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The Growing Gap: A Study of Sleep, Encoding, and Consolidation of New Words in Chronic Traumatic Brain Injury

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Abstract

Word learning is an iterative and dynamic process supported by multiple neural and cognitive systems. Converging evidence from behavioral, cellular, and systems neuroscience highlights sleep as an important support for memory and word learning over time. In many lab-based word learning experiments, participants encode and subsequently retrieve newly learned words in a single session. These designs are inadequate to capture the full dynamic word learning process, making them less ecologically valid. Single timepoint studies also limit investigation of the role of behavioral and lifestyle factors, like sleep, in supporting word learning over time. Adults with a history of traumatic brain injury (TBI), who commonly exhibit deficits in the memory systems that support word learning and report concomitant sleep disturbance, provide a unique opportunity to examine the link between memory, sleep, and word learning. Here we examined word learning over time and the influence of sleep on short- and long-term word recall in 50 adults with chronic moderate-severe TBI and 50 demographically matched neurotypical peers. We used a randomized within-participant crossover design to assess immediate encoding of new words and the consolidation of those words over time across intervals that did or did not involve sleep. Participants completed this study over the course of two weeks in their own homes to capture the iterative, dynamic process of real-world word learning. We also measured sleep in free living conditions using actigraphy throughout the experiment. Participants with TBI exhibited a word learning deficit that began at encoding and persisted across time. Critically, this deficit grew over the course of the week. The performance gap between groups was larger at the 1-week post-test than the immediate post-test, suggesting deficits in both encoding and consolidation of new words in individuals with TBI. Participants with and without TBI remembered more words when they

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slept after learning. Ecologically valid research designs that examine the relationship between memory, sleep, and word learning over time promise to advance mechanistic accounts of word learning and improve the long-term retention of new words in individuals with and without brain injury.

Keywords

learning; memory; sleep; consolidation; traumatic brain injury

1.1 Memory and Word Learning

Word learning is an iterative and dynamic process. 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). Word learning is also inherently relational in nature, requiring the binding and flexible use of the arbitrary relations between orthographic and phonetic forms and physical and conceptual referents (Davis & Gaskell, 2009; Duff et al., 2020; N. B. Klooster et al., 2020) across variable contexts of use.

The relational nature of word learning places high demands on the declarative memory system (Davis & Gaskell, 2009; Duff et al., 2020; Eichenbaum & Cohen, 2001; McGregor et al., 2013). The declarative memory system supports 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). Evidence for the role of declarative memory in word learning comes from the observation of profound word learning deficits in individuals with adult-onset hippocampal damage and declarative memory deficits (e.g., Gabrieli et al., 1988; Warren & Duff, 2014). We note that many studies of declarative memory focus on specific aspects of declarative knowledge including semantic memory (memory for words, facts, and general knowledge) and episodic memory (memory for context specific autobiographical events) (Tulving, 1972). Word learning, both in naturalistic contexts and in laboratory experiments, requires episodic and semantic memory processes. Indeed, in this study we use well-established episodic memory paradigms to measure the encoding and retrieval of semantic information over time. Consistent with perspectives pointing to the interdependence and shared neural mechanisms of semantic and episodic memory (Duff et al., 2020; Greenberg & Verfaellie, 2010; Irish & Piguet, 2013; Renoult et al., 2019), we do not attempt to separate them. As such, we describe word learning as depending broadly on the processes of declarative memory.

Historical attempts to study the role of memory in word learning in both neurotypical and clinical populations have largely occurred in a single experimental session during which

participants encode and subsequently retrieve newly learned words (see Duff et al., 2020, for review). Yet, 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, single-session designs are inadequate to capture the full dynamic word learning process over time, making them less ecologically valid (Morrow & Duff, 2022). Single-session experiments also constrain the context of learning to a single setting and time of day, which is in direct contrast to the way that learning plays out across context, time, and space (Morrow & Duff, 2022). Moreover, single timepoint designs also limit the ability to investigate behavioral and lifestyle factors (e.g., sleep, exercise) that may promote new word learning over time. By contrast, multi post-test experimental designs have become the gold standard for studying word learning and sleep consolidation benefits because they offer a robust way to examine learning of word form and meaning, as well as sleep's role in supporting memory consolidation, over time (Davis & Gaskell, 2009; Dumay & Gaskell, 2007; Gaskell et al., 2019; Morrow & Duff, 2022).

In this study, we examined the word learning process over time in adults with and without a chronic history of traumatic brain injury (TBI). We used a multi post-test schedule to study the encoding and retrieval of novel words using a well-established paradigm (Dumay et al., 2004; Dumay & Gaskell, 2007; McGregor et al., 2013). This design allowed examination of how TBI affects multiple stages of word learning in free living contexts, as well as how neurological injury affects the role of sleep in supporting the learning process over time.

1.2 Sleep Supports Memory and Learning

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; Schechtman et al., 2022; 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 and learning (Cousins & Fernández, 2019; Guttesen et al., 2022; 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). Sleep is critical to memory and learning in the neurotypical brain, but there is limited research exploring the effects of neurological injury on the relationship between sleep and memory, especially with regard to the role of sleep in long-term recall and the memory process over time. Sleep may present a critical, and malleable, target for examining and supporting memory and learning in patients following brain injury (Morrow & Duff, 2020). However, more research using ecologically valid sleep and learning measurements is needed to assess whether sleep supports learning in those with neurological injury, as it does in neurotypical individuals.

1.3 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 (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 (McClelland, 2013; McClelland & McNaughton, 1995). 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; Schechtman et al., 2022). Sleep is thought to be particularly critical for the consolidation phase of learning (Antony & Paller, 2017; Schechtman et al., 2022; 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; Cohen & Banich, 2003). 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 neurotypical 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 (Morrow & Duff, 2022).

