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Detecting Cognitive Impairments in Idiopathic Intracranial Hypertension using Neuropsychological and Ocular Motor Testing

Dr. Wendy Wang
Bachelor of Medicine and Surgery, Fellow of the Royal Australasian College of Physicians

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Neurosciences Department, Alfred Hospital Melbourne

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General Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Name: Dr. Wendy Wang

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Abstract

Idiopathic intracranial hypertension (IIH) is a neurological syndrome associated with high morbidity that primarily affects young overweight women. Although often referred to as a rare disorder, its prevalence is increasing[1]. Although the pathophysiology of IIH is unknown, current theories include the involvement of factors such as sex hormones and adipokines (including 11β-hydroxysteroid dehydrogenase type 1 and leptin[2]), resulting in generalised cerebrospinal fluid (CSF) dysregulation[3]. While headache and visual symptoms are common features of IIH, occurring in more recent years cognitive changes have also been reported, with the few studies demonstrating impairments across a range of cognitive functions. However, it is unclear whether these cognitive changes are a unique symptom and/or a consequence of other symptoms (i.e., headache, visual changes, mood), and whether they are chronic.

Accordingly, this study aimed to characterise cognitive impairments in individuals with IIH, ascertaining whether they are related to the clinical features of the disorder and whether they fluctuate over time.

To address these aims, both traditional neuropsychological tests and ocular motor tasks were used to measure cognitive function in patients with newly diagnosed IIH and at three and six months. Neuropsychological tests assessed verbal learning, working memory, processing speed and cognitive inhibition. Ocular motor tasks assessed the processing of visual information under conditions that increased inhibitory demands, attentional control, and cognitive flexibility. Patients also completed headache and mood questionnaires, to determine the impact on cognition, and additional questionnaires to determine the impact of IIH on quality of life.

IIH patients performed worse than controls on all neuropsychological tests (verbal learning, working memory, processing speed and inhibition of cognitive interference), at all time-points, demonstrating the persistence of cognitive impairments. These impairments were not related to IIH clinical features (weight, waist circumference, disease duration, CSF opening pressure, visual acuity, retinal nerve fibre layer (RNFL) thickness and Humphrey visual field (HVF) values). Despite being highly prevalent, headache and mood disorders were also unrelated to cognitive impairments.

Ocular motor tasks revealed distinct impairments in the processing of visual information under conditions requiring increased inhibitory control, cognitive flexibility and attentional control. Interestingly, these impairments were only evident when a cognitive load was introduced, with basic visual processing and formation of an eye movement intact. Interestingly, RNFL elevation predicted worse performance particularly on ocular motor tasks of inhibitory control. Further, as RNFL elevation improved over the study period, ocular motor performance improved, suggesting that RNFL elevation affected the processing of visual information under increased cognitive loads. Finally, impaired inhibitory control on ocular motor tasks was associated with reduced quality of life in IIH patients; quality of life was similarly influenced by increased headache and reduced mood.

Overall, cognitive impairments are present and persistent in newly diagnosed IIH, occurring independently from most clinical features including headache. However, RNFL elevation is associated with impaired visual-cognitive processing and poorer quality of life. Collectively, these results suggest that IIH may cause dysfunction of widespread fronto-striatal networks manifesting as impairments across a range of cognitive domains contributing to high morbidity. These results also highlight the need for cognitive assessment to form part of clinical management and should be routinely monitored, regardless of clinical features. This research represents the necessary first step in determining the types of cognitive deficits that occur in IIH, as well as the best methods for assessment and improvement of patient care.

Acknowledgements

I have many people to thank for this meaningful experience. According to Dr. Viktor Frankl who founded logotherapy (with “logos” being Greek word for meaning), we find meaning in life through three core mechanisms:
1) By creating a work or doing a deed;
2) By experiencing something or encountering someone;
3) By choosing one’s attitude in any given set of circumstances.

Thank you to my supervisors Dr. Joanne Fielding, A/Prof. Anneke Van Der Walt, Dr. Meaghan Clough and Prof. Owen White for their time, patience, support and mentorship. Each of you inspire me to be better in different ways; it has been a privilege working with you. Thanks to the Neurosciences Department, the Neuro-Ophthalmology team at the Alfred Hospital and the Royal Victorian Eye and Ear Hospital, for making this enjoyable fellowship possible. I have to of course thank my family, friends and loved ones for their unwavering encouragement. Lastly, thanks to the patients who were involved in this study for donating their time.

Completing this thesis as part of my Neuro-Ophthalmology fellowship has not only taught me a lot about research and IIH, but also about life. I have an added dimension of respect for those who have completed a postgraduate degree. Unexpected challenges can occur in both research and life. I have learned that challenges in both can be approached with a growth mindset; these are the moments that our future selves will reflect on with nostalgia. In addition, both research and life can be unpredictable, which can teach us about what really matters.

Main Abbreviations

IIH – Idiopathic Intracranial Hypertension

BMI – Body Mass Index

CSF – Cerebrospinal Fluid

NPH – Normal Pressure Hydrocephalus

ICP – Intracranial Pressure

MRI – Magnetic Resonance Imaging

OM – Ocular Motor

CVLT – California Verbal Learning Test

SDMT – Symbol Digit Modalities Test

SCWT – Stroop Colour and Word Test

HVF – Humphrey Visual Fields

OCT – Ocular Computed Tomography

RNFL – Retinal Nerve Fibre Layer

Overview of thesis

The objective of this thesis is to comprehensively study cognitive impairment during the early course of IIH. This involves determining which cognitive domains are impaired in IIH, whether or not common clinical features and comorbidities of IIH are related to the cognitive impairments revealed, whether cognitive impairments change over time, and how they impact quality of life.

In Chapter 1, I provide a detailed overview of IIH. The epidemiology, pathophysiology and clinical features of IIH will be discussed. This includes a review of evolving areas in IIH, such as theories on pathogenesis and strategies for optimising patient care. Preliminary studies have reported cognitive impairment in IIH patients, which may increase morbidity[4-9]. I discuss the existing literature on cognitive impairment in IIH, in the context of study limitations and future research directions. This is followed by a description of how neuropsychological tests and ocular motor tasks can be utilised to further characterise cognitive impairments in IIH.

Chapter 2 outlines the general methods used to characterise cognitive impairments in my study. I explain how patients were recruited and assessed clinically, before introducing the specific neuropsychological tests and ocular motor tasks used. This chapter also includes a summary of the questionnaires that were administered to IIH patients to evaluate headache, depression, anxiety, quality of life and impulsivity levels.

The majority of results from neuropsychological testing and ocular motor tasks are presented in Chapter 3, in manuscript format. Chapter 4 presents additional results in detail, and includes supplementary ocular motor data, as well as responses from headache, mood, quality of life and impulsivity questionnaires.

Finally, Chapter 5 explains the results from my study, their significance, and recommendations on how they can be applied in future research and clinical settings. Study limitations will be considered before concluding remarks.

Chapter 1 Literature review

1.1 Idiopathic Intracranial Hypertension

Idiopathic intracranial hypertension (IIH) is characterised by increased cerebrospinal fluid pressure of an unclear aetiology. It is associated with significant morbidity and tends to affect overweight women of child-bearing age. Historically, IIH was called 'benign intracranial hypertension', 'serous meningitis' or 'pseudotumour cerebri'. In contemporary nomenclature, the term 'pseudotumour cerebri' may be used to encompass both primary raised intracranial pressure of unclear aetiology, otherwise known as IIH, or raised intracranial pressure from an identifiable secondary cause[10]. The term 'benign intracranial hypertension' was deemed inappropriate after it was recognised that some patients experience serious consequences, such as visual impairment or chronic disabling headaches[11]. Fulminant cases can quickly progress to permanent vision loss[12] and chronic headaches can be problematic, leading to extended time off work and/or loss of employment[13].

In recent years, cognitive impairment has become recognised as a potential symptom of IIH. Although the existing literature regarding cognitive impairment in IIH is limited, the few studies that have been conducted have found impairments across a range of cognitive domains, with impairments found to correlate with decreased quality of life[14-17]. However, what is not clear is how these cognitive impairments are related to other clinical symptoms of IIH such as visual changes (i.e., visual acuity, retinal nerve fibre layer (RNFL) and Humphrey visual field (HVF)), headache and low mood, which are known to affect cognitive performance as well as other disease characteristics (waist circumference, disease duration, CSF opening pressure). Further, it is similarly unclear whether cognitive impairments persist over time or resolve along with other symptoms of the disease. My thesis addressed these areas of uncertainty by characterising the cognitive impairments present in IIH and evaluating how they relate to common clinical features of the disorder.

The following review (Chapter 1) includes an overview of IIH epidemiology, clinical features, diagnosis and management, as well as providing a summary of existing studies on cognitive impairment in IIH. This is followed by an introduction to ocular motor testing as a novel method of assessing visual-cognitive processing, which was used here in conjunction with traditional neuropsychological testing.

1.1.1 Epidemiology

The prevalence of IIH is increasing and as obesity rates continue to rise globally[18], it is likely that the number of cases will continue to grow[19]. The demographic most commonly afflicted with this condition are young overweight women in their prime of life[3, 20]. A recent study in the United Kingdom found that between 2005 and 2017, the incidence of IIH in females increased from 2.5 to 9.3 per 100,000 person-years and prevalence increased from 26 to 79 per 100,000 women[21]. In the general population, the incidence is at a lower rate of 0.5-2 per 100,000 people per year[22]. Cohort studies have reported that the majority of patients with IIH are obese[23 24 25] and the incidence of IIH rises significantly above a body mass index of 30[21]. IIH may be associated with significant morbidity, as well as socioeconomic consequences. Many patients experience severe chronic headaches and visual symptoms, resulting in loss of productivity. In addition, there is a threat of permanent vision loss[26]. It is therefore vital that patients engage with management strategies for IIH. While there are medical and surgical therapies for IIH, most patients are advised to lose weight, which can be extremely challenging[27]. Little is known of the comorbidities of IIH beyond visual problems and headache.

In the United States alone, the economic burden of IIH was estimated at $444 million per year from hospitalisations and effects on employment. Thirty-one percent of IIH patients required a career change and fifty-seven percent became dependent on the disability pension[13]. Anecdotal evidence indicates that many IIH patients require time off work or school, resulting in loss of productivity. Decreased productivity may be due to symptoms such as chronic headaches and visual disturbance, however cognitive impairment may also play a role.

1.1.2 Pathophysiology

The pathophysiology of IIH remains unknown, however it appears to involve intracerebral pressure (ICP) dysregulation associated with metabolic and hormonal factors, including altered adipokine profiles[28] (Figure 1.1.2). Excessive weight may influence leptin levels, which were found to be elevated in CSF specimens from IIH patients compared to controls and raised the possibility of leptin resistance[29]. Women with IIH have been shown to have an excess of circulating androgens, with significantly higher levels of active testosterone, but lower levels of the androgen precursors dehydroepiandrosterone and androstenedione, compared to women with simple obesity or polycystic ovarian syndrome[30]. Additionally, elevated serum levels of interleukin-1β, decreased serum levels of interleukin-8 and decreased serum levels of tumour

necrosis factor-α have been reported in IIH[31]. Such metabolic and hormonal dysregulation may contribute to altered CSF dynamics[20] and an enzyme, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) has been identified as potential therapeutic target.

Recently, there has been increasing interest in how factors underlying IIH pathogenesis could be targeted on a molecular level. 11β-HSD1 is found in the choroid plexus and functions to increase cortisol availability, as well as regulating CSF production[32]. Overexpression of 11β-HSD1 has been linked to excessive abdominal weight[2]. IIH patients with resolution of disease, as reflected by improvements in papilloedema, headaches and reduced ICP, were reported to have reduced 11β-HSD1 activity[33]. Given these findings, inhibition of 11β-HSD1 has been proposed as a potential method of lowering ICP in patients with IIH[34]. A multi-centre phase II randomised, double-blind, placebo-controlled trial was recently conducted in the UK and demonstrated that over twelve weeks, seventeen IIH patients taking an 11β-HSD1 inhibitor (AZD4017) had greater reductions in ICP compared to fourteen patients on placebo treatment[32]. Future studies of 11β-HSD1 inhibition in IIH with a larger cohort, over longer periods of time are required.

An alternate theory regarding the underlying mechanism of raised ICP in IIH pertains to venous sinus stenosis. In conditions with known increased CSF production or decreased CSF drainage, patients can develop obstructive hydrocephalus and enlargement of the cerebral ventricles. Interestingly, IIH patients do not develop features of obstructive hydrocephalus[35]. CSF flow is thought to be rhythmic in nature and CSF absorption relies on a negative pressure gradient between the venous sinus and subarachnoid space[36]. Conversely, increased venous pressure and venous sinus stenosis is commonly seen in IIH[37]. Abdominal obesity increases intra-abdominal pressure, which may result in raised venous sinus pressure[20]. Although it is unclear whether venous sinus stenosis occurs as a *consequence* of increased ICP, *causes* increased ICP, or both. These two entities might also exacerbate each other.

Figure 1.1.2 Proposed pathophysiological mechanisms of IIH[20].

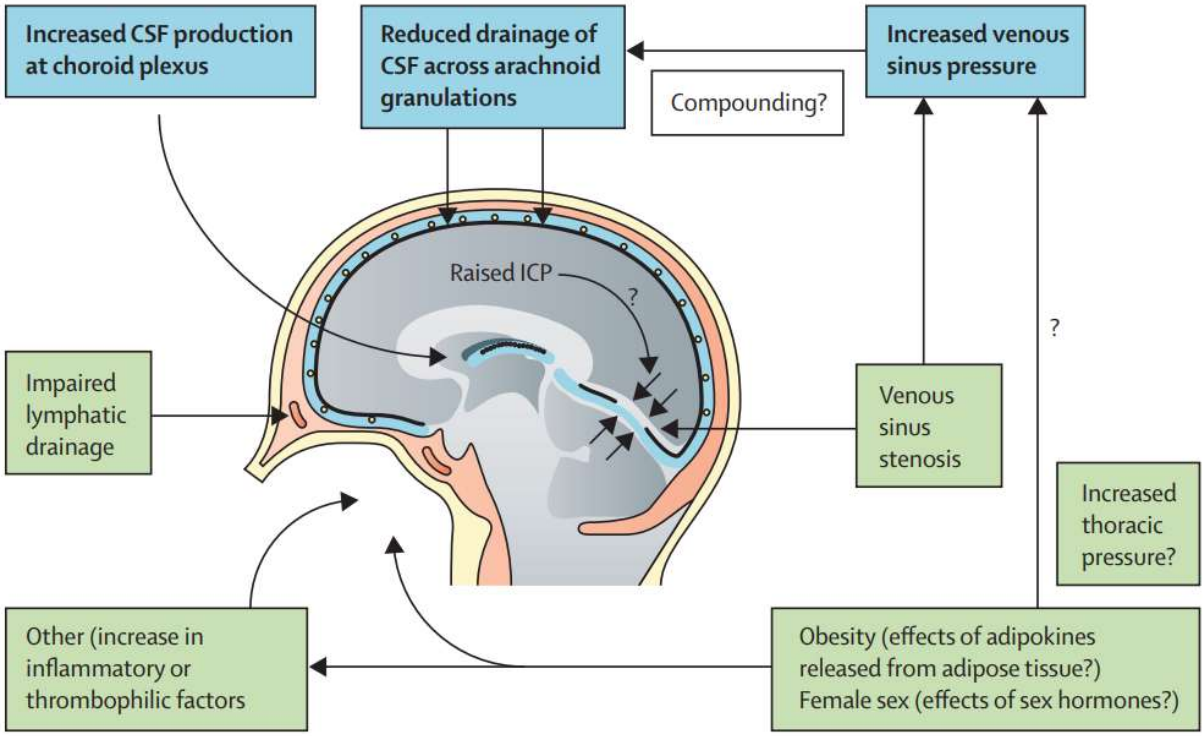


Figure 1.1.2. Markey et al 2016 illustrates three main mechanisms of increased ICP in IIH, specifically, increased venous sinus pressure, decreased CSF drainage through lymphatics or the arachnoid granulations and increased CSF production at the choroid plexus. Contributory factors likely include adipokines and sex hormones, given the major risk factors of obesity and female sex in IIH. In addition, inflammatory and thrombophilic processes could feature in IIH pathogenesis[20]

1.1.3 Clinical Features

The cardinal clinical features of IIH reflect raised ICP and therefore include headache and visual impairment. However, it is important to note that some patients present atypically and may not exhibit these characteristic features[38]. Diagnosis and assessment need to occur expediently to decrease the risk of permanent vision loss that can evolve rapidly in fulminant cases[39]. CSF dysregulation is a hallmark of IIH, typically manifesting as elevated opening CSF pressure evident by lumbar puncture and often normal or slit-like ventricles on MRI[40]. The following section discusses each of the primary clinical features of IIH in turn, leading to an outline of the current diagnostic criteria in section 1.1.4.

1.1.3.1 Headache

Headache is the most common symptom of IIH, affecting an estimated 75-94% of patients[20]. Specifically, patients frequently report nocturnal or early morning headaches, with an increase in headache severity when recumbent[41]. However, IIH patients often experience headaches that are heterogenous and multi-factorial in nature. These headaches can be non-specific, with most cases exhibiting features of migraines and/or chronic tension headaches[42, 43]. The majority of patients with IIH report that their headaches are exacerbated by straining, coughing and physical activity[44], although this can also be found in association with other headache syndromes[45-47]. Short-term relief in headache severity after lumbar puncture is often reported by IIH patients, due to decreased ICP immediately following the procedure[44]. However, therapeutic lumbar punctures are not generally recommended as a treatment for IIH due to the rapid re-accumulation of CSF, patient discomfort and the risks of the procedure[43].

Many patients with IIH experience a protracted clinical course, with prominent headaches and psychological stress due to the impact of the condition on their lives[48]. Headaches appear to be a key determinant of perceived quality of life[49]. Predictive factors for less headaches in IIH include young age at diagnosis and paradoxically, high CSF opening pressure[50]. Chronic daily headaches can be an unfortunate outcome in IIH and be further complicated by medication overuse headaches[51]. The relationships between headaches and intracranial pressure are likely complex and non-linear[52]. IIH may trigger allodynia via similar pain pathways as chronic migraines[53]. Optimal headache management relies heavily on maintaining a healthy lifestyle and medication adherence, which may be challenging.

1.1.3.2 Visual Manifestations

Detection of papilloedema is critical in the evaluation of possible IIH, and a diagnosis is rarely made without this clinical finding. Detecting papilloedema can be challenging for clinicians inexperienced with fundoscopy and fundus photography is therefore a very useful tool for detection and monitoring in ambulatory clinic settings. Given the variability of clinical skills in fundoscopy, there could be a role for new technologies such as using non-mydriatic retinal photography in the acute assessment of neurological patients in the Emergency Department[54]. Serial visual field monitoring, ideally using the same form of perimetry at each visit, is essential in the management of IIH and can be underestimated when clinical assessment alone is used. Visual field deficits may manifest as enlarged physiologic blind spots, or peripheral vision loss progressing to central vision loss. Patients could also experience transient visual obscurations,

particularly with postural changes, which are presumably due to optic nerve head ischaemia[55]. In severe cases, permanent vision loss can ensue. A relative afferent pupillary light defect (RAPD) may be observed if one optic nerve is injured more severely than the other. Other examination findings in IIH may include abducens nerve palsies. There are also rare presentations like trigeminal nerve involvement and pseudo-radiculopathies[56].

1.1.3.3 Cognitive Impairment

Cognitive impairment is a largely under-recognised feature of IIH that has been investigated by few studies[4-9]. Currently, standard IIH management does not include screening for cognitive impairment. Section 1.2 discusses cognitive impairment in more detail.

1.1.4 Diagnosis

IIH is a clinical diagnosis, however diagnostic criteria are helpful to differentiate between definite and probable cases, as well as highlighting atypical features that may be suggestive of an alternative cause. The initial diagnostic criteria for IIH was proposed by Dandy in 1937, which outlined a CSF opening pressure greater than or equal to 25 centimetres of water[57]. Proposed contemporary diagnostic criteria distinguishes between definite and probable cases[58]. The entity of IIH without papilloedema has also been described[10]. Panel 1.1.4.1 summarises the current diagnostic criteria for IIH.

Table 1.1.4.1 IIH diagnostic criteria[58] [10].

Criteria required for definite diagnosis of IIH

- Papilloedema
- Normal neurologic examination except for cranial nerve abnormalities
- Neuroimaging: normal brain parenchyma (no hydrocephalus, masses or structural lesions), no abnormal meningeal enhancement on MRI with gadolinium contrast and mandatory exclusion of venous thrombosis
- Normal CSF composition
- Lumbar puncture opening pressure greater than 25 cm of water in adults

Probable diagnosis of IIH

Above criteria met, but lumbar puncture opening pressure < 25 cm of water

IIH without papilloedema

Above criteria met, but no papilloedema AND

- The patient has a unilateral or bilateral abducens nerve palsy OR the patient has three neuroimaging features of high ICP (empty sella, flattening of posterior globe, peri-optic subarachnoid space distension, transverse sinus narrowing)

Misdiagnosis can result in serious consequences. Patients with wrongly presumed IIH will be subjected to inappropriate management and potentially have a separate treatable condition that is then neglected[48]. Multiple conditions need to be excluded before a diagnosis of IIH is made, as summarised in panel 1.1.4.2. Mimickers of papilloedema, such as optic nerve head drusen, should also be considered. A detailed history, clinical examination, neuroimaging, blood tests and lumbar puncture are required as part of IIH evaluation.

