# Uncovering the Latent Structure of Visuospatial Ability and Predicting Visuospatial Dysfunction From Lesion Location

by

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This dissertation is dedicated to my Opa, Judge Alan Sternberg, for demonstrating the importance of intellectualism, critical thinking, and the pursuit of one's greatest passions; my mom, Dawn Lee, for providing a loving and nurturing environment that fostered my curiosity about the world around me; and my Grammy, Sharon Sternberg, for her unending love and support when I need it most.

“Time and space are modes by which we think and not conditions in which we live.”
Albert Einstein

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# ABSTRACT

Visuospatial ability is the ability to perceive, understand, and utilize visual sensory data to construct a spatial map of one's environment. Visuospatial dysfunction commonly occurs following brain lesions and often improves in the first few months post-injury; however, some patients continue to have chronic visuospatial dysfunction which can have a devastating impact on recovery trajectory, the ability to live independently, and quality of life. Prognoses for these patients are often made based on clinical intuition, but an evidence-based approach for predicting long-term visuospatial dysfunction in the acute epoch of recovery remains elusive. This study sought to identify the latent structure of visuospatial ability, investigate brain regions and networks involved in visuospatial ability independent of the tests used to measure it, and develop a model to predict long-term visuospatial dysfunction in two out-of-sample cohorts. Exploratory factor analysis was used to identify potential latent variables representing domain-general visuospatial ability across twelve neuropsychological tests in patients from the Iowa Neurological Patient Registry (n = 480). One latent variable, "domain-general visuospatial ability", described variance in this sample best. Brain regions and networks associated with domain-general visuospatial ability were identified using multivariate lesion-symptom mapping and lesion network mapping. Finally, models were compared to determine the best predictors of long-term visuospatial dysfunction in the Benton Neuropsychology Clinic cohort (n = 80) and the Washington University cohort (n = 104). Domain-general visuospatial ability was associated with right hemisphere damage to the putamen and bilateral damage to posterior white matter tracts constituting the dorsal visual stream in the lesion-symptom map. After controlling for

general cognitive ability, only right white matter damage was implicated. Damage to regions in the dorsal attention network and visual network along with posterior inter- and intra-hemispheric white matter was also associated with visuospatial dysfunction. A model including functional lesion network mapping, structural lesion network mapping, and lesion volume best predicted outcomes in both validation cohorts. This study provides novel evidence for the right putamen's importance in visuospatial ability and confirms the previously identified involvement of the dorsal visual stream, dorsal attention network, and visual network in visuospatial ability. Furthermore, my predictive model is one step towards the broader goal of predicting long-term outcomes of brain damage in the acute epoch.

## PUBLIC ABSTRACT

The brain processes information from the eyes to create a map of spatial relationships that is used for things like navigation, drawing, rotating objects in one's mind, and guiding movement to avoid running into objects. Damage to the brain can affect someone's ability to do this, a deficit called visuospatial dysfunction. After brain damage, this problem can resolve on its own in some, but not all, people. Visuospatial dysfunction can impact multiple areas of everyday life, and predicting long-term recovery in the days following brain damage is challenging. This study had three main goals: 1) identify which sub-processes comprise visuospatial ability, 2) identify regions and networks in the brain that support visuospatial ability, and 3) develop mathematical models that can predict long-term visuospatial dysfunction. Analyses were performed in 664 people with brain damage. I identified regions in the brain, the right putamen and the dorsal visual stream, and networks in the brain, the dorsal attention network and the visual network that are important for visuospatial ability. The significance of the dorsal visual stream for visuospatial ability has been well described, but the involvement of the right putamen in visuospatial ability has not been reported in humans. These results were used to create a mathematical model that predicts visuospatial dysfunction using brain networks and the size of a brain lesion as predictors. My findings contribute to the broader goals of predicting outcomes from brain injury using mathematical models and better understanding the functional neuroanatomy of visuospatial ability.

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# PREFACE

I proudly present my doctoral dissertation, “Uncovering the Latent Structure of Visuospatial Ability and Predicting Visuospatial Dysfunction From Lesion Location”, written to fulfill the graduation requirements of the Interdisciplinary Graduate Program in Neuroscience at the University of Iowa in Iowa City, Iowa. I researched this topic and wrote this dissertation from April 2022 to August 2023.

My interest in space and time began in preschool when I routinely begged my mom to take me to the library to check out an unending pile of books on outer space and physics. She always entertained my young scientific musings and quickly became a captive audience to my rants about planets, black holes, and how space and time can be thought of as two sides of the same coin. While my field of interest has pivoted from theoretical physics to neuroscience over the years, my interest in the relationship between space and time has not. How does the brain construct a sense of space and time using multimodal sensory information in concert with experience? As a PhD candidate, I have been fortunate to investigate the functional neuroanatomy of visuospatial ability and time perception from a neuroscientific perspective in patients with focal, acquired brain lesions.

I have never been short on research questions, but the skills needed to investigate my interests needed to be further developed when I entered the Neuroscience Program. It was only through the excellent mentorship of Dr. Aaron Boes and Dr. Daniel Tranel that I could succeed in pursuing this line of research I am so enthusiastic about. I was concerned that I would not be able to pick my own research topics when I entered graduate school, and the independence to develop my own project

was paramount when selecting a lab to join. Aaron and Dan struck a perfect balance between encouraging my scientific creativity and guiding me through my proposed projects' practical and their technical aspects. Mentorship by others in the lab, especially Joel Bruss who kickstarted my love for computer science, has also made a tremendous impact.

As I wrap up my career as a PhD candidate, I am filled with profound gratitude for the people in my life who have invested in me. Science is never a one person endeavor; it takes a team of diverse and excellent individuals to push the boundaries of the field to discover more about the beautiful reality we live in. To those that have helped me along the way, I have one final sentiment: “Never gonna’ give you up. Never gonna’ let you down. Never gonna’ run around and desert you.”[1].

So Long, and Thanks for All the Fish[2],

Jax D. Skye

Iowa City, April 27, 2023

[1] Astley, R. & Waterman, S.A. (1987). Never Gonna Give You Up [Song]. On *Whenever You Need Somebody*. RCA Records.
[2] Jennings, G. (Director). (2005). *The Hitchhiker’s Guide to the Galaxy* [Film]. Touchstone Pictures, Spyglass Entertainment, Hammer & Tongs Productions, Everyman Pictures.

# CHAPTER 1: LITERATURE REVIEW

## 1.1. Neuropsychological Assessment of Visuospatial Ability

### 1.1.1. Definition of Visuospatial Ability

Visuospatial ability describes the ability to perceive, understand, and utilize visual information to generate a useful internal model of one's spatial environment. This umbrella term includes constructs like mental rotation of objects, spatial attention, visuoconstruction, and spatial memory among other faculties. Deficits in visuospatial ability, sometimes called vision-for-action, can lead to non-useful perceptions of spatial relationships that cannot appropriately guide action. Importantly, visuospatial dysfunction is not a byproduct of damage to the eyes, optic nerve, or primary visual cortex (V1). Instead, visuospatial dysfunction describes a cognitive problem that affects one's ability to use visual information to identify spatial relationships (Bauer, 2014; Lezak et al., 2012).

Several clinical syndromes are included under the umbrella of "visuospatial dysfunction". Some of these include topographic disorientation (failure to find one's way in the environment), visuospatial inattention/hemispatial neglect (inattention to the contralesional side of space, typical), deficits in drawing to dictation (i.e., the patient cannot accurately draw a clock when prompted), impairment in two-dimensional and three-dimensional block design construction, and visuospatial dysgnosia (inability to sense the relative location between oneself and the environment or the spatial relationship between objects and other objects). Since human brains exhibit interindividual variability and each lesion is unique, lesions affecting visuospatial function often produce several co-occurring deficits that do not strictly follow the

categories described above. For example, patients with Balint's syndrome experience simultanagnosia (inability to perceive multiple objects at once), oculomotor apraxia (defect in voluntary eye movements), optic ataxia (defect in visually guided reaching), and defective judgment of distance (Bálint, 1909; Lezak et al., 2012). Topographic disorientation commonly co-occurs with visuospatial dysgnosia (Suzuki et al., 1998) and visuospatial inattention commonly co-occurs with anosognosia (unawareness or inaccurate awareness of one's condition) (Grattan et al., 2018). Therefore, the profile of impairment across multiple neuropsychological assessments of visuospatial function will vary between patients. This must be considered when making more specific predictions about the long-term outcomes of brain damage.

### 1.1.2. Clinical Importance of Visuospatial Ability

Impairment on measures of visuospatial ability has clinical significance. Visuospatial cognition is heavily relied upon, and if lost, the patient's quality of life and ability to live independently can be severely impacted. Everyday tasks like grabbing an object, getting dressed, finding one's way in a building, driving a car, walking, and drawing rely on intact visuospatial ability. For example, deficits in understanding spatial relationships could make driving dangerous and increase the risk of falls. An inability to grasp objects makes caring for oneself without assistance difficult or impossible. Inattention to one side of space could cause issues like neglecting to clean one side of one's body, bumping into objects on the neglected side, and only reading one side of a page, making long-term care a necessity. Deficits in this domain can result in a financial burden for families and insurance companies, decrease the number of years worked, and take an emotional toll on those close to the patient in addition to the substantial

impact these deficits have on the patient themself. Therefore identifying specific deficits a patient is experiencing, and ideally accurately predicting them, is critical to create realistic expectations for recovery and provide proper treatment and care. This research builds upon the field's current knowledge of the impact of brain injury on visuospatial function, adds to our understanding of functional neuroanatomy, and takes steps towards developing a clinical tool to predict visuospatial dysfunction.

### 1.1.3. Approaches to Studying Visuospatial Ability in Humans with Brain Lesions

Neuropsychological assessments sensitive to visuospatial ability are the most common way of assessing visuospatial function, providing information critical for diagnosing neurological disorders and providing treatment recommendations to patients and their caregivers. Early neuroscientists and neuroanatomists learned that damage to specific brain areas across patients produced similar cognitive and behavioral impairments. Before the widespread availability of neuroimaging tools like positron emission tomography (PET), computerized tomography (CT), and magnetic resonance imaging (MRI), clinicians relied on neuropsychological assessment to localize lesions while the patient is alive. This proved to be an invaluable and reliable tool that often accurately identified the location of a brain lesion which was confirmed post-mortem. The same principle is still used today: hypotheses about lesion location based on neuropsychological test performance can be confirmed with neuroimaging. Neuropsychological assessment is a component of the field of clinical neuropsychology which seeks to identify specific behavioral and cognitive manifestations of neurological defects (Lezak et al., 2012). Standardized behavioral assessment is an essential component in the "lesion method", an approach whereby regions of stable, focal brain

damage are correlated with a defect in cognitive or behavioral function that was not present before the onset of the lesion (Koenigs et al., 2007). This also allows researchers to better understand which brain areas are involved in specific cognitive domains.

Dozens of reliable and valid assessments of visuospatial function have been developed over the past several decades, many of which have been associated with specific loci of brain damage. Impairments in other cognitive domains like memory and language are often more evident to the patient and those around them compared to visuospatial dysfunction. Furthermore, this deficit can be more challenging to identify without proper testing due to a higher rate of co-occurring anosognosia and spatial cognition's inherent first-person perceptual quality. Failure to correctly identify visuospatial dysfunction early can lead to real-world consequences like traffic accidents, falls, and occupational problems depending on the patient’s line of work.

The lesion method has several unique qualities that will contribute to the success of this project. First, the brain exhibits functional localization (meaning that different regions of the brain perform different functions) (Lezak et al., 2012) and small-world network architecture (individual nodes are not adjacent to each other but are highly connected, requiring few steps between nodes) (Bassett & Bullmore, 2017; Watts & Strogatz, 1998). However, it is important to remember that a single brain region can be involved in multiple seemingly different functions. Modularity in the brain is well described in primary and secondary visual cortex (S. Zeki & Bartels, 1998). Other components of vision including form, color, and motion are processed by modular but connected brain areas despite the subjective perception of a unitary visual world (A. L.

Benton & Tranel, 1993; Galletti & Fattori, 2018; Tranel et al., 2009). For example, damage to an area of the brain that processes color while sparing regions that process form and motion can cause achromatopsia, a disorder of color perception wherein the patient experiences the visual world in a limited array of colors (Bartels & Zeki, 2000). Functional distinction between regions allows researchers and clinicians to make accurate assumptions about lesion location from behavioral deficits to aid in identifying clinical syndromes. Relatedly, double dissociation describes an instance where two cognitive processes occur independently of each other such that a focal lesion to area A produces measurable behavioral outcome 1 and damage to area B produces measurable behavioral outcome 2 while preserving behavior 1 (Plaut, 1995). Groundbreaking research by Ungerleider and Mishkin showed a double dissociation in non-human primates where lesions to the posterior parietal lobe affected spatial recognition but not form recognition and lesions to the temporal lobe affected form recognition but not spatial recognition (Ungerleider, 1982) (see section 1.324). But significant limitations in animal research exist, especially when studying complex cognitive processes unique to humans or vastly more complex in humans. While there is a degree of evolutionary conservation of brain structure between species, animals do not have some cognitive capabilities and cannot report their experience like humans can (Tecott, 2003). Some aspects of visuospatial function, like navigation, can be studied quite well in rodents. However, more complex faculties like mental rotation of objects cannot be probed as effectively in animal models as in humans (if non-human animals have this capability at all). From a research perspective, the lesion method in humans allows us to understand better the functional neuroanatomy of complex

processes like visuospatial ability while providing indispensable information for diagnosing and treating specific neurological deficits. However, some limitations exist to using patients with brain lesions instead of healthy subjects. This study is limited in its generalizability to the cognitive architecture of healthy adults' brains due to reorganization of function following brain damage, learned compensatory mechanisms to circumvent dysfunction, and commonly occurring co-impairments that may suggest two co-occurring functions are a single function. In other words, the latent variables identified in this study might not accurately reflect how visuospatial ability is represented in neurologically normal brains. There could be other confounds related to the consequences of a brain injury that are not accounted for, driving certain tests to be grouped.

### 1.1.4. Neuropsychological Tests Sensitive to Visuospatial Dysfunction

Many neuropsychological assessments sensitive to visuospatial dysfunction have been developed over the last several decades. Different laboratories and clinics across the globe use various behavioral measures, and only some commonly administered tests are included in this study due to data availability. But, all neuropsychological assessments included in this study are widely administered (Lezak et al., 2012).

The Wechsler Adult Intelligence Scale (WAIS) is a commonly administered standardized intelligence test for adults and adolescents that assesses various domains of cognition (Wechsler, 1955). It is a valuable tool and commonly administered assessment that can inform diagnoses and treatment recommendations for patients with brain injuries while remaining sensitive to the abilities of highly intelligent healthy adults, which reduces floor/ceiling effects. Various subtests of the WAIS probe

visuospatial function and scores from these subtests were used in this study. Developed in the 1950s, this assessment improved upon existing intelligence measures like the Wechsler-Bellevue Intelligence Scale (Balinsky et al., 1939) and the Stanford-Binet intelligence test (Terman, 1916) by offering scores for individual tests, categories of intelligence, and general intelligence. Four full-length versions of the WAIS have been developed as of 2022: the original version (Wechsler, 1955), revised version (WAIS-R) (Wechsler, 1981), WAIS-III (Wechsler, 1997), and WAIS-IV (Wechsler & Assessment, 2008). Each version differs slightly by adding/removing subtests, making subtle changes to test items, and providing different index scores. The current version (WAIS-IV) contains ten core subtests with five supplemental subtests. When scored, patients receive four index scores that represent performance on a group of the subtests: Verbal Comprehension Index (Similarities, Vocabulary, Information, Comprehension), Perceptual Reasoning Index (Block Design, Matrix Reasoning, Visual Puzzles, Figure Weights, Picture Completion), Working Memory Index (Digit Span, Arithmetic, Letter-Number Sequencing), and Processing Speed Index (Symbol Search, Coding, Cancellation) in addition to a Full Scale Intelligence Quotient (FSIQ) score. The WAIS-III included a Verbal IQ score and Performance IQ score instead of index scores to represent performance across categories of intelligence. A score of 10 on a subtest and a full-scale IQ of 100 are considered average using demographic-adjusted normative data.

#### *1.1.4.1. Block Design*

Block Design is a timed test where the subject is presented with a set of two, four, or nine red and white blocks (Lezak et al., 2012; Wechsler, 1955, 1981, 1997;

Wechsler & Assessment, 2008). Each block has two white sides, two red sides, and two white and red sides bisected along the diagonal. The subject must replicate the design shown by the examiner using the provided blocks, and test items are increasingly difficult as the test progresses. The time taken to complete each item of this subtest is considered when generating the subtest's score. Performance on this subtest has increased over time (Flynn effect (Trahan et al., 2014)) and is influenced by age, sex, and education (Lezak et al., 2012).

Block Design assesses visuospatial ability, problem-solving, and visuomotor construction. More specifically block design tests two-dimensional visuoconstruction, which differs from three-dimensional visuoconstruction in that subjects can have impairment in one but not the other (A. L. Benton & Fogel, 1962). Administration of assembling tasks like block design in concert with drawing tasks in the same battery better characterizes a person's relative impairment in the spatial and constructional aspects of visuoconstructional dysfunction (Lezak et al., 2012). Beyond the quantitative data available via the subject's score, qualitative characteristics of how the test was performed can provide valuable insight into the specific nature of a subject's dysfunction in addition to their planning and problem-solving abilities. The types of errors on this test (e.g., rotational errors, positional errors, etc.) can provide further information on the underlying cause of a low score. Subjects who complete this test quickly, accurately, and with relative ease likely have a better mental conceptualization of spatial relationships than those who are more hesitant and use a trial-and-error approach (Lezak et al., 2012).

#### *1.1.4.2. Digit-Symbol Coding*

Digit-Symbol Coding, sometimes referred to as just “Coding”, consists of rows of small blank boxes paired with single-digit numbers (Lezak et al., 2012; Wechsler, 1955, 1981, 1997; Wechsler & Assessment, 2008). The top of the page contains a key indicating symbols assigned to each of the nine digits. The subject must fill in the box below each number with the corresponding nonsense symbol on this paper and pencil test. In the WAIS-IV, there are three demo questions where the examiner demonstrates the principle of the test followed by six practice items for the subject to demonstrate that they understand the task. Subjects are scored on their ability to perform this task accurately and quickly, finishing as many test items as possible in the two-minute testing period.

Several cognitive functions are necessary in this speed-dependent test including motor precision, visual scanning, associative memory, and visuomotor coordination. If the subject demonstrates motor slowness in other tasks, a low score may reflect motor disability and not visual scanning or visuomotor ability impairments. People with impaired vision are also at a disadvantage in this task. Furthermore, the ability of this task to evaluate visual search ability can wane if the subject begins to memorize which symbol corresponds with which digit; this can be determined by comparing the number of items completed in the first half of the test with the latter half of the test (Milberg et al., 1996). Finally, selective attention may also play a role in test performance. The test shows high test-retest reliability and is not influenced by education, but is influenced by age and frequency of aerobic exercise (Lezak et al., 2012).

#### *1.1.4.3. Matrix Reasoning*

In the Matrix Reasoning subtest, subjects are presented with increasingly difficult visual puzzles that follow a pattern (Lezak et al., 2012; Wechsler, 1955, 1981, 1997; Wechsler & Assessment, 2008). For example, the question may contain four boxes, each with a dot in the corner. The dot shifts to the next corner in a clockwise fashion for the first three boxes (i.e., dot in the top-left corner, dot in the top-right corner, dot in the bottom-right corner) and the subject must indicate which of several multiple-choice options best completes the pattern shown on that test item. In this example, the correct choice would be a box with a dot in the bottom-left corner.

Matrix Reasoning tests nonverbal abstract problem-solving and inductive reasoning through visual pattern matching, similar to Raven's Progressive Matrices (Raven & Court, 1938, 1998). The subject must conceptualize the design and spatial relationships shown on the test item non-verbally. Fluid intelligence is also measured as patterns range from evident to highly complex, changing between each test item. The examiner must be careful when administering this test to subjects suspected of having unilateral visuospatial inattention so as not to penalize them. Matrix Reasoning is a good indicator of premorbid intelligence and is highly correlated with other tests sensitive to premorbid intelligence (Lezak et al., 2012). This untimed test shows excellent internal consistency and high test-retest reliability. Older subjects tend to perform worse than younger subjects (Lezak et al., 2012).

#### *1.1.4.4. Picture Completion*

In the Picture Completion subtest, the subject is shown incomplete images of everyday things like objects, scenes, and human faces and must indicate to the

examiner what is missing in the image (Lezak et al., 2012; Wechsler, 1955, 1981, 1997; Wechsler & Assessment, 2008). Test items increase in difficulty; large, colored images are shown and the subject must respond within a 20-second time limit. For example, a test item may include a picture of a grandfather clock missing the minute and hour hands and the subject would be prompted to tell the examiner what is missing. This test probes the subject's ability to quickly notice visual differences showing sensitivity to visual searching, visual organization, concentration, visual recognition of detail, memory, and processing speed. While this test predominantly measures alertness to detail, effort is also a critical component. Suppose a patient demonstrates low effort through formal measures like Dot Counting (Boone et al., 2002) and has a low score on picture completion. In that case, alternative explanations outside of visuospatial dysfunction should be considered. Scores on this test decline with age and sex differences (superior performance in males) are most pronounced in mid-adulthood. Test-retest reliability for Picture Completion is lowest among WAIS-IV subtests but is most correlated with Full Scale IQ (Lezak et al., 2012).

#### *1.1.4.5. Symbol Search*

On this timed paper and pencil test, subjects must indicate whether the two nonsense probe symbols appear in an adjacent horizontal array (Bauer, 2014; Lezak et al., 2012). If one of the two probe symbols matches one of the five symbols in the array of options, the subject must cross out the appropriate symbol. If neither of the two probe symbols matches symbols in the array, the subject must mark "no".

Symbol search is a timed test of processing speed, visual search, and visuomotor function. Patients with hemispatial inattention will likely struggle with Symbol

Search, particularly in cases of left-sided neglect, which are most common (where probe symbols are displayed). Lower scores may not indicate visuospatial dysfunction if motor slowing or poor graphomotor ability is apparent from other assessments. Therefore, it is essential to administer Symbol Search along with other visuospatial tests to further evaluate the cause of a low score. Older adults tend to perform worse on this test compared to younger individuals as is common with tests of processing speed (Lezak et al., 2012).

#### *1.1.4.6. Benton Facial Recognition Test*

Apart from the WAIS, a host of other neuropsychological assessments probe visuospatial function, some of which are not mentioned in this research proposal. Apart from those described in this dissertation other commonly administered assessments sensitive to visuospatial dysfunction include the Mini-Mental State Examination, Dementia Rating Scale, Visual Object and Space Perception Battery, Gestalt Completion Test, Dot Counting, Line Bisection Test, and a variety of cancellation tests like Line Cancellation and Bell's Cancellation. The tests mentioned in the following subsections are not WAIS subtests as the five above named tests are.

The Benton Facial Recognition Test probes face perception independent of memory of faces (A. L. Benton et al., 1994). The subject must match black and white images of an unfamiliar human face to the front of the same person's face, the side of the same person's face, or the front of the same person's face under a different lighting condition. Some test items ask for one match-to-sample response and other items ask for three match-to-sample responses. In a lesion-symptom mapping study comparing the face processing as measured by the Benton Facial Recognition Test and line

orientation as measured by the Judgment of Line Orientation test, damage to ventral regions in posterior cortex and dorsolateral regions around the parieto-occipital junction are associated with face processing and line orientation processing respectively, suggesting this test is especially sensitive to ventral visual stream dysfunction (Tranel et al., 2009). However, this test is still important to include when evaluating visuospatial function since reciprocal communication between the dorsal and ventral visual streams has been noted (see section 1.3.2). Practice effects on this test are negligible, and age is negatively correlated with test performance (Lezak et al., 2012).

#### *1.1.4.7. Benton Visual Retention Test*

The Benton Visual Retention Test (BVRT) is widely used to assess visuospatial memory and visuospatial inattention (A. L. Benton & Sivan, 1992). Most test items have two large shapes and one small shape lined up next to each other horizontally. After each test item is shown for 10 seconds, the subject must draw the stimulus on a sheet of paper. For example, a test item might show two large semi-overlapping circles to the left and a small square on the right. To get the item correct, the subject would have to remember each shape's position and relative size. The BVRT has correct and error scores for each test item. An alternate form of scoring can provide a score based on the type of error made, which provides a more detailed evaluation of specific deficits contributing to poor performance.

Hemispatial inattention could affect how patients encode information about the shapes on the affected side because the shapes may not be consciously perceived; therefore, a low score may not reflect a deficit in visuospatial memory but a deficit in visual attention. Furthermore, graphomotor impairments or visuoconstructional

impairments may affect a patient's ability to draw the test item accurately, even if their memory of the item is correct. Like other tests, a comprehensive battery of tests is required to identify the cause of poor performance. Older adults typically have fewer correct items, and education drastically affects performance. This test shows high test-retest reliability if the test is retaken within the same year to avoid the impact of age-related effects on BVRT performance (Lezak et al., 2012).

#### *1.1.4.8. Clock Drawing*

Originally designed to identify visuospatial inattention, Clock Drawing was later shown to be sensitive to various neurological deficits (Battersby et al., 1956; Freedman et al., 1994; Tranel et al., 2008). The subject is instructed to draw a circular analog clock face depicting numbers in the appropriate positions and draw hour and minute hands to depict a time given by the examiner. Impairments in clock drawing can be striking, especially since patients may need to recognize their drawing is flawed. In patients with have left-sided hemispatial inattention, the circular clock face may only contain numbers on the right side (Freedman et al., 1994; Tranel et al., 2008).

Clock drawing deficits can result from a variety of different types of dysfunction. In addition to visuoconstruction this test is sensitive to deficits in working memory, executive function, numerical knowledge, and receptive language. Patients with working memory difficulties may be unable to remember the time they were supposed to indicate with the hour and minute hands. Executive function deficits could lead to poor planning such that the placement of numbers is off. Patients with receptive language dysfunction may not understand the test instructions correctly. There are different ways to score this test, but all show high interrater reliability (Lezak et al., 2012). The nature of the error

(hand placement or visuospatial error) may indicate which hemisphere is lesioned (Tranel et al., 2008). Performance does not change much with age, and poor education can impact test performance (Lezak et al., 2012).

#### *1.1.4.9. Hooper Visual Organization Test*

The Hooper Visual Organization Test (HVOT) consists of 30 test items, each including a cut-up, readily identifiable two-dimensional black and white line drawing (Hooper, 1983). The subject must name the object depicted for each individually administered test item The HVOT measures visuospatial integration, wherein the subject mentally rotates the pieces that comprise everyday objects. Visual organization necessary for this test involves making sense of fragmented or ambiguous figures, relying on multiple cognitive faculties like conceptual knowledge, memory, visuoperceptual differentiation, and visuoconstruction. Subjects must name the object once they realize what the fragmented pieces comprise, making this test sensitive to naming deficits too. Performance on the HVOT, subtests of the WAIS measuring perceptual organization, and tests of object naming are highly correlated (Lanca et al., 2003). This test also shares variance with other tests of visuospatial ability (Johnstone & Wilhelm, 1997). The HVOT has a high test-retest reliability, and test performance decreases with age. Performance does not significantly differ between sexes or in level of education. The HVOT is particularly useful in identifying brain disease because false positive test performances are rare (Lezak et al., 2012).

#### *1.1.4.10. Judgement of Line Orientation*

The Judgment of Line Orientation Test (JLO) tests basic visuospatial function (A. Benton et al., 1975; A. L. Benton et al., 1978, 1994). Subjects must match two probe

line segments in the same location and point in the same direction as two lines within a series of eleven lines. The probe segments in the multiple-choice array are either the lines' proximal, middle, or distal section. Responses are scored as correct if the subject identifies the orientation of both lines in this 30-item test. The JLO is particularly sensitive to early visual processing and, unlike other commonly administered visuospatial measures, does not rely on visuoconstruction or graphomotor skills. Therefore, impairment on the JLO may predict impairment on other visuospatial tests that depend on accurate processing of line orientation, like the Complex Figure Test. Several short forms of the JLO exist for screening purposes. One short form developed using Item Response Theory (Reise & Waller, 2009) shows promise as a replacement for the complete JLO form (Calamia et al., 2011; Spencer et al., 2013). High internal consistency and test-retest reliability makes the JLO a good option for testing cognitive decline in patients with neurodegenerative diseases that affect visuospatial ability. Healthy women tend to perform worse than healthy men by two points; regardless of sex, performance declines with age and is higher in those who are better educated (Lezak et al., 2012).

