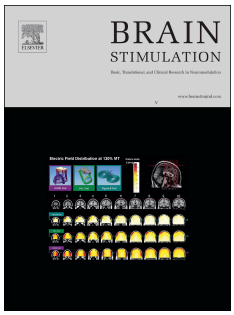


Anterior thalamic stimulation improves working memory precision judgments

Jiali Liu, Tao Yu, Jinfeng Wu, Yali Pan, Zheng Tan, Ruobing Liu, Xueyuan Wang, Liankun Ren, Liang Wang

PII: S1935-861X(21)00144-3

DOI: https://doi.org/10.1016/j.brs.2021.07.006

Reference: BRS 2004

To appear in: *Brain Stimulation*

Received Date: 10 February 2021

Revised Date: 25 June 2021

Accepted Date: 15 July 2021

Please cite this article as: Liu J, Yu T, Wu J, Pan Y, Tan Z, Liu R, Wang X, Ren L, Wang L, Anterior thalamic stimulation improves working memory precision judgments, *Brain Stimulation* (2021), doi: https://doi.org/10.1016/j.brs.2021.07.006.

Credit Author Statement

Jiali Liu: Data collection, Data curation, Formal analysis, Writing - original draft, Revising the manuscript critically for important intellectual content, Approval of the version of the manuscript to be published. **Tao Yu:** Data collection, Writing - original draft, Revising the manuscript critically for important intellectual content, approval of the version of the manuscript to be published. **Jingfeng Wu:** Data collection, Approval of the version of the manuscript to be published. **Yali Pan:** Task design, Data collection, Approval of the version of the manuscript to be published. **Zheng Tan:** Data curation, Formal analysis, Approval of the version of the manuscript to be published. **Ruobing Liu:** Data collection, Revising the manuscript critically for important intellectual content, Approval of the version of the manuscript to be published. **Xueyuan Wang:** Data collection, Data curation, Approval of the version of the manuscript to be published. **Liankun Ren:** Data collection, Writing - original draft, Approval of the version of the manuscript to be published. **Liang Wang:** Conceptualization, Funding acquisition, Data curation, Formal analysis, Writing – original draft, revising the manuscript critically for important intellectual content, Approval of the version of the manuscript to be published.

Anterior thalamic stimulation improves working memory precision judgments

Jiali Liu[1,2#], Tao Yu[3,4#], Jinfeng Wu[1,2], Yali Pan[1], Zheng Tan[1,2], Ruobing Liu[1,2], Xueyuan Wang[3,4], Liankun Ren[3,4], Liang Wang[1,2*]

[1]CAS Key Laboratory of Mental Health, Institute of Psychology, Beijing, China.

[2]Department of Psychology, University of Chinese Academy of Sciences, Beijing, China.

[3]Beijing Institute of Functional Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, China

[4]Comprehensive Epilepsy Center of Beijing, The Beijing Key Laboratory of Neuromodulation, Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China

[#]these authors have equal contribution

*Correspondence: Liang Wang, CAS Key Lab of Mental Health, Institute of Psychology, 16 Lincui Rd., Chaoyang District, Beijing 100101, China. Tel: +86-10-64888632, Fax: +86-10-64872070, Email: lwang@psych.ac.cn

Abstract:

Background: The anterior nucleus of thalamus (ANT) has been suggested as an extended hippocampal system. The circuit of ANT and hippocampus has been widely demonstrated to be associated with memory function. Both lesions to each region and disrupting inter-regional information flow can induce working memory impairment. However, the role of this circuit in working memory precision remains unknown.

Objective: To test the role of the hippocampal-anterior thalamic pathway in working memory precision, we delivered intracranially electrical stimulation to the ANT. We hypothesize that ANT stimulation can improve working memory precision.

Methods: Presurgical epilepsy patients with depth electrodes in ANT and hippocampus were recruited to perform a color-recall working memory task. Participants were instructed to point out the color they were supposed to recall by clicking a point on the color wheel, while the intracranial EEG data were synchronously recorded when participants performed the task. For randomly selected half trials, a bipolar electrical stimulation was delivered to the ANT electrodes.

Results: We found that compared to non-stimulation trials, working memory precision judgements were significantly improved for stimulation trials. ANT electrical stimulation significantly increased spectral power of gamma (30-100Hz) oscillations and decreased interictal epileptiform discharges (IED) in the hippocampus. Moreover, the increased gamma power during the pre-stimulus and retrieval period predicted the improvement of working memory precision judgements.

Conclusion: ANT electrical stimulation can improve working memory precision

judgements and modulate hippocampal gamma activity, providing direct evidence on the role of the human hippocampal-anterior thalamic axis in working memory precision.

Keywords: anterior nucleus of thalamus, electrical stimulation, hippocampus, neural oscillations, working memory precision

Highlight:

- Electrical stimulation to ANT induced the improvement of working memory precision.
- Electrical stimulation to ANT increased gamma activity and decreased IED in the hippocampus.
- Increased post-stimulation gamma predicted the improvement of working memory precision.

Introduction

Working memory is a critical cognitive function[1] in supporting a lot of daily behavior including learning[2], decision making[3], and language comprehension[4]. Recent studies suggest that the hippocampus was involved in working memory[5-8].According to the multiplexing buffer model, working memory contents are represented by neural assemblies synchronized in gamma oscillations locked to specific phases of low frequency oscillations[9-11]. Consistent with this, several studies have found increased hippocampal gamma activity with working memory load [6, 7] and prominent theta-gamma coupling in the hippocampus when multiple items are retained[5]. A rodent study reported that successful working memory was linked to synchronized gamma oscillations within hippocampal formation[8]. Furthermore, human intracranial EEG study revealed that hippocampal gamma power during memory retrieval was predictive of memory precision[12].

With dense and reciprocal connections with the hippocampus[13-15], and its involvement in cognitive function[15-17], the anterior nucleus of thalamus (ANT) has been suggested as an extended hippocampal system[18-20]. A rodent study found that disrupting information flow between the hippocampal and ANT impaired spatial working memory performance[21]. Electrical stimulation directly targeted to the hippocampus can disrupt memory performance[22, 23]. Given the evidence that stimulating a critical node within a functional network may modulate the network function[24], targeting hippocampal afferent projections may be a more efficient strategy to drive the downstream structure in order to modulate memory

performance[25]. Thus, it is possible to modulate working memory performance by electrically stimulating the ANT.

The current study was to examine whether directly electrical stimulation of ANT can modulate working memory precision. A classic color recall paradigm[26, 27] was performed by drug-resistant epileptic patients with implanted depth electrodes, while a bipolar electrical stimulation was delivered to the ANT electrodes for a half of trials. Given the evidence that extensive functional and anatomy connections between the hippocampus and ANT and the hippocampus also plays a role in working memory, we hypothesized that ANT electrical stimulation may improve working memory precision judgements.

