Sleep and Word Learning Over Time in Adults with Moderate-Severe Traumatic Brain Injury

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DEDICATION

For my grandparents,

Mary Jeannine (Goldey) O'Nan
Jesse Ralph O'Nan
Martha Joyce (Benton) Morrow
John Andrew Morrow, Sr.

And my parents,

Miriam Jayne (O'Nan) Morrow
John Andrew Morrow, Jr.

Who showed me the importance of knowing where I came from
and going where I can be of service.

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PREFACE

Every 21 seconds, one person in the United States sustains a traumatic brain injury (TBI) (Centers for Disease Control and Prevention, 2015). Although there has been a significant decrease in the number of deaths caused by TBI in the last 20 years, there has been no corresponding reduction in the rate of disability (Roozenbeek et al., 2013). Fewer than half of people with moderate-severe TBI return to work after injury (Gormley et al., 2019), and many struggle to return to school or vocational training (Duff & Stuck, 2015; E. M. Frank et al., 1997; Ownsworth & McKenna, 2004; Todis et al., 2011; Ylvisaker et al., 2003). Currently, 6.2 million Americans live with brain injury-related disability at enormous personal and societal cost (Centers for Disease Control and Prevention, 2015).

A major barrier to rehabilitation after TBI is the challenge of predicting long-term outcome. Despite the prevalence of chronic disability after TBI, the current medical model manages it as an acute injury (Dahdah et al., 2016; Morrow et al., 2021; Ylvisaker, Adelson, et al., 2005). Rehabilitation services, when available, are front-loaded for intensive therapy courses in the weeks or months after injury (Morrow et al., 2020a, 2021; Ylvisaker, Turkstra, et al., 2005). Due to limitations in access or insurance, some individuals with TBI do not receive rehabilitation services at all beyond the acute hospital stay (Ylvisaker, Adelson, et al., 2005; Ylvisaker et al., 2003). Yet, speech-language pathologists who manage TBI in acute care report limited confidence in making predictions about long-term outcome in TBI or in targeting therapies to individuals based on clinical characteristics (Morrow et al., 2020b). This system leaves individuals with TBI and stakeholders to independently cope with chronic disability without a clear of idea of how that disability will manifest over time (Morrow et al., 2021).

A central challenge to predicting outcome and targeting treatments in TBI is significant inter-individual variability in symptom profiles and the complex interactions between symptoms (Covington & Duff, 2020; Dahdah et al., 2016; Duff et al., 2022). Speech-language pathologists treat and study cognitive-communication deficits, which often persist long after physical manifestations of TBI subside (MacDonald, 2017; Morrow et al., 2021). However, individuals with TBI also experience a range of related symptoms that may impair cognition (e.g., chronic pain, mood disorders, sleep disruptions) (Morrow & Duff, 2020). When we treat and study cognitive-communication symptoms in isolation, we may miss opportunities to intervene in related areas and potentially improve intransigent components of cognition.

Untangling the complex web of symptoms in individuals with TBI may seem an overwhelming task, but there are clear opportunities to begin with a single skill that may be particularly impactful for functional outcome. For example, the ability to (re)learn information is critical for successful rehabilitation after TBI, as it underlies a person's potential to benefit from any medical recommendations or therapy. Memory deficits are among the most commonly-reported and disruptive symptoms reported by individuals with TBI and those close to them. Yet, the last several decades have seen limited progress in developing restorative therapies for memory and learning deficits in this population

(Velikonja et al., 2014). In fact, some learning processes that rely on memory systems routinely impaired in TBI and could underlie outcomes in academic, vocational, and social spheres (e.g., word learning) have not been studied as intervention targets after TBI at all.

Perhaps it is time to expand our study of memory and consider how related systems might support learning over time. Converging evidence from behavioral, cellular, and systems neuroscience provides a clue as to where to start: sleep. Sleep supports the formation of new memories, and the strengthening of those memories over time, in neurotypical individuals (Stickgold, 2005). Although approximately half of individuals with TBI report sleep deficits after injury, sleep has not been fully explored as a potential contributor to memory deficits in this population (Grima et al., 2017; Morrow & Duff, 2020).

Study designs that involve learning and assessment in a single session are inadequate to capture the full process of learning, and sleep's contributions to it, over time. This thesis combined theories of psycholinguistics, cognitive neuroscience of memory, and rehabilitation with well-established word learning protocols (Dumay et al., 2004; Dumay & Gaskell, 2007; McGregor et al., 2013) and objective measurement of sleep via actigraphy to ask how TBI affects word learning over time and its interactions with sleep. Findings could support the design of rehabilitation interventions and the targeting of those interventions to individuals at risk for learning- and sleep-related disruptions of functional outcome after TBI.

This thesis is composed of four chapters. **Chapters 1-3** are each adapted from articles developed for publication and present a theoretical introduction to this work. **Chapter 1** details the rationale and framework for focusing on word learning as a window to memory and functional outcomes after TBI. **Chapter 2** discusses the role of sleep in memory and learning, and how the field of speech-language pathology might capitalize on this interaction in both research and clinic to improve rehabilitation outcomes. **Chapter 3** describes the use of mediation and moderation analysis approaches to understand the interactions of related factors in producing outcome and to increase the clinical-translational implications of research findings for improving rehabilitation precision. **Chapter 4** has also been developed for publication and provides a summary of the rationale for the presented work, the study's methods, results, and a general discussion and perspectives on the presented work. Each of these chapters contains a box summarizing conclusions and open questions in its respective area. Additional visualizations and analyses are provided in the **Supplementary Appendix**.

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I feel like, after my brain injury,
it's harder to make connections.

To connect with people, or the world,
or even to connect these words in my brain.

(extract from a conversation with study participant)

1 Word Learning as a Window to Memory and Rehabilitation Outcomes in Traumatic Brain Injury

1.1 The Importance of Words

Word learning is a lifelong human endeavor. It is estimated that the average English speaker has acquired 12.5 million bits of information, the majority relating to word forms and meanings, by adulthood (Mollica & Piantadosi, 2019). In early life, vocabulary is key to educational attainment and represents a gateway to reading and learning over the lifetime (Masrai & Milton, 2018; Milton, 2013; Nagy et al., 2012). In older adults, vocabulary and semantic richness are the only cognitive skills that continue to grow, rather than decline, with age (Salthouse, 2019). The central role of vocabulary to learning and communication makes it key to academic, vocational, and social outcomes throughout a person's life.

Despite the importance of words across the lifespan, word learning in the field of speech-language pathology has largely been the purview of pediatrics and developmental language research (e.g., McGregor et al., 2002, 2007, 2020; Munro et al., 2012) and is understudied in adults with neurogenic communication disorders like traumatic brain injury (TBI). Studying word learning offers a unique window into memory and learning processes that unfold over time and in rich and diverse contexts (Horst, 2013; Klooster et al., 2020; Klooster & Duff, 2015; McGregor et al., 2007; Munro et al., 2012). Here, we briefly describe the word learning process and the unique opportunities afforded by studying each component and stage. We describe how word learning may underlie a variety of functional outcomes after TBI, making it a promising target for rehabilitation. Finally, we discuss principles that may guide study in this critical area to advance outcomes after TBI for children and adults. The empirical study of word learning and rehabilitation of word learning deficits in TBI present a promising new direction in understanding the breadth of neurogenic cognitive-communication disorders and improving long-term functional outcomes.

1.2 Word Learning is a Multifaceted Cognitive Process

Learning a new word is a complex and multifaceted phenomenon (Davis & Gaskell, 2009; Gupta, 2005). Fully knowing a word means recalling its spoken and written form, its conceptual meaning, and related morphology, syntax, and pragmatics. Foundationally, learning a word means remembering its form (e.g., *poodle* or pudəl), its meaning (e.g., curly-haired dog breed), and the arbitrary link between them (Davis & Gaskell, 2009; Gupta, 2012; McGregor et al., 2013). However, vocabulary is more than a bag of words; individuals must also learn how to combine and manipulate words to complete cognitive tasks and communicate effectively (Duff et al., 2020b; Klooster et al., 2020). Thus, a

disruption at the level of basic word learning can have catastrophic effects for vocabulary and the full range of communication.

Word learning takes place over time and in multiple stages (Dumay et al., 2004; Dumay & Gaskell, 2007; Klooster et al., 2020; McGregor et al., 2007; Munro et al., 2012). Encoding is the formation of a new memory (e.g., a new word). Over time, the new word may be forgotten, or it may strengthen and become established in the brain via a process called consolidation (McGregor et al., 2007; Munro et al., 2012). Through consolidation, a new memory becomes independent of the hippocampus and is stored in the neocortex, making it less vulnerable to interference from new information (Cohen & Banich, 2003). For example, a child may hear hundreds of words every day. A subset of those words might be encoded, but even fewer will become consolidated so that they become a part of the child's vocabulary and can be used later (e.g., to ask one's parents for a poodle). Thus, consolidation is a critical learning phase for long-term retention, flexible use, and the formation of one's vocabulary (Cohen & Banich, 2003).

Word learning is also iterative. Each time a child retrieves and uses a word, the representation of that word is changed and strengthened (Cohen & Banich, 2003; Duff et al., 2020b). Studies in children and adults show that multiple exposures and diverse opportunities for retrieval support learning, consolidation, and incorporation of new information into a person's existing knowledge base (Goossens et al., 2014; Gordon, 2020; Horst, 2013; Middleton et al., 2019; Stark et al., 2005). For example, hearing and using a word in different contexts and at different times supports the incorporation of that word into one's vocabulary.

Mental representations of words do not exist in isolation. Rather, vocabulary involves understanding the rules and statistical regularities among words to create grammatical and meaningful utterances (see Duff et al., 2020b for review). A single word can have multiple meanings or senses, multiple words can mean the same thing (i.e., synonyms), and combinations of words can take on meanings beyond the meanings of the individual words (i.e., metaphors) (Duff et al., 2020b). Through experience and exposure, the acquisition of individual words and the relations among them creates a vast network of vocabulary that speakers draw on to create novel combinations for expressing and negotiating meaning.

1.3 Word Learning Requires a Confluence of Memory Systems

Multiple memory systems support different elements of word learning (Davis & Gaskell, 2009; Gupta, 2005, 2012). Binding a word's form to its meaning requires the declarative memory system to support the linking of two elements with no perceptual ties (Davis & Gaskell, 2009; Duff et al., 2020b; Klooster et al., 2020). Declarative memory, which depends critically on the hippocampus and medial temporal lobes, binds arbitrary elements of an experience (e.g., word forms and meanings, memory for facts and experiences, world knowledge) into lasting mental representations and facilitates the use of those representations in novel contexts (Eichenbaum & Cohen, 2001). The flexibility of the declarative memory system underlies not only the learning of words, but also

understanding how words can be used and combined functionally. For example, the declarative memory system supports both the ability to remember a word's meaning and to use the word in new sentences and contexts (e.g., if a child learns that a cute dog is called a "poodle" and later asks her parents to get a "poodle" as a pet, or distinguishes Artie the poodle from Gus the poodle) (Duff et al., 2020b).

As a complex behavior requiring the confluence of multiple memory systems, word learning makes a fascinating target of study. Although the declarative memory system is central to word learning, other memory systems also contribute. For example, word learning requires declarative, non-declarative, and working memory at the time of initial encoding (to learn the sequence of sounds that make up a word's form, its meaning, and bind them together) (Davis & Gaskell, 2009; Gupta, 2012). Strengthening a word's connections with existing vocabulary is also a learning process that requires memory. Prior work by our research group supports the claim that declarative memory is key to adding a word to a person's lexicon and strengthening its ties with existing word representations (Covington & Duff, 2016; Duff et al., 2020b; Hilverman & Duff, 2021). Although many clinical interventions are aimed at targeting memory systems in isolation, real world cognitive communication involves systems working in concert, in cooperative or competitive ways, to guide complex behavior (Eichenbaum & Cohen, 2001; Poldrack & Packard, 2003). Word learning offers a clinically relevant target that leverages those dynamics in a cognitive domain (memory) that is critical for rehabilitation.

1.4 TBI Impairs Memory Systems Critical for Word Learning

The memory systems that support word learning in neurotypical individuals are among the most vulnerable to TBI. The hippocampus and medial temporal lobes, which critically underlie the declarative memory system and word learning, are highly exposed to external injury mechanisms (Bigler et al., 1996; Palacios et al., 2013; Rabinowitz & Levin, 2014). In fact, declarative memory deficits are consistently identified in both empirical studies and patient report as major disruptors to daily life after TBI (Rabinowitz & Levin, 2014; Vakil, 2005; Velikonja et al., 2014). The importance of the declarative memory system for word learning and the prevalence of declarative memory deficits after TBI suggest that word learning deficits are likely common after injury. Yet, this foundational skill is under-studied in TBI. It is unclear when, how, and why word learning breaks down in TBI. Understanding which components of word learning are affected by TBI is key to designing interventions that improve word learning and functional outcomes after brain injury. This knowledge could also support leveraging the interactions of memory systems involved in TBI both directly (e.g., supporting the non-declarative memory system to compensate for impaired declarative memory) and indirectly (e.g., leveraging external factors like timing of encoding, sleep, and exercise that may support learning). Given its potential as both a single rehabilitation target and an avenue to understand the interactions of multiple memory systems after TBI, we propose that word learning should be a primary target of study for improving functional outcomes after brain injury.

1.5 Word Learning May Support Functional Outcomes in Traumatic Brain Injury

Approximately 6.2 million Americans currently live with disability related to TBI, with significant inter-individual variability in functional outcomes (Centers for Disease Control and Prevention, 2015; Dahdah et al., 2016). For example, some people return to work after injury, but more than half do not (Gormley et al., 2019). Some people report that their lives are largely unchanged after brain injury, but people with a history of TBI also face increased risk for social isolation (Rigon et al., 2019), housing insecurity (Stubbs et al., 2020), interpersonal violence (Ivany & Schminkey, 2016), and interactions with the legal system (McIsaac et al., 2016). This heterogeneity in post-injury trajectory presents a significant challenge in outcome prognostication and in targeting interventions to a given individual for the clinical management of TBI (Covington & Duff, 2020).

In parsing inter-individual variability after TBI, it is easy to imagine that intervening in even a single skill could improve a variety of functional outcomes. The importance of words to daily life persists after TBI, even as the cognitive systems that support the word learning process are disrupted. The ability to learn words and concepts is key to success in most workplaces (e.g., for learning new job-related skills or communicating with clients). Word learning is foundational to academic success for individuals who are in school or may wish to return after injury. Learning words and concepts is also key to making a successful transition to a new setting. For example, if a person is unable to return to the same job after TBI due to physical or cognitive limitations, learning words and concepts is a prerequisite of the vocational rehabilitation process and transitioning into a new position. Given increased focus on supporting individuals with cognitive-communication deficits in their communications with medical providers and in the legal system (Wszalek, 2021), it is critical to note that the ability to learn new words and concepts is key to understanding medical and legal jargon and self-advocating in these settings.

A disruption in word learning could have significant implications for outcomes in a variety of spheres, making word learning a key target for advancing long-term community-based outcomes after injury. Focusing on word learning in rehabilitation may support the identification of functional rehabilitation targets, e.g., considering the types of activities that people must engage in to be successful at school or work. Thus, targeting interventions around word learning may improve the precision of rehabilitation to improve community outcomes more broadly.

1.6 Principles and Opportunities for Studying Word Learning in TBI

There is an established word learning literature that is ripe for adaptation to studying this process in TBI. Because word learning plays out in multiple components and phases, a single-visit study is inadequate to capture all elements of the process (Dumay et al., 2004; Dumay & Gaskell, 2007; Klooster et al., 2020; McGregor, 2014;

McGregor et al., 2013). Studies providing multiple opportunities to demonstrate knowledge of word elements (e.g., form, meaning) and multiple time points for retrieval are the strongest in fully depicting word learning and the factors that influence it over time. For example, a study in which individuals learn words and then are tested on those words over the course of a week may capture consolidation patterns that are key to rehabilitation. If the gap between a group of individuals with TBI and their neurotypical peers were to grow with time over the course of a study, such a finding may suggest that individuals with TBI are not only impaired at encoding new words, but also do not consolidate words at the same rate as their neurotypical peers. A single-timepoint study would be inadequate to capture this pattern, potentially leading to interventions that are designed on incorrect or incomplete information about what participants will remember in the long term. A study that did capture the pattern of learning over time could lead to more appropriate interventions aimed at increasing retrieval and exposures to support disrupted patterns of memory consolidation.

Word learning is not unimodal and thus requires multi-component study designs (Davis & Gaskell, 2009; Gupta, 2005). For example, a post-test in a word learning study should assess multiple aspects of word learning and provide a range of opportunities for success. A mix of free recall tasks and cued recall tasks allows participants who cannot recall a full representation of a word (i.e., on a free recall task) to demonstrate some knowledge on a cued recall task (e.g., by choosing that form from a field of two on forced choice). A post-test should also include tasks designed to separately assess recall of word forms, word meanings, and the links between them. This design allows assessment of which basic elements of word learning are disrupted immediately at encoding and later at consolidation. Individuals or groups could show distinct patterns of deficits, which would inform specific intervention directions. Studies may also advance knowledge of word learning after TBI by studying semantic integration at the usage level in two potential areas: 1) tasks designed to assess which learned words integrate and relate to other words into a person's lexicon (Tamminen & Gaskell, 2013) and 2) designs assessing which new words are available and used across communicative settings (i.e., in conversation). Such an exploration moves beyond basic memory processes to examine how newly learned words integrate functionally with a person's existing lexicon.

1.6.1 Manipulating Behavioral and Lifestyle Interventions to Improve Word Learning

Studying word learning may also underlie future work aimed at capitalizing on external factors to support memory and learning broadly after TBI. There have been no measurable gains in improving post-TBI memory outcomes through direct restorative interventions for decades (Roozenbeek et al., 2013; Vakil, 2005; Velikonja et al., 2014). Therefore, it is appealing to understand how external factors that support memory in neurotypical individuals (e.g., sleep, exercise, gesture, multiple retrieval opportunities spaced out over time (Clough & Duff, 2020; Erickson et al., 2011a; Middleton et al., 2019; Morrow & Duff, 2020)) do or do not support memory in TBI. Some of these factors may represent malleable targets that can improve memory and learning after brain injury.

The word learning literature has established paradigms for testing the role of other systems in word learning (Dumay & Gaskell, 2007; McGregor et al., 2013; McGregor & Alper, 2015). For example, participants may learn words in two conditions: just before going to bed (so that they slept before their first post-test) and in the morning (so that they did not sleep before the first post-test) (Dumay & Gaskell, 2007; McGregor et al., 2013). Examining differences between these conditions may elucidate whether timing learning around sleep confers a significant sleep-learning benefit in a clinical population, as it does in neurotypical individuals (Morrow & Duff, 2020). The same design could be applied using the manipulation of other factors that support learning in neurotypical individuals, like exercise. Use of this multi-post-test paradigm, in concordance with manipulating an external factor that could support memory, could open the door to external interventions in a manipulable area to improve memory after TBI.

1.7 Pediatric Populations, Word Learning, and Academic Achievement

Although this manuscript focuses on word learning in adults, there is also a robust literature on studying word learning in pediatric populations (McGregor, 2014; McGregor et al., 2002, 2007; Munro et al., 2012). Studying word learning in children with TBI using these existing paradigms may be particularly impactful, as TBI during the developmental years disrupts learning and academic performance long into the future (Ylvisaker, 1998; Ylvisaker, Adelson, et al., 2005; Ylvisaker et al., 2003, 2007). Given the importance of word learning to academic achievement, understanding how and when word learning is affected after pediatric TBI may support future interventions that help children with TBI to return to the classroom more successfully. Considering the role of other systems (e.g., sleep, exercise) in learning via multi post-test study designs may also increase academic success in children with TBI. For example, based on recommendations from the American Academy of Pediatrics, school districts across the country have delayed start times to better match students' circadian rhythms, with initial success in boosting academic achievement (Dunster et al., 2018). Early work has also identified the benefits of exercise for learning words in school-aged children and could be extended to explore how exercise supports long-term word retention (Pruitt & Morini, 2021). Thus, understanding word learning after pediatric TBI, and how other systems support it, may underlie future interventions that improve learning and academic success for children whose development is disrupted by brain injury.

1.8 Conclusions

Given the critical role of vocabulary in communication and achievement throughout a person's life, studying word learning in TBI is a vital opportunity to explore a potential driver of functional outcome and impactful rehabilitation target. Considering word learning in its full complexity in study design allows for assessment of the

contributions of multiple cognitive systems to the learning process, as well as how other manipulable factors (e.g., sleep, exercise, retrieval opportunities) influence learning. Resultant findings could guide future clinical decision-making that could directly support improved memory, learning, and functional outcomes for individuals with TBI across the lifespan.

Chapter 1: Main Conclusions, Opportunities, and Open Questions

Word learning is key to success in functional spheres across the lifespan. The importance of words to daily life remains after TBI, even as the memory systems that support word learning are disrupted.

Word learning is a complex cognitive process that requires the confluence of multiple memory systems over several learning stages. Thus, researching word learning presents the opportunity to parse the relative contributions of multiple memory systems to different phases and components of word learning, in both neurotypical individuals and clinical populations. However, single-timepoint designs are insufficient to capture the full word learning process, which occurs over time and across contexts.

As a process that occurs over time, word learning presents an opportunity to assess the contributions of behavioral and lifestyle factors (e.g., sleep, exercise) to different memory phases. Understanding these interactions could drive clinical interventions aimed at improving memory through manipulable external behaviors.

The nature and severity of word learning disruptions in TBI are open questions. Given the critical role of vocabulary in communication and achievement throughout a person's life, studying word learning in TBI is a vital opportunity to explore a potential driver of functional outcome and impactful rehabilitation target.

2 Sleep Supports Memory and Learning: Implications for Research and Clinical Practice in Speech-Language Pathology

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2.1 Sleep's Role in Mental and Physical Health

Sleep is critical for mental and physical well-being. In addition to long-standing intuition, the role of sleep in health and wellness is increasingly evident in popular press (e.g., Arianna Huffington's bestseller *The Sleep Revolution*) (Huffington, 2017) and empirical science (e.g., a dozen articles focused on sleep published in the journal *Nature* in the last year alone) (McAlpine et al., 2019; Tall & Jelic, 2019). The fact that sleep matters is not news to any practicing speech-language pathologist (SLP). Every SLP, working in the schools or in a medical setting, has seen the therapeutic benefits of a well-rested client and has observed that the sleepy client cannot participate well in treatment. Indeed, SLPs frequently see the effects of sleep deprivation in therapy, given that sleep disturbance is concomitant with many developmental language disorders and neurological disorders (e.g., TBI, stroke).

Critically, recent developments in the neuroscience literature suggest that sleep disturbance may pose more pervasive and systematic challenges to our clients' progress, beyond just their participation in therapy. Research increasingly points to the importance of sleep quality and quantity to memory and learning (Batterink & Paller, 2017; Stickgold, 2005). All SLP interventions, whether we are addressing delays in normal language acquisition or working with clients to relearn skills following neurological injury, rely on our clients' capacity to learn (or relearn). Any systemic factors that affect these abilities demand our attention. If sleep quality and quantity is linked to our clients' memory and learning ability, then they are also critically linked to their treatment outcomes.

In this paper, we highlight key findings from the cognitive neuroscience of memory, the neurophysiology of sleep, and how they interact to benefit learning. We then discuss how this interaction affects learning for clinical populations, as well as the SLP's role in addressing the potential implications of sleep disturbance for therapy success.

2.2 Neuroscience of Sleep and its Enhancement of Memory and Learning

2.2.1 Cognitive Neuroscience of Memory

Memory is critical to intervention because it supports the acquisition, maintenance, and use of the knowledge and skills required to communicate and to be

successful at school, work, and in the community. Memory allows our clients to take advantage of direct interventions and to gain new knowledge or improve existing skills in therapy. Memory, however, is not a unitary function, but rather is composed of multiple functionally and anatomically distinct systems that support different aspects of knowledge and behavior (Eichenbaum & Cohen, 2001; Stickgold, 2005).

Broadly speaking, memory can be divided into short-term memory (retention of a period of seconds) and long-term memory (retention over longer periods of time) (Baddeley & Warrington, 1979; Cohen & Squire, 1980). Short-term (and working) memory play an important role in our ability to keep information active in our minds and in transferring information to long-term memory. Our focus in this discussion will be on long-term memory, as it is of particular interest to clinicians. That is, we want the skills and knowledge our clients gain in therapy to be used over long periods of time and in new contexts, not just in the treatment session itself. Many of the domains we treat depend on functions that are also supported by long-term memory (e.g., vocabulary; syntax; learning and utilizing compensatory strategies for dysphagia, dysarthria, or cognitive-linguistic deficits). Moreover, the bulk of the research on the benefits of sleep for memory and learning come largely from studies of long-term memory, suggesting that sleep may be critical to generalization and therapy success via this memory system (Antony & Paller, 2017; Stickgold, 2005).

Long-term memory can be broken down into declarative memory and non-declarative memory (see **Figure 1**). These memory systems are separated in the type of information processed, as well as the time course of memory formation and the flexibility of memory retrieval (Eichenbaum & Cohen, 2001). Declarative memory, which depends critically on the hippocampus and other medial temporal lobe structures, comprises the ability to acquire relational knowledge (such as semantic knowledge, temporal and spatial relationships, and information about the autobiographical events of our lives) and to use that information flexibly in novel contexts (i.e., generalization) (Cohen & Squire, 1980; Eichenbaum & Cohen, 2001). In treatment contexts, declarative memory is critical in learning new information such as vocabulary and facts, compensatory strategies, and names of therapists or co-workers and in using that information across new and varied settings. Non-declarative memory, which depends on the cortical and subcortical structures that support experience-dependent learning (e.g., basal ganglia), is an umbrella term describing priming, skill or procedural learning, and conditioning. Non-declarative memory supports skills and habits (including rules and sequences) that are learned unconsciously and incrementally (Cohen & Squire, 1980; Eichenbaum & Cohen, 2001). Unlike declarative memory, skills learned via non-declarative memory are inflexible in their recall and use (Reber et al., 1996; Ullman & Lovelett, 2018). Clients rely on the non-declarative memory system to learn routines or procedures and to acquire the sequences of sounds and rules that make up phonotactic knowledge and the grammar of a language (Ullman & Lovelett, 2018).

While these divisions and taxonomies of memory have held up for decades, it is important to note that more recent work in the cognitive neuroscience of memory literature has blurred some of the lines that differentiate memory systems. A key finding is that the hippocampus appears to contribute to a range of memory processes and tasks

that cut across the previously-established declarative and procedural division (Eichenbaum & Cohen, 2014; Rubin et al., 2017). For example, the hippocampus supports relational binding, or the linking of different elements of an experience in memory, even when learning unconscious, rule-based sequences previously attributed solely to procedural memory and the basal ganglia (e.g., statistical learning) (Covington et al., 2018a; Rubin et al., 2017). These newly-identified hippocampal contributions to multiple memory functions mean that any process affecting hippocampal function may be critical to learning and behavior across a range of domains. This expanded understanding of the role of the hippocampus across memory systems has implications for the link between sleep and memory, as the hippocampus may play a key mediating role in the relationship between the two.