#### *1.1.4.11. Rey-Osterrieth Complex Figure Test*

The Rey-Osterrieth Complex Figure Test (CFT) copy trial probes perceptual organization and visuoconstruction (Rey, 1941). Subjects must copy a complex figure using a pencil and paper while the stimulus is in front of them. The subject cannot rotate the stimulus or their paper and the time it takes for them to copy the figure is timed (although time to complete does not affect the CFT copy score). Many types of errors could lead to a poor score including but not limited to distortions in size/shape of the

figure or parts of the figure, failure to copy one side of the figure, and failure to include all details in the figure to name a few. More recently developed scoring methods can better elucidate the nature of the subject's deficit; a poor score is based on how the figure is drawn. Errors on this test could be due to graphomotor deficits, deficits in visual organization, hemispatial inattention, or deficits in short-term visual memory. Performance on the CFT gradually declines after approximately age 50 and the time it takes to copy the figure increases. However, this decline in performance is not drastic in healthy aging adults. Men outperform women and IQ is significantly correlated with CFT performance. Individuals with a background in science or mathematics perform better on this test than others (Lezak et al., 2012).

#### *1.1.4.12. Spatial Span*

Spatial span is a Corsi-style measure of visuospatial working memory (Berch et al., 1998). Ten cubes are placed in an irregular arrangement on a pedestal and the examiner taps the blocks in a predetermined order. The subject must repeat the pattern of tapping forwards or backwards depending on the portion of the test. Spatial span is also sensitive to motor deficits like ataxia, hemiplegia, and apraxia which can be circumvented in part by administering the assessment over a computer. This test is similar to the WAIS subtest Digit Span, but subjects tend to perform worse by one or two items on Spatial Span. Performance on this test decreases with age. Lesion laterality can be evaluated by comparing Digit Span and Spatial Span scores: right hemisphere dysfunction may be present if Spatial Span is much worse than Digit Span, and left hemisphere dysfunction may be present if Digit Span is much worse than Spatial Span (Lezak et al., 2012).

### 1.1.5. Influence of Attribute Variables on Visuospatial Ability

When interpreting neuropsychological test scores and referencing scores of healthy people, it is essential to consider scores in context. Demographic characteristics like gender, age, level and quality of education, handedness, and race/culture may impact performance. Population-level differences do not necessarily translate to the level of individual patients but nonetheless should be considered, especially in research. Moreover, lateralization of cognitive function can be influenced by attribute variables like handedness and gender. Attribute variables can be controlled for in analyses, ensuring results are driven by differences in the location of brain injury, not differences in attribute variables.

At a population level, men outperform women on tests of visuospatial ability and are more likely to hold jobs that require visuospatial skills (Hedges & Nowell, 1995; Linn & Petersen, 1985; Ramírez-Uclés & Ramírez-Uclés, 2020; Strand et al., 2006; Voyer & Saunders, 2004). This gender disparity is most consistently reported in adult populations (Linn & Petersen, 1985) and for aspects of visuospatial ability relating to mental rotation (Hines et al., 2003; Linn & Petersen, 1985). The age at which these sex differences appear varies between studies and is based upon which aspect of visuospatial ability is being measured (e.g., mental rotation versus visuoconstruction versus line orientation, etc.) (Hespos & Rochat, 1997; Möhring & Frick, 2013; Moore & Johnson, 2008; Quinn & Liben, 2008). A more recent study with a large sample size did not find sex differences in mental rotation children. Still, differences were apparent in adults (Barel & Tzischinsky, 2018), which supports the idea that superior visuospatial ability in males may be due to hormonal differences. This hypothesis is further

supported by positive correlations between visuospatial ability and an individual's serum testosterone level. After administering testosterone to young women, Aleman and colleagues noted significant improvement in visuospatial memory (Aleman et al., 2004).

Visuospatial ability changes with age in healthy adults (Rowe et al., 2008) and this change in performance over time may be further magnified in the context of brain damage. Some studies suggest that mental rotation and spatial visualization are conserved in healthy older adults. However, they may perform tasks slower than healthy younger adults (de Bruin et al., 2016) but others suggest visuospatial performance declines with age (Bendayan et al., 2017; Jenkins et al., 2000). Neurodegenerative diseases must also be considered in older populations since dementia and other age-related neurodegenerative diseases can affect visuospatial function (Pal et al., 2016; Salimi et al., 2018). Using scaled scores and age-matched normative datasets can help account for age in group-level analyses. When this is not possible and there are age-related differences in test performance, age can be used as a covariate when comparing performance between groups.

More years of education and better quality of education are associated with higher scores on neuropsychological tests of visuospatial ability (Bendayan et al., 2017; Ostrosky-Solís et al., 2004). For example, two fictitious patients with comparable lesions and different educational backgrounds (one with ten years of formal education and one with eighteen years of formal education) may both perform in a low-average range on a test of visuospatial function. However, it is likely that the score is a greater reduction from baseline in the patient with eighteen years of formal education. It may suggest the lesion had a greater impact on test performance compared to the patient with ten years

of education. Visuospatial ability is critical within science, technology, engineering, and mathematics (STEM) fields (e.g., concepts are represented and communicated spatially). Those with better visuospatial ability tend to be drawn to STEM and education in STEM topics improves visuospatial function (Castro-Alonso & Uttal, 2019). In fact, innate visuospatial ability predicts academic achievement in maths and reading in school-age children (Liu et al., 2021).

Handedness has long been associated with differences in hemispheric specialization and performance on cognitive tasks. 90% - 95% of people exhibit single-hand dominance with right hand preference (Lezak et al., 2012), which appears to be genetic (Annett, 2002). It is common for people to use their non-dominant hand for simple tasks, though (Lezak et al., 2012). An over-generalization by non-experts in cognitive neuroscience is that the left hemisphere is language dominant, and the right hemisphere supports non-verbal abilities. While there is some truth to this, the story is much more nuanced. Most right-handed people have left-lateralized language representation (>95%) as measured by Wada testing (Borod et al., 1985; Branch et al., 1964; Loring et al., 1990). The same is true for ~70% - 80% of left-handed individuals (Branch et al., 1964; Loring et al., 1990); however, those who are not left-hemisphere language dominant typically exhibit bilateral language dominance instead of right-lateralized language dominance as measured by Wada testing (Risse et al., 1997). Right-hand dominant individuals typically outperform left-handers on visuospatial tasks (Bradshaw, 1989; Nicholls et al., 2010; Snyder & Harris, 1993) but there is an interaction with sex. This may be due to a more diffuse but inefficient representation of spatial ability in both hemispheres in left-handed people as in females. In contrast,

spatial ability is more consistently represented in the right hemisphere in right-handed people. One study showed that strongly left-handed males had higher spatial scores than strongly right-handed males, an opposite effect in females (Sanders et al., 1982).

Race, culture, and ethnicity are often used interchangeably and inconsistently within neuropsychology and cognitive neuroscience literature (Lezak et al., 2012). This is something to be aware of when examining the literature on racial, cultural, and ethnic differences in cognitive performance regardless of cognitive domain. It is important to remember, though, that differences in performance on visuospatial tests due to race are most likely due to a mediating variable like socioeconomic status, access to education, and cultural importance of visuospatial ability (e.g., Indigenous Pame and Maya people have superior visuospatial skills compared to non-Indigenous people of the same region since their culture prioritizes farming and basketry (Ostrosky-Solís et al., 2004)).

### 1.2. Investigating the Cognitive Architecture of Visuospatial Ability

Neuropsychological assessments were not designed to test the function of specific brain regions. Therefore, a single neuropsychological test may be sensitive to deficits in multiple cognitive abilities. For example, the WAIS subtest Symbol Search is a timed test sensitive to visuospatial ability and processing speed. An impaired score could reflect deficits in either capacity. On the other hand, multiple neuropsychological tests could measure a single underlying construct. This would be reflected in behavioral data as impairments in test performance that covary between tests across a large number of patients. Covariance in scores between tests could point to a neuroanatomical similarity between individual functions being tested (regions that support each function are typically lesioned together) or the tests assess the same

function. It is essential to understand the underlying construct being measured, also called a “factor” or “latent variable”, to identify the neural correlates of cognitive abilities and not merely the neural correlates of performance on a neuropsychological test. From a clinical perspective, identifying latent variables measured by visuospatial tests could reduce redundancy in test administration and maximize a testing session to cover more domains of cognition in less time.

The Cattell-Horn-Carroll (CHC) theory is a theory of the structure of human cognitive abilities that offers a way of understanding aspects of cognition (e.g., language, memory, visuospatial ability, etc.) as components of an overarching concept: intelligence (Carroll, 1993; Cattell, 1941). A vital part of the CHC theory is Carroll’s Three Stratum Theory which was developed using a psychometric approach and factor analytic techniques (Carroll, 2003). Psychometric theories posit that intelligence/general cognitive ability can be understood in terms of its constituents. Intelligence is a latent variable that cannot be measured directly but can be better understood using mathematical modeling like factor analysis. Factor analysis is a data reduction technique that describes variability within a data set using fewer variables (Kyriazos, 2018). In the context of this project, multiple neuropsychological tests can measure one or a few latent variables of visuospatial ability (Bowren et al., 2020). Tests that covary would be grouped into a single factor. The Three Stratum Theory hypothesizes a three-tier hierarchical structure of cognitive abilities where general intelligence (stratum III), also called *g*, is composed of several broad cognitive abilities (stratum II) (Carroll, 2003). Examples of abilities within stratum II include comprehension knowledge (the depth and breadth of acquired knowledge and the ability to communicate/apply it), fluid

reasoning (the ability to form concepts, reason, and solve unfamiliar problems), processing speed (the ability to perform cognitive tasks requiring maintained focused attention quickly), and visual processing (the ability to perceive, analyze, synthesize, and think using visual patterns). Within each broad cognitive ability of stratum II lies multiple more specific narrow cognitive abilities (stratum I). For example, visual processing (also called *Gv*) consists of narrow abilities like visual memory, spatial scanning, length estimation, and mental rotation to name a few (Carroll, 1993). Different neuropsychological tests assess different narrow abilities within the domain of visuospatial function.

Data-reduction techniques seek to understand aspects of cognition that are not directly measured and have been widely applied in psychology and neuropsychology. Methods like factor analysis, which is similar in principle to independent component analysis and principal component analysis, allow researchers to probe phenomena independent of individual tests and individual test questions (Bechtoldt et al., 1962). Exploratory Factor Analysis (EFA) is a data-driven statistical method that identifies the underlying structure of data when there are many variables (Comrey, 1978; E. Ferguson & Cox, 1993). When applied to psychological research, EFA can identify latent variables not directly measured by behavioral assessments (Cattell, 1966; Pires et al., 2018). Factor analysis has been used to understand the structure of intelligence (Bowren et al., 2020), personality (Greene, 2000; John et al., 1991), and other aspects of the mind (Fabrigar et al., 1999). How the field describes cognitive functions linguistically is not necessarily related to how the brain represents them. Since the goal of this project aims to understand better how the brain supports visuospatial function, I want to define types

of dysfunction through latent variables and not specific neuropsychological tests or behavioral descriptions, most of which were coined to describe healthy brains.

Factor analysis has been used to characterize general intelligence from multiple domain-specific measures for decades (Stephenson, 1935). General intelligence, also referred to as general cognitive ability or "*g*", is a psychometric construct that captures general cognitive ability as a summation of positive correlations across multiple cognitive tasks (Spearman, 1904). While neurologically healthy people have minor relative strengths and weaknesses across cognitive domains, performance on one cognitive task is typically comparable to performance on another cognitive task (Spearman, 1904). Research in patients with brain lesions provides the unique opportunity to disentangle constituents of *g*. A recent study investigated the localization of *g* in patients with brain lesions and showed that damage to posterior white matter in the left hemisphere, specifically the arcuate fasciculus, is associated with impairment across neurological domains, even in patients with relatively small lesions (Bowren et al., 2020). The visuospatial ability factor localized to the right posterior putamen, right subinsula/claustrum, and white matter superior to these regions (Bowren et al., 2020). Some patients in Bowren and colleagues' cohort overlap with patients in the Iowa Registry cohort.

### 1.3. Neuroanatomy of Visuospatial Ability

Visuospatial ability, or vision-for-action, is typically considered a function of the right posterior parietal lobe with information flowing from primary visual cortex through the occipitoparietal "dorsal visual stream", terminating in the posterior parietal lobe. However, this is a gross oversimplification of the neuroanatomical correlates of

visuospatial ability. Differences in functional specialization between hemispheres can be broadly described as verbal or non-verbal information coding. In right-handed people, the left hemisphere is dominant for processing verbal, analytical, detail-oriented information; the right hemisphere is associated with non-verbal, intuitive, emotional thought (Hécaen & Angelergues, 1961). Hemispheric specialization is further supported by differences in cellular organization between hemispheres (Galuske et al., 2000; Gazzaniga, 2000). While the right hemisphere is commonly believed to dominate visuospatial processing, contradictory evidence suggests that the reality of the spatial representation in the brain is more nuanced (Prohovnik, 1978) and requires further investigation. The “left for language” and “right for visuospatial” dichotomy of hemispheric asymmetry fails to account for left hemisphere lesions associated with visuospatial disturbance and the effects of handedness on hemispheric specialization. Furthermore, cases of visuospatial dysfunction associated with anterior cortical and subcortical lesions in the absence of posterior cortical damage have been reported (Carrera & Bogousslavsky, 2006; Kashyap et al., 2011). As described in previous sections, numerous narrow cognitive abilities like mental rotation and visuospatial memory contribute to what the field calls “visuospatial ability”. Each narrow cognitive ability likely relies upon different but sometimes overlapping neural substrates. Thus, the term “visuospatial ability” must be further parsed into its constituents to understand better how different brain regions contribute to each aspect of visuospatial function. This is particularly important when predicting specific visuospatial deficits from lesion location. Finally, considering visuospatial ability as an exclusively dorsal visual stream

function fails to consider how reciprocally connected regions modulate this pathway's activity and how damage to these connected regions may affect visuospatial function.

### 1.3.1. Representation of Space From the Retina to Neocortex

Higher-order visual dysfunction can be categorized as disturbances in vision-for-action and disturbances in vision-for-perception that can result from damage to regions outside of the eye, optic nerve, or primary visual cortex. According to the two-stream model of visual processing, there are two anatomically and functionally distinct higher-order visual pathways: 1) an occipitoparietal "dorsal" visual stream originating in primary visual cortex (V1/Broadmann's area 17) and terminating in the parietal lobe and 2) an occipitotemporal "ventral" visual stream originating in V1 and terminating in the temporal lobe (Mishkin et al., 1983; Ungerleider M., 1982). The dorsal visual stream is colloquially referred to as the "where pathway" and the ventral visual stream is called the "what pathway". These descriptions were slightly altered a decade later, redefining the dorsal stream as necessary for visually guided action (Goodale & Milner, 1992). While it will be mentioned when relevant, this work will not focus on the ventral visual stream or its functions as it is outside of this project's scope dissociation between object location processing in the dorsal visual stream and object feature processing in the ventral visual stream begins early in the visual system. Photoreceptors are selectively tuned to different aspects of visual stimuli, starting the dissociation between types of visual information at the level of the retina. Associated with the parvocellular and magnocellular layers of the lateral geniculate nucleus of the thalamus (LGN) respectively, P and M retinal ganglion cells have different response properties and selectively fire in response to different stimuli (Purves, 2018). P cells are color-sensitive,

receiving input from cones in center-surround style receptive fields common in retinal cells. For example, the center of a P cell may be sensitive to medium-wavelength cones, whereas the surround may be sensitive to long-wavelength cones. Contrarily, M cells are indifferent to the type of cone they receive input from, making them largely color insensitive and are instead sensitive to low contrast stimuli. Compared to P cells, M ganglion cells have larger cell bodies, larger receptive fields, and a larger axonal diameter, making their conduction velocity faster. This is functionally significant because cells sensitive to motion must carry information rapidly the brain so the organism can react quickly. M cells also exhibit a more transient response profile; whereas, P cells fire in a more sustained manner. M and P cells terminate on the magnocellular (layers I and II) and parvocellular (layers III–VI) of the LGN, respectively, suggesting that these two central streams contribute differently to visual processing. In non-human primate lesion studies, selective damage to magnocellular layers affects the individual's ability to process movement with little effect on color perception or visual acuity. A double dissociation is seen with damage to the parvocellular layer of the LGN, which affects color perception and visual acuity but not motion perception (Merigan et al., 1991).

Tracing the central visual pathways from the LGN to primary visual cortex, the parvocellular pathway terminates on cytochrome oxidase blobs in layer 4Cβ of V1. These cylindrical columns of cells are sensitive to color (Wong-Riley, 1979). The magnocellular pathway terminates on neurons between blobs in layers 4Cα and 4B of V1, called interblobs, which are sensitive to stimulus orientation and less sensitive to wavelength information. Information from interblobs then travels to thick stripes of V2 before ending up in extrastriate cortex. The next stop in the dorsal visual stream is the

middle temporal visual area (V5/MT) which contains direction-sensitive neurons (Born & Bradley, 2005). V5 is best known for its role in motion perception (S. Zeki, 2015), discovered first in non-human primates (Cragg, 1969; S. M. Zeki, 1969) and then in humans (S. Zeki et al., 1991). Direction-sensitive neurons were also identified in the lateral suprasylvian gyrus of cats (Hubel & Wiesel, 1962). In the original conception of the dorsal visual stream, the pathway continues through occipitoparietal cortex and terminates in the inferior parietal lobule (IPL) (Mishkin et al., 1983; Ungerleider M., 1982). Later research in humans and non-human primates suggests that two dorsal visual stream pathways may exist: one flowing from extrastriate visual cortex to MT/V5 and terminating in the IPL and a second pathway from extrastriate visual cortex to V6 to the superior temporal lobule (SPL) (Rizzolatti & Matelli, 2003). However, this has been contested by Galletti and colleagues who demonstrate two pathways: 1) a dorsolateral pathway from V6 to MT/V5 and other regions of extrastriate cortex including V3A, V4T, and medial superior temporal area (MST) and 2) a dorsomedial pathway from V6 to V6A, medial intraparietal area (MIP), and ventral intraparietal area (VIP) (Galletti et al., 2001). Other regions, including the superior frontal lobe, are connected to the IPL and are also thought to be involved in visuospatial function (Macko et al., 1982). Despite differences in proposed pathways, cortical regions involved in visuospatial function are reciprocally connected and in constant communication (Galletti & Fattori, 2018).

### 1.3.2. Brain Networks and Visuospatial Ability

The previous section shows that intact visuospatial function in healthy adults relies on multiple communicating brain areas. There are disagreements within the field regarding the exact pathways information used for visuospatial processing travels after

it reaches extrastriate visual cortex. One model posits a dorsolateral and dorsomedial visual stream that may exhibit neuroanatomical and functional differences (Galletti & Fattori, 2018). In the Galletti model, neurons from the extrastriate cortex synapse onto neurons in area V6, a retinotopically organized region representing the contralateral visual field (Galletti et al., 1993). V6 is highly sensitive to visual motion (Pitzalis et al., 2009), outputs to several areas including MT/V5, and receives input from V1 and extrastriate cortex (Desimone & Ungerleider, 1986). All four regions included in the dorsolateral visual stream (V6, MT/V5, MST, and V3A) are involved in motion perception and contain cells that respond to real movement of objects, not merely movement across the retina (Galletti & Fattori, 2018). Regions in the dorsomedial visual stream (V6A, MIP, and VIP) contain cells that respond to the position of objects independent of head position (Galletti et al., 1993) which is essential for reaching and grasping (Galletti & Fattori, 2018). Damage to the dorsolateral and dorsomedial streams sensitive to object motion and object position respectively would, in theory, cause a double dissociation between motion detection and vision for action. This is supported by human lesion studies where lesions affecting MT/V5 cause akinetopsia, or motion blindness (Zihl et al., 1983), and electrical stimulation to regions in the dorsolateral path causes sensations of motion (Pitzalis et al., 2009). Lesions to the dorsomedial pathway result in optic ataxia (Perenin & Vighetto, 1988). In another study, patient D.F. had an extensive posterior occipital lesion affecting the ventrolateral occipital lobes due to carbon monoxide poisoning (Milner et al., 1991). The dorsomedial visual stream remained largely intact. This resulted in visual form agnosia, amongst other impairments. Since the dorsomedial visual stream was spared, she retained the

ability to grasp objects. It is important to note that the same cortical areas and neurons within them can serve multiple purposes (Galletti & Fattori, 2018) so considering whole brain networks is essential.

Experientially, vision is unitary meaning that aspects of vision like color, shape, and movement are experienced simultaneously and inseparably in healthy humans despite being processed in discrete brain regions. This may be due to the high degree of connectivity needed for communicating information between regions. Neither the dorsal visual stream nor the ventral visual stream works in isolation. Building upon the original two-stream hypothesis that suggested visuospatial processing occurs in a hierarchical flow of information, modern conceptions of visuospatial function suggest a stage-wise flow of information with reciprocally connected nodes (Trés & Brucki, 2014). Reciprocal connections between spatially disparate areas, including regions outs of the canonical dorsal visual stream (Barrash et al., 2000), seem to represent space. Current evidence may support three separate pathways within the dorsal stream terminating in prefrontal cortex, premotor cortex, and medial temporal cortex associated with spatial working memory, visually guided self-motion, and navigation respectively (Kravitz et al., 2011). Extensive reciprocal connectivity between the ventral visual stream and dorsal visual stream in visuospatial tasks has also been noted in the literature (Kravitz et al., 2011; Migliaccio et al., 2016; van Polanen & Davare, 2015) and makes sense in terms of function. In the real world, lesions do not follow boundaries of the dorsal and ventral visual streams. Hence, lesions often cross this anatomical boundary resulting in clinical syndromes exhibiting deficits in both visuospatial and visuoperceptual domains. Presumably, damage anywhere within the nodes of the visuospatial network can affect

function. Therefore, it is critical to examine the impact of brain lesions not only from a regional perspective but from a network perspective. Results from this study will help to further the field's understanding of how damage to structurally and functionally connected regions impacts visuospatial function.

Some research groups have conceptualized specific visuospatial impairments as disconnection syndromes. A disconnection syndrome describes a neurological disorder caused by severing white matter pathways connecting two intact cortical regions. One of the most well-known examples of a disconnection syndrome is conduction aphasia. This acquired language deficit arises from the structural disconnection of the arcuate fasciculus connecting Broca's area and Wernicke's area (areas associated with speech production and speech comprehension, respectively). Patients with conduction aphasia have intact speech production and comprehension yet cannot repeat words or phrases. This is because information understood cannot be transmitted to regions responsible for producing speech. Next, visuospatial inattention, also called hemispatial neglect, describes a disorder in which a patient is inattentive to stimuli on one side of space. This syndrome typically occurs after a stroke affecting the right cerebral hemisphere and causes inattention to the contralesional side of space (Li & Malhotra, 2015). Patients can be inattentive to stimuli on their left side (egocentric neglect) or in relation to the left side of objects (allocentric neglect) regardless of where they are in the patient's visual field (Leyland et al., 2017). While the mechanism of visuospatial inattention is hotly debated, some researchers hypothesize it is a disconnection syndrome. Damage to long-range white matter tracts due to stroke often precedes visuospatial inattention, suggesting that visuospatial attention may depend on a

distributed network of structurally connected regions (Bartolomeo et al., 2007). Simultanagnosia, a disorder in which a patient cannot perceive more than one object at once, may also be caused by lesions that disconnect the visuospatial attention network (Chechlacz et al., 2012).

### 1.3.3. Visuospatial Ability Through Lesion Studies

Several lesion studies have examined the neuroanatomical correlates of visuospatial ability, typically using one or a few neuropsychological tests to measure behavior. Impairments across multiple areas of visual perception are most common following brain lesions (Riddoch & Humphreys, 2001; Zihl, 1989) making it more difficult to pin down precise neural correlates, especially in studies with small cohorts of patients. However, large cohort human studies have replicated findings in non-human primate lesion research, furthering the field's understanding of the neural correlates of visuospatial ability. A double dissociation between dorsal visual stream and ventral visual stream has been confirmed in human lesion patients using the JLO and Benton Facial Recognition Test, respectively, to measure higher-order visual function (Tranel et al., 2009). Localization of impairment on the JLO was compared to the Rey-Osterrieth Complex Figure Test indicating overlapping neural correlates in the frontal lobe, superior temporal lobe, and supramarginal gyrus in judging line orientation and visuoconstruction (Biesbroek et al., 2014). Damage to the right superior parietal lobe and angular and middle occipital gyri impaired visuoconstruction showing that earlier visual processing (of line orientation) is insufficient for, but intimately related to, visuoconstruction (Biesbroek et al., 2014). The common notion of visuospatial ability as a right hemisphere function has been disproven. Developmental onset lesions to the left

hemisphere (Lidzba et al., 2006) and adult-onset lesions to the left hemisphere (Ng et al., 2000) are also associated with visuospatial impairment. The cerebellum (Molinari et al., 2004) and basal ganglia (Mohr et al., 1997) also seem to play a role, further emphasizing the necessity of a network-based understanding of visuospatial function. Some studies suggest that damage to the superior longitudinal fasciculus (Nakajima et al., 2017) and functional disconnection in alpha and beta bands are associated with chronic visuospatial dysfunction across etiologies (D'Andrea et al., 2019; Ros et al., 2022). These findings must be considered in the context of patients' attribute variables. While some aspects of visuospatial ability may be strongly right-lateralized, others are not (Vogel et al., 2003) which could lead to inaccurate predictions like a minimal risk for visuospatial dysfunction following left hemisphere damage. For example, mental versus physical manipulation of objects in a block design task relied on the right and left hemispheres, respectively (Kee et al., 1984). Simple tasks involving visuospatial cognition could be performed by both hemispheres (Dick, 1976), suggesting that there could be preservation of visuospatial function by the left hemisphere following right-sided damage. Regardless of the large body of lesion research investigating visuospatial function, studies are often confined to single cohorts of patients using one or few behavioral assessments. This project addresses this limitation by including analyses in three patient cohorts across eleven behavioral measures.

### 1.4. Predicting Visuospatial Dysfunction From Lesion Location

Much of the current research on the effects of brain lesions focuses on the contribution of discrete brain regions to cognitive function. Most lesion studies use lesion-symptom mapping to perform group-level analyses of the impact of brain damage

on behavior. Lesion-symptom mapping associates regions of focal, stable brain damage with impairment on a standardized neuropsychological test. Before the advent of neuroimaging, cognitive neuroscientists relied on post-mortem examination of a patient's brain to confirm hypotheses about brain-behavior relationships. Earlier research was dominated by case studies or small group studies which evolved to include larger datasets, often combining data from several institutions. More data are now available in part due to the widespread use of neuroimaging in clinical settings, the higher survival rate of patients with brain injuries in recent decades due to tPA administration, and a field-wide push towards open science and data sharing. This paved the way for larger group-level analyses of brain-behavior relationships using modern neuroimaging. One of the first techniques to determine the association between lesion location and behavioral deficits across patients involved overlapping the lesion mask of each patient impaired on the task of interest and finding regions of peak overlap. This process was enhanced with the advent of the proportional subtraction method (Rudrauf et al., 2008). The proportion of patients impaired on some task relative to all patients is calculated on a voxel-wise basis. The same is done for unimpaired patients. The difference map of the impaired and unimpaired proportional maps is generated such that each voxel in the proportional subtraction map is weighted from -1 to 1, with voxel weights closer to 1 indicating a stronger relationship between damage at that voxel and impairment on the task of interest. One major pitfall of the proportional subtraction method is that continuous scores are binarized, which may cause the analysis to lose granularity compared to methods that treat continuous data as

continuous. Additionally, proportional subtraction does not typically employ a statistical test of significance, although this is possible to do.

