Low-frequency direct cortical stimulation of left superior frontal gyrus enhances working memory performance

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Abstract

The neural substrates of working memory are spread across prefrontal, parietal and cingulate cortices and are thought to be coordinated through low frequency cortical oscillations in the theta (3 – 8 Hz) and alpha (8 – 12 Hz) frequency bands. While the functional role of many subregions have been elucidated using neuroimaging studies, the role of superior frontal gyrus (SFG) is not yet clear. Here, we combined electrocorticography and direct cortical stimulation in three patients implanted with subdural electrodes to assess if superior frontal gyrus is indeed involved in working memory. We found left SFG exhibited task-related modulation of oscillations in the theta and alpha frequency bands specifically during the encoding epoch. Stimulation at the frequency matched to the endogenous oscillations resulted in reduced reaction times in all three participants. Our results support the causal role of SFG in working memory and suggest that SFG may coordinate working memory through low-frequency oscillations thus bolstering the feasibility of targeting oscillations for restoring cognitive function.

Introduction

Working memory (WM), the ability to flexibly maintain and manipulate information for a short

period of time, forms an important component of cognition. It supports other higher-order cognitive

functions and has been tightly linked to fluid intelligence [1, 2]. Impairment in WM accompanies

many neurological and psychiatric disorders and significantly reduces the quality of life of affected

patients [3-7]. A mechanistic understanding of the causal role of circuit dynamics in WM will open

new therapeutic avenues.

Functional imaging studies have revealed that the neural substrate of WM is spread across

multiple cortical regions including dorsolateral prefrontal cortex, posterior parietal cortex and

anterior cingulate cortex. While early studies have suggested superior frontal gyrus (SFG) to be

involved in working memory [8-10], subsequent studies have often found the middle frontal gyrus

(MFG) to be the key node in working memory [11-15]. However, lesions in SFG have been shown

to result in working memory deficits [16]. In addition, electroencephalography (EEG) and

magnetoencephalography (MEG) studies have shown that oscillations in the theta frequency

band (4 – 8 Hz) observed on fronto-central regions [17-21] coordinate working memory. The

source of these oscillations is thought to be medial prefrontal cortex which includes SFG.

Modulations in WM performance by non-invasive brain stimulation like repetitive transcranial

magnetic stimulation (rTMS) [22, 23] and transcranial alternating current stimulation (tACS) [24-

27] targeting prefrontal cortex also provide indirect evidence for the role of SFG in WM

performance.

Electrocorticography (ECoG) allows identification of activity signatures at temporal scale of a few

milliseconds with a spatial resolution of a few centimeters is an ideal tool to map functions of

cortical regions. Direct cortical stimulation, in which stimulation is applied through ECoG

electrodes ,allows for focal probing of cortex providing additional information through reversible

microlesions [28]. Combined recording and stimulation with implanted electrodes have greatly

contributed to revealing the substrate of long-term memory [29-32]. Low amplitude periodic

stimulation at 10 Hz has been demonstrated to engage ongoing cortical oscillations in a state-

dependent manner and enhance oscillation strength measured by signal power [33]. In this study,

we employed a similar experimental paradigm to delineate the role of SFG on working memory.

We present results from three participants with subdural electrodes over left and right SFG in

whom we assessed the electrophysiological signatures of SFG and applied periodic stimulation

during a verbal working memory task. We found that left SFG exhibited a task-related modulation

in oscillation power and stimulation matched to the frequency of oscillation resulted in an

improvement in working memory performance.

