GDS-15 is suitable for use in this population since it de-emphasises the somatic symptoms associated with depression, therefore avoiding misattributing signs of physical disability or normal aging to depression (Sheikh & Yesavage, 1986). The GDS-15 is a self-rated scale consisting of 15 yes/no questions. A score of 6 or higher is suggestive of depression (Herrmann et al., 1996). A score of 12 or higher was defined as severe depression (Israelsson et al., 2016). See Appendix C for items and instructions.

*The National Adult Reading Test (NART; Nelson, 1982)*

The NART is a measure of pre-morbid verbal IQ, testing proper pronunciation of irregular English words. Since pronunciation of words has been shown to be relatively unaffected by neurodegenerative diseases and normal aging, NART scores should be representative of the patient’s IQ prior to the onset of NPH (Crawford, Deary, Starr, & Whalley, 2001).

### 3.2.4. Statistical analysis

Differences in the prevalence of apathetic and depressive symptoms between pre- and post-shunt assessments were evaluated in a within-subjects manner. That is, the same patients were assessed at both pre- and post-shunt. Therefore, McNemar’s test was used to evaluate differences in prevalence. Scores in the AES-S and GDS-15 were correlated with cognitive test scores at pre- and post-shunt. Pre-operative BCRs were correlated with patients’ pre-operative AES-S score, and GDS-15 score for comparison. BCR was also correlated with pre-operative MMSE score, IQ and age. Bivariate correlations were conducted using Spearman’s rho. Mean pre- and post-operative neuropsychological test scores were compared using paired samples t-tests. One outlier was identified and removed from the phonemic fluency analysis as the pre-operative score was >2.5 SDs above the mean. Scores in the AES-S, GDS-15, HVLT delayed,
and MMSE violated assumptions of normality. Wilcoxon signed-rank tests were therefore used to compare scores in these tests. To investigate the relationship between change in apathy (AES-S) with change in neuropsychological test scores pre-operative scores were subtracted from post-operative scores to obtain a “change” (difference) score for each test. Correlations were then conducted using Spearman’s rho. Correlations between change in depression (GDS-15) and change in neuropsychological test scores were conducted for comparison.

3.3. Results

3.3.1. Demographic information

Fourteen patients were male and eight were female. Mean (SD) age in years was 68.3 (10.80). Mean IQ and years of education was 109.4 (11.38) and 12.1 (2.49), respectively. Mean baseline MMSE was 25 (3.52). Mean pre-operative BCR was 0.29 (0.03) (significant ventriculomegaly = BCR ≥ 0.25). Individual patient details are shown in Table 3.1.

3.3.2. Prevalence of apathy and depression

One patient did not complete the AES-S at either pre- or post-shunt. Three additional patients did not complete the AES-S at pre-shunt. Therefore, 18 patients completed the AES-S at pre-shunt, and 21 patients completed the AES-S at post-shunt. One patient did not complete the GDS-15 at either pre- or post-shunt. An additional one patient did not complete the GDS-15 at post-shunt. Therefore, 21 patients completed the GDS-15 at pre-shunt, and 20 completed the GDS-15 at post-shunt.

Frequency and severity of apathetic and depressive symptoms at pre- and post-shunt are shown in Figure 3.2. Cut-off points for the AES-S and GDS-15 for determining severity of symptoms are detailed in section 3.2.3. Eight patients scored within the apathetic range of the AES-S at pre-shunt (44.44%). Specifically, four patients scored within the mild apathetic symptoms range (22.22%) and four patients scored within the moderate apathetic symptoms range (22.22%). At post-shunt, three patients scored within the apathetic range of the AES-S (14.29%; all scoring in the moderate apathetic symptoms range).

The GDS-15 scores for eleven patients at pre-shunt were suggestive of depression (52.38%). Within those patients, three scored within the severe depressive symptoms range
At post-shunt, the GDS-15 scores for five patients were suggestive of depression (25%). Three out of those five patients scored within the severe depressive symptoms range (15%).

Frequency of apathetic and depressive symptoms did not change significantly from pre- to post-shunt (AES-S, $p = 0.092$; GDS-15, $p = 0.302$).

At pre-shunt the percentage of patients who scored within the apathetic range of the AES-S without also scoring in the depressive range of the GDS-15 was 11.76% (2/17), while the percentage of patients scoring in the depressive range of the GDS-15 without also scoring within the apathetic range of the AES-S was also 11.76% (2/17). 29.41% (5/17) of patients scored both within the apathetic range of the AES-S and within the depressive range of the GDS-15, at pre-shunt.

At post-shunt, one patient (5.26%) scored within the apathetic range of the AES-S but did not score in the depressive range of the GDS-15, and two patients (10.53%) scored in the depressive range of the GDS-15 without scoring in the apathetic range of the AES-S. Two patients (10.53%) scored both in the apathetic range of the AES-S and the depressive range of the GDS-15.

![Figure 3.2: Frequency and severity of apathetic and depressive symptoms at pre- and post-shunt]
### Table 3.1: Normal pressure hydrocephalus patient demographics

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age</th>
<th>Sex</th>
<th>IQ</th>
<th>Years Edu</th>
<th>Time to retest (months)</th>
<th>Aetiology</th>
<th>Gait Disturb</th>
<th>Incontinence</th>
<th>MMSE Pre</th>
<th>MMSE Post</th>
<th>Pre BCR^a</th>
</tr>
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<tr>
<td>1</td>
<td>61</td>
<td>M</td>
<td>120</td>
<td>12</td>
<td>3</td>
<td>Idiopathic</td>
<td>+</td>
<td>+</td>
<td>23</td>
<td>26</td>
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</tr>
<tr>
<td>2</td>
<td>49</td>
<td>M</td>
<td>112</td>
<td>n/a</td>
<td>4</td>
<td>Secondary to IV ventricular outlet obstruction</td>
<td>+</td>
<td>-</td>
<td>26</td>
<td>26</td>
<td>0.23^c</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>M</td>
<td>117</td>
<td>11</td>
<td>3</td>
<td>Secondary to Pineal tumour and radiotherapy</td>
<td>+</td>
<td>-</td>
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<tr>
<td>4</td>
<td>73</td>
<td>M</td>
<td>98</td>
<td>11</td>
<td>3</td>
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<td>+</td>
<td>+</td>
<td>18</td>
<td>24</td>
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<tr>
<td>5</td>
<td>74</td>
<td>F</td>
<td>100</td>
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<td>9</td>
<td>Idiopathic</td>
<td>+</td>
<td>-</td>
<td>28</td>
<td>25</td>
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<td>M</td>
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<td>-</td>
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<tr>
<td>11</td>
<td>76</td>
<td>M</td>
<td>103</td>
<td>11</td>
<td>5</td>
<td>Idiopathic</td>
<td>+</td>
<td>+</td>
<td>23</td>
<td>21</td>
<td>0.29</td>
</tr>
<tr>
<td>12</td>
<td>52</td>
<td>M</td>
<td>109</td>
<td>11</td>
<td>3</td>
<td>Aqueduct stenosis</td>
<td>+</td>
<td>-</td>
<td>27</td>
<td>29</td>
<td>0.29</td>
</tr>
<tr>
<td>13</td>
<td>62</td>
<td>F</td>
<td>100</td>
<td>11</td>
<td>2</td>
<td>Secondary to Chiari malformation, Aqueduct stenosis</td>
<td>+</td>
<td>-</td>
<td>29</td>
<td>25</td>
<td>0.27</td>
</tr>
<tr>
<td>14</td>
<td>82</td>
<td>F</td>
<td>115</td>
<td>9</td>
<td>3</td>
<td>Idiopathic</td>
<td>+</td>
<td>+</td>
<td>26</td>
<td>27</td>
<td>0.26^c</td>
</tr>
<tr>
<td>15</td>
<td>56</td>
<td>F</td>
<td>111</td>
<td>16</td>
<td>3</td>
<td>Idiopathic</td>
<td>+</td>
<td>n/a</td>
<td>21</td>
<td>24</td>
<td>0.30^c</td>
</tr>
<tr>
<td>16</td>
<td>77</td>
<td>M</td>
<td>115</td>
<td>9</td>
<td>3</td>
<td>Idiopathic</td>
<td>+</td>
<td>n/a</td>
<td>27</td>
<td>28</td>
<td>0.30</td>
</tr>
<tr>
<td>17</td>
<td>79</td>
<td>F</td>
<td>124</td>
<td>12</td>
<td>8</td>
<td>Idiopathic</td>
<td>++^b</td>
<td>n/a</td>
<td>26</td>
<td>27</td>
<td>0.33</td>
</tr>
<tr>
<td>18</td>
<td>75</td>
<td>M</td>
<td>125</td>
<td>14</td>
<td>3</td>
<td>Idiopathic</td>
<td>+</td>
<td>-</td>
<td>27</td>
<td>30</td>
<td>0.28</td>
</tr>
<tr>
<td>19</td>
<td>81</td>
<td>M</td>
<td>120</td>
<td>14</td>
<td>3</td>
<td>Idiopathic</td>
<td>+</td>
<td>-</td>
<td>27</td>
<td>28</td>
<td>0.26^c</td>
</tr>
<tr>
<td>20</td>
<td>52</td>
<td>F</td>
<td>109</td>
<td>18</td>
<td>8</td>
<td>Aqueduct stenosis</td>
<td>+</td>
<td>-</td>
<td>24</td>
<td>27</td>
<td>0.29</td>
</tr>
<tr>
<td>21</td>
<td>66</td>
<td>M</td>
<td>92</td>
<td>12</td>
<td>5</td>
<td>Idiopathic</td>
<td>+</td>
<td>+</td>
<td>26</td>
<td>27</td>
<td>0.24</td>
</tr>
<tr>
<td>22</td>
<td>71</td>
<td>F</td>
<td>126</td>
<td>17</td>
<td>4</td>
<td>Idiopathic</td>
<td>+</td>
<td>-</td>
<td>27</td>
<td>26</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Note: ^a = pre-operative bicaudate ratio (greater BCR = greater degree of ventriculomegaly; significant ventriculomegaly = BCR ≥ 0.25), ^b = patient in a wheelchair, ^c = taken from CT scans, n/a = information not available.
3.3.3. Correlation between neuropsychological test scores and apathy and depression

Table 3.2 shows results of correlations between scores in AES-S and GDS-15 with neuropsychological test scores at pre-shunt. Scores in AES-S and GDS-15 were significantly positively correlated (greater levels of apathy were associated with greater levels of depression). AES-S score was significantly negatively correlated with phonemic and semantic fluency scores. GDS-15 score was significantly negatively correlated with IQ, phonemic fluency score, and scores in the immediate and total subtests of the HVLT. For all significant negative correlations, greater levels of apathy or depression were associated with poorer performance in the corresponding cognitive tests (as well as lower IQ). There were no other significant correlations.

Table 3.3 shows results of correlations between scores in AES-S and GDS-15 with neuropsychological test scores at post-shunt. Again, scores in AES-S and GDS-15 were significantly positively correlated (greater levels of apathy were associated with greater levels of depression). AES-S score was significantly negatively correlated with phonemic fluency, HVLT immediate, HVLT total, HVLT delayed, and MMSE score. GDS-15 score was significantly negatively correlated with phonemic fluency score, only. As with at pre-shunt, for all significant negative correlations, greater levels of apathy or depression were associated with poorer performance in the corresponding cognitive tests.

Table 3.2: Bivariate correlations between AES-S and GDS-15 ratings with neuropsychological test scores at pre-shunt

<table>
<thead>
<tr>
<th>Scale</th>
<th>Age</th>
<th>IQ</th>
<th>GDS-15</th>
<th>Phonemic fluency</th>
<th>Semantic fluency</th>
<th>HVLT immediate</th>
<th>HVLT total</th>
<th>HVLT delayed</th>
<th>MMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AES-S</td>
<td>0.19</td>
<td>-0.29</td>
<td>0.66**</td>
<td>-0.47*</td>
<td>-0.51*</td>
<td>-0.34</td>
<td>-0.46</td>
<td>-0.30</td>
<td>-0.40</td>
</tr>
<tr>
<td>GDS-15</td>
<td>-0.03</td>
<td>-0.45*</td>
<td>--</td>
<td>-0.51*</td>
<td>-0.33</td>
<td>-0.56**</td>
<td>-0.71**</td>
<td>-0.31</td>
<td>-0.37</td>
</tr>
</tbody>
</table>

Note: Results represent Spearman’s rho values. *p < 0.05, **p < 0.01.
Table 3.3: Bivariate correlations between AES-S and GDS-15 ratings with neuropsychological test scores at post-shunt

<table>
<thead>
<tr>
<th>Scale</th>
<th>Age</th>
<th>IQ</th>
<th>GDS-15</th>
<th>Phonemic fluency</th>
<th>Semantic fluency</th>
<th>HVLT immediate</th>
<th>HVLT total</th>
<th>HVLT delayed</th>
<th>MMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AES-S</td>
<td>0.10</td>
<td>-0.03</td>
<td>0.49*</td>
<td>-0.53*</td>
<td>-0.38</td>
<td>-0.51*</td>
<td>-0.57**</td>
<td>-0.54*</td>
<td>-0.55**</td>
</tr>
<tr>
<td>GDS-15</td>
<td>0.21</td>
<td>-0.27</td>
<td></td>
<td>-0.48*</td>
<td>-0.33</td>
<td>-0.27</td>
<td>-0.27</td>
<td>-0.22</td>
<td>-0.28</td>
</tr>
</tbody>
</table>

Note: Results represent Spearman’s rho values. *p < 0.05, **p < 0.01.

3.3.4. Pre-operative bicaudate ratio

Significant positive correlations were observed between pre-operative BCR and pre-operative AES-S score, \( r_s = 0.51, p = 0.03 \), and between pre-operative BCR and pre-operative GDS-15 score, \( r_s = 0.52, p = 0.02 \), (Figure 3.3). These significant correlations indicate that greater pre-operative BCR (greater degree of ventriculomegaly) was associated with greater levels of apathy and depression. Pre-operative BCR was not significantly correlated with MMSE score (\( p = 0.76 \)) or with age (\( p = 0.74 \)). Although there was no significant correlation between BCR and age, partial correlations were conducted for both analyses controlling for age. Both AES-S score and GDS-15 score remained significantly positively correlated with pre BCR when controlling for effects of age.

3.3.5. Neuropsychological outcome

There were significant within-group differences between pre-operative and post-operative scores in phonemic fluency, semantic fluency, and HVLT delayed, all in the direction of improvement following shunt surgery (Table 3.4). No other significant group differences were observed. A Wilcoxon signed-ranks test demonstrated a non-significant trend for decreased apathy (AES-S) post-operatively, \( Z = -1.87, p = 0.06 \). A post-hoc power calculation was conducted using G*Power 3 to determine an estimate of the sample size required to achieve a significant difference in AES-S score from pre- to post-shunt. With alpha set at 0.05 and power set at 0.80, approximately 34 participants would be needed to achieve a medium effect size (\( d = 0.45 \)).
Figure 3.3: Scatterplots of the relationships between bicaudate ratio and apathy and depression at pre-shunt

Greater BCR = greater degree of ventriculomegaly; a higher AES-S rating (A.) suggests more severe levels of apathy; a higher GDS-15 rating (B.) suggests more severe levels of depression.
Table 3.4: Neuropsychological tests results at baseline and three to nine months post-operatively

<table>
<thead>
<tr>
<th>Neuropsychological Test</th>
<th>Pre-operative</th>
<th>Post-operative</th>
<th>t / Z</th>
<th>df</th>
<th>p</th>
<th>change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apathy Evaluation Scale*</td>
<td>18</td>
<td>17.50 (10.5)</td>
<td>10.00 (9.5)</td>
<td>-1.87</td>
<td>0.06</td>
<td>+</td>
</tr>
<tr>
<td>Geriatric Depression Scale*</td>
<td>21</td>
<td>6.00 (6)</td>
<td>2.00 (4.5)</td>
<td>-1.29</td>
<td>0.20</td>
<td>+</td>
</tr>
<tr>
<td>Phonemic Fluency*</td>
<td>21</td>
<td>27.90 ± 10.97b</td>
<td>34.14 ± 16.43b</td>
<td>-2.38</td>
<td>20</td>
<td>0.03</td>
</tr>
<tr>
<td>Semantic Fluency**</td>
<td>22</td>
<td>12.32 ± 5.79b</td>
<td>15.82 ± 7.02b</td>
<td>-3.06</td>
<td>21</td>
<td>0.006</td>
</tr>
<tr>
<td>HVLT Immediate</td>
<td>22</td>
<td>4.95 ± 1.86b</td>
<td>5.05 ± 2.14b</td>
<td>-0.20</td>
<td>21</td>
<td>0.85</td>
</tr>
<tr>
<td>HVLT Learning</td>
<td>22</td>
<td>17.27 ± 5.42b</td>
<td>18.91 ± 6.82b</td>
<td>-1.26</td>
<td>21</td>
<td>0.22</td>
</tr>
<tr>
<td>HVLT Delayed**</td>
<td>22</td>
<td>1.00 (3)</td>
<td>3.00 (7)</td>
<td>-2.14</td>
<td>0.03</td>
<td>+</td>
</tr>
<tr>
<td>MMSE*</td>
<td>22</td>
<td>26.00 (4)</td>
<td>26.50 (3.75)</td>
<td>-1.72</td>
<td>0.09</td>
<td>+</td>
</tr>
</tbody>
</table>

Note: *p < 0.05; **p < 0.01; a nonparametric test, b mean ± SD, c direction of change (+ = improvement, - = decline).

3.3.6. Correlation between change in neuropsychological test scores with change in apathy and depression

Table 3.5 shows results of correlations between AES-S and GDS-15 change scores with change scores in the remaining neuropsychological tests. A significant positive correlation was observed between AES-S change and GDS-15 change, as AES-S score decreases so does GDS-15 score (both improve). Additionally, there was a significant negative correlation between AES-S change and MMSE change. The nature of this relationship can be seen in Figure 3.4. As AES-S score decreases, MMSE score increases. That is, a reduction in apathy is associated with increased functional level as measured by the MMSE. No significant correlation was observed between GDS-15 and MMSE change.
Table 3.5: Correlations between change in neuropsychiatric symptoms and change in neuropsychology

<table>
<thead>
<tr>
<th>Variables</th>
<th>Age</th>
<th>IQ</th>
<th>Time to Retest</th>
<th>BCR</th>
<th>AES-S change</th>
<th>GDS-15 change</th>
<th>Phonemic fluency change</th>
<th>Semantic fluency change</th>
<th>HVLT immediate change</th>
<th>HVLT total change</th>
<th>HVLT delayed change</th>
<th>MMSE change</th>
</tr>
</thead>
<tbody>
<tr>
<td>AES-S change</td>
<td>0.05</td>
<td>0.21</td>
<td>0.28</td>
<td>-0.36</td>
<td>--</td>
<td>0.51*</td>
<td>-0.38</td>
<td>-0.43</td>
<td>-0.24</td>
<td>-0.27</td>
<td>0.09</td>
<td>-0.70**</td>
</tr>
<tr>
<td>GDS-15 change</td>
<td>0.27</td>
<td>0.10</td>
<td>0.25</td>
<td>-0.08</td>
<td>0.51*</td>
<td>--</td>
<td>-0.16</td>
<td>-0.30</td>
<td>0.03</td>
<td>-0.18</td>
<td>-0.05</td>
<td>-0.41</td>
</tr>
</tbody>
</table>

Note: Results represent Spearman’s rho values. *p < 0.05, **p < 0.01. “Change” scores were calculated by subtracting pre- scores from post-shunt scores.

Figure 3.4: Scatterplot showing the relationship between change in MMSE and change in AES-S

A positive MMSE difference score indicates improvement in global cognitive functioning from pre- to post-shunt, while a negative AES-S difference score indicates a reduction in apathy severity from pre- to post-shunt.

3.4. Discussion

The present study investigated whether bicaudate ratio (degree of ventriculomegaly) relates to degree of apathy in patients with NPH, and whether there is a relationship between cognitive outcome and change in apathy severity following shunt treatment. The prevalence of apathetic and depressive symptoms was also investigated. BCR was significantly positively correlated with levels of apathy and depression at baseline. Additionally, there were significant group improvements from baseline to follow-up in tests of phonemic and semantic fluency, and
delayed verbal recall. Prevalence of apathy and depression was not significantly different at post-shunt compared to pre-shunt, although there was a non-significant trend for improved group apathy scores following shunt surgery. Importantly, a reduction in apathy was associated with improved performance in a measure of global cognitive function. No relationship was observed between changes in global cognitive function performance with changes in depressive symptoms.

These findings highlight the importance of assessing apathy in patients with NPH. Apathy is associated with striatal dopaminergic pathology (David et al., 2008). Since pre-operative BCR was positively associated with degree of apathy the symptom of apathy may indicate greater subcortical brain atrophy, possibly leading to impaired functioning of fronto-striatal dopaminergic pathways in patients with NPH. Indeed, caudate atrophy has been observed in NPH patients (DeVito et al., 2007). BCR has previously been shown to be associated with caudate atrophy in patients with Huntington’s disease (Aylward et al., 1991) although this has not been confirmed in patients with NPH. However, the relationship between caudate volume and apathy in NPH should be investigated further.

Additionally, the present findings suggest that alleviation of the symptom of apathy following shunt surgery is linked to improved functional level as measured by the MMSE. This effect may be modulated by dopaminergic activity (Keenan et al., 2005; Nakayama et al., 2007). For example, Keenan and colleagues (2005) found that administration of the psychostimulant drug methylphenidate was associated with reduced apathetic symptoms and increased performance in a Spatial Recognition task in a patient with NPH. Methylphenidate inhibits dopamine reuptake in the brain by blocking dopamine transporters (del Campo et al., 2013; Volkow et al., 1998), meaning the increase in dopamine level in the brain following methylphenidate administration may account for the observed reduction in apathy (Keenan et al., 2005). Therefore, a reduction in apathy severity following shunt may indicate improved functioning in areas of the brain which are associated with dopaminergic activity.