Materials and Methods

Participants

Eight patients with medically refractory temporal lobe epilepsy who were stereotactically implanted the stereo-electroencephalography (SEEG) depth electrodes to identify epileptogenic zones at Xuanwu hospital were recruited in the current study. Demographic information for each patient was shown in Table 1. All patients reported normal or corrected to normal acuity and normal color vision. Informed consent was obtained from all subjects and study procedures were approved by the ethical committee of Xuanwu Hospital, Capital Medical University.

Electrode Localization

Postoperative CT was co-registered to the preoperative MRI using FreeSurfer Software Suite[28] (http://surfer.nmr.mgh.harvard.edu) and FMRIB Software

Library(https://fsl.fmrib.ox.ac.uk)[29]. The implanted electrodes were reconstructed using the stereotactic localization software[30]. Then all electrodes were mapped onto a standard MNI space. All hippocampal contacts (56 contacts from 8 patients, red circles) in the MNI space were visualized using BrainNet viewer[31].

Electrophysiological recordings and data preprocessing

Intracranial EEG data were recorded by Blackrock Neuroport recording system during the experiment, with a sample rate at 2000 Hz. Artifact periods were identified by visual inspection and rejected from the raw signals. Bipolar re-reference was employed to reduce volume conduction as well as confounding interactions between neighboring contacts. The resultant data were broken into event-related epochs for further analysis.

Electrical stimulation

Electrical stimulation was delivered extra operatively by an external stimulator (CereStim R96, Blackrock Microsystems) while the participants performed the task. The stimulation was entered to the paired neighbor contacts in the ANT using biphasic rectangular pulses with a width of 300 μs and an amplitude of 0.2mA at the frequency of 50Hz (Fig. 1B-C). Pat2 receives 50Hz stimulation at the amplitude of 0.5mA (Table 1).

Experimental paradigm

The working memory task was presented on a 14-in laptop monitor at a viewing distance of about 60 cm with a grey background. A trial started with the display of a white fixation cross (0.3°) on the center of the screen, lasting for 4.2 - 5.2 s (Fig. 1A).

Two colored squares (1.5° × 1.5°) were displayed centrally and sequentially, each of which lasted for 0.3 s and was followed by an interval of 0.4-0.5 s in which only the fixation cross was showed centrally. The two colors were chosen at random from nine pre-selected colors, each of which was spaced at least 40 degrees on a color wheel comprising a circularly gradient subset of colors. After that, a cued Arabic numeral (1 or 2) was evenly shown for 0.55 s, indicating which color to be recalled afterwards. The cue was followed by another interval of 2.5-3 s only with the fixation cross. Then a color wheel was displayed and consisted of continuous colors (a thick of 1.5° and a radius of 9.5°). Participants were instructed to point out the color they were supposed to recall by using a mouse to click a point on the color wheel. To eliminate the contribution of spatial memory, the color wheel rotated randomly across trials. One second electrical stimulation were implemented in randomly selected trials across all 10 blocks (90 trials for stimulation trials, 90 trials for non-stimulation trials). Each block was composed of 18 trials and the participants can rest during the interval of blocks. The first and last 4 trials (8trials) from the whole 180 trials that did not contain stimulation. Pre-stimulus statement is important for the subsequent task, as recent studies suggested[32-34]. Previous studies applying stimulation during task generally disrupt memory[22-24]. Exogenous stimulation might disrupt the ongoing organized cognitive activities inside the brain. Multiple studies have shown that pre-stimulus neural activity is important for the subsequent task[32-36]. Therefore, electrical stimulation was applied beginning 2.2-2.7 s before the first color square onset trying to modulate the mental state in the pre-stimulus, as referred to the recent

study[25]. The subjects were not informed which trials were sham and which contained stimulation and they also can't report the occurrence of stimulation. Before the formal experiment, we initially tested the used parameter of electrical stimulation. We asked the patients whether they felt any differences when electrical stimulation was silently delivered or not. None of the patients reported they feel anything different when electrical stimulation was delivered.

Data processing and statistical analysis

Working memory precision

We estimated the precision of working memory based on the Swap model in which three responses were measured: target response when participants correctly reported the color of the probed item with some variability, non-target response when subjects mistakenly reported the color that was not supposed to recall (e.g., though the second color was cued, the first color was recalled) and guessing response for the probe item completely not in memory[37]. Both target responses and non-target responses fit to a Von Mises distribution centered on the color value of probed and misreported item, respectively, with the same standard deviation since target and non-target colors will on average be stored with the same precision[37]. The guessing response was assumed to be a uniform distribution because subjects may response randomly when no color information was memorized (Fig. 1D). The model can be described in the equation：

$$p(\hat{\theta}) = (1-\gamma-\beta)\phi_\sigma(\hat{\theta}-\theta) + \gamma\frac{1}{2\pi} + \beta\frac{1}{m}\sum_{i}^{m}\phi_\sigma(\hat{\theta}-\theta_i)$$

where $\hat{\theta}$ is the reported color value (in radians), θ is the target color value, and θ_i is the non-target color value. γ is the proportion of trials on which the subject responds at random, and β is the probability of misremembering the target location. ϕ_σ denotes the Von Mises distribution with mean of zero and standard deviation (SD). The SD of the Von Mises distribution reflects the overall precision of responses, which we referred as Recall SD in the following. For each patient, we first used the Bays' lab toolbox to obtain an estimation of concentration parameter (K)[37]. K was further converted to the circular standard deviation of the Von Mises distribution with the function k2sd. (https://bayslab.com/code.php).

Oscillatory power

We calculate the power prior stimulus onset as follows. We created the sham stimulation time point (2.2-2.7 s before the first color square) for trials without stimulation according to the electrical stimulation onset in trials with stimulation. The sham stimulation had the same time window as the true stimulation. We measured oscillatory power in the LFP signals with Morlet wavelets (wave number = 5) at 40 log-spaced frequencies between 1 and 200 Hz using Fieldtrip toolbox [38]. The power (P) per frequency at each time point was log transformed and corrected to the averaged baseline power (P0) across all trials (-1.5 to -0.5 s prior to electrical stimulation onset or sham electrical stimulation onset) and time 10 to obtain the normalized power (dB) (i.e., 10×log10(P/P0)). Gamma power (30-100Hz) was measured in 0.8 s time window

(i.e., 0.2 s to 1 s after stimulation offset for trials with stimulation, 0.2 s to 1 s after sham stimulation offset for trials without stimulation).