Panel 1.1.4.2 Secondary causes of elevated ICP[20].

Secondary causes of elevated ICP

Medications

- Antibiotics (tetracyclines, nitrofurantoin, sulphonamides, nalidixic acid)
- Hormones (thyroxine, growth hormone, tamoxifen)
- Excess vitamin A and retinoids
- Others (corticosteroids, lithium, ciclosporin)

Medical comorbidities

- Venous sinus thrombosis
- Metabolic disorders (anaemia, renal failure)
- Obstructive sleep apnoea, hypercapnia
- Elevated CSF protein or hypercellularity
- Chromosomal disorders (Down's syndrome and Turner's syndrome)
- Endocrinopathies (Addison's disease, Cushing's disease and thyroid dysfunction)
- Autoimmune disorders (systemic lupus erythematous and Sjogren's syndrome)

1.1.5 Special Investigations

MRI brain and orbits with gadolinium contrast venography can adequately exclude intracranial structural abnormalities and show features that are suggestive of raised ICP[58]. These features are particularly useful for supporting the diagnosis in situations where patients partially meet the diagnostic criteria for IIH. However, it is important to note that none of the MRI features of elevated ICP are specific for IIH when considered in isolation. Patients are occasionally referred for possible IIH based on incidental findings detected on neuroimaging. Table 1.1.5 summaries the reported sensitivities and specificities of MRI brain findings associated with high ICP.

Table 1.1.5. Predictive values for elevated ICP based on MRI brain findings[37, 59-61]

MRI brain finding	Estimated sensitivity (%)	Estimated specificity (%)
Posterior globe flattening	66	36
Optic nerve head protrusion	98	99
Area of sellar enlargement	100	90
Foramen ovale widening	81	50
Peri-optic CSF ring width > 2mm	58	89
Venous sinus stenosis	93	93

If no contraindications are seen on neuroimaging, a lumbar puncture performed in the lateral decubitus position can be performed for diagnosis of IIH. This may confirm the presence of elevated CSF opening pressure, exclude secondary causes of raised ICP and be a therapeutic procedure for the patient. It is important that the patient is as relaxed as possible, so that the opening pressure is not falsely elevated[62]. CSF analysis should include cell count, protein and glucose at a minimum. If the opening pressure is inconsistent with the patient's overall clinical picture, a repeat lumbar puncture should be considered, as CSF pressures can fluctuate[48].

1.1.6 Visual Monitoring

Clinical investigations that objectively monitor visual and ocular parameters are important in IIH management. Neuro-ophthalmic assessments include visual acuity, formal visual field perimetry, fundoscopy, pupillary examination and colour vision assessment. In addition, fundal photos and optical coherence tomography (OCT) are often useful for comparison at follow-up review[48].

OCT is widely used in ophthalmology as a non-invasive method of obtaining cross-sectional images of the retina. It is a particularly useful way of objectively quantifying papilloedema in IIH and can be used as a surrogate measure of raised ICP[63]. Standard measurements on OCT include peripapillary retinal nerve fibre layer (RNFL) and optic nerve head (ONH) volume. The RNFL is formed from retinal ganglion cell axons that extend from the optic nerve head. In IIH patients with papilloedema, the RNFL increases in thickness due to retinal ganglion cell axoplasmic stasis[55]. RNFL thickness normalises and has been demonstrated to correlate with

improvements in visual field parameters after treatment of IIH[64]. However, reductions in RNFL values should be evaluated with caution, since it could also be the consequence of optic nerve atrophy related to retinal ganglion cell injury[65].

1.1.7 Management of IIH

Management of IIH can be challenging and there are controversies regarding which therapies are optimal[48]. A consensus statement on IIH management was published in 2018 and cognitive impairment was mentioned as a possible co-existing feature of IIH[66]. However, details were lacking and there were no recommendations on cognitive screening in IIH, due to limited research in this area. The following section will discuss concepts of IIH management that are currently recognised in clinical practice.

1.1.7.1 Surgical Management

Approximately 10% of IIH patients will experience fulminant disease, with permanent vision loss without prompt surgical intervention[67]. Potentially vision-saving procedures include CSF shunting and optic nerve sheath fenestration. There have been no trials comparing outcomes from CSF shunting to optic nerve sheath fenestration. A systematic review concluded that there is not enough evidence to recommend either surgical approach over the other; the preferred procedure varies regionally, depending on local expertise[68]. Venous sinus stenting has been reported through case series and retrospective studies to improve IIH symptoms[69]. However, further research is required to clarify these outcomes before venous sinus stenting becomes recommended practice. There is also recent interest in the role of temporary lumbar drainage, which led to resolution of IIH in a case series of 14 patients[70].

1.1.7.2 Medical Management

Non-invasive management options in IIH include medications such as acetazolamide and topiramate. Both acetazolamide and topiramate can be associated with cognitive impairment. Up to 10% of patients on topiramate experience cognitive disturbances[71] such as decreased memory span, working memory and verbal fluency[72]. Language impairment from topiramate has been described in healthy controls and also patients with epilepsy, with changes seen on functional MRI brain[73]. Topiramate has an effect as a carbonic anhydrase inhibitor, acts as a chronic migraine preventer and can result in appetite suppression, which are useful in IIH management. In a prospective open label study of 40 IIH patients comparing topiramate to acetazolamide, there were no significant differences in visual field outcomes[74]. Initiating

topiramate at a low dose, slow up-titration and being on the minimum effective dose could help to decrease the degree of cognitive side effects experienced[75].

Similarly, but to a lesser extent, negative effects on cognition have been reported in association with acetazolamide. In a study of cognition at high-altitude, participants were found to have decreased cognitive functioning after taking acetazolamide, even though the medication helps with altitude acclimatisation[76]. In the multicentre randomised, double-blinded placebo controlled Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), acetazolamide with dietary changes improved papilloedema and visual fields more than dietary changes alone. Interestingly, acetazolamide did not have a significant impact on headache morbidity[52]. Other diuretics are used by some for IIH treatment, however, evidence is limited[66].

1.1.7.3 Weight Loss

Over 90% of patients with IIH are overweight[77], however it is important to recognise that some are not. Generally, weight loss is considered a disease modifying treatment in IIH and can result in improved papilloedema, intracranial pressure and symptoms[77]. However, prolonged periods of caloric restriction may be unstainable. Currently, bariatric surgery may be the most effective method for morbidly obese people to lose weight[78]. A case review reported resolution of IIH in 92% of patients following bariatric surgery, however further studies are required before bariatric surgery can be recommended as standard treatment[79]. Weight-loss maintenance is very challenging and strategies to overcome re-gaining weight over time are being explored[80]. IIH remission can result from approximately 6-10% of loss in body weight[77], although some studies show that up to 15% of weight loss may be required[81].

1.1.7.4 Minimising Headache Morbidity

Headaches contribute significantly to IIH morbidity. Management of headaches in IIH remains challenging and is an evidence-free zone[82]. Patients can develop chronic daily headaches during or after resolution of IIH. There appears to be a complex relationship between headaches in IIH and CSF pressure, with conflicting evidence[43]. The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) demonstrated that CSF opening pressure was not related to headaches both at baseline and follow up[52]. High ICP at diagnosis has been found to be protective rather than predictive of long-term chronic headaches[50]. It is possible that other mechanisms other than high ICP may propagate chronic headaches in IIH, such as the development of allodynia[53]. Although it is unclear why some IIH patients experience residual chronic headaches and not

others, medical comorbidities such as mood disorders, other headache syndromes such as migraine or tension-type headaches and medication overuse may contribute[83]. Studies examining the effects of acetazolamide on headache reduction in IIH have shown mixed results[84, 85].

1.1.8 Section Summary

IIH is a prevalent neuro-ophthalmic disorder with areas of uncertainty in patient management, pathogenesis and clinical features. In recent years, cognitive impairment has been seen as a common and prominent symptom for IIH patients. However, little is known about how cognitive impairment manifests and relates to the other symptoms of IIH. Consequently, while the assessment of cognition does not form part of clinical management of patients, it represents an important area to understand. The following section will focus on cognitive impairments in IIH.

1.2 Idiopathic Intracranial Hypertension and Cognitive Impairment

As mentioned previously, there is a scarcity of literature on cognitive impairments in IIH and the potential impact on patients, as well as the health care system. The six studies that address cognitive changes in IIH are summarised in Table 1.2.1, with study outcomes presented in table 1.2.2. All studies detected impairment across multiple domains, with the exception of one case report. Notably, most of these studies are case studies of either single patients or a small group of patients. Only a few are prospective case-controlled studies. The following section reviews these studies.

1.2.1 Case Studies

Case series papers have been published by Kharkar et al in 2011 and Sorensen et al in 1986. Kharkar et al reviewed the medical records of ten IIH patients who had baseline cognitive testing at presentation. These patients were found to have significant cognitive impairments, especially in learning and memory[8]. In a separate case series, Sorensen et al tested five consecutive IIH patients with self-reported cognitive impairment. The results showed below-average scores that were most significant with verbal tests, and which affected all five of the study patients. Re-testing of these patients a year later indicated improvement in verbal test results, with four out of five patients achieving a score above normative cut-offs[5]. However,

these case studies are subject to many limitations and co-founding factors, such as mood disorders and headache, and the absence of a control group. In addition, patients in the Sorensen et al study had CSF opening pressures of 8, 18, 20, 25 and 30 centimetres of water, and would thus be unlikely to meet the contemporary diagnostic criteria for typical IIH[86].

Table 1.2.1. Literature on cognitive impairment in IIH

Study	Design	Participants	Testing	Limitations
Kaplan et al 1997	Case report	1 patient	Neuropsychological	Single patient
Kharkar et al 2011	Case series	10 patient records	Cognitive screening tests	Small numbers, limited testing, co-founders, no controls
Sorensen et al 1986	Case series	5 patients	Neuropsychological	Small numbers, varying definition of IIH, no controls
Yri et al 2014	Prospective case control	31 patients, 31 controls without headache > 4 days per month	Neuropsychological	Small numbers, short follow up period
Elbanhawy et al 2018	Cross-sectional case control	20 patients, 20 controls	MMSE, P300	Small numbers, heterogenous IIH clinical activity
Zur et al 2015	Cross-sectional case control	30 patients	Computerised cognitive battery, 'NeuroTrax'	Small numbers, heterogenous IIH clinical activity, no controls

MMSE = mini-mental state examination, P300 = neurophysiology testing.

1.2.2 Case Controlled Studies

There have been only three prospective case-controlled studies investigating cognitive function in IIH. Overall, these studies highlight significant cognitive impairments across a range of

cognitive domains. In the largest of these studies published by Yri et al (2014), 31 newly diagnosed IIH patients and 31 matched controls were examined at baseline and at three months after treatment, using a comprehensive battery of neuropsychological tests. The key results of this study were impaired learning, memory, language, perceptual motor ability and complex attention, with the authors suggesting that patients may have prefrontal dysfunction. Similar cognitive impairments were reported by Zur et al, who used a comprehensive computerised cognitive testing battery[6] called 'NeuroTrax'. This study reported impairments in all domains with the exception of memory, with the most affected domains being attention and visual spatial processing. Interestingly, the severity of cognitive impairment did not appear to correlate with patient age, disease duration, BMI or treatment with acetazolamide. However, at the time of testing it was unclear whether or not patients had active IIH, an important consideration since cognitive impairment in IIH could be impacted by certain clinical features. Lastly, a case control study by Elbanhawy and colleagues demonstrated that IIH patients with lower mini mental state examination (MMSE: a brief measure of attention, memory and language impairment commonly used to screen for dementia) scores correlated with prolonged latencies and reduced amplitude of P300 values, which is a known neurophysiological marker indicative of poorer cognitive function[7].

Overall, it is clear from these studies that cognitive function is affected in IIH to varying degrees. However, what is not clear is which domains are routinely affected and, importantly, how these cognitive impairments are related to other clinical symptoms of IIH such as visual changes (i.e., visual acuity, retinal nerve fibre layer (RNFL) and Humphrey visual field (HVF)), headache, and mood as well as other disease characteristics (waist circumference, disease duration, CSF opening pressure). Further, it is also unclear whether cognitive impairments persist over time or resolve along with other symptoms of the disease. The following sections will discuss the proposed link between cognitive function and hallmark features of IIH.

Table 1.2.2 Cognitive domains affected in IIH

	Kaplan et al 1997 (n=1)	Kharkar et al 2011 (n=10)	Sorensen et al 1986 (n=5)	Yri et al 2014 (n=31)	Elbanhawy et al 2018 (n=20)	Zur et al 2015 (n=30)
Learning + Memory	✓	✓	✓	✓	✓*	✓
Language	✓	✓	✓	✓	✓*	
Perceptual Motor	✓	✓	✓	✓	✓*	✓
Executive Function	✓	✓		✓	✓*	✓
Complex Attention	✓		✓	✓		✓
Social Cognition	✓			✓		

✓ Tested ✓ Area of impairment ✓ Major area of impairment

* Mini-mental state examination screening only, correlated with P300 neurophysiology

1.2.3 CSF Dynamics and Cognition

While CSF dysregulation and cognitive function has not been explicitly investigated in IIH these features are also the hallmark of normal pressure hydrocephalus (NPH). While the abnormal CSF dynamics in NPH is not identical to IIH, in NPH there is ventricular dilation with normal CSF opening pressure[87], NPH patients have similar cognitive impairments to IIH particularly in regards to attention, visuospatial perception and executive abilities[88]. In a study of NPH patients, improvement in cognitive impairment after CSF diversion therapy was found[89]. Altered CSF dynamics could stress vulnerable cognitive networks in the brain by producing subtle structural changes[90]. Neuroanatomically, cognitive networks in the brain are

widespread[91] and alterations in CSF dynamics are therefore likely to impact at least some, if not most, cognitive domains (Figure 1.2.1.1). Further, it has been reported that high intracranial pressure from secondary causes such as intracranial haemorrhage results in cognitive deficits[92].

Figure 1.2.1.1. DSM-5 Neurocognitive domains[93]

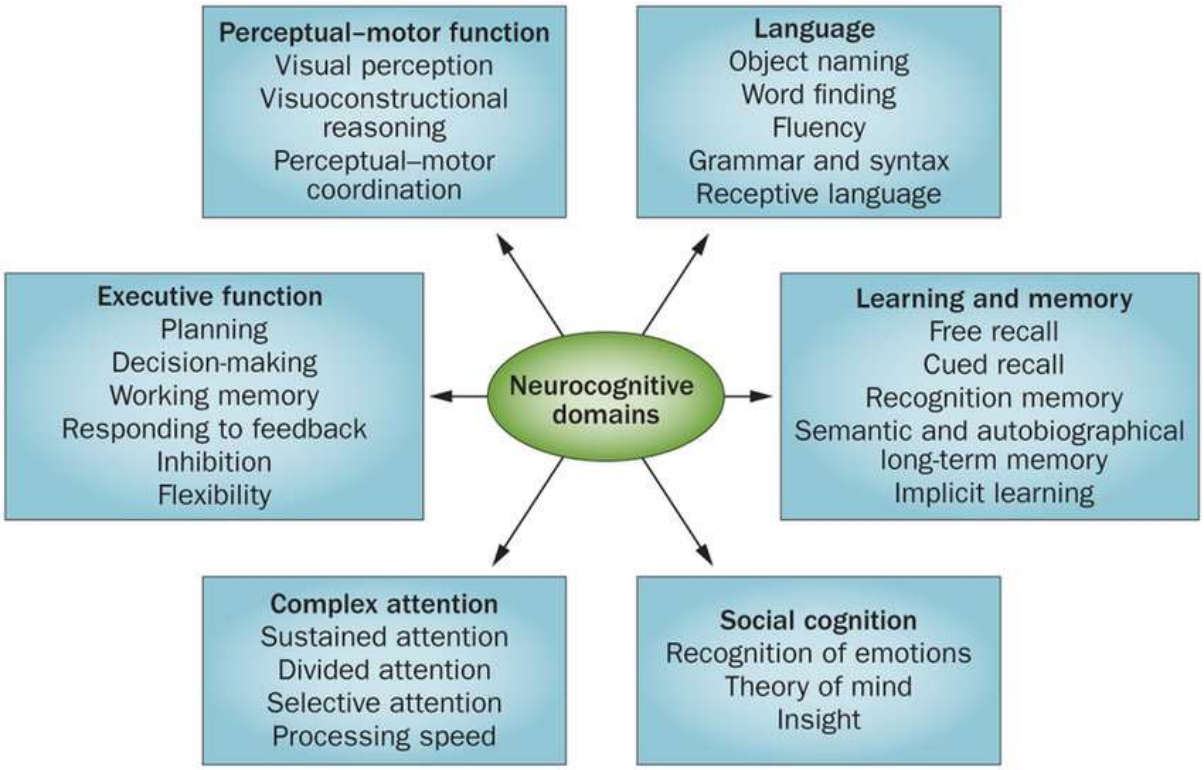


Figure 1.2.1.1. Neurocognitive domains can be broadly classified into six categories, as shown in this diagram. Mechanisms associated with CSF dysregulation may impair multiple cognitive domains in IIH.

1.2.4 Obesity and Cognition

There is a well-established yet complex relationship between obesity and IIH, with excess adiposity a major risk factor for IIH, and modest amounts of weight loss often leading to disease remission[1]. Obesity has been shown to be associated with cognitive impairments[94, 95], with obese individuals reported to have impaired attention and inhibitory control that manifests as impulsivity[95]. Inhibitory control is an important executive function that enables us to resist impulses, in favour of more difficult and productive goal-oriented behaviour[96]. There appears to be neuroanatomical changes in obesity that exacerbate inhibitory control deficits[97]. Obesity and binge-eating disorder are related to decreased striatal responses to food, and heightened

frontostriatal responses to food cues[98]. These findings have similarities to states of drug addiction, where frontal circuits are associated with cravings and the striatum responds with reward cues[99]. High dietary sugar and fat is proposed to cause hippocampal stress due to altered intracellular protein expression[100], which decreases inhibitory control, increases food cravings and results in further excessive calorie consumption; resulting in a vicious cycle[101].

Obesity has been associated with neural atrophy in mid-life, according to brain imaging studies that link elevated body mass index (BMI) to decreased brain volume[102]. Obese individuals in mid-life are at increased risk of developing Alzheimer's Disease and vascular dementia in later life[103, 104]. Central adiposity may be particularly detrimental to health. For example, risks of peripheral neuropathy in normoglycemic obese individuals were reported to correlate with increased waist circumference but not general obesity[105]. There is also evolving evidence that mortality rates are increased by central, rather than generalised adiposity[106]. The effects of central obesity on cognition and health in IIH is unclear. However, the high prevalence of obesity and corresponding hormonal dysregulation and pro-inflammatory states found in IIH [107-109], may affect neuronal function within vulnerable cognitive networks.

1.2.5 Headache and Cognition

Around 75-94% of people with IIH will experience headaches that are often multi-factorial[52]. Headaches experienced by IIH patients often involve migrainous symptoms and may also mimic chronic tension type headaches[42]. Despite mixed results, most studies have found that migraine patients have poorer cognitive performance than healthy controls. The most frequently reported cognitive changes are impaired visuo-spatial function, verbal memory, attention and inhibitory control[110]. Although it is unclear *why* cognitive impairment occurs in migraine patients, it has been suggested that it might reflect central nervous system dysfunction associated with migraine pathophysiology in combination with pain, reduced quality of sleep and mood changes.

1.2.6 Mood and Cognition

Depression and anxiety are highly prevalent in IIH patients compared to controls, which cannot be explained by obesity alone[111]. It has been observed that some patients can appear disengaged with the management of their IIH[4]. Apathy could be a symptom of comorbid mood disorders, but can also be related to prefrontal dysfunction. Cognitive impairment has been demonstrated in individuals diagnosed with depression and anxiety[112, 113]. Both conditions can result in

executive dysfunction[114-116], which can persist even after treatment of the underlying mood disorder[117]. One theory is that pro-inflammatory cytokines facilitate mood disorders, such as major depressive disorder, by causing hippocampal neuroinflammation[118]. It is possible that neuroinflammation could be contributory to cognitive impairment in both mood disorders and IIH.

1.2.7 Visual Processing and Cognition

Visual changes are a key symptom of IIH. Vision is our most dominant sense with approximately 50% of all neurons entering and leaving the central nervous system (CNS) related to the processing of visual information. This extends from (1) the acquisition and transmission of visual information from our eyes to the visual cortices, to (2) the integration and interpretation of this information within cognitive networks, and (3) the use of this information to inform a behaviourally relevant response. Thus, disruption to the efficiency of visual processing, at any stage, can adversely affect cognitive function. At present no IIH study has looked at the association between visual processing changes and cognitive function.

The assessment of saccade generation, the fast movement that shifts the eye from one location to another, implicates all three stages of visual processing (afferent, cognitive, and efferent), with the degree of cognitive processing dependent upon the conditions under which the saccade is generated [119]. This type of assessment is known as ocular motor assessment and has been used to investigated visual-cognitive processing in many disorders of the central nervous system[120 121-123]. In a review published in 2012 by White and Fielding, patients with MS have abnormal visual-cognitive processing evident on cognitive ocular motor tasks of inhibitory control, visual spatial ability, processing speed and attention. Similarly, oculomotor deficits have been reported in concussion[121], schizophrenia[124], stroke[125], attention deficit hyperactivity disorder[122] and neurodegenerative conditions[126].