Results

We leveraged the access to ECoG signals in three patients with epilepsy undergoing long term

monitoring in the Epilepsy monitoring unit at the N.C. Neurosciences Hospital, UNC Medical

Center, Chapel Hill. The participants (P1, P2 and P3) had electrodes over frontal, temporal and

parietal regions on both hemispheres (Figure 1A). The participants performed a Sternberg verbal

working memory task that has been previously used in ECoG research [34, 35] (Figure 1B). The

cognitive load, measured by the number of items (English letters) in a list to be held in memory (3,

4, or 5 for P1 and 3 or 5 for P2 and 5 or 7 for P3), was varied randomly for each trial. In participant

P1, we observed an increase in reaction times with increasing cognitive load (list length 3: 824 ±

31 ms, list length 4: 1119 ± 105 ms, list length 5: 1140 ± 78 ms) in the sham trials (Linear model

factor list length: $F_{(2,34)} = 4.864$; $p = 0.014$). In participant P2, who performed a separate baseline

session of the task without stimulation, there was no significant difference between reaction times

for different cognitive loads ($F_{(1,20)} = 0.060$; $p = 0.809$). In participant P3, who also performed a

separate baseline session without stimulation, there was a significant effect of cognitive load

(Linear mixed model factor list length: $F_{(1,45)} = 4.646$; $p = 0.036$). The reaction time for trials with

5 items in the list was lower than trials with 7 items in the list (785 ± 26 ms vs 902 ± 48 ms).

Figure 1. (A) Surface model showing the coverage of electrodes for the three participants. (B) Schematic of a single trial of the working memory task used. The task consisted of 3 epochs – Encoding, Retention and Retrieval. Stimulation was applied through the entire trial. (C) Schematic of the periodic pulse stimulation. Stimulation consisted of train of biphasic pulses 400 µs in duration every 100 ms (P1 and P2) or 200 ms (P3) for 5s.

Oscillations in the theta (3 – 8 Hz) and alpha (8 – 12 Hz) bands have been shown to be modulated during working memory tasks [19, 34, 36]. Spectral analysis revealed oscillations with a peak frequency around 5 Hz in P1 and P3 and 9.5 Hz in P2. To assess if these observed oscillations were modulated by the task, we computed power spectra for baseline, encoding and retention epochs when no stimulation was being delivered (sham trials in P1 and baseline session trials in P2 and P3). Modulation indices were computed relative to baseline epoch. The retrieval epoch was not included in analysis as the epoch may be confounded with action planning and action. We found that electrodes in frontal, temporal and parietal regions exhibited an enhancement of power relative to baseline during sham trials in the theta band (3 – 8 Hz) in P1 and P3 and in alpha band (8 – 10 Hz) in P2 (one sample t-test with FDR correction; p < 0.05). Specifically, electrodes over the left superior frontal gyrus (lSFG) exhibited the task relevant enhancement of oscillation across

all three participants. Spectrograms of sample electrodes over SFG illustrating task-related

modulation are depicted in Figure 2A. Further analysis of data from electrodes over lSFG revealed

that power modulation during the encoding epoch was influenced by list length (Figure 2B; Linear

mixed model factor list length: F(3,370) = 3.417; p = 0.017). Post-hoc analysis revealed a

significant difference between modulation indices from list lengths 3 and 5 in participants P1 and

P2 (Pairwise t-test, p < 0.05). In contrast, power modulation during the retention epoch was not

influence by list length (Linear mixed model factor list length: F(3,228) = 1.029; p = 0.38). Taken

together, these results imply that the oscillations indeed reflect task relevant processing and

specifically contribute to encoding.

Figure 2. (A) Cortical model showing electrodes that exhibited task-related modulation. Red circle denotes
the three electrodes in lSFG whose event related spectral perturbation are plotted. observed in left superior
frontal gyrus electrodes during sham trials for P1 and baseline session trials for P2 and P3 indicating the
modulation of signal in the band 3 – 12 Hz. Hot (red) colors indicate an increase and cold (blue) colors
indicate a decrease in signal power relative to baseline. (B) Modulation indices during encoding epoch
across all lSFG electrodes that exhibited significant task related modulation of signal power. In P1 and P2
there was a significant difference between modulation indices for list length 3 and list length 5.

