Developing Process-Specific Verbal Memory Interventions for Veterans with TBI

Protocol

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1. Project Title: Developing Process-Specific Verbal Memory Interventions in Veterans with TBI

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3. Abstract: Memory dysfunction can result from impairments along a continuum of information processing, from poor initial acquisition of information during learning to disturbed retrieval of stored memory when it is later needed to perform a task[1]. There is a critical need to better understand disease heterogeneity in order to enhance diagnosis and therapeutic management[2]. Several subtypes of memory dysfunction after TBI have been identified[3,4]. First, some TBI survivors exhibit impaired memory acquisition/encoding (e.g., frontal system damage)[5]. Second, some exhibit impaired memory consolidation/storage impairment (e.g., prominent damage to temporal lobe systems[6]). Third, some show impairment in retrieval of information[5,7]. This heterogeneity results from the variable nature and severity of underlying brain trauma resulting from unpredictable mechanical forces[2,8]. This study attempts to determine whether these subtypes of memory respond better to treatments that are focused specifically on the constituent cognitive deficit than to other treatments. There are existing training protocols for training these three components of memory processing, as follows: encoding (memory strategy training[9]), consolidation (errorless learning[10]), and retrieval (retrieval practice[11], but their efficacy has not been tested in TBI survivors with documented impairments in each component. That is, to our knowledge, there is no solid evidence for memory training in TBI survivors that supports the widely held belief that specifically matching the patient impairment to the treatment leads to better treatment outcomes. This project attempts to fill this gap in our knowledge. In an alternating treatments design, TBI survivors with encoding, consolidation, or retrieval deficits will undergo (a) a treatment matched to their deficit and (b) a treatment that addresses a different deficit. High resolution imaging and neurocognitive biomarkers will be used to predict response to treatment. Results will be used as a basis for a larger clinical trial of memory rehabilitation in brain injured populations.

4. Background:

Traumatic brain injury (TBI) has emerged as a “signature injury” of the OIF-OEF-OND combat experience. Enduring cognitive deficits after TBI present barriers to full recovery and re-entry into societal roles, with executive dysfunction, poor attention-concentration, and memory difficulties being the most persistent disabilities faced by TBI survivors[12].

Current Knowledge. There is considerable heterogeneity in the nature and severity of memory disorders after moderate-severe TBI(M-STBI)[8], resulting not only from variability in severity and etiology of TBI, but also from variable loci of neuroanatomic damage[13]. Chronic episodic memory deficits after M-STBI are often rooted in deficient encoding and/or consolidation of to-be-learned information[5,14], or from retrieval deficits associated with frontal-executive damage[4]. Meta-analytic reviews of memory rehabilitation studies show that memory strategy training may improve TBI-related memory deficits of any severity, leading to its recommendation by ACRM as a practice standard[15]. More limited data on errorless learning (EL), which rebuilds learning/memory skills in a way that prevents errors, suggests that EL is a promising approach to treating severe memory deficits[10,16,17]. Retrieval practice (in which participants practice the act of retrieving information with appropriate cueing and support) improves paired-associate

learning in the TBI population[18,19]. Other memory therapies with promising but unproven efficacy in RCT's include spaced retrieval[20,21] and the method of vanishing cues[22,23].
Gaps in Knowledge. Although these protocols may lead to improved learning and memory after M-STBI, little is known about their mechanism(s) of action or whether they would be differentially effective in TBI survivors with deficits at different stages of the memory process. There have been no comparative effectiveness studies involving these treatments, and no group studies have attempted to match patients to treatments that specifically target the locus of memory impairment in encoding, consolidation, or retrieval. If, in fact, some patients suffer from consolidation failure[6], while others have prominent encoding or retrieval deficits[5,24,25], it is likely that alternative memory interventions, each matched to the patient's primary deficit, may be needed to maximize individual rehabilitation outcomes. Stage of recovery/time since injury may also be important, as encoding deficits and consolidation deficits recover differentially in severely injured patients, with poor encoding representing the more enduring problem[13].
Relevance: Managing and alleviating residual effects of traumatic brain injury is a key priority area and represents a critically important public health problem facing the veteran population. Differential efficacy of specific rehabilitation programs may be an important factor for clinicians to consider when offering health services to veterans with cognitive impairment.
Benefit to Veterans. A better understanding of the efficacy of memory rehabilitation may provide clinicians with better decision-making support for prescribing different available therapies to alleviate TBI-related cognitive and memory dysfunction. Better understanding of individual differences in TBI-related memory dysfunction, and of underlying structural and functional brain dysfunction may also explain the neural basis for heterogeneous memory difficulties veterans suffer after M-STBI.

