

**EFFICACY OF ENDOSCOPIC THIRD VENTRICULOSTOMY TO TREAT
COGNITIVE SYMPTOMS IN ADULTS WITH CHRONIC OBSTRUCTIVE
HYDROCEPHALUS**

by

Nicholas Salterio

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The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, a thesis/dissertation entitled:

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submitted by Nicholas Salterio in partial fulfillment of the requirements for

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Examining Committee:

Dr. Thomas Zwimpfer, Neurosurgery, Clinical Professor
Supervisor

Dr. Dean Foti, Neurology, Clinical Assistant Professor
Supervisory Committee Member

Dr. Nicholas Bogod, Neuropsychology, Clinical Assistant Professor
Supervisory Committee Member

Dr. Christopher Honey, Neurosurgery, Clinical Professor
Additional Examiner

Abstract

Hydrocephalus is a neurological disease caused by an overaccumulation of cerebrospinal fluid (CSF) within the ventricles of the brain. This produces expansion of the ventricles (ventriculomegaly) and compression of the surrounding brain tissue. Obstructive hydrocephalus is the result of a macroscopic blockage within the ventricular system distal to the arachnoid villi and can produce cognitive decline. Endoscopic third ventriculostomy (ETV) has been shown to be a safe surgical treatment in obstructive hydrocephalus, however the efficacy of ETV to improve cognition has limited evidence. In order to determine how ETV affects cognition in adults who have chronic obstructive hydrocephalus, this thesis had the following objectives: 1) to determine the sufficiency of primary ETV to safely improve global cognition in adults with chronic obstructive hydrocephalus, and 2) to determine which cognitive domains ETV produces clinically meaningful changes in adults with chronic obstructive hydrocephalus.

To complete the first objective, we conducted a multicenter study using the Montreal Cognitive Assessment (MoCA) and Symbol Digit Modality Test (SDMT), measures of global cognition and processing speed, before and twice after ETV at 5-months and 14-months follow-up. We found that global cognition was only clinically improved at 14-months follow-up and processing speed was unaffected. Global cognitive worsening was rare at both follow-up assessments.

To complete the second objective, we conducted a single-center study using the RBANS to measure global cognition in better detail and five cognitive domains before and after ETV. We found patients with chronic obstructive hydrocephalus treated with ETV have a clinically and statistically significant improvement in global cognition, attention, and delayed memory domains

at 4-months follow-up. Clinical worsening was rare in all domains except visuospatial/constructional, where although there was no statistical difference, 50% of patients had a clinical worsening post-ETV. Lastly, a potential predictor of post-ETV global cognitive improvement was discovered. The likelihood of global cognition improvement was 100% when the difference between immediate and delayed memory indexes were three points or less.

Further validation of this predictor is required. Future studies should expand on the neurocognitive testing to include anatomical correlates to elucidate the mechanism of cognitive decline seen in chronic obstructive hydrocephalus.

Lay Summary

Hydrocephalus is a treatable disease that when left untreated, can cause permanent thinking-related disabilities and eventually brain swelling, coma, and death. Hydrocephalus can affect all ages. The problem comes from a blockage and backup of the normal fluid spaces that exist within the brain.

An endoscopic third ventriculostomy (ETV), is a brain surgery that can treat the disease and reduce many of the symptoms. There is important information missing about what happens to adults who have an ETV. This is especially true for thinking and memory problems caused by hydrocephalus. We used state-of-the-art thinking and memory tests before and after surgery to figure out that ETVs are safe and improve parts of memory and attention.

Preface

This thesis comprises works with the attempt to determine the efficacy of ETV to improve cognition in adults with chronic obstructive hydrocephalus.

Chapter 2. A version of this material has been submitted for publications as “Zwimpfer, T.J., **Salterio, N.**, Holubkov, R., Katzen, H., Luciano, M.G., Nagel, S.J., Williams, M.A., Wisoff, J.H., McKhann, G.M., Edwards, R., and Hamilton, M.G. *Cognitive and Gait Outcomes after Primary Endoscopic Third Ventriculostomy in Adults with Chronic Obstructive Hydrocephalus*”.

This study was conducted as a part of the Adult Hydrocephalus Clinical Research Network with Dr. Zwimpfer as the project lead. I was involved in data collection at our center. I designed and managed the analyses and figure design. I wrote the first draft of the manuscript and was involved in editing the final version for submission. Statistical supervision was completed by Dr. Holubkov. All authors reviewed the final version of the manuscript.

Chapter 3. A version of this material is being submitted for publication “**Salterio, N.**, Foti, D., Bogod, N., Katzen, K., and Zwimpfer, T.J. *Chapter 3: Improved Global Cognition, Attention, and Delayed Memory After Endoscopic Third Ventriculostomy in Adult Chronic Obstructive Hydrocephalus Using The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)*”. Dr. Zwimpfer, Dr. Katzen, and I conceived the study. I collected the data, completed the analyses, created the tables and figures, and wrote the first draft of the manuscript. Dr. Foti, Dr. Bogod, and Dr. Zwimpfer provided supervision, assistance with results interpretation, and editorial support.

The University of British Columbia Clinical Research Ethics Board approved the study contents of Chapter 2 (H14-02127) and Chapter 3 (H19-01434). The patients provided informed consent for participation in these studies.

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List of Abbreviations

AHCRN: Adult Hydrocephalus Clinical Research Network

ARAS: Anterior Reticular Activating System

CPC: Choroid Plexus Cauterization

CSF: Cerebrospinal Fluid

DLPFC: Dorsolateral prefrontal cortex

ETV: Endoscopic Third Ventriculostomy

FA: Fractional Anisotropy

GABA: Gamma Aminobutyric Acid

HCRN: Hydrocephalus Clinical Research Network

ICP: Intracranial Pressure

iNPH: idiopathic Normal Pressure Hydrocephalus

IQ: Intelligent Quotient

MCID: Minimum Clinically Important Difference

MMSE: Mini Mental Status Exam

MoCA TS: MoCA Total Score

MoCA: Montreal Cognitive Assessment

MTG: Middle Temporal Gyrus

RBANS TS: RBANS Total Score

RBANS: Repeatable Battery for the Assessment of Neuropsychological Status

RCI: Reliable Change Index

SDMT: Symbol Digit Modality Test

STG: Superior Temporal Gyrus

TPS: Total Percentile Score

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Chapter 1: Introduction

Cognition is the capacity to use prior knowledge to inform current and future decision making. Few causes of cognitive decline have a safe surgical option for treatment and improvement in cognitive symptoms. Hydrocephalus is a category of neurological disease stemming from an overaccumulation of cerebrospinal fluid (CSF) within the ventricles of the brain. This produces expansion of the ventricles (ventriculomegaly) and compression of the surrounding brain tissue (Pong et al., 2017). Obstructive hydrocephalus is the result of a macroscopic blockage within the ventricular system distal to the arachnoid villi and can produce cognitive decline. Endoscopic third ventriculostomy (ETV) has been shown to be a safe surgical treatment in obstructive hydrocephalus (Isaacs et al., 2016; Waqar et al., 2016), yet the efficacy of ETV to improve cognition has limited evidence (Burtscher et al., 2003; Locatelli et al., 2014; Hader et al., 2014; Baroncini et al., 2019).

This chapter will begin with a brief summary of known epidemiology. Description of the different etiologies of hydrocephalus and pathophysiology of symptomatology will follow. Cognitive domains will be defined and a detailed review of ventricular anatomy and potential anatomical correlates to cognition will be described. The surgical treatment options for obstructive hydrocephalus and methods of cognitive testing will be compared. A full review of the current literature of cognition outcomes and ETV in adults will be presented highlighting the gaps that exist. Lastly, the rationale, hypotheses, and objectives of the thesis are stated.

1.1 Hydrocephalus Epidemiology:

An estimated 70,000 Canadian adults currently suffer from an etiology of hydrocephalus (Isaacs et al., 2018). The global prevalence is 84.7/100,000 [95% CI 61.9 to 115.9]. The continents with the highest prevalence include Asia, Africa, and South America. The Asian prevalence is largely due to the increased elderly prevalence of 656.9/100,000 [95% CI 46.6 to 9257.9] compared to Europe and North America's combined, 52.8/100,000 [95% CI 11.8 to 237.0]. The African prevalence of pediatric hydrocephalus is also higher (104.0/100,000 [95% CI 33.3 to 324.77]) compared with the North American (55.6/100,000 [95% CI 41.4 to 74.7]). Prevalence is not uniform across the lifespan with a global pediatric prevalence of 88/100,000, adult prevalence of 11/100,000, elderly prevalence of 175/100,000, and possible prevalence of >400/100,000 above the age of 80.

The incidence of surgical intervention varies based on etiology with idiopathic normal pressure hydrocephalus (iNPH), communicating hydrocephalus, and obstructive hydrocephalus having rates of 2.2 ± 0.8 , 1.9 ± 0.3 , and $0.8 \pm 0.1/100,000/\text{year}$ (Sundström et al., 2017). However, the incidence of ETV surgery is only $0.4 \pm 0.1/100,000/\text{year}$ compared to 4.7 ± 0.8 shunt surgeries. This shows the disparity of patients with obstructive hydrocephalus that are not receiving ETV surgery.

The initial cost for shunt insertion and ETV is similar, but with shunts requiring more revisions it is more cost-effective to treat obstructive hydrocephalus with an ETV (Reddy et al., 2014; Isaacs et al., 2016; Waqar et al., 2016; Pham et al., 2013). If more obstructive hydrocephalus patients are treated with ETV, this could significantly reduce the estimated \$1.1 billion dollars per year

cost of hydrocephalus treatment in the United States, which a Manitoba Canada study found a similar cost per population (Patwardhan & Nanda, 2005; Del Bigio, 1998). As the Canadian population continues to grow, the social and economic burden of hydrocephalus will continue to rise. Effective and cost-efficient treatment modalities, like ETVs, are required to aid in reducing this burden going forward.

1.1.1 The Different Etiologies of Hydrocephalus

Hydrocephalus can be produced by different mechanisms of disease development. There are three main types of hydrocephalus: obstructive/non-communicating, communicating, and iNPH. The major distinction between the types of hydrocephalus is based on where along the ventricular system the obstruction is found. If the obstruction is at the level of the arachnoid villi, where cerebrospinal fluid is absorbed into the venous system, CSF is able to flow through the system unimpeded, but is not adequately absorbed. This is termed communicating hydrocephalus. Conversely, if there is a macroscopic blockage within the ventricular system distal to the villi, then it is termed obstructive or non-communicating hydrocephalus. The pathophysiology for each type of hydrocephalus is varied by the specific etiology and the resulting anatomical changes.

Etiology by level of obstruction:

Obstructive hydrocephalus can be the result of congenital abnormality (aqueductal stenosis or webbing) or malformation (e.g. myelomeningocele, Arnold-Chiari, Dandy-Walker). Aqueductal stenosis or atresia, is a narrowing or absence of the cerebral aqueduct of Sylvius. This reduces or stops the flow of CSF through the aqueduct. Commonly, this is due to developmental

malformations and can produce hydrocephalus in utero up-to and including the elderly. The latter termed “arrest hydrocephalus” is a form of unrecognized congenital hydrocephalus as the obstruction has persisted since development, but symptoms only presented in adulthood. The reason for this delay is symptom presentation is currently unproven. It may be due to the inability for neural networks to continue to compensate at a certain degree of age-related atrophy. Tumours (primary benign, neoplastic and metastases), cysts (arachnoid, colloid), abscesses (rare), within the ventricular system from lateral ventricles blocking foramen of Monro to the outlets of the fourth ventricle can also cause obstructive hydrocephalus through the same mechanism.

Until the recent awareness around folate supplementation during pregnancy, myelomeningocele and its variants were a common pediatric cause of hydrocephalus. Myelomeningocele is an abnormal protrusion of the dural sac with spinal root involvement past the vertebral column. It is often associated with hydrocephalus due to aqueductal stenosis and Chiari malformations (Avagliano et al., 2019). The caudal displacement of the brainstem and commonly malformed tectum (beaked tectum) is likely the cause of the narrowing of the aqueduct. Encephalocele is thought to cause hydrocephalus by similar mechanism (Avagliano et al., 2019). Although hydrocephalus was originally part of the Dandy-Walker malformation triad, it is only present in 80% of cases when the cyst causes obstruction within the fourth ventricle (Spennato et al., 2011). Hydrocephalus is usually only seen in syndromic craniosynostosis and is thought to be caused by hypoplastic posterior fossa and skull base venous outlet occlusion (Collmann et al., 2005).

Communicating hydrocephalus is the result of microscopic obstruction at the level of the arachnoid granulations, the portion of the neuroaxis that absorbs cerebrospinal fluid into the circulation. Communicating hydrocephalus is generally thought to be an acquired etiology, occurring after an insult to the arachnoid villi. Inter-/intra-cerebral infection (ie. meningitis, ventriculitis, encephalitis) can cause the villi to scar and can result in malabsorption of CSF and results in communicating hydrocephalus. Hemorrhage within the cranial vault can cause hydrocephalus through the same mechanism. Post-traumatic brain injury requiring decompressive craniotomy is associated with hydrocephalus in 11.9-36% who undergo decompressive craniotomy (Fattahian et al., 2018), however the mechanism is still unclear (Satyarthee, 2018)

iNPH is a form of communicating hydrocephalus but is not associated with an increase in intracranial pressure (ICP). This form of hydrocephalus is chronic and occurs by definition over the age of 60 (although debate exists on the appropriate age for classification) without meeting the criteria for any of the aforementioned etiologies (Marmarou et al., 2005; Mori et al., 2012; Halperin et al., 2015; unpublished AHCRN guidelines). Although the mechanism behind it is unknown, there have been some hypotheses presented based on vascular, hemodynamic, and metabolic aspects (Bräutigam et al., 2019). iNPH presents chronically with a well-defined clinical finding known as Hakim's triad: gait, urinary, and cognitive dysfunction.

In rare instances, choroid plexus hyperplasia (23 cases reported) and choroid plexus papilloma/carcinoma have been suggested to cause an overproduction and lower absorption of CSF leading to hydrocephalus (Hallaert et al., 2012).

For completeness, there exists a third population of patients who appear to have both communicating and obstructive forms, but there is no method of determining if a patient has both forms until after surgical treatment. This is likely the reason why approximately 13-27% of ETV fail (Isaacs et al., 2016; Waqar et al., 2016). The obstruction to CSF flow has been bypassed with a patent ETV, however there is reduced absorption at the arachnoid villi requiring shunting of the CSF to a different body cavity.

1.1.2 Symptomatology in Acute and Chronic Obstructive Hydrocephalus

Obstructive hydrocephalus patients can present acutely with raised ICP symptomatology.

Alternatively, chronic obstructive hydrocephalus can present with normal pressure symptoms (Hakim's triad) alone or in combination with some symptoms from raised ICP. It is important to note that although chronic obstructive hydrocephalus may present similarly to iNPH and results in chronic ventriculomegaly, the etiology of the disease and preferred treatment is different.

Thus, the presentation of symptoms severity and efficacy of treatment cannot be equivocated to those of iNPH. iNPH has an idiopathic cause of CSF malabsorption, whereas chronic obstructive hydrocephalus has a defined macroscopic obstruction limiting the amount of CSF that is able to be absorbed. It likely for this reason why ETV has been shown to be ineffective in iNPH in a randomized controlled trial and systematic review (Tudor et al., 2015).

1.2 Pathophysiology of Acute Hydrocephalic Symptomatology

The symptomatology of hydrocephalus is varied by the acuity of symptom onset, with the most acute presentations consisting primarily of raised ICP symptoms. As the presentation becomes more chronic, normal pressure symptoms dominate.

Raised intracranial pressure symptoms vary in severity from headache to nausea and vomiting, loss of consciousness, papilledema, brain herniation, coma, and eventually death.

The mechanism for these symptoms is based off the Monro-Kellie hypothesis, which states that there is a defined and limited volume within the skull (Monro, 1783). The brain parenchyma, blood, and CSF each make up a part of this volume. If any of the three increases in size (tumour, hematoma, CSF backup in hydrocephalus) the total volume will exceed the volume available within the skull. The compensatory mechanism is to raise ICP to force more fluid (blood, CSF, extracellular fluid, and intracellular fluid) out of the skull. Once this compensation has been exhausted and ICP continues to increase, pressure gradients between different compartments of the brain within the skull emerge. Namely, the falx cerebri and tentorium cerebelli. With raised ICP, herniation of different components occurs.

