Functional and anatomical connectivity predict brain stimulation's mnemonic effects

Abbreviated Title: Mediators of stimulation's effect on memory

Youssef Ezzyat[1], James E. Kragel[2], Ethan A. Solomon[3], Bradley C. Lega[4], Joshua P. Aronson[5], Barbara C. Jobst[6], Robert E. Gross[7], Michael R. Sperling[8], Gregory A. Worrell[9], Sameer A. Sheth[10], Paul A. Wanda[11], Daniel S. Rizzuto[11], Michael J. Kahana[11]

[1]Dept. of Psychology, Wesleyan University, Middletown CT 06459
[2]Dept. of Neurology, University of Chicago, Chicago IL 60637
[3]Perelman School of Medicine, University of Pennsylvania, Philadelphia PA 19104
[4]Dept. of Neurosurgery, University of Texas Southwestern, Dallas TX 75390
[5] Dept. of Neurosurgery and [6] Dept. of Neurology, Dartmouth-Hitchcock Medical Center, Lebanon NH 03756
[7]Dept. of Neurosurgery, Emory University Hospital, Atlanta GA 30322
[8]Dept. of Neurology, Thomas Jefferson University Hospital, Philadelphia PA 19107
[9]Department of Neurology, Mayo Clinic, Rochester, MN 55905, USA
[10]Dept. of Neurosurgery, Columbia University Medical Center, New York, NY 10032
[11]Dept. of Psychology, University of Pennsylvania, Philadelphia PA 19104

Corresponding Author:
Youssef Ezzyat
Department of Psychology
Wesleyan University
207 High Street
Middletown, CT 06459
yezzyat@wesleyan.edu

Abstract

Direct electrical stimulation of the brain, when applied or optimized in a closed-loop manner, can lead to improvements in memory (Ezzyat et al., 2018) and mood (Scangos et al., 2021a). In these approaches, brain states control the timing of stimulation or the choice of parameters, which build off the notion that stimulation's neural and behavioral effects depend on brain state at the time of delivery (Ezzyat et al., 2017; Scangos et al., 2021b). Although closed-loop algorithms provide greater control over stimulation's physiological and behavioral effects, variability in outcomes remains a primary challenge for using stimulation for clinical and experimental neuromodulation. Here, we evaluate the hypothesis that stimulation's behavioral and physiological effects depend on the anatomical and functional network properties of the stimulation target. Closed-loop stimulation was delivered via intracranially-implanted electrodes as neurosurgical patients studied and recalled word lists. Multivariate classifiers, trained to predict momentary lapses in memory function, triggered stimulation of the lateral temporal cortex (LTC) during the study phase of the task. We found that stimulating LTC locations with high functional network connectivity led to greater physiological and behavioral effects of stimulation. Further, stimulation specifically improved memory performance when delivered to targets near white matter pathways. These data reveal how functional and anatomical networks mediate stimulation's physiological and behavioral effects, provide further evidence that closed-loop LTC stimulation modulates episodic memory, and suggest future strategies for stimulation targeting for effective neuromodulation.

Significance Statement

Direct electrical stimulation, when applied in closed-loop, can improve cognitive function (Ezzyat et al., 2018; Scangos et al., 2021a), however variability in outcomes remains a key challenge. We examined how the anatomical and functional network characteristics of the stimulation target predict variability in stimulation's physiological and behavioral effects, focusing on stimulation of the lateral temporal cortex (LTC) during an episodic memory task. Stimulating LTC locations with high functional network connectivity produces greater physiological and behavioral effects of stimulation, while stimulating targets near white matter pathways produced the most robust behavioral improvement. The data reveal how functional and anatomical networks mediate stimulation's physiological and behavioral effects and suggest future strategies for optimal targeting of stimulation for neuromodulation.

Introduction

Direct electrical stimulation is a powerful method for manipulating neural circuits underlying human perceptual, motor, and cognitive systems (Siddiqi et al., 2022). Focal electrical stimulation has been used to treat non-focal syndromes of brain dysfunction (Mayberg et al., 2005; Scangos et al., 2021a; Limousin et al., 1998; Bouthour et al., 2019; Deuschl et al., 2006; Geller et al., 2017; Jobst et al., 2017), suggesting that stimulation influences a broader network of brain regions beyond the stimulated location (McIntyre and Hahn, 2010; Lozano and Lipsman, 2013). Beyond these clinical syndromes, direct electrical stimulation can also modulate the brain's ability to learn and remember (Mankin and Fried, 2020), which, like other cognitive functions (Voytek and Knight, 2015), depends on the coordinated activity of several key brain regions (Burke et al., 2013; Das and Menon, 2021; Solomon et al., 2017; Kim, 2011; Keerativittayayut et al., 2018; Staresina and Wimber, 2019).

Although increasingly used as a therapeutic and experimental tool, variability in outcomes poses a critical challenge, in part because stimulation's mechanisms of action remain poorly understood. Following the success of stimulation for Parkinson's, initial theoretical accounts of stimulation's effects evolved from models of local disruption of pathological activity (Benabid et al., 2004) to modulation of the broader network of areas linked in circuit with the stimulated location (Ashkan et al., 2017). If stimulation's effects are best understood at the network level, it raises the possibility that variability in individual network structure could explain the variability in physiological and behavioral outcomes reported in the literature.

Anatomically, whether stimulation targets gray matter, the gray-white matter boundary, or specific white matter fibers determines the spread of physiological effects through the network (Paulk et al., 2022; Solomon et al., 2018). Compared to gray matter stimulation, white matter stimulation leads to more broadly distributed excitation in downstream areas (Crocker et al., 2021; Paulk et al., 2022; Mohan et al., 2020). White matter pathways also constrain stimulation's downstream functional effects (Lujan et al., 2013; Khambhati et al., 2019; Stiso et al., 2019). Behaviorally, stimulation of white matter has led to remission in depression (Mayberg et al., 2005), slowed cognitive decline in Alzheimer's (Lozano et al., 2016; Hamani et al., 2008), and memory enhancement in epilepsy (Suthana et al., 2012; Mankin et al., 2021; Titiz et al., 2017).

Functional connectivity may also mediate direct brain stimulation's effects on the broader brain network (Keller et al., 2011; Fox et al., 2020; Fox et al., 2014). For example, functional connectivity also explains the persistence of stimulation-evoked changes in neural excitability (Keller et al., 2018). Building upon research showing how low-frequency activity supports cognitive function (Colgin, 2013; Solomon et al., 2017), previous work has also shown that stimulation can modulate activity in specific frequency bands. In particular, stimulating brain regions that are network hubs (i.e. that show strong whole-brain low-frequency functional connectivity) produces greater downstream changes in low-frequency activity (Solomon et al., 2018). This suggests that stimulating low-frequency network hubs could reliably modulate whole-brain low-frequency activity, which predicts variability in cognitive function, including episodic memory (Donoghue et al., 2020; Koster and Gruber, 2022; Griffiths et al., 2021; Herweg et al., 2020).