BCR was also positively correlated with degree of depression in the patient sample and as level of apathy reduced (improved) post-operatively so did level of depression. Additionally, levels of apathy and depression were significantly positively correlated at both pre- and post-shunt. Distorted reward processing, an aspect of depression (Roiser, Elliott, & Sahakian, 2012), likely overlaps with symptoms of apathy and therefore delineating these two symptoms is challenging. However, no association was observed between change in depression level and change in MMSE score (unlike with change in apathy severity). This suggests that apathy and
depression are differentially involved in the symptomology of NPH, and that alleviation of the symptom of apathy may be particularly important for cognitive outcome. Future studies should aim to disentangle depression and apathy in patients with NPH.

The prevalence of apathetic symptoms in the present study was 44% at baseline, and 14% at post-shunt. This difference in frequency of apathetic symptoms was not statistically significant (using McNemar’s test), likely due to the small sample size given that only 18 of the 22 patients completed the AES-S at both pre- and post-shunt. However, such a reduction in the frequency of apathetic symptoms does suggest that there is a beneficial effect of shunt surgery on apathetic symptoms in patients with NPH. The prevalence of apathetic symptoms was only reported twice before, with both studies using the Neuropsychiatric Inventory to assess apathy (Kanemoto et al., 2016; Kito et al., 2009). Kanemoto et al. reported a prevalence of 86% at baseline and 73% three months following shunt surgery in 22 patients and Kito et al. reported a prevalence of 70.3% at baseline in 64 patients. The prevalence of apathy was lower in the present study and likely reflects the use of different assessment measures. The prevalence of depressive symptoms in the present study was 52% at baseline, and 25% at post-shunt. This is similar to levels reported by Israelsson et al. (2016) (pre-shunt 56%; post-shunt 46%) also using the GDS-15, but greater than those reported by Kito et al. (pre-shunt 14%) and Kanemoto et al. (pre-shunt 36%; post-shunt 5%), both using the NPI. Therefore, the differences are again likely due to variations in assessment measures used.

3.4.1. Limitations

The present study did not include a measure of disease duration. Disease duration is often difficult to determine in patients with NPH due to the gradual nature of cognitive and functional decline, however it may relate to the magnitude of brain structural changes as well as to levels of apathy and depression. Future studies should attempt to examine whether disease duration relates to BCR and/ or neuropsychiatric symptoms in patients with NPH. In addition, common to investigations of NPH, the sample size is small meaning that results should be interpreted with caution.
3.5. Conclusions

BCR is an easily obtainable measure of degree of ventriculomegaly in patients with NPH and may tentatively provide information about volume of subcortical regions (although this should be clarified in future studies). Greater BCR (greater degree of ventriculomegaly) was associated with more severe levels of apathy and depression at pre-shunt. It was speculated that apathy in NPH may be related to atrophy or dysfunction of the subcortical or fronto-subcortical regions (e.g. the caudate). The relationship between caudate volume and apathy in NPH should be examined further. Additionally, the findings suggest a potential role of apathy in patients’ post-shunt functional outcome, as improved performance on the MMSE was associated with a reduction in severity of apathetic symptoms.

Overall, the present study highlights the importance of assessing apathy in patients with NPH (a symptom which currently is not commonly assessed). Neither the prevalence of apathy, nor the effect of shunt surgery on severity of apathetic symptoms in patients with NPH are well established. Future research into the significance of apathy in NPH may provide important findings relevant for aiding differential diagnosis, as well as for informing treatment options.
Chapter 4

Brain structural correlates of cognitive dysfunction and neuropsychiatric symptoms in normal pressure hydrocephalus

4.1. Introduction

The pathological bases for the cognitive and behavioural symptoms in normal pressure hydrocephalus (NPH) have not been elucidated. However, the symptoms may indicate dysfunction of subcortical regions. Chapter 3 reported associations between pre-operative bicaudate ratio (BCR) with levels of apathy and depression in patients with NPH. Specifically, greater BCR (greater ventriculomegaly) was associated with more severe levels of self-rated apathy and depression at pre-shunt. It was hypothesised that BCR may be related to subcortical atrophy or dysfunction of fronto-subcortical regions in NPH, and that this may underlie the symptom of apathy. Indeed, caudate atrophy has previously been observed in NPH patients (DeVito et al., 2007). To test this further, a structural magnetic resonance imaging (MRI) study was conducted to investigate global and regional volumetric changes in NPH and their association with apathy and cognitive dysfunction.

Global and regional brain volumetric changes in NPH have not been extensively investigated using quantitative MRI techniques. A well as ventriculomegaly, brain volume in patients with NPH may be related to disease severity, brain damage/dysfunction, or atrophy. Previous research of volumetric changes in NPH are outlined below.

4.1.1. Total brain volume in NPH

It has not been established whether brain volume in NPH relates to clinical symptoms. One study investigated whether pre-operative intracranial compartment volumes (specifically, total intracranial volume, ventricular volume, brain volume, and pericerebral CSF volume) are related to post-shunt outcome (Palm et al., 2006). No statistically significant pre-operative volumetric differences were found between patients who improved following shunt and those who did not. Therefore, the researchers concluded that volumetric assessment had no utility for identifying shunt responders. However, relationships between volumes and clinical measures
at pre-shunt were not reported. Another study (Singer et al., 2012) reported increased global brain volume following diagnostic CSF removal (via lumbar puncture or external lumbar drainage) which they suggested may be clinically meaningful. However, they did not examine whether volumetric changes were related to clinical scores or clinical outcome. The present study extracted pre-operative total brain volume, total grey matter volume, and total white matter volume in a group of patients with NPH in order to examine whether volumes were related to cognitive function. Additionally, this study investigated whether total brain volume was reduced in patients with NPH compared to controls.

4.1.2. Subcortical volumetric changes in NPH

Periventricular regions are frequently implicated in studies of NPH and subcortical pathology has been suggested to contribute to the symptomology (Del Bigio, 1993; Momjian et al., 2004). The pattern of cognitive decline is consistent with dysfunction of subcortical structures and may indicate disruption to the subfrontal white matter, limbic connections, or connections between the frontal lobe and the subcortical deep grey matter (SDGM) structures (N. C. H. Keong et al., 2016). Indeed, impaired rCBF has been found in the periventricular white matter and in the basal ganglia (Owler et al., 2004; Ziegelitz et al., 2014).

The presence of apathy (impaired goal-directed behaviour) in NPH is consistent with fronto-subcortical pathology. Apathy can result from lesions affecting fronto-subcortical circuitry (Mega & Cohenour, 1997; Tekin & Cummings, 2002), or from focal lesions of the basal ganglia (Levy & Czernecki, 2006; Tekin & Cummings, 2002), including lesions located in the caudate nucleus (Bhatia & Marsden, 1994). Diminished caudate volume in NPH patients was observed by DeVito et al. (2007) and hypothesised to contribute to the clinical symptoms of cognitive impairment and apathy. Chapter 3 found evidence for an association between greater bicaudate ratio (greater ventriculomegaly) with increased levels of apathy and depression in NPH patients. Additionally, evidence for associations between apathy and rCBF in the anterior cingulate cortices and the right caudate nucleus has been reported (Kanemoto et al., 2015).

Subcortical volumes in NPH have not been extensively investigated using quantitative MRI techniques. The periventricular regions may be distorted due to enlargement of the ventricles. Atrophy may also occur over time due to ischaemia and subsequent cell death (Momjian et al., 2004; Vanneste, 1994). The few studies that have examined morphologic
changes to subcortical structures in NPH focused only on individual structures or did not relate volumetric data to clinical information (DeVito et al., 2007; Golomb et al., 1994; Savolainen et al., 2000). DeVito et al. observed reduced caudate volumes in NPH patients, however clinical information was not included in the study. Golomb et al. extracted hippocampal volumes in patients with NPH and correlated these with MMSE scores. They observed a significant reduction in hippocampal volume in the NPH patients compared to controls. Further, there was a significant positive correlation between hippocampal size and MMSE score in the NPH group. It was concluded that hippocampal atrophy may contribute to cognitive decline in some patients with NPH. Savolainen et al. also observed reduced hippocampal volume in NPH patients compared to healthy controls, but only on the left side. However, both Golomb et al. and Savolainen et al. extracted hippocampal volumes only. Therefore, total brain volume or volumes of other subcortical regions may also have been reduced and related to clinical or cognitive measures.

The present study investigated subcortical volumetric change in NPH in a larger range of SDGM structures, compared to previous investigations, using both automated (FSL FIRST; www.fmrib.ox.ac.uk/fsl) and manual (ITK-SNAP; www.itksnap.org) segmentation techniques. Initially, subcortical volumes were estimated using automated segmentation techniques, however, in some of the patients there was displacement of the caudate nuclei due to ventriculomegaly. Therefore, manual tracing of the caudate was conducted to supplement automated caudate segmentation. This study aimed to investigate (i) volumetric differences in SDGM structures compared to healthy controls at pre- and post-shunt; (ii) pre- to post-shunt change in SDGM structure volumes; and (iii) whether SDGM structure volumes are related to cognitive function/ outcome or neuropsychiatric symptoms.

This study is in two parts. Part I utilised automated segmentation techniques to extract pre-operative total brain volume, grey matter volume, white matter volume, and pre- and post-shunt SDGM structure volumes for patients with NPH. Volumes were also extracted for a control group at a single time point. Associations with cognitive dysfunction and neuropsychiatric symptoms were then investigated. Part II more closely examines the relationship between caudate volume and apathy by supplementing the automated subcortical segmentation with manually segmented caudate volumes.
4.2. Methods

4.2.1. Ethical approval

Ethical approval for this study, as part of a larger research project entitled ‘Functional, Vascular and Structural Correlates of Reversible Dementia in Normal Pressure Hydrocephalus (NPH)’, was obtained from the Cambridgeshire 2 Local Research Ethics Committee (LREC No: 06/Q0108/330).

4.2.2. Participants

Patients

Patient participants were patients who were given a diagnosis of possible or probable NPH at the CSF disorders clinic, Addenbrooke’s Hospital. Patients with NPH were referred to be included in the study by a neurosurgeon (JDP). Sixteen of these patients were included in the analyses that follow, based on having been assessed and scanned both before and following shunt surgery (mean = 6 months post-shunt). There is an overlap of five patients in Chapter 3 and Chapter 4. One patient was subsequently excluded from the following analyses as they had comorbid Alzheimer’s disease. One additional patient was excluded due to a complicated clinical course.

Controls

Healthy controls were recruited to take part in the project entitled ‘Functional, Vascular and Structural Correlates of Reversible Dementia in Normal Pressure Hydrocephalus’ via friends and family of patients recruited into the same study (to ensure that both groups are within similar age brackets), and via advertisement in the local area. Eight healthy controls were recruited into the study and were scanned at one time-point.

4.2.3. Neuropsychological assessment

Patients completed the Mini-Mental State Examination (MMSE), the Hopkins Verbal Learning Test (HVLT), the Controlled Oral Word Association Test (COWAT), the Cambridge State Apathy Evaluation scale (self-rated; AES-S), and the short form of the Geriatric Depression
Scale (GDS-15) pre- and post-operatively. IQ was assessed using the National Adult Reading Test (NART). To minimise practice effects, alternate versions of the phonemic and semantic fluency categories and the HVLT word list were used during the follow-up assessment. The tests are described in detail in section 3.2.3.

4.2.4. MR imaging protocol

MR Imaging was performed on a 3T Siemens Tim Trio using a 12 channel head matrix radio frequency receive coil. The MR imaging protocol included a PDT2, FLAIR, MPRAGE and DTI. The FLAIR (Fluid Attenuated inversion recovery) and PDT2 (Proton Density-T2 weighted) fast spin echo pulse sequence was acquired with FOV 224mmx168mm, 5mm slice separation, giving a voxel size 0.7x0.7x5mm. The PDT2 had TR/TE1/TE2, 4600ms/12ms/104ms and the FLAIR TR/TE of 7840/95ms with an inversion time T1=2500 ms. The T1 weighted structural sequence (MPRAGE) was acquired with TR/TE of 2300/2.98ms, with a resolution of 1x1x1mm. The DTI data set was acquired by using a spin echo diffusion-weighted echo planar imaging sequence with the following parameters: TR/TE, 8300ms/98ms, matrix dimensions 96x96, FOV 192x192, slice thickness 2mm giving a voxel size of 2x2x2mm. Diffusion weighted images were acquired in 12 non collinear directions each at 5 b-values of 350, 650, 1000, 1300 and 1600 s/mm$^2$, along with 4 b-0 images.
Part I: Global and regional volumetric analysis in normal pressure hydrocephalus: association with cognitive function and neuropsychiatric symptoms

4.3. Methods

4.3.1. Image analysis

Total brain volume estimation

Total brain volume estimation was conducted for the NPH group at pre-shunt only. This is because a shunt-induced artefact is visible at post-shunt.

Before processing, all images were manually inspected and reviewed for artefact. Brain tissue volume, normalised for subject head size, was estimated with SIENAX (Smith et al., 2002; Smith, De Stefano, Jenkinson, & Matthews, 2001), part of FSL (Smith et al., 2004). SIENAX starts by extracting brain and skull images from the single whole-head input data (Smith, 2002). The brain image is then affine-registered to MNI152 space (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001) (using the skull image to determine the registration scaling); this is primarily in order to obtain the volumetric scaling factor to be used as a normalisation for head size. Next, tissue-type segmentation with partial volume estimation is carried out (Zhang, Brady, & Smith, 2001) in order to calculate total volume of brain tissue (including separate estimates of volumes of grey matter (GM), white matter (WM), peripheral grey matter and ventricular CSF).

Subcortical segmentation

An automated subcortical registration and segmentation tool in FSL (FSL FIRST; www.fmrib.ox.ac.uk/fsl) was used to extract subcortical volumes as described in (Patenaude, Smith, Kennedy, & Jenkinson, 2011). All automated segmentations were thoroughly individually reviewed for accuracy.

SDGM structure and ventricular volumes were extracted for both groups. Volumes for the NPH group were extracted at two time-points: pre- and post-shunt, as they were below the level of the shunt artefact (therefore, segmentation was unaffected). FSL FIRST was used to segment the amygdala, caudate, hippocampus, nucleus accumbens, pallidum, putamen, and
thalamus from 3D T1-weighted images. Examples of subcortical segmentation are shown in Figure 4.1. SIENAX was used to obtain ventricular volumes normalised for head size, and volumetric scaling factors (as described above) for normalizing SDGM structure volumes for head size. SDGM structure volumes were normalised for head size by multiplying by the volumetric scaling factors. As laterality effects were not hypothesised, normalised right and left volumes of the SDGM structures were combined to yield a single total volume for each structure.

![Image of FIRST segmentation of subcortical structures](image)

**Figure 4.1:** Representative FIRST segmentation of subcortical structures in a patient with normal pressure hydrocephalus (left) and a healthy control subject (right)

### 4.3.2. Statistical analysis

**Demographic data**

Independent samples *t*-tests were conducted to test for group differences in age and ventricular volume. Pearson’s *r* correlations were conducted to investigate associations between demographic data and volumetric data; and with demographic data and neuropsychological test scores. Independent samples *t*-tests were conducted to investigate effects of sex on total brain, GM, and WM volume.

**Total brain volume**

One-way analyses of covariance (ANCOVAs) were conducted to test for group differences in total brain volume, GM, and WM volume while controlling for age and ventricular volume.
Pearson’s $r$ correlations were conducted to investigate associations between neuropsychological test scores and total brain, GM, and WM volume in the NPH group. Partial correlations were conducted where appropriate.

**Subcortical deep grey matter structures**

ANCOVAs were conducted to test for group differences in SDGM structure volumes while controlling for age and ventricular volume. Paired samples $t$-tests were conducted to test for differences in SDGM volumes between pre- and post-shunt in the NPH group. Pearson’s $r$ correlations were conducted to investigate associations between neuropsychological test scores and SDGM volumes in the NPH group. Partial correlations were conducted where appropriate. For ventricular volume, SDGM structures showing significant volumetric differences from pre- to post-shunt, and neuropsychological test scores showing significant differences from pre- to post-shunt percent change scores were calculated according to the following: $\frac{(\text{follow-up value} - \text{baseline value})}{\text{baseline value}} \times 100$. Subsequently, Pearson’s $r$ correlations were conducted to investigate relationships between percent change neuropsychological test scores with percent volumetric changes and demographic data.

**Neuropsychological tests**

Paired samples $t$-tests were conducted to test for differences in neuropsychological test scores between pre- and post-shunt in the NPH group.

### 4.4. Results

#### 4.4.1. Demographic information

The final patient group consisted of fourteen patients (nine male and five female). Demographic information for the NPH group are summarised in Table 4.1. Four healthy controls were male and four were female. The NPH group was older than the control group: NPH group mean ($SD$) age in years = 76.43 (3.90), range = 70 – 84; control group mean ($SD$) age in years = 70.25 (6.56), range = 64 – 80; and this difference was statistically significant ($t$ (9.89) = 2.43, $p = 0.036$).
4.4.2. Ventricular volumes

Mean (SD) ventricular volume for the NPH group at pre-shunt was 160405.9 (15666.8) mm$^3$ and at post-shunt was 135820 (28012.3) mm$^3$. Ventricular volume was reduced following shunt surgery for all patients (mean = -15.67%, range -1.97% to -48.94%). A paired samples $t$-test indicated that the mean ventricular volume for the NPH group at post-shunt was significantly smaller than at pre-shunt ($t$ (13) = 4.39, $p$ = 0.001). The mean (SD) ventricular volume for the control group was 71187 (17198.3) mm$^3$. Independent samples $t$-tests indicated that the mean ventricular volume of the NPH group was significantly larger than that of the control group at both pre-shunt ($t$ (20) = 12.41, $p$ < 0.001) and post-shunt ($t$ (20) = 5.89, $p$ < 0.001).

Table 4.1: Demographic information for the NPH group

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>76.4</td>
<td>3.9</td>
</tr>
<tr>
<td>IQ</td>
<td>110.8</td>
<td>10.4</td>
</tr>
<tr>
<td>MMSE</td>
<td>24</td>
<td>3.3</td>
</tr>
<tr>
<td>Years of education</td>
<td>11.1</td>
<td>2.2</td>
</tr>
</tbody>
</table>

4.4.3. Correlation of demographic data with volumetric data

*NPH group*

Age was significantly negatively correlated with pre-operative WM volume ($r = -0.60$, $p = 0.024$) and total brain volume ($r = -0.61$, $p = 0.021$; Figure 4.2), but was not significantly correlated with GM volume or ventricular volume. IQ and years of education were not significantly correlated with total brain, GM, or WM volume (all $p > 0.05$). Total brain, WM and GM volumes were not significantly different between males and females. Ventricular volume did not significantly correlate with pre-operative GM, WM, or total brain volume.

IQ was significantly negatively correlated with volume of the pallidum at post-shunt ($r = -0.62$, $p = 0.040$). There were no significant correlations between age, years of education, or ventricular volume with SDGM structure volumes in the NPH group at pre-shunt or at post-shunt (all $p > 0.05$).
**Control group**

There were no significant correlations between age or ventricular volume with GM volume, WM volume, or total brain volume in the control group. Additionally, there was no significant correlation between age and ventricular volume. Age was not significantly correlated with volume of any of the SDGM structures. Ventricular volume was significantly negatively correlated with volume of the hippocampus ($r = -0.82$, $p = 0.013$), but was not significantly correlated with volume of any of the remaining SDGM structures.

![Figure 4.2: Scatterplots showing relationships between age and brain volume (ml) in NPH](image)

White matter volume (A.) and total brain volume (B.) extracted from pre-shunt scans.
4.4.4. Correlation of demographic data and ventricular volume with neuropsychological test scores in the NPH group

IQ was significantly positively correlated with MMSE score at pre-shunt ($r = 0.80$, $p = 0.003$), and with semantic fluency at post-shunt ($r = 0.60$, $p = 0.049$). Age, years of education, and ventricular volume were not significantly correlated with scores in any of the neuropsychological tests at pre- or post-shunt.

4.4.5. Baseline total brain volume, grey matter volume, and white matter volume

**Volumetric comparisons between patients with NPH at pre-shunt and controls**

There were no significant group differences in grey matter, white matter, or total brain volume after controlling for age and ventricular volume (Table 4.2). Similarly, there were no significant group differences in grey matter, white matter, or total brain volume when only controlling for age (all $p > 0.05$).

**Table 4.2: Results of ANCOVAs for group differences in grey matter, white matter, and total brain volume**

<table>
<thead>
<tr>
<th></th>
<th>NPH Mean (SD) volume</th>
<th>Control Mean (SD) volume</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grey matter</td>
<td>673247.5 (40433)</td>
<td>707765.6 (47196.2)</td>
<td>0.142</td>
</tr>
<tr>
<td>White matter</td>
<td>640772.1 (33456.7)</td>
<td>667535.5 (40409.8)</td>
<td>0.264</td>
</tr>
<tr>
<td>Total brain</td>
<td>1314019.5 (59379)</td>
<td>1375301.1 (71061.3)</td>
<td>0.094</td>
</tr>
</tbody>
</table>

Note: Volumes are in mm$^3$

**Correlation with cognitive test scores in the NPH group (pre-shunt)**

White matter volume was significantly positively correlated with GDS-15 score ($r = 0.65$, $p = 0.029$). That is, greater white matter volume was associated with more severe depressive symptoms. Additionally, white matter volume was significantly negatively correlated with scores on the HVLT learning ($r = -0.59$, $p = 0.035$) and delayed ($r = -0.60$, $p = 0.031$) subtests. That is, greater white matter volume was associated with poorer performance on the two
subtests. Grey matter volume and total brain volume were not significantly correlated with scores in any of the cognitive tests.

Since age was significantly negatively correlated with white matter volume in the NPH group, partial correlations were conducted to investigate relationships between white matter volume with GDS-15, HVLT learning, and HVLT delayed scores after controlling for age. White matter volume and GDS-15 score were no longer significantly correlated ($r = 0.58, p = 0.080$). There was a slight but non-significant negative relationship between white matter volume and HVLT learning score ($r = -0.57, p = 0.054$). The negative correlation between white matter volume and HVLT delayed score remained statistically significant ($r = -0.69, p = 0.014$). The nature of the relationship is shown in Figure 4.3.

