Clinical Cognitive Screening

A Study Done with Chiari Malformation I Patients

Phillip Vorster

Advised by Christopher Benjamin, PhD, Yale Neurology

Submitted to the faculty of Cognitive Science in partial fulfillment of the requirements for the degree of Bachelor of Science

Yale University

Abstract

Chiari Malformation Type I is a neurological disorder which presents in 0.1% of the general population. The disorder is principally characterized by significant (usually >5mm) cerebellar tonsillar descent through the foramen magnum, crowding the brainstem. A myriad of physical symptoms is present in many people with this disorder, but research has recently focused on the cognitive deficits that also appear. This study characterizes the performance of patients with Chiari on a simple cognitive screening tool, the Montreal Cognitive Assessment (MOCA), and documents a key neurological change (cerebellar descent). Results from a sample of thirty patients with Chiari Malformation Type I (M_{age} = 37.2 years; SD_{age} = 12.4; 23 females) show that patients with Chiari do obtain scores on the MOCA consistent with Mild Cognitive Impairment (MCI), with specific deficits in delayed recall / memory, attention, and certain language and visual processing areas. Surgical status was not found to be influential on overall scores, while age was (with negative correlation). The mean cerebellar descent for the entire sample was found to be 7.8 ± 8.6mm (6.4 ± 4.1mm with an outlier included). These findings are consistent with recent literature on the cognitive deficits associated with Chiari.

Contents

1. Introduction

1.1 Clinical Cognitive Testing

Cognition can be understood as the mental action or process of acquiring and displaying knowledge and understanding through thought, experience, and the senses (Oxford English Dictionary). Accordingly, deficits in cognition are central to a range of neurological disorders. The number of, and variation in, available cognitive tests to screen for these disorders is exceedingly large. According to a 2015 listing by Beacon Health Options, there are already over 350 available tests for researchers and clinicians to use (Beacon Health Options Psychological Test Listing, 2015). Of course, many of these tests have very different applications, ranging from detailed indices of intelligence (e.g., the Wechsler Adult Intelligence Scale) to specific measures of memory (e.g., the Rey Auditory Verbal Learning Task) (Wechsler, 2008, Schmidt 1996). However, there is a need in certain situations to employ a test that serves as a general screen for a range of cognitive skills, and an entry point for further testing. A good example of a situation wherein this would apply is a patient's first interaction in a clinical consultation setting – especially one in an area such as neurology or neurosurgery (Burch, 1987).

For the purposes of this paper, it can be assumed that there are three potential "levels" at which such a general test can be administered. At the highest level lies the neuropsychological evaluation. This is an in-depth evaluation, usually achieved using a combination of interview and paper tests, administered by a neuropsychologist. Testing like this can last upward of 6 hours and is highly individualized to the patient in question (Sweet, 2015). This testing is normally tailored to a clinical referral, and the professional administering the evaluation analyzes patterns of strengths and weaknesses in the patient's performance.

Since this type of testing is time-consuming and work-intensive, there is a notable advantage in having a similarly structured examination paradigm that can be performed more quickly. This is where more simplified paradigms such as the RBANS (Repeatable Battery for the Assessment of Neuropsychological Status) come to the foreground (Kimbell, 2013). Standardized test batteries such as these allow an efficient and practical way to get cognitive data on patients. These types of evaluative paradigms have proven especially useful when screening for aging and degenerative diseases, such as Alzheimer's, Parkinson's, or Dementia (Cullen et al., Woodford et al., 2007). However, the completion time [for the RBANS] still lies at 30 minutes. This may not seem like an arduous commitment, but even so may prove too impractical or time-consuming for everyday clinical use. Further, the abbreviated nature of the assessment means the findings are comparably less reliable than a neuropsychological evaluation, thus increasing the chance of mis-diagnosis in clinical decision-making.

The simplest "level" of testing, and the one that is most important for this current study, is what is known as cognitive screening. Two prominent examples of this type of testing paradigm are the Mini-Mental State Examination (MSE) and the Montreal Cognitive Assessment (MOCA). Each test takes about 10 minutes to complete and uses only a couple of items to assess each of a range of cognitive domains. These types of evaluations are most often used as cognitive screens: tests that can be given quickly by anyone trained in their administration, and can be used to identify impairments warranting higher-level testing.

Nasreddine et al. (2005) determined that the MOCA had a sensitivity of 90% in detecting Mild Cognitive Impairment (MCI), whereas the MMSE only had a sensitivity of 18%. These sensitivities were determined using the established MOCA cut-off score of <26/30 for MCI. Another study (Borland et al., 2017) sought to confirm that 26 was indeed an appropriate cut-off value. Using a large population-based cohort, they established that the MCI cut-off for elderly people (age 65-85) with MCI lay in the 21-25 range for low levels of education and in the 24-26 range for high levels of education. They did find however, that age is a significant predictor of MOCA score, and that these cut-offs only apply to the elderly population. A recent study which sought to reevaluate the cutoff values for MCI, used a meta-analysis (across 304 studies) to determine the best cutoff value to avoid as many false-positives as possible (Carson, 2017). Their results suggest that a cutoff of <23/30 might be more appropriate across geriatric groups and for those with lower levels of education. Since these groups were minimally represented in the present study, the current MOCA-suggested cutoff value of <26/30 was used.

1.2 Chiari Malformation Type I

In the current study we chose the use of the MOCA to detect cognitive impairment in Chiari Malformation Type I. One in 1000 people have the disorder, which suggests a number of 300,000 people in the United States (Conquer Chiari, 2017). It is also very likely that the disease affects more women than men. There are approximately 10,000 Chiari surgeries per year (Conquer Chiari, 2017).

Chiari malformation is a neurological disorder in which the cerebellum descends downwards to crowd the brain-stem/spinal area. Put more specifically, the cerebellar tonsils descend into the foramen magnum, a large opening at the base of the skull. This restricts the flow of cerebrospinal fluid (CSF), causing pressure on both the brain and the spine. Symptoms are myriad and include headaches, neck pain, balance problems, muscle weakness, dizziness, difficulty swallowing or speaking, vomiting, tinnitus, insomnia, depression, and problems with fine motor skills, to name a few (Labuda, 2012). It is important to note, however, that many (and potentially all) of these symptoms may be absent in a patient that would technically qualify for Chiari Malformation Type I. The surgery completed to treat Chiari I usually involves decompression at the base of the skull, allowing the CSF to flow more freely. It is typically recommended to patients whose symptoms, particularly the *physiological* ones, have been worsening over time, such as muscle weakness or eyesight deficits (Conquer Chiari, 2012).

There are two different pathological components that may cause the symptoms associated with Chiari Malformation I**:** tonsillar ectopia (tonsillar descent) and the expansion of a syrinx (a fluid-filled cavity in the spinal cord or brainstem) (Oldfield, 2017). For the purposes of this paper, we will focus on the principal marker, tonsillar ectopia, only. The tonsillar descent can cause pressure on the dura, brainstem and spinal cord. It can also obstruct the flow of cerebrospinal fluid (CSF). In terms of this pathological component, it is believed that most of the symptoms are a result of pressure on the brain stem due to pulsatile flow, obstruction, and cerebellar impact. The cerebellar tonsils are located at the most posterior location of the cerebellum, adjacent to lobule IX. Lobule X of the cerebellum (which has been found to have associations with the decision-making areas of the cerebrum) actually contains the cerebellar tonsils themselves (Buckner et al., 2011). This is the area which has descended into the foramen magnum and is actively blocking CSF in patients with Chiari.

There is a lack of concrete evidence linking these pathological components of Chiari I to the Mild Cognitive Impairment that is present in many of these patients (Allen et al. 2014). One theory is that the repeated pulsatile impact damages tissue in the cerebellum, and since the cerebellum is functionally connected to the pre-frontal cortex, this could disrupt higher cognitive function. This relationship is discussed further in section 1.4. Alternatively, brainstem-related symptoms, such as muscle weakness, difficulty breathing or speaking, or headaches, might be dampening a patient's ability to concentrate, thus resulting in an MCI-like presentation (Allen et al., 2017, Conquer Chiari).