To test if targeting oscillations that exhibited task-related modulation in SFG, periodic pulse

stimulation was applied between pairs of electrodes over the left SFG. Stimulation consisted of

pulse trains 2 mA in amplitude and 5 seconds in duration (Figure 1C) and the electrode pair being

stimulated was randomly changed for each trial. Stimulation and sham trials were randomly

interleaved and trial initiation was time-locked to stimulation initiation. Stimulation frequency was

10 Hz for P1 (chosen a priori), 9 Hz for P2 (due to technical issues) and 5 Hz for P3. A total of two

different pairs of electrodes in left SFG were stimulated in P1, one pair of electrodes in P2 and P3

(blue electrodes in Figure 1A). During the stimulation session, participants P1, P2 and P3

performed the task in which trials consisted of 3, 4 or 5 items, 3 or 5 items, 5 items respectively.

As a first step, the effect of stimulation on reaction times of participants P1 and P2 was analyzed

using a linear mixed model with fixed factors list length and stimulation condition and participant

as random factor as these participants had trials with 3 and 5 items. While there was no significant

effect of stimulation ($F(2,108) = 1.042$; $p = 0.356$), there was a significant effect of list length (

$F(1,108) = 9.072$; $p = 0.003$) and interaction between list length and stimulation condition (

$F(2,108) = 6.536$; $p = 0.002$). Next analysis was restricted to only trials with 5 items and the

reaction times of all 3 participants in sham trials were compared with that in stimulation trials. The

effect of stimulation was statistically significant (Linear Mixed Model $F(1,97) = 13.414$; $p < 0.001$)

with all participants showing a significant decrease in reaction times (P1: 1140 ± 78 ms vs $852 \pm$

111 ms; P2: 1188 ± 93 ms vs 954 ± 54 ms; P3: 841 ± 48 ms vs 727 ± 27ms; Figure 3A) confirmed

by post-hoc analysis (Pairwise t-test, $p < 0.05$). Analysis of accuracy using chi-squared tests did

not reveal any significant interactions (Figure 3B) suggesting stimulation served to reduce reaction

times without affecting accuracy.

In most studies involving electrical stimulation, artifacts caused by stimulation prevent the analysis

of electrophysiological signals during stimulation. To overcome this, we developed an independent

component analysis (ICA) based method (see Methods and Experimental Procedures).

Stimulation artifacts were sufficiently suppressed (Figure S1) allowing us to study the signals in

the frequency band of interest. Power spectra and modulation indices in the endogenous

oscillation frequency band (3 – 8 Hz in P1 and P3 and 8 – 12 Hz in P2) were computed as

described before. Analysis of modulation indices of the electrodes over lSFG (restricted to trials

with 5 items in the list) across all participants did not reveal any significant effect of stimulation

(Figure 3C; Linear mixed model factor condition $F(1,459) = 0.612$; $p = 0.434$). To explore the

effects of stimulation on other regions that exhibited modulation of task-relevant oscillations, we

ran analysis on individual participant data including list length as a factor. In P1, stimulation

induced a differential change in modulation indices (Linear mixed model factor condition $F(1,672)$

= 20.827; p <0.001, factor list length F(1, 672) = 15.793; p = 0.001, interaction F(1,672) = 10.536;

p = 0.004). Further analysis revealed that there was a significant effect of stimulation in trials with

5 items in list, with stimulation inducing a decrease in modulation indices (Linear mixed model

factor condition F(1,305 = 27.742; p< 0.001). Similarly in P2, stimulation induced a difference

change in modulation indices (Linear mixed model factor condition F(1,1738) = 0.495; p = 0.482,

factor list length F(1, 1738) = 33.190; p < 0.001, interaction F(1,1738) = 11.134; p < 0.001).

Stimulation caused significant decrease in modulation indices in trials with 3 items (Factor

condition F(1,908) = 9.04; p = 0.003) while stimulation caused a trend-level significant increase in

modulation indices in trials with 5 items (Factor condition F(1,830) = 3.13; p = 0.077). There was

no significant effect of stimulation in P3 (Factor condition F(1,215) = 0.005; p = 0.946).

Figure 3. (A) Reaction times in trials with 5 items showing a decrease with stimulation. (B) Accuracy was not affected by stimulation (C) Stimulation did not result in any changes in modulation indices in electrodes over lSFG. (D) Differential effect of stimulation on modulation indices in electrodes that exhibited task-relevant modulation of low frequency oscillations.

