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

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A B S T R A C T

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 provide evidence for SFG playing a functional role in working memory and suggest that SFG may coordinate working memory through low-frequency oscillations thus bolstering the feasibility of using intracranial electric stimulation for restoring cognitive function.

1. 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 (Ackerman et al., 2005; Unsworth et al., 2014). Impairment in WM accompanies many neurological and psychiatric disorders and significantly reduces the quality of life of affected patients (Campo et al., 2013; Forbes et al., 2009; Lee and Park, 2005; Snyder, 2013; Uhlhaas and Singer, 2012). 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 (Awh et al., 1995; Braver et al., 1997; Cornette et al., 2001), subsequent studies have often found the middle frontal gyrus (MFG) to be the key node in working memory (Curtis, 2006; Curtis and D'Esposito, 2003; D'Esposito, 2007; Ranganath et al., 2004; Wager and Smith, 2003). However, lesions in SFG have been shown to result in working memory deficits (du Boisgueheneuc et al., 2006). 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 (Gevins et al., 1997; Hsieh and Ranganath, 2014; Jensen et al., 2002; Krause et al., 2000; Tesche and Karhu, 2000) 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) (Mottaghy et al., 2002; Oliveri et al., 2001) and transcranial alternating current stimulation (tACS) (Jausovec et al., 2014; Polania et al., 2012; Violante et al., 2017; Vosskuhl et al., 2015) 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 (Borchers et al., 2012). Combined recording and stimulation

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with implanted electrodes have greatly contributed to revealing the substrate of long-term memory (Kim et al., 2016; Kucewicz et al., 2018; Suthana and Fried, 2014; Suthana et al., 2012). 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 (Alagapan et al., 2016). 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.

2. Material and methods

2.1. 1 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 Fig. 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.

Table 1
Clinical information of participants.

Participant	Age	Sex	Handedness	Clinical Seizure Focus
P1	23	F	R	Bilateral parahippocampal gyri
P2	57	M	R	Bilateral inferior occipital, posterior temporal
P3	26	M	R	Unknown Seizure Focus

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 s 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 Fig. 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 (see Table 2).