Chiari Malformation I is notoriously hard to define in explicit and detailed anatomical terms (Labuda, 2012). The classic method of defining the condition – cerebellar descent of greater than 3-5mm below the foramen magnum - has been called into question, because it is often the case that patients with a large magnitude of descent will have minimal symptoms or present as asymptomatic, whereas others will have a small magnitude of descent but be plagued with severe symptoms (Labuda, 2012).[1] These symptoms are also hard to pinpoint, as many of those mentioned above are present in many other conditions, such as intracranial hypertension or tethered cord syndrome (Chiari Comorbidities, 2018). Even so, strong and usually occipitally-located headaches are the most defining symptom (Labuda, 2012, Symptoms).

1.3 Classic associations with cerebellar damage

Cerebellar damage has been, and still is, primarily associated with movement and coordination disorders such as ataxia (Gonzalez-Usigli, 2017). Ataxia is primarily characterized by trouble coordinating balance, gait, movements in the extremities or eyes, and dysarthria (slurred speech). These basic relationships were established centuries ago by Rolando and Flourens (Contrary of the ideas of Franz Gall, who postulated that the cerebellum was the "seat

[1] Researchers and surgeons have shifted their focus onto the CSF flow around the tonsils, rather than their pure physical descent. The theory is that tonsils with larger volume blocking the hole, even if there is not a large amount of vertical descent, will cause harsher symptoms than relatively thin ones (Houston, In Press).

of sexual function") and have been confirmed by a plethora of modern physicians and researchers (Schmahmann, 2004). Depending on the severity of the damage, any of a myriad of symptoms can present: dysmetria, impairment of alternating movements, and general errors regarding most motor-specific tasks requiring coordination/precision. Cerebellar dysfunction is not only the result of cerebellar lesions, however, as there are also a great number of diseases implicating the cerebellum (including Chiari Type I).

Even though there is a new wave of research suggesting the cerebellum is also involved in higher cognitive function, the vast majority of physicians and researchers would agree that the structure is first and foremost devoted to motor control (Buckner, 2013). Thus, there are many telling papers in the medical literature that have contributed to, and built upon our understanding of the cerebellum as the motor-coordination powerhouse of the brain (Lang et. Al., 1996). There is, however, new and growing support for the relationship between the cerebellum and the inferior frontal cortex (as well as the precuneus, sometimes described as the medial area of the superior parietal cortex). Both areas are highly involved in executive-level decision-making. Effects on the pre-frontal cortex have also become increasingly linked to cerebellar efficiency and function.

1.4 Newer associations with cerebellar damage

Chiari Malformation is associated with symptoms reminiscent of cerebellar and brainstem damage, given the pulsatile impact of the cerebellar tonsils on and around the brainstem area (Labuda, 2012, Symptoms). Thus, it is critical to analyze any and all of the symptomatic relationships that cerebellar damage has. As mentioned above, newer findings have suggested that there is more to the cerebellum than just motor coordination and control. A pioneer in understanding the link between higher-level cognition and the cerebellum, Jeremy Schmahmann (2004), summarizes the possible effects of cerebellar damage as follows:

> *"The cerebellar cognitive affective syndrome (CCAS) includes impairments in executive, visual-spatial, and linguistic abilities, with affective disturbance ranging from emotional blunting and depression, to disinhibition and psychotic features. The cognitive and psychiatric components of the CCAS, together with the ataxic motor disability of cerebellar disorders, are conceptualized within the dysmetria of thought hypothesis."* (pg. 367)

This concept of "dysmetria of thought" has come to represent a new way of understanding cerebellar damage. This parallel is meant to frame the executive function implications of the cerebellum in terms of its classic association with motor coordination. Schmahmann suggests that just as cerebellar damage causes coordination trouble in many aspects of motor function, so too can it cause coordination trouble with many aspects of higher cognition. The principal cognitive symptoms of cerebellar impairment can include deficits in "planning, set-shifting (unconsciously shifting attention between tasks), verbal fluency and abstract reasoning" as well as "the blunting of affect or disinhibited and inappropriate behavior" (Schmahmann, 2004, pg. 371)

This symptom set is very similar to one that summarizes the error characterization of patients with damage to the ventromedial prefrontal cortex– an area of the brain heavily associated with decision-making and judgment (Bechara et al., 2000). This study found that patients with ventromedial prefrontal cortex lesions “are insensitive to future consequences, positive or negative, and are primarily guided by immediate prospects”. This phrasing mirrors Schmahmann’s later report on the effects of cerebellar damage.

In the last decade, anatomical data has shed light upon the theorized connections between the cerebellum and the frontal cortex. Work using fMRI, in particular, has demonstrated functional connectivity between the cerebellum and pre-frontal cortex (Krienen et al., 2009). Further research has suggested a far stronger relationship between the cerebellum and cerebral cortex. For example, almost one half of the cerebellum targets cerebral networks that are heavily involved in executive function and memory (Buckner et al., 2011). A primary somatomotor cerebellar map of the cerebral cortex was outlined in the same paper (the map begins in the anterior lobe of the cerebellum and progresses towards the posterior) as well as two additional cerebellar maps. One of these additional maps found in the posterior lobe was found to chart the full cerebrum, whereas the third map originated from lobules IX and X. These lobules make up the most posterior portion of the cerebellum, with lobule X containing the cerebellar tonsils themselves (Buckner et al., 2011).

Their evidence for the tertiary map was consistent with earlier work which outlined dense efferent connections between Brodmann’s area 46 and Lobules IX and X. Brodmann’s area 46, which corresponds to the dorsolateral prefrontal cortex, has been correlated with short-term memory, planning and organization, and response activation and inhibition (Kelly & Strick, 2003).

Together, the work of Bechara, Krienen, and Buckner suggests that the cerebellum, and perhaps specifically the posterior of the cerebellum containing lobules IX and X, is an important factor in higher cognitive abilities. These results corroborate Schmahmann's (2004) findings that,

> *"Behavioral changes were clinically prominent in patients with lesions involving the posterior lobe of the cerebellum and the vermis, and in some cases they were the most noticeable aspects of the presentation."(pg. 561)*

1.5 Present Study and Goals

This study aims to replicate past findings on the cognitive deficits of Chiari. In a study by Allen et al. (2014), it was found that Chiari patients *with* alleviative decompression surgery[2] still exhibit cognitive dysfunction (deficits in response inhibition) when compared to healthy controls. Even after controlling for anxiety and depression, they found that the effect persisted. In a related study by Allen et al. (2017), it was found that chronic pain, as well as the patient's relative degree of rumination and reflectiveness may be significant additional influencing factors towards cognitive dysfunction. This is suggested by the finding that even though all Chiari patients performed worse than healthy controls on a delayed recall task, within the Chiari group the levels of recall were further influenced by pain and degree of negative introspection, both of which are described as being significantly alleviated by surgery. This suggests that surgery can have a positive and individualized effect on general cognition, through the vehicle of pain relief. More recently, a study in press (Houston et al., In Press) found that using the RBANS, Chiari

---

[2] This surgery involves removing a portion of the occipital skull bone to reduce pressure and restore CSF flow.

patients exhibited statistically significant reductions in the attention domain. Interestingly, they also found that the extent of cognitive impairment may be correlated with the degree of cerebellar tonsillar herniation. Thus, using more in-depth cognitive assessments than those in Allen and colleagues' work has yielded convincing evidence for domain-specific mild cognitive impairment in patients with Chiari.

The current study aimed to use one of the simplest cognitive screening tests – the MOCA – to see if similar results could be replicated. There are 8 modalities tested on the MOCA: Visuospatial/Executive, Naming, Memory, Attention, Language, Abstraction, Delayed Recall, and Orientation. The goal then was to see whether this simple test could produce results that align with the general body of knowledge on the cognitive effects of Chiari. Testing was performed on both pre-operative and post-operative patients. As previous studies have suggested, there should be no cognitive difference between these two samples (Allen et al., 2014), though scores between these groups was also compared.

Drawing on the aforementioned factors, we developed five specific hypotheses:

1. Patients with Chiari will perform worse than normal (i.e. score below 26 on average) on the MOCA.
2. MOCA scores for pre-operative and post-operative patients will not differ significantly.
3. Age will be negatively correlated with MOCA scores.
4. Cerebellar tonsillar descent will be negatively correlated with MOCA scores.