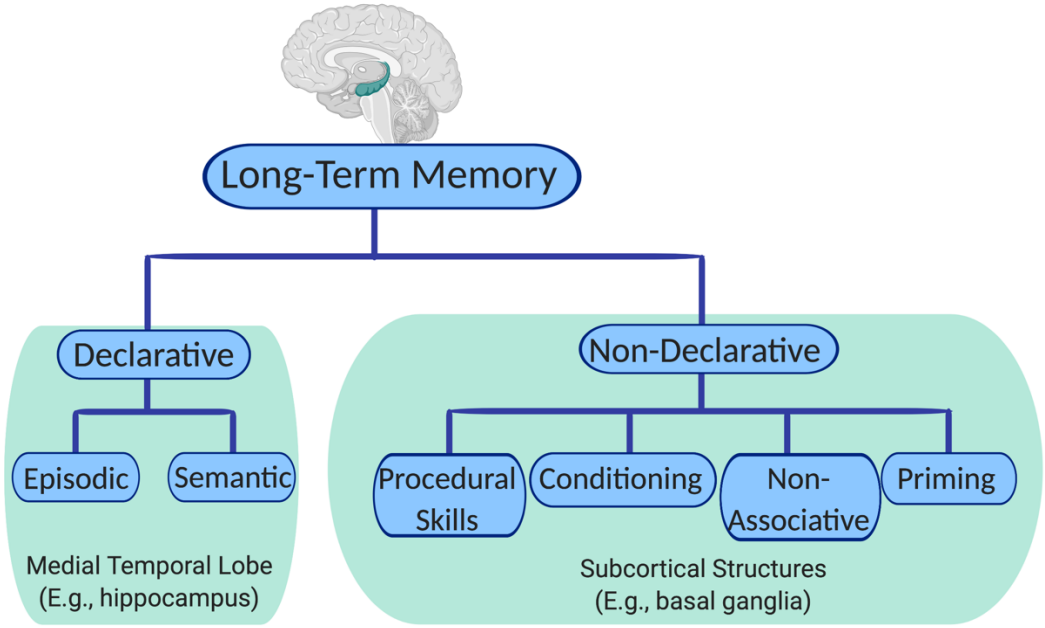

Figure 1 Taxonomy of long-term memory. The hippocampus is shown in blue. Adapted from Stickgold (2005) and Squire (1982).

Learning something new requires progression through at least three phases (encoding, consolidation, retrieval; see **Table 1**) (Eichenbaum & Cohen, 2001; Prince & Abel, 2013). Encoding involves converting a fact or experience into a memory that may be stored in the brain. Once a memory is encoded, consolidation is the process by which it is stabilized and strengthened so that it may later be retrieved and used. While the hippocampus plays a critical role in the initial encoding of new declarative (relational) memory, consolidation represents the process by which knowledge becomes independent of the hippocampus and is stored in the neocortex. The process of consolidation also makes a memory less vulnerable to interference from newly learned information (Antony

& Paller, 2017). For example, a young child might hear hundreds of new words in a day. Although many of those words may be encoded, only some of them will be consolidated, so that the child is later able to retrieve and use those words. The words that are consolidated will remain in the child's vocabulary, even as new words are encoded. Consolidation, then, is critical to learning and therapy success.

Memory Phases	
Phase	**Definition**
Encoding	The process by which a perceived item or event is converted into a mental representation, or memory, that can be stored in the brain.
Consolidation	The process by which memories become independent of the hippocampal system and are strengthened and stabilized in the neocortex.
Retrieval	The process by which we access a stored memory.

Table 1 Memory phases. Adapted from Cohen & Banich, 2003.

Reactivation of a memory trace is likely critical to the consolidation process. Whereas memories are initially vulnerable to interference and are dependent on the hippocampus, reactivation of the memory results in repeated interaction between the hippocampus and the neocortex. These repeated interactions strengthen, reorganize, and stabilize the memory, all of which support later retrieval (Antony & Paller, 2017). Memory reactivation may occur when the brain replays a memory during conscious or unconscious retrieval. For example, people who show a strong hippocampal-cortical response after learning (even without consciously retrieving the newly-learned information) are more likely to remember what they've learned later (Tambini et al., 2010). Just as it is involved in multiple memory systems, the importance of the hippocampus in new learning and consolidation suggests it may also play a critical role in therapy success.

2.2.2 Neuroscience of Sleep

Sleep is an active, dynamic cognitive process. A night's sleep contains multiple 90-minute cycles with distinct phases of brain activity. A person transitions from wakefulness to non-rapid eye movement (NREM sleep): light sleep in stages 1 and 2, followed by deep sleep (known as slow-wave sleep) in stage 3 (Stickgold, 2005; Wickwire et al., 2018). Before the cycle is complete, there is a subsequent return to light sleep, followed by rapid eye movement (REM) sleep. Circadian rhythms influence the occurrence of these phases, such that a person experiences more slow-wave sleep earlier in the night and more REM sleep in later cycles (Antony & Paller, 2017).

These stages differ not only in depth of sleep, but also in physiological properties (e.g., eye movements, muscle tone), neurological processes (e.g., regional brain activation

and communication between memory systems), and intensity of dreaming (see **Figure 2**) (Stickgold, 2005). Notably, NREM sleep, which comprises 75-80% of sleep, is a distinct and mutually exclusive neurophysiological state from REM sleep. Whereas REM sleep is characterized by chaotic, high-amplitude brain activation (similar to when a person is awake), NREM sleep is notable for slower, more synchronized neural activity. Stages 1 and 2 of NREM sleep involve a mix of high-amplitude activation (short bursts of activity known as sleep spindles), originating in the thalamus, and slower oscillations, originating in the frontal cortex. These signals transition to NREM Stage 3, or slow wave sleep, which represents the most synchronous neural stage, with slow, high-amplitude waves of activation viewed on EEG, in addition to ongoing sleep spindles (Antony & Paller, 2017; Wickwire et al., 2018). This slow wave, or deep sleep, comprises at least 20 percent of a person's total sleep time. This period is characterized by heavy interaction between the hippocampus and neocortex, with input from the hippocampus likely influencing the initiation and frequency of the neural activation waves (Wei et al., 2016). In REM sleep, the EEG shows higher-frequency, low-amplitude activity, although brain areas involving self-monitoring show dramatically lowered activity, and emotional areas reach higher levels than wake. Although early research on sleep was focused on what happens physiologically during each of these sleep phases, the question of how these changes affect health and cognition is now central.

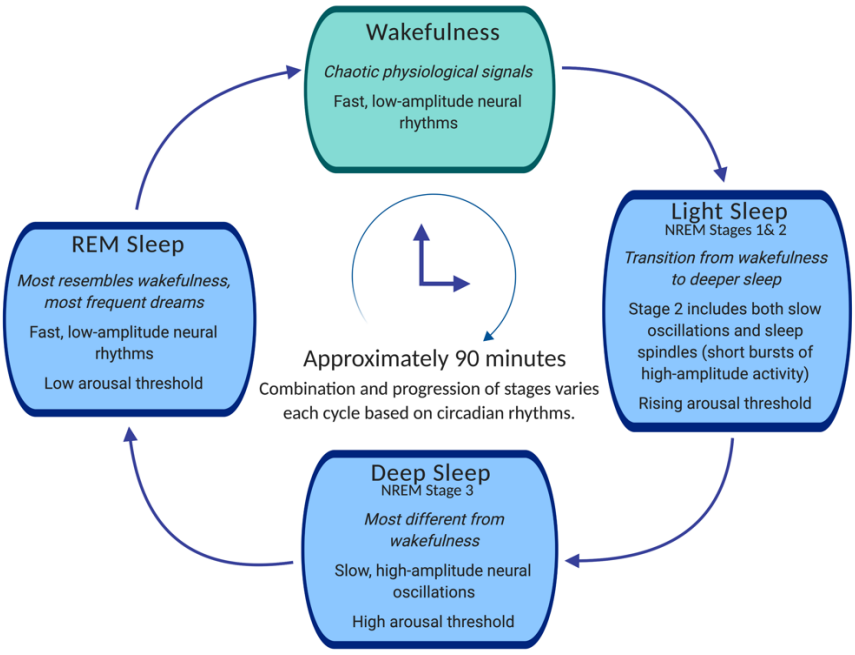

Figure 2 Phases of sleep cycle. Phases of REM (rapid eye movement) sleep and NREM (non-rapid eye movement) sleep combine differently in each cycle throughout the night based on circadian rhythms. Adapted from Antony & Paller (2017) and Stickgold (2005).

2.2.3 Sleep's Support of Memory and Learning

Converging evidence from behavioral, cellular, and systems neuroscience has increasingly implicated sleep in memory and learning (Stickgold, 2005; Antony & Paller, 2017). Specifically, although sleep may play a role in all phases of memory (Cousins & Fernández, 2019), memory reactivation during sleep has been most strongly implicated in the consolidation of newly-learned information (Antony & Paller, 2017; Stickgold, 2005). Although initial memory reactivation may also occur during wake, behavioral studies have shown that people who sleep after learning get a "learning boost" and are able to remember more information later (Jenkins & Dallenbach, 1924). This remembering has even been related to certain physiological properties of sleep. For example, learning has increased the density of spindles in subsequent sleep, and the density of those sleep spindles is related to performance on post-sleep memory tests (Gais et al., 2002; Schabus et al., 2004, 2008). Thus, memory reactivation during sleep is likely a significant contributor to the consolidation of new learning.

In neurotypical individuals, research has suggested that sleep supports nearly every type of memory. Sleep has been implicated in the formation and generalization of new long-term declarative memories, e.g., language learning (Batterink & Paller, 2017; Cousins & Fernández, 2019; Dumay & Gaskell, 2007; Gaskell et al., 2019; Jenkins & Dallenbach, 1924; Stickgold & Walker, 2013). Researchers have also linked sleep to procedural memory (Huber et al., 2004; Tamaki et al., 2008) and visual/auditory perceptual learning (Brawn et al., 2013; Frank et al., 2001; Stickgold et al., 2000). Sleep's role in multiple memory systems likely makes it critical to therapy success. For example, sleep after learning makes newly-learned vocabulary words less vulnerable to interference (Dumay & Gaskell 2007). When working on language learning or relearning with our clients, adequate sleep may play an important role in allowing them to retain and generalize new words. Memory reactivation and consolidation during sleep may also allow our clients to retain stabilized information acquired in our sessions for later use in novel contexts, making sleep critical to therapy success (McGregor & Alper, 2015).

Both sleep and memory consist of multiple phases, which interact in complex ways. The time course of memory reactivation during sleep and its place in the sleep cycle, however, remain under investigation (Mölle & Born, 2011; Prince & Abel, 2013). To date, REM, stage 2, and slow wave sleep have been implicated in memory reactivation during sleep, as the synchronous neural activation thought to support consolidation occurs during these stages (Stickgold, 2005). Recent research has suggested that certain sleep phases may be closely linked with specific memory systems, but the literature in this area is developing (Antony & Paller, 2017). For example, REM sleep has been linked to procedural learning, as deprivation of REM sleep negatively affects learning on operant conditioning tasks (Smith & Wong, 1991). However, newer evidence has also implicated slow wave sleep in learning for simpler procedural tasks (like visual sequence learning) (Huber et al., 2004; Landsness et al., 2009). Likewise, there is also evidence strongly implicating slow wave sleep in the consolidation of declarative memories. REM sleep has

been implicated in declarative memory for more complex information, such as full stories, but not in learning simple associations (Antony & Paller, 2017; Empson & Clarke, 1970). One possible explanation for REM sleep's role in cognition more broadly, which will require further investigation, is that REM sleep is critical for more complex tasks (such as learning full stories) but not simpler ones (such as learning simple associations or simpler procedural tasks) (Antony & Paller 2017). Like the cognitive neuroscience of memory literature, the literature on the interaction between sleep and memory is robust in its foundation (linking sleep and memory) but is evolving in further understanding the mechanisms and time course of this connection (Stickgold, 2005).

2.3 Consequences of Sleep Disturbance in Neurotypical Individuals

Sleep disturbance of any kind (see **Table 2**), in the absence of other co-morbidities, has been linked to structural brain changes and associated disturbances in functional cognition (Antony & Paller, 2017). For example, sleep deprivation has been linked to reduced hippocampal synaptic plasticity (or reduced flexibility of neurons to make new connections when a person learns something new). Because memory consolidation depends critically on new connections between the hippocampus and the neocortex, this reduced plasticity makes it more difficult for the brain to reorganize to accommodate new learning and form long-term memories (Cousins & Fernández, 2019; Prince & Abel, 2013; Yoo et al., 2007). Unsurprisingly given these neural effects, even

Clinical Sleep Disorder Categories	
Category	**Characteristics**
Insomnias	Inability to fall or stay asleep
Hypersomnias	Excessive sleepiness, falling asleep at inappropriate times
Sleep-Related Breathing Disorders	Difficulty breathing during sleep (e.g., obstructive sleep apnea)
Circadian Rhythm Sleep-Wake Disorders	Misaligned sleep schedule, such that one does not sleep at regular hours
Parasomnias	Unwanted events or experiences that occur while falling asleep, sleeping, or waking up
Sleep Movement Disorders	Movement during or prior to sleep, making it difficult to fall asleep, stay asleep, or get restful sleep

Table 2 Clinical sleep disorder categories. Adapted from National Healthy Sleep Awareness Project, 2019.

moderate chronic sleep deprivation has been linked to significant cumulative, dose-dependent declines in neuropsychological performance (Van Dongen et al., 2003). People with even mild sleep problems, or poor sleep habits, may have problems with cognition (especially attention and memory), in the absence of other diagnoses. In part due to this link between sleep and cognition, age-related sleep changes in neurotypical older adults (e.g., decreased slow wave sleep) may warrant clinical management and have become a frequent topic in the medical literature (Suzuki et al., 2017).

This neuropsychological decline with loss of sleep has been linked to changes in functional cognition. For example, sleep quality and quantity have been closely linked to student learning capacity and related academic performance across settings and age groups (Curcio et al., 2006; Eliasson et al., 2002; Sadeh et al., 2001; Trockel et al., 2000). The science around sleep and learning has led to recommendations from the American Academy of Pediatrics, among others, to delay school start times for middle and high schoolers to optimize learning depending on students' age, hormones, and resultant circadian patterns (Carskadon et al., 1998; Epstein et al., 1998; Owens, 2014). School districts around the country have acted on this knowledge by delaying school start times for high schoolers, with initial results indicating that delaying school start times by as little as an hour allows students to get more sleep and is associated with improved academic performance (Dunster et al., 2018; Neighmond, 2018).

Given the established role of sleep in health and cognition, the American Academy of Sleep Medicine has established a public awareness campaign regarding the importance of sleep for health (the National Healthy Sleep Awareness Project) to provide the general public with basic information regarding sleep's importance and sleep hygiene techniques (*National Healthy Sleep Awareness Project*, 2019). Sleep's established importance to memory and learning in people without neurological disturbance, and the related changes to public policy around this issue, raise the question as to what steps SLPs can take to improve sleep, memory, and learning potential in our clients.

2.4 Sleep Disturbance and Clinical Populations

Because sleep implicates so many neural systems, individuals with even mild damage or impaired development in associated structures are at increased risk for sleep disturbance (Sandsmark et al., 2017). Sleep's fragility means that sleep disturbance frequently co-occurs with a number of disabilities treated by SLPs, including developmental language disorder (McGregor, 2014; McGregor et al., 2013), autism (Liu et al., 2006; Schreck et al., 2004), Down syndrome (Carter et al., 2009; Levanon et al., 1999), Parkinson's disease (Chaudhuri et al., 2006; Kumar et al., 2002), and neurogenic disorders such as dementia with Lewy bodies (Murray et al., 2013; Turner et al., 2000), TBI (Dachtyl & Morales, 2017; Lundine et al., 2019; Mathias & Alvaro, 2012; Sandsmark et al., 2017; Wiseman-Hakes et al., 2019) and stroke (Hermann et al., 2008; Stern & Bachman, 1991). When sleep disturbance co-occurs with a condition, it may account for some of the delayed or aberrant learning associated with that condition. However, even when the primary disorder is not associated with memory impairment, sleep disturbance

may interfere with our clients' ability to participate in therapy, which is dependent on memory and learning ability.

Our colleagues specializing in developmental language disorders have noted that the link between sleep and learning may affect symptom presentation. There is a growing literature on how developmental language disorders frequently co-occur with disturbed sleep, as well as how sleep disorders interact with and/or disrupt language learning (Earle et al., 2018; McGregor, 2014; McGregor et al., 2013; McGregor & Alper, 2015). Even in children without diagnoses of developmental language disorder, those with reported sleep problems present with poorer language by parent and teacher report. This effect remains even after controlling for potential confounding factors, such as deficits in behavior or attention (McGregor & Alper, 2015; Quach et al., 2009). Given sleep's implication in memory consolidation, some researchers have explored consolidation of newly-learned language in adults diagnosed with language impairment. In studies of word form learning (McGregor et al., 2013) and speech sound learning (Earle et al., 2018), adults with language disorder performed comparably to neurotypical peers during training (encoding) but did not experience the same memory gains after overnight rest periods (consolidation), resulting in a gap in long-term recall of new language. Although research in this area is ongoing, these results suggest that impaired sleep, or a disturbance in memory reactivation during sleep, may contribute independently to deficits in language learning considered hallmarks of developmental language disorder.

Some preliminary work has also suggested that sleep disturbance may be associated with increased social skills deficits in autism (Schreck et al., 2004), which is of interest given the importance of memory and learning to appropriate social interaction. However, additional research will be required to determine the nature and direction of this relationship (Schreck et al., 2004).

An emerging literature suggests that a similar link between sleep disturbance and impaired learning may also exist for adult-onset neurological disorders. For example, this is especially salient for people with TBI, as current estimates indicate that approximately 50% of people with TBI have concomitant sleep disturbance (Duclos et al., 2014, 2017; Grima et al., 2017; Mathias & Alvaro, 2012; Ouellet et al., 2015; Ponsford et al., 2012). Despite the literature suggesting that sleep disturbance contributes to cognitive impairment in neurotypical individuals, the link between sleep disturbance and functional cognitive outcomes has not been fully explored in clients with TBI (Orff et al., 2009; Wickwire et al., 2016). To date, research on acute sleep-wake disturbances has suggested that sleep disturbance may be a contributor to duration of post-traumatic amnesia, as well as length of rehabilitation stay (Nakase-Richardson et al., 2013). A small body of evidence suggests that sleep disturbance associated with TBI exacerbates broader injury-related cognitive-communication disturbances, as measured via neuropsychological testing (Mahmood et al., 2004; Wiseman-Hakes et al., 2009, 2011, 2013). However, more investigation with larger sample sizes is needed to further elucidate the link between sleep and learning in individuals with TBI and the best intervention options to address it (Wiseman-Hakes et al., 2013).

Sleep disturbance has also been associated with adult-onset neurodegenerative diseases, such as Parkinson's disease (Chaudhuri et al., 2006; Kumar et al., 2002), and is a

common feature suggestive of dementia with Lewy bodies (Murray et al., 2013; Turner et al., 2000). More research will be needed to assess how sleep may contribute to progressive cognitive decline in these disorders.

2.5 Next Steps in Addressing Sleep Disturbance for SLPs

The basic science findings from research in neurotypical individuals relating sleep to cognition are robust, holding promise for advancing our knowledge of the relation between sleep and cognition in special populations. Yet, to date, there is a limited evidence base addressing sleep's effects on cognition outside of neurotypical populations. For example, in the field of TBI, there is growing evidence that brain injury affects sleep, but we know significantly less about how sleep disturbance may influence long-term outcomes in TBI and which interventions improve long-term outcomes related to sleep disturbance (Wiseman-Hakes et al., 2009). Given the literature linking sleep and learning in neurotypical individuals, more study is needed to better understand the nature of this link in individuals with developmental or neurogenic disorders to drive intervention planning.

Clinical Symptoms of Sleep Disturbance
Difficulty falling or staying asleep
Daytime somnolence (excessive tiredness or falling asleep during the day)
Shortness of breath or headache on waking
Irregular sleep and wake cycles
Irritability or anxiety
Difficulty concentrating

Table 3 Clinical symptoms of sleep disturbance. Adapted from Mayo Clinic, 2019.

Although interventions targeting sleep seem promising to support learning, there is a limited grade of evidence supporting use of these strategies. For example, preliminary casework has suggested the utility of integrating sleep self-report with medical and pharmacological intervention to address sleep disturbance in individuals with TBI (Wiseman-Hakes et al., 2011), although more work with larger sample sizes is needed. Exercise, which benefits sleep, has also been linked independently to memory and learning benefits (also due to its support of hippocampal function), suggesting that sleep is part of a complex web of interacting factors that influence memory and learning abilities in our clients (Erickson et al., 2011b). As we target this new frontier in addressing sleep as a systemic factor in memory and learning, researchers in the field of speech-language pathology have the opportunity to create an evidence base that will benefit clients across settings, ages, and disorders. In the meantime, clinicians should follow this literature as we develop our knowledge about the basic science of sleep, how it breaks down after injury, and how that breakdown underlies memory

and learning.

Although SLPs do not treat sleep disturbance, we play a critical role in recognizing the signs and symptoms of sleep disturbance (see **Table 3**) and making appropriate referrals, as undiagnosed and untreated sleep disturbance may limit our clients' success in therapy. Whether evaluating a child with developmental language disorder or an adult with a neurogenic communication disorder, SLPs should ask about sleep as part of a clinical protocol, consider its clinical effects, and refer clients for medical follow-up as warranted (McGregor & Alper, 2015). As clinical intervention strategies develop in the literature, SLPs can take an active role in client, family, and team education to share our knowledge about how sleep disturbance may affect memory and learning. All SLPs, regardless of setting or patient population, depend on our clients' ability to learn or relearn therapy targets. By considering how related factors affect memory and learning, we have the opportunity to take a whole client approach to maximizing therapy potential and functional progress. It is starting to look like sleep may be one of the key ingredients in treatment success.

Chapter 2: Main Conclusions, Opportunities, and Open Questions

Converging evidence from behavioral, cellular, and systems neuroscience highlights the importance of sleep as a memory and learning support. Getting more sleep and timing learning to occur just before sleep both promote long-term retention in neurotypical individuals.

Both sleep and memory depend critically on the hippocampus, which is routinely damaged in TBI. Hippocampal-neocortical interactions during sleep support the strengthening of memories in the brain. However, we do not know how hippocampal damage in TBI may affect the interactions of sleep and memory.

At least half of people with TBI report some form of sleep disturbance, but we do not know how sleep disturbance affects memory after TBI. There have been no studies to determine if people with TBI get the same sleep-learning benefit as neurotypical peers. Understanding the contributions of sleep to learning after TBI may support the targeting of future interventions aimed at capitalizing on the interaction of these two hippocampal-based systems

3 Matching Analytic Approach for Improved Precision in Cognitive-Communication Rehabilitation Research

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This manuscript is in revision at the *Journal of Speech-Language Hearing Research* (Morrow, Duff, & Mayberry, in revision).

3.1 Opportunities to Maximize Clinical-Translational Implications of Results in Cognitive-Communication Rehabilitation Research

Researchers in the field of communication sciences and disorders routinely ask questions about causality to understand relationships driving clinical outcomes and determine which treatments work (Duffy et al., 1981; Hayes & Rockwood, 2017). For example, a researcher specializing in cognitive-communication rehabilitation might assess whether a given treatment is effective in improving memory performance after traumatic brain injury (TBI). To identify the treatment effect, researchers typically assess how a given independent variable (e.g., the memory treatment being tested) is related to a given outcome or dependent variable (e.g., performance on a standardized or real-world memory task). To focus on the effect of interest (the effect of the independent variable on the dependent variable), researchers might treat other individual characteristics (e.g., demographic characteristics like sex or age, or behavioral characteristics like exercise or sleep) as noise by removing their associated variability from the statistical model (Schisterman et al., 2009). This gives researchers an idea of whether a treatment works at the group level, removing the effects of other characteristics that might affect treatment outcome. In other words, this approach provides the treatment effect for the average person in the study sample.

However, this common analytic approach may be contributing to the current reckoning in the field of cognitive-communication rehabilitation as to whether, and if so for whom, our existing treatments work (Lu et al., 2012; Spell et al., 2020). In rehabilitation research, we study *groups,* but we use the findings from those studies to treat *individuals*. Therefore, the most functional clinical research should tell us more than whether a given effect exists for an "average person" in the group of interest. When we adjust for individual characteristics in our models, we may be removing key clues that could help us to develop targeted treatment plans for our individual clients (Hayes & Rockwood, 2017). For example, we may conduct a clinical trial with a null result at the group level, when in fact the treatment worked well for some participants in the study sample (e.g., those in a certain age group). By contrast, a significant treatment effect in a clinical trial may reflect treatment gains in only a subset of the study sample, meaning that the treatment would only be appropriate for clients whose characteristics match that subgroup and should not be implemented in all clients with the overarching diagnosis.

Moreover, when studies of treatments show no effect on targeted outcomes, we do not maximize our learning from those studies if we move on to examine other treatments without considering the active ingredients producing our results (Hayes & Rockwood,

2017). If we adjust for the factors driving relationships between our independent and dependent variables, rather than including them as causal variables in our statistical models, we may not find a treatment effect when in fact it exists. Alternatively, if a treatment indeed was not effective, considering the conditions under which our treatment does or does not affect outcomes can inform next steps for intervention development. By testing treatments at the whole-group level without considering individual differences and factors that drive treatment outcomes, we risk setting aside treatments that may work, or over-prescribing treatments to a whole group when they will only benefit some members of that group (Covington & Duff, 2020; Hayes & Rockwood, 2017; Kraemer et al., 2001).

Fortunately, there is potential to maximize clinical outcomes from cognitive-communication research by implementing methods from the social sciences that provide information about factors that drive treatment outcomes and context for treatment success (Covington & Duff, 2020; Maas et al., 2012). For example, mediation analyses help us to understand the active ingredients that make a treatment work, and moderation analyses help us to determine which circumstances, contexts, or individual characteristics might make that treatment most beneficial. Understanding an effect's active ingredients and boundary conditions is at the heart of the push for precision medicine, in which treatments are not only matched to a patient's diagnosis, but also individual characteristics like genes, lifestyle, and environment (Denny & Collins, 2021). Given limited progress in developing successful treatments using a group-based approach in the last several decades (Lu et al., 2012), it is time that we extend this analytic approach, and combine it with larger sample sizes, to improve the precision of research and treatment in the field of cognitive-communication disorders.

Moving beyond group-level analysis is especially important for researchers interested in complex disorders like TBI, wherein population heterogeneity belies the efficacy of a one-size-fits-all approach (Covington & Duff, 2020; Maas et al., 2012). For decades, researchers have cited population heterogeneity and complex symptom interactions as barriers when treatments fail to stand up to assessment via clinical trial (Covington & Duff, 2020; Dahdah et al., 2016; Hart et al., 2014; Lu et al., 2012). However, a targeted approach using moderation analyses allows us to turn this thinking on its head by capitalizing on, rather than ignoring or adjusting for, this population heterogeneity (Hayes & Rockwood, 2017; Kraemer et al., 2001; Maas et al., 2012; Preacher & Hayes, 2008a). For example, using moderation analyses to identify meaningful clinical subgroups might allow us to mitigate health disparities (e.g., based on health literacy, socioeconomic status, or education) by ensuring that treatments work for patients across demographic categories (Kraemer et al., 2001; Mayberry et al., 2014, 2018). In addition, using mediation to investigate the active ingredients that make treatments succeed or fail can help us to learn from null findings and understand what targets are more or less important to ensure maximum effects in designing the next treatments and trials (Hayes & Rockwood, 2017; Kraemer et al., 2001).