1.4 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. 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. The short time course of differential sleep effects for the word form tasks suggested that sleep promotes consolidation, and there may be a shorter time course for consolidation of word form than meaning.

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).

In each of these experimental protocols, multi post-test designs supported a robust examination of learning of word form and meaning, as well as sleep's role in supporting memory consolidation, over time. These protocols may also promote better understanding of how learning of words and concepts develop over time after brain injury, advancing mechanistic accounts and rehabilitation of word learning.

1.5 The Relation Between Sleep and Word Learning in Individuals with Traumatic Brain Injury

The memory systems that support word learning in neurotypical individuals are among the most vulnerable to traumatic brain injury (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, word learning has received little attention in the TBI literature despite its importance in academic, vocational, and rehabilitation success (Morrow & Duff, 2022).

An understanding of the role of sleep in word learning may be particularly consequential for individuals with TBI (Lowe et al., 2020; Wiseman-Hakes et al., 2009). Current estimates indicate that ~ 50% of (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). 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).

Despite findings 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 that objectively measure and experimentally test how sleep affects learning, and word learning specifically, in individuals with TBI. Furthermore, the severity and nature of word learning deficits, and sleep's role in learning over time for people with TBI, remain unknown

1.6 The Current Study

To address these gaps in the literature, we used actigraphy to objectively measure sleep in participants' daily routines, then combined that measurement with long-term word learning protocols, to determine how sleep supports word learning over time in individuals with TBI relative to neurotypical comparison (NC) peers. To increase ecological validity, we moved beyond single-timepoint designs by evaluating learning over time and in participants' home environments using established protocols from the word learning literature (Dumay et al., 2004; Dumay & Gaskell, 2007; McGregor et al., 2013). 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 NCs 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 two specific aims:

1. **To investigate word learning in individuals with 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 NCs when tested immediately after training (i.e., impaired encoding). We expected this deficit to extend across domains and over the course of the experiment. We planned to explore how patterns in word learning differed over time between participants with TBI and neurotypical peers.
2. **To determine how sleep affects word learning in individuals with 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 expected that TBI would attenuate the sleep-learning benefit, such that individuals with TBI would show a smaller benefit from sleep than NCs.

2. Methods

2.1 Participants

Participants were 50 adults in the chronic phase (>6 months post-injury, mean time since injury = 5.4 years (SD: 5.4)) of moderate-severe TBI (28 female) and 50 demographically matched NCs (28 female). They were recruited from the Vanderbilt Brain Injury Patient Registry (Duff et al., 2022) 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. All participants had normal or corrected-to-normal hearing and vision per lab screening protocols or self-report.

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) <13 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 1 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), so no participants sustained developmental TBIs. 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.

2.1.2 Participant Matching—

NCs 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); $t(98) = .000$, $p = 1.0$).

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.

2.2.1 Study Timeline—

Participants completed 8 sessions over 2 weeks. During the first week, each participant was randomly assigned to complete 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

[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.

& 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 2). 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).

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 2.2.3 Sleep Measurement via 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.

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). We primarily used actigraphy to verify that participants did or did not sleep in the appropriate conditions, so the ability to monitor participants' sleep patterns in their home environments was a key manipulation check.

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.

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% for form recall and 94% for meaning association.

2.3 Measures

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 1). 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.

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. Each block consisted of 1 exposure to each of the 16 words, for a total of 12 exposures for each word during the training. The words were presented via visual and auditory stimuli. Participants saw the image depicting each word for a total of 8 seconds. During that time, they heard the word, the definition of the word, and a sentence containing the word (see Figure 1). After a 1.5 second pause, they saw the next word. The 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):

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).

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.

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.

For this study, we 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).

2.4 Statistical Analyses

2.4.1 Inclusion—To be included in analyses, participants had to answer at least 80% of the attention check questions correctly during both training sessions.

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 sleep analysis (Aim 2) using form recall as the outcome measure.

Aim 1: To investigate word learning in individuals with 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 TBI and NCs. This analysis combined performance across two sessions, as we pooled immediate scores in the Wake and Sleep conditions because 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 charted group 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.

Finally, we explored how patterns of word learning differed over time between participants with TBI and NC peers. We compared performance on form recall at the immediate post-test to the 1-week post-test for both groups using a mixed effects linear model. In this 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.

Aim 2: To determine how sleep affects word learning in individuals with 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 the same test for NCs. Next, we conducted two between-groups independent-samples t-tests (one in the Wake and one in the Sleep condition) comparing participants with TBI to NCs2. Our sample size was adequate to detect a medium effect size (0.5) at alpha .05 for each of these group comparisons.

We conducted an exploratory mixed-effects linear regression model to assess whether the difference in effect sizes between groups was statistically significant, indicating that sleep moderated the relationship between TBI and word learning. In this model, the outcome was form recall score at the 12 hour post-test. Predictors were group (TBI vs. NC), condition (Sleep vs. Wake), and their interaction. We also included random intercepts to account for variability nested within participants.

[2]Our primary analysis included all participants who had completed the immediate trainings and 12-hour post-tests in both the Wake and Sleep 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.

3. Results

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 one 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 80.0% 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), 2 for calibration failure as reported by the GGIR package, and 1 for insufficient wear (i.e., < 7 days of complete actigraphy data from the experiment period). The remaining 95 participants (46 participants with TBI and 49 NCs) had actigraphy data to verify sleep in each condition.

3.2 Aim 1: To investigate word learning in individuals with TBI

3.2.1 Primary Word Learning Task—To assess encoding of the novel words, we examined performance on the form recall task at the immediate post-test. When performance was collapsed across the Wake and Sleep conditions, participants with TBI recalled a 3.8 (SD: 2.8) words, on average, compared to 6.4 (SD: 3.7) words, on average, for NCs, with a statistically significant difference with a large effect size [$t(91.53)=3.96$, $p<.001$, Cohen's $d=.79$].