Statistically grounded methods like voxel-wise lesion-symptom mapping (VLSM) became more popular because they enhanced the ability to detect brain-behavior relationships and utilized more available data without relying on cutoff scores (Bates et al., 2003). In this mass-univariate method, behavioral data can be kept continuous while identifying which voxels are more associated with behavioral impairment when lesioned. VLSM uses voxel-wise statistical testing to generate a t-score for each voxel which represents the importance of that voxel for the tested function (Rajashekar et al., 2020). The large number of statistical tests between voxels makes corrections for multiple comparisons (like parametric false discovery rate or family-wise error rate) essential to avoid Type I errors (Mirman et al., 2018). Despite corrections for multiple comparisons in mass univariate methods, multivariate approaches to lesion-symptom mapping are more accurate (Pustina et al., 2018). The LESYMAP package in R employs a multivariate lesion-symptom mapping algorithm using sparse canonical correlation analysis for neuroimaging (SCCAN) (Pustina et al., 2018). Across real and simulated analyses, SCCAN outperformed mass-univariate methods; this approach was used for lesion-symptom mapping in this study. Lesion-symptom mapping has limitations, though. Lesion-symptom mapping 1) requires large sample sizes and adequate lesion coverage across the brain with relatively equal power (i.e., not areas with lots of overlapping lesions and areas with few overlapping lesions), 2) can only identify regional correlates of behavior when lesions to the same region cause the same behavioral impairment (not adequately accounting for the effect of lesions on networks),

and 3) may offer more limited predictive value compared to lesion network mapping in some cognitive domains.

Over the past couple of decades, research has emphasized that lesions can impair the function of distant intact brain regions (Carter et al., 2010) and can influence whole-brain network dynamics (Grefkes & Fink, 2011). Considering the network effects of lesions associated with visuospatial dysfunction is paramount. Lesion network mapping is a technique that allows researchers further probe the impact of lesions on anatomically distant intact brain regions. Significant regions identified via a lesion-symptom map or whole lesions are used as seed regions of interest (ROIs) to assess their intrinsic functional connectivity using data from a normative resting state functional connectivity MRI (rs-fcMRI) dataset (Boes, 2020; Boes et al., 2015; Bowren et al., 2020). This allows for retrospective functional connectivity analyses from structural MRI and CT without requiring additional scans, which are costly and not often available clinically. This technique gained popularity after functional lesion network mapping identified the network correlates of neurological syndromes caused by small lesions (Boes et al., 2015). That is, lesions producing common clinical syndromes did not overlap at the site of the lesion but did share the same functional network. Structural lesion network mapping, also called white matter tractography, uses a similar approach to evaluate the impact of lesions to white matter retrospectively by using the results of a lesion-symptom analysis or whole lesions to create seed ROIs as is done in functional lesion network mapping. Both methods of lesion network mapping have effectively predicted cognitive and motor outcomes in other patient cohorts (Boes, 2020; Boes et al., 2015; Bowren Jr et al., 2022; Reber et al., 2021; Salvalaggio et al., 2020). Lesion

network mapping overcomes a major limitation of lesion-symptom mapping by considering the impact of lesions on connected non-lesioned regions. This was particularly advantageous in this study since visuospatial ability is thought to draw on brain-wide networks. Lesion network mapping may explain how lesions outside the dorsal visual stream can still impair visuospatial function. It is essential to consider intrinsic connectivity changes that compensate for tissue loss after brain injuries. Therefore, using a normative dataset of healthy adults is a limitation of this method that must be considered when interpreting results.

Interindividual variability in the outcomes of brain injuries makes predicting long-term behavioral and cognitive deficits particularly challenging. Brain damage can cause a diverse set of deficits acutely, some of which may resolve over time in some patients. However, evidence-based tools to accurately predict chronic (> 3 months after the onset of brain damage) outcomes of focal brain damage based on lesion location are not currently used in clinical settings. Lesion-symptom mapping (Bowren et al., 2020; Weaver et al., 2021) and lesion network mapping (Boes, 2020; Boes et al., 2015; Bowren Jr et al., 2022; Reber et al., 2021; Salvalaggio et al., 2020) have successfully predicted cognitive deficits from brain lesions in multiple cohorts of patients.

To predict dysfunction, lesion-symptom maps are created from one set of behavioral scores in a large dataset of patients. The weighted matrix of voxel values and accompanying eigenvalue created by LESYMAP are multiplied by the binary matrix representing a patient's lesion to create predicted scores for each individual in the validation cohorts. To test predictions using lesion network mapping, lesion load values were generated by summing the voxel intensities of voxels that overlap between the

lesion network map and a patient's lesion mask. The predicted scores from the lesion-symptom map and lesion load values from lesion-symptom maps are transformed to z-scores using Fisher's transformation and compared with the observed scores to determine whether the predicted scores/lesion load values accurately reflect the observed scores. This approach allowed me to use lesion-symptom mapping, functional lesion network mapping, and structural lesion network mapping as predictors in linear regression models.

### 1.5. Knowledge Gap

Despite decades of high-quality research on visuospatial ability and its neuroanatomical correlates, much remains to be discovered regarding the localization of underlying constructs measured by visuospatial tests. Notably, the field needs to gain more knowledge of how lesions outside the dorsal visual stream impact visuospatial function and how to empirically predict long-term visuospatial dysfunction in patients with focal brain damage. To the best of my knowledge, no current studies examine the local and network impacts of brain lesions on visuospatial dysfunction across such a wide array of neuropsychological assessments or use factor-based approaches to predict dysfunction.

This research addresses gaps in the literature in several ways. First, most lesion studies investigate the localization of performance on one or a few neuropsychological assessments. Even with modern lesion-symptom mapping techniques like VLSM or SCCAN, current studies typically map test performance to brain regions. This is limiting because multiple assessments can probe the same function, and a single test can probe multiple functions. In predicting dysfunction in lesion patients, it would be more

beneficial to map the neuroanatomical correlates of latent variables instead of individual test scores. Then, these results can be applied to other datasets regardless of which specific tests are used to assess a patient. Eventually, the generalizability of this approach could inform the development of a clinical tool for predicting chronic visuospatial dysfunction utilizing a patient's acute structural image. The size of the Iowa Neurological Patient Registry is particularly beneficial in this research. Data from 480 patients were used to create the lesion-symptom maps and lesion network maps needed to predict dysfunction in two demographically different validation cohorts. This increases the likelihood that the results of this study can be applied to patient populations across the United States. The large sample size, all of whom have taken the same or similar set of neuropsychological tests, also bodes well for investigating how the brain represents space.

Methods used in this project extend beyond regional localization of function by considering the impact of lesions on functionally connected intact regions. Functional lesion network mapping is a relatively new technique that has shown great promise in understanding how brain-wide networks support cognitive functions and how lesions to separate areas within the same network can lead to similar behavioral outcomes. To the best of my knowledge, this technique has yet to be applied to a large lesion dataset to investigate visuospatial ability until now.

Finally, this research paves the way for developing an evidence-based tool to accurately predict specific visuospatial deficits from lesion location soon after lesion onset. Ideally, this tool would be used in a hospital setting using clinically acquired neuroimaging data. Predictions from this tool can better inform diagnoses and treatment

recommendations for patients and families about recovery trajectories. Cognitive rehabilitation must occur early in recovery for the best results. Knowing which patients are less likely to recover function spontaneously is particularly useful when deciding how to allocate time spent in a cognitive rehabilitation program.

## 1.6. Research, Objectives, Hypotheses, and Significance

### 1.6.1. Research Objectives

This research project aims to identify visuospatial dysfunction independent of neuropsychological tests used to measure it, better understand brain regions and networks associated with visuospatial ability, and predict chronic visuospatial dysfunction in two validation cohorts of patients with focal brain damage. This project has three primary aims. **Aim 1** will use exploratory factor analysis to identify and describe relationships between constituent processes that comprise visuospatial ability. Latent variables identified through factor analysis will indicate covariance in performance across groups of tests, suggesting the tests measure the same or similar underlying processes. **Aim 2** will identify neural correlates of latent variables identified in Aim 1 using multivariate lesion-symptom mapping and network correlates of latent variables using functional lesion network mapping and structural lesion network mapping to uncover functional networks associated with visuospatial dysfunction. **Aim 3** will evaluate the predictive ability of factor-derived lesion-symptom maps and lesion network maps in two separate datasets using lesion load. This study provides more detailed insight into the neuroanatomy of visuospatial ability and how this function is impacted following brain damage at a regional and network level. An enhanced view of the cognitive architecture and neuroanatomical correlates of visuospatial ability will help

pave the way for developing an evidence-based tool to predict chronic visuospatial dysfunction from lesion location in neurological patients.

### 1.6.2. Hypothesis

It is hypothesized that a combined approach of factor-derived lesion-symptom maps and factor-derived functional and structural lesion network maps will best predict chronic visuospatial dysfunction in two validation cohorts. Each patient's lesion mask from the validation cohorts was tested against these statistical maps. Several stepwise regression and linear regression models were used to assess whether lesion-symptom mapping, functional lesion network mapping, or structural lesion network mapping of factors best predicts visuospatial dysfunction in the validation cohorts. The model with the best fit determined by RMSE, AIC, BIC, and R2 was deemed the best. I hypothesize that the model using a combination of lesion-symptom mapping, structural lesion network mapping, and functional lesion network mapping of factors will best predict visuospatial dysfunction in validation cohorts. The hypothesis will be falsified if the model is non-specific, meaning it predicts general cognitive function or language instead of or as well as visuospatial ability.

### 1.6.3. Significance

Brain damage due to stroke affects approximately 795,000 Americans yearly (*Stroke Facts*, n.d.). Brain damage due to traumatic brain injury hospitalizes more than 223,000 Americans every year (*Traumatic Brain Injury & Concussion*, n.d.). The most common cause of brain injury, stroke, creates a $53 billion financial burden including the cost of medical treatment and missed days of work (Tsao et al., 2022) and is a leading cause of disability. The rate of ischemic stroke is likely to continue to increase

due to rising rates of hyperlipidemia, high blood pressure, and obesity in the United States (Akil & Ahmad, 2011). Brain injuries of all types substantially impact patients' quality of life by limiting mobility, reducing independence, and worsening their emotional state (von Steinbüchel et al., 2010). Visuospatial dysfunction is a common consequence of brain damage, can become a long-term disability, and contributes to a reduced quality of life in patients (Bosma et al., 2020; Corbetta et al., 2005; Nijboer et al., 2018; Vossel et al., 2013).

Early detection of visuospatial impairment is essential to guide cognitive rehabilitation and ultimately recovery. Cognitive rehabilitation can aid in reorganizing and redistributing function to surviving tissue in patients with neglect and other visuospatial impairments (Funk et al., 2012; Kerkhoff, 1998). As more therapies are developed, functional outcomes are likely to improve. Increased neural plasticity during the first few months following a brain lesion makes cognitive rehabilitation most effective early in recovery (Kim et al., 2009), meaning early identification of visuospatial dysfunction is crucial. However, cognitive rehabilitation is time-consuming, costly, and requires expert intervention. Moreover, health insurance coverage for outpatient cognitive rehabilitation is limited or unavailable to most, withholding life-changing treatment from people based on money instead of morals. Insurance companies sometimes refuse to cover early outpatient cognitive rehabilitation because visuospatial dysfunction can resolve independently of treatment in some patients. An evidence based tool to identify patients that are likely to have chronic impairment based on lesion location may help support patients in getting insurance companies to cover cognitive

rehabilitation so patients with a lower socioeconomic status can have equal access to life-changing effective treatment.

Aside from the clinical implication of this research, much can be learned about functional neuroanatomy from this study. Most lesion studies of visuospatial function seek to localize impairment on specific tests, an approach that has two major pitfalls. First, a single neuropsychological test can be sensitive to several domains of cognition and multiple neuropsychological tests can measure the same underlying process. This limits the generalizability of findings in lesion studies to how cognitive processes are described linguistically based on apparent differences in behavior instead of how the brain represents cognitive processes. Predictions using one or a few neuropsychological tests to predict real-world cognitive outcomes outside of test performance may be more limited compared to predicting outcomes using the neural correlates of latent variables. Second, lesion-symptom mapping does not adequately account for the impact of a brain injury on network dynamics. The brain is currently understood in terms of “small-world” networks, sets of nodes connected by edges (Bassett & Bullmore, 2017). However, lesion studies restricted to lesion-symptom mapping often fail to consider how damage outside of peak regions can impact test performance. Lesion network mapping can offer explanatory value for how damage to areas outside of findings of a lesion-symptom map can still result in behavioral impairment, enhancing the amount of variance explained by the predictive model. Damage anywhere within a shared functional network can result in the same behavioral outcome (Boes et al., 2015). In context of the domain of interest, this research may

provide deeper insight into how functionally connected regions outside the dorsal visual stream can support visuospatial ability.

### 1.6.4. Expected Results

Based on prior literature and findings in the preliminary analysis, I expect two factors to emerge from the analysis: one factor containing Block Design, Digit-Symbol Coding, Matrix Reasoning, Judgment of Line Orientation, Symbol Search, Benton's Facial Recognition Test, and Hooper Visual Organization Test and a second factor containing Picture Completion, Symbol Search, Benton Visual Retention Test, Complex Figure Test, and Spatial Span. I expect both factors to localize to the right putamen and superior longitudinal fasciculus on both sides of the brain. I expect factor one to localize to regions in the left dorsolateral prefrontal cortex and posterior white matter on both sides, while factor two will localize to predominantly white matter regions along the longitudinal fasciculus. I hypothesize that a combined method of lesion-symptom mapping, white matter tractography, and functional lesion network mapping will account for the most variance and best predict visuospatial dysfunction in the validation cohorts.

# CHAPTER 2: METHODS

## 2.1. Behavior and Neuroimaging Data

### 2.1.1. Behavioral Data

Neuropsychological test data and neuroimaging data for patients with chronic acquired focal brain lesions available through the Iowa Neurological Patient Registry (n = 480) were used to identify latent variables, create lesion-symptom maps, and seed lesion network maps (Table 2.1). Patients in the Registry gave informed written consent prior to testing and this study is approved by the Institutional Review Board of the University of Iowa. Patients were administered an extensive battery of neuropsychological tests designed to assess major domains of behavior and cognition in accordance with Benton Neuropsychology Laboratory protocols (Tranel et al., 2007). Behavioral and neuroimaging data were collected for this retrospective study during the chronic epoch of recovery (> three months after lesion onset) in adult patients. Patients are screened for pre-existing neurological and psychiatric conditions before enrollment in the Registry.

Neuropsychological tests used in this study were selected if they are sensitive to some aspect of visuospatial ability and a large number of Registry patients had been administered the behavioral measure. Tests included were Block Design, Digit-Symbol Coding (Coding), Matrix Reasoning, Picture Completion, Symbol Search, Benton Facial Recognition Test (BFRT), Benton Visual Retention Test (BVRT), Judgment of Line Orientation (JLO), Hooper Visual Organization Test (HVOT), Clock Drawing, Rey-Osterrieth Complex Figure Test (CFT, copy trial), and Spatial Span. For a patient to be included in this study, they had to have scores for at least eight of the twelve behavioral

measures selected. 113 Iowa Registry patients were administered all twelve neuropsychological tests and 114 Iowa Registry patients were missing a score for only one test. The cutoff of eight tests (75%) was selected per previously published methods (Bowren et al., 2020) to reduce the amount of imputed data required while maintaining a large sample size. If a patient was administered the same assessment multiple times, the score most contemporaneous with the scan date was used. If a patient was administered multiple versions of the WAIS, WAIS-IV scores were used preferentially followed by WAIS-R and WAIS-III. Scaled total scores were used for all WAIS subtests and Spatial Span. Hooper Visual Organization Test scores were reported as t-scores, Judgment of Line Orientation and Benton Facial Recognition Test scores were reported as the raw scores plus correction, Complex Figure Test scores were reported as raw scores, Benton Visual Retention Test scores were reported as the number of correct items, and Clock Drawing scores were categorical (impaired, borderline, and unimpaired).

| | | Iowa Registry Cohort (n=480) | Benton Clinic Cohort (n=80) | Washington University Cohort (n=104) |
|---|---|---|---|---|
| Age (in years) | mean (sd) | 52.5 (15.0) | 57.8 (14.7) | 53.6 (10.4) |
| Education (in years) | mean (sd) | 13.6 (2.67) | 12.9 (2.31) | 13.1 (2.36) |
| Gender | Men | 258 | 37 | 55 |
| | Women | 222 | 43 | 49 |
| Handedness | Right | 437 | 72 | 95 |
| | Left | 34 | 6 | 9 |
| | Both | 9 | 1 | 0 |
| Race | African American | 6 | 1 | 69 |
| | American Indian | 2 | 0 | 0 |
| | Caucasian | 470 | 79 | 35 |
| | Other/Unknown | 2 | 0 | 0 |
| Ethnicity | Hispanic | 2 | 1 | 2 |

| | | | | |
|---|---|---|---|---|
| | Non-Hispanic | 477 | 79 | 102 |
| | Unknown | 1 | 0 | 0 |
| Lesion volume (in $mm^3$) | mean (sd) | 46,066 (66,880) | 47,329 (82,938) | 29,814 (42,511) |
| Lesion laterality | Right | 183 | 42 | 54 |
| | Left | 196 | 31 | 50 |
| | Bilateral | 101 | 7 | 0 |
| Etiology | Ischemic stroke | 260 | 72 | 104 |
| | Hemorrhage | 104 | 7 | 0 |
| | Tumor resection | 87 | 1 | 0 |
| | Focal contusion | 16 | 0 | 0 |
| | Herpes simplex or limbic encephalitis | 12 | 0 | 0 |
| | Multiple etiologies | 1 | 0 | 0 |

Table 2.1 A demographics table for all 664 patients across the three cohorts of patients in the study is shown. One limitation of the Iowa dataset is that patients are predominantly white non-Hispanic Iowans which may limit the generalizability to other groups. This was partly addressed by including a validation cohort with different attribute variables. However, more homogenous datasets such as this one can limit noise in the data due to unaccounted for attribute variables and can be a strength. Patients in the WashU cohort acquired their lesions through stroke. Since the group is predominantly African American, this validation cohort can determine whether findings translate across racial groups independent of etiology, which is expected.

One of two validation cohorts includes stroke patients from a previously described study recruited from Washington University - St. Louis (henceforth referred to as the WashU cohort) (Corbetta et al., 2015). Participants in this validation cohort provided written informed consent before participation in the study approved by the Washington University Internal Review Board. Patients in the WashU cohort were administered Clock Drawing, Mesulam's Symbol Cancellation Test, Posner's Spatial Cueing Task, and the Star Cancellation Test.

The second validation dataset includes clinically acquired data from the Iowa Benton Neuropsychology Lab (henceforth referred to as the Benton Clinic cohort). Patients in the Benton Clinic cohort were administered the same behavioral measures

as those from the Iowa Registry, save for Hooper's Visual Organization Test, and provided written informed consent before participation.

The exploratory factor analysis was performed in R using the 'psych' package (W. R. Revelle, 2017). Missing data were imputed using Multivariate Imputation by Chained Equations (https://github.com/amices/mice). The number of factors extracted was determined using a parallel analysis and confirmed using eigenvalues plotted in a scree plot. Minimum residual was used to estimate parameters in the parallel analysis; using maximum likelihood to estimate parameters produced the same result ensuring the number of factors to be retained was not dependent on the method of parameter estimation. A one-factor EFA solution was indicated by the parallel analysis. Minimum residual was used to estimate parameters in the EFA and oblimin rotation was used to extract factors. The results of this analysis include factor loadings for each test (the amount of variance explained by the test) and factor scores for each patient (one factor score per factor per patient). Domain-general visuospatial ability was estimated in two ways, first using composite z-scores and second using factor scores. Composite z-scores were calculated by summing the z-score for each test and dividing by twelve. Factor scores account for the relative influence of each test on a factor. Separate analyses using composite z-scores and factor scores were used in place of individual test scores for the LESYMAP analysis. Results from this analysis can be used to determine which tests contribute most to the latent variable. Tests with higher factor loadings for a given factor (a quantification of the extent to which a variable relates to a factor) are weighted more heavily compared tests with lower factor loadings. One limitation of using exploratory factor analysis is that the output only provides groupings

of neuropsychological assessments. It is up to the researcher to determine the underlying commonality between tests, which can introduce bias into the interpretation of results.

A supplementary agglomerative hierarchical clustering analysis was performed using the hclust function in R with the average agglomeration method to show relationships between tests as an alternative way of representing grouped data (W. Revelle, 1979). The results of this analysis are represented as a dendrogram with multiple clades (arranged according to similarity between data) containing one or more leaves (each leaf being one neuropsychological test). The hierarchical clustering analysis evaluates the similarity between tests without selecting a specific number of factors through a parallel analysis, as is necessary for exploratory factor analyses. If the groupings from the hierarchical clustering analysis are similar to those in the EFA, it would suggest that the test groupings are analysis-independent and reflect true cognitive architecture in the Iowa Registry cohort. This will not be possible to evaluate in the main analysis since a one-factor EFA solution best fit the data.

### 2.1.2. Neuroimaging Data

All patients in this study underwent structural neuroimaging, most often magnetic resonance imaging unless contraindicated. Structural neuroimaging was obtained for each patient in the Iowa cohorts three months or more after lesion onset. The boundaries of the lesions were manually segmented using standard procedures (Frank et al., 1997). Lesion masks for neuroimaging data acquired before 2006 were generated using the MAP-3 method (Damasio & Frank, 1992), wherein the boundaries of the lesion are traced onto a template brain. Lesions in neuroimaging data acquired in 2006

and after were manually traced onto the patient's T1 native scan in FSL (Smith et al., 2004) and subsequently transformed into MNI152 space using ANTs. The anatomical accuracy of the native trace and the transformed lesion mask were confirmed and edited if necessary by a neurologist (A.D.B.) who was to all demographic and cognitive data. MRI data for the WashU cohort were processed as previously described (Corbetta et al., 2015). Lesions in each cohort were overlapped to show relative power across the brain (Figure 2.1).

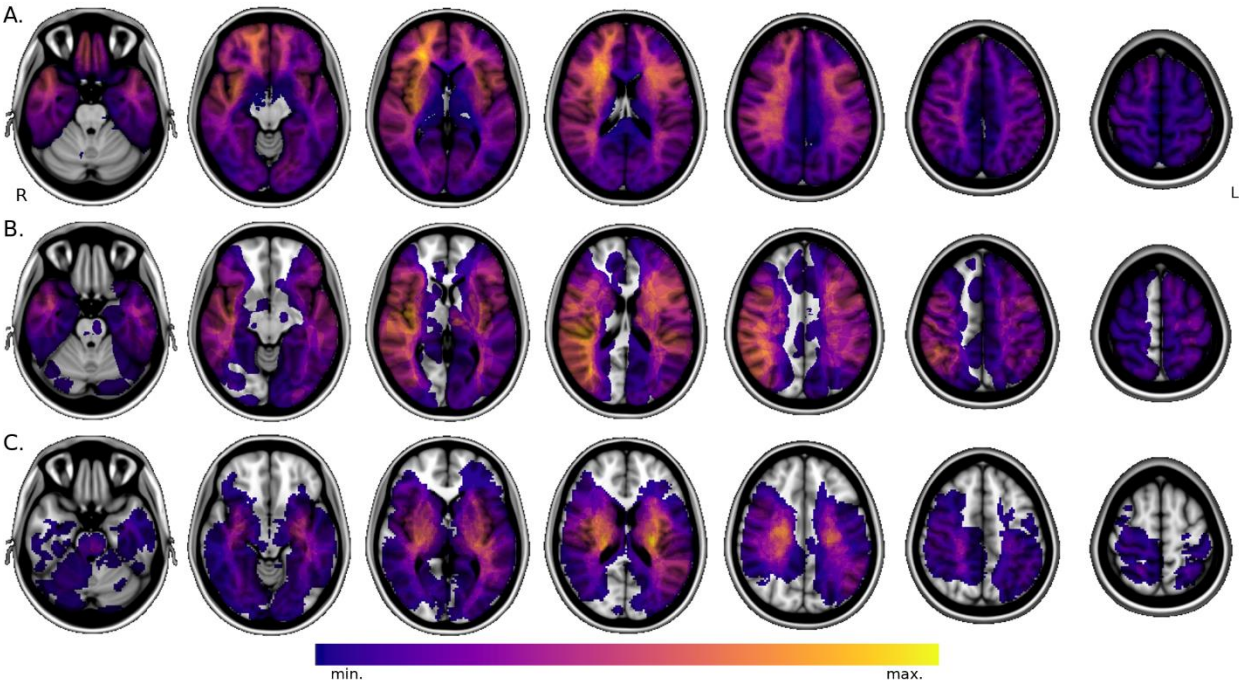



Figure 2.1 Transverse slices -24, -10, 4, 18, 32, 46, and 60 are shown in all panels. The lesion masks of all patients in the Iowa Registry cohort (n = 480) were overlapped to show lesion coverage across virtually the entire cortex (Fig A). Cerebellar and brainstem regions were underrepresented in this sample. The region of peak lesion overlap was in right frontal white matter (MNI coordinates 26 37 5, maximum overlap = 55 lesions). 12 lesions overlapped in the right posterior insula and white matter deep to this region (43 -9 9 and 36 -10 9) in the Benton Clinic cohort (Fig B). More medial cortical regions, the brainstem, and the cerebellum were underrepresented in this sample as well as the WashU sample. 18 lesions overlapped in left deep white matter (-25 -22 18) in the WashU cohort (Fig C). There was a high concentration of lesions in the basal ganglia compared to the other two cohorts.

### 2.2. Lesion-Symptom Mapping and Lesion Network Mapping

Multivariate lesion-symptom mapping was performed using sparse canonical correlation analysis for neuroimaging (SCCAN) via the R package LESYMAP (Pustina et al., 2018). SCCAN implemented via LESYMAP is an optimization procedure that derives voxel weights by maximizing the multivariate correlation between individual patient scores and voxel values from lesion masks (i.e., binary values indicating whether or not that voxel is damaged in that patient). SCCAN sets a sparseness value, or the proportion of voxels retained in the final solution, which is empirically determined through 4 fold cross-validations and gives the best predictive value. A model wherein 75% of the subjects and their behavioral scores are used to predict the remaining 25% provides a sparseness value with the highest cross-validation correlation between predicted and measured behavioral scores. This procedure is more accurate than mass-univariate methods, including situations where there is functional dependency on multiple regions, different sample sizes, and a variety of multi-area combinations regardless of the correction for multiple comparisons used (Pustina et al., 2018). Outputs of LESYMAP analyses are in arbitrary units from -1 to 1, indicating regions associated with minimal risk of impairment and regions associated with a higher risk of impairment on the behavioral measure of interest. As there is no consensus within the field regarding the meaning of findings associated with minimal risk of impairment, lesion-symptom maps shown in the results section will only highlight regions associated with risk of impairment unless otherwise stated. Composite z-scores and factor scores were used as behavioral scores in two sets of lesion-symptom mapping analyses. The identity of grey matter regional peaks was confirmed using the MMP1 atlas (Glasser et al., 2016).

Resting-state functional connectivity MRI (rs-fcMRI) data from a normative database (n = 1000 healthy right-handed subjects; 500 female subjects, ages 18-36 years) was used (A. Cohen et al., 2020). The rs-fcMRI data were processed in accordance with previously described methods (Buckner et al., 2014; A. Cohen et al., 2020). Each lesion mask was entered as a seed ROI which generated a brain-wide network map of z-scores that represented voxel-wise positive and negative correlations with the average BOLD signal time course within the lesion volume. Structural lesion network mapping was performed in DSI studio, where each lesion mask was used as a seed ROI in a deterministic tractography analysis using normative diffusion MRI data as performed previously (Bowren Jr et al., 2022). Normative DTI data from the Human Connectome Project's MGH 32-fold group connectome was used (https://ida.loni.usc.edu/login.jsp; Horn et al., 2017).

Functional and structural lesion network mapping analyses were performed using MATLAB's FSL Permutation Analysis of Linear Models (PALM) tool (Winkler et al., 2014). Lesion masks and behavioral data were included in a permutation-based voxel-wise two-tail linear model using 2,000 permutations with tail approximation and Threshold Free Cluster Enhancement as previously described (Cotovio et al., 2020; Reich et al., 2022; Winkler et al., 2014). Functional and structural lesion network maps were corrected for multiple comparisons using False Discovery Rate.