Increased adoption of mediation and moderation approaches may accelerate progress in rehabilitation research at this critical time when our field must develop new, targeted treatment approaches that work. Importantly, these approaches can be

completed in steps, allowing preliminary mediation and moderation analyses to be completed in smaller sample sizes that are attainable for researchers studying cognitive-communication disorders and later confirmed in larger sample sizes once preliminary studies have determined the best allocation of resources. With this promise in mind, the dual goals of this tutorial are: 1) to increase awareness and use of mediation and moderation models in cognitive-communication rehabilitation research by describing options, benefits, attainable statistical approaches, and how to appropriately interpret and build on findings, and 2) to illustrate how these models may be interpreted so that clinicians may optimally apply research findings to enhance clinical care.

Although we focus on the field of cognitive-communication rehabilitation here as our area of expertise and a section of the field that urgently needs to implement new approaches for increased precision and progress, these principles apply to science and treatment across many communication disorders and have in fact gained traction in other heterogeneous clinical populations such as autism (Contaldo et al., 2020; Davis et al., 2011; Lombardo et al., 2019; Sievers et al., 2018). We hope that increased implementation of these analytic approaches will lead to faster advances in treatment design and improved outcomes for patients with cognitive-communication disorders.

3.2 Understanding a Variable's Role for Improved Analytic Models: Adjusting Isn't Enough

As statistical tests are agnostic to causation, conclusions made based on statistics rely on careful constraint of those tests by experimental design. When researchers are focused on identifying the presence or absence of a given effect (e.g., whether a treatment works), data analysis often involves a linear model assessing the relationship between the independent variable and dependent variable (Preacher & Hayes, 2008a). For example, researchers might use an ANOVA or regression model to assess the relationship between a manipulated variable like treatment condition, or a measured variable like time since injury onset, and performance on a neuropsychological assessment or real-world task. In many cases, in this standard linear model, researchers may "adjust" for individual differences, including demographic or behavioral characteristics that could affect treatment outcomes, by treating them as covariates or confounders. Although this is a common statistical approach, it is important to be selective in adjusting for variables that may explain part of treatment outcomes, as described below.

3.2.1 Including Covariates and Confounders to Assess the Relationship of Interest

A covariate affects the outcome variable but is not related to the independent variable (**Figure 3**) (Salkind, 2010). Covariates are included in models to enhance precision because they remove the variability in the outcome associated with the covariate, making it easier to identify the target effect (Bloom et al., 2007; Field-Fote, 2019; Fisher, 1949). For example, say that we are interested in how stroke and TBI differentially affect performance on a given memory outcome. We recruit two groups of people, half with a history of TBI and half with a history of stroke, to complete the

assessment. In this case, our independent variable (*X*) would be whether a person has a history of TBI or stroke, and our dependent variable (*Y*) would be performance on the memory outcome. In this model, researchers may treat time since onset as a covariate: time since onset may affect a person's performance on a memory outcome (*Y*), but it is not causally associated with the presence or absence of a TBI or stroke (*X*). It may be that a researcher would "adjust for" time since onset as a covariate to assess how TBI and stroke affect performance on the memory outcome, regardless of time since onset.

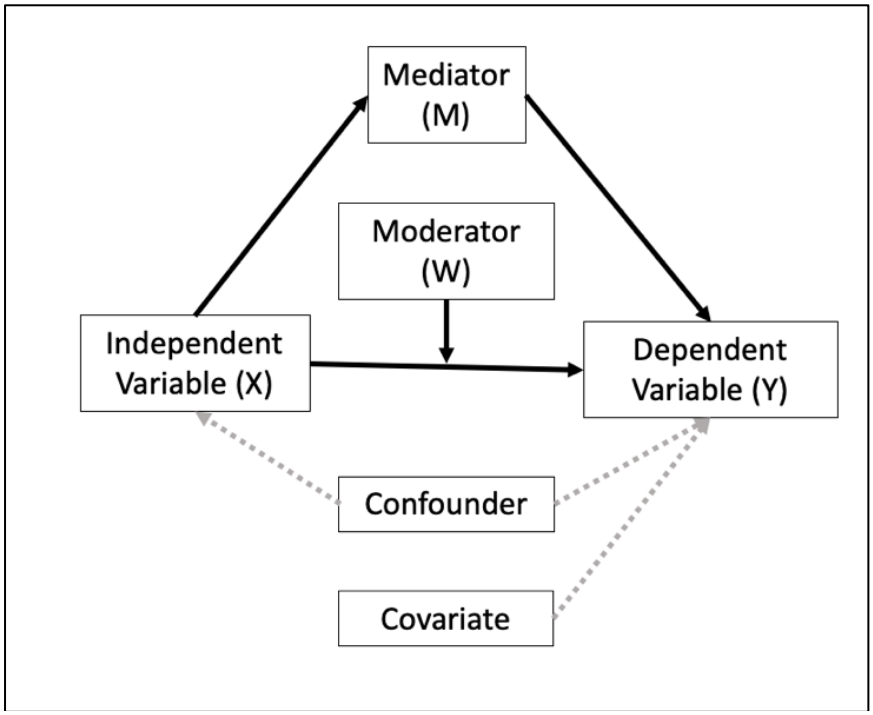

Figure 3 Relationships of variables to the independent variable (X) and dependent variable (Y). The causal pathway is in black. Mediators (M) lie on the causal pathway, such that X affects M, which then affects Y, and are a mechanism driving the relationship between X and Y (e.g., why a treatment works). Moderators affect the size or direction of the relationship between X and Y and determine the contexts in which X affects Y (e.g., under what circumstances or for what types of people). Covariates explain some of the variability in Y but are not related to X or on the causal pathway. Confounders drive variability in both X and Y but do not drive the relationship between them. Adapted from Field-Fote (2019).

In contrast, a confounder is causally associated with both the independent and dependent variables but does not drive the association between them (**Figure 3**) (Ananth & Schisterman, 2017; Field-Fote, 2019; Schisterman et al., 2009). Consider how age might play a role in the model from the above example. Increasing age is associated with both an increased risk of TBI and stroke (Kissela et al., 2012; Thompson et al., 2006) (*X*) and poorer performance on many memory outcomes (Grady & Craik, 2000) (*Y*). However,

TBI or stroke does not affect a person's age. Age might be driving some of the variation in both *X* (TBI or stroke diagnosis) and *Y* (memory performance), but it could not be causing the association between them. In this case, a researcher might treat age as a confounder and adjust for it in a linear model to remove age-related variability when estimating the association between TBI or stroke diagnosis and memory performance. This approach works best if the researcher does not believe that age is of interest for affecting the relationship between the independent and dependent variables; we need a different approach if it is (described below) (Ananth & Schisterman, 2017; Field-Fote, 2019; Schisterman et al., 2009).

Key Terms	
Covariate	A variable that affects the outcome/dependent variable but is not related to the independent variable. Covariates are included in models to enhance precision because they remove the variability in the outcome associated with the covariate, making it easier to identify the target effect.
Confounder	A variable that is causally associated with both the independent and dependent variables but does not drive the association between them. Researchers often adjust for confounders in linear models to remove their associated variability from the outcome.
Overadjusting	Treating a variable as a covariate (i.e., adjusting for it to remove its variability from the model) when it is on the causal pathway or is of interest in affecting the relationship between independent and dependent variables. Overadjusting risks slowing progress in clinical-translational research when we may instead gain valuable information by analyzing variables of interest as mediators or moderators.

Table 4 Key terms for variable types.

3.2.2 Choosing Covariates Wisely for a Targeted Analytical Approach

We make some key assumptions when we adjust for a variable as a covariate or confounder: 1) we assume that the covariate/confounder is not causing the association between our independent and dependent variables, and 2) we assume that the covariate/confounder is not of clinical interest for affecting the relationship between our independent and dependent variables. We may be ignoring key information when we take this approach in violation of those assumptions, which slows our progress on patient outcomes.

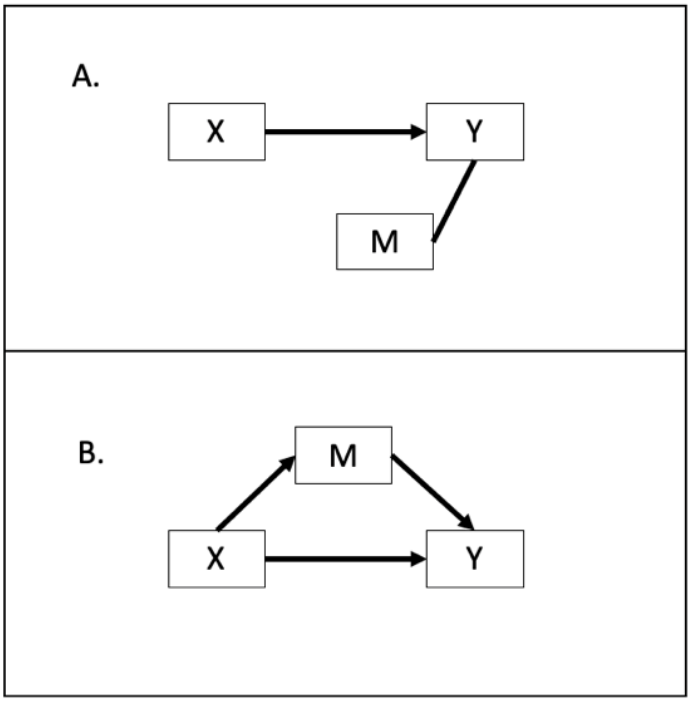

Figure 4 A) A standard linear model, in which the independent variable (X) affects the dependent variable (Y), and researchers adjust for a covariate (M). B) If M explains part of the relationship between X and Y, it is on the causal pathway and should be treated as a mediator, not adjusted for as a covariate.

Consider another potential variable in our example: the amount of exercise a person gets in a week might affect memory performance (Erickson et al., 2011b). In a standard linear model, a researcher might adjust for exercise as a covariate to assess whether TBI affects memory performance without the effects of exercise (Figure **4A**). But what if exercise is, in fact, a key part of the picture? Maybe TBI causes people to exercise less, and this reduction in exercise in turn affects memory performance. In this case, exercise is on the causal pathway: our independent variable (*X*, TBI) affects exercise (*M*), which in turn affects our dependent variable (*Y*, memory performance, Figure **4B**) (Preacher & Hayes, 2008a; Schisterman et al., 2009). If exercise is on the causal pathway, we should treat it as a mediator (as described below) instead of a covariate, to account for its role in explaining the relationship between our independent and dependent variables.

3.3 Matching Analytic Approach: Treating Variables of Interest as Mediators and Moderators

3.3.1 Mediators Are Stops on the Causal Pathway

A key piece of determining a variable's appropriate role in a statistical model is understanding its place on the causal pathway. In the above example, exercise is an intermediate variable on the causal pathway because TBI (*X*) may affect how much a

person exercises (*M*), which in turn affects memory performance (*Y*). Mediation, by definition, requires the causal assertion: the assertion that the independent variable (*X*) is a theoretical cause of the mediator (*M*), which in turn affects the dependent variable (*Y*) (Hayes & Rockwood, 2017).

3.3.2 Risks of Overadjusting for Variables on the Causal Pathway

Treating variables on the causal pathway (mediators) as covariates is counterproductive to our goals. If we control for exercise when it is on the causal pathway, we remove key explanatory power from our model and bias our results towards the null (Schisterman et al., 2009). For example, if TBI by itself explains 25% of variability in memory performance, and exercise explains another 50%, a model that includes exercise on the causal pathway will explain 75% of variability in memory scores. If we treat exercise as a covariate and adjust for it, we remove the variability that it explains from our model, thereby only explaining 25%/75%, or 33%, of the variability in our outcome. This form of overadjustment, or treating a variable as a covariate when it is on the causal pathway, may be key to understanding why many clinical trials in cognitive-communication research do not have significant results, as we may be removing variables that explain part of the target effects (Schisterman et al., 2009).

3.3.3 Using Mediation Models to Maximize Learning in Clinical-Translational Research

Instead of overadjusting, mediation analysis helps researchers to understand why treatments work and to improve them (Hayes & Rockwood, 2017; Kraemer et al., 2001). Continuing the above example, if exercise is on the causal pathway and mediates the relationship between TBI and memory, then researchers might design an intervention to target exercise as a path to improving memory after injury. The researchers could then use a mediation framework to assess a) whether the intervention effectively increased exercise and b) whether the intervention's effect on memory worked through the increase in exercise, and to what extent. The mediation model provides key context to accelerate and maximize what we learn from a study. If there were no mediation model, and the intervention did not improve memory, it would be unclear if the intervention did not increase exercise or if it increased exercise, but doing so did not result in memory gains. Findings from the mediation model would help researchers to design their next study iteration if the initial design failed to improve memory, as they would know whether the new version of their treatment needed to be better at improving exercise or if they needed to add other components in addition to or instead of the exercise intervention to improve memory.

Importantly, mediation modeling is not limited to intervention research. A researcher can still make and test the theoretical causal assertion about a variable that is measured and not manipulated (e.g., keeping track of the amount of exercise without manipulating it, then assessing it as a mediator of memory performance after TBI) (Hayes & Rockwood, 2017; Preacher & Hayes, 2008a). This observational research often guides design future treatment studies.

3.3.4 Moderators Are Key to Understanding Context

In some cases, a variable that is not on the causal pathway may prove crucial to creating a model that explains outcome variability. A moderator is not on the causal pathway but interacts with the independent variable in a way that influences the outcome (**Figure 5**). A moderator determines the context (*under what circumstances*, or *for what types of people*) in which an effect exists or does not, and in what magnitude (Field-Fote, 2019; Hayes & Rockwood, 2017). A moderation model differs from controlling or adjusting for a covariate in that it asks what effect a treatment has on outcomes *at different levels of the moderator*, whereas adjusting for a covariate asks what effect the treatment would have on outcome *if the value of the covariate was held constant*. Thus, a moderation analysis allows us to identify meaningful conditions under which an effect is strongest in keeping with the principles of precision medicine (Denny & Collins, 2021; Kraemer et al., 2001).

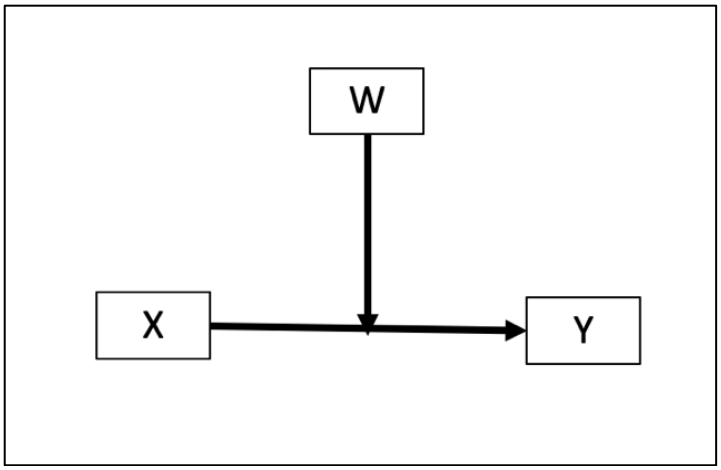

Figure 5 The moderation model. The moderator, W, determines the direction or magnitude of the effect of independent variable X on dependent variable Y.

3.3.5 Risks of Removing Key Variables of Clinical Interest from the Model

We may have inaccurate results for trials in heterogeneous populations when we adjust for variables that could be of key interest to the clinical picture without considering them as moderators. Say, for example, that we have designed a memory intervention for people with TBI and will test it in a group of 100 people with TBI, 50 of whom also have a diagnosis of depression (which can also affect memory (Burt et al., 1995)). The treatment is not very effective for people who also have a diagnosis of depression, with an effect size of .10 which is not statistically significant, but it is effective for those who do not, with an effect size of .45 and a *p* value indicating significance at <.05. If we conduct a study on this entire group and adjust for depression diagnosis instead of assessing it as a meaningful contributor to the treatment's effectiveness, we will identify a relatively modest effect size of .33 for our treatment (.10 x 35% + .45 x 65%). From this, we might conclude the treatment was moderately effective, and it may be incorporated into clinical care. However, if we recognize depression as a moderator, we

will learn that our treatment is more effective in people who do not have depression and not at all effective in people who do. From this knowledge, we would proceed differently: we may move forward refining and applying the treatment for adults who do not have depression and designing a different intervention for those who do. There is incentive, then, to use moderation analyses to identify meaningful clinical subgroups and optimize treatment success.

Key Terms	
Causal assertion	The assertion that the independent variable is a theoretical cause of the mediator, which in turn is causally associated the dependent variable. The causal assertion is necessary to consider a variable a mediator.
Mediator	A variable driving the association between the independent and dependent variable. By definition, a mediator must lie on the causal pathway, such that the independent variable is causally associated with the mediator, which in is causally associated with the dependent variable. Mediation analyses help us to understand the mechanisms by which treatments do or do not work.
Moderator	A variable that determines the context (*under what circumstances*, or *for what types of people*) in which an effect exists or does not, and in what magnitude. A moderator does not cause the association between the independent and dependent variables (i.e., does not lie on the causal pathway), but it interacts with the independent variable to determine the nature of their association. Moderation analyses help us to understand the contexts or subgroups in which treatments work best.

Table 5 Key terms for mediation and moderation analyses.

3.3.6 Using Moderation Analyses to Increase the Precision of Clinical-Translational Results

Many variables that are treated as covariates or confounders in common linear models should be analyzed as moderators as well (Ananth & Schisterman, 2017; Schisterman et al., 2009). In fact, very few variables represent "noise" when assessing a treatment effect, although there may be theoretical reason to adjust for some of them. When a variable affects our treatment outcome but is not our independent variable, we should ask if that variable could be key to the clinical picture before adjusting for it. For example, both age and time since onset (from our covariate and confounder examples above) could affect whether a treatment works for certain subgroups of a sample. The

same is true for study conditions; rather than adjusting for when a treatment is administered (e.g., time of day, or location of administration), it might be important to assess whether participants scored better in a certain context (e.g., in the morning or evening). This has particular significance for clinical-translational research, as many treatments are focused on translating gains made in controlled clinical environments to "real world" circumstances. Treating context as a moderator in analyzing outcomes can help us to determine if our treatments move beyond the controlled treatment setting in producing functional results. Moderation analyses can also be used to address healthcare disparities, e.g., by helping ensure that a treatment works for people of all ethnicities or levels of education (Kraemer et al., 2001; Mayberry et al., 2018). If, for example, a treatment works only for people with higher levels of educational attainment, we may need to assess the accessibility of our treatment materials.

In many cases, researchers may adjust for a variable to determine the group average treatment effect, then conduct a moderation analysis to identify meaningful subgroups that benefit more or less from the treatment. For example, researchers might adjust for education to estimate the overall treatment effect at the group's average level of education, then separately estimate the treatment effect for subgroups with higher and lower levels of education. This dual analysis approach allows researchers to both assess group average treatment effects and to conduct analyses based on meaningful subgroups that will result in tailored treatments that work better for individuals with complex, heterogeneous cognitive-communication disorders.

3.4 Designing a Theory-Based Model

Once a researcher determines a variable's theoretical role on the causal pathway, the next step is to match the analytic approach. Below, we provide some preliminary guidance for conducting mediation and moderation analyses in real-world settings.

3.4.1 Mediation: Modeling the Causal Pathway and Conducting Exploratory Path Analysis in Smaller Sample Sizes

To statistically model mediation, the gold standard model involves a path analytic framework using bootstrapping, a resampling method, to estimate the mediated effect (also called the indirect effect, or effect of *X* on *Y* that operates via mediator *M*) (Preacher & Hayes, 2004, 2008b; Zhao et al., 2010). Several "paths," or effect estimates, are critical for understanding and interpreting a mediation model. First, the total effect (*c* path in **Figure 6**) is simply the effect of *X* on *Y* (Preacher & Hayes, 2004, 2008b). This total effect can be decomposed into a direct effect – the effect of *X* on *Y* when adjusted for *M* (*c'* path in **Figure 6**) – and the indirect effect – the effect of *X* on *Y* via *M*. The indirect effect is a product of the *a* path and the *b* path (**Figure 6**). The *a* path is the effect of *X* on *M* (Preacher & Hayes, 2004, 2008b). In the intervention context, this path tells you if your intervention had the intended effect on the target (e.g., did your treatment increase exercise?). The b path is the effect of *M* on *Y*, adjusted for *X* (Preacher & Hayes, 2004, 2008b). In the intervention context, this path tells you if changes in M were associated

with changes in the outcome (e.g., was increased exercise associated with improved memory?).

The *c, c'*, *a* and *b* path estimates can use either a *p* value or confidence interval to determine statistical significance. *p* values rely on a normal distribution for the estimates. Because both the *a* and *b* paths have normal distributions, multiplying them with each other to obtain an indirect effect often results in a non-normal distribution. Therefore, bootstrapping is used to generate a confidence interval for the indirect effect, instead of a *p* value. A bootstrapped indirect effect with a confidence interval of 95% excluding zero provides evidence of mediation (Preacher & Hayes, 2004, 2008b). Estimating the indirect effect using bootstrapping requires a large sample size and can be conducted using any structural equation modeling program, most commonly the PROCESS macro in SPSS or SAS (Preacher & Hayes, 2004). Interested readers can learn more about mediation analysis using bootstrapping in more detail here: (Preacher & Hayes, 2008b).

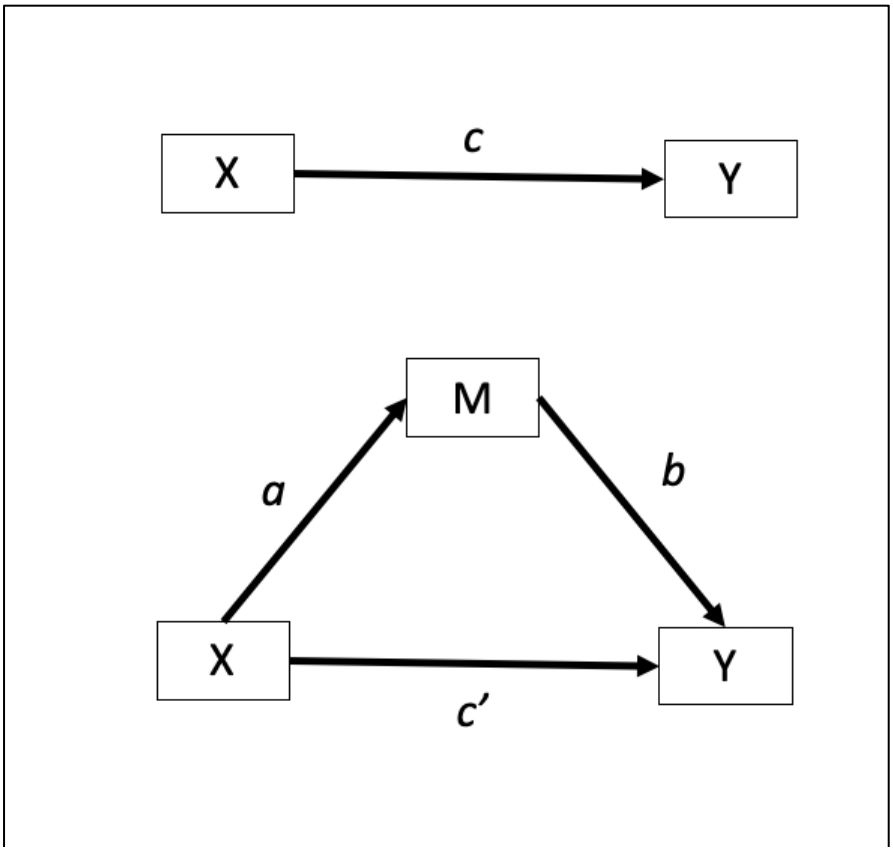

Figure 6 Analytic pathways in mediation model.

Exploratory analyses to identify potential causal factors/mediators can be illuminating even in much smaller samples, although they are preliminary and should be followed up with larger studies for confirmation. The underlying paths can be estimated with a series of four regression models to estimate the *c, a, b*, and *c*' paths (**Figure 6**) (Hayes & Rockwood, 2017). If the *a* and *b* paths are significant in the expected direction, the study has yielded preliminary evidence for mediation in the designated framework.

Common rules of thumb for regression models suggest number of predictor variables to sample size ratios of 1:15 to 1:20 for studies in which the effect size is expected to be at least moderate. Therefore, regression models underlying formal tests of mediation can be tested with samples as small as 30-40 (the *b* path and *c* paths require two predictors in the model, as they include both the independent variable and the mediator) (Austin & Steyerberg, 2015). Of course, if the effect size is expected to be smaller, or if additional covariates are needed in the models, they should be accommodated as well in the sample size calculation.

This exploratory analytic approach may allow researchers interested in rare disorders or smaller study populations, including many populations with cognitive-communication disorders, to determine where evidence for mediation exists and decide where to put their resources when developing treatments or pursuing larger studies aimed at more fully testing mediation using the bootstrapping method. Furthermore, in pilot intervention work, testing the *a* and *b* paths with regression can illuminate if the intervention is effectively improving the targets (e.g., *a* path, did we increase exercise?) and if it is the right target to improve (e.g., *b* path, was increased exercise associated with improved memory?) before running a large trial with null results.

3.4.2 Moderation: Interaction Effect and Subgroups Analysis in Smaller Sample Sizes

Moderation is tested with an interaction effect between the predictor and the moderator (*X* interacts with *W,* **Figure 5**). It is common for people to not look at potential moderators because they fear they are "underpowered to test an interaction effect." That is often true but does not preclude the ability to conduct preliminary analysis assessing which factors moderate an outcome.

For example, researchers may conduct preliminary analyses of meaningful subgroups without testing an interaction effect. In many cases, determining the effect size in each subgroup will give the researchers all the information they need to move forward with refining an intervention. The interaction term answers the question "is the difference in the effect size between the two groups (e.g., older and younger persons) significantly different from zero?," whereas the subgroups analysis answer the questions "what was the effect size in younger persons? What was the effect size in older persons?" or, stated more succinctly, "was the treatment effective in both subgroups?" Often the subgroups question is as interesting as the interaction question, particularly when working to develop and improve therapies for heterogeneous groups.

For example, if we were testing the efficacy of a memory treatment in TBI, it may be that participants who do not have a co-occurring diagnosis of depression benefit more from the intervention than those who also have depression. If our treatment has an effect size of .10 for people who also have depression and .45 for people who do not, we would need to be powered to detect an effect size of .35 (the difference between the two) to be "powered" to detect an interaction. If the study was designed to detect an overall treatment effect that was small to moderate (~.35), then it will not be powered to detect an interaction term of that same magnitude. However, in this scenario the magnitude of the difference between effects in people with and without depression is not the most

important result. What matters more is whether the treatment works both for people who do not have depression and those who do (whether there is a strong effect size in both groups), which can be determined without a study that was designed to test for an interaction effect.

