Closed-loop stimulation of temporal cortex rescues functional networks and improves memory

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Memory failures are frustrating and often the result of ineffective encoding. Using a closed-loop system to monitor and decode memory encoding activity from direct brain recordings in humans, we applied targeted stimulation to rescue periods of poor memory encoding. This led to improved later recall, revealed the lateral temporal cortex to be a reliable target for memory enhancement, and suggests a therapeutic approach for treating memory dysfunction.

Research on human episodic memory has shown that whether information is remembered or forgotten depends on neural events that transpire during encoding. Spectral power recorded using intracranial electrophysiology [1] and blood-oxygen-level dependent (BOLD) fMRI signal [2] show that activity in many cortical and subcortical regions differentiates learned information that is likely to be remembered from information that is likely to be forgotten. Differences in neural activity during encoding therefore predict intra-individual variability in later memory performance, suggesting that modulating neural activity when the brain is unlikely to encode successfully could improve overall performance by rescuing network activity.

A promising tool for modulation of neural activity is direct brain stimulation, in which electrical current is applied via electrodes implanted on or directly in the brain parenchyma. Direct brain stimulation is a standard tool in the treatment of motor dysfunction in Parkinson’s Disease, epilepsy, and some psychiatric conditions [3, 4, 5, 6] and is thought to act by disrupting pathological resonant activity in thalamo-cortico-basal ganglia circuits [7]. Direct brain stimulation treatment commonly involves continuous high-frequency stimulation and recent work has suggested improved effectiveness when applying stimulation in response to specific brain states (i.e. closed-loop [8, 9]).

Several studies have used direct brain stimulation of the hippocampus and medial temporal lobes (MTL) to modulate neural activity during memory tasks. While some have suggested that stimulation of these areas can improve performance [10, 11, 12], many others have failed to show improvements or have shown disruption [13, 14, 15, 16, 17, 18, 19]. This literature suggests that there may be other more effective targets for applying stimulation for memory enhancement.

Activity in the lateral temporal cortex (LTC), including the middle portions of the inferior, middle, and superior temporal gyri, predicts memory performance [1, 2, 20, 21], and stimulation mapping of this area has been shown to evoke memory-like recollective phenomena [22]. Prior invasive [23] and non-invasive [24] stimulation studies also suggest this region to be a prime target.
for memory modulation.

Here, we evaluate the use of LTC as a stimulation target by deploying a closed-loop architecture for sensing and stimulating the brain during the performance of a free recall memory task. We use multivariate classifiers that are individualized to each subject to decode neural activity during memory encoding, and trigger stimulation online in response to patterns of neural activity that are associated with later forgetting. By using classification within a closed-loop system, we account for the fact that direct brain stimulation has distributed effects on physiology [25, 26] that depend on the state of the brain at the time of stimulation delivery [27, 28, 29, 30, 31].

![Figure 1: Closed-loop approach.](image)

(a) For each list of the free recall task, subjects encoded 12 nouns presented sequentially, followed by an arithmetic distractor, and the verbal recall phase. Subjects performed at least three sessions of record-only free recall. (b) After collecting at least three sessions of record-only data, we use spectral decomposition to measure power at a set of frequencies ranging from 3 to 180 Hz for each encoded word. We used the patterns of spectral power across electrodes to train a penalized logistic regression classifier to discriminate encoding activity during subsequently recalled words from subsequently forgotten words. (c) In later closed-loop sessions, we applied spectral decomposition to each word encoding period while subjects performed the task. This produced a set of frequency × electrode features to which we applied the classifier trained on the record-only data. If the resulting estimated probability of recall was below 0.5, we triggered 500 ms of stimulation stimulation to either the lateral temporal cortex or a control target.

We recruited 26 neurosurgical patients undergoing clinical monitoring for epilepsy to participate in sessions of a delayed free recall memory task (Fig. 1a). Subjects performed at least three record-only sessions of free recall from which we trained a multivariate classifier to discriminate patterns of neural activity during encoding that predicted recall. We fit penalized logistic regres-
sion classifiers to at least three sessions of record-only data from each subject, producing a set of model weights that map features of intracranial EEG (iEEG) activity to an output probability of later word recall (Fig. 1b). These classifiers trained on encoding activity discriminated recalled from not recalled words (leave-one-session-out cross-validated $AUC = 0.61, P < 10^{-7}$, Fig. 2).