### 2.3. Predicting Visuospatial Dysfunction in External Cohorts

Lesion load values were generated from lesion-symptom maps and lesion network maps, respectively, in order to test the ability of each to predict dysfunction in validation cohorts. Lesion-symptom mapping lesion loads were calculated by multiplying the

matrix of voxel values weighted via the association with the behavioral score of interest by the eigenvalue for that lesion-symptom map by the binary matrix representing an individual patient's lesion. Observed and predicted scores were transformed to z-scores using the Fisher transformation and compared using a permutation test with 100,000 permutations. Lesion load values were created from the functional and structural lesion network maps in a similar fashion as previously described (Albazron et al., 2019; Reber et al., 2021; Zhu et al., 2010). The voxel intensities for voxels where a patient's lesion mask overlaps with the lesion network map were summed, transformed to z-scores, and compared to observed scores. Next, linear regression models were generated for domain-general visuospatial ability: 1) a model using lesion-symptom map lesion load; 2) a model using functional lesion network map lesion load; 3) a model using structural lesion network map lesion load; 4) a combination of 1 and 2; 5) a combination of 1 and 3; 6) a combination of 2 and 3; and 7) a combination of 1, 2, and 3. Iterations of these models with and without lesion volume as a predictor were compared. RMSE, AIC, BIC, and $R^2$ were used to determine model fit. The best model was confirmed using backward stepwise regression.

### 2.4. Controlling for General Intelligence (*g*)

General intelligence was estimated in this cohort via patients' performance on other neuropsychological tests. Neuropsychological tests administered to at least 75% of patients in the Iowa Registry cohort were included. 28 tests/trials met these criteria, 9 of which were excluded. Orientation to time, place, and personal information; grooved pegboard, and the Beck Depression Inventory were excluded as they are largely unrelated to general cognitive ability. Clinical assessments of fluency of speech,

paraphasias, prosody, and articulation were also excluded since they are not standardized and aspects of language related to intelligence (e.g., verbal fluency) are captured by other tests included in the calculation of *g*. Trail Making Test A & B; Rey's Auditory Verbal Learning Test trial 5, 30-minute delayed recall trial, and recognition trial; Rey-Osterrieth Complex Figure 30-minute delayed recall and time to complete copy trial; Boston Naming Test; Token Test; the reading comprehension section of the Boston Diagnostic Aphasia Examination, Controlled Oral Word Association; Benton Laboratory Assessment of Writing; and multiple subtests of the WAIS including Information, Vocabulary, Arithmetic, Similarities, Digit Span, Comprehension, and Picture Arrangement were used to estimate *g*. Missing data were imputed using the same procedure as described previously.

# CHAPTER 3: RESULTS

## 3.1. Exploratory Factor Analysis

Exploratory factor analysis was used to investigate the latent factor structure of visuospatial ability. Of the 480 patients in the Iowa Registry cohort, 113 were administered all twelve neuropsychological tests sensitive to visuospatial dysfunction. Missing data were imputed in the remaining 387 patients. A parallel analysis was used to determine the number of factors to retain for the EFA, which revealed a single-factor solution best fit the data (Figure 3.1 A). To ensure this was not an artifact of data imputation, a secondary parallel analysis was performed in the subset of patients with no missing data (n = 113; Figure 3.1 B), again showing one factor best captures variance across all the tests. Parameter estimation using minimum residual and maximum likelihood both indicated that a one-factor solution best fits the data. This single factor is referred to as “domain-general visuospatial ability” for the rest of the document.

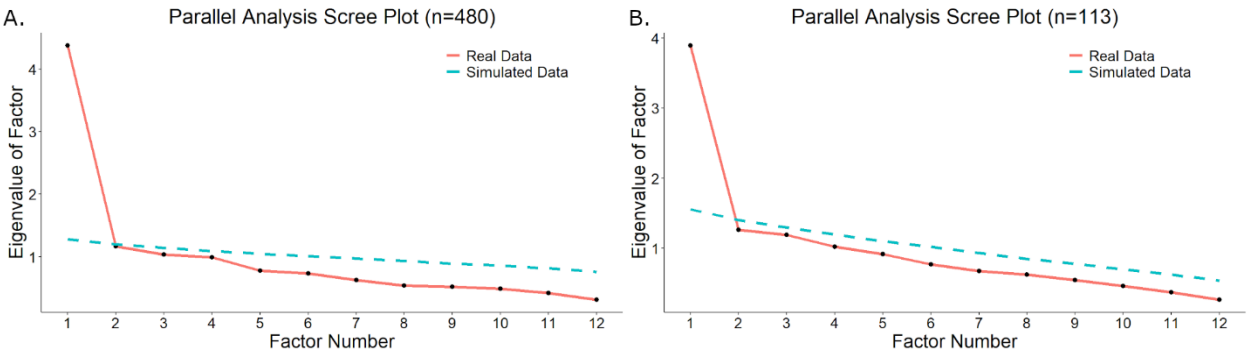



Figure 3.1 The blue line in both panels reflects simulated principal component data and the red line represents actual data. Figure A shows the parallel analysis in the full cohort of patients with imputed data and figure B shows the analysis in the subset of patients with data for all twelve tests.

In the full cohort of 480 patients, one factor comprised of all twelve tests explained 31.0% of the variance ($X^2(54, 480) = 323$, $p = 5.36 \times 10^{-40}$, Figure 3.2 A). The root mean square of the residuals (RMSR) was .07, and the degrees-of-freedom-corrected RMSR was .08. In patients without imputed data, one factor explained 26.7% of the variance in the data ($X^2(54, 113) = 104$, $p = 5.72 \times 10^{-5}$, RMSR = .08, df-corrected RMSR = .09; Figure 3.2 B).

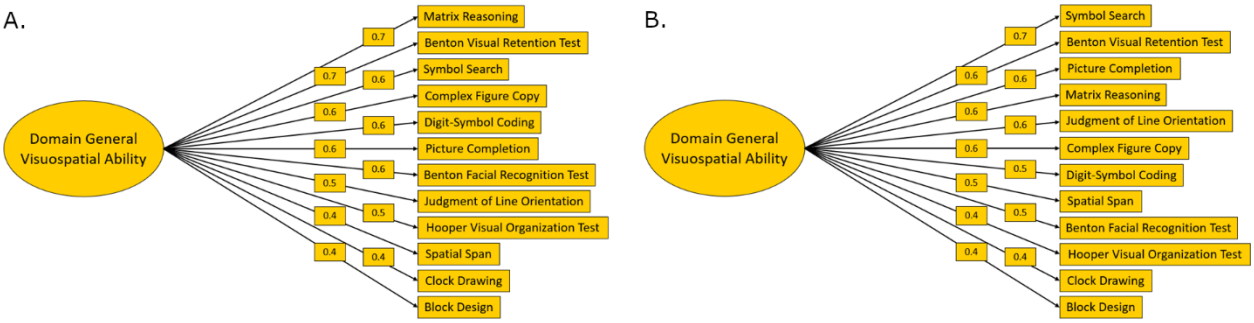



Figure 3.2 All tests loaded onto the single factor with positive factor loadings for every test. The analysis was performed in the whole Iowa Registry cohort (Figure 3.2 A, n = 480) and the sub-cohort without imputed data (Figure 3.2 B, n = 113). While factor loading values varied for some tests, the strength with which each test loaded onto the domain-general visuospatial ability factor remained similar in both analyses, suggesting imputed data were not driving the results.

Composite z-scores were used to estimate domain-general visuospatial ability. Age ($r = -.148$, $p = 1.16 \times 10^{-3}$), education ($r = .293$, $p = 5.86 \times 10^{-11}$), and lesion volume ($r = -.366$, $p = 1.19 \times 10^{-16}$) are correlated with domain-general visuospatial ability, but there are no gender differences ($t(462) = .518$, $p = .605$). Z-scores for all tests contributing to the estimate of domain-general visuospatial ability are displayed in Figure 3.3.

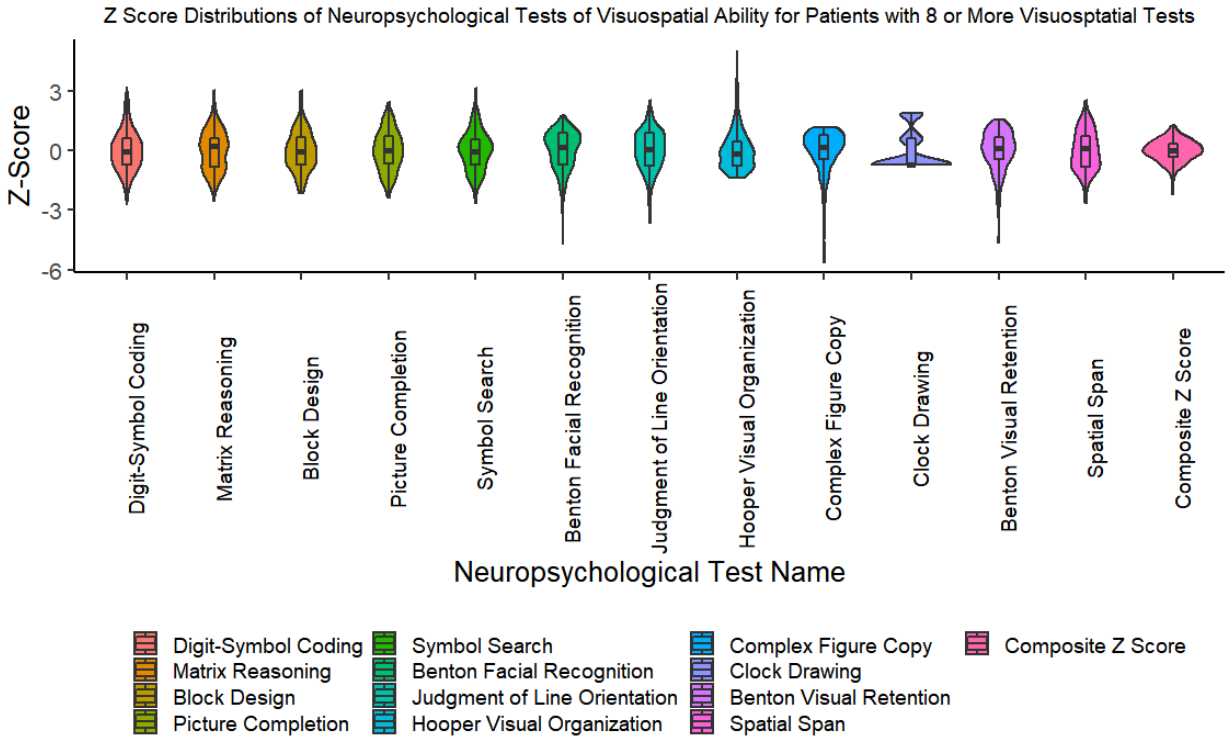



Figure 3.3 The distributions of individual test z-scores and the composite z-score after data imputation are shown.

Since a single factor emerged per the parallel analysis, a hierarchical clustering algorithm was applied to the data to evaluate how the tests grouped together. A correlation matrix between the tests is shown in Figure 3.4.

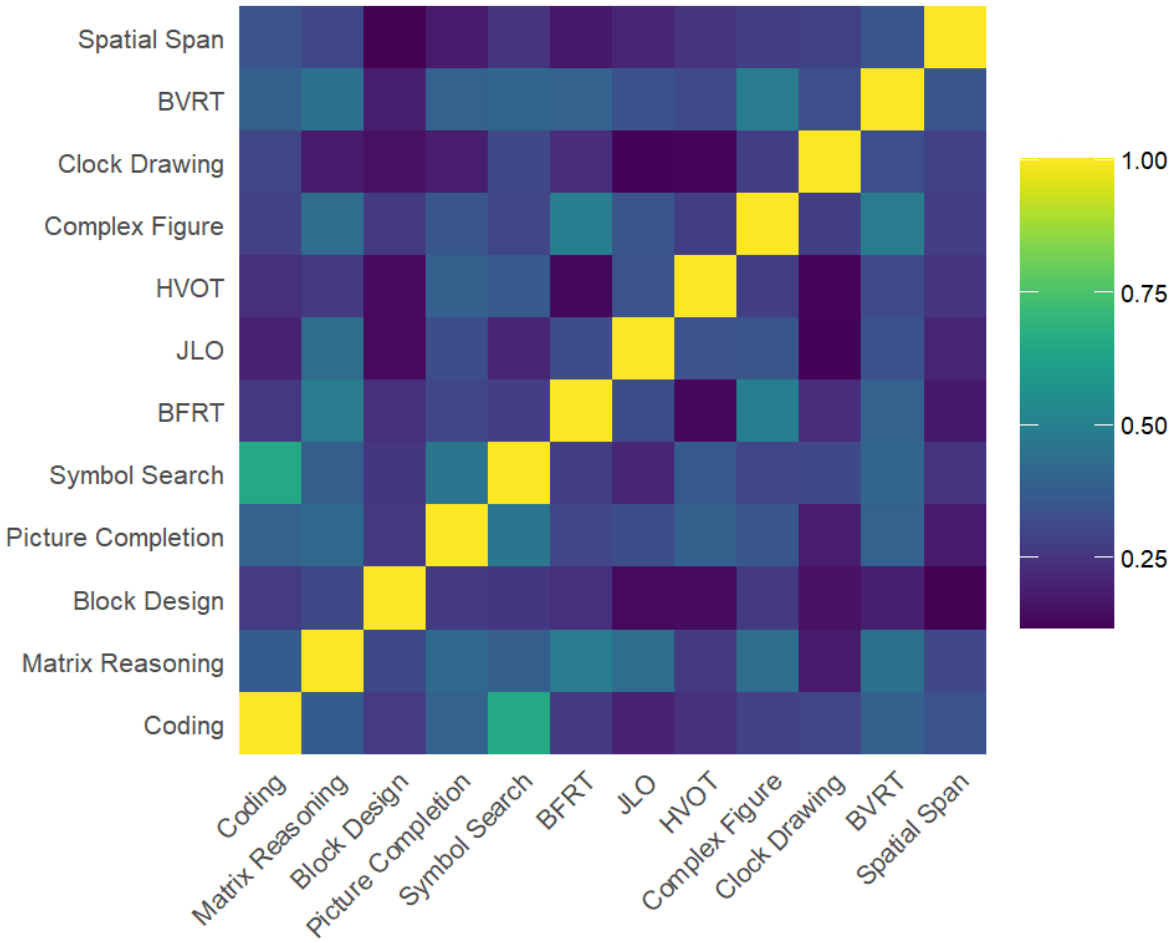



Figure 3.4 The correlation values between each test in the Iowa Registry cohort after data imputation are shown. Higher correlation values indicate that two tests are more correlated with each other.

A distance matrix was derived from the correlation matrix and was used as the input to an agglomerative hierarchical clustering algorithm. The distance matrix computes the similarities between tests to determine which tests covary. The results of the hierarchical clustering analysis were plotted as a dendrogram (Figure 3.5).

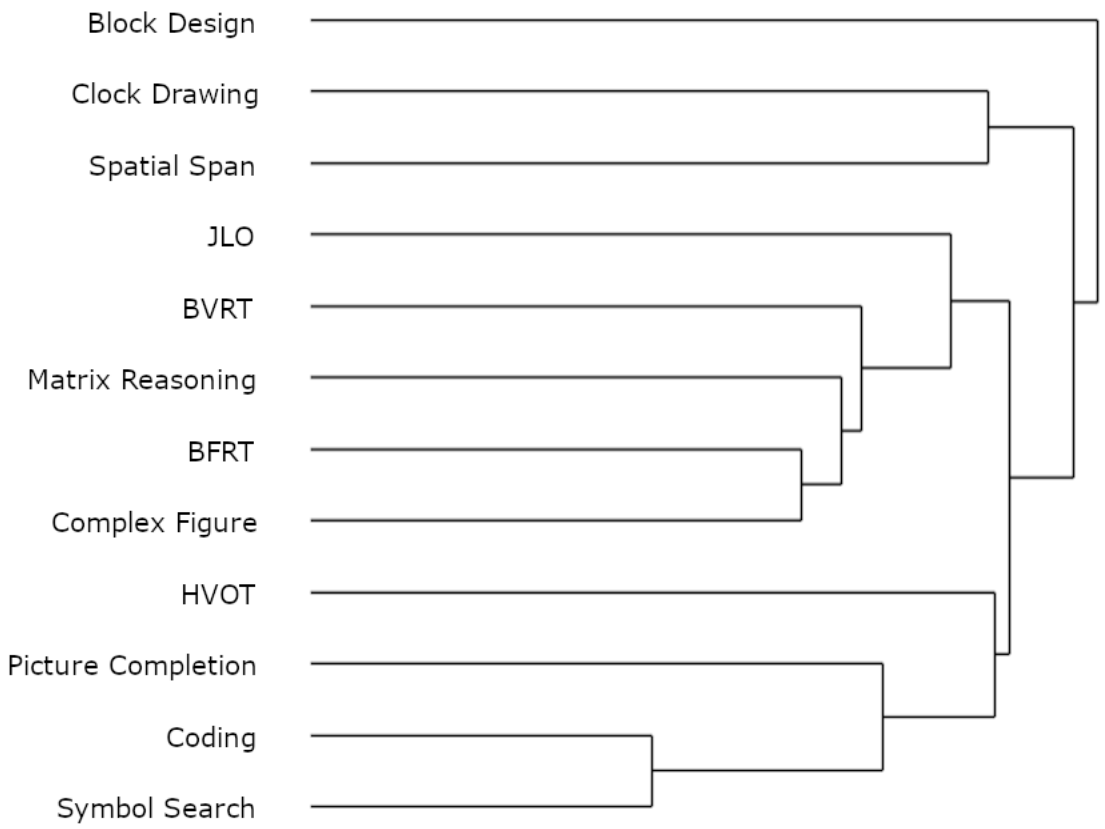



Figure 3.5 This dendrogram, the most important output of a hierarchical clustering analysis, shows which tests cluster together. Clusters are interpreted subjectively, as opposed to the parallel analysis used prior to the EFA to determine the number of factors to be retained in the final solution. The clusters could be interpreted as follows: cluster one contains only Block Design; cluster two contains Clock Drawing and Spatial Span; cluster three contains Judgement of Line Orientation, Benton Visual Retention Test, Matrix Reasoning, Benton Facial Recognition Test, and Complex Figure copy; and cluster four contains Hooper Visual Organization Test, Picture Completion, Digit-Symbol Coding, and Symbol Search.

### 3.2. Lesion-Symptom Mapping and Lesion Network Mapping of Individual Tests of Visuospatial Function

Lesion-symptom mapping analyses of each of the twelve tests of visuospatial ability were performed, eight of which implicated the right putamen in visuospatial ability.

### 3.2.1. Block Design

The Block Design lesion-symptom mapping analysis was performed using scaled scores (n = 475, mean = 10.3, sd = 4.74, min = 4, max = 19). The peak region is in the right posteroventral putamen at MNI coordinates (X Y Z) 33 -12 -2 (r = 0.169, p = $2.10x10^{-4}$), which can be seen in Figure 3.6.

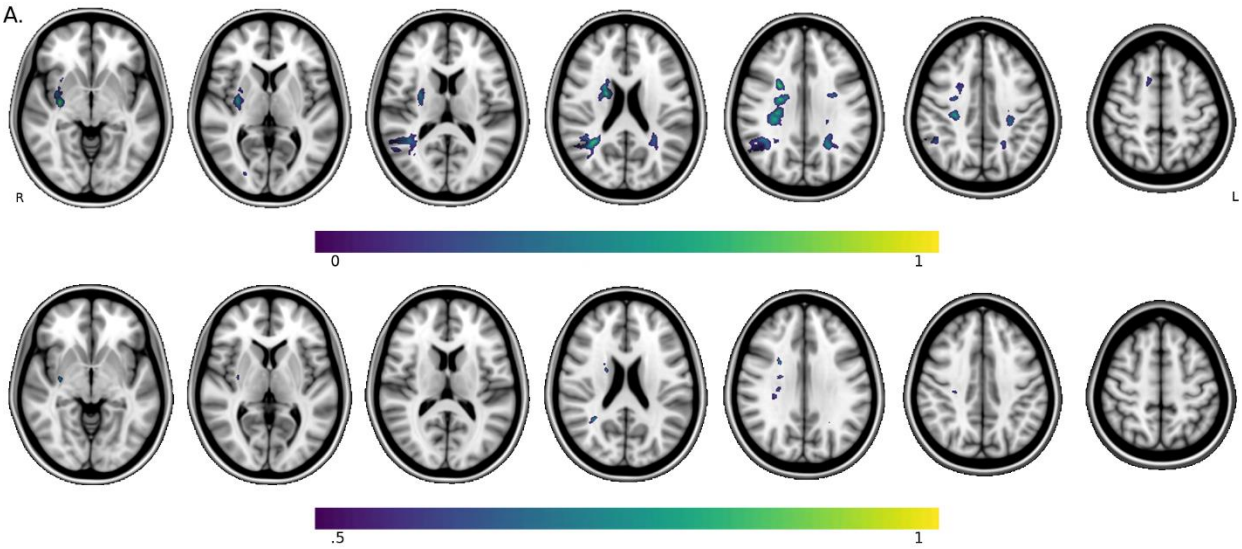



Figure 3.6. Slices -4, 6, 14, 22, 31, 40, and 53 show that white matter superior to the right posterior putamen is most associated with impairment on Block Design in addition to the posteroventral right putamen. Damage to right hemisphere white matter tracts connecting the right anterior occipital lobe to the right posterior frontal lobe through the parietal lobe also contributes to impairment on Block Design. Figure A shows all statistically significant results on an arbitrary scale from 0 to 1. Larger voxel values are associated with stronger findings. Figure B highlights the strongest findings by thresholding the voxel values of the same lesion-symptom map from 0.5 to 1. This format for panels A and B will remain consistent for all lesion-symptom maps presented.

### 3.2.2. Digit-Symbol Coding

The Digit-Symbol Coding lesion-symptom mapping analysis was performed using scaled scores (n = 471, mean = 9.18, sd = 3.05, min = 1, max = 19). The peak region is in the left longitudinal fasciculus at MNI coordinates -28 1 25 (r = 0.386, p = $3.39x10^{-18}$), which can be seen in Figure 3.7.

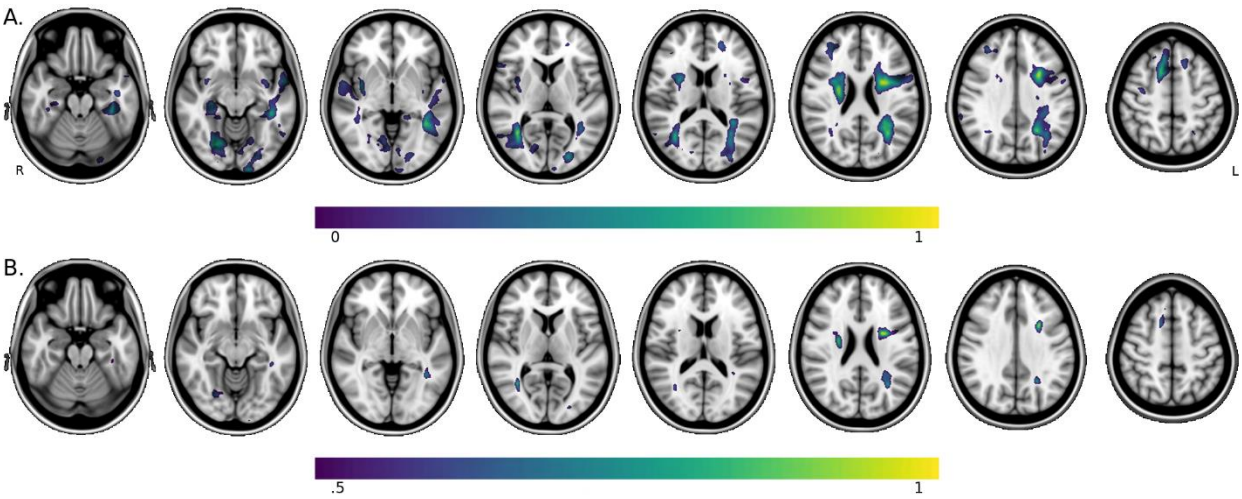



Figure 3.7. Slices -20, -10, -2, 8, 16, 24, 34, and 52 are shown. Regional peaks in the left posterior parietal and left posterior frontal lobes intersect with the left superior longitudinal fasciculus. Regional peaks are present bilaterally in posteroventral white matter of the temporal and occipital lobes.

### 3.2.3. Matrix Reasoning

The Matrix Reasoning lesion-symptom mapping analysis was performed using scaled scores (n = 356, mean = 10.3, sd = 2.88, min = 3, max = 19). The peak region is in the right superior longitudinal fasciculus at MNI coordinates 33 -28 33 ($r = 0.196$, $p = 1.94 \times 10^{-4}$), which can be seen in Figure 3.8.

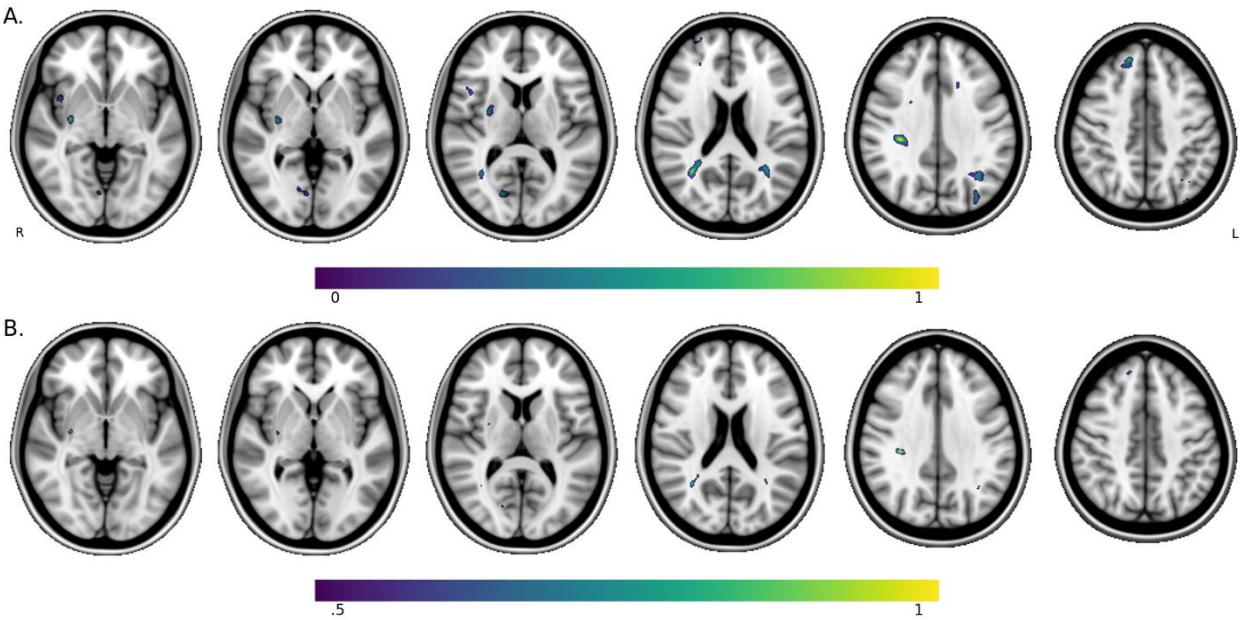


Figure 3.8. A region in the right superior longitudinal fasciculus is most associated with Matrix Reasoning impairment, shown in slices -4, 0, 10, 20, 33, and 42. Regional peaks are also present in the right posterior putamen and in posterior white matter bilaterally.

### 3.2.4. Picture Completion

The Picture Completion lesion-symptom mapping analysis was performed using scaled scores (n = 410, mean = 9.95, sd = 2.91, min = 3, max = 17). The peak region is in left frontal white matter at MNI coordinates -27 44 7 (r = 0.261, p = $8.29 \times 10^{-8}$), which can be seen in Figure 3.9.