In spite of evidence suggesting network mechanisms of action of stimulation, previous work has yet to link stimulation of functional and anatomical networks, evoked physiology, and modulation of behavioral performance. Our goal was to offer a coherent account of how stimulation interacts with functional and structural networks to produce changes in neural activity and behavior. We hypothesized that anatomical and functional characteristics of the stimulation target represent key variables that control the effect of stimulation on the brain's memory network. We applied stimulation in closed-loop in 47 patients while they participated in an episodic memory task (free recall). We stimulated 57 targets located in the lateral temporal cortex (LTC), with the timing of stimulation determined by multivariate classification of neural activity during the encoding phase of the memory task. Using patient-specific data, we characterized each stimulation target based on its proximity to the nearest white matter pathway, as well as its low-frequency resting-state functional connectivity with the rest of the brain. We found that closed-loop LTC stimulation improves memory performance relative to random stimulation, extending prior evidence that LTC stimulation modulates episodic memory (Ezzyat et al., 2018; Kucewicz et al., 2018). Further, we reveal that stimulation target proximity to white matter and functional connectivity predict both stimulation's effects on memory performance and changes in rhythmic low-frequency activity involved in successful memory encoding.

Experimental Procedures

Participants

Forty-seven patients undergoing intracranial electroencephalographic monitoring as part of clinical treatment for drug-resistant epilepsy were recruited to participate in this study. In total, $N = 57$ brain locations were stimulated: 38 patients were stimulated in one location, 8 patients were stimulated in two separate locations, and 1 patient was stimulated in three separate locations. Only one location was stimulated per session. Of the current dataset, data from 14 patients were included in an earlier publication (Ezzyat et al., 2018); data from all other patients have not been previously published, and all of the presently reported analyses and results are novel.

Data were collected as part of a multi-center project designed to assess the effects of electrical stimulation on memory-related brain function. Data were collected at the following centers: University of Texas Southwestern Medical Center (Dallas, TX), Dartmouth-Hitchcock Medical Center (Lebanon, NH), Thomas Jefferson University Hospital (Philadelphia, PA), Emory University Hospital (Atlanta, GA), Mayo Clinic (Rochester, MN), Hospital of the University of Pennsylvania (Philadelphia, PA), and Columbia University Medical Center (New York, NY). The research protocol was approved by the IRB at each hospital and informed consent was obtained from each participant. Electrophysiological data were collected from electrodes implanted subdurally (grid/strip configurations) on the cortical surface and/or electrodes within the brain parenchyma (depth electrodes). The clinical team determined the placement of the electrodes based on the epileptogenic monitoring needs of the patient.

Anatomical localization

Cortical surface regions were delineated on pre-implant whole brain volumetric T1-weighted MRI scans using Freesurfer (Fischl et al., 2004) according to the Desikan-Kiliany atlas (Desikan et al., 2006). Whole brain and high resolution medial temporal lobe volumetric segmentation was also performed using the T1-weighted scan and a dedicated hippocampal coronal T2-weighted scan with Advanced Normalization Tools (ANTS) (Avants et al., 2008) and Automatic Segmentation of Hippocampal Subfields (ASHS) multi-atlas segmentation methods (Yushkevich et al., 2015). Coordinates of the radiodense electrode contacts were derived from a post-implant CT and then

registered with the MRI scans using ANTS. Subdural electrode coordinates were further mapped to the cortical surfaces using an energy minimization algorithm (Dykstra et al., 2012). Two neuro-radiologists reviewed cross-sectional images and surface renderings to confirm the output of the automated localization pipeline. Stimulation targets that were localized to the left inferior, middle, and superior temporal gyri were classified as LTC. For region of interest analyses, electrodes were assigned to regions using Freesurfer atlas labels (IFG: inferior frontal gyrus; MFG: middle frontal gyrus; SFG: superior frontal gyrus; MTLC: medial temporal lobe cortex; HIPP: hippocampus; ITG: inferior temporal gyrus; MTG: middle temporal gyrus; STG: superior temporal gyrus; IPC: inferior parietal cortex; SPC: superior parietal cortex; OC: occipital lobe).

Verbal memory task

Across participants, data were collected from two behavioral tasks: standard delayed free recall and categorized delayed free recall. In both tasks, participants were instructed to study lists of words for a later memory test; no explicit encoding task was used. Lists were composed of 12 words presented in either English or Spanish, depending on the participant's native language. In the standard free recall task, words were selected randomly from a pool of common nouns (`https://memory.psych.upenn.edu/Word_Pools`). In the categorized free recall task, the word pool was constructed from 25 semantic categories (e.g. fruit, furniture, office supplies). Each list of 12 items in the categorized version of the task consisted of four words drawn from each of three categories. Overall, $N = 19$ participated in standard free recall only; $N = 26$ participated in categorized free recall only; and $N = 2$ participated in both free and categorized recall (in separate sessions).

Immediately following the final word in each list, participants performed a distractor task (to attenuate the recency effect in memory, length = 20 seconds) consisting of a series of arithmetic problems of the form A+B+C=??, where A, B and C were randomly chosen integers ranging from 1-9. Following the distractor task participants were given 30 seconds to verbally recall as many words as possible from the list in any order; vocal responses were digitally recorded and later manually scored for analysis. Each session consisted of 25 lists of this encoding-distractor-recall

procedure.

EEG recording and analysis

Electrophysiological recording and stimulation was conducted using a variety of systems across the years and sites over which the project was conducted. Recording and stimulation equipment included clinical EEG systems (Nihon Kohden EEG-1200, Natus XLTek EMU 128 or Grass Aura-LTM64), equipment from Blackrock Microsystems, as well as the External Neural Stimulator (ENS) (Medtronic, Inc.). Data were sampled at 500, 1000, or 1600 Hz (depending on the clinical site). During the sessions, a laptop recorded behavioral responses (vocalizations, key presses), synchronized to the recorded EEG via transmitted network packets.

Intracranial electrophysiological data were filtered to attenuate line noise (5 Hz band-stop fourth order Butterworth, centered on 60 Hz). We referenced the data using a bipolar montage (Burke et al., 2013) by identifying all pairs of immediately adjacent contacts on every depth, strip and grid and taking the difference between the signals recorded in each pair. The resulting bipolar timeseries was treated as a virtual electrode and used in all subsequent analysis. For the purposes of anatomical localization, we used the midpoint of the bipolar pair as the location for this virtual electrode. We used the same midpoint approach to localize stimulation targets.

Multivariate classification of memory

We performed spectral decomposition (8 frequencies from 3-180 Hz, logarithmically-spaced; Morlet wavelets; wave number = 5) for 1366 ms epochs from 0 to to 1366 ms relative to word onset. Mirrored buffers (length = 1365 ms) were included before and after the interval of interest to avoid convolution edge effects. The resulting time-frequency data were then log-transformed, averaged over time, and z-scored within session and frequency band across word presentation events. For a subset of participants, we also performed the same spectral decomposition procedure on record-only data from the memory recall phase of each list. These data were then used along with the encoding data to train the classifier (Kragel et al., 2017). To do so, we computed spectral power for the 500 ms interval preceding a response vocalization, as well as during unsuccessful periods of memory search (the first 500 ms of any 2500 ms interval in which no recall response was made).

For both trial types (correct vocalizations and unsuccessful search periods), we further stipulated that no vocalization onsets occurred in the preceding 2000 ms.