3.2.2 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, on average, for NCs. This was a moderate effect size [$t(97.29)=2.56$, $p=.01$, Cohen's $d=.51$].

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 $d=.60$].

3.2.3 Word Learning Over Time

3.2.3.1 Primary Word Learning Task: Form Recall: Next, we examined patterns of word learning over time. On the form recall task, participants with TBI produced fewer

words, on average, than NCs at every post-test (collapsed across the Wake and Sleep conditions) (Figure 2; Table 3). 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 1-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.

3.2.3.2 Secondary Word Learning Task: Meaning Association: On the cued meaning association task, participants with TBI recalled fewer word meanings than NCs at every post-test (collapsed across the Wake and Sleep conditions) (Table 3). At the 12-hour post-test, participants with TBI recalled an average of 8.9 word meanings (SD: 4.1), and NCs recalled an average of 11.4 word meanings (SD: 3.5). At 24 hours, participants with TBI recalled, on average, 9.6 word meanings (SD: 4.1), compared to 12.3 word meanings (SD: 3.4) for NCs. One week after learning, participants with TBI recalled an average of 8.2 word meanings (SD: 3.9), compared to 11.7 word meanings (SD: 3.5) for neurotypical peers. See Table 3 for group means on form recall and meaning association, averaged across the Wake and Sleep conditions, at each post-test.

3.2.3.3 Exploratory Model Assessing Patterns of Word Learning Over Time: In our exploratory model comparing group performance on form recall at the immediate and 1-week post-tests, 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 the performance gap between groups was larger at the 1-week post-test than the immediate post-test (interaction estimate = −1.289, $t = -3.583$, $p < .001$).

3.2.4 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 3 for a visualization of individual differences in word learning performance.

3.3 Aim 2: To determine how sleep affects word learning in individuals with TBI

3.3.1 Sleep—Although actigraphy was used primarily to verify that participants did or did not sleep in the appropriate conditions, for completeness we also examined sleep quantity over the course of the study. 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, $t(88.76) = .448$, $p = .655$]].

3.3.2 Primary Word Learning Task—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 4 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 4], See Supplementary Appendix Figures 1-2 for visualization of form recall and meaning association performance, broken down by sleep condition, over time.

3.3.3 Exploratory Model Assessing Group Differences in Sleep-Learning Benefit—

Given difference in sleep-learning benefit between groups, we conducted an exploratory interaction analysis to assess whether sleep moderated the relationship between TBI and word learning. In this model, there was a fixed effect of group, such that NCs remembered more words at the 12-hour post-test than participants with TBI (estimate = −2.100, $t=-3.096$, $p<.001$). There was also a fixed effect of condition, such that all participants remembered more at the 12-hour post-test in the Sleep condition than the Wake condition (estimate = 2.00, $t=4.457$, $p<.001$). We also tested the group * condition interaction to assess whether the sleep-learning benefit differed between groups (interaction estimate = −1.020, $t=-1.607$, $p=.108$).

3.3.4 Individual Differences in Sleep-Learning Benefit—

There were substantial individual differences within each group and condition at the 12-hour post-test. See Figure 5 for a visualization of individual differences in performance.

3.4 Supplementary Data and Exploratory Analyses[3]

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 1 and 2). Briefly, we visualize that the gap in performance between the two participant groups at the immediate and 1-week post tests (reported in Figure 2 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. These analyses, which are available in the Supplementary Appendix, concerned the association between demographic variables and performance on neuropsychological assessments of short-term memory (i.e., Weschler Adult Intelligence Scale Digit Span and Letter-Number Sequencing subtests) and long-term memory (i.e., Rey

[3]Per reviewer request, we performed a post hoc mixed ANOVA to replicate the aim-specific planned analyses. For this ANOVA, we combined data at all word learning timepoints in both sleep conditions. In this model, the outcome was form recall score. Group (TBI vs NC) was a between-subjects factor. Condition (Sleep vs. Wake) and timepoint (immediate, 12-hour, 24-hour, and 1 week) were within-subject factors. There were significant main effects of group ($F=22.33$, $p<.001$) and post-test ($F=60.64$. $p<.001$). There were also significant interactions of group * time ($F=6.90$, $p<.001$) and time * condition ($F=10.19$, $p<.001$).

Auditory Verbal Learning Test) with the word learning task. Although these were not part of our planned analyses, we believe these explorations are important in examining the data to guide future hypothesis testing.

4. Discussion

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 NCs. 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 (Centers for Disease Control and Prevention, 2015; Dahdah et al., 2016; Finset et al., 1995; Gormley et al., 2019; Todis et al., 2011; Tomberg et al., 2005; Ylvisaker et al., 2003, 2005), word learning has not been examined for people with TBI. We found that people with TBI recalled fewer word forms and meanings than NCs both immediately after learning and over time. This performance gap observed at initial encoding grew over the study period. Like NCs, people with TBI remembered more words when they slept after learning than when they did not. Below we discuss each of these findings and their implications for theories of word learning and improving word learning abilities in individuals with and without TBI.

4.1 TBI Disrupts Word Learning at Encoding and Consolidation

People with TBI exhibited a 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 on TBI (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 different components of the word learning process. 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 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 unsuccessful in retrieval in free and cued recall conditions.

In populations with memory impairments and well-documented word learning deficits (e.g., individuals with amnesia), word learning tasks have historically followed a single session

study-test format and not taken advantage of the opportunity to examine how encoding and consolidation develop over longer timescales (see Duff et al., 2020, for review). In this study, we moved beyond single-timepoint designs by incorporating protocols from the word learning literature. Consequently, we observed that deficits in word learning existed over time for participants with TBI, and the performance gap grew over the course of the experiment (i.e., before the 1-week post-test). This growing gap suggests that individuals with TBI have disruptions in both encoding and in the consolidation of new knowledge over time relative to their neurotypical peers.