1.2.1 Herniation:

The three types of herniation are as follows: transtentorial, subfalcine, and tonsillar (Dunn, 2002). Transtentorial herniation can be subdivided into uncal or central. Uncal herniation occurs when the uncus of the temporal lobe, the medial extent of the parahippocampal gyrus, is pushed under the tentorium and places pressure onto the midbrain of the brainstem.

Central herniation consists of diencephalon (thalamus, hypothalamus, subthalamus, and epithalamus) being pushed under the central (medial) aspect of the tentorium. Again, pressure on the midbrain results.

Subfalcine or cingulate/transfalcine herniation comprises the frontal aspect of the cingulate cortex being pushed laterally under the falx cerebri into the contralateral hemisphere. Unlike the other forms of herniation, subfalcine does not result in brainstem compression. Instead, anterior cerebral artery compression can occur leading to an ischemic injury to the medial and paramedial aspects of the hemispheres including the frontal poles. Subfalcine herniation can also result in central herniation.

Tonsillar herniation is the result of the tonsils of the cerebellum being pushed through the foramen magnum. Compression of the lower medulla and upper cervical cord can lead to dysfunction of the cardiac and respiratory centers within the medulla. These forms of herniation account for the later phases of raised ICP, coma, and death.

1.2.2 Respiratory centers:

The respiratory centers of the brain are controlled by the three groups of nuclei: the dorsal, ventral, and pontine respiratory groups. The dorsal and ventral groups are located within the medulla, and the pontine group is found within the pons (Saether et al., 1987). The dorsal group is responsible for inhalation and under the influence of the solitary nucleus. The ventral group is responsible for exhalation and is under the influence of both the nucleus ambiguus and retro-ambiguus nucleus. The pontine group is divided into the pneumotatic and the apneustic center,

which are interconnected and are under another component of the solitary nucleus. The pneumotaxic center manages breathing rate and pattern of the respiratory system (Song et al., 2006). The apneustic center manages the intensity of breathing. Therefore, dysfunction of this system leads to depression and eventual cessation of breathing, causing a hypoxic environment throughout the brain and body. When this occurs, intubation and forced oxygen via machine ventilation is mandatory for sustained life.

1.2.3 Cardiac centers:

The cardiac centers of the brain are contained within the solitary nucleus, ventrolateral depressor area, and the ventrolateral pressor area (Maeda et al., 1994). The solitary nucleus is located in the dorsal medulla, while as their names suggest, the ventrolateral depressor and pressor areas are found more ventrally within the medulla. This is slightly counterintuitive as ventral medulla is typically thought of as purely motor fibers running down the pyramids. However, just posterior to the pyramids in the rostral medulla are where these ventrolateral areas are found. Originally, the cardiac centers were thought to only control the regulation of systemic blood pressure and heart rate. But, Maeda et al. (1994) showed that these centers also control cerebrovascular vasoconstriction. This could explain one of the causes of brain ischemia with raised ICP.

1.2.4 Papilledema:

Papilledema is the swelling of the optic disk. The optic nerves can be thought of as extensions of the brain. Papilledema in adults is 100% sensitive and 98% specific for raised ICP (Tuite et al., 1996). The optic canal is the bony structure where the optic nerve and ophthalmic artery reside, running along the skull base before entering the orbital cavity. They are surrounded by the optic

sheath made of dural and arachnoid layers. The subarachnoid space and the optic sheath are communicating structures with respect to the CSF flow (Hayreh, 1984). As ICP increases, the axonal fibers within the sheath become damaged and a reduced axoplasmic flow of the optic disk results in papilledema (Schirmer & Hedges, 2007). This can cause transient reduced visual acuity and chronically can cause permanent blindness if left untreated.

1.2.5 Nausea and vomiting:

The pathophysiology of nausea and vomiting associated with raised ICP is related to pressure being put onto the medullary structure responsible for emesis, the area postrema (Irwin & Rippe, 2008; Maule, 1990). This can occur with tonsillar herniation as mentioned above. The area postrema is located just superior and ventral to the obex of the medulla (Miller & Leslie, 1994). The obex can be thought of as the transition zone between the floor of the fourth ventricle and the ventral aspect of the central canal. This cervicomedullary junction is at the level of the foramen magnum and thus can be compressed with tonsillar herniation.

The area postrema's primary connection is to the solitary nucleus. This nucleus has many connections to other autonomic centers within the brainstem. Together the area postrema and the solitary tract are the primary centers for autonomic emesis control. When functioning normally, both these centers have permeable capillaries, which allows for gross autonomic regulation of hormones, proteins, and toxins. Specifically, within the area postrema, the chemoreceptor trigger zone is located. It is this area that controls nausea and vomiting activation. In response to an emetic stimulus, the chemoreceptor trigger zone is activated which has outputs to the nucleus of the solitary tract. From here, more than 25 different nuclei may be activated to coordinate the

complex motor movement of vomiting. This is the start of the final common pathway to initiate vomiting from any emetic stimulus, be it an emetic drug or compression from raised ICP.

Two known and important components of this pathway are the activation of the retrofacial nucleus and the dorsal motor nucleus of the vagus cranial nerve. The former is the impetus for the required respiratory pattern of emesis. The latter connects to the gastrointestinal system and prepares it for emesis. Additionally, secondary neuronal activation of the trigeminal, facial, and glossopharyngeal cranial nerves occurs for the motor action of emesis.

1.2.6 Headache:

Headache associated with raised intracranial pressure is thought to be due to the pain receptors on the meninges (including the falx) surrounding the brain (Yamada et al., 2018). As the brain itself does not contain pain receptors, the expansion of the brain parenchyma against the meninges and the inner plate of the skull causes the meninges to stretch. This stretching is thought to be an irritant to the meningeal nerves and the impetus of the headaches experienced with raised ICP. A good example is the “thunderclap” headache associated with a subarachnoid hemorrhage. A large amount of bleeding into the cranial vault causes quick expansion of the arachnoid and dura. The nociceptors along the tentorial nerve, the first branch of the ophthalmic branch of the trigeminal nerve that innervate the meninges, are activated by the stretching. This signal is relayed to the subnucleus caudalis of the spinal trigeminal nucleus, where pain is processed. From here, the signal travels along the anterior trigeminal-thalamic tract to the contralateral ventral posterior medial nucleus of the thalamus and continues on to the primary somatosensory cortex. This cortex has been shown to be involved in both pain perception and modulation, given this pain circuit (Bushnell et al., 1999).

1.2.7 Loss of consciousness:

Loss of consciousness in an acutely raised ICP scenario is a result of brain herniation onto the brainstem's nuclei responsible for maintaining consciousness. This grouping of more than 20 nuclei is referred to as the anterior reticular activating system (ARAS) and is located within the superior tegmentum (midbrain and superior pons) of the brainstem. Multimodal sensory input from the spinoreticular pathway as well as the olfactory, optic, trigeminal, and vestibulocochlear nerves synapse onto the various nuclei within the ARAS (Iwańczuk & Guźniczak, 2015). These sensory inputs all reach the diencephalon but can travel directly through the medial column of the reticular formation or diffusely through non-specific pathways. Within the diencephalon, these projections separate into paths towards the thalamus and hypothalamus. At the level of the thalamus, the reticular and interlaminar thalamic nuclei act as the relay station between the brainstem and cerebral hemispheres. The reticular thalamic nuclei are mostly specific to pain signals and the interlaminar thalamic nuclei projects the ARAS signals to the cortex, forming part of the thalamocortical network. This network is one of the primary excitatory signals to the cerebral cortex, which at its baseline state is heavily depressed via gamma aminobutyric acid (GABA) inhibition. Therefore, with compression to the ARAS from brain herniation, excitatory signals are reduced to the cerebral cortex leading to a lower level of consciousness. If severe, longstanding, or bilateral this leads to coma and eventually death. Death results from an unprotected airway, requiring intubation to force oxygen into the lungs.

Additionally, raised ICP can lead to cerebral hemisphere ischemia due to decreased cerebral perfusion pressure in response to raised ICP (Bor-Seng-Shu et al., 2013). If both hemispheres

become dysfunctional then consciousness can be impaired. This is due to widespread apoptosis and autophagy of neuronal and vascular cells within the cerebral hemispheres. Many circuits and networks will become dysfunctional, leading to eventual brain death.

1.3 Pathophysiology of Chronic Hydrocephalic Symptomatology

As the acuity of the initial presentation of hydrocephalic symptoms lessens, normal pressure symptoms dominate. These chronic symptoms can be easily distilled into the classic triad: gait, urinary, and cognitive dysfunction.

1.3.1 Gait dysfunction:

The prevailing theories surrounding gait dysfunction in iNPH are centered around the subcortical and periventricular white matter, deep grey nuclei, intracortical circuits, and midbrain's mesencephalic locomotor region (MLR), and recent work on circulation and neurotransmitter involvement.

The corticospinal tract runs along the edges of the lateral ventricles. These fibers control leg movement (Lee et al, 2005; Mocco et al, 2006). The corticospinal tract starts with activation of Betz cells in layer V of the primary motor cortex. The axons travel through the corona radiata, around the lateral ventricles to the posterior limb of the internal capsule. They continue through the crus cerebri, to the pyramids and decussate before entering the superior cervical spinal cord. The lumbar and a portion of the sacral spinal cord lead to efferent motor nerves that stimulate the musculature in the legs, causing movement. Due to the proximity of the corticospinal tract within the corona radiata to the lateral ventricles, compression or atrophy of these upper motor neurons

could result in gait dysfunction. MRI analyses of corticospinal tract have found evidence of axonal compression, stretching, and damage in the corticospinal tract which is partially reversed post-shunting (Assaf et al., 2006; Hattingen et al., 2010, Jang et al., 2011, Hattori et al., 2011, Scheel et al., 2012; Jurcoane et al., 2014; Kamiya et al., 2017; Irie et al., 2017; Ades-Aron et al., 2018)

Intracortical connection dysfunction in the hydrocephalic patient is a new line of evidence for the mechanism of gait dysfunction. Chistyakov et al. (2012) used transcranial magnetic stimulation over the medial aspect of the primary motor cortex (ie. lower extremity representation) to show that resting motor threshold was increased and short intracortical inhibition was decreased prior to surgical treatment in iNPH patients. This resulted in an overexcited primary motor cortex, leading to disturbances in corticospinal motor outputs. After ventricular shunting, both these metrics improved along with expected gait improvement. This study provided initial evidence that upper motor neuron dysfunction via intracortical connection compression from lateral ventricle ventriculomegaly may play a role in the gait dysfunction seen in iNPH patients.

The MLR is located proximal to the cuneiform nucleus, and ventral to the inferior colliculus. It is suggested that the pontine tegmental nucleus and extrapyramidal area are the functional areas within the MLR. Grossly, the MLR can be divided into a dorsal and ventral portion. The dorsal extent is paramedial and ventral to the periaqueductal grey encasing the cerebral aqueduct of Sylvius. The ventral extent is further ventral and lateral. Sherman et al. (2015) showed that the dorsal portion of the MLR is responsible for locomotion and the ventral portion for standing. Due to the closeness of these nuclei to the aqueduct, it is logical to suggest that enlargement of

the aqueduct could cause dysfunction of these nuclei and lead to gait dysfunction. Imaging studies using MRI, CT, and newer modeling techniques show conflicting evidence of atrophy in these areas (Lee et al., 2005; Mocco et al., 2006; Hiraoka et al., 2011). Cadaver based studies should be performed to provide insight into the precise anatomical changes in a hydrocephalic patient. Additionally, patients with obstructive hydrocephalus with obstruction rostral to the anterior aspect of the cerebral aqueduct should not display this compression. Follow-up studies comparing these populations should also be conducted.

A handful of hypotheses have been suggested to explain the gait dysfunction seen in the hydrocephalic patient, from simple corticospinal tract dysfunction as ventricular size increases, to intracortical and midbrain nuclei compression. However, a causal mechanism is yet to be determined.

1.3.2 Urinary dysfunction:

Unfortunately, urinary dysfunction is understudied in hydrocephalus. It is a common notion that urinary dysfunction is a side effect of aging. However, urinary dysfunction is always pathogenic and can typically be improved with treatment of the underlying cause (Rigamonti, 2014). The study methods are also a deterrent for researchers and participants; urinary logs to the weighing of soiled pads. As such, the pathophysiology behind urinary dysfunction is limited in chronic hydrocephalus. The current hypothesis is non-specific to hydrocephalus as it is directly taken from other diseases.

Micturition (or urinary) reflexes are the set of neural loops that control urination. They are dependent on the spino-bulbo-spinal reflex (Lee et al., 2011). Suprapontine structures including the frontal cortex and basal ganglia suppress the pontine centers via the periaqueductal grey matter that surrounds the cerebral aqueduct of Sylvius. This descending information synapses onto the pontine micturition center (Barrington's nucleus) within the rostral pons. When it is activated, motor neurons through the spinal cord trigger concomitantly the smooth muscle constrictors of the bladder and the striated muscle dilators of the urinary sphincter allowing for micturition. Moreover, sensations of a filled bladder ascends the spinal cord to the pontine micturition center and through the periaqueductal grey matter to the suprapontine structures, completing the reflex loop.

Since the suprapontine networks are not well understood, there is the potential for the ventriculomegaly of the lateral and third ventricles to disrupt part of this network and cause downstream effects. Alternatively, cerebral aqueduct enlargement may disturb the periaqueductal grey matter, which acts as a relay between ascending and descending urinary information. This would account for why patients with hydrocephalus display both incontinence from being unaware of the filled bladder and frequency symptoms. However, at this time, no evidence has been put forth supporting these ideas. More work is needed to understand this aspect of Hakim's triad.

1.3.3 Cognitive dysfunction:

Cognitive dysfunction has no specific mechanism identified for symptom development in hydrocephalus. First, definitions of cognitive domains will be presented. Then, a description of

the features of cognitive impairment found in chronic obstructive hydrocephalus will be reviewed from a neuropsychological perspective. The following section will review potential anatomical correlates to these cognitive domains in the context of ventriculomegaly. Together they will form a framework from which to study cognitive change in chronic obstructive hydrocephalus post-ETV.

1.3.3.1 Definitions of Cognitive Domains

To assess the current neuropsychology literature surrounding chronic obstructive hydrocephalus and ETV, a clear understanding of the domains tested is required. There are six cognitive domains commonly tested in this literature: executive function, attention, immediate memory, delayed memory, visuospatial/constructional, and language.

Executive Functions

Executive functions combine a collection of complex processes in a system that provides supervision atop the brain's hierarchical processing structure, especially in novel contexts (Strauss et al., 2006). In addition, executive functions contain the skills required for purposeful, goal-directed behaviour. This allows individuals to create strategies specific to the context and evaluate their effectiveness. Executive dysfunction may consist of inappropriate social behaviour, poor decision making and judgment, and planning and organizational difficulties. Executive, attentional, and immediate memory dysfunction may coexist together causing executive function problems in a memory context (ie. memory of prior planning), distractibility, or poor task shifting.

Attention

Attention is the intrinsic quantity and speed limiter for processing information in the brain (Strauss et al., 2006). It can be thought of as a gateway for information flow (Cohen, 1993). Conceptualization of attention has resulted in many different models of attention being proposed (Mesulam, 1981; Posner & Petersen, 1990; and Mirsky, 1996). Mirsky's (1996) model of attention was formed from validated commercially available neuropsychological assessments and is the only model to have putative neuroanatomy from lesional studies for each element. The same elements have been found through factor-analytic studies (Kremen et al., 1992; Mirsky et al., 1991; Strauss et al., 2000). Mirsky's elements of attention include focus-execute (selective attention and rapid perceptual-motor output), shifting (change attentional focus, cognitive flexibility and adaptability), sustained/stable (vigilance and consistency of attentional effort), and encode (short-term memory; Kent, 2016) (Zillmer et al., 2008).

Additionally, arousal can be linked to attention as the prerequisite for attentional processing (Zillmer et al., 2008). Detailed anatomy pertaining to arousal and loss of consciousness can be found in *Section 1.2.7 Loss of Consciousness*.

Memory

Memory is the process of encoding (storing), consolidation (strengthening), and retrieving information (Strauss, 2006). Memory is often modelled based on specific subdivisions relating to the type of information to be remembered. The first subdivision of memory is into short-term and long-term memory.

