Improved autobiographical memory with central thalamic deep brain stimulation in traumatic brain injury

Eun Young Choi,[1] Brian Levine,[2,3] Jonathan D. Victor,[4,5] Linda M. Gerber,[6] Jaimie M. Henderson,[1] and Nicholas D. Schiff[4,5]

Abstract

Memory impairment is a common, debilitating consequence of moderate-to-severe traumatic brain injury, affecting daily life functions. There are few treatment options for memory impairment, particularly for real-life autobiographical memory. Recently, in a first-in-human phase I clinical trial, we demonstrated the improvement of executive attention and arousal in five participants with moderate-to-severe traumatic brain injury using deep brain stimulation of the central thalamus, specifically the central lateral nucleus and its projecting fibers within the medial portion of the dorsal tegmental tract.[1] Here in this within-subject study, we report a concomitant improvement in autobiographical memory in all five participants.

Participants were tested on their ability to recall autobiographical memories using a cue word-based recall task, and on the specificity of memories using the Autobiographical Interview,[2] before the start of treatment and at sessions approximately 3, 6, 9, or 13 months thereafter. Participants also provided self-reports of autobiographical memory changes during treatment.

All five participants showed an increase in the average number of autobiographical memories recalled with treatment (range: 12-100%, average: 45.9%, $P = 0.032$). Autobiographical Interview testing of the last four participants showed an average increase with treatment in the specificity of the recalled AMs, as measured by the percent of episodic (temporally- and spatially-specific to the memory) details out of the total episodic and semantic (factual, not memory-specific) details (18.7% improvement; main effect of treatment time $F(3,9) = 5.85$, $P = 0.017$). In subjective self-reports, four of the five participants clearly endorsed autobiographical memory improvements in their daily lives, collectively in the detail and vividness of the memories, the frequency of memories recalled, and the recollection of memories from time periods of post-traumatic retrograde amnesia.

These results raise the possibility that the central thalamus modulates the autobiographical memory system, potentially via the glutamatergic connections of the targeted fibers emanating

from the central lateral nucleus. The increased recall and specificity of autobiographical memories following treatment suggest that central thalamic deep brain stimulation may work to stabilize and refine the multi-faceted process of autobiographical memory retrieval, resulting in improved memory and, in turn, more effective everyday function. These findings support the possible use of central thalamic deep brain stimulation for improving autobiographical memory in moderate-to-severe traumatic brain injury.

Author affiliations:

1 Department of Neurosurgery, Stanford University, Stanford, CA, 94305, USA

2 Rotman Research Institute, Baycrest Academy for Research and Education, Toronto, ON, M6A 2E1, Canada

3 Departments of Psychology and of Medicine (Neurology), University of Toronto, Toronto, ON, M6A 2E1, Canada

4 Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York City, NY, 10065, USA

5 Department of Neurology, New York Presbyterian Hospital, New York City, NY, 10065, USA

6 Departments of Population Health Sciences and of Medicine, Weill Cornell Medicine, New York City, NY, 10065, USA

Correspondence to: Eun Young Choi, PhD

Department of Neurosurgery, 300 Pasteur Drive, MC5327, Stanford, CA, 94305, USA

E-mail: eychoi@stanford.edu

Running title: Thalamic DBS for autobiographical memory

Keywords: central thalamus; deep brain stimulation; autobiographical memory; traumatic brain injury; central lateral nucleus

Abbreviations:

AI = Autobiographical Interview; AM = autobiographical memory; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BA = Brodmann Area; BOLD = bold oxygenation level-dependent; CL = central lateral; CM = centromedian; dACC = dorsal anterior cingulate cortex; DBS = deep brain stimulation; dmPFC = dorsomedial prefrontal cortex; DTTm = medial portion of the dorsal tegmental tract; GCS = Glasgow Coma Scale; GOS-E = Glasgow Outcome Scale-Extended; TBI = traumatic brain injury; MD = mediodorsal; mPFC = medial prefrontal cortex; msTBI = moderate-to-severe traumatic brain injury; MTL = medial temporal lobe; PCC = posterior cingulate cortex; Rsp = retrosplenial cortex; TMT-B = Trail Making Test-B; VPL = ventral posterior lateral

Introduction

Moderate-to-severe traumatic brain injury (msTBI; Glasgow Coma Scale [GCS] = 3-12, Glasgow Outcome Scale-Extended [GOS-E] = 5-7) results in a broad array of behavioral deficits, including poor memory, poor executive function, and fatigue.[3,4] While most memory research in msTBI concerns memory as assessed by laboratory tasks,[5] real-life mnemonic tasks necessary for core life functions, such as social interactions and future planning, rely on autobiographical memory (AM; memory for facts and events from one's life).[6-9] In TBI, AMs have fewer memory-specific details, reduced temporal scope, and are associated with disruptions to such core life functions.[10-12] Despite the importance of AM deficits in msTBI, only a few studies have explored treatments, such as behavioral,[13] pharmacological,[14] and neurofeedback[15] interventions.

The multi-faceted nature of AM retrieval is reflected in the dynamic engagement of distributed brain regions underlying mnemonic search, retrieval, monitoring, and narrative coherence.[16] These regions include the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), retrosplenial cortex (Rsp), precuneus, and the medial temporal lobe (MTL) memory system, which overlap with regions of the default mode network.[17,18] In TBI, structural, functional, and metabolic abnormalities have been observed in these regions, including reduced brain

volume,[19-21] reduced neuronal glucose uptake,[22,23] evidence for partial deafferentation and functional down-regulation underlying executive dysfunction,[24-26] and abnormalities in functional connectivity.[27,28]

How might AM deficits arise in TBI? A prominent process that occurs following a TBI is the downregulation of the central lateral (CL) nucleus of the thalamus and the broader arousal regulation system.[29,30] CL is a key node in the arousal regulation system that receives inputs from the brainstem arousal centers, including the reticular nuclei,[31,32] and is connected with regions throughout the brain, including in the cerebral cortex and striatum,[33] primarily via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor glutamatergic connections.[34] The mesocircuit hypothesis posits that based on CL's widespread connections, the diffuse axonal damage following a TBI disproportionately downregulates CL, which in turn downregulates CL's targets.[35] Chief among CL's targets are attention-related regions in the dorsomedial prefrontal cortex (dmPFC) and dorsal anterior cingulate cortex (dACC). This mechanism is thought to underlie the commonly observed cognitive deficits in TBIs, despite heterogeneity in the primary structural damage; as well as several demonstrations of instrumental improvements in arousal and cognitive function following CL stimulation. Evidence for the critical role of CL includes a macaque study in which CL stimulation rescued fatigue-induced performance deficits in an attentional vigilance task[36] and two human studies in which CL stimulation restored a minimally conscious participant to a conscious, behaving state[37] and improved executive attention and arousal in five msTBI participants.[1]

While CL's attention and motor-related connections are well known, its connections pertaining to memory are less recognized, but nonetheless present. Animal tract-tracing shows that CL is not directly connected to any structures in the MTL memory system.[33,38-42] However, in macaques, a subset of CL's projections target cortical midline areas that are homologous to regions of the human default network involved in AM.[43-46] In macaques, demonstrated targets include areas in the mPFC (Monkey Brodmann Area [BA] 24b), PCC (Monkey BA 23a), Rsp (Monkey BA 30), and precuneus (Monkey BA 31, PGm, PEc, PEci[44,47,48]; see also rodent study[33]) (Note: tracer studies thus far report that CL receives afferents from, but does not send efferents to, the caudal inferior parietal lobule, another region of the default network[49,50]). In turn, mPFC, PCC, and Rsp are connected with the subicular complex,[51-53] entorhinal cortex,[54-57] perirhinal cortex (Monkey BA 35, 36), and parahippocampal cortex (Monkey areas TF, TH).[51,56-60] Thus, downregulation of CL in TBI may lead to the downregulation of mPFC, PCC, and Rsp, which in turn downregulate MTL structures, thereby reducing functions related to

AM. Indeed, rat studies have shown that DBS of CL improves object recognition memory,[61] as well as rescues spatial memory in an amyloid beta-infused rodent model of Alzheimer disease.[62] In addition, although CL is not directly connected to the hippocampus, these studies, respectively, reported gene expression changes and rescue of glutamatergic spine density in the hippocampus following CL stimulation, indicating CL's ability to indirectly modulate the hippocampus. However, it is yet unknown whether CL and its downstream glutamatergic pathways modulate a high-order form of memory such as AM.

Here, we tested the hypothesis that CL stimulation remediates AM deficits in five msTBI participants. These participants underwent DBS of the central thalamus, specifically targeting the central lateral nucleus of the thalamus and its projection fibers within the medial portion of the dorsal tegmental tract (CL/DTTm) in a phase I clinical trial (CENTURY-S) designed to test its effects on dysexecutive attention and fatigue.[1,63] Our test battery separately assessed distinct AM processes: AM generation (searching for a memory based on a cue) and AM elaboration (the richness of AM given an identified memory).[16,64] To assess the generative component, we used a cue word-based AM Recall Task closely adapted from a well-validated paradigm[65,66] to test AM recall ability before and after the start of CL/DTTm DBS treatment. To assess the specificity of the elaborative component, we examined the percentage of episodic (spatiotemporally-specific to the memory) out of the total number of episodic and semantic (factual, non-specific to the memory) details quantified using the Autobiographical Interview (AI),[2] a well-established method for dissociating these canonical categories of AM content that is sensitive to changes in AM in aging and neurodegenerative disease,[67] medial temporal lobe damage,[68] and the AM network in numerous structural and functional neuroimaging studies.[69-73] Among chronic-phase TBI participants administered the AI, reduced specificity (i.e., reduced episodic and increased semantic autobiographical details) was evident in those with severe TBI,[74] a pattern associated with distributed volume loss in the above-described default mode network regions. On the basis of these findings, we hypothesized that CL/DTTm DBS would address these mnemonic changes by increasing the number and specificity of recalled AMs in narrative AM. These measures were supplemented by self-reports of AM improvements experienced by the participants in their daily lives.

Materials and methods

Study Design

This study examined the effects of CL/DTTm DBS treatment on AM in the five participants using a within-subject design. Participants were enrolled in a clinical trial examining this treatment on executive attention and arousal (Schiff *et al.*[1]). Participants were tested on AM measures before the start of treatment and at sessions approximately 3, 6, 9, or 13 months thereafter while receiving treatment during and after the clinical trial. AM Recall Task data, comprised of a single measure, were analyzed using the Wilcoxon signed-rank test. AI data, comprised of multiple measures, were analyzed using a repeated-measures ANOVA and Page's L test.

Participants

Six participants (P1-P6) with msTBI were enrolled in the NIH Brain Initiative CENTURY-S phase I clinical trial (NIH BRAIN UH3NS095554; ClinicalTrial.gov NCT02881151) investigating the safety and feasibility of CL/DTTm DBS in restoring executive function[1]. Briefly, all participants provided informed consent according to protocols approved by Stanford University's Institutional Review Board in accordance with the Declaration of Helsinki. Participant inclusion and exclusion criteria included an age of 22-60 years, a history of msTBI as assessed by a GCS (a measure of consciousness level after TBI) score of 3-12 within the first 48 hours of injury, current GOS-E (a measure of functional outcome after TBI) score of 5-7, being two or more years post-injury, and failure to return to the pre-injury level of vocational or educational function. Participant P2 had her DBS system removed due to safety reasons and did not participate further in the trial, resulting in five participants who completed the study. Table 1 shows the demographic information of the participating participants. All participants demonstrated evidence of diffuse axonal injury with generalized atrophy, asymmetric volume loss, and focal injuries (Supplementary Fig. 1-5). Of note, P6 demonstrated marked bifrontal structural lesions, including large left hemispheric volume loss within the medial frontal lobe (Supplementary Fig. 5). See Schiff *et al.*[1] for further details on eligibility criteria and recruitment.