Of note, we were only able to capture the disruption in consolidation over time by employing a long-term study design. 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. Future studies could also move beyond task-based assessments like those used here to assess functional integration and usage of newly-learned words in conversational settings over the course of the experiment. Future research should also examine the relation between word learning ability and functional long-term outcomes (e.g., vocation, academic success, independent living).

4.2 Sleep Supports Word Learning, But Timing of Learning 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 (Antony & Paller, 2017; Batterink & Paller, 2017; Schechtman et al., 2022; Stickgold, 2005). Because our sample encompassed a wider range of ages than earlier word learning studies in young adults (i.e., college students), we extended this finding to an older population of NCs than was included in previous work.

A critical question here was whether individuals with TBI would receive a similar sleep-learning boost to NCs. Like NCs, 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). There was not a statistically significant difference in the sleep-learning benefit between participants with and without TBI in our exploratory analysis (p=.108), but our findings support the need for larger, well-powered studies to assess group differences in sleep-learning benefit. There is emerging evidence that the strength and circumstances of initial encoding may affect the consolidation process during sleep (Antony & Schechtman, 2022; Baena et al., 2020; Denis et al., n.d., 2021; Schoch et al., 2017), which would be of interest given disrupted consolidation in the TBI group. Further exploration of the direction and nature of this relationship is needed in individuals with and without TBI.

We replicated the sleep-learning boost for NC participants and extended those findings to participants with TBI. We note that it is possible that interference by exposure to other stimuli throughout the day may have also affected memory performance at the 12-hour post-test for the Wake group. However, given the well-established sleep-learning benefit in neurotypical individuals and work indicating that even a short nap is more supportive of learning than wakeful rest (Heim et al., 2017; van Rijn et al., 2020), sleep was likely key to the performance difference between the Wake and Sleep groups at the 12-hour post-test.

We also note that 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.

Individuals with TBI got a short-term boost from sleep after learning, however, the growing gap in performance at the 1-week post-test between participant groups suggests that a single well-timed exposure is likely not enough to remediate a word learning deficit in individuals with TBI. 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 pre-sleep 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 better long-term retention of information in individuals with and without TBI.

Another important consideration for the timing of sleep is the role of naps. 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). 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). We note that actigraphy allowed us to identify these individuals, whereas prior studies relied on participant report for compliance with study protocol. In our study, the sleep-learning benefit existed even when we included this napping group in the sample, and removing them did not change the significance or direction of the sleep effect. Given initial evidence from this study for a sleep-learning boost in individuals with TBI, future studies should consider the role of

napping on overall sleep quantity and if napping may support initial encoding and long-term memory consolidation for people with TBI. It is also possible that the influence of naps evolves over recovery from TBI. For example, in rehabilitation settings, a focus on regaining a regular sleep schedule often leads to attempts to keep individuals with TBI awake all day. An open question is if naps during the earliest stages of recovery would result in better learning during rehabilitation and lead to better long-term outcomes.

4.3 Possible Mechanisms of Disrupted Encoding and Consolidation After TBI

There are multiple potential mechanisms behind the disrupted long-term memory consolidation observed in the TBI group. 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 encoding and consolidation on their own. The hippocampus has long been associated with encoding and consolidation, and hippocampal damage impairs both (Cohen & Eichenbaum, 1993; Hannula & Duff, 2017; Nadel & Moscovitcht, 1997). Although this study did not include neuroimaging data to confirm hippocampal damage in participants with TBI, the demonstrated deficits in encoding and poor performance on a neuropsychological test of declarative memory (i.e., the Rey Auditory Verbal Learning test; see Supplementary Appendix Figure 4) are consistent with hippocampal dysfunction. Future work might relate assessments of word learning over time to neuroimaging findings to elucidate how neural systems, and specifically if the extent of hippocampal damage, contribute to encoding and long-term consolidation deficits in individual with TBI. Such work would also inform the proposal that hippocampal damage not only impairs acquisition of new words but can also disrupt the long-term re-consolidation and maintenance of lexical knowledge acquired long before a person experiences hippocampal damage and memory impairment (Hilverman & Duff, 2021; Klooster & Duff, 2015). It is also possible that individual differences in other cognitive skills, like attention or information processing, may affect memory performance. Here, we included an attention check to limit the influence of inattention to task on encoding. However, future work might relate performance in other cognitive domains to word learning to further elucidate the complex cognitive profiles of individuals with and without TBI.

Alternatively, 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. Although approximately half of individuals with TBI report sleep disturbance (Mathias & Alvaro, 2012), there was no significant difference in sleep quantity, as measured via actigraphy, between participants with and without TBI in this study. 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. It is possible that this sample included a subpopulation of individuals with TBI in which sleep disturbance was less prevalent. It is equally possible that actigraphy, which measures overt sleep-wake cycle disruptions, is insensitive to sleep disruption in chronic TBI. In this study, we gained

ecological validity by using actigraphy to capture sleep-wake cycles in participants' own homes (i.e., to determine purely whether they slept in each condition). However, sleep-wake cycle measurement is 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). For example, 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 captured by other measures like self-report and polysomnography may persist. Future studies should relate memory to polysomnography as a more sensitive measure of sleep phase disruption in chronic TBI. This will elucidate which sleep measures capture the largest proportion of self-reported sleep disruptions, and which measures correspond most to memory and learning performance. Such data are critical for determining who benefits most from sleep before learning and for identification of the potential factors that influence individual differences in performance, like those observed here, and that are hallmark to individuals with TBI more broadly (Covington & Duff, 2020; Dahdah et al., 2016).

It is also possible that interactions between hippocampal damage and sleep disturbance produce memory consolidation deficits after TBI. Future work on the underlying mechanism of disrupted memory consolidation in TBI is warranted. Understanding the mechanism(s) of disrupted memory consolidation will advance our understanding of the neurobiology of consolidation and provide targets for improving consolidation to increase long-term memory outcomes following neurological injury.