Short-term memory, immediate memory, working memory and attentional encoding are often conflated (Kent, 2016). Short-term memory is specific to encoding information before consolidation and is made up of sensory memory (registration of sensory inputs) and immediate memory (initial phase of temporary storage of sensory memory) (Lezak et al., 2012). Immediate memory last between 30 seconds to several minutes. Short-term memory can also last for up to two days through different mechanisms. Working memory is specific to processing information and can involve short-term and long-term memory components, as such it is associated with executive functioning. The encoding element of attention is temporary storage of information through a “span of attention” and is therefore short-term memory. Sensory inputs difference (Strauss et al., 2006) and theoretical models of working memory have also been proposed (Baddeley & Hitch, 1974), but are unnecessary for the contents of this thesis.

Long-term memory or delayed memory contains permanent or extended storage of information. It is first divided into declarative/explicit memory and non-declarative/implicit memory. Explicit memory contains information that requires conscious awareness to remember (Zillmer et al., 2008; Camina & Güell, 2017). This can be further divided into episodic and semantic memory (Zillmer et al., 2008). Episode memory contains autobiographical information with spatial and temporal components. Semantic memory contains factual based information without temporal components.

Implicit memory contains certain actions and skills, and unconscious memories (Camina & Güell, 2017). It is better defined through each of the four types of implicit memory: procedural, associative, non-associative, and priming. Procedural memory contains the motor and executive

function information required to perform a specific skill. Associative memory is simply the result of classical and operant conditioning. Non-associative memory is evolutionarily one of the more basic forms of memory resulting from habituation and sensitization. Habituation is when repeated stimulus leads to a decrease in response. Sensitization is the opposite, where repeated stimulus leads to an increase in response. Priming occurs when a primary stimulus alters the future response to a secondary stimulus after the primary stimulus has been forgotten from conscious recall.

Visuospatial and Constructional

Visuospatial and constructional condition is defined as the ability to break down an object or picture into parts (visuospatial perception) and construct a replica based on these parts (constructional) (Mervis et al., 1999). It also requires integration from the attention and executive functions domains (Biesbroek et al., 2014).

Language

The classical model of the language domain consists of Broca's area for speech production, Wernicke's area for language comprehension and the arcuate fasciculus as the white matter connection (Fujii et al., 2016). However, as our understanding of language has increased the classical model has required expansion. The current accepted model of language consists of the dorsal and ventral streams of language processing. The dorsal stream is associated with phonological processing. The ventral stream is associated with semantic processing. The anatomy associated with the parts of language will not be discussed beyond this section, therefore a review of the dorsal and ventral systems is found below.

Language processing is initiated with low-level auditory processing at Heschl's gyrus (Middlebrooks et al., 2016; Fujii et al., 2016). Anterior, middle, and posterior (Wernicke's area) aspects of the superior temporal gyrus (STG) perceive phonemes from speech sounds from Heschl's gyrus and is the beginning of the dorsal stream. The middle STG has been shown to contain a phonetic alphabet. Therefore, bilateral damage to this area results in pure word deafness. After phoneme perception, phonological retrieval occurs in the posterior STG and posterior superior temporal sulcus. Since these are large areas of Wernicke's area, Wernicke's aphasia results from damage in the dominant hemisphere. Next, the supramarginal gyrus is responsible for preservation of phonologic information and verbal working memory. The ventral segments of the arcuate fasciculus connects the STG and supramarginal gyrus along the superior longitudinal fasciculus to the frontoparietal operculum including the pars opercularis (Broca's area) and ventral premotor cortex, and in 40% of people to the pars triangularis. The pars opercularis is responsible for syntax. The ventral premotor cortex is important for speech output and phonological processing bilateral and results in dysarthria/anarthria when damaged in 83% of left and 55% of right hemispheres in patients (Tate et al., 2014). Pars triangularis (Broca's area) functions as both semantic and phonologic processing center along an anterior-posterior orientation.

The ventral stream initiates in the middle temporal gyrus (MTG) (Middlebrooks et al., 2016; Fujii et al., 2016). The posterior MGT is responsible for lexical-semantic processing (bilaterally) and prosody (non-dominant hemisphere) (Karunanayaka et al., 2007; Friederici et al., 2015). Moving anteriorly along the MGT is associated with more semantic processing. The inferior

temporal gyrus is also thought to be involved in semantic processing. The temporal pole is involved in the semantics of living things (proper names and famous face naming), theory of mind, and sentence-level semantics (Binder et al., 2009; Bi et al., 2011; Binder et al., 2011, Barnett et al., 2014). The angular gyrus is responsible for syllable discrimination, identification, and lexical-semantic processing (Yagmurlu et al., 2016). The inferior fronto-occipital fasciculus connects the MTG, interior temporal gyrus, and angular gyrus to the dorsolateral prefrontal cortex (DLPFC), pars orbitalis, and pars triangularis. The DLPFC is an integration center and is responsible for the semantic stream of language and verbal working memory (Binder et al., 2009; Yagmurlu et al., 2016). The pars orbitalis is connected to the semantic network however the exact function has not been elucidated.

Dorsal and ventral streams can be examined through neurocognitive testing of picture naming and semantic fluency, respectively. Additionally, orthography follows a different stream and can be individually tested through different assessment but will not be discussed in this thesis (see Middlebrooks et al., 2016 for a detailed anatomical review).

1.3.3.2 Features of Cognitive Impairment in Chronic Obstructive Hydrocephalus

Cognitive dysfunction in chronic hydrocephalus has been shown to follow a frontal-subcortical pattern (Ogino et al., 2006). Chronic obstructive hydrocephalus lacks large studies to provide the specific cognitive domain deficits. Of the studies that use multi-domain cognitive testing, 70-100% patients had a deficit in at least one of the following cognitive domains: executive, attention, immediate memory, delayed memory, visuospatial/constructional, and language either

pre- and/or post-ETV (Burtscher et al., 2003; Lacy et al., 2009; Al-Jumaily et al., 2012; Hader et al., 2014).

Burtscher et al. (2003) found that none of the six patients with unrecognised congenital obstructive hydrocephalus had fully intact cognition pre-ETV. Overall, two patients had isolated memory impairments with the remainder having multiple impaired domains. Episodic verbal learning and memory was impaired in five patients, recognition was impaired in two patients, figural memory was impaired in four patients, executive function (including verbal fluency, cognitive flexibility, or attention) was impaired in three patients, and visuospatial/constructional impaired was found in one patient. Orientation and auditory working memory were preserved in all patients. Locatelli et al. (2014) found 8/13 patients with unrecognized congenital aqueductal stenosis had a pre-ETV cognitive deficit. Hader et al. (2014) found 11/13 patients with chronic obstructive hydrocephalus had at least one cognitive domain with borderline (≤ 16 percentile) or impaired (≤ 7 percentile) performance. They also found a mean percentile of 51 for intelligence with no patient having borderline or impaired performance. Another study used the MMSE in 15 patients with chronic obstructive hydrocephalus and found a pre-ETV mean of 25.7/30 (Baroncini et al., 2019). However, the MMSE had been shown to be an insensitive measure of the pattern of cognitive deficits observed in hydrocephalus (Golomb et al., 1994; Iddon et al., 1999).

1.4 Cerebral Ventricular Anatomy and Related Neurocognitive Correlates

Knowledge of the cerebral ventricles, CSF, and meninges has been known for millennia. The latter two were described in an Egyptian papyrus dated approximately 3500 BC (Schiller, 1997; Clarke & O'Malley, 1996).

“Smashing his skull...opening to the interior...the membrane enveloping his brain so that it breaks open his fluid in the interior of his head.”

Aristotle (384-322 BC) mentions the “hollow inside as well as of some membrane surrounding it”. Herophilus (290 BC) and Erasistratus (280 BC) are credited with the first full descriptions of the four ventricles and their connections to each other.

Contemporary gross description of the ventricular system is based off four fluid filled cavities within the brain (Standring, 2008). The two lateral ventricles (previously termed first and second ventricle) are each found within a cerebral hemisphere. The foramen of Monro/interventricular foramen connects the lateral ventricles to the third ventricle. The aqueduct of Sylvius connects the third ventricles to the fourth ventricle located posterior to the brainstem. The fourth ventricle has three apertures and is continuous inferiorly with the central canal of the spinal cord.

The lateral ventricles can be further divided into five sections from anterior to posterior: frontal/anterior horn, body, trigone/atrium, temporal/inferior horn, occipital/posterior horn.

Frontal Horns of Lateral Ventricles

The frontal horns lie within the frontal lobe of the cerebral hemisphere (Standring, 2008). The anterior wall and roof are formed by the genu and anterior body of the corpus callosum. The frontal horns are separated medially by the septum pellucidum. The posterior boundary is the foramen of Monro where the continuous body of the lateral ventricles commences. The floor mainly consists of the head of the caudate nucleus with the rostrum of the corpus callosum forming a section of the medial aspect. Deep to the caudate nucleus is the internal capsule and lenticular nucleus.

The dorsolateral prefrontal circuit emerges from the dorsolateral prefrontal cortex (Brodmann's area 9 & 10) and projects to the dorsolateral head of the caudate nucleus (Tekin & Cummings, 2002). These fibers continue to the lateral dorsomedial globus pallidus interna and rostromedial substantia nigra pars reticulata. Pallidal fibers project to the ventral anterior and mediodorsal thalamus, which returns fibers to the dorsolateral prefrontal cortex. Disruptions anywhere in this circuit results in dorsolateral prefrontal syndrome resulting in executive cognitive dysfunction. This can result in poor organizational strategies, poor memory search strategies, environmental dependency, impaired set shifting, and verbal/manual dissociation.

Specific disruption along the circuit results in certain cognitive ability dysfunction (Tekin & Cummings, 2002). Disruption along the DLPFC and caudate results in poor recall with preserved recognition. Pallidal disruption, like in Huntington's and Parkinson's disease, also results in retrieval type memory loss. The thalamus is involved in both the temporal-limbic and frontal-subcortical circuits, so disruption results in poor recall and poor recognition causing an amnesic syndrome. As previously mentioned, the head of the caudate forms the floor of the frontal horns

and is therefore susceptible to compression which may resulting in the specific cognitive dysfunction of poor recall with preserved recognition.

In adults with iNPH, ventriculomegaly resulted in displacement of caudate nuclei and decreased volumes associated with worse neurocognitive performance and severity of neuropsychiatric symptoms (Peterson et al., 2019). Abnormal regional network parameters were also significantly different in pediatric hydrocephalus patients in many regions including the medial frontal gyrus for all parameters and caudate nucleus for a subset of parameters (Yuan et al., 2015). Chronic hydrocephalic patients were also found to have an increased fractional anisotropy (FA) value, indicative of compression, in the caudate nucleus compared to controls with ex vacuo ventriculomegaly (Osuka et al., 2010). Moreover, FA values returned to normal post-shunting. An experimental study showed that kaolin induced hydrocephalus in rats caused decreased cortical gray matter thickness with microstructure rearrangement, decreased caudate-putamen cross-sectional area, compression of caudate-putamen and ventral internal capsule, and alternation of corpus callosum and periventricular white matter microstructure (Lugé et al., 2016). These three studies provide evidence of disruption in regions of the dorsolateral prefrontal circuit and associated changes in neurocognitive testing. This is suggestive of a potential neuroanatomical correlate for some of the cognitive dysfunction seen in hydrocephalic patients.

Bodies & Atria of Lateral Ventricles

The bodies extend throughout the frontal and parietal lobes (Standring, 2008). The septum pellucidum continues to separate the lateral ventricles throughout the body. The body of the fornix forms the inferior limit and medial wall of the body. Lateral to the body of the fornix is

the thalamus, which are separated from each other by the choroidal fissure containing the choroid plexus and superior choroidal vein. The choroid plexus produces CSF. ETV and choroid plexus cauterization (CPC) has been shown to be effective in African pediatric post-infectious hydrocephalus, but the Hydrocephalus Clinical Research Network (HCRN) has found higher revision rates compared to ETV alone (Kulkarni et al., 2017; Pindrik et al., 2020).

The lateral walls of the bodies of the lateral ventricles are formed from the thalamus inferiorly and body of the caudate nucleus superiorly (Standring, 2008). The groove between the caudate nucleus and thalamus contains the stria terminalis and thalamostriate vein. The stria terminalis is a white-matter bundle and major output pathway of the amygdala to the septal nuclei, ventromedial nucleus of the hypothalamus, and thalamic areas. It is thought to serve an important role in delayed or unpredictable threats (~10 minute) stress responses including cardiovascular responses and a potential site of deep brain stimulation for severe obsessive-compulsive disorder (Goode et al., 2020; Gomes-de-Souza et al., 2020; Luyten et al., 2016). The thalamostriate vein is an important landmark for intra-operative ventricular navigation as it marks the direction of the lateral wall of the body from the foramen of Monro. This allows for identification of which lateral ventricle the endoscope has entered.

As the bodies widen from anterior to posterior and the continuous temporal and occipital horns start to form, the central aspect connecting these three areas together is the atrium (Standring, 2008).

Occipital Horns of Lateral Ventricles

The occipital horns extend past the atrium into the occipital lobe (Standring, 2008). The splenium of the corpus callosum (forceps major) forms the upper medial wall, however the calcar avis (previously hippocampus minor) forms the majority of the medial wall which separates the occipital horn from the calcarine fissure (Flores, 2002). The most common floor of the inferior horn consists of the collateral eminence, the white matter associated with the indentation of the collateral sulcus (97% of people), but variations including the inferolateral surface from the occipitotemporal sulcus, both collateral eminence and inferolateral surface and neither can exist as well (Switka et al., 1999). The tapetum of the corpus callosum (most posterior aspect of forceps major) forms the roof and lateral wall of the occipital horns. The tapetum connects the hippocampi bilaterally (Maller et al., 2019). Limited research has shown the tapetum in patients with Alzheimer's disease to have reduced FA and increased mean diffusivity in diffusion weighted imaging indicative of neurodegeneration (Mayo et al., 2016). FA was also reduced in the tapetum of posttraumatic stress disorder patients, as hippocampal dysfunction is consistently associated with this disorder (Dennis et al., 2019). This limited evidence may point to another potential correlate to hippocampal memory dysfunction as found in hydrocephalus and other diseases.

Temporal Horns of Lateral Ventricles

Lastly, the temporal horn extends infero-laterally from the atrium into the temporal lobe around the pulvinar nucleus of the thalamus (Standring, 2008). It extends anteriorly to within 2.5 cm of the temporal pole adjacent to the uncus. The superior temporal sulcus can be used as a cortical landmark for the temporal horn. The roof from medial to lateral consists of the stria terminalis, tail of caudate nucleus, and tapetum which extends laterally to form the lateral wall. The floor is

formed by the collateral eminence. The medial wall is formed by the alveus of the hippocampus with CA 1 deep to it. The alveus is a thin layer of white matter with ependymal lining that form the ventricular surface of the hippocampus, it is continuous with the fimbria hippocampi.

Hippocampus volume has been associated with verbal learning abilities (Aslaksen et al., 2018; Bähler et al., 2017 & Antoniadou et al., 2017; Ajilore et al., 2015; Cao et al., 2016).

Experimental hydrocephalus animal models have shown volumetric, neurotransmitter, and morphological changes in the hippocampus suggestive of compression and axonal apoptosis (Kondziella et al., 2009; Taveira et al., 2012). Expansion of temporal horn and hippocampal dysfunction may underlie short-term memory problems seen in hydrocephalic patients.

Foramen of Monro

This crescent or oval passageway between the lateral ventricles and the third ventricle was discovered by Alexander Monro (1733-1817), who is also known for creating the Monro-Kellie doctrine (Tubbs et al., 2014). The superior border consists of the body of the fornix posteriorly and one of the columns of the fornix traveling in an arc in an anterior-inferior fashion. The posterior-inferior aspect is formed from the convex of the anterior pole of the thalamus (Tubbs et al., 2014). The choroid plexus and branches of the medial posterior choroidal arteries pass through the foramen. As well, the thalamostriate, superior choroidal, and septal veins join into the internal cerebral veins on the roof of the third ventricle (Torres-Corzo et al., 2016). The foramen of Monro is a common site for ventricular obstruction. The endoscope is passed through the foramen of Monro during ETV and contains the eloquent memory structure of the fornix which can become damaged. The fornix is a part of the Papez circuit and important for episodic memory (Senova et al., 2020). The fornix has lateralized function with the left fornix responsible

for verbal memory and the right fornix for visual memory. ETV are commonly conducted through a right sided approach putting the visuospatial domain at risk. This highlights the need for domain specific neurocognitive testing.