5. Specific Aims:

Aim 1. Aim 1 is to refine and validate three separate, process-specific memory rehabilitation treatments that focus on improving information-processing at the encoding, consolidation, or retrieval stage for Veterans with chronic moderate/severe TBI.
Objective 1.1. Generate treatment manuals for three process-specific memory treatments.
Objective 1.2. Test and refine treatment fidelity so that each of the three interventions can be reliably delivered by different clinicians.

Aim 2. Aim 2 is to provide a preliminary test of the response to the three memory interventions. At baseline, TBI survivors will be evaluated for memory function in each of these three memory component processes using established neuropsychometric methods. Their experimental treatment allocation will be to the treatment targeting their most impaired memory component. In addition, each subject will serve as his/her own control, by engaging in a treatment targeted to another memory component ('mismatched' group).

Hypothesis A. The matched vs. mismatched group will show differential improvement in memory component function, with the former group benefitting to a significantly greater degree. (Primary measures: Memory component performance, encoding, consolidation, retrieval; secondary: cognitive function and quality of life).

Aim 3. Aim 3 is to establish links between the behavioral taxonomy of the three memory components and differences in brain structure and function documented with diffusion tensor imaging and functional connectivity analysis. This is a key first step in establishing brain-based metrics of neuroplastic change after memory therapy in our research program.

Objective 3.1. Identify specific and unique imaging signatures that distinguish patients with deficits in encoding, consolidation, and retrieval, respectively. Primary measures: structural measures of morphometry and white matter integrity (FA) and functional connectivity (cross correlation and total interdependence) in identified brain networks damaged in TBI.

Clinical Implications. This research has the potential to devise a method to match specific

subcomponents of memory impairment to specifically targeted memory interventions, thus maximizing recovery of memory and function. The results of this investigation will be used to refine the interventions, to evaluate cognitive and functional endpoints, and to power a larger clinical trial that will yield data enabling clinicians to match TBI patients to effective treatments based on their individual profile of memory dysfunction.

6. Research Plan:

6.1. Study Design. The proposed research will be conducted in three phases: Intervention Development, Patient Characterization and Classification, and Initial Testing of Treatment Efficacy.

6.2. Phase 1: Intervention Development. During the first 6 months of the project, we will formalize, manualize, and perform preliminary fidelity testing on three memory interventions targeting process-specific memory deficits after TBI in Veterans: (a) memory strategy training (to boost encoding), (b) errorless learning (to improve consolidation, and (c) retrieval practice (to rehabilitate deficits in retrieval).

6.2.1. Materials Common to Memory Interventions. Each of the three treatment conditions will utilize the same training materials, a set of verbal paired-associates (VPA) and a set of face-name pairs (FNP), both presented for training in associative learning. Each session will involve training utilizing two 12-item VPA lists and two sets of 12 FNP's, for an overall total of 144 unique VPAs and 144 FNPs. The VPA's are weak paired associates[26,27] (have a forward association strength of <.01[28]), and that do not contain words from clinical memory tests given in Phase 2. FNP's are constructed by pairing face-front black and white photographs from Stringer's Ecologically-Oriented Neurorehabilitation of Memory (EON-MEM) protocol[29]. Training stimuli will be presented on a desktop computer using E-prime software.