4.4 Capitalizing on Ecologically Valid Research Designs to Improve TBI Research on Sleep and Memory

Research designs that examine behavior across time and functional contexts promises to improve the ecological validity and the generalizability of research on sleep and memory. 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. 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. Remote data collection can also increase ecological validity by promoting recruitment of a diverse sample. We were able to recruit a geographically diverse set of participants from 8 states and Puerto Rico, as attending sessions at a physical location was not a limiting factor. Completing sessions online paired with actigraphy 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 a lab to complete sessions multiple times during the experiment period. 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. 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 to study sleep, memory, and learning.

Rehabilitation settings are an important context for memory and learning following brain injury. Indeed, 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). In the current study, we examined the effect of sleep on word learning in individuals with TBI in the chronic phase of recovery; people with chronic TBI got a learning boost when they slept after learning. These findings lead to testable hypotheses and ecological research designs that could be adapted to examine the link between sleep, memory, and learning during the acute and subacute stages of recovery (i.e., when individuals are in in-patient rehabilitation) and to test if individuals benefit from more repetitions, and well-timed repetitions, of information over time and across contexts (i.e., distributed practice (Cepeda et al., 2006.; Middleton et al., 2019). Such studies promise to inform our understanding of how early in recovery a sleep-dependent learning boost is possible and if targeting sleep during rehabilitation (e.g., sleep hygiene, timing of learning around sleep) can improve memory and learning, and in turn, advance post-TBI memory outcomes.

4.5 Conclusions

People with TBI exhibit a word learning deficit, at both the encoding and consolidation phases, that persists across domains and grows over time. Like NCs, people with TBI get a learning boost from sleeping after they learn. Ecologically valid research designs that examine the relationship between memory, sleep, and word learning over time promises to advance mechanistic accounts of word learning and improve the long-term retention of new words in individuals with and without brain injury.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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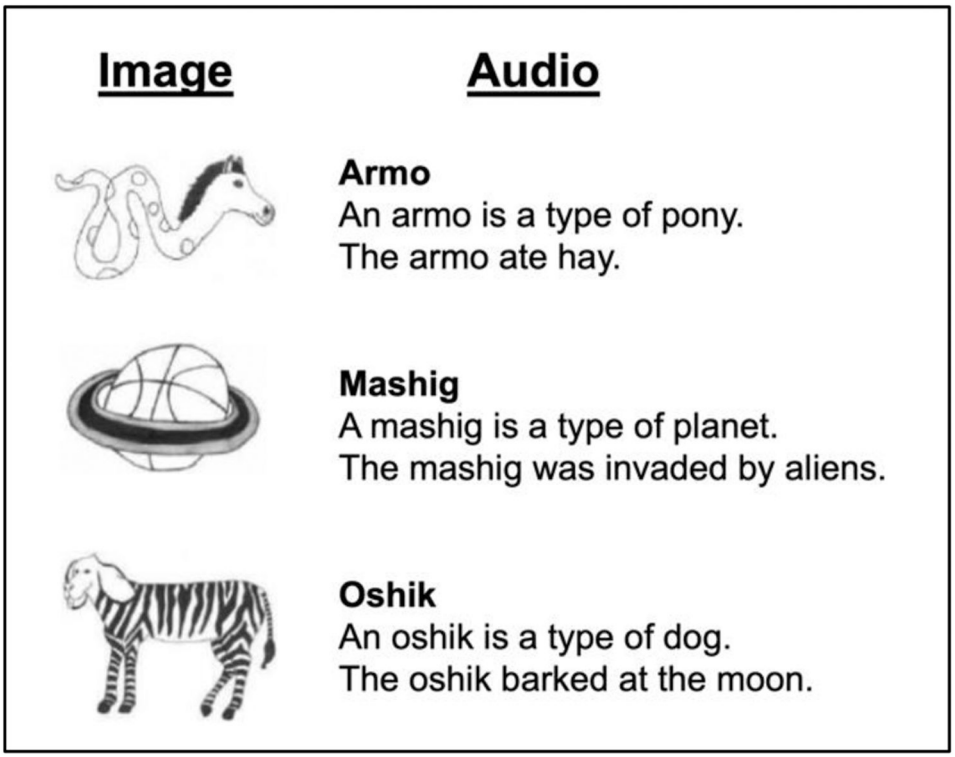

Figure 1.
Sample word-referent stimuli.

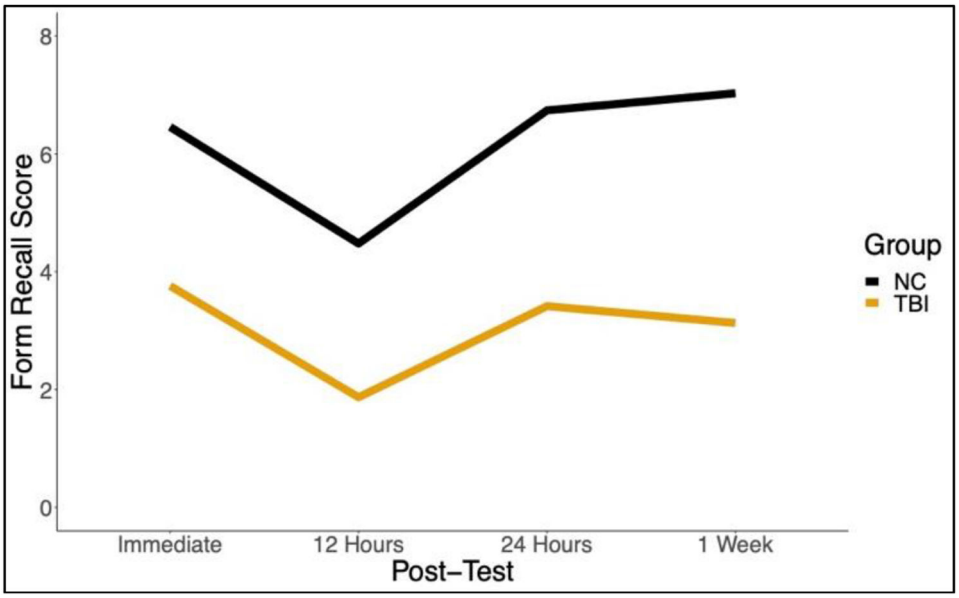

Figure 2.