Discussion

In this study, we show evidence for the role of superior frontal gyrus (SFG) in working memory

using a combination of ECoG and DCS. Electrodes over left SFG exhibited modulation of cortical

oscillations in the canonical theta and alpha frequency bands. The degree of modulation,

measured using modulation index, depended on the cognitive load, specifically in the encoding

epoch. Stimulation of lSFG with frequency matched to the fundamental frequency or harmonic of

the endogenous oscillations, led to an enhancement in working memory performance. However,

analysis of data obtained during stimulation did not provide any conclusive evidence for

modulation of task-relevant oscillations. Taken together, the results suggest SFG may be an

important node in brain network that coordinates working memory.

While there is an abundance of evidence for the role of middle frontal gyrus (MFG; Brodmann

Area 9/46) in working memory from neuroimaging studies [11, 15, 37, 38], the role of SFG is not

clear. There have been a few neuroimaging studies that suggest SFG may be involved in working

memory [8-10, 39]. SFG gray matter volume has been linked to working memory activation in

intra-parietal sulcus [40]. The strongest evidence for the role of SFG in working memory has come

from a lesion study [16] in which patients with lesions in lSFG exhibited deficits in working memory

involving verbal, spatial and face stimuli. Our results strengthen the evidence for SFG's role in

working memory. However, the proximal location our stimulation targets to MFG may confound

our interpretation of the results. Diffusion tensor tractography has revealed that SFG can be

divided into subregions with strong connectivity to ACC, a key node in cognitive control network

and MFG, a key node in executive control network [41]. As both networks are essential to working

memory processes [42-44], stimulation of SFG may have distributed effects across multiple

regions including MFG. The lack of sufficient coverage of these areas in these three patients

limited our ability to examine this idea. Previous studies have observed oscillations in the range 3

– 15 Hz to be modulated during working memory tasks [34, 45, 46] and the strength of oscillations

to reflect working memory load [19, 35, 36]. Frontal midline theta (FMT) is a commonly observed

oscillatory signature in EEG studies of working memory [18] typically in Fz and neighboring

electrodes in the 10-20 electrode system. The sources of FMT are thought to include lateral PFC

and ACC [47]. The theta oscillations we observed in our study may be related to FMT although we

did not have any scalp electrodes to confirm this. We found task-related modulation specifically in

the encoding period. Analysis of oscillation strength in the retention epoch did not reveal any

significant difference between the cognitive loads. This suggests that SFG may play a role that is

different from that of MFG/IFG which is known to predominantly be active during the retention

epoch [15].

To the best of our knowledge, this is the first study where effects of intracranial stimulation on

working memory and on oscillation strength were investigated. Periodic pulse stimulation of

entorhinal region has been shown to improve performance in a spatial learning task [31].

Concurrently there was an increase in theta-phase resetting. In another study, stimulation with

very weak sinusoidal currents (0.01mA) produced trend level effects in memory performance

although no improvement compared to sham was seen [48]. Impairment of performance has been

more commonly reported than improvement especially for hippocampal stimulation. One study

showed that single pulse stimulation of hippocampus impaired episodic memory [49]. In another

study, stimulation at 50 Hz impaired recognition of specific stimuli depending on whether left or

right hippocampus was stimulated [50]. More recently, stimulation of entorhinal/ hippocampal and

medial temporal regions was shown to affect both verbal and spatial memory [32, 51]. One key

difference between the studies described above and our current study is the frequency of

stimulation used. Often, 50 Hz was chosen as the stimulation frequency as opposed to the low

frequency used in our study. A study that utilized low frequency stimulation showed that

stimulation at 5 Hz resulted in improvement of delayed recall [52]. Another study in which theta

burst stimulation (100 ms trains of 0.1 ms pulses at 200 Hz repeated 5 times per second) of fornix

resulted in improvement of visual-spatial memory [53]. These results suggest that frequency of

stimulation might be crucial to the effects observed. Intracranial stimulation studies have often

focused on episodic memory and stimulation of hippocampus. In contrast, non-invasive stimulation

studies have focused on working memory specifically and target cortical regions such as dlPFC,