Assessment of saccadic movements provides information on both stimulus-initiated responses, as well as cortically-driven intentional movements[127] that reflect executive function, attention, working memory and inhibitory control[119]. There are numerous studies on active saccadic eye movements and there is also increasing interest regarding the role of inhibitory ocular actions[128]. The term ‘antisaccade’ refers to an eye movement made away from a suddenly appearing visual stimulus, instead of made towards it. This has been shown as a particularly useful method for challenging inhibitory control[129]. Ocular movements can be considered a

'microcosm' in relation to the brain, as one needs to incorporate decision-making skills, visual localisation and force control in order to perform a precise eye movement[130]. Additional tasks that increase cognitive loading, such as adding a memory component and generating a prosaccade or antisaccade depending on the cue given, further increases the scope of brain regions tested[119].

In IIH we know the visual system is affected. It therefore, stands to reason that visual processing will be affected. However, this has not as yet been investigated.

1.3 Rationale for Thesis

While the existing literature and anecdotal clinical experience suggests that IIH is associated with cognitive impairment, the number of studies assessing this important symptom are sparse and the patient numbers small. Previous studies comprise of case reports, cross-sectional studies and cohorts with short follow-up periods[4-8, 131]. More data is required to establish the significance and pattern of these impairments so that necessary changes can be made to patient management.

Further research will help to determine whether or not common clinical features of IIH such as altered CSF dynamics, obesity, headache, mood disorders and impaired visual processing contribute to cognitive impairment. Visual processing changes could be particularly relevant, since IIH is almost always associated with papilloedema. As such, specialised testing of visual-cognitive processing may reveal unique patterns of cognitive impairment.

Ocular motor deficits correlate with cognitive impairment in a wide range of neurological conditions and provide an objective method of quantifying impairments, particularly in relation to changes in visual-cognitive processing[121, 125, 132, 133]. Novel methods of cognitive assessment require validation with well-established methods, such as traditional neuropsychological testing. Both methods of cognitive assessment will help to characterise cognitive impairment in IIH patients.

1.4 Aims and Hypotheses

To characterise:

(i) Cognitive changes in IIH using neuropsychological testing and ocular motor testing

(ii) Relationships between common IIH clinical features and cognitive changes, as well as impacts on quality of life

(iii) How and if cognitive deficits change during the early course of IIH

Hypotheses

(i) Widespread cognitive changes will be present in IIH

(ii) Certain IIH clinical features may negatively impact cognitive function and quality of life

(iii) Cognitive deficits likely persist during the early course of IIH

Chapter 2 General Methods

2.1 Ethics

Primary ethics approval for this prospective single centre study was obtained from the Alfred Health Ethics, project number 129/19. Involvement in the study was voluntary and consent was obtained from all participants prior to testing, in accordance with the Declaration of Helsinki.

2.2 Recruitment

2.2.1 IIH Participants

IIH patients were recruited from the Neuro-Ophthalmology Clinic and the inpatient Neurology services at the Alfred Hospital. Additionally, external clinic referrals were accepted if inclusion criteria were met. The study was verbally discussed with patients during their initial clinic appointment. A follow up email was sent to interested participants, which contained the consent form for reference and detailed information regarding the study. Research testing sessions were primarily booked in conjunction with subsequent IIH clinical reviews for patient convenience.

2.2.2 Controls Participants

Control data were pooled from existing ocular motor and neuropsychological result databases at the Alfred Hospital.

2.2.3 General Information

All participants were informed that their involvement in the study was completely voluntary and would not affect treatment received from the Alfred Hospital. They were aware that data collected would be strictly confidential and de-identified when published. Opting out of the study was possible at any stage, however any data collected up to that point could be utilised.

2.3 Compensation

Parking vouchers for testing attendance at the Alfred Hospital were provided to participants if required, as a method of compensation for involvement in the study.

2.4 Measures

Table 2.4 summarises the testing battery and the corresponding cognitive domains assessed. Each measure will be described later in this section.

Table 2.4. Testing battery and cognitive domains assessed

Testing Battery	Cognitive Domains Assessed
Neuropsychological Testing	
- National Adult Reading Test	Baseline cognitive function estimate [134]
- California Verbal Learning Test II	Verbal learning, working memory [135]
- Symbol Digit Modalities Test	Information processing speed [136]
- Digit Span	Working memory [137]
- Stroop Test	Inhibition of cognitive interference [138]
Ocular Motor Testing	
- Visually Guided	Baseline assessment of visual pathway integrity [139]
- Antisaccade	Inhibitory control [140]
- Simon Task	Cognitive flexibility, attention [141, 142]
- Switch Task	Attention, working memory [132, 143-145]
Questionnaires	
- Patient Health Questionnaire 9	Depression [146]
- Penn State Worry Questionnaire	Anxiety [147]
- Headache Impact Test 6	Headache [148]
- National Eye Institute Visual Function 25	Visual functioning [149]

Table 2.4. The cognitive battery included comprehensive neuropsychological testing to cover widespread cognitive domains. Ocular motor tasks evaluated simple, as well as more complex, visual-cognitive processing. Common IIH comorbidities and quality of life were assessed using self-administered questionnaires.

2.4.1 Clinical Characteristics

Recruited IIH patients were assessed clinically at baseline, 3-months and 6-months. In addition to routine history and examination, patients completed specialised neuro-ophthalmic testing. Data recorded included symptomatology, medications, weight, waist circumference, visual acuity, time from diagnosis, CSF opening pressure, neuroimaging findings, Humphrey Visual Fields (HVF) and Ocular Computed Tomography (OCT) values. Clinical data were monitored over time, with exceptions of CSF opening pressure and neuroimaging, which were performed at as part of the initial diagnostic work-up only.

2.4.2 Neuropsychological Assessments

2.4.2.1 National Adult Reading Test (NART)

The NART consists of 50 irregularly spelled words (e.g. syncope, quadruped) and provides an estimate of baseline cognitive ability[134].

Participants are instructed to read aloud a standardised list of words, which are displayed on a card. With reference to a pronunciation guide, the researcher marks whether or not the words are read correctly. Each incorrectly pronounced word is counted as an error and the sum of this forms a total error score. The Full Scale IQ score is derived from the formula 127.7 – 0.826 x NART error score[134].

2.4.2.2 California Verbal Learning Test

The CVLT examines verbal learning and working memory[135]. Participants are read two lists of words and assessed on short-term, cued, as well as delayed recall.

List A and B each comprises of sixteen words, with four words from four different semantic categories (modes of transport, vegetables, furniture, animals). The standardised list does not present two words from the same category consecutively. The first five trials involve the examiner reading List A, followed by the participant reciting as many words as possible aloud. Each correct response from the participant is recorded. List B is then presented to participants, who are asked to recall words from List B only. After one trial of List B, delayed recall testing of List A is conducted after twenty minutes. During the last short-term recall trial and the long-term recall trial of List A, participants are given the semantic categories of the words, as a memory prompt.

2.4.2.3 Digit Span

The digit span task tests working memory[137]. It is a sub-test of the Wechsler Adult Intelligence Scale – third edition (WAIS-III: (Wechsler, 1997)). It involves digit forward and digit backward tasks.

With the digit forward task, the researcher reads a number sequence aloud and participants are asked to repeat the sequence verbatim. Number sequences start at two digits and increases to nine digits incrementally. There are two sequences of the same digit length. When completing

the digit backward task, participants are instructed to repeat the number sequence that the researcher read aloud backwards. For both tasks, if the participant incorrectly recites two consecutive number sequences of the same length, the task is discontinued.

2.4.2.4 Stroop Colour and Word Test (SCWT)

The SCWT assesses inhibition of cognitive interference[138]. Participants are asked to read three different tables as quickly as possible, with each table having a forty-five second time limit.

The first table consists of colour words (red, green or blue) written in black ink and participants are asked to read the words aloud. The second table consists of coloured crosses and require participants to state the colour of the crosses aloud. The third table contains colour words with incongruous colouring, for example the word may spell 'red', but be coloured blue. Participants must read the colour of the word and not what the word spells.

2.4.2.5 Symbol Digit Modalities Test (SDMT)

The SDMT assesses attentional control and processing speed[136].

Participants are given a coding key with nine abstract symbols that each correspond to a number. A series of the symbols arranged in eight rows, each containing fifteen symbols, is located below the coding key. Participants are instructed to put the corresponding number beneath each symbol. The first ten symbols are used as practice. Once understanding of the task has been confirmed, participants are told to complete as many symbol-number matches as possible in ninety seconds. The number of correct symbol-number matches within ninety seconds becomes the participant's score.

2.4.3 Ocular Motor Assessments

2.4.3.1 Ocular Motor Apparatus and Data Analysis

Ocular motor tasks were conducted in a darkened room, with participants seated on a chair adjusted for height, 950mm from a 60 Hz LCD monitor (resolution: 1920 x 1080). Task stimuli were green, blue and purple crosses presented on a black background. Horizontal eye movements were recorded using an Eyelink 1000 plus dark pupil video-oculography system, which has high resolution (noise limited at <0.01 degrees) and an acquisition rate of 1000 Hz.

Eye movement analysis was completed using a custom Matlab program. Values were obtained from a monocular eye trace. Latency was defined as the time between stimulus presentation and saccade onset in milliseconds (ms), as illustrated in Figure 2.4.3.1. Errors were expressed as a percentage and recorded if participants performed any trials incorrectly.

For all tasks, trials were excluded from analysis if an error was recorded, a blink occurred prior to saccade onset, no eye movement was made, or fixation was lost. In addition, trials in the Simon and switch tasks were excluded if the preceding trial was an error, which was required in order to calculate the Simon and switch effect[150].

Figure 2.4.3.1. Sample eye movement trace from healthy control[151]

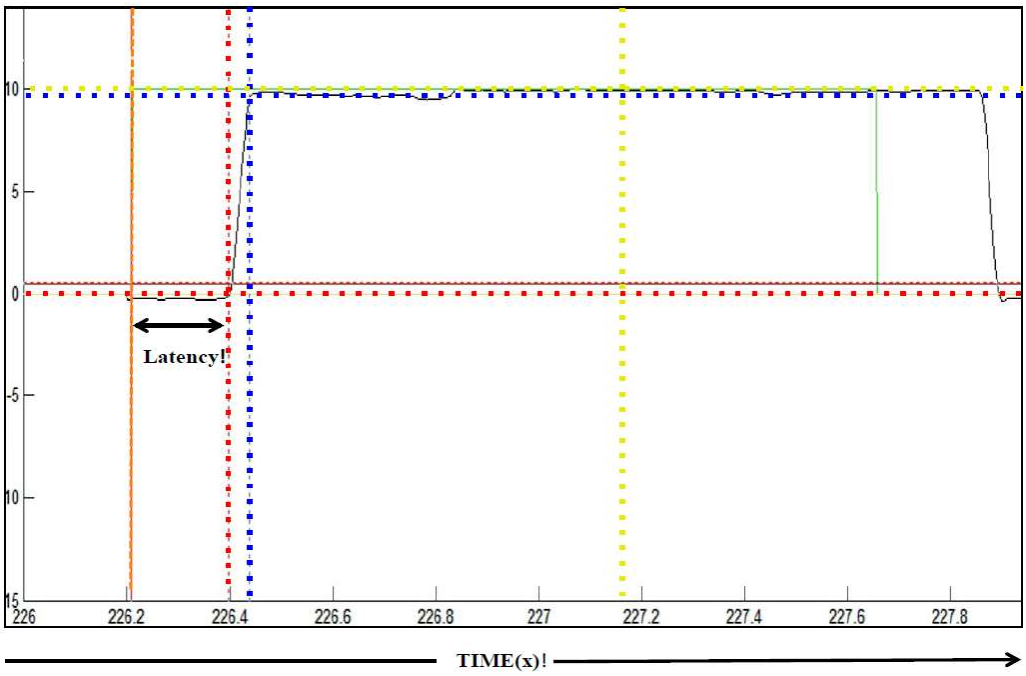


Figure 2.4.3.1. The solid black line signifies the trajectory of a saccade during a trial. The solid orange vertical line marks the presentation of a visual stimulus. The dotted red vertical line represents saccade onset and the dotted blue vertical line represents saccade offset. Latency is the time between the presentation of a visual stimulus and saccade onset, measured in milliseconds.

2.4.3.2 Ocular Motor Tasks

Ocular motor tasks consisted of visually guided saccades (Figure 2.4.3.2a), antisaccades (Figure 2.4.3.2b), the Simon task (Figure 2.4.3.2c) and the switch task (Figure 2.4.3.2d).

Figure 2.4.3.2a. Visually guided saccades

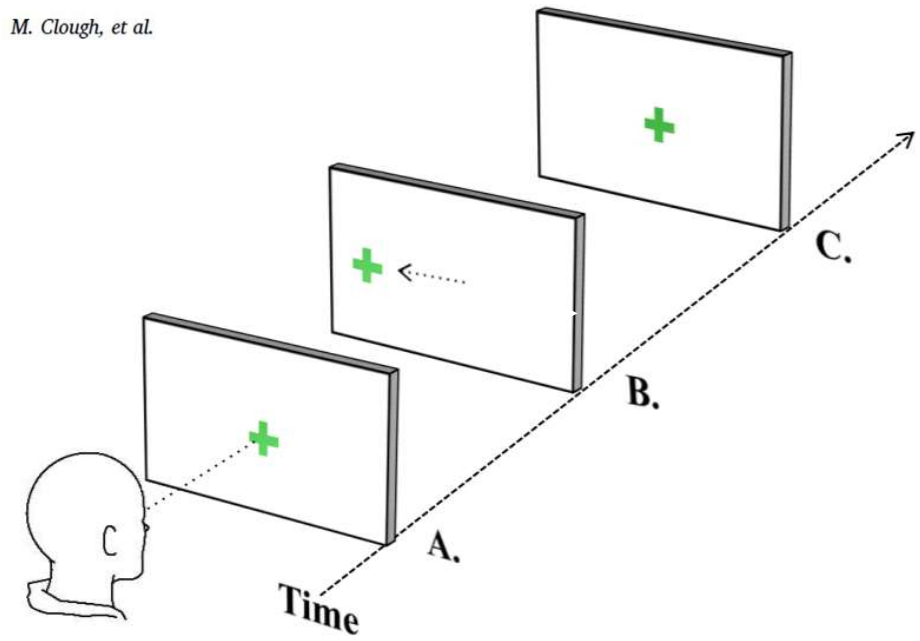


Figure 2.4.3.2a. Visually guided saccades assessed baseline visual pathway integrity[139]. Participants fixated on a central green cross (A), which moved right or left and back to centre (B and C). They were instructed to follow the cross with their eyes as accurately as possible (B).

Figure 2.4.3.2b. Antisaccades

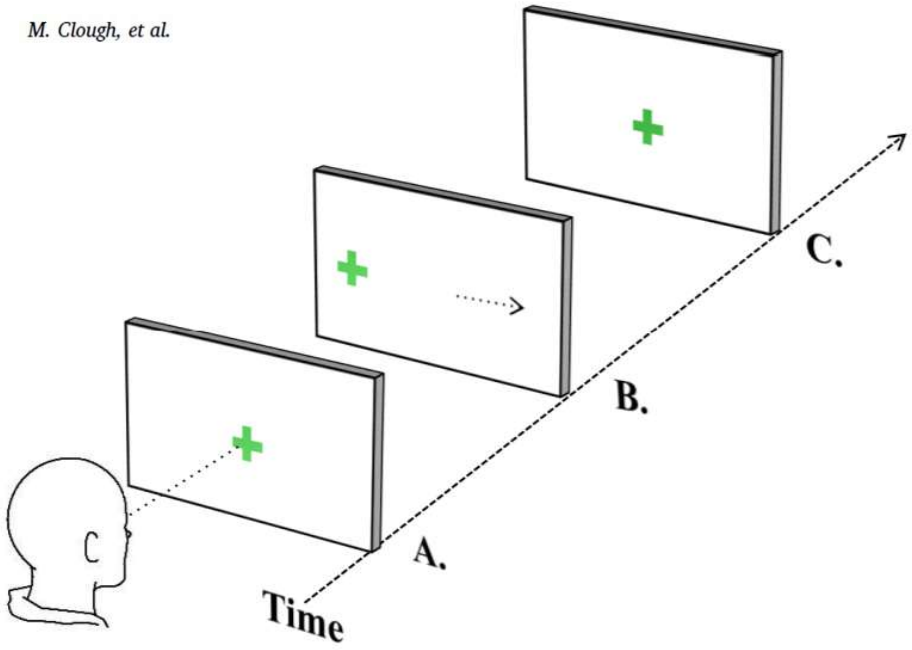


Figure 2.4.3.2b. Antisaccades assessed inhibitory control; the ability to inhibit an automatic response, in favour of performing a goal-oriented response that required more effort[140]. Participants fixated on a central green cross (A), which moved right or left and back to centre (B and C). They were instructed to look at the mirror opposite location of the green cross as it moved peripherally, rather than towards it (B).

Figure 2.4.3.2c. Simon task

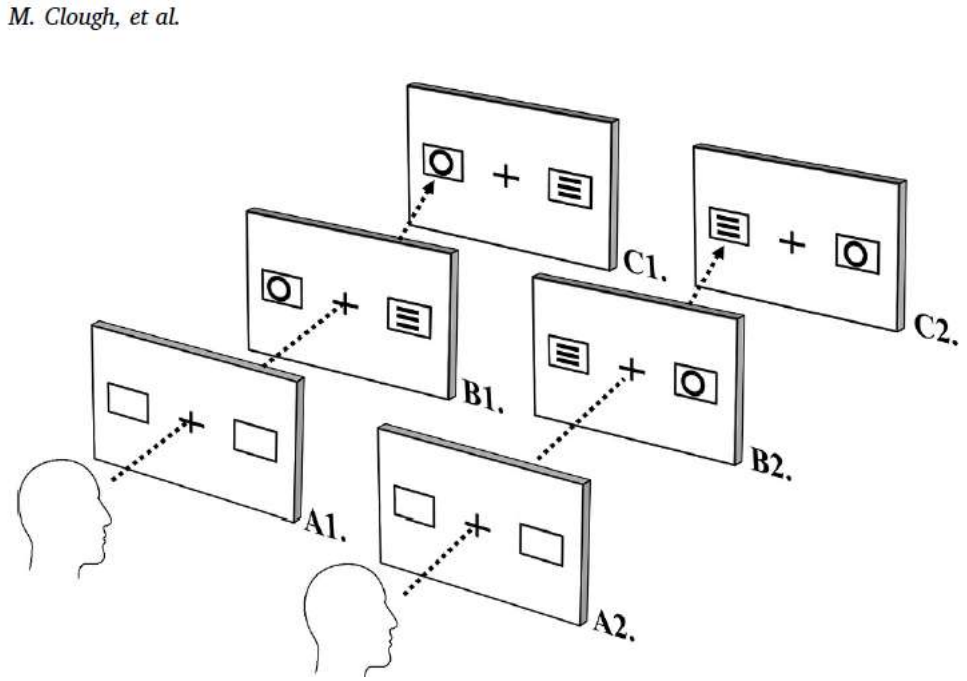


Figure 2.4.3.2c. The Simon task assessed cognitive flexibility by measuring responses to trials with congruent and incongruent conditions[141, 142]. Participants fixated on a central green cross (A1 and A2) and two boxes were located peripherally. A green circle or square appeared in either box, at the same time three horizontal green lines appeared in the opposite box (B1 and B2). The shape acted as the eye movement cue. If the circle appeared in either box, participants were instructed to look at the left box (C1 and C2). If the square appeared in either box, the correct saccade was toward the right box.

Trials in which the green circle or square appeared in the same box that participants needed to look at were termed “congruent” (C1). If the shape appeared in the opposite box, the trial was “incongruent” (C2). For example, a “congruent-incongruent” trial is a congruent trial followed by an incongruent trial.

Figure 2.4.3.2d. Switch task

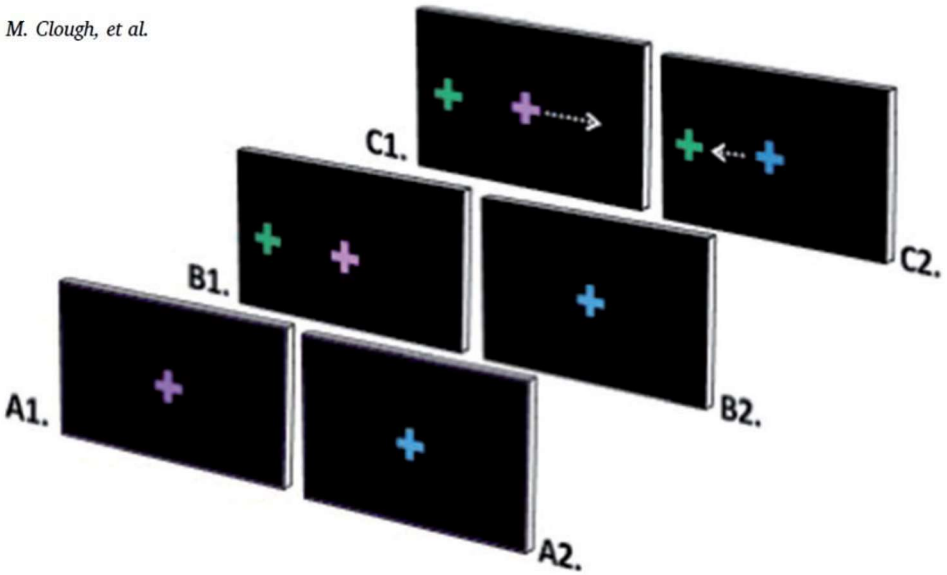


Figure 2.4.3.2d. The switch task assessed attention and working memory by presenting a stimulus, which cued participants to respond in one of two ways[132, 145]. Participants fixated on the centre of the screen, and either a purple (A1) or blue (A2) cross appeared. A green cross then appeared peripherally (B1). Participants performed a prosaccade or antisaccade movement, depending on the colour of the initial cross. An antisaccade movement when the green cross appeared was cued by an initial purple cross (C1) and a prosaccade by an initial blue cross (C2).