Our closed-loop stimulation approach was based on using individualized memory classifiers to control the timing of stimulation in response to brain activity. Thus, after collecting at least three record-only sessions from an individual patient, we then used the data as input to a logistic regression classifier that would trigger closed-loop stimulation during the later stimulation session(s). To build the classifier, we used patterns of brain activity collected during memory encoding (N = 14 participants) or memory encoding and retrieval (N = 33) and trained the classifier to discriminate words that were recalled vs. not recalled. The input features were spectral power at the eight analyzed frequencies $\times$ N electrodes. We used L2-penalization to prevent overfitting (Hastie et al., 2001) and set the penalty parameter (C) to 2.4×10^{-4} based on the optimal penalty parameter calculated across our large pre-existing dataset of free-recall participants (Kragel et al., 2017; Ezzyat et al., 2018). We weighted the penalty parameter separately for each participant in inverse proportion to their number of recalled and not recalled words; this was done so that the model would learn equally from both classes (Hastie et al., 2001).

We used leave-one-session-out cross-validation to assess classifier performance and estimate the model's ability to generalize to the subsequent closed-loop stimulation session. Thus, we trained the classifier on $M - 1$ sessions and tested the trained classifier on the held-out session. This process was then iterated until all sessions had been held out as test data. We then assessed the model's performance by calculating area under the curve (AUC) using these cross-validated model outputs and comparing it to chance AUC = 0.50. To do so, we conducted a permutation test by generating a null distribution for AUC by retraining the classifier 1000 times using randomized labels for the recalled/not recalled words. Classification analyses were programmed using either the Matlab implementation of the LIBLINEAR library (Fan et al., 2008) or the Python library scikit-learn (Pedregosa et al., 2011).

For the Closed-loop group (34 participants, N = 40 stimulation targets), classifiers were trained using the true mapping of features (spectral power $\times$ electrodes) to recall outcomes. In contrast, for the Random group (13 participants, N = 17 stimulation targets), a technical error in labeling features during classifier training led to classifiers that were trained on permuted data, eliminating the true mapping between neural activity on each trial and recall outcomes. This provided a natural

experiment for testing whether the closed-loop nature of stimulation enhanced the efficacy of LTC stimulation.

To assess the importance of individual features to the classifier's performance, we calculated a forward model (Haufe et al., 2014):

$$A = \frac{\Sigma_{\mathbf{x}}\mathbf{w}}{\sigma^2_{\hat{\mathbf{y}}}}$$

where $\Sigma_{\mathbf{x}}$ is the data covariance matrix, $\mathbf{w}$ is the vector of feature weights from the trained classifier, and $\sigma^2_{\hat{\mathbf{y}}}$ is the variance of the logit-transformed classifier outputs for all recalled/not recalled events $\hat{\mathbf{y}}$. Positive values in A suggest a positive relation between power for a given feature and successful memory recall. We computed A separately for each participant (averaging features within anatomical regions of interest based on the Freesurfer labels derived from anatomical localization of electrodes) before conducting across-participant statistical tests (Fig 1D.

Closed-loop stimulation

Before beginning the closed-loop stimulation session, we used the participant's full set of record-only data to train a memory classifier using the parameters described in the previous section. At the start of each stimulation session, we determined the safe amplitude for stimulation using a mapping procedure in which stimulation was applied at 0.5 mA while a neurologist monitored for afterdischarges. This procedure was repeated, incrementing the amplitude in steps of 0.5 mA, up to a maximum of 1.5 mA for depth contacts and 3.5 mA for cortical surface contacts. These maximum amplitudes were chosen to be below the afterdischarge threshold and below accepted safety limits for charge density (Shannon, 1992). For each stimulation session, we passed electrical current through a single pair of adjacent electrode contacts. The locations of implanted electrodes were determined strictly by the monitoring needs of the clinicians (recording sites depicted in Figure 1B). We therefore used a combination of anatomical and functional information to select stimulation sites, prioritizing (if available) targets in the middle temporal gyrus (stimulation locations depicted in Figure **??**A). This choice was guided by prior work identifying the middle temporal gyrus as an effective target for modulating memory with stimulation (Ezzyat et al., 2018; Kucewicz et al., 2018). Stimulation was delivered using charge-balanced biphasic rectangular

pulses (pulse width = 300 μs) at either 50, 100 or 200 Hz frequency (a single frequency was chosen for each subject), and was applied for 500 ms in response to classifier-detected poor memory states (see below). Participants performed one practice list followed by 25 task lists: lists 1-3 were used as a baseline for normalizing the classifier; lists 4-25 consisted of 11 lists each of Stim and NoStim conditions, randomly interleaved. On NoStim lists, stimulation was not triggered in response to classifier output.

To determine (in actuality) how well the classifier predicted recalled and forgotten words in a given participant's stimulation session, we again used AUC. We used the true classifier outputs and true recall outcomes from the NoStim lists to calculate the classifier generalization AUC for the stimulation sessions. To generate the corresponding receiver operating characteristic curves for visualization (Figure 1C), we modeled the classifier outputs for recalled and not recalled words using signal detection theory (Wixted, 2007). We did this by using the classifier outputs to estimate the mean and variance of hypothetical (normal) distributions of memory strength for recalled and not recalled words. We then generated a curve relating true and false positive rates by varying the assumed decision criterion (Wixted, 2007).

Analysis of memory performance

All participants completed at least three sessions of the record-only task (for purposes of classifier training) and at least one session of the stimulation task. For the stimulation session(s) we calculated stimulation's effect on recall performance as follows:

$$\Delta = \frac{R_S - R_{NS}}{R_{NS}} \times 100$$

where R_S is the average recall for stimulated lists and R_{NS} is the average recall for non-stimulated lists. Because the first three lists of every stimulation session were always non-stimulated (used for normalization of the classifier input features for that session), we excluded these lists from the calculation of R_{NS} to avoid introducing a temporal order confound (Ezzyat et al., 2018). All participants were required to demonstrate a minimum R_{NS} = 8.33% (1 out of 12 words per list) for inclusion in the sample.

Calculation of stimulation target distance to white matter

Using Freesurfer to segment patients' T1 MRI scan, we identified white-matter vertex locations, then calculated the distance between the stimulation location and the nearest white matter vertex. These distances were then split into thirds in order to categorize stimulation sites as Near, Middle, or Far relative to the nearest white matter (Solomon et al., 2018; Mohan et al., 2020).

Calculation of stimulation target node strength

We used a previously reported method for calculating the node strength of stimulation targets using the MNE-Python software package (Gramfort et al., 2014; Solomon et al., 2018). We extracted data from the record-only sessions of each patient and used the data to calculate the coherence between each pair of bipolar channels in the patient's montage. The coherence (C_{xy}) between two signals is the normalized cross-spectral density. This measure reflects the consistency of phase differences between signals at two electrodes, weighted by the correlated change in spectral power at both sites:

$$C_{xy} = \left| \frac{S_{xy}}{S_{xx} S_{yy}} \right|$$

where S_{xy} is the cross-spectral density between signals at electrodes x and y; S_{xx} and S_{yy} are the auto-spectral densities at each electrode. We used the multitaper method to estimate spectral density (Bronez, 1992). We used a time-bandwidth product of 4 and a maximum of 8 tapers (tapers with spectral energy < 0.9 were removed), computing coherence for frequencies between 5 and 13 Hz. We computed inter-electrode coherence within non-overlapping 1-s windows of data collected during a 10-second baseline (countdown) period that occurred at the start of each word list. The resulting coherence values between each pair of electrodes were then regressed on the Euclidean distance between each pair of electrodes, to account for the correlation between inter-electrode coherence and distance (Solomon et al., 2018). This distance-residualized measure of coherence was then used in the node-strength calculation.