We further examined the hippocampus activity during the first encoding, the second encoding, retrieval. The preprocessed hippocampal data were grouped into event-related epochs. We then did time-frequency decomposition and baseline correction exactly the same way as above. The baseline correction time window was -1.5 to -0.5 s prior to electrical stimulation onset for trials with stimulation, -1.5 to -0.5 s prior to sham electrical stimulation onset for trials without stimulation. Gamma power (30-100Hz) was extracted for the first encoding (i.e., 0.25 to 0.7 s after first color onset), the second encoding (i.e., 0.25 to 0.7 s after second color onset), retrieval (i.e., 0.5 to 1.5 s after the cue onset). The start of the encoding window was based on the finding that stimulus-evoked activity was shown to emerge in the hippocampus 0.25 s after external stimulus onset[12, 39, 40]. We chose the time window of retrieval according to a recent study indicating that memory retrieval happened between 0.5 s and 1.5 s after the cue presentation[41].

Interictal epileptiform discharges analysis

Abnormal electrical activity during interictal intervals, i.e., interictal epileptiform discharges (IED), was found in the hippocampus for patients with temporal lobe epilepsy[42] which can impair memory function[43, 44]. In the current study, an automated detection algorithm developed in a previous study[45] was used to identify IEDs for all patients. In brief, the preprocessed data were downsampled to 200 Hz, then band-pass filtered from10 Hz to 60 Hz. Instantaneous envelope of each channel

was obtained by calculating the absolute value of the Hilbert transform of the filtered data. The signal envelope was segmented using sliding windows with a width of 5 s and an overlap of 80%. The time varying threshold of k×(Mode + Median) was used to detect IED, where k was 5 in this study and Mode and Median was obtained through a maximal likelihood estimation of a log-normal statistical distribution of the signal envelope in each segment. Each channel had its own envelope and its own threshold curve now. Local maxima at intersections between envelope and threshold curves were marked as detected IEDs. Originally, the performance of the automated detector performance was evaluated by experienced neurophysiologists which showed high detective sensitivity and low false positive rate[45]. To eschew the possibility that the stimulation artifacts (in stim trials) affected the variability of LFP signals, which may consequently reduce the sensitivity of IED detection. We removed the instantaneous envelope when electrical stimulation was implemented. The removed time window was from 0.2 s before stimulation onset to 0.2 s after stimulation offset. In the current study, to examine the effect of ANT stimulation to the occurrence rate of hippocampal IEDs during the working memory task, we detected IED during the entire recording. After that, the number of IEDs detected from the first color square onset until the response action were summed up and then divided by the total time length to calculate the IED rate (count/sec). Afterwards, the IED rate was compared between trials with and without stimulation.

Statistical analysis

Statistical analysis was processed using custom scripts combined with open source toolboxes developed in MATLAB (MathWorks, Natick, MA, USA). Wilcoxon signed-rank test was performed to measure the effect of stimulation and difference in memory precision of the probed color. The comparison of gamma power and IED rate of the hippocampus between electrical stimulation and non-stimulation were carried out using linear mixed-effect (LME) model. The LME model is a sort of regression model in which the variation of a dependent variable is modeled as a function of both fixed and random effects[46]. LME model is very suitable for our dataset because it can be used at a group level, while accounting for repeated measurements from one sample, which occurred as we tested the stimulation effects at the same contact. Furthermore, the LME model can account for the uneven sampling across conditions and groups. This characteristic is important for our analysis because participants had different number of contacts in the hippocampus. The LME model was defined as follows:

$$Y \sim condition + (1|subject) + (1|subject:electrode)$$

The condition was fixed effect variable, while subject and electrode were random effect variable. We compared gamma power (Y) between trials with and without electrical stimulation during the pre-stimulus fixation, the first encoding, the second encoding, retrieval and the trial offset period separately. The condition referred to the trial type (trials with stimulation and trials without stimulation). To examine the change of IED rate, the condition was trials with and without stimulation, while Y

was IED rate under the corresponding condition. The LME model was implemented using the *fitlme* function in MATLAB. The correlation between the changed electrophysiological activity (i.e., gamma power/IED with electrical stimulation - gamma power/IED without electrical stimulation) and precision change (i.e., SD with electrical stimulation - SD without electrical stimulation) was measured by Spearman correlation.

Results

Electrical stimulation enhanced working memory precision judgements

For each subject, the recall SD calculated by fitting the error distributions using the Swap model, in which smaller recall SD indicated better memory precision[37] (Fig 1D). To determine the behavioral effects of stimulation, we compared recall SD between trials in which subjects did and did not receive stimulation using Wilcoxon signed-rank test. We found that electrical stimulation significantly improved memory performance ($z = 2.240$, $p = 0.025$) (Fig. 2A). Furthermore, the working memory precision improvements were highly consistent across subjects (7/8) (Fig. 2B). These results indicated that stimulation delivered to the ANT during the pre-encoding fixation can improve working memory precision judgement.

Increased hippocampus gamma activity

Given that the hippocampus has been proposed involving in processing memory

precision[12], we analyzed the neural changes of 56 hippocampal contacts (Fig. 3A) related to ANT stimulation. Recent studies found that electrical stimulation enabled to induce high-frequency activity and that the induced gamma activity was associated with memory performance[47]. In the current study, pre-stimulus gamma power (30-100Hz) in stimulation trials were compared with that in the non-stimulation trials using the LME model. The analysis showed an increased gamma power in the hippocampus after ANT stimulation during pre-stimulus fixation (β = -0.155, $t(110)$ = -3.447 , $p < 0.001$) (Fig. 3B-C). We also found hippocampus gamma power was higher during the first encoding (β = -0.101, $t(110)$ = -2.990, $p = 0.003$, supplementary Fig. 1B), the second encoding (β = -0.101, $t(110)$ = -3.526, $p < 0.001$, supplementary Fig. 1D) and retrieval (β = -0.104, $t(110)$ = -3.471, $p < 0.001$) in the trial with stimulation (Fig. 3F). However, the theta, alpha and beta power were not significant between trials with and without stimulation during different stages (all p values > 0.05, supplementary Fig. 1A-D).

Decreased IED rate in the hippocampus

Considering the subjects recruited in the current study was patients with temporal lobe epilepsy, we further examined whether electrical stimulation improved memory precision by reducing epilepsy discharges. IED was recognized as the biomarker of epileptogenic tissue and hippocampal IED can cause cognitive impairments[42, 43]. We computed IED incidence for each hippocampal contact between trials with and without stimulation. Using the LME model, we found statistically reliable reduction

in IED rate as a result of electrical stimulation (β = 0.010, $t(110)$ = 2.782, p = 0.006) (Fig. 4).