5. Chiari Patients will perform worse on attention and delayed recall as evaluated by the MOCA.

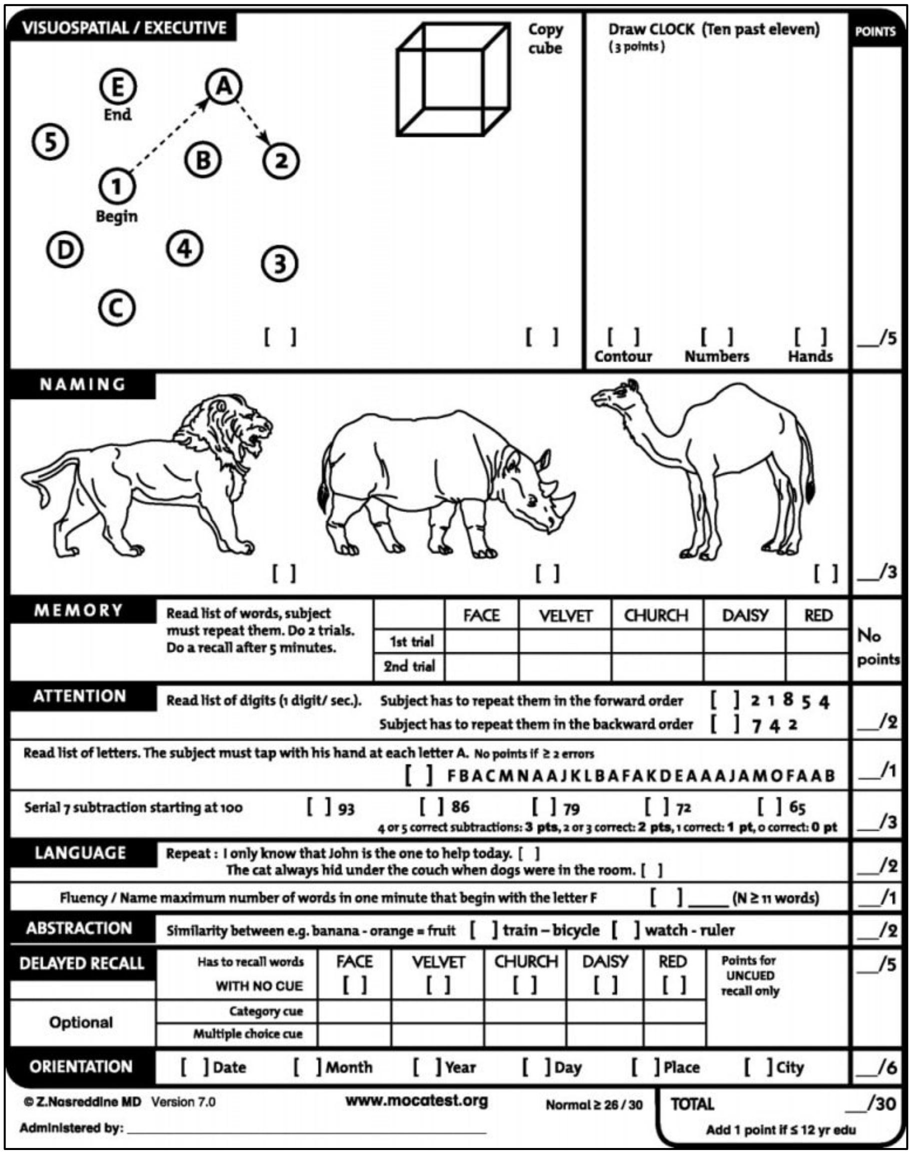
2. Method

2.1 Participants

Thirty patients with Chiari Malformation Type I (M_{age} = 37.2 years; SD_{age} = 12.4; 23 females) who received a neurosurgical or neurological consultation at the Cleveland Clinic Fairview Neurological Institute completed the MOCA evaluation. Of these 30 subjects, 9 had already undergone decompression surgery, and 21 were unoperated. One subject was exempted from the study due to emotional instability, as this may have impacted scoring results negatively, and independently of CMI. Comorbidities, or other clinical conditions were not used as grounds for exemption.

2.2 Design and Procedure

The subjects were given the MOCA evaluation during the waiting period before clinical consultation. Before test-taking, the age and sex of the patient was recorded. The test was administered as per the official MOCA instructions.



VISUOSPATIAL / EXECUTIVE

E End, A, 5, B, 2, 1 Begin, D, 4, 3, C [ ]

Copy cube [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS ___/5

NAMING

[ ] [ ] [ ] ___/3

MEMORY	Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.		FACE	VELVET	CHURCH	DAISY	RED	No points
		1st trial						
		2nd trial						

ATTENTION Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 ___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] FBACMNAAJKLBAFAKDEAAAJAMOFAAB ___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** ___/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] ___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) ___/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler ___/2

DELAYED RECALL	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only	___/5
Optional	Category cue							
	Multiple choice cue							

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City ___/6

© Z.Nasreddine MD Version 7.0 www.mocatest.org Normal ≥ 26 / 30 TOTAL ___/30
Administered by: ____________ Add 1 point if ≤ 12 yr edu

Figure 1. Image of the exact MOCA variation given to patients.

The entire test was given in a single sitting, and each category was considered as a separate score. Specifically, for scoring purposes, the test was split into 12 segments: Visuospatial1 (trail making), Visuospatial2 (cube copying), Visuospatial3 (clock drawing), Naming (animal naming), Attention1 (simple mathematical repetitions), Attention2 (appropriate reaction to letter reading), Attention3 (serial subtraction), Language1 (sentence repetition), Language2 (fluency/word synthesis), Abstraction (similarity analysis), Memory (only scoring the patients on delayed recall), and Orientation.

Additionally, the degree of cerebellar tonsillar descent was transcribed for each patient from the clinical MRI report. These measurements are typically done by making a perpendicular measurement from the McRae line down to the tip of the cerebellar tonsil on a mid-sagittal MRI scan of the head (Gaillard, 2019).

All statistical analysis was done using Minitab.

3. Results

3.1 Hypothesis 1: Patients with Chiari will perform worse than normal (i.e. score, on average, below 26) on the MOCA.

A one-sided, one-sample t-test was performed on the total MOCA scores for the entire sample ($M_{total} = 24.97$, $SD_{total} = 2.75$) with H_0: $\mu = 26$ and H_a: $\mu < 26$. There was a significant effect for Chiari Malformation I, $t(29) = -2.06$, $p < .05$, with Chiari patients receiving lower scores than 26/30. This suggests that, as a group, patients with Chiari will score on average below the MOCA cutoff score for MCI (26) (Figure 2). It is notable, however, that the median was 26, so that at the level of individual patients a total of 43% actually received scores below 26 (Figure 2).