Eighteen healthy adults (7M, 11F, mean age 43.3 +/- 12.1 years) were recruited as comparison participants for a study of AM in depression using the AI.[75] As part of an unpublished follow-up study, their memory for distinct autobiographical events was serially assessed and scored using the AI, providing an independent estimate of the degree to which AM performance

changes over time in healthy adults with no intervention. This study was approved by the Baycrest Institutional Review Board, and all participants provided informed consent.

Insert Table 1 About Here

Surgery and CL/DTTm DBS Treatment

Detailed descriptions of the clinical trial, surgery, and treatment are in Schiff *et al*.[1] Briefly, participants underwent surgery consisting of two stages: (1) implantation of DBS leads (Medtronic, Minneapolis, MN) into the central thalamus (Supplementary Fig. 6), targeting CL and its connections with the dorsomedial frontal cortex located in the DTTm; and (2) placement of an implantable neurostimulator (P1: Medtronic Activa PC+S; P3-P5: Activa PC; P6: Percept) connected to the DBS leads by extension wires tunneled from the scalp down to the chest. After post-operative recovery, therapeutic stimulation settings for each participant were determined based on performance on a neuropsychiatric battery (which did not include a test of AM) and avoidance of side effects. Once the therapeutic stimulation setting was determined (Supplementary Table 1), participants underwent a 90-day treatment period in which stimulation was on for 12hrs during the day and off for 12hrs at night.

Autobiographical Memory Recall Task

The AM Recall Task was presented combined with a visually-guided attentional vigilance task ("Vigilance-AM task"; data not reported here). There were two runs, each run consisting of six blocks of eight vigilance trials that were interleaved with six blocks of three AM recall trials (Fig. 1; the interleaved design was originally selected to time-efficiently administer both tasks in the intraoperative setting). A vigilance trial consisted of a variable delay "vigilance" fixation period (1-3 seconds, mean = 2 seconds) with a centrally located crosshair, and then a 1-second saccade target presented at the top, bottom, left, or right part of the screen at 10 degrees of visual field eccentricity from the center, to which the participant was required to saccade within

the 1-second window. All four saccade targets were randomly presented with equal frequency within one block (6 trials per target per block).

Insert Figure 1 About Here

An AM recall trial consisted of a 3-second fixation period with a centrally located crosshair, followed by a 15-second period in which the central crosshair remained on the screen, while a cue word appeared immediately above the crosshair and one of two memory time periods ("distant" pre-injury and "recent" post-injury within the last 6-12 months; see Supplementary Table 2 for participant-specific distant time periods) appeared immediately below the crosshair. A script of the task instructions was read by the experimenter to the participants prior to testing at each time point. Participants were instructed to keep their eyes fixated on the crosshair at all times. Once the cue word and memory time period appeared, they were instructed to maintain fixation while reading the words with their peripheral vision. This was done to minimize muscle and eye movement during the simultaneously recorded EEG for P1 and P6 who were tested in the clinic (data not reported here), and to maintain consistency in the task for P3, P4, and P5 who were tested without EEG via video conferencing due to COVID-19 pandemic restrictions on in-person testing. Participants were instructed to recall an AM that occurred within the indicated time period. The AM did not have to be related to the cue word above the crosshair. Once an AM was remembered, participants pressed a button to indicate successful recall, after which they were instructed to relive the AM in as much detail as possible until the trial ended. Participants were given the opportunity to take a 5-minute rest between the two runs, although not all participants rested for the full time. After the completion of both runs, participants took a post-test questionnaire that reviewed each AM trial and asked whether an AM had been recalled; and if so, briefly what its content was, the participant's alertness during the memory recall, and the valence of the memory. Alertness was measured on a 5-point scale consisting of 1 ("Not at all"), 2 ("Slightly"), 3 ("Moderately"), 4 ("Very"), and 5 ("Extremely"). Valence was measured on a 5-point scale consisting of -2 ("Strongly negative"),

-1 (“Somewhat negative”), 0 (“Neutral”), +1 (“Somewhat positive”), and +2 (“Strongly positive”).

Five versions of the Vigilance-AM task were created for a pre-treatment start time point and 3, 6, 9, or 13 months after treatment start time points. Each version had a different schedule of saccade targets and variable delay fixation periods, as well as novel sets of 18 cue words. Cue words were culled from the Toronto Word Bank and matched for imagery, concreteness, and frequency in the English language, both across the two memory time periods within a task version and across the four task versions.

Insert Table 2 About Here

Testing occurred prior to the start of treatment, and at 3, 6, 9, or 13 months after the start of treatment. Table 2 shows each participant’s specific time points and small deviations in these time points for Participants 3 and 5 due to scheduling issues, as well as two baseline time points for P6. Table 2 also indicates whether CL/DTTm DBS was on or off at each testing session. In general, participants who were tested in the clinic (P1 and P6) had their CL/DTTm DBS turned off for testing and back on afterwards by the investigators. P3, P4, and P5 had to be tested remotely due to COVID-19 safety restrictions. For these remote testing sessions, CL/DTTm DBS was left on either at the participant’s request to not interrupt treatment or due to concerns that the therapeutic stimulation might not be reliably turned back on by the participant after testing.

For in-clinic testing, tasks were presented on a computer screen using Labview. Participants wore a 256-channel high density EEG cap (Electrical Geodesics, Inc.) (data not presented) and observed the screen while resting their heads on a chin rest to reduce head movement. Eye movements were tracked by an Eyelink 1000 eyetracker (data not presented). Millisecond precise task timing was achieved using a photodiode detecting luminance changes on the computer screen corresponding to different task epochs and connected to a National Instruments data acquisition card. Button-press responses were made with a hand-held button

responder that was also connected to the data acquisition card. Response times were measured by post-test reconstruction of these events. For testing via video conferencing (Zoom Communications, Inc.), tasks were run on the experimenter's laptop and presented by screen share; EEG, eyetracking, and millisecond response times were not measured. However, saccades during the vigilance task were observed by the experimenter and button press responses during the AM Recall Task were recorded instead by key presses in the chat window. All testing sessions in the clinic and over video conferencing were video and audio recorded.

AM recall scores were calculated for each time point as the number of trials in which AMs were successfully recalled out of a total of 36 trials. Successful AM recall was defined as the recollection of a personally occurred event that occurred within a specific time and place, was from the cued memory time period, was retrieved within the 15-second time window as indicated by button press, and was confirmed as such in the post-test questionnaire. Recollections were counted as not successful AM recalls if they did not meet these criteria, if the participant provided a vague post-test description that could not confirm a successful AM recall, or if the AM was a repeat of a previously recalled AM within the same testing session. See Supplementary Table 3 for the number of trials with successful AM recall ("Correct"), no successful AM recall ("Incorrect"), or nothing recalled ("Omit"). A significant difference between the baseline and average treatment memory recall scores was assessed across participants with a one-tailed Wilcoxon signed rank test (*signrank* function; Matlab R2020b, The Mathworks, Inc.).[76] The effect size for the Wilcoxon signed rank test was calculated as r = abs(Z-statistic) / sqrt(number of participants).[77] The one-tailed test was selected based on prior human and rodent stimulation work[1,37,61,62] indicating that CL/DTTm DBS would improve cognitive functions, including memory. The average treatment memory recall score was analyzed to at least partially average out confounds related to differing testing timepoints and COVID-related alterations in testing (such as DBS on/off status) that might have affected performance at certain timepoints.

Autobiographical Interview Task

Beginning with P3, the AI task[2] was added to the study procedure. The AI task was administered to P3, P4, P5, and P6 at baseline and at approximately 3, 6, and 9 months (Table 2), one week after completing the Vigilance-AM task. Exceptions were P3, who was tested only at baseline at 6 months of treatment, and P4 who was tested only at baseline, 6 months,

and 9 months of treatment. CL/DTTm DBS was on or off during testing as indicated in Table 2. For each time point, six AMs were selected from the preceding Vigilance-AM task, comprised of three AMs from each of the distant/pre-injury and recent/post-injury time periods, matched as a group by time period for alertness, valence, and importance ratings (Exception: P6 was tested on four, two, and three AMs for the two baseline and 3-month time points, respectively, due to insufficient AMs available from the preceding Vigilance-AM task). AMs were also selected to not have been recalled in AI testing from a prior time point, not be embarrassing or traumatic, and not potentially reveal personal information that the participant may not want to share. The AI was administered using standardized instructions[2]. Briefly, for each AM, participants were asked to recall the memory in three stages: a free recall in which the participant recalled the memory with no prompting by the experimenter, a general probe in which the experimenter prompted open-endedly for more details (e.g., "Tell me more about…", "Can you remember anything else about …"), and a specific probe in which the experimenter asked specific questions seeking further details ("Where did this memory take place?", "What colors, smells, or tastes do you recall in the memory?", "Where were you situated in the room?"). Personal health information was removed from the responses, which were then transcribed by a medical transcription company (TranscribeMe; www.transcribeme.com). In order to avoid introducing bias, transcribed text was separated into individual memories, de-identified, and scored in a random order such that the independent scorer, who had not collected the data, was blind to participant identity and test session. AI scoring entails identification of details (grammatical clauses) that are classified as internal (i.e., episodic, pertaining to events or happenings, temporal, spatial, perceptual, or emotion/thought details specific to the event) or external (i.e., semantic information, repetitions, commentary, or details about other events). For simplicity, the internal and external detail categories are hereafter referred to as episodic and semantic. The scorer had established high inter-rater reliability (intra-class correlation coefficients > 0.90) for internal and external details on the AI scoring method. See Levine *et al*.[2] for additional details of the AI task.

For each participant's AM, the total numbers of episodic or semantic details across the three stages (free recall, general probe, specific probe) were counted and used to calculate the percent of episodic details (out of the total episodic and semantic details). These values were averaged across all AMs to obtain the average total numbers of episodic and of semantic details, which were used to compute the average percent of episodic details out of the total episodic and semantic details at each time point for each participant (AMs were pooled across both baseline

timepoints for P6). For P3 and P4, who were tested at a subset of the time points, the missing data were imputed with the mean of the average total number of episodic or semantic details across timepoints and subjects; this is a conservative approach as it would tend to underestimate significance and effect size. The results obtained with this method were similar to those obtained by imputing the missing data with data only from the subject, as well as by analyzing only the timepoints with data from all four subjects. Percent change from baseline was calculated using the baseline (average baseline for P6) and average treatment values. Data were further analyzed with a repeated-measures ANOVA with Time treated as a categorical variable, Time On Treatment as a fixed-effect factor, and Participant as a random-effect factor. Normality of the data was confirmed using the Shapiro-Wilk test of the data at each timepoint, of the difference scores between timepoints, and of the pooled data across all timepoints. The per-timepoint analysis showed that 11 of 12 timepoints were normally distributed, with only the number of semantic details measure at the 3-month timepoint showing non-normality (P = 0.005). Most importantly, the difference score analysis, which is most theoretically relevant for repeated-measures ANOVA assumptions, showed normality for all nine difference score comparisons across all three measures. Effect sizes were determined using partial η^2. Results of the repeated-measures ANOVA were confirmed with the non-parametric Page's L test. Significance was determined using critical L values for 4 subjects and 4 timepoints (for an increasing trend, critical L = 114 for $P < 0.01$ and 111 for $P < 0.05$; for a decreasing trend, critical L = 89 for $P < 0.05$).[78]

For the eighteen healthy participants, the AI was administered at 0, 1.5, and 2.5 months. While these time intervals differ from those in the present study, the methods of cueing and scoring were comparable to the present study, including the selection of different events at each assessment. These data therefore provide a benchmark as to how much interval change is expected in healthy adults' successive testing of AM recall without intervention. For each measure, the average scores of AMs extracted from the 1 year (range: 6-18 months) and 10 year (range: 5-15 years) time periods were averaged for each participant at each timepoint. Paired t-tests were performed on the data from the 0 and 1.5 months timepoints and from the 1.5 and 2.5 months timepoints.