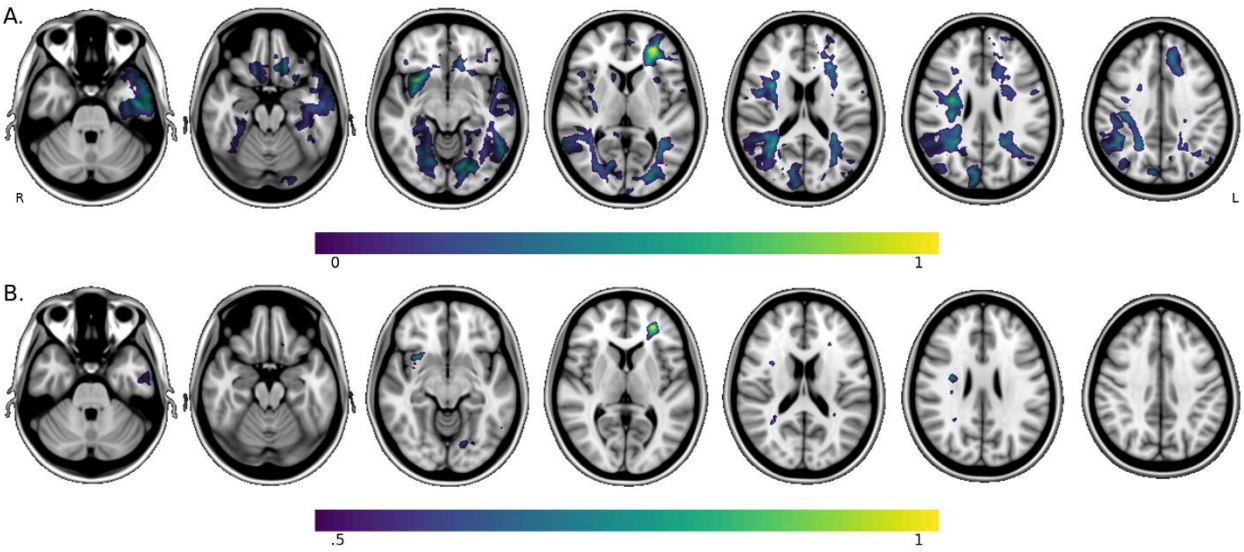



Figure 3.9. Slices -30, -20, -10, 6, 18, 26, and 37 are shown. Findings are distributed across a large portion of the brain but are strongest in left frontal white matter, the right external capsule, and the right superior longitudinal fasciculus.

### 3.2.5. Symbol Search

The Symbol Search lesion-symptom mapping analysis was performed using scaled scores (n = 335, mean = 9.19, sd = 3.11, min = 1, max = 19). The peak region is in left frontal white matter deep to the dorsolateral prefrontal cortex at MNI coordinates -26 12 33 (r = 0.383, p = $3.53 \times 10^{-13}$), which can be seen in Figure 3.10.

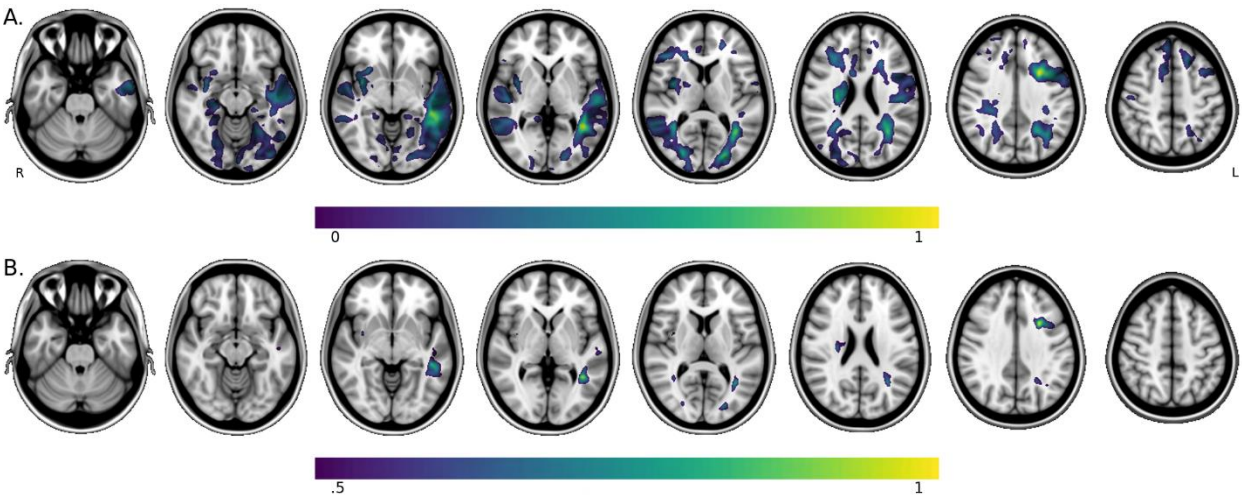



Figure 3.10. Slices -27, -13, -6, 1, 9, 24, 34, and 49 are shown. Findings are distributed bilaterally but are stronger in the left hemisphere, namely in posterior frontal white matter and white matter of the temporal lobe, including the temporo-parieto-occipital junction.

### 3.2.6. Benton's Facial Recognition Test

The Benton Facial Recognition Test lesion-symptom mapping analysis was performed using raw scores plus corrections (n = 470, mean = 44.7, sd = 4.84, min = 27, max = 57). The peak region is in the right putamen at MNI coordinates 27 -1 10 (r = 0.287, $2.22 \times 10^{-10}$), which can be seen in Figure 3.11.

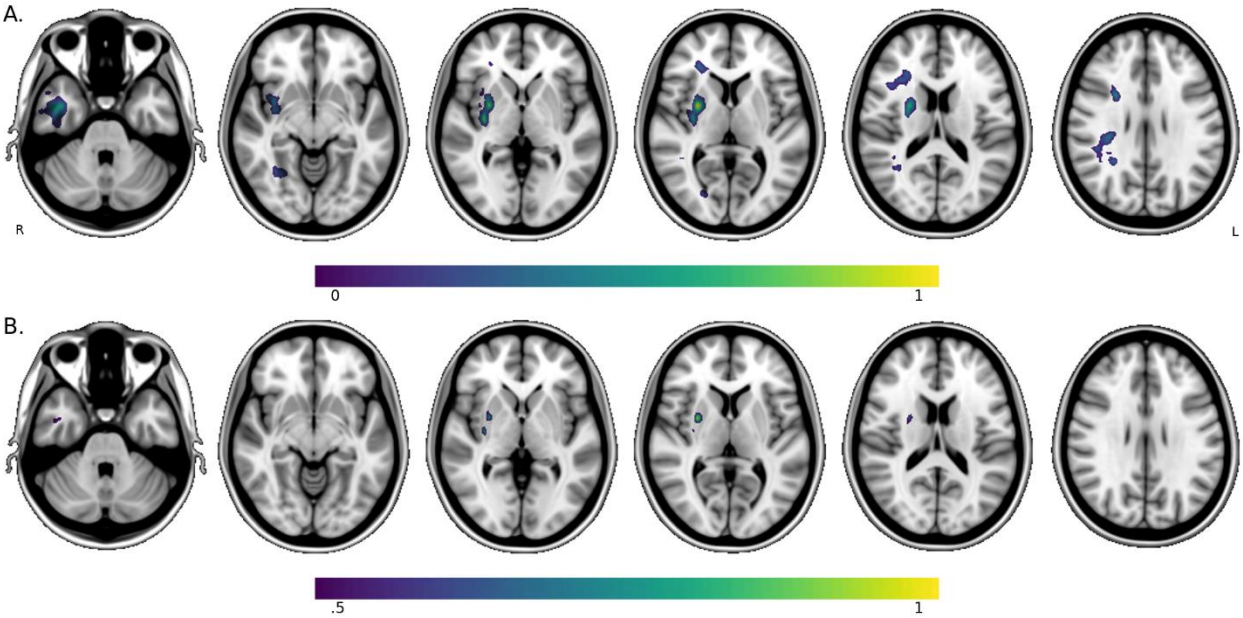


Figure 3.11. Slices -31, -8, 0, 6, 16, and 28 are shown. The right putamen and white matter of the superior longitudinal fasciculus superior to the right putamen are most associated with Benton's Facial Recognition Test.

### 3.2.7. Benton Visual Retention Test

The Benton Visual Retention Test lesion-symptom mapping analysis was performed using the number of correct responses (n = 475, mean = 6.56, sd = 1.89, min = 0, max = 10). The peak region is in the left inferior longitudinal fasciculus at MNI coordinates -24 -54 29 ($r = 0.278$ $7.12 \times 10^{-10}$), which can be seen in Figure 3.12.

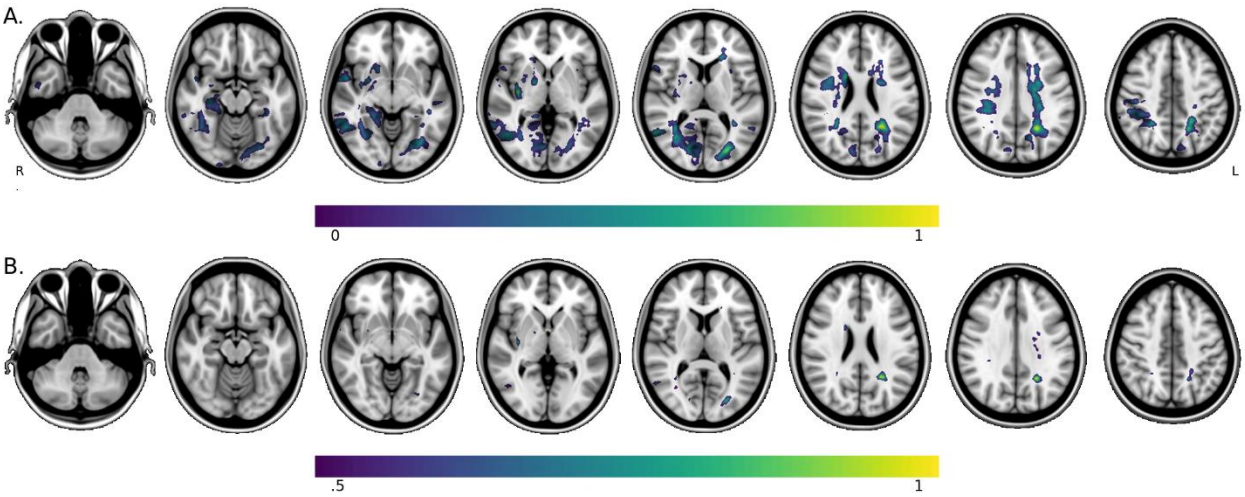



Figure 3.12. Slices -35, -14, -6, 1, 10, 25, 33, and 45 are shown. Regions significantly associated with the BVRT are widely distributed across cortical white matter, especially compared to lesion-symptom maps with more focal findings like that of the BFRT.

### 3.2.8. Clock Drawing

The Clock Drawing lesion-symptom mapping analysis was performed using categories of impairment (1 is unimpaired, 2 is borderline impaired, and 3 is impaired) (n = 373, mean = 1.54, sd = .78, min = 1, max = 3). The peak region is in deep left frontal white matter at MNI coordinates -21 29 16 ($r = 0.264$, $p = 2.32 \times 10^{-7}$), which can be seen in Figure 3.13. Distributed findings are consistent with prior literature (Tranel et al., 2008).

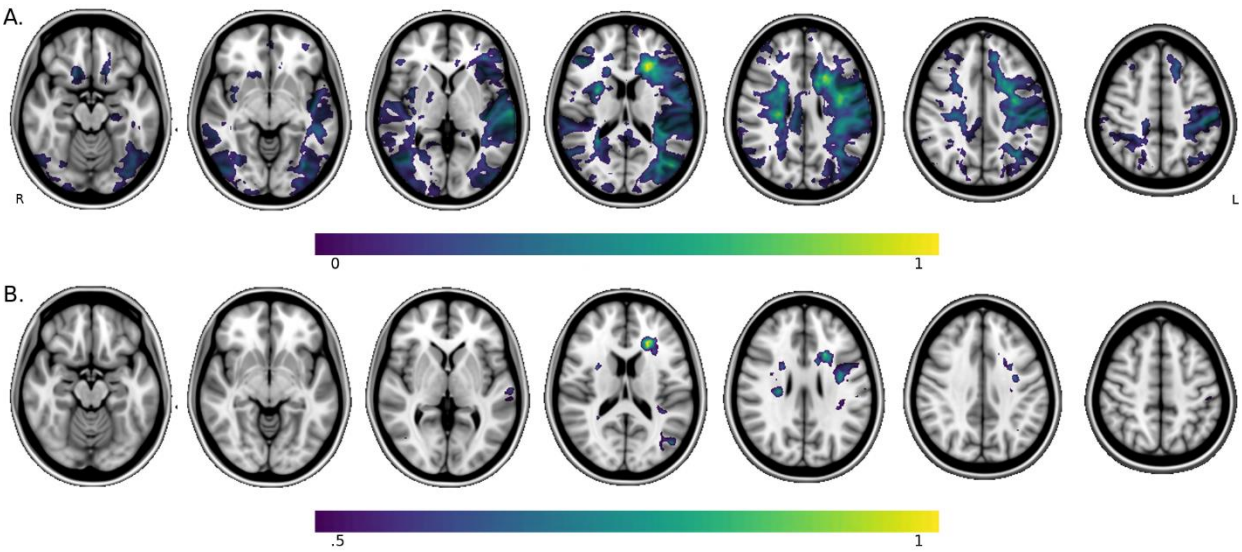



Figure 3.13. Slices -16, -7, 2, 16, 27, 36, and 49 are shown. While distributed across much of the cortex, left hemisphere lesions are most associated with poor performance on clock drawing. This reflects, in part, the many cognitive abilities that contribute to clock drawing.

### 3.2.9. Hooper Visual Organization Test

The Hooper Visual Organization Test lesion-symptom mapping analysis was performed using t-scores (n = 377, mean = 52.2, sd = 8.10, min = 41, max = 93). The peak region is in the right external capsule at MNI coordinates 32 0 -8 (r = 0.333, p = $3.33 \times 10^{-11}$), which can be seen in Figure 3.14.

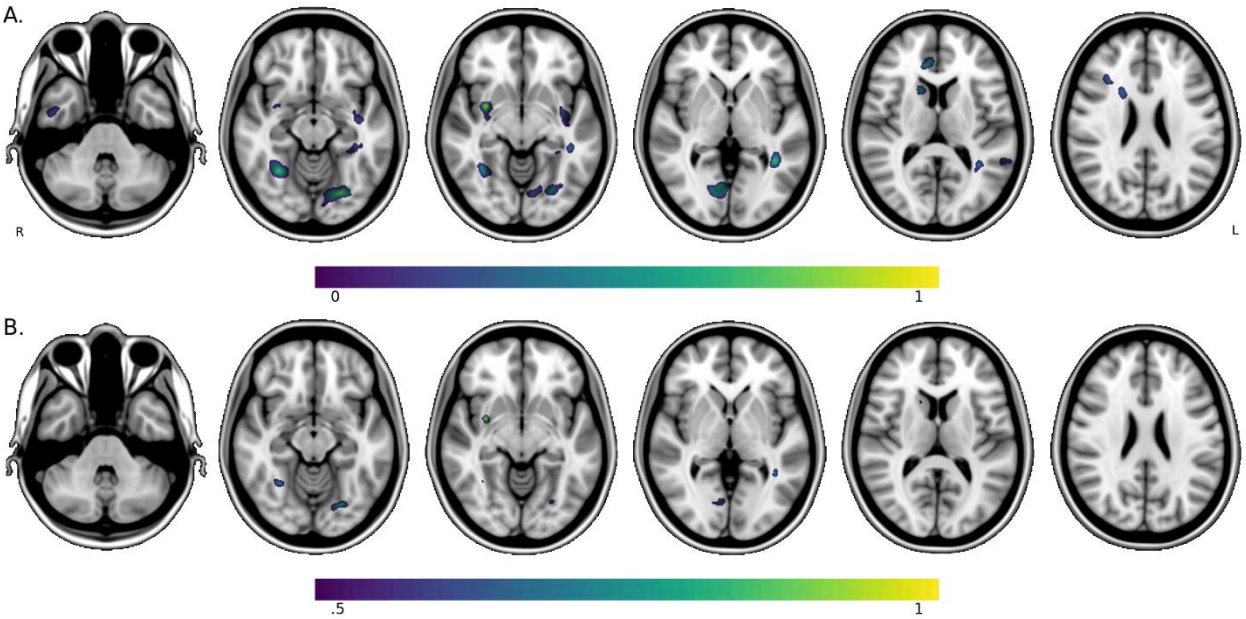



Figure 3.14. Slices -36, -13, -8, 0, 11, and 24 are shown. Regions of the inferior temporal and occipital lobes in addition to posterior white matter and the right putamen are associated with impairment on the HVOT.

### 3.2.10. Judgment of Line Orientation

The Judgment of Line Orientation lesion-symptom mapping analysis was performed using corrected scores (n = 465, mean = 25.1, sd = 4.49, min = 4, max = 33). The peak region is in the right posterior putamen at MNI coordinates 31 -13 2 (r = 0.277, p = $1.31 \times 10^{-9}$ ) and which can be seen in Figure 3.15. Early visual areas are known to process line orientation (Hubel & Wiesel, 1962), yet are not a significant finding in this analysis.

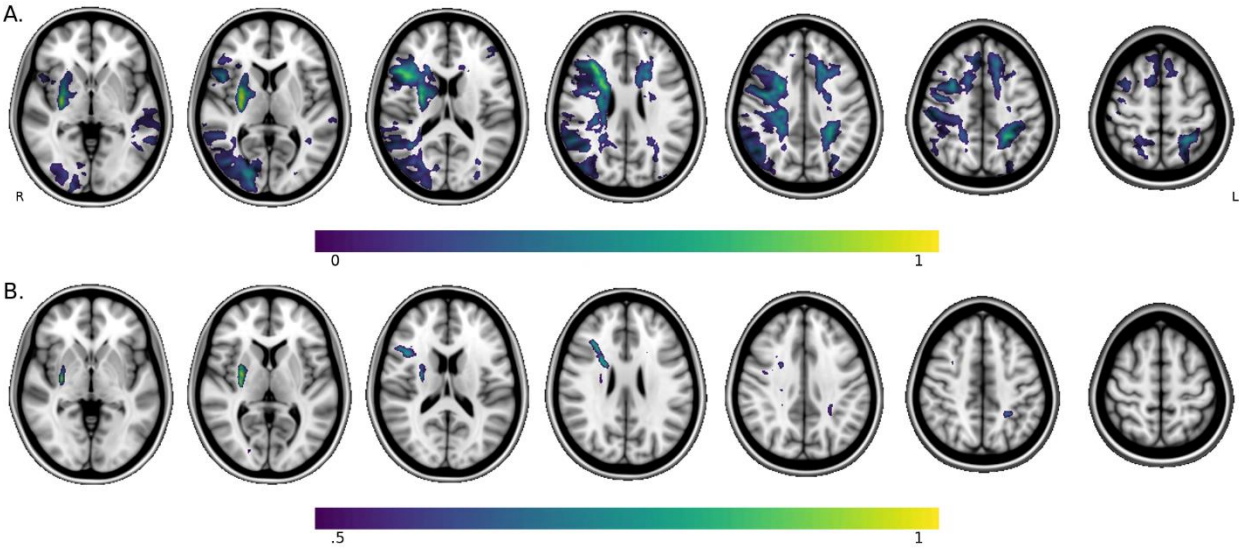



Figure 3.15. Slices -2, 6, 16, 26, 36, 46, and 56 are shown. Regions significantly associated with worse JLO performance were mainly in the right hemisphere.

### 3.2.11. Rey-Osterrieth Complex Figure Test

The Rey-Osterrieth Complex Figure lesion-symptom mapping analysis was performed using raw scores (n = 479, mean = 30.2, sd = 5.03, min = 2, max = 36). The peak region is in the right inferior putamen at MNI coordinates 28 -1 -9 (r = 0.231, p = $3.03x10^{-7}$) and which can be seen in Figure 3.16.

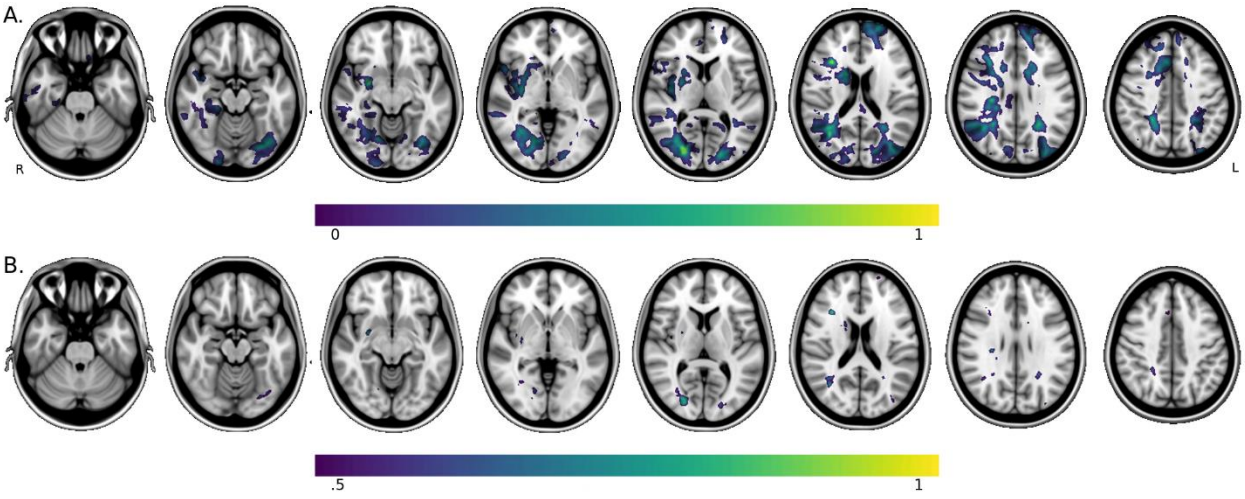



Figure 3.16. Slices -26, -15, -9, -1, 9, 20, 29, and 43 are shown. Regions significantly associated with poor CFT are present bilaterally but stronger in the right hemisphere. Damage to posterior white matter and the superior longitudinal fasciculus are associated with worse CFT performance.

### 3.2.12. Spatial Span

The lesion-symptom mapping analysis of the age-corrected scaled Spatial Span total scores (n = 171, mean = 10.27, sd = 3.10, min = 3, max = 17) was not significant (r = 0.12, p = 0.11). Further analyses of the total backward score (r = 0.08, p = .32), total forward score (r = 0.11, p = .15), longest backward span (r = 0.12,p = .11), longest forward span (r = 0.10, p = .21), and uncorrected total score (r = 0.12, p = .11) were also nonsignificant.

## 3.3. Lesion-Symptom Mapping and Lesion Network Mapping of Domain-general Visuospatial Ability

### 3.3.1. Lesion-Symptom Mapping

Lesion-symptom mapping was performed to identify regions of damage associated with domain-general visuospatial dysfunction. Missing data were imputed for patients who did not have scores for at least eight of the twelve neuropsychological tests. After missing data were imputed, a composite z-score representing domain-general visuospatial ability was computed for all 480 patients which was used as the behavioral variable in lesion-symptom mapping and lesion network mapping analyses. The lesion-symptom map was significant at r = .237, p = $1.52 \times 10^{-7}$ in the right dorsal putamen (MNI coordinates 27 -3 12), which was most associated with deficits in domain-general visuospatial ability (Figure 3.17 A&B). Other regional peaks included the right posterior putamen (32 -11 -2), right caudate nucleus (19 -2 22), left V4 (-27 -77 -15 & -25 -84 9), white matter in the right ventral visual stream (34 -61 -4), right primary visual cortex (22 -78 7), and left occipital white matter (-23 -56 33). Factor scores were also used as the behavioral predictor in a lesion-symptom mapping analysis as a complementary measure of domain-general visuospatial ability (Figure 3.17 C&D). Unlike composite z-

scores, factor scores the relative weight of a given test in calculating a patient's composite score. This analysis was most significant in left occipital white matter deep to V4 (r = .209, p = $3.68x10^{-6}$; -25 -83 10) with other strong regional peaks in right occipital white matter deep to primary visual cortex (22 -78 7) and the right putamen (27 -3 12).

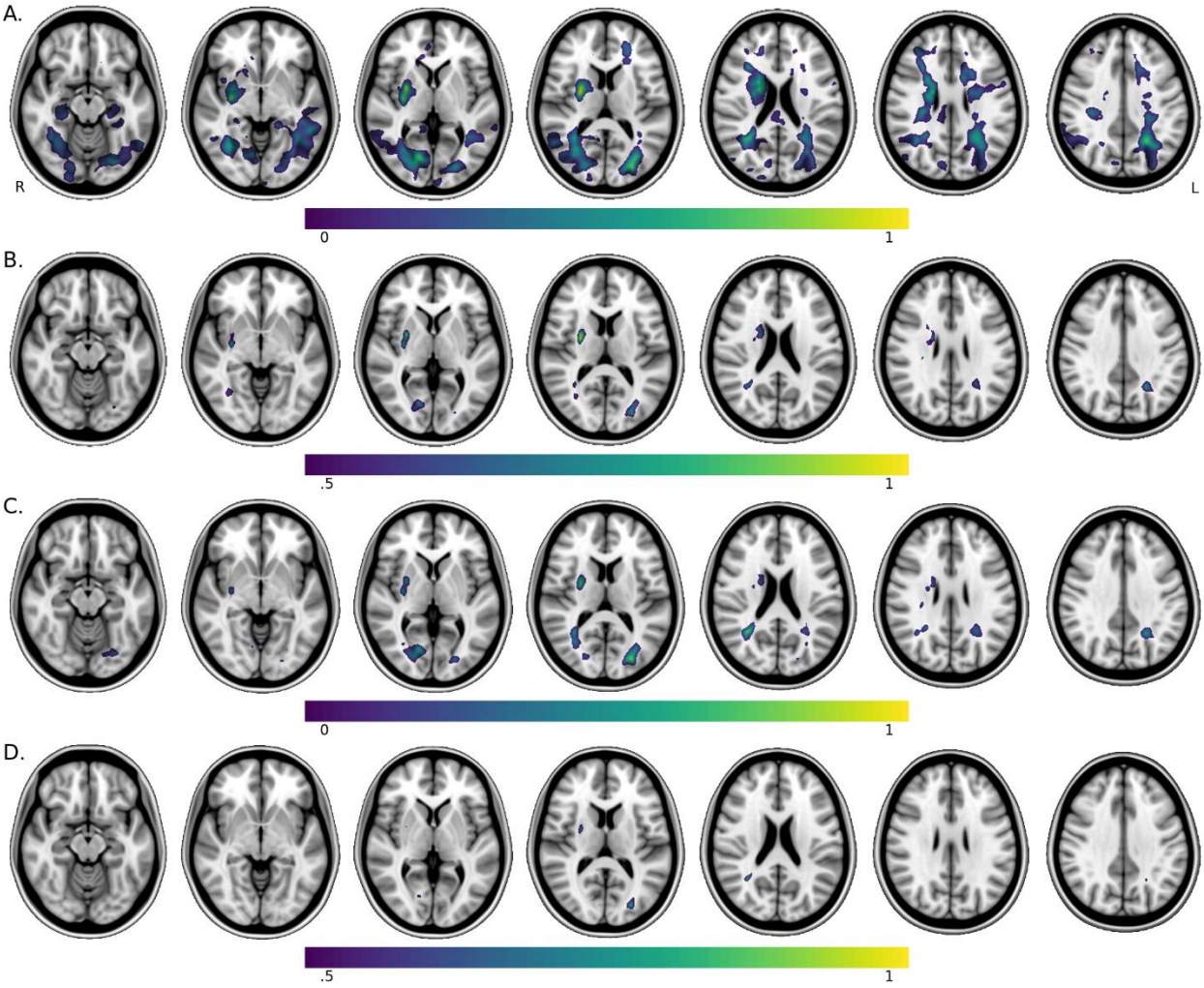



Figure 3.17. Slices -13, -4, 4, 13, 22, 28, and 35 are shown in all four panels. Composite z-scores were used as predictors in a lesion-symptom mapping analysis, shown in A & B (n = 480). Bilateral regional peaks across white matter in all four lobes are present in A. The analysis was thresholded at 0.5 on an arbitrary scale from 0 to 1 to show the strongest findings, which are in the right putamen and white matter bilaterally (Fig B). Findings from the factor score-derived analysis (Figs C & D) were less distributed compared to the analysis using composite z-scores but retained the same strong regional peaks in the right putamen and bilateral posterior white matter.

Since most of the significant regional peaks were in the right hemisphere, the lesion-symptom mapping analysis was repeated in 153 Iowa Registry patients with right unilateral lesions ($r = .440$, $p = 1.26x10^{-8}$). Composite z-scores were used as the behavioral variable of interest. Regional peaks were strongest in the right posterior putamen (32, -13, 2) and several peaks in deep parietal white matter superior to the putamen, including but not limited to MNI coordinates 27, -6, 23 and 27, -5, 17.