6.2.2. Memory Strategy Training (MST). MST, in which persons with brain injury are taught specific strategies useful for encoding new information at the point of learning, is a widely used rehabilitative technique[9,30,31] that is an *ACRM practice standard*[15]. While specific strategies vary across studies, most teach the participant to form meaningful cognitive associations between memoranda through the use of imagery or semantic encoding, building a form of memory encoding known as relational memory[32]. Relational encoding, a key process that enhances the strength and durability of episodic memory[33,34], can be reduced or impaired after TBI[35]. Successful relational memory involves two distinct mnemonic mechanisms: the generation of an association between to-be-encoded items (a frontal/executive function)[36,37] and the binding of that association into a cohesive memory trace (a function of the hippocampal memory system)[33,38]. MST may be particularly useful in enhancing the first of these two processes.

6.2.2.1. Procedure. Six biweekly sessions of MST will be conducted. Two VPA lists and two FNP lists will be used in each session. During MST, VPAs (e.g., "candle-table") or FNPs will be presented in horizontal arrangement on a computer screen at a rate of 1 per 6 seconds (this may be modified based on participant processing speed). For ***VPA learning***, participants will be asked to generate a memorable sentence (first list) or form a distinctive mental image (second list) that links the two VPA items together. The therapist will help the participant generate sentences and images that are distinctive or unusual, and therefore more memorable. Specific examples of distinctive sentence-based and imagery-based encoding will be given (e.g., "The wax from the candle poured onto the table", or an image of a candle scorching a table) and will be developed as the treatment is manualized. Immediately following list presentation, the cue word will be presented without the target (e.g., "candle-_____") and the participant will be asked to generate the target. Spontaneous production of targets will be recorded. For each item not spontaneously recalled, participants will be asked to retrieve the

sentence (first list) or image (second list) that they created during encoding, and will then be asked to retrieve the target word again. Unsuccessful retrieval will be initially cued by the therapist. Prompted recall will also be recorded. This procedure will be repeated five times for each list, each followed by a retrieval phase. For each session, the dependent measure is the percentage of correct target words (out of 12) in spontaneous and cued recall for each list during the final exposure trial. For ***FNP learning***, we will use a training approach adapted from Hampstead[39] and Stringer[9]. Training teaches patients to self-generate cues linking faces and names; patients will also be provided cues to standardize procedures and to encourage strategy development. For each FNP, participants will be directed to a salient facial feature (a visual cue like a long nose) and given a nickname that rhymes with the actual name (verbal cue) linking the feature to the name. Patients will be instructed to associate the visual and verbal cues by creating mental images that emphasize or exaggerate the relationship between cues. After initial learning, FNP's will be repeated five times. On each presentation, participants will be asked to recall the visual cue, then the verbal cue, and then finally the name. Dependent measure is the percent correct recall of visual cues, verbal cues, and names on the final trial of each list.

6.2.3. Errorless Learning (EL). EL refers to a group of techniques that promote recovery of memory abilities using procedures that explicitly prevent the patient from making errors during learning[10]. EL is based on the premise that errors during training become primed in long term memory via implicit memory mechanisms relatively spared in amnesia[40]. Because of impairment in explicit memory consolidation that would normally provide corrective influence, these errors exert an unusually strong detrimental effect on relearning. While the standard interpretation of EL is that implicit memory is responsible for the treatment effect[41,42], it has been more recently shown that the EL advantage results from residual, though impaired, episodic memory consolidation due to temporal lobe damage[43,44]. EL has been shown to be a promising tool in memory rehabilitation[15,40,45], at least for individuals without severe executive deficits[46].

6.2.3.1. Procedure. Six biweekly sessions of EL will be conducted, each using two VPA lists and two FNP lists. During EL, the word pairs (e.g., "candle-table") or face-name pairs will be presented in horizontal arrangement on a computer screen at a rate of 1 per 6 seconds with no encoding instructions. After initial presentation, the cue will be presented without the target. For VPA learning, the cue word in each pair ("candle - _____") will be presented, and the participant will be asked to provide the second (target) word, ***but only if they are certain they can retrieve it accurately***. ***Guessing is explicitly discouraged***. If the participant cannot provide the word within 3 seconds, the word appears on the screen for 3 seconds and the participant is asked to read the pair aloud. During training, each list will be presented five times in this fashion. The dependent measure is the percent correct target words produced (out of 12) during the fifth exposure trial for each list. The procedure will be repeated for the second VPA list and then for the two FNP lists, yielding 4 accuracy measures (percent correct) for each session.