Correlation between electrophysiological activity and behavioral performance

Next, we performed the correlation analysis between electrophysiological activity (gamma power and IED) and behavioral performance. We did not find that hippocampal IED rate change was related to working memory precision change (IED: r = -0.262, p = 0.536). However, the correlation between pre-stimulus hippocampal gamma power change and working memory precision change was significant (*rho* = -0.738, p = 0.046) (Fig. 3D). Further, the increased gamma power during the retrieval period was also correlated with working memory improvement (*rho* = -0.881, p = 0.007 Fig. 3E). The increased gamma power during the first encoding and second encoding was not correlated with working memory improvement (all $p>0.05$).

Discussion

The current study revealed that electrical stimulation targeted to ANT was effective in improving working memory precision. Indeed, we found that ANT stimulation can increase hippocampal gamma power, and decrease IED occurrence rate in the hippocampus. Increased hippocampal gamma power significantly correlated with the working memory precision judgements, which provided the causal role of the hippocampal-anterior thalamic axis in working memory precision.

A large number of studies attempted to improve memory via electrical

stimulation delivered to hippocampus related structures and yielded inconsistent results[22, 23, 25, 48]. The current study applied electrical stimulation to ANT, one of the primary components in the circuit of Papez. The Papez circuit was proposed as the anatomical basis of memory[49]. Researchers has proposed that modulating the neural activity in the Papez circuit can affect hippocampal activity and thus change memory performance. Consistent with this, we found electrical stimulation improved working memory precision, which can be predicted by the increased hippocampal gamma power. Our results supported the growing consensus that direct electrical stimulation can enable to modulate the activity of a distributed network connected to the stimulation site[24, 50]. This inference was line with the perspective from noninvasive stimulation used to investigate global brain network dynamics and organization[51].

We delivered electrical stimulation to ANT, and found stimulation improve working memory precision. Given this result indicates hippocampal-anterior thalamic axis is causally involved, there are two possibilities accounting for working memory precision improvement. First, ANT stimulation itself may improve memory directly as it is a critical component of the extended hippocampal system supporting memory[19, 20]. Furthermore, ANT was reported to play a vital role in memory-guided attention[16, 17, 52]. Moreover, a recent study revealed shared neural mechanisms between attention and working memory[53]. Second, working memory precision was improved by the modulated activity in the hippocampus. ANT is densely connected to the hippocampus[13, 15]. Recent study suggests that it is essential to modulate

cognitive function by stimulating one of connected nodes comprising a functional network[24]. Indeed, we found that ANT stimulation can increase hippocampal gamma power and the increased gamma power was predictive of the improved working memory precision. The hippocampus has been suggested to be involved in working memory processing either when multiple items were maintained or when objects were presented sequentially[5, 54]. Both human and animal studies have shown that working memory is linked to gamma activity in the hippocampus[5, 6, 8]. Thus, the modulated activity in the hippocampus may contribute to working memory improvement.

It was possible that electrical stimulation delivered to ANT may change the patient's mental state by increasing alertness or attention prior to the stimulus input. Multiple studies have shown that pre-stimulus neural activity can explain the trial-by-trial variability in perceptual and cognitive performance[32-35]. Consistent with this, the increased pre-stimulus hippocampal gamma power was correlated with memory improvement. In addition, gamma power during the encoding and retrieval period were also enhanced by electrical stimulation. The increased gamma power during retrieval was also predictive of memory improvement. Our results were consistent with previous study that hippocampus gamma power was necessary for working memory execution[8]. Taken together, it is possible that electrical stimulation delivered to ANT may increase patient's alertness or attention during the pre-stimulus stage and further affect subsequent memory encoding and retrieval.

We also observed that ANT stimulation may suppress hippocampal pathological,

consistent with our previous clinical study[14]. However, the decrease of IED can't predict working memory improvement, although multiple studies have demonstrated that hippocampal IED was associated with memory performance[43, 44, 55]. It is possible that IED may primarily affect long-term memory, while our task is working memory.

There are three limitations in this study. First, the sample size is relatively small. Confirmation of the stimulation effect observed required further investigation by recruiting a large number of participants. Also, this small sample size limited us to further investigate the laterality effect of ANT stimulation. Second, all of the individuals in the present study were patients with drug-resistant epilepsy. Hence generalizing the current results to other groups should be treated with caution. On the other hand, a lot of patients with epilepsy have reported memory deficits and improving memory for them is essentially a therapeutic goal. Third, this study found that ANT stimulation can improve working memory precision in humans. However, it is unknow whether other stimulation parameters such as intensity, duration and stimulation period may also modulate working memory performance. Fourth, it is possible that electrical stimulation delivered to ANT may increase patient's alertness or attention during the pre-stimulus stage and further affect subsequent memory encoding and retrieval. However, in this study we can't determine which stage is more important for the working memory improvement. Future studies may directly test this by delivering electrical stimulation during different stages separately.

Conclusion

This study showed that intracranial electrical stimulation to the anterior nuclear of thalamus can improve working memory precision and increase hippocampal gamma activity. The increased hippocampal gamma activity during pre-stimulus and retrieval was predicted by the subsequent improvement of working memory precision. These results suggest the critical roles of the hippocampal-anterior thalamic axis in working memory precision.

Competing interests: The authors report no competing interests.

Acknowledgements: The authors thank Dr. Weiwei Zhang for advice on color rendering and task design. This study was supported by the National Natural Science Foundation of China (31771255, 81771395, 32020103009), the Strategic Priority Research Program of Chinese Academy of Science (XDB32010300) and CAS Interdisciplinary Innovation Team (JCTD-2018-07).

References

[1] Baddeley A. Working memory. Science 1992;255(5044):556-9. https://doi.org/10.1126/science.1736359.

[2] Janacsek K, Nemeth D. Implicit sequence learning and working memory: correlated or complicated? Cortex 2013;49(8):2001-6. https://doi.org/10.1016/j.cortex.2013.02.012.

[3] Finn PR. Motivation, working memory, and decision making: a cognitive-motivational theory of personality vulnerability to alcoholism. Behav Cogn Neurosci Rev 2002;1(3):183-205. https://doi.org/10.1177/1534582302001003001.

[4] Baddeley A. Working memory and language: an overview. J Commun Disord 2003;36(3):189-208. https://doi.org/10.1016/s0021-9924(03)00019-4.

[5] Axmacher N, Henseler MM, Jensen O, Weinreich I, Elger CE, Fell J. Cross-frequency coupling supports multi-item working memory in the human hippocampus. Proc Natl Acad Sci U S A 2010;107(7):3228-33. https://doi.org/10.1073/pnas.0911531107.