PPC, inferior frontal gyrus. Transcranial magnetic stimulation, which produces local

suprathreshold effects, i.e., evoking action potentials like those expected in intracranial

stimulation, has been shown to enhance working memory performance based on the stimulation

frequency, location and specific epoch within the task or before the task [54-61]. It must also be

noted that many studies report impairments of working memory and episodic memory by TMS as

well [62-65]. Transcranial alternating current stimulation, which likely produces more global

subthreshold effects, has been shown to increase performance by targeting dlPFC and PPC [24,

26]. The neurophysiological underpinnings of the effects in these studies are often unclear [27,

60]. Recently, rTMS applied at theta frequency to left intraparietal sulcus was shown to entrain

theta oscillations with a concurrent improvement in auditory working memory [66].

As any scientific study, our study has a set of limitations. First, the results presented here are from

three participants. The major obstacle in our case was the heterogeneity in electrode distribution

as the electrode locations were dictated by clinical needs. Second, although the stimulation

frequency was 10 Hz, oscillations in the frequency band 3 – 8 Hz were significantly modulated

concurrently with changes in WM performance. This discrepancy is hard to reconcile if

entrainment is thought to be the underlying mechanism of interaction between stimulation and

oscillation [67, 68]. However, the interaction between stimulation and an ongoing oscillation has

been found to be nonlinear and the effects depend on the strength of the prevailing oscillations

[33]. When there is a strong ongoing oscillation, stimulation tends to increase the strength of the

endogenous oscillation and only in cases where the strength of the oscillation is low, entrainment

is possible. This state-dependent effect of stimulation is likely the underlying mechanism in the

current study as well. Alternatively, 10 Hz stimulation may have engaged with the strong 5 Hz

oscillation through subharmonic entrainment as predicted in computational models [69].Third, the

present experimental paradigm is limited to applying stimulation during the entire trial due to

technical limitations of the FDA-approved cortical stimulator used in the study. This limitation

precluded us from identifying if stimulation during an epoch within a trial, i.e. encoding or retention,

is more effective than stimulation during the entire trial. Moreover, the frequency of stimulation

was restricted to a few discrete frequencies that did not allow matching of the stimulation

frequency to frequency of endogenous oscillations in P1. Fourth, a limitation of the current study

design is that it used only a single stimulation amplitude and stimulation frequency. Given the

large parameter space, it is prohibitively difficult to try all possible parameters in studies with

limited participant pools as the current study. For P1, we chose stimulation regions based on

previous literature due to technical limitations. A more effective strategy was followed for P2 and

P3 where we identified electrodes that exhibited task-related modulation in low frequency bands

and applied stimulation accordingly. Also, the stimulation used in our study was restricted to a

single site. However, memory processes are distributed across different brain regions and the

most effective strategy would likely involve stimulation of multiple regions to produce more of a

network effect [29, 70] or an adaptive approach using closed-loop stimulation based on the state

of the network [71, 72]

In conclusion, we show that periodic pulse stimulation of cortex through subdural electrodes at low

frequency can enhance working memory. Despite the limitations, the study provides valuable

insights into the feasibility of using oscillations as brain stimulation targets. The importance is

highlighted by the emerging interest in using invasive recordings and electrical stimulation to

understand and alter pathological signatures of brain activity, whether it be neurological disorders,

like epilepsy and Parkinson's disease, or psychiatric disorders, like depression and obsessive-

compulsive disorder. Our results suggest that the same technology could be leveraged to also

address cognitive impairment.

Experimental Procedures

ECoG Data Collection and Direct Cortical Stimulation

All experimental procedures were approved by the Institutional Review Board of University of

North Carolina at Chapel Hill (IRB Number 13-2710) and written informed consent was obtained

from the participant. The participants underwent implantation of intracranial EEG electrodes followed by long-term monitoring at the Epilepsy Monitoring Unit in UNC Neuroscience hospital for surgical resection planning.