6.2.4. Retrieval Practice (RP). Some authors have argued that practicing retrieval during learning is an essential feature of successful learning[10,47]. Effects of RP are most robust when retrieval is effortful, successful and spaced over time [48,49]. If retrieval of a learned item is practiced shortly after it is learned, but before it is forgotten, subsequent recall is enhanced, a phenomenon known as the "testing effect"[47]. RP has been used recently to improve performance of memory-impaired patients with multiple sclerosis[50] and M-STBI[11,19].

6.2.4.1. Procedure. Six biweekly sessions of RP will be conducted. We will follow procedures outlined in Sumkowski et al[19], who demonstrated efficacy of RP in a small group of patients with M-STBI and chronic memory deficits. For each session, two sets of 12 VPA's and 12 FNP's will be used. Paired stimuli will be presented together for 6s on a computer screen, and the participant will be asked to read the VPA or say the name (FNP) aloud. Following this, 3 6s filler pairs (other VPA's or FNP's) will be presented. Then, a 5s cued

recall test (candle-_____), followed by a 1-s feedback screen (candle-table) will be presented, followed by another six 6s filler trials and another 5s cued recall test and 1s feedback. This continues until all 12 VPA's or FNP's are given. After VPA is complete, FNP is administered (counterbalanced). After a brief delay, the participant completes two separate delayed cued recall tests (VPA, FNP, counterbalanced). The procedure is repeated for the second set of VPA's and FNP's. Dependent measure: Percent correct scores on the delayed recall test for each of the two VPA and two FNP sets, recorded each session.

6.2.5 Manualization and Fidelity Testing. During Phase 1, session-by-session procedures, including instructions to therapists and patients, stimuli and stimulus presentation schedules, methods of data collection, and permissible procedural variations will be formalized into a treatment manual for each of the three interventions. Six Master's level therapists will be trained in all three interventions, and will practice administering them to volunteer participants. At the end of Phase 1, each therapist will administer each treatment to a Veteran participant with M-STBI. Each session will be video recorded for evaluation of treatment fidelity by the study team[51,52], which will review session recordings and will rate the degree to which the therapist adhered to the following aspects of the protocol: communication of content to the participant (consent, rationale for treatment, instructions for engaging in training), accurate use of cues, selection of stimulus materials, recording of data, and adherence to designated treatment schedules. We will develop a rating sheet that provides feedback to therapists on their adherence to the manualized protocol[53].

6.3. Phase 2: Patient Characterization and Classification

6.3.1. Participants. Veterans aged 25-65 who are post-deployment, having served in OIF, OEF, or OND, who meet criteria for moderate or severe TBI during deployment, are eligible to participate. *Patients will meet the 2007 VA/DoD criteria[54], supplemented by data from the VA TBI Identification Semi-Structured Interview[55].* All patients will have gone through Level I and II assessments with positive findings. Inclusion/Exclusion criteria: *Primary inclusion criteria:* M-STBI (blast and blunt), ≥ 6 months post-injury, no receptive aphasia (impairing ability to comprehend task instructions), able to participate in return visits. *Primary exclusion criteria*: No MRI contraindications, not claustrophobic, no current or past history of disabling Axis I psychiatric disorders (except for PTSD and depression), no active substance abuse, not pregnant.

6.3.2. Procedure. Phase 2 consists of three components. **First**, after informed consent is obtained, participants undergo ***standardized neuropsychological screening*** to characterize their neurocognitive deficits, enabling comparisons with other Veterans whose memory rehabilitation outcomes have been reported in the literature. **Second**, we will use an established neuropsychometric algorithm to ***classify patients into process-specific groups*** that locates their primary memory deficit at the encoding, consolidation, or retrieval stage. **Third**, we will conduct ***high-resolution structural and resting state functional MRI (RS-fMRI)*** to determine whether our group classification is associated with different neuroimaging signatures. In this pilot proposal, we will not evaluate pre-post structural or functional brain changes resulting from our interventions, though this will be a key feature of a subsequent MERIT proposal based on our preliminary outcomes here.