[6] Axmacher N, Mormann F, Fernández G, Cohen MX, Elger CE, Fell J. Sustained neural activity patterns during working memory in the human medial temporal lobe. J Neurosci 2007;27(29):7807-16.
https://doi.org/10.1523/jneurosci.0962-07.2007.
[7] van Vugt MK, Schulze-Bonhage A, Litt B, Brandt A, Kahana MJ. Hippocampal gamma oscillations increase with memory load. J Neurosci 2010;30(7):2694-9.
https://doi.org/10.1523/jneurosci.0567-09.2010.
[8] Yamamoto J, Suh J, Takeuchi D, Tonegawa S. Successful execution of working memory linked to synchronized high-frequency gamma oscillations. Cell 2014;157(4):845-57.
https://doi.org/10.1016/j.cell.2014.04.009.
[9] Jensen O, Lisman JE. Hippocampal sequence-encoding driven by a cortical multi-item working memory buffer. Trends in Neurosciences 2005;28(2):67-72.
https://doi.org/https://doi.org/10.1016/j.tins.2004.12.001.
[10] Lisman John E, Jensen O. The Theta-Gamma Neural Code. Neuron 2013;77(6):1002-16.
https://doi.org/https://doi.org/10.1016/j.neuron.2013.03.007.
[11] Lisman JE, Idiart MA. Storage of 7 +/- 2 short-term memories in oscillatory subcycles. Science 1995;267(5203):1512.
https://doi.org/10.1126/science.7878473.
[12] Stevenson RF, Zheng J, Mnatsakanyan L, Vadera S, Knight RT, Lin JJ, et al. Hippocampal CA1 gamma power predicts the precision of spatial memory judgments. Proc Natl Acad Sci U S A 2018;115(40):10148-53.
https://doi.org/10.1073/pnas.1805724115.
[13] Aggleton JP, O'Mara SM, Vann SD, Wright NF, Tsanov M, Erichsen JT. Hippocampal-anterior thalamic pathways for memory: uncovering a network of direct and indirect actions. Eur J Neurosci 2010;31(12):2292-307.
https://doi.org/10.1111/j.1460-9568.2010.07251.x.
[14] Yu T, Wang X, Li Y, Zhang G, Worrell G, Chauvel P, et al. High-frequency stimulation of anterior nucleus of thalamus desynchronizes epileptic network in humans. Brain 2018;141(9):2631-43.
https://doi.org/10.1093/brain/awy187.
[15] Aggleton JP, Brown MW. Episodic memory, amnesia, and the hippocampal–anterior thalamic axis. Behavioral and Brain Sciences 1999;22(3):425-44.
https://doi.org/10.1017/S0140525X99002034.
[16] Leszczyński M, Staudigl T. Memory-guided attention in the anterior thalamus. Neurosci Biobehav Rev 2016;66:163-5.
https://doi.org/10.1016/j.neubiorev.2016.04.015.
[17] de Bourbon-Teles J, Bentley P, Koshino S, Shah K, Dutta A, Malhotra P, et al. Thalamic control of human attention driven by memory and learning. Curr Biol 2014;24(9):993-9.
https://doi.org/10.1016/j.cub.2014.03.024.
[18] Dalrymple-Alford JC, Harland B, Loukavenko EA, Perry B, Mercer S, Collings DA, et al. Anterior thalamic nuclei lesions and recovery of function: Relevance to cognitive thalamus. Neurosci Biobehav Rev 2015;54:145-60.
https://doi.org/10.1016/j.neubiorev.2014.12.007.
[19] Wolff M, Gibb SJ, Dalrymple-Alford JC. Beyond spatial memory: the anterior thalamus

and memory for the temporal order of a sequence of odor cues. J Neurosci 2006;26(11):2907-13.
https://doi.org/10.1523/jneurosci.5481-05.2006.
[20] Nelson AJD. The anterior thalamic nuclei and cognition: A role beyond space? Neurosci Biobehav Rev 2021;126:1-11.
https://doi.org/10.1016/j.neubiorev.2021.02.047.
[21] Nelson AJD, Kinnavane L, Amin E, O'Mara SM, Aggleton JP. Deconstructing the Direct Reciprocal Hippocampal-Anterior Thalamic Pathways for Spatial Learning. J Neurosci 2020;40(36):6978-90.
https://doi.org/10.1523/jneurosci.0874-20.2020.
[22] Jacobs J, Miller J, Lee SA, Coffey T, Watrous AJ, Sperling MR, et al. Direct Electrical Stimulation of the Human Entorhinal Region and Hippocampus Impairs Memory. Neuron 2016;92(5):983-90.
https://doi.org/10.1016/j.neuron.2016.10.062.
[23] Lacruz ME, Valentín A, Seoane JJ, Morris RG, Selway RP, Alarcón G. Single pulse electrical stimulation of the hippocampus is sufficient to impair human episodic memory. Neuroscience 2010;170(2):623-32.
https://doi.org/10.1016/j.neuroscience.2010.06.042.
[24] Kim K, Schedlbauer A, Rollo M, Karunakaran S, Ekstrom AD, Tandon N. Network-based brain stimulation selectively impairs spatial retrieval. Brain Stimul 2018;11(1):213-21.
https://doi.org/10.1016/j.brs.2017.09.016.
[25] Titiz AS, Hill MRH, Mankin EA, Z MA, Eliashiv D, Tchemodanov N, et al. Theta-burst microstimulation in the human entorhinal area improves memory specificity. Elife 2017;6:e29515.
https://doi.org/10.7554/eLife.29515.
[26] Zhang W, Luck SJ. Discrete fixed-resolution representations in visual working memory. Nature 2008;453(7192):233-5.
https://doi.org/10.1038/nature06860.
[27] Bays PM, Husain M. Dynamic shifts of limited working memory resources in human vision. Science 2008;321(5890):851-4.
https://doi.org/10.1126/science.1158023.
[28] Fischl B. FreeSurfer. Neuroimage 2012;62(2):774-81.
https://doi.org/10.1016/j.neuroimage.2012.01.021.
[29] Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. FSL. Neuroimage 2012;62(2):782-90.
https://doi.org/10.1016/j.neuroimage.2011.09.015.
[30] Qin C, Tan Z, Pan Y, Li Y, Wang L, Ren L, et al. Automatic and Precise Localization and Cortical Labeling of Subdural and Depth Intracranial Electrodes. Front Neuroinform 2017;11:10.
https://doi.org/10.3389/fninf.2017.00010.
[31] Xia M, Wang J, He Y. BrainNet Viewer: a network visualization tool for human brain connectomics. PLoS One 2013;8(7):e68910.
https://doi.org/10.1371/journal.pone.0068910.
[32] Fell J, Ludowig E, Staresina BP, Wagner T, Kranz T, Elger CE, et al. Medial temporal