Repeat consecutive trials ('non-switch') were generally considered easier than changing tasks between trials ('switch'). The differences in performance between non-switch and switch trials provided an indication of task-switching ability ('switch-cost')[143, 144].

2.4.4 Headache, Mood and Quality of Life Questionnaires

IIH patients completed self-administered questionnaires at each testing session, regarding their degree of headache, depression, anxiety, visual functioning and quality of life.

2.4.4.1 Headache Impact Test

Headache severity was evaluated by the Headache Impact Test, Version 6 (HIT-6)[148]. HIT-6 was developed as a tool for screening and monitoring headache, in both clinical and research settings[152]. Areas assessed by the HIT-6 include daily functioning (such as social, role-specific, cognitive), vitality, psychological distress and headache severity. The HIT-6 is internally consistent and has good test-retest reliability[148]. It has been widely applied in clinical trials and is useful for monitoring patients with headache[153, 154]. Each response in the HIT-6 is assigned 6-13 points and the sum of all points forms the overall score[153].

2.4.4.2 Patient Health Questionnaire

Depression was assessed using the Patient Health Questionnaire, Version 9 (PHQ-9)[146]. The PHQ-9 has been reported as a reliable instrument for criteria-based assessment of depression, which was validated with 3000 patients from primary care and 3000 patients from obstetrics and gynaecology clinics[155, 156]. Criteria contained in the PHQ-9 are based on diagnostic criteria for depression from the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV). In addition to being a useful diagnostic tool, the PHQ-9 also grades depression severity[146]. Raw scores in the PHQ-9 are multiplied by either 0, 1, 2 or 3 and then added to form a total score that ranges between 0-27[146].

2.4.4.3 Penn State Worry Questionnaire (PSWQ)

The Penn State Worry Questionnaire provided a marker of anxiety[147], by measuring excessive worry and depressive rumination, which are associated with the development and propagation of psychological disorders. This 16-item instrument has high internal consistency, good test-retest reliability and is able to distinguish patients with generalised anxiety disorder (GAD) from other anxiety disorders[157]. Brief versions and cross-cultural versions of the PSWQ have also been generated[158, 159]. In scoring the PSWQ, responses are assigned a value 1-5 depending on if the answer was worded positively or negatively. Some questions are reverse-scored. The total score is obtained by adding all scores together and ranges from 16-80[158].

2.4.4.4 National Eye Institute Visual Functioning Questionnaire

Visual impacts on quality of life were evaluated by the 25-item National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25)[149]. The NEI VFQ-25 was derived from the 51-item version of the NEI VFQ, based on early feedback from users that a shorter version is needed for research and clinical settings. Subsequent studies have validated the NEI VFQ-25 and found that scores in the short and long versions of the NEI VFQ appear strongly correlated[149]. In the NEI VFQ-25, questions are grouped into 12 subscales. Scores from each subscale are averaged to form an overall score (Table 2.4.4.4)[160].

Table 2.4.4.4 NEI-VFQ-25 scoring algorithm[149]

Scale	**Number of items**	**After recoding, average the following items**
General health	1	1
General vision	1	2
Ocular pain	2	4, 19
Near activities	3	5, 6, 7
Distance activities	3	8, 9, 14
Vision specific: - Social functioning - Mental health - Role difficulties - Dependency	 2 4 2 3	 11, 13 3, 21, 22, 25 17, 18 20, 23, 24
Driving	3	15c, 16, 16a
Colour vision	1	12
Peripheral vision	1	10

2.4.4.5 Short Form 36

The Short form 36 (SF-36) was used to determine health related quality of life and consists of 8 sub-categories[161]. The SF-36 has been translated into 120 languages and is widely used, as a reliable and validated instrument[162]. Scoring the SF-36 involves re-coding responses to a value between 0-100 according to standardised instructions, and then averaging values from the same scale to obtain a score for that category (Table 2.4.4.5).

Table 2.4.4.5 SF-36 scoring algorithm[161]

Scale	Number of items	After recoding, average the following items
Physical functioning	10	3, 4, 5, 6, 7, 8, 9, 10, 11, 12
Role limitations due to physical health	4	13, 14, 15, 16
Role limitations due to emotional problems	3	17, 18, 19
Energy/fatigue	4	23, 27, 29, 31
Emotional well-being	5	24, 25, 26, 28, 30
Social functioning	2	20, 32
Pain	2	21, 22
General health	5	1, 33, 34, 35, 36

2.4.5 Barratt Impulsiveness Scale (BIS-11)

The BIS-11[163] was an additional questionnaire that was emailed and/or verbally administered to all participants after the bulk of recruitment and testing had concluded, to assess impulsivity levels. This was conducted given the striking inhibitory control deficits seen on ocular motor testing, as impulsivity could be an associated feature[164].

Impulsivity-related research has utilised the BIS-11 for over fifty years. It is widely regarded as the gold-standard self-reported instrument for evaluating impulsiveness[165]. The BIS-11 is divided into three major second order factors, which are further classified into six first order factors[163]. The scoring algorithm for BIS-11 is displayed in Table 2.4.5.

Table 2.4.5 BIS-11 scoring algorithm[163]

Barratt Impulsiveness Scale 11 – Factor Structure and Scoring			
2nd Order Factors	**1st Order Factors**	**# of items**	**Items contributing to each subscale**
Attentional	Attention	5	5, 9*, 11, 20*, 28
	Cognitive Instability	3	6, 24, 26
Motor	Motor	7	2, 3, 4, 17, 19, 22, 25
	Perseverance	4	16, 21, 23, 30*
Non-planning	Self-Control	6	1*, 7*, 8*, 12*, 13*, 14
	Cognitive Complexity	5	10*, 15*, 18, 27, 29*

*reverse scored items

2.5 Testing Schedule

IIH patients were initially screened for eligibility and if inclusion criteria were met, informed consent was obtained. The testing schedule is outlined in Table 2.5. Testing at baseline and six months involved clinical neuro-ophthalmic assessments and included all neuropsychological tests and ocular motor tasks. At three months, neuropsychological testing was slightly abbreviated, to avoid test re-test effects on the CVLT and NART.

Table 2.5 Testing schedule

	Screening	Baseline	3 months	6 months
Informed consent	X			
Clinical review		X	X	X
Ocular motor: VG, AS, ST, SwT (40 min)		X	X	X
Neuropsychological: SDMT, Digit Span, Stroop, CVLT, NART (1hr)		X		X
Neuropsychological: SDMT, Digit Span, Stroop (40 min)		X	X	X
Questionnaires* (15 min)		X	X	X

VG = Visually Guided saccades, AS = Antisaccade, ST = Simon Task, SwT = Switch Task

SDMT = Symbol Digit Modalities Test, CVLT = Californian Verbal Learning Test, NART = National Adult Reading Test

*Mood, headache and visual function questionnaires: Patient Health Questionnaire 9, Penn State Worry Questionnaire, Headache Impact Test 6, National Eye Institute Visual Functioning Questionnaire 25.

2.6 Statistical Analyses

Data analyses was conducted using IBM SPSS Statistics Version 26. Group comparisons were performed using Mann-Whitney U tests, as normality was violated according to Shapiro-Wilks analyses. Results from the IIH and control groups were compared for all cognitive assessments separately with Mann-Whitney U tests. In the IIH cohort, high error rates on the switch and Simon ocular motor tasks resulted in the exclusion of many trials. Switch cost (differences in performance between non-switch and switch trials) and Simon effect (differences in performance between congruent and incongruent trials) could not be determined due to the high proportion of excluded trials.

Multivariate linear regressions were performed to determine whether certain clinical variables (weight, waist circumference, depression, anxiety, headache, RNFL) predicted cognitive performance on neuropsychological tests or ocular motor tasks. Wilcoxon-signed rank testing compared longitudinal data within the IIH cohort. Correction for multiple comparisons were performed using the Benjamini-Hochberg methodology [166], with a false discovery rate of 80%. All significant findings and p-values presented survived corrections and those that did not were stated as non-significant.

Chapter 3 Results: Manuscript

Most results are presented as a manuscript submitted for publication, which are listed below. Please excuse an inevitable amount of repetition due to the nature of manuscripts. Additional results not covered in this Chapter will be presented in Chapter 4.

Results presented in Chapter 3: Manuscript

- National Adult Reading Test (NART)
- Stroop Colour and Word Test (SCWT)
- Symbol Digit Modalities Test (SDMT)
- California Verbal Learning Test (CVLT)
- Digit span test
- Visually guided saccades
- Antisaccades
- Switch task
- Brief summary of results from self-administered questionnaires (detailed discussion in Chapter 4, section 4.3 Comorbidities and Quality of Life).

Manuscript under review at Therapeutic Advances in Neurological Disorders (TAND).

Ocular motor inhibitory control deficits in Idiopathic Intracranial Hypertension are predicted by RNFL thickness but not by clinical characteristics.

ABSTRACT

Objective: To determine whether cognitive impairments in patients with Idiopathic Intracranial Hypertension (IIH) are correlated with changes in visual processing, weight, waist circumference, mood or headache and whether they change over time.

Methods: Twenty-two newly diagnosed IIH patients participated, with a subset assessed longitudinally at 3 and 6 months. Both conventional and novel ocular motor tests of cognition were included: Symbol Digit Modalities Test (SDMT), Stroop Colour and Word Test (SCWT), Digit Span, California Verbal Learning Test (CVLT), prosaccade (PS) task, antisaccade (AS) task, interleaved antisaccade-prosaccade (AS-PS) task. Patients also completed headache, mood and visual functioning questionnaires.

Results: IIH patients performed more poorly than controls on the SDMT ($p<.001$), SCWT ($p=.021$), Digit Span test ($p<0.001$) and CVLT ($p=.004$) at baseline, and generated a higher proportion of AS errors in both the AS ($p<.001$) and AS-PS tasks ($p=.007$). Further, IIH patients exhibited prolonged latencies on the cognitively complex AS-PS task ($p=.034$). While weight, waist circumference, headache and mood did not predict performance on any experimental measure, increased retinal nerve fibre layer (RNFL) was associated with AS error rate on both the block ($F(3, 19)=3.22, B=0.30, p=0.022$) and AS-PS task ($F(3, 20)=2.65, B=0.363, p=0.013$). Unlike ocular motor changes, impairments revealed on conventional tests of cognition persisted up to 6 months.

Conclusion: We found multi-domain cognitive impairments in IIH patients that were unrelated to clinical characteristics. Marked ocular motor inhibitory control deficits were predicted by RNFL thickness but remained distinct from other cognitive changes, underscoring the significance of visual processing changes in IIH.

INTRODUCTION

Idiopathic intracranial hypertension (IIH) is characterised by increased cerebrospinal fluid pressure with an unclear aetiology. IIH affects predominantly young women, and is associated with serious consequences, including loss of vision, disabling headache, and loss of employment[11]. Evidence is emerging that IIH patients also experience a range of cognitive impairments[13-17, 167] that, despite effects on decreased quality of life and poor treatment outcomes[15], remain under-recognised and poorly understood. Whether cognitive changes are independent or a consequence of other features of the disorder, such as changes in visual processing, headache, mood disorders, weight and medication, is unknown.

Here we assessed cognitive changes in IIH using conventional neuropsychological measures and novel ocular motor tasks that examine visual processing changes associated with saccade generation[168]. Ocular motor tasks were the simple prosaccade (PS) task, which requires a gaze shift towards a suddenly-appearing stimulus, reflecting simple sensorimotor processing, and the more complex antisaccade (AS) task that additionally implicates cognitive networks required to inhibit a saccade towards a suddenly-appearing stimulus and then move the eyes in the opposite direction[169]. Task demands were modified using the interleaved AS-PS task that recruits a broader cognitive network, enabling assessment of the interaction between changes in visual processing and cognitive function more broadly[170]. Relationships were assessed between cognitive impairments and common comorbid IIH features, such as headache, mood, weight, waist circumference and visual processing changes.

METHODS

Participants

Twenty-two patients diagnosed with IIH based on revised diagnostic criteria proposed by Friedman et al[10] were recruited from a tertiary neuro-ophthalmology clinic in Melbourne, Australia. Fourteen IIH patients completed testing at three months and five at six months.

To decrease additional confounding factors, or barriers to testing, patients were excluded if they had severe vision-threatening IIH, were pregnant, or had co-existing severe neurological or mental health disorders.

All IIH patients underwent comprehensive neurological and neuro-ophthalmic assessment, including tests of visual acuity, perimetry and optical computed tomography (OCT). Baseline patient characteristics are displayed in Table 1.

Healthy control data were sourced from existing ocular motor and neuropsychological databases[171]. Twelve ocular motor and twenty-two neuropsychological control datasets were included. IIH and ocular motor control groups were matched for age and sex. IIH and neuropsychological control groups were matched for age, sex and intelligence as estimated by the National Adult Reading Test (NART)[134].

Standard protocol approvals, registrations, and patient consents.

Ethics approval was granted by the Alfred Health Research Ethics Committee. Participants provided written informed consent prior to participation in the study in accordance with the declaration of Helsinki.

Data availability statement

Relevant data not published within the article can be made available by the corresponding author on reasonable request.

Equipment, stimuli, and procedures

All testing took place at the Central Clinical School in the Alfred Centre at Monash University.

Clinical assessments and Optical Coherence Tomography

Visual assessments were completed by qualified orthoptists and neuro-ophthalmologists. Perimetry was conducted using a Humphrey Visual Field analyser, set at 30-2. OCT was performed in all participants using Zeiss Cirrus technology according to published standards[172]. Scans were acquired on the same day as clinical and cognitive assessments at a single centre, on a single machine using semi-automatic settings, by a single operator. Testing was performed undilated in a brightly lit room. Quality control using the OSCAR-IB criteria[173] was applied and all scans were included for analysis. RNFL thickness was derived from Zeiss Windows 7 Version 11 software.

Questionnaires

Patient rated outcomes included assessments of headache (Headache Impact Test 6: HIT-6)[152], anxiety (Penn State Worry Questionnaire: PSWQ)[147], depression (Patient Health Questionnaire 9: PHQ-9)[146] and visual functioning (National Eye Institute Visual Functioning Questionnaire 25: NEI-VFQ 25)[149].

Conventional cognitive assessments

The Symbol Digit Modalities Test (SDMT) assesses information processing speed[136], Stroop Colour and Word Test (SCWT) provides a marker of inhibition of cognitive interference[138], and both the Digit Span[137] and California Verbal Learning Test (CVLT)[135] assess working memory.

Ocular motor assessments

Ocular motor tasks were conducted in a darkened room, with participants seated on a chair adjusted for height, 950mm from a 60 Hz LCD monitor (resolution: 1920 x 1080). Task stimuli were green, blue and purple crosses presented on a black background. Horizontal eye movements were recorded using an Eyelink 1000 plus dark pupil video-oculography system, which has high resolution (noise limited at <0.01 degrees) and an acquisition rate of 1000 Hz.

Block prosaccade (PS) task: The PS task consisted of 96 randomly presented trials completed in a single block. Participants initially fixated a centrally located green cross and were instructed to follow the cross with their eyes as it moved to one of four peripheral locations (5 or 10 degrees to the right or left of centre, presented for 1500ms) and back to centre. To reduce anticipatory responses, the central cross was presented for 1000, 1250, or 1500ms.

Block antisaccade (AS) task: The AS task consisted of 24 randomly presented trials in 2 blocks. Participants initially fixated a centrally located green cross. After either 1000, 1250 or 1500ms, the central cross disappeared and re-appeared at either 5 or 10 degrees left or right of centre for 1500ms. Participants were instructed to look at the mirror opposite position of the peripherally located cross, rather than directly at the cross.

Interleaved antisaccade-prosaccade (AS-PS) task: The AS-PS task consisted of 16 PS trials and 16 AS trials, presented in 3 blocks in a pseudo-random order. Prior to testing, participants performed a practice block of 5 PS trials and 5 AS trials. During the task, participants initially fixated a centrally located blue or purple cross for 1000, 1250, or 1500ms. The central cross then disappeared and a green cross appeared either 5 or 10 degrees to the left or right of centre for 1500ms. A blue central cross indicated that participants should look towards the peripheral green cross (PS). A purple central cross indicated that participants should look at the mirror opposite position of the green cross (AS). The second of two consecutive trials of the same trial type (e.g. PS followed by PS) was classified as a repeat trial, while the second of two consecutive trials of different types (e.g. PS followed by AS) was classified as a switch trial. The first trial of each block was excluded from repeat or switch trial type analyses, since there was no preceding trial.

Data analysis

A custom Matlab program was utilised to analyse eye movement data. Saccade latency (ms) was calculated from a monocular eye trace as the time difference between the onset of a target and onset of a saccade. The onset of a saccade was determined by a visual change in the baseline saccade trace and calculated using a velocity criterion of 30° per second. An error, calculated as a percentage of the total number of trials, was recorded if participants generated a saccade of greater than 1.5 degrees in the wrong direction (e.g. PS movement during an AS trial). Errors were not applicable to PS block trials. Trials that involved an error, blink artefact, absent response, or fixation loss of 2 degrees from the central target, were excluded from latency analysis.

All data were analysed using IBM SPSS Statistics Version 26. Due to violations of normality using Shapiro-Wilks analyses, group comparisons were conducted using Mann-Whitney U. Mann-Whitney U tests separately compared IIH and control groups for all cognitive assessments. For the AS-PS task, switch cost (differences in performance between non-switch and switch trials) could not be determined due to the high proportion of excluded trials for the IIH cohort as a result of error. Multivariate linear regressions were performed to determine whether certain clinical variables (weight, waist circumference, depression, anxiety, headache, RNFL) predicted cognitive performance (either neuropsychological test or ocular motor). Correction for multiple comparisons were performed using the Benjamini-Hochberg methodology [166], with a false discovery rate of 80%. All significant findings and p-values presented survived corrections. Those that did not have been stated as non-significant.

RESULTS

All 22 participants were phenotypically typical of IIH and were tested at a mean of 2.7 months from diagnosis (*standard deviation (SD)=1.4*). 13 patients were managed with acetazolamide, 5 with topiramate and 4 were not on medications for IIH. Additional clinical characteristics and baseline demographics are shown in Table 1. Table 2 summarises group means and standard deviations for all tasks.

Table 1. Demographic information for all participants.

	IIH	OM Controls	NP Controls
	Mean (SD)	*Mean* (SD)	*Mean* (SD)
	n=22	*n=12*	*n=22*
Female / Male	22 / 0	12 / 0	22/0
Age / distribution	27.32 / 19-46	23.58 / 21-30	31.43 / 20-42
Mean NART FSIQ / distribution	118 / 97-128		116 / 109-128
Idiopathic intracranial hypertension			
Duration (months)	2.7 (1.4)		
CSF opening pressure (cm)	29.5 (4.8)		
Weight (kg)	103.6 (33.3)		
Waist (cm)	107.9 (20.9)		
Headache / Visual symptoms (%)	91 / 18		
Acetazolamide / Topiramate (%)	59 / 23		
VA right / left (LogMAR)	-0.1 (0.1) / -0.1 (0.1)		
HVF 30-2 right / left (PSD)	2.7 (2.5) / 3.1 (2.9)		
RNFL right / left (μm)	125.1 (46.9) / 119.9 (36.5)		

OM = Ocular Motor, NP = Neuropsychological, NART FSIQ = National Adult Reading Test Full Scale Estimated IQ, VA = Visual Acuity, OD = Right, OS = Left, HVF = Humphrey Visual Fields, PSD = Pattern Standard Deviation, RNFL = Retinal Nerve Fibre Layer

Table 2. Ocular motor and neuropsychological means and standard deviations

	Control	IIH baseline	IIH 3-month	IIH 6-month
	Mean (SD)	*Mean* (SD)	*Mean* (SD)	*Mean* (SD)
	n=12	*n*=22	*n*=14	*n*=5
Ocular Motor				
Prosaccade latencies (ms)				
PS block	213.22 (26.24)	205.22 (21.27)	206.14 (19.08)	202.34 (14.36)
Repeat PS	230.79 (36.07)	211.37 (28.36)	217.17 (41.13)	213.18 (19.23)
Switch PS	237.03 (51.99)	242.12 (59.64)	236.86 (48.51)	216.96 (20.28)
Prosaccade error rate (%)				
Repeat PS	1.00 (2.11)	5.22 (19.74)	0.36 (1.34)	0.00 (0.00)
Switch PS	3.20 (3.16)	6.78 (16.47)	2.00 (2.08)	0.00 (0.00)
Antisaccade latencies (ms)				
AS block	312.88 (33.96)	335.56 (41.78)	354.49 (62.78)	317.31 (32.52)

Repeat AS	305.85 (43.00)	346.26 (60.62)	343.06 (50.70)	375.80 (98.72)
Switch AS	300.38 (48.53)	**349.32 (63.50)***	338.38 (49.33)	329.49 (38.76)
Antisaccade error rate (%)				
AS block	6.06 (8.25)	**34.33 (21.47)***	**22.05 (22.22)***	25.83 (38.00)
Repeat AS	5.22 (9.12)	**29.49 (23.96)***	17.70 (26.28)	32.17 (27.85)
Switch AS	9.60 (8.88)	22.26 (22.81)	15.14 (17.62)	18.40 (16.32)
Neuropsychological				
SDMT (score)	74.59 (12.27)	**47.90 (14.02)***	**51.08 (13.84)***	**57.40 (12.90)***
SCWT (t-score)	53.77 (12.20)	**45.73 (6.13)***	**42.36 (5.27)***	**39.40 (7.27)***
Digit Span (score)	12.68 (3.05)	**9.55 (2.22)***	**8.79 (2.29)***	**8.20 (2.28)***
CVLT (t-score)	43.05 (10.71)	**36.09 (17.49)***	N/A	N/A

***Sig p<.05, compared to controls**

PS: prosaccade; AS: antisaccade. SDMT: symbol digit modalities test; SCWT: Stroop colour and word test; CVLT: California Verbal Learning Test

Questionnaires

At baseline, responses from the HIT-6 indicated that participants generally experienced prominent headaches, with a mean score of 57.8 (*SD=11.6, range = 36-76, prominent if score >50*)[152]. The PSWQ and PHQ-9 revealed moderate levels of anxiety and depression in the IIH cohort, with mean scores of 51.1 (*SD=14.3, range = 32-75, moderate if score 40-59*) and 11.8 (*SD=15.0, range = 0-75, moderate if score 10-14*), respectively[146, 147].