6.3.2.1. Pre-Treatment Neuropsychological Screening. Table 1 lists key neuropsychological measures. Participants will be offered $50 for participation in neuropsychological screening.

Domain	Measure
Effort	Test of Memory Malingering (TOMM)
Intelligence	North American Adult Reading Test (NAART) Wechsler Abbreviated Scale of Intelligence (WASI 2-subtest)
Memory	California Verbal Learning Test II (CVLT-II) Rey Complex Figure Test (Meyers version) – includes forced-choice effort measure Logical Memory, Visual Reproduction I, II (WMS-III LM, VR)
Attention	*WAIS-III Subtests yielding Working Memory Index (WMI); WMS-R DS*
Processing Speed	*WAIS-III Subtests yielding Processing Speed Index*
Frontal/Executive	Controlled Oral Word Association Test (COWAT) – FAS, Animal Fluency Delis-Kaplan Executive Function System -Tower Test (DKEFS-Tower) *Trail Making Test*
Motor Speed and Dexterity	Finger Tapping Test (FTT) Grooved Pegboard Test (GPT)
Emotional/Psychiatric	PTSD Checklist-Military (PCL-M) Beck Depression Inventory

6.3.2.2. Classifying Participants into Process-Specific Groups

We aim to identify M-STBI patients whose injuries produce primary deficits in encoding/acquisition, consolidation/retention, or retrieval. While we expect that many patients may have some problems in more than one domain, many studies have concluded that memory problems after M-STBI are *primarily* rooted in one of these domains at the individual level[5-7,56,57]. Three studies[4,7,58] report distinct deficit patterns attributable to encoding, consolidation, and retrieval deficits using the CVLT[59]. Crosson et al[7] found that encoding deficits were marked by a high false positive (FP) rate and reduced hits on recognition, while consolidation deficits were marked by lower hit rates and lower FP (also see[58]). Curtiss et al[56], using hierarchical clustering of CVLT and WMS-R variables, found three memory-impaired groups corresponding to acquisition/encoding, retention, and retrieval deficits. Millis and Ricker[4] used Delis'[59] six-factor solution of CVLT performance variance to identify patterns of verbal learning deficit after moderate-severe TBI. They found 4 identifiable clusters: a ***Disorganized*** type (n = 22; encoding deficit) who exhibited a haphazard learning style, elevated FP rate, reduced discriminability on recognition testing and increased susceptibility to proactive interference, an ***Active*** type (n = 15; retrieval deficit) who showed good semantic encoding, good acquisition rate, and disproportionate improvement on recognition (discriminability), a ***Passive*** type (n = 11; consolidation deficit) whose recall showed prominent serial position effects and rapid forgetting, and a ***Deficient*** type (n = 13; encoding deficit) who showed slow rate of learning, recency effects in free recall, and an excessively high FP rate on recognition. These results were subsequently replicated and extended[3]. We will use this classification scheme, summarized in Table 2. Deficient and Disorganized groups will be collapsed, as both suffer from encoding deficits. Characteristics of each class (encoding, consolidation, and retrieval) will be combined in multivariate fashion, creating a composite score. Participants will be assigned to the group corresponding to the most impaired composite score. We will also investigate other algorithms for classifying patients, with the goal of deriving the most accurate and stable method.

Table 2. Scheme for Classifying TBI patients into deficit categories.

Deficit	Encoding Deficit	Consolidation Deficit	Retrieval Deficit
Millis/Ricker/Deshpande Grouping	Disorganized (I) Deficient (IV)	Passive (III)	Active (II)
CVLT Factor Score Comparisons	Serial cluster <III, =II Primacy <III, =II Slope < II, =III FR Intrus =II, III List B v. A <II, =III	Serial cluster >I,IV,=III Primacy <I,II, >II Slope =I,IV, <II FR Intrus <IV, =II List B v. A =I,III,IV	Serial cluster =I, >III Primacy <III, =I,IV Slope >I,III,IV FR Intrus <III,=I,IV List B v. A >I, =III,IV
CVLT Performance Features	False pos >II,III Recency >II,III Recog Discrim <II,III	False pos <I,II,IV Recency <I Recog Discrim <I Semantic cluster <II SDFR v. Trial 5 >II	Semantic cluster >III,IV SDFR v. Trial 5 <III,IV FR Consist >I,IV Total (1-5) >I,IV List B >I,IV