Third Ventricle

This midline cavity is the location where the ETV occurs. The endoscope enters superior-anteriorly through the foramen of Monro. The anterior commissure crosses midline anterior to the columns of the fornix and foramen of Monro and is located antero-inferior to the globus pallidus (Lavrador et al., 2019). It contains three divisions into the anterior crus containing olfactory fibers and the posterior crus containing a temporal and occipital portion which may be involved in non-visual communication (Larador et al., 2018; Gerrish et al., 2014). Continuing anteriorly, the lamina terminalis forms the most anterior aspect of the third ventricle. It forms a thin sheet from the optic chiasm to the rostrum of the corpus callosum (Standring, 2008). Fenestration of the lamina terminalis has been used as a surgical corridor for tumour resection, anterior communicating artery clipping, or as an alternative when ETV cannot be performed without obvious functional deficits (Silva et al., 2013; Mao et al., 2019; Giussani et al., 2017). Lastly, the optic recess is formed as a crevice superio-anterior to the optic chiasm.

The roof of the third ventricle commences at the foramen of Monro and continues posteriorly to the suprapineal recess (Standring, 2008). Interhemispheric transcallosal approaches can be used to enter the third ventricle through the four-layer roof: neuronal fornix, two layers of telacoroidea membrane, and blood vessels (medial posterior choroidal arteries and the internal cerebral veins) (Greenwood, 1949).

The floor of the third ventricle is sectioned into two parts: diencephalon and midbrain (Standring, 2008). The most anterior aspect of the floor is the infundibulum, then tuber cinereum, mammillary bodies, posterior perforated substance, followed by medial cerebral peduncles and superior tectum. The tuber cinereum is the location where the ETV is made (Torres-Corzo et al., 2016). Once a sufficiently large opening is achieved, CSF will preferentially flow into the prepontine cistern bypassing the distal obstruction. An additional layer of arachnoid membrane (Lillquist membrane) must be dissected through so the CSF can freely flow through the ventriculostomy. The infundibulum and mammillary bodies are millimeters anterior and posterior to the ETV. Although the risk of injury is low, reported cases of pituitary hormonal dysfunction and visual memory deficits have been recorded post-ETV (Bouras & Sgouros, 2011; Bouras & Sgouros, 2013; Benabarre et al., 2001). Mammillary body function is divided by medial and lateral aspects in each body (Tanaka et al., 2020). The medial aspect is responsible for spatial memory and the lateral aspect is responsible for spatial navigation as it contains head-direction cells. The medial aspect is most at risk during ETV again highlight the need for visuospatial domain testing in these patients.

The posterior wall of the third ventricle contains five components from superior to inferior: superpineal recess, habenular commissure, pineal body and recess, and posterior commissure (Standring, 2008). The habenular complex consists of a nucleus on each side of the commissure and is thought to play a role in addiction (Lavrador et al., 2019; Fakhoury et al., 2014). The pineal body is responsible for melatonin release to regulate circadian rhythm (Nichols, 2017). The posterior commissure mediates consensual pupillary light reflex (Lavrador et al., 2019).

The lateral walls of the third ventricle consist of the hypothalamus and thalamus with delineation at line with the foramen of Monro via the hypothalamic sulcus (Standring, 2008). Lastly, the massa intermedia/interthalamic adhesion crosses the third ventricle. It contains neurons cell bodies and tracts but is thought to have no or minimal functional significance (Standring, 2008; Damle et al., 2017; Borghei et al., 2020).

Cerebral Aqueduct

This narrow canal connects the third and fourth ventricles (Standring, 2008). It lies between the tectum and tegmentum. It is a common area of obstruction causing aqueductal stenosis (if narrowed) or aqueductal atresia (if absent). Previous attempts at aqueductoplasty and stenting the aqueduct have been attempted, however the re-occlusion rate is as high as 50% with aqueductoplasty alone and due to the eloquence of this area, complications include dysconjugate gaze, as well as stent migration, infection, ventriculitis, and subdural hygroma (Torres-Corzo et al., 2016). No evidence shows any benefit to aqueductoplasty and stenting over ETV.

Fourth Ventricle

The roof of the fourth ventricle consists of the superior and inferior medullary vela, which separate the ventricles from the cerebellum posteriorly (Standring, 2008). The floor is termed the fossa rhomboidei and consists of the posterior aspect of the tegmentum. The fourth ventricle opens into the two lateral recesses of Luschka into the cerebropontine angle and one medial recess of Magendie leading to the cisterna magna. The most inferior aspect of the fourth ventricle is at the level of the obex, where the open medulla oblongata closes and transitions into the

cervical spinal cord. The fourth ventricle narrows into the central canal at this stage. Possible obstructions can result along the fourth ventricle or one of the recesses (termed fourth ventricular outlet syndrome). Obstructions posterior to the tuber cinereum including fourth ventricular obstructions and outlet syndromes meet the anatomical requirements for an ETV to be attempted.

1.5 Surgical Treatments of Obstructive Hydrocephalus: CSF Shunting vs ETV

Obstructive hydrocephalus is unique in that it has two different surgical treatment options, ETV and CSF shunting. CSF shunting actively drains the CSF out of the cerebral ventricles to another location for absorption, typically the peritoneum (Reddy et al., 2014). Although the pleural cavity (Craven et al., 2017), cardiac atrium (Borgbjerg et al., 1998), gallbladder (Demetriades et al., 2013), venous system (Ayaz et al., 2010), and urinary bladder (Ibrahim, 2014) have been used. Lumbo-peritoneal shunting is also often used for iNPH and idiopathic intracranial hypertension (Kazui et al., 2015; Krishnan et al., 2020).

For more than seven decades CSF shunting in hydrocephalus has been shown to be effective at treating neurological and cognitive symptoms of hydrocephalus (Nulsen & Spitz, 1951; Laurence, 1969). However, shunting is also associated with non-trivial infection and blockage rates leading to reoperation for shunt revision. The mean number of shunt revisions per adult patient is 0.6, with 32.5% of total patients requiring revisions, and comprising 39.3% of all shunt surgeries (Reddy et al., 2014). This stratifies into 19.8% of patients requiring a single shunt revision, and 12.7% requiring two or more revisions. Wu et al. (2019) retrospective review of complication post-shunt for iNPH found an overall complication rate of 19% from: misplaced proximal catheters (5%), asymptomatic catheter tract hemorrhages (3%), bilateral hygromas

(4%), subdural hematomas (6%), CSF leak (1%), repeat surgery due to complication (3%). In a European multicenter study using programmable valves, the one-year post-shunt overall complication, subdural hematoma, and infection rates requiring surgery were found in 15%, 1%, and 1% of iNPH patients (Klinge et al., 2012). An additional 13% of patients had complications that did not require surgery, of which 5% were subdural hematomas.

ETV is a minimally invasive bypass procedure using a flexible or rigid endoscopy to perforate the tuber cinereum at the base of the third ventricle. This allows CSF to preferentially flow through the ventriculostomy into the open cisternal spaces creating a pathway around the obstruction to allow for restoration of homeostatic CSF absorption.

ETV is effective at relieving symptoms of raised ICP in adult obstructive hydrocephalus (Isaacs et al., 2016; Waqar et al., 2016). The reported success rate for primary ETV in adults with untreated obstructive hydrocephalus, defined as not needing a subsequent shunt or repeat ETV, ranges from 73% to 87% 10 years post-ETV (Isaacs et al., 2016; Waqar et al., 2016). ETV failure predominately occurs early, with 78% of failures seen within six months after surgery (Dusick et al., 2008; Labidi et al., 2015). It is uncommon for a primary ETV to fail after two years (Isaacs et al., 2016; Waqar et al., 2016).

ETV complications are largely transient having an overall morbidity rate of 8.5% (range: 0-31.2%), but permanent morbidity of 2.38% (Bouras & Sgouros, 2011; Bouras & Sgouros, 2013; Kawsar et al., 2015; Schroeder et al., 2002). The overall mortality rate is 0.28-1.28% but is rarely reported in the literature (Jung et al., 2017). The five most commonly reported complication

categories include: cognitive, vascular and neurological injury, hemodynamic alterations, endocrinologic abnormalities, electrolyte imbalances, cerebrospinal fluid leakage, fever and infection.

Cognitive complications after neuroendoscopy has also been recently summarized in a systematic review finding transient and permanent cognitive complications in 2.0% and 1.04% in 2804 neuroendoscopy procedures (Soleman et al., 2020). Although the complication rates are relatively low, three of the initial publications about ETV illustrate the severity of the complications that can occur, including: organic personality disorder, immediate memory and executive function impairment from MRI confirmed fornix and mammillary body damage (Benabarre et al., 2001); severe psychotic depression (van Aslst et al., 2002); and permanent episodic memory impairment and bulimia due to right fornix column complete section and hypothalamic lesion to the left wall of the third ventricle (Bonanni et al., 2004).

The major vascular injury rate is 0.49% due to perforation of the basilar artery and its perforators, or septal and thalamostriate veins (Kawsar et al., 2015). Permanent neurological morbidity ranges from 0.5-1.4% (Bouras & Sgouros, 2011; Bouras & Sgouros, 2013; Kulkarni et al., 2016).

Changes in ICP from aggressive irrigation and during ventriculostomy can cause intraoperative hemodynamic changes that are common and largely transient (Kawsar et al., 2015). For example, bradycardia during ventriculostomy stage is reported between 26.8-43.0% (Baykan et al., 2005; Kawsar et al., 2015). However, case reports of intraoperative cardiac arrest and post-operative

uncontrollable high-frequency tachypnea have been reported (Bernard et al., 2010; Handler et al., 1994).

Hormonal changes due to hypothalamic and pituitary injury have an overall morbidity of 0.94% (Bouras & Sgouros, 2011; Bouras & Sgouros, 2013). Diabetes insipidus, weight gain, and precocious puberty have been reported in 0.64%, 0.27%, and 0.04% in pediatric cases (Bouras & Sgouros, 2011). Electrolyte disorders may occur transiently post-ETV (Anandh et al., 2002; Bouras & Sgouros, 2011; Kawsar et al., 2015). Transient post-operative fever is also common and typically resolves within three days (de Kunder et al., 2016; Kinoshita et al., 2013).

Pediatric CSF leak has an overall reported rate of 1.7% and pediatric intracranial infections occur in 1.81-6.1% of cases (Bouras & Sgouros, 2011; Bouras & Sgouros, 2013).

ETV may represent a superior treatment to shunt procedure in adults with chronic obstructive hydrocephalus due to higher patency rate (73-87% vs 67.5%) and lower frequency of permanent complications requiring surgery (2.38% vs 15%). However, the paucity of literature on the efficacy of ETV to improve chronic hydrocephalic symptoms (cognitive, gait, and urinary dysfunction) limits comparability. If it can be demonstrated that ETV improves these chronic symptoms as effectively as shunting, it would make ETV the preferred initial option to treat obstructive hydrocephalus.

1.6 Testing Cognition in Obstructive Hydrocephalus

Cognitive testing can vary greatly by the level of detail required for the clinical assessment or research question. Short ten-minute global assessments like the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) or Mini Mental Status Exam (MMSE; Folstein et al., 1975) can be used to determine whether there exists mild cognitive impairment. However, only the global score that is made up of all the individual tests has clinical validity (Bruijnen et al., 2020). This essentially allows for a binary outcome, either cognitively impaired or normal. Logically, significantly lower scores indicate more severe cognitive impairment. But, without additional empirical categories this limits these global assessments to provide more detailed insight into the cognitive abilities of the patient. Additionally, the MMSE is not considered a very sensitive cognitive test to measure the pattern of cognitive deficits observed in hydrocephalus (Golomb et al., 1994; Iddon et al., 1999).

Using more extensive cognitive testing that is still able to be performed at the bed side is crucial for inpatient assessment and in outpatient clinics where detailed full neurocognitive assessment is not possible due to time restraints or when the patient is unable to complete lengthy multi-hour assessments. The Repeatable Battery for the Assessment of Neuropsychological Status revised (RBANS; Randolph et al., 1998) was designed specifically with these constraints in mind. It provides a portable, 20-30-minute assessment with a global cognition score made up of five individually validated cognitive domains: Immediate Memory, Visuospatial and Constructional, Language, Attention, and Delayed Memory. The RBANS allows for comparison to the normal population with percentile rankings from age-grouped normal populations every 8-12 years starting at age 12. As well, there are multiple validated versions to allow for repeated measures

testing with high test-retest reliability. This allows for greater interpretation of the global cognition and domain scores.

The greatest level of detail is only achievable with a trained neuropsychologist at an outpatient clinic, typically outside of the initial neurosurgical clinic or emergency room. A full cognitive assessment can take between 3-4 hours or even longer in some cases. As a result, this limits patient populations that are unable to attend additional clinics or are unable to undergo prolonged testing. Amongst the many benefits that do exist with detailed cognitive testing, the thorough nature of many different tests allows for a more holistic understanding of the patients cognitive and behavioural capacities, which can allow for discrimination between psychiatric and neurological symptoms. In addition, extensive domain specific testing allows for the most accurate and specific domain abilities and allows for changes over time to be easily tracked with clinically meaningful changes often available for interpretation.

Based on the chronic obstructive hydrocephalus patient population being studied in this thesis, it is essential that portable and relatively short assessments are selected able to be completed. The MoCA allows for quick and easy global assessment and the RBANS allows for a subset of patients to undergo more detailed testing at the bed side and is within the limited testing length this population is able to endure.

1.7 Evidence of ETV to Improve Cognition in Obstructive Hydrocephalus

The study of cognitive changes in chronic obstructive hydrocephalus treated with ETV is quite limited. Modern ETV was first described in 1978 by Vries and later made popular by Jones et al.

(1990). Teo (1998) reported 13 patients underwent neuropsychological testing but did not publish the results. Larsson et al. (1999) reported two patients with unrecognized congenital aqueductal stenosis had some improvement based on their overall symptom score. However, whether there existed any cognitive change post-ETV is not possible to determine based on the reported data.

The first paper on cognitive outcomes post-ETV was not published until Burtscher et al. (2003) provided pre- and post-ETV detailed cognitive testing in six adult patients with unrecognized congenital aqueductal stenosis. All six patients improved in multiple cognitive tests by means of individual analysis with descriptive statistics. Despite this being the first paper on cognitive outcomes, there was not another study using pre- and post-ETV cognitive assessments until Locatelli et al. (2014) evaluated eight patients with unrecognized congenital aqueductal stenosis and pre-ETV cognitive deficit pre- and post-ETV. They found three patients had improved and two patients had complete resolution of their cognitive deficit. However, the method of assessment was not reported, nor was there any indication of objective cognitive evaluation. Hader et al. (2014) used neuropsychology assessments evaluated with a Reliable Change Index in five pediatric and eight adult patients with chronic obstructive hydrocephalus pre- and post-ETV. Nine of 13 patients demonstrated improvement in at least one of six cognitive domains tested. Baroncini et al. (2019) used the MMSE in 15 patients with chronic obstructive hydrocephalus and found no significant difference in mean MMSE scores post-ETV. However, the MMSE is not considered a very sensitive cognitive test to measure the pattern of cognitive deficits observed in hydrocephalus (Golomb et al., 1994; Iddon et al., 1999).

Hamada et al., (2009), provided a case report of an unrecognized congenital aqueduct stenosis with normal pre-ETV scores on the MMSE (29/30), an intelligence quotient of 115, and normal RBANS domains, except visuospatial and constructional domains which was just outside of normal (84; 85-115 normal range). Post-ETV all cognitive domains significantly improved. This case report provided the first evidence against the idea that normal cognition pre-ETV excludes possible improvement post-ETV. The second evidence came from Hong et al. (2016), who presented a case report of unrecognized congenital aqueduct stenosis found incidentally and remained asymptomatic for ten years and underwent baseline neuropsychological testing. Thereafter, the patient was treated with ETV for increasing headache, memory loss, gait instability, and urinary and fecal incontinence. 15-month post-ETV neuropsychological testing had significantly improved compared to the pre-ETV baseline.

Lacy et al., (2009) conducted post-ETV cognitive assessments in ten patients with obstructive hydrocephalus. The assessments included the RBANS showing 40% of patients had >2SD cognitive deficit in two or more domains, 50% of patients had emotional testing suggestive of depression, and 30% of patients had anxiety-related symptoms. They noted specific deficits in processing speed, response inhibition, cognitive flexibility, and verbal and visual memory. However, intelligence quotient was found to be normal (study mean = 97; normal = 100 with SD =15) using the Weschsler Test of Adult Reading. Al-Jumaily et al. (2012) also used the RBANS in a group of twenty unrecognized congenital obstructive hydrocephalus post-ETV to determine how they compared to the normal population. The mean RBANS total score and domains scores were all below the normal range. Xhu et al., (2013) found seven of nine adults who underwent

ETV and biopsy have post-operative normal cognitive scores on the MMSE and Rivermead Behavioural Memory Test.