Analysis of physiological effects of stimulation

To assess the effect of LTC stimulation on neural activity, we analyzed recording channels (i.e. those that were not stimulated) and we compared spectral power in the theta band (4-8 Hz) on Stim lists vs. NoStim lists. We first excluded electrodes exhibiting non-physiological post-stimulation artifacts (such as amplifier saturation/relaxation) using three different measures of the EEG timeseries before and after stimulation. We compared intervals before and after stimulation for changes in variance using an F-test and for changes in signal amplitude using a t-test. We additionally fit a polynomial function to the timeseries before and after each stimulation event and used a t-test to compare the resulting betas for the quadratic term. We calculated these three measures using the signal from -400 ms to -100 ms relative to stimulation onset and 100 ms to 400 ms relative to stimulation offset. In order to select statistical thresholds for each measure, we conducted the same analysis on each participant's record-only data. We then selected P-value thresholds associated with a 5% detection rate in the record-only data (i.e. false positives). Any channel that was significant on any of the three measures was excluded from analysis.

To measure stimulation's effect on theta power, we extracted spectral power from -600 ms to -100 ms relative to stimulation onset and 100 ms to 600 ms relative to stimulation offset. We used Morlet wavelets (wave number = 5) to estimate spectral power for 45 logarithmically-spaced frequencies from 4 to 200 Hz (Long et al., 2014). We used mirrored buffers to eliminate edge artifacts. The resulting spectral power estimates were then z-scored within each frequency, separately for each session. We then averaged power within the 4-8 Hz band across the time dimension for each 1000 ms pre-stimulation period and for each matched 1000 ms post-stimulation period. We then subtracted the pre-stimulation data from the post-stimulation data to yield a distribution of change in spectral power.

We compared the distribution of power changes for stimulation events to the analogous power changes from NoStim lists. To do so, we extracted and calculated 4-8 Hz power using identical parameters. However, because there were no actual stimulation events in NoStim lists, we generated a synthetic distribution of onset times by extracting the lag (in ms) between each word onset and stimulation event in Stim lists, and sampling randomly from that distribution of onset times to determine when to extract data relative to word onset events in NoStim lists. We did so for all

NoStim lists excluding the first three to avoid temporal order confounds (see *Analysis of memory performance*).

Finally, we used an independent samples t-test to compare the distribution of Stim list power differences to the distribution of NoStim list power differences. The resulting distribution of t-statistics was then averaged across all electrodes to estimate stimulation-evoked change in power (Figure **??**).

Statistics

Data are presented as mean ± standard error of the mean; scatterplots show the standard error of the estimate. All statistical comparisons were conducted as two-tailed tests. Non-parametric tests (Mann-Whitney; Spearman rank correlation) were used for non-normally distributed variables (e.g. white matter distance, Figure **??**B); parametric tests (t-tests and Pearson correlation) were used for the remaining analyses. Data distributions were visually inspected or assumed to be normal for parametric tests.

Results

Multivariate classifiers identify memory lapses

Our stimulation strategy sought to intercept and rescue periods of poor memory encoding. To do so, we trained participant-specific multivariate classifiers to discriminate patterns of neural activity during record-only sessions of free recall (Figure 1A). For the Closed-loop group (N = 40), classifiers were trained using the true mapping of features (spectral power × electrodes) to recall performance; for the Random group (N = 17), due to a technical error in labeling features (see *Methods*), classifiers were trained on permuted features. The recording electrode locations for the Closed-loop and Random groups appear as spheres in Figure 1B. After having trained the classifiers on record-only data, we used them in later (independent) sessions to identify poor memory states for targeting with stimulation.

Our stimulation approach relies on the classifier successfully identifying poor memory states

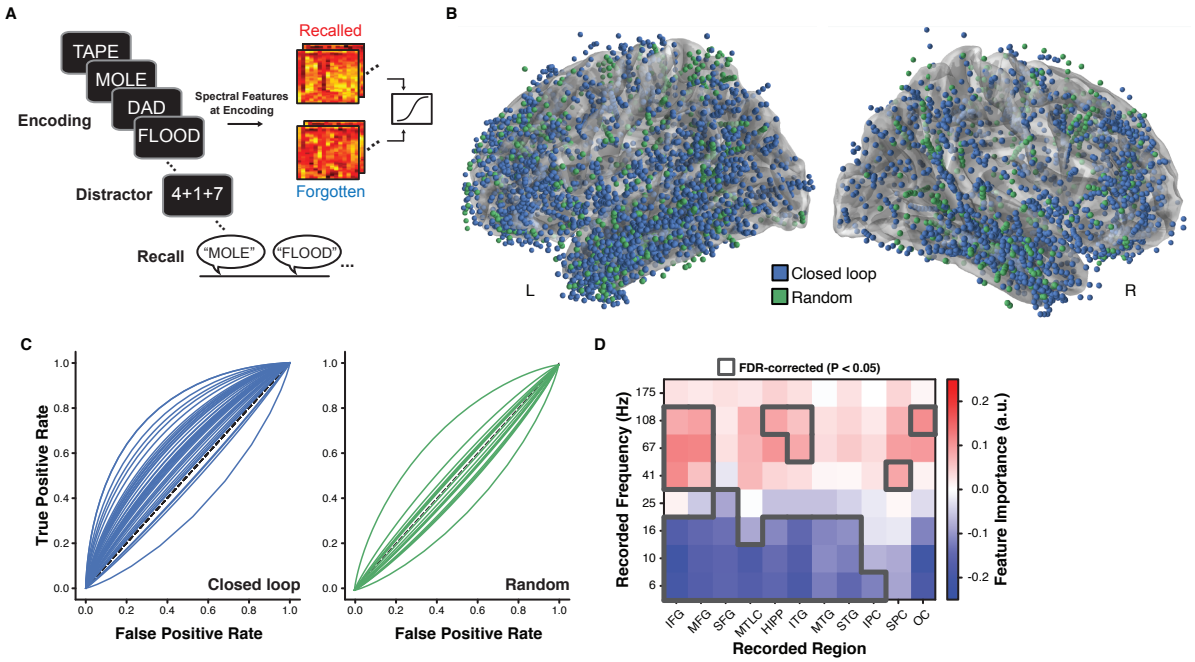

Figure 1: Stimulation strategy and classifier performance. **A.** Participants performed at least three sessions of the free recall task while being monitored with intracranial EEG. Multivariate classifiers trained on whole-brain patterns of spectral activity predicted subsequent recalled vs. not recalled words. **B.** Recording electrode locations for all participants in the Closed-loop (blue) and Random (green) groups, rendered on the Freesurfer average brain. **C.** Each participant's multivariate classifier then served as their personalized model to trigger stimulation. Classifiers trained on record-only data generalized to the stimulation session(s) for the Closed-loop group ($P = 6.14 \times 10^{-7}$) and outperformed classifiers for the Random group ($P = 2.73 \times 10^{-5}$). **D.** An analysis of feature importance for classifiers from the Closed-loop group showed that successful memory states were associated with decreases in low-frequency activity and increases in high-frequency activity.