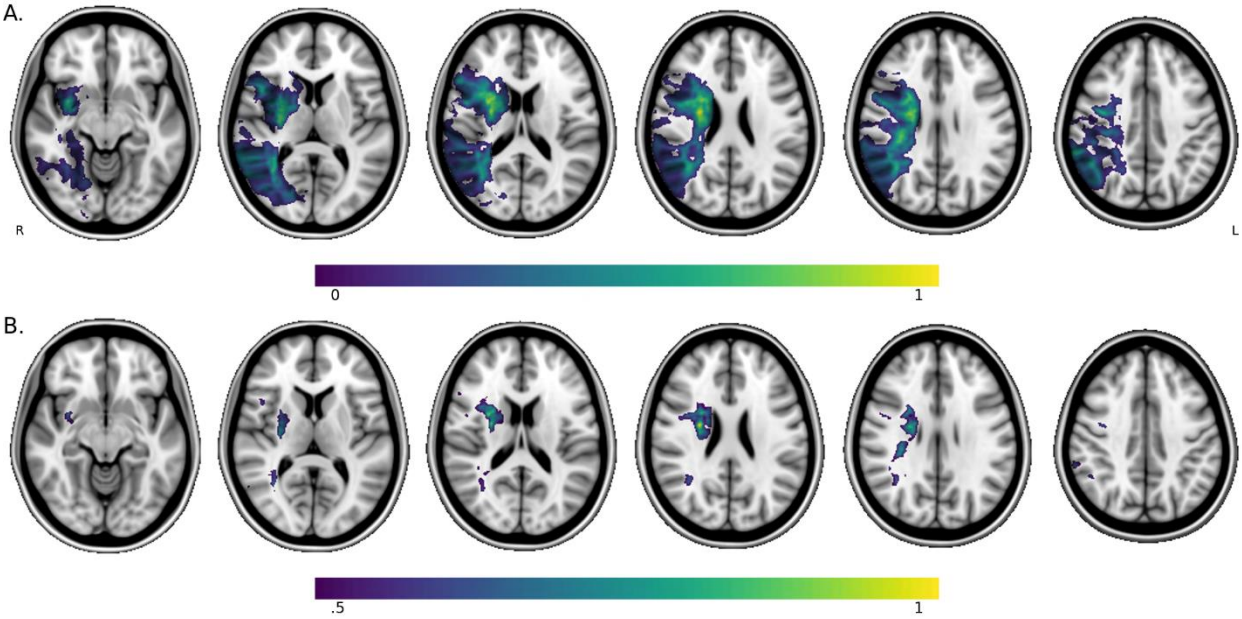



Figure 3.18 Slices -10, -2, 9, 17, 24, 28, and 39 are shown. The putamen and white matter superior to the putamen are most associated with domain-general visuospatial dysfunction in patients with right unilateral lesions.

To ensure imputed data were not driving these results, the lesion-symptom mapping analysis was repeated the a subset of patients with data for all twelve tests (n = 113; Figure 3.19 A&B). The lesion-symptom map using composite z-scores was most significant in the right putamen ($r = .249$, $p = 7.88x10^{-3}$; 30 0 3). Other regional peaks were scattered through the right putamen, white matter lateral to the right putamen (32 11 -7), and the right caudate nucleus (15 -2 19). A lesion-symptom map of the same sub-cohort (n = 113) using factor scores as the predictor ($r = .308$, $p = 9.00x10^{-4}$) shared

the strongest regional peak in the right putamen (30 0 3), demonstrating that both ways of representing a patient's domain-general visuospatial ability produce similar results (Figure 3.19 C&D). Additional peaks were seen in in the right posterior putamen (34 -9 -2), white matter lateral to the right putamen (32 11 -7), and the right caudate nucleus (19 -4 21).

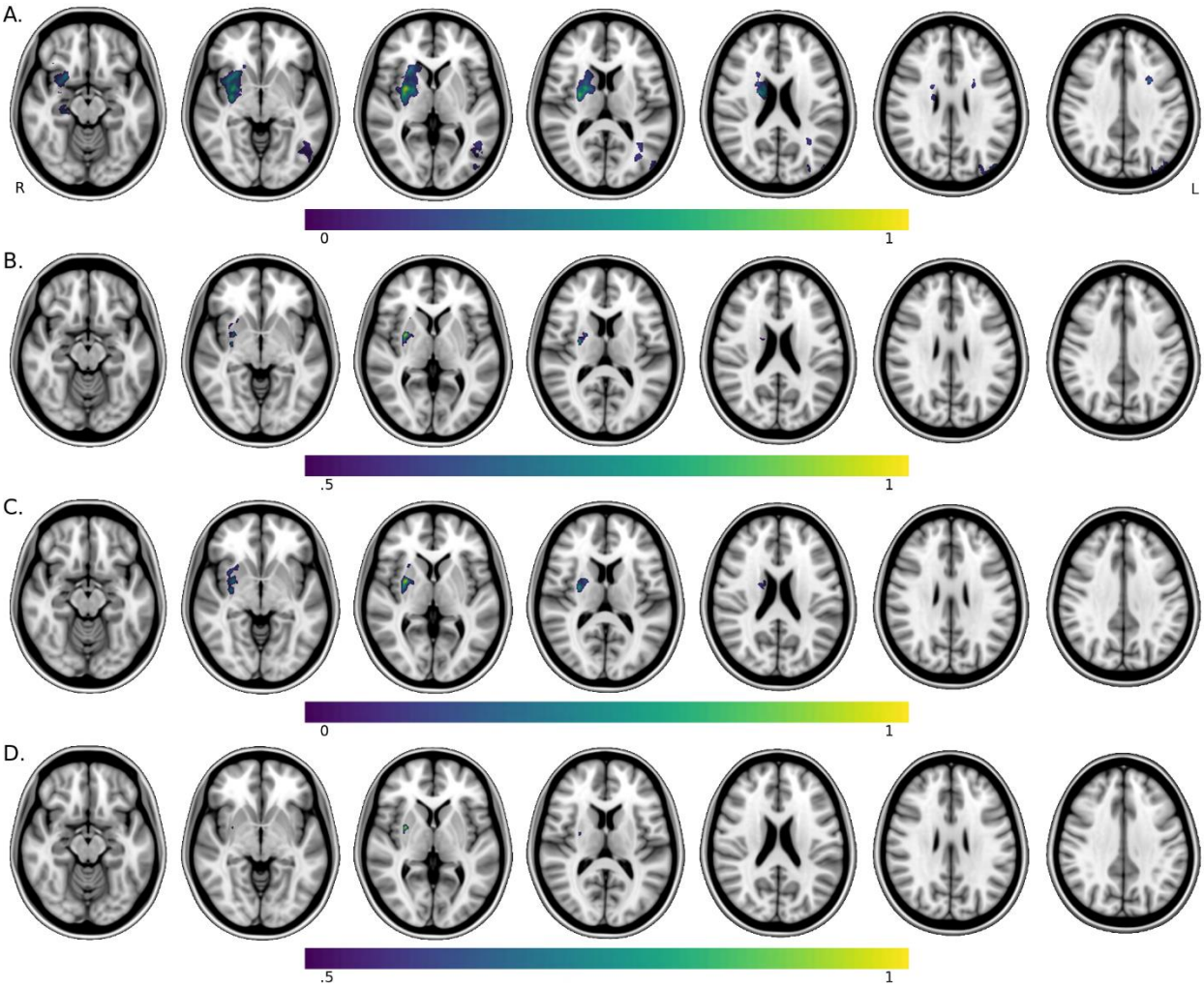
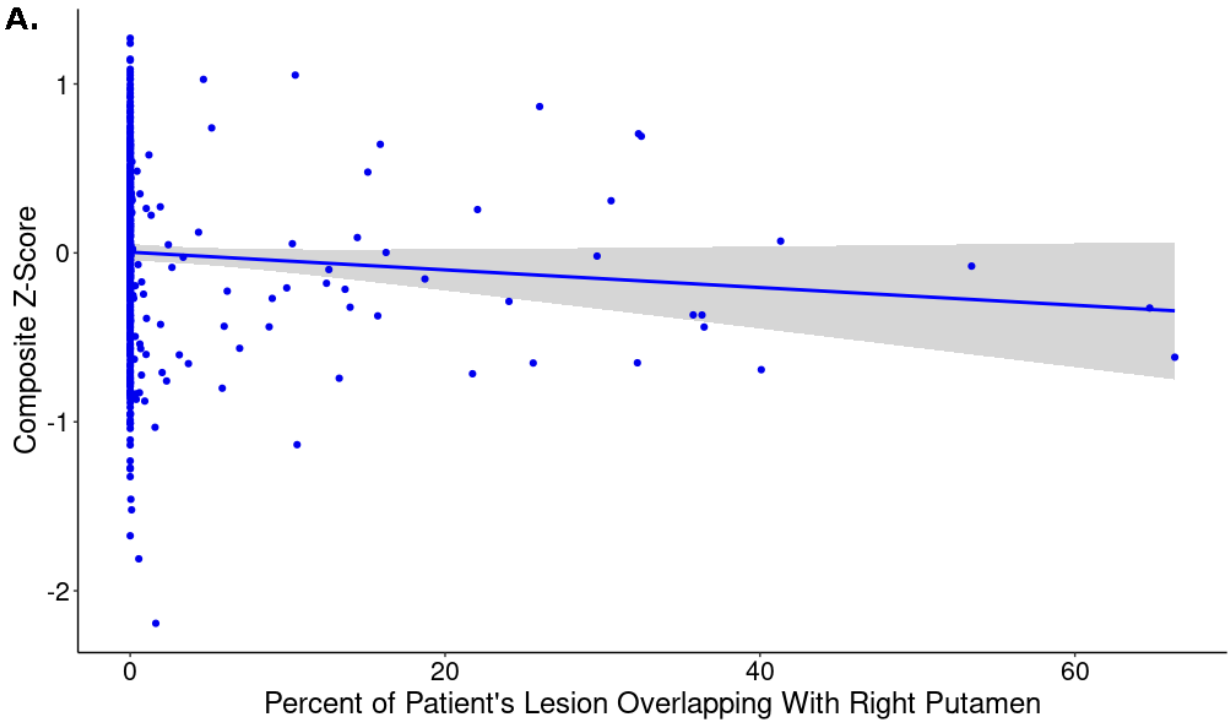


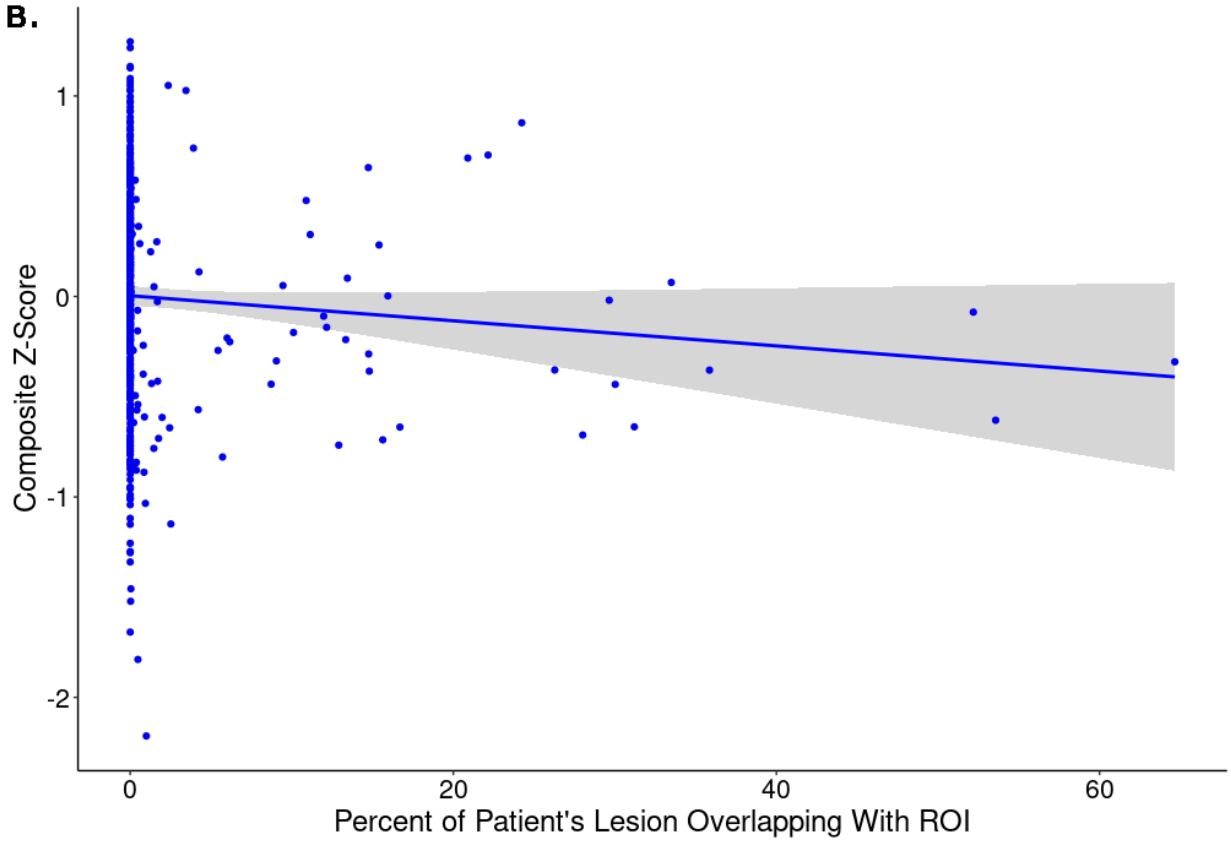

Figure 3.19. The same slices are displayed here as in Figure 3.17. A subset of the Iowa Registry patients were administered all twelve tests (n = 113) and were included in these lesion-symptom mapping analyses. As before, figures A&B show lesion-symptom maps generated from composite z-scores and figures C&D were generated from factor scores. There were fewer and more focal peaks in both analyses shown, which highlights the importance of the right putamen and surrounding white matter in domain-general visuospatial ability.

Additional analyses were performed to further probe the specificity of the relationship between right putamen damage and visuospatial dysfunction. Each patient's lesion was overlapped with the entire right putamen and in a separate analysis, the portion of the putamen significantly associated with deficits in domain-general visuospatial ability as identified in the above lesion-symptom mapping analysis (henceforth referred to as the putamen ROI). 21.5% of patients in this cohort had a lesion intersecting with the right putamen; all lesions intersecting with the right putamen also intersected with the putamen ROI. Lesion volume was significantly associated with domain-general visuospatial ability ($F(1,478) = 44.3$, $p = 7.87 \times 10^{-11}$, adj. $R^2 = .0828$) and thus was used as a covariate in all of the following linear models. First, a linear model was used to identify a potential relationship between the proportion of lesioned voxels intersecting with the right putamen ($v_{\text{right putamen}} = 6005\ mm^3$) to a patient's total lesion volume and the composite z-score representing domain-general visuospatial ability. The percent of a patient's lesion intersecting with the right putamen was significantly associated with worse visuospatial function (adj. $R^2 = .0925$, $F(2,477) = 25.4$, $p = 3.30 \times 10^{-11}$; Figure 3.20 A), even after removing an outlier whose lesion covered 96.7% of the right putamen (patient's total lesion volume = 357,299 $mm^3$) and a had a composite z-score of -2.19 (adj. $R^2 = .0760$, $F(2, 476) = 20.7$, $p = 2.51 \times 10^{-9}$). The same analysis was performed using the lesion-symptom mapping-based ROI instead of the whole putamen, again showing that greater damage to the putamen is significantly associated with worse domain-general visuospatial ability (adj. $R^2 = .0927$, $F(2, 477) = 25.5$, $p = 3.07 \times 10^{-11}$; Figure 3.20 B). The intersection between a patient's lesion and the putamen ROI was then treated as a binary variable. Domain-general visuospatial ability

of patients with a lesion to the putamen ROI (mean = -.233, sd = .590) was worse than patients without a lesion to the putamen ROI (mean = .0469, sd = .506; $T(122) = -4.17$, $p = 5.62 \times 10^{-5}$).

The ratio of lesioned voxels in the right putamen to total voxels in the right putamen and domain-general visuospatial ability was also characterized while controlling for lesion volume. The amount of the putamen that was damaged was associated with worse visuospatial dysfunction (adj. $R^2 = .0984$, $F(2, 477) = 27.1$, $p = 6.95 \times 10^{-12}$; Figure 3.20 C), even after removing the same outlier as before (adj. $R^2 = .0771$, $F(2, 476) = 21.0$, $p = 1.87 \times 10^{-9}$). The amount of the putamen ROI that was damaged was also associated with worse visuospatial dysfunction (adj. $R^2 = .102$, $F(2, 477) = 28.1$, $p = 3.04 \times 10^{-12}$; Figure 3.20 D).


A.
Composite Z-Score
1
0
-1
-2
0
20
40
60
Percent of Patient's Lesion Overlapping With Right Putamen


B.
Composite Z-Score
1
0
-1
-2
0
20
40
60
Percent of Patient's Lesion Overlapping With ROI

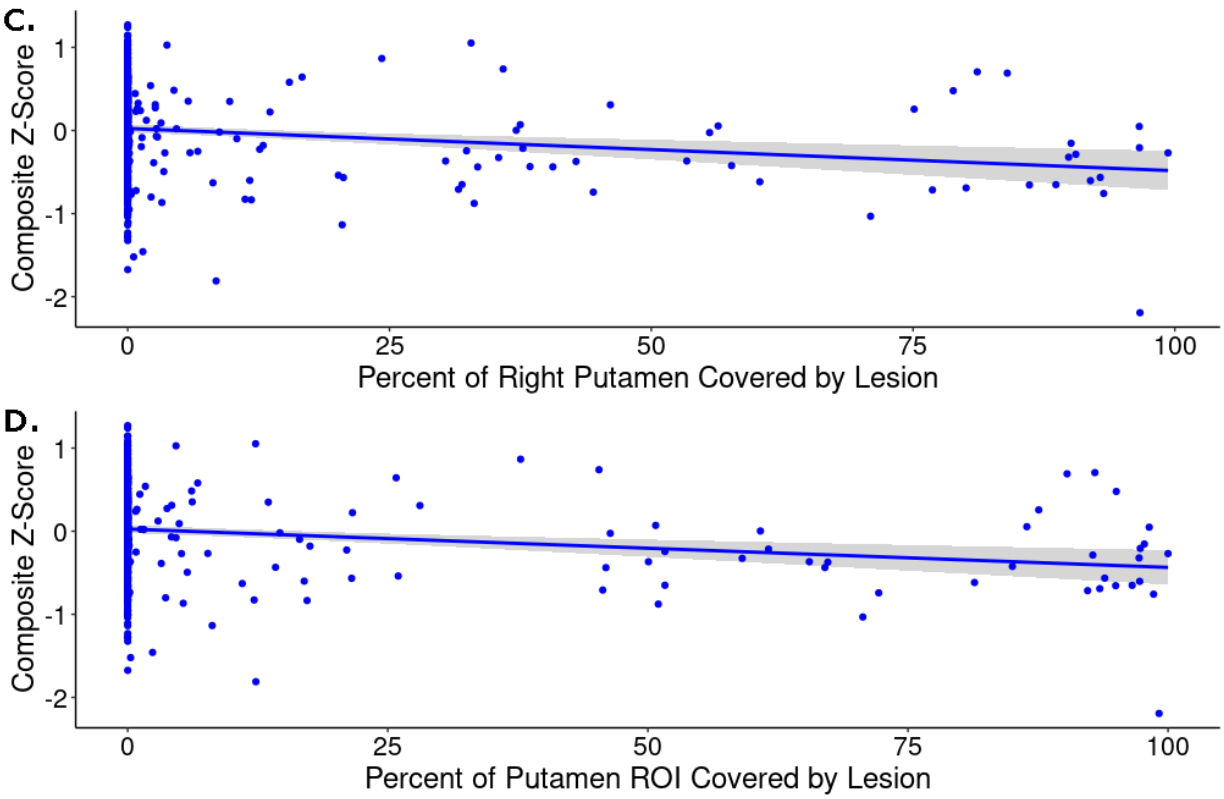



Figure 3.20 The percentage of a patient's lesion intersecting with the right putamen (Fig A) and the putamen ROI (Fig B) are associated with worse visuospatial function. The amount of damage to the right putamen (Fig C) and the putamen ROI (Fig D) are associated with worse visuospatial function.

### 3.3.2. Lesion Network Mapping

Structural and functional lesion network mapping were performed to determine networks associated with domain-general visuospatial ability, represented by composite z-scores in one analysis and factor scores in a separate analysis. The functional lesion network map generated from composite z-scores ($t = 5.10$, $p = 1.94 \times 10^{-3}$) overlaps most with the dorsal attention and visual networks ($r = .462$ and $r = .343$ respectively; Figure 3.21 A) as defined by Yeo and colleagues (Thomas Yeo et al., 2011). The distribution of results in the dorsal attention ($r = .440$) and visual ($r = .387$) networks was similar when using factor scores as the behavioral variable ($t = 5.08$, $p = 2.59 \times 10^{-3}$; Figure 3.21 B).

The same analysis was repeated in the sub-cohort without imputed data; the results were nonsignificant after False Discovery Rate (FDR) correction.

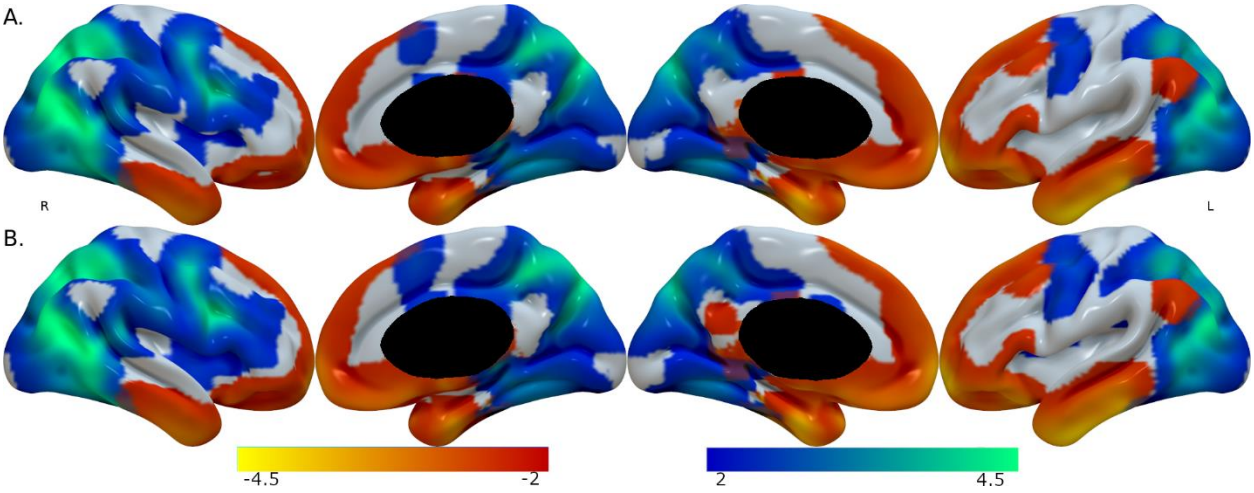



Figure 3.21 Cool colors show significant t-values of functional lesion networks associated with domain-general visuospatial ability. Hot colors show anti-correlated networks (A & B). The analyses using composite z-scores (Fig A) and factor scores (Fig B) showed nearly identical results and overlapped most with the dorsal attention and visual networks.

White matter tractography showed non-specific tracts across most of the cortex bilaterally using composite z-scores ($t = 10.8$, $p = 3.98 \times 10^{-4}$, Figure 3.22 A&B) and factor scores ($t = 11.0$, $p = 2.06 \times 10^{-4}$; Figure 3.22 C&D) after FDR correction. Since both approaches to estimating domain-general visuospatial ability produced similar results using lesion-symptom mapping and both types of lesion network mapping, only the results generated from composite z-scores will be referenced for brevity.

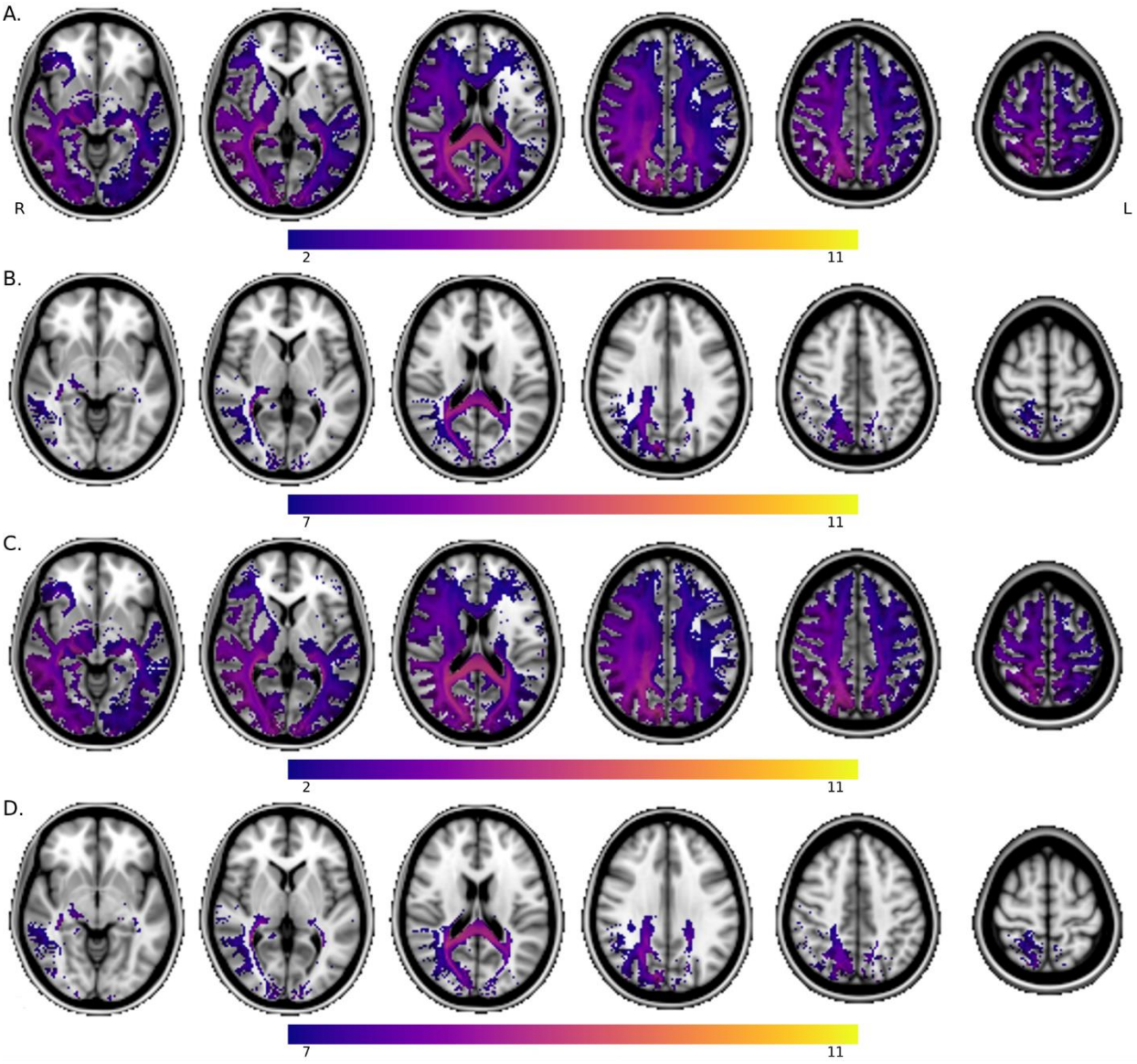



Figure 3.22 Slices -6, 4, 18, 30, 44, and 60 show significant t-values from the white matter tractography analysis. Domain-general visuospatial ability was associated with diffuse white matter in both hemispheres, but the findings were stronger in the right hemisphere (Fig A). The t-values were further thresholded to highlight the strongest results in posterior interhemispheric tracts (Fig B). As in prior analyses, using factor scores did not appreciably change the results (Figs C&D).

The functional lesion network mapping analysis in the sub-cohort of 113 individuals was nonsignificant after FDR correction. In the structural lesion network mapping analysis, significant white matter tracts were strongly right-lateralized in patients with scores for all tests ($n = 113$; $t = 6.68$, $p = 7.33 \times 10^{-4}$; Figure 3.23).