Data availability

The data underlying this article are available in the article and its online supplementary material, and upon reasonable request. All analyses were conducted with MATLAB R2020b (www.mathworks.com).

Results

Autobiographical Memory Recall Task

All participants showed an increase in the average number of memories recalled with CL/DTTm DBS treatment (Fig. 2), with a significant group improvement of 45.9% (one-tailed Wilcoxon signed-rank W = 0, $P < 0.032$) with a large effect size (r = 0.90) (Table 3). Individually, there was considerable variation in baseline memory recall score (3-21, out of 36 possible total points) and improvement with CL/DTTm DBS treatment (11.8-100%). P1 and P5 had the highest baseline recall scores (21 and 17, respectively), while P3, P4, and P6 had relatively low scores (9, 8, and 3, respectively). However, baseline recall did not predict improvement with CL/DTTm DBS treatment (Fig. 2). P1 and P6, who had the highest and lowest baseline recall scores, respectively, were the highest improvers (61.9% and 100%, respectively); while P3, P4, and P5, who had intermediate baseline recall scores, were the lower improvers (18.5%, 37.5%, and 11.8% improvement, respectively). Across participants, there was no significant difference in the memory time period (pre-injury or post-injury) (Supplementary Table 4), or in the ratings for alertness during the recall or valence of the memory, for successfully recalled AMs at baseline versus with treatment (Supplementary Table 5).

Insert Figure 2 About Here

Insert Table 3 About Here

Autobiographical Interview Task

In order to understand if CL/DTTm DBS treatment affects the specificity of recalled AMs, we measured the percentage of episodic details (out of the total number of episodic and semantic details) for P3, P4, P5, and P6 at baseline and 3, 6, and 9 months of treatment (Fig. 3A; Table 4). All four participants showed an increase in specificity from baseline and across the treatment timepoints with a large overall effect size (average 18.7% improvement, main effect of time $F(3,9) = 5.85$, $P < 0.017$, partial $\eta^2 = 0.66$). Examining the underlying numbers of episodic and semantic details (Fig. 3B, C) showed that this increased specificity was driven by a large (but not quite significant) reduction of semantic details over time for P4, P5, and P6 (-33.3%, -45.1%, and -30.4%, respectively) (average 23.4% reduction, main effect of time $F(3,9) = 3.12$, $P < 0.081$, partial $\eta^2 = 0.51$). The change in the number of episodic details was mixed across the participants, increasing for P3 and P4 (54.4% and 33.9%, respectively) and decreasing for P5 and P6 (-16.0% and -21.5%, respectively). This led to a small, non-significant increase in episodic details with treatment (average 12.7% improvement, main effect of time $F(3,9) = 0.83$, $P < 0.51$, partial $\eta^2 = 0.22$). These results were confirmed with the non-parametric Page's L test: specificity significantly increases ($L = 114$, $P < 0.01$), the number of semantic details has a trend towards significantly decreasing ($L = 91$), and the number of episodic details does not significantly change ($L = 101$) with treatment. There was no change in the average vividness rating of the AMs recalled with treatment (Supplementary Table 6).

Insert Figure 3 About Here

Insert Table 4 About Here

Even though the patients retrieved different events at each time point, it is possible that repeated practice with the AI task (and not the intervention) accounted for their improved

performance over serial assessments. We therefore analyzed AI data from an independent cohort of healthy participants tested at 0, 1.5, and 2.5 months using methods similar to those used in the msTBI cohort. These results showed an average specificity of 72.9 +/- 8.2% of episodic details, with 56.6 +/- 20.7 episodic details and 22.6 +/- 11.7 semantic details, across all timepoints. We found that healthy controls did not systematically improve between timepoints in specificity as assessed by the percentage of episodic details (Baseline to 1.5 months: $P = 0.45$; 1.5 months to 2.5 months: $P = 0.34$; Fig. 4B) or in the numbers of episodic and semantic details (Baseline to 1.5 months: $P = 0.10$ and 0.70; 1.5 months to 2.5 months: $P = 0.12$ and 0.20, respectively), suggesting that there are no significant practice effects when AM for distinct events is serially assessed in healthy adults without intervention.

Participant Self-Reports (Box)

Participants, and their families when available, were asked for their subjective observations of any changes in autobiographical memory (AM) in their daily lives over the course of central lateral thalamic nucleus / medial portion of the dorsal tegmental tract (CL/DTTm) deep brain stimulation (DBS) treatment. All participants and their families endorsed an improvement in AM at various times during treatment; no participant reported a decrement in AM at any time. P1 reported the greatest improvement, reporting that at four months of treatment, there was an "explosion" in her ability to remember "highly detailed, very vivid" AMs, particularly from a pre-injury period that was previously "blank." P1's mother stated that "she started remembering all this stuff… once her mind found the way. It's happening all the time on a regular basis. It's just becoming normal, like we're normal with our memories. … I think [she is] remembering pretty much everything now." P1 stated, "I remember everything about it. … It's not like I just know a little bit… [it's] like a picture." At around one year of treatment, P1 additionally reported a 1-2 week period with intense, movie-like AM recollections. These recollections included remembering her grandfather's wake, such as the green color of the carpet and the smell of incense in the air, and remembering all the faces and names of the children in her first grade class.

At three and five months of treatment, P3 did not endorse a strong improvement in AM. However, he reported that his dreams, occurring almost every night, were more vivid and frequent, and included childhood events that he had forgotten about. At ten months of

treatment, P3 reported continuing to have vivid dreams almost every night and added that his recalled AMs were more vivid, as well.

At three months of treatment, P4 reported, "I believe [AMs have] improved a bit … [there is] a bit more variety of memories from back then I'm recalling…" However, he still could not remember well the order in which autobiographical events had happened within a constrained time period (e.g., Thanksgiving season).

At two months of treatment, P5 reported that he had recalled a few AMs from the six months prior to his injury, which was a period of post-traumatic amnesia. At five months of treatment, P5 reported that his AMs were "brighter" and more visually detailed, and that he could more thoroughly assess the AM ("look at it from different angles"), but not necessarily recall more AMs than prior to treatment. At seven months of treatment, P5 reported having some dreams, which was more frequent than prior to the treatment when dreams were "few and far between and can't [be remembered] one hour after being awake."

P6 did not strongly endorse an improvement in AMs with treatment. However, at three months of treatment, his mother reported an instance of his recalling where he was living and with whom during college, which had surprised her as something he could not have done prior to the treatment.

Discussion

In the present study, we report that CL/DTTm DBS led to the improvement of AM in all five participants who completed the CENTURY-S trial, in addition to the increase in executive attention[1] and decrease in fatigue[63] reported earlier. There was evidence for CL/DTTm-DBS-related improvement in both generative (search and retrieval) and elaborative (quantity of specific details) elements of AM retrieval. The AM Recall Task showed an overall 45.9% increase in retrieved memories in response to non-specific cues. The AI task showed that the participants had an average 18.7% increase in specificity with CL/DTTm DBS treatment, potentially by reducing non-specific, semantic detail. These results suggest that CL/DTTm DBS treatment induces greater fluency, focus, and richness of AMs, which are known to be affected in msTBI (as well as other conditions) and with downstream effects on everyday function. Qualitatively, participants and their families reported AM improvements to varying degrees in the fluency of recall, vividness and detail, and accessibility of AMs from periods of post-traumatic retrograde amnesia (Box 1). Remarkably, P1 reported a return to pre-injury

levels of AM functioning after 3 months of treatment, as well as several weeks of highly vivid, multi-sensory AM recollections at home during a period of post-trial adjustment of stimulation settings, which resolved when the stimulation voltage was lowered (Box 1). These self-reports are consistent with qualitative improvements broadly in memory reported by all participants and their families in a structured, prospective narrative study accompanying the phase I trial.[63,79]

Studies from the literature provide context to the present results (Fig. 4) using similar versions of the AM Recall Task and AI to those used here. For the AM Recall Task, healthy participants performed at the highest range (~40-84 +/- ~10-14%)[65,66,80-87] , followed by participants with depression-associated conditions and bipolar disorder (~30-50 +/- ~10-16%)[81-88]; as seen in the figure, our participants are at the lowest range (~10-60% range). Interestingly, two studies by Young et al. examined the effects of potential interventions on recall (specifically, the effects of modulating cortisol levels with various cortisol receptor antagonists[14] and of neurofeedback-based real-time fMRI modulation of amygdala activity[15]); the manipulations modulated recall by ~7-17 percentage points, which is on the same scale as the improvement in our participants (~5-36 percentage points) with CL/DTTm DBS. For the AI, healthy controls and mild-to-moderate TBI participants performed similarly at ~70 +/- 10%.[74,75] Our participants started in the lower range of 44-60% episodic details, consistent with their having cognitive disabilities in the moderate-to-severe TBI range, and had treatment-related improvements ranging ~60-70%. Altogether, our participants initially performed overall worse than healthy and depression-associated populations, and improved either to levels similar to those of healthy participants or by amounts that are similar to or greater than those observed by other interventions.

Given that different events were selected at each time point, there is no reason to expect that memory performance would improve without intervention. Accordingly, no significant practice effects were observed on the AM Recall Task in 19 MDD participants who were tested twice at an interval of 5-7 days,[15] as well as on the AI of 18 healthy participants tested at intervals of 1 and 1.5 months (Fig. 4). This lack of practice effects suggests that the improvements we observed are likely due to CL/DTTm DBS, and that the degree of improvement eclipsed the expected variability due to the differing contents of the AMs tested at different time points.

We do not believe that the AM improvements are merely due to improved verbal or language function. This is because the participants show an increase in the percent of episodic details, which corrects for overall verbal output, due to an underlying decrease in semantic details, rather than an increase in both semantic and episodic details, as would be the case if the treatment were simply improving verbal or language function. In addition, no participants had any expressive language impairments at any timepoint in the trial, nor did any endorse verbal or language deficits.

There are several anatomical pathways through which CL/DTTm DBS effects on AM could occur. As CL does not directly connect to the hippocampus and adjacent medial temporal areas,[33,38-42] the CL/DTTm DBS enhancement of AM recall likely occurs via CL's connections with cortical regions that process AM, including mPFC, PCC, Rsp, and precuneus of the default network. Indeed, CL stimulation in rats was associated with improvements in unrewarded object recognition and spatial memory, and induced changes in gene expression and synaptic density in the hippocampus, indicating the ability of CL stimulation to create long-term changes to this central node of the memory system, despite the lack of direct connections.[61,62] Consistent with this, CL stimulation in rats lead to an increase in functional MRI blood oxygenation level-dependent (BOLD) activity in the hippocampus and enhanced CL-hippocampal functional connectivity as measured by resting-state functional connectivity MRI; these effects were also seen for regions of direct connectivity, such as the anterior cingulate cortex, somatomotor cortex, and Rsp.[89] However, we note that Liu *et al*.[90] did not find hippocampal changes in BOLD activity following optogenetic stimulation of CL in rats, although they also observed BOLD activity changes in the anterior cingulate, somatomotor cortex, and Rsp; this difference from the Li *et al*.[89] study could be due to differences in the anesthesia used or the extent of stimulation from the differing stimulation methods.