We then used this model in subsequent sessions to decode the probability of recall from neural activity on-line during the encoding phase of the task (Fig. 1c). On Stim lists, if the predicted probability of recall was below 0.5, the system triggered 500 ms of bipolar stimulation across an adjacent pair of channels. We predicted that this would disrupt poor encoding states and improve memory performance. On NoStim lists, we used the classifier to estimate recall probabilities but did not trigger stimulation. This allowed us to control for the memory state when comparing the effect of stimulation on recall probability of stimulated items.

We used a generalized linear mixed effects model (binomial distribution) to model the individual trial-level data across subjects to estimate how stimulation affected the probability of word recall. Stimulation of LTC increased the odds of recalling stimulated words compared to matched non-stimulated words ($\Delta$ odds = 18.1%, $P < 0.05$, Fig. 3a) and compared to Non-LTC ($P < 0.01$). The decrease in recall odds in the Non-LTC group was not significant ($\Delta$ odds = -13.2%, $P = 0.23$). The stimulation targets that led to increased memory performance clustered in the middle portion of the ROC curve.
Figure 3: Stimulation affects behavior and physiology. (a) Stimulation delivered to LTC targets increased the probability of recall compared to matched unstimulated words in the same subject ($P < 0.05$) and stimulation delivered to Non-LTC targets in an independent group ($P < 0.01$). (b) The change in classifier output post-LTC stimulation was greater than for matched intervals on NoStim lists.

We observed these different stimulation-related memory outcomes in spite of the fact that the groups were matched in several ways. LTC and Non-LTC subjects showed equivalent memory performance during the record-only sessions (LTC = 26.1%, Non-LTC = 29.8%, $t(24) = -0.87, P = 0.39$). We also analyzed subsequent memory effects at the stimulated electrodes in the record-only data, to determine whether the stimulated electrodes showed different contributions to memory performance across the groups. We found that power across the frequency spectrum (2-200 Hz) was similarly predictive of memory for the LTC and Non-LTC groups (Fig. S1 a,b), indicating no difference between groups in the stimulated electrode’s involvement in encoding processes. We also did not find any relation between the size of the subsequent memory effect at the stimulated electrode and stimulation’s effect on behavior (Fig. S1 c).

We hypothesized that stimulation of LTC influenced memory by perturbing the subject’s encoding state via modulation of activity across the brain, rather than solely at the locus of stimulation. We assessed this by computing the change in whole-brain classifier output for words $w_{i+1}$ and $w_i$, for all stimulated words. We did the same for matched words on NoStim lists and compared $\Delta$ classifier between the Stim and NoStim conditions for the LTC group. This analysis showed larger
Figure 4: Stimulation targets rendered on an average brain surface. Stimulation targets showing numerical increase (decrease) in free recall performance are shown in red (blue). Memory-enhancing sites clustered in the middle portion of the middle temporal gyrus.

Increases in classifier output following stimulation compared to the control non-stimulated condition ($estimate = 0.009, P < 0.04$, Fig. 3b), suggesting that stimulation increased list-level memory in the LTC group by increasing whole-brain neural activity supporting successful encoding.

Supplementary Figure 1: Subsequent memory effect at stimulated electrode pair. (a,b) The subsequent memory effect during the record-only sessions at the stimulated electrode pair did not differ between the LTC and Non-LTC groups. (c) We computed the slope of the frequency spectrum to estimate the spectral tilt [1] at the stimulated electrode pair and found this measure did not correlate with the effect of stimulation on memory performance in later closed-loop sessions.

Our findings make several contributions to the field of brain stimulation for memory modulation. In observing that closed-loop stimulation improves performance in the free recall task, we show that stimulation improves memory by intercepting and rescuing poor memory states. We also identify the lateral temporal cortex as a prime target for memory enhancement, moving beyond prior work that has attempted to modulate episodic memory focusing on the hippocampus and MTL [11, 19, 14, 13]. Our system also provides a framework for developing therapies to treat memory dysfunction.
Experimental Procedures

Participants

Twenty six patients undergoing intracranial electroencephalographic monitoring as part of clinical treatment for drug-resistant epilepsy were recruited to participate in this study. 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: Thomas Jefferson University Hospital (Philadelphia, PA), University of Texas Southwestern Medical Center (Dallas, TX), Emory University Hospital (Atlanta, GA), Dartmouth-Hitchcock Medical Center (Lebanon, NH), Hospital of the University of Pennsylvania (Philadelphia, PA), and Mayo Clinic (Rochester, MN). 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 on the cortical surface as well as depth electrodes within the brain parenchyma. In each case, the clinical team determined the placement of the electrodes so as to best localize epileptogenic regions. Subdural contacts were arranged in both strip and grid configurations.