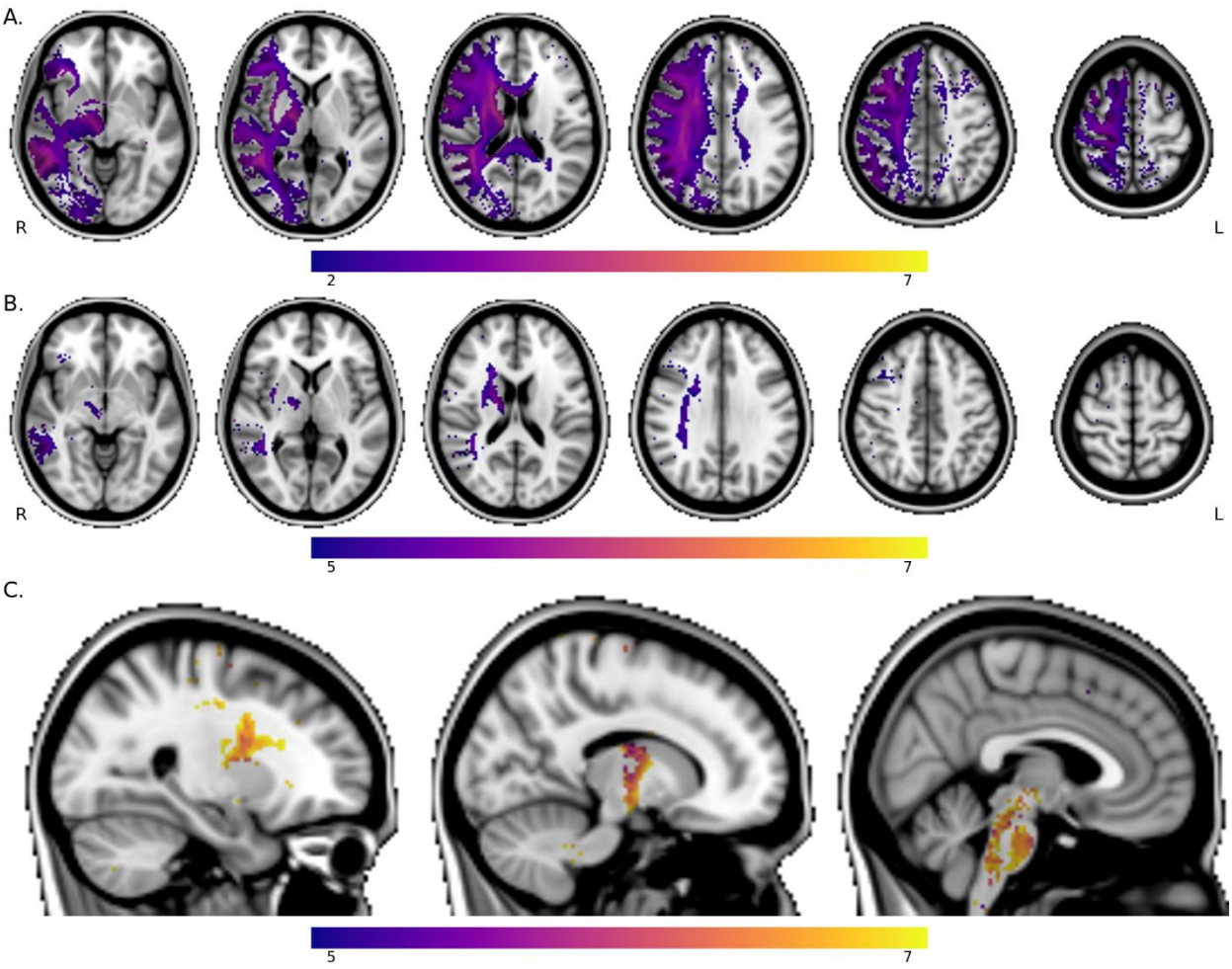



Figure 3.23 Axial slices -6, 4, 18, 30, 44, and 60 are shown in figures A&B. Sagittal slices 26, 14, and 4 are shown in figure C. Long range right posterior white matter tracts are strongly associated with visuospatial dysfunction. Tracts most strongly associated with visuospatial dysfunction appear to surround the right posterior putamen before terminating in deep parietal white matter.

### 3.4. General Intelligence and Visuospatial Ability

An EFA was used to extract *g* from 19 tests sensitive to a variety of cognitive domains. The number of factors was first determined using a parallel analysis which indicated four factors best explained variance across the 19 tests. Eigenvalues for each potential factor are plotted in Figure 3.24 A. All but one test (Picture Arrangement) loaded onto these four factors (Figure 3.24 B). The largest eigenvalue for the first factor is 7.37, followed by 2.22, 1.52, and 1.37 for the subsequent three factors. Based on

eigenvalues, a one-factor solution may still represent the data well, so a secondary EFA was performed using a single factor (Figure 3.24 C) to extract an estimate of *g*.

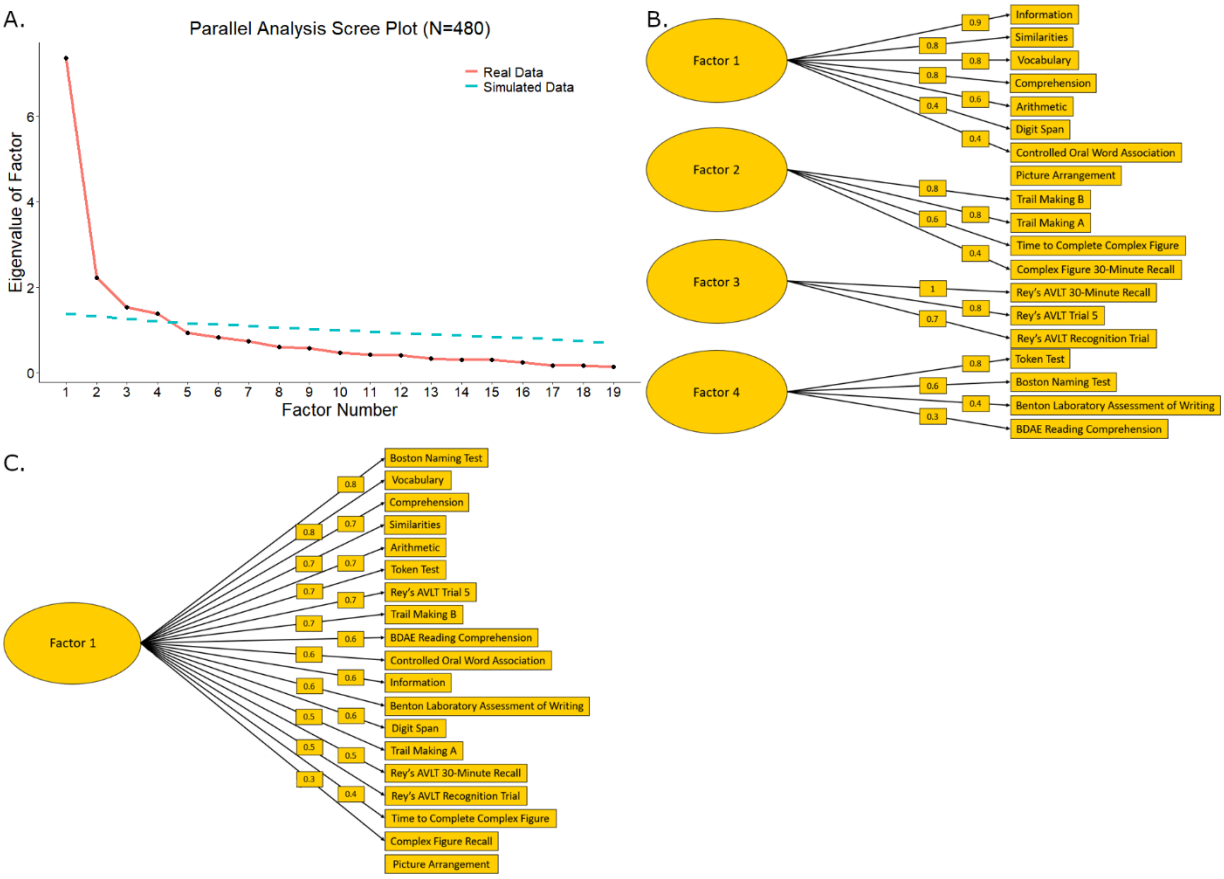



Figure 3.24. The parallel analysis indicated that four factors should be used in the exploratory factor analysis (Fig A). The four-factor (Fig B) and one-factor (Fig C) solutions both excluded picture arrangement.

Factor scores were used to estimate *g* for all lesion-symptom mapping analyses of general intelligence. The regional peak for the one-factor solution ($r = .459$, $p = 2.06 \times 10^{-26}$; Figure 3.25 A&B) was in white matter deep to the left insula/inferior frontal gyrus (-29 7 19). White matter deep to the posterior middle temporal gyrus (-48 -40 -6), left posterior white matter (-31 -47 19), and left auditory association area/posterior insula (-31 13 6) were also associated with *g*. The factor that explained the most variance in the four-factor EFA solution (Figure 3.25 C&D) was also most strongly

associated with damage to left frontoparietal white matter (r = .317, p = $1.18x10^{-12}$; -28 7 20) in addition to the left anterior insula (-31 13 7), white matter deep to the left posterior middle temporal gyrus (-49 -40 -6), and white matter deep to the left temporo-parieto-occipital junction (-35 -36 29).

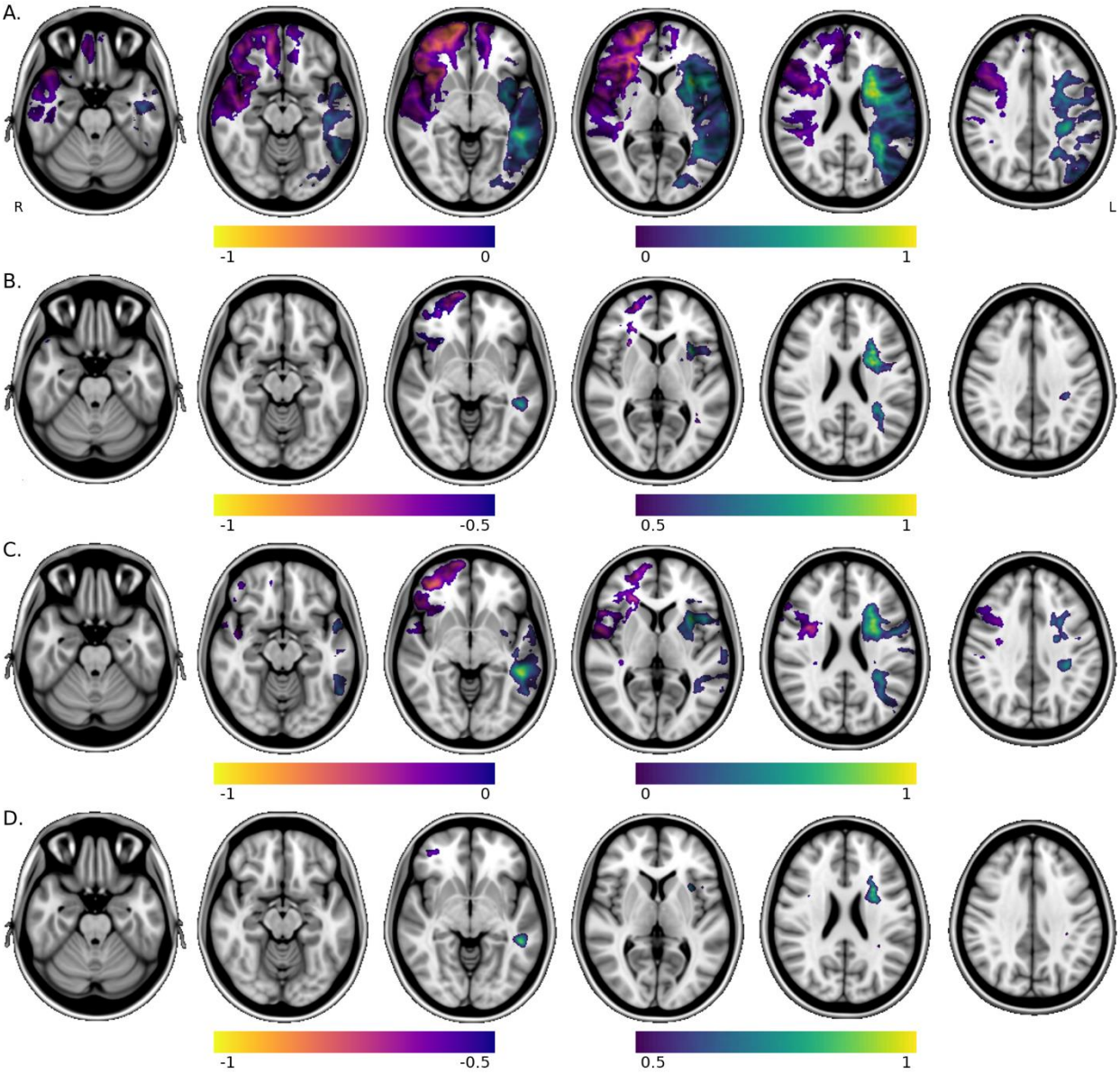



Figure 3.25 Slices -24, -14,-6, 5, 23, and 35 are shown. Regions associated with impairments in general cognitive ability are shown in cool colors and regions significantly not associated with impairments in general cognitive ability are displayed in warm colors. The localization of the 1-factor solution used to estimate *g* is shown in figures A&B. The factor that explains the most variance in the 4-factor solution (Figs

C&D) localizes similarly to the 1-factor solution, expectedly. In both analyses, posterior white matter lesions are associated with worsening *g*, consistent with prior literature. Contrarily, regions not associated with impairments in *g* localize to largely right hemisphere frontal areas, including parts of the putamen and white matter of the internal/external capsule and claustrum.

Domain-general visuospatial ability was highly correlated with *g* regardless of whether the 1-factor solution ($r = .569$, $p = 1.36 \times 10^{-42}$) or first factor of the 4-factor solution ($r = .521$, $p = 1.06 \times 10^{-34}$) was used to estimate *g*. Visuospatial ability was also correlated with the second factor of the 4-factor solution ($r = .592$, $p = 9.19 \times 10^{-47}$), the third factor ($r = .337$, $p = 3.47 \times 10^{-14}$), and the fourth factor ($r = .172$, $p = 1.58 \times 10^{-4}$). Full-scale IQ was available for 338 of the 480 patients in the Iowa Registry sample (mean = 99.69, SD = 14.4, min = 69, max = 146) and was significantly correlated with visuospatial ability ($r = .747$, $p = 1.62 \times 10^{-61}$) and *g* as estimated by the 1-factor solution ($r = .808$, $p = 3.20 \times 10^{-79}$). Since the anatomical distribution of results was largely the same regardless of which of the two factor analyses was used, the 1-factor estimation of *g* was regressed out of the domain-general visuospatial composite z-scores. The residuals were used as the behavioral variable in a lesion-symptom mapping analysis (Figure 3.26), and the right posterior putamen remains the strongest regional finding ($r = .425$, $p = 1.75 \times 10^{-22}$; 32 -11 -2). Other peak regions include the right superior putamen (27 1 13), white matter just superior to the right putamen (26 9 27), right anterior insula (40 8 -5), and occipital (32 -52 21) and parietal white matter (32 -28 31).

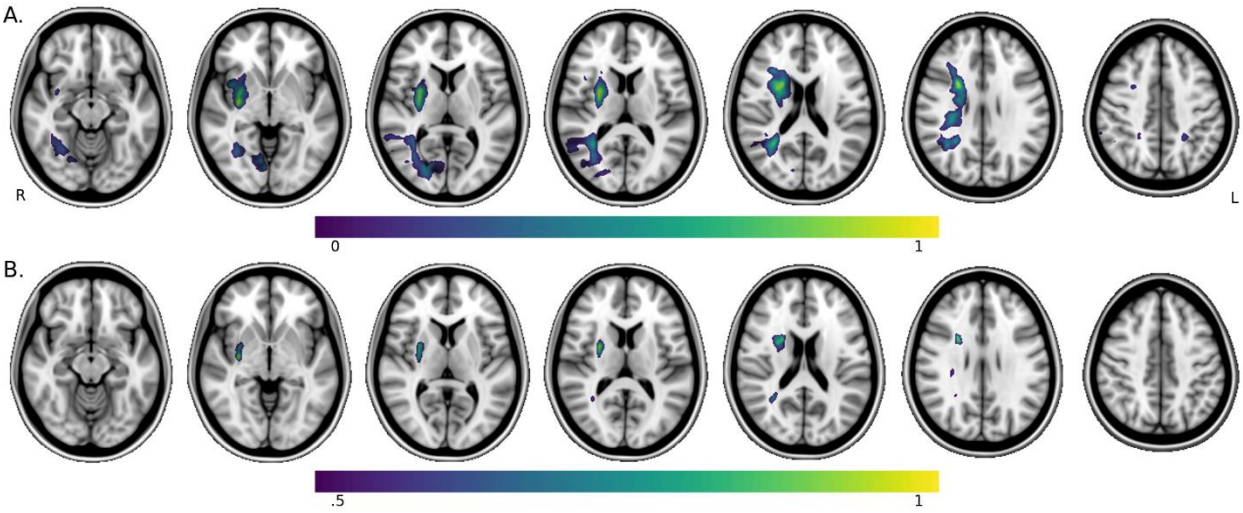



Figure 3.26 Slices -12, -3, 8, 13, 20, 29, and 44 are shown. Lesion-symptom mapping results in figure A are significant but unthresholded on a scale of 0 to 1. The strongest findings are highlighted in figure B.

## 3.5. Predicting Visuospatial Dysfunction in External Datasets

### 3.5.1. Benton Clinic Cohort

Lesion-symptom mapping of domain-general visuospatial ability in the Benton Clinic cohort (n = 80) was significantly associated with damage to left hemisphere posterior white matter, right hemisphere white matter superior to the putamen, and the right posterior frontoparietal operculum (r = .287, p = .00984; Figure 3.27).

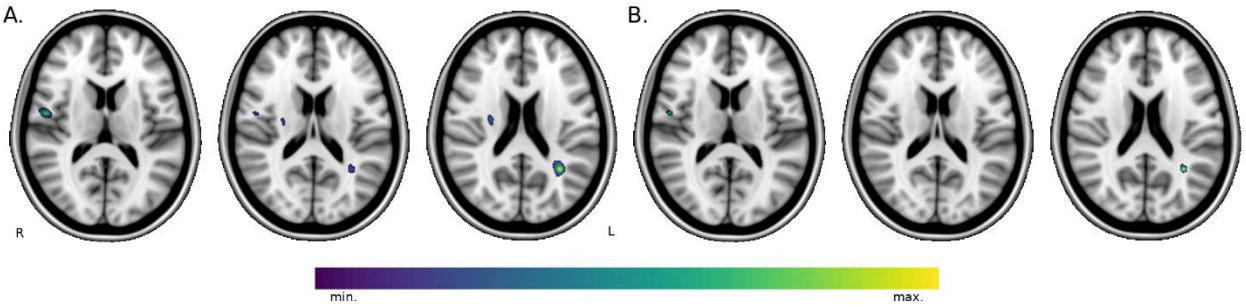



Figure 3.27 Axial slices 13, 17, and 20 are shown. Figure A shows voxel values between 0 and 1; figure B shows voxel values between .5 and 1. Damage to left hemisphere posterior deep white matter at MNI coordinates -33 -54 20 is most associated with domain-general visuospatial dysfunction in the Benton Clinic cohort.

The same analyses were used to probe the specificity of the putamen findings in this cohort as in the Iowa Registry cohort. 25.0% of patients in this cohort had a lesion intersecting with the right putamen, compared to 21.5% in the Iowa Registry cohort. A linear model was used to identify any potential correlation between the proportion of lesioned voxels in the right putamen ($v_{\text{right putamen}} = 6005\ mm^3$) to a patient's total lesion volume and the composite z-score representing domain-general visuospatial ability. Lesion volume was not significantly associated with domain-general visuospatial ability (adj. $R^2 = .00965$; $F(1,78) = 1.77$; $p = .187$). The amount of the lesion covering the right putamen is significantly associated with worse visuospatial ability (adj. $R^2 = -.0121$, $F(1,78) = .0563$, $p = .813$). The relationship between the ratio of lesioned to total voxels in the right putamen and domain-general visuospatial ability was also characterized while controlling for lesion volume (adj. $R^2 = -.0127$, $F(1,78) = .0108$, $p = .917$).

The lesion-symptom map and lesion network maps of domain-general visuospatial ability in the Iowa Registry cohort (n = 480) were used to generate out-of-cohort predictions in the Benton Clinic cohort (n = 80). Lesion-symptom mapping, functional lesion network mapping, and structural lesion network mapping were included as predictors in all possible combinations to determine which predictor(s) best fit the data. Lesion volume was significantly correlated with functional lesion network map lesion load ($r = .539$, $p = 2.43 \times 10^{-7}$) and structural lesion network map lesion load ($r = .896$, $p = 3.75 \times 10^{-29}$) but not domain-general visuospatial dysfunction ($r = -.215$, $p = .056$) and lesion-symptom map lesion load ($r = .0430$, $p = .705$) in the Benton Clinic cohort. The latter non-significant correlation makes sense as this in lesion-symptom mapping analysis controlled for lesion volume. Although lesion volume is not significantly

associated with visuospatial dysfunction, models with and without lesion volume as a covariate were explored because the p-value was trending towards significance (Table 3.1 and Table 3.2). A backwards stepwise linear regression was also used to determine possible predictors of domain-general visuospatial ability from the same four candidates. AIC set the limit for possible predictors in the model. This approach showed a model with lesion-symptom mapping, functional lesion network mapping, structural lesion network mapping, and lesion volume as predictors best fit the data best predicts visuospatial dysfunction (adj. $R^2 = .109$, $F(4,75) = 3.43$, $p = .0130$).

| Test of Model Fit | LSM | fLNM | sLNM | LSM + fLNM | LSM + sLNM | fLNM + sLNM | LSM + fLNM + sLNM |
|---|---|---|---|---|---|---|---|
| RMSE | .654 | .650* | .650 | .656 | .650 | .656 | .656 |
| $R^2$ | .112 | .123* | .113 | .101 | .115 | .115 | .103 |
| AIC | 163 | 161* | 162 | 162 | 161 | 163 | 163 |
| BIC | 170 | 169* | 169 | 171 | 171 | 173 | 175 |
| p-value | .0381 | .0194* | .0281 | .0266 | .0224 | .0592 | .0526 |

*indicates best model fit

Table 3.1 Better model fit is associated with lower RMSE, higher $R^2$, lower AIC, and lower BIC values. Five models significantly predicted outcomes, but all metrics of model fit suggest functional lesion network mapping best fit the data.

| Test of Model Fit | LSM + LV | fLNM + LV | sLNM + LV | LSM + fLNM + LV | LSM + sLNM + LV | fLNM + sLNM + LV | LSM + fLNM + sLNM + LV |
|---|---|---|---|---|---|---|---|
| RMSE | .647* | .660 | .668 | .660 | .665 | .670 | .670 |
| $R^2$ | .115 | .110 | .0916 | .0971 | .0915 | .112 | .127* |
| AIC | 160 | 163 | 164 | 162 | 162 | 164 | 160* |
| BIC | 170* | 172 | 174 | 174 | 174 | 176 | 174 |
| p-value | .0143 | .0481 | .0906 | .0314 | .0370 | .0720 | .0130* |

*indicates best model fit

Table 3.2 Lesion volume was included as a predictor in all models shown. The interpretation of the tests of model fit was less clear since RMSE and BIC suggest the lesion-symptom map lesion load and lesion volume model. R2 and AIC suggest the model including lesion-symptom map lesion load, functional lesion network mapping lesion load, structural lesion network mapping lesion load, and lesion volume as predictors best fit the data.

The same approach was used to determine model fit from the sub-cohort without imputed data (n = 113) with lesion-symptom mapping, structural lesion network mapping (the functional lesion network map was nonsignificant after correcting for multiple comparisons), and lesion volume as potential predictors. The best model includes lesion-symptom mapping and lesion volume as predictors (adj. $R^2$ = .0338, F(1,78) = 3.76, p = .0560).

| Test of Model Fit | LSM | sLNM | LSM + sLNM | LSM + LV | sLNM + LV | LSM + sLNM + LV |
|---|---|---|---|---|---|---|
| RMSE | .672 | .661* | .673 | .672* | .678 | .691 |
| $R^2$ | .0697 | .0880* | .0563 | .0773 | .0817* | .0579 |
| AIC | 167 | 164* | 166 | 165 | 165* | 167 |
| BIC | 174 | 172* | 176 | 175 | 174* | 179 |
| p-value | .869 | .102* | .257 | .150 | .132 | .242 |

*indicates best model fit

Table 3.3 None of the models significantly predicted outcomes, regardless the inclusion of lesion volume as a predictor. However, the model using only structural lesion network mapping lesion load as a predictor explained the most variance out of all six tested models.

### 3.5.2. Washington University Cohort

Lesion-symptom mapping of domain-general visuospatial ability in the Washington University cohort (n = 104) was most significant in left deep parietal white matter (r = .193, p = .0493; MNI coordinates -26 -20 31) with other distributed regional peaks in the right inferior frontal gyrus and insula (46 -4 11), the left thalamus (-12 -11 7; Figure 3.28).

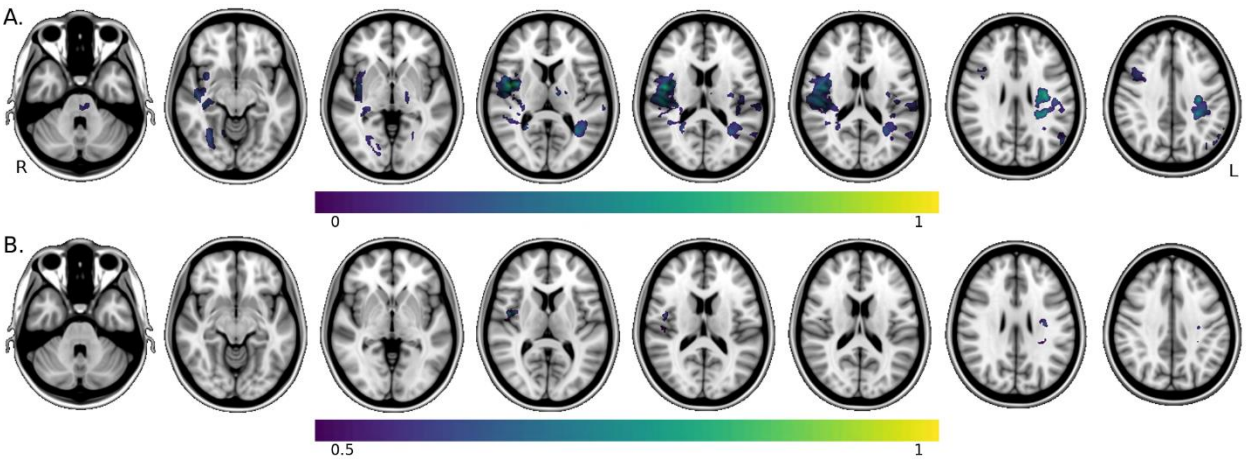



Figure 3.28 Slices -31, -9, -1, 10, 16, 28, and 37 are shown. Lesion-symptom mapping of visuospatial ability in the Washington University cohort shows bilateral peaks in the right inferior frontal gyrus and deep parietal white matter in the left hemisphere.