theta/alpha power enhancement precedes successful memory encoding: evidence based on intracranial EEG. J Neurosci 2011;31(14):5392-7.
https://doi.org/10.1523/jneurosci.3668-10.2011.
[33] Guderian S, Schott BH, Richardson-Klavehn A, Düzel E. Medial temporal theta state before an event predicts episodic encoding success in humans. Proc Natl Acad Sci U S A 2009;106(13):5365-70.
https://doi.org/10.1073/pnas.0900289106.
[34] Sweeney-Reed CM, Zaehle T, Voges J, Schmitt FC, Buentjen L, Kopitzki K, et al. Pre-stimulus thalamic theta power predicts human memory formation. Neuroimage 2016;138:100-8.
https://doi.org/10.1016/j.neuroimage.2016.05.042.
[35] Linkenkaer-Hansen K, Nikulin VV, Palva S, Ilmoniemi RJ, Palva JM. Prestimulus oscillations enhance psychophysical performance in humans. J Neurosci 2004;24(45):10186-90.
https://doi.org/10.1523/jneurosci.2584-04.2004.
[36] Iemi L, Busch NA, Laudini A, Haegens S, Samaha J, Villringer A, et al. Multiple mechanisms link prestimulus neural oscillations to sensory responses. Elife 2019;8:e43620.
https://doi.org/10.7554/eLife.43620.
[37] Bays PM, Catalao RF, Husain M. The precision of visual working memory is set by allocation of a shared resource. J Vis 2009;9(10):7.1-11.
https://doi.org/10.1167/9.10.7.
[38] Oostenveld R, Fries P, Maris E, Schoffelen JM. FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011;2011:156869.
https://doi.org/10.1155/2011/156869.
[39] Mormann F, Fell J, Axmacher N, Weber B, Lehnertz K, Elger CE, et al. Phase/amplitude reset and theta–gamma interaction in the human medial temporal lobe during a continuous word recognition memory task. Hippocampus 2005;15(7):890-900.
https://doi.org/https://doi.org/10.1002/hipo.20117.
[40] Staresina BP, Fell J, Do Lam ATA, Axmacher N, Henson RN. Memory signals are temporally dissociated in and across human hippocampus and perirhinal cortex. Nature Neuroscience 2012;15(8):1167-73.
https://doi.org/10.1038/nn.3154.
[41] Staresina BP, Wimber M. A Neural Chronometry of Memory Recall. Trends Cogn Sci 2019;23(12):1071-85.
https://doi.org/10.1016/j.tics.2019.09.011.
[42] Pillai J, Sperling MR. Interictal EEG and the diagnosis of epilepsy. Epilepsia 2006;47 Suppl 1:14-22.
https://doi.org/10.1111/j.1528-1167.2006.00654.x.
[43] Kleen JK, Scott RC, Holmes GL, Roberts DW, Rundle MM, Testorf M, et al. Hippocampal interictal epileptiform activity disrupts cognition in humans. Neurology 2013;81(1):18-24.
https://doi.org/10.1212/WNL.0b013e318297ee50.
[44] Gelinas JN, Khodagholy D, Thesen T, Devinsky O, Buzsáki G. Interictal epileptiform discharges induce hippocampal-cortical coupling in temporal lobe epilepsy. Nat Med

2016;22(6):641-8.
https://doi.org/10.1038/nm.4084.
[45] Janca R, Jezdik P, Cmejla R, Tomasek M, Worrell GA, Stead M, et al. Detection of interictal epileptiform discharges using signal envelope distribution modelling: application to epileptic and non-epileptic intracranial recordings. Brain Topogr 2015;28(1):172-83.
https://doi.org/10.1007/s10548-014-0379-1.
[46] Baayen RH, Davidson DJ, Bates DM. Mixed-effects modeling with crossed random effects for subjects and items. Journal of Memory and Language 2008;59(4):390-412.
https://doi.org/https://doi.org/10.1016/j.jml.2007.12.005.
[47] Kucewicz MT, Berry BM, Kremen V, Miller LR, Khadjevand F, Ezzyat Y, et al. Electrical Stimulation Modulates High γ Activity and Human Memory Performance. eNeuro 2018;5(1): e0369-17.2018.
https://doi.org/10.1523/eneuro.0369-17.2018.
[48] Ezzyat Y, Kragel JE, Burke JF, Levy DF, Lyalenko A, Wanda P, et al. Direct Brain Stimulation Modulates Encoding States and Memory Performance in Humans. Curr Biol 2017;27(9):1251-8.
https://doi.org/10.1016/j.cub.2017.03.028.
[49] Aggleton JP, Pralus A, Nelson AJ, Hornberger M. Thalamic pathology and memory loss in early Alzheimer's disease: moving the focus from the medial temporal lobe to Papez circuit. Brain 2016;139(7):1877-90.
https://doi.org/10.1093/brain/aww083.
[50]McIntyre CC, Hahn PJ. Network perspectives on the mechanisms of deep brain stimulation. Neurobiol Dis 2010;38(3):329-37.
https://doi.org/10.1016/j.nbd.2009.09.022.
[51] Dayan E, Censor N, Buch ER, Sandrini M, Cohen LG. Noninvasive brain stimulation: from physiology to network dynamics and back. Nat Neurosci 2013;16(7):838-44.
https://doi.org/10.1038/nn.3422.
[52] Wright NF, Vann SD, Aggleton JP, Nelson AJ. A critical role for the anterior thalamus in directing attention to task-relevant stimuli. J Neurosci 2015;35(14):5480-8.
https://doi.org/10.1523/jneurosci.4945-14.2015.
[53] Panichello MF, Buschman TJ. Shared mechanisms underlie the control of working memory and attention. Nature 2021;592(7855):601-5.
https://doi.org/10.1038/s41586-021-03390-w.
[54] Roux F, Uhlhaas PJ. Working memory and neural oscillations: α-γ versus θ-γ codes for distinct WM information? Trends Cogn Sci 2014;18(1):16-25.
https://doi.org/10.1016/j.tics.2013.10.010.
[55] Khan OI, Zhao Q, Miller F, Holmes GL. Interictal spikes in developing rats cause long-standing cognitive deficits. Neurobiol Dis 2010;39(3):362-71.
https://doi.org/10.1016/j.nbd.2010.05.002.

578 **Table 1:** Demographic information and electrical stimulation parameters for each patient.