Verbal memory task

Each subject participated in a delayed free-recall task in which they were instructed to study lists of words for a later memory test; no encoding task was used. Lists were composed of 12 words chosen at random and without replacement from a pool of high frequency nouns (either English or Spanish, depending on the participant’s native language; http://memory.psych.upenn.edu/WordPools). Each word remained on the screen for 1600 ms, followed by a randomly jittered 750-1000 ms blank inter-stimulus interval (ISI).

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. Some subjects completed sessions of the free recall task using categorized word lists, which were included in the electrophysiological analyses. The categorized recall task is identical to the free recall task, with the exception that the word pool was drawn 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. Subject counts by task: N = 17 free recall only; N = 2 categorized free recall only; N = 7 both free and categorized recall (in separate sessions).

**Stimulation methods**

At the start of each session, we determined the safe amplitude for stimulation using a mapping procedure in which stimulation was applied at .5 mA while a neurologist monitored for after-discharges. This procedure was repeated, incrementing the amplitude in steps of .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 [32]. For each stimulation session, we passed electrical current through a single pair of adjacent electrode contacts. Because the electrode locations were determined strictly by the monitoring needs of the clinicians, we used a combination of anatomical and functional information to select stimulation sites. If available, we prioritized electrodes in lateral temporal cortex (LTC), in particular the middle portion of the middle temporal gyrus. To choose among these regions in cases in which more than one was available, we selected the electrode demonstrating the largest subsequent memory effect (SME), in the high frequency range (70-200 Hz). In cases in which no LTC contacts were available, we selected the contact with the largest SME elsewhere in the brain. We used a mapping procedure at the start of each session to determine the safe amplitude for stimulation. 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
Anatomical localization

Cortical surface regions were delineated on pre-implant whole brain volumetric T1-weighted MRI scans using Freesurfer [33] according to the Desikan-Kiliany atlas. 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) [34] and Automatic Segmentation of Hippocampal Subfields (ASHS) multi-atlas segmentation methods [35]. 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 [36]. Two neuroradiologists reviewed cross-sectional images and surface renderings to confirm the output of the automated localization pipeline. Targets that were localized to the left inferior, middle, and superior temporal gyri were classified as LTC. Any target outside these regions was classified as Non-LTC.

Electrophysiological data processing

Intracranial data were recorded using one of the following clinical electroencephalogram (EEG) systems (depending the site of data collection): Nihon Kohden EEG-1200, Natus XLTek EMU 128 or Grass Aura-LTM64. Depending on the amplifier and the preference of the clinical team, the signals were sampled at either 500, 1000 or 1600 Hz and were referenced to a common contact placed either intracranially, on the scalp or mastoid process. Intracranial electrophysiological data were filtered to attenuate line noise (5 Hz band-stop fourth order Butterworth, centered on 60 Hz). To eliminate potentially confounding large-scale artifacts and noise on the reference channel, we re-referenced the data using a bipolar montage [1]. To do so, we identified all pairs of immediately adjacent contacts on every depth, strip and grid and took 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. We performed spectral decomposition (8 frequencies from 3-180 Hz, logarithmically-spaced; Morlet wavelets; wave number = 5) for 1366 ms epochs from 0 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.