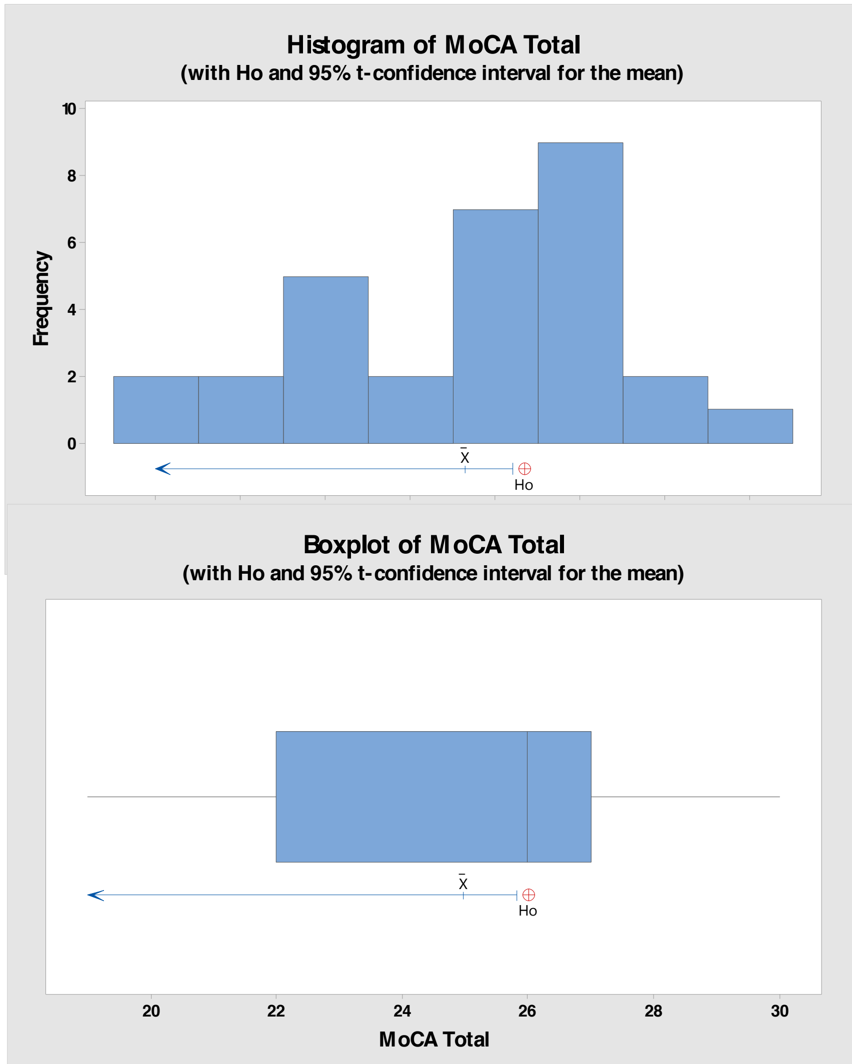


Figure 2. Data and t-test visualizations (histogram and boxplot) for total MOCA scores for all subjects.

3.2 Hypothesis 2: MOCA scores for Pre-operative and Post-operative patients will not differ significantly.

A two-sided, two-sample t-test was performed on the total MOCA scores of the pre-operative ($\mu2$: $M_{pre} = 24.62$, $SD_{pre} = 2.48$, $n = 21$) and post-operative Chiari patients ($\mu2$: $M_{post} = 25.78$, $SD_{post} = 3.31$, $n=9$) with H_0: $\mu1 - \mu2 = 0$ and H_a: $\mu1 - \mu2 \neq 0$. MOCA scores did not differ significantly according to operative status ($t_{(12)} = 0.94$, $p = .36$). There is no clear evidence to suggest that the MOCA scores for pre-operative and post-operative patients with Chiari are significantly different in this sample (Figure 3).

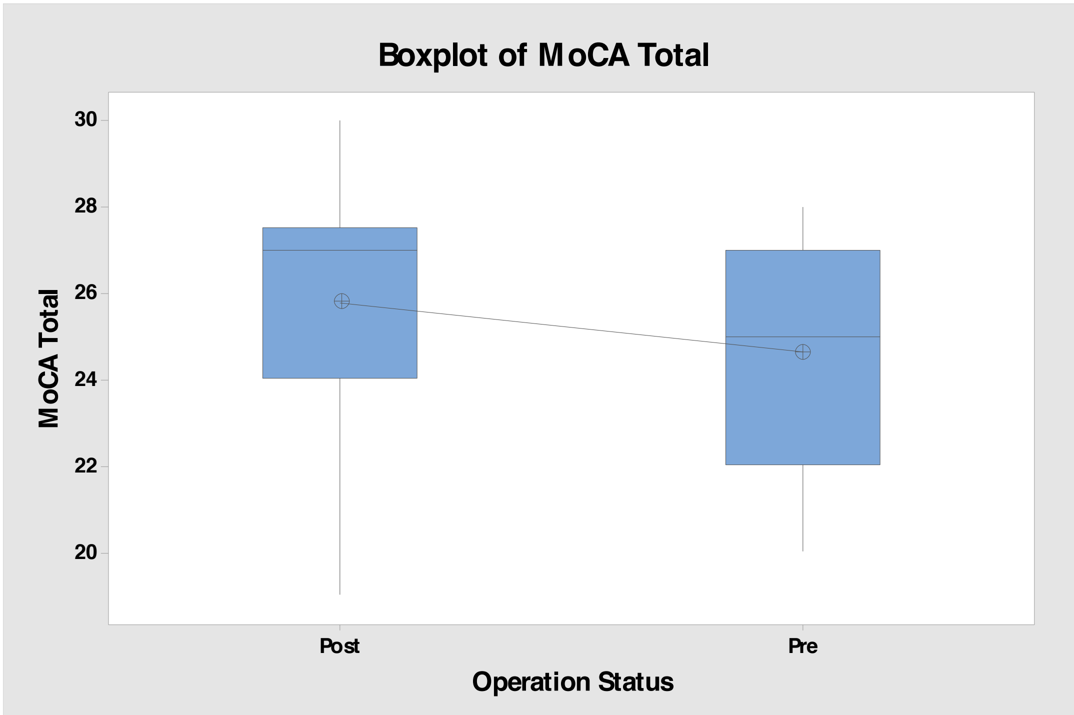


Figure 3. Data and t-test visualizations (boxplot) for total MOCA scores between pre-operative and post-operative patients with Chiari.

3.3 Hypothesis 3: Age will be negatively correlated with MOCA scores.

Linear regression was completed using Age to predict MOCA Total Score. A significant negative correlation was found between "Age" and "MOCA Total Score" ($p<0.05$) (Figure 4). Age also explained a significant proportion of variance in MOCA scores $R^2 = 16.18\%$ This indicates a majority of the total MOCA scores is explained by other underlying factors. The residuals for analysis appear to be independent, and follow a normal distribution, indicating a good fit of model assumptions (Figure 5).

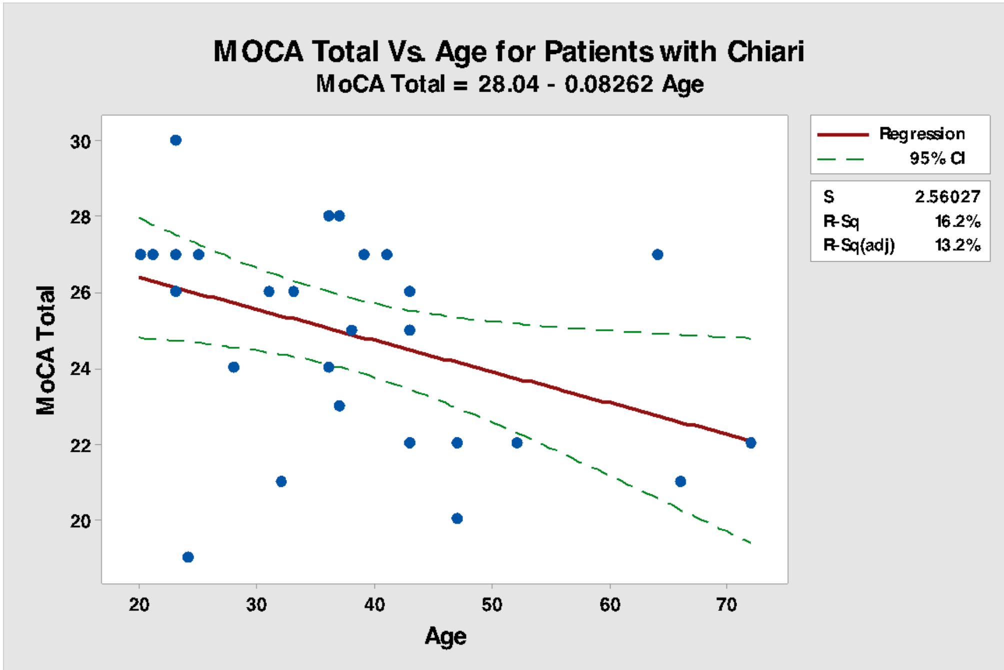


Figure 4. Scatterplot showing MOCA score and patient age, and the results of the significant linear regression using age as a predictor (red; 95% confidence intervals in green).