![Figure 4.3: Scatterplot showing the relationship between white matter volume (ml) and score on Hopkins Verbal Learning Test - Delayed](image)

4.4.6. Subcortical volumetric comparisons between patients with NPH at pre-shunt and controls

Results of ANCOVAs are shown in Table 4.3. Mean volume of the caudate was significantly reduced in the NPH group at pre-shunt compared to healthy controls after controlling for age and ventricular volume.
Table 4.3: Results of ANCOVAs for group differences in pre-shunt SDGM structure volumes

<table>
<thead>
<tr>
<th>SDGM structure</th>
<th>NPH Mean (SD) volume</th>
<th>Control Mean (SD) volume</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>13141.5 (883.4)</td>
<td>17590.6 (1865.1)</td>
<td>0.147</td>
</tr>
<tr>
<td>Caudate</td>
<td>6720.4 (485.1)</td>
<td>8627.6 (726.8)</td>
<td>0.045*</td>
</tr>
<tr>
<td>Putamen</td>
<td>7150.3 (1771.8)</td>
<td>11658.7 (1269.2)</td>
<td>0.076</td>
</tr>
<tr>
<td>Pallidum</td>
<td>2903 (639)</td>
<td>4139.9 (562.4)</td>
<td>0.073</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>5356.7 (1142.8)</td>
<td>9211.9 (1271.5)</td>
<td>0.491</td>
</tr>
<tr>
<td>Amygdala</td>
<td>2631.4 (605.9)</td>
<td>3148.5 (638.9)</td>
<td>0.807</td>
</tr>
<tr>
<td>Nucleus Accumbens</td>
<td>483.7 (100.9)</td>
<td>1010.6 (237.9)</td>
<td>0.720</td>
</tr>
</tbody>
</table>

Note: Volumes are in mm$^3$; * p < 0.05.

4.4.7. Correlation between SDGM structure volumes and cognitive test scores at pre-shunt

Volume of the caudate was significantly positively correlated with MMSE score ($r = 0.73$, $p = 0.040$), and volume of the nucleus accumbens was significantly positively correlated with HVLT immediate score ($r = 0.70$, $p = 0.035$). That is, greater caudate volume was associated with better performance on the MMSE, and greater nucleus accumbens volume was associated with better performance on HVLT immediate. There were no other significant correlations between SDGM structures and cognitive test scores at pre-shunt.

Since IQ and pre-operative MMSE score were significantly correlated, a partial correlation was conducted to investigate the relationship between caudate volume and MMSE after controlling for IQ. The relationship was no longer significant ($r = 0.65$, $p = 0.160$).
4.4.8. Subcortical volumetric comparisons between patients with NPH at post-shunt and controls

Results of ANCOVAs are shown in Table 4.4. Mean volumes of the putamen, pallidum, hippocampus, and nucleus accumbens were significantly reduced in the NPH group at post-shunt compared to healthy controls after controlling for age and ventricular volume.

Table 4.4: Results of ANCOVAs for group differences in post-shunt SDGM structure volumes

<table>
<thead>
<tr>
<th>SDGM structure</th>
<th>NPH Mean (SD) volume</th>
<th>Control Mean (SD) volume</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>14112.4 (1287.1)</td>
<td>17590.6 (1865.1)</td>
<td>0.092</td>
</tr>
<tr>
<td>Caudate</td>
<td>6965.3 (822.6)</td>
<td>8627.6 (726.8)</td>
<td>0.165</td>
</tr>
<tr>
<td>Putamen</td>
<td>8737.2 (1410.2)</td>
<td>11658.7 (1269.2)</td>
<td>0.039*</td>
</tr>
<tr>
<td>Pallidum</td>
<td>3226.5 (646.5)</td>
<td>4139.9 (562.4)</td>
<td>0.045*</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>6302.9 (1051.6)</td>
<td>9211.9 (1271.5)</td>
<td>0.045*</td>
</tr>
<tr>
<td>Amygdala</td>
<td>2889.4 (642.2)</td>
<td>3148.5 (638.9)</td>
<td>0.363</td>
</tr>
<tr>
<td>Nucleus Accumbens</td>
<td>531 (182)</td>
<td>1010.6 (237.9)</td>
<td>0.028*</td>
</tr>
</tbody>
</table>

Note: Volumes are in mm$^3$; * $p < 0.05$.

4.4.9. Correlation between SDGM structure volumes and cognitive test scores at post-shunt

Volume of the caudate was significantly positively correlated with semantic fluency ($r = 0.67$, $p = 0.035$), and significantly negatively correlated with AES-S ($r = -0.73$, $p = 0.026$). Volume of the nucleus accumbens was significantly positively correlated with MMSE score ($r = 0.61$, $p = 0.028$), HVLT immediate ($r = 0.58$, $p = 0.039$), HVLT learning ($r = 0.68$, $p = 0.011$), and HVLT delayed ($r = 0.61$, $p = 0.027$). For all significant positive correlations, greater volumes were associated with better performance on cognitive tests, while greater caudate volume was associated with less severe level of self-rated apathy.
Since IQ and post-operative semantic fluency score were significantly correlated, a partial correlation was conducted to investigate the relationship between caudate volume and semantic fluency after controlling for IQ. The relationship was no longer significant ($r = 0.53$, $p = 0.182$).

### 4.4.10. Pre- and post-shunt volumetric comparisons

Paired samples $t$-tests indicated significant increase in volume of the thalamus, $t (10) = -2.85$, $p = 0.017$; and hippocampus, $t (10) = -3.02$, $p = 0.013$, following shunt surgery. The mean pre- and post-shunt volumes of the remaining SDGM structures were not significantly different. Pearson’s $r$ correlations revealed no relationship between age, IQ, or years of education with percent change in volumes of the thalamus or hippocampus. Percent change in ventricular volume (from pre- to post-shunt) was significantly negatively correlated with percent change in volume of the thalamus ($r = -0.88$, $p < 0.001$), but did not correlate with percent change in volume of the hippocampus.

### 4.4.11. Neuropsychological outcome

Neuropsychological outcome in the NPH group following shunt is summarised in Table 4.5. Scores for all tests were in the direction of improvement following shunt surgery (apart from GDS-15 score which was unchanged). Paired samples $t$-tests indicated significant improvement in scores for semantic fluency, HVLT immediate, and HVLT learning.

### 4.4.12. Correlation of percent change in cognitive test scores with SDGM structure and ventricular volumes

There were no significant correlations between percent change in volumes of the thalamus and hippocampus, with percent change scores in semantic fluency, HVLT immediate, or HVLT learning. Further, percent change scores in semantic fluency, HVLT immediate, and HVLT learning were not significantly correlated with percent change in ventricular volume (all $p > 0.05$).
Table 4.5: Neuropsychological outcome following shunt surgery

<table>
<thead>
<tr>
<th>Test</th>
<th>N</th>
<th>Pre-shunt Mean (SD)</th>
<th>Post-shunt Mean (SD)</th>
<th>t</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>12</td>
<td>23.92 (3.40)</td>
<td>24.58 (3.92)</td>
<td>-0.70</td>
<td>11</td>
<td>0.497</td>
</tr>
<tr>
<td>AES-S</td>
<td>10</td>
<td>18.60 (7.95)</td>
<td>15.60 (9.06)</td>
<td>1.15</td>
<td>9</td>
<td>0.278</td>
</tr>
<tr>
<td>GDS-15</td>
<td>10</td>
<td>5.10 (2.51)</td>
<td>5.10 (3.93)</td>
<td>0.00</td>
<td>9</td>
<td>1.000</td>
</tr>
<tr>
<td>Phonemic fluency</td>
<td>12</td>
<td>29.75 (14.20)</td>
<td>30.33 (16.96)</td>
<td>-0.19</td>
<td>11</td>
<td>0.853</td>
</tr>
<tr>
<td>Semantic fluency</td>
<td>11</td>
<td>10.00 (3.98)</td>
<td>13.45 (3.83)</td>
<td>-2.40</td>
<td>10</td>
<td>0.038*</td>
</tr>
<tr>
<td>HVLT immediate</td>
<td>12</td>
<td>3.83 (1.40)</td>
<td>4.58 (1.68)</td>
<td>-3.00</td>
<td>11</td>
<td>0.012*</td>
</tr>
<tr>
<td>HVLT learning</td>
<td>12</td>
<td>13.83 (4.86)</td>
<td>17.50 (6.07)</td>
<td>-2.70</td>
<td>11</td>
<td>0.020*</td>
</tr>
<tr>
<td>HVLT delayed</td>
<td>12</td>
<td>2.17 (2.76)</td>
<td>3.08 (4.17)</td>
<td>-0.74</td>
<td>11</td>
<td>0.473</td>
</tr>
</tbody>
</table>

Note: MMSE = Mini-Mental State Examination; AES-S = self-rated State Apathy Evaluation; GDS-15 = Geriatric Depression Scale short form; HVLT = Hopkins Verbal Learning Test; * p < 0.05.

4.5. Summary

Part I of the present study conducted a volumetric assessment in patients with NPH using automated segmentation techniques. Total brain volume and volumes of subcortical structures in NPH patients were compared to healthy controls; and associations between volumetric data and cognitive function/outcome were investigated.

4.5.1. Pre-operative total brain volume

Total brain, GM, and WM volumes were extracted at pre-shunt in the NPH group. As would be expected, age was significantly negatively correlated with WM volume and total brain volume in the NPH group. However, ventricular volume was not significantly correlated with total brain, GM, or WM volume. The average total brain, GM, and WM volumes of the NPH group were smaller than those for the control group but the differences were not statistically significant.
One previous study (Serulle et al., 2014) compared GM, WM, and ventricular volumes in patients with NPH, patients with Alzheimer’s disease (AD), and healthy controls. They found a statistically significant reduction in GM volume in patients with AD compared to NPH patients and controls. Although the mean GM volume for the NPH group was smaller than the control group mean, the difference was not statistically significant. No significant differences in WM volume were observed across the three groups. Ventricular volume in the NPH group was significantly larger than in the two remaining groups. Therefore, the results of the present study support the findings by Serulle et al.

These results might suggest that, despite the ventriculomegaly, total brain volume in patients with NPH is not markedly reduced, or that brain atrophy is absent or mild in NPH. However, as the sample sizes in these studies were small, a larger study is needed to verify this finding. Another explanation could be that the patients in the present study and in the previous study had relatively short disease durations but that brain atrophy could occur as the disease progresses. The relationship between disease duration and total brain volume in NPH would be an interesting topic for future research. Finally, brain atrophy may only occur in a subgroup of NPH patients, such as those with comorbid AD (Serulle et al., 2014).

The present study also investigated whether total brain, GM, and WM volumes were associated with cognitive performance. After controlling for the effect of age, WM volume was significantly negatively correlated with HVLT delayed score, and there was a trend towards a significant negative correlation between WM volume and HVLT learning score. That is, reduced WM volume was associated with better performance on a measure of delayed recall. The reason for this relationship is unclear and warrants further investigation. However, GM and total brain volume did not significantly correlate with scores in any of the cognitive tests.

4.5.2. Subcortical deep grey matter structure volumes

Volumetric assessment of SDGM structures was conducted in patients with NPH at both pre- and post-shunt. At baseline, mean volume of the caudate nucleus was significantly reduced in NPH patients compared to healthy controls after controlling for age and ventricular volume. Correlations between subcortical volumes and neuropsychological test scores in the NPH patient group at pre-shunt revealed that greater caudate volume was associated with better performance on the MMSE, and greater nucleus accumbens volume was associated with better performance on the HVLT immediate subtest. However, after controlling for IQ, the
relationship between caudate volume and MMSE score was no longer significant. At post-shunt, volumes of the putamen, pallidum, hippocampus and nucleus accumbens were significantly reduced in the NPH group compared to controls after controlling for age and ventricular volume. Additionally, at post-shunt, greater caudate volume was associated with better semantic fluency performance and less severe levels of apathy; and greater nucleus accumbens volume was associated with better performance on the MMSE as well as better performance on the immediate, learning and delayed subtests of the HVLT. After controlling for IQ, the relationship between caudate volume and semantic fluency was no longer significant.

Reduced caudate volume was previously noted by our laboratory in a group of NPH patients who had not yet undergone shunt surgery (DeVito et al., 2007). While the previous study segmented the caudate nuclei only, in the present study, volumes for a greater range of SDGM structures were extracted. Despite this, at pre-shunt, the caudate was the only SDGM structure showing a statistically significant volume reduction compared to controls. DeVito et al. (2007) further hypothesised that caudate volume loss may contribute to cognitive decline and apathy in NPH. In the present study, caudate volume was associated with apathy at post-shunt.

At post-shunt, while there was no significant difference in mean caudate volume compared to pre-shunt, mean caudate volume was no longer significantly reduced compared to controls. Instead, the putamen, pallidum, hippocampus, and nucleus accumbens showed significant volume reductions compared to controls. Further, volume of the nucleus accumbens was associated with performance on the MMSE at post-shunt, and with verbal learning and memory at pre- and post-shunt. The nucleus accumbens forms part of the ventral striatum and has been linked to learning and memory (Setlow, 1997), and dementia (de Jong et al., 2012). Thus, the associations between caudate and nucleus accumbens volume with scores on neuropsychological tests and apathy suggest that striatal volume reductions in NPH may be related to functional impairment of these areas. While volumes of the putamen and pallidum did not correlate with performance in cognitive tests, both of these regions have been shown to play a role in movement (DeLong et al., 1984; Heimer, Switzer, & Van Hoesen, 1982; Marchand et al., 2008; Mogenson, Jones, & Yim, 1980). Therefore, future studies should investigate whether gait dysfunction in NPH is related to volumes of the pallidum and putamen.

Although there were significant group improvements in tests of semantic fluency, and verbal learning and memory following shunt surgery; as well as significant volume increases
in the thalamus, and hippocampus, percent change in these variables were not significantly correlated. Therefore, SDGM volumetric change following shunt surgery cannot account for the observed cognitive improvement in the present study. However, regional volumetric changes following shunt may be associated with other measures of cognitive or functional outcome.

It is unclear why volumes of specific SDGM structures might increase following shunt surgery. While percent increase in volume of the thalamus was significantly correlated with percent reduction in ventricular volume, reduced ventricular volume was not significantly correlated with increased volume of the hippocampus. Therefore, ventricular reduction may not be the sole mechanism leading to SDGM volumetric changes. A previous study investigating whole brain volume change following diagnostic CSF removal found an increase in global brain volume which was particularly evident in periventricular, frontal, and temporal regions (Singer et al., 2012). The researchers hypothesised that increased brain volume may be due to increased cerebral blood volume, and that this in turn might lead to improved cerebral perfusion. However, further research is needed to investigate whether regional volumetric changes are associated with changes in rCBF.

Overall, the results suggest there is reduction of volumes of subcortical structures both before and following shunt surgery in NPH that is not solely due to ventricular enlargement. Striatal volumes in particular appear to be associated with cognitive performance and apathy in NPH. These results suggest that at least some of the cognitive decline in patients with NPH may be due to subcortical dysfunction.

4.5.3. Rationale for Part II

There was a significant negative correlation between caudate volume and apathy at post-shunt (that is, a reduction in caudate volume was associated with increased apathy severity), but this relationship was not observed at pre-shunt. However, due to problems with caudate segmentation in particular (due to ventriculomegaly), caudate volumetric information was not available for five of the patients at pre-shunt, and three of the patients at post-shunt, considerably reducing the sample size for caudate volume analyses. Therefore, in order to further investigate the relationship between caudate volume and apathy in NPH patients (at pre- and post-shunt), Part II of the present study was conducted in which the caudate nuclei were segmented manually for the NPH group. Specifically, Part II aimed to investigate whether
caudate volume is related to apathy at pre-shunt (i.e. whether the reduced sample size explains the lack of a relationship at pre-shunt in Part I), as well as at post-shunt.
Part II: Volume of the caudate nucleus in NPH: association with apathy and cognition

4.6. Introduction

Part 1 of the present study reported an association between caudate volume and apathy at post-shunt, but not at pre-shunt, in patients with NPH. Apathy was not significantly correlated with volume of any other subcortical deep grey matter (SDGM) structure at either pre- or post-shunt. However, at pre-shunt the caudate nuclei were not reliably extracted for five of the patients (and were therefore not included in the analysis) and this might explain the lack of relationship between caudate volume and apathy at pre-shunt. Previous research has suggested a link between caudate dysfunction and apathy in NPH (Kanemoto et al., 2015) and in other dementias (Bruen, McGeown, Shanks, & Venneri, 2008; Levy & Czernecki, 2006). Therefore, in order to further investigate the relationship between caudate volume and apathy, manual segmentation of the caudate was conducted from both pre- and post-shunt scans.

4.7. Methods

4.7.1. Image analysis

Caudate segmentation was performed on T1-weighted images using ITK-SNAP version 3.4.0 (www.itksnap.org; Yushkevich et al., 2006). The right and left caudate nuclei were traced manually on contiguous axial slices as described by Looi et al., (2008). Segmentation began with the most inferior slice where the caudate nucleus was visible, bounded by the frontal white matter anteriorly, the anterior commissure posteriorly, and the internal capsule laterally (Looi et al., 2008). Tracing proceeded superiorly from the head to the tail of the caudate until the tail of the caudate was no longer distinguishable from the wall of the lateral ventricle. Caudate segmentation was then checked in the coronal and sagittal views where any errors were corrected. Finally, a 3D view of the segmented caudate nucleus is compiled and this was checked for abnormalities (Figure 4.4).

The volumetric scaling factors obtained using SIENAX in Part I of the present study (see section 4.3.1) were used to normalise the volumes for head size (volumes were normalised
for head size by multiplying by the volumetric scaling factors). As laterality effects were not hypothesised, normalised right and left volumes of the caudate were combined to yield a single total volume. Estimates of ventricular volume were also obtained using SIENAX (section 4.3.1).

### 4.7.2. Statistical analysis

Pearson’s $r$ correlations were conducted to investigate associations between caudate volumes obtained via automated segmentation and via manual tracing. Independent samples $t$-tests were conducted to investigate differences in volumes in patients who were included in Part I and those who were excluded. Pearson’s $r$ correlations were conducted to investigate associations between demographic data and neuropsychological test scores; demographic data and volumetric data; and between volumetric data and neuropsychological test scores. Partial correlations were conducted where appropriate. Independent samples $t$-tests were conducted to investigate effects of sex on caudate volume at pre- and post-shunt. A paired samples $t$-test was conducted to investigate differences in caudate volume at pre- and post-shunt.

Figure 4.4: Segmented right caudate in (A) axial section, (B) sagittal section, and (C) coronal section in a representative NPH patient; (D) 3D rendering of caudate volume
4.8. Results

4.8.1. Demographic information

As detailed in section 4.4.1, one patient from the initial sample was excluded due to comorbid AD and one patient was excluded due to having a complicated post-operative course. Therefore, the final patient group for Part II of the present study was fourteen (nine male and five female). Demographic information is presented in Table 4.1.

4.8.2. Comparison of volumes obtained via automated and manual segmentation

Caudate volumes obtained via manual tracing and via automated segmentation (section 4.3.1) were significantly correlated at both pre- \((r = 0.74, p = 0.035)\) and post-shunt \((r = 0.76, p = 0.011)\). Mean \((SD)\) volumes obtained by manual tracing and automated segmentation are shown in Table 4.6. Mean caudate volumes obtained via manual tracing were smaller than those obtained via automated segmentation. To examine whether this was due to the inclusion of additional patients in the manual tracing analysis, the patients were split into those who were included in the automated segmentation analyses in Part I of the present study, and those who had been excluded (due to failure of automated caudate segmentation). Manual tracing of the caudate was conducted for an additional six patients at pre-shunt, and an additional four patients at post-shunt in comparison to automated segmentation in Part I. Independent samples \(t\)-tests indicated that the mean (manually segmented) caudate volumes for the patients who had been excluded from the automated segmentation were not significantly different from those for whom automated segmentation was successful at pre- \((p > 0.05)\) or at post-shunt \((p > 0.05)\) (see Table 4.7). Therefore, the reduced volumes obtained via manual tracing are not due to the inclusion of additional participants.

Table 4.6: Caudate volumes obtained via automated segmentation and manual tracing

<table>
<thead>
<tr>
<th>Method</th>
<th>Pre-shunt caudate volume</th>
<th>Post-shunt caudate volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ((SD); N)</td>
<td>Mean ((SD); N)</td>
</tr>
<tr>
<td>Automated segmentation</td>
<td>6720.4 (485.1); 8</td>
<td>6965.3 (822.6); 10</td>
</tr>
<tr>
<td>Manual tracing</td>
<td>6288.7 (1386.2); 14</td>
<td>5610 (901.5); 14</td>
</tr>
</tbody>
</table>

Note: Volumes are in \(\text{mm}^3\); volumes shown have been normalised for head size.
Table 4.7: Caudate volumes obtained via manual tracing for patients included or excluded from automated segmentation

<table>
<thead>
<tr>
<th>Patient subgroup</th>
<th>Pre-shunt caudate volume</th>
<th>Post-shunt caudate volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD); N</td>
<td>Mean (SD); N</td>
</tr>
<tr>
<td>Included in automated segmentation analysis</td>
<td>6191.9 (1643.4); 8</td>
<td>5470.6 (1044.9); 10</td>
</tr>
<tr>
<td>Excluded from automated segmentation analysis</td>
<td>6417.7 (1086.1); 6</td>
<td>5958.5 (138.1); 4</td>
</tr>
</tbody>
</table>

Note: Volumes are in mm³; volumes obtained via manual tracing method.

4.8.3. Correlation between demographic data and neuropsychological test scores

At pre-shunt, years of education was significantly positively correlated with semantic fluency ($r = 0.68, p = 0.015$). At post-shunt, years of education was significantly positively correlated with MMSE score ($r = 0.53, p = 0.050$). At pre-shunt, IQ was significantly positively correlated with MMSE score ($r = 0.80, p = 0.002$). At post-shunt, IQ was significantly positively correlated with semantic fluency ($r = 0.60, p = 0.039$) and HVLT learning ($r = 0.61, p = 0.035$). Age was not significantly correlated with scores in any of the neuropsychological tests at pre- or post-shunt (section 4.4.4).