ID	Age/ Gender	Supposed seizure zone	Stimulation site	Electrodes/ Total contacts	Stimulation current (mA)
Pat1	23/M	Bi-MTL	L-ANT	4/40	0.2
Pat2	18/F	R-MTL	R-ANT	8/124	0.5
Pat3	26/F	R-TL	R-ANT	6/92	0.2
Pat4	29/F	R-MTL	R-ANT	7/123	0.2
Pat5	26/M	Bi-MTL	L-ANT	5/84	0.2
Pat6	35/F	R- MTL	R-ANT	7/99	0.2
Pat7	17/F	R-aTL, Hipp, pTL	R-ANT	8/124	0.2
Pat8	27/M	L-TL	L-ANT	7/112	0.2

579 Pat: patient; F: female; M: male; L: left hemisphere; R: right hemisphere; ANT: anterior nucleus

580 of thalamus; Bi: bilateral hemisphere; aTL: anterior temporal lobe; MTL: medial temporal lobe;

581 TL: temporal lobe; FL: frontal lobe; Hipp: hippocampus; pTL = posterior temporal lobe;

582

583 **Figure legends**

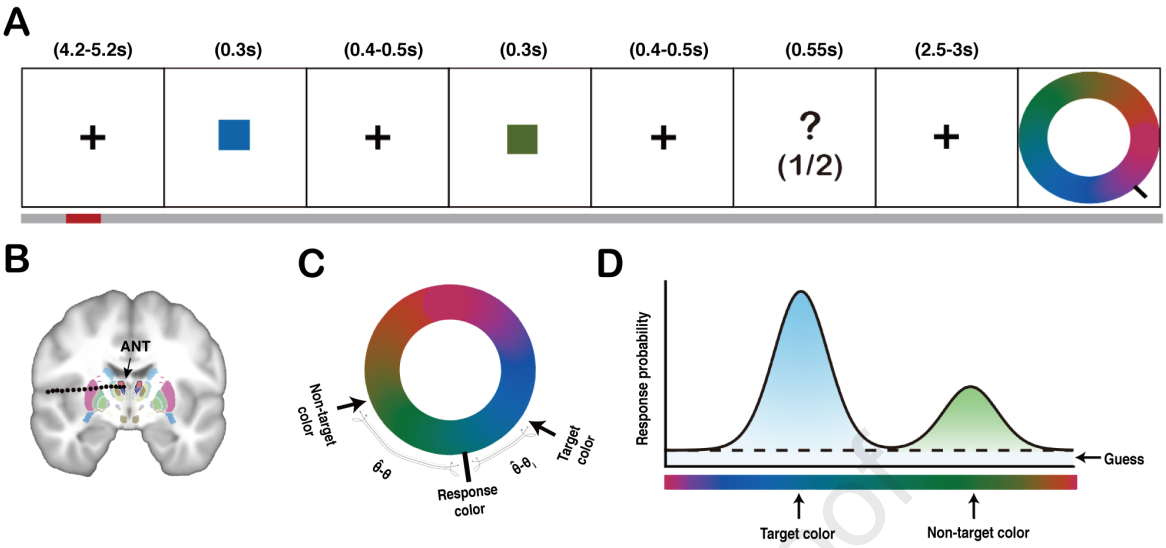
584 **Figure 1.** Task design. (A) Trials started with a white fixation cross on the center of the
585 screen. Two colored squares were displayed sequentially. Then a cued Arabic numeral (1 or
586 2) was evenly and randomly showed, indicating which color to be recalled afterwards. After
587 an interval, participants were instructed to point out the color they were supposed to recall by
588 using a mouse to click a point on the color wheel. Electrical stimulation was applied
589 beginning 2.2–2.7 s before the first color square onset (red bar). (B) An example electrode
590 (black filled circles) is display for Pat 3. The most medial contact is located in the ANT
591 (black arrow). (C) Stimulation patterns. Stimulation was implemented using of biphasic
592 rectangular pulses with a width of 300 μs and an amplitude of 0.2mA (inter-pulse interval of
593 60 μs) at the frequency of 50Hz. (D) Swap model fitting the behavior responses. An
594 exemplary response (black bar) was represented on the color wheel (left). A probabilistic
595 model was used to fit the performance in which there are three possible sources: Von Mises
596 variability centered at target color, another von Mises distribution with the same
597 concentration but centered at nontarget color and a fixed probability of simply guessing at
598 random (right).

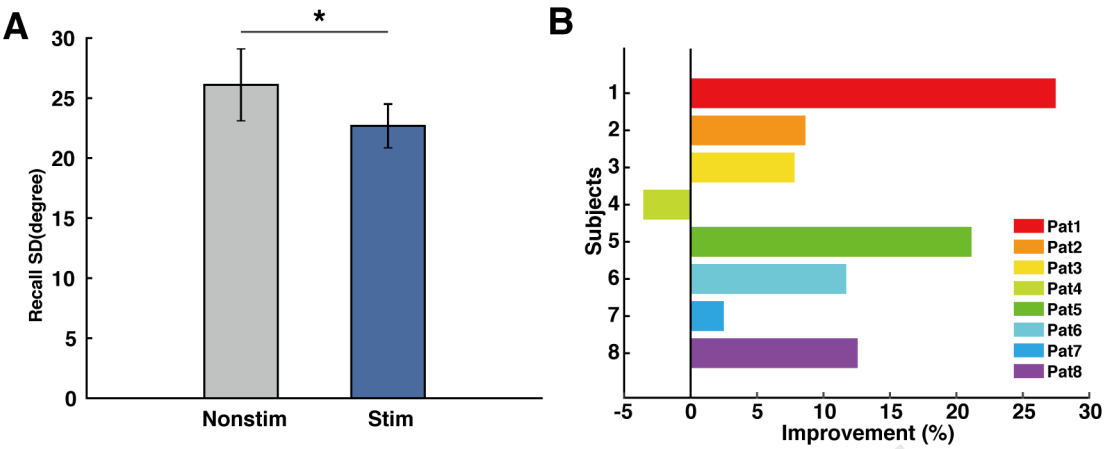
599 **Figure 2.** ANT stimulation enhances working memory precision. (A) Working memory
600 precision (Recall SD) of trials with (Stim) and without stimulation (Nonstim) (z = 2.240, p=
601 0.025). (B) Percentage change in working memory precision for each participant.