Strips of electrodes were implanted over bilateral frontal, temporal and parietal lobes as shown in Figure 1A. Depth electrodes were implanted in bilateral parahippocampal gyri in P1 and strip electrodes were implanted over bilateral occipital lobe in P2 (not shown in figure). The locations of the electrodes were completely dictated by the clinical needs of the participant. The electrodes, 4 mm in diameter (2.5 mm exposed), were made of platinum-iridium alloy and embedded in silicone (Ad-Tech Medical, Racine, Wisconsin, United States). The electrodes in each strip were separated by 10 mm. Signals from electrodes that were over seizure foci (Table 1) were excluded from analysis.

ECoG data from participant P1 was recorded using a 128-channel acquisition system (Aura LTM 64, Grass Technologies, Warwick, Rhode Island, United States) at 800 Hz sampling rate. Electrical stimulation consisted of 5 second train of biphasic pulses, 2 mA in amplitude, 400 µs in duration and 10 Hz in frequency. The pulses were generated by a cortical stimulator (S12x cortical stimulator, Grass Technologies, Warwick, Rhode Island, United States) and applied between pairs of adjacent electrodes (blue electrodes in Figure 1A).

 ECoG data from participants P2 and P3 were recorded using a different 128-channel EEG system (NetAmps 410, Electrical Geodesics Inc, Eugene, Oregon, United States) at 1000 Hz sampling rate. Stimulation was delivered using Cerestim M96 cortical stimulator (Blackrock Microsystems, Salt Lake City, Utah, United States). Stimulation parameters (except frequency) remained the same as in P1 except for the duration which was adjusted to encompass the encoding and retention epochs.

Table 1. Clinical Information of Participants

Participant	Age	Sex	Handedness	Clinical Seizure Focus	Stimulation Frequency	Number of Trials
P1	23	F	R	Bilateral parahippocampal gyri	10 Hz	24 Sham, 13 Stimulation
P2	57	M	R	Bilateral inferior occipital, posterior temporal	9 Hz	27 Sham, 26 Stimulation
P3	26	M	R	Unknown Seizure Focus	5 Hz	30 Sham, 30 Stimulation

Working Memory Task

We adopted a classical Sternberg working memory task previously used in other ECoG studies [34, 35, 73] (Figure 1C). The task consisted of 3 epochs. In the first epoch, lists of 3 to 5 pseudo-randomly chosen letters from the English alphabet were presented sequentially. This was termed the encoding epoch and each alphabet was displayed for 500 ms with 200 ms between each alphabet (the inter-alphabet interval was not present for P2 and P3). Following this, was a retention epoch where a blank screen was presented for 1 second. The final epoch was the retrieval epoch where a single probe (another English alphabet) was shown for 5 seconds and the participants had to indicate if they thought that the probe was present in the list by pressing a specified key on the keyboard. If they did not think the probe was present in the list, they did not have to press any key. The task was programmed in Matlab using Psychtoolbox [74] and presented in a laptop. For the experiment in which P1 participated, triggers from the cortical stimulator were detected by an ethernet DAQ (National instruments, Austin, TX, USA) connected to the task computer and used to initiate trials. Sham trials, in which no electrical pulses were delivered, were initiated using a pulse generator and were randomly interleaved with stimulation trials. For the experimental session in which P2 and P3 participated, triggers were generated within the Psychtoolbox task code and sent to Cerestim through the ethernet DAQ. In sham trials,

no triggers were sent to Cerestim. Stimulation was applied for 5 seconds in P1 and the duration of

encoding and retention epochs in P2 and P3. In P1 electrodes over right SFG and bilateral

temporal cortices were stimulated as well. However, the low number of stimulation trials did not

allow any meaningful analysis to be performed and hence was not included in the study here. In

P2, a pair of electrode over right SFG was stimulated and the results are not included here.

Participants P2 and P3 completed 2 sessions – a baseline session and a stimulation session. The

baseline session did not include any stimulation and consisted of 40 trials of two different list

lengths to assess the baseline performance level as well as determine the parameters for the

stimulation session.