4.8.4. Pre- and post-operative volumetric results

Caudate volume was not significantly correlated with ventricular volume, IQ or age at pre- or post-shunt ($p > 0.05$). Mean caudate volumes of males and females were not significantly different at pre- or post-shunt ($p > 0.05$). Years of education was significantly positively correlated with caudate volume at both pre- ($r = 0.57, p = 0.035$) and post-shunt ($r = 0.60, p = 0.023$). There was no significant difference in caudate volume between pre- and post-shunt (means and standard deviations are shown in Table 4.6).
4.8.5. Correlation with neuropsychological test scores and neuropsychiatric symptoms

*Pre-shunt*

Caudate volume was significantly positively correlated with MMSE score ($r = 0.63, p = 0.022$), phonemic fluency ($r = 0.64, p = 0.019$), semantic fluency ($r = 0.78, p = 0.003$), and HVLT delayed ($r = 0.59, p = 0.035$) at pre-shunt. Since pre-operative MMSE score was significantly correlated with IQ, and caudate volume at pre-shunt was significantly correlated with years of education, a partial correlation was conducted to investigate the relationship between caudate volume and MMSE while adjusting for IQ and years of education. The correlation between caudate volume and MMSE was no longer significant ($r = 0.50, p = 0.138$). After adjusting for years of education, the relationships between caudate volume and phonemic and semantic fluency remained significant ($p = 0.006$ and $p = 0.019$, respectively; see Figure 4.5 and Figure 4.6), while the relationship between caudate volume and HVLT delayed was no longer significant ($p = 0.198$).

![Figure 4.5: Scatterplot showing the relationship between caudate volume and phonemic fluency performance (pre-shunt)](image_url)
At post-shunt, caudate volume was significantly positively correlated with MMSE score ($r = 0.78, p = 0.001$), meaning greater caudate volume was associated with better performance on the MMSE. Additionally, caudate volume was significantly negatively correlated with AES-S ($r = -0.69, p = 0.009$) and GDS-15 ($r = -0.55, p = 0.042$), meaning greater caudate volume was associated with less severe levels of apathy and depression. Following partial correlations adjusting for years of education, the relationship between caudate volume and AES-S score remained significant ($r = -0.65, p = 0.023$; Figure 4.7), however caudate volume was no longer significantly correlated with MMSE ($p = 0.080$) or GDS-15 ($p = 0.165$).
Figure 4.7: Scatterplot showing the relationship between caudate volume and apathy (post-shunt)

4.8.6. Distribution of AES-S ratings at pre- and post-shunt

Distributions of AES-S ratings at pre- and post-shunt are shown in Figure 4.8. As shown in the figure, the range of AES-S ratings at post-shunt is greater than at pre-shunt.
Figure 4.8: Box-plot diagram showing AES-S ratings in patients with NPH at pre- and post-shunt

Pre-shunt – $n = 11$; median = 15; range = 10-32. Post-shunt – $n = 13$; median = 11; range = 7-36.

4.9. Discussion

In Part I of the present study, an association between apathy and caudate volume was found in patients with NPH at post-shunt but not at pre-shunt. However, the automated segmentation method used failed to accurately segment the caudate in a number of patients, particularly from pre-operative MRI scans, reducing the sample size considerably. Therefore, Part II of the present study was conducted to supplement the analyses related to the caudate. In Part II, the caudate was segmented via manual tracing in order to further investigate associations with apathy and cognition and, specifically, to investigate whether caudate volume is related to apathy at pre-shunt.

The results from Part II of the present study supported those from Part I in that there was a significant correlation between caudate volume and apathy at post-shunt, but not at pre-shunt. The nature of the correlations indicated that, at post-shunt, greater caudate volume was associated with less severe levels of apathy. DeVito et al. (2007) found evidence for caudate atrophy in patients with NPH, and the researchers pointed out that the symptoms of NPH (including executive dysfunction and apathy) have been associated with dysfunction of the caudate. Additionally, O provided evidence for a relationship between bicaudate ratio (which was suggested to possibly relate to subcortical atrophy) with apathy. The results of the present
study provide support to the notion that caudate dysfunction occurs in NPH, and that this contributes to the behavioural symptomology. Kanemoto et al., (2015) recently found evidence for an association between improvement in apathy following shunt surgery with improved regional cerebral blood flow (rCBF) in the anterior cingulate cortices and the right caudate nucleus. Therefore, caudate volume reduction might relate to reduction in rCBF.

It is unclear why the association between apathy and caudate volume was specific to post-shunt. The sample size was reduced at pre-shunt in Part I of the study, however, pre- and post-shunt sample sizes were equal for Part II. Therefore, the lack of relationship at pre-shunt was not due to the reduced sample size in Part I. The distributions of AES-S ratings at pre- and post-shunt were plotted in Figure 4.8. As shown in the figure, the range of ratings was larger at post-shunt, perhaps indicating that the pre-operative range was not broad enough for a statistically significant relationship to be detected. Another explanation might be that some of the more cognitively impaired patients at pre-shunt lack insight into their apathetic symptoms, meaning their AES-S ratings were unreliable. However, the above findings should be verified in a larger sample size before investigating these issues further.

Caudate volume was further associated with performance in neuropsychological tests. While a number of the correlations in Parts I and II did not remain statistically significant after controlling for the effects of IQ and years of education, manually traced caudate volumes were significantly correlated with phonemic and semantic fluency at pre-shunt after controlling for years of education. Additionally, volume of the nucleus accumbens was significantly correlated with MMSE score at post-shunt, and with performance on tests of verbal learning and memory at pre- and post-shunt. Taken together, these results provide evidence for the importance of striatal volume loss in the cognitive and behavioural symptoms in NPH.

4.9.1. Structural MR imaging of NPH

Caudate volumes obtained via automated segmentation were significantly correlated with those obtained via manual tracing at both pre- and post-shunt suggesting that automated segmentation was reasonably accurate for at least a subgroup of patients. However, a number of patients had to be excluded from the analyses in Part I of the present study due to inaccurate segmentation of the caudate (or of multiple subcortical structures). Therefore, in cases of more extreme ventriculomegaly, the automated segmentation method was unreliable. Of course, there are trade-offs for each method. While automated segmentation is less time consuming compared to
manual tracing and reduces observer bias, this method was not always reliable in the NPH patients due to ventriculomegaly. Manual tracing is more accurate, however, it is time-consuming to trace in three planes, and there are recognised difficulties with tracing the tail of the caudate due to its small volume (Looi et al., 2008).

4.9.2. Limitations

There are a number of limitations to the present study. The sample sizes were small meaning that results should be interpreted with caution. Additionally, the small sample sizes combined with the fact that not all patients completed all neuropsychological tests meant that regression analyses could not be used. A third limitation concerns the use of self-rated scales. Future research should aim to verify these findings using informant- or clinician-rated scales, in addition to self-rated scales. Finally, the present study did not include a measure of disease duration which may relate to the magnitude of brain structural changes in patients with NPH.

4.10. Conclusions

Chapter 4 found evidence for volume reductions in a range of subcortical structures in patients with NPH. Striatal volume loss in particular appears to play a role in the cognitive and behavioural symptomology in NPH.
Chapter 5

Investigating the efficacy of a novel rewarding learning task as an objective measure of motivation and apathy in patients with normal pressure hydrocephalus

5.1. Introduction

Apathy is a common symptom in patients with dementia, including patients with Alzheimer’s disease (Landes et al., 2001), Parkinson’s disease (Leentjens et al., 2008), frontotemporal dementia (Chow et al., 2009), and vascular dementia (Fuh, Wang, & Cummings, 2005). The prevalence of apathy in patients with NPH has also been shown to be high (44% - 86%; see section 3.3.2, Kanemoto et al., 2016; Kito et al., 2009). Apathy is most commonly measured using rating scales (see section 1.4.4). These can be self-rated (by the patient), informant-rated (by a family member or caregiver), or clinician-rated; or a combination of these. However, rating scales may be problematic for use with patients who have dementia. For example, self-rated apathy scales may be unreliable if patients lose insight into their apathetic symptoms (i.e. as a result of cognitive decline; Aalten, Van Valen, Clare, Kenny, & Verhey, 2005; Starkstein, Jorge, Mizrahi, & Robinson, 2006a), while a disadvantage of informant-rated scales is that a caregiver may be unreliable or unavailable (Sockeel et al., 2006). Additional complications are associated with testing-retesting paradigms. For example, when investigating the effect of a treatment using informant-rated scales there is a risk of bias towards a positive treatment effect due to informants’ expectations or a placebo effect (Kanemoto et al., 2016; Kaufer, Cummings, & Christine, 1996). Therefore, there is a need to develop an objective measure of apathy, or motivation, for use with dementia patients (including patients with NPH).

Chapter 3 investigated change in apathy following shunt surgery using the State Apathy Evaluation scale (Blackwell et al., 2008) which is a modified version of the self-rated Apathy Evaluation Scale (AES-S; Marin et al., 1991) in patients with NPH. While there was a significant relationship between improvement in AES-S score and improvement in Mini-Mental State Examination score, AES-S score did not significantly improve (reduce) following shunt surgery (mean time between shunt and reassessment was 4.17 months). Chapter 4 also did not find evidence for significant improvement in apathy following shunt surgery. Similarly, Kito et al. (2009) investigated change in neuropsychiatric symptoms in 10 iNPH patients using
the Neuropsychiatric Inventory (NPI; Cummings et al., 1994) but did not find a significant improvement in apathy following shunt. However, Kanemoto et al. (2016), investigating the effect of lumboperitoneal shunt surgery on neuropsychiatric symptoms in 22 patients with iNPH using the NPI, observed a significant improvement in apathy at 3 months post-shunt.

The conflicting results to date are likely due to a combination of small sample sizes and the use of different rating scales. While the patients in Chapters 3 and 4 may not have shown significant group improvements in apathy due to the low average baseline scores (median scores were 17.5 and 18.6, respectively; cut off for apathetic symptoms = 19, using 0 to 54 scoring range), Kanemoto et al. (2016) point out that the self-rated AES may be unreliable due to patients’ loss of insight into their symptoms. However, the informant-rated NPI may be biased towards a positive effect of shunt treatment (Kanemoto et al., 2016; Kaufer et al., 1996). As the problems associated with apathy scales are largely due to subjectivity, there is a need to develop an objective measure of apathy or motivation. This would be especially useful for assessing apathy in patients who have dementia and for evaluating effects of treatments.

The challenge for developing an objective measure of motivation for use with dementia patients is that it should be simple enough for patients with cognitive decline to understand and complete. The present study investigated whether a reward learning paradigm, the simple Salience Attribution Test (sSAT), could be used as an objective measure of motivation. Apathy is associated with dysfunction of the dopaminergic reward system and linked to reward learning ability and motivation (Mitchell, Herrmann, & Lanctôt, 2011). The sSAT is a simplified version of the Salience Attribution Test originally devised by Roiser et al. (2009) which has provided useful information about motivation in healthy individuals and in patients with schizophrenia. The task was simplified for use in patients with dementia, and the present study assessed how well it measured motivation in healthy volunteers.

First, the original Salience Attribution Test from Roiser et al. (2009) is described in section 5.1.1, and the simplified version of the task (the sSAT) is then presented briefly. The sSAT is then described in detail in section 5.2.2.
5.1.1. The Salience Attribution Test (Roiser et al. 2009)

The Salience Attribution Test taps stimulus-reinforcement association learning by measuring response times to stimuli of differing reward contingencies. **Stimulus-reinforcement associations** are associations between environmental stimuli and outcomes (e.g. reward/punishment/no outcome). Learning of stimulus-reinforcement associations can be investigated using conditioning experiments in which a neutral stimulus is repeatedly paired with a reward. Over time, the association between the previously neutral stimulus with a reward is learned and begins to affect behaviour (Schultz, Dayan, & Montague, 1997). Learning of stimulus-reinforcement associations is modulated by dopaminergic pathways in the brain which code reward prediction errors (Murray, Corlett, et al., 2008; Schultz et al., 1997), and reward information is processed primarily in frontal regions of the brain as well as in the basal ganglia. The previously neutral stimulus is called the **conditioned stimulus** because its association with a reward triggers a conditioned response (e.g. salivating/approach).

The Salience Attribution Test is a computerised reward learning task in which participants must respond (press a button) as quickly as possible to the onset of a target (a black square in the centre of the screen; see Figure 5.1). Pictures appear on the screen just before the onset of the target, and they signal the likelihood that a participant will win a monetary reward on a given trial. The pictures vary on two dimensions: colour (blue or red); and shape (animal or household object). Therefore, there are four types of pictures: blue animals; red animals; blue household objects; red household objects. In the task, one dimension of the picture is task-relevant (e.g. colour) while the other is task-irrelevant (e.g. shape). The task-relevant dimension gives information about the likelihood of a reward. That is, a reward is more likely to follow one level of the task-relevant domain (colour, in this example) than the other. For example, blue pictures (regardless of shape) are reinforced on 87.5% of trials, while red pictures are reinforced on only 12.5% of trials. If shape is the task-irrelevant domain, it means that both types of shape are equally likely to precede a reward (50%). The **reward contingency** of a stimulus is the likelihood that it will be followed by a reward. Participants are not told about the reward contingencies of the different stimuli (pictures) but learn these over the course of the task.

The pictures that precede the target are the (previously neutral) conditioned stimuli which indicate the probability of a reward. Stimuli with high reward contingencies have been shown to be associated with faster response times relative to stimuli that do not predict a reward (Cools et al., 2005; Murray, Corlett, et al., 2008; O’Doherty et al., 2004). This effect has been termed **reinforcement-related speeding**, and is attributed to increased motivation in
anticipation of a (predicted) reward (Murray, Corlett, et al., 2008). As described by Roiser et al. (2009) this effect reflects **adaptive motivational salience** (or the correct assignment of salience to stimuli) where the learned association between a previously neutral stimulus and a reward can affect behaviour.

![Diagram of the Salience Attribution Test](image)

**Figure 5.1: The Salience Attribution Test (from Roiser et al. 2009)**

The conditioned stimuli are either coloured blue or red. Participants respond to the target (black square) which is preceded by conditioned stimuli of varying reward contingencies. Following a response, feedback is presented on the screen.

Roiser et al. (2009) measured adaptive motivational salience in two ways: **implicit motivational salience** - *behavioural* adaptive motivational salience defined as the speeding of responses to high-probability rewarding stimuli relative to low-probability rewarding stimuli; and **explicit motivational salience** – *subjective* learning of the reward contingencies of stimuli, defined as the increase in probability rating for high-probability rewarding stimuli relative to low-probability rewarding stimuli. The participants in their study showed a reinforcement-related speeding effect, and they also rated high-probability rewarding stimuli as more likely to be followed by a reward than low-probability rewarding stimuli. Therefore, the task was successful in tapping both implicit and explicit motivational salience. Attenuated adaptive motivational salience, on the other hand, may be associated with a motivational deficit such as apathy (Roiser et al., 2009). Indeed, Roiser et al. found that medicated patients with schizophrenia showed a reduction in implicit motivational salience compared to controls, and this was related to a measure of anhedonia.

Using functional magnetic resonance imaging, Roiser, Stephan, den Ouden, Friston, and Joyce (2010) found that the presentation of high- versus low-probability rewarding cues elicited hemodynamic responses in regions of the brain associated with the ‘affective’ cortico-striatal-thalamic loop including the ventral tegmental area, the medial dorsal thalamus, and the ventral
striatum, regions which respond to the rewarding associations of stimuli. The researchers hypothesised that dopaminergic activity mediates learning of stimulus-reward associations.

It should be noted that the Salience Attribution Test can also provide a measure of aberrant motivational salience, or the incorrect assignment of salience to task-irrelevant stimuli, a process which may underlie the positive symptoms in schizophrenia (such as delusions). However, for the purposes of the present study, the sSAT was simplified to measure adaptive motivational salience, only, as it is linked to goal-directed behaviour or motivation. This meant that the conditioned stimuli in the sSAT varied on only one dimension (colour) instead of two (colour and shape).

Like the Salience Attribution Test, the sSAT features a target (a black box) to which participants must respond quickly in order to win money, and which is preceded by pictures (two circles appearing at the top and bottom of the screen) which signify the probability that a reward will follow (see Figure 5.2). The circles vary in colour (blue, yellow, or red) in a task-relevant fashion, that is, the colour of the cue signals the probability that money will be awarded in a given trial. One level of the cue (e.g. blue) is reinforced in 80% of trials (high availability); another level (e.g. yellow) is reinforced in 50% of trials (medium availability); and the last level (e.g. red) is reinforced in only 20% of trials (low availability).

As with in Roiser et al. (2009) this task allows us to calculate two measures of adaptive motivational salience; these are explicit (or subjective) salience, and implicit (or behavioural) salience. Explicit motivational salience is measured using a visual analogue scale (VAS) in which participants estimate the reinforcement contingencies of each of the three coloured cues. Implicit motivational salience is measured using participants’ response times. It is expected that control participants would show both implicit and explicit adaptive motivational salience using this task, while patients with NPH would show attenuated adaptive implicit motivational salience compared to healthy controls, reflecting their apathetic symptoms. However, the present study investigated whether the sSAT is sensitive to implicit and explicit adaptive motivational salience in healthy controls.
Figure 5.2: Screenshots from the simple Salience Attribution Test
The pictures (blue circles) appear on the screen before the onset of the target (black square). Participants respond to the target and on-screen feedback is given.

Since patients with NPH are typically elderly, the sSAT was piloted in both younger and older healthy adults to investigate whether there are age-related differences in performance. Normal aging is associated with structural atrophy as well as reductions in dopaminergic neurotransmission which may affect stimulus-reward learning (Mell et al., 2005, 2009). There were two research objectives in the present study: (1) to investigate whether the sSAT is sensitive to explicit and implicit adaptive motivational salience in healthy participants and whether, therefore, it could be an appropriate task for measuring motivation in patients with NPH; and (2) whether there were age-related differences in performance. The hypotheses were that: (1) participants would rate high-probability reward cues as more rewarding than medium- or low-probability reward cues; (2) participants would respond faster to the high-probability reward cues relative to medium- or low-probability reward cues; and (3) older adults would show reduced adaptive implicit motivational salience compared to younger adults.
5.2. Methods

5.2.1. Participants

Two groups of healthy volunteers were assessed using the sSAT: younger adults (aged 21 to 35, \( n = 25 \)); and older adults (aged 50 to 90, \( n = 19 \)). Participants were recruited via advertisement within Cambridge. This study received ethical approval from the University of Cambridge Psychology Research Ethics Committee.

5.2.2. The simple Salience Attribution Test (sSAT)

The sSAT was presented using MATLAB on a Paceblade. Participants began with a tutorial which featured instructions for the task, and built-in practice sessions allowing participants to familiarise themselves with the task and also providing a baseline measure of response time (RT).

The first practice session consisted of two blocks of 20 trials. During this session, a fixation cross appeared in the centre of the screen. After a short interval (0.5 – 1.5 seconds, variable), the probe appeared and participants were instructed to try to respond as quickly as possible, by pressing the right shift key, before it disappeared. The mean RT from the first block was used as the mean probe duration in the second block. The standard deviation of the quickest half of the trials (SDF) in the first block was used to set the maximum and minimum probe durations in the second block (mean from first block \( \pm 2 \times \text{SDF} \)). The RT and standard deviation from the second trial were used to calculate the mean, maximum and minimum probe durations for the main game in the same way. Participants received the following feedback during the practice session: “Good” if a response is made before the box disappears; “Try to respond faster” if a response is made after the box disappears; and “Too early” if a response was made before the onset of the box. However, no monetary rewards were given during the practice session.

Participants then completed a second practice session followed by the main game which consisted of two blocks of 60 trials. For the second practice session, participants were instructed to respond to the probe, as in the first practice session. However, in this session cues (pink circles) preceded the probe. Instructions for this part of the task informed the participants that the cue has a specific reward contingency, giving a reward on only a certain percentage of trials, but they were not told what the reward contingency was. The second practice session consisted
of 4 trials and participants were rewarded in 3 of these. Followed the second practice session, participants were asked to indicate the percentage of trials in which the pink circle gave a reward using a visual analogue scale (75% being the correct response). At this point, the experimenter could discuss with the participant how often a reward was given in the second practice session so that participants were clear on how to estimate the reward contingency of a cue.

For the following two blocks of trials in the main game blue, yellow or red cues appeared, signalling the onset of the probe. The reward contingencies for the different coloured cues were 20%, 50% and 80%. The colours associated with each of the reward contingencies were counterbalanced between participants. The order in which the coloured cues appeared was fully randomised to eliminate order effects. At the beginning of each trial, a fixation cross appeared in the centre of the screen. After 1000ms one of the three coloured cues appeared at the top and bottom of the screen and remained until the end of the trial. After a variable interval (500-1500ms) the probe appeared in the centre of the screen replacing the fixation cross and participants attempted to respond by pressing the right shift key.

Participants received feedback and a monetary reward dependant on cue type. If no reward was available for a given trial the following appeared: “Sorry no money available”. If a reward was available (reinforced trial), participants could win between 5 and 100 pence depending on speed of response. If a response was made after the probe had disappeared, or not at all, during a reinforced trial, the message “Missed: 5 pence” appeared. If a response was made too soon (less than 100ms after onset of probe) then the message “Too early: 5 pence” appeared. If participants responded slower than their mean RT, but before the probe disappeared, “Good: 10 pence” was displayed. For responses up to 1.5 SDFs faster than a participants’ mean RT, the message “Quick: X pence” appeared, and for responses over 1.5 SDFs faster than their mean RT, “Very quick: X pence” appeared. The amount of reward given was calculated as follows: \( X = 10 + 90 \times (\text{mean RT} – \text{trial RT})/(3 \times \text{SDF}) \), up to 100 pence per trial. The amount of money awarded per trial was added to the participants’ running total for the block and displayed below the feedback.

After each block of trials a 10mm VAS scale was displayed in which participants indicated how often they thought each level of the cue was followed by a monetary reward (the estimated reinforcement probabilities of each cue). The three scales ranged from 0-100%.
5.2.3. Statistical analysis

A two-way repeated measures analysis of variance (ANOVA) was used to analyse the effect of cue reward probability on response times for blocks 1 and 2. The two within-group factors were cue reward probability (High; Medium; Low), and block (1; 2). A repeated measures ANOVA was used to analyse VAS ratings to three levels of cue reward probability for blocks 1 and 2. The two within-group factors were cue reward probability (High; Medium; Low), and block (1; 2).