Headache, anxiety and depression in the IIH group remained statistically comparable to baseline at 3 and 6-months; HIT-6 (*mean = 55, SD = 10.9, range = 38-78*), PSWQ (*mean = 55, SD = 14.7, range = 28-80*) and PHQ-9 (*mean = 9.3, SD = 6.1, range = 2-20*).

IIH patients had no significant impairment of activities of daily living due to visual limitations, based on responses from the NEI-VFQ 25 questionnaire [149], at any time-point.

Neuropsychological assessments

At baseline, IIH patients performed more poorly than healthy controls on the SDMT (*U=27, p<.001*), SCWT (*U=143.5, p=.021*) Digit Span (*U=94, p<0.001*) and CVLT (*U=114, p=.004*). For IIH patients, performance remained significantly poorer than controls at 3-months (*SDMT: U=28, p<.001, Stroop: U=65.5, p=.003, Digit Span: U=43.5, p<.001*) and 6-months (*SDMT: U=19.5, p=.023, Stroop: U=14.5, p=.008, Digit Span: U=11, p=.004*); with the exception of the CVLT, which was tested at baseline only due to practice effects.

Ocular motor assessments

Prosaccades: There were no significant differences in latency between IIH and control groups for either the block PS task, or PS trials on the more cognitively complex AS-PS task, at any time-point (baseline, +3 months, +6 months). In addition, there was no significant group difference in error for PS trials in the AS-PS task, at any time-point.

Antisaccades: There was no significant difference in latency between IIH and control groups for the block AS task at baseline. In contrast, AS latencies were significantly prolonged for IIH patients on the more cognitively complex AS-PS task, compared to controls (*U=58, p=.034*). In addition, IIH patients generated significantly more AS errors than controls on both the block (*U=7.5, p<.001*) and AS-PS tasks (*U=44, p=.007*).

At 3-months, AS latencies on the AS-PS task for IIH patients had reduced to within the normal range, with no statistically significant group difference (*U=37, p=.056*). While AS error rates remained significantly higher for IIH patients at 3-months on the block AS task (*U=31.5,*

p=.032), at 6 months and with only 5 patients available for testing, values had reduced to within the normal range (*U=22, p=.583*).

Effect of clinical variables on cognitive performance

Multivariate analyses demonstrated that IQ, headache, depression, anxiety, weight and waist circumference did not predict any significant ocular motor or neuropsychological result at baseline. However, increased RNFL thickness predicted increased baseline AS error rate, both in the block (*F(3, 19)=3.22, B=0.30, p=0.022*) and AS-PS task (*F(3, 20)=2.65, B=0.363, p=0.013*). At 3-months, RNFL elevation did not clearly predict block AS error (*F(5, 12)=1.763, B=.553, p=.056*), although continued to predict AS-PS antisaccade error (*F(5, 13)=3.186, B=0.589, p=.008*).

Patient numbers were insufficient for multivariate analyses of 6-month data, or multivariate analyses of medication effect. When comparing means, interleaved antisaccade task latencies appeared more prolonged in patients taking topiramate compared to those on acetazolamide (*404ms vs. 326ms, U=10, p=0.027*), however medications did not appear to impact performance on any other cognitive measure.

DISCUSSION

We reveal a range of cognitive impairments in IIH patients both on conventional neuropsychological and novel ocular motor tests of cognition. At baseline, as well as 3 and 6 months, IIH patients performed more poorly than controls on the Stroop test, indicating poorer inhibition of cognitive interference[138], on the SDMT, indicating reduced cognitive processing speed[136], and on the Digit Span and CVLT, indicating reduced working memory[135, 137].

At baseline, IIH patients found it more difficult to inhibit a saccade towards a suddenly appearing stimulus (AS error), irrespective of task difficulty. However, eye movements made directly towards a visual stimulus (PS) were comparable to controls for both tasks, at all time-points. For the more cognitively complex interleaved saccade task, AS latencies were significantly prolonged for IIH patients, suggesting reduced cognitive processing speed[168]. At 3 months, IIH patients exhibited partial improvement for AS error and normal antisaccade latencies. In five patients followed for 6-months, all ocular motor results were similar to controls, although these results must be interpreted with caution given the significant cohort attrition over time.

Although IIH patients reported high rates of headache, anxiety and depression, none of these factors predicted performance on any neuropsychological or ocular motor measure, at any time-

point. Notably, rates of headache and mood disturbances remained similar over time. However, increased AS error rates were associated with changes in structures involved in afferent visual transduction (i.e., increased RNFL thickness). Increased RNFL thickness was not associated with performance on any other cognitive measure. Further, RNFL thickness reduced significantly over time, in-line with observed improvements in ocular motor results. On the contrary, poorer performance on neuropsychological assessments for IIH patients persisted at 6 months, suggesting that cognitive functions less reliant on visual processing are independent of the clinical features of the disorder. It is plausible that subclinical visual processing changes may not impact conventional tests of cognition or perceived visual functioning, but may be revealed using more direct testing of the visual processing system using ocular motor tasks.

With the exception of a single case report[174], all prior studies have reported cognitive impairments in IIH[6, 8, 9, 167, 175, 176]. Yri and colleagues, in a study of 31 IIH patients, described decreased processing speed and reaction times as well as cognitive flexibility deficits[167]. When considered in combination with our findings of prominent inhibitory control deficits and impaired cognitive flexibility, it is conceivable that impaired frontostriatal function may underlie cognitive impairments in IIH[177].

Frontostriatal circuits support cognitive functions and neuroanatomically encompass the frontal cortex, thalamus and basal ganglia[178]. Three of five major frontostriatal circuits are thought to mediate non-motor, cognitively driven behaviours, namely the dorsolateral prefrontal, medial orbitofrontal and lateral orbitofrontal circuits[179]. The dorsolateral pre-frontal cortex is primarily responsible for executive functioning, which is comprised of cognitive domains impaired in our IIH cohort, such as inhibitory control, processing speed and working memory[180]. Although IIH pathophysiology is not fully understood, there is a complex yet well-established relationship between IIH and obesity, with the pathology of obesity postulated to affect striatal networks[181].

Weight gain and obesity increase the risk of IIH, while modest amounts of weight loss can lead to disease resolution[1]. In our cohort, weight and waist circumference did not predict cognitive performance. Similarly, Yri et al found that IIH patient body mass index (BMI) did not predict cognitive performance[167] suggesting that cognition appears to be influenced by the presence of, rather than the magnitude of weight excess in IIH. However, obesity by itself, or when present in other neurological diseases, has been associated with a number of adverse cognitive outcomes[182, 183] and larger cohorts may be needed to resolve this association. Functional Magnetic Resonance Imaging (fMRI) suggests that obesity and binge-eating disorder is associated with decreased striatal responses to food, yet heightened frontostriatal responses to

food cues[98]. This supports the hypothesis that frontostriatal changes in obesity may facilitate decreased inhibitory control[97].

A further potential pathophysiological factor in obesity and IIH-related cognitive changes is metabolically active adipose tissue, which can produce a range of adipokines and inflammatory cytokines[107]. Such an inflammatory milieu may contribute to cognitive impairment by interfering with neuronal network function. This has been demonstrated in other conditions such as multiple sclerosis, where obesity independently contributes to cognitive dysfunction as assessed by clinical testing, biomarkers and MRI[184]. Obesity-related systemic inflammation as well as increased mechanical strain on frontostriatal networks from raised intracranial pressure may therefore both contribute to cognitive dysfunction in IIH[185]. Since IIH patients exhibited no PS deficits, basic visual processing appears intact. Visual processing changes must therefore relate to the interaction of signals from the afferent visual pathway and widely distributed cognitive networks that are utilised in generating an AS[186]. This is clinically relevant, since high rates of AS errors are associated with decreased concentration and high distractibility [187]. Surprisingly, we found no correlation between any ocular motor measure and neuropsychological test results in our study. This was especially surprising for tests of inhibitory control like the AS task and Stroop test. However, the Stroop test and AS task assess inhibitory control differently. Unlike the AS task, there are no absolute penalties for errors in the Stroop test[138], which records errors as a correct/incorrect binary variable. The Stroop test and AS task are also timed differently; the Stroop test is concluded when a time limit is reached, while the AS task measures the time taken to complete a task. While we might expect a relationship between saccade latency and deficits revealed by neuropsychological testing, as has been reported previously[188], this is conceivably confounded by high error rates due to impaired inhibitory control, excluding a large number of trials from latency analyses for our IIH cohort.

Our study was limited by a relatively homogenous group of IIH patients, with mild to moderate clinical characteristics. Longitudinal testing was impacted by Covid19 restrictions, and a larger, more heterogenous cohort of IIH patients would help to confirm trends and clarify clinical associations identified in our study. Ideally controls would be weight matched to the IIH group in addition to being age and sex matched, since cognitive impairments may be associated with obesity[97]. Further, ocular motor tasks less reliant on inhibitory control would be useful in future IIH research, identifying impairments obscured by the high AS errors in our study.

While our results were largely consistent with previous studies in IIH patients, we also revealed a unique subclinical cognitive profile in IIH, that elucidates the difficulties some IIH patients have with maintaining employment and engaging in lifestyle alterations[1, 167]. Although it is increasingly acknowledged that cognitive impairments are likely in IIH, cognitive screening is absent from management guidelines[189]. The Mini Mental State Examination (MMSE) has been proposed as a screening test[176], however it lacks sensitivity[190]. The SDMT is quick, simple to administer and easy to score[136], and could be considered as an alternative screening test for IIH-specific cognitive changes, such as reduced information processing speed[167].

Weight, waist circumference, anxiety, depression and headache do not appear to underlie cognitive impairments in mild to moderate IIH but need to be studied in larger cohorts. Here, RNFL elevation was associated with ocular motor deficits, that might represent subclinical changes in visual-cognitive processing and future inclusion of more severely affected IIH patients would be of interest. Exploration of frontostriatal pathways, given impairments of inhibitory control, processing speed and working memory, may provide insights into IIH pathophysiology. Our work adds to the importance of the inclusion of cognitive screening in IIH management to enable targeted neurorehabilitation and employment support, leading to improved patient care.

Chapter 4 Additional Results

Participant characteristics and results from neuropsychological tests and most ocular motor tasks were presented in Chapter 3 (briefly revisited in this chapter in sections 4.1 and 4.2). Additional data from my study are presented in sections 4.3 and 4.4, which expands upon results that were not covered comprehensively in the manuscript.

Results presented in section 4.3 Comorbidities and Quality of Life

- Headache Impact Test 6 (HIT 6)
- Patient Health Questionnaire 9 (PHQ 9)
- Penn State Worry Questionnaire (PSWQ)
- Short from 36 (SF-36)
- National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25)

Results presented in section 4.4 Attentional Control and Impulsiveness

- Simon Task
- Barratt Impulsiveness Scale (BIS-11)

4.1 Clinical Characteristics

Twenty-two IIH patients participated in baseline testing (Table 4.1a). Neuropsychological and ocular motor results were compared to age and sex matched controls from an existing database.

Table 4.1a Baseline Demographics

	Number	Mean age in years (Range, SD)	Sex	Mean NART FSIQ (Range, SD)
IIH	22	27.32 (19-46, 5.99)	All Female	118 (97-128, 6.14)
OM Controls	12	23.58 (21-30, 2.94)	All Female	-
NP Controls	22	31.43 (20-42, 6.83)	All Female	116 (109-128, 5.11)

OM = Ocular Motor, NP = Neuropsychological, SD = standard deviation
NART FSIQ = National Adult Reading Test Full Scale Estimated IQ

Included patients were assessed within three months of being diagnosed with IIH, based on revised diagnostic criteria proposed by Friedman et al[10]. All participants were of typical IIH phenotype. Clinically, included patients did not have any significant visual impairment; those with fulminant vision-threatening IIH were excluded from the study due to logistics and testing barriers.

Baseline IIH patient clinical features are presented in Table 4.1b. 91% (*n=20*) of IIH patients reported headache. 18% (*n=4*) had intermittent visual symptoms, consisting of blurred vision (*n=3*) and diplopia (*n=1*). In general, IIH patients had preserved visual acuity, mild-moderate papilloedema and mild-moderate changes on Humphrey visual field (HVF) perimetry.

Neuroimaging of the brain with dedicated venography was obtained for all patients. Transverse venous sinus stenosis was reported in 45% of patients (*n=10*), pituitary flattening in 64% (*n=14*), optic nerve sheath distention in 23% (*n=5*) and posterior globe flattening in 5% (*n=1*). 23% (*n=5*) of IIH patients had normal neuroimaging, without features suggestive of raised intracranial pressure. 59% (*n=13*) patients received acetazolamide for IIH, 23% (*n=5*) were taking topiramate and 18% (*n=4*) were not on any medications for IIH.

Table 4.1b Baseline IIH patient clinical characteristics

Patient	Weight (kg)	Waist (cm)	Diagnosis (months)	CSF Pressure (cm of water)	Imaging Findings (TVS = transverse venous stenosis)	Symptoms	Visual Acuity (OD/OS)	HVF 30-2 PSD dB (OD/OS)	Optic Disc Swelling Grade (OD/OS), RNFL Average	Treatment
1	147.5	131	3	25	R) TVS, pituitary flattening	Headache	-0.2, -0.2	1.48, 1.66	(1/0). 99, 100	Acetazolamide
2	76.1	86.5	5	28	ON distension, bilateral TVS, pituitary flattening	Asymptomatic	-0.1, -0.1	1.50, 1.49	(1/1). 99, 91	Observation
3	76.5	106	4	24	Pituitary flattening	Headache	-0.1, -0.1	2.03, 1.88	(3/3). 305, 243	Acetazolamide
4	97.2	112	1	34	Pituitary flattening	Headache	-0.1, -0.1	2.12, 1.71	(2/2). 122, 122	Acetazolamide
5	85	92	1	25	Bilateral TVS, pituitary flattening	Headache	0, +0.2	1.38, 1.35	(2/2). 100, 111	Topiramate
6	89.4	87	5	39	Pituitary flattening	Headache	0, -0.1	0.99, 1.03	(1/1). 99, 104	Acetazolamide
7	138.3	140	3	30	ON distension, pituitary flattening	Headache	-0.1, -0.1	2.15, 2.40	(2/2). 67, 75	Acetazolamide
8	79.8	90	1	23	Bilateral TVS	Headache	0, -0.1	1.28, 1.85	(2/2). 110, 115	Observation
9	149.1	141	1	26	Normal	Headache, visual blurring	0, 0	8.25, 6.17	(1/1). 127, 119	Acetazolamide
10	208	155	1	37.5	Globe flattening, ON distension, pituitary flattening, bilat TVS	Headache	-0.1, -0.2	2.21, 1.49	(1/1) 104, 111	Acetazolamide
11	78.5	85.5	2	33	Normal	Headache, visual blurring	0, 0	11.51, 10.95	(2/1). 150, 110	Acetazolamide
12	123.9	122	3	29	Normal	Headache	0, 0	1.41, 1.70	(1/1). 110, 114	Acetazolamide
13	103.2	106	4	26	Normal	Headache	0, 0	1.61, 1.19	(0/1). 100, 97	Topiramate
14	104.2	115	1	38	Pituitary flattening, bilat TVS	Headache	0, 0	5.33, 8.85	(1/2) 120, 159	Acetazolamide
15	130.8	137.5	5	25	Pituitary flattening	Headache	0, 0	2.63, 1.65	(2/2). 136, 136	Topiramate
16	65.3	87.5	2	30	Pituitary flattening R) TVS	Headache	0, 0	1.42, 1.51	(2/1) 104, 86	Acetazolamide
17	69	84	2	29	Bilateral TVS	Headache	0, 0	1.67, 2.60	(0/0). 112, 91	Observation
18	82.3	94	4	31	Pituitary flattening	Headache	-0.1, -0.1	1.23, 1.54	(2/2). 136, 118	Acetazolamide
19	78.8	100	3	34	Normal	Headache, diplopia	-0.1, -0.1	2.38, 9.68	(2/1). 140, 133	Acetazolamide
20	99.6	91	2	27	Pituitary flattening	Asymptomatic	0, 0	1.64, 1.82	(1/1). 95, 94	Observation
21	100.7	99	4	33	ON sheath distension, pituitary flattening, bilateral TVS	Headache	-0.2, -0.2	1.45, 1.55	(2/2). 201, 192	Topiramate
22	96	111	2	22.5	ON sheath distension, bilateral TVS	Headache, visual blurring	-0.1, 0	4.00, 4.64	(1/1). 116, 116	Topiramate
Mean (SD)	103.6 (33.3)	107.9 (20.9)	2.7 (1.4)	29.5 (4.8)	-	-	-0.05, -0.05	2.71, 3.12	125, 120	-

OD = Right, OS = Left. Visual acuity measured in Log MAR
HVF = Humphrey Visual Fields, PSD dB = Pattern Standard Deviation. RNFL = Retinal Nerve Fibre Layer

Wilcoxon signed-rank testing found a significant reduction in average RNFL thickness in the IIH cohort from mean of 122.48 micrometres (*SD=40.9*) at baseline, to a mean of 110.04 micrometres (*SD=34.98*) at 3-months (*Z=-3.181, p=.001*). A significant reduction in RNFL thickness was also found at 6-months, with a group mean of 102.3 micrometres (*SD=11.22*), compared to baseline (*Z=-2.02, p=0.043*). There were no significant changes in headache, anxiety, depression, weight, or waist circumference in the IIH cohort observed over time, according to Wilcoxon signed-rank testing.

4.2 Neuropsychological and Ocular Motor Assessments

The majority of neuropsychological and ocular motor results were incorporated into a manuscript for publication, as detailed in Chapter 3. This section revisits the main results.

4.2.1 Neuropsychological Assessments

At baseline, IIH patients performed worse than healthy controls in all neuropsychological tests (SDMT: *U=27, p<.001*, SCWT: *U=143.5, p=.021*, Digit Span: *U=94, p<0.001* and CVLT: *U=114, p=.004*).

Neuropsychological results remained significantly worse than controls at 3-months (*SDMT: U=28, p<.001, Stroop: U=65.5, p=.003, Digit Span: U=43.5, p<.001*) and 6-months (*SDMT: U=19.5, p=.023, Stroop: U=14.5, p=.008, Digit Span: U=11, p=.004*); with the exception of the CVLT, which was tested at baseline only due to practice effects.

4.2.2 Ocular Motor Assessments

There were no significant differences in prosaccade (PS) latencies between IIH and control groups in simple or complex tasks, at any time-point (baseline, +3 months, +6 months).

There were no significant antisaccade (AS) differences in latency between IIH and control groups for the simple block AS task at baseline. However, AS latencies were significantly prolonged for IIH patients on the more cognitively complex AS-PS task, compared to controls (*U=58, p=.034*). In addition, IIH patients generated significantly more AS errors than controls on both the block (*U=7.5, p<.001*) and AS-PS tasks (*U=44, p=.007*).

At 3-months, AS latencies on the AS-PS task for IIH patients had reduced to within the normal range, with no statistically significant group difference (*U=37, p=.056*). While AS error rates

remained significantly higher for IIH patients at 3-months on the block AS task (*U=31.5, p=.032)*, at 6 months and with only 5 patients available for testing, values had reduced to within the normal range (*U=22, p=.583*).

4.2.3 Effect of Clinical Variables on Cognitive Performance

Multivariate analyses demonstrated that IQ, headache, depression, anxiety, weight and waist circumference did not predict any significant ocular motor or neuropsychological result at baseline.

However, increased RNFL thickness predicted increased baseline AS error rate, both in the block (*F(3, 19)=3.22, B=0.30, p=0.022*) and AS-PS task (*F(3, 20)=2.65, B=0.363, p=0.013*). At 3-months, RNFL elevation did not clearly predict block AS error (*F(5, 12)=1.763, B=.553, p=.056*), although continued to predict AS-PS antisaccade error (*F(5, 13)=3.186, B=0.589, p=.008*).

Patient numbers were insufficient for multivariate analyses of 6-month data, or multivariate analyses of medication effect. When comparing means, interleaved antisaccade task latencies appeared more prolonged in patients taking topiramate compared to those on acetazolamide (*404ms vs. 326ms, U=10, p=0.027*), however medications did not appear to impact performance on any other cognitive measure.