6.3.2.3. Structural/Functional Neuroimaging. A long-term goal of our research is to provide evidence of neuroplastic changes after memory interventions by documenting treatment-related change in structural integrity and functional brain connectivity. In this study, we will collect pre-treatment MRI data to provide brain-based biomarkers of our 3-group classification. Participants will be offered $50 for participation in each of two MRI acquisitions, once before treatment, and again 1 month post-treatemtn.

6.3.2.3.1. Acquisition Protocol. The MRI acquisition protocol is outlined in Table 3.

6.3.2.3.2. Structural MRI. Our laboratory uses tractography and tract-based spatial statistics[60,61] along with reliable manual segmentation of memory-relevant grey matter structures to analyze structural damage after TBI. Fiber orientation is estimated using the Mixture of Wishart (MOW) distribution method[62], capable of estimating fiber orientation in regions of crossing fibers. Tractography will be performed by seeding the whole brain with 64 uniformly-spaced seeds within each voxel. The tracking algorithm (based on FACT[63]) creates **connectivity streamlines** using single and multi-fiber directionality. ROI's of key brain networks are defined anatomically and connected by streamlines. The streamlines with structural region masks will create a graph from which **network edge weight (NEW)**[64] will be computed. NEW controls for ROI surface area, seeding density, and voxel volume, and is a measure of network connection strength independent of image resolution, fiber length, and ROI size. NEW provides a quantitative measure of network connections that will be used together with FA and measures of radial and axial diffusivity to quantify structural brain integrity.

6.3.2.3.3. Resting-State Functional MRI. RS-fMRI, which measures intrinsic BOLD fluctuations in the absence of an explicit task, evaluates the degree to which activity in structurally connected brain regions co-varies (i.e., increases or decreases together) during rest. We will focus on resting state network connections between inferior frontal and medial temporal areas (shown to be prominent neural substrate of successful encoding[65,66]) and other resting state networks, including default mode network (DMN), task-positive network (TPN), and

salience network (SN). The ***DMN*** consists of interconnected regions in the posterior cingulate cortex, medial and lateral parietal cortex, and medial prefrontal cortex, which show *deactivation* during active task conditions[67]. The ***TPN***, centered on connections between medial and dorsal regions of the frontal and parietal lobes, becomes more activated when the brain is presented with an attentionally demanding task[68]; activity within this region during encoding is associated with accurate retrieval later on[69]. The ***SN***, comprised of dorsal anterior cingulate and the bilateral insula, responds to salient events and provides interaction between cortical, limbic, and subcortical structures essential for learning[70]. M-STBI is associated with abnormalities in the DMN[71-74], TPN[73], and SN[75]. It has been suggested[73] that TBI disrupts the normal segregation of the DMN and TPN through white matter damage to large corticortical pathways[76,77] and through damage to pathways that link the SN with the DMN and TPN. Such abnormalities are related to memory dysfunction[73] and show experience-dependent improvements after memory training[31,78].

Table 3. MRI Protocol – UF AMRIS 3T Philips System; 32 Channel Head Coil Total Scan Time = 43m 55s

Sequences	Purpose	Parameters
3D T1	Gray-white matter segmentation	176 continuous slices, voxel=1mm^3, TR/TE=7.0/3.2ms, flip angle=8^o, FOV=240x240mm, matrix=240x240x176mm, time: 4m 34s
3D FLAIR	Structural lesion identification, segmentation	180 continuous slices, voxel=1mm^3, TR/TE=8000/338ms, IR=2400ms, flip angle=90^o, FOV=240x240mm, matrix= 240x240x180mm, time: 7m 12s
T2	Brain extraction	176 continuous slices, voxel=1mm^3; TR/TE=2500/363ms; FOV=240x240, flip angle=90^o; matrix=240x240x165; time: 5m 27s
SWI	Micro-hemorrhage detection	Flow-compensated gradient echo; TR/TE1/ΔTE=59/8/6ms, FOV=240x192mm, flip angle=22^o, matrix=240x192x170mm, voxel=1x1x2mm^3, time = 5m 31s
HARDI	Fiber integrity, fiber modeling	74 continuous slices, 64 directions (1000s/mm^2), 6 directions (100/mm^2), voxel=2mm^3, TR/TE=4840/86ms, flip angle=90^o, FOV=224x224mm, matrix=224x224x140mm, time: 13m 1s
RS-BOLD	Resting state functional connectivity	36 slices, Single-shot EPI sequence, TR/TE=2500/30ms, flip angle=90^o, FOV=252x252mm, matrix=72x72x36mm, slice thickness=3.5mm, voxel=3.5mm^3, time: 8m 10s