This relative lack of studies that assess cognition in a systematic prospective manner, both pre- and post-ETV, has limited our ability to quantitatively assess both the potential cognitive benefits and risks of ETV. This provides weak and conflicting evidence of cognitive change post-ETV due to their heterogeneous results, small sample size, and variation in cognitive testing.

1.8 Research Question

To address the gaps in the literature, we proposed to use neurocognitive assessments pre- and post-ETV in prospective cohorts to demonstrate how global cognition and multiple cognitive domains are affected by ETV treatment of chronic obstructive hydrocephalus in adults.

We hypothesize that ETV will improve global cognition based on the existing literature and expert opinion. Hydrocephalus is thought to follow a frontal-subcortical dementia pattern therefore we hypothesize that ETV will improve immediate memory, delayed memory, and attention domains, but not the cortically driven language domain. Additionally, ETV may cause damage to visuospatial networks as has been described in the literature and based on surgical manipulation around important anatomy to these systems.

Using this framework, this thesis will meet the following specific objectives:

O1. *To determine the sufficiency of primary ETV to safely improve global cognition in adults with chronic obstructive hydrocephalus.* We will use the MoCA to measure global cognitive changes pre-ETV and twice post-ETV prospectively in a multicenter study.

O2. *To determine which cognitive domains ETV produces clinically meaningful changes in adults with chronic obstructive hydrocephalus.* We will use the RBANS to individually measure five cognitive domains pre-ETV and once post-ETV in a prospective single center study.

Chapter 2: Short- and Long-term Follow-up of Cognitive Outcomes after Primary ETV in Adult Chronic Obstructive Hydrocephalus

The first objective of this thesis is to determine if ETV safely improves cognition in adult patients with chronic obstructive hydrocephalus. The MoCA and SDMT allows for assessment of global cognition, processing speed and task switching with short assessment time. This will allow for multi-center data collection within the Adult Hydrocephalus Clinical Research Network (AHCRN). Results from this paper will provide the first prospective data, solely in adults with both pre- and post-ETV testing over three time points.

2.1 Methodology

The details of the AHCRN registry and its methods have been previously described (Williams et al., 2019). Subjects were enrolled prospectively; however, not all patients seen at each center could be enrolled.

2.1.1 Inclusion and Exclusion Criteria

Subjects for this study enrolled in the AHCRN registry between December 2014 and January 2019 and had primary ETV procedures between April 2015 and January 2019, with a minimum of three months follow-up after the procedure. From subjects in the Unrecognized Congenital and Acquired categories, we identified those with obstructive hydrocephalus, potentially amenable to ETV, based on brain CT or MRI with evidence of obstruction to CSF flow at the cerebral aqueduct, within the 4th ventricle, or at the foraminae of Luschka and/or Magendie.

The purpose of this study was to examine the effect of primary ETV on cognition in adults with chronic obstructive hydrocephalus. Therefore, subjects were excluded if: 1) The hydrocephalus had previously been treated either with an ETV or a shunt; 2) Pre- and post-ETV MoCA was unavailable; or 3) The patient required a subsequent shunt procedure or repeat ETV, within five months of the primary ETV.

2.1.2 Baseline Evaluations

MoCA versions 7.1, 7.2, and 7.3 (Nasreddine et al., 2005) and SDMT original version, alternative 1, and alternative 2 were used to assess global cognition and processing speed (Smith, 1982; Benedict et al., 2017). The MoCA contains 12 items that fit into seven cognitive domains and sum into a total score between 0-30. A total score of greater than 25 is considered normal. Although the total score has good psychometric properties, the cognitive domains should be interpreted with caution (Bruijnen et al., 2020). Therefore, only the MoCA total score (MoCA TS) was used in this study. A change in MoCA TS of ≥ 2 points was defined as clinically significant (Krishnan et al., 2017). A clinically significant change in SDMT was defined as ≥ 4 points (Smith, 1982; Benedict et al., 2017). Only primary ETV patients that had documentation of a pre- and post-ETV MoCA were included in the analysis.

2.1.3 Intraoperative Data

Data recorded included: type and size of endoscope used, bleeding during procedure, any surgical parenchymal contusion, vascular/vessel injury, if a biopsy was performed, if the procedure was abandoned, the method and instrument used to create and enlarge the opening in the floor of the third ventricle, any additional procedure performed, CSF appearance at the

beginning and end of the procedure, whether an open pre-pontine cisternal space was achieved with basilar visualization, estimated size of fenestration and if an EVD was inserted. Any additional intra-operative or subsequent post-operative complications were also recorded.

2.1.4 Statistical Analysis

Binary and categorical data are presented as numbers and percentages. Continuous outcomes, which tended to have skewed and/or long-tailed distributions, are presented using medians and the interquartile range (IQR). IQRs are presented using the notation [X-Y], indicating that approximately one-quarter of observations have values less than X, one-quarter have values greater than Y, while the middle 50% of observations lie in the interval [X-Y]. The within-patient change medians for MoCA TS were determined by subtracting the pre-ETV score from the post-ETV score of each patient and taking the median of the resulting change scores. Assessments of whether within-patient change scores differ significantly from zero were performed using the Wilcoxon signed rank test. All reported *p*-values are two-sided, with a significance level of $\alpha = 0.05$.

2.2 Results

2.2.1 Patient Population (Figure 1)

A total of 74 patients underwent primary ETV, of which 38 patients were analyzed. Thirty-six ETV patients were excluded from this study as they could not complete either a pre- and/or post-ETV MoCA assessment. The most common reasons for exclusion included drowsiness or cognitive deficits that precluded their ability to follow instructions to complete cognitive assessments. However, this group of 36 patients was still followed and assessed at four months

post-ETV. Compared to pre-ETV, 12/36 could complete a MoCA test post-ETV. Therefore, many of these 36 excluded ETV patients did demonstrate substantial improvement in cognition post-ETV, but this improvement could not be measured due to the lack of objective pre-ETV data.

Of the 38 patients, 17 (45%) were female. The mean age was 51.9 ± 17.1 years. Most patients were Caucasian (n=33; 87%), with the remainder Asian.

The most common hydrocephalus category was Unrecognized Congenital (n=28, 74%), which included aqueduct stenosis (n=21, 55%), aqueductal pattern (n=6, 16%) and arachnoid cyst (n=1, 3%). The remaining 10 patients (26%) were in the Acquired category, which included brain tumour (n=6, 16%; 2 malignant and 4 benign), intraventricular adhesion or web (n=3, 8%), and other masses or vascular anomalies (n=1, 3%).

Pre-operative symptoms included: cognitive problems (n=26, 68%), gait disturbance (n=22, 58%), headache (n=19, 50.0%), and urinary dysfunction (n=18, 47%). Nineteen patients (50.0%) presented with combined dysfunction of cognition, gait, and urination.

An open pre-pontine cisternal space with basilar visualization was recorded by the surgeon in 33 procedures (87%). In the remaining five patients, the ETV was felt to be successful based on improvement of baseline signs and symptoms, decreased ventricular size on post-ETV imaging and absence of the patient requiring an additional CSF diversion procedure within five months of the primary ETV.

The mean early post-ETV assessment was at 4.6 ± 4.0 months (n=38) and is labelled as “5-Months Follow-up” (Tables 1 & 2; Figures 1, 2 & 3). The mean late post-ETV assessment was at 14 ± 3.1 months (n=15) and is labelled as “14-Months Follow-up”.

2.2.2 MoCA (Table 1 and Figure 2)

5-Months Follow-up (n=38): The baseline median MoCA TS score was 24/30 [23-27]. The 5-months follow-up median MoCA TS score was 26/30 [24-28]. The median within patient change was +1 point [0-2], $p < 0.001$, which does not meet the threshold of ≥ 2 points for clinical significance (Krishnan et al., 2017).

14-Months Follow-up (n=15): The baseline median MoCA TS was 23/30 [22-27]. The 14-months follow-up MoCA TS was 26/30 [25-28]. The median within patient change was +2 points [1-3], $p = 0.007$, which is also clinically significant.

2.2.3 SDMT (Table 2)

The SDMT scores did not change following ETV at either the 5-months or 14-months follow-up (Table 2). For the 5-Months follow-up (n=32), the baseline median SDMT score was 39 [29-48], 5-months follow-up median was 45 [35-50], and the median within patient change was +3 [-1-6], $p = 0.084$. For the 14-Months follow-up (n=14), the baseline median SDMT score was 32 [28-43], the 14-months follow-up median score was 38 [30-46], and the within patient change was +3.0 [1.0-8.0], $p = 0.138$. Both the 5-months and 14-months follow-up change scores failed to meet the clinical significance criterion of ≥ 4 points (Smith, 1982; Benedict et al., 2017).

2.3 Discussion

Our prospective and multicenter study shows that when adults with untreated chronic obstructive hydrocephalus present with cognitive impairment, treatment with ETV results in significant and sustained improvement for as long as 14 months. Although, early clinically significant improvements were not seen at 5-months follow-up. This suggests that longer follow-up is needed to identify this gradual cognitive improvement.

Our study provides the largest dataset to date on cognitive impairment at the time of presentation in adults with chronic obstructive hydrocephalus, as well as its response to ETV. This relative lack of studies that assess cognition in a systematic manner, both pre- and post-neuroendoscopy (Soleman & Guzman, 2020), has limited our ability to quantitatively assess both the potential cognitive benefits and risks of neuroendoscopy. Only four relevant cohort studies have included pre- and post-ETV cognitive assessment (Burtscher et al., 2003; Locatelli et al., 2014; Hader et al., 2014; Baroncini et al., 2019). One study stated that 5/8 patients, who had pre-ETV cognitive impairment, improved post-ETV but the method of assessment was not provided, and an objective evaluation of change was not reported (Locatelli et al., 2014). Nine of 13 adult and pediatric patients demonstrated improvement in at least one of six cognitive domains using neuropsychology assessments evaluated with a Reliable Change Index (Hader et al., 2014). Burtscher et al. (2003) found 6/6 patients demonstrated some cognitive improvement post-ETV, utilizing a large battery of cognitive tests, however only used descriptive statistics and individual analysis. Baroncini et al. (2019) found no significant difference in mean MMSE scores post-ETV in 15 patients. However, the MMSE is not considered a very sensitive cognitive test to measure

the pattern of cognitive deficits observed in hydrocephalus (Golomb et al., 1994; Iddon et al., 1999). These studies provide weak and conflicting evidence of cognitive change post-ETV due to their heterogeneous results, small sample size, and variation in cognitive testing.

In our study, the change in median MoCA score at the 5-months follow-up was overall not clinically significant, although 40% of patients did have an increase score of at least two points. This could be due to insufficient power or subgroup differences. However, the improvement at 14-months follow-up was clinically significant and indicates that treating chronic obstructive hydrocephalus with ETV results in long-term improvement in cognition, although 40% of the group had no change and one patient (7%) worsened. Increased numbers in our long-term cohort will improve the validity of any cognitive changes seen in chronic obstructive hydrocephalus patients post-ETV.

Cognitive processing speed and efficiency, as measured by SDMT, was not improved at either the 5-months or 14-months follow-up. This test has been shown to be sensitive to processing speed in the multiple sclerosis population (Benedict et al., 2017). Detailed cognitive assessment with a comprehensive neuropsychological battery should be carried out in the future.

In summary, statistically significant but not clinically significant improvement in cognition may not be evident at 5-months post-ETV but becomes both clinically and statistically significant by one-year post-ETV. In addition, our data demonstrate that ETV can be performed safely with a low rate of cognitive deterioration: worsening of global cognition was rare, both at 5-months (2 patients) and at 14-months (1 patient) following ETV.

Chapter 3: Improved Global Cognition, Attention, and Delayed Memory After Endoscopic Third Ventriculostomy in Adult Chronic Obstructive Hydrocephalus Using The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The second objective of this thesis was to determine which cognitive domains are affected after ETV for adult chronic obstructive hydrocephalus. The RBANS allows for assessment of global cognition and five major cognitive domains: immediate memory, visuospatial/constructional, language, attention, and delayed memory. This will allow for determination of which domains of cognition are causing the global changes seen with the MoCA. Additionally, a novel pre-ETV predictor of post-ETV global cognition improvement will be discussed.

3.1 Methodology

3.1.1 Inclusion and Exclusion Criteria

Subjects were enrolled prospectively as they presented to our outpatient clinic or emergency department between April 2018 and March 2020, with a minimum of three months follow-up after the procedure. We identified those with obstructive hydrocephalus, potentially amenable to ETV or endoscopic resection, based on brain MRI with evidence of obstruction to CSF flow at the foramen of Monroe, cerebral aqueduct, within the 4th ventricle or at the foraminae of Luschka and/or Magendie. Subjects were excluded if they could not complete pre- or post-ETV assessments or if the patient required subsequent resection, shunt procedure, or repeat ETV within five months.

3.1.2 Assessments

The patient underwent the following assessments pre-ETV and once post-ETV. The MoCA is a five- to ten-minute global cognitive assessment (Nasreddine et al., 2005). It is based on 12 items that fit into seven cognitive domains and sum into a total score between 0-30. A total score greater than 25 is considered normal. Although the total score has good psychometric properties, the cognitive domains should be interpreted with caution (Bruijnen et al., 2020). Therefore, we have elected to only consider the total score in our analysis. A change in MoCA total score (MoCA TS) of ≥ 2 points was defined as clinically significant (Krishnan et al., 2017). MoCA versions 7.1, 7.2, and 7.3 were used.

The RBANS is a 25-minute neurocognitive assessment (Randolph et al., 1998). It is based on 12 subtests that fits into five cognitive domains (immediate memory, visuospatial and constructional, language, attention, and delayed memory) and sum into a total score for global cognition with percentile. The total score and indexes are based on age-grouped normal populations with a mean of 100 and standard deviation of 15. We elected not to determine whether our population was significantly different from the normal population, as the purpose of this study was to establish initial data on how cognitive domains change within patient post-ETV.

There is exist some controversy on the psychometric properties of the original domain groupings, with many suggesting new grouping of the subtest (Wild et al., 2006; Duff et al., 2006; Carlozzi et al., 2008; Garcia et al., 2008; Yang et al., 2009; Duff et al., 2010; Schmitt et al., 2010; King et al., 2012; Torrence et al., 2016; Vogt et al., 2017). But, many of these studies were conducted on

mixed group or normal populations, which leads to ceiling effects during testing. Two recent papers that assessed the RBANS on Alzheimer's and suspected cognitive impairment patients found good psychometric proprieties in the five original domains (Emmert et al., 2018; Holden et al., 2020). Therefore, we selected to keep the original five domains as well as the total score as our primary outcome variables. Secondary analysis included the 12 subtests and the effect of age.

There exist neither a perfect Minimum Clinically Important Difference (MCID) or Reliable Change Index (RCI) for the RBANS that fits our sample's needs. Phillips et al. (2015) MCID has been critiqued for design compared to the available RCI (O'Connell, 2019). However, the cohorts were not equal in cognitive performance (healthy controls vs dementia) and all domains except for the visuospatial/constructional domain MCIDs were satisfactory. Nonetheless, careful interpretation of the visuospatial/constructional domain should be utilized, and subtest interpretation can be used for more precise interpretation of subdomain changes. In contrast, the RCI available is based on an elderly (>65 years old) population and is less robust at percentile extremes (Duff, 2004 & Duff, 2005). Since our sample's mean age is 34 and the percentiles for the primary outcomes are extremely low, the MCID was selected as the clinically changed cut-off. This will allow for a general idea of how the sample changed clinically. Although further validation of the MCIDs and RCIs of RBANS on hydrocephalus patients is required for more robust results. The MCID are as follows: RBANS TS ≥ 8 , Attention ≥ 4 , Delayed Memory ≥ 10 , Language ≥ 9 , Immediate Memory ≥ 10 , Visuospatial/Constructional ≥ 6 .

3.1.3 Intraoperative Data

Data recorded included: type and size of endoscope used, bleeding during procedure, any surgical parenchymal contusion, vascular/vessel injury, if a biopsy was performed, if the procedure was abandoned, the method and instrument used to create and enlarge the opening in the floor of the third ventricle, any additional procedure performed, CSF appearance at the beginning and end of the procedure, whether an open pre-pontine cisternal space was achieved with basilar visualization, estimated size of fenestration, and if an EVD was inserted. Any additional intra-operative or subsequent post-operative complications were also recorded.