Lesion volume is correlated with lesion-symptom map lesion load ($r = .469$, $p = 5.11 \times 10^{-7}$), functional lesion network map lesion load ($r = .686$, $p = 9.78 \times 10^{-16}$), and structural lesion network map lesion load ($r = .898$, $p = 4.56 \times 10^{-38}$) but not domain-general visuospatial dysfunction ($r = .0293$, $p = .768$) in the Washington University cohort. Using the same measures of model fit, a model including functional lesion network mapping, structural lesion network mapping, and lesion volume but not lesion-symptom mapping as predictors best fits the data (adj. $R^2 = .144$, $F(3,100) = 6.76$, $p = 3.39 \times 10^{-4}$). The backwards stepwise linear regression produced the same results.

| Test of Model Fit | LSM | fLNM | sLNM | LSM + fLNM | LSM + sLNM | fLNM + sLNM | LSM + fLNM + sLNM |
|---|---|---|---|---|---|---|---|
| RMSE | 0.569* | 0.589 | 0.586 | 0.596 | 0.597 | 0.604 | 0.604 |
| $R^2$ | 0.0916 | 0.111 | 0.146* | 0.0854 | 0.0963 | 0.118 | 0.112 |
| AIC | 186.6* | 190.1 | 187.9 | 188.2 | 188.5 | 186.6* | 187.6 |
| BIC | 194.6* | 198.0 | 195.8 | 198.8 | 199.0 | 197.1 | 200.8 |
| p-value | .0602 | .677 | .129 | .141 | .159 | .0631 | .0919 |

*indicates best model fit

Table 3.4 Models in the WashU dataset are included above, none of which reached statistical significance without including lesion volume as a predictor.

| Test of Model Fit | LSM + LV | fLNM + LV | sLNM + LV | LSM + fLNM + LV | LSM + sLNM + LV | fLNM + sLNM + LV | LSM + fLNM + sLNM + LV |
|---|---|---|---|---|---|---|---|
| RMSE | 0.598 | 0.620 | 0.586 | 0.626 | 0.599 | 0.584* | 0.584* |
| $R^2$ | 0.0875 | 0.146* | 0.0952 | 0.0927 | 0.0806 | 0.115 | 0.105 |
| AIC | 188.2 | 192.1 | 183.6 | 190.1 | 185.5 | 175.1* | 176.7 |
| BIC | 198.8 | 202.61 | 194.2 | 203.3 | 198.7 | 188.3* | 192.5 |
| p-value | .138 | .917 | .0152 | .258 | .0371 | $3.39 \times 10^{-4}$ | $8.46 \times 10^{-4}$ |

*indicates best model fit

Table 3.5 Lesion volume was included as a predictor in all models shown and based on RMSE, AIC, and BIC the model with functional lesion network mapping, structural lesion network mapping, and lesion volume as predictors best fits the data.

The same approach was used to determine model fit from the Iowa Registry cohort analyses without imputed data (n = 113). By metrics of model fit and per the stepwise linear regression, a model with structural lesion network mapping and lesion volume as predictors is best (adj. $R^2$=.0983, $F(2,101)=6.61$, $p = 2.00 \times 10^{-3}$).

| Test of Model Fit | LSM | sLNM | LSM + sLNM | LSM + LV | sLNM + LV | LSM + sLNM + LV |
|---|---|---|---|---|---|---|
| RMSE | 0.558 | 0.557 | 0.560* | 0.582 | 0.563* | 0.568 |
| $R^2$ | 0.152* | 0.151 | 0.133 | 0.0943 | 0.125* | 0.112 |
| AIC | 182.0 | 181.2 | 181.0* | 183.8 | 179.5* | 179.7 |
| BIC | 190.0 | 189.1* | 191.5 | 194.4 | 190.0* | 192.9 |
| p-value | .311 | .252 | .297 | .0165 | $2.00 \times 10^{-3}$ | $2.84 \times 10^{-3}$ |

*indicates best model fit

Table 3.6 Structural lesion network mapping and lesion volume are the best predictors in the sub-cohort with all twelve tests (n = 113).

# CHAPTER 4: DISCUSSION

The main findings of my analyses are that damage to the right putamen, right subinsula/claustrum, dorsal visual stream, dorsal attention network, and visual network is associated with chronic visuospatial dysfunction. Lesion-symptom mapping of individual neuropsychological tests sensitive to visuospatial dysfunction and of domain-general visuospatial dysfunction further support the importance of the right putamen in visuospatial ability. The functional lesion network mapping results show that the dorsal attention and visual networks are most associated with visuospatial dysfunction. Structural lesion network mapping revealed that damage to distributed white matter in posterior regions, particularly in the right hemisphere, is associated with domain-general visuospatial dysfunction. I also estimated general intelligence in this cohort which showed anatomical localization to left hemisphere regions. After accounting for *g*, damage to the right putamen was still most associated with visuospatial dysfunction in the Iowa Registry cohort. Lesion-symptom mapping, functional lesion network mapping, structural lesion network mapping, and lesion volume best predicted visuospatial dysfunction in the Benton Clinic cohort. Functional lesion network mapping, structural lesion network mapping, and lesion volume but not lesion-symptom mapping best predicted visuospatial dysfunction in the WashU cohort. Together, these findings suggest that bilateral posterior white matter and the right putamen are involved in visuospatial function independent of *g* and a combination of lesion-symptom mapping and lesion network mapping can predict chronic visuospatial dysfunction in external datasets.

Significant lesion-symptom maps were produced for all but one neuropsychological test: Spatial Span. This may be due to the relatively small sample size used in this analysis (n = 179) compared to the other eleven tests that did localize, which included from 337 to 480 patients. Lesion-symptom maps of Block Design, Matrix Reasoning, Symbol Search, Benton Facial Recognition Test, Benton Visual Retention Test, Hooper Visual Organization Test, Judgment of Line Orientation, and Rey-Osterrieth Complex Figure Test all show significant peaks in the right putamen, suggesting that this neuroanatomical correlate is task-independent. Damage to right hemisphere white matter in the dorsal visual stream and/or the superior longitudinal fasciculus was also associated with worse performance on Block Design, Digit-Symbol Coding, Matrix Reasoning, Picture Completion, Symbol Search, Benton Facial Recognition Test, Benton Visual Retention Test, clock drawing, Hooper Visual Organization Test, Judgement of Line Orientation, and Rey-Osterrieth Complex Figure Test. Despite the lateralization of visuospatial ability to the right cerebral hemisphere widely reported for decades, most individual test analyses showed left hemisphere findings too. This was especially true in tests with more distributed neural correlates including Digit-Symbol Coding, Picture Completion, Symbol Search, Benton Visual Retention Test, clock drawing, Judgement of Line Orientation, and Rey-Osterrieth Complex Figure Test. A larger set of regions associated with performance on a given test could be because the test relies on other cognitive abilities. Moreover, functions also necessary for intact test performance on some tests recruit left hemisphere regions including visual search, letter representation, working memory, language comprehension, and visuoconstruction. Prior studies have highlighted the involvement

of left hemisphere regions in general cognitive ability which is highly correlated with visuospatial ability (Bowren et al., 2020). Lesion-symptom maps of multiple tests suggested similar neural correlates in the right putamen and right posterior white matter, providing preliminary evidence that these findings are task-independent.

Exploratory factor analysis was used to determine the latent structure of visuospatial ability. Tests selected were sensitive to various constructs including visuospatial working memory, visuoconstruction, face processing, processing speed, mental rotation, and spatial visualization. Despite this, one factor, dubbed “domain-general visuospatial ability”, best explained variance across all tests. This suggests that tests commonly used to assess visuospatial ability are sensitive to a common construct in addition to more specific cognitive abilities. Prior studies found more than one factor representing visuospatial ability in different sets of tests (Chen et al., 2000; Mammarella et al., 2013; Miyake et al., 2001; Pellegrino et al., 1984); however, these studies were not performed in patients with brain lesions. The one-factor solution in this study may be due to the influence of general cognitive ability on performance on tests of visuospatial ability, which are strongly correlated constructs (Lynn et al., 1988; Miyake et al., 2001).

Composite z-scores and factor scores were used to estimate domain-general visuospatial ability in lesion-symptom mapping and lesion network mapping analyses in the Iowa Registry cohort. Both methods of estimating domain-general visuospatial ability produced similar regional peaks. Visuospatial ability was most strongly associated with damage to the right putamen and posterior white matter bilaterally, including the dorsal visual stream. Regional peaks in the lesion-symptom map are present bilaterally along the dorsal visual stream, which spans from primary visual

cortex through V5/MT to posterior parietal cortex. The involvement of the dorsal visual stream in vision-for-action has been well established and replicated for over four decades, including by this study. However, the putamen is not typically considered an area related to visuospatial ability. The specificity of the right putamen in visuospatial ability was probed in an additional analyses. Patients in the Iowa Registry cohort with lesions that overlap more with the right putamen and have a damage to more of the right putamen have significantly worse performance on tests of visuospatial ability.

Ungerleider and Mishkin provided the first conclusive evidence for at least two cortical visual streams in a primate lesion study, identifying the dorsal and ventral visual streams as the “where” and “what” pathways, respectively (Mishkin et al., 1983; Ungerleider M., 1982). The conception of the dorsal visual stream as the “where” pathway has been refined over the past few decades, particularly after studies in a famous patient with brain damage, D.F. (Goodale & Milner, 1992; James et al., 2003). D.F. had hypoxic brain damage to the lateral occipital cortex, white matter connecting the lateral occipital cortex to other regions, and shrinkage in the intraparietal sulcus due to carbon monoxide exposure (Goodale & Milner, 1992; James et al., 2003); regions in the ventral visual stream like the fusiform face area were preserved. D.F. demonstrated a deficit in reaching and grasping, which partially led to the reconsideration of the dorsal visual stream as processing information related to vision-for-action, contrasted to vision-for-perception in the ventral visual stream. The role of a motor control region, the putamen, in visuospatial ability becomes clearer when considering vision-for-action processing as a function represented by the dorsal visual stream.

While the right putamen is not canonically associated with visuospatial function, it was the strongest regional peak in the lesion-symptom map. The putamen is one of five nuclei in the basal ganglia. Combined with the globus pallidus, these two structures form the lentiform nucleus; the putamen and caudate nucleus form the dorsal striatum. The caudate nucleus, putamen, globus pallidus, nucleus accumbens, and olfactory tubercle comprise the basal ganglia, most well-known as part of the motor control system. Motor functions of the basal ganglia more broadly include initiating movements, suppressing non-synergistic movements, chunking elements into action sequences, encoding procedural memories, and controlling the activation of locomotor pattern generators (Sipla, 2020). The putamen receives input from primary motor and primary sensory cortices (Parent & Hazrati, 1995). These excitatory glutamatergic cortico-striate projections synapse onto inhibitory GABAergic medium spiny neurons in the striatum, which require activation by cortical inputs (Walker et al., 1993). At least in the motor domain, the putamen receives sensory and motor input, making this region a good candidate for processing vision-for-action. Indeed, connectivity between extrastriate visual cortex, including area V5 (Riecansky, 2004), and the putamen has been observed in non-human primates (Yeterian & Pandya, 1995).

Non-motor functions of the putamen have been noted, but the role of the putamen in cognitive function is still an open area of investigation. Unrelated to vision-for-action, the putamen is associated with language (Viñas-Guasch & Wu, 2017), reward learning (Muranishi et al., 2011), and emotion (Talati et al., 2022) in humans. Structural and functional abnormalities in the putamen are associated with an increased risk of depression (Talati et al., 2022). One patient with a perinatal left putamen lesion

showed deficits in working memory, executive function, and sequence learning (Sefcsik et al., 2009). Finally, visuospatial attention is correlated with activity in the putamen (Umarova et al., 2010).

Although it is not typically considered a “visuospatial area”, several studies have suggested that the putamen is important for vision-for-action. Electrophysiologic activity in the primate putamen has been observed in tasks associating sensory stimuli with movement (Kimura, 1986). A related study later demonstrated that neurons in the primate putamen were vital for the visuospatial and temporal organization of movements (Ueda & Kimura, 2003). Neurons sensitive to vision and not movement have also been measured in monkeys (Vicente et al., 2012), further emphasizing the involvement of the putamen in higher-order visual processing. In humans, structural and functional differences in the right putamen in older adults are systematically related to proprioception (Goble et al., 2012). Along with findings from this study, it is clear that the right putamen supports visuospatial ability and damage to this region and regions along the dorsal visual stream can lead to visuospatial dysfunction.

The advent of functional lesion network mapping (Boes et al., 2015) has been vital to understanding how damage brain networks impacts cognitive function, including networks associated with visuospatial dysfunction. The visuospatial ability functional lesion network map shared a similar spatial distribution to the dorsal attention network and visual network. The dorsal attention network canonically encompasses the intraparietal sulcus, frontal eye fields, V5/MT, superior parietal lobule, supplementary eye field, and ventral premotor cortex (Uddin et al., 2019). This task-positive network is associated with voluntary control of visuospatial attention (Corbetta & Shulman, 2002)

and interacts with regions in the visual system (Yeo et al., 2011). Thus, its relevance to visuospatial dysfunction is not surprising. The visual network as defined by Yeo and colleagues includes primary and extrastriate visual cortex (Yeo et al., 2011). Damage to these earlier visual areas can impact downstream information processing in V5/MT and posterior parietal cortex, which manifests behaviorally as changes in visuospatial function. My robust findings in the dorsal attention network and visual network may be one reason why functional lesion network mapping significantly predicted visuospatial dysfunction in the WashU cohort, even though their measures of visuospatial ability were tests of neglect. It is important to note that the dorsal attention network is not the only network involved in visuospatial attention (Bartolomeo et al., 2012).

Structural lesion network mapping in the Iowa Registry cohort generated relatively non-specific results that were stronger in posterior white matter connecting both cerebral hemispheres. These significant regions were slightly more pronounced in the right hemisphere. Some researchers have suggested that visual neglect could be due to interhemispheric disconnection (Bartolomeo et al., 2007). While this study focuses on visuospatial ability more broadly, some patients in this sample do have visual neglect, which may be partly driving these findings. Alternatively, some forms of visuospatial dysfunction may be due to an intrahemispheric disconnection syndrome. In the cohort without imputed data, findings were strongly right lateralized and showed tracts running along the caudal-rostral axis. The most significant results appeared to be a tract projecting through brainstem regions around the right putamen before terminating in deep parietal white matter superior to the putamen in the right hemisphere. Since the direction of information flow cannot be established using DTI,

these findings could represent a mixture of inputs and outputs from the putamen. However, this cannot be determined conclusively using these methods.

General cognitive ability, defined psychometrically as shared variance across multiple measures and cognitive domains (Bowren et al., 2020; Spearman, 1904), is correlated with visuospatial ability in healthy (Mervis et al., 1999) and lesion (Gläscher et al., 2009) populations. As such, general cognitive ability impacts performance on a range of cognitive tests. Thus, ensuring that *g* was not driving the visuospatial ability lesion-symptom mapping results was important. In fact, tests that heavily rely on visuospatial function like Raven's Progressive Matrices (Carpenter et al., 1990; Raven & Court, 1938), a test similar to Matrix Reasoning from the WAIS, are used by some as a quick estimate of intelligence. The strong association between *g* and visuospatial ability (Lynn et al., 1988; Miyake et al., 2001) makes this relationship particularly difficult to disentangle in healthy adults. A major strength of lesion studies like this one is the ability to dissociate constructs that are typically indivisible in healthy populations.

Previous studies on the functional localization of general cognitive ability showed that left posterior white matter damage is most associated with acquired deficits in *g* (Bowren et al., 2020). This is important to consider since damage to left posterior white matter was associated with deficits in domain-general visuospatial ability. As expected, *g* localized to predominantly left hemisphere regions across all four lobes of the cerebral cortex. One of the most significant regional peaks was in left posterior white matter, but it was more ventral than the peak from the visuospatial ability lesion-symptom map. After covarying for general cognitive ability, the left hemisphere posterior white matter peak was no longer significant. The right putamen, long-range white matter fibers

superior to the right putamen extending from the superior posterior parietal lobe to the posterior frontal lobe, and right hemisphere occipital white matter remained associated with visuospatial ability independent of general cognitive ability. Based on the results of this analysis, left posterior white matter identified in the lesion-symptom map of domain-general visuospatial ability may be reflective of *g*, not visuospatial ability specifically.

The lesion-symptom map of domain-general visuospatial ability in the Benton Clinic cohort again highlighted the importance of left posterior white matter, white matter superior to the right putamen, and the right posterior frontoparietal operculum. While the right putamen was not a significant peak of the lesion-symptom map, damage to the right putamen was still associated with worse visuospatial function. The peak in left posterior white matter was of particular interest. This region has been associated with lower *g* scores in a semi-overlapping cohort of patients (Bowren et al., 2020). A future analysis could estimate and covary for *g* in the Benton Clinic cohort to disentangle regions involved in visuospatial ability from regions involved in general intelligence.

The lesion-symptom map of visuospatial ability in the WashU cohort was most significant in the right insula, right inferior frontal gyrus, and left superior white matter, the former of which may also be explained by *g*. The current analysis cannot confirm this hypothesis, although it could be investigated further by estimating and covarying for *g* in the WashU cohort before performing the lesion-symptom mapping analysis. The right putamen was not significantly associated with visuospatial dysfunction in the WashU cohort. The four tests that comprise the estimate of domain-general visuospatial ability in this cohort are sensitive to visuospatial neglect as opposed to visuospatial

function more generally. Based on these results, visuospatial attention may not recruit the right putamen, but other aspects of visuospatial function might.

Functional lesion network mapping, structural lesion network mapping, and lesion volume but not lesion-symptom mapping significantly predicted visuospatial dysfunction in the WashU cohort. Although I hypothesized lesion-symptom mapping would also be a significant predictor, these results are unsurprising. Recent studies show that lesion network mapping (Boes, 2021; A. L. Cohen et al., 2021; Salvalaggio et al., 2020) is quite valuable in predicting outcomes from stroke. Several approaches have been used to predict long-term behavioral outcomes after brain injury including lesion-symptom mapping (Campana et al., 2015; Thye & Mirman, 2018), functional lesion network mapping (A. L. Cohen et al., 2021; M. A. Ferguson et al., 2019), white matter tractography (Bowren Jr et al., 2022; Forkel et al., 2014; Kaminski et al., 2022; Reber et al., 2021), latent disconnectome prediction (Talozzi et al., 2023), and connectome-based predictive modeling (Jiang et al., 2023) to name a few. Regardless of approach, studies of this type are invaluable in better understanding functional neuroanatomy and the long-term impact of brain injury on patients.

To the best of my knowledge, this is the most extensive study of domain-general visuospatial ability in patients with focal brain lesions to date. Results of this research further the field's understanding of the latent structure and functional neuroanatomy of visuospatial ability and the impact of brain damage on visuospatial function. These results are a steppingstone towards the broader goal of using data-driven approaches to predict long-term outcomes of brain damage. These data can be used to create a clinical tool for generating empirically supported prognoses for recovery from brain

damage using similar approaches to predict outcomes in other cognitive domains (Bowren Jr et al., 2022; Reber et al., 2021; Sullivan et al., 2022).

The lesion method is a powerful approach to understanding brain-behavior relationships that can carve nature at its joints in ways other methods in cognitive neuroscience cannot. However, some limitations to the lesion method are still pervasive, one of which is mapping neuropsychological test performance to brain regions instead of cognitive functions as represented by the brain independent of a test. While this approach has been a powerful tool in human brain mapping, neuropsychological tests are usually sensitive to multiple cognitive functions. For example, patients can have impaired performance on Block Design due to deficits in visuoconstruction, mental rotation, motor planning/control, executive function, or receptive language. The lesion-symptom map of Block Design could reflect regions associated with the set of functions used for the task. Using a factor analytic approach to investigate neuroanatomical correlates of latent variables measured across multiple tests addresses this concern while working towards developing a cognitive ontology based on neuroanatomy instead of behavior. Task-independent lesion-behavior analyses are clinically useful too. Clinicians have limited time to gather as much information as possible about a patient's cognitive status. Shortening test batteries without compromising information gleaned from the assessment session can maximize information used to make diagnoses and treatment recommendations while mitigating other factors like insurance covering limited testing sessions and patient burnout. If a primary goal of testing is to assess visuospatial function broadly, administering a set of

tests that all load strongly onto the domain-general visuospatial ability factor may not be as information-rich as including tests sensitive to other functions under time constraints.

### 4.1. Limitations and Future Directions

This study has limitations, some of which are present in most lesion studies. First, a patient's lesion sometimes appears larger if several years pass from lesion onset to the scan date. Chronic lesions are stable but neuroplastic recovery, small vessel ischemia, and sub-clinical neurodegenerative disease can slightly alter the boundaries of the lesion (Alexander et al., 2010). However, this is negligible in studies with large sample sizes. Next, some brain regions are more or less likely to be impacted by lesions (e.g., watershed zones are less likely to be lesioned by ischemic stroke; white matter shearing and damage to frontal/occipital poles is common following traumatic brain injury), which can lead to unequal lesion coverage in some brain areas. In this study there was a difference in the distribution of lesions across the Iowa Registry, Benton Clinic, and WashU cohorts. Differences in power across the brain could impact lesion-symptom mapping and lesion network mapping results, even though my findings did not consistently overlap with regions that are overpowered in these samples. Power could be accounted for by first creating a power map to determine which areas of the brain are adequately powered in the brain. A similar approach is used in fMRI research to constrain claims about tissue function to only reliable areas. Patients' lesion masks could then be weighted on a voxel-wise basis such that lower weights are applied to overpowered regions and higher weights are applied to less powered regions. Only lesion-symptom map results in powered regions would be retained. However, the external validity of this technique is currently unknown.

Relatedly, the Iowa Registry cohort and both out-of-sample validation cohorts were underpowered in some areas that are thought to be involved in visuospatial dysfunction including the thalamus (Carrera & Bogousslavsky, 2006) and cerebellum (Molinari & Leggio, 2007). This can be addressed in future research by using a more extensive multi-site database with structural imaging and comprehensive standardized neuropsychological evaluation.

A single factor best explained variance in visuospatial ability in the Iowa Registry cohort, contrary to what prior studies have reported (Carroll, 2003; Chen et al., 2000; Voyer & Saunders, 2004). This finding was not due to data imputation. Since general cognitive ability and domain-general visuospatial ability are correlated, the one-factor solution suggested by the parallel analysis may capture variance in both. The lesion-symptom map of domain-general visuospatial ability differed after accounting for general cognitive ability, namely left hemisphere regional peaks no longer reached significance, but right hemisphere peaks present in the original lesion-symptom map were retained. There is likely overlap in the behavioral and anatomical characteristics of *g* and visuospatial ability. Covarying for *g* prior to running the parallel analysis and EFA might result in multiple factors emerging, which would be consistent with prior findings (Carroll, 2003; Chen et al., 2000; Voyer & Saunders, 2004).

My models significantly predicted outcomes in both validation cohorts but explained more variance in the WashU cohort, contrary to my expectation. Patients in the Benton Clinic cohort were administered a nearly identical set of tests as those in the Iowa Registry cohort, whereas patients in the WashU dataset were only administered tests designed to screen for visuospatial inattention. I hypothesized that a greater overlap

between tests in the training and validation datasets would result in stronger model predictions, but that was not the case. Lesions of patients in the WashU cohort predominantly affected subcortical white matter and the basal ganglia but did not affect cortical grey matter as much as in the other two cohorts. One of the main findings of the Iowa Registry lesion-symptom map was the involvement of posterior white matter in visuospatial ability, which may drive model prediction in the WashU cohort.

A model with all predictors tested explained the most variance in the Benton Clinic. This emphasizes the importance of lesion network mapping in addition to lesion-symptom mapping in predicting outcomes (Boes, 2020; Boes et al., 2015; Bowren Jr et al., 2022; Reber et al., 2021; Salvalaggio et al., 2020). In the WashU cohort, the best model included structural and functional lesion network mapping lesion load but not lesion-symptom mapping lesion load. Posterior interhemispheric white matter was represented bilaterally by the structural lesion network map. Thus, the overrepresentation of white matter lesions and basal ganglia lesions in the WashU cohort compared to the Benton Clinic cohort could be responsible for more variance explained in the WashU cohort. Models predicting domain-general visuospatial ability using individual test performance lesion-symptom map lesion load and lesion network map lesion load could be compared to the factor-derived lesion load values. If my models using domain-general visuospatial ability better predict outcomes in the Benton Clinic and WashU cohorts, it would be strong evidence that using latent factors as predictors enhances the generalizability of predictions regardless of which specific tests were used to measure visuospatial dysfunction.

Lesion-symptom mapping of Spatial Span produced nonsignificant results, possibly because regions implicated in the task are diffuse or because fewer patients were administered Spatial Span compared to other tests included in calculating domain-general visuospatial ability. A future analysis will remove Spatial Span as a component of domain-general visuospatial ability, which may be introducing noise to the dataset.

Future analyses will further investigate the role of *g* as it relates to visuospatial ability, use alternative approaches to lesion-symptom mapping and lesion network mapping, use other methods of generating and testing predictive models, and use computational modeling to characterize the impact of lesions on information processing to continue to investigate the neuroanatomical correlates of visuospatial ability.

The lesion method is one approach to causal brain mapping, but targeted brain stimulation through transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), or intracranial electrical stimulation in neurosurgical patients can further elucidate relationships between brain structure and function. TMS and tDCS are limited to targeting regions near the brain's surface, so stimulation of the putamen would require intracranial stimulation. Neuropsychological tests sensitive to visuospatial dysfunction could be administered before surgery while a “virtual lesion” is imposed upon the right putamen via stimulation. If patients perform significantly worse on measures of visuospatial ability during stimulation, it would be further evidence for the involvement of the right putamen in visuospatial ability.

Alternative approaches to lesion-symptom mapping and lesion network mapping may help further probe the functional neuroanatomy of visuospatial ability and increase the amount of variance explained by predictive models. As already mentioned,

regressing out *g* prior to performing the EFA will further support the notion that the latent variable represented by the composite z-score is specific to domain-general visuospatial ability and not to cognitive performance more broadly. The residuals can be used as the behavioral variable in lesion-symptom mapping and lesion-symptom mapping analyses. The lesion-symptom map for domain-general visuospatial ability in the Benton Clinic cohort was most significant in left posterior white matter, which may be due to the influence of *g*. A future analysis could covary for *g* in the Benton Clinic cohort to disentangle the relative contribution of general intelligence and domain-general visuospatial ability to these findings. Lesion network mapping in the validation datasets can also be performed; a spatial correlation analysis between the lesion network maps from the Iowa Registry cohort and the lesion network maps for each validation cohort could probe potential similarities in network localization of domain-general visuospatial ability across cohorts.

Other approaches to lesion network mapping could provide insight into the functional and structural connectivity between the right putamen in other brain regions. The right putamen could be used as a seed ROI in functional lesion network mapping and white matter tractography analyses to see if it is connected to networks implicated in domain-general visuospatial ability. Functional lesion network mapping could also be replicated using seeds from the domain-general visuospatial ability lesion-symptom map. Since the strongest findings are in the right putamen, the results would likely be similar to the functional lesion network map analysis using the right putamen as a seed. I expect the results of an ROI-based approach to functional lesion network mapping to

be similar to the results of functional lesion network mapping using FSL PALM, as has been demonstrated in other studies (Skye et al., 2022).

Predictive models can be generated and validated in other ways too. Patients in the Iowa Registry cohort and patients in the Benton Clinic cohort could be pooled to increase the sample size of the domain-general visuospatial ability lesion-symptom map and lesion network maps. A subset of the pooled cohort would be used as a validation dataset and the other portion as a training dataset to create lesion-symptom maps and lesion network maps which would minimize potential differences between the predictor and predicted groups. This approach would also benefit from a multisite lesion dataset using a variety of neuropsychological tests to enhance the generalizability of the models. Second, additional attribute variable predictors like years of education, age, gender, handedness, and lesion laterality can be added to the models which may help explain more variance in the data. However, adding more predictors could worsen the problem of overfitting already present in linear models (Hawkins, 2004). This could be combatted using machine learning approaches or ridge regression, methods that can reduce the problem of overfitting.

Computational modeling approaches have been making their way into lesion research over the past few years (Parr et al., 2018). Developing task-dependent and task-independent models of cognitive functions is one way to test hypotheses about how information is processed by the brain, often using item-level data instead of raw or scaled scores to enhance the granularity of behavioral data. This also helps to address a major limitation of using a single score to sum up a patient's performance on a test: the patient could be performing poorly for any number of reasons (e.g., a low score on

the Complex Figure Test could be due to graphomotor impairment, visuoconstruction impairment, attentional deficits, lack of planning, early visual processing dysfunction, etc.). Combined with the lesion method, computational modeling provides an unprecedented opportunity to evaluate how lesions impact information processing, not just test performance. This has been applied to studies of visuospatial neglect to assess the relationship between visuospatial attention and saccadic eye movements (Parr & Friston, 2018). Future research could apply this same line of thought to visuospatial ability more broadly.

In conclusion, this research demonstrates the importance of the right putamen, posterior white matter tracts, dorsal attention network, and visual network in supporting domain-general visuospatial ability. Some left hemisphere correlates of domain-general visuospatial ability may be explained by general cognitive ability more broadly. Finally, lesion-symptom map lesion load, lesion network map lesion load, and lesion volume significantly predict visuospatial dysfunction in external validation cohorts. I am optimistic that a better understanding of the cognitive architecture and neural correlates of visuospatial ability will continue to inform how the field thinks about vision-for-action and predictive models of long-term recovery from brain damage.

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