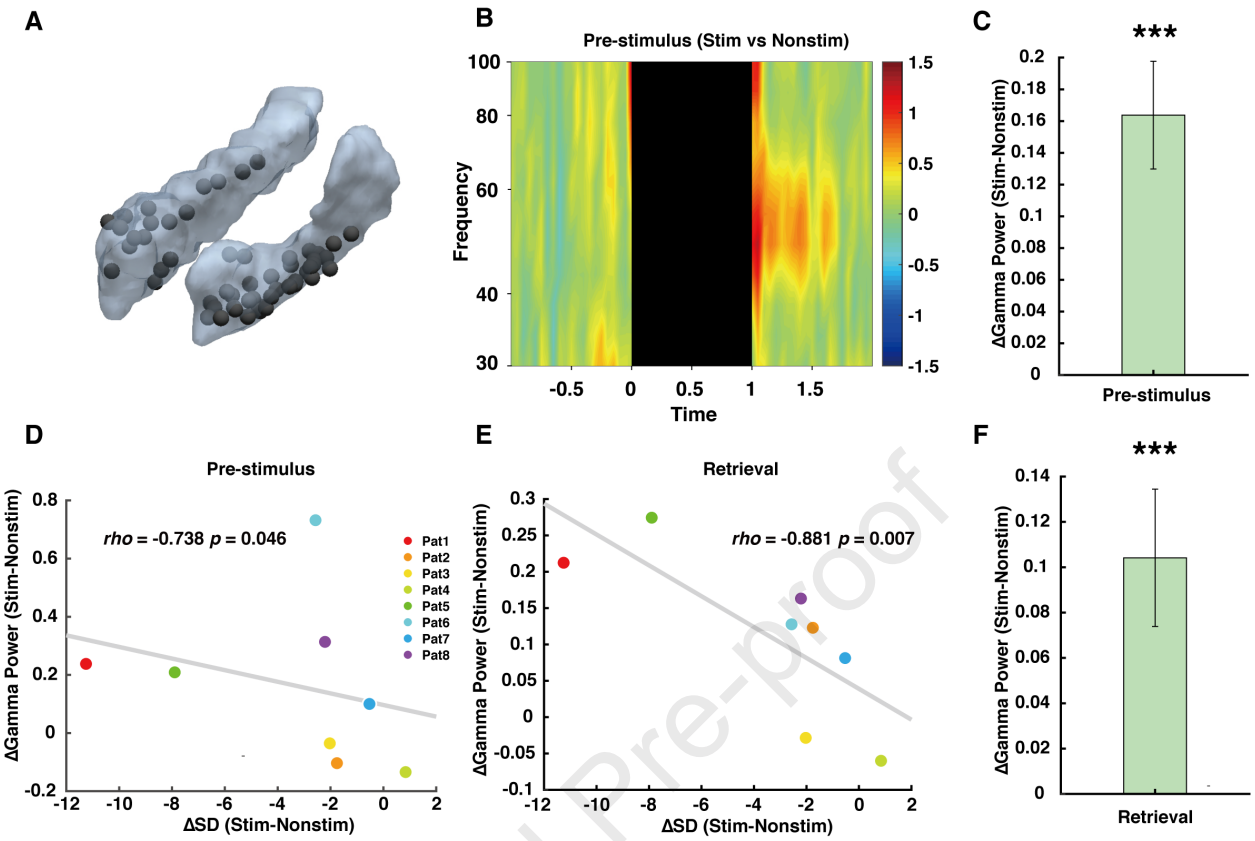
602 **Figure 3**. ANT stimulation increases hippocampal gamma activity. (A) All hippocampal
603 contacts (56 contacts from 8 patients) are delineated in the MNI space. (B) Pre-stimulus gamma

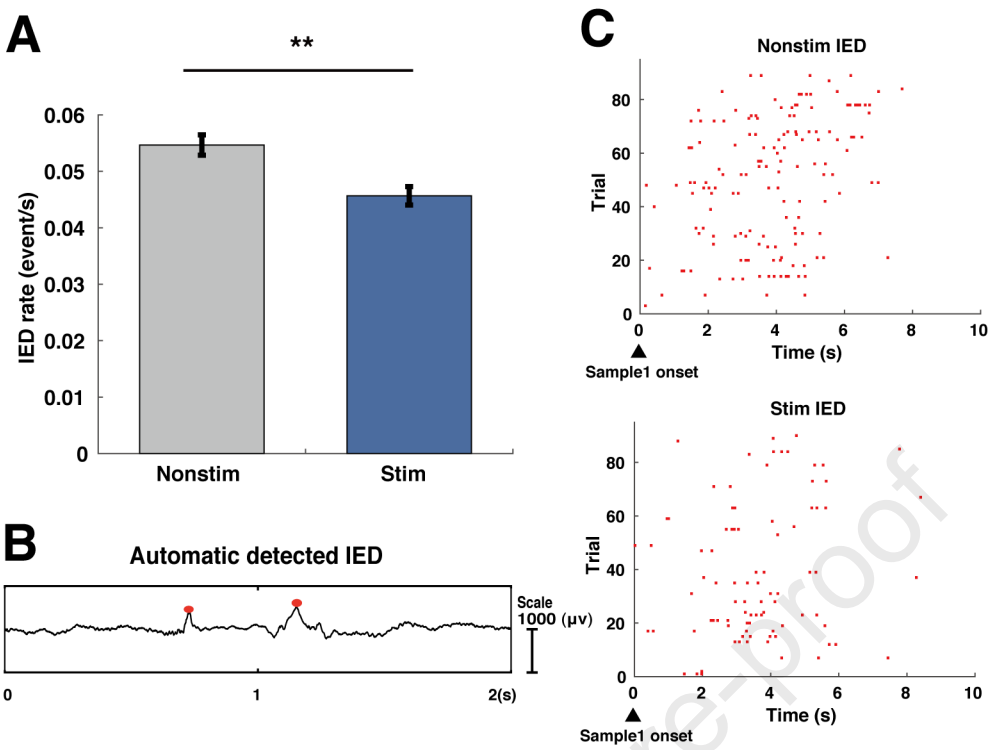
power (trials with stimulation vs trials without stimulation). The blackout (0-1 s) is the electrical stimulation duration. (C) Gamma power (30-100Hz) was significant higher for trials with stimulation than trials during pre-stimulus fixation based on the LME model (β = -0.155, t(110) = -3.447 , p<0.001). (D) Correlation between gamma power change (i.e., gamma power with electrical stimulation - gamma power without electrical stimulation) during pre-stimulus fixation and memory recall SD change (*rho* = -0.738, p = 0.046). (E) Significant correlation between gamma power change during retrieval (i.e., gamma power with electrical stimulation - gamma power without electrical stimulation) and memory recall SD change (i.e., SD with electrical stimulation - SD without electrical stimulation) (*rho* = -0.881, p = 0.007). Each colored circle denotes one patient. (F) Gamma power was significant increased during retrieval in trials with stimulation based on the LME model (β = -0.104, t(110) = -3.471, p < 0.001). ***p <0.001

Figure 4. ANT stimulation decreases hippocampal IED rate. (A) Averaged IED rate from the first color square onset to response action is significantly decreased for trials with electrical stimulation compared with trials without electrical stimulation (β = 0.010, t(110) = 2.782, p = 0.006). (B) Two example IEDs (marked in red circles) using an automatic detection method. (C) Raster plot of detected IEDs across trials without stimulation (upper) and with stimulation (lower) for patient 2. Each vertical red bar denotes an IED detected at a specific time.









Highlight:

Electrical stimulation to ANT induced the improvement of working memory precision.

Electrical stimulation to ANT increased gamma activity and decreased IED in the hippocampus.

Increased post-stimulation gamma predicted the improvement of working memory precision.

Competing interests: The authors report no competing interests.