5.3. Results

One younger adult participant and one older adult participant were excluded from analyses because their RTs were more than three standard deviations away from the mean. Mean (SD) age in years was 25.60 (4.18) for the younger adult group, and 66.10 (7.89) for the older adult group.

5.3.1. Younger adults

Younger adults’ (n = 24) mean response times and VAS ratings for the three reward-probability cues in blocks 1 and 2 are shown in Table 5.1.
Table 5.1: Younger adults’ mean (SD) response times (ms) and VAS ratings for high, medium, and low reward probability cues in blocks 1 and 2

<table>
<thead>
<tr>
<th>Cue Reward Probability</th>
<th>Block</th>
<th>RT (ms) mean (SD)</th>
<th>VAS rating mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>1</td>
<td>290.66 (39.28)</td>
<td>64.17 (17.49)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>292.32 (33.82)</td>
<td>63.75 (15.48)</td>
</tr>
<tr>
<td>Medium</td>
<td>1</td>
<td>289.94 (38.20)</td>
<td>42.92 (17.75)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>287.40 (40.80)</td>
<td>39.79 (12.89)</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>292.40 (41.40)</td>
<td>18.75 (15.27)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>289.93 (46.16)</td>
<td>16.04 (13.75)</td>
</tr>
</tbody>
</table>

Implicit motivation

There was no significant main effect of reward probability on RT, $F(2, 46) = .21, p = .81, \eta_p^2 = .009$, thus younger adults did not demonstrate adaptive implicit salience. There was no significant main effect of block, $F(1, 23) = .07, p = .79, \eta_p^2 = .003$, and there was no significant interaction between reward probability and block, $F(2, 46) = .29, p = .75, \eta_p^2 = .01$.

Explicit motivation

There was a significant main effect of probability, $F(2, 46) = 83.75, p < .001, \eta_p^2 = .79$, with participants rating high, medium, and low probability-reinforcement cues significantly differently. Pairwise comparisons using the Bonferroni correction revealed that mean VAS rating of the high-probability reward cue was significantly higher than mean VAS rating of the medium-probability reward cue ($p < .001$) and of the low-probability reward cue ($p < .001$). Additionally, mean VAS rating of the medium-probability reward cue was significantly higher than mean VAS rating of the low-probability reward cue ($p < .001$). Therefore, younger participants were roughly estimating the correct reward contingencies of the three cues, thus demonstrating adaptive explicit salience. There was no main effect of block, $F(1, 23) = 1.58, p = .22, \eta_p^2 = .06$, and no interaction was observed between cue reward probability and block $F(2, 46) = .22, p = .80, \eta_p^2 = .01$. 

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5.3.2. Older adults

Older adults’ \( n = 19 \) mean response times and VAS ratings for the three reward-probability cues in blocks 1 and 2 are shown in Table 5.2.

<table>
<thead>
<tr>
<th>Cue Reward Probability</th>
<th>Block</th>
<th>RT (ms) mean (SD)</th>
<th>VAS rating mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>1</td>
<td>312.73 (42.53)</td>
<td>55.00 (20.86)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>296.97 (42.83)</td>
<td>56.67 (14.95)</td>
</tr>
<tr>
<td>Medium</td>
<td>1</td>
<td>320.09 (46.04)</td>
<td>42.22 (13.53)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>285.02 (37.76)</td>
<td>35.83 (14.37)</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>303.82 (38.73)</td>
<td>23.61 (16.16)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>301.82 (54.43)</td>
<td>23.61 (14.43)</td>
</tr>
</tbody>
</table>

Implicit motivation

There was no significant main effect of reward probability on RT, \( F(2, 34) = .11, p = .90, \eta^2_p = .006 \), thus older adults did not demonstrate adaptive implicit salience. There was a significant main effect of block, \( F(1, 17) = 6.62, p = .02, \eta^2_p = .28 \) with participants responding faster in Block 2 than in Block 1 perhaps demonstrating a practice effect.

There was a significant interaction between reward probability and block, \( F(2, 34) = 4.18, p = .02, \eta^2_p = .197 \). Further analysis of the interaction revealed that in block 1 participants responded slower to the medium-probability reward cue compared to high- and low-probability reward cues, while in block 2 participants responded faster to the medium-probability reward cue compared to high- and low-probability reward cues. Paired samples \( t \)-tests were conducted to compare response times to each reward probability cue in blocks 1 and 2. There was a significant difference in response times to the medium-probability reward cue in block 1 \( (M = 320.09, SD = 46.04) \) and block 2 \( (M = 285.02, SD = 37.76); t(17) = 3.99, p = .001 \). There were no other significant differences. Therefore, differences in response times to the medium-probability reward cue could account for the main effect of block on response times.
Explicit motivation

There was a significant main effect of probability, $F(2, 34) = 27.53, p < .001, \eta^2_p = .62$, with participants rating high, medium, and low probability-reinforcement cues significantly differently. Pairwise comparisons using the Bonferroni correction revealed that mean VAS rating of the high-probability reward cue was significantly higher than mean VAS rating of the medium-probability reward cue ($p = .003$) and of the low-probability reward cue ($p < .001$). Additionally, mean VAS rating of the medium-probability reward cue was significantly higher than mean VAS rating of the low-probability reward cue ($p = .001$). This reflects the observation that participants were roughly estimating the correct reward contingencies of the three cues, thus demonstrating adaptive explicit salience. There was no main effect of block, $F(1, 17) = .50, p = .49, \eta^2_p = .03$, and no interaction was observed between cue reward probability and block $F(2, 34) = 1.36, p = .27, \eta^2_p = .07$.

5.4. Discussion

The aim of the present study was to evaluate the suitability of a reward learning task, a simplified version of the Salience Attribution Test (Roiser et al., 2009), to act as an objective measure of motivation for assessing apathy in patients with normal pressure hydrocephalus. The present study piloted the task in younger and older healthy adult participants to investigate whether participants would show adaptive explicit and implicit motivational salience similar to that found using the Salience Attribution Test (Roiser et al., 2009), and whether there are age-related differences in performance. The hypotheses were that: (1) participants would rate high-probability reward cues as more rewarding than medium- or low-probability reward cues; (2) participants would respond faster to the high-probability reward cues relative to medium- or low-probability reward cues; and (3) older adults would show reduced adaptive implicit motivational salience compared to younger adults. The first hypothesis was supported as both younger and older adults rated high-probability reward cues as more rewarding than medium- and low-probability reward cues, and thus they demonstrated adaptive explicit salience. However, the second hypothesis was not supported as neither group responded faster to the high-probability reward cues relative to medium- or low-probability reward cues. Consequently, the third hypothesis was not supported as neither group demonstrated adaptive implicit motivational salience. As the healthy participants in the present study did not
demonstrate adaptive implicit motivational salience, the sSAT would be unsuitable for use as an objective measure of motivation in NPH.

The sSAT was simplified from the original Salience Attribution Test which may be the reason that the reinforcement-related speeding effect (which has previously been reported in healthy participants; Cools et al., 2005; Murray, Clark, et al., 2008) was not found in the present study. The task was simplified (1) to measure adaptive motivational salience only, and not aberrant motivational salience; and (2) so that the task would be appropriate for patients with NPH who are typically elderly. However, as a result, the task was likely too easy for the healthy participants, meaning that a ceiling effect was observed whereby participants responded equally quickly to all stimuli regardless of their reward contingencies.

5.4.1. Alternative measures

A possible alternative task which could be used as an objective measure of motivation in patients with dementia could be The Progressive Ratio Task from the recently developed EMOTICOM test battery (Bland et al., 2016). The task comprises a simple ‘odd one out’ paradigm and participants are rewarded during successful trials. However, the reward gets progressively smaller over the course of the task. Participants are told that they can discontinue the task at any point, but that if they do so they will have to sit facing the screen for the remainder of the session. From this, a ‘motivational breakpoint’ can be calculated which is the maximum effort expended in order to receive a reward. This task is a good candidate for objectively measuring motivation in patients with NPH as the task is simple enough that it would be appropriate for older participants, and comparable normative data is already available for healthy adult participants (Bland et al., 2016).

Alternatively, wearable technologies may provide useful information for quantifying apathy or motivation in patients with dementia, such as those which measure patients’ activity levels (Goldfine et al., 2016), or even wearable recording technologies for caregivers for capturing behavioural symptoms (Matthews et al., 2015).
5.5. Conclusions

The present study investigated whether a novel reward learning task, the sSAT: a simplified version of the Salience Attribution Test, was sensitive to adaptive implicit and explicit motivational salience in younger and older healthy adults and whether, therefore, it could be used as an objective measure of motivation in patients with NPH. Both groups demonstrated subjective understanding of the reward contingencies for each cue (explicit motivational salience), however no corresponding behavioural changes were observed in either group. That is, participants did not respond faster to the target when it was preceded by a more rewarding cue and, thus, did not demonstrate adaptive implicit motivational salience. The sSAT is therefore unsuitable as an objective measure of motivation for patients with NPH.
6.1. **Summary of the thesis**

This thesis aimed to expand on the neuropsychological and the neuropsychiatric research relating to normal pressure hydrocephalus, with specific emphasis on investigating the effect of shunt surgery on neuropsychological performance in patients, and investigating the significance of the symptom of apathy. Three studies that investigated cognitive function and apathy in patients with normal pressure hydrocephalus were reported, and a further feasibility study of a novel reward learning task to determine whether it might be useful as an objective measure of motivation and apathy for patients with dementia was reported.

Study 1 (Chapter 2, ‘The effect of shunt surgery on neuropsychological performance in normal pressure hydrocephalus: A systematic review and meta-analysis’) used meta-analytic techniques to investigate neuropsychological outcome following treatment for NPH. Specifically, Study 1 examined whether specific aspects of neuropsychological functioning are more likely than other aspects to show improvement following shunting and whether, therefore, a consistent pattern of neuropsychological change emerges. Study 2 (Chapter 3, ‘Apathy, ventriculomegaly and neurocognitive improvement following shunt surgery in normal pressure hydrocephalus’) investigated the significance of the symptom of apathy for cognitive outcome in NPH, prevalence of apathy in patients with NPH, and whether a simple measure of ventricular enlargement was related to level of apathy. Study 3 (Chapter 4, ‘Brain structural correlates of cognitive dysfunction and neuropsychiatric symptoms in normal pressure hydrocephalus) used structural imaging analysis techniques to investigate whole brain and subcortical volumetric changes in NPH and associations with cognitive dysfunction and apathy. Study 4 (Chapter 5, ‘Investigation into the efficacy of a novel rewarding learning task as an objective measure of motivation and apathy in patients with normal pressure hydrocephalus’) examined performance in a novel reward learning task (the simple Salience Attribution Test; sSAT) by younger and older healthy adults in order to investigate the task’s utility as an objective measure of apathy or motivation for use with patients with dementia.
6.2. Main contributions of this research

The main findings of this thesis were as follows:

Study 1, Chapter 2:

(i) Meta-analyses were conducted on average difference scores (from pre-to post-shunt) for seven neuropsychological tests spanning global cognition, learning and memory, executive function, and psychomotor speed. Statistically significant estimated average difference scores were observed for all seven tests in the direction of improved performance following shunt surgery. However, detailed examination of the results suggested that the evidence for improvement in two of the tests (two tests of executive function) was not robust. Therefore, while there was good evidence for improvements in tests of global cognition, learning and memory, and psychomotor speed following shunt surgery, the evidence for improved performance in tests of executive function was less clear.

(ii) Meta-regressions revealed no significant effect of age, sex, or time between shunt and reassessment on outcome in a measure of global cognitive functioning.

Study 2, Chapter 3:

(i) The frequency of apathetic symptoms (as measured using the self-rated Cambridge State Apathy Evaluation scale; AES-S) was 44% at pre-shunt and 14% at post-shunt. The frequency of depressive symptoms (measured using the short form of the Geriatric Depression Scale; GDS-15) was 52% at pre-shunt and 25% at post-shunt.

(ii) Frequency of apathetic and depressive symptoms did not change significantly from pre- to post-shunt.

(iii) AES-S and GDS-15 ratings were significantly correlated at both pre- and post-shunt. AES-S and GDS-15 scores were also correlated with neuropsychological test scores.

(iv) The bicaudate ratio (a measure of ventricular enlargement) was significantly positively correlated with self-rated levels of apathy and depression at pre-shunt. That is, greater degree of ventriculomegaly was associated with greater levels of self-rated apathy and depression.
There were significant post-operative group improvements in performance in tests of phonemic fluency, semantic fluency, and delayed recall.

There was a non-significant trend for a reduction in mean apathy rating at post-shunt compared to pre-shunt.

Following shunt treatment, a reduction in apathy severity was significantly correlated with improved performance in a measure of global cognitive function.

Study 3, Chapter 4:
Part I:

(i) Total brain volume, total grey matter (GM) volume, and total white matter (WM) volume were not significantly different between patients with NPH (pre-shunt) and controls.

(ii) WM volume was significantly negatively correlated with performance on a measure of delayed verbal recall, after controlling for age, in patients with NPH at pre-shunt. That is, reduced WM volume was associated with better performance on the task.

(iii) At pre-shunt, mean volume of the caudate was significantly reduced in the NPH group compared to healthy controls after controlling for age and ventricular volume.

(iv) At pre-shunt, volume of the nucleus accumbens was significantly positively correlated with performance on a measure of immediate verbal recall in the NPH group. That is, greater nucleus accumbens volume was associated with better performance on the task.

(v) At post-shunt, mean volumes of the putamen, pallidum, hippocampus, and nucleus accumbens were significantly reduced in the NPH group compared to healthy controls after controlling for age and ventricular volume.

(vi) At post-shunt, volume of the caudate was significantly negatively correlated with AES-S rating. That is, greater caudate volume was associated with less severe level of self-rated apathy. Additionally, volume of the nucleus accumbens was significantly positively correlated with performance on tasks of global cognitive function and verbal learning and memory. That is, greater nucleus accumbens volume was associated with better performance on the tasks.

(vii) Volumes of the thalamus and the hippocampus were significantly larger at post-shunt compared to pre-shunt. Percent change in ventricular volume was significantly
correlated with percent change in volume of the thalamus, but not with percent change in volume of the hippocampus.

(viii) There were significant post-operative group improvements in performance in tests of semantic fluency, immediate and total verbal recall.

(ix) Percent change in volumes of the thalamus and hippocampus were not significantly correlated with percent change in semantic fluency, immediate and total verbal recall scores.

Part II:

(i) Caudate volumes obtained via manual tracing and via automated segmentation were in good agreement.

(ii) There was no significant difference in caudate volume between pre- and post-shunt.

(iii) At pre-shunt, caudate volume was significantly positively correlated with performance on tasks of phonemic and semantic fluency, after controlling for years of education. That is, greater caudate volume was associated with better performance on the tasks.

(iv) At post-shunt, caudate volume was significantly negatively correlated with AES-S rating, after controlling for years of education. That is, greater caudate volume was associated with less severe levels of apathy.

Study 4, Chapter 5:

(i) Both older and younger healthy adults demonstrated adaptive explicit salience. That is, they correctly estimated the relative reward contingencies of the three stimuli in the sSAT task. However, neither group demonstrated adaptive implicit motivational salience during the task (their behaviour did not change to reflect learning of the reward contingencies of the stimuli). The sSAT task is, therefore, deemed to be unsuitable as an objective measure of motivation or apathy in NPH.
6.3. Interpretation and integration of findings

6.3.1. Neuropsychological outcome following treatment for NPH

The first aim of this thesis was to investigate the effect of shunt surgery on neuropsychological performance in patients with NPH. A number of studies have found evidence for impaired neuropsychological functioning in patients. In particular, patients show impairments in memory, executive function, psychomotor speed, and visuospatial abilities (DeVito et al., 2005; Duinkerke et al., 2004; Gleichgerrcht et al., 2009; Iddon et al., 1999; Katzen et al., 2011; Mataró et al., 2003; Saito et al., 2011; Solana et al., 2012b). However, the pattern of neuropsychological change following treatment for NPH has not been established.

In order to investigate neuropsychological outcome following treatment for NPH, Chapter 2 conducted meta-analyses of outcome for the most frequently used neuropsychological tests in studies of NPH. The tests spanned global cognitive function, learning and memory, executive function, and psychomotor speed. A significant problem facing investigations into the neuropsychology of NPH to date concerns the small sample sizes contained in many studies. Chapter 2 pooled results from 23 studies and 1059 patients to gain a clearer picture of neuropsychological outcome. Results indicated statistically significant estimated average difference scores for all tests in the direction of improvement following shunt surgery. However, despite the significance levels, the results for two of the studies (two measures of executive function) did not appear to be robust.

The results suggested that, on average, shunt surgery leads to improvements in neuropsychological functioning. This is in agreement with a number of studies which find improvements on neuropsychological tests following shunting (Chaudhry et al., 2007; Duinkerke et al., 2004; Gleichgerrcht et al., 2009; Hellström et al., 2008; Katzen et al., 2011; Raftopoulos et al., 1994; Solana et al., 2012b; Stambrook et al., 1988; Thomas et al., 2005). Regarding the pattern of post-shunt improvement, there was good evidence for improvements on tests of global cognitive functioning, learning and memory, and psychomotor speed, while the results concerning outcome on tests of executive function were less clear. One of the three tests of executive function included in the meta-analyses showed good evidence for improvement following shunt surgery. However, the evidence for improvement in performance on the remaining two tests was not considered to be robust. Therefore, the results might suggest that, on average, performance on tasks of executive function is less likely to improve following shunt surgery.
Some studies have found that performance on tests of executive function does not improve following shunt (Iddon et al., 1999; Thomas et al., 2005) or is less likely to improve compared to other cognitive domains (Solana et al., 2012b). Additionally, there is large variability in results relating to outcome in tests of executive function following shunt (see section 2.4). If executive dysfunction is less likely to improve following shunt compared to impairments in other domains, it might reflect irreversible impairment to fronto-subcortical connectivity resulting from NPH (Iddon et al., 2004). Accordingly, executive dysfunction may only improve in a subgroup of patients with NPH (such as those who have mild executive dysfunction at baseline, as opposed to those with more severe executive dysfunction which might indicate greater disease severity/ longer disease duration and thus greater structural damage to the brain). This could explain why some studies find good evidence for improvement in tests of executive functions (e.g. Gleichgerrcht et al., 2009; Saito et al., 2011). However, it should be noted that the three tests of executive function included in the meta-analyses do not adequately tap higher-level executive functions such as planning or decision making. Therefore, there is a need to assess high-level executive functions in patients with NPH before and after shunt surgery in order to investigate this finding further.

Establishing an expected pattern of neuropsychological change following shunt surgery is important for a number of reasons. Firstly, it is useful for providing patients with realistic information regarding the likely benefits of treatment. Secondly, it could inform further treatment or care options. For example, residual cognitive deficits (such as executive dysfunction) following shunt surgery can have significant implications for patients’ quality of life, and could impact on their ability to complete daily tasks meaning that patients might require assistance from a carer. Alternatively, targeted treatment of residual cognitive deficits could be an option for some patients, e.g. via non-pharmacological treatment methods such as targeted cognitive training (Sahakian et al., 2015); or via pharmacological treatments such as cognitive enhancing drugs (Keenan et al., 2005). Thirdly, an established pattern of neuropsychological change could aid in diagnosis of NPH, as well as quantifying outcome following shunt treatment.

Does NPH represent a reversible form of dementia?

Whether or not NPH represents a reversible dementia is debated. The results of Chapter 2 provide support to the notion that neuropsychological performance is improved following shunt
surgery in patients with NPH. However, the results do not provide information about the extent of cognitive recovery. Very few studies of long-term cognitive outcome have been conducted and therefore it is not known whether patients ever return to “normal”. Although current evidence suggests this is unlikely (Hellström et al., 2008, 2012b). Nevertheless, for many patients, there is considerable improvement in the cognitive symptoms following shunt treatment which can have a substantial impact on patients’ quality of life.

6.3.2. The symptom of apathy in NPH

The second aim of the thesis was to investigate the significance of the symptom of apathy for cognitive function and outcome since this symptom is under-researched in NPH. Chapter 3 reported evidence that levels of apathy and depression were related to neuropsychological functioning at both pre- and post-shunt. However, when investigating whether change in apathy or depression was related to cognitive improvement, improved global cognitive functioning was associated with change in apathy levels but not with change in depression severity. Therefore, apathy may be a significant obstacle for cognition and functional outcome.

How common is apathy in NPH?

In Chapter 3, the prevalence of apathy was investigated by examining the frequency of patients scoring within the apathetic range of the AES-S. Based on this criteria, apathy was present in 44% of patients at pre-shunt, and in 14% at post-shunt. In comparison, prevalence of depression was 52% at pre-shunt, and 25% at post-shunt. Only two studies have previously investigated prevalence of apathy in NPH (Kanemoto et al., 2016; Kito et al., 2009) and they found higher rates of apathy (70-86% at pre-shunt). The same studies reported lower rates of depression (14-36% at pre-shunt).

This discrepancy is likely due to the different assessment measures used. Both Kanemoto et al. (2016) and Kito et al. (2009) used the Neuropsychiatric Inventory (NPI) to assess apathy and depression (see section 1.4.4 for a description). The NPI relies on informant reporting whereas AES-S and GDS-15 are both rated by the patients themselves.