when they occur. Therefore, our first question was how well the classifiers predicted memory outcomes during the stimulation sessions (i.e. out-of-sample generalization). To answer this question, we used NoStim lists to calculate the area under the receiver operating characteristic curve as an index of classification accuracy (AUC; see *Methods*). Classifiers for the Closed-loop group significantly exceeded chance [Mean AUC = 0.62 (chance AUC = 0.50), Wilcoxon signed rank test $P = 5.73 \times 10^{-7}$] and outperformed classifiers for the Random group [Mann-Whitney $U = 586.0, P = 1.85 \times 10^{-5}$]. As expected, Random classifiers did not exceed chance [Mean AUC = 0.49, Wilcoxon signed rank test $P = 0.55$; Figure 1C].

To understand what features the classifier used to discriminate good vs. poor memory encoding states, we used a forward model for each participant to derive importance estimates for each feature

(Haufe et al., 2014). We averaged the feature importance values within a set of regions of interest (ROIs) separately for each classifier frequency. Across participants, classifiers predicted successful memory encoding based on increased high-frequency activity and decreased low-frequency activity (Figure 1D). This pattern, which we refer to as the spectral tilt, has been observed in previous studies to be a biomarker of successful episodic memory encoding and retrieval (Ezzyat et al., 2017; Burke et al., 2014; Long et al., 2014).

Closed-loop LTC stimulation improves memory

Having established that classifiers in the Closed-loop group reliably discriminate memory encoding states, we next asked if we could increase memory performance by stimulating targets in the LTC (Figure 2A). Our stimulation strategy was based on detecting and intercepting poor memory encoding states with stimulation (Figure 2B). For the Closed-loop and Random groups, we compared recall performance for lists in which we delivered closed-loop stimulation (Stim lists) vs. identically structured lists in which we did not stimulate (NoStim lists). In the Closed-loop group, recall was higher on Stim lists compared to NoStim lists [$\Delta = 10.6\% \pm 4.3; t(39) = 2.45, P = 0.02$, Figure 2C], suggesting that intercepting poor memory encoding states enhanced later recall. In contrast, there was no difference in memory performance for the Random group [$\Delta = -3.2\% \pm 5.5; t(16) = -0.59, P = 0.57$]. There was a trend for greater memory enhancement for the Closed-loop compared to the Random group [$t(55) = 1.83, P = 0.07$]. These findings are the first to directly compare closed-loop LTC stimulation with a random/open-loop stimulation control and, in a larger replication sample, demonstrate the robustness of previous studies showing memory enhancement via LTC stimulation (Ezzyat et al., 2018; Kucewicz et al., 2018; **?**).

White matter proximity mediates stimulation's effect on memory

Our first main question, motivated by physiological studies of electrical stimulation's effects on downstream targets (Mohan et al., 2020; Solomon et al., 2018; Keller et al., 2018) was whether stimulating close to white matter tracts produces greater positive or negative effects on memory. If so, this would suggest that the brain's anatomical network structure plays a key role in determining

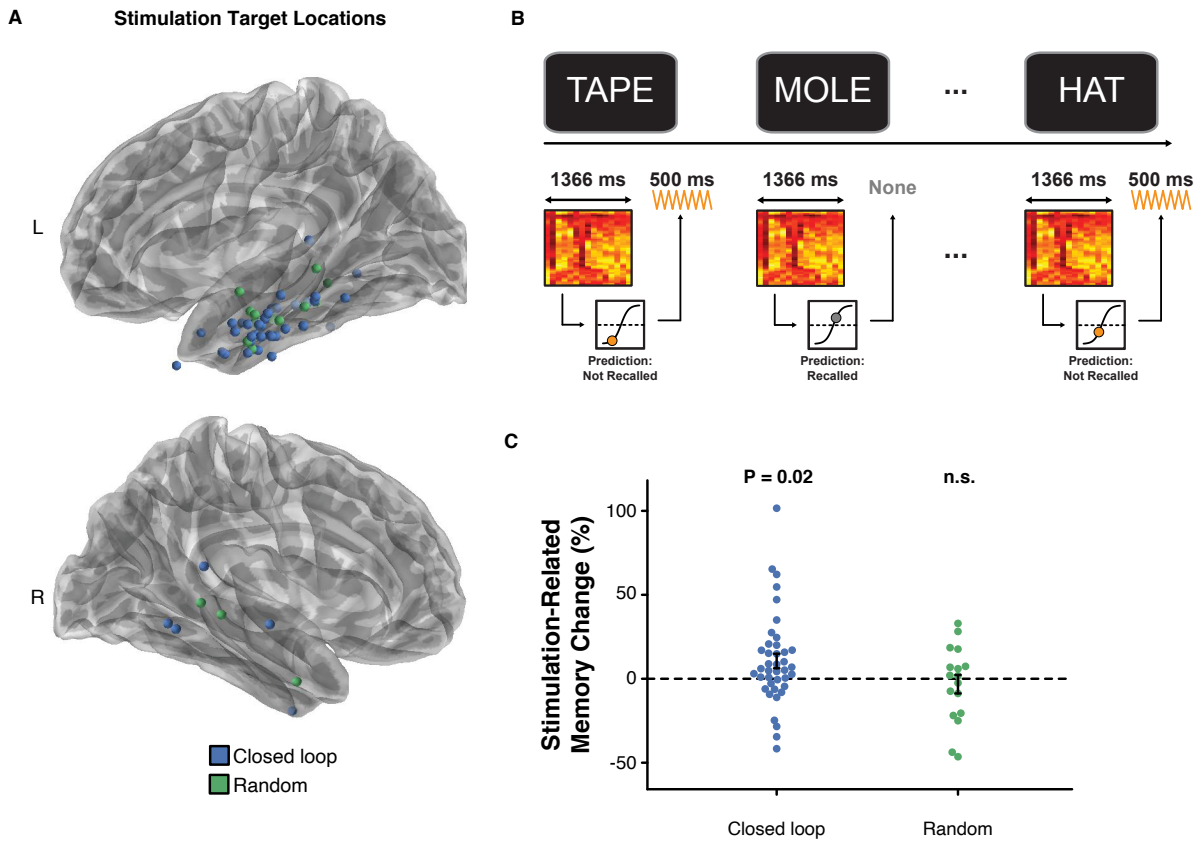

Figure 2: **Closed-loop stimulation improves memory performance. A.** Stimulation target locations for the Closed loop (blue) and Random (green) groups. **B.** Closed-loop stimulation strategy. **C.** Closed-loop LTC stimulation improved memory performance ($P = 0.02$) while Random stimulation did not. Error bars in *C* reflect s.e.m.

how effective stimulation can modulate memory (Stiso et al., 2019; Crocker et al., 2021). To answer this question, we examined how stimulation's effect on memory performance varied as a function of the stimulation target's proximity to white matter (see Figure 3A). These analyses revealed that for closed-loop stimulation, increased proximity to white matter predicted greater stimulation-related memory improvement [Spearman $\rho(38) = -0.42, P = 0.007$; Figure 2B]. In contrast, distance to white matter did not correlate with the memory effect when LTC stimulation was randomly timed (Spearman $\rho(15) = -0.17, P = 0.52$). There was no difference between the distances to white matter for the Closed loop and Random groups [Mann-Whitney $U = 331.0$, $P = 0.44$] and the median distance was in fact numerically greater for the Closed loop (1.58 mm) compared to the Random group (1.39 mm). This suggests that distance to white matter does not on its own explain the finding of improved memory in the closed-loop group.