Mean form recall performance, averaged across the Wake and Sleep conditions, for both groups (total possible = 16).

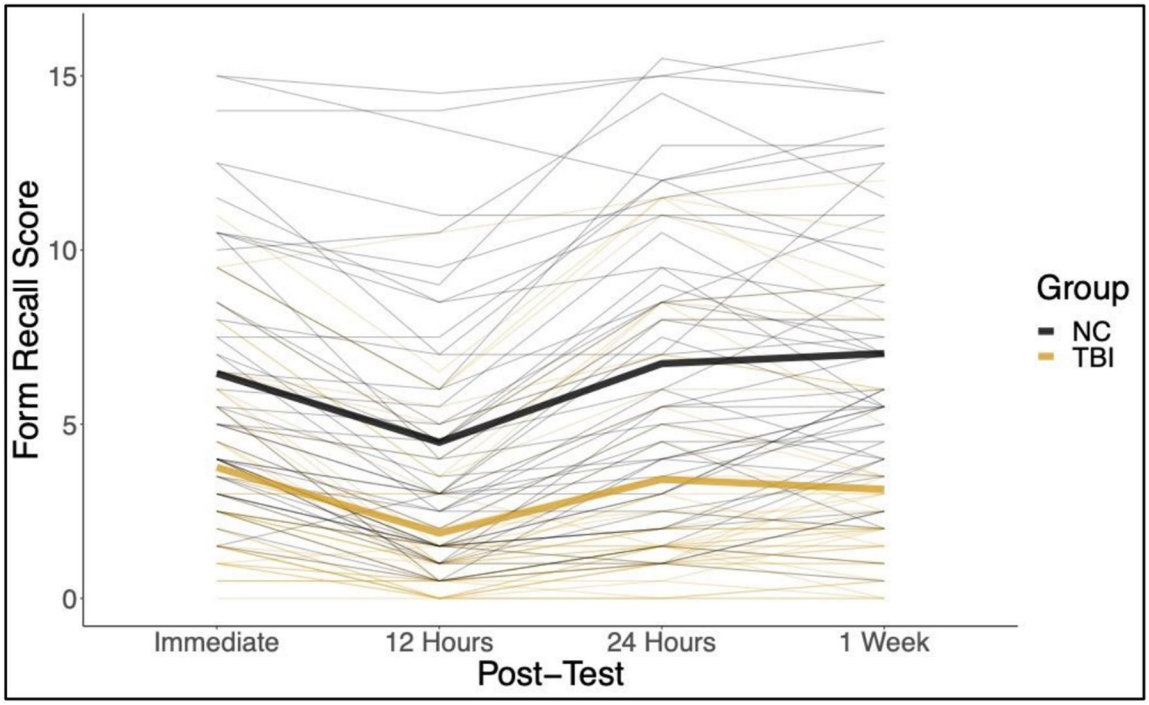

Figure 3.

Line graph showing group and individual performance on form recall, averaged across conditions, at each post-test (total possible = 16). Thin lines represent performance for an individual participant, and thick lines represent group means.

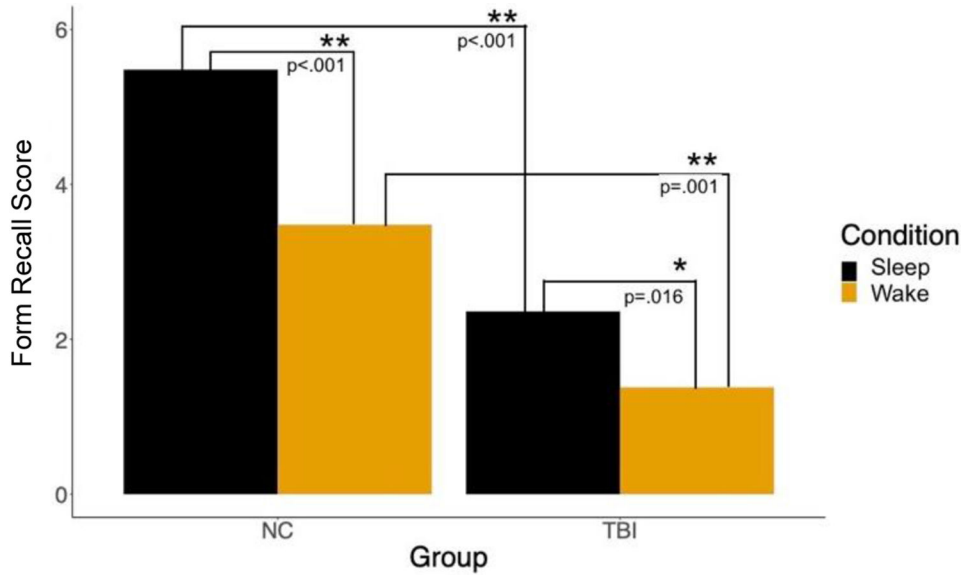

Figure 4.

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. (Total possible = 16).