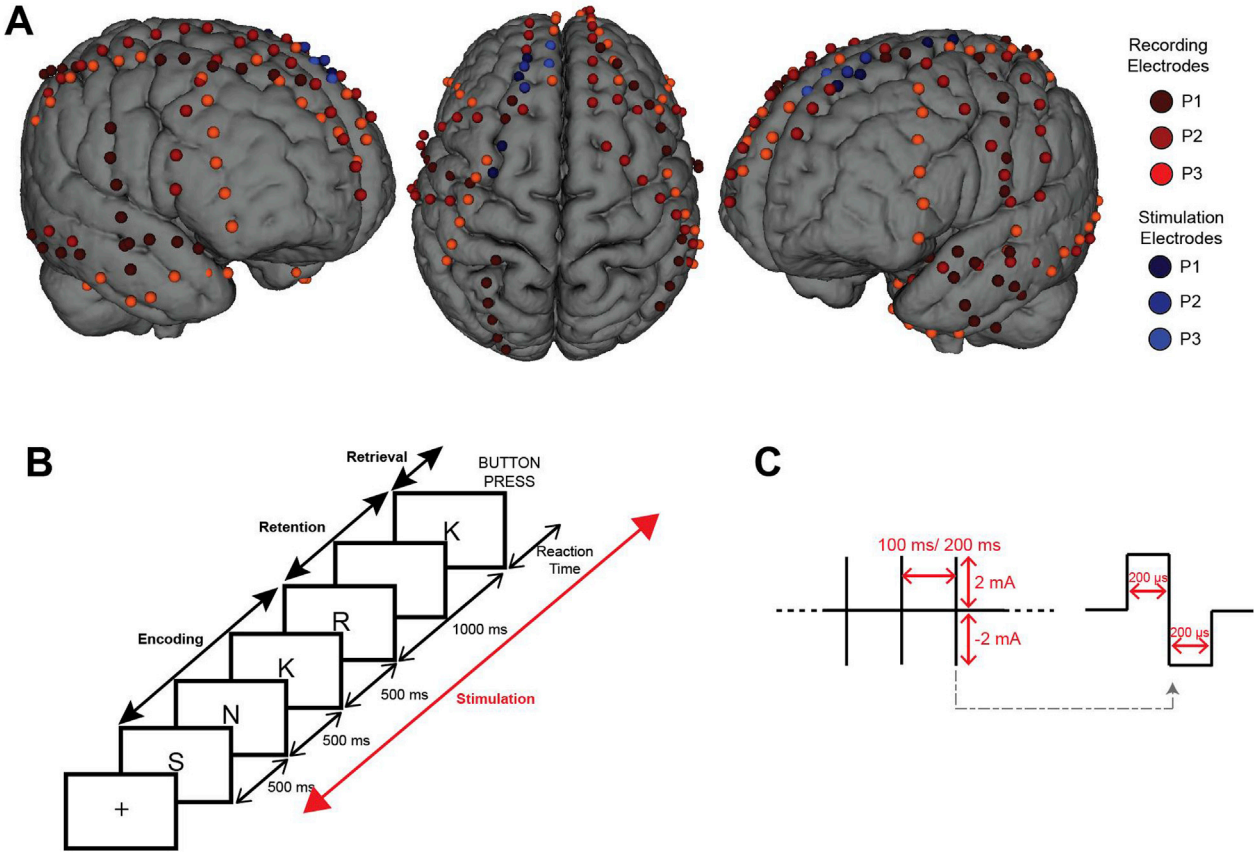

Fig. 1. (A) Surface model showing the coverage of electrodes for the three participants. (B) Schematic of a single trial of the working memory task used. The task consisted of 3 epochs – Encoding, Retention and Retrieval. Stimulation was applied through the entire trial. (C) Schematic of the periodic 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.

Table 2
Experimental Parameters for the three participants.

Participant	Duration (ms)			List Lengths	Response	Stimulation Frequency	Number of Trials		lSFG Electrode Pairs Stimulated
	Encoding	Inter-item	Retention				Sham	Stim	
P1	500	200	1000	3, 4, 5	Only probe present	10 Hz	24	13	2
P2	500	0	1000	3, 5	Both probe present and probe absent	9 Hz	27	26	1
P3	500	0	1000	5, 7	Both probe present and probe absent	5 Hz	30	30	1

Stimulation frequencies were determined based on the peaks in power spectra during the baseline session in P2 and P3. In P1, we chose the stimulation frequency a priori without any knowledge of the endogenous frequency as baseline stimulation session was not possible. The stimulation frequencies did not match the endogenous frequency exactly as power spectral density was determined with a frequency resolution of 1 Hz. Fig. 2B illustrates the power spectral density for the different list lengths and the stimulation frequency.

2.2. Working memory task

We adopted a classical Sternberg working memory task previously used in other ECoG studies (Meltzer et al., 2008; Raghavachari et al., 2001, 2006) (Fig. 1C). The task consisted of 3 epochs. In the first epoch, lists of 3–5 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). The task was initially designed based on Raghavachari et al. (2001) in which the inter-item interval was present. However, to reduce the overall duration of the task, we decided to remove the inter-item interval in subsequent participants. This modification did not significantly deviate from other implementations of the Sternberg task. Following this, was a retention epoch where a blank screen was presented for 1 s. The final epoch was the retrieval epoch where a single probe (another English alphabet) was shown for 5 s 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 different list lengths correspond to different levels of cognitive load that enabled us to identify task-related modulation in terms of electrode locations as well as frequency band. We adjusted the list lengths for each participant according to their performance in a shortened practice version of the task. We chose the list length at which the participant's performance was at or below 80 percent. The task was programmed in Matlab using Psychtoolbox (Brainard, 1997) 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. Sham trials were trials during which no triggers were sent to Cerestim and hence no stimulation was applied. Only flags were sent to the recording system to denote the trial epochs. Stimulation was applied for 5 s 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. In contrast to P2 and P3 where baseline sessions were possible, P1 had a time constraint at the epilepsy monitoring unit due to which it was not possible to acquire baseline data before the stimulation experiment. Therefore, stimulation was applied to two electrode pairs over lSFG, as the exact electrodes which exhibited task-related modulation were not known. To ensure targeting of potential regions, the stimulation electrodes were randomly changed over each trial. In P2 and P3, stimulation was applied to the task-modulated electrodes determined from baseline session.

2.3. 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 S1). 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 (Lee et al., 2000) available as a part of EEGLab toolbox (Delorme and Makeig, 2004) 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 (Bokil et al., 2010). To quantify the change induced by stimulation, modulation index was computed as

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

where $\bar{S}_e$ and $\bar{S}_b$ 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 s 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

$$\boldsymbol{ERSP} = 10\boldsymbol{log}_{10}\left(\frac{\boldsymbol{S}_e}{\bar{\boldsymbol{S}}_b}\right)$$

where $\boldsymbol{S}_e$ is the spectra at each time point within an epoch and $\bar{\boldsymbol{S}}_b$ is the average power in the baseline epoch.