Participants will be asked to keep still during the entire scan to minimize motion artifacts. During resting state recording, participants will be asked to close their eyes, relax their body and mind, but not to fall asleep or focus on any specific thought. Total Interdependence (TI; developed by Co-I Ding), will be used to quantify the functional connectivity between pairs of ROIs. Compared with Cross Correlation (CC), which exploits the covariance structures of zero-lag data but ignores temporal relations that extend beyond zero-lag, TI estimates the total amount of mutual information between the two extracted BOLD time series[79]. The statistical treatment of TI is similar to that applied CC estimates, but it has been shown that, by revealing additional temporal relationships not captured by CC, TI reproduces more precise task activated networks, and provides greater sensitivity in correctly deciding network membership[79].

6.4. Phase 3: Initial Testing of Treatment Efficacy

6.4.1. Overview. In this phase, appropriately classified patients will be assigned to participate in two memory interventions, one matched to their primary deficit, the other

mismatched, in counterbalanced order. The overall framework is outlined in Table 4; shaded cells are "matched" conditions.

6.4.2. Design. The overall approach is a ***multiple-subject Alternating Treatment Design***, effective for determining the relative efficacy of two treatments in a single individual[80]. One participant will be assigned to each treatment order in Table 4, such that 4 patients per classification group (12 total) will participate. Each participant will receive 1 matched and 1 mismatched treatment, in counterbalanced order. Therapists will be blinded to patient classification.

Table 4. Treatment Schedule

Memory Deficit	**Treatment Strategy/Target**			**Treatment Orders (one matched, one mismatched; counterbalanced)**
	Memory Strategy Training (1)	Errorless Learning (2)	Retrieval Practice (3)	
Encoding	+/+	+/-	+/-	12, 13, 21, 31
Consolidation	-/+	+/+	+/-	21, 23, 12, 32
Retrieval	-/+	-/+	+/+	31, 32, 13, 23

Although this design is subject to multiple-treatment interference[81] (the notion that the effects of each of the interventions might be affected by the presence of another intervention), such carryover effects are typically small and counterbalancing the order of treatments should further reduce treatment carryover[80]. The design permits comparison of treatment effects in conditions in which a treatment is given first vs. second. New methods for calculating treatment effect size and possible confounding factors are available[82-85]. ***It is hypothesized that greater gains in memory will be seen in matched, as compared to unmatched, treatments.*** This is illustrated by hypothetical data presented in Figure 1, where a patient with encoding deficits (blue) benefits more [greater elevation and slope] from memory strategy training than from retrieval practice, while the opposite pattern is seen in the patient with retrieval deficits (red). Each treatment will be conducted twice weekly for 3 weeks (6 sessions). Thus, each participant's involvement in actual treatment will span 6 weeks (2 treatments). Participants will be offered $20/session for participation as inconvenience cost and to help them defray travel expenses. We will conduct a 1-month follow-up at which time performance on proximal outcomes (performance on VPA and FNP tasks) and secondary outcomes (see below) will be evaluated.