The AM tasks used in this study entail complex cognitive operations requiring integrated activity across distributed brain regions, including the mPFC (initiation, arousal, and self-related processes), posteromedial regions (multimodal perceptual-mnemonic integration), and distributed cortical regions involved in the reconstruction of the sensory aspects of mnemonic experiences.[16] One of the consequences of CL downregulation following TBI may be disruptions to the synchrony in neural activity necessary amongst these regions for successful AM retrieval.[91-93] Consequently, CL/DTTm DBS may concurrently drive these regions, promoting synchrony amongst these regions and, in turn, driving hippocampal processing and the distributed brain-wide synchrony needed for successful AM retrieval.[68,94] Accordingly, the

present treatment effects showed an increase in the episodic details of AM, which are mediated by hippocampal-neocortical connectivity,[91,93] whereas semantic details reflecting generic or off-task content did not increase with treatment. Indeed, the significant decline in these semantic details reflects an increased fidelity of recall in response to the task instructions to recall a specific event. It is the episodic elements of AM that are most strongly connected to the representation of the self across time,[95] which in turn is crucial for self-regulation in everyday situations.[64,96]

It is notable that AMs are predominantly visual[97] and that CL has several established roles in visual processing (see reviews[98,99]). While we did not observe any changes with treatment in the vividness ratings of the AI (Supplementary Table 6), several participants self-reported changes in the vividness of AMs and dreams in their daily lives (Box 1). CL neurons code eye movement information[100] and have monosynaptic projections to visual cortex.[101] Modulation of CL has been demonstrated to alter both the contrast sensitivity of V1 neurons (when electrically stimulated[102]) and orientation tuning when lesioned[103] or electrically stimulated at low frequencies.[99,104] Finally, as noted above, CL projects to the precuneus,[48] which is involved in visuo-spatial imagery and attention[105] and is a modulatory node of AM recall.[93] We also note that alongside P3's report of enhanced vividness in AMs and dreams, functional improvement in P3's vision emerged with continued treatment after the trial. Prior to the trial, P3 had a large left posterior lesion within the primary visual cortex (Supplementary Fig. 2), along with hemianopia and visual disability requiring a white cane for walking. Within 18 months of CL/DTTm DBS treatment, P3 stopped his use of the walking cane and reported improvements on the Goldmann visual field test in comparison to his pre-surgical baseline score. Taken together, these observations suggest CL/DTTm DBS may enhance visual processing via one or more of these mechanisms, leading to improvements in visual aspects of AM. Further study is needed to specifically examine this hypothesis.

The individual improvements in AM seen with CL/DTTm DBS did not closely parallel the individual improvements in executive function (primary outcome measure: Trail Making Test-B [TMT-B]) in Schiff *et al*.,[1] consistent with a prior report of no significant correlation between TMT-B and AM.[74] This variability likely reflects individual differences in the complex underlying connectivity and heterogeneity in TBI-related damage. It also suggests that even though executive attention is a component of AM retrieval, there is some degree of independence between the neural processing underlying AM and executive attention, at least as measured here. Despite this individual variability, we nonetheless found statistically

significant group-level AM improvements. A fuller understanding of individual response variability and its implications will require a larger sample size.

The therapeutic potential of the present findings is considerable. Currently, although AM deficits are a major complaint in msTBI and reduce core life functions,[10-12] there are no established effective treatments for AM deficits in msTBI. The majority of prior studies on the memory effects of DBS have targeted the medial temporal lobe and associated memory circuitry or the cholinergic system via the nucleus basalis of Meynert using laboratory-based episodic memory, such as verbal memory of word lists (see [106] for review), in Alzheimer Disease and epilepsy. To our knowledge, the present study is the first to quantify improvements in AM with DBS, here in msTBI via the CL-mediated glutamatergic system. Interestingly, P1's spontaneous at-home episodes of multi-sensory, movie-like re-experiencing of AMs (Box 1) is similar to reports from a fornix DBS study of 42 Alzheimer Disease participants, where 20 participants reported spontaneous vivid AM recollections.[107,108] Of these 20 participants, 6 had multi-sensory recollections involving imagery, smells, and ambient temperature experiences, similar to P1's experiences. Our finding that stimulating the arousal system at the CL node leads to improvements in AM, as well as arousal and attention-related functions,[1] indicates that CL/DTTm DBS improves a wide array of cognitive deficits experienced in msTBI. This may differentiate CL/DTTm DBS as a memory treatment from DBS approaches that directly target the memory system.

These data have implications for trial design, specifically the importance of testing at longer timepoints, potentially up to a year. For example, had we stopped data collection after three months of treatment, we would not have observed the improvements in AM at later timepoints, and may have concluded that there was no improvement in AM with treatment. In addition, there is evidence that CL/DTTm DBS treatment effects accumulate over the long-term.[37,109,110] Thus, we suggest that trial designs could benefit from extending over a longer time period to fully capture treatment benefits.

While the present findings provide striking evidence that CL/DTTm DBS improves AM, we note the following caveats. There are only five participants and a number of factors underlying individual variability amongst these participants, including the nature and degree of injury, duration of retrograde amnesia, demographic and premorbid factors such as age, education, and pre-injury cognitive abilities, and day-to-day fluctuations in function due to varying fatigue, mood, and environmental stressors. In addition, due to COVID-related restrictions on

being able to turn DBS on and off in the participants who were tested remotely, we can only speculate as to the acute effect of DBS on and off versus chronic effects. Given the known phenomenon of transient symptom improvement due to implant-related microlesion effects in DBS for disorders such as essential tremor and Parkinson's disease, it is worth considering whether these effects could play a similar role in this study. However, microlesion effects generally persist for only a few days after electrode implantation,[111] whereas AM improvements in this study occurred many months after implantation – well outside the window of potential transient postoperative symptom improvement. Altogether, these factors necessitate caution when making generalizations from these findings. Further study is needed to understand the impact of these factors with a larger sample size, healthy control data at the same timepoints, and a measure of clinical significance corresponding to improvements in the AM Recall Task and AI (e.g., using a Reliable Change Index).

We note that there was no confirmation of the veracity of the recall, which could lead to an apparently successful recall of a memory when in fact the memory was recalled in a faulty manner. We followed Addis *et al.*'s standard protocol of ascertaining twice whether they recalled an AM - the first report is the button press during each trial after a successful AM recall and the second report is the post-hoc questionnaire asking for details of what they recalled in order to verify that an AM meeting our criteria was recalled.[66]

We also note that DBS delivers a relatively large volume of stimulation, and that structures, other than those explicitly targeted, may be affected. Here, the CL/DTTm axons projecting forward to frontal lobe structures were targeted, as noted in Schiff *et al.*[1]: the primary, executive attention-related effects of CL/DTTm stimulation likely depend on activation of large, myelinated axons within CL/DTTm, perhaps with additional contribution from axons from the adjacent paralaminar portion of the MD nucleus, which has similar characteristics to CL.[34] In contrast to paralaminar MD, the medial magnocellular portion of MD is implicated in episodic memory,[34] and bilateral lesions to this structure produces a profound paramnesia ('thalamic chronotaraxis') that alters the memory of time and personal identity.[112] Nonetheless, we propose that the present findings are less likely to be due to driving magnocellular MD due to its distance from CL/DTTm. In addition, our modeling of the DBS activation of each participant's connectivity indicated that CL/DTTm DBS maximized activation of CL/DTTm fibers and minimized activation of the adjacent fibers from MD (including both magnocellular and paralaminar MD), CM, and VPL nuclei in P1, P3, P4, and P6 participants, and avoided MD fiber activation entirely in P5.[1] Nonetheless, we cannot eliminate the possibility that the

observed AM improvements were due to the stimulation of MD and its memory-related connections.

Finally, based on CL's neuroanatomical connections to cortical default network regions, we have focused on the effects of CL/DTTm DBS on AM, in addition to executive attention in our prior work.[1] However, CL/DTTm DBS may improve cognition more generally, including improvements to episodic memory more broadly. Given limited testing time, we prioritized autobiographical memory over traditional episodic memory tests due to its greater ecological validity and potential clinical significance. We also reasoned that CL/DTTm DBS would be better suited for improving autobiographical memory, which requires activity across these distributed areas, as opposed to the more limited areas involved in traditional episodic memory tasks.[16] However, future study is needed to understand the full extent of CL/DTTm DBS on episodic memory and cognition more broadly.

Conclusion

CL/DTTm DBS treatment improved the recall and specificity of AMs in five msTBI participants, causally demonstrating a new mechanism of interaction between the arousal and AM systems that likely involves long-range cortico-cortical systems modulated by thalamocortical glutamatergic neurotransmission. CL/DTTm DBS may be a promising new treatment for improving both AM and executive attention deficits in msTBI. Future work is needed with additional participants to understand the factors mediating these responses and the potential effect of CL/DTTm DBS on cognition more broadly.

Acknowledgements

We thank Alissa Papadopoulos for scoring memories in the Autobiographical Interview task. We are grateful to the participants for participating in this study.

Funding

This work was funded by NIH NINDS UH3 NS95554 (EYC, LMG, JMH, NDS), DOD W81XWH-20-PRARP-CSRA (EYC), and the Canadian Institutes of Health Research MOP-148940 (BL).

Competing interests

JMH and NDS are co-founders and shareholders of a company under development (Re-EmergeDBS) to develop central thalamic DBS to treat msTBI. EYC, JMH, and NDS are co-inventors on a patent held jointly by Stanford University, Cornell University, and the University of Utah for the use of CL/DTTm DBS to treat msTBI. NDS is an inventor on additional patents held by Cornell University for the use of CL/DTTm DBS to treat msTBI.

Supplementary material

Supplementary material is available at *Brain Communications* online.