4.3 Comorbidities and Quality of Life

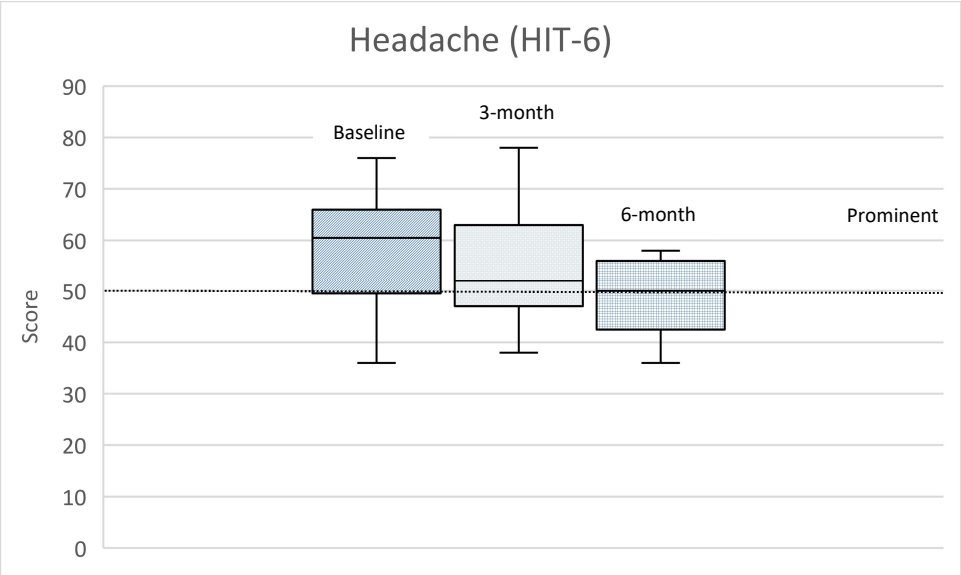
Common IIH comorbidities include chronic headache and mood disorders, such as depression and anxiety[111]. Self-administered questionnaires assessing the extent of headaches, mood disorders, quality of life and visual functioning were given to IIH patients to further explore these associations. Questionnaire results are expanded upon in this section.

4.3.1 Headache Impact Test 6 (HIT-6)

Headaches were prominent in the IIH cohort (Figure 4.3.1), with a mean HIT-6 score of 57.8 at baseline (*SD 11.3*). HIT-6 scores of >50 indicate prominent levels of headache. 77.3% of IIH patients experienced prominent headaches at baseline according to HIT-6 scores.

At 3-months, the IIH cohort had a mean HIT-6 score of 54.8 (*SD=10.9*) and 61.5% continued to experience prominent levels of headache. Headache remained a prominent issue at 6-months for 60% of IIH patients, with a mean HIT-6 score of 49.5 (*SD=7.4*).

Figure 4.3.1. Headache Impact Test 6 Scores



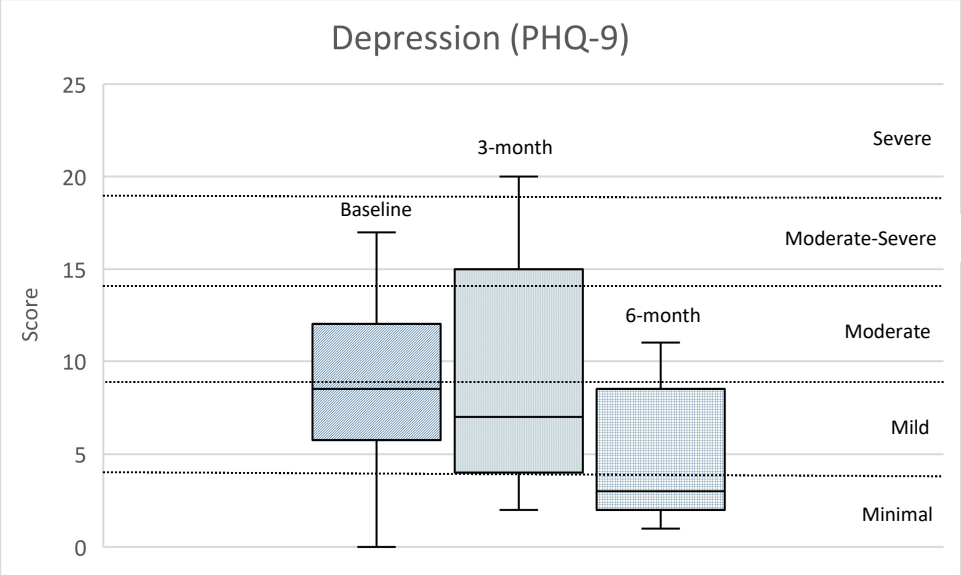
Wilcoxon signed-rank tests of HIT-6 scores at baseline, 3-months and 6-months did not show any significant changes in headache over time. Multivariate analyses revealed that headache severity was not predicted by IIH clinical features such as weight, waist circumference, CSF opening pressure, disease duration, visual acuity, RNFL thickness or HVF values, at baseline or 3-months. There were no relationships between headache and neuropsychological and ocular motor results at baseline or 3-months, according to multivariate analyses. Patient numbers were insufficient for multivariate analyses at 6-months (*n=5*).

4.3.2 Patient Health Questionnaire 9 (PHQ-9)

IIH patients exhibited a high prevalence of depression according to the PHQ-9 (Figure 4.3.2). In the PHQ-9, degrees of depression are categorised into minimal (score 0-4), mild (score 5-9), moderate (score 10-14), moderate-severe (score 15-19) and severe (score 20-27). At baseline according to PHQ-9 scores, 36.4% of IIH patients had mild depression, 27.3% had moderate depression and 18.3% had moderate-severe depression. As a cohort, IIH patients had a mean baseline PHQ-9 score of 8.9 (*SD=4.87*).

At 3-months, the IIH cohort had a mean PHQ-9 score of 9.3 (*SD=6.09*). Depression was reported by the majority of patients, with 30.8% scoring as experiencing mild depression, 15.4% as moderate, 7.7% as moderate-severe and 15.4% falling into the severe category. Of the 5 patients assessed at 6-months, 20% continued to report mild depression and 20% had moderate depression. Mean PHQ-9 score at 6-months was 4.8 (*SD=3.49*).

Figure 4.3.2. Patient Health Questionnaire 9 Scores



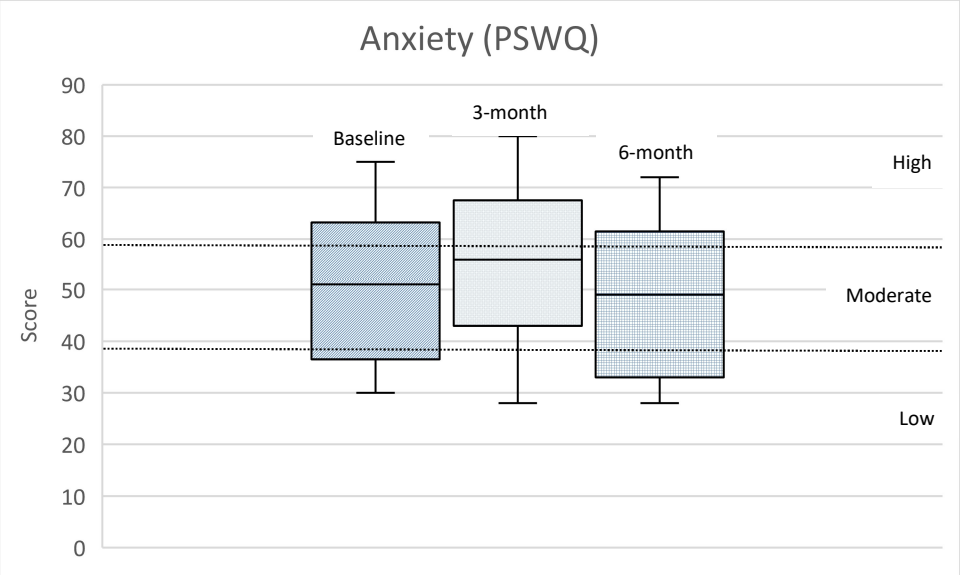
As a cohort, IIH patients had no significant changes in composite PHQ-9 scores at baseline, 3-months and 6-months, according to Wilcoxon signed-rank testing. Multivariate analyses showed that weight, waist circumference, CSF opening pressure, IIH disease duration, visual acuity, RNFL thickness and HVF values did not predict PHQ-9 scores at baseline or 3-months. Additionally, multivariate analyses ascertained that PHQ-9 scores did not predict significant neuropsychological or ocular motor results at baseline or 3-months. Patient numbers were insufficient for multivariate analyses at 6-months (*n=5*).

4.3.3 Penn State Worry Questionnaire

Self-reported anxiety was prominent in the IIH cohort based on responses in the PSWQ (Figure 4.3.3). The PSWQ categorises levels of anxiety into low worry (score 16-39), moderate worry (score 40-59) and high worry (score 60-80). At baseline, IIH patients had a mean PSWQ score of 51.1 (*SD=13.9*). This consisted of 27.3% of IIH patients scoring as experiencing low worry, 36.4% as moderate worry and 36.4% as high worry.

At 3-months, mean PSWQ score in the IIH cohort was 55.0 (*SD=14.7*), with 15.4% of patients scoring as low worry, 53.8% as moderate worry and 30.8% as high worry. Mean PSWQ score at 6-months was 47.7 (*SD=3.49*), with 40.0% of IIH patients scoring as low worry, 40.0% as moderate worry and 20.0% as high worry.

Figure 4.3.3. Penn State Worry Questionnaire Scores



Wilcoxon signed-rank testing did not demonstrate any significant changes in IIH cohort PSWQ scores at baseline, 3-months and 6-months. Multivariate analyses showed that clinical features such as weight, waist circumference, CSF opening pressure, IIH disease duration, visual acuity, RNFL thickness or HVF values did not predict PSWQ scores at baseline and 3-months. Further multivariate analyses found that PSWQ scores did not predict significant neuropsychological and ocular motor results at baseline and 3-months. Patient numbers at 6-months were insufficient for multivariate analyses (*n=5*).

4.3.4 Short Form 36 (SF-36)

For the SF-36, lower scores indicate worse quality of life. IIH patients reported worse quality of life in all areas of the SF-36 at all time-points, compared to results from an existing group of 1274 healthy control participants, all women, aged 25-34 [191] (Table 4.3.4).

Table 4.3.4. Short Form 36 Scores

	Physical	Physical limits	Emotional limits	Energy	Mental	Social	Pain	General
IIH Baseline								
Mean	**83.64**	**67.05**	**69.70**	**44.77**	**62.95**	**72.73**	**68.98**	**52.05**
SD	14.55	40.86	38.81	21.77	22.22	26.55	31.58	21.19
IIH 3-month								
Mean	**87.14**	**76.79**	**61.90**	**40.83**	**60.57**	**69.64**	**74.29**	**53.21**
SD	14.60	38.34	41.51	21.78	21.05	28.63	25.27	20.67
IIH 6-month								
Mean	**87.00**	**85.00**	**80.00**	**47.00**	**60.80**	**85.00**	**76.50**	**57.00**
SD	9.80	20.00	26.67	16.91	22.26	18.37	25.96	22.27
Controls[191]								
Mean (SD)	**92.9 (13.3)**	**86.9 (29.2)**	**80.6 (34.0)**	**58.3 (19.5)**	**71.6 (15.2)**	**87.1 (18.9)**	**82.1 (21.1)**	**77.3 (18.5)**

Wilcoxon signed-rank testing did not show any significant changes in SF-36 scores at baseline, 3-months or 6-months in the IIH cohort. This was the case for all SF-36 categories, which were analysed separately.

Multivariate analyses of baseline results demonstrated that less reported pain in the SF-36 was predicted by high CSF opening pressure (*f(df 8, 21)=1.674, B=3.40, p=.035*). Baseline SF-36 scores were not predicted by most clinical features including weight, waist circumference, IIH duration, visual acuity, RNFL thickness or HVF values, nor by significant neuropsychological or ocular motor results. However, worse headache in the HIT-6 questionnaire predicted more physical limitations (*f(df 3, 21)=5.32, B=-2.49, p=.005*) and more reported pain (*f(df 3, 21)=6.11, B=-1.68, p=.009*) in the SF-36 at baseline. Depression and anxiety did not predict any baseline SF-36 scores.

At 3-months, SF-36 scores were not predicted by any clinical features; CSF opening pressure was not repeated at this time-point. Significant neuropsychological and ocular motor results did not predict SF-36 scores at 3-months, nor did headache and depression. However, high anxiety levels predicted more physical limitations (*f(df 3, 12)=4.84, B=-1.17, p=.027*) and worse general health (*f(3, 12)=13.94, B=-1.01, p=.037*) in the SF-36 at 3-months. Patient numbers were insufficient for multivariate analyses at 6-months (*n=5*).

4.3.5 National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25)

Lower scores in the NEI-VFQ-25 indicate worse functioning. While IIH patients generally had sufficient vision to carry out activities of daily living, scores in the general health category of the NEI-VFQ-25 appeared particularly low at all time-points (Table 4.3.5).

Table 4.3.5. NEI-VFQ-25 Scores

	Health	Vision	Ocular Pain	Near Activity	Distance Activity	Social	Mental	Role Difficulty	Dependency	Driving	Colour vision	Peripheral vision
IIH Baseline Mean	**38.64**	**71.59**	**72.73**	**85.98**	**86.74**	**96.02**	**82.95**	**83.52**	**87.50**	**71.59**	**96.59**	**81.82**
IIH Baseline SD	19.55	20.36	20.17	17.48	17.53	10.91	21.00	22.10	14.16	35.94	11.42	21.56
IIH 3-month Mean	**39.29**	**73.21**	**78.57**	**89.88**	**91.07**	**98.21**	**88.39**	**92.86**	**89.29**	**77.98**	**98.21**	**94.64**
IIH 3-month SD	18.21	11.43	18.56	11.43	12.39	4.37	17.50	13.95	14.58	33.13	6.44	13.95
IIH 6-month Mean	**40.00**	**65.00**	**72.50**	**90.00**	**91.67**	**95.00**	**97.50**	**92.50**	**93.33**	**58.33**	**100.00**	**90.00**
IIH 6-month SD	20.00	25.50	18.37	8.16	7.45	10.00	3.06	10.00	6.24	36.51	0.00	20.00

Wilcoxon signed-rank testing demonstrated reported improvement in peripheral vision at 3-months compared to baseline (*Z=-2.121, p=.034*) in the IIH cohort, however no significant changes in other categories of the NEI-VFQ-25.

At baseline, multivariate analyses showed that better general health scores in the NEI-VFQ-25 were predicted by lower waist circumference (*f(df 8, 21)=2.71, B=-1.19, p=.031*) and lower HVF PSDdB values (*f(df8, 21)=2.71, B=-4.16, p=.027*). Significant neuropsychological results, headache severity and mood disturbance did not predict baseline NEI-VFQ-25 general health scores. Less errors in the block antisaccade task predicted better general health scores in the NEI-VFQ-25 (*f(df(5, 20)=1.30, B=-.829, p=.039*) at baseline, however other significant ocular motor results did not.

At 3-months, multivariate analyses demonstrated that NEI-VFQ-25 general health scores were not predicted by any clinical features, significant neuropsychological or ocular motor results, headache severity or anxiety. However, lower levels of depression predicted better NEI-VFQ-25 general health scores at 3-months (*f(df(3, 12)=5.38, B=-2.70, p=.037*). Patient numbers were insufficient for multivariate analyses at 6-months (*n=5*).

4.4 Attentional Control and Impulsiveness

4.4.1 Simon Task

While no group differences in latency were demonstrated in the Simon task (Table 4.4.1), the IIH cohort performed significantly more errors compared to controls on congruent-congruent (*U=75.5, p=.04*) and incongruent-incongruent (*U=45, p=.001*) trials at baseline, as determined

by Mann-Whitney U tests. There was also a trend of increased error rate in the IIH cohort with incongruent-congruent (*U=89, p=.12*) and congruent-incongruent trials (*U=85, p=.93*), but this did not reach statistical significance. High error rates in the IIH cohort resulted in many excluded trials and thus the Simon Effect could not be determined.

At 3-months, Mann Whitney U tests showed that IIH patients continued to perform more errors than controls on incongruent-incongruent trials (*U=33.5, p=.008*) but not congruent-congruent trials (*U=77, p=.742*). IIH patient numbers were limited at 6-months, however showed possible persistence of high error rates compared to controls on incongruent-incongruent trials (*U=11.5, p=.048*) and congruent-congruent trials (*U=4.5, p=.004*). However, when comparing results within the IIH group, Wilcoxon signed-rank tests showed no significant changes in Simon task latency or error rates at 3-months or 6-months compared to baseline.

Multivariate analyses showed that clinical features (including headache, depression, anxiety, weight, waist circumference, disease duration, CSF opening pressure, visual acuity, visual fields and RNFL thickness) did not predict congruent-congruent errors in the IIH cohort at baseline. However, increased incongruent-incongruent errors were predicted by shorter IIH duration (*f(11,20)=3.78, B=-6.39, p=.008*) and increased RNFL thickness (*f(11, 20)= 3.78, B=0.18, p=.03*) at baseline. Increased RNFL thickness continued to predict high incongruent-incongruent errors in the Simon task at 3-months (*f(9,13)=6.40, B=.394, p=.008*), while IIH duration did not (*f(9,13)=6.40, B=3.75, p=.16*). Patient numbers were insufficient for multivariate analyses at 6-months (*n=5*).

Table. 4.4.1 Simon Task means and standard deviations

	Measurement Latency (ms), Error (%)	**Controls (n=12)** Mean (SD)	**IIH Baseline (n=22)** Mean (SD)	**IIH 3-month (n=14)** Mean (SD)	**IIH 6-month (n=5)** Mean (SD)
Simon Task	Latency CC	505.61 (115.35)	446.10 (94.81)	459.94 (117.21)	417.71 (115.13)
	Latency CI	508.38 (95.39)	446.18 (108.17)	440.83 (89.29)	412.84 (120.10)
	Latency IC	494.31 (100.32)	446.96 (92.46)	446.66 (120.84)	431.15 (130.57)
	Latency II	489.67 (97.20)	441.68 (118.73)	430.56 (76.76)	420.98 (154.61)
	Error CC	**9.34 (8.01)***	**21.49 (15.81)***	13.64 (13.59)	**29.10 (15.24)***
	Error CI	14.08 (12.94)	23.70 (19.83)	18.11 (14.45)	24.29 (14.81)
	Error IC	11.61 (10.23)	23.70 (19.83)	18.11 (14.45)	24.29 (14.81)
	Error II	**7.60 (9.25)***	**24.33 (16.84)***	**23.53 (18.74)***	**23.52 (18.25)***

***Sig, p<.05 compared to controls**

CC = congruent-congruent, CI = congruent-incongruent, IC = incongruent-congruent, II = incongruent-incongruent.

4.4.2 Barratt Impulsiveness Scale (BIS-11)

Higher BIS-11 scores indicate higher levels of impulsiveness. Twelve IIH patients completed the BIS-11 questionnaire. Compared to responses from 1184 healthy female controls from an existing result database (*mean age 21.6, SD=5.3*)[192], IIH patients reported more impulsiveness in settings requiring self-control (Table 4.4.2). Multivariate analyses of BIS-11 self-control scores in the IIH cohort showed that high levels of impulsiveness did not predict weight, waist circumference, or neuropsychological and ocular motor inhibitory control results at baseline or 3-months. Patient numbers were insufficient for multivariate analyses at 6 months (*n=5*).

Table 4.4.2 BIS-11 results

	Attentional		Motor		Non-planning	
Patient	**Attention**	**Cognitive instability**	**Motor**	**Perseverance**	**Self-Control**	**Cognitive Complexity**
1	7	5	12	4	8	8
2	13	9	14	7	14	12
3	10	4	14	4	10	10
4	15	9	22	8	21	11
5	10	7	16	7	18	15
7	12	9	15	8	18	11
8	8	8	17	5	9	8
9	12	10	15	9	19	11
10	12	6	13	8	13	10
11	8	4	12	5	10	8
12	11	3	13	7	10	9
IIH Mean (SD)	10.7 (2.3)	6.7 (2.3)	14.8 (2.7)	6.5 (1.6)	13.64 (4.4)	10.27 (2.0)
Controls[192] Mean (SD)	10.4 (2.9)	6.3 (1.9)	15.0 (3.4)	6.8 (1.7)	12.0 (3.3)	11.6 (2.6)

4.5 Results Summary

Cognitive impairment was demonstrated in IIH patients using neuropsychological testing and ocular motor testing, which appeared to be persistent during the early course of the condition. A distinctive pattern of inhibitory control deficits related to altered visual-cognitive processing was evident on ocular motor tasks. Whether or not inhibitory control deficits on ocular motor testing translate to behavioural consequences require further investigation. Headache and mood disorders were prominent in the IIH cohort. While these co-morbidities were not associated with cognitive impairment, they appear to negatively impact certain areas of quality of life.