**Multivariate classification**

We included only data collected in record-only sessions as input to a logistic regression classifier trained to discriminate encoding-related activity predictive of whether a word was later remembered or forgotten. We used spectral power averaged across the time dimension for each word encoding epoch (0-1600ms relative to word onset) as the input data. Thus, the features for each individual word encoding observation were the average power across time, at each of the 8 analyzed frequencies \( \times N \) electrodes. We used L2-penalization [37] and selected the penalty parameter for each subject based on the best penalty parameter (in terms of maximizing area under the curve, AUC) across the entire distribution of subjects. To do this, we began with a set of 22 possible penalty parameters spaced logarithmically between \( 10^{-6} \) and \( 10^{4} \) and, for each penalty parameter, fit the classifier using maximum likelihood and used \( N - 1 \) cross-validation to assess performance using AUC. For the majority of subjects that completed more than one session, \( N - 1 \) was applied over sessions; for subjects that completed a single session \( N - 1 \) was applied over lists within the session. This procedure yielded a distribution of AUCs across subjects for each penalty parameter. Then, for each subject we conducted a final cross-validated training in which we selected the penalty parameter with the highest mean AUC across the distribution of all subjects except the one whose classifier was being trained. We then computed AUC [37] to quantify classifier performance and repeated this procedure for all subjects. AUC measures a classifier’s ability to identify true positives while minimizing false positives, where chance AUC = 0.50. To ensure the classifier learned equally from both classes (given the imbalance between recalled and not recalled exemplars), we also weighted the penalty parameter in inverse proportion to the number of exemplars of each class [37]. We assessed the significance of each classifier within-subject using a permutation test in which we randomized the labels of recalled/not recalled events in the training data, computed AUC and repeated the randomization 1000 times to generate a null distribution.
of AUCs.

**Generalized Linear Mixed Effects Model**

We used generalized linear mixed effects (GLME) models using MatLab’s `fitglme` function to estimate the effect of stimulation on memory performance. In the full model assessing the interaction of stimulation and group on memory, we modeled the recalled/not recalled status of each encoding trial for all subjects as a function of list type (Stim/NoStim) and group (LTC/Non-LTC), with random slopes and intercepts for the effect of stimulation for each subject and unique stimulation target site (three subjects were stimulated at two different targets in separate sessions). We included in the model stimulated words and matched words from NoStim lists. The NoStim words were matched based on whether classifier output during the closed loop session was below threshold (i.e. stimulation would have been applied had it been a Stim list). To estimate the effect of stimulation within each of the LTC/Non-LTC groups we then fit the same model separately for each group without the group predictor.

**Analysis of post-stimulation classifier**

To assess the effect of LTC stimulation on neural activity we used the classifier to decode the stimulation-evoked change in physiology. We fit a GLME model to predict classifier output for the word encoding period immediately following delivery of a stimulation train. We included matched intervals from NoStim lists by identifying periods following words that would have been stimulated and modeled the Stim/NoStim list status of the observations, with separate slopes and intercepts for each subject and and unique stimulation target site.

**Statistics**

Data are presented as mean ± standard error of the mean. Unless otherwise specified, all statistical comparisons were conducted as two-tailed tests. Data distributions were either visually inspected or assumed to be normal for parametric tests. For both the record-only and stimulation samples, we included any enrolled subject that completed at least one full session of the task. We used linear mixed effects models of the trial-level data to estimate the effect of stimulation on behavior and
classifier output (Fig. 3), while accounting for repeated subject and subject-stimulation location
across observations.

Author Contributions

A.B., C.I., M.A.G., and M.T.K. performed data collection, recording, and annotation of behavioral
responses. I.P. programmed the closed-loop system. M.R.S., A.D.S., B.C.L., R.E.G., B.C.J., K.A.D.,
and G.A.W. recruited participants and provided general assistance. J.M.S, R.G., and S.R.D. local-
ized the electrodes. Y.E. and M.J.K. wrote the manuscript. All authors provided feedback on the
manuscript. D.S.R. and M.J.K. supervised the research.

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Department of Defense or the U.S. Government. B.C.J. receives research funding from NeuroPace
and Medtronic not relating to this research. M.J.K. and D.S.R. are in the process of organizing Nia
Therapeutics, LLC (“Nia”), a company in- tended to develop and commercialize brain stimulation
therapies for memory restoration. Currently, Nia has no assets and has not commenced operations.
M.J.K. and D.S.R. each holds a greater than 5% equity interest in Nia.
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Clinical Site: D: Dartmouth-Hitchcock Medical Center, E: Emory University Hospital, J: Thomas Jefferson University Hospital, M: Mayo Clinic, P: Hospital of the University of Pennsylvania, T: University of Texas Southwestern Medical Center

Ictal Onset: L: Left, R: Right, NA: Not Reported/Undetermined


Memory Task: FR: free recall, CatFR: categorized free recall