References

1. Schiff ND, Giacino JT, Butson CR, *et al*. Thalamic deep brain stimulation in traumatic brain injury: a phase 1, randomized feasibility study. *Nat Med*. Dec 2023;29(12):3162-3174. doi:10.1038/s41591-023-02638-4
2. Levine B, Svoboda E, Hay JF, Winocur G, Moscovitch M. Aging and autobiographical memory: dissociating episodic from semantic retrieval. *Psychol Aging*. Dec 2002;17(4):677-689.
3. Dikmen SS, Corrigan JD, Levin HS, Machamer J, Stiers W, Weisskopf MG. Cognitive outcome following traumatic brain injury. *J Head Trauma Rehabil*. 2009;24(6):430-438. doi:10.1097/HTR.0b013e3181c133e9
4. Levine B, Kovacevic N, Nica EI, Schwartz ML, Gao F, Black SE. Quantified MRI and cognition in TBI with diffuse and focal damage. *Neuroimage Clin*. Apr 10 2013;2:534-541. doi:10.1016/j.nicl.2013.03.015
5. Vakil E, Greenstein Y, Weiss I, Shtein S. The effects of moderate-to-severe traumatic brain injury on episodic memory: a meta-analysis. *Neuropsychol Rev*. Sep 2019;29(3):270-287. doi:10.1007/s11065-019-09413-8
6. Baerger DR, McAdams DP. Life story coherence and its relation to psychological well-being. *Narrative Inquiry*. 1999;9(1):69-96.
7. Bluck S, Alea N, Habermas T, Rubin DC. A tale of three functions: the self-reported uses of autobiographical memory. *Social Cognition*. 2005;23(1):91-117.
8. Pillemer DB. Remembering personal circumstances: a functional analysis. In: Winograd E, Neisser U, eds. *Affect and Accuracy in Recall: Studies of "Flashbulb" Memories*. Cambridge University Press; 1992:236-264:chap 12.
9. Schacter DL, Addis DR, Buckner RL. Remembering the past to imagine the future: the prospective brain. *Nat Rev Neurosci*. Sep 2007;8(9):657-661. doi:10.1038/nrn2213
10. Dritschel BH, Kogan L, Burton A, Burton E, Goddard L. Everyday planning difficulties following traumatic brain injury: a role for autobiographical memory. *Brain Inj*. Oct 1998;12(10):875-886. doi:10.1080/026990598122098
11. Rochat L, Renaud O, Arnould A, *et al*. Self-defining memories after severe traumatic brain injury: a preliminary study. *J Neuropsychol*. Mar 2021;15(1):112-128. doi:10.1111/jnp.12212

12. Rasmussen KW, Berntsen D. Autobiographical memory and episodic future thinking after moderate to severe traumatic brain injury. *J Neuropsychol*. Mar 2014;8(1):34-52. doi:10.1111/jnp.12003
13. Hewitt J, Evans JJ, Dritschel B. Theory driven rehabilitation of executive functioning: improving planning skills in people with traumatic brain injury through the use of an autobiographical episodic memory cueing procedure. *Neuropsychologia*. 2006;44(8):1468-1474. doi:10.1016/j.neuropsychologia.2005.11.016
14. Young KD, Preskorn SH, Victor T, Misaki M, Bodurka J, Drevets WC. The effect of mineralocorticoid and glucocorticoid receptor antagonism on autobiographical memory recall and amygdala response to implicit emotional stimuli. *Int J Neuropsychopharmacol*. Sep 2016;19(9):1-11. doi:10.1093/ijnp/pyw036
15. Young KD, Siegle GJ, Zotev V*, et al*. Randomized clinical trial of real-time fMRI amygdala neurofeedback for major depressive disorder: effects on symptoms and autobiographical memory recall. *Am J Psychiatry*. Aug 01 2017;174(8):748-755. doi:10.1176/appi.ajp.2017.16060637
16. Fan CL, Simpson S, Sokolowski HM, Levine B. Autobiographical memory. In: Kahana MJ, Wagner AD, eds. *The Oxford Handbook of Human Memory, Two Volume Pack: Foundations and Applications*. Oxford University Press; 2024:1140–1170:chap 39.
17. Svoboda E, McKinnon MC, Levine B. The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia*. 2006;44(12):2189-2208. doi:10.1016/j.neuropsychologia.2006.05.023
18. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci*. Mar 2008;1124:1-38. doi:10.1196/annals.1440.011
19. Levine B, Kovacevic N, Nica EI*, et al*. The Toronto traumatic brain injury study: injury severity and quantified MRI. *Neurology*. Mar 04 2008;70(10):771-778. doi:10.1212/01.wnl.0000304108.32283.aa
20. Zhou Y, Kierans A, Kenul D*, et al*. Mild traumatic brain injury: longitudinal regional brain volume changes. *Radiology*. Jun 2013;267(3):880-90. doi:10.1148/radiol.13122542
21. Irimia A, Goh SM, Wade AC, Patel K, Vespa PM, Van Horn JD. Traumatic brain injury severity, neuropathophysiology, and clinical outcome: insights from multimodal neuroimaging. *Front Neurol*. 2017;8doi:10.3389/fneur.2017.00530
22. Kato T, Nakayama N, Yasokawa Y, Okumura A, Shinoda J, Iwama T. Statistical image analysis of cerebral glucose metabolism in patients with cognitive impairment following diffuse traumatic brain injury. *J Neurotrauma*. Jun 2007;24(6):919-926. doi:10.1089/neu.2006.0203
23. García-Panach J, Lull N, Lull JJ*, et al*. A voxel-based analysis of FDG-PET in traumatic brain injury: regional metabolism and relationship between the thalamus and cortical areas. *J Neurotrauma*. Sep 2011;28(9):1707-1717. doi:10.1089/neu.2011.1851
24. Kawai N, Maeda Y, Kudomi N, Yamamoto Y, Nishiyama Y, Tamiya T. Focal neuronal damage in patients with neuropsychological impairment after diffuse traumatic brain injury: evaluation using ^{11}C-flumazenil positron emission tomography with statistical image analysis. *J Neurotrauma*. Dec 2010;27(12):2131-2138. doi:10.1089/neu.2010.1464
25. Kang Y, Jamison K, Jaywant A*, et al*. Longitudinal alterations in gamma-aminobutyric acid ($GABAA_)$ receptor availability over ~ 1 year following traumatic brain injury. *Brain Commun*. 2022;4(4):fcac159. doi:10.1093/braincomms/fcac159
26. Woodrow RE, Grossac J, Hong YT*, et al*. Outcomes and mechanisms associated with selective thalamic neuronal loss in chronic traumatic brain injury. *JAMA Netw Open*. Aug 01 2024;7(8):e2426141. doi:10.1001/jamanetworkopen.2024.26141

27. De Simoni S, Grover PJ, Jenkins PO*, et al*. Disconnection between the default mode network and medial temporal lobes in post-traumatic amnesia. *Brain*. Dec 2016;139(Pt 12):3137-3150. doi:10.1093/brain/aww241
28. Sharp DJ, Scott G, Leech R. Network dysfunction after traumatic brain injury. *Nat Rev Neurol*. Mar 2014;10(3):156-66. doi:10.1038/nrneurol.2014.15
29. Schiff ND. Central thalamic contributions to arousal regulation and neurological disorders of consciousness. *Ann N Y Acad Sci*. 2008;1129:105-118. doi:10.1196/annals.1417.029
30. Maxwell WL, MacKinnon MA, Smith DH, McIntosh TK, Graham DI. Thalamic nuclei after human blunt head injury. *J Neuropathol Exp Neurol*. May 2006;65(5):478-488. doi:10.1097/01.jnen.0000229241.28619.75
31. Steriade M, Paré D, Parent A, Smith Y. Projections of cholinergic and non-cholinergic neurons of the brainstem core to relay and associational thalamic nuclei in the cat and macaque monkey. *Neuroscience*. Apr 1988;25(1):47-67. doi:10.1016/0306-4522(88)90006-1
32. Steriade M, Glenn LL. Neocortical and caudate projections of intralaminar thalamic neurons and their synaptic excitation from midbrain reticular core. *J Neurophysiol*. Aug 1982;48(2):352-371. doi:10.1152/jn.1982.48.2.352
33. Berendse HW, Groenewegen HJ. Restricted cortical termination fields of the midline and intralaminar thalamic nuclei in the rat. *Neuroscience*. 1991;42(1):73-102. doi:10.1016/0306-4522(91)90151-d
34. Jones EG. *The Thalamus*. Second ed. Cambridge University Press; 2007.
35. Schiff ND. Recovery of consciousness after brain injury: a mesocircuit hypothesis. *Trends Neurosci*. Jan 2010;33(1):1-9. doi:10.1016/j.tins.2009.11.002
36. Baker JL, Ryou JW, Wei XF, Butson CR, Schiff ND, Purpura KP. Robust modulation of arousal regulation, performance, and frontostriatal activity through central thalamic deep brain stimulation in healthy nonhuman primates. *J Neurophysiol*. Nov 01 2016;116(5):2383-2404. doi:10.1152/jn.01129.2015
37. Schiff ND, Giacino JT, Kalmar K*, et al*. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature*. Aug 02 2007;448:600-603. doi:10.1038/nature06041
38. Amaral DG, Cowan WM. Subcortical afferents to the hippocampal formation in the monkey. *J Comp Neurol*. Feb 15 1980;189(4):573-591. doi:10.1002/cne.901890402
39. Aggleton JP, Desimone R, Mishkin M. The origin, course, and termination of the hippocampothalamic projections in the macaque. *J Comp Neurol*. Jan 15 1986;243(3):409-421. doi:10.1002/cne.902430310
40. Saunders RC, Mishkin M, Aggleton JP. Projections from the entorhinal cortex, perirhinal cortex, presubiculum, and parasubiculum to the medial thalamus in macaque monkeys: identifying different pathways using disconnection techniques. *Exp Brain Res*. Nov 2005;167(1):1-16. doi:10.1007/s00221-005-2361-3
41. Yeterian EH, Pandya DN. Corticothalamic connections of paralimbic regions in the rhesus monkey. *J Comp Neurol*. Mar 01 1988;269:130-146. doi:10.1002/cne.902690111
42. Insausti R, Amaral DG, Cowan WM. The entorhinal cortex of the monkey: III. Subcortical afferents. *J Comp Neurol*. Oct 15 1987;264(3):396-408. doi:10.1002/cne.902640307
43. Öngür D, Ferry AT, Price JL. Architectonic subdivision of the human orbital and medial prefrontal cortex. *J Comp Neurol*. Jun 02 2003;460(3):425-449. doi:10.1002/cne.10609
44. Vogt BA, Pandya DN, Rosene DL. Cingulate cortex of the rhesus monkey: I. Cytoarchitecture and thalamic afferents. *J Comp Neurol*. Aug 08 1987;262(2):256-270. doi:10.1002/cne.902620207