Chapter 5 Discussion

5.1 Overview of Thesis Aims

IIH can be a debilitating condition associated with high morbidity and serious consequences, such as permanent vision loss[86]. Its prevalence is increasing in accordance with rising rates of obesity[1, 25]. IIH typically affects young overweight women of childbearing age, who are in their prime of life. Comorbidities such as chronic headaches and mood disorders likely contributes to time off from work and in some cases, loss of employment[13]. It is necessary to explore other morbidities related to IIH that could worsen quality of life and place limitations on functional capacity. While it has been reported that cognitive impairments are present in IIH[4-8], the nature of these deficits and their relationships to common clinical features of IIH remain unclear. Both clinicians and patients are generally unaware of the associations between cognitive impairment and IIH. To provide comprehensive patient care, we need to increase our understanding of cognition in IIH, particularly in the context of the clinical features of the disorder.

My thesis aimed to evaluate patterns of cognitive impairment in IIH (Aim 1) and clarify if any deficits are related to particular clinical features of the disorder, or quality of life (Aim 2). Further, cognition was monitored during the early course of IIH, to determine if there are any changes over time (Aim 3). Table 5.1 summarises the key cognitive domains impaired in IIH.

Neuropsychological testing demonstrated widespread cognitive impairments in IIH patients and ocular motor testing revealed additional distinct impairments of inhibitory control, which were predicted by increased retinal nerve fibre layer (RNFL). There was significant attrition of the IIH cohort over time, in the context of the Covid-19 pandemic. However, widespread cognitive impairment appeared persistent at three and six months from IIH diagnosis according to neuropsychological testing. RNFL elevation, which was reflective of papilloedema severity in our cohort, was the only clinical feature observed that improved over time. Interestingly, ocular motor inhibitory control deficits also appeared to resolve over time as papilloedema improved, while neuropsychological impairments remained persistent.

Table 5.1. Key cognitive impairments in IIH

Cognitive Domain	Key Results (IIH vs. Controls)	Conclusions
Verbal learning	Worse CVLT score at baseline (not repeated longitudinally due to test relearning effect) CVLT score not predicted by IIH clinical features	Impaired verbal learning[135] present at IIH diagnosis Deficits independent of IIH clinical features
Working memory	Worse Digit Span scores at baseline, 3 and 6 months Worse CVLT score Digit Span and CVLT scores not predicted by IIH clinical features More antisaccade errors on the Switch task in repeat trials at baseline and 3 months More prolonged antisaccade latencies on the Switch task in switch trials at baseline only RNFL elevation predicted more errors in the Switch task at baseline and 3 months in the IIH cohort	Impaired working memory evident in multiple cognitive tests[132, 135, 137]. Working memory deficits persisted over time in neuropsychological testing, independent of IIH clinical features Ocular motor deficits improved over time, related to improvement in raised intracranial pressure represented by reduction in RNFL elevation

Information processing	Worse scores in the SDMT at baseline, 3 and 6 months SDMT scores not predicted by IIH clinical features	Impaired information processing speed[136] at diagnosis and during early course of IIH Deficits independent of IIH clinical features
Inhibitory control	Worse Stroop test scores at baseline, 3 and 6 months Stroop test scores not predicted by IIH clinical features More block antisaccade errors at baseline and 3 months RNFL elevation predicted more antisaccade block errors at baseline in IIH cohort	Impaired inhibitory control[138, 140] present at baseline and during early course of IIH Inhibitory control deficits persisted over time in neuropsychological testing, independent of IIH clinical features Ocular motor deficits improved over time, related to improvement in raised intracranial pressure represented by reduction in RNFL elevation

Cognitive flexibility	More errors in the Simon task at baseline only RNFL elevation predicted more Simon task errors at baseline and 3 months in IIH cohort	Impaired cognitive flexibility[180] present at IIH diagnosis, related to RNFL elevation
Attention	More errors in the Switch and Simon tasks that trended towards improvement over time RNFL elevation predicted more errors in the Switch and Simon tasks in the IIH cohort	Impaired attention[181, 53] present at diagnosis and early course of IIH Deficits partially improved over time, related to improvement in RNFL elevation

5.2 Explanation of Findings

5.2.1 Clinical Characteristics

All patients included in our study were of typical IIH phenotype, which is consistent with the observation that increased weight and female sex are key risk factors. Patients generally had significantly high waist circumferences and were overweight in our IIH cohort. Central adiposity is seen in both IIH and simple obesity. Truncal fat mass has been demonstrated to correlate with CSF opening pressure in IIH patients and weight loss, predominantly from the truncal region rather than the limbs, resulted in a significant reduction of IIH disease activity[193]. Neither weight nor body mass index (BMI) in isolation are indicative of body composition, whereas waist circumference could be the best simple indicator of central adiposity[194]. As a group, IIH participants did not have any significant changes in weight over time. Some participants were able to lose weight, however most found weight loss challenging to achieve.

This reflects the difficulties surrounding sustained weight loss in developed countries[195], which remains a significant issue in IIH management.

Almost all IIH participants reported headache and some had intermittent visual symptoms. The most common symptom in IIH is headache[49] and thus it was expected that headache would be prominent in our cohort. However, headache did not predict neuropsychological or ocular motor performance in our study (discussed further in section 5.2.4). Patients with fulminant IIH were excluded from our study, given the necessity for prompt interventions to preserve vision and associated logistical barriers to cognitive testing. Neuro-ophthalmic examination revealed mild to moderate papilloedema in the IIH cohort and the severity of optic nerve head swelling was quantitatively measured by RNFL thickness. RNFL thickness, measured in micrometres, is a sensitive tool for monitoring IIH patients and assessing responses to treatment[196]. RNFL thickness and other parameters, such as the retinal pigment epithelium and ganglion cell layer can be evaluated in detail using OCT scanning. OCT is a promising non-invasive method of evaluating ICP changes and has an evolving role in the diagnosis and management of IIH[55]. Humphrey visual fields and visual acuity were generally preserved in out IIH cohort, consistent with mild to moderate disease severity.

IIH patients in our study were recruited soon after diagnosis to capture cognitive impairment at baseline, so that any changes over time could be observed. IIH was diagnosed after secondary causes of raised ICP were excluded, according to standardised criteria[10]. Neuroimaging revealed typical features of raised ICP in almost all IIH patients; transverse sinus stenosis was the most common finding in our cohort, which has been well described in existing literature[197]. Very high CSF opening pressures may correlate with increased IIH severity and poor responses to treatment[198]. IIH patients in our study had elevated CSF opening pressures, however these readings were not excessively high. Clinically, included patients had mild to moderate IIH and objectively responded to medical therapy.

A useful test for facilitating IIH diagnosis and monitoring disease activity is OCT scanning[199]. RNFL thickness was the only IIH clinical feature that changed significantly and reduced over time, which signified improving optic disc swelling. Interestingly, we found that increased RNFL thickness appeared to predict poor ocular motor performance on tests requiring inhibitory control. As RNFL thickness decreased over time, ocular motor inhibitory control deficits partially resolved (discussed in section 5.2.3). Reductions in RNFL thickness usually

indicates improvement in papilloedema in IIH, however caution should be taken in cases where there is ganglion cell layer loss, as in these cases a reduction in RNFL thickness could reflect optic nerve atrophy[200]. IIH patients included in our study did not have significant ganglion cell layer loss and therefore, reductions in RNFL thickness represented improving papilloedema.

Unlike RNFL thickness, the other clinical features monitored in our study (including headache, anxiety, depression, weight and waist circumference) remained statistically similar at three and six months following IIH diagnosis. Our results are consistent with other studies that reported prominent headaches, and mood disturbances in chronic illness[201]. In particular, chronic daily headaches can be problematic in IIH and worsens perceived quality of life[49]. Headaches in IIH are challenging to manage and are often multifactorial[66]. It remains unclear why some patients experience severe headaches in the absence of conventionally elevated ICP, although central sensitisation may be involved[52].

5.2.2 Neuropsychological Assessments

Multiple cognitive domains are impaired in IIH, according to neuropsychological testing results from our study. This was consistent with previous studies that reported impairment of multiple cognitive domains on neurocognitive testing[4-8]. Additionally, ocular motor testing highlighted unique inhibitory control deficits (discussed further in section 5.2.3). IIH patients in our study performed worse compared to controls on all of the neuropsychological measures, at all time-points (baseline, +3, +6 months from diagnosis). Specifically, impaired inhibition of cognitive interference was seen on the Stroop test[138], reduced cognitive processing speed was evident on the SDMT[136] and reduced working memory was revealed on the Digit Span and CVLT[135, 137].

Our results demonstrate that cognitive changes in IIH appear to fall under the general category of executive control dysfunction. This is supported by work done by Yri and colleagues where decreased processing speed and complex attention were the main findings. Executive control refers to a collection of mental processes required for directing attention and concentration[202]. These cognitive functions require effort and are essential for achieving purposeful goals, as opposed to acting impulsively based on intuition only, which can be counter-productive in certain circumstances. Executive control is proposed to consist of three core functions; inhibitory control, cognitive flexibility and working memory[202]. These functions are related to each other and also to cognitive processes such as attention, processing speed, learning and

memory[203]. In a case series of ten IIH patients by Kharkar et al, learning and memory were significantly impaired[8]. Additionally, IIH patients were found to have particular impairments of attention and visual spatial processing, detected using a computerised cognitive battery, in a study by Zur et al[6]. These findings could be related to executive control dysfunction, which are largely mediated by frontostriatal circuits[202].

Neuroanatomically, frontostriatal circuits encompasses the frontal cortex, thalamus and basal ganglia[178]. Within this widespread network, cognitive functions are predominantly mediated by the dorsolateral prefrontal, medial orbitofrontal and lateral orbitofrontal circuits[179]. The dorsolateral prefrontal circuit is primarily responsible for executive functions and facilitates cognitive processes such as inhibitory control, processing speed and working memory[180], which were impaired in our IIH cohort. Alterations in frontostriatal circuitry are observed on functional MRI (fMRI) and on neuropsychological testing involving states of addiction, such as smoking[204]. Similarly, over-eating has been conceptualised by some as a form of psychological and physical dependence on high-fat and high-sugar foods[99]. Excessive weight increases the risk of IIH, while modest amounts of weight loss can lead to disease resolution[1]. Thus, potential frontostriatal dysfunction in IIH may have clinical implications associated with over-eating in some patients, as well as contributing to cognitive impairment.

There is a clear, yet complex relationship between IIH and obesity. Interestingly, results from neuropsychological testing in our IIH cohort were not predicted by waist circumference. Similarly, Yri et al reported that IIH patient body mass index (BMI) were unrelated to the severity of cognitive impairment observed[167]. It is therefore plausible that cognition may be impacted by the presence, rather than magnitude of, obesity in IIH. Obesity in itself may impact striatal networks[181]. Decreased frontostriatal responses to food, yet heightened responses to food cues, have been described on fMRI studies of obese individuals[98]. Increased connectivity between regions of the brain involved in cues and reward signalling could result in behaviours to satisfy cravings[205, 206]. Obesity is associated with impairments in executive functioning, such as inhibitory control and decision-making, which may add to the challenges of sustained weight loss[207]. Including weight-matched controls in future IIH studies will help to clarify how much obesity contributes to cognitive impairment.

A major feature of IIH is its tendency to affect young overweight women. This has generated increasing interest in the role of cytokines and hormones in IIH. In particular, a modulator of

glucocorticoids called 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) may have an important role in IIH pathogenesis by altering CSF production[2]. At a cellular level, 11β-HSD1 regulates the availability of active cortisol and is most active in adipose and hepatic tissue[208]. Features of metabolic syndrome (visceral obesity, dyslipidaemia and glucose intolerance) are observed in mice that overexpress 11β-HSD1[209].

The link between IIH pathophysiology, obesity and cognitive function is further complicated by work that demonstrate the metabolic activity in adipose tissue. A wide variety of adipokines and inflammatory cytokines[107] are produced, supporting the theory that IIH could be associated with a generalised pro-inflammatory state[2, 31, 210]. Neuroinflammation may disrupt the normal functioning of widespread frontostriatal networks, which could be compounded by mechanical strain from raised intracranial pressure[211], and result in cognitive impairment.

In our IIH cohort, cognitive impairments were evident on neuropsychological testing at diagnosis and were persistent at three and six months, compared to controls. There were no significant changes in the severity of cognitive impairment noted over time. This is in contrast to a study performed by Sorensen et al in 1986, which reported possible improvement in cognition with treatment of IIH. Sorensen's study included five IIH patients, who were re-tested one year from diagnosis[5]. Three of these patients had CSF opening pressures below 25 cm of water (8, 18, 20cm of water) and it is unclear whether or not they would meet the contemporary diagnostic criteria for IIH. It is possible that cognitive impairments in IIH resolve over longer periods of observation, since our study only had prospective data at three months and a limited dataset at six months. Our results demonstrate that cognitive impairments appear to be persistent during the early course of IIH. Similarly, persistent cognitive deficits were present in Yri et al's IIH cohort at three months from baseline assessment[4].

Common clinical features of IIH (headache, anxiety, depression, weight, waist circumference, CSF opening pressure, disease duration, visual acuity, RNFL thickness and HVF values) did not predict performance on neuropsychological testing in our study. With the exception of Yri et al's study, previous research has not comprehensively evaluated whether or not clinical features of IIH can impact cognition. Yri et al did not find correlations between cognitive impairment and baseline ICP, depression and chronic headache. It is surprising that we also did not find any correlations between cognitive impairment and anxiety, depression, or headache in IIH. Increased anxiety levels may be related to reduced working memory[212],

although results have been mixed in previous studies, particularly if acute stressors were involved[213]. Depression can cause 'pseudodementia' in an older population[112], however it is unclear if these findings can be translated to a younger cohort, such as IIH patients. Impairment of memory, attention and information processing speed has been recognised in migraine[214], but may not be present in other headache syndromes, such as tension-type or cluster headache[215]. While there is overlap between headaches in IIH and migraines, it is possible that chronic headaches in IIH do not correlate directly with cognitive impairment.

We explored differences in cognition based on medication exposure but lacked the power to do a formal subgroup analysis. Although medications used in IIH may affect cognition[71, 76], IIH itself seems to produce multidomain cognitive impairment, based on a study by Yri and colleagues, during which IIH medications were withheld at the time of cognitive testing[4].

None of the clinical features measured in our study changed significantly over time, except for RNFL thickness, which reduced and reflected improving papilloedema in out IIH cohort. While there were no clear relationships between RNFL thickness and neuropsychological results, RNFL elevation was associated with more ocular motor errors in the IIH cohort. This highlighted how ocular motor and neuropsychological tasks assess cognition differently, which will be discussed in the following section (5.2.3 Ocular Motor Assessments). While neuropsychological testing showed widespread cognitive impairments, specialised assessment of visual-cognitive processing using ocular motor testing detected distinct inhibitory control deficits, which seemed to correlate with RNFL elevation.

5.2.3 Ocular Motor Assessments

IIH patients performed significantly worse than controls on all tests requiring antisaccades (AS), while prosaccades (PS) remained intact. This demonstrated a distinct pattern of inhibitory control deficits[140]. Inhibitory control is a key executive function, mediated by the frontostriatal network[202]. Ocular motor inhibitory control deficits are present in neurological conditions known to involve the frontostriatal network, such as Parkinson's Disease[216]. Further research is required to evaluate if obesity, independent of IIH, is associated with worse rates of AS error. It is difficult to determine whether the pathophysiological mechanisms of obesity could result in inhibitory control deficits, or if individuals with pre-existing inhibitory control deficits are more likely to be obese, or both. Once inhibitory control deficits are present, regardless of its primary cause, individuals may find it more difficult to control impulsive behaviour such as

overeating[217]. Given the links between obesity and IIH[1], inhibitory control deficits detected by ocular motor testing may have behavioural and clinical consequences.

IIH participants in our study appeared to have particular impairments of executive functions, mediated by the frontostriatal network, which may have behavioural implications[202]. Cognitive impairment appears to be present in IIH despite clinically intact afferent and efferent visual processing pathways. Ocular motor testing measures three levels of visual processing, which can be classified into: (1) sensory afferent, (2) cognitive and (3) efferent[171]. In this systematic ocular motor model, (1) sensory afferent refers to visual inputs received at the retina transmitted through the optic nerve and related pathways to the visual cortex. (2) Cognitive, incorporates visual information with intentional goal-oriented behaviour, which is dependent on widespread cortical connections within the frontostriatal network. Outcomes of (1) sensory afferent and (2) cognitive integration is (3) efferent action; such as an eye movement. Therefore, the generation of a correct saccade requires all three levels of visual-cognitive processing to be intact[132].

IIH patients performed prosaccades normally compared to controls in all tasks, which implies that visual processing levels (1) sensory afferent and (3) efferent pathways are intact, regardless of task complexity. However, it was clear that IIH patients found it difficult to perform even simple AS tasks correctly. AS tasks add a degree of cognitive loading and assesses the more widely distributed (2) cognitive network[186]. We can therefore localise the basis of cognitive impairment in IIH to possible dysfunction of the widespread frontostriatal cortical networks. This is consistent with findings from both neuropsychological testing and ocular motor testing in our study, which detected impairments largely related to executive control. White matter tracts of the frontostriatal network may be vulnerable to factors involved in IIH pathophysiology. It has been observed that IIH patients have significant changes of periventricular white matter microstructures seen on diffusion tensor imaging, which may result from tissue compression, compared to controls with normal CSF pressure[218].

In addition, an evolving area of research in IIH pertains to elevated levels of pro-inflammatory cytokines, chemokines and adipokines in CSF and serum[34]. It has been reported that cytokines such as interleukin 2 and 7 are elevated in the CSF of IIH patients, compared to controls[219]. Pro-inflammatory pathways in both CSF and serum seem to be upregulated in IIH, according to studies using micro-ribonucleic acid (miRNA) analyses[220]. As mentioned in the previous section, chronic inflammation is linked to cognitive impairment in Alzheimer's disease and

vascular dementia, possibly from direct brain tissue damage[221]. Further, elevated serum inflammatory markers in mid-life is correlated with cognitive decline in later life[222]. It is plausible that chronic inflammation and increased CSF pressure could result in dysfunction of the widespread frontostriatal networks, forming the basis of cognitive impairment in IIH.

While neuropsychological testing and ocular motor testing both showed significant executive control impairments in our study, it was surprising that there were no correlations between the two testing modalities. This was particularly the case with the Stroop Colour and Word test (SCWT) and the AS task, since both assess inhibitory control[169, 223]. While both tests assess inhibitory control, they do so in different ways. The SCWT is timed differently to the AS task and unlike the AS task, it does not record error as a binary correct/incorrect variable[138]. There have been correlations found between prolonged ocular motor saccade latencies and impaired neuropsychological results in other neurological conditions, such as multiple sclerosis[224]. This relationship may have been potentially obscured in our study by high error rates, since a large number of trials were subsequently excluded from latency analyses.

Interestingly, we found that high AS error rates in both simple and complex ocular motor tasks appeared to be predicted by increased RNFL thickness. Other clinical features of IIH, such as headache, mood disorders, weight, waist circumference, CSF opening pressure, disease duration, visual acuity and HVF values did not predict any significant ocular motor results. Increased RNFL thickness quantified increased optic nerve head swelling in our IIH cohort, which reflected worse papilloedema[64]. While mild to moderate papilloedema did not produce overt clinical deficits in visual processing, it seemed to result in subclinical visual-cognitive processing impairments that manifested as poor performance in AS tasks. RNFL thickness was not associated with any neuropsychological results, yet predicted high AS error rates. This implied that unique cognitive impairments related to RNFL elevation may only be evident on specialised testing methods, such as ocular motor tasks. Ocular motor AS errors partially resolved at three and six months after IIH diagnosis, in the context of RNFL thickness decreasing significantly over time. While none of the other IIH clinical features changed significantly over time; it is known that refractory headaches and mood disorders can be particularly challenging to manage[66, 225].

5.2.4 Headache and Mood Questionnaires

More than three-quarters of our IIH cohort reported prominent headaches at baseline, according to HIT-6 questionnaire responses. Significant neuropsychological testing and ocular motor results were unrelated to headache severity. Headaches remained prominent at three- and six-months after IIH diagnosis and were not predicted by other clinical characteristics at any time-point. Chronic headaches are common in IIH and is a major morbidity, affecting up to 90% of patients in some studies[226, 227]. Additionally, headaches are strongly correlated with poor perceived quality of life in IIH[49]. Headaches in IIH were previously considered to be primarily related to raised ICP. However, in the IIH treatment trial, no correlations were found between headache disability and CSF opening pressure[52]. The most common headache phenotype in IIH is now understood to be migrainous[43].

Migraine headaches have been associated with cognitive impairment during attacks, although it is unclear whether or not cognitive changes are also present between migraine episodes[215]. Cognitive domains affected in migraine are broad, including executive functioning, attention, processing speed, memory and verbal skills[228, 229]. We did not find any associations between headache and cognitive impairment on neuropsychological testing or ocular motor testing in IIH. Similarly in Yri et al's study, cognitive impairment was present in IIH patients after adjustment for headache, which persisted at three months despite improvements in headache[4]. Cognitive impairment has not been described in other headache syndromes such as cluster and tension-type headaches[215]. There have been no trials evaluating optimal treatment strategies for IIH-related headaches. While many IIH patients report headaches with migrainous features and are managed accordingly[43], IIH-related headaches may have distinct underlying mechanisms. Co-existing conditions such as depression and anxiety may also contribute to cognitive impairment in this cohort[230].