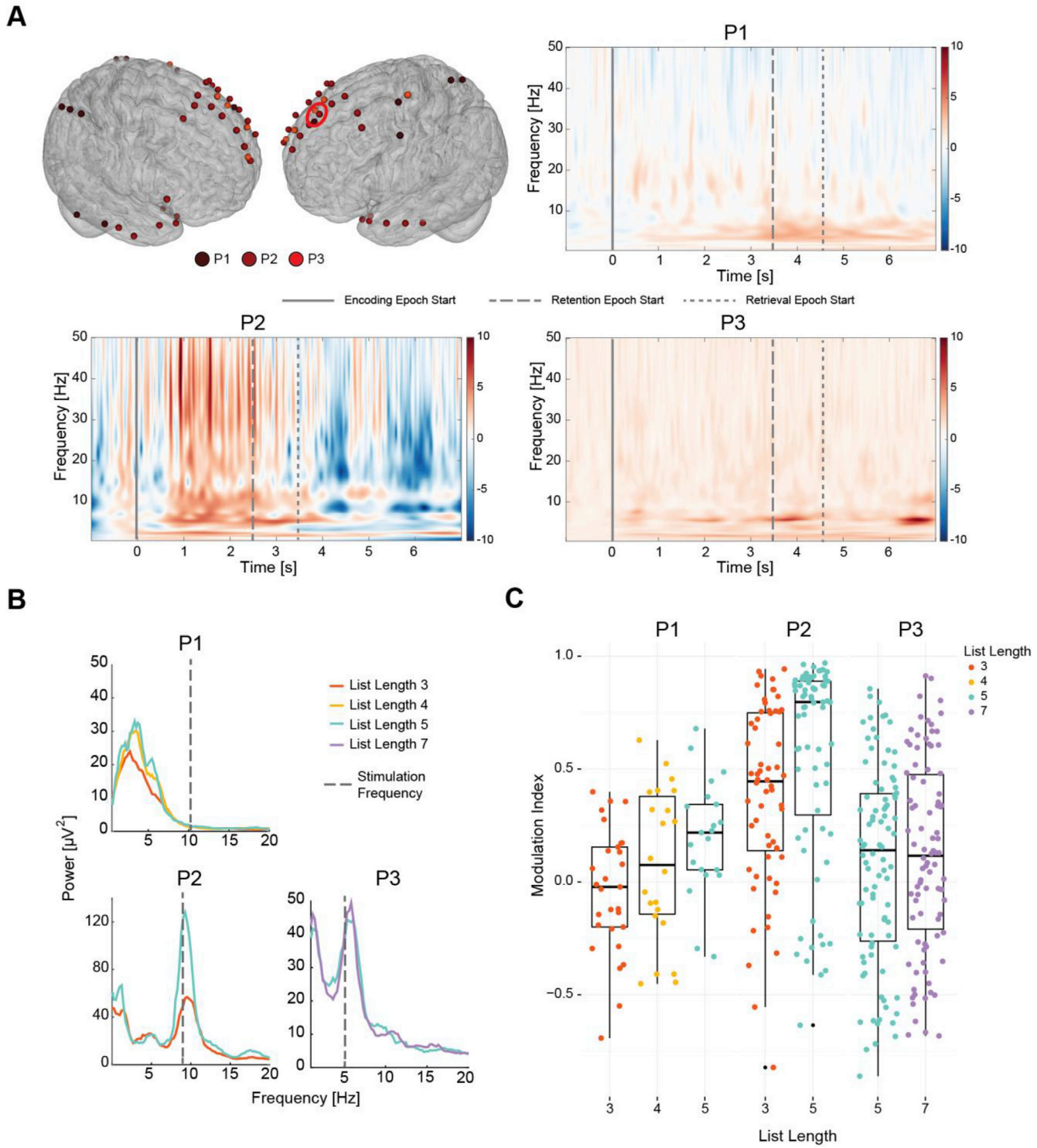

Fig. 2. (A) Cortical model showing electrodes that exhibited task-related modulation. Red circle denotes the three electrodes in lSFG whose event related spectral perturbation are plotted. observed in left superior frontal gyrus electrodes during sham trials for P1 and baseline session trials for P2 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) Power spectral density of lSFG electrodes