45. Vincent JL, Patel GH, Fox MD, *et al*. Intrinsic functional architecture in the anaesthetized monkey brain. *Nature*. May 03 2007;447:83-86. doi:10.1038/nature05758
46. Mantini D, Gerits A, Nelissen K, *et al*. Default mode of brain function in monkeys. *J Neurosci*. Sep 07 2011;31(36):12954-12962. doi:10.1523/JNEUROSCI.2318-11.2011
47. Hsu DT, Price JL. Midline and intralaminar thalamic connections with the orbital and medial prefrontal networks in macaque monkeys. *J Comp Neurol*. Sep 10 2007;504(2):89-111. doi:10.1002/cne.21440
48. Buckwalter JA, Parvizi J, Morecraft RJ, Van Hoesen GW. Thalamic projections to the posteromedial cortex in the macaque. *J Comp Neurol*. Apr 10 2008;507:1709-1733. doi:10.1002/cne.21647
49. Yeterian EH, Pandya DN. Corticothalamic connections of the posterior parietal cortex in the rhesus monkey. *J Comp Neurol*. Jul 15 1985;237:408-426. doi:10.1002/cne.902370309
50. Schmahmann JD, Pandya DN. Anatomical investigation of projections from thalamus to posterior parietal cortex in the rhesus monkey: a WGA-HRP and fluorescent tracer study. *J Comp Neurol*. May 08 1990;295:299-326. doi:10.1002/cne.902950212
51. Aggleton JP, Wright NF, Vann SD, Saunders RC. Medial temporal lobe projections to the retrosplenial cortex of the macaque monkey. *Hippocampus*. Sep 2012;22:1883-1900. doi:10.1002/hipo.22024
52. Insausti R, Muñoz M. Cortical projections of the non-entorhinal hippocampal formation in the cynomolgus monkey (Macaca fascicularis). *Eur J Neurosci*. Aug 2001;14:435-451. doi:10.1046/j.0953-816x.2001.01662.x
53. Parvizi J, Van Hoesen GW, Buckwalter J, Damasio A. Neural connections of the posteromedial cortex in the macaque. *Proc Natl Acad Sci U S A*. Jan 31 2006;103(5):1563-1568. doi:10.1073/pnas.0507729103
54. Insausti R, Amaral DG, Cowan WM. The entorhinal cortex of the monkey: II. Cortical afferents. *J Comp Neurol*. Oct 15 1987;264:356-395. doi:10.1002/cne.902640306
55. Mohedano-Moriano A, Pro-Sistiaga P, Arroyo-Jimenez MM, *et al*. Topographical and laminar distribution of cortical input to the monkey entorhinal cortex. *J Anat*. Aug 2007;211:250-260. doi:10.1111/j.1469-7580.2007.00764.x
56. Muñoz M, Insausti R. Cortical efferents of the entorhinal cortex and the adjacent parahippocampal region in the monkey (Macaca fascicularis). *Eur J Neurosci*. Sep 2005;22:1368-1388. doi:10.1111/j.1460-9568.2005.04299.x
57. Kobayashi Y, Amaral DG. Macaque monkey retrosplenial cortex: III. Cortical efferents. *J Comp Neurol*. Jun 10 2007;502:810-833. doi:10.1002/cne.21346
58. Lavenex P, Suzuki WA, Amaral DG. Perirhinal and parahippocampal cortices of the macaque monkey: projections to the neocortex. *J Comp Neurol*. Jun 10 2002;447:394-420. doi:10.1002/cne.10243
59. Kondo H, Saleem KS, Price JL. Differential connections of the perirhinal and parahippocampal cortex with the orbital and medial prefrontal networks in macaque monkeys. *J Comp Neurol*. Dec 26 2005;493:479-509. doi:10.1002/cne.20796
60. Kobayashi Y, Amaral DG. Macaque monkey retrosplenial cortex: II. Cortical afferents. *J Comp Neurol*. Nov 03 2003;466:48-79. doi:10.1002/cne.10883
61. Shirvalkar P, Seth M, Schiff ND, Herrera DG. Cognitive enhancement with central thalamic electrical stimulation. *Proc Natl Acad Sci U S A*. Nov 07 2006;103(45):17007-17012. doi:10.1073/pnas.0604811103
62. Tsai S-T, Chen S-Y, Lin S-Z, Tseng G-F. Rostral intralaminar thalamic deep brain stimulation ameliorates memory deficits and dendritic regression in β-amyloid-infused rats. *Brain Struct Funct*. Mar 2020;225:751-761. doi:10.1007/s00429-020-02033-6

63. Gerber LM, Shulman KS, Wright MS, Schiff ND, Fins JJ. Qualitative analysis of symptoms from the central thalamic deep brain stimulation trial for traumatic brain injury. *NeuroRehabilitation*. 2025:1-9.
64. Conway MA, Pleydell-Pearce CW. The construction of autobiographical memories in the self-memory system. *Psychol Rev*. Apr 2000;107(2):261-288. doi:10.1037/0033-295x.107.2.261
65. Conway MA, Pleydell-Pearce CW, Whitecross SE, Sharpe H. Neurophysiological correlates of memory for experienced and imagined events. *Neuropsychologia*. 2003;41:334-340. doi:10.1016/s0028-3932(02)00165-3
66. Addis DR, Wong AT, Schacter DL. Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. *Neuropsychologia*. Apr 08 2007;45:1363-1377. doi:10.1016/j.neuropsychologia.2006.10.016
67. Simpson S, Eskandaripour M, Levine B. Effects of healthy and neuropathological aging on autobiographical memory: a meta-analysis of studies using the autobiographical interview. *J Gerontol B Psychol Sci Soc Sci*. Oct 09 2023;78(10):1617-1624. doi:10.1093/geronb/gbad077
68. Miller TD, Chong TT, Davies AMA*, et al*. Human hippocampal CA3 damage disrupts both recent and remote episodic memories. *eLife*. Jan 24 2020;9:e41836. doi:10.7554/eLife.41836
69. Setton R, Mwilambwe-Tshilobo L, Sheldon S, Turner GR, Spreng RN. Hippocampus and temporal pole functional connectivity is associated with age and individual differences in autobiographical memory. *Proc Natl Acad Sci U S A*. Oct 11 2022;119(41):e2203039119. doi:10.1073/pnas.2203039119
70. Clark IA, Mohammadi S, Callaghan MF, Maguire EA. Conduction velocity along a key white matter tract is associated with autobiographical memory recall ability. *eLife*. Sep 27 2022;11:e79303. doi:10.7554/eLife.79303
71. Hodgetts CJ, Postans M, Warne N, Varnava A, Lawrence AD, Graham KS. Distinct contributions of the fornix and inferior longitudinal fasciculus to episodic and semantic autobiographical memory. *Cortex*. Sep 2017;94:1-14. doi:10.1016/j.cortex.2017.05.010
72. Palombo DJ, Bacopulos A, Amaral RSC*, et al*. Episodic autobiographical memory is associated with variation in the size of hippocampal subregions. *Hippocampus*. Feb 2018;28(2):69-75. doi:10.1002/hipo.22818
73. Gilmore AW, Quach A, Kalinowski SE, Gotts SJ, Schacter DL, Martin A. Dynamic content reactivation supports naturalistic autobiographical recall in humans. *J Neurosci*. Jan 06 2021;41(1):153-166. doi:10.1523/JNEUROSCI.1490-20.2020
74. Esopenko C, Levine B. Autobiographical memory and structural brain changes in chronic phase TBI. *Cortex*. Apr 2017;89:1-10. doi:10.1016/j.cortex.2017.01.007
75. Söderlund H, Moscovitch M, Kumar N*, et al*. Autobiographical episodic memory in major depressive disorder. *J Abnorm Psychol*. Feb 2014;123(1):51-60. doi:10.1037/a0035610
76. Murphy R. On the use of one-sided statistical tests in biomedical research. *Clin Exp Pharmacol Physiol*. Jan 2018;45:109-114. doi:10.1111/1440-1681.12754
77. Rosenthal R. Parametric measures of effect size. In: Cooper H, Hedges LV, eds. *The handbook of research synthesis*. Russell Sage Foundation; 1994:231-244.
78. Page EB. Ordered hypotheses for multiple treatments: a significance test for linear ranks. *J Amer Stat Assoc*. 1963;58(301):216-230.
79. Fins JJ, Wright MS, Shulman KS, Henderson JM, Schiff ND. Subject and family perspectives from the central thalamic deep brain stimulation trial for traumatic brain injury: part II. *Camb Q Healthc Ethics*. Oct 18 2023:1-24. doi:10.1017/S0963180123000518

80. Holland AC, Addis DR, Kensinger EA. The neural correlates of specific versus general autobiographical memory construction and elaboration. *Neuropsychologia*. Oct 2011;49(12):3164-3177. doi:10.1016/j.neuropsychologia.2011.07.015
81. Young KD, Erickson K, Nugent AC*, et al*. Functional anatomy of autobiographical memory recall deficits in depression. *Psychol Med*. Feb 2012;42(2):345-357. doi:10.1017/S0033291711001371
82. Young KD, Bellgowan PS, Bodurka J, Drevets WC. Behavioral and neurophysiological correlates of autobiographical memory deficits in patients with depression and individuals at high risk for depression. *JAMA Psychiatry*. Jul 2013;70(7):698-708. doi:10.1001/jamapsychiatry.2013.1189
83. Young KD, Bellgowan PS, Bodurka J, Drevets WC. Functional neuroimaging of sex differences in autobiographical memory recall. *Hum Brain Mapp*. Dec 2013;34(12):3320-3332. doi:10.1002/hbm.22144
84. Young KD, Bellgowan PS, Bodurka J, Drevets WC. Neurophysiological correlates of autobiographical memory deficits in currently and formerly depressed subjects. *Psychol Med*. Oct 2014;44(14):2951-2963. doi:10.1017/S0033291714000464
85. Young KD, Bellgowan PS, Bodurka J, Drevets WC. Autobiographical deficits correlate with gray matter volume in depressed and high risk participants. *Soc Cogn Affect Neurosci*. Nov 2015;10(11):1588-1595. doi:10.1093/scan/nsv047
86. Young KD, Bodurka J, Drevets WC. Differential neural correlates of autobiographical memory recall in bipolar and unipolar depression. *Bipolar Disord*. Nov 2016;18(7):571-582. doi:10.1111/bdi.12441
87. Young KD, Drevets WC, Dantzer R, Teague TK, Bodurka J, Savitz J. Kynurenine pathway metabolites are associated with hippocampal activity during autobiographical memory recall in patients with depression. *Brain Behav Immun*. Aug 2016;56:335-342. doi:10.1016/j.bbi.2016.04.007
88. Young KD, Bodurka J, Drevets WC. Functional neuroimaging of sex differences in autobiographical memory recall in depression. *Psychol Med*. Nov 2017;47(15):2640-2652. doi:10.1017/S003329171700112X
89. Li S-J, Lo Y-C, Lai H-Y*, et al*. Uncovering the modulatory interactions of brain networks in cognition with central thalamic deep brain stimulation using functional magnetic resonance imaging. *Neuroscience*. Aug 01 2020;440:65-84. doi:10.1016/j.neuroscience.2020.05.022
90. Liu J, Lee HJ, Weitz AJ*, et al*. Frequency-selective control of cortical and subcortical networks by central thalamus. *eLife*. Dec 10 2015;4:e09215. doi:10.7554/eLife.09215
91. Fuentemilla L, Barnes GR, Düzel E, Levine B. Theta oscillations orchestrate medial temporal lobe and neocortex in remembering autobiographical memories. *Neuroimage*. Jan 15 2014;85 Pt 2:730-737. doi:10.1016/j.neuroimage.2013.08.029
92. Fuentemilla L, Palombo DJ, Levine B. Gamma phase-synchrony in autobiographical memory: evidence from magnetoencephalography and severely deficient autobiographical memory. *Neuropsychologia*. Feb 2018;110:7-13. doi:10.1016/j.neuropsychologia.2017.08.020
93. Hebscher M, Meltzer JA, Gilboa A. A causal role for the precuneus in network-wide theta and gamma oscillatory activity during complex memory retrieval. *eLife*. Feb 11 2019;8:e43114. doi:10.7554/eLife.43114
94. Stieger JR, Pinheiro-Chagas P, Fang Y*, et al*. Cross-regional coordination of activity in the human brain during autobiographical self-referential processing. *Proc Natl Acad Sci U S A*. Aug 06 2024;121(32):e2316021121. doi:10.1073/pnas.2316021121
95. Tulving E. Episodic memory: from mind to brain. *Annu Rev Psychol*. 2002;53:1-25. doi:10.1146/annurev.psych.53.100901.135114