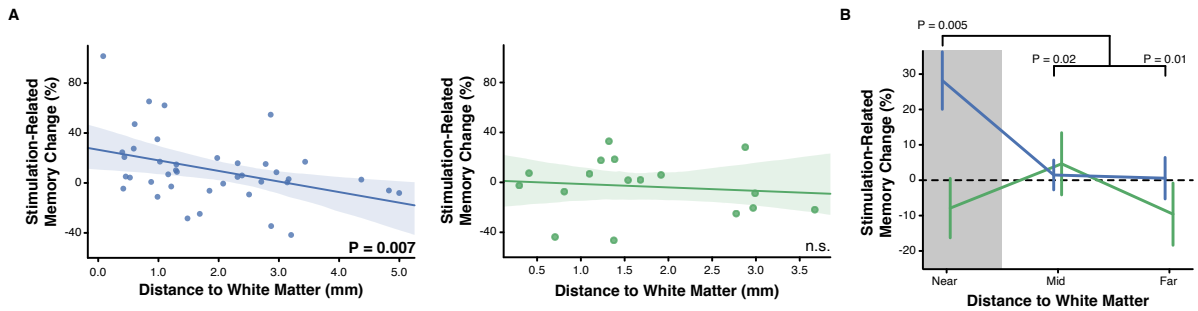

Figure 3: **Closed-loop stimulation near white matter enhances memory. A.** For the Closed-loop group, stimulation's effect on memory depended on the target distance from the nearest white matter [*left*, $P = 0.007$]. The correlation was not significant for the Random group [*right*, $P = 0.52$]. **B.** Closed-loop LTC stimulation improved memory performance for targets located nearest to white matter ($P = 0.005$). There was no effect for the Random group ($P = 0.62$). Error regions in *A* reflect the standard error of the estimate. Error bars in *B* reflect s.e.m.

To further evaluate this apparent distinction between closed-loop and random stimulation, we divided stimulation targets into terciles and asked whether stimulation near white matter was particularly effective in modulating memory performance. Indeed, closed-loop stimulation improved memory when delivered to electrodes nearest to white matter compared to electrodes in the middle [$M = 1.55\% \pm 4.22\%, t(24) = 2.67, P = 0.01$] and farthest [$M = 0.64\% \pm 5.87\%, t(26) = 2.65, P = 0.01$] thirds of the distance distribution [Closed-loop $M = 28.25\% \pm 8.14\%$, Random $M = -7.89\% \pm 8.40\%, t(17) = 2.36, P = 0.03$, Figure 2C. Closed-loop stimulation near white matter improved memory compared to NoStim lists within-participant [$t(13) = 3.23, P = 0.005$]. In contrast, there was no effect of stimulation in any white matter distance bin in the Random group (all $P > 0.38$). These data suggest that stimulating near white matter leads to greater modulation of memory, and complement previous work that showed that stimulating near white matter led to greater modulation of electrophysiology (Mohan et al., 2020; Solomon et al., 2018; Keller et al., 2018; Stiso et al., 2019; Crocker et al., 2021).

Stimulation target functional connectivity predicts the change in memory

We next asked why stimulation delivered near white matter reliably modulated memory function. One possibility is that stimulating near white matter allows more reliable and direct access to the broader memory network connected to the stimulated location (Khambhati et al., 2019; Stiso et al., 2019; Solomon et al., 2018; Mohan et al., 2020). We therefore measured functional connectivity