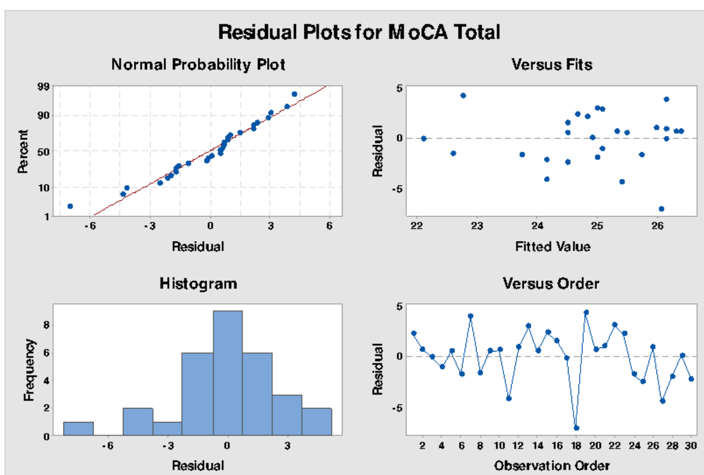


Figure 5. Four-in-one residual analysis for the linear regression in Figure 4.

3.4 Hypothesis 4: Cerebellar tonsillar descent will be negatively correlated with MOCA scores.

Linear regression was completed using cerebellar tonsillar descent to predict MOCA Total Score. A non-significant negative correlation was found between “Tonsillar Descent” and “MOCA Total Score” ($p = .31$) (Figure 6), $R^2 = 3.6\%$. Important to note is the large x-value outlier – only one subject had a degree of descent below 20mm (48mm). This point alters the linear trend from a non-significant positive one to the aforementioned non-significant negative one.

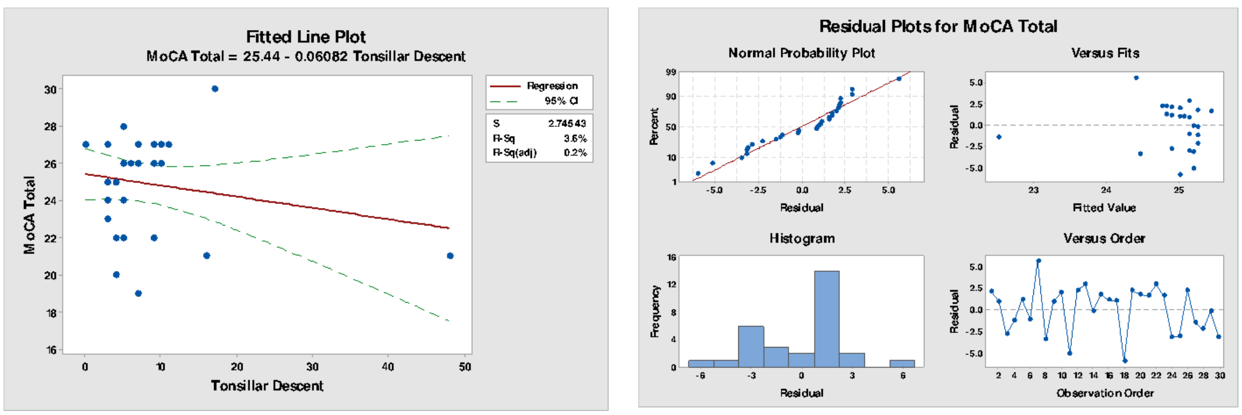


Figure 6. Scatterplot showing MOCA score and degree of tonsillar descent, and the results of the non-significant linear regression using this descent as a predictor (red; 95% confidence intervals in green). Four-in-one residual analysis for the linear regression in Figure 6 are included.

3.5 Hypothesis 5: Chiari Patients will perform worse on the attention and delayed recall subsections (MOCA).

As mentioned above, each portion (modality) of the MOCA was scored separately. Given the sample size and the exploratory nature of this hypothesis, the overall pattern of results across these groups is simply described. For each patient, each subsection score was divided by the total possible score in that subsection and this value was then averaged across the sample (n=30) (Figure 7).

In this sample, patients performed worst on a measure of verbal fluency (Language2: rapidly listing words beginning with “F” for 1 minute; total possible score was 3 points). The average score for this section across the sample was 50%. The Memory/Delayed Recall subsection was also relatively poor, with an average performance of 59% (Perfect possible score = 5 items). Visuoapatial2 (70%) – copying a cube - was another section on which patients struggled, followed by Attention3 (74%), Language1 (78%), and Attention2 (80%). On all other subsections, the patients had a >88% chance of receiving a perfect score (Figure 7, next page).

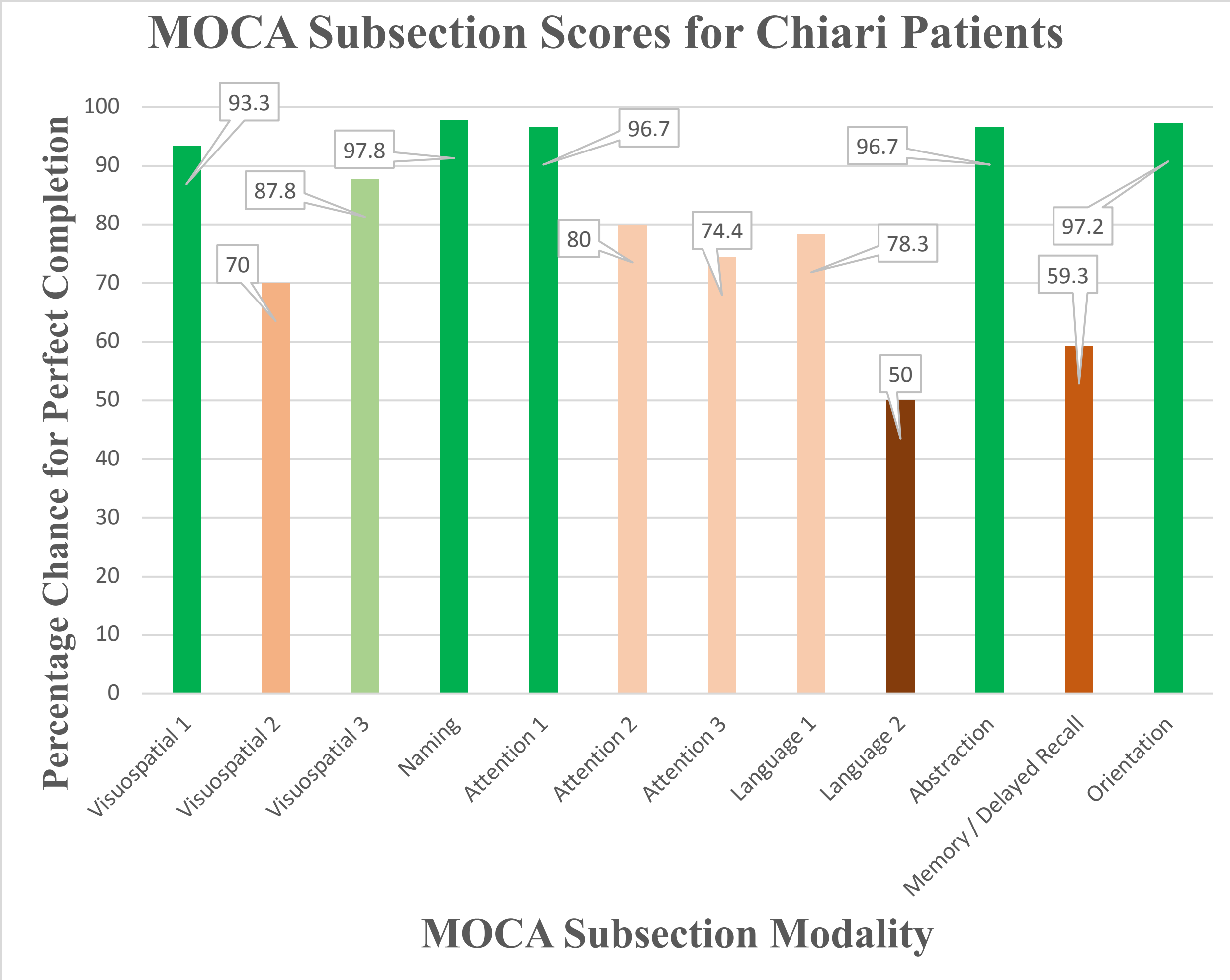


Figure 7. Average performance (percentage correct) on each MOCA subsection for patients with Chiari. Bars are differentially colored based on percentage values: Dark Green (>90%), Light Green (>80%), Light Tan (>70%), Dark tan (>60%), Brown (>50%), Dark Brown (>40%). In general, a healthy control is expected to get at or near 100% on each section.