3.1.4 Statistical Analysis

Binary and categorical data are presented as numbers and percentages. Continuous outcomes with skewed and/or long-tailed distributions, are presented using medians and the interquartile range (IQR). IQRs are presented using the notation [X-Y], indicating that approximately one-quarter of observations have values less than X, one-quarter have values greater than Y, while the middle 50% of observations lie in the interval [X-Y]. Otherwise, 95% confidence interval are displayed as (lower bound, upper bound). The within-patient change medians were determined by subtracting the pre-ETV score from the post-ETV score of each patient and taking the median of the resulting change scores. Assessments of whether within-patient change scores differ significantly from zero were performed using the Wilcoxon signed rank test. All reported p -values are two-sided, with a significance level of $\alpha = 0.05$. Correlations were computed with Pearson's r . No familywise correction was used due to the exploratory nature of the study design.

3.2 Results

3.2.1 Patient Population (Figure 3)

A total of 29 ETV candidates underwent pre-ETV RBANS testing, of which 17 underwent primary or secondary ETV, with one patient receiving an endoscopic resection without ventriculostomy. Ten patients completed the follow-up assessment, of which seven primary ETVs were performed, two secondary ETVs and one endoscopic resection without ventriculostomy. Twenty ETV patients were excluded from this study as they did not undergo an ETV or did not complete any post-ETV testing. The most common reasons for exclusion included: incomplete testing either pre-ETV, lack of symptomology to indicate surgery (n=4), and ETV requiring subsequent diversion procedure before post-ETV assessment (n=4). However, this group of 20 patients is still being followed for standard clinical follow-up.

Of the ten patients analyzed, seven were female. The mean age was 34.00 years (SD: ± 16.98 , range: 17-68). Patients were Caucasian (n=9) or Asian (n=1). The most common hydrocephalus category was the acquired category (n=6), which included brain tumour (n=3, 1 benign midbrain tectal glioma, 1 benign thalamic tumour, 1 hemangioblastoma), colloid cyst (n=1), pineal cyst (n=1), and cavernous malformation (n=1). Two patients (20%) were in the unrecognized congenital category, which included aqueduct stenosis (n=1) and arachnoid cyst (n=1). Two secondary ETVs were conducted on etiologies of previously shunted aqueductal stenosis (n=2).

Pre-operative symptoms included: decreased level of consciousness (n=2), headache (n=7), nausea and vomiting (n=2), and cognitive problems (n=6).

An open pre-pontine cisternal space with basilar visualization was recorded by the surgeon in all nine ETVs. The endoscopic resection of a 3rd ventricular colloid cyst was felt to be successful based on successful near total resection, improvement of baseline symptoms and signs, decreased ventricular size on post-operative imaging, and absence of the patient requiring an additional CSF diversion procedure within 3-months.

Pre-ETV assessment was at 22.6 ± 44.5 days before ETV. The follow-up assessment was at 3.8 ± 2.3 months and is labelled as 4-Month Follow-up (Table 2).

3.2.2 MoCA (Table 2 and Figure 4)

The 4-month (n=9) follow-up median within patient change in MoCA TS was not significantly different, 0 point (-2, +1), $p = 0.7204$ (Table 2; Figure 6). The baseline and post-ETV median MoCA TS were 23/30 and 24/30, which is outside the normal range of $\geq 26/30$. At baseline, 2/9 patients had MoCA TS in the normal range. Post-ETV only one patient had a normal score. Individual clinical change shows 2/9 patients had a clinically significant improvement and 3/9 patients had clinically significant worsening of ≥ 2 points (Krishnan et al., 2016).

3.2.3 RBANS (Table 2 and Figure 5)

In contrast to the MoCA data, RBANS Total Score (RBANS TS) post-ETV was significantly improved with median a within patient change of $+8.0 [+4.25, +15.50]$, $p = 0.0125$. This also met the MCID criteria of ≥ 8 as being clinically improved. Individually, 50% (5/10) showing clinically significant differences in total score and no significant worsening. However, the

median RBANS TS was still > 1SD below normal (100) at pre-ETV, 72 [55-81], and post-ETV, 77 [66-89].

The Total Score Percentile (TSP) was also significantly improved from a median of 3.5 [0.33-11] to 6.5 [1.25-23.5], with a change score of +3.45 [+0.30, +18.00], $p = 0.0284$. It should be noted that since the total score was significantly different, the TSP will likely be significant as well since they contain the same data in different unit conversions (ie. colinear). The magnitude of within patient change in TSP was strongly correlated to the pre-ETV TSP, $r = 0.83$ (0.43, 0.96), $p = 0.0027$ (Figure 6).

The standard five-factor analysis of the 12 subtests showed that the improvement in global cognition came from the Attention and Delayed Memory Index Scores, $p = 0.0058$ and $p = 0.0143$. Both index scores also met their MCIDs. Pre-ETV medians for Attention and Delayed Memory and the Attention post-ETV median were 1 SD below the normal population mean. Delayed Memory was the only domain to improve into the normal range post-ETV. Immediate Memory, Visuospatial/Constructional, and Language were not significantly different, nor did they meet their respective MCIDs. Language was the only other domain whose median scores were within ± 1 SD of normal: Pre-ETV, 88.0 [57.00-95.25]; Post-ETV, 85.5 [76.0,105.0].

The Attention Index Score is a composite of the digit span and coding subtests. Digit span was significantly improved by +1.5 points [0.25, 2.75], $p = 0.0397$. As subtests do not have half points, interpretation of median changes will be a range from the closest two whole numbers. This equates to an extra one or two second-string repetition on the test or one additional first-

string item out of eight items. This is a median 9.375% improvement on this subtest. The Coding subtests was nearly statistically significant at +5.5 [2.5, 7.5], $p = 0.0523$. Six additional correct matching is a 6.74% improvement on this test.

The Delayed Memory Index Score is a composite of four subtests using a summed score from three recall subtests (Figure Recall, List Recall, and Story Recall) and the List Recognition subtest. The Figure Recall was significantly improved by +5.0 points [2.5-5.75], $p = 0.0049$. This is an additional five correct drawing or placement items and a median 22.5% improvement on the subtest. List Recall was trending towards significance at +1 point [0.00, 2.75], $p = 0.0790$. This represents a 10% improvement in remembering ten items without cueing. Story Recall was not significant, $p = 0.2736$. However, when summed together there was a statistically significant improvement of +5.5 point [4.25, 11.50], $p = 0.0058$. The total possible summed score is 42, therefore a median 13% improvement was seen in delayed memory recall. However, List Recognition was not significantly improved, $p = 0.6989$. Thus, the Delayed Memory index score interpretation should be limited to improved figure recall and potentially list recall, but not recognition.

Picture naming was significantly improved by +4 [1.0,5.0], $p = 0.0162$. It is one of the components for the language index score, the other being semantic fluency, which was not significant, $p = 0.3571$. Story memory, a part of the Immediate Memory index, is the only other subtest to be marginally trending towards significance at $p = 0.1000$. All other subtests were not significantly different.

3.2.4 Pre-ETV Memory Domains as a Predictor of Post-ETV RBANS TS Improvement

When compared individually, all five of the patients who had clinically improved RBANS TS post-ETV also had similar Immediate and Delayed Memory index scores, within ± 3 points. The Immediate Memory and Delayed Memory Index Scores were subtracted from each other and the difference was plotted against their paired change in RBANS TS (Figure 7). Retrospectively, the memory difference score perfectly separates those who had clinically significant improvement from those who did not. No other pre-ETV indexes were similar to each other to suggest a different predictor.

3.2.5 Individual Analysis

Individual analysis shows that when the MoCA TS and RBANS TS were compared in this small sample, the MoCA TS showed three patients who had clinically significant worsening, but their RBANS TS did not. In fact, one of the three patients had an improved RBANS TS and was the only patient to improve in 4/5 domains. The other two patients had no clinically different RBANS TS. These two patients had 1-3 domains clinically improve and 0-1 clinically worsened domain. Both patients who had a significant improvement in the MoCA TS also had a significant improvement in RBANS total score. Of the four patients who had no significant change in MoCA TS, two had significant improvements in RBANS TS.

RBANS TS and Delayed Memory had 5 patients who met the MCID for clinical improvement and no patient worsened. Attention had seven patients clinically improve and no worsening. Immediate memory had four patients clinically improve and no worsening. Language had five patients clinically improve and one who had clinically worsened. Visuospatial/Constructional

had two patients clinically improve and five who clinically worsened. The patients who had Language worsening also had clinically worse visuospatial/constructional domain.

Overall, all patients had at least one significantly improved domain, seven patients had at least two significantly improved domains, four patients had at least three significantly improved domains, and one had four significantly improved domains. No one improved in all five domains.

3.3 Discussion

This prospective study with multidomain cognitive testing shows that when adults with chronic obstructive hydrocephalus undergo treatment with ETV, clinically and statistically significant improvements in Attention and Delayed Memory domains are present at 4-months follow-up. Global cognitive changes showed conflicting results depending on method of assessment, however more robust testing suggests significant improvement in global cognition. Although not statistically significant, individual analysis revealed the Visuospatial/Constructional domain may be worsened initially post-ETV. Lastly, pre-ETV memory domains may predict post-ETV global cognitive improvement.

3.3.1 MoCA

In this follow-up study to the previous chapter, the median baseline MoCA TS was the similar at 23/30 and 24/30, suggesting that these two samples had comparable pre-ETV cognitive symptoms. The median short-term (4/5-months) follow-up scores were similar, showing no clinically significant change. The percentages of patients that showed clinical improvement

differed from 20% (2/10) to 40% (15/38). The striking difference was that this sample had 30% (3/10) patients who clinically worsened versus 5% (2/38) in the previous study. Due to the small sample size it is unclear whether these differences were simply due to sampling error or whether selection bias played a role. The bias for continued follow-up in those who may be still symptomatic could be overrepresented in those who complete the follow-up assessment and are available for analysis. It is likely that the small sample size led to a component of both sampling error and selection bias. Since this is an exploratory study, more conservative estimates of improvement will not lead to exaggerated conclusions. Mindful interpretation of the generalizability is still required.

3.3.2 RBANS TS and TSP

This is the first study on ETV cognitive outcome that used validated multi-domain cognitive testing with good psychometric properties collected prospectively solely in adults pre- and post-ETV. This small study helped to bridge the gap within the limited literature surrounding cognitive changes post-ETV. By using the RBANS TS we provided additional evidence for global cognitive improvement in 50% (5/10) of patients at short-term follow-up. Additionally, the RBANS TS found 0% (0/10) of patients had clinically or statistically significant worsening of global cognitive.

Only four cohort studies had both pre- & post-ETV cognitive testing (Baroncici et al., 2019; Locatelli et al., 2013; Hader et al., 2014; Burtscher et al., 2003). They showed no significant difference, 63%, 69%, and 100% improvement in cognition post-ETV. However, Baraoncici et al., (2019) found used the MMSE, which has been shown to have poor sensitivity in

hydrocephalus patients (Golomb et al., 1994; Iddon et al., 1999). Hader et al. (2014) showed that 69% (9/13) mixed-aged patients improved in at least one of six cognitive domains tested, with 17% worsening in executive function. Burtscher et al (2003) by way of descriptive statistics and individual analysis found 100% of patients improved in some of their pre-ETV deficits, with two patients returning to normal scores, three patients with improved but abnormal scores, and one patient with continued deficits in some domains with improvement in others. Locatelli et al. (2014) listed 63% (5/8) patients with pre-ETV cognitive deficit had improved (3/8) or resolved (2/8) symptoms post-ETV. However, the method of assessment was not included and no objective evaluation of change was reported. Similarly, the RBANS TS in our sample had > 1 SD deficit in 8/10 patients pre-ETV and 6/10 patients post-ETV. In this view, two patients returned to normal scores. But, by looking at the RBANS TS MCID 50% (5/10) of patients improved in global cognition. Included in those improved patients were the two patients who had normal scores of 99 and 100 pre-ETV, which improved by 9 and 16 points respectively post-ETV. Therefore, normal scores on the RBANS TS does not limit the patient from improving post-ETV. Thorough history and examination should still be done to determine each patient's own normal and any deviations from it.

The Total Score Percentile (TSP) is an alternative representation of the RBANS TS that does not rely on MCID, but instead is compared to an age-matched normal population. The TSP demonstrated the extremely low median global cognitive percentiles this population has before (3.5%) and after surgery (6.5%). Burtscher et al (2003) also found all six patients had multiple tests scores below the 3rd percentile pre-ETV. Hader et al. (2014) also found that 11/12 patients pre-ETV had at least one 'borderline' domain \leq 16th percentile (one patient excluded as four of

six domains were not tested) and 8/12 patients had at least one 'impaired' domain $\leq 7^{\text{th}}$ percentile.

Although statistical and clinical improvement in global cognition was seen in the RBANS TS, the median within patient change in TS percentile was only +3.45% with 7/10 patients still under the 10th percentile and 2/10 patients >50th percentile post-ETV. These are the same two patients with normal RBANS TS. The magnitude of change was strongly correlated with Pre-ETV TSP ($r = 0.83$). Showing that those with a higher pre-ETV percentile tend to improve the most. This may have implications for treating those with minimal or mild cognitive dysfunction and evidence of obstructive hydrocephalus. A case report found that a 39-year-old woman with a pre-ETV intelligence quotient (IQ) of 115, MMSE =29/30, and RBANS TS and domains within +/- 1SD of norms with the exception of visuospatial and constructional, had significant improvement in immediate and delayed memory, and visuospatial and constructional domains (Hamada et al., 2009). Hong et al. (2016) also presented case report of incidental, asymptomatic, unrecognized congenital aqueduct stenosis for normal baseline neuropsychological testing. Ten years later, the patient presented with increasing headache, memory less, gait instability, and urinary and fecal incontinence and was treated with ETV. The 15-month post-ETV neuropsychological testing showed significant improvements compared to the pre-ETV baseline scores. As well, delaying treatment until further cognitive dysfunction may limit the amount of improvement seen post-ETV, as has been shown in the shunting literature (Kazui et al, 2015 (ie. Siphoni trial); Yamada et al., 2017 (post-hoc Siphoni trial); and Andren et al., 2014).-In sum, a normal RBANS TS does not exclude patients from improvement as those with the highest pre-ETV scores may see the greatest improvements.

3.3.3 Index Scores

Using the standard indexing, attention and delayed memory were statistically and clinically improved at 4-months follow-up. Individual analysis showed that 70% of patients had clinically improved attention and 50% showed clinically improved delayed memory. No one had clinical worsening in these domains. However, both pre- and post-ETV median were below the normal range.

Attention domain improvements post-ETV have been shown previously (Hader et al., 2014). This study found improvement in the attention domain with 33% improving with no worsening post-ETV. Their median pre-ETV attention percentile was 27th but did not reach their definition of borderline or impaired. Improvements in attention post-shunting in iNPH has been previously seen as well (Liu & Su, 2020). However, long-term attention problems may persist more than 20 years after shunt insertion in pediatric patients (Gmeiner et al., 2019). Although there was improvement in attention post-ETV, it is possible that attentional problems may persist throughout life.

The Attention domain is derived from the Digit Span (forwards) subtest and the Coding subtest. The functional implication of improvements in these subtests and therefore the index scores are increased working memory storage capacity (McGrew, 2009) and improved processing speed and task switching (Smith, 1982). Working memory storage capacity can be thought of as the ability to guide behaviour by using and retaining information over short time intervals (Drew & Vogel, 2009; Goldman-Rakic, 1987). The coding subtest is similar to the SDMT used in the

previous study. Interestingly, there was a near significant difference in this cohort ($p = 0.0523$) and a trend towards significance at 4-months using the SDMT in the larger cohort ($p = 0.084$). Future studies evaluating the long-term attentional outcomes are needed. As well, the impact of attentional improvements on quality of life is warranted.

Delayed memory recall but not recognition was improved in our study. This may be indicative of different networks being affected. Recall has been causally associated with the hippocampal-cortical network (Wang et al., 2014; Nilakantan et al., 2019). Recognition is based on two distinct processes, recall and familiarity discrimination (Brown, 2015). The latter has been shown to be found in the perirhinal cortex of the temporal lobe (Brown, 2015). Chronic hydrocephalus cognitive dysfunction typically follows a frontosubcortical dementia pattern (Ogino et al., 2006). This difference in location between subcortical networks and temporal cortex may explain why recall but not recognition is improved.

Visuospatial and constructional index had the largest amount of clinically worsened scores by individual analysis (50%), but was not statistically changed, $p = 0.3850$. The figure copy subtest had two patients achieve max scores post-ETV and two patients worsen post-ETV (-1 and -3 points). Line orientation subtest had six patients with a negative change score. This suggest that this subtest makes up a large proportion of worsening in the visuospatial/constructional index score. Line orientation is a basic visuospatial task. Worsening scores in 50% of patients regardless of statistical significance is concerning for post-ETV deficits in this domain.

