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Title: Pilot and Feasibility of MEMI for Chronic Traumatic Brain Injury

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1.0 Rationale and Specific Aims

While the barriers to community reintegration after traumatic brain injury (TBI) are multifactorial, memory and learning deficits are the most frequent targets for intervention in patients with TBI. The ability to (re)learn information is critical to a person's potential to benefit from therapy, to follow medical recommendations, to maintain positive social relationships, and to be successful at school or work. Yet, the last several decades have seen limited progress in developing restorative therapies for memory and learning deficits in this population.

In the cognitive neuroscience literature, evidence has accumulated that people with and without brain damage learn more when the context of learning is varied across time and space. Yet, rehabilitation typically occurs in a constrained context (i.e., the same therapy room at the same time of day). In memory rehabilitation, each opportunity to retrieve information strengthens that information in the neocortex, and is thus both an opportunity for assessment and intervention. Increasing the contextual variance of learning opportunities (i.e., in the daily lives and contexts of patients) may improve the rehabilitation potential of patients with TBI, in addition to increasing the potential for interventions that extend beyond an acute timeframe for service delivery.

There is critical need for technologies that move beyond the constrained therapy context to deliver interventions across time and space. In the proposed study, we focus on developing a technology-delivered system that extends the timing and context of memory exposures beyond current service delivery models. We aim to refine the technology for future use in research assessment and intervention contexts, with the long-term goal of improving memory care for individuals with TBI in their daily lives and across the lifespan. After taking into account feedback from real users, this system may also eventually be extended to other areas of TBI management and has the potential to improve both short-term and chronic care for the millions of Americans currently living with brain injury-related disability.

This is a pilot and feasibility study for a mobile phone-delivered intervention for memory, called MEMI (memory ecological momentary intervention), that was designed to support adults with chronic traumatic brain injury with their memory. The goal of the study is to examine the feasibility and acceptability of MEMI and to assess preliminary efficacy as to whether technology-delivered spaced memory retrieval opportunities improve memory in people with and without a history of chronic traumatic brain injury.

2.0 Inclusion/Exclusion Criteria

Inclusion criteria:

For participants with TBI:
• Moderate-severe TBI. All participants sustained an injury of adequate effect to have been hospitalized. Severity is determined per the Mayo Classification System.
• All participants are at least 6 months post-injury at the time of study enrollment and thus exhibit chronic and stable neuropsychological profiles.
• All participants sustained their TBIs in adulthood (i.e., 18 years old or older) and are 60 years old or younger to limit the effects of age-related cognitive decline.

For all participants:
• Oral and written language skills sufficient for the study tasks.
• Participants must own a smartphone to access the Gorilla online behavioral experiment platform from their mobile phones.

Exclusion criteria:

For participants with TBI:
• History of medical or neurological disease affecting the brain or language, before or after the qualifying TBI.

For non-injured comparison peers:
- History of neurological or cognitive disability, including TBI

For all participants:
• Any disability (e.g., vision impairment, hard of hearing, aphasia or other neurologic condition) that limits ability to read, type, or verbally communicate.
• Demonstrates inability to receive and respond to a text message.

3.0 Enrollment/Randomization

No randomization will occur. The order of condition/word list combination will be pre-determined, and participants will be assigned to the next available combination based on when they join the study (i.e., a counterbalanced within-person crossover design).

4.0 Study Procedures

The technology being tested involves receiving intermittent text messages over the course of a week with links to respond to memory prompts on the Gorilla mobile behavioral experiment webpage.

This pilot will include 40 participants: 20 with a history of chronic moderate-severe TBI and 20 demographically-matched non-injured peers. Participation in the study will last two weeks for each person, with one week in each of two conditions:

- **Blocked (Active Comparator) Condition:** Participants complete their initial learning session on the target words, then immediately receive all of the exposures to each of the items in a single block. They do not complete any more retrieval sessions until one week later, when they complete a 15-minute test for their memory of all of the trained items.
- **MEMI Spaced Rerieval (Intervention) Condition:** Participants complete their initial learning session, and the subsequent retrieval sessions are spaced out over the course of the week (two short retrieval sessions each day) using MEMI. Then, they complete a 15-minute test for their memory of all of the trained items at the end of the week.

Outcome measures include:

- **Acceptability (Primary): Acceptability of Intervention Measure:** At the end of each week, participants complete this four-item measure regarding the acceptability of each intervention condition. Scores range from 4 to 20, with higher scores indicating higher acceptability.
- **Feasibility (Primary): Session Engagement:** In each condition, we measure the number of possible sessions that each participant completes. In the Blocked condition, the total number of possible sessions is two. In the MEMI condition, the number of possible sessions is 12. Higher number of sessions completed indicates better engagement and higher feasibility.
- **Efficacy (Secondary/Preliminary): Memory at 1 week:** At the end of each week, participants complete memory tasks to assess their memory for the trained information. Measures include:
    - *Free recall of word forms:* The number of target word forms that participants can free type without cueing (0=did not remember any words- worse to 16=remembered all the words - better)
    - *Cued recall of word forms:* The number of target word forms that participants remember in response to prompting (i.e., typing the word that labels a given image) (0=did not remember any words- worse to 16=remembered all the words - better)
    - *Cued recall of word meanings:* The number of target word meanings that participants remember in response to prompting (i.e., typing the definition for a given word) (0=did not remember any words- worse to 16=remembered all the words - better)
- **Other: Number of Spatial Contexts:** At the beginning of each retrieval session, we ask participants to give their spatial context (the physical location in which they are completing the session, e.g., home or work). We report the number of different spatial contexts in which participants

completed sessions in each condition. A higher number of spatial contexts indicates more variance in the contexts of retrieval opportunities, which is a goal of this technology.

5.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Although serious adverse events are unanticipated given the nature of this study, the PI will evaluate all participant concerns for severity, relationship to the research, and actions to be taken, and immediately report any serious adverse events or unanticipated problems involving risks to participants to the IRB.

6.0 Study Withdrawal/Discontinuation

Participants are free to withdraw from the study at any time by contacting the PI. There is no penalty for early withdraw, and participants will receive payment proportional to the amount of the study completed. This is made clear during the informed consent process.

7.0 Statistical Considerations

This phase of the study is descriptive and is designed to inform the research team regarding which aspects of using MEMI are challenging, or represents a barrier to use, for individuals with TBI. We collect preliminary pilot data on acceptability, feasibility, and the effects of technology-delivered spaced retrieval on memory in TBI. These findings will be used to refine the technology for future research and clinical trials.

8.0 Privacy/Confidentiality Issues

Only KSP approved by the IRB will have access to research information. Participant survey data will be entered and stored electronically in REDCap. KSP will assign participants a unique subject ID associated with their identifiable information in REDCap. Original paper copies of any surveys will be de-identified and filed in a locked file cabinet. Participant contact information will be password protected and stored separately from research data, without any health information, on a secure VUMC server. Participant information collected for payment purposes will be stored separate from research data in a locked file cabinet.

In order to minimize the risks of loss of privacy, all research-related conversations with participants will take place in private testing rooms on a private web conference session or phone call when data are collected remotely. Recordings from participant interviews will be saved with the unique subject ID

on a secure VUMC server. Twilio, the platform that delivers the mobile phone intervention, is integrated into REDCap in order to initiate and tailor the intervention (e.g., name, cell phone number, preferred time of day to receive text messages). Twilio will be used to send text messages at pre-designated times. Each of these messages contains a link to the secure web platform where participants will complete the memory task. Individual participant responses to the memory task are only accessible by KSP through a secure password protected portal.