The scores for Memory/Delayed Recall were further examined given the relatively large number of items (5) and the fact that the data is discretely analyzable. Mean performance was 2.967 out of 5 words correct, with a relatively large standard deviation of ~ 1.497.

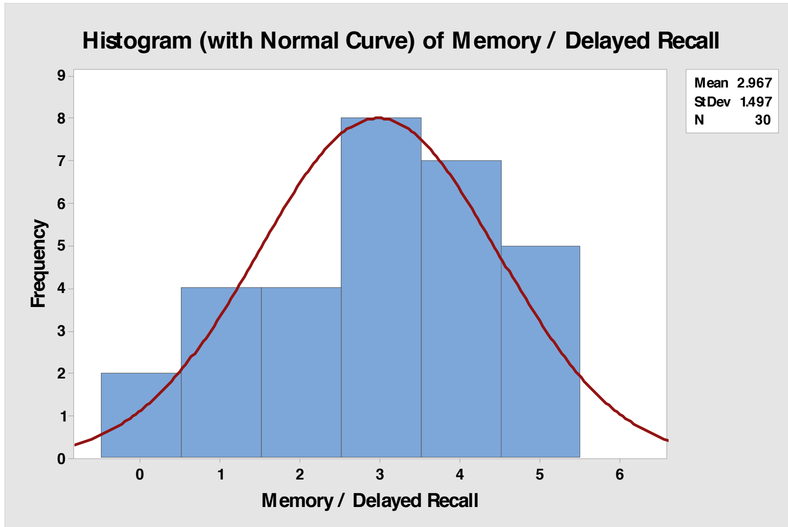


Figure 8. Histogram of the data collected from the Memory/Delayed Recall subsection. The data appears to follow a normal distribution centered around "2.967".

3.6 Results Unrelated to the 5 Principal Hypotheses

An additional exploratory review of the data was completed. Two other demographic data points of interest were captured: the frequencies of men and women encountered through the study (76.7% Female), as well as the mean degree of cerebellar tonsillar descent for the entire sample (Figure 10, next page).

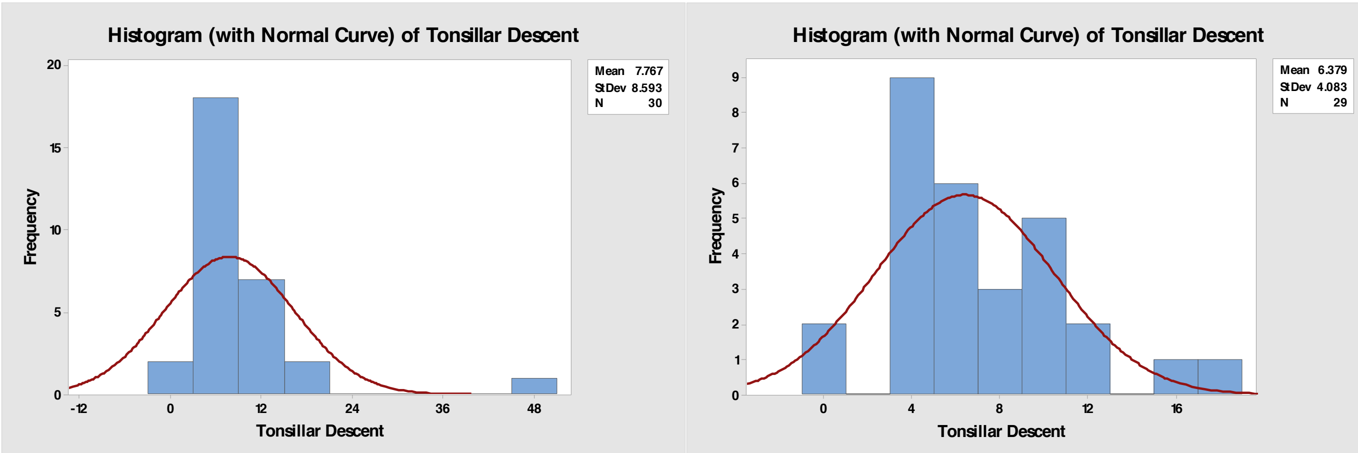


Figure 10. Histograms and predicted normal curves of cerebellar tonsillar descent across the entire sample. The outlier point of "48mm" is included on the left-hand graph and excluded on the right-hand graph. On this right-hand graph, the mean lies at 6.379mm, with a standard deviation of 4.083mm.

4. Discussion

The results from this study provide tentative evidence that patients with Chiari may present with MCI, scoring on average below 26 on the MOCA. Further, this MCI may be characterized by specific deficits in the language, memory, and attention domains. Additionally, past findings are corroborated in that surgical status does not seem to significantly (or directly) change cognitive effects in patients with Chiari (Allen et al., 2014, 2017), that age is negatively correlated with MOCA scores (Borland et al., 2017), and that there appear to be specific deficits in the attention and memory domains (Houston et al., In Press, and Allen et al. 2014/2017)

4.1 On Result 1- Patients with Chiari performed worse than normal (i.e. score, on average, below 26) on the MOCA.

In this sample, there is evidence that the mean MOCA score of patients with Chiari Type I will lie below the cutoff score of 26 for Mild Cognitive Impairment. However, it is important to note that the 1st quartile of this data set lies at 22/30, and the 3rd quartile lies at 27/30. Given the relatively high sensitivity of the MOCA in identifying MCI (90% in Nasreddine et al, 2005), this suggests patients with Chiari Malformation Type I have a high likelihood of presenting with MCI. This likelihood can be assumed by comparing the MOCA failure rate (43.3%) in patients with Chiari to the incidence of MCI in the general population = a conservative estimate of 7.7% (Luck et al., 2010).

4.2 On Result 2 - MOCA scores for Pre- and Post-operative patients are the same

There was no significant difference between pre-operative and post-operative MOCA scores in patients with Chiari. This result appears to corroborate Allen et al. (2014), which found that Chiari patients *with* alleviative decompression surgery continue to exhibit cognitive dysfunction when compared to healthy controls. Primarily, this finding suggests that decompressive surgery alleviates the more pressing physical symptoms associated with the disorder, but does not alleviate the more evasive cognitive symptoms. However, as with result 4.1, it is important to take into account the possibility that the MOCA is simply not sensitive enough to truly differentiate the two groups. At a glance, the mean for the post-operative distribution is more than a point higher than that of the pre-operative distribution. The standard deviation, however, is much larger, and this then leads to the significant overlap of the two sample distributions.

Interpretation of these data is critically limited by our sample size (9 post-operative; 21 pre-operative) so our findings here are tentative. Nevertheless, it is notable that in this small sample, on a general cognitive screening test (the MOCA), there was no evidence that patients experienced cognitive decline after decompression surgery.

4.3 On Result 3 - Age is significantly related to MOCA score, but not strongly.

When the linear regression model was calculated for "Age" vs. "MOCA Total Score", the R^2 value was indeed low at 16.2% though age did significantly predict performance. This value makes sense when thinking about what factors should be contributing most to MOCA score totals. Age, while an important factor in natural mental decline is among a multitude of variables that could account for a decrease in cognitive health. Since the MOCA is indeed testing for MCI, and not age, this interpretation supports the MOCA as a general measure for cognitive health that is sensitive to age differences but does not let that factor overwhelm the scoring scale.

This conclusion rests on the assumption that a linear model is the best description of the relationship between MOCA score and age. It is very possible that a non-linear model is a better descriptor of the data, or that there are multiple other confounding variables such as operative status, or education level. Given all of this, one possible conclusion is that while age is indeed a significant negative predictor of MOCA score, it is a weak one, and does not effectively capture all variance in performance.