Through lesion-mapping, subcortical fibers associated with performance on line orientation and figure copy have been associated with the right frontal area when the endoscope is advanced through the brain (Biesbroek et al., 2014). However, the lesion-mapping studies produce large areas of fMRI activity and are not conclusive as anatomical correlates. Additionally, the subcortical pathway for visuospatial function is poorly understood. More detailed visuospatial assessments should be performed and compared to left versus right endoscope placement and whether right forniceal and medial mammillary body injury intra-operatively is correlated to these outcomes.

Lastly, although the language domain was found to be not significantly changed, $p = 0.2300$. There may exist a ceiling effect as picture naming was found to be significantly improved from a within patient median of 9/10 pre-ETV to a within patient median of 10/10 post-ETV, and a within patient change of +1 (0, +1), $p = 0.0162$. The significance was largely drawn from two patients who had +7 and +9 point improvements, all other patients had improvements of 0 or +1. Seven of ten patients achieved max scores, thus limiting the assessment of potential improved gained. Semantic fluency was found to not significantly changed, $p = 0.3571$. However, four patients had worse post-ETV semantic fluency scores. Three of these four patients achieved max scores in picture naming and the other scoring 9/10 both pre- and post-ETV. The patient with clinically worsened language index score achieved max score on picture name and -9 words on semantic fluency.

3.3.4 Retrospective prediction of global cognition improvement based on memory scores

In iNPH, the RBANS was used pre- and post-external lumbar drain to predict cognitive improvement after shunting (Nakatsu et al., 2016). They found that when both baseline immediate and delayed memory index scores were below 80, they could retrospectively predict 13/19 patients who improved post-shunting. In our study, the difference between immediate and delayed memory index scores was within three points of each other in all patients who showed clinically significant improvement in the RBANS TS.

Remembering that the delayed memory index scores was based off recall and not recognition, with the knowledge that immediate memory and recall delayed memory are symptoms of subcortical dementia, it fits with the expected symptomatology of chronic obstructive hydrocephalus and these patients would therefore expect to improve. However, the three patients with worse delayed memory scores when compared to immediate memory present with an amnesic pattern of dementia. So, these patients do not fit with the subcortical dementia symptoms of chronic obstructive hydrocephalus and unlikely to improve in their cognitive symptoms post-ETV. The last group represent those with delayed memory scores greater than their immediate memory scores. This does not mean that they remembered more after a delay than immediately after presenting the stimuli, it is the relative difference in capacity. This is an uncommon symptom presentation that can be seen in those with high test anxiety or where questions of effort may exist. This dementia paradigm suggests that pre-ETV determination of those with frontosubcortical dementia symptomatology and chronic obstructive hydrocephalus may predict who will have global cognitive improvements post-ETV.

3.3.5 MoCA vs RBANS

In this cohort, the MoCA TS was not statistically or clinically changed. Whereas, the RBANS TS was both clinically and statistically improved. Individual analysis shows the MoCA TS was clinically worsened in 30% (3/10) and clinically improved in 20% (2/10). The RBANS TS had 50% (5/10) of patients clinically improved with no worsening. This finding highlights the benefits of extended neurocognitive testing. Individual analysis found no trend in MoCA subdomains leading to the clinical worsening or improvement.

Chapter 4: Conclusions

4.1 Summary of Thesis Objectives

This thesis aimed to determine the efficacy of ETV to improve cognition in chronic obstructive hydrocephalus. The literature to date consists of retrospective, underpowered, post-operative, global cognitive assessments (Al-Jumaily et al., 2012; Burtscher et al., 2003; Hader et al., 2014; Lacy et al., 2009; Takahashi, 2006; Azab et al., 2016 for review.) The published evidence for cognitive improvement post-ETV is weak and conflicted. So, we designed two studies accounting for those previous limitations with the following objectives:

O1. To determine the sufficiency of primary ETV to safely improve global cognition in adults with chronic obstructive hydrocephalus.

O2. To determine which cognitive domains ETV produces clinically meaningful changes in adults with chronic obstructive hydrocephalus.

4.2 Objective 1: Conclusions and Limitations

Primary ETV can safely improve symptoms of cognitive dysfunction in adults with chronic obstructive hydrocephalus. ETV resulted in significant and clinically meaningful long-term improvement in global cognition in some adults with chronic obstructive hydrocephalus.

Deterioration of global cognition was rare following ETV. ETV is an effective treatment for patients with chronic obstructive hydrocephalus and may be superior to shunt procedures given the potentially lower failure and complication rates of ETVs. Future evaluations of the AHCRN registry patients undergoing ETV should further strengthen these observations.

A limitation of this study comes from incomplete registry data relevant both to patients who were too impaired to undergo assessment either at baseline (36 patients), 5-months post-ETV (13 patients), and due to a small number of patients with only either a pre- or post-ETV MoCA. An additional limitation is the modest population size. However, the results were obtained using standardized methodology for cognitive assessment with within patient analysis, thus maximizing the power of the sample size.

4.3 Objective 2: Conclusions and Limitations

Patients with chronic obstructive hydrocephalus treated with ETV have a clinically and statistically significant improvement in global cognition, attention and delayed memory cognitive domains at 4-months follow-up. There was no worsening in global cognition, attention, delayed memory, or immediate memory indexes. Although there were no statistically worsened cognitive domains, 50% of patients had a clinical worsening in visuospatial index scores. A potential predictor of post-ETV global cognitive improvement was discovered. The likelihood of RBANS TS clinical improvement was 100% when the difference between immediate and delayed memory indexes was three or less. Further validation of this predictor is required. Future studies should expand on the neurocognitive testing to include anatomical correlates in an effort to elucidate the mechanism of cognitive decline seen in chronic obstructive hydrocephalus.

The largest limitation of this study is the exploratory nature of the statistics and small sample size. Larger studies are required to validate the results. Special attention should be given to minimize the chance of selection bias. Longer follow-up is also essential to determine how these

cognitive domains change over time in order to determine the sufficiency of ETV to provide long-term symptom relief. The digit span subtest has previously been noted to often have a ceiling effect when tested on “normal” populations, leading to the potential for it to be a less robust subtest for measuring the cognitive construct (Costello & Osborne, 2005). Despite this potential ceiling effect, our population was sufficiently poor pre-ETV that none of the patients achieved maximum scores, but two patients did achieve maximum scores by improving by +3 and +4 points at the four-month follow-up. Even though in our analysis statistical and clinical significance was reached, it should be noted that this is a possible limitation of this subtest. The picture naming subtest may also have a ceiling effect as 70% of patient achieve max scores post-ETV. Additionally, MCIDs have not been validated in this population and may not be have high accuracy to clinical change in the visuospatial domain.

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Appendices
Appendix A Tables

Table 1. MoCA Total Score and Symbol Digit Modalities Test (SDMT)

	Follow-up	Sample Size (n)	Pre-ETV Median [Q1-Q3]	Post-ETV Median [Q1-Q3]	Within Patient Change [Q1-Q3]	P-value	Clinical Improvement n (%)	Clinical Worsening n (%)
MoCA Total Score	5 Months	38	24 [23-27]	26 [24-28]	+1 [0-2]	< 0.001	15 (40%)	2 (5%)
	14 Months	15	23 [22- 27]	26 [25-28]	+2 [1-3]	0.007	8 (53%)	1 (7%)
SDMT	5 Months	32	39 [29-48]	45 [35-50]	+3 [-1-6]	0.084	14 (44%)	9 (28%)
	14 Months	14	32 [28-43]	38 [30-46]	+3 [1-8]	0.138	7 (50%)	3 (21%)

Table 2. Neurocognitive assessments: MoCA and RBANS Domains						
	Pre-ETV Median [Q1-Q3]	Post-ETV Median [Q1-Q3]	Within Patient Change [Q1-Q3]	P-value	Clinical Improvement n (%)	Clinical Worsening n (%)
MoCA Total Score	24 [21-27]	24 [18-25]	0.00 [-2.00, +1.00]	0.7204	2 (20%)	3 (30%)
RBANS Total Score	72 [55-81]	77 [66-89]	+8.0 [+4.25, +15.50]	0.0125	5 (50%)	0
RBANS Total Scale Percentile	3.5 [0.33- 11]	6.5 [1.25- 23.5]	+3.45 [+0.30, +18.00]	0.0284	N/A	N/A
RBANS: Immediate Memory Index Score	76.5 [66- 84.5]	81.5 [65- 101.2]	+2.50 [0.00, +14.25]	0.1322	4 (40%)	0
RBANS: Visuospatial Constructional Index Score	98.0 [63.75- 107.75]	84.9 [73.5- 98.0]	+5.5 [-3.0, +9.0]	0.3850	2 (20%)	5 (50%)
RBANS: Language Index Score	88.0 [57.00- 95.25]	85.5 [76.0,105.0]	+5.0 [-6.50, +16.5]	0.2399	5 (50%)	1 (10%)
RBANS: Attention Index Score	70.0 [56.75- 80.25]	71.5 [64.0, 98.5]	+10 [+3.25, +19]	0.0058	7 (70%)	0
RBANS: Delayed memory Index Score	75.5 [55.0, 83.0]	92.5 [76.25, 98.75]	+11.50 [+4.50, +20.25]	0.0143	5 (50%)	0

Appendix B Figures

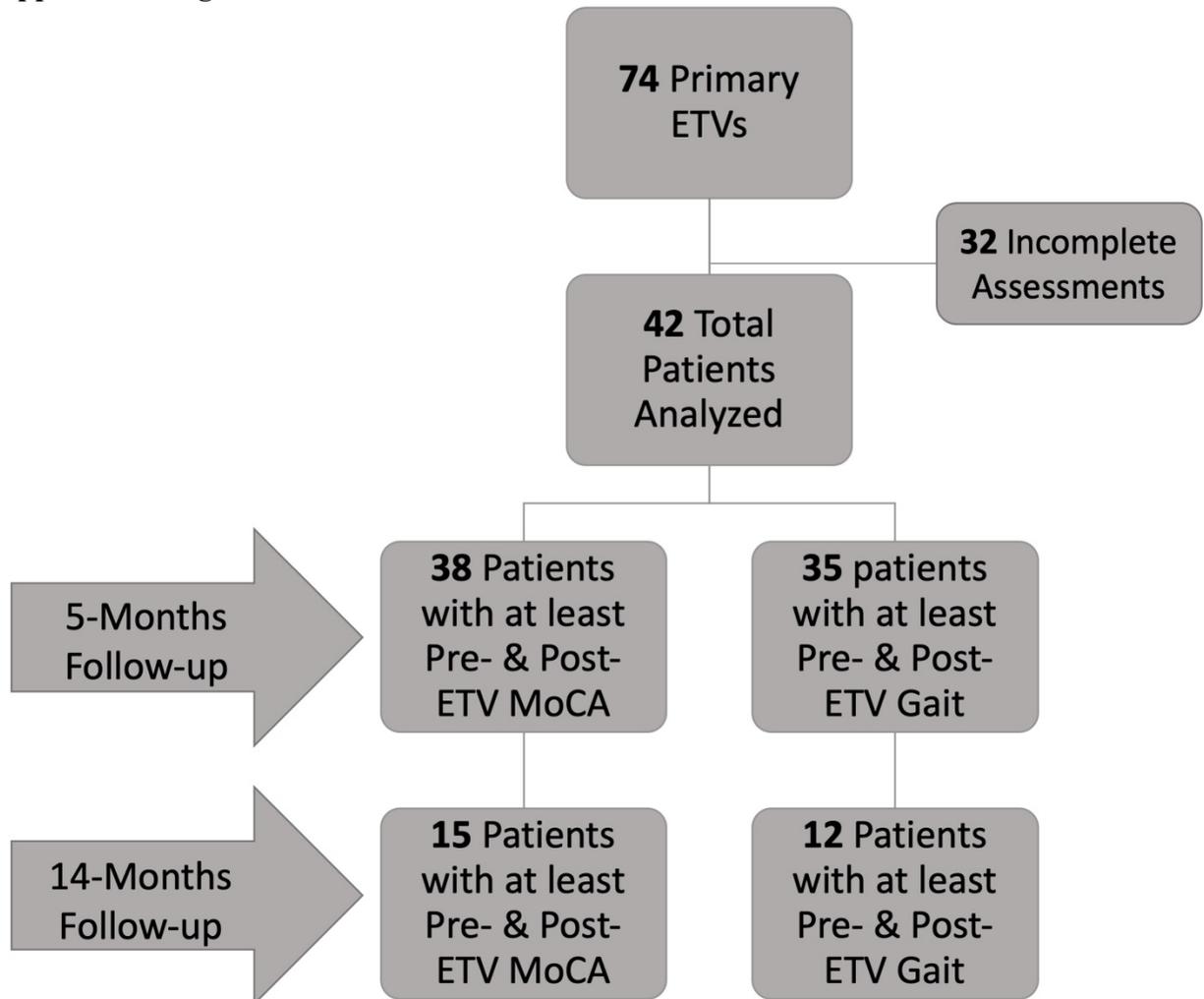


Figure 1. Flow diagram of patient inclusions, exclusions and follow-up.
MoCA: Montreal Cognitive Assessment. ETV: Endoscopic Third Ventriculostomy.

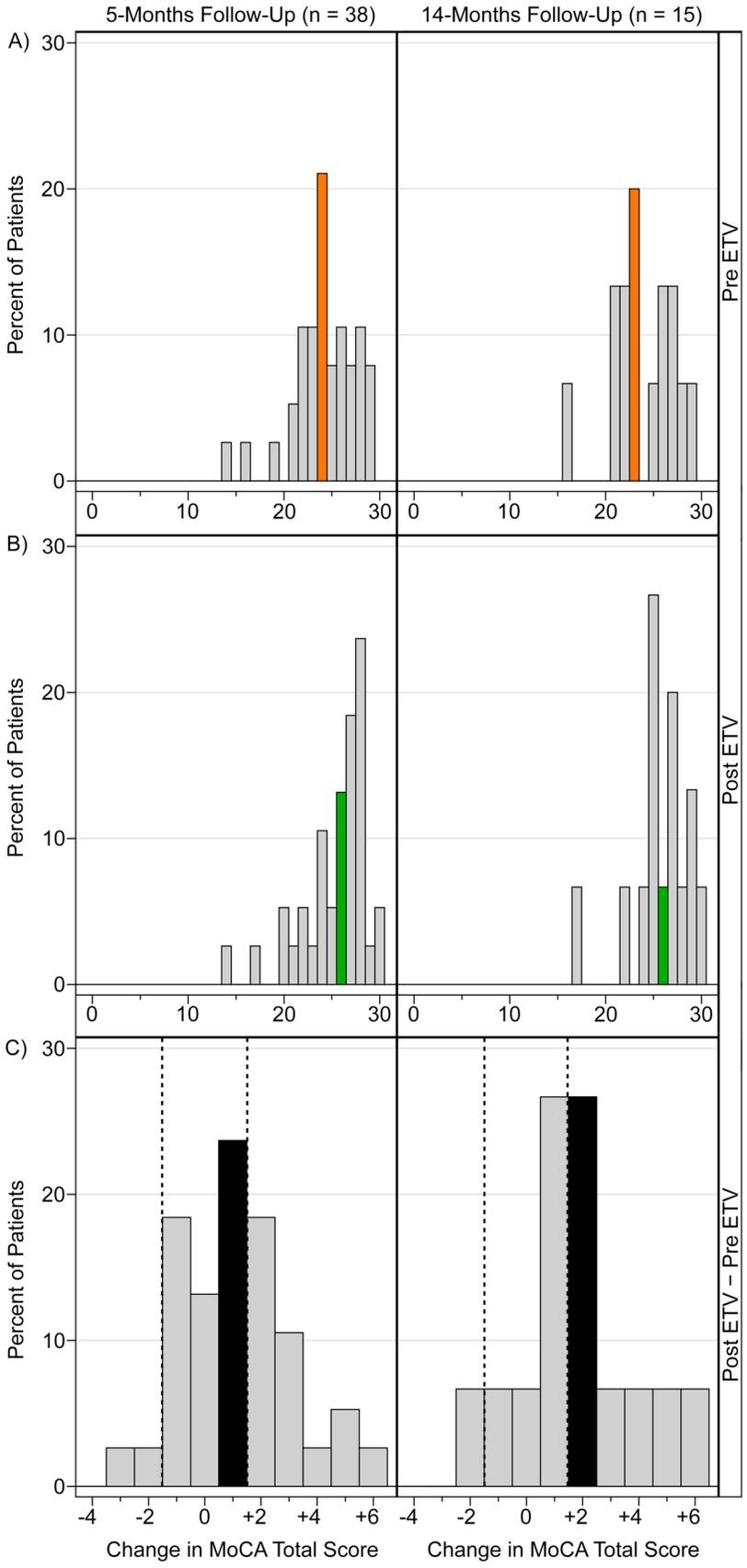


Figure 2. MoCA Total Score for 5-Months Follow-up (n=38; left) and 14-Months Follow-up (n=15; right)

5-Months Follow-up: Median pre-ETV MoCA score of 24/30 (orange bar) improved to 26/30 post ETV (green bar). Median within patient change was +1 point (black bar; $p < 0.001$). Dotted lines show a clinically significant change of $\geq \pm 2$ points (Krishnan et al., 2017).