Data Analysis

Data analysis was performed using custom written Matlab scripts (The MathWorks Inc., Natick,

MA, United States). The recording setup consisted of switching circuits designed to protect the

amplifier during stimulation which prevented recording of data from stimulating electrodes. Hence,

data from stimulating electrodes were not included in the analysis.

Stimulation artifacts, present in channels adjacent to stimulated electrodes, were removed using

an independent component analysis (ICA) based approach (Figure S). Since artifacts were

observed as stereotypical waveforms, ICA resulted in components that contained only artifact

waveforms which were then rejected, and the remaining components were used to reconstruct

artifact free signals. We used the infomax algorithm [75] available as a part of EEGLab toolbox

[76] for computing independent components. Following artifact suppression, the signals were low

pass filtered with an FIR filter (cutoff frequency 50 Hz) and re-referenced to common average.

Signal power spectra was computed with a multi-taper fft based approach using Chronux toolbox

[77]. To quantify the change induced by stimulation, modulation index was computed as

$$\textbf{Modulation Index} = \frac{(\overline{S}_e - \overline{S}_b)}{(\overline{S}_e + \overline{S}_b)}$$

Where $\overline{S_e}$ and $\overline{S_b}$ are average power in specified frequency band in specific epoch (task,

encoding or retention) and baseline epoch respectively. The baseline epoch was defined as 5

second interval before the beginning of encoding epoch.

Time-frequency representations were computed by convolving Morlet wavelets with the time

series of each trial. Event related spectral perturbation was calculated as

$$ERSP = 10log_{10}(\frac{S_e}{\overline{S_b}})$$

Where S_e is the spectra at each time point within an epoch and $\overline{S_b}$ is the average power in the

baseline epoch.

Statistics

All statistical analyses were performed using R. Linear mixed effects models were fitted using the

lmertest package [78] which uses Satterthwaite's approximation to degrees of freedom to

determine the F statistics of the fixed effects.

For the effect of list length on reaction times, we fitted a linear model with reaction time as

dependent variable and list length as the factor for each participant separately. For the effect of list

length on modulation indices, we fitted linear mixed model with modulation index as the dependent

variable and list length as the fixed factor and participant and electrodes as nested random

factors. To study the effect of stimulation on reaction time, we fitted a linear mixed model with

reaction time as dependent variable and stimulation as fixed factors and participant as the random

factor. As post hoc analysis we performed a two-sample t-test to compare the difference between

reaction times during sham and stimulation trials for each participant. To study the effect of

stimulation on modulation index, we fitted linear mixed models with modulation index as

dependent variable, stimulation as fixed factor and electrodes and participants as nested random

factors and also with modulation index as dependent variable and list length (3 levels) and

stimulation regions (3 levels – sham, frontal region, temporal region) as fixed factors and

electrodes as a random factor. As post-hoc analysis, we performed paired t-tests.

Extraction of Electrode Location from Neuroimaging Data

3D Slicer [79] was used to analyze and extract electrode locations from CT images obtained after

implantation of subdural electrodes. The post-operative MRI was co-registered to post-operative CT

in Slicer followed by registering to standard MNI atlas [80]. Skull stripping was performed using

ROBEX [81], and the gray matter and white matter were then segmented using ITK-Snap [82]. The

surface model of the MNI atlas brain was generated using Slicer and used for visualization

purposes. The anatomical locations of the electrodes were determined by co-registering the MRI

Image to the MNI Atlas [83], recomputing electrode locations in the MNI space, transforming these

locations to Talairach space, and using the Talairach Client [84] to obtain the label of the gray matter

nearest to the coordinate representing electrode location.

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Supplementary Figures

Figure S1: An example illustrating performance of ICA based artifact suppression algorithm. (A) Raw signal from channels adjacent to stimulation channels before artifact suppression (B) Signal after removal of stimulation artifacts. Visually, the artifact has been reduced to noise level. (C) Trace from a single channel highlighting the suppression of artifact waveform (D) Power spectra computed from the signal shown in (C) before and artifact suppression.

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