Particularly when the moderator of interest is categorical and is roughly evenly distributed across the sample, the sample can be split for an exploratory subgroup analysis. In our example, the subgroups analysis would reveal that our treatment is not very effective for people who have a co-occurring diagnosis of depression, with an effect size of .10, but it is effective for those who do not have depression, with an effect size of .45. If researchers notice a big difference between the effect sizes they identify in each subgroup, they might move forward to directly test moderation with an interaction effect in a larger independent sample, but they could also work on developing the treatment for the groups that exhibited a larger effect size (those without depression) and identifying alternative treatments for the groups that did not experience a benefit (those who also have depression). It is important to note that separately examining effect sizes without the interaction term does not provide evidence of a difference between the two subgroups, but it does show if the treatment was effective for each of the subgroups separately. Thus, conducting an exploratory moderation analysis using subgroups makes this more attainable for researchers facing the practical constraints of conducting research in clinical-translational settings.

Before conducting a subgroups analysis on a continuous variable, it is critical to consider which differences produce meaningful, well-defined subgroups. For example, dichotomizing some continuous variables (e.g., income, such that one group has income below the poverty line and the other above) may produce meaningful subgroups for assessing treatment effects in some contexts. However, there is danger in dichotomizing a continuous variable without a meaningful reason to do so (Altman & Royston, 2006; Royston et al., 2006). For example, if we were hoping to determine if a treatment worked for both younger and older adults and split our groups at age 60 (i.e., people 60 and younger are in the younger group, older than 60 in the older group), the oldest members of the younger group and the youngest members of the older group would be more likely to experience similar treatment effects than to average-aged members of their assigned groups. Thus, dichotomizing age would be inappropriate, and we require an alternate analysis strategy. Using bootstrapping or Bayesian modeling (Stephan et al., 2009; Wasserman, 2000) to support simulations that examine a range of sample sizes and effect sizes for both the treatment and the moderator, which is beyond the scope of this paper, may be a more appropriate approach for estimating treatment effects in sample sizes that do not lend themselves to dichotomization but are underpowered for testing a moderation interaction effect.

3.5 Is it a Mediator or a Moderator?

How do you know if your variable should be examined as a mediator or a moderator? The causal assertion differentiates the two (Field-Fote, 2019; Hayes &

Rockwood, 2017). A mediator lies on the causal pathway between *X* and *Y*. A moderator, by contrast, affects the relationship between *X* and *Y* (e.g., changes the magnitude or direction of the effect) but does not form part of the causal chain linking them. Importantly, a mediator must vary with the independent variable (Hayes & Rockwood, 2017). Therefore, stable characteristics like sex or ethnicity are never mediators, as they cannot be caused by nor vary with the independent variable, but they may be important moderators. However, constructs such as behaviors, symptoms, and functional status often are potential mediators, but they could be moderators as well. In our example, TBI may affect the amount that a person exercises, meaning that it could lie on the causal pathway as a mediator. If findings indicate that TBI does not affect exercise (i.e., we do not find support for the causal assertion), we may then shift our research question to consider whether exercise might be a moderator. For instance, we may ask if exercise protects against the detrimental effects of brain injury on memory (i.e., people with brain injuries who exercise more do better on memory tests than people with brain injuries who do not). In this case, exercise is not a mediator but rather a moderator of the relationship between brain injury and memory.

Whether or not a specific behavior, symptom, or functional state is a potential mediator should be determined by the existing literature, prior research, and – most importantly – theory. It is certainly possible for mediators and moderators to coexist in the same model, or for there to be multiple mediators of the relationship between two variables (e.g., for both diet and exercise to mediate the relationship between TBI and memory) (Kraemer et al., 2001; Preacher & Hayes, 2007). Discussing analytic approaches for these multi-component models is beyond the scope of this tutorial, but researchers may consider building multi-component models in some cases when addressing the complexities present in many cognitive-communication disorders.

3.6 A Note on Statistical Power, Interpretation of Findings, and Team Science

In this tutorial, we have described some practical first steps to conduct *preliminary* mediation and moderation analyses for researchers who work with rare disorders and smaller sample sizes. However, these preliminary approaches are meant to inform the development and refinement of interventions for testing in larger sample sizes. Conducting a step-wise approach in which a treatment is first refined using preliminary analyses may allow researchers who work with smaller sample sizes to parse heterogeneity in smaller samples and direct resources for larger-scale studies to better-developed interventions. However, the first steps of the approach are not substitutes for the last (i.e., formal tests of mediation and moderation), and conducting preliminary analyses without careful follow-up could further contribute to replication challenges by sampling subsets of heterogeneous populations (Covington & Duff, 2020). Consequently, it may be prudent to combine preliminary mediation and moderation analyses with a team science approach in some cases. For example, smaller labs conducting preliminary analyses could feed information and data to larger initiatives aimed at sampling a more representative sample of a given population (e.g., large and well-designed registries for

patients with TBI (Duff et al., 2022)). By combining well-matched and practical analysis approaches with a collaborative model, we stand to make significant gains in improving treatment precision for the management of a variety of cognitive-communication disorders.

3.7 For Clinicians: Interpreting the Results of Mediation and Moderation Analyses for Clinical Practice

Mediation analyses tell clinicians where to focus to improve the results of their interventions (Hayes & Rockwood, 2017; Kraemer et al., 2001). For example, if another manipulable factor like exercise proved to be a mediator on the causal pathway between TBI and memory, clinicians might focus on increasing exercise to improve memory performance rather than attempting restorative memory treatments with limited proven efficacy (Lu et al., 2012). Understanding the factors that support treatment efficacy, then, gives clinicians the tools to adjust the focus of those treatments in real-world clinical settings.

A moderator, by contrast, tells clinicians who should get a treatment and under what circumstances (Hayes & Rockwood, 2017; Kraemer et al., 2001). This supports application of the principles of precision medicine to improve the efficacy of cognitive-communication treatment plans. In our example, clinicians should use our hypothetical memory treatment in individuals with TBI who do not have depression but consider another approach for those who also have depression and do not receive the same benefit. Further, we can use moderation analyses to ensure that our treatments work across groups. For example, if we determine that a treatment works for people with more educational attainment but not less, we might consider altering our materials so that they are digestible for a broader audience. This approach can increase our focus on equity by ensuring our treatments do not widen and perpetuate existing disparities by benefiting least the persons already at risk for worse outcomes.

When a study's analytic plan does not consider individual differences, it is unclear if subgroups differed in their response to a given treatment. In studies with high variability in treatment response within the sample, moderation analyses can help to determine if individual differences or meaningful subgroups drive part of that variability (Hayes & Rockwood, 2017). Designing an analytic plan that takes individual differences into account represents a key area for collaboration between researchers and clinicians, as clinicians may provide valuable insights as to which individual differences could be most meaningful and should be analyzed for driving treatment outcomes. Collaborating on these new analytic approaches could guide and advance thinking by reducing the research-to-practice gap in cognitive-communication disorders (Douglas & Burshnic, 2019; Olswang & Prelock, 2015).

3.8 Increasing the Use of Mediation and Moderation Models in Cognitive-Communication Rehabilitation Research

In a field that has made limited progress in developing successful interventions in the last several decades, it is critical that we harness mediation and moderation approaches to make sense of clinical-translational research results and to improve the precision of cognitive-communication rehabilitation research. Path analysis and subgroup analysis allow for preliminary assessment of mediation- and moderation-based hypotheses in smaller sample sizes that are more attainable in the field of cognitive-communication disorders. These analyses should be considered the first step in assessing the potential for mediators and moderators of treatment outcome and should be used to target resources for larger-scale studies to confirm effects (e.g., via team science and patient registries). Now is the time for researchers interested in cognitive-communication disorders to take steps toward selecting appropriate covariates and using mediation and moderation analyses to identify the active ingredients and contexts that affect treatment outcomes. A targeted analytic plan may be part of a framework underlying much-needed breakthroughs that result in treatments that work in diverse clinical populations with cognitive-communication disorders.

Chapter 3: Main Conclusions, Opportunities, and Open Questions

Common approaches to linear modeling may be slowing progress in cognitive-communication rehabilitation research. Adjusting for variables that represent meaningful differences in predicting treatment outcome may limit our ability to parse heterogeneity in complex clinical populations.

In rehabilitation research, we study *groups,* but we use the findings from those studies to treat *individuals*. The most functional clinical research is about more than establishing only whether a given effect exists for an "average person" in the group of interest. It is critical to understand the mechanisms by which a given treatment works (mediation), and to know which circumstances, contexts, or individual characteristics might make that treatment most beneficial (moderation).

Matching analysis approach may increase the precision of rehabilitation research results. For example, mediation and moderation analyses can be used to explore how symptoms interact to produce functional outcomes after TBI.

4 Sleep and Word Learning Over Time in Adults with Moderate-Severe Traumatic Brain Injury

4.1 Theoretical Introduction

Cognitive-communication impairment is a common and chronic consequence of TBI linked to negative outcomes in academic, vocational, and interpersonal realms (MacDonald, 2017; Ownsworth & McKenna, 2004). One central aspect of cognitive communication that is largely unexamined in TBI is word learning. Word learning draws on memory systems and processes that are routinely impaired in TBI (Bigler et al., 1996; Davis & Gaskell, 2009; Palacios et al., 2013; Rabinowitz & Levin, 2014) and is critical to a person's ability to benefit from therapy, to understand medical recommendations, and to participate in academic and vocational settings (MacDonald, 2017; Meulenbroek & Turkstra, 2016; Ylvisaker et al., 2003; Ylvisaker & Feeney, 1998). Deficits in the ability to learn words, concepts, and the relations among them could explain negative outcomes in many functional spheres. However, the nature and severity of word learning deficits in TBI are unknown.

Examining word learning over time presents a unique opportunity to explore how related systems interact with memory and learning and how those interactions may be affected by brain injury. Of particular interest recently has been the role of sleep in memory and learning, including the benefits of sleep for learning new words and concepts (Dumay & Gaskell, 2007; Gaskell et al., 2019; McGregor et al., 2013; McGregor & Alper, 2015). Although approximately half of individuals with TBI report sleep disturbance, the relation between sleep and learning in TBI has not been experimentally evaluated (Mathias & Alvaro, 2012; Morrow & Duff, 2020). This study fills a critical gap in understanding word learning in TBI and advances our basic understanding of the relationships between sleep, memory, and word learning.

4.1.1 Memory and Word Learning

Word learning is a complex and multifaceted phenomenon. At its most basic level, learning a word involves remembering its form (e.g., *cactus or* kæktəs), its meaning (e.g., desert plant), and the arbitrary link between them (Davis & Gaskell, 2009; McGregor et al., 2013). To fully know a word is to recall its spoken and written form and its conceptual meaning, as well as related morphology, syntax, and pragmatics (Davis & Gaskell, 2009; Gupta, 2005; McGregor et al., 2013) across variable contexts of use. Learning a word is a protracted process spanning days and weeks (Carey, 2010; McMurray et al., 2012), with additional information added over the course of the lifespan (Klooster et al., 2020). Thus, many lab-based word learning experiments where participants encode and subsequently retrieve newly learned words in a single session are inadequate to capture the full dynamic word learning process over time.

Learning a word's form, meaning, and the link between them requires the declarative memory system (Davis & Gaskell, 2009; Duff et al., 2020a; Eichenbaum & Cohen, 2001; McGregor et al., 2013). The declarative memory system comprises the

acquisition of relational knowledge (e.g., memory for facts, world knowledge, and autobiographical experiences) and the use of that knowledge in novel contexts (Eichenbaum & Cohen, 2001). This system depends on the hippocampus and medial temporal lobe structures to bind arbitrary elements of experiences into lasting mental representations (Eichenbaum & Cohen, 2001; Rubin et al., 2017). Critically, the hippocampal declarative memory system is frequently disrupted after TBI due to the hippocampus's vulnerability to injury mechanisms (Bigler et al., 1996; Palacios et al., 2013; Rabinowitz & Levin, 2014). The importance of the declarative memory system for word learning and the prevalence of declarative memory deficits following TBI (Bigler et al., 1996; Irimia & Van Horn, 2015; Palacios et al., 2013; Rabinowitz & Levin, 2014) suggest that word learning is an area of vulnerability with significant functional implications for individuals with TBI. However, this study is the first comprehensive evaluation of word learning, and its many components, in TBI.

4.1.2 Sleep Supports Memory and Learning in Neurotypical Individuals

Converging evidence from behavioral, cellular, and systems neuroscience highlights sleep as an important memory support. Sleep supports memory and learning across domains and throughout the lifespan (Antony & Paller, 2017; Morrow & Duff, 2020; Stickgold, 2005; Stickgold & Walker, 2013). Sleep disturbance, in the absence of other comorbidities, has also been linked to structural hippocampal changes and thus related disruptions in memory, learning, and functional cognition (Cousins & Fernández, 2019; Prince & Abel, 2013; Yoo et al., 2007). Even moderate chronic sleep deprivation has been linked to significant cumulative, dose-dependent declines in neuropsychological performance in healthy individuals (Van Dongen et al., 2003). The body of evidence highlighting sleep's support of learning has led to recommendations from the American Academy of Pediatrics to delay school start times to optimize learning around students' circadian rhythms, with initial results indicating that delaying school start times and allowing students to get more sleep is associated with improved academic performance (Carskadon et al., 1998; Dunster et al., 2018). Thus, sleep is critical to memory and learning in the neurotypical brain and may be a critical, and malleable, target to support memory and learning in patients requiring rehabilitation after neurological injury.

4.1.3 The Relation Between Sleep Disturbance and Learning in TBI is an Open Question

Sleep's support of learning may be particularly consequential for individuals with TBI (Lowe et al., 2020; Wiseman-Hakes et al., 2009). Current estimates indicate that many (~ 50% (Mathias & Alvaro, 2012) individuals with TBI report concomitant sleep disturbance, which may relate to quantity, quality, or variability of sleep (Duclos et al., 2014; Grima et al., 2017; Ouellet et al., 2015; Ponsford et al., 2012; Sandsmark et al., 2017). The literature indicates that individuals with TBI exhibit sleep disturbance across the time spectrum of recovery and levels of severity, with some individuals exhibiting sleep disturbance years post-injury (Wiseman-Hakes et al., 2009). However, estimates vary depending on patient characteristics, measures used, and duration of follow up (Duclos et

al., 2014; Wiseman-Hakes et al., 2009). For example, studies using patient report identify more cases of insomnia than those using objective measures of sleep (e.g., polysomnography, actigraphy) (Beaulieu-Bonneau & Morin, 2012; Duclos et al., 2014; Ouellet & Morin, 2006; Wiseman-Hakes et al., 2009). As studies have varied in their identification of sleep disturbance, delineation of injury severity, and stratification of time since onset, it is difficult to discern from the existing literature how each of these factors may affect sleep disturbance (Duclos et al., 2014; Wiseman-Hakes et al., 2009).

Despite the literature suggesting that sleep disturbance disrupts memory in typical adults, the link between sleep, memory, and learning in individuals with TBI has not been explored (Lowe et al., 2020; Morrow & Duff, 2020; Orff et al., 2009; Wickwire et al., 2018; Wiseman-Hakes et al., 2009). A limited body of evidence links sleep disturbance to increased duration of post-traumatic amnesia in the acute phase of injury and poorer neuropsychological outcomes, including attention and reaction time, in the subacute and chronic phases of injury (Beaulieu-Bonneau et al., 2017; Bloomfield et al., 2010; Mahmood et al., 2004; Nakase-Richardson et al., 2013; Sinclair et al., 2013; Wiseman-Hakes et al., 2011, 2013, 2019). However, to date there have been no studies to objectively measure sleep over time and relate it to an experimental learning measure in individuals with TBI.

4.1.4 Word Learning is a Window to Sleep's Contributions Across Learning Phases

Exploring how word learning develops over time represents a unique opportunity to identify sleep's contributions during each part of the learning process. Word learning takes place over multiple phases (Carey, 2010; Davis & Gaskell, 2009; McGregor et al., 2013). Encoding is the process of forming a new memory (Cohen & Banich, 2003; Eichenbaum & Cohen, 2001). Over time, the representation of the word may be forgotten, or it may strengthen and stabilize via consolidation. Consolidation is the process by which knowledge becomes independent of the hippocampus and is stored in the neocortex, making it less vulnerable to interference (Cohen & Banich, 2003; Eichenbaum & Cohen, 2001). For example, a child may hear hundreds of new words daily. Many of those words will be encoded, but only some will be consolidated so that the child can later retrieve and use them (thus becoming a part of the child's vocabulary) (Morrow & Duff, 2020). Consolidation, then, is critical to learning and long-term retention.

Research in neurotypical individuals has indicated that sleep makes unique contributions to each learning phase (Antony & Paller, 2017). Sleep is thought to be particularly critical for the consolidation phase of learning (Antony & Paller, 2017; Stickgold, 2005). Consolidation occurs through reactivation of the memory trace for repeated interactions between the hippocampus and neocortex to strengthen, reorganize, and stabilize memory (Antony & Paller, 2017). This reactivation may occur during conscious or unconscious (i.e., during sleep) retrieval (Antony & Paller, 2017). Although initial memory reactivation may occur during wake, behavioral studies have shown that healthy people get a "learning boost" if they sleep after encoding and are able to remember more information later (Antony & Paller, 2017; Jenkins & Dallenbach, 1924). Thus, experimental protocols that capture learning across stages, and manipulate the

presence or absence of sleep during those stages, are well-suited to identify the differential role of sleep in establishing and strengthening memories over time.

4.1.5 Established Protocols for Investigating Sleep and Word Learning Over Time

A growing body of research demonstrates that sleep supports language and word learning in neurotypical individuals (Antony & Paller, 2017; Batterink & Paller, 2017; Davis & Gaskell, 2009; Dumay & Gaskell, 2007; Gaskell et al., 2019). The protocol for this study was based on established methods in the word learning literature designed to explore the links between sleep and memory over time. Particularly influential was work by Dumay, Gaskell, and colleagues (2004, 2007) in neurotypical individuals and work by McGregor and colleagues (2013) in adults with developmental language impairment. Dumay, Gaskell, and Feng (2004) trained neurotypical adults on novel word forms and their meanings, then tested them on the words one day and one week after training. Among others, meaning association effects (i.e., participants' ability to give a semantically related definition after hearing a target word) were stronger one week after training, but not one day after training, suggesting that consolidation of word meaning happens over more than one day (Dumay et al., 2004).

These protocols also allow for assessment of how sleep contributes to different components of learning a word. In a subsequent study, Dumay and Gaskell (2007) taught neurotypical adults word forms (without associated meanings) via phoneme monitoring. Participants were tested immediately after learning (to capture encoding) and again 12 and 24 hours later (to assess consolidation). Critically, half of participants trained in the evening and slept before the 12 hour post-test, and the other half trained in the morning and did not sleep before the 12 hour post-test per their self-report. Participants completed a lexicalization test (making speeded decisions as to whether pauses have been inserted into target words), form recall task (free recall task in which participants said aloud as many word forms as they could remember in three minutes), and a recognition forced choice task (choosing the target word from a field of 2 spoken words) at each post-test. Forced choice was near ceiling for all post-tests, but participants who slept in advance of the 12-hour post-test performed better on the lexicalization test and form recall task than those who had not. Given the short time course of differential sleep effects for the word form tasks, the authors suggested that sleep has a role in promoting consolidation of word forms over a shorter time course than the consolidation of word meanings.

McGregor and colleagues (2013) integrated procedures from both Dumay, Gaskell, & Feng (2004) and Dumary and Gaskell (2007) to examine learning of both form and meaning targets in young adults with and without developmental language impairment. Participants learned new words and completed post-tests immediately after training, then 12 hours, 24 hours, and 1 week post-training, to capture how encoding and consolidation of words developed over time. Half of participants were assigned to complete their training in the evening, with the first interval of sleep before the 12 hour post-test, whereas half completed their training in the morning and did not sleep before the 12 hour post-test per their self-report. Participants with language impairment performed more poorly on both form and meaning recall at an immediate post-test, suggesting that their

encoding of the novel words was impaired. However, participants with language impairment did not differ from neurotypical participants in their recall for word meanings over the course of the week. Participants with and without language impairment who slept before the 12 hour post-test remembered more word meanings than those who did not. In contrast, the gap between groups for form recall (such that individuals with language impairment remembered fewer word forms than neurotypical peers) grew over the week. Given the similarity in patterns of meaning recall between the two groups over the course of the experiment, the authors concluded that consolidation of declarative memory for words is a strength for adults with language impairment (McGregor et al., 2013).

Multi post-test experimental designs offer a robust way to examine learning of word form and meaning, as well as sleep's role in supporting memory consolidation, over time. These designs have become the gold standard for studying word learning and sleep consolidation benefits (& Gaskell, 2009; Dumay et al., 2004; Dumay & Gaskell, 2007; McGregor et al., 2013), and implementation of such a design in TBI may promote better understanding of how learning of words and concepts plays out over time after injury.

4.1.6 Matching Analysis Approach for Clinical-Translational Significance in Rehabilitation Context

Word learning is a potentially impactful rehabilitation target post-TBI that remains unexplored. From a rehabilitation science perspective, it is critical to understand the effects of TBI on memory, including word learning, and to develop interventions to improve learning in functional settings. As word learning represents a window into sleep's contributions to learning over time, understanding how sleep does or not contribute to word learning may support the development of clinical recommendations and interventions that target multiple interacting domains after TBI. For example, interventions may target the timing of learning to maximize sleep benefits or treat sleep as a malleable component of the memory and learning process (e.g., via sleep hygiene or pharmaceutical intervention). To maximize the clinical-translational utility of our findings in this study, we combine established word learning protocols with mediation and moderation analyses that consider sleep, both as manipulated before learning and as naturally occurring over the course of multiple weeks. These analyses will underpin future clinical-translational research by allowing us to understand *when, how*, and *why* sleep-related interventions could improve memory and learning in TBI (Hayes & Rockwood, 2017).

4.1.7 The Current Study

The severity and nature of word learning deficits, and sleep's role in learning over time post-TBI, remain unknown. In the current study, we integrated procedures established in the word learning literature (Dumay et al., 2004; Dumay & Gaskell, 2007; McGregor et al., 2013) to assess word learning, and sleep's contributions, over time in adults with TBI. Specifically, we asked how timing of learning and the influence of sleep affect short- and long-term word recall in adults with TBI and neurotypical peers.

Our protocol closely followed McGregor and colleagues (2013), which was adapted from procedures used by Dumay and colleagues (Dumay et al., 2004; Dumay & Gaskell, 2007). Adults in the chronic phase of moderate-severe TBI and demographically matched neurotypical comparison (NC) peers trained on a group of novel words and were assessed immediately on their encoding of word forms and meanings. Next, they participated in ongoing assessment of their consolidation of the novel words over regular time intervals that did or did not involve sleep. This design allowed for analysis of differential performance on encoding and consolidation of word forms and meanings, as well as assessment of the role of sleep in consolidation over time.

This study had three specific aims:

(1) **To investigate word learning following TBI.** We hypothesized that word learning is impaired in individuals with TBI and predicted that adults with TBI would exhibit impaired word learning relative to neurotypical peers when tested immediately after training (i.e., impaired encoding). We expected this deficit to extend across domains and delays over the course of the experiment.
(2) **To determine how sleep affects word learning in TBI.** Given prior findings that sleep after novel word training promotes consolidation (Dumay & Gaskell, 2007; McGregor et al., 2013), we predicted that both groups would remember more words on a post-test with an interim period of sleep than without. However, we hypothesized that TBI would attenuate the sleep-learning benefit and expected individuals with TBI to show a smaller benefit than neurotypical peers.
(3) **To explore sleep's role as a mediator of the relationship between TBI and word learning.** We predicted that TBI would impair both sleep and word learning and that individuals with less sleep or more variable sleep will show diminished learning over time.

4.2 Methods

4.2.1 Participants

Participants were 50 adults in the chronic phase of moderate-severe TBI (28 female) and 50 demographically matched neurotypical comparison (NC) participants (28 female). They were recruited from the Vanderbilt Brain Injury Patient Registry and the community using social media ads and flyers. All participants were native English speakers, as the word learning stimuli follow English phonetic conventions (Dumay et al., 2004; Dumay & Gaskell, 2007; McGregor et al., 2013). All participants were 18 or older to limit the effects of developmental changes and were younger than 55 to conservatively limit the effects of expected age-related cognitive decline.

4.2.1.1 TBI Characteristics

Participants with TBI each sustained a single moderate-severe TBI, as determined using the Mayo Classification System (Malec et al., 2007). All met at least one of the following criteria: (1) Glasgow Coma Scale (GCS) <1 within the first 24 hours of acute care

admission, (2) positive neuroimaging finding (acute CT findings, or lesions visible on chronic MRI), (3) loss of consciousness (LOC) >30 minutes, or (4) post-traumatic amnesia (PTA) >24 hours. Injury information was determined from available medical records and a semi-structured participant interview; see **Table 6** for demographic and injury information for participants with TBI.

Participants with TBI were in the chronic phase of injury (>6 months post-injury, mean time since injury = 5.4 years (SD: 5.4)). Thus, participants' neuropsychological profiles were in the chronic and stable phase (Salmond et al., 2006). All sustained their injuries in adulthood (i.e., after age 18). Injury etiologies included motor vehicle accidents (*n*=24), motorcycle accidents (*n*=7), ground-level falls (*n*=5), non-motorized vehicle accidents (e.g., bicycle, *n*=4), falls from height (*n*=3), assault (*n*=3), being hit by a car while walking (*n*=2), and being struck by a moving object (*n*=2). Five participants with TBI had a self-reported pre-injury diagnosis of attention deficit hyperactivity disorder (ADHD)[1]; no other participants had a history of neurological or cognitive disability prior to the qualifying brain injury. Aphasia was ruled out via clinical assessment by a certified speech-language pathologist.

4.2.1.2 Participant Matching

NC participants had no history of neurological or cognitive disability and were matched pairwise to participants with TBI on sex, age (+-5 years), and educational attainment (+-2 years) to reduce between-group demographic variability and ensure similar within-group demographic variability. The groups did not differ statistically on age (TBI mean = 38.5 years (SD: 11.3), NC mean = 37.7 years (SD: 11.6; $t(98) = .376$, $p = .708$) or years of educational attainment (TBI mean = 15.0 years, (SD: 2.5); NC mean = 15.0 years (SD: 2.6); $t(98) = .000$, $p = 1.0$).

ID	Age	Sex	Edu	Etiology	TSO	LOC	GCS	Neuroimaging	PTA
5002	44	F	16	Non-motorized vehicle accident	250	LOC >30 minutes	3	Intracranial hemorrhage	>24 hours
5003	30	F	18	Ped vs. auto	41	Unknown or not available	11	Subdural hematoma	>24 hours
5014	52	M	16	MVA	204	LOC >30 minutes	Not available	Not available	>24 hours
5016	23	F	16	MVA	38	LOC >30 minutes	13	Subarachnoid hemorrhage	>24 hours

[1] Participants with ADHD were included in this sample to increase representativeness, as there is a high diagnosis rate of ADHD in people who sustain TBIs (Ilie et al., 2015). All analyses were conducted both with the full sample and removing these participants with ADHD and their matched pairs. As there were no changes to significance or direction of results, we report data for the full sample throughout this paper.