A criticism of the use of self-rated scales in studies of NPH is that the patients may have impaired insight into their symptoms meaning that their ratings are unreliable. Insight or self-assessment has been shown to be associated with functioning of the frontal regions (Hornberger
et al., 2014; van der Meer, Costafreda, Aleman, & David, 2010). Hornberger et al. (2014) conducted a voxel-based morphometry analysis in patients with neurodegenerative conditions and found that atrophy of ventromedial and frontopolar prefrontal cortical regions was associated with loss of insight. Further, loss of insight was most severe in patients with behavioural variant frontotemporal dementia (which is characterised by degeneration of the frontal and temporal lobes) compared to patients with language subtypes of frontotemporal dementia and patients with Alzheimer’s disease (AD). Although there is evidence for impairments in frontal functioning in patients with NPH (Iddon et al., 1999; Sasaki et al., 2007), this appears to be mediated by a primary dysfunction of fronto-subcortical mechanisms (Iddon et al., 1999; Momjian et al., 2004; Shprecher, Schwalb, & Kurlan, 2008; Waldemar et al., 1993) and there is limited evidence for cortical atrophy in NPH (Serulle et al., 2014). Nevertheless, a recent study investigated cortical thickness in patients with iNPH who were either cerebrospinal fluid tap test (CSF-TT) responders or non-responders (Kang, Yoon, Lee, & Lee, 2013). Kang et al. (2013) found that CSF-TT non-responders showed increased cortical thinning in most areas of the brain compared with CSF-TT responders but particularly in the left superior frontal gyrus (an area which has been associated with self-awareness; Goldberg, Harel, & Malach, 2006). However, there were no significant differences in cortical thickness between CSF-TT non-responders and patients with AD, which the researchers suggested might indicate the presence of comorbid AD pathology in this group. Therefore, impaired insight may not be as prominent in NPH as it is in other neurodegenerative conditions. However, an early study of 23 patients with hydrocephalic dementia (most of whom had a known or tentative cause of hydrocephalus; age range: 36-70) reported that impaired insight was a prominent symptom (Gustafson & Hagberg, 1978) and so there is a need to investigate whether this is a problem for the use of self-rated scales in patients with NPH.

Although there is a need to investigate this issue further, in the CSF disorders clinic at Addenbrooke’s care is taken to ensure that the information obtained from self-rated scales is as accurate as possible. The following measures are in place: patients are advised that they may complete the scales privately if they wish; the statements contained within the rating scales can be read aloud by the research psychologist if needed; patients are encouraged to consider their responses to the statements (e.g. by thinking of examples of how they do or don’t meet a behaviour); and finally, the scoring of the AES allows the research psychologist to check whether patients have not read the questions (that is, each statement is scored out of four indicating least to most severity of apathy, apart from two for which the scoring is reversed).
On the other hand, the nature of the scoring on the NPI may make it biased towards a false positive result and could explain the higher prevalence reported by Kanemoto et al. (2016) and Kito et al. (2009). However, it should be noted that the sample size in Chapter 3 was small and, in addition, a number of patients did not complete the AES-S at pre-shunt, possibly affecting the results.

Does shunt surgery lead to a reduction in apathy?

Chapters 3 and 4 provided information about the effect of shunt surgery on apathetic symptoms. While mean group apathy rating was reduced following shunt surgery in both Chapters, neither showed a statistically significant reduction in apathy severity. However, it should be noted that there was an overlap of five patients in Chapters 3 and 4. Additionally, the difference in prevalence of apathetic symptoms between pre- and post-shunt was examined in Chapter 3. While prevalence was reduced following shunt surgery, the difference was not statistically significant.

Kanemoto et al. (2016) previously reported a significant reduction in apathy severity but not in prevalence, at three months post-shunt. In contrast, Kito et al. (2009) assessed change in apathy severity only, and did not find a statistically significant reduction in apathy severity at three months post-shunt. Kito et al. suggested that the patients in their study may have been at an early disease stage meaning levels of apathy at baseline were mild. Additionally, the mean baseline apathy ratings in Chapters 3 and 4 were below the cut-off for apathetic symptoms and so this could explain the lack of improvement of apathy severity in these studies.

As yet, the effect of shunt surgery on apathetic symptoms in NPH has not been elucidated. Larger studies with better assessment measures are required in order to examine this issue further.

Is apathy distinct from depression in NPH?

AES-S and GDS-15 ratings were significantly correlated at both pre- and post-shunt in Chapter 3. Additionally, both were related to scores in cognitive tests and bicaudate ratio. Therefore, the symptoms of apathy and depression likely overlap. However, improvement in global cognitive function was associated with a reduction in apathy but not depression, suggesting that the two are differentially related to cognitive outcome.
However, few studies have investigated both apathy and depression together in patients with NPH. Depression is more commonly assessed in patients (without also including a measure of apathy), so the co-occurrence and significance of each has not been determined. Additionally, if a measure of apathy is not included, apathetic symptoms may be misdiagnosed as depression. In Chapter 3, the proportions of patients scoring only in the depressive range of the GDS-15 and not in the apathetic range of the AES-S, and vice versa, was small (although this was not compared to the general population). However, the self-rated nature of both scales means that patients themselves may have falsely attributed apathetic symptoms to depression (or depressive symptoms to apathy). Therefore, in order to investigate this further, objective assessment measures are needed.

A better understanding of this issue is of primary importance as it could have implications for treatment options. For example, apathy could be a target for treatment using cognitive enhancing drugs (Keenan et al., 2005).

How to measure apathy

The problems outlined above in relation to measurement of apathy generally relate to (1) the differences in assessment measures being used across studies, and (2) the subjective nature of the tests. In order to more accurately investigate the significance of the symptom of apathy in NPH (including prevalence and outcome) more reliable assessment measures are needed. Of greatest help would be an objective measure of motivation which would be easy to use for patients with dementia, and could be used in conjunction with apathy rating scales. Additionally, when measuring apathy using rating scales, where possible it is important to include both self- and informant-ratings in order to obtain a more cohesive picture of the symptomology. Finally, assessments of neuropsychiatric/behavioural symptoms in patients with NPH should include measures of both apathy and depression.

6.3.3. Structural correlates of cognitive dysfunction and apathy

Chapter 3 examined relationships between bicaudate ratio (BCR; a measure of ventricular enlargement and possibly related to subcortical atrophy) and apathy and depression; and BCR and global cognitive function in patients with NPH at pre-shunt. BCR was significantly correlated with levels of apathy and depression. That is, greater pre-operative ventriculomegaly
was associated with more severe levels of apathy and depression. BCR was not significantly correlated with global cognitive function. Since evidence for caudate atrophy in patients with NPH has previously been found (DeVito et al., 2007), a structural MR imaging study was conducted in Chapter 4 to investigate structural correlates of cognitive dysfunction and apathy in NPH with a particular focus on subcortical volumetric assessment. Both automated segmentation and manual tracing methods were used.

The results from Chapter 4 suggested that striatal volume loss in particular was associated with cognitive dysfunction and neuropsychiatric symptoms in patients with NPH. Further, caudate volume was significantly correlated with levels of apathy at post-shunt, with larger caudate volumes being associated with less severe levels of apathy. The results, therefore, provide support to the notion that the cognitive and behavioural symptoms in NPH result from subcortical pathology.

6.4. Summary of the limitations of the investigations

There are a number of limitations to the current work and these are discussed below.

6.4.1. Classification of significant improvement following shunt

There is no consensus as to how to classify significant improvement in cognition following shunt surgery in patients with NPH. In Chapters 3 and 4, improvement was based on assessment of differences in group means from pre- to post-shunt. However, other studies have used different criteria for improvement. For example, Chang et al. (2006) examined improvement on the individual patient level. Significant improvement in each task was defined as at least 25% improvement in score, or reduction in time taken to complete the task (where appropriate). An individual was classified as ‘improved’ if they showed at least 25% improvement on more than 50% of the tasks. By analysing changes on the group level, only, some important patterns in the data may have been missed. However, due to the small sample sizes in this thesis, this kind of analysis is likely inappropriate.

This also has implications for interpretation of the meta-analysis results where difference scores in neuropsychological tests from pre- to post-shunt were also examined on the group level.
6.4.2. Practice effects

Practice effects is an important issue for consideration when investigating outcome following shunt surgery. This thesis did not analyse neuropsychological performance in a control group in order to investigate the influence of practice effects on follow-up scores. However, parallel versions of neuropsychological tests were used in order to mitigate practice effects. Additionally, a number of studies have provided evidence that practice effects are minimal in investigations of cognitive outcome following shunt surgery (Katzen et al., 2011; Saito et al., 2011; Solana et al., 2010). Nevertheless, it is important that future studies include a control group to undergo repeated testing in order to investigate the influence of practice.

6.4.3. Heterogeneity of groups

Heterogeneity of patients is a significant problem for NPH research. Patients often have comorbid disorders such as Alzheimer’s disease, or cerebrovascular risk factors. Although it is desirable to conduct investigations on ‘pure’ NPH, excluding patients on the basis of comorbid disorders is problematic for a number of reasons. Firstly, small sample sizes is a pervasive problem in NPH research and excluding further patients reduces the statistical power in studies. Secondly, excluding participants based on comorbidities means that results may not be generalizable to all patients with NPH.

Additionally, it has been recommended that patients with idiopathic NPH (iNPH) and patients with secondary NPH (sNPH) be separated in studies of cognitive outcome following shunt (Larsson et al., 1991; Thomas et al., 2005) as the two have been shown to respond differently to shunt surgery. Specifically, patients with sNPH are more likely to respond positively to shunt surgery than those with iNPH (Larsson et al., 1991; Thomas et al., 2005). In Chapters 3 and 4, patients with iNPH and sNPH were not separated and so this could have affected the results.

6.4.4. Assessment methods

As discussed previously, apathy and depression were measured using self-rated measures in Chapters 3 and 4 which may be problematic. The development of objective measures of neuropsychiatric or behavioural changes in NPH would be of high clinical value.
6.5. Directions for future work

6.5.1. Post-shunt neuropsychological functioning

Future studies should investigate the extent of cognitive recovery that occurs in patients with NPH following shunt surgery. If significant cognitive impairments remain, they may be a target for treatment. For example, future studies could investigate the efficacy of cognitive training paradigms for reducing residual cognitive impairment in NPH. Cognitive rehabilitation has shown to produce measurable benefits in functioning in patients with dementia (Clare et al., 2010) and brain injury (Rohling, Faust, Beverly, & Demakis, 2009), thus it could be a viable option for patients with NPH. Alternatively, the efficacy of pharmacological treatment with cognitive enhancing drugs could be investigated further. One case study has demonstrated that the cognitive enhancer methylphenidate may be a promising treatment for alleviating cognitive dysfunction and apathy in patients with NPH (Keenan et al., 2005).

Additionally, it is important for future studies to investigate whether executive function improves following shunt surgery. Specifically, higher-level executive functions such as decision making or planning should be assessed in patients with NPH before and following shunt surgery to better quantify changes in executive function.

6.5.2. Apathy

Future studies should aim to determine the optimal method for assessing apathy in patients with NPH (and other dementias). Initially, future studies should aim to determine whether the different assessment scales produce different results regarding prevalence and outcome of apathy. Secondly, insight into apathy should be investigated in patients with NPH in order to investigate whether self-ratings are reliable. Thirdly, the development of an objective measure of apathy for use in patients with dementia should be a priority. Finally, future studies should aim to elucidate the effects of apathy on cognition and vice versa.

6.5.3. Structural imaging in NPH

Future studies should investigate whether subcortical volume loss is related to impaired regional cerebral blood flow in subcortical regions, and whether volume increase is related to
improved blood flow. Longitudinal volumetric assessment is also of value to investigate whether brain atrophy continues after shunt surgery as well as the clinical implication of this.

6.6. Achievement of the aims of this thesis

This thesis aimed to expand on the neuropsychological and neuropsychiatric research in NPH. More specifically, this thesis aimed to investigate (i) the effect of shunt surgery on neuropsychological performance in patients with NPH; (ii) the significance of the symptom of apathy in NPH; (iii) structural correlates of cognitive dysfunction and apathy in NPH; and (iv) the efficacy of current apathy assessment measures.

The results of this thesis provided evidence that there is a beneficial effect of shunt surgery on neuropsychological performance in patients with NPH. Although a number of studies found that patients improved on neuropsychological tests following shunt, a consistent pattern of improvement had failed to emerge. A meta-analysis was conducted to pool the available data in order to provide a clearer picture of post-shunt cognitive change. From the results, it appears that, on average, patients improve on tests of learning and memory, global cognitive function, and psychomotor speed. However, there is a need to further investigate the effect of shunt surgery on executive function.

In evaluating the significance of the symptom of apathy, Chapter 3 found evidence that apathy in NPH is related to cognitive function and outcome, as well as degree of ventriculomegaly at baseline. Importantly, reduction in apathetic symptoms following shunt in Chapter 3 was associated with improved performance on a measure of global cognitive functioning. This might suggest that the symptom of apathy may be a barrier to functional recovery in patients with NPH which could have implication for treatment options. The most important conclusion from these investigations is that apathy should be objectively measured in patients with NPH in addition to depression.

The results of the structural imaging project provided evidence for the role of subcortical pathology in the cognitive and behavioural symptomology in NPH. Specifically, the impaired functioning of the caudate appears to underlie the symptom of apathy in NPH. This might suggest that cognitive dysfunction and apathy in NPH have shared neural underpinnings.

Finally, this thesis provided an evaluation of a possible objective measure of apathy, something which would be of great clinical utility, particularly for assessing apathy in patients
with dementia or cognitive decline. Although the task described here was ultimately deemed to be unsuitable for this purpose, some alternative measures were proposed.
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**APPENDIX A. The Cambridge State Apathy Evaluation scale (self-rated)**

*Indicate how much you agree with each statement right now. INSTRUCTIONS: For each statement below, circle one number to indicate how true you think each statement is for you in the past couple of weeks. Is the statement (0) not at all true, (1) slightly true, (2) somewhat true, or (3) very true? Please provide one rating for every statement, even if you are not confident of your answer.*

*NOTE: This questionnaire is asking how you FEEL. So, for example, if you FEEL like getting things done but struggle to because of other factors, you should answer the question based on what you feel like doing, not what you actually do.*

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>Slightly</th>
<th>Somewhat</th>
<th>Very</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel interested in things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>I feel like getting things done (rather than putting them off)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Getting things started on my own is important to me</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>I am interested in having new experiences</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>I am interested in learning new things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>I don’t feel like putting any effort into anything</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>I feel like approaching tasks whole-heartedly</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>I feel it is important to see a job through to its end</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>I feel like spending time pursuing my interests/ hobbies</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>I feel that I need someone to tell me what to do (otherwise I’d do nothing)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>I am less concerned about my problems than I ought to be</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>I would like to meet new people</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>I feel like spending time with friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>I would be excited if good things were to happen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>I think I have an accurate understanding of my problems</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>I feel like doing a good job and achieving something</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>I feel full of initiative</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>I feel motivated</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
APPENDIX B. Meta-analyses results when assuming alternative correlations between average pre- and post-operative scores

Results of meta-analyses of the average difference between pre-operative and post-operative neuropsychological test scores when assuming alternative correlations (between the average pre-operative and post-operative scores) of 0.4 and 0.8 are presented in Table B-1 and Table B-2, respectively.

Table B-1: Results of meta-analyses when assuming an alternative correlation of 0.4

<table>
<thead>
<tr>
<th>Test</th>
<th>n of Studies</th>
<th>Estimated average difference</th>
<th>95% CI</th>
<th>p</th>
<th>Cochran’s Q (d.f.; p)</th>
<th>$I^2$</th>
<th>Estimated between-study variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>19</td>
<td>2.17 points</td>
<td>1.42, 2.92</td>
<td>&lt; 0.001</td>
<td>75.20 (18; &lt; 0.001)</td>
<td>76.1%</td>
<td>1.77</td>
</tr>
<tr>
<td>RAVLT total</td>
<td>7</td>
<td>5.55 words</td>
<td>3.76, 7.33</td>
<td>&lt; 0.001</td>
<td>12.29 (6; 0.06)</td>
<td>51.2%</td>
<td>2.44</td>
</tr>
<tr>
<td>RAVLT delayed</td>
<td>7</td>
<td>1.42 words</td>
<td>0.57, 2.27</td>
<td>0.001</td>
<td>40.55 (6; &lt; 0.001)</td>
<td>85.2%</td>
<td>0.97</td>
</tr>
<tr>
<td>Backwards digit span</td>
<td>6</td>
<td>0.34 digits</td>
<td>0.04, 0.65</td>
<td>0.03</td>
<td>30.10 (5; &lt; 0.001)</td>
<td>83.4%</td>
<td>0.10</td>
</tr>
<tr>
<td>Phonemic verbal fluency</td>
<td>8</td>
<td>2.41 words</td>
<td>0.76, 4.07</td>
<td>0.004</td>
<td>7.57 (7; 0.37)</td>
<td>7.6%</td>
<td>0.45</td>
</tr>
<tr>
<td>TMT-B</td>
<td>9</td>
<td>-41.54 sec</td>
<td>-80.73, -2.36</td>
<td>0.04</td>
<td>27.92 (8; &lt; 0.001)</td>
<td>71.3%</td>
<td>2.2e+03</td>
</tr>
<tr>
<td>TMT-A</td>
<td>13</td>
<td>-26.03 sec</td>
<td>-35.64, -16.42</td>
<td>&lt; 0.001</td>
<td>14.42 (12; 0.28)</td>
<td>16.8%</td>
<td>48.71</td>
</tr>
</tbody>
</table>

Note: MMSE, Mini-mental state examination; RAVLT, Rey Auditory Verbal Learning Test; TMT, trail making test.
Table B-2: Results of meta-analyses when assuming an alternative correlation of 0.8

<table>
<thead>
<tr>
<th>Test</th>
<th>n of Studies</th>
<th>Estimated average difference</th>
<th>95% CI</th>
<th>p</th>
<th>Cochran’s Q (d.f.; p)</th>
<th>$I^2$</th>
<th>Estimated between-study variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>19</td>
<td>2.22 points</td>
<td>1.47, 2.97</td>
<td>&lt; 0.001</td>
<td>158.56 (18; &lt; 0.001)</td>
<td>88.6%</td>
<td>2.23</td>
</tr>
<tr>
<td>RAVLT total</td>
<td>7</td>
<td>5.84 words</td>
<td>4.04, 7.64</td>
<td>&lt; 0.001</td>
<td>17.56 (6; 0.007)</td>
<td>65.8%</td>
<td>3.05</td>
</tr>
<tr>
<td>RAVLT delayed</td>
<td>7</td>
<td>1.44 words</td>
<td>0.51, 2.37</td>
<td>0.002</td>
<td>97.45 (6; &lt; 0.001)</td>
<td>93.8%</td>
<td>1.33</td>
</tr>
<tr>
<td>Backwards digit span</td>
<td>6</td>
<td>0.37 digits</td>
<td>0.04, 0.70</td>
<td>0.03</td>
<td>62.42 (5; &lt; 0.001)</td>
<td>92.0%</td>
<td>0.15</td>
</tr>
<tr>
<td>Phonemic verbal fluency</td>
<td>8</td>
<td>3.24 words</td>
<td>1.09, 5.40</td>
<td>0.003</td>
<td>18.87 (7; 0.009)</td>
<td>62.9%</td>
<td>5.52</td>
</tr>
<tr>
<td>TMT-B</td>
<td>9</td>
<td>-46.41 sec</td>
<td>-87.44, -5.37</td>
<td>0.03</td>
<td>54.86 (8; &lt; 0.001)</td>
<td>85.4%</td>
<td>2.9e+03</td>
</tr>
<tr>
<td>TMT-A</td>
<td>13</td>
<td>-25.47 sec</td>
<td>-35.89, -15.05</td>
<td>&lt; 0.001</td>
<td>29.04 (12; 0.004)</td>
<td>58.7%</td>
<td>163.02</td>
</tr>
</tbody>
</table>

Note: MMSE, Mini-mental state examination; RAVLT, Rey Auditory Verbal Learning Test; TMT, trail making test.
APPENDIX C. The Geriatric Depression Scale (short form)

Instructions: Circle the answer that best describes how you felt over the past week.

1. Are you basically satisfied with your life?  yes  no
2. Have you dropped many of your activities and interests?  yes  no
3. Do you feel that your life is empty?  yes  no
4. Do you often get bored?  yes  no
5. Are you in good spirits most of the time?  yes  no
6. Are you afraid that something bad is going to happen to you?  yes  no
7. Do you feel happy most of the time?  yes  no
8. Do you often feel helpless?  yes  no
9. Do you prefer to stay at home, rather than going out and doing things?  yes  no
10. Do you feel that you have more problems with memory than most?  yes  no
11. Do you think it is wonderful to be alive now?  yes  no
12. Do you feel worthless the way you are now?  yes  no
13. Do you feel full of energy?  yes  no
14. Do you feel that your situation is hopeless?  yes  no
15. Do you think that most people are better off than you are?  yes  no

Total Score ____________
APPENDIX D. Published papers

Original Article

Apathy, ventriculomegaly and neurocognitive improvement following shunt surgery in normal pressure hydrocephalus

Katie A. Peterson1, Charlotte R. Housden1,3, Clare Killikelly1, Elise E. DeVito1,2,4, Nicole C. Keong2, George Savulich1, Zofia Czosnyka1, John D. Pickard2 & Barbara J. Sahakian1,5

1Department of Psychiatry, University of Cambridge, Addenbrooke’s Hospital, Cambridge, UK, 2Department of Neurosurgery, University of Cambridge, Addenbrooke’s Hospital, Cambridge, UK, 3Cambridge Cognition Ltd, Cambridge, UK, 4Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA, and 5MRC/Wellcome Trust Behavioural and Clinical Neurosciences Institute, University of Cambridge, Cambridge, UK

Abstract

Introduction. Apathy – impaired motivation and goal-directed behaviour – is a common yet often overlooked symptom in normal pressure hydrocephalus (NPH). Caudate atrophy often yields atypical symptoms; however, this structural and functional relationship has not yet been explored in NPH. Additionally, little is known about the relationship between apathy and post-shunt cognitive recovery. Methods. This audit investigated whether apathetic symptoms improve following shunt surgery in NPH, and whether this relates to cognitive response. In addition, we assessed the relationship between ventriculomegaly and apathy using the bicaudate ratio. Twenty-two patients with NPH completed the Mini-Mental State Examination (MMSE), the Apathy Evaluation Scale (AES) and the Geriatric Depression Scale (GDS) before and 3–9 months after shunt surgery. Pre-operative ventriculomegaly was correlated with pre-operative AES and GDS scores. Difference scores (post-shunt minus baseline values) for AES and GDS were correlated with cognitive outcome. Results. Greater pre-operative ventriculomegaly was associated with increased level of apathy and depression. A reduction in apathetic symptoms following shunt surgery was associated with improved performance on the MMSE. Conclusions. Apathy may be indicative of a greater degree of subcortical atrophy in NPH and may relate to functional outcome.