14-Months Follow-up: Median pre-ETV MoCA of 23/30 (orange bar) improved to 26/30 post ETV (green bar). Median within patient change was +2 points (black bar; $p = 0.007$), which is also clinically significant.

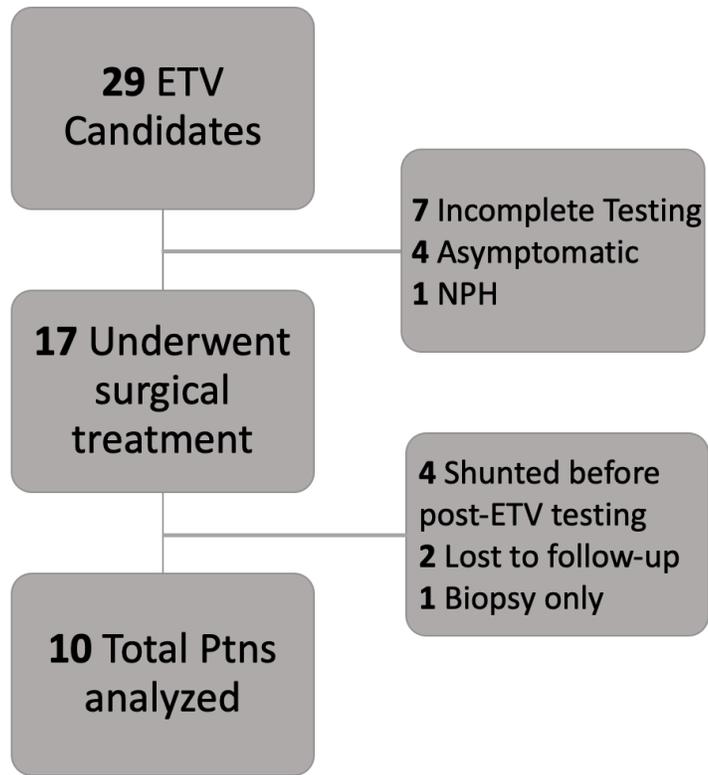


Figure 3. Flow diagram of patient inclusions, exclusions and follow-up in Chapter 3 study.

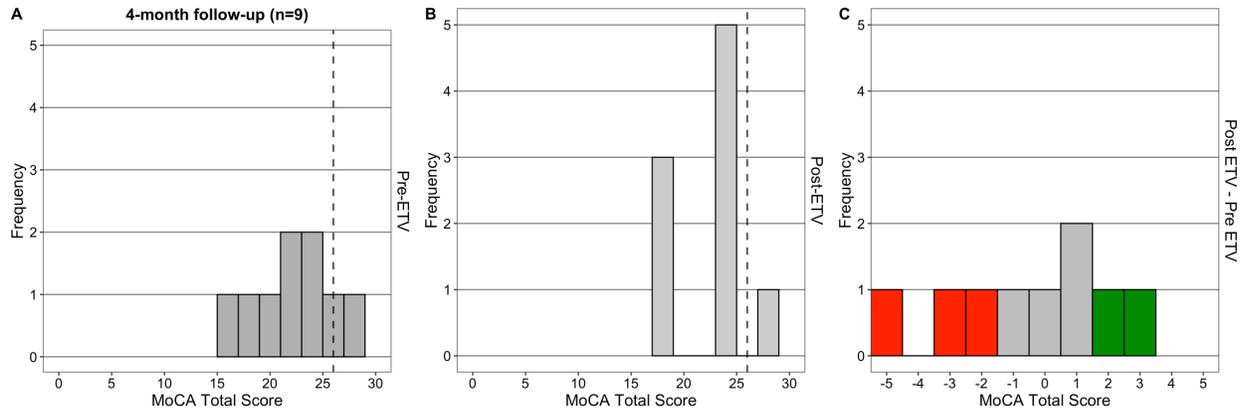


Figure 4. MoCA Total Score, not significantly changed at 4-Months Follow-up. Each column contains data one time point. N = 9 for all time points. Dotted line (A & B) shows lowest normal score of 26/30. Red bins represent clinically worsened scores. Green bin represents the clinically improved score. Clinically significant change is $\geq \pm 2$ points (Krishnan et al., 2017).

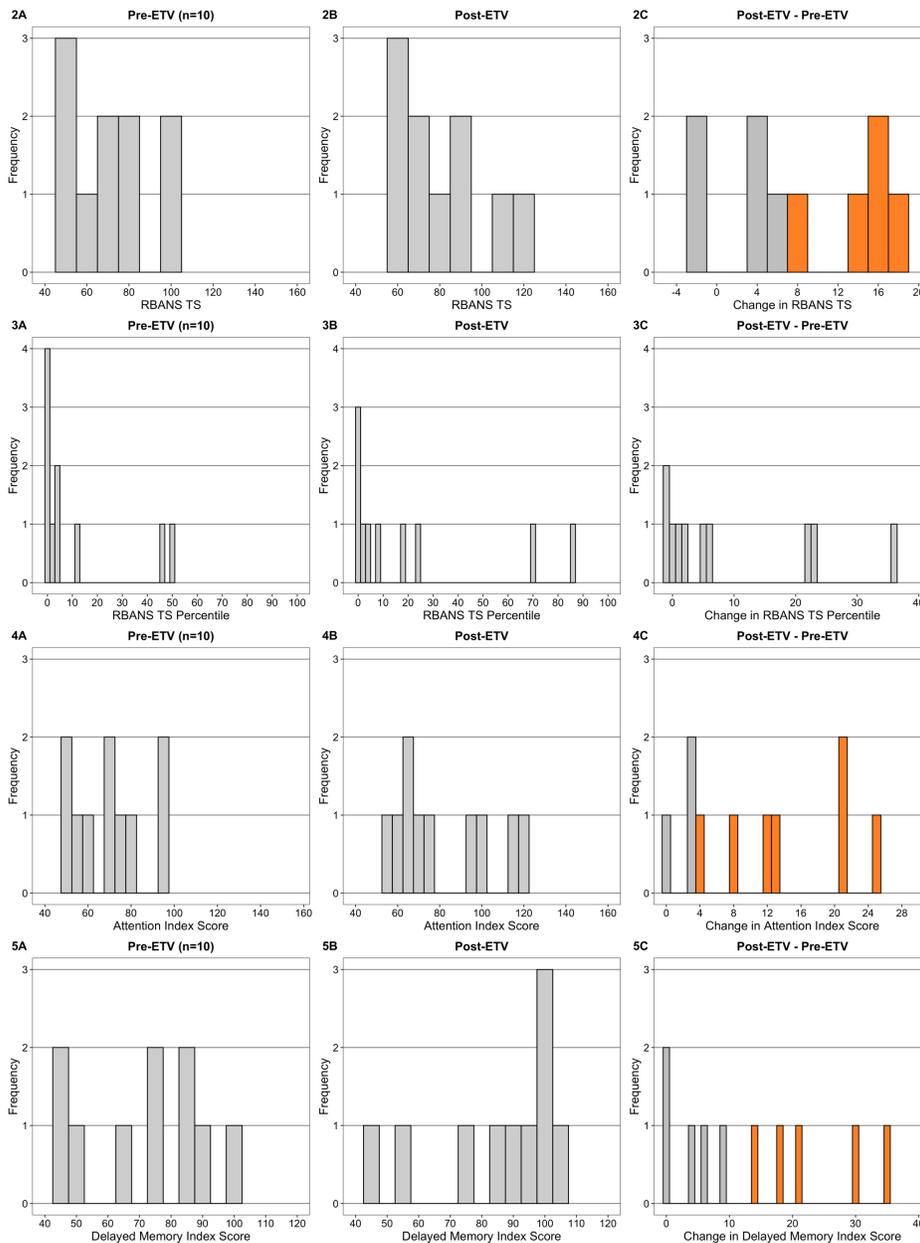


Figure 5. Statistically significant changes in primary outcomes: RBANS Total Score, Total Score Percentiles or index scores (attention and delayed memory). Each column contains data one time point. Each row displays histograms for one score. Change scores that meet the MCID are highlighted in orange. N = 10 for all scores.

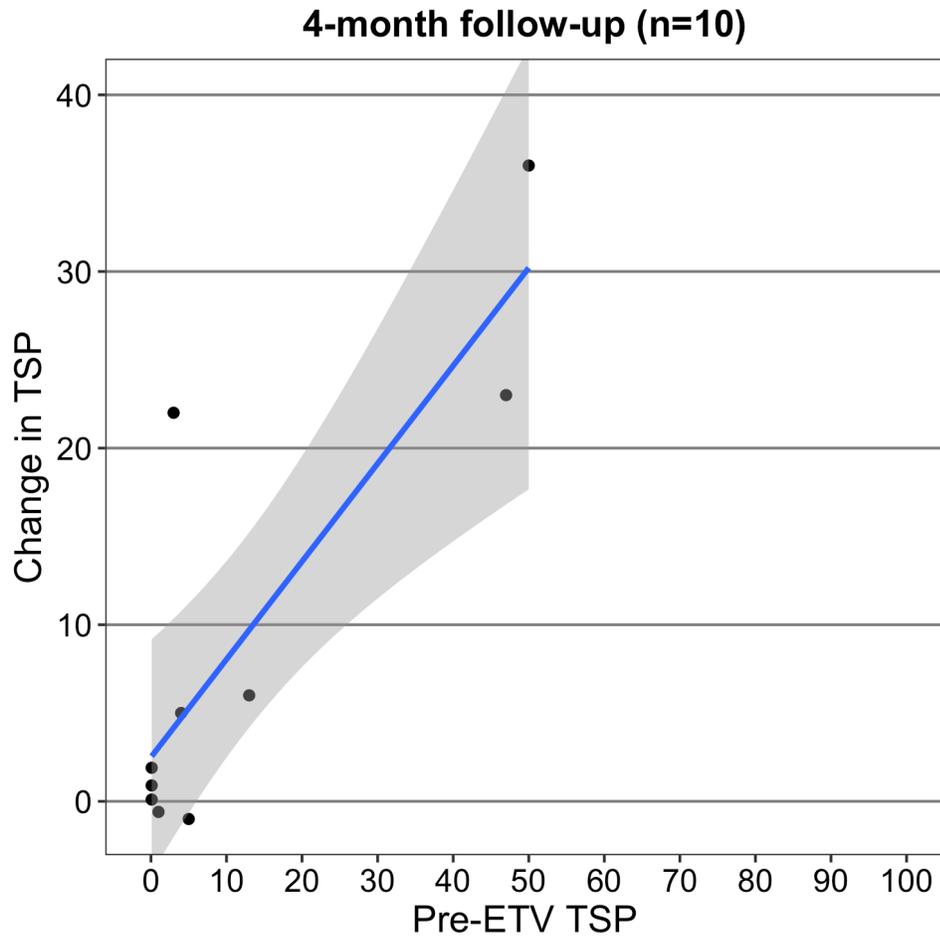


Figure 6. Correlation between Pre-ETV Total Score Percentile and Change in Total Scale Percentile. The blue line is the linear model (x~y) regression line. The grey shading is the standard error based on the linear model.

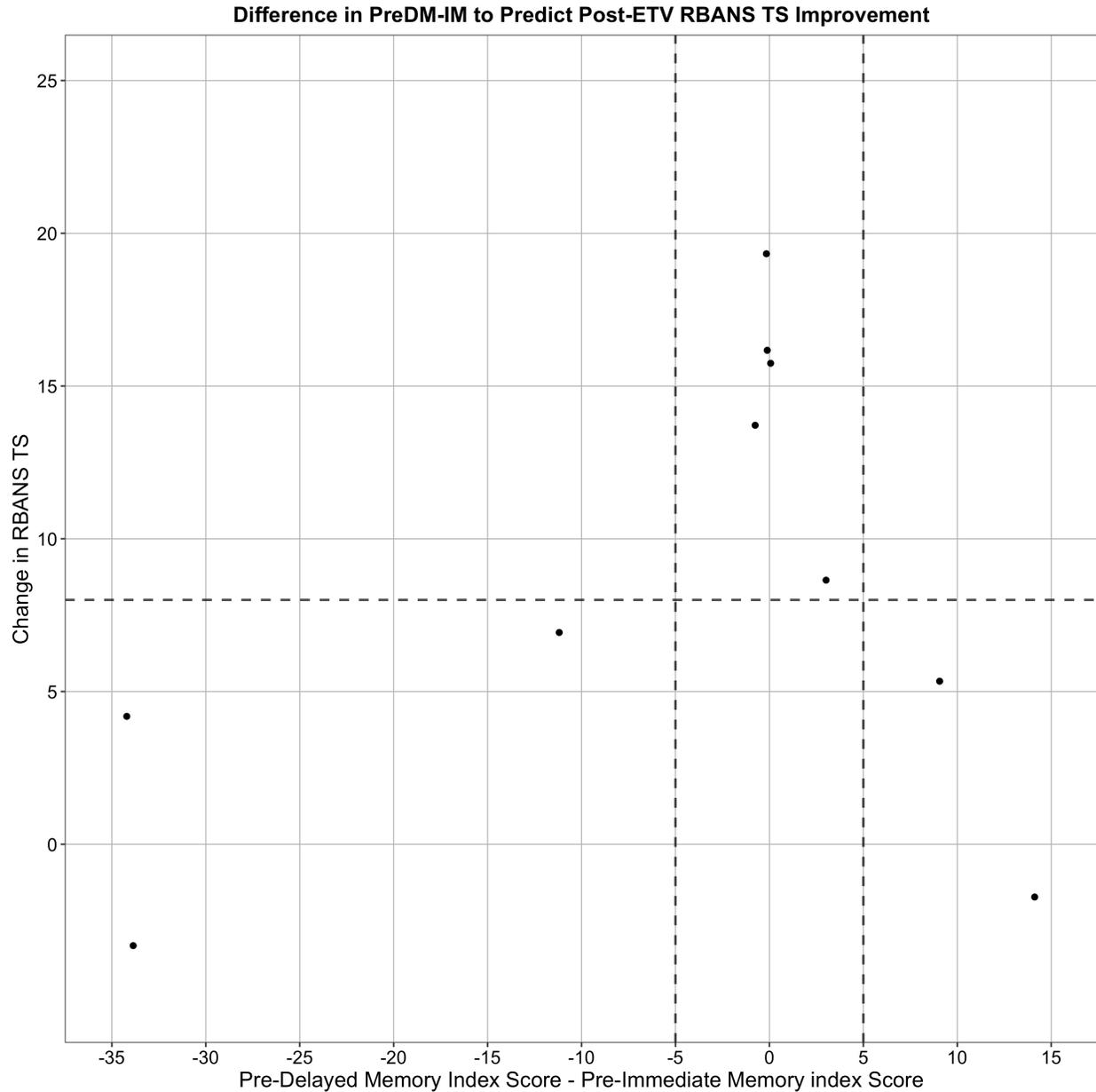


Figure 7: The difference between pre-ETV delayed memory and immediate memory index scores accurately predict clinically significant improvement in post-ETV RBANS TS (MCID ≥ 8). Vertical lines divide the differences between delay memory and immediate memory index scores into three groups: amnesic (left), subcortical dementia (center), and uncommon combination (right). Horizontal line indicates MCID for RBANS TS ≥ 8 . The dots above the horizontal line and between the two vertical lines are the five patients that had improved RBANS TS post-ETV. They also had very similar delayed and immediate memory scores, with three patients having the same scores, one with a difference of one, and the third patient with a difference of three points. Those with larger differences to either side failed to improve in RBANS TS post-ETV. This may be indicative of a different pathology causing the global cognitive dysfunction, which has a greater effect on either delayed or immediate memory.