5021	42	F	18	MVA	62	LOC >30 minutes	3	Epidural hematoma; subarachnoid hemorrhage	>24 hours
5027	31	M	16	Ground-level fall	30	LOC >30 minutes	9	Subarachnoid hemorrhage	>24 hours
5034	36	F	16	MVA	63	LOC >30 minutes	3	Subarachnoid hemorrhage	>24 hours
5038	41	M	16	Ground-level fall	36	LOC >30 minutes	Not available	Subdural hematoma; multifocal hemorrhages; post-traumatic hemorrhagic contusions	>24 hours
5041	32	F	16	MVA	79	No LOC	10	No acute intracranial findings	>24 hours
5047	30	M	16	Assault	41	LOC < 30 minutes	15	Subdural hematoma	< 24 hours
5050	32	M	18	Ground-level fall	35	LOC >30 minutes	15	Subarachnoid hemorrhage; intraparenchymal hemorrhages	< 24 hours
5051	52	F	16	MVA	20	LOC < 30 minutes	14	Subarachnoid hemorrhage; subdural hematoma	< 24 hours
5058	35	F	12	MCC	121	LOC < 30 minutes	8	Subarachnoid hemorrhage; Subdural hematoma; parenchymal hemorrhage	>24 hours
5070	47	F	16	Fall from height	66	LOC < 30 minutes	15	Subarachnoid hemorrhage; hemorrhagic contusions	>24 hours
5082	49	M	12	Assault	89	LOC >30 minutes	14	Subdural hematoma; subarachnoid hemorrhage; bifrontal contusions	< 24 hours
5095	41	M	12	Ground-level fall	52	LOC >30 minutes	3	Intracranial hemorrhage, parenchymal contusions, subarachnoid hemorrhage, subdural hematoma	>24 hours

5098	52	M	14	Struck by object	165	LOC < 30 minutes	Not available	Front-temporal contusion; intraparenchymal hemorrhage; subarachnoid hemorrhage; intracerebral hemorrhage	< 24 hours
5099	33	F	20	Assault	39	LOC >30 minutes	13	Subdural hemorrhage	< 24 hours
5100	54	F	18	Non-motorized vehicle accident	28	LOC >30 minutes	3	Intraventricular hemorrhage; intraparenchymal hemorrhage;	>24 hours
5104	37	M	20	Struck by object	21	LOC < 30 minutes	15	Subdural hemorrhage; scattered subarachnoid hemorrhage; right temporal hemorrhage	< 24 hours
5109	26	M	14	MVA	101	LOC >30 minutes	5	Subdural hemorrhage; intraparenchymal hemorrhage; intraventricular hemorrhage	>24 hours
5111	26	F	16	MVA	73	LOC < 30 minutes	Not available	Shear Injury; diffuse axonal injury	>24 hours
5112	55	M	16	MVA	49	LOC >30 minutes	10	Frontal hematoma; intraparenchymal hemorrhages; intraventricular hemorrhage	>24 hours
5115	39	F	12	MVA	207	No LOC	Not available	Subarachnoid hemorrhage;	>24 hours
5117	47	M	12	MCC	114	LOC < 30 minutes	15	Diffuse axonal injury	>24 hours
5118	28	F	18	MVA	44	LOC >30 minutes	10	Subdural hemorrhage	>24 hours
5119	37	F	16	MVA	223	LOC >30 minutes	Not available	Subarachnoid hemorrhage; right frontal contusion	>24 hours
5121	53	M	12	MCC	12	LOC < 30 minutes	12	Subarachnoid hemorrhage; subdural hemorrhage;	>24 hours

								parenchymal Hemorrhages	
5122	54	M	18	Non-motorized vehicle accident	21	LOC < 30 minutes	15	Subarachnoid hemorrhage;	>24 hours
5123	53	M	12	MCC	22	LOC < 30 minutes	14	Intraparenchymal hemorrhage, subdural hemorrhage, subarachnoid hemorrhage	>24 hours
5124	23	M	12	Fall from height	31	LOC >30 minutes	3	Intracerebral hemorrhage; intraventricular hemorrhage	>24 hours
5125	53	F	12	Ground-level fall	11	No LOC	15	Subdural hemorrhage; subarachnoid hemorrhage	No
5126	45	F	12	MVA	25	LOC >30 minutes	3	Subdural hemorrhage	>24 hours
5128	39	F	16	MVA	184	LOC >30 minutes	Not available	Medical records currently unavailable. Participant reports brain bleed.	>24 hours
5129	53	F	12	Non-motorized vehicle accident	8	LOC < 30 minutes	12	Subdural hemorrhage; subarachnoid hemorrhage	< 24 hours
5131	41	F	12	MVA	9	LOC >30 minutes	12	Subdural hemorrhage	>24 hours
5133	25	M	12	MCC	23	LOC < 30 minutes	15	Contusions; subdural hemorrhage; intraventricular hemorrhage	< 24 hours
5134	50	M	16	MCC	10	LOC < 30 minutes	12	Intraparenchymal hemorrhage	< 24 hours
5137	26	M	16	Ped vs. auto	9	LOC >30 minutes	3	Epidural hematoma; subdural hemorrhage; subarachnoid hemorrhage	>24 hours
5141	27	M	12	MVA	8	LOC >30 minutes	13	Subdural hemorrhage	< 24 hours

5145	32	M	20	MVA	116	LOC>30 minutes	12	Not available	>24 hours
5148	25	F	16	MVA	23	LOC >30 minutes	3	Subdural hemorrhage; subarachnoid hemorrhage	>24 hours
5149	21	F	14	MVA	11	LOC < 30 minutes	3	Intraparenchymal hemorrhage; subarachnoid hemorrhage; shear injury	>24 hours
5152	55	F	18	MCC	174	LOC >30 minutes	7	Subdural hemorrhage; subarachnoid hemorrhage; shear injuries	>24 hours
5153	47	F	16	MVA	154	LOC >30 minutes	3	Parenchymal hemorrhage; intraparenchymal hemorrhage; intracerebral hemorrhage; subarachnoid hemorrhage;	>24 hours
5155	20	F	12	MVA	17	LOC >30 minutes	Not available	Not available	>24 hours
5156	54	F	12	MVA	41	LOC >30 minutes	15	Subdural hemorrhage	No
5158	31	F	16	MVA	10	LOC < 30 minutes	15	Subarachnoid hemorrhage;	Unknown or not available
5159	24	F	16	Fall from height	11	No LOC	15	Epidural hematoma	No
5161	25	M	12	MVA	7	LOC>30 minutes	10	Subdural hemorrhage; parenchymal hemorrhage; diffuse axonal injury	>24 hours

Table 6 Demographic and injury information for participants with TBI. ID = participant ID number. Education (edu) reflects years of highest degree obtained. MVA = motor vehicle accident. MCC includes both motorcycle and snowmobile accidents. Non-motor = non-motorized vehicle accident. Ped vs. auto = participant was hit by car while walking or running. Time since onset (TSO) is presented in months. LOC = loss of consciousness. Glasgow Coma Scale (GCS) is total score at time of first post-injury measurement. PTA = post-traumatic amnesia.

4.2.1.3 Sleep Characteristics

Two participants with TBI reported a pre-injury diagnosis of mild sleep apnea. Otherwise, participants with TBI reported no pre-injury sleep diagnoses. Five participants with TBI reported new-onset sleep disorders post-injury: 3 diagnoses of sleep apnea and 2 of chronic insomnia. Thirty-one participants with TBI (62%) reported a change in sleep post-injury. Twenty-four (48%) reported that their sleep is worse, whereas 7 (14%) reported that their sleep has improved post-injury. Ten participants with TBI (20%) and 4 NCs (8%) reported taking a sleep aid (e.g., melatonin, prescription sleep aid) over the course of the study.

4.2.2 Procedures

The experiment had a randomized within-participant crossover design. Participants completed the word learning task online and were tested on their memory for words with and without interim periods of sleep. They wore an activity monitor throughout the two-week experiment period to objectively measure quantity and variability of sleep. The study protocol was approved by the Vanderbilt University Human Research Protections Program.

4.2.2.1 Study Timeline

Participants completed 8 sessions over 2 weeks. During the first week, each participant was randomly assigned to completed one hour training on a group of novel words either in the morning (Wake condition) or evening (Sleep condition). After training, they completed an immediate post-test lasting 10-15 minutes. The post-test structure provided multiple opportunities for success across different levels of representation and forms of learning (e.g., cued and uncued recall, recognition). The structure followed the word learning and memory literatures (Davis & Gaskell, 2009; Dumay et al., 2004; Dumay & Gaskell, 2007; McGregor et al., 2013) and standardized memory test formats (Schmidt, 1996).

Over the course of the next week, we assessed participants' consolidation of the novel words via the same post-test structure at 12 hours, 24 hours, and 1 week post-training. The manipulation between the Wake and Sleep conditions was that participants slept before the 12-hour post-test in the Sleep condition, but not in the Wake condition (see **Table 7**). During the second week, participants learned a new word list in the opposite training condition from their first week and completed the 12 hour, 24 hour, and 1 week post-tests for that condition. Starting condition (Wake or Sleep) and starting word list were counterbalanced so that equal proportions of the experimental groups began in each condition and word list combination. This crossover design allowed for both within-participant comparisons (i.e., performance in the Wake versus Sleep conditions) and between-participant comparisons (i.e., differences in performance between the TBI and NC groups).

Wake Condition			
	Training Day	**Next Day**	**1 Week Later**
Morning	Novel Word Training Immediate Post-Test	24 Hour Post-Test	1 Week Post-Test
Evening	12 Hour Post-Test	--	--
Sleep Condition			
	Training Day	**Next Day**	**1 Week Later**
Morning	--	12 Hour Post-Test	--
Evening	Novel Word Training Immediate Post-Test	24 Hour Post-Test	1 Week Post-Test

Table 7 Experimental schedule for Wake and Sleep conditions. Each participant experienced both conditions, with the condition order randomly assigned (i.e., a randomized within-participant crossover design).

4.2.2.2 Remote Data Collection

Experimental sessions occurred remotely using the Gorilla online behavioral experiment platform (Anwyl-Irvine et al., 2020). Prior to study initiation, we mailed each participant a box containing a set of noise-cancelling headphones to use as needed during the experiment, a pre-programmed activity monitor to wear between experimental sessions (see **Actigraphy**), and a prepaid return shipping label. Participants completed sessions on their own devices, supervised 1:1 by an experimenter via Zoom. We offered a laptop loan program to reduce technology barriers for interested participants who did not have a computer available, and 3 participants completed the study using a loaned laptop.

We began remote data collection due to the COVID-19 pandemic. However, continuing remotely allowed participants, including those who could not come to the lab due to physical or cognitive barriers (e.g., unable to drive or navigate public transportation), to conveniently participate. We were able to recruit a geographically diverse set of participants from 8 states and Puerto Rico, as attending sessions at our lab in Nashville was not a limiting factor. Completing sessions online also increased ecological validity, as participants learned and were tested on the novel words in their own homes, and we captured their sleep routines without the confines of traveling to our lab to complete sessions multiple times during the experiment period.

4.2.2.3 Sleep Measurement via Actigraphy

We objectively tracked participants' sleep-wake patterns using actigraphy. Participants received Actigraph GT9X Link activity monitors (ActiGraph, 2020), which they were asked to wear on their non-dominant wrists, 24 hours a day, throughout the entire experiment period. These 3-axis accelerometers are approximately the size of a wristwatch and capture physical activity and rest levels in free-living conditions (i.e., in a participant's own home and daily life) over extended time periods (Buxton et al., 2017; Tracy et al., 2018). Although detailed analysis of sleep phases requires the use of polysomnography, actigraphy is considered a reliable and valid alternative for estimating sleep-wake patterns (Cellini et al., 2013; Sadeh, 2011; Tracy et al., 2018). In this study,

actigraphy allowed for minimally-invasive assessment of sleep and strong ecological validity, as participants wear the monitors in their own homes over time (versus a polysomnography study at a set time and location) (Buxton et al., 2017; Tracy et al., 2018).

4.2.2.4 Compensation

Participants were compensated $15/hour for each online data collection session (i.e., the 8 word learning sessions) they attended. They received an additional $10 for each 24 hour period they spent wearing the activity monitor, for a maximum $290 compensation. Final compensation amount was determined upon receipt of participants' return shipment.

4.2.2.5 Coding Reliability

Coding on the form recall and meaning association tasks (see below) was performed by experimenters with clinical training in speech-language pathology, including phonetics and semantics. Inter-rater reliability was performed on 25% of the data. Inter-rater reliability was 91.5% for form recall and 94% for meaning association.

4.2.3 Measures

4.2.3.1 Word Learning

The word learning task closely followed McGregor and colleagues (2013) to examine learning of word forms, meanings, and their links over time.

Trained stimuli were two sets of 16 novel words (form) and their referents (meaning) (one set per week). Each novel word was a pseudoword derived from a disyllabic, monomorphemic English word (e.g., *army* became *armo*). Each novel word was randomly assigned to a fantasy referent/meaning. Referents were created by combining two animate objects (e.g., a pony and snake) or two inanimate objects (e.g., a planet and a basketball) and depicted by line drawings (see **Figure 7**). To ensure familiarity, both the bases for the novel words and base categories for the fantasy referents were selected from children's books (McGregor et al., 2013). See **Supplementary Appendix Table 1** for novel words and their referents.

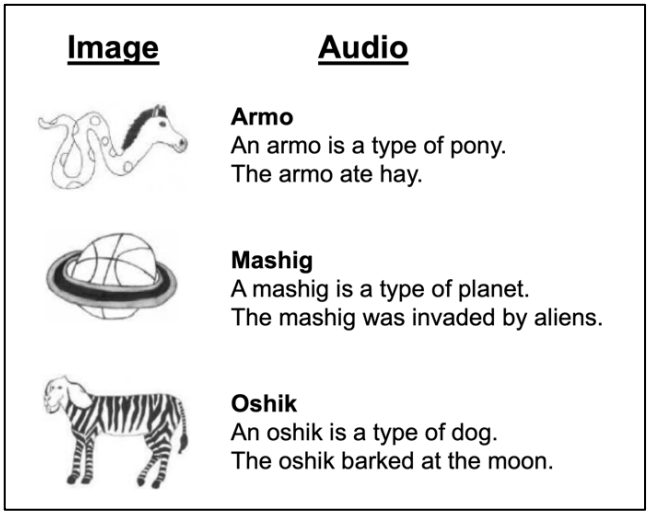

Figure 7 Sample word-referent stimuli.

Each week, participants completed a 12-block training exercise (approximately 1 hour in duration) designed to introduce them to the set of 16 novel words and their meanings. The words were presented via visual and auditory stimuli (see **Figure 7**), and training included intermittent yes/no questions (e.g., "Does it have wheels?") to ensure attention to task. Next, participants completed a 10-15 minute post-test via multiple recall/recognition tasks (in this order):

4.2.3.1.1 Primary Outcome: Free Recall Task

Form Recall Task: Participants had two minutes to verbally recall as many of the trained words as possible with no cueing. All responses were digitally recorded, then transcribed and scored offline. The primary outcome was the number of exact form productions a participant replicated (maximum score: 16).

4.2.3.1.2 Secondary Outcomes: Cued Recall and Recognition Tasks

Meaning Association Task*:* Trained word forms were presented via audio recording in a fixed random order, and the participant had seven seconds to verbally define each. Responses were recorded, transcribed offline, and coded for correct semantic relationship (maximum score: 16). The primary outcome was how many exact word meanings (i.e., the exact definition provided in the training) each participant produced.

Two-Item Alternative Forced Choice Tasks:

Word (Form): Participants heard trained words (e.g., *armo*), paired with untrained lexical neighbors that diverged in the final syllable (e.g., *armu*). They indicated which of the two words was familiar via mouse click (maximum score: 16).

Referent (Meaning): Participants saw a trained referent (e.g., snake-pony), paired with an untrained semantic neighbor (e.g., shark-pony) and indicated which is familiar via mouse click (maximum score: 16).

Link: For half of the items, participants heard a trained word (e.g., *armo*) and indicated which of two trained referents matches it via mouse click. For the other half, participants saw a trained referent and heard two trained words. They indicated which

word matched the given referent via mouse click (maximum score: 16). For this task, item recall was insufficient for a correct response, as both possible responses were familiar. Rather, participants had to rely on declarative memory (Konkel & Cohen, 2009; Monti et al., 2014) to identify which response was correctly paired with the target item.

There was no response time limit on any of the forced choice tasks, which took participants an average of 1-2 minutes to complete. The post-test provided multiple opportunities for success with cued and uncued recall, as well as recognition tasks.

4.2.3.2 Sleep

We processed data from the activity monitors using the GGIR package (version 2.5.0) in R (Migueles et al., 2019; van Hees et al., 2014). GGIR is a research community-driven, open-source R package for generating activity and sleep measures from multi-day accelerometer data. The package comprises a validated autocalibration algorithm to assess the quality of accelerometer data and correct for calibration error (van Hees et al., 2014). It also includes an algorithm to assess sleep duration, which has been validated against both participant questionnaires and polysomnography (van Hees et al., 2015). Broadly, the algorithm determines sustained inactivity (rest) and wake times using the variance in the estimated z-axis angle from the accelerometer, such that a period of more than 5 minutes with less than a 5 degree change in the z-axis angle is considered rest (van Hees et al., 2018). We chose GGIR rather than a device-specific count-based analysis method because, as an open-source package with a generic algorithm, it allows more direct comparison across studies (Migueles et al., 2019; van Hees et al., 2015). Our GGIR calibration file is included in **Supplementary Appendix Table 2**.

We generated two primary sleep measures using the GGIR algorithm:

(1) Average nightly sleep duration throughout the study period served as a measure of quantity of nightly sleep.
(2) The standard deviation of nightly sleep duration throughout the experiment captured variability in nightly sleep.

We also used actigraphy to verify that participants stayed awake before the 12-hour post-test in the Wake condition and slept before the 12-hour post-test in the Sleep condition. For this purpose, sleep was a yes/no in each condition. More than 90 minutes of sustained daytime inactivity in the first 12 hours of the Wake condition was considered a nap, consistent with study protocols on the effects of napping in the memory literature (Heim et al., 2017; van Schalkwijk et al., 2019).

4.2.4 Statistical Analyses

4.2.4.1 Inclusion

To be included in analyses using the word learning task, participants had to answer at least 80% of the attention check questions correctly during both training sessions. To be included in the actigraphy analysis, participants had to wear the activity monitor for at least 7 full days (of 14 days total) during the experiment period.

4.2.4.2 Analyses

For all analyses, the primary outcome measure was the form recall task, which was a free recall task and thus captured the most robust form of word learning (Cohen & Banich, 2003; Eichenbaum & Cohen, 2001). Performance on cued recall and recognition tasks were secondary outcomes to measure multiple facets of word learning (Aim 1). We conducted our moderation (Aim 2) and mediation (Aim 3) using form recall as the outcome measure.

Aim 1: To investigate word learning following TBI: To assess how well participants encoded the novel words, we used an independent-samples t-test to compare performance on the immediate form recall task between individuals with and without a history of TBI. This analysis combined performance across two sessions, as we pooled immediate scores in the Wake and Sleep conditions. (All participants completed the training and post-test in both conditions. At this immediate post-test, participants had not yet slept in either condition.) We also used independent samples t-tests to assess performance on the secondary word learning outcomes to determine how TBI affected immediate word learning across domains. Our sample size was adequate to detect a medium effect size (0.5) at alpha .05.

We also assessed group differences in performance on both form recall and meaning association, averaged across the Wake and Sleep conditions, at each post-test to examine consolidation of the novel words. We conducted an exploratory analysis to examine how the magnitude of group differences changed over the course of the week using a mixed-effects linear regression model.

Aim 2: To determine how sleep affects word learning in TBI: We conducted a paired samples t-test on form recall at the 12 hour post-test between the Wake and Sleep conditions among participants with TBI to assess how sleeping before post-test affects their learning. For rigor, we also conducted a paired samples t-test on form recall at the 12 hour post-test between the Wake and Sleep conditions for neurotypical participants to ensure replication of the sleep-learning benefit established in the prior literature. Finally, we conducted two between-groups independent-samples t-tests (one in the Wake and one in the Sleep condition) and compared effect sizes to determine if sleeping before post-test affects the nature of word learning deficits in TBI[2]. Our sample size was adequate to detect a medium effect size (0.5) at alpha .05 for each of these group comparisons.

[2] Our primary analysis included all participants who had completed the immediate trainings and 12-hour post-tests in both the AM and PM conditions of the word learning task, as earlier versions of this protocol (Dumay et al., 2004; Dumay & Gaskell, 2007; McGregor et al., 2013) did not objectively verify whether participants did or did not sleep in each condition. However, we also used actigraphy to objectively verify that participants slept before 12 hour post-test in the Sleep condition but not in the Wake condition. All participants slept more than 90 minutes in the before the post-test in the Sleep condition, but 8 participants with TBI and 7 NCs slept more than 90 minutes before the post-test in the Wake condition. We conducted a secondary version of the analysis only including participants who did not nap in the Wake condition. As there was no change in the significance or direction of results, we report data from the entire sample here.

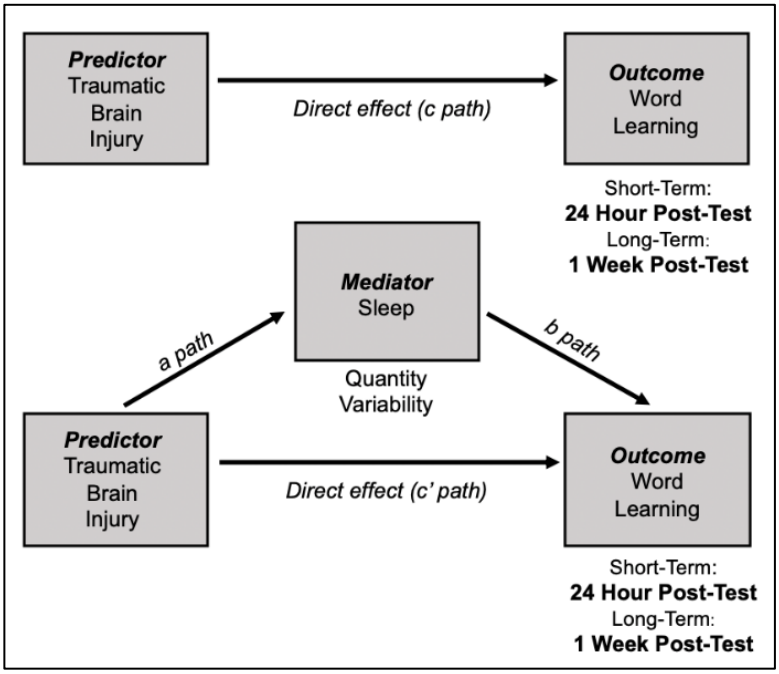

Figure 8 Mediation model of TBI, sleep, and word learning over time.

<u>Aim 3: To explore sleep's role as a mediator of the relationship between TBI and word learning</u>: Using the lavaan package in R (Rosseel, 2012), we conducted two sets of mediation models with form recall as the primary outcome, one in the short term (24-hour post-test, a single night's duration) and one in the long term (1-week post-test, 7 nights' duration and variability). Before both of these post-tests, participants had slept as per their normal routine and without manipulation. We tested each mediator separately: sleep quantity (average nightly sleep duration) and variability (standard deviation of nightly sleep). Although we were not powered to test the significance of the indirect effect (e.g., bootstrap the confidence interval on the indirect effect, as in a formal mediation analysis), we examined each of the paths in the mediation model to understand the potential role of sleep as a mediator (as shown in **Figure 8)**. We conducted a series of regression models to estimate each of the individual paths shown in Figure 3 (*a, b, c* and *c' paths* where *c* is also called the total effect and *c'* is also called the direct effect*).* Regression models included 1 predictor for the *a* and *c* paths (word learning as a function of TBI, sleep as a function of TBI), and 2 predictors for the *b* path (predicting word learning as a function of sleep, adjusted for TBI) and the *c*' path (predicting word learning as a function of TBI, adjusted for sleep) (Hayes & Montoya, 2016). Preliminary evidence for potential mediation would be significant *a* and *b* paths, and/or a substantive difference between *c* and *c'* path.

4.3 Results

4.3.1 Inclusion

The 100 participants in this study represented 800 scheduled online sessions. Of those 800 scheduled sessions, we successfully completed 798, resulting in a 99.8% session completion rate. Both missed sessions involved a participant with TBI missing the 24 hour post-test. Additionally, form recall data were missing for 1 NC at an immediate post-test due to recording device failure. Otherwise, all participants had data for all post-tests. All participants answered more than 80% of the embedded attention questions correctly for both training conditions (TBI group mean: 92.2% (SD: 3.3), NC group mean: 93.7% (SD: 2.4)), so all participants were included in the word learning analysis.

Of the 100 participants, 5 were excluded from the actigraphy analysis: 2 for device failure (e.g., device failing after submersion in water, broken device band resulting in inadequate data quality), 1 for calibration failure as reported by the GGIR package, 1 for failure to return device in time for analysis, and 1 for insufficient wear (i.e., participant did not have 7 days of complete actigraphy data from the experiment period). The remaining 95 participants (46 participants with TBI and 49 NCs) were included in the actigraphy analysis. For these included participants, the TBI group averaged 1.7% nonwear (SD: 1.7) during the included study period, and the NC group averaged 2.0% nonwear (SD: 4.0). There was no significant difference between the groups in nonwear percentage ($t(93)=.538$, $p=.592$).

4.3.2 Overview

4.3.2.1 Word Learning

Participants with TBI produced fewer words than NCs on the form recall task at every post-test in both conditions. See **Figure 9** for performance on the form recall task at each post-test, averaged across conditions, for both groups. Participants with TBI recalled an average of 3.8 word forms (SD: 2.8) immediately, relative to 6.4 word forms (SD: 3.7) for NCs. At the 12 hour post-test, participants with TBI recalled an average of 1.9 word forms (SD: 2.2), and NCs recalled an average of 4.5 word forms (SD: 3.7). At 24 hours, participants with TBI recalled, on average, 3.4 word forms (SD: 3.4), compared to 6.7 word forms (SD: 4.2) for NCs. One week after learning, participants with TBI recalled an average of 3.1 word forms (SD: 2.9), compared to 7.0 word forms (SD: 3.9) for neurotypical peers. At the one week post-test, 40 (80%) participants with TBI recalled fewer than 5 word forms, compared to 8 (16%) NCs who recalled fewer than 5 word forms.

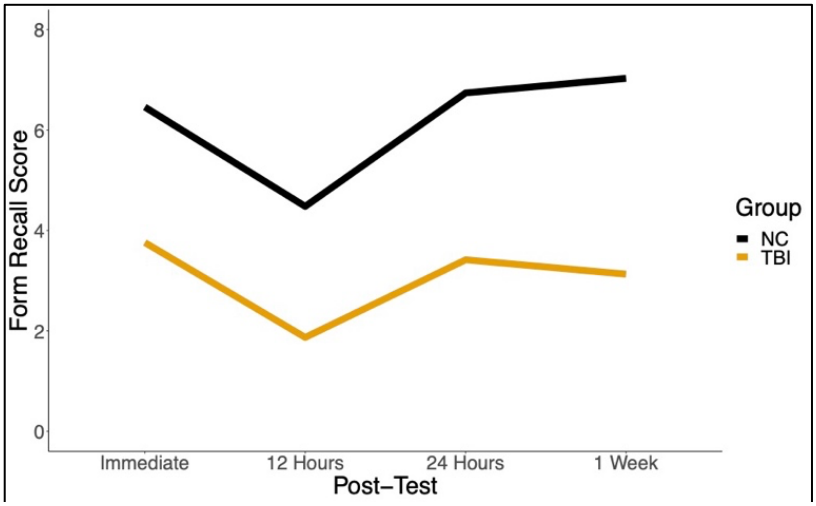

Figure 9 Form recall performance, averaged across the Wake and Sleep conditions, for both groups.