Keywords: apathy; audit; caudate nucleus; cognitive function; normal pressure hydrocephalus

Introduction

Normal pressure hydrocephalus (NPH) is a clinical syndrome resulting from a buildup of cerebrospinal fluid (CSF) in the brain. It is characterised by gait apraxia, cognitive decline, urinary incontinence, ventriculomegaly (ventricular enlargement) and apparently normal CSF pressure at lumbar puncture. Although cognitive decline is commonly associated with NPH, the nature of NPH-related dementia is difficult to characterise. Following treatment with a ventriculoperitoneal shunt to divert CSF, cognitive function has been shown to improve.2,3 Hence, NPH represents a reversible form of dementia.2 Problematically, apathy is often observed in NPH patients.2,4 This symptom may be a significant obstacle for cognition and functional outcome. Increased apathy is associated with decreased functional level across a range of disorders (e.g. Alzheimer’s disease and stroke)9 and should thus be an important consideration for NPH treatment.

It has been argued that symptoms associated with NPH may be attributed to subcortical pathology.2 For example, the caudate nucleus, a subcortical structure and part of the fronto-subcortical dopaminergic system, plays a role in reward processing and motivation. Importantly, damage to these areas has been associated with apathy.2,4 Diminished caudate volume has been observed in patients with NPH; it is therefore possible that caudate atrophy and damage to associated striatal circuitry in NPH may underlie apathetic behaviour. It is not yet established whether caudate atrophy relates to degree of ventriculomegaly. Ventriculomegaly may be assessed using the bicaudate ratio (BCR) – the width of the lateral ventricles at the level of the body of the caudate nuclei as a percentage of the width of brain across the same line (Fig. 1). BCR is a useful measure as it is easily obtainable without complex computerised techniques. This audit investigates whether BCR relates to degree of apathy in patients with NPH. In addition, cognition and apathy were assessed before and after shunt surgery to explore the relationship

Correspondence: Katie A. Peterson, Department of Psychiatry, University of Cambridge, Addenbrooke’s Hospital, Level 4 Box 189, Cambridge CB2 0QQ, UK.
Tel: + 44 (0)1223 747 840. E-mail: kapt@mcchi.cam.ac.uk
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between apathy and cognitive outcome, and to provide a clearer profile of the mechanisms driving post-shunt recovery.

**Materials and methods**

**Patients**

As part of an ongoing audit, a clinically representative sample of 22 patients with NPH was included in the present study. Patients were assessed using a brief neuropsychological test battery as part of their normal clinical pathway prior to shunt surgery and 3-9 months after surgery (M = 4.17 months).

Patients were referred by a neurosurgeon (IDP) based on the presence of a clinical picture of NPH. Neuropsychological test data were collected at the CSF clinic led by IDP, Addenbrooke's Hospital.

**Imaging analysis and neuropsychological assessment**

Patients were scanned using magnetic resonance imaging (MRI) or computed tomography (CT) prior to shunt surgery as part of the standard diagnostic procedure. MRI scans were used by a neurosurgeon (IDP) to calculate BCRs. Where these were unavailable, CT scans were used (n = 5). Figure 1 provides an illustration of BCR before and following shunt surgery.

**Table 1. NPH patients demographics.**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Sex</th>
<th>IQ</th>
<th>Years of education</th>
<th>Time to retest (months)</th>
<th>Aetiology</th>
<th>Gait Disturb</th>
<th>Incontinence</th>
<th>MMSE</th>
<th>Pre BCR</th>
<th>Post BCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>M</td>
<td>120</td>
<td>12</td>
<td>3</td>
<td>Idiopathic</td>
<td>+</td>
<td>-</td>
<td>23</td>
<td>26</td>
<td>0.32</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>M</td>
<td>n/a</td>
<td></td>
<td>4</td>
<td>Secondary to IV ventricular outlet obstruction</td>
<td>+</td>
<td>-</td>
<td>26</td>
<td>26</td>
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</tr>
<tr>
<td>3</td>
<td>56</td>
<td>M</td>
<td>117</td>
<td>11</td>
<td>11</td>
<td>Secondary to pineal tumour and radiotherapy</td>
<td>-</td>
<td>28</td>
<td>28</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
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<td>11</td>
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<td>+</td>
<td>18</td>
<td>24</td>
<td>0.27</td>
</tr>
<tr>
<td>5</td>
<td>74</td>
<td>F</td>
<td>100</td>
<td>9</td>
<td>3</td>
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<td>+</td>
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<td>3</td>
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<td>-</td>
<td>28</td>
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<td>0.30</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>M</td>
<td>92</td>
<td>10</td>
<td>8</td>
<td>Aqueduct stenosis</td>
<td>+</td>
<td>n/a</td>
<td>28</td>
<td>23</td>
<td>0.29</td>
</tr>
<tr>
<td>8</td>
<td>83</td>
<td>M</td>
<td>110</td>
<td>11</td>
<td>5</td>
<td>Idiopathic</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>23</td>
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<tr>
<td>9</td>
<td>79</td>
<td>F</td>
<td>100</td>
<td>11</td>
<td>5</td>
<td>Idiopathic</td>
<td>+</td>
<td>-</td>
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<tr>
<td>10</td>
<td>74</td>
<td>M</td>
<td>87</td>
<td>10</td>
<td>2</td>
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<td>18</td>
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<tr>
<td>11</td>
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<td>M</td>
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<td>+</td>
<td>23</td>
<td>21</td>
<td>0.29</td>
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<tr>
<td>12</td>
<td>52</td>
<td>M</td>
<td>109</td>
<td>11</td>
<td>3</td>
<td>Aqueduct stenosis</td>
<td>+</td>
<td>-</td>
<td>27</td>
<td>28</td>
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</tr>
<tr>
<td>13</td>
<td>62</td>
<td>F</td>
<td>100</td>
<td>11</td>
<td>2</td>
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<td>-</td>
<td>29</td>
<td>25</td>
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</tr>
<tr>
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<td>82</td>
<td>F</td>
<td>115</td>
<td>9</td>
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<td>Idiopathic</td>
<td>+</td>
<td>+</td>
<td>26</td>
<td>27</td>
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</tr>
<tr>
<td>15</td>
<td>56</td>
<td>F</td>
<td>111</td>
<td>16</td>
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<td>+</td>
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<td>24</td>
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</tr>
<tr>
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<td>77</td>
<td>M</td>
<td>115</td>
<td>9</td>
<td>3</td>
<td>Idiopathic</td>
<td>+</td>
<td>n/a</td>
<td>27</td>
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<td>0.30</td>
</tr>
<tr>
<td>17</td>
<td>79</td>
<td>F</td>
<td>124</td>
<td>12</td>
<td>8</td>
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</tr>
<tr>
<td>18</td>
<td>75</td>
<td>M</td>
<td>123</td>
<td>14</td>
<td>3</td>
<td>Idiopathic</td>
<td>+</td>
<td>-</td>
<td>27</td>
<td>30</td>
<td>0.28</td>
</tr>
<tr>
<td>19</td>
<td>81</td>
<td>M</td>
<td>120</td>
<td>14</td>
<td>3</td>
<td>Idiopathic</td>
<td>+</td>
<td>-</td>
<td>27</td>
<td>28</td>
<td>0.20</td>
</tr>
<tr>
<td>20</td>
<td>52</td>
<td>F</td>
<td>109</td>
<td>18</td>
<td>3</td>
<td>Aqueduct stenosis</td>
<td>+</td>
<td>-</td>
<td>24</td>
<td>27</td>
<td>0.29</td>
</tr>
<tr>
<td>21</td>
<td>66</td>
<td>M</td>
<td>92</td>
<td>12</td>
<td>5</td>
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<td>+</td>
<td>+</td>
<td>35</td>
<td>27</td>
<td>0.24</td>
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<tr>
<td>22</td>
<td>71</td>
<td>F</td>
<td>126</td>
<td>17</td>
<td>4</td>
<td>Idiopathic</td>
<td>+</td>
<td>-</td>
<td>27</td>
<td>26</td>
<td>0.26</td>
</tr>
</tbody>
</table>

*Pre-operative BCR (higher BCR = greater degree of ventriculomegaly), † patient in a wheelchair, ‡ taken from CT scans, n/a = information not available.
surgery in NPH. IQ and global function were assessed using the National Adult Reading Test (NART)\(^9\) and the Mini-Mental State Examination (MMSE),\(^{10}\) respectively. Phonemic and semantic fluency were measured using the Controlled Oral Word Association Test (COWAT).\(^{11}\) Verbal memory and learning were measured using the Hopkins Verbal Learning Test (HVLT).\(^{12}\) Mood was assessed by the Geriatric Depression Scale (GDS short form)\(^{13}\) and/or the self-report version of the Apathy Evaluation Scale (AES).\(^{14}\)

**Statistical analysis**

Pre-operative BCRI was correlated with patients’ pre-operative AES score, and GDS score for comparison. BCR was also correlated with pre-operative MMSE score, IQ and age. Bivariate correlations were conducted using Spearman’s rho. Pre- and post-operative neuropsychological test scores were compared using paired samples t-tests. One outlier was identified and removed from the phonemic fluency analysis as the pre-operative score was >2.5 standard deviations (SDs) above the mean. Scores in the AES, GDS, HVLT delayed, HVLT recognition and MMSE violated assumptions of normality; Wilcoxon signed-rank tests were therefore used to compare scores in these tests. To investigate the relationship between change in apathy (AES) and change in neuropsychological test scores, pre-operative scores were subtracted from post-operative scores to obtain a ‘change’ (difference) score for each test. Correlations were then conducted using Spearman’s rho. Correlations between change in depression (GDS) and change in neuropsychological test scores were conducted for comparison.

**Results**

Fourteen patients were male and eight were female. Mean (SD) age in years was 68.3 (10.8). Mean IQ and years of education were 109.4 (11.38) and 12.1 (2.49), respectively. Mean baseline MMSE was 25 (3.52). Mean pre-operative BCR was 0.29 (0.03). Individual patient details are shown in Table I.

Significant positive correlations were observed between pre-operative BCR and pre-operative AES score, \(r = 0.61, p < 0.03\), and between pre-operative BCR and pre-operative GDS score, \(r = 0.52, p < 0.02\). These significant correlations indicate that greater pre-operative BCR (greater degree of ventriculomegaly) was associated with greater levels of apathy and depression. Although there was no significant correlation between BCR and age, partial correlations were conducted for both analyses controlling for age. Both AES score and GDS score remained significantly positively correlated with pre-operative BCR when controlling for effects of age.

There were significant within-group differences between pre-operative and post-operative scores in phonemic fluency, semantic fluency, HVLT delayed and HVLT recognition, all in the direction of improvement after shunt surgery (Table II). No other significant group differences were observed. A Wilcoxon signed-ranks test demonstrated a non-significant trend for decreased apathy (AES) post-operatively, \(Z = -1.87, p = 0.06\). A post-hoc power calculation was conducted using G\(^*\)Power 3 to determine an estimate of the sample size required to achieve a significant difference in AES scores before and 3-9 months after the operation. With alpha set at 0.05 and power set at 0.80, approximately 34 participants would be needed to achieve a medium effect size (\(d = 0.45\)).

Table III shows results of correlations between AES and GDS change scores with change scores in the remaining neuropsychological tests. A significant positive correlation was observed between AES change and GDS change, as AES score decreases so does GDS score (both improve). Additionally, there was a significant negative correlation between AES change and MMSE change. The nature of this relationship can be seen in Fig. 2. As AES score decreases, MMSE score increases. That is, a reduction in apathy is associated

---

**Table II. Neuropsychological tests results at baseline and 3-9 months post-operatively.**

<table>
<thead>
<tr>
<th>Neuropsychological test</th>
<th>Pre-operative</th>
<th>Post-operative</th>
<th>change$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQ8)</td>
<td>Median (IQ8)</td>
<td>t/Z</td>
</tr>
<tr>
<td>AES$^a$</td>
<td>18</td>
<td>17.56 (10.5)</td>
<td>10.90 (9.5)</td>
</tr>
<tr>
<td>GDS$^b$</td>
<td>21</td>
<td>6.00 (3)</td>
<td>2.90 (4.5)</td>
</tr>
<tr>
<td>Phonic fluency$^{**}$</td>
<td>21</td>
<td>27.98 ± 10.37</td>
<td>34.14 ± 16.43</td>
</tr>
</tbody>
</table>
| Semantic fluency$^{**}$ | 22            | 12.32 ± 5.79  | 15.82 ± 7.02  | -2.06 | 21   | 0.006 | +
| HVLT immediate          | 22            | 4.95 ± 1.89   | 5.05 ± 2.44  | -0.20 | 21   | 0.85 | |
| HVLT learning           | 22            | 17.27 ± 5.43  | 18.01 ± 6.89  | -1.26 | 21   | 0.22 | +
| HVLT delayed$^{**}$     | 22            | 1.00 (3)      | 3.90 (7)     | -2.14 | 0.03 | + |
| HVLT recognition$^{***}$| 22            | 21.00 (3)     | 23.90 (2)    | -2.00 | 0.003 | + |
| MMSE$^c$                | 22            | 28.00 (4)     | 26.50 (3.75) | -1.72 | 0.09 | + |

*\(p < 0.05\), \*\(p < 0.01\), \*\*\*parametric test, \(\text{mean} ± \text{SD}, \text{direction of change (} + \text{improvement, } - \text{decline}).

---

**Table III. Bivariate correlations in apathy and depression with change in neuropsychological tests.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>AES change</th>
<th>GDS change</th>
<th>Phonemic fluency change</th>
<th>Semantic fluency change</th>
<th>HVLT immediate change</th>
<th>HVLT delayed change</th>
<th>HVLT recognition change</th>
<th>MMSE change</th>
</tr>
</thead>
<tbody>
<tr>
<td>AES change</td>
<td>0.05</td>
<td>0.21</td>
<td>0.28</td>
<td>-0.36</td>
<td>-0.51*</td>
<td>-0.38</td>
<td>-0.43</td>
<td>-0.24</td>
</tr>
<tr>
<td>GDS change</td>
<td>0.27</td>
<td>0.10</td>
<td>0.25</td>
<td>-0.08</td>
<td>0.51*</td>
<td>-0.16</td>
<td>-0.30</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Results represent Spearman’s rho values.

\*\(p < 0.05\), \*\(p < 0.01\). 'Change' scores were calculated by subtracting pre-shunt scores from post-shunt scores.
with increased functional level as measured by the MMSE. No significant correlation was observed between GDS and MMSE change.

Discussion

This audit investigated whether BCR (degree of ventriculomegaly) relates to degree of apathy in patients with NPH, and the relationship between changes in cognition with change in apathy after shunt treatment. Results revealed significant improvements from baseline to follow-up in tests of phonemic and semantic fluency, delayed verbal recall and recognition memory. Additionally, pre-operative BCR was positively correlated with pre-operative degree of apathy and depression. There was a non-significant trend for improved apathy scores following shunt surgery. Importantly, we found that a reduction in apathy was associated with improved global cognition. No relationship was observed between change in global cognition and changes in depressive symptoms.

These findings highlight the importance of assessing apathy in patients with NPH. Apathy is associated with striatal dopaminergic pathology. Since pre-operative BCR was positively associated with degree of apathy, the symptom of apathy may indicate greater subcortical brain atrophy, possibly leading to impaired functioning of striatal dopamine pathways in patients with NPH. Additionally, our findings suggest that alleviation of the symptom of apathy following shunt surgery is linked to improved functional level as measured by the MMSE. Keenan et al. found that administration of the psychostimulant drug: methylphenidate was associated with reduced apathetic symptoms and increased performance in a spatial recognition task in a patient with NPH. Methylphenidate inhibits dopamine reuptake in the brain by blocking dopamine transporters and it was concluded that increased dopamine level in the brain following methylphenidate administration may account for the observed reduction in apathy. These findings suggest a possible dopaminergic link to apathy and the cognitive deficits observed in NPH.

BCR also positively correlated with degree of depression in our patient sample and as level of apathy reduced (improved) post-operatively so did the level of depression. However, no association was observed between change in depression level and MMSE score. Distorted reward processing, an aspect of depression, likely overlaps with symptoms of apathy and therefore this aspect could improve simultaneously with reduced apathetic symptoms following shunt surgery.

Conclusions

BCR is an easily obtainable measure of degree of ventriculomegaly in patients with NPH. We observed a relationship between pre-operative BCR and degree of apathy. Additionally, our findings suggest a potential role of apathy in patients’ post-shunt functional outcome, highlighting the importance of assessing this symptom in NPH (a symptom which currently is not commonly assessed). These results may also demonstrate that to some extent apathetic symptoms improve following shunt treatment. The relationship between BCR and caudate atrophy in NPH should be examined further.

Acknowledgments

The authors would like to thank the administrative staff at the Departments of Psychiatry and Neurosurgery, University of Cambridge, Addenbrooke’s Hospital for their assistance.
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References

The effect of shunt surgery on neuropsychological performance in normal pressure hydrocephalus: a systematic review and meta-analysis

Katie A. Peterson1 · George Savulich1 · Dan Jackson2 · Clare Killikelly1 · John D. Pickard1 · Barbara J. Sahakian1,4

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Abstract We conducted a systematic review of the literature and used meta-analytic techniques to evaluate the impact of shunt surgery on neuropsychological performance in patients with normal pressure hydrocephalus (NPH). Twenty-three studies with 1059 patients were identified for review using PubMed, Web of Science, Google scholar and manual searching. Inclusion criteria were prospective, within-subject investigations of cognitive outcome using neuropsychological assessment before and after shunt surgery in patients with NPH. There were statistically significant effects of shunt surgery on cognition (Mini-Mental State Examination; MMSE), learning and memory (Rey Auditory Verbal Learning Test; RAVLT, total and delayed subtests), executive function (backwards digit span, phonemic verbal fluency, trail making test B) and psychomotor speed (trail making test A) all in the direction of improvement following shunt surgery, but with considerable heterogeneity across all measures. A more detailed examination of the data suggested robust evidence for improved MMSE, RAVLT total, RAVLT delayed, phonemic verbal fluency and trail making test A only. Meta-regressions revealed no statistically significant effect of age, sex or follow-up interval on improvement in the MMSE. Our results suggest that shunt surgery is most sensitive for improving global cognition, learning and memory and psychomotor speed in patients with NPH.

Keywords Normal pressure hydrocephalus · Shunt surgery · Cognition · Neuropsychology · Neuropsychological tests

Introduction

Normal pressure hydrocephalus (NPH) is characterized by a build-up of cerebrospinal fluid (CSF) in the brain despite apparently normal CSF pressure at lumbar puncture [1]. Idiopathic NPH (iNPH) typically occurs in later life and without any obvious cause [2, 3]. Symptoms include gait disturbance, urinary incontinence and progressive dementia [1]. Dementia-related symptoms are characterised by deficits in memory, visuospatial abilities, psychomotor speed and executive function [2, 4–10].

The effect of shunt treatment on cognitive performance in patients with NPH is controversial. While CSF drainage is generally considered to relieve problems with gait and incontinence, cognitive impairment is reported to be the least likely symptom to improve [2]. Rates of cognitive improvement range from 0 to 80 % of patients in a given series [2, 11–14]. However, methodological limitations have been identified which could explain the variability observed between studies. These include unclear patient
selection criteria, inconsistent follow up intervals and use of subjective measures of improvement [15]. Additionally, due to the lack of standardized clinical guidelines for assessing cognitive function in this patient group, assessment methods often vary between centres with functional grading scales, clinical rating scales, and neuropsychological testing being employed [15]. Studies that have focused on neuropsychological test performance generally show a beneficial effect of shunt surgery on cognitive function. However, again, the pattern of post-operative neuropsychological improvement varies widely between studies [e.g., 2, 5, 9, 11].

Understanding the neuropsychology of NPH may be useful for differential diagnosis as well as interpretation of outcome following treatment [9]. We combined data from the most frequently used neuropsychological tests in an attempt to determine the effect of shunt surgery on neuropsychological performance in patients with NPH. We included studies using neuropsychological tests to assess cognition before and after shunt surgery. We conducted meta-analyses on pre- and post-operative scores for each test. Additionally, we conducted exploratory analyses to investigate effects of moderator variables on cognitive outcome.

Methods

Search strategy

A systematic search of the electronic databases PubMed and Web of Science was conducted in October 2015 using the key words: 'NPH', 'normal pressure hydrocephalus', 'cognition', 'shunt outcome', 'neuropsychological outcome' and 'neuropsychological assessment' (separately and in combination) for studies published before October 2015. Due to the limited pool of papers recovered, Google Scholar was included in the search strategy. Reference lists of relevant studies were searched manually. Our review did not have a registered protocol but followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16].

Study selection

Selection of studies

Titles and abstracts of articles were scanned independently by two researchers to identify articles to retrieve in full. Disagreement was dealt with by discussion including a third person.

Inclusion criteria

Inclusion criteria were: (1) prospective investigations of cognitive outcome following shunt surgery; (2) patients were adults with a diagnosis of NPH; (3) within-subjects design; and (4) report of pre- and post-operative neuropsychological test scores.

Exclusion criteria

Exclusion criteria were: (1) case studies; (2) studies which did not use neuropsychological tests; (3) used neuropsychological tests which were not analysed based on insufficient data; (4) reported composite scores. One study [12] was excluded due to patient overlap with Poca et al. (2004) [17]. Three other papers [18–20] were excluded due to likely patient overlap with other papers that involve larger patient numbers and were included in the review and the analyses that follow.

Primary outcome measures

Meta-analyses were conducted on pre-operative and "difference" scores in seven neuropsychological tests: the Mini-Mental State Examination (MMSE); the Rey Auditory Verbal Learning Test (RAVLT) total verbal recall and delayed verbal recall subtests; backwards digit span; phonemic verbal fluency; trail making test A (TMT-A); and trail making test B (TMT-B). These were selected as each had at least five studies providing supporting data. Follow-up intervals ranged from 3 to 12 months post-shunt (Table 1). The majority of studies reported follow-up data from one post-operative assessment period. However, one study reported outcome data from more than one post-operative assessment [21]. In this case, data from the earliest follow-up assessment (3 months) were included. Analyses were performed using Stata v13.