96. Bluck S. Autobiographical memory: exploring its functions in everyday life. *Memory*. Mar 2003;11(2):113-23. doi:10.1080/741938206
97. Rubin DC, Umanath S. Event memory: A theory of memory for laboratory, autobiographical, and fictional events. *Psychol Rev*. Jan 2015;122(1):1-23. doi:10.1037/a0037907
98. Purpura KP, Schiff ND. The thalamic intralaminar nuclei: a role in visual awareness. *The Neuroscientist*. 1997;3:8-15.
99. Shah SA, Schiff ND. Central thalamic deep brain stimulation for cognitive neuromodulation - a review of proposed mechanisms and investigational studies. *Eur J Neurosci*. Oct 2010;32(7):1135-1144. doi:10.1111/j.1460-9568.2010.07420.x
100. Schlag J, Schlag-Rey M. Visuomotor functions of central thalamus in monkey. II. Unit activity related to visual events, targeting, and fixation. *J Neurophysiol*. Jun 1984;51(6):1175-1195. doi:10.1152/jn.1984.51.6.1175
101. Miniacchi D, Granato A, Santarelli M, Macchi G. Different weights of subcortical-cortical projections upon primary sensory areas: the anterior intralaminar system. In: Miniacchi D, Molinari M, Macchi G, Jones EG, eds. *Thalamic Networks for Relay and Modulation*. Pergamon Press Ltd; 1993:209-226:chap 19.
102. Hunsperger RW, Roman D. The integrative role of the intralaminar system of the thalamus in visual orientation and perception in the cat. *Exp Brain Res*. Jun 18 1976;25(3):231-246. doi:10.1007/BF00234015
103. Tsumoto T, Freeman RD. Ocular dominance in kitten cortex: induced changes of single cells while they are recorded. *Exp Brain Res*. 1981;44(3):347-351. doi:10.1007/BF00236575
104. Schiff ND, Purpura KP, Kalik SF, Victor JD. Intralaminar thalamic stimulation alters tuning properties of primary visual cortex neurons. In: *Society for Neuroscience Abstracts*. Society for Neuroscience; 1998:1875.
105. Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain*. Mar 2006;129:564-583. doi:10.1093/brain/awl004
106. Mankin EA, Fried I. Modulation of human memory by deep brain stimulation of the entorhinal-hippocampal circuitry. *Neuron*. Apr 22 2020;106(2):218-235. doi:10.1016/j.neuron.2020.02.024
107. Deeb W, Salvato B, Almeida L*, et al*. Fornix-region deep brain stimulation-induced memory flashbacks in Alzheimer's Disease. *N Engl J Med*. Aug 22 2019;381(8):783-785. doi:10.1056/NEJMc1905240
108. Hamani C, McAndrews MP, Cohn M*, et al*. Memory enhancement induced by hypothalamic/fornix deep brain stimulation. *Ann Neurol*. Jan 2008;63(1):119-123. doi:10.1002/ana.21295
109. Adams ZM, Forgacs PB, Conte MM, Nauvel TJ, Drover JD, Schiff ND. Late and progressive alterations of sleep dynamics following central thalamic deep brain stimulation (CT-DBS) in chronic minimally conscious state. *Clin Neurophysiol*. Sep 2016;127(9):3086-3092. doi:10.1016/j.clinph.2016.06.028
110. Gottshall JL, Adams ZM, Forgacs PB, Schiff ND. Daytime central thalamic deep brain stimulation modulates sleep dynamics in the severely injured brain: mechanistic insights and a novel framework for alpha-delta sleep generation. *Front Neurol*. 2019;10(20):1-14. doi:10.3389/fneur.2019.00020
111. Sitburana O, Almaguer M, Ondo WG. A pilot study: microlesion effects and tremor outcome in the ventrointermediate deep brain stimulation (VIM-DBS). *Clin Neurol Neurosurg*. Feb 2010;112(2):106-109. doi:10.1016/j.clineuro.2009.10.004
112. Spiegel EA, Wycis HT, Orchinik C, Freed H. Thalamic chronotaraxis. *Am J Psychiatry*. Aug 1956;113(2):97-105. doi:10.1176/ajp.113.2.97

Figure legends

Figure 1 Autobiographical memory recall task structure. The task consisted of two runs of AM recall blocks interleaved with Vigilance (V) blocks (not reported here).

Figure 2 Autobiographical memory recall performance with CL/DTTm DBS treatment. AM recall scores, out of 36 possible total points on the AM Recall Task, are plotted for each participant (P) at various timepoints of treatment. P6's baseline score is an average of two baseline scores of 3 and 4. There was a group improvement of 45.9% (one-tailed Wilcoxon signed-rank W = 0, $P < 0.032$) with an effect size of r = 0.90. Connecting lines are added to aid in the observation of trends and dashed to indicate that the measures are not continuous.

Figure 3 Autobiographical Interview performance with CL/DTTm DBS treatment. Plots show patient scores at varying treatment timepoints for **(A)** specificity (percent of episodic details out of the total number of episodic and semantic details), **(B)** the total number of episodic details, and **(C)** the total number of semantic details are shown at each time point. Connecting lines are added to aid in the observation of trends and dashed to indicate that the measures are not continuous. Following treatment, the specificity increased (average 18.7% improvement, ANOVA: main effect of time $F(3,9) = 5.85$, $P < 0.017$, partial $\eta^2 = 0.66$), driven largely by a reduction in the number of semantic details (average 23.4% reduction, ANOVA: main effect of time $F(3,9) = 3.12$, $P < 0.081$, partial $\eta^2 = 0.51$), indicating more focused and specific recall of AMs. There was no significant change in the number of episodic details with treatment (average 12.7% improvement, ANOVA: main effect of time $F(3,9) = 0.83$, $P < 0.51$, partial $\eta^2 = 0.22$). Note: imputed values at missing timepoints for P3 and P4 (see Table 4) used in the statistical tests are not plotted here. P = Participant.

Figure 4 Comparison of AM recall and specificity improvements with CL/DTTm DBS to the literature. Baseline and average treatment performances on the **(A)** AM Recall Task (recall: percent of all trials with successful recall) and **(B)** AI (specificity: the percent of episodic details out of the total episodic and semantic details) are compared with group average performances in the literature of patients and healthy controls and under various interventions. AM recall tasks from the literature had the same general structure as the present task, differing in relatively minor ways, such as the number of total trials and the valence of the cue words. The AI also differed in minor ways, such as the number of examined memories. For the healthy control dataset related to Söderlund et al.,[75] only data from the 1 year and 10 year time periods were used in order to match the time periods of the present study. Dashed lines indicate repeat

testing in the same cohort. Data from the literature show the group average and standard deviation of individual scores. HC = healthy controls. MC = mineralocorticoid. GC = glucocorticoid. MDD = major depressive disorder. rtfMRI = real-time fMRI neurofeedback. msTBI = moderate-to-severe TBI. CL/DTTm DBS = central lateral/medial dorsal tegmental tract deep brain stimulation. P = Participant. *No standard deviation reported. †Each data point in this cluster is from a separate study by Young et al.[81-88] ‡Baseline data were previously published in Söderlund et al.[75]

Participant Self-Reports (Box)

Participants, and their families when available, were asked for their subjective observations of any changes in autobiographical memory (AM) in their daily lives over the course of central lateral thalamic nucleus / medial portion of the dorsal tegmental tract (CL/DTTm) deep brain stimulation (DBS) treatment. All participants and their families endorsed an improvement in AM at various times during treatment; no participant reported a decrement in AM at any time. P1 reported the greatest improvement, reporting that at four months of treatment, there was an "explosion" in her ability to remember "highly detailed, very vivid" AMs, particularly from a pre-injury period that was previously "blank." P1's mother stated that "she started remembering all this stuff… once her mind found the way. It's happening all the time on a regular basis. It's just becoming normal, like we're normal with our memories. … I think [she is] remembering pretty much everything now." P1 stated, "I remember everything about it. … It's not like I just know a little bit… [it's] like a picture." At around one year of treatment, P1 additionally reported a 1-2 week period with intense, movie-like AM recollections. These recollections included remembering her grandfather's wake, such as the green color of the carpet and the smell of incense in the air, and remembering all the faces and names of the children in her first grade class.

At three and five months of treatment, P3 did not endorse a strong improvement in AM. However, he reported that his dreams, occurring almost every night, were more vivid and frequent, and included childhood events that he had forgotten about. At ten months of treatment, P3 reported continuing to have vivid dreams almost every night and added that his recalled AMs were more vivid, as well.

At three months of treatment, P4 reported, "I believe [AMs have] improved a bit … [there is] a bit more variety of memories from back then I'm recalling…" However, he still could not remember well the order in which autobiographical events had happened within a constrained time period (e.g., Thanksgiving season).

At two months of treatment, P5 reported that he had recalled a few AMs from the six months prior to his injury, which was a period of post-traumatic amnesia. At five months of treatment, P5 reported that his AMs were "brighter" and more visually detailed, and that he could more thoroughly assess the AM ("look at it from different angles"), but not necessarily recall more AMs than prior to treatment. At seven months of treatment, P5 reported having some dreams,

which was more frequent than prior to the treatment when dreams were "few and far between and can't [be remembered] one hour after being awake."

P6 did not strongly endorse an improvement in AMs with treatment. However, at three months of treatment, his mother reported an instance of his recalling where he was living and with whom during college, which had surprised her as something he could not have done prior to the treatment.

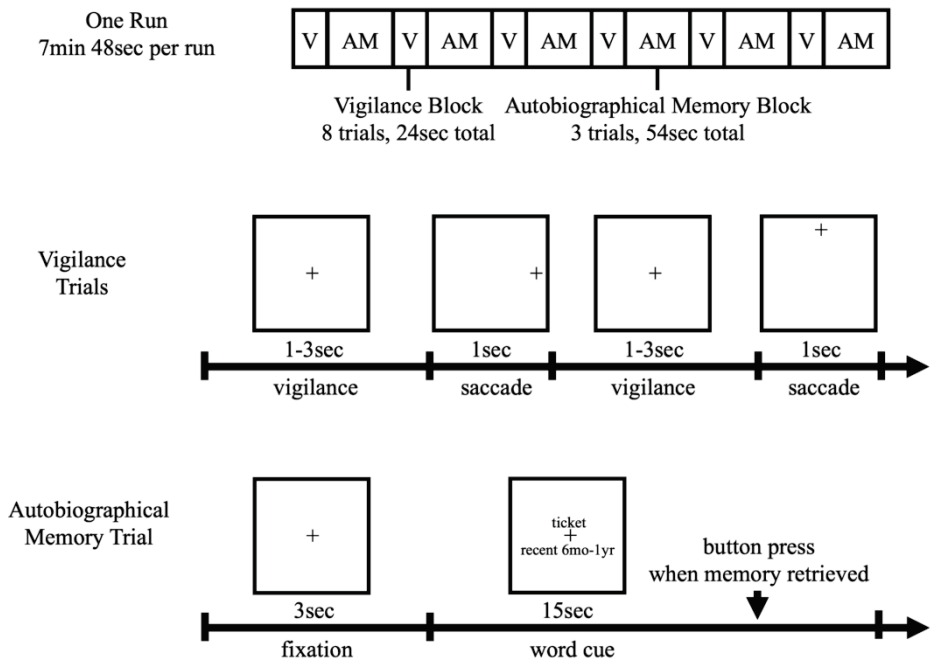

Figure 1 Autobiographical memory recall task structure. The task consisted of two runs of AM recall blocks interleaved with Vigilance (V) blocks (not reported here).