4.4 On Result 4 – No significant evidence was found to establish a correlation between tonsillar descent and MOCA score.

There was no evidence from statistical tests to suggest that the degree of cerebellar tonsillar descent is correlated with lower MOCA scores. In fact, without the negative outlier of 48mm, the correlation (albeit still non-significant) is actually *positive*. This suggests that either there is no significant correlation between cerebellar tonsillar descent and MOCA score, or that the data set is simply not large enough to establish a meaningful relationship. Results in this section are decidedly inconclusive.

Yet, this data does corroborate recent findings that CSF flow could be far more important than relative cerebellar cognitive descent. It has been hypothesized that descent of the cerebellum is in fact a contributory symptom to physically blocking CSF flow through the foramen magnum. Having wider cerebellar tonsils, then, could perhaps be more important (as opposed to just their descent magnitude).

4.5 On Result 5 - Chiari Patients performed worse on the delayed recall, attention, and language subsections (MOCA).

Chiari patients performed very well on half of the MOCA sections, but performed poorly on measures of language (Language2; 50%; Language 1 78%), Memory/Delayed Recall (59%), and relatively poorly on measures of visuospatial (70%) and attentional function (74-80%).

The results from the delayed recall section mirror the findings of Allen et al. (2017), and the results across the attention subsections mirror the results from Houston et al. (In Press). Interestingly, a deficit was also uncovered in the language domain, which has not been a significant finding in previous studies using more robust cognitive measures.

In general, these results provide tentative support for the use of the MOCA as a general cognitive screening for patients. Additionally, very specific subsections were seen to have significant performance deficits, indicating that the MOCA might be able to serve as a *selective* initial screen for certain Chiari-associated deficits. Further statistical testing must be performed to confirm this hypothesis.

Looking at the results for the memory and delayed recall section, the mean score being just under 3 (2.967) correct out of 5 is of note. When compared to typical ratings given for a similar task on a concussion screening protocol (SAC), one finds that the Chiari patients may indeed score similarly to people who have experienced concussions. In a study completed to determine the baseline scores for delayed recall tests (also out of 5) for normal and injured people, it was found that healthy controls remembered on average 4 out of 5 words, whereas people that were concussed remembered 3 out of 5 (McCrea, 2001). While there are many caveats in comparing these studies–the age of the patients, the difficulty of the words to be remembered, and the type of task administration–these data raise the possibility that the MOCA is indeed identifying a meaningful delayed recall deficit in Chiari Patients.

Finally, there is the curious finding that patients with Chiari seem to be deficient on language measures, and to an extreme degree in the "Language2" section (saying as many words as possible that begin with "F" in one minute). This is surprising given that there is no strong evidence in the literature to suggest that language production or comprehension is heavily affected in people with Chiari Malformation Type I, although the nature of this task also incorporates executive function.

However, after analyzing the "Language2" section, it is clear that there is a specific aspect of this section which may be the cause of the unusually low score – time pressure. This is the only section on the MOCA which requires the participant to work under strict time pressure. The pressure in the section may produce more anxiety (and thus lower scores) for the patient. Additionally, it also requires a fast processing speed, which is a separate modality entirely. Indeed, in Allen et al. (2014), when taking into account anxiety and depression factors, it was found that Chiari patients exhibit significant processing speed deficits. This may be the root cause behind the deficit in this, and perhaps all, language sections on the MOCA. It may also be the root cause of the poor performance on the memory subtask, where the individual is required to quickly encode the words that are presented to them.

4.6 Additional Discussion

The demographic statistics recorded with regards to sex align very well with the findings from Arnautovic et al. (2015), which describe a 1:3 male to female ratio. Our study found exactly a 1:3 male to female ratio, providing further support for a sex-based specificity to the disorder.

As depicted in figure 10, the mean cerebellar tonsillar descent (after removal of the 48mm outlier) was 6.379mm (SD 4.083mm). The large standard deviation reflects the fact that some of these patients had indeed undergone successful decompression surgery, thus minimizing their tonsillar descent to below diagnosable values.

4.7 Improvements to be Made and the Future of Basic Cognitive Screening

Overall, the MOCA shows promise as an effective tool to highlight some of the cognitive deficiencies associated with Chiari Malformation Type I. As suggested above, both general and specific deficiencies appear to be screen-able using this simple test.

However, there are aspects to the test that must be examined further. These aspects should be analyzed not just in terms of Chiari-related deficits, but also in terms of the overall interpretation of the MOCA.

The first aspect is that of processing speed. Ideally, all sections should be timed, giving the examiner some idea of the speed at which the patient is answering the questions. In more than one case – in the trail making task, for example - the patient would take an unusually long time to complete the assignment, but get the final answer correct. Although it would be possible for them to get a perfect score on a section, this type of behavior should also allow for information to be extracted as to whether the patient's general processing speed is at a normal level. The most obvious reflection of this phenomenon is the result that Chiari patients performed terribly on a specific section (language). This section involved a modality that, according to literature, should not have been impaired, but it is likely that this processing speed confounding interaction skewed the data. Even so, the degree to which patients performed badly on this section warrants further investigation into both language and processing speed deficits in Chiari. Interestingly, this bad performance on timed or pressured sections may serve as further support for Schmahmann's "Dysmetria of thought" hypothesis, in that while some cognitive modalities remain intact, it may be difficult for CMI patients to coordinate their thoughts appropriately.

The second aspect of the MOCA that must be reexamined is related to subsection scoring. Specifically, the manner in which subjects fail subsections should impact their maximum score somehow. As an example, there were multiple patients who performed extremely poorly on the executive/visuospatial subsections (**Drawing examples are in the Appendix)**. This performance, if bad enough, should be taken into account immediately. Especially as a general cognitive screening tool, the MOCA should require that the examiner make note of these unusual performances on certain sections to warrant further cognitive testing, or even fail the entire sub-section (for e.g. Language or Memory).

The future of general cognitive screening is bright – just in this small sample of Chiari patients, it appears that the MOCA detected difficulties on the test present in a large portion of the population indicative of MCI (43%<26 cutoff score). Descriptively, specific deficits highlighted by other, more in-depth, testing paradigms were also detected. If combined with a digital timing method which allows for the measurement of other modalities such as processing speed (as is indeed currently being done by the MOCA team, who are starting to use tablet-based testing), then general cognitive screens could indeed become a David to the Goliaths of tests such as RBANS or neuropsychological evaluations. Not only is there a possibility for general (and standardized) quick cognitive screens to pick up on specific cognitive deficits, but they can also be completed in under ten minutes, making them directly available for easy clinical application.

4.8 Limitations

There are several limitations that must be taken into account concerning this study. First and foremost, sample size is of significant concern. Specifically, the analysis for post-op patients (currently n=9) would greatly benefit from an increase in this sample size. While for the most part the entire sample was treated as uniform in terms of operation status, more precise analysis would clearly warrant using far higher sample sizes.

Second, the true nature of the patients' cognitive deficits was never confirmed. That is to say, it is unknown whether the patients who scored below the cut-off value of 26 on the MOCA actually would be clinically diagnosable with MCI. Having patients receive further detailed and in-depth testing with regards to cognitive deficits (i.e. neuropsychological evaluation) would both increase the strength of the present results as well as support the power of the MOCA to detect deficits such as MCI.

In this same vein, detailed statistical analysis was not performed in this study with the aim of controlling for confounding effects such as pain or anxiety. Additionally, as mentioned in the methods section, exemption from the study was not considered for patients with other medical conditions. In order to avoid this for a future study, a far larger sample size should be used, especially given the wide degree of comorbidities that Chiari patients typically present with (Chiari Comorbidities, 2018).

Finally, as mentioned in the discussion section on result 5, the findings and analysis in that section are purely descriptive. Thus, further statistical analysis and testing are necessary in that area. This analysis was not performed in the case of this present study due to the small sample size tested, an over-complexity of the model required to capture multi-variate / non-consistent subsections, and the amount of time that would be required.

Acknowledgements

Many thanks to Dr. Philip Allen for introducing me to and teaching me about the subject matter in this paper, to Dr. Christopher Benjamin for assisting me in the thesis process, and to the Neurological Institute at Cleveland Clinic Fairview. Additional thanks to Prof. Mark Sheskin and Prof. Joshua Knobe for guiding me through the Cognitive Science major.