Statistical analysis

Random-effects meta-analyses were performed using the average difference between pre-operative and post-operative scores (difference scores) as outcome data and the standard method of DerSimonian and Laird [22]. Average difference scores were provided by some studies, while for others these were calculated from average pre-operative and post-operative scores. In all meta-analyses, a positive difference indicates that the average post-operative score is more than the pre-operative score. Hence in some meta-analyses positive estimates indicate patient improvement and in others positive estimates indicate deterioration. However, pooled estimates from all seven meta-analyses
Table 1 Characteristics of the studies included in meta-analyses

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient n</th>
<th>Patient selection</th>
<th>Age of patients mean (SD) years</th>
<th>Follow-up interval</th>
<th>% males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andén et al. [23]</td>
<td>69</td>
<td>Patients with idiopathic NPH</td>
<td>70 (48-84)</td>
<td>3 months</td>
<td>54</td>
</tr>
<tr>
<td>Dunkerke et al. [2]</td>
<td>10</td>
<td>Patients with idiopathic NPH who showed improvement in at least one clinical symptom with temporary lumbar drainage</td>
<td>70.9 (10.26)</td>
<td>6-12 months</td>
<td>40</td>
</tr>
<tr>
<td>Foss et al. [24]</td>
<td>27</td>
<td>Patients with idiopathic NPH</td>
<td>72 (46-81)</td>
<td>6-9 months</td>
<td>29.6</td>
</tr>
<tr>
<td>Gleichgericht et al. [5]</td>
<td>10</td>
<td>Patients with idiopathic NPH who showed clinical response to continuous CSF drainage</td>
<td>69.4 (9.3)</td>
<td>6-8 months</td>
<td>70</td>
</tr>
<tr>
<td>Hellström et al. [11]</td>
<td>47</td>
<td>Patients with idiopathic NPH</td>
<td>73 (24-84)</td>
<td>3 months</td>
<td>47</td>
</tr>
<tr>
<td>Hellström et al. [21]</td>
<td>142</td>
<td>Patients with idiopathic NPH</td>
<td>72.3 (30-87)</td>
<td>3 months</td>
<td>51</td>
</tr>
<tr>
<td>Hiraoka et al. [25]</td>
<td>11</td>
<td>Patients with idiopathic NPH</td>
<td>77.9 (4.1)</td>
<td>3 months</td>
<td>40</td>
</tr>
<tr>
<td>Iddon et al. [6]</td>
<td>11</td>
<td>Patients with idiopathic NPH</td>
<td>69.64 (6.14)</td>
<td>6 months</td>
<td>72.7</td>
</tr>
<tr>
<td>Katzen et al. [7]</td>
<td>12</td>
<td>Patients with idiopathic NPH</td>
<td>74.92 (7.72)</td>
<td>6 months</td>
<td>33.3</td>
</tr>
<tr>
<td>Kacoi et al. [26]</td>
<td>49</td>
<td>Patients with idiopathic NPH</td>
<td>76.4 (4.4)</td>
<td>3 months</td>
<td>41</td>
</tr>
<tr>
<td>Lundin et al. [27]</td>
<td>35</td>
<td>Patients with idiopathic NPH</td>
<td>73 (49-81)</td>
<td>3 months</td>
<td>45.7</td>
</tr>
<tr>
<td>Mutaró et al. [10]</td>
<td>8</td>
<td>Patients with idiopathic NPH</td>
<td>73.4 (6.8)</td>
<td>6 months</td>
<td>50</td>
</tr>
<tr>
<td>Mutaró et al. [28]</td>
<td>18</td>
<td>Patients with idiopathic NPH</td>
<td>74.56 (7.06)</td>
<td>6 months</td>
<td>50</td>
</tr>
<tr>
<td>Moriya et al. [29]</td>
<td>32</td>
<td>Patients with idiopathic NPH</td>
<td>73.7 (6.8)</td>
<td>12 months</td>
<td>71.9</td>
</tr>
<tr>
<td>Peterson et al. [30]</td>
<td>22</td>
<td>Patients with NPH</td>
<td>68.3 (10.8)</td>
<td>3-9 months</td>
<td>63.6</td>
</tr>
<tr>
<td>Peca et al. [17]</td>
<td>43</td>
<td>Patients with idiopathic NPH</td>
<td>71.1 (6.9)</td>
<td>6 months</td>
<td>69.8</td>
</tr>
<tr>
<td>Saito et al. [8]</td>
<td>32</td>
<td>Patients with idiopathic NPH who showed ≥ 1 point reduction on the total INPH Grading Scale following shunt surgery</td>
<td>75.7 (4.5)</td>
<td>12 months</td>
<td>50</td>
</tr>
<tr>
<td>Savolainen et al. [31]</td>
<td>51</td>
<td>Patients with idiopathic NPH</td>
<td>67.5</td>
<td>3-12 months</td>
<td>52.9</td>
</tr>
<tr>
<td>Solana et al. [9]</td>
<td>185</td>
<td>Patients with idiopathic NPH</td>
<td>73.96 (6.3)</td>
<td>6 months</td>
<td>60</td>
</tr>
<tr>
<td>Stambrook et al. [52]</td>
<td>14</td>
<td>Patients with NPH</td>
<td>66.0 (14.16)</td>
<td>Mean = 23.73 weeks</td>
<td>64.3</td>
</tr>
<tr>
<td>Thomas et al. [14]</td>
<td>42</td>
<td>Patients with idiopathic NPH</td>
<td>73 (10)</td>
<td>3-9 months</td>
<td>45.2</td>
</tr>
<tr>
<td>Virhammar et al. [33]</td>
<td>173</td>
<td>Patients with idiopathic NPH</td>
<td>74 (54-88)</td>
<td>12 months</td>
<td>53</td>
</tr>
<tr>
<td>Yamamoto et al. [34]</td>
<td>16</td>
<td>Patients with idiopathic NPH</td>
<td>75.8 (4.9)</td>
<td>3 months</td>
<td>50</td>
</tr>
</tbody>
</table>

CSF: cerebrospinal fluid, NPH: normal pressure hydrocephalus

* Median (range)

* Mean (range)

* Treatment-as-normal group
lie in the direction where post-operative scores are better than the corresponding pre-operative score.

To include all studies providing relevant outcome data, medians were used as means where these were reported. Where interquartile ranges or ranges were reported instead of standard deviations, these were converted to standard deviations by assuming that their bounds correspond to appropriate quantiles from a normal distribution.

The within-study variances of the average differences were calculated using the reported standard deviations and the numbers of patients. For studies that did not give average difference scores directly, we calculated variances of the average pre-operative and post-operative scores in the same way and allowed for a correlation between these two scores when calculating within-study variances of their difference; this is important because scores from the same patients will generally be positively correlated. We assumed a moderate correlation of 0.6 between the average pre-operative and post-operative scores. Our conclusions were robust when assuming alternative correlations of 0.4 and 0.8 (results not shown).

Due to the small numbers of patients comprising the studies, the approximations that underlie the random-effects model are not especially precise. This is evident when, for example, studies’ statements about the statistical significance of their difference scores are not necessarily reflected in the forest plots. Therefore, we carefully assess whether the results are robust below.

Random-effects meta-analyses were also performed using average pre-operative scores to investigate whether instances of lack of improvement were due to ceiling effects. Finally, three random-effects meta-regression models were fitted using the average difference in MMSE as outcome data to assess the evidence that three covariates may be useful predictors of cognitive change.

We did not use any statistical method to assess publication bias. Whilst recognising this as an important issue for meta-analyses, not all studies contribute outcome data to all meta-analyses. Hence the sample sizes are inadequate to assess this issue formally. Furthermore, it is plausible to assume an absence of publication bias in our systematic review. This is because publication bias is usually thought to occur because studies indicating a treatment effect are more likely to be published but our studies do not compare treatment groups in this way.

Results

Search results

Seventy-one studies were identified following a systematic literature search. Forty-eight were excluded (Fig. 1) and twenty-three met criteria for inclusion in meta-analyses (Table 1). A subset of these studies provide outcome data for each neuropsychological test. Nineteen studies provide outcome data for the MMSE; seven studies provide outcome data for RAVLT total and delayed recall subscores; six studies provide outcome data for backwards digit span; eight studies provide outcome data for phonemic verbal fluency; 13 studies provide outcome data for TMT-A; and nine studies provide outcome data for TMT-B (Table 2; supplementary figures).

Average pre-operative scores

The estimated average pre-operative score for each test was as follows: MMSE = 23.10 points (95% CI 22.13–24.08); RAVLT total verbal recall = 22.73 words (95% CI 19.86–25.61); RAVLT delayed verbal recall = 1.90 words (95% CI 1.22–2.57); backwards digit span = 2.92 digits (95% CI 2.38–3.46); phonemic verbal fluency = 19.67 words (95% CI 13.60–25.74); TMT-B = 293.03 s (95% CI 221.09–364.97); and TMT-A = 132.48 s (95% CI 108.48–156.49) (Table 2).

Average difference scores (pre- to post-operative)

There was a statistically significant effect of shunt surgery on cognition (MMSE: pooled average difference = 2.20 points, 95% CI 1.45–2.95, p < 0.001; \( \bar{F} = 81.9 \% \), Suplemental Figure 1), memory (RAVLT total verbal recall: pooled average difference = 5.64 words, 95% CI 3.86–7.43; \( p < 0.001 \); \( \bar{F} = 57.2 \% \), Supplemental Figure 2); delayed verbal recall: pooled average difference = 1.43 words, 0.55–2.31; \( p = 0.001 \); \( \bar{F} = 89.3 \% \), Supplemental Figure 3); executive function (backwards digit span: pooled average difference = 0.36 digits, 0.04–0.67; \( p = 0.03 \); \( \bar{F} = 87.0 \% \), Supplemental Figure 4); phonemic verbal fluency: pooled average difference = 2.73 words, 95% CI 0.84–4.63, \( p = 0.005 \); \( \bar{F} = 33.6 \% \), Supplemental Figure 5); TMT-B: pooled average difference = 43.46 s, 95% CI −83.23 to −3.70, \( p = 0.03 \); \( \bar{F} = 77.7 \% \), Supplemental Figure 6); and psychomotor speed (TMT-A: pooled average difference = −25.90 s, 95% CI −36.11 to −15.69; \( p < 0.001 \); \( \bar{F} = 36.1 \% \), Supplemental Figure 7).

Interpretation of difference scores

All analyses show statistically significant estimated average differences in the direction of improvement following shunt surgery in the presence of moderate to high heterogeneity (Table 2). There is strong evidence for five of these average differences: MMSE (\( p < 0.001 \)), RAVLT total verbal recall (\( p < 0.001 \)), RAVLT delayed verbal recall
Table 2 Meta-analyses results

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Test</th>
<th>n of studies</th>
<th>Estimated average pre-shunt score</th>
<th>95 % CI</th>
<th>Estimated average difference</th>
<th>95 % CI</th>
<th>p</th>
<th>Cochran’s Q (df, p)</th>
<th>$I^2$ (%)</th>
<th>Estimated between-study variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global function</td>
<td>MMSE</td>
<td>19</td>
<td>23.10</td>
<td>22.13, 24.08</td>
<td>2.20 points</td>
<td>1.45, 2.95</td>
<td>&lt;0.001</td>
<td>99.62 (18; &lt;0.001)</td>
<td>81.9</td>
<td>1.99</td>
</tr>
<tr>
<td></td>
<td>Learning and memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RAVLT total</td>
<td>7</td>
<td>22.73</td>
<td>19.86, 25.61</td>
<td>5.64 words</td>
<td>3.86, 7.43</td>
<td>&lt;0.001</td>
<td>14.02 (6; 0.03)</td>
<td>57.2</td>
<td>2.68</td>
</tr>
<tr>
<td></td>
<td>RAVLT delayed</td>
<td>7</td>
<td>1.90 words</td>
<td>1.22, 2.57</td>
<td>1.43 words</td>
<td>0.55, 2.31</td>
<td>0.001</td>
<td>56.31 (6; &lt;0.001)</td>
<td>89.3</td>
<td>1.11</td>
</tr>
<tr>
<td>Executive function</td>
<td>Backwards digit span</td>
<td>6</td>
<td>2.92 digits</td>
<td>2.38, 3.46</td>
<td>0.36 digits</td>
<td>0.04, 0.67</td>
<td>0.03</td>
<td>38.61 (5; &lt;0.001)</td>
<td>87.0</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Phonemic verbal fluency</td>
<td>8</td>
<td>19.67</td>
<td>13.60, 25.74</td>
<td>2.73 words</td>
<td>0.84, 4.63</td>
<td>0.005</td>
<td>10.55 (7; 0.16)</td>
<td>33.6</td>
<td>2.32</td>
</tr>
<tr>
<td>Psychomotor speed</td>
<td>TMT-B</td>
<td>9</td>
<td>293.03 s</td>
<td>221.03, 364.97</td>
<td>−43.46 s</td>
<td>−83.23, −3.70</td>
<td>0.03</td>
<td>35.89 (8; &lt;0.001)</td>
<td>77.7</td>
<td>2494.80</td>
</tr>
<tr>
<td></td>
<td>TMT-A</td>
<td>13</td>
<td>132.48 s</td>
<td>108.48, 156.49</td>
<td>−25.90 s</td>
<td>−36.11, −15.69</td>
<td>&lt;0.001</td>
<td>18.78 (12; 0.09)</td>
<td>36.1</td>
<td>104.03</td>
</tr>
</tbody>
</table>

MMSE Mini-Mental State Examination, RAVLT Rey Auditory Verbal Learning Test, TMT trail making test

(p = 0.001), phonemic verbal fluency (p = 0.005) and TMT-A (p < 0.001). The remaining tests (backwards digit span, and TMT-B) show weaker significance levels (p = 0.03; 0.03; respectively). Given the problems associated with repeated testing, and because of the approximations made by the statistical methods used, we suggest that the statistical significance of these two tests be treated with caution and we do not view them as robust. The $I^2$ statistics range from 33 to 90 %, indicating considerable between-study heterogeneity in all outcomes and meaning that the studies estimate substantially different effects. This means that any single study is susceptible to producing results that differ from the estimated average differences. The pooled estimates must therefore be interpreted as population average differences, and not study specific differences, in accordance with the random effects model for meta-analysis.

Visual analysis of the forest plots supports the above interpretations. For all forest plots, average scores across studies are in very good directional agreement with the estimated average difference scores, but this is less clear for backwards digit span and TMT-B.
Moderator variables

All nineteen studies included in the analysis of moderator variables provided information about average age, time-to-retest and % males. Random effects meta-regressions using average difference in MMSE as outcome data were all non-significant (Table 3). We did not find evidence that average age, time-to-retest or sex predict improvement in the MMSE.

Discussion

The aim of the current review was to determine the effect of shunt surgery on neuropsychological test performance in patients with NPH. Twenty-three studies were eligible for inclusion within one or more meta-analyses. Meta-analyses were conducted on average pre-operative and average “difference” scores for seven neuropsychological tests. Statistically significant estimated average difference scores were observed for all tests in the direction of improvement following shunt surgery. However, detailed examination of the results suggested robust evidence for improved MMSE, RAVLT total verbal recall, RAVLT delayed verbal recall, phonemic verbal fluency and TMT-A only. Meta-regressions revealed no significant effects of age, time-to-retest or sex on average MMSE difference score.

Memory

Post-shunt improvement in memory is frequently reported in patients with NPH. Significant improvement has been found for visual recall [35, 36], spatial memory [6], and in various subtests of the Wechuler Memory Scale [2, 9, 14, 37]. However, the RAVLT appears to be highly sensitive to cognitive improvement in NPH. We found robust evidence for improvement in the total and delayed verbal recall subtests and significant improvement has also been documented in RAVLT retention score [2, 37].

Executive function

It is unclear whether executive function improves following shunt surgery. Some studies report significant improvement in the backwards digit span test [5, 9, 11, 28], whilst others report no change [10, 12, 17, 19]. Similarly, improvements in the Stroop test have been observed in some studies [2, 11, 21], but not in others [10, 14, 28, 31]. A ceiling effect has been suggested to underlie the absence of improved executive function [37]. However, studies have found performance in tests of executive function to be disproportionately impaired in NPH patients at baseline [6, 8], and suggested that lack of improvement reflects an irreversible frontal executive impairment.

Only one of three tests of executive function in our meta-analyses showed robust evidence for improvement (phonemic verbal fluency). The remaining two (backwards digit span and TMT-B) had weaker significance levels, and supporting studies did not indicate agreement in the direction of improvement. We performed meta-analyses using average pre-operative scores to investigate whether instances of lack of improvement were due to ceiling effects. The estimated average pre-operative score for backwards digit span was 2.92 digits. Median score in this test by 159 healthy controls in a study by Hellström et al. [11] was 4 digits. Estimated average pre-operative score for TMT-B was 293.03 s. Normative data provided by Tombaugh [38] suggests individuals aged 70–74 complete this test in 109.95 s (less time indicates better performance). Estimated average pre-operative scores for both tasks indicated that, on average, patients were impaired in these tests compared to age-matched normative data. This suggests that ceiling effects cannot explain the lack of robust evidence for improvement in these tests following shunt. Nevertheless, robust evidence for improvement was observed for phonemic verbal fluency. However, phonemic verbal fluency is simplistic compared to executive tests with strategic or problem solving aspects. Therefore, improvement in this test likely reflects improved attentional capacity rather than higher level executive function. Overall, given the tests we could include in the analyses, our results do not provide strong evidence for improvement in executive function following shunt surgery, tentatively supporting the hypothesis that executive impairment in NPH may reflect irreversible damage to fronto-subcortical connectivity. However, further investigation using more sensitive tests of executive function are needed as improvements in this domain have been found [5].

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Estimate</th>
<th>Standard error</th>
<th>p value</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-to-retest (months)</td>
<td>0.01</td>
<td>0.13</td>
<td>0.96</td>
<td>-0.24, 0.25</td>
</tr>
<tr>
<td>Av. age (years)</td>
<td>-0.15</td>
<td>0.15</td>
<td>0.29</td>
<td>-0.44, 0.13</td>
</tr>
<tr>
<td>% male</td>
<td>0.05</td>
<td>0.03</td>
<td>0.09</td>
<td>-0.01, 0.11</td>
</tr>
</tbody>
</table>
Psychomotor speed

We found good evidence for improvement in psychomotor speed, as measured by the TMT-A. Due to lack of data, we were unable to include other tests of psychomotor speed, although improvements have also been documented in the Grooved pegboard test [21], the Purdue pegboard test [10], and the Line-tracing test [14].

Global cognitive functioning

We found robust evidence for improved performance on the MMSE. This test is commonly used to assess cognitive function in NPH, although results vary with some studies finding significant improvements [14, 28, 34], and others finding no change [5, 8, 12, 17]. A ceiling effect may explain why some studies find no change on the MMSE. High functioning patients can perform well on this test while specific cognitive deficits may be missed unless detailed neuropsychological testing is conducted [39]. Indeed, in their study, Iddon et al. [6] split patients according to their pre-operative MMSE scores. Patients who scored in the dementing range of the MMSE at baseline (<24 points) improved to the normal range post-operatively. However, no significant difference was observed between baseline and outcome scores for patients who did not score in the dementing range at baseline. Therefore, it is important that cognitive assessments include a battery of neuropsychological tests in addition to the MMSE.

Practice effects

Studies with test-retest control groups provide evidence that improvements following shunt surgery are due to treatment effects rather than practice effects. Katzen et al. [7] found greater improvement in measures of mental tracking speed and sustained attention in shunted iNPH patients than in healthy controls who had undergone repeated testing. Saito et al. [8] found evidence for improvements in executive function following shunt which were not ascribable to practice effects. Furthermore, Solana et al. [40] investigated the effect of testing-retesting in patients with NPH using a battery of neuropsychological tests administered over four consecutive days. No learning effect was observed for any of the tests and it was concluded that improvements following shunt reflect a true treatment effect.

Predicting improvement

Since shunt surgery is an invasive procedure and patients are often elderly, it is important to identify factors which predict positive outcome following treatment. We found no significant effects of age, sex, or time between shunt and reassessment on outcome in the MMSE. However, this was an exploratory analysis and effects may be observed using other measures of cognitive or functional outcome.

Extent and duration of improvement

Although cognitive improvement has been observed in patients with NPH following shunt surgery, patients remain impaired in neuropsychological tests compared to age-matched controls. Shunted patients have shown to perform significantly poorer than healthy controls in tests of psychomotor speed, memory and executive function at both three and 12 months post-shunt [11, 21]. We investigated outcome between three and 12 months post-shunt, however, from the available data, we were unable to assess outcome at longer durations. To determine the extent of cognitive recovery, longer-term monitoring of patients is required using multiple post-operative assessments as improvements have been documented as late as 5 years post-shunt [41].

Limitations and methodological considerations

We have not attempted to formally assess the risk of bias because of the difficult nature of determining what constitutes study quality in this area and so leave it to the reader to assess study quality if they wish to consider this issue.

Methodological differences across studies complicate interpretation of results. Variability within tests used meant that our analyses were limited to seven neuropsychological tests when others may show improvement following shunt surgery. Furthermore, higher level executive functions could not be assessed with the restricted set of tests used to date. Additionally, time between shunt and reassessment varied with 3, 6 and 12 month delays being used. Consistency here is pertinent as different patterns of improvement may be seen at different intervals. Improvement may be observed more readily at shorter intervals due to immediate effect of the shunt, whereas initial improvement may be missed at longer intervals due to effects of comorbid disorders or increasing age [9].

Conclusions

We found evidence for improved performance in global cognitive function, verbal learning and memory and psychomotor speed following shunt surgery. However, we did not find strong evidence for improvement in tests of
executive function based on the available data. To clarify these findings, we suggest that there is a need to assess high-level executive functions in patients with NPH before and after shunt surgery. Additionally, longer-term monitoring of patients is required to determine the extent to which cognitive functions may improve. The MMSE, the RAVLT, phonemic verbal fluency and trail making test A may be useful for assessment of cognitive outcome following treatment for NPH.

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Compliance with ethical standards

Ethical approval In accordance with NRES and MRC guidance, this study does not require ethical approval as it does not directly involve human participants.

Conflicts of interest RJS consults for Cambridge Cognition, Peak (Brainbow), Servier, Otsuka, and Lundbeck, holds a grant from Janssen/Johnson & Johnson, and has share options in Cambridge Cognition. JDP reports grants from NIHR Senior Investigator Award, and grants from NIHR Cambridge Brain Injury HTIC. All other authors have nothing to declare.

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