4.3.2.2 Sleep

Actigraphy analyses revealed no significant differences between the two groups on quantity or variability of sleep over the course of the study. Participants with TBI slept an average of 7.53 (SD: 1.34) hours per night, compared to 7.64 hours (SD: 1.14) for NCs [independent samples t-test, $t(88.76) = .448$, $p=.655$]].

4.3.3 Aim 1: To investigate word learning following TBI

For our primary analysis, we assessed encoding of the 16 trained words by conducting an independent-samples t-test on the form recall task at the immediate post-test, collapsed across the Wake and Sleep conditions. Participants with TBI recalled a mean of 3.8 (SD: 2.8) words, compared to 6.5 (SD: 3.6) words for NCs, resulting in a statistically significant difference with a large effect size [$t(91.53)=3.96$, $p<.001$, Cohen's $d=.79$].

4.3.3.1 Secondary Word Learning Tasks

On the cued meaning association task, participants with TBI recalled an average of 9.6 (SD: 3.8) out of 16 trained word meanings at the immediate post-test (collapsed across the Wake and Sleep conditions), relative to 11.5 (SD: 3.5) word meanings for NCs. This resulted in a significant independent-samples t-test result with a moderate effect size [$t(97.29)=2.56$, $p=.01$, Cohen's $d=.51$]. See **Table 8** for group means and t-test results on the meaning association task at each post-test.

Participants in both groups were near ceiling on all forced choice tasks throughout the experiment, so we pooled performance across post-tests. Participants in both groups scored best on the forced choice referent task: 99.3% (SD: 1.8) for participants with TBI and 99.8% (SD: 0.6) for NCs [$t(113.24)=2.25$, $p=.021$, Cohen's $d=.34$]. Participants with TBI answered correctly on 94.0% (SD: 5.8) of forced choice word items, compared to 97.3% (SD: 3.4) for NCs [$t(143.60)=4.74$, $p<.001$, Cohen's $d=.70$]. On the forced choice link task,

participants with TBI were correct for 93.6% (SD: 8.1) of items, relative to 97.4% (SD: 3.4) for NCs[t(119.52)=4.05, p<.001, Cohen's d=.60].

4.3.3.2 Growing Word Learning Gap Over Time

See **Table 8** for group means and differences on form recall and meaning association, averaged across the Wake and Sleep conditions, at each post-test.

Task / Time Point	Group	Performance Correct (SD)	p / effect size
Form Recall – Immediate	NC	6.4 (3.7)	p <.001 Cohen's d = .792
	TBI	3.8 (2.8)	
Form Recall – 12 hours	NC	4.5 (3.7)	p <.001 Cohen's d = .862
	TBI	1.9 (2.2)	
Form Recall – 24 hours	NC	6.7 (4.2)	p <.001 Cohen's d = .866
	TBI	3.4 (3.4)	
Form Recall – 1 week	NC	7.0 (3.9)	p <.001 Cohen's d = 1.134
	TBI	3.1 (2.9)	
Word Association – Immediate	NC	11.5 (3.5)	p = .012 Cohen's d = .511
	TBI	9.6 (3.8)	
Word Association – 12 hours	NC	11.4 (3.5)	p = .001 Cohen's d = .671
	TBI	8.9 (4.1)	
Word Association – 24 hours	NC	12.3 (3.4)	p <.001 Cohen's d = .716
	TBI	9.6(4.1)	
Word Association – 1 week	NC	11.7 (3.5)	p <.001 Cohen's d = .947
	TBI	8.2 (3.9)	

Table 8 Task performance by group at each post-test. T-tests reveal significant between-groups differences at every time point for both form recall and meaning association. Effect size (Cohen's d) increases to >1.0 for form recall and >.90 for word association by one week.

We conducted an exploratory analysis to assess the growing numerical gap in performance between the TBI and NC groups at the 1 week post-test. We compared form recall performance at the immediate post-test to the 1 week post-test for both groups using a mixed effects linear model. The outcome was form recall score. Predictors were group (TBI vs. NC), post-test (immediate vs. 1 week), and their interaction. We also included random intercepts to account for variability nested within participants. In this model, there was no fixed effect of post-test (estimate = .659, t = 2.578, p = .964). However, there was a fixed effect of group such that NCs recalled more words than participants with TBI (estimate = -2.612, t = -3.933, p <.001). There was also a group * post-test interaction, such that there the performance gap between groups was larger at

the one-week post-test than the immediate post-test (estimate = -1.289, t = -3.583, p <.001).

4.3.3.1 Individual Differences in Word Learning Over Time

There were considerable individual differences within each group for word learning over the course of the experiment. See **Figure 10** for a visualization of individual differences in word learning performance.

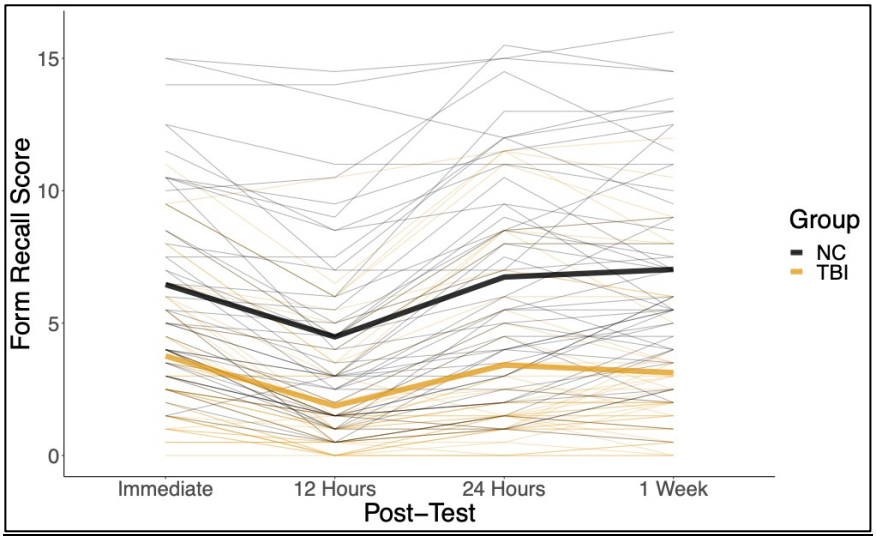

Figure 10 Line graph showing group and individual performance, averaged across conditions, at each post-test. Thin lines represent performance for an individual participant, and thick lines represent group means.

4.3.4 Aim 2: To determine how sleep affects word learning in TBI

On form recall at the 12-hour post-test, NC participants recalled more word forms than participants with TBI in both the Sleep (TBI mean: 2.4 (SD: 3.1), NC mean: 5.5 (SD: 4.3)) and Wake (TBI mean: 1.4 (SD: 2.0), NC mean: 3.5 (SD: 3.9)) conditions. This resulted in significant independent-samples t-tests with moderate-to-large effect sizes [Sleep: t(89.18)=4.19, p <.001, Cohen's d =.84; Wake: t(71.70)=3.39, p = .001, Cohen's d = .68]. See **Figure 11** for graph of group means and comparisons.

Both groups performed better at the 12-hour post-test in the Sleep condition than in the Wake condition. On average, participants with TBI recalled 1.0 more words in the Sleep Condition, whereas NC peers recalled 2.0 more words in the Sleep condition. This resulted in significant paired-samples t-tests with small-to-moderate effect sizes in both groups [TBI: t(49) = -2.49, p = .016, Cohen's d =.35; NC: t(49) = -3.95, p < .001, Cohen's d = .56; see **Figure 11**].

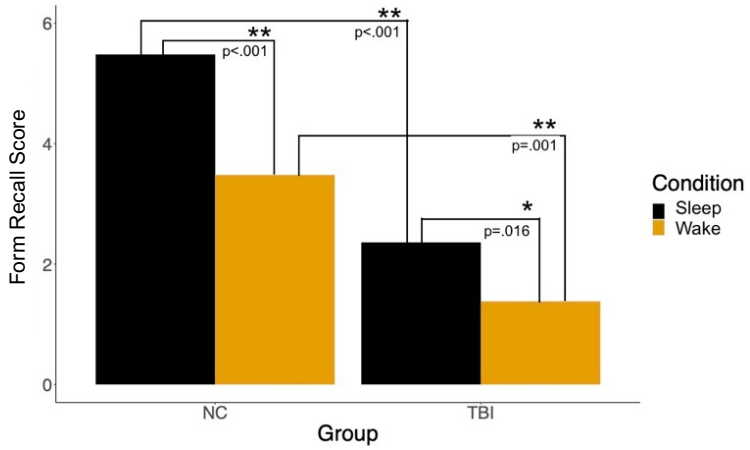

Figure 11 Form recall performance at the 12 hour post-test by condition. ** indicates a comparison significant at p<.01. * indicates a comparison significant and p<.05.

4.3.4.1 Individual Differences in Sleep-Learning Benefit

There were substantial individual differences within each group and condition at the 12 hour post-test. See **Figure 12** for a visualization of individual differences in performance.

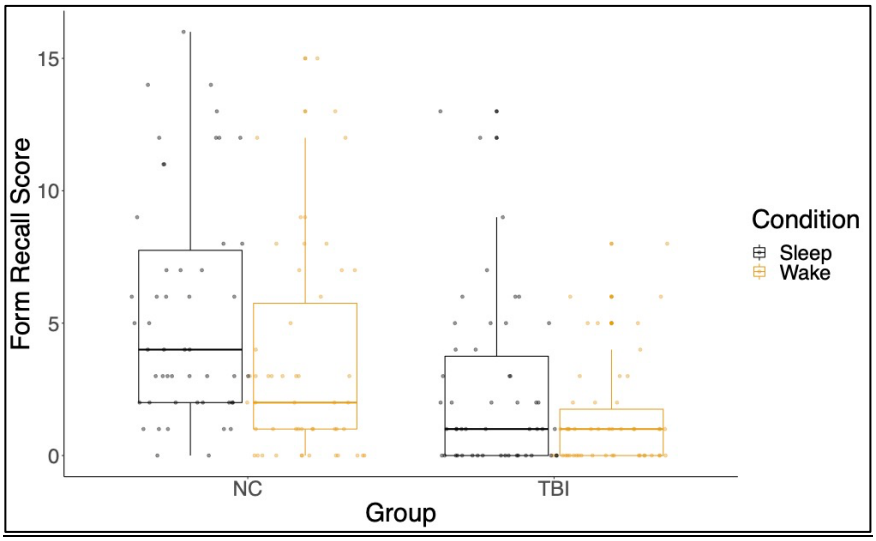

Figure 12 Boxplot showing group and individual performance by condition at the 12 hour post-test (Aim 2). Central lines represent medians, and points represent scores for each individual participant.

4.3.5 Aim 3: To explore sleep's role as a mediator of the relationship between TBI and word learning

We conducted path analyses to explore sleep's role as a potential mediator in TBI's effect on word learning. In each model, TBI was the predictor, sleep variables were mediators, and word learning (form recall scores at the 24 hour and 1 week post-tests) were the outcomes. Each model included only 1 mediator and 1 outcome.

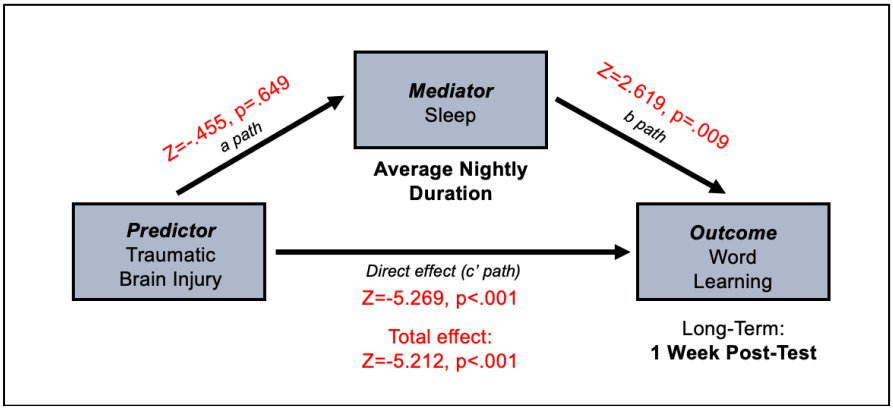

Figure 13 Path estimates for model assessing sleep duration as a mediator of the relationship between TBI diagnosis and form recall at the 1 week post-test.

We first conducted path analysis to explore average nightly sleep duration as a potential mediator for the relationship between TBI and form recall at the long-term (one week) post-test (see **Figure 13**). In this model, TBI diagnosis was predictive of poorer form recall scores at the one week post-test (estimate = -3.605, Z = -5.269, p<.001). There was an association between average nightly sleep duration and word learning, such that people who slept more, on average, each night remembered more words at one week (estimate = .729, Z = 2.619, p = .009). However, there was no association between TBI diagnosis and average nightly sleep duration over the course of the experiment (estimate = -.115, Z = -.455, p=.649). Thus, nightly sleep duration was not a potential mediator of the relationship between TBI and long-term word learning. See **Figure 13** for a depiction of path analyses for this model.

We next conducted path analyses on models to explore variability in sleep schedules (standard deviation in nightly sleep) as a potential mediator of the relationship between TBI and word learning. TBI diagnosis was predictive of poorer form recall scores at the 24 hour post-test (estimate = -3.559, Z = -5.050, p <.001). However, TBI diagnosis was not associated with sleep variability (estimate = .162, Z = 1.198, p = .231), and sleep variability was not associated with long-term form recall (estimate = -.798 , Z= -1.504 , p = .133). Thus, sleep variability was not a potential mediator of the relationship between TBI and long-term word learning. See **Supplementary Appendix Figure 1a** for depictions of path analyses for each model.

Finally, we analyzed a model assessing how sleep affects word recall in the short term (24 hour post-test). In this model, TBI diagnosis was again predictive of poorer form recall performance at the 24 hour post-test (estimate = -2.753, Z= -3.493, p < .001). Sleep duration was not associated with form recall in the short term (estimate = .542, Z=1.904, p=.057). TBI diagnosis was not associated with sleep duration in the short term (estimate = -.522, Z=-1.853, p=.064). Thus, nightly sleep duration was not a potential mediator of the relationship of the relationship between TBI and short-term word learning. See **Supplementary Appendix Figure 1b** for depictions of path analyses for this model.

4.3.6 Supplementary Data and Exploratory Analyses

In the Supplementary Appendix, we present additional task performance data visualizations of form recall and meaning association performance separated by group and condition over the course of the experiment (**Supplementary Appendix Figures 2 and 3**). Briefly, we visualize that the growing gap in performance between the two participants groups (reported in **Figure 9** for form recall, collapsed across condition) is present across the Sleep and Wake conditions, and the gap extends to meaning association as well.

We performed additional ad hoc analyses that were beyond the scope of the original study questions and design. Although these were not part of our planned analyses, we believe these explorations are important in examining the data to guide future hypothesis testing and clinical decision making. We assessed the associations between age, education, and word learning performance for all participants. There was no significant association between age and long-term form recall, but there was an association between educational attainment and long-term recall such that participants with more education recalled more word forms at the one week post-test. Additionally, we explored whether performance on canonical, standardized, neuropsychological assessments of declarative and working memory is associated with immediate and long-term word learning. Form recall at both the immediate and one week post-tests was associated with standardized assessment of declarative memory with similar task demands, and immediate form recall was associated with performance on a standardized working memory assessment. Finally, we found that sleep duration and variability were not associated with age in the entire participant sample or time since onset for participants with TBI.

4.4 Discussion

The ability to learn new words is critical for academic, vocational, and interpersonal success. Although individuals with TBI have well-documented negative outcomes in each of these spheres, word learning has not been examined for people with TBI, and the nature and severity of word learning deficits in TBI are unknown. In this study, we asked how TBI affects word learning and if sleep contributes to word learning over time in people with TBI as it does for neurotypical peers.

People with TBI recalled fewer word forms and meanings than neurotypical peers both immediately after learning and over time. Like neurotypical peers, people with TBI remembered more words when they slept after learning than when they did not. For all participants, sleeping more each night was associated with better long-term word recall, but participants with TBI did not differ from neurotypical peers in their amount or variability of nightly sleep as measured objectively via actigraphy over the course of the experiment.

4.4.1 Word Learning Deficits Extend Across Domains and Delays

People with TBI exhibited a striking disruption in word learning relative to NCs, even when tested immediately after learning, as evidenced by statistically significant group differences across measures of both word form and meaning at the immediate post-test. This disruption was present regardless of when people encoded new information (i.e., regardless of how learning is timed relative to sleep). Although deficits in memory and learning are well-documented in the scientific literature (both from standardized assessments and stakeholder report (Vakil, 2005; Velikonja et al., 2014)), this is the first study to extend understanding of those deficits to word learning.

We selected multiple assessments to capture each component of the multifaceted word learning process. Consistent with the memory literature, performance for both groups was poorest on free recall of word forms (form recall) across conditions and delays. The form recall task represents the most robust measure of learning because participants provided their answered uncued, so this was the most challenging task in our post-test and the best at capturing variability in performance. Meaning association, a cued recall task for word meanings, captured the semantic facet of word learning and was the second most difficult task for both groups. Finally, participants in both groups performed quite well (group means above 90%) on forced choice tasks assessing recognition of word form, meaning, and the links between them. Forced choice, then, may be a specific measure for the most severe memory deficits but is not as sensitive as form recall or meaning association for capturing the full spectrum of word learning disruption. However, including forced choice in the study protocol allowed us to determine that most participants with TBI had some representation of the novel words after learning, even if they were not able to retrieve the representation in free and cued recall conditions.

Strikingly, these deficits in word learning across domains existed over time for participants with TBI and grew over the course of the experiment (i.e., before the one week post-test). This growing gap suggests that, in addition to disruptions in encoding, people with TBI do not strengthen their memories through consolidation in the same way as neurotypical peers. Hippocampal and medial temporal lobe damage, which are common in TBI due to the vulnerability of these networks to injury mechanisms (Bigler et al., 1996; Palacios et al., 2013; Rabinowitz & Levin, 2014), may disrupt the consolidation process on their own. However, it may also be that some form of sleep disruption after injury (either caused by or contributing to hippocampal damage) interacts to produce disrupted memory consolidation. Irrespective of the mechanism(s), which are beyond the scope of the current study, these results demonstrate that individuals with TBI have disruptions in both encoding and in the consolidation of new knowledge over time. Studying word learning at a single time point is inadequate to capture the full breadth of word learning deficits in TBI beyond initial encoding and how those deficits manifest in long-term retention.

4.4.2 Sleep Supports Word Learning, But Time Also Plays a Role

In our study sample, we replicated findings in the cognitive neuroscience literature that neurotypical individuals remember more when they sleep after they learn. Because

our sample encompassed a wider range of ages than earlier word learning studies in young adults, we extended this finding to an older population of neurotypical individuals than was included in previous work.

A critical question here was whether individuals with TBI would receive a similar sleep-learning boost to their neurotypical peers. Like their neurotypical peers, participants with TBI got a short-term learning boost (i.e., a statistically significant difference between the Wake and Sleep conditions at the 12 hour post-test) when they slept after they learned (small effect size for participants with TBI and moderate effect size for NCs). The gap in word learning performance for participants with TBI relative to NCs grew, as evidenced by an increasing gap in numerical form recall and meaning association scores, over the course of the week in both the Wake and Sleep conditions.

Although we replicated the sleep-learning boost for participants with and without TBI, performance in this study's sample differed from some prior examinations of sleep and timing of word learning in young adults. In one previous examination of form recall in young adults (Dumay & Gaskell, 2007), those who slept before the 12 hour post-test remembered more word forms than they had at the immediate post-test. In contrast, both groups in the current study exhibited performance consistent with McGregor and colleagues (2013), who in their sample of neurotypical college students showed a decline in form recall performance at the 12 hour post-test for all conditions, which is attenuated by sleeping before the post-test, with a subsequent boost at the 24 hour mark. Our sample was more demographically diverse than in Dumay & Gaskell (2007) but also in McGregor and colleagues (2013) (i.e., both participants with TBI and NCs ranged in age from 19 to 55 in our study, as compared to the young adults and college student samples in these earlier studies). Rather, the similarity between our findings and the McGregor finding follows logically, as our task more closely mirrored the materials used in that study (i.e., we had a mix of free and cued recall tasks for both word forms and meanings, whereas Dumay & Gaskell focused only on recall of word forms via free recall and lexicalization tests). It may be that when participants are learning both a word's form and meaning, time and sleep interact to produce robust word learning via memory consolidation. That is, there may be competition between a word's form and meaning in the early stage of learning that slows the acquisition process and results in a dip in performance at the 12 hour post-test for studies that include both components, whereas participants who must learn only word forms show a gain at the 12 hour post-test. However, it is worth considering whether the combination of word form and meaning leads to more robust learning over time once the two are linked in a mental representation. This proposal warrants further consideration in future study designs to improve understanding of word learning in individuals with TBI.

4.4.2.1 Patterns in Learning Form and Meaning May Point to Shifting Memory System Contributions Over Time

Our exploratory visualization of task performance at each post-test revealed that participants in the Wake condition caught up to performance on the Sleep condition by the one week post-test for form recall. However, participants remembered numerically more word meanings in the Sleep condition than the Wake condition over the course of

the entire week. In fact, both groups, on average, showed a slight increase in meaning association score at the 12 hour post-test in the Sleep condition and a marked decline in the Wake condition. Although we conducted our primary analysis on form recall because free recall is the most robust demonstration of learning, it is worth considering how this changing pattern may reflect differential contributions of the declarative memory system, with its well-documented reliance on sleep, for each component and stage of learning a word. Perhaps the meaning association task, which hinges on the binding of word form to meaning, depends most critically on the declarative memory system and is thus most influenced by an initial bout of sleep, whereas the non-declarative memory system makes a larger contribution to learning the sequence of sounds in the early stages of form recall. Although, other work has pointed to the benefits for the non-declarative memory system as well (Brawn et al., 2013; Frank et al., 2001; Huber et al., 2004; Stickgold et al., 2000; Tamaki et al., 2008). It is unclear from the sleep-memory literature if sleep has similar benefits on each memory system, or if the timing of those benefits is the same. Future studies are warranted to better understand these dynamics, and word learning is an ideal behavior for such exploration as it requires the confluence of multiple memory systems over time.

Relatedly, it may be that the hippocampus's contribution to word learning (influenced by sleep) is strongest in the earliest stages, with shifting contributions from other memory systems over time. For example, the hippocampus makes contributions to sequence learning in statistical tasks (which are not unlike learning the sequence of sounds that make up a word form) but also requires slow, incremental contributions from the non-declarative memory system over time for the consolidation of those representations, which could explain the strengthening of form recall at the 24 hour post-test (Covington et al., 2018b). Future research designs could change levels of cueing for form and meaning tasks to further parse the relative effects of sleep on areas of rehabilitation relying heavily on non-declarative memory (e.g., physical and occupational therapy).

4.4.3 Measurement Matters in Capturing Sleep Disruption Across Phases of Chronicity

People who got more sleep each night over the course of the study remembered more words at the one week post-test. This was expected given the established body of literature showing that getting more sleep benefits memory (Cousins & Fernández, 2019; Prince & Abel, 2013; Yoo et al., 2007). Both participant group's average nightly sleep durations fell squarely in the window recommended by the Centers for Disease Control and Prevention and with age-based norms in the general population (Centers for Disease Control and Prevention, 2017; Ohayon et al., 2004).

In contrast to duration, regularity of nightly sleep quantity was not associated with word learning performance during the study period. Because actigraphy is most reliable for capturing sleep-wake cycle disruptions, whereas polysomnography is the gold standard for measuring sleep phase disruptions, it may be that this analysis did not capture changes in sleep quality or sleep phases that may contribute more to word learning (Sadeh, 2011).

Although increased sleep duration was associated with better long-term word recall for all participants, we did not find evidence for sleep as a mediator of the relationship between TBI and word learning because there were no group differences in amount or variability of nightly sleep over the course of the study period. This finding was unexpected given both subjective reports of sleep disruption extending well into the chronic phase of TBI (Duclos et al., 2014; Wiseman-Hakes et al., 2009) and a few existing actigraphy studies showing that people with TBI exhibit sleep disruption (especially hypersomnia) in the acute (Chiu et al., 2013; Duclos et al., 2017, 2020) and subacute (6 months post (Baumann et al., 2007; Imbach et al., 2015)) phases of injury.

In interpreting this result, it is important to note that this was one of only a few existing studies to objectively measure sleep for adults in chronic phase of TBI using actigraphy. Earlier studies in this population have found that adults with TBI report increased sleep need (El-Khatib et al., 2019; Imbach et al., 2016) but show limited evidence of alterations to sleep efficiency as measured via actigraphy (El-Khatib et al., 2019). In actigraphic examinations of sleep in chronic TBI, concordance with self-report has been poor (El-Khatib et al., 2019; Imbach et al., 2016; Nazem et al., 2016). Concordance between actigraphy and polysomnography, which is considered the gold standard for measuring sleep phase disturbances, is also limited in TBI (Zeitzer et al., 2020). Taking these results together, it may be that actigraphy, with its focus on sleep-wake cycle disruptions but limited ability to measure sleep phases or quality (Sadeh, 2011), does not capture the alterations in sleep phase that lead to increased sleepiness, more time in bed, and low self-perceived quality of sleep in adults with chronic TBI.

The prevalence of overt sleep-wake cycle disruption (capturable by actigraphy) may fade in the chronic phase of TBI, though disruptions to quality or efficiency of sleep via other measures like self-report and polysomnography persist. In this sample, 8 participants with TBI (16%) still slept less than 6 hours per night over the course of the study period. There was no correlation between time since onset and the included measures of sleep quantity or variability, suggesting that some subset of people with TBI will persist with overt sleep-wake deficits well into the chronic phase of injury, whereas more could persist with self-reported sleep disruptions that do not manifest in overt changes to sleep-wake cycle. Future studies examining which sleep measures capture the largest proportion of self-reported sleep disruptions, and which measures correspond most to learning performance, will help to pinpoint who benefit most from sleep interventions in the chronic phase of injury.

4.4.4 Sleep as a Manipulable Target for Improved Memory and Learning in Chronic TBI

Although there was no group difference in quantity or variability of sleep, this study represented a key contribution to the literature by objectively measuring sleep and relating it to an experimental measure of word learning for all participants, including participants in the chronic phase of TBI. Previous research shows that sleep is related to persistence of post-traumatic amnesia and neuropsychological performance in the acute and sub-acute phases of injury (Beaulieu-Bonneau et al., 2017; Bloomfield et al., 2010; Mahmood et al., 2004; Nakase-Richardson et al., 2013; Sinclair et al., 2013; Wiseman-

Hakes et al., 2011, 2013, 2019). These prior studies linking sleep to cognition in the acute phase are critical, as rehabilitation after TBI is front-loaded to the first weeks and months after injury in the current medical model. However, the acute phase is when memory, learning, and sleep are most unstable (Salmond et al., 2006). We build on these earlier findings by examining how sleep relates to memory in the chronic phase of TBI, when this connection is most stable, we know more about a person's plans for return to school or work where word learning is critical, and both sleep and the timing of learning may represent manipulable targets to improve memory and learning in functional settings. In this way, this study represents a key first step in determining the role of sleep in learning and identifying who can benefit from sleep-based learning interventions in chronic TBI.