Depression and anxiety were highly prevalent in our IIH cohort at all time-points. Most patients fell into the categories of mild-moderate depression in the PHQ-9 and low-moderate levels of anxiety in the PSWQ. Mood disturbances appeared unrelated to IIH clinical characteristics or significant neuropsychological testing and ocular motor results. In a survey of 28 women with IIH, rates of depression were found to be higher in comparison to 30 weight- and age-matched women without IIH and 30 age-matched women of normal weight[111]. Therefore, independent from the effects of obesity, IIH likely increases the risk of mood disorders. Compared to the general population, mood disorders may be up to sevenfold more common in IIH patients and

worsen subjective prognostic outcomes[225]. It has been hypothesised that pro-inflammatory cytokines may propagate major depressive disorder by causing neuroinflammation, particularly of the hippocampus[118]. While headaches are associated with mood disorders in migraineurs[231], we did not find any relationships between headaches and mood disorders in our study. This suggests that mood disorders in IIH are not primarily related to headache.

Cognitive impairment is common in individuals diagnosed with depression and anxiety[112, 113] and both conditions may result in executive function deficits[114-116]. The relationships between mood disorders and cognition are complex and may be synergistic; for example, depression may result in cognitive impairment, however cognitive impairment may also cause depression. Given the high prevalence of depression and anxiety in IIH and the potential relationships with cognitive impairment, it was surprising that mood disorders did not predict performance on neuropsychological testing and ocular motor tasks in our study. Subgroup analysis within the IIH cohort in Yri et al's study also did not demonstrate any differences in cognitive performance, when comparing results from patients with and without depression. IIH patients are typically younger than those with mild cognitive impairment and co-existing mood disorders[232]. IIH patients included in our study may have been experiencing symptoms of depression and anxiety related to acute stressors, which could explain why there were no correlations between self-reported mood disorders and cognitive testing results. However, IIH patients with higher levels of depression and anxiety had worse perceived quality of life according to questionnaire responses in our study.

5.2.5 Quality of Life Questionnaires

IIH patients reported persistently worse quality of life compared to controls, in all sections of the SF-36 at all time-points. Poor quality of life was also reflected in the general health section of the NEI-VFQ. These questionnaires were important to include in our study, since cognitive impairments are associated with worse quality of life in a range of neurological conditions[233]. Poor performance on neuropsychological testing did not predict quality of life responses in our IIH cohort. However, on ocular motor testing, high antisaccade errors predicted worse general health scores in the NEI-VFQ-25. High rates of antisaccade error may reflect poor inhibitory control, which is a key executive function that could translate to maladaptive behaviours[186]. People with robust executive functions generally enjoy a better quality of life[202]. Specifically, inhibitory control enables self-regulation, which plays a crucial role in successful relationships,

learning and employment[234]. Since these important areas of life require inhibitory control, it is evident that impairments could result in decreased quality of life.

Other clinical features that predicted worse NEI-VFQ-25 general health scores were increased waist circumference and increased HVF pattern standard deviation values. This is consistent with existing literature that correlated high waist circumference with poorer quality of life in adults of all-ages and in the setting of chronic disease[235-237]. Pattern standard deviations seen on HVF testing may represent focal visual field deficits, which could have been a consequence of relatively more severe IIH in our cohort[238]. Patients with visual field deficits are considered to have moderate to severe IIH and require more frequent clinical reviews[66]. Clinical features associated with increased IIH severity may subsequently result in worse quality of life.

It was interesting to observe that higher CSF opening pressures predicted less reported pain on the SF-36 in our IIH cohort. This finding appeared counterintuitive, however was similar to a previous study that showed higher initial CSF opening pressures paradoxically decreased the risk of chronic headaches in IIH[50]. It is widely acknowledged that headaches in IIH are often multifactorial and not directly related to raised ICP[43]. Papilloedema was not correlated with worse headaches or quality of life in our IIH cohort. Patients included in our study had mild to moderate papilloedema, which may not be severe enough to directly impact perceived quality of life. In addition, it has been reported that chronic headaches can be problematic in cases of IIH without papilloedema and that patients can experience disabling chronic headaches despite having normal ICP[66, 239]. As expected, IIH patients with worse headaches according to HIT-6 scores reported worse pain and physical limitations on the SF-36.

IIH patients with higher levels of anxiety according to the PSWQ were more likely to report worse physical limitations and general health on the SF-36 at 3-months from diagnosis, but not at baseline assessment. Anxiety levels increased (although not statistically significantly) from baseline to 3-months, which may have negatively impacted quality of life. Similarly, higher depression levels predicted worse NEI-VFQ-25 general health scores at 3-months. Depression and anxiety are associated with worse quality of life and these relationships may be even more prominent in cohorts with clinically diagnosed mood disorders[111, 240]. There were no significant changes in the any of the SF-36 or NEI-VFQ-25 categories over time, with the exception of peripheral vision, which improved on the NEI-VFQ-25 at 3-months compared to baseline.

While IIH patients were able to carry out most activities of daily living, responses from both the SF-36 and NEI-VFQ-25 indicated that perceived quality of life was significantly reduced. Decreased quality of life seemed to be persistent despite objective improvements in IIH disease activity based on neuro-ophthalmic findings. IIH co-morbidities such as headache and mood disorders, appeared particularly influential on perceived quality of life. Additionally, worse perceived general health may be associated with inhibitory control deficits detected on ocular motor testing. The potential behavioural implications of impaired cognitive functions related to inhibitory control will be discussed in the next section (5.2.6).

5.2.6 Attentional Control and Impulsiveness

Decreased attention span is correlated with increased impulsivity, which may have behavioural consequences[241]. Attention was primarily assessed in the IIH cohort by ocular motor testing; namely, the Simon and switch tasks[150, 242]. Results from the switch task were presented in Chapter 3 (Manuscript) and previously discussed in section 5.2.3. (Ocular Motor Assessments). To avoid duplication, the Simon task was not included in Chapter 3 (Manuscript). This section discusses results obtained from the Simon task and also the Barratt Impulsiveness Scale (BIS-11).

IIH patients performed significantly more errors on the Simon task compared to controls, on both congruent and incongruent trial types. Usually, individuals find incongruent trials more difficult than congruent trials[141]. Difficulty performing both trial types accurately may be due to impairments in attention and related functions such as cognitive flexibility[243]. Previous studies have also detected attentional deficits in IIH patients using neuropsychological testing[4, 6]. Difficulties performing the Simon task, particularly when antisaccades were required, further highlighted attentional and inhibitory control deficits in IIH patients[96]. High error rates were persistent in the Simon task at 3-months in the IIH cohort. This reflected ongoing impairments of core executive functions such as attention, inhibitory control and cognitive flexibility[202]. As previously discussed (in section 5.2.2 Neuropsychological Assessments and 5.2.3 Ocular Motor Assessments), executive functions are facilitated by widespread frontostriatal pathways and may be vulnerable to mechanisms involved in the pathophysiology of IIH.

Errors in the Simon task were not predicted by most IIH clinical features. However, increased incongruent trial errors were predicted by shorter IIH duration and increased RNFL thickness at baseline. RNFL thickness was the only IIH clinical feature that significantly changed over

time in the IIH cohort. Reductions in RNFL thickness over time represented responses to IIH therapy and improving papilloedema[86]. At baseline, when patients were recently diagnosed with IIH, RNFL thickness were at its highest values. It was interesting to observe that RNFL elevation predicted more errors in the Simon task, as well as more errors in simple antisaccade ocular motor tasks[186]. When considering the three-tier ocular motor model of visual-cognitive processing, this refers to particular deficits of level 2; cognitive integration (detailed in section 5.2.3 Ocular Motor Assessments)[171]. Despite significant improvements in RNFL values, RNFL elevation continued to predict high rates of incongruent trial errors at 3-months in the complex Simon task, indicating persistent attentional impairments with increased cognitive loading. Persistent deficits were also observed in simple ocular motor tasks that specifically assessed inhibitory control at 3-months in the IIH cohort, although there were partial improvements compared to baseline.

Given the striking findings of attentional and inhibitory control impairments in the IIH cohort, we evaluated levels of impulsiveness using the BIS-11 questionnaire as an additional test[192]. This was an important outcome to assess further, since high levels of impulsiveness may lead to maladaptive behaviours such as overeating and substance dependence[244, 245]. IIH patients reported more impulsiveness than controls in the self-control category of the BIS-11[192]. Low levels of self-control may lead to obesity and obesity is a major risk factor for IIH. However, BIS-11 self-control scores did not predict weight or waist circumference in our IIH cohort at any time-point. Limited participant numbers may have blunted any significant relationships between BIS-11 scores and IIH clinical features in our study. BIS-11 scores also did not predict any significant neuropsychological and ocular motor results at any time point. This was somewhat surprising, given the pattern of inhibitory control deficits in the IIH cohort. It has been observed that self-reported measures of self-control often do not correlate with tasks requiring inhibition, which raises the possibility that questionnaires and tests of inhibition evaluate different aspects of self-control[246]. This could explain why higher levels of self-reported impulsivity in our IIH cohort were unrelated to any clinical features or cognitive impairments.

5.2.7 Summary

In summary, cognitive impairments are present in IIH (Aim 1), independent from most clinical features. Neuropsychological testing detected impairment of widespread cognitive domains in IIH that were not predicted by any clinical features. However, ocular motor testing revealed a

unique pattern of visual-cognitive processing deficits that were associated with papilloedema severity, which may negatively impact self-perceived general health and quality of life (Aim 2). Cognitive impairments seen on neuropsychological testing persisted at three and six months from baseline testing in the IIH cohort, while ocular motor deficits partially resolved over time as papilloedema improved (Aim 3).

It was interesting that cognitive impairments in our IIH cohort appeared to be largely unrelated to most clinical features. Included IIH patients has similar clinical characteristics and disease severity. A larger cohort, with more variance in clinical features, may reveal more relationships to cognitive testing results. The only IIH clinical feature related to cognitive testing results was RNFL elevation, which provided a quantitative assessment of papilloedema in our cohort[64]. IIH patients with worse papilloedema performed worse on ocular motor tasks with increased cognitive loading. Ocular motor testing provides a specialised assessment of visual-cognitive processing, in contrast to neuropsychological testing. Cognitive impairments remained persistent on neuropsychological testing for up to six months from IIH diagnosis, despite improvements in papilloedema and some ocular motor results. This highlighted the importance of monitoring cognition despite improving clinical parameters such as papilloedema in IIH.

Cognitive impairment is linked to poor quality of life in other neurological conditions such as multiple sclerosis and has not been previously characterised in IIH[247]. IIH patients in our study had mild to moderate disease with no significant visual impairments, yet reported reduced quality of life. Poor quality of life was more likely if patients had co-morbidities of chronic headaches and mood disturbance. Additionally, worse inhibitory control deficits on ocular motor testing appeared to negatively impact perceptions of general health. Potential links between inhibitory control deficits and quality of life warrant further investigation, since there may be behavioural implications[248]. Impaired inhibitory control and attention could theoretically relate to increased impulsivity[249]; however, this was not observed in our IIH cohort. Cognitive impairments in IIH appear to be multi-faceted and independent from most clinical features or personality traits of increased impulsivity, although these findings require further observation in a larger cohort of patients. Comprehensive IIH management should include longitudinal monitoring of cognition, regardless of clinical features and co-morbidities.

5.3 Clinical Significance

Our results support the inclusion of cognitive monitoring in the comprehensive management of IIH patients. Unrecognised cognitive impairment is associated with a range of consequences, which will be discussed in section 5.3.1. Subsequently, the importance of raising awareness will be outlined in section 5.3.2.

5.3.1 Consequences of Cognitive Impairment

Cognitive impairments in IIH appear to be widespread and include major facets of executive functioning, such as working memory, cognitive flexibility and inhibitory control[202]. These core cognitive domains are required for related processes such as effective verbal learning, information processing and attention, which were also impaired in our IIH cohort[250].

Impaired executive functioning may result in reduced logical reasoning, increased stress and difficulties with emotional regulation[251]. Treatment non-adherence can be problematic in IIH management despite the risks of uncontrolled disease. Reduced capacity for logical reasoning may result in counter-productive behaviours[252], particularly if patients do not fully understand the consequences of treatment non-adherence. In addition, weight loss is often advised as part of IIH management, however can be particularly challenging in the context of increased stress and emotional lability[253]. Both treatment adherence and weight management are important in IIH and rely on effective executive functioning.

Related cognitive processes that can be negatively impacted by executive functioning deficits include verbal learning, information processing and attention[250]. These cognitive processes are vital for productivity and impairments may result in reduced work capacity[254]. While most IIH patients in our study did not report any major employment issues, other studies have described loss of income related to IIH[13]. Employment difficulties due to cognitive impairment and IIH co-morbidities such as headache and mood disorders may be more evident in a larger cohort of patients. Additionally, those with severe vision-threatening IIH may experience employment loss, however were excluded from our study due to barriers to cognitive testing. Cognitive rehabilitation and employment support may benefit some IIH patients (discussed in section 5.4.3 Management). Impaired executive functions and related cognitive processes in our IIH cohort were persistent for at least six months from diagnosis, which highlights the importance of cognitive monitoring in management.

5.3.2 Raising Awareness

Current IIH consensus management guidelines acknowledge that cognitive dysfunction may be present and that medications, particularly topiramate, may exacerbate cognitive deficits[66]. It is likely that many clinicians, including neurologists, are unaware of the potential effects of IIH on cognition since research has been limited in this area. In practice, cognitive monitoring is not yet recommended as part of routine IIH patient care. Our study adds to the evidence base of cognitive impairment in IIH and demonstrates that neuropsychological testing deficits may be persistent, existing separately from most clinical features. Further research would be useful to ascertain how much medications such as topiramate contributes to cognitive impairment in IIH (discussed in section 5.4.1). Patients may not disclose that they have cognitive issues if they do not recognise that their symptoms could be related to IIH. As we increase our understanding of IIH and cognition, both clinicians and patients will become more aware of impairments so that they can be managed.

Cognitive impairment negatively impacts quality of life in other neurological conditions, such as multiple sclerosis (MS), Parkinson's disease and epilepsy[247, 255, 256]. IIH is commonly encountered in neurological clinics and is increasing in prevalence[257], however its relationships with cognitive impairment is likely under-recognised. Publishing research, clinical teaching, patient education and support groups are some methods of increasing awareness. Increasing awareness enables necessary changes in patient management. For example, raising awareness of cognitive impairment in MS has led to research initiatives on how computerised cognitive testing batteries can be implemented clinically[258, 259]. Increased awareness of how IIH impacts cognition will encourage further research on how impairments can be monitored and addressed, leading to more comprehensive patient care.

5.3.3 Patient Care

Clinical features such as RNFL thickness are one of the key measures of treatment response in IIH. Increased RNFL thickness in IIH patients typically reflects increased papilloedema and optic disc swelling[64]. In the absence of significant optic nerve atrophy, such as in our IIH cohort, reductions in RNFL thickness correlates with improving papilloedema[63]. However, our study demonstrated persistent cognitive impairments in IIH patients on neuropsychological testing, despite improvements in papilloedema. Clinically, cognition should be monitored in IIH so that affected patients have access to support services and cognitive rehabilitation.

Our study suggests that cognitive screening and monitoring should be included in IIH patient care. Patients who report overt cognitive impairments that impact their daily activities could be referred for formal neuropsychological assessment. Affected patients may also benefit from psychological counselling, which can provide practical tools for improving coping strategies and regulating emotions. Mindfulness is a common psychological tool that helps to attain non-judgemental awareness of the present moment, including acceptance of one's current state with openness and curiosity[260]. Interestingly, mindfulness may improve cognitive functions such as verbal learning and memory by enhancing encoding compared to controls, according to a study that utilised the Rey Auditory Verbal Learning Task (RAVLT)[261]. Mindfulness-based therapy was also moderately effective at improving depression and anxiety in a meta-analyses of 1140 participants[262], which are highly prevalent co-morbidities in IIH. The future of comprehensive IIH patient care may involve neuropsychological and psychological interventions for patients who require cognitive rehabilitation.

To date, there have been no studies on cognitive rehabilitation strategies in IIH. However in MS, group cognitive rehabilitation therapy for ten sessions over twelve weeks significantly improved working memory on neuropsychological testing and had high patient satisfaction[263]. In another study, MS patients who engaged in six weeks of home-based computerised cognitive rehabilitation had significant improvements in visuospatial memory and demonstrated altered cortical activation on functional MRI[264]. Similar rehabilitation strategies could potentially be applied to IIH patients. For IIH specifically, cognitive rehabilitation targeting inhibitory control may be particularly relevant, since we detected impairments on neuropsychological testing that were also striking on ocular motor assessments. Inhibitory control deficits are associated with obesity[265], which can be problematic for some IIH patients. Targeting inhibitory control in a laboratory setting using neuropsychological tests such as Stop-Signal task training appears to moderate eating behaviours in the short-term, however, post-intervention eating patterns and body mass index may not improve[266]. Adapting cognitive rehabilitation results from research settings to sustained behavioural changes remains a challenge.

5.4 Limitations and Future Directions

5.4.1 Limitations

Our study was limited by relatively small patient numbers and significant attrition of the IIH cohort over time, in the context of the Covid19 pandemic. This was particularly the case for data obtained at the six-month time-point, which should be substantiated with further research. The effects of chronic IIH on cognition beyond six months was not examined in our study and could be clinically relevant.

A larger cohort is also required to determine if and how IIH medications impact cognition. Yri et al detected cognitive impairments in IIH patients despite withholding medications prior to neuropsychological testing[4]. However, both topiramate and acetazolamide may impair cognition and are commonly used in IIH[71, 76]. It would be informative to compare cognitive testing results between patients on different medications for IIH, as well as no medications. In our study, only five patients were taking topiramate and four were not taking IIH medications, which limited statistical analyses.

Patients in our study were of typical IIH phenotype, fulfilled diagnostic criteria and had similar mild-moderate disease activity. This was both a strength and a weakness, since it remains unclear how variations in IIH disease activity, particularly more severe cases of IIH, influences cognitive impairment. In addition, variations in clinical characteristics such as CSF opening pressures were limited in our IIH cohort. A larger, more varied group of IIH patients may detect additional relationships between clinical features and cognitive impairments.

While our study demonstrated widespread cognitive impairment on neuropsychological testing, these results could not be correlated with ocular motor testing, which largely showed marked inhibitory control deficits. Potential deficits on ocular motor testing such as increased saccadic variation or prolonged latencies could have been obscured by high error rates due to inhibitory control impairment, which resulted in many excluded trials. Finally, control groups in IIH research should ideally be weight-matched, since obesity itself may impair cognition[109].

5.4.2 Future Directions

Our study results generate an exciting platform for future research on cognition in IIH. Since cognitive impairments were persistent and independent from most IIH clinical features in our cohort, it is important to monitor cognition longitudinally for comprehensive IIH management. Research addressing how long cognitive impairments persist for in IIH are required, including prognostic features for protracted cases. Evaluating whether or not cognitive impairments are present in patients with chronic IIH or IIH in remission would be worthwhile, as this would add to our study findings that showed persistent cognitive impairments in recently diagnosed IIH patients. More patient numbers are required to substantiate the longitudinal results from our study.

Future studies could evaluate strategies for including cognitive screening and monitoring in IIH management. Tests such as the SDMT are simple, quick and easy to administer. The SDMT assesses processing speed[136], which was impaired in our cohort and was also a major area of impairment in Yri et al's study[4]. There is also increasing interest in the role of computerised cognitive testing, which can be performed in a range of settings, including from home[267, 268]. In addition, computerised cognitive testing can be 'gamified', which may be more engaging for participants[269, 270]. Telehealth medicine has boomed in the Covid19 era[271] and may provide another accessible method of assessing cognition.

Ocular motor inhibitory control deficits, predicted by RNFL thickness/papilloedema severity, were a unique finding in our study. The severity of inhibitory control impairments in our IIH cohort were striking and may have obscured other potential findings on ocular motor testing, such as prolonged latencies. As such, it would be interesting to perform ocular motor studies on IIH patients that are less reliant on inhibitory control, to potentially unmask further cognitive deficits. Conducting ocular motor testing on a healthy, obese cohort would also be informative. Obesity may be particularly associated with inhibitory control deficits[97, 265], however studies in this area are limited and it is unclear whether or not impairments translate to behaviours on a practical level[272]. Ocular motor testing provides a novel and sensitive method of assessing inhibitory control, which may reveal clinical and behavioural associations in obesity that are undetected by neuropsychological testing.

5.5 Concluding Remarks

IIH is a condition associated with significant morbidity and patients may experience cognitive impairments, which remain largely unaddressed. While a limited number of previous studies have described cognitive impairments in IIH, there is uncertainty surrounding which cognitive domains are most affected, whether these impairments are related to clinical features of IIH and if cognition fluctuates over time. The research presented in this thesis demonstrates that widespread cognitive impairments are present in IIH and appear to be persistent, occurring independently from most clinical features.

Impairments of multiple cognitive domains related to executive functioning were detected on neuropsychological testing, which occurred independently from clinical features of IIH. Ocular motor testing revealed additional distinctive inhibitory control deficits. Specifically, compared to controls, IIH patients performed high rates of error on complex cognitive ocular motor tasks, yet completed simple reflexive ocular motor tasks normally. This suggests that while simple visual processing is intact, integration of higher cognitive functioning is impaired.

Ocular motor deficits in the IIH cohort partially resolved at three and six months, which seemed related to improvements in papilloedema. However, cognitive impairments remained persistent on neuropsychological testing and highlighted the importance of cognitive monitoring in IIH longitudinally. Cognitive impairment may result from dysfunction of widespread fronto-striatal networks related to IIH pathophysiology. A larger IIH cohort, followed over a longer period of time, is necessary to substantiate our findings. Our research supports the inclusion of routine cognitive monitoring as part of comprehensive IIH management and encourages research on potential interventions that could be implemented to improve patient care.

Chapter 6 References

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