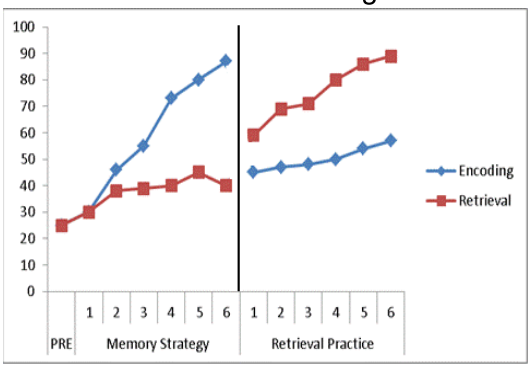

Figure 1. Hypothetical data of two patients, one with encoding deficit (blue), the other with retrieval deficit (red).

6.5. Secondary Outcome Measures

We will collect preliminary data on secondary outcome measures (Table 5) derived from the Interagency Traumatic Brain Injury Outcomes Workgroup recommendations[86]. Measures will be collected before treatment, immediately after the conclusion of each treatment (during the last treatment session), and 1 month after treatment has concluded. The $50 paid to the participant to undergo post-treatment MRI scanning will also cover the collection of 1-month post-treatment secondary outcome measures, since they will be collected on the same day.

Table 5. Secondary Outcome Measures

Domain	Purpose	Measure
Global Outcome	Summarize overall TBI impact	MPAI-4
Memory Impairment	Characterize memory deficits	RAVLT, BVMT-R, Everyday memory simulations from EON-MEM[a]
Social Role Participation	Evaluate involvement and participation in life situations	CHART-SF
Self-reported and general Quality of Life	Perceived satisfaction and well-being	SWLS, QUOLIBRI
Patient Reported Outcomes	Evaluate outcome from patient evaluation perspective	PROMIS[b] and Neuro-QOL[c] Item Banks

[a]Address/Phone Number, News Article, Face-Name Learning simulations; [b]Applied Cognition-Abilities, Applied Cognition-General Concerns; [c]Executive Function, General Concerns

7. Possible Discomforts and Risks:

7.1 **Risks Associated with MRI**: Magnetic resonance imaging (MRI) is a procedure that allows doctors to look inside the body by using a scanner that sends out a strong magnetic field and radio waves. This procedure is used routinely for medical care and is very safe for most people, but you will be monitored during the entire MRI scan in case any problems occur. The risks of MRI are:

- The MRI scanner contains a very strong magnet. Therefore, you may not be able to have the MRI if you have any type of metal implanted in your body, for example, any pacing device (such as a heart pacer), any metal in your eyes, or certain types of heart valves or brain aneurysm clips. Someone will ask you questions about this before you have the MRI.

- There is not much room inside the MRI scanner. You may be uncomfortable if you do not like to be in closed spaces ("claustrophobia"). During the procedure, you will be able to talk with the MRI staff through a speaker system, and, in the event of an emergency, you can tell them to stop the scan.
- The MRI scanner produces a loud hammering noise, which has produced hearing loss in a very small number of patients. You will be given earplugs to reduce this risk.

- If you are a woman of childbearing potential, there may be unknown risks to the fetus. Therefore, before you can have the MRI, you must have a pregnancy test.

7.2 **Risks Associated with Memory/Cognitive Testing**: When undergoing memory and cognitive ability testing, there is the risk of fatigue and frustration while taking the tests. Our trained examiners attempt to provide frequent breaks and utilize techniques to minimize frustration.

7.3 **Risks Associated with Participation in the Memory Treatment Program**: There are no known risks associated with participating in the memory treatment program.

7.4 **Other Risks**: Other possible risks to you may include: Normal risk associated with travel to and from UF and VA facilities.

8. Possible Benefits:

Patients may or may not benefit from participating in this research study. This research tests the effectiveness of memory rehabilitation therapies for helping Veterans with TBI-related memory problems. Since we are testing these treatments, we do not know how effective they are. Each participant will be given at least two such therapies, which may bring some benefit in memory by teaching strategies for remembering new information. The patient may also gain a better understanding of the effects of brain injury on memory function.

Other nonparticipating patients may benefit from our increased understanding of patterns of memory difficulty after mild traumatic brain injury that might respond better to particular memory rehabilitation therapies. Once we understand these patterns, we can better match patients to effective treatments designed to alleviate memory dysfunction.

9. Conflict of Interest: None, other than the typical benefit the PI and Co-I's get from presenting or publishing research results.

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