4.4.4.1 Memory and Word Learning Underlie Rehabilitation

Memory and learning are critical for successful rehabilitation after TBI, as all therapy depends on a person's ability to learn and relearn skills (Morrow & Duff, 2020). Yet, although there has been a decrease in the number of deaths caused by TBI in the last 20 years, there has been no corresponding reduction in the rate of brain injury-related disability, including memory and learning deficits (Roozenbeek et al., 2013). Fewer than half of people with moderate-severe TBI return to work after injury (Gormley et al., 2019), and many struggle to return to school or vocational training (Duff & Stuck, 2015; Frank et al., 1997; Ownsworth & McKenna, 2004; Todis et al., 2011; Ylvisaker et al., 2003).

This study is the first demonstration of a disruption in word learning for people with TBI. This word learning disruption is consistent with well-documented deficits in memory and learning after TBI (Bigler et al., 1996; Davis & Gaskell, 2009; Palacios et al., 2013; Rabinowitz & Levin, 2014) and has significant implications for rehabilitation across functional spheres (e.g., academic and vocational settings). After injury, the ability to (re)learn words and concepts is critical to a person's potential to benefit from therapy, to follow medical recommendations, and to be successful at school or work (Morrow & Duff, 2020). For people who are unable to return to their previous vocation after TBI, the ability to learn new things is critical to transitioning to a more suitable position or engaging in vocational training. Learning words and concepts is also key to success in any therapy (e.g., completing prescribed exercises and strategies). Demonstrating and examining word learning deficits in TBI is an important step in establishing new links to understand functional outcomes and develop new intervention approaches. Our exploratory analysis also revealed correlations between word learning and performance on standardized declarative memory assessments, suggesting that these assessments may be used to identify who is most at risk for word learning disruptions after TBI.

4.4.4.2 Capitalizing on Sleep in the Rehabilitation Framework

In this study, people with TBI got a learning boost when they slept after learning, and people with and without TBI who slept more over the course of the week remembered more words in the long term. These findings suggest that rehabilitation professionals should advocate for individuals with TBI, and those who care for them, to prioritize sleep across settings and phases of injury. For example, in the acute and subacute phases of TBI, the practice of interrupting sleep with frequent nightly checks in

inpatient rehabilitation may be undermining rehabilitation potential or prolonging early-stage memory disruptions. Speech-language pathologists who work with individuals with TBI as they recover might consider recommendations that center around capitalizing on a sleep-learning boost (e.g., going over a memory book or other important information before bed). In the chronic phase, it seems that a subset of people with TBI will persist with overt sleep-wake cycle disruptions years post-injury, and others may experience sleep disturbance that is not captured in an objective measurement of sleep-wake cycle. Many of these individuals could benefit from behavioral and medical interventions that target sleep (e.g., sleep hygiene or medication) to improve a range of domains, including memory and learning. However, more research is needed to determine which objective and subjective sleep measures most relate to memory and learning and to determine candidacy for an intervention focused on sleep as a malleable target to improve memory in patients with chronic TBI.

People with TBI got a short-term boost from sleeping after learning, but that boost did not remain stable over the course of a week. Further, the TBI group's gap in performance relative to NCs grew over the course of the week in both the Wake and Sleep conditions, as evidenced by numerical score differences on form recall and meaning association. Although timing learning to coincide with sleep may present an initial learning boost, a single well-timed exposure is likely not enough to remediate a memory deficit in this population. Rather, individuals with TBI may benefit from more repetitions, and well-timed repetitions, of critical information that occurs over time and across contexts (i.e., distributed practice (Cepeda et al., 2006.; Middleton et al., 2019)). For example, it may be that multiple bedtime exposures are required to capitalize on a sleep effect for long-term retention. Examining memory and learning as phenomena that occur over time, and manipulating the presentation of information over time, may lead to more functional rehabilitation schedules for people with TBI.

Another important consideration in examining sleep after TBI is the role of naps. In inpatient rehabilitation, a focus on regaining a regular sleep rhythm often leads to attempts to keep individuals with TBI awake all day. It may be that napping in inpatient rehabilitation would in fact allow patients to benefit more from therapy in the earliest stage of injury. In this study, 8 participants with TBI and 7 NCs took a nap during the first day of their Wake condition (i.e., before the 12 hour post-test where sleep-learning benefit was assessed). Actigraphy allowed us to capture this group, whereas other prior studies relied on participant report and compliance with study protocol. In this study, the sleep-learning benefit existed even when including this napping group in the sample, and removing them did not change the significance or direction of the sleep effect. However, there is a literature in both children and adults showing that naps and rest support memory (Heim et al., 2017; van Rijn et al., 2020; van Schalkwijk et al., 2019). Given initial evidence from this study that a sleep-learning boost exists in TBI, future studies should consider how napping plays into overall sleep quantity and how it may support initial encoding and long-term memory consolidation for people with TBI. Assessing the role of naps is another important future direction in TBI research and may be particularly impactful for clinical recommendations in acute and subacute rehabilitation settings.

4.4.5 Opportunities for Further Study

The learning patterns captured in this study underscore the need for multi-post-test studies to fully understand the role of sleep and timing in long-term retention. The data for this study represent 800 scheduled sessions, 400 of which included participants with TBI. Research sessions for participants with TBI were conducted by rehabilitation specialists with clinical training, and we used a variety of techniques to promote session attendance, including mailing participants a checklist with session dates and phone and text reminders. Conducting this study online also made study participation more convenient for participants, but we used a laptop loan program to ensure that technology was not a barrier to participation. The combination of these techniques resulted in a session attendance rate above 99%. The strategies may be applied to increase success of future multi-post-test studies that examine cognitive phenomena as they occur over time and in the real world in participants with TBI. Future studies should also consider how timing of repeat exposures might extend the sleep-learning boost over time in people with and without TBI. Studies may also relate assessments of word learning over time to neuroimaging findings to elucidate how neural systems contribute to encoding and consolidation in TBI. To assess functional memory integration, future studies could also move beyond task-based assessments like those used in this study to assess usage of newly-learned words in conversational settings over the course of the experiment.

In this study, we gained ecological validity by using actigraphy to capture sleep-wake cycles over time and in participants' own homes. However, sleep-wake cycles are not sensitive to a range of sleep disruptions, including disruptions in sleep quality and reduced time spent in sleep phases critical for memory consolidation (Antony & Paller, 2017; Sadeh, 2011). Future studies should relate memory to polysomnography as a more sensitive measure of sleep phase disruption in chronic TBI. Studies that include neuroimaging will also help to elucidate how disruptions to related neural systems, such as the hippocampus and medial temporal lobes, play a role in sleep disruption, memory deficits, and their interactions in chronic TBI.

Consistent with the heterogeneity of the population of individuals with chronic TBI, there was considerable variability in word learning performance in this study sample. Future analyses and studies should harness individual differences to understand the factors that drive word learning success and to guide clinical decision making at the level of the individual. More study is also needed to understand if word learning ability is predictive of general outcomes (e.g., vocation, academic success, independent living).

4.4.6 Conclusions

People with TBI exhibit a striking word learning deficit that persists across domains and over time, representing a critical rehabilitation target. Like their neurotypical peers, people with TBI get a learning boost from sleeping after they learn and remember more when they sleep more in the long term. Rehabilitation across TBI chronicity should consider sleep and timing of learning as malleable targets to improve long-term retention. More research is needed to explore how neural systems contribute to learning and sleep deficits in TBI, how timing and repetition of exposures might contribute to maintenance of a sleep-learning boost, and which measures of sleep are

most effective in determining who will benefit from sleep-based interventions to improve memory after TBI.

Chapter 4: Main Conclusions, Opportunities, and Open Questions

People with TBI exhibit a striking word learning disruption relative to neurotypical peers. This deficit extends across word learning domains (form, meaning) and grows with time, suggesting that individuals with TBI are impaired in both encoding and consolidation of novel words. This deficit has significant functional implications across settings and represents a key target for rehabilitation.

People with and without TBI remember more when they sleep after they learn. TBI does not abolish the sleep-learning benefit. This finding has implications for clinical recommendations around timing learning to maximize benefits from sleep, although more work is needed to understand which types and intervals of exposure will best support long-term retention.

People with and without TBI remember more in the long term when they get more sleep. Although there were no group differences in quantity or variability of sleep, all participants remembered more at the 1 week post-test when they slept more over the course of the week. This finding points to the importance of sleep-related interventions in the subset of individuals with TBI who do persist with overt sleep-wake cycle disturbance in the chronic phase of injury.

We may need more sensitive measures to understand exactly how sleep affects learning after TBI. This study makes a key contribution to the literature by linking sleep-wake cycles, as objectively measured via actigraphy, to memory in chronic TBI. However, sleep-wake measurements are not sensitive to the full range of sleep disruptions, especially disruptions in sleep phases key to memory and learning. Future studies can build on this work by measuring sleep phase to determine which measures are most sensitive to 1) participant reports of sleep disruptions and 2) the components of sleep most critical for learning and long-term retention.

CONCLUDING REMARKS

In this thesis, we set out to assess how word learning, and sleep's contributions to it, may be affected by chronic moderate-severe TBI. Word learning represents both an impactful potential target for functional rehabilitation and an established avenue for exploring components and phases of learning over time. We used mediation and moderation analyses to assess the relations among TBI symptoms (word learning disruption, sleep), with the goal of untangling the complex web of post-injury symptoms to underlie future clinical-translational work aimed at improving learning by manipulating external behaviors (e.g., sleep, timing of exposure).

In this study, people with TBI exhibited a striking word learning deficit that existed across domains and delays. People with and without TBI remembered more when they slept after learning and got more sleep over the course of a week, but there were no group differences in overt sleep-wake cycles as measured via actigraphy. Future work can build on these contributions by assessing how repeat exposures across time and context can support long-term retention, how neuroimaging corresponds with sleep-learning benefit, which sleep measures best correspond with learning disruptions after injury, and how individual differences in learning and sleep can lead to more targeted interventions.

We chose these study objectives based on what individuals with TBI identified as functionally meaningful targets in conversation with the author of this thesis. Many participants in this study reported that they enjoyed the word learning task because it allowed them to "test" their own abilities in an area of great challenge: learning new things and using that knowledge over time. We hope that these findings will underlie future work in this clinically meaningful area and address remarks from one of our study participants:

"I love doing this stuff.
It helps me to understand my brain and the connections it's trying to make.
I hope we can figure out how to make those connections stronger."

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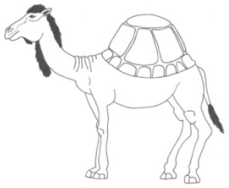
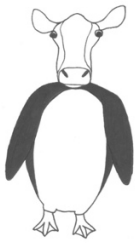
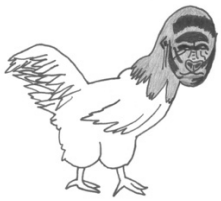
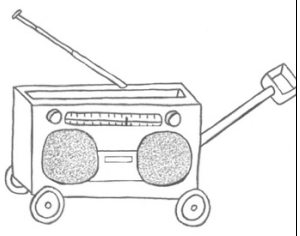
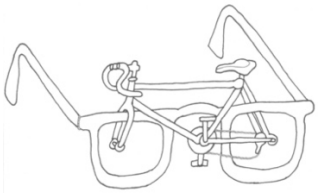
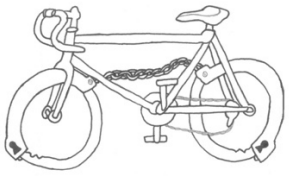
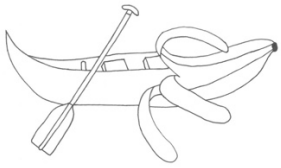
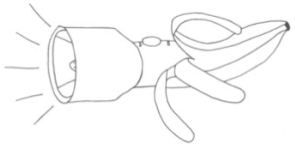
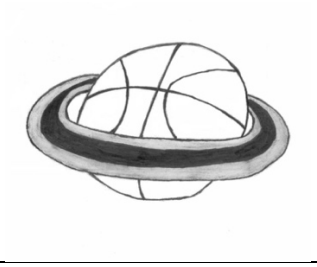
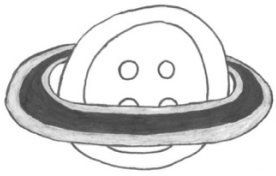
Materials and Analysis Documentation

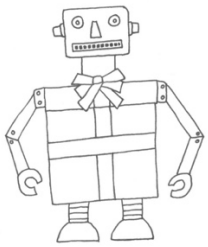
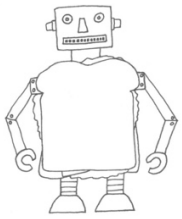
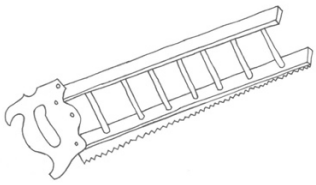
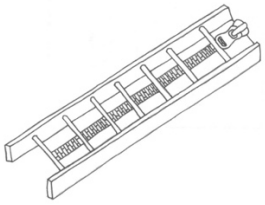
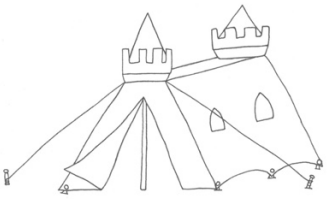
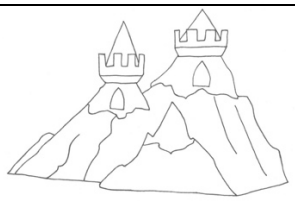
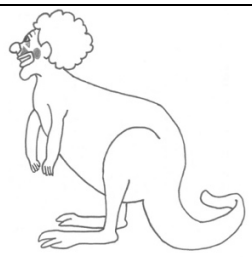
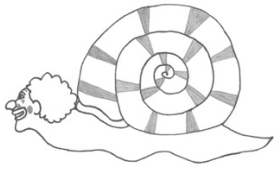
Full Stimulus Set

Stimuli were adapted from McGregor and colleagues (2013). Order of word lists was counterbalanced so that an equal proportion of participants in each group received each word list in each condition.

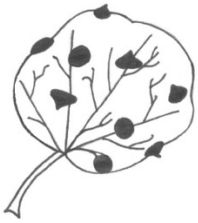
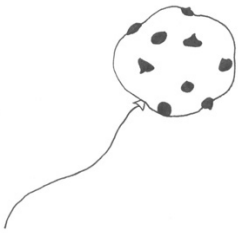
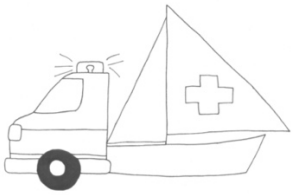
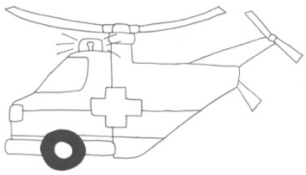
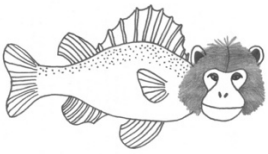
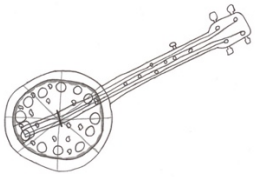
Supplementary Appendix Table 1a: List A Stimuli

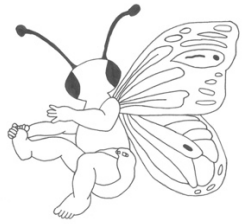
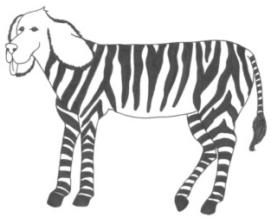
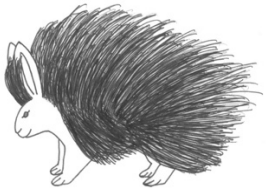
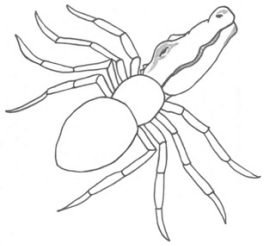
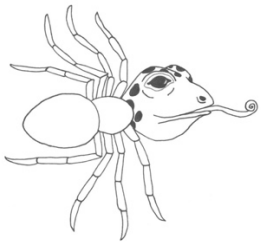
Word	Image	Training Audio	Forced Choice Word Foil	Forced Choice Referent Foil
Armo		An armo is a type of pony. The armo ate hay.	Armu	
Buckedge		A buckedge is a type of turtle. The buckedge moved slowly.	Buckev	
Fingep		A fingep is a type of sherriff. The fingep arrested the criminal.	Fingess	
Garak		A garak is a type of phone. The garak rang incessantly.	Garam	

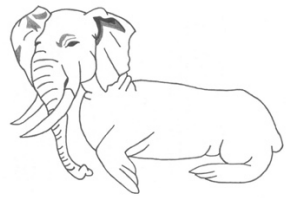
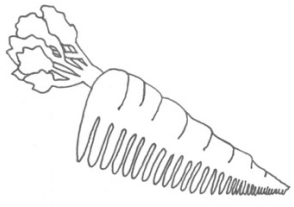
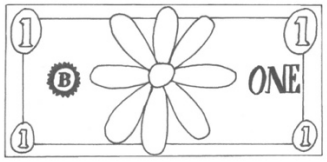
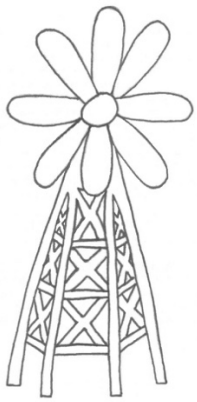
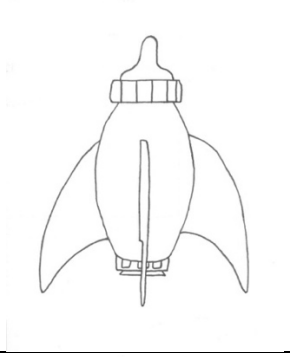
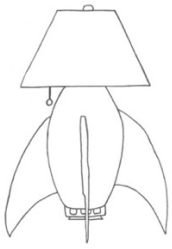
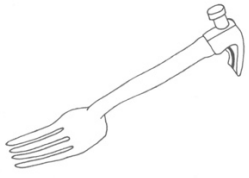
Huna		A huna is a type of penguin. The huna swam in the icy water.	Huno	
Kabib		A kabib is a type of chicken. The kabib ran from the farmer.	Kabif	
Klazem		A klazem is a type of wagon. The klazem was hard to pull.	Klazeg	
Leida		A leida is a type of bicycle. The leida had ten speeds.	Leidai	
Letev		A letev is a type of banana. The letev was not yet ripe.	Letel	
Mashig		A mashig is a type of planet. The mashig was invaded by aliens.	Mashiz	

Muvu		A muvu is a type of robot. The muvu was state- of-the-art.	Muvo	
Ofid		An ofid is a type of ladder. The ofic was dangerous to climb.	Ofik	
Partrip		A partrip is a type of monster. The partrip was kinder than he looked.	Partrim	
Pilu		A pilu is a type of castle. The pilu was drafty in the winter.	Pili	
Puzum		A puzum is a type of clown. The puzum was a bit freaky.	Puzuv	
Winteg		A winteg is a type of angel. The winteg flew through the clouds.	Winten	

Supplementary Appendix Table 1a List A stimuli.

Word	Image	Training Audio	Forced Choice Word Foil	Forced Choice Image Foil
Baskel		A baskel is a type of dragon. The baskel frightened the prince.	Baskem	
Buttep		A buttep is a type of cookie. The buttep was homemade .	Butel	
Cartook		A cartook is a type of ambulance. The cartook transported the patient.	Cartoos	
Kaptidge		A kaptidge is a type of monkey. The kaptidge amused the tourists.	Kaptik	
Kitchet		A kitchet is a type of pizza. The kitchet is a data-night favorite.	Kitchef	

Musib		A musib is a type of baby. The musib napped every afternoon.	Musin	
Oshik		An oshik is a type of dog. The oshik barked at the moon.	Oshil	
Oved		An oved is a type of rabbit. The oved hopped through the garden.	Ovek	
Pockem		A pockem is a type of spider. The pockem gave the girl the creeps.	Pocker	
Pumpkit		A pumpkit is a type of cat. The pumpkit purred loudly.	Pumpkis	
Rived		A rived is a type of paddle. The rived fell off the canoe.	Rives	

Sito		A sito is a type of elephant. The sito charged the jeep.	Sita	
Stomas		A stomas is a type of carrot. The stomas was not ripe enough to eat.	Stomab	
Tennib		A tennib is a type of flower. The tennib blooms only in early spring.	Tennitch	
Tickem		A tickem is a type of rocket. The tickem left for outer space.	Tickef	
Womal		A womal is a type of hammer. The womal was the wrong size for the carpenter's hand.	Womat	

Supplementary Appendix Table 1b List B stimuli.

Actigraphy Analysis Information

argument	value	context
R_version	R version 3.6.1 (2019-07-05)	not applicable
backup.cal.coef	retrieve	Calibration, Feature extraction, Epoch size, Time zone
chunksize	1	Calibration, Feature extraction, Epoch size, Time zone
configtz	c()	Calibration, Feature extraction, Epoch size, Time zone
dayborder	0	Calibration, Feature extraction, Epoch size, Time zone
do.anglex	FALSE	Calibration, Feature extraction, Epoch size, Time zone
do.angley	FALSE	Calibration, Feature extraction, Epoch size, Time zone
do.anglez	TRUE	Calibration, Feature extraction, Epoch size, Time zone
do.bfen	FALSE	Calibration, Feature extraction, Epoch size, Time zone
do.cal	TRUE	Calibration, Feature extraction, Epoch size, Time zone
do.dev_roll_med_acc_x	FALSE	Calibration, Feature extraction, Epoch size, Time zone
do.dev_roll_med_acc_y	FALSE	Calibration, Feature extraction, Epoch size, Time zone
do.dev_roll_med_acc_z	FALSE	Calibration, Feature extraction, Epoch size, Time zone

do.en	FALSE	Calibration, Feature extraction, Epoch size, Time zone
do.enmo	TRUE	Calibration, Feature extraction, Epoch size, Time zone
do.enmoa	FALSE	Calibration, Feature extraction, Epoch size, Time zone
do.hfen	FALSE	Calibration, Feature extraction, Epoch size, Time zone
do.hfenplus	FALSE	Calibration, Feature extraction, Epoch size, Time zone
do.lfen	FALSE	Calibration, Feature extraction, Epoch size, Time zone
do.lfenmo	FALSE	Calibration, Feature extraction, Epoch size, Time zone
do.mad	FALSE	Calibration, Feature extraction, Epoch size, Time zone
do.roll_med_acc_x	FALSE	Calibration, Feature extraction, Epoch size, Time zone
do.roll_med_acc_y	FALSE	Calibration, Feature extraction, Epoch size, Time zone
do.roll_med_acc_z	FALSE	Calibration, Feature extraction, Epoch size, Time zone
dynrange	c()	Calibration, Feature extraction, Epoch size, Time zone
hb	15	Calibration, Feature extraction, Epoch size, Time zone
lb	0.5	Calibration, Feature extraction, Epoch size, Time zone

minloadcrit	72	Calibration, Feature extraction, Epoch size, Time zone
myfun	c()	Calibration, Feature extraction, Epoch size, Time zone
print.filename	FALSE	Calibration, Feature extraction, Epoch size, Time zone
printsummary	TRUE	Calibration, Feature extraction, Epoch size, Time zone
windowsizes	c(5,900,3600)	Calibration, Feature extraction, Epoch size, Time zone
acc.metric	ENMO	General parameters
bout.metric	6	General parameters
config_file_in_outputdir	/Users/emilylmorrow/Desktop/Output//output_WordLearning/config.csv	General parameters
data_cleaning_file	c()	General parameters
datadir	/Volumes/Drive/WordLearning/	General parameters
desiredtz		General parameters
do.bfx	FALSE	General parameters
do.bfy	FALSE	General parameters
do.bfz	FALSE	General parameters
do.hfx	FALSE	General parameters
do.hfy	FALSE	General parameters
do.hfz	FALSE	General parameters
do.lfx	FALSE	General parameters
do.lfy	FALSE	General parameters
do.lfz	FALSE	General parameters
do.parallel	TRUE	General parameters
do.report	c(2,4,5)	General parameters
do.sibreport	FALSE	General parameters
do.zcx	FALSE	General parameters
do.zcy	FALSE	General parameters
do.zcz	FALSE	General parameters
excludefirst.part4	FALSE	General parameters

excludelast.part4	FALSE	General parameters
f0	1	General parameters
f1	101	General parameters
frag.metrics	c()	General parameters
GGIRversion	2.5-0	General parameters
HASIB.algo	vanHees2015	General parameters
HASPT.algo	HDCZA	General parameters
HASPT.ignore.invalid	FALSE	General parameters
i	39	General parameters
idloc	1	General parameters
includedaycrit.part5	7	General parameters
interpolationType	1	General parameters
longitudinal_axis	c()	General parameters
LUX_cal_constant	c()	General parameters
LUX_cal_exponent	c()	General parameters
LUX_day_segments	c()	General parameters
LUXthresholds	c(0,100,500,1000,3000,5000,10000)	General parameters
maxNcores	c()	General parameters
minimum_MM_length.part5	7	General parameters
minimumFileSizeMB	2	General parameters
mode	c(1,2,3,4,5)	General parameters
MX.ig.min.dur	10	General parameters
outputdir	/Users/emilylmorrow/Desktop/Output/	General parameters
overwrite	FALSE	General parameters
part5_agg2_60seconds	FALSE	General parameters
qwindow_dateformat	%d-%m-%Y	General parameters
relyonguider	FALSE	General parameters

rmc.bitrate	c()	General parameters
rmc.check4timegaps	FALSE	General parameters
rmc.col.acc	c(1,2,3)	General parameters
rmc.col.temp	c()	General parameters
rmc.col.time	c()	General parameters
rmc.col.wear	c()	General parameters
rmc.dec	.	General parameters
rmc.desiredtz		General parameters
rmc.doresample	FALSE	General parameters
rmc.dynamic_range	c()	General parameters
rmc.firstrow.acc	c()	General parameters
rmc.firstrow.header	c()	General parameters
rmc.format.time	%Y-%m-%d %H:%M:%OS	General parameters
rmc.header.length	c()	General parameters
rmc.header.structure	c()	General parameters
rmc.headername.recordingid	c()	General parameters
rmc.headername.sf	c()	General parameters
rmc.headername.sn	c()	General parameters
rmc.noise	FALSE	General parameters
rmc.origin	1/1/70	General parameters
rmc.sf	c()	General parameters
rmc.unit.acc	g	General parameters
rmc.unit.temp	C	General parameters
rmc.unit.time	POSIX	General parameters
rmc.unsignedbit	TRUE	General parameters
Sadeh_axis		General parameters
save_ms5raw_format	csv	General parameters

save_ms5raw_without_invalid	TRUE	General parameters
selectdaysfile	c()	General parameters
sensor.location	wrist	General parameters
sleeplogsep	,	General parameters
sleepwindowType	SPT	General parameters
storefolderstructure	FALSE	General parameters
studyname	c()	General parameters
week_weekend_aggregate.part5	FALSE	General parameters
anglethreshold	5	Parameters sleep detection
constrain2range	TRUE	Parameters sleep detection
ignorenonwear	TRUE	Parameters sleep detection
timethreshold	5	Parameters sleep detection
colid	1	Parameters sleep period time detection with or wihout sleeplog
coln1	1	Parameters sleep period time detection with or wihout sleeplog
criterror	3	Parameters sleep period time detection with or wihout sleeplog
def.noc.sleep	1	Parameters sleep period time detection with or wihout sleeplog
do.visual	TRUE	Parameters sleep period time detection with or wihout sleeplog
excludefirstlast	FALSE	Parameters sleep period time detection with or wihout sleeplog
includenightcrit	ll	Parameters sleep period time detection with or wihout sleeplog

loglocation	c()	Parameters sleep period time detection with or wihout sleeplog
nnights	c()	Parameters sleep period time detection with or wihout sleeplog
outliers.only	FALSE	Parameters sleep period time detection with or wihout sleeplog
relyonsleeplog	FALSE	Parameters sleep period time detection with or wihout sleeplog
sleeplogidnum	TRUE	Parameters sleep period time detection with or wihout sleeplog
boutcriter.in	0.8	Parameters time-use variables
boutcriter.lig	0.8	Parameters time-use variables
boutcriter.mvpa	0.8	Parameters time-use variables
boutdur.in	1	Parameters time-use variables
boutdur.lig	1	Parameters time-use variables
boutdur.mvpa	1	Parameters time-use variables
excludefirstlast.part5	FALSE	Parameters time-use variables
save_ms5rawlevels	FALSE	Parameters time-use variables
threshold.lig	44.8	Parameters time-use variables
threshold.mod	100.6	Parameters time-use variables
threshold.vig	428.8	Parameters time-use variables
timewindow	c(MM,WW)	Parameters time-use variables
boutcriter	0.8	Study design, Parameters descriptive analysis
closedbout	FALSE	Study design, Parameters descriptive analysis