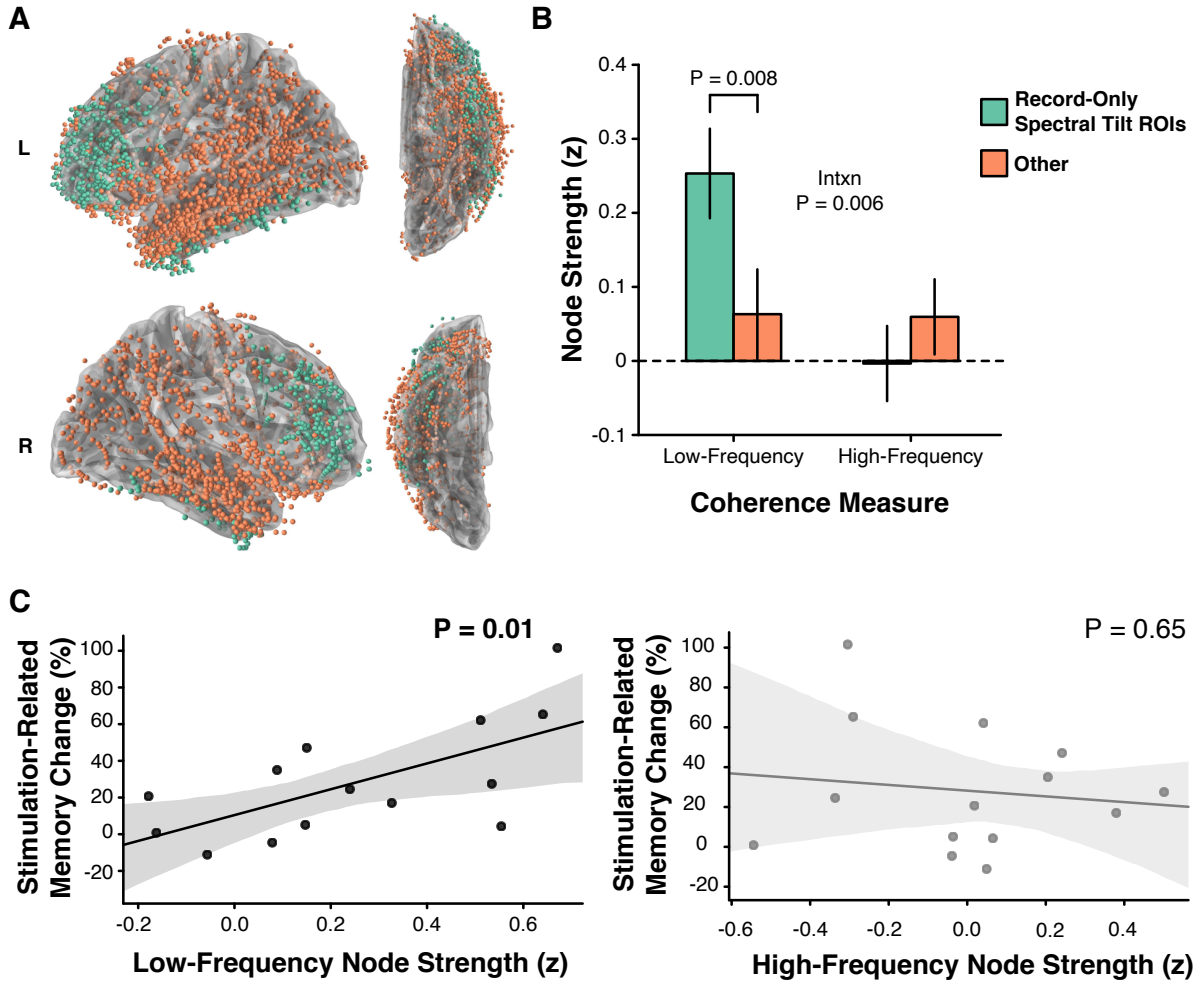

Figure 4: **Stimulation target functional connectivity.** **A.** We assigned each patient's record-only electrodes to two ROIs based on whether the electrode was located in a region that showed a memory-related spectral tilt or not (Other). **B.** Low-frequency connectivity was higher between the stimulation target and electrodes in Spectral Tilt regions, compared to electrodes in Other regions. In contrast, there was no difference in stimulation target high-frequency network connectivity. **C.** For closed-loop targets nearest to white matter, there was a significant correlation between the stimulation target distance to white matter and stimulation's effect on memory [$r(12) = 0.648, P = 0.01$].

between the memory encoding brain network and the stimulation targets located near white matter. We measured connectivity using coherence and tested whether stimulation target node strength differed for low vs. high-frequency networks (see *Methods*). To isolate the brain's memory encoding network, we identified all electrodes that were in brain regions that showed a significant spectral tilt that predicted memory success, assessed using classifier feature importance Figure 3A. We then compared stimulation target connectivity (Node Strength) In vs. Out of the memory

network, for both low and high-frequency coherence. Stimulation targets showed stronger low-frequency connectivity to electrodes in the memory network than to electrodes outside of the memory network [$t(13) = 3.14, P = 0.008$, Figure 3B]. In contrast, stimulation targets showed equivalent high-frequency connectivity In vs. Out of the memory network [interaction: $F(1, 13) = 10.54, P = 0.006$, Figure 3B].

Although stimulation targets near white matter showed greater overall low-frequency connectivity with memory-predicting brain areas, this finding leaves open the question of whether variability in connectivity strength predicts variability stimulation's effect on memory. To answer this question, we correlated low-frequency node strength with stimulation-related memory change. To determine whether stimulation-target connectivity predicted memory modulation, we measured functional connectivity between the stimulation target and all other electrodes in the patient's montage (see *Methods*). Using target-node strength as our measure of functional connectivity (Solomon et al., 2018), we correlated node strength with the stimulation-related change in memory performance. We found that low-frequency node strength predicted closed-loop stimulation's effect on memory [$r(12) = 0.648, P = 0.01$, Figure 3C] while high-frequency node strength did not ($P = 0.65$). The difference in correlation for low vs. high-frequency node strength was also significant (two-tailed permutation test $P = 0.03$). For all other targets that were further from white matter, there was no relation between node strength and stimulation-related memory change (all $P > 0.21$).

Functional connectivity mediates stimulation's effect on downstream physiology

The preceding results indicate that white-matter proximity and low-frequency functional connectivity to the (classifier identified) memory network predict stimulation's mnemonic effects. Our closed-loop system entrained the timing of stimulation to the waxing and waning of successful memory states as determined by the classifier. We therefore hypothesized that stimulation's effects on memory would be further related to changes in memory-related physiological activity across this memory network. To test this prediction we correlated each stimulation target's connectivity to the memory network with the stimulation-evoked spectral power in this network (Figure 5A). Two participants' data were excluded due to excessive stimulation artifact on the recording channels.

In the remaining participants, we found that stimulation-target functional connectivity predicted stimulation-related changes in low-frequency power [$P = 0.02$, Figure 5B). The correlation was not significant when using high-frequency connectivity and evoked power (Figure 5C).

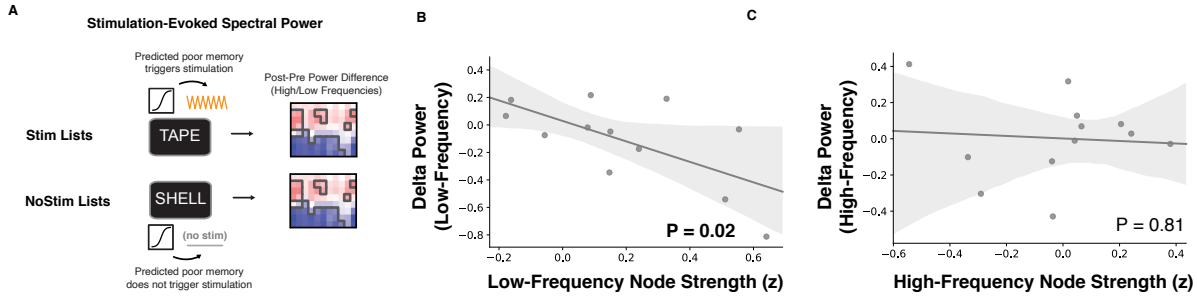

Figure 5: **Memory network connectivity predicts physiology. A.** Schematic of spectral tilt analysis. **B.** For stimulation targets near white matter, low-frequency functional connectivity predicted the stimulation evoked change in spectral tilt ($P = 0.02$). **C.** High-frequency network connectivity did not predict stimulation's effect on the spectral tilt memory biomarker.

Discussion

Direct electrical stimulation has emerged as a powerful tool for manipulating neural activity. The present study evaluated the hypothesis that network properties of a stimulated brain location predict stimulation's effects on both memory and network physiology. Prior studies suggest that stimulating white matter correlates with stimulation's physiological or behavioral effects (Paulk et al., 2022; Solomon et al., 2018; Mohan et al., 2020; Khambhati et al., 2019; Stiso et al., 2019). Other studies demonstrate that measures of structural and functional connectivity predict stimulation's effects on downstream targets (Keller et al., 2011; Fox et al., 2020; Solomon et al., 2018). However, none have simultaneously linked structural/functional connectivity with both (1) a reliable improvement over baseline cognitive functioning and (2) concomitant changes in neurophysiology that explain the behavioral effect. To directly address these open questions, we asked whether white-matter proximity and functional connectivity underlie the degree to which stimulation of LTC produces improvements or impairments of memory, alongside changes in oscillatory signatures of mnemonic function.

We found that closed-loop stimulation of LTC reliably improved memory as seen in better recall performance on stimulated vs. non-stimulated lists. Consistent with the hypothesis that white-matter pathways convey the effects of stimulation to the broader memory network, we found the benefits of closed-loop LTC stimulation to arise principally from stimulating in, or near, white matter pathways. For the upper tercile of white matter proximity, stimulation yielded a 28% increase in recall performance, whereas we failed to observe any reliable increase when delivering stimulation far from these pathways (−8%). In a subgroup of subjects who received randomly timed stimulation in LTC targets we failed to observe any improvement in memory performance.