184x137mm (300 x 300 DPI)

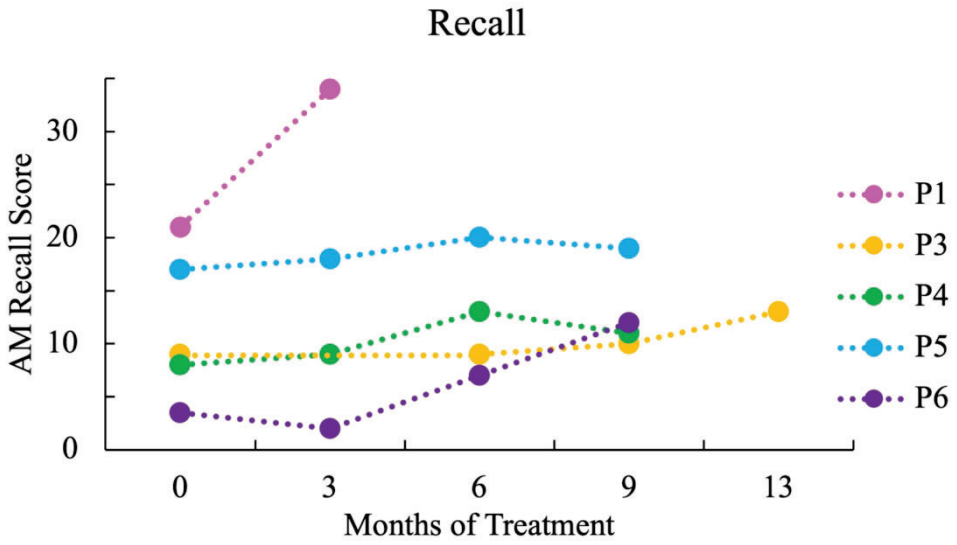

Figure 2 Autobiographical memory recall performance with CL/DTTm DBS treatment. AM recall scores, out of 36 possible total points on the AM Recall Task, are plotted for each participant (P) at various timepoints of treatment. P6's baseline score is an average of two baseline scores of 3 and 4. There was a group improvement of 45.9% (one-tailed Wilcoxon signed-rank W = 0, $P < 0.032$) with an effect size of r = 0.90. Connecting lines are added to aid in the observation of trends and dashed to indicate that the measures are not continuous.

135x79mm (300 x 300 DPI)

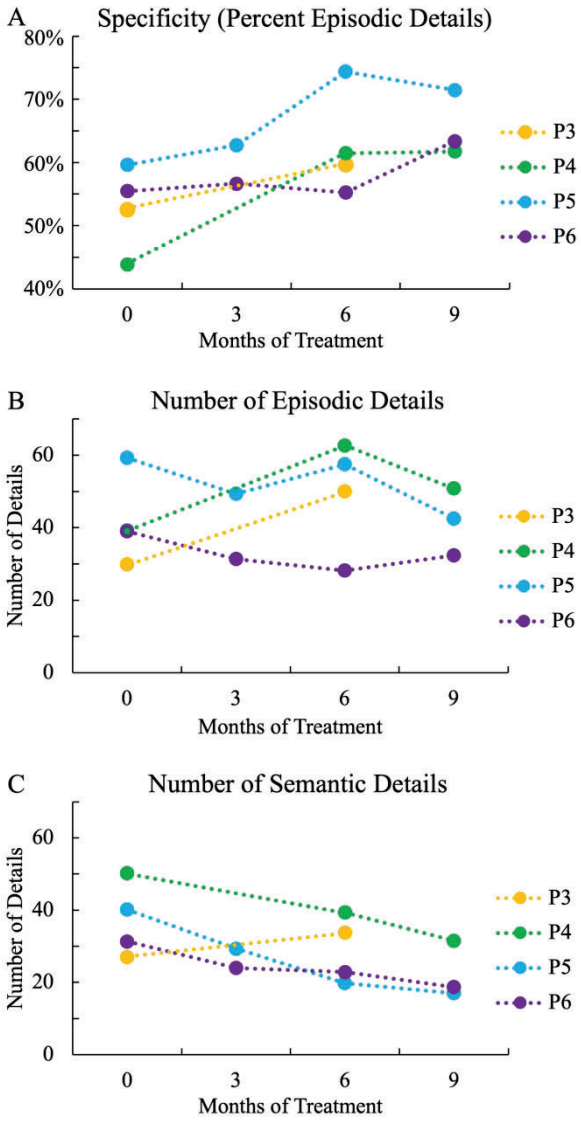

Figure 3 Autobiographical Interview performance with CL/DTTm DBS treatment. Plots show patient scores at varying treatment timepoints for (A) specificity (percent of episodic details out of the total number of episodic and semantic details), (B) the total number of episodic details, and (C) the total number of semantic details are shown at each time point. Connecting lines are added to aid in the observation of trends and dashed to indicate that the measures are not continuous. Following treatment, the specificity increased (average 18.7% improvement, ANOVA: main effect of time $F(3,9) = 5.85$, $P < 0.017$, partial $\eta^2 = 0.66$), driven largely by a reduction in the number of semantic details (average 23.4% reduction, ANOVA: main effect of time $F(3,9) = 3.12$, $P < 0.081$, partial $\eta^2 = 0.51$), indicating more focused and specific recall of AMs. There was no significant change in the number of episodic details with treatment (average 12.7% improvement, ANOVA: main effect of time $F(3,9) = 0.83$, $P < 0.51$, partial $\eta^2 = 0.22$). Note: imputed values at missing timepoints for P3 and P4 (see Table 4) used in the statistical tests are not plotted here. P = Participant.

137x232mm (300 x 300 DPI)

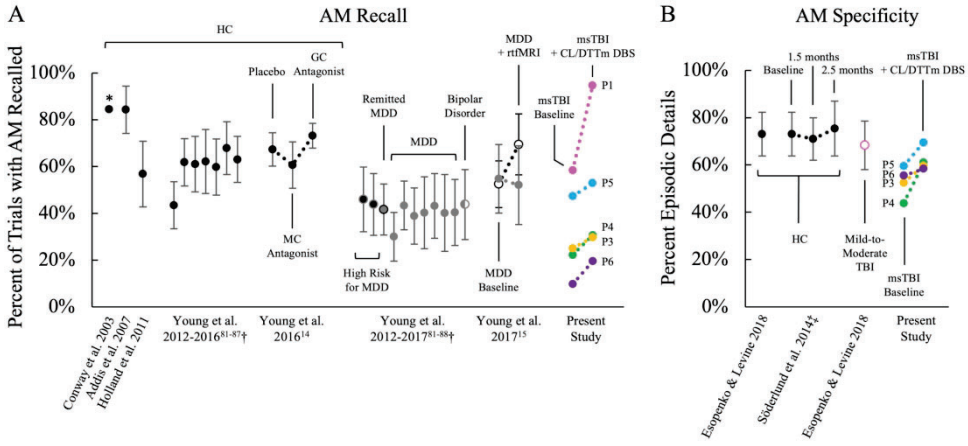

Figure 4 Comparison of AM recall and specificity improvements with CL/DTTm DBS to the literature. Baseline and average treatment performances on the (A) AM Recall Task (recall: percent of all trials with successful recall) and (B) AI (specificity: the percent of episodic details out of the total episodic and semantic details) are compared with group average performances in the literature of patients and healthy controls and under various interventions. AM recall tasks from the literature had the same general structure as the present task, differing in relatively minor ways, such as the number of total trials and the valence of the cue words. The AI also differed in minor ways, such as the number of examined memories. For the healthy control dataset related to Söderlund et al.,[75] only data from the 1 year and 10 year time periods were used in order to match the time periods of the present study. Dashed lines indicate repeat testing in the same cohort. Data from the literature show the group average and standard deviation of individual scores. HC = healthy controls. MC = mineralocorticoid. GC = glucocorticoid. MDD = major depressive disorder. rtfMRI = real-time fMRI neurofeedback. msTBI = moderate-to-severe TBI. CL/DTTm DBS = central lateral/medial dorsal tegmental tract deep brain stimulation. P = Participant. *No standard deviation reported. †Each data point in this cluster is from a separate study by Young et al.[81-88] ‡Baseline data were previously published in Söderlund et al.[75]

212x104mm (300 x 300 DPI)

Table 1 Demographic information

Participant	Sex	Age (years)	Education (Years)	Time Since Injury (Years)	Pre-surgical GOS-E Score
P1	F	39	16	20	5
P3	M	60	13	3	5
P4	M	22	13	5	5
P5	M	30	14	10.5	6
P6	M	28	14	9	6

Table 2 Testing timepoints

Participant		Baseline 1	Baseline 2	3 Months Treatment	6 Months Treatment	9 Months Treatment	13 Months Treatment
P1							
	Timepoint Exceptions						
	DBS on/off during testing	OFF		OFF			
	AM Recall Task	X		X			
	AI Task						
P3							
	Timepoint Exceptions				5 months*	8 months*	
	DBS on/off during testing	OFF			ON	ON	ON
	AM Recall Task	X			X	X	X
	AI Task	X			X		X
P4							
	Timepoint Exceptions						
	DBS on/off during testing	OFF		ON	ON	OFF	
	AM Recall Task	X		X	X	X	
	AI Task	X			X	X	
P5							
	Timepoint Exceptions				7 months*	10 months*	
	DBS on/off during testing		OFF	ON	ON	ON	
	AM Recall Task		X	X	X	X	
	AI Task		X	X	X	X	
P6							
	Timepoint Exceptions						
	DBS on/off during testing	OFF	OFF	OFF	ON	OFF	
	AM Recall Task	X	X	X	X	X	
	AI Task	X	X	X	X	X	

*Small deviations in the 6-month and 9-month time points for P3 and P5.

Table 3 Autobiographical Memory Recall performance with CL/DTTm DBS treatment

Participant	Baseline	3 Months Treatment	6 Months Treatment	9 Months Treatment	13 Months Treatment	Average Treatment Score	Average Treatment – Baseline Score	Average Percent Improve-ment	Average Improve-ment Effect Size (r)
P1	21	34				34	13	61.9	
P3	9		9	10	13	10.7	1.7	18.5	
P4	8	9	13	11		11	3	37.5	
P5	17	18	20	19		19	2	11.8	
P6	3.5*	2	7	12		7	3.5	100.0	
Average							4.6	45.9	0.90
							$W = 0, P < 0.032$		

AM Recall scores are out of 36 total points. *P* value was determined using the one-tailed Wilcoxon signed rank test of baseline and average treatment scores.
*Average score of two baseline timepoints.

Table 4 Autobiographical Interview performance with CL/DTTm DBS treatment

Participant	Baseline	3 Months Treatment	6 Months Treatment	9 Months Treatment	Average Treatment	Average Treatment – Baseline	Average Percent Improve-ment	*F*-statistic *P*-value	Average Improvement Effect Size (Partial η^2)
	Number of Episodic Details								
P3	29.8	44†	50.0	44†	46.0	16.2	54.4		
P4	39.2	44†	62.7	50.8	52.5	13.3	33.9		
P5	59.3	49.3	57.5	42.5	49.8	-9.5	-16.0		
P6	39.0*	31.3	28.2	32.3	30.6	-8.4	-21.5		
Average						2.9	12.7	$F(3,9) = 0.83$ $P < 0.51$	0.22
	Number of Semantic Details								
P3	27.0	29.6†	33.8	29.6†	31.0	4.0	14.8		
P4	50.2	29.6†	39.3	31.5	33.5	-16.7	-33.3		
P5	40.1	29.3	19.8	17.0	22.0	-18.1	-45.1		
P6	31.3*	24.0	22.8	18.7	21.8	-9.5	-30.4		
Average						-10.1	-23.4	$F(3,9) = 3.12$ $P < 0.081$	0.51
	Percent Episodic Details (Specificity)								
P3	52.5	59.8†	59.6	59.8†	59.7	7.2	13.8		
P4	43.8	59.8†	61.4	61.7	61.0	17.1	39.0		
P5	59.6	62.7	74.4	71.4	69.5	9.9	16.6		
P6	55.5*	56.6	55.2	63.4	58.4	3.0	5.3		
Average						9.3	18.7	$F(3,9) = 5.85$ $P < 0.017$	0.66

F and *P* values were determined using the repeated measures ANOVA.
*Average score of two baseline timepoints.
†The mean value of episodic or semantic details across all participants and all timepoints was used for imputing the data at this missing time point.