References

[Beacon Health Options Psychological Test Listing]. (2015, December 15). Unpublished raw data.

Arnautovic, A., Splavski, B., Boop, F. A., & Arnautovic, K. I. (2015). Pediatric and adult Chiari malformation Type I surgical series 1965–2013: A review of demographics, operative treatment, and outcomes. Journal of Neurosurgery: Pediatrics, 161-177. doi:10.3171/2014.10.peds14295

Allen, P. A. et al. (2014). Task-Specific and General Cognitive Effects in Chiari Malformation Type I. *PLOS one, 9*(4), e94844.

Allen, P. A. et al. (2017). Chiari 1000 Registry Project: assessment of surgical outcome on self-focused attention, pain, and delayed recall. *Psychological Medicine*.

Bechara, A. et al. (2000). Characterization of the Decision-Making Deficit of Patients with Ventromedial Prefrontal Cortex Lesions. *Brain, 123*, 2189-2202.

Borland, E., Nägga, K., Nilsson, P., Minthon, L., Nilsson, E. D., & Palmqvist, S. (2017). The Montreal Cognitive Assessment: Normative Data From A Large Swedish Population-Based Cohort. Alzheimers & Dementia, 13(7). doi:10.1016/j.jalz.2017.06.1498

Buckner, R. L. et al. (2011). The organization of the human cerebellum estimated by intrinsic functional connectivity. *Neurophysiology, 106*, 2322-2345.

Buckner, R. (October 30, 2013). The Cerebellum and Cognitive Function: 25 Years of Insight from Anatomy and Neuroimaging. Neuron, 80(3), 807-815. doi:10.1016/j.neuron.2013.10.044

Burch, E. A., & Andrews, S. R. (1987). Cognitive Dysfunction in Psychiatric Consultation Subgroups. *Southern Medical Journal,80*(9), 1079-1082. doi:10.1097/00007611-198708090-00003

Carson, N., Leach, L., & Murphy, K. J. (2017). A re-examination of Montreal Cognitive Assessment (MoCA) cutoff scores. International Journal of Geriatric Psychiatry, 33(2), 379-388. doi:10.1002/gps.4756

Chiari Comorbidities & Etiological/Pathological Co-factors. (2018, November 11). Retrieved March 25, 2019, from https://chiaribridges.org/overview-chiari-comorbidities-etiological-pathological-cofactors/

Chiari Malformation Fact Sheet. (n.d.). Retrieved Feb 4, 2019, from http://www.conquerchiari.org/index.html

Conquer Chiari (n.d.). Retrieved Feb 4, 2019, from http://www.conquerchiari.org/index.html

Cullen, B., O'Neill, B., Evans, J. J., Coen, R. F., & Lawlor, B. A. (2007). A review of screening tests for cognitive impairment. Journal of Neurology, Neurosurgery, and Psychiatry, 78, 790-799.

Gaillard, F. (2019). Chiari I malformation | Radiology Reference Article. Retrieved March 25, 2019, from https://radiopaedia.org/articles/chiari-i-malformation?lang=us

Gonzalez-Usigli, H. A. (2017, February). Cerebellar Disorders - Neurologic Disorders. Retrieved October 27, 2017, from http://www.merckmanuals.com/professional/neurologic-disorders/movement-and-cerebellar-disorders/cerebellar-disorders

Goodlett, C. R., & Lundahl, K. R. (1996). Temporal determinants of neonatal alcohol-induced cerebellar damage and motor performance deficits. *Pharmacology Biochemistry and Behavior,55*(4), 531-540. doi:10.1016/s0091-3057(96)00248-1

Houston et al. Type I Chiari Malformation, RBANS Performance, ad Brain Morphology: Connecting the Dots of Cognition and Macro-Level Brain Structure. *Neuropsychology*. In Press.

Kelly R. M., & Strick, P. L. (2003). Cerebellar Loops with Motor Cortex and Prefrontal Cortex of a Nonhuman Primate. *The Journal of Neuroscience, 23*. Retrieved November 27, 2017, from http://www.jneurosci.org/content/23/23/8432.long#T1

Kimbell, A. (2013, July 24). Cognitive Testing Using the RBANS Update. Retrieved March 24, 2019, from http://images.pearsonclinical.com/images/pdf/webinar/rbansjuly2013webinarhandout.pdf

Krienen, F. M., & Buckner, R. L. (2009). Segregated Fronto-Cerebellar Circuits Revealed by Intrinsic Functional Connectivity. *Cerebral Cortex, 19*, 2485-2497.

Labuda, R. (2012). Chiari Malformation: Symptoms. Retrieved March 25, 2019, from https://www.conquerchiari.org/documents/presentations/SYMPTOMS Presentation.pdf C&S Patient Education Foundation

Labuda, R. (2012). Chiari Malformation: Diagnosis. Retrieved March 25, 2019, from https://www.conquerchiari.org/documents/presentations/DIAGNOSIS%20Presentation.pdf C&S Patient Education Foundation

Lang, C. E., & Bastian, A. J. (2002). Cerebellar Damage Impairs Automaticity of a Recently Practiced Movement. *Journal of Neurophysiology, 87*(3), 1336-1347. doi:10.1152/jn.00368.2001

Luck, T., Luppa, M., Briel, S., & Riedel-Heller, S. G. (2010). Incidence of Mild Cognitive Impairment: A Systematic Review. Dementia and Geriatric Cognitive Disorders, 29(2), 164-175. doi:10.1159/000272424

Mccrea, M. (2001). Standardized Mental Status Assessment of Sports Concussion. Clinical Journal of Sport Medicine, 11(3), 176-181. doi:10.1097/00042752-200107000-00008

Middleton, F. (2000). Basal ganglia and cerebellar loops: motor and cognitive circuits. *Brain Research Reviews, 31*(2-3), 236-250. doi:10.1016/s0165-0173(99)00040-5

Nasreddine, Z. S., Phillips, N. A., BãcDirian, V., Charbonneau, S., Whitehead, V., Collin, I., . . . Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. Journal of the American Geriatrics Society, 53(4), 695-699. doi:10.1111/j.1532-5415.2005.53221.x

Neuropsychological Evaluation FAQ. (n.d.). Retrieved February 22, 2019, from https://www.med.unc.edu/neurology/divisions/movement-disorders/npsycheval/

Oldfield, E. H. (2017). Pathogenesis of Chiari I – Pathophysiology of Syringomyelia: Implications for Therapy: A Summary of 3 Decades of Clinical Research. *Neurosurgery,64*(CN_suppl_1), 66-77. doi:10.1093/neuros/nyx377

Randolph, C. (2012). Clinical Psychology. Retrieved February 22, 2019, from https://www.pearsonclinical.com/psychology/products/100000726/repeatable-battery-for-the-assessment-of-neuropsychological-status-update-rbans-update.html#tab-details

Schmahmann, J. D. (2004). Disorders of the Cerebellum: Ataxia, Dysmetria of Thought, and the Cerebellar Cognitive Affective Syndrome. *The Journal of Neuropsychiatry and Clinical Neurosciences, 16*, 367-378.

Schmahmann, J. D., & J. C. (1998). The cerebellar cognitive affective syndrome. *Brain, 121*, 561-579.

Schmidt, M. (1996). Rey Auditory Verbal Learning Task. NY, USA: Western Psychological Services.

Sweet, J. J., Benson, L. M., Nelson, N. W., & Moberg, P. J. (2015). The American Academy of Clinical Neuropsychology, National Academy of Neuropsychology, and Society for Clinical Neuropsychology (APA Division 40) 2015TCNProfessional Practice and ‘Salary Survey’: Professional Practices, Beliefs, and Incomes of U.S. Neuropsychologists. *The Clinical Neuropsychologist,29*(8), 1122. doi:10.1080/13854046.2016.1140228

Wechsler, D (2008), “Wechsler Adult Intelligence Scale-Fourth Edition.” USA: Pearson.

Woodford, H., & George, J. (2007). Cognitive assessment in the elderly: A review of clinical methods. Qjm, 100(8), 469-484. doi:10.1093/qjmed/hcm051

Appendix

<u>Example Patient-Drawn Diagrams from the MOCA</u>