To evaluate the hypothesized relation between functional connectivity and stimulation's mnemonic effects we leveraged analyses of large-scale neural recordings obtained during prior record-only sessions. Building on evidence that brain networks become theta-coherent during successful memory encoding and retrieval (Solomon et al., 2017; Kragel et al., 2021a) we asked whether theta connectivity between LTC targets and the rest of the brain resulted in greater (or weaker) effects of stimulation on memory performance. Consistent with the hypothesized role of theta connectivity we found a strong positive correlation (r = 0.595, see Figure 2D) between theta connectivity and

stimulation-related memory improvement. Finally, LTC stimulation engaged low-frequency activity across a broader brain network in a way that matched the network position of the stimulated location.

Our data highlight how precise targeting improves stimulation efficacy by showing that delivering stimulation near LTC white-matter leads to greater stimulation-related memory gains (Figure 2C). By linking low-frequency network connectivity with physiological and behavioral outcomes (Figure **??**), our study also points to a neural mechanism for modulating memory with stimulation. This result extends earlier work that demonstrated the potential to modulate episodic memory by targeting LTC with stimulation (Ezzyat et al., 2018; Kucewicz et al., 2018). Directly comparing closed-loop and open-loop stimulation strategies in the same study helps to establish a causal role for the closed-loop approach (Hampson et al., 2018; Ezzyat and Rizzuto, 2018). Finally, our data from 57 stimulation targets (across 47 patients) also represents a substantial increase compared to sample sizes described in related prior studies (Ezzyat et al., 2018; Hampson et al., 2018).

Prior work has linked successful memory function with increased theta power and coherence (Burke et al., 2013; Solomon et al., 2017; Herweg et al., 2020; Griffiths et al., 2019; Kragel et al., 2021b; Ter Wal et al., 2021; Osipova et al., 2006; Guderian and Düzel, 2005; Klimesch et al., 1997; Staudigl and Hanslmayr, 2013). Here, we investigated this physiological correlate of memory function by testing how memory-modulating LTC stimulation affects low-frequency physiology. We found that stimulation's effect on low-frequency (theta) activity depends on the low-frequency functional connectivity of the stimulation target. This suggests that identifying hubs within the brain's low-frequency network will lead to stronger modulation of low-frequency activity. Furthermore, we found that stimulation that modulated low-frequency activity also modulated memory performance.

Several prior studies, including one based upon a subset of these data, found potential therapeutic benefits of closed-loop stimulation triggered by decoding of intracranial brain recordings (Ezzyat et al., 2018; Scangos et al., 2021a; Hampson et al., 2018). However, with some exceptions (Hampson et al., 2018), this work has lacked an open-loop or random stimulation control condition, leaving open the question of what *specific* role the closed-loop nature of stimulation played in its therapeutic effects. Here, we compared the effects of closed-loop stimulation with a

random stimulation condition. Closed-loop participants received stimulation only for those items predicted to be forgotten, while participants in the random group followed the same protocol, but using classifiers trained on permuted data, resulting in stimulation being applied without regard to predicted memory success. This led to reliable memory improvement for the closed-loop group and none for the random group, despite following an otherwise identical protocol (Figure 1C).

We found that closed-loop stimulation improved memory the most when it was delivered to LTC targets in or near white matter. This finding builds on a growing literature that indicates that stimulation is most effective when it is delivered in or near white matter pathways (Khambhati et al., 2019; Stiso et al., 2019; Mohan et al., 2020; Solomon et al., 2018; Paulk et al., 2022). One explanation for this phenomenon is that only stimulation of white matter pathways successfully engages broader brain networks, perhaps via oscillatory synchronization. In contrast, gray matter stimulation tends to cause more local effects (Mohan et al., 2020; Paulk et al., 2022). Though purely local effects may sometimes be desirable, the key cognitive and pathophysiological processes of greatest interest to neuroscientists tend to involve multiple interconnected brain regions.

Among its many applications for modulating cognition and behavior (Siddiqi et al., 2022; Fox et al., 2020; Sreekumar et al., 2017) a number of recent studies have evaluated stimulation's potential for enhancing episodic memory (Mankin and Fried, 2020; Suthana and Fried, 2014; Curot et al., 2017; Lee et al., 2013; Sankar et al., 2014). While our study investigated numerous stimulation targets within the LTC, future work should compare stimulation of this region to other brain areas within the broader episodic memory network. Recent work suggests that stimulating white matter pathways in the medial temporal lobe, for example, can also improve memory (Titiz et al., 2017; Mankin et al., 2021; Suthana et al., 2012). However, these previous studies used visual and/or spatial memoranda, while the present study focused on encoding and retrieval of verbal material. Thus, future research should compare stimulation to the lateral and medial temporal lobes, to determine whether stimulation target location interacts with the modality of the to-be-remembered information.

We delivered stimulation using macroelectrodes, consistent with its clinical applications (Krauss et al., 2021; Morrell, 2011; Sun et al., 2008). Macroelectrode stimulation alters local activity at the spatial scale of the distance between the anode and cathode (approximately 1 cm), but can also alter more distant regions. Because memory relies on a broad network of cortical

and subcortical regions, including the hippocampus (Kim, 2011; Keerativittayayut et al., 2018), stimulating a broader network may be necessary to impact cognitive function. On the other hand, memory also relies on the recapitulation of specific patterns of neuronal activity, especially within the hippocampus (Foster, 2017; Staresina and Wimber, 2019). Thus, other work has stimulated through microelectrodes to mimic and reinstate memory-related hippocampal activity using a model-based closed loop approach (Hampson et al., 2018; Hampson et al., 2013; Deadwyler et al., 2017). An avenue for future work could use macroelectrode stimulation in a similar vein, by triggering stimulation at multiple macroelectrode contacts in order to synchronize a particular spatiotemporal pattern of activity across key memory-related regions (Kim et al., 2016; Kim et al., 2018).

In relating low-frequency network connectivity, physiology, and behavior, our study contributes to methodological development for invasive stimulation (Krauss et al., 2021; Cagnan et al., 2019) that illuminates the critical role of low-frequency networks in cognition (Voytek and Knight, 2015). In addition, the present study also suggests that other methods that manipulate low-frequency activity could be leveraged to modulate neural and cognitive function. Several recent studies using non-invasive methods have leveraged low-frequency theta-patterned stimulation to modulate episodic and working memory (Nilakantan et al., 2017; Hermiller et al., 2020; Tambini et al., 2018; Warren et al., 2019; Grover et al., 2022). Such low-frequency stimulation modulates electrophysiology perhaps by entraining low-frequency oscillations that are associated with cognitive function function (Solomon et al., 2021; Reinhart and Nguyen, 2019; Reinhart et al., 2017; Hanslmayr et al., 2019).

In summary, our demonstration of improved memory with closed-loop stimulation supports the idea that memory function is dynamic, and that closed-loop algorithms which account for moment-to-moment variability in the brain's memory state can selectively deliver stimulation only when it is needed. The present study also links closed-loop stimulation efficacy to white matter targeting, brain-wide evoked physiology, and changes in episodic memory performance. The findings suggest future strategies for using the functional and anatomical network profile of putative stimulation targets to optimize downstream changes in oscillatory activity and cognition.

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