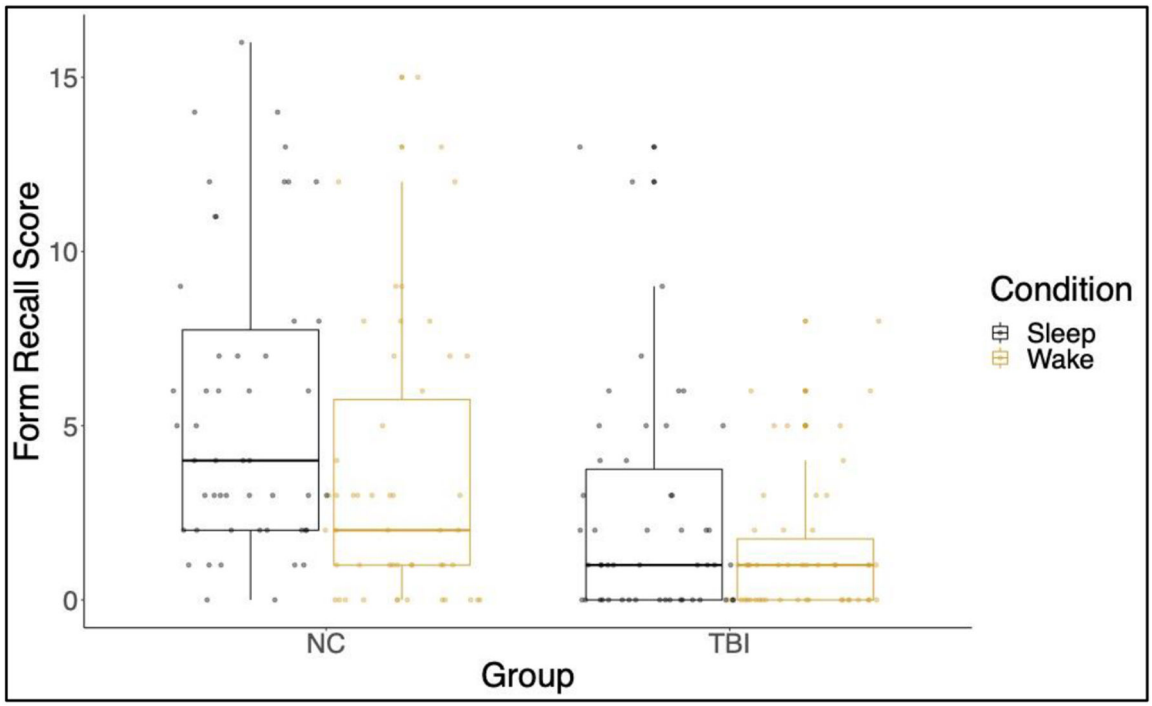

Figure 5.

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. (Total possible = 16).

Table 1

Demographic and Injury Information for Participants with TBI

ID	Age	Sex	Edu	Etiology	TSO	LOC	GCS	Neuroimaging	PTA
5002	40-44	F	16	Non-motorized vehicle accident	250	LOC >30 minutes	3	Intracranial hemorrhage	>24 hours
5003	30-34	F	18	Ped vs. auto	41	Unknown or not available	11	Subdural hematoma	>24 hours
5014	50-54	M	16	MVA	204	LOC >30 minutes	Not available	Not available	>24 hours
5016	20-24	F	16	MVA	38	LOC >30 minutes	13	Subarachnoid hemorrhage	>24 hours
5021	40-44	F	18	MVA	62	LOC >30 minutes	3	Epidural hematoma; subarachnoid hemorrhage	>24 hours
5027	30-34	M	16	Ground-level fall	30	LOC >30 minutes	9	Subarachnoid hemorrhage	>24 hours
5034	35-39	F	16	MVA	63	LOC >30 minutes	3	Subarachnoid hemorrhage	>24 hours
5038	40-44	M	16	Ground-level fall	36	LOC >30 minutes	Not available	Subdural hematoma; multifocal hemorrhages; post-traumatic hemorrhagic contusions	>24 hours
5041	30-34	F	16	MVA	79	No LOC	10	No acute intracranial findings	>24 hours
5047	30-34	M	16	Assault	41	LOC < 30 minutes	15	Subdural hematoma	< 24 hours
5050	30-34	M	18	Ground-level fall	35	LOC >30 minutes	15	Subarachnoid hemorrhage; intraparenchymal hemorrhages	< 24 hours
5051	50-54	F	16	MVA	20	LOC < 30 minutes	14	Subarachnoid hemorrhage; subdural hematoma	< 24 hours
5058	35-39	F	12	MCC	121	LOC < 30 minutes	8	Subarachnoid hemorrhage; Subdural hematoma; parenchymal hemorrhage	>24 hours
5070	45-49	F	16	Fall from height	66	LOC < 30 minutes	15	Subarachnoid hemorrhage; hemorrhagic contusions	>24 hours
5082	45-49	M	12	Assault	89	LOC >30 minutes	14	Subdural hematoma; subarachnoid hemorrhage; bifrontal contusions	< 24 hours
5095	40-44	M	12	Ground-level fall	52	LOC >30 minutes	3	Intracranial hemorrhage, parenchymal contusions, subarachnoid hemorrhage, subdural hematoma	>24 hours
5098	50-54	M	14	Struck by object	165	LOC < 30 minutes	Not available	Front-temporal contusion; intraparenchymal hemorrhage; subarachnoid hemorrhage; intracerebral hemorrhage	< 24 hours
5099	30-34	F	20	Assault	39	LOC >30 minutes	13	Subdural hemorrhage	< 24 hours
5100	50-54	F	18	Non-motorized vehicle accident	28	LOC >30 minutes	3	Intraventricular hemorrhage; intraparenchymal hemorrhage;	>24 hours
5104	35-39	M	20	Struck by object	21	LOC < 30 minutes	15	Subdural hemorrhage; scattered subarachnoid	< 24 hours