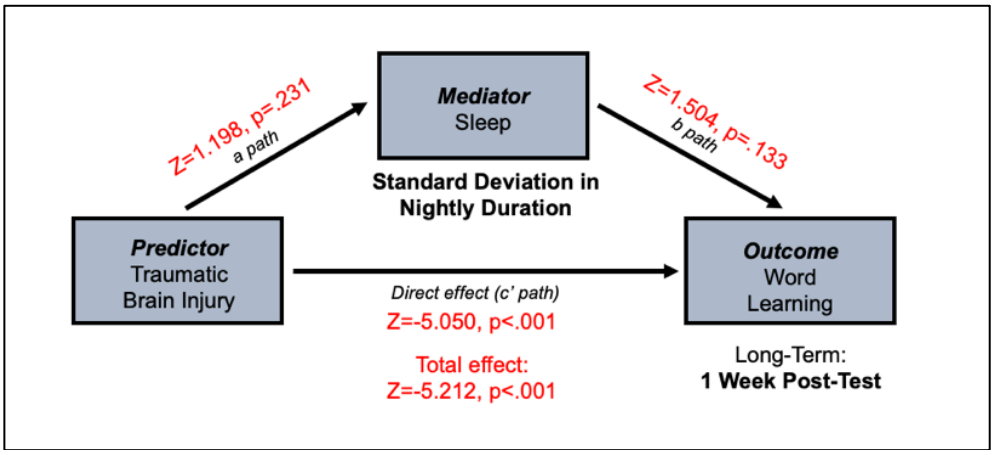
do.imp	TRUE	Study design, Parameters descriptive analysis
do.part3.pdf	TRUE	Study design, Parameters descriptive analysis
epochvalues2csv	FALSE	Study design, Parameters descriptive analysis
hrs.del.end	1	Study design, Parameters descriptive analysis
hrs.del.start	1	Study design, Parameters descriptive analysis
iglevels	c()	Study design, Parameters descriptive analysis
ilevels	c()	Study design, Parameters descriptive analysis
includedaycrit	11	Study design, Parameters descriptive analysis
IVIS_epochsize_seconds	NA	Study design, Parameters descriptive analysis
IVIS_windowsize_minutes	60	Study design, Parameters descriptive analysis
IVIS.activity.metric	2	Study design, Parameters descriptive analysis
M5L5res	10	Study design, Parameters descriptive analysis
maxdur	14	Study design, Parameters descriptive analysis
mvpadur	c(1,5,10)	Study design, Parameters descriptive analysis
mvpathreshold	100.6	Study design, Parameters descriptive analysis
ndayswindow	7	Study design, Parameters descriptive analysis
qlevels	c()	Study design, Parameters descriptive analysis
qM5L5	c()	Study design, Parameters descriptive analysis
qwindow	c(8,20,24)	Study design, Parameters descriptive analysis
strategy	1	Study design, Parameters descriptive analysis
TimeSegments2ZeroFile	c()	Study design, Parameters descriptive analysis

window.summary.size	10	Study design, Parameters descriptive analysis
winhr	5	Study design, Parameters descriptive analysis
dofirstpage	TRUE	Visual report
viewingwindow	1	Visual report
visualreport	TRUE	Visual report

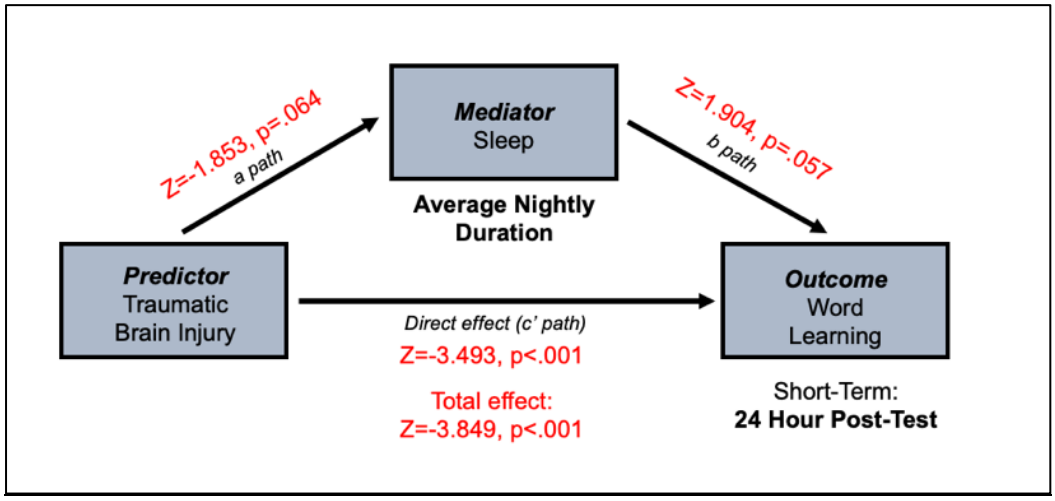
Supplementary Appendix Table 2 GGIR configuration information.

Results Visualizations

Supplementary Appendix Figure 1 Visualizations of path analyses for mediation models.

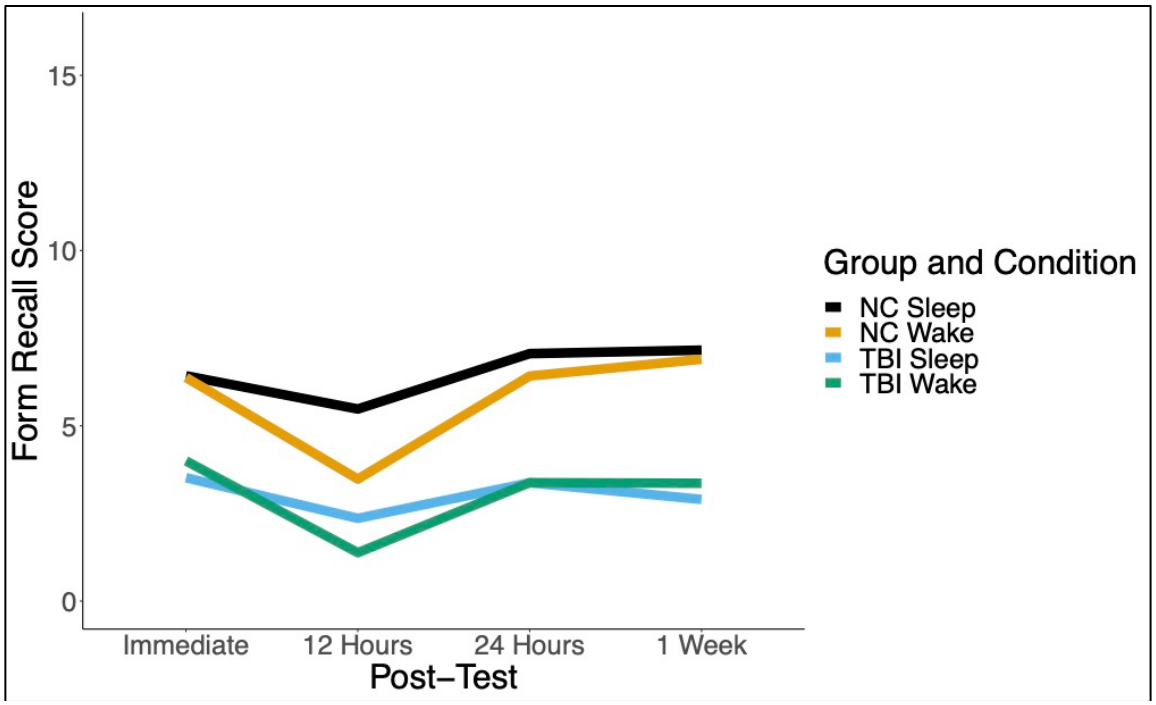


Supplementary Appendix Figure 1a Path estimates for model assessing standard deviation in nightly sleep duration as a potential mediator of the relationship between TBI diagnosis and long-term word recall (form recall at the one week post-test).

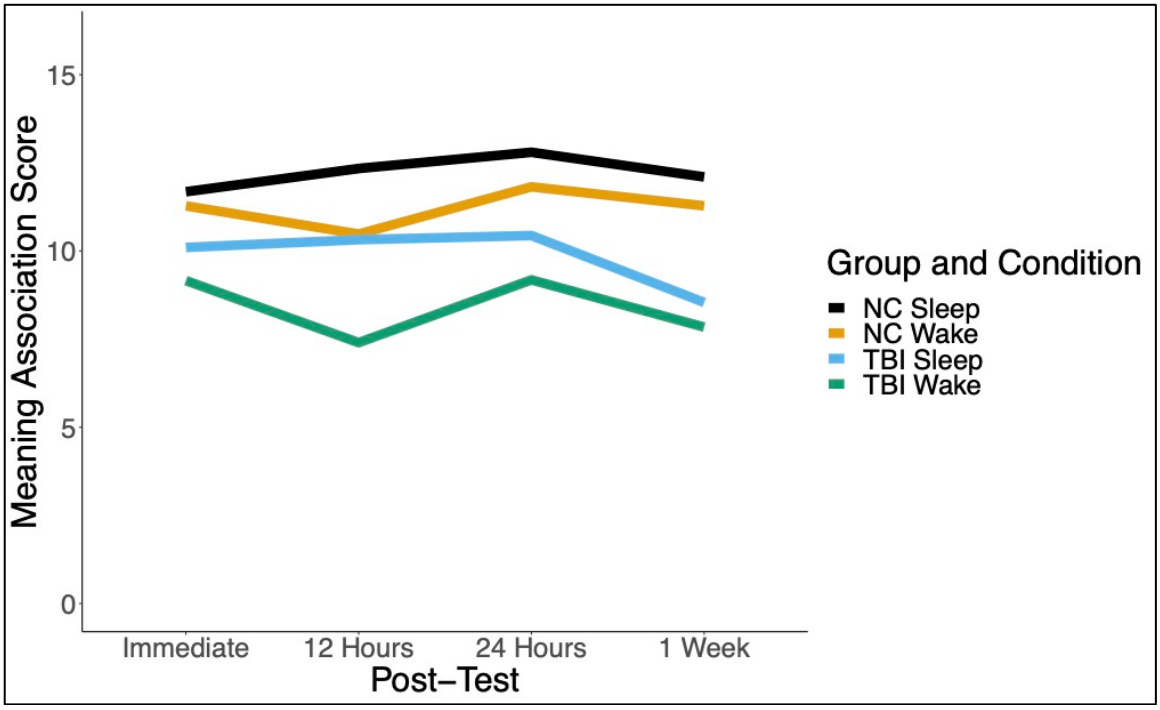


Supplementary Appendix Figure 1b Path estimates for model assessing average nightly sleep duration as a potential mediator of the relationship between TBI diagnosis and short-term word recall (form recall at the 24 hour post-test).

Additional Task Performance Data



Supplementary Appendix Figure 2 Form recall scores by group and condition at each post-test.



Supplementary Appendix Figure 3 Meaning association scores by group and condition at each post-test.

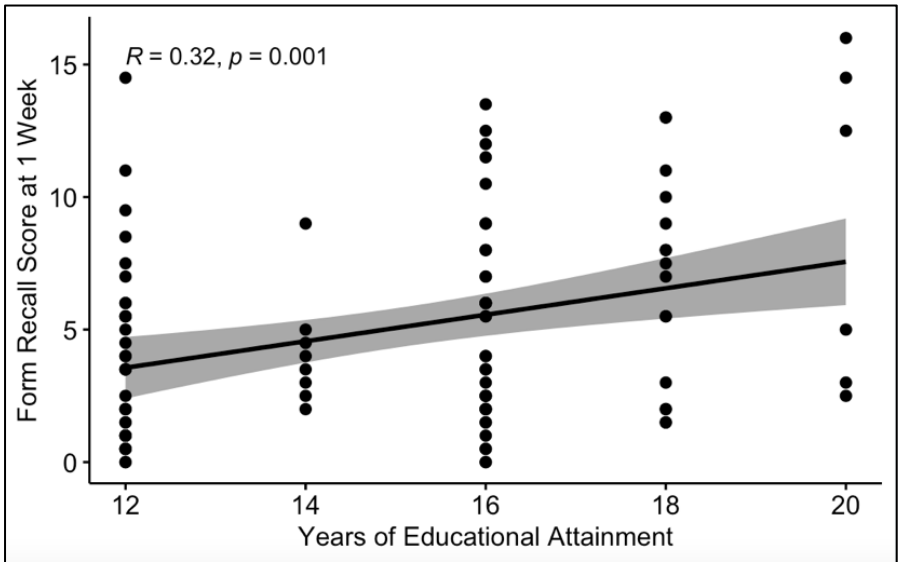
Exploratory Analyses of Demographic and Neuropsychological Variables

Relations between Word Learning, Age, and Education

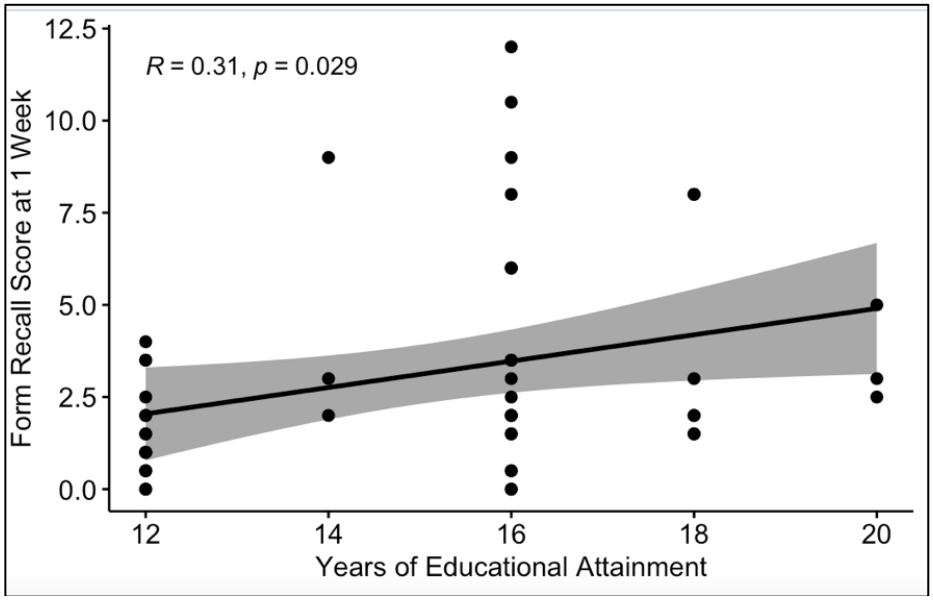
This study represents a contribution to the word learning literature on neurotypical individuals, as well, as we sampled a wider range of age and educational attainment than typical word learning studies conducted in young adults (Dumay et al., 2004; Dumay & Gaskell, 2007; McGregor et al., 2013).

There are strong associations in the scientific literature between age and memory and learning abilities (Grady & Craik, 2000; Mitchell et al., 2000). We conducted an ad hoc analysis to assess whether age was related to form recall at the long-term (one week) post-test for all participants (with and without a history of TBI). Age was not correlated with form recall performance at one week (R=-.086, p=.39). The same was true within the group of participants with TBI (R=.24, p=.10).

Supplementary Appendix Figure 4 Correlations between word learning and demographic variables.



Supplementary Appendix Figure 4a There is an association in the literature between education and task performance/recovery in TBI (Gauthier et al., 2018), and the ability to learn new words and concepts is critical to academic success. We conducted an ad hoc analysis to assess whether educational attainment was related to form recall at the long term (one week) post-test for all participants (with and without a history of TBI). Educational attainment was correlated with form recall scores at one week (R=-.32, p=.001).



Supplementary Appendix Figure 4b Educational attainment was also correlated with form recall scores within the group of participants with TBI (R=.31, p=.029).

Relations between Word Learning Task and Canonical Neuropsychological Measures for Participants with TBI

There are increasing calls in the scientific literature to assess how experimental tasks relate to performance on canonical neuropsychological measures. Such analyses may motivate the development of certain experimental tasks into more sensitive, specific, or functional measures of cognition that may be deployed in a clinical setting (McAndrews et al., 2020). Participants in this study (49 participants with TBI and 44 NCs) completed the following neuropsychological measures in addition to their participation in the word learning task:

Auditory Verbal Learning Test (AVLT): Participants completed the AVLT as a standardized measure of declarative memory (Schmidt, 1996). The AVLT is one of the most widely-used verbal learning tests in both research and clinical practice. Participants hear a list of 15 real words five times and attempt to free recall the words after each repetition. We test free recall for the 15 words again after a 30 minute filled delay. We use immediate (repetition of the target words after hearing the list once) and delayed (repetition of the target words after a 30 minute filled delay) recall from the AVLT in exploratory analyses to assess how the experimental word learning task compares to a widely-used standardized verbal learning assessment.

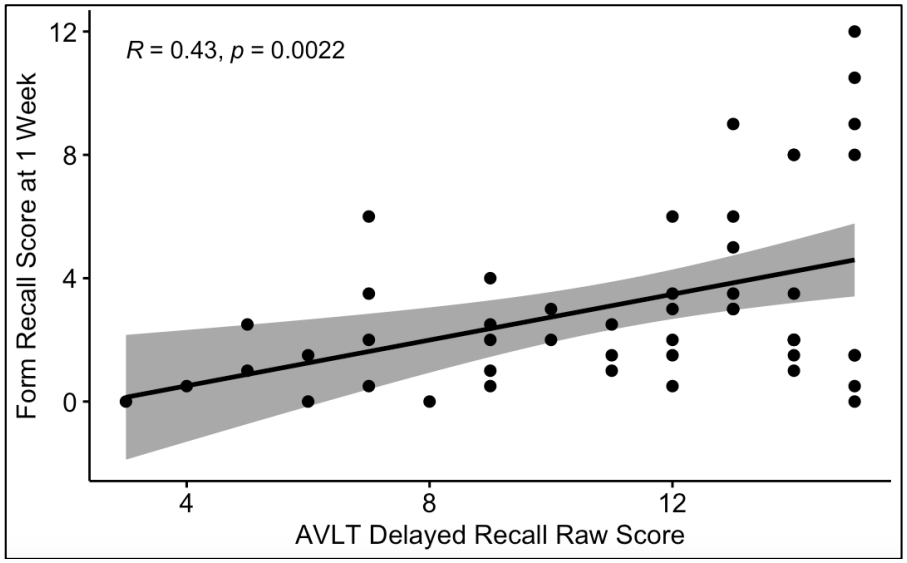
Weschler Adult Intelligence Scale (WAIS)- IV Digit Span and Letter-Number Sequencing: Participants also completed the Digit Span and Letter-Number Sequencing subtests of the Weschler Adult Intelligence Scale (WAIS-IV) as standardized assessments of working memory (Weschler, 2008). In the Digit Span task, the experimenter reads aloud strings of numbers of increasing length, and participants repeat them in three sections: forward (in the same order the experiment said them), backward (in reverse order), and rearranged to be in numerical order. In Letter-Number sequencing, the experimenter reads aloud strings of letters and numbers, and participants repeat them with the numbers first in numerical order, then the letters in alphabetical order. We used age-corrected standard scores from both subtests to assess how the experimental word learning task compares to a widely-used standardized working memory assessment.

Neuropsychological Measure	Group	Performance Correct (SD)	p / effect size
AVLT Trial I Raw Score	NC	9.4 (2.6)	p <.001 Cohen's d = .954
	TBI	7.2 (2.0)	
AVLT Delayed Recall Raw Score	NC	13.5 (1.7)	p <.001 Cohen's d = .864
	TBI	11.1 (3.4)	
WAIS Digit Span Scaled Score	NC	12.4 (2.6)	p = .062 Cohen's d = .394
	TBI	11.3 (2.9)	
WAIS Letter-Number Sequencing Scaled Score	NC	12.8 (3.6)	p <.001 Cohen's d = .780
	TBI	10.3 (2.7)	

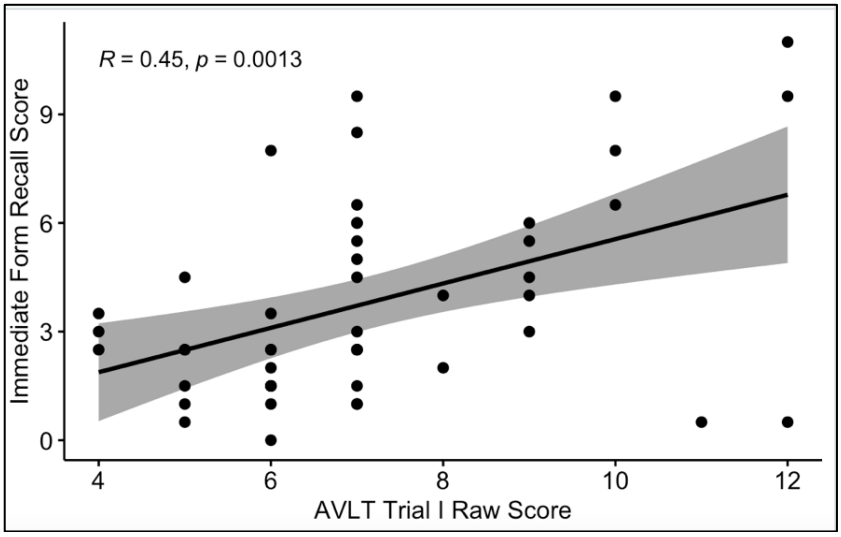
Supplementary Appendix Table 3 Group means for neuropsychological measures.

We assessed relations between the neuropsychological measures and the word learning task for participants with TBI using Pearson's correlations. The NC and TBI groups differed significantly on all measures except the WAIS Digit Span Scaled Score.

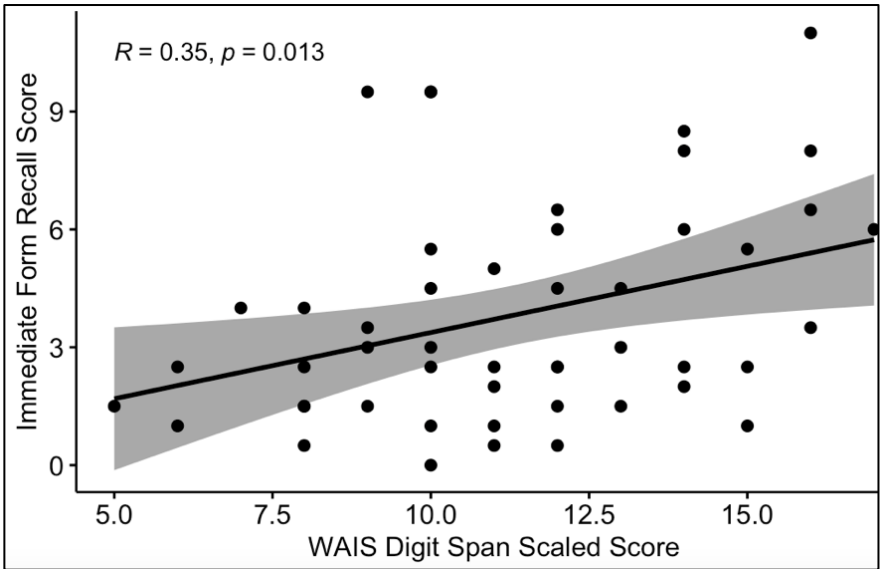
Supplementary Appendix Figure 5 Correlations between neuropsychological measures and word learning performance within the TBI group.



Supplementary Appendix Figure 5a We first assessed the correlation between the Delayed Recall score on the AVLT (raw score representing the number of words recalled after a 30 minute filled delay, out of a possible 15) and form recall score (raw score representing the number of word forms recalled, out of a possible 16) at the one week post-test. The two were related, such that participants with TBI who scored higher on the AVLT also performed better on the word learning task (R=.43, p<.001).



Supplementary Appendix Figure 5b We next assessed the correlation between the Trial I score on the AVLT (raw score representing the number of words recalled when repeating them immediately after learning, out of a possible 15) and form recall (raw score representing the number of word forms recalled out of a possible 16) at the immediate post-test. The two were related, such that participants with TBI who scored higher on the AVLT also performed better on the word learning task (*R*=.45, *p*=.001).



Supplementary Appendix Figure 5c Next, we assessed whether the scaled score on Digit Span (a working memory measure, adjusted for participant age) was related to form recall (raw score representing the number of word forms recalled out of a possible 16) at the immediate post-test. The two were related (*R*=.35, *p*=.01).

Finally, we assessed whether the scaled score on WAIS Letter-Number Sequencing (a working memory measure, adjusted for participant age) was related to form recall (raw score representing the number of word forms recalled out of a possible 16) at the immediate post-test. The two were not related (R=.35, p=.14).

Relations Between Sleep, Demographic, and Injury Characteristics

Given the established literature showing that age affects sleep quantity and variability (Ohayon et al., 2004), we assessed whether age was correlated with sleep quantity or variability in our entire sample. Age was not correlated nightly sleep duration (R=.017, p=.87) or standard deviation of nightly sleep duration (R=-.19, p=.06.

As earlier studies using actigraphy to objectively measure sleep occurred in the more acute phases of TBI (Baumann et al., 2007; Duclos et al., 2017; Imbach et al., 2015), we assessed whether time since onset was correlated with sleep quantity in this sample of participants with TBI. It was not (R=-.14, p=.36).