ID	Age	Sex	Edu	Etiology	TSO	LOC	GCS	Neuroimaging	PTA
								hemorrhage; right temporal hemorrhage	
5109	25-29	M	14	MVA	101	LOC >30 minutes	5	Subdural hemorrhage; intraparenchymal hemorrhage; intraventricular hemorrhage	>24 hours
5111	25-29	F	16	MVA	73	LOC < 30 minutes	Not available	Shear Injury; diffuse axonal injury	>24 hours
5112	55-59	M	16	MVA	49	LOC >30 minutes	10	Frontal hematoma; intraparenchymal hemorrhages; intraventricular hemorrhage	>24 hours
5115	35-39	F	12	MVA	207	No LOC	Not available	Subarachnoid hemorrhage;	>24 hours
5117	45-49	M	12	MCC	114	LOC < 30 minutes	15	Diffuse axonal injury	>24 hours
5118	25-29	F	18	MVA	44	LOC >30 minutes	10	Subdural hemorrhage	>24 hours
5119	35-39	F	16	MVA	223	LOC >30 minutes	Not available	Subarachnoid hemorrhage; right frontal contusion	>24 hours
5121	50-54	M	12	MCC	12	LOC < 30 minutes	12	Subarachnoid hemorrhage; subdural hemorrhage; parenchymal Hemorrhages	>24 hours
5122	50-54	M	18	Non-motorized vehicle accident	21	LOC < 30 minutes	15	Subarachnoid hemorrhage;	>24 hours
5123	50-54	M	12	MCC	22	LOC < 30 minutes	14	Intraparenchymal hemorrhage, subdural hemorrhage, subarachnoid hemorrhage	>24 hours
5124	20-24	M	12	Fall from height	31	LOC >30 minutes	3	Intracerebral hemorrhage; intraventricular hemorrhage	>24 hours
5125	50-54	F	12	Ground-level fall	11	No LOC	15	Subdural hemorrhage; subarachnoid hemorrhage	No
5126	45-49	F	12	MVA	25	LOC >30 minutes	3	Subdural hemorrhage	>24 hours
5128	35-39	F	16	MVA	184	LOC >30 minutes	Not available	Medical records currently unavailable. Participant reports brain bleed.	>24 hours
5129	50-54	F	12	Non-motorized	8	LOC < 30 minutes	12	Subdural hemorrhage; subarachnoid hemorrhage vehicle accident	< 24 hours
5131	40-44	F	12	MVA	9	LOC >30 minutes	12	Subdural hemorrhage	>24 hours
5133	25-29	M	12	MCC	23	LOC < 30 minutes	15	Contusions; subdural hemorrhage; intraventricular hemorrhage	< 24 hours
5134	50-54	M	16	MCC	10	LOC < 30 minutes	12	Intraparenchymal hemorrhage	< 24 hours
5137	25-29	M	16	Ped vs. auto	9	LOC >30 minutes	3	Epidural hematoma; subdural hemorrhage; subarachnoid hemorrhage	>24 hours
5141	25-29	M	12	MVA	8	LOC >30 minutes	13	Subdural hemorrhage	< 24 hours
5145	30-34	M	20	MVA	116	LOC>30 minutes	15	Negative	>24 hours
5148	25-29	F	16	MVA	23	LOC >30 minutes	3	Subdural hemorrhage; subarachnoid hemorrhage	>24 hours

ID	Age	Sex	Edu	Etiology	TSO	LOC	GCS	Neuroimaging	PTA
5149	20-24	F	14	MVA	11	LOC < 30 minutes	3	Intraparenchymal hemorrhage; subarachnoid hemorrhage; shear injury	>24 hours
5152	55-59	F	18	MCC	174	LOC >30 minutes	7	Subdural hemorrhage; subarachnoid hemorrhage; shear injuries	>24 hours
5153	45-49	F	16	MVA	154	LOC >30 minutes	3	Parenchymal hemorrhage; intraparenchymal hemorrhage; intracerebral hemorrhage; subarachnoid hemorrhage;	>24 hours
5155	20-24	F	12	MVA	17	LOC >30 minutes	Not available	Not available	>24 hours
5156	50-54	F	12	MVA	41	LOC >30 minutes	15	Subdural hemorrhage	No
5158	30-34	F	16	MVA	10	LOC < 30 minutes	15	Subarachnoid hemorrhage;	Unknown or not available
5159	20-24	F	16	Fall from height	11	No LOC	15	Epidural hematoma	No
5161	25-29	M	12	MVA	7	LOC>30 minutes	10	Subdural hemorrhage; parenchymal hemorrhage; diffuse axonal injury	>24 hours

Note: ID = participant ID number. Age is provided in five-year ranges to protect participant confidentiality. Education (edu) reflects years of highest degree obtained. MVA = motor vehicle accident. MCC includes both motorcycle and snowmobile accidents. Non-motor = non-3 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. PTA = post-traumatic amnesia.

Table 2

Experimental Schedule for Wake and Sleep Conditions

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

Note: Each participant experienced both conditions, with the condition order randomly assigned (i.e., a randomized within-participant crossover design).

Table 3

Performance by Task and Group at Each Post-test

Task / Time Point	Group	Performance Correct (SD)
Word Form Recall – Immediate	NC	6.4 (3.7)
	TBI	3.8 (2.8)
Word Form Recall – 12 hours	NC	4.5 (3.7)
	TBI	1.9 (2.2)
Word Form Recall – 24 hours	NC	6.7 (4.2)
	TBI	3.4 (3.4)
Word Form Recall – 1 week	NC	7.0 (3.9)
	TBI	3.1 (2.9)
Word Meaning Association – Immediate	NC	11.5 (3.5)
	TBI	9.6 (3.8)
Word Meaning Association – 12 hours	NC	11.4 (3.5)
	TBI	8.9 (4.1)
Word Meaning Association – 24 hours	NC	12.3 (3.4)
	TBI	9.6(4.1)
Word Meaning Association – 1 week	NC	11.7 (3.5)
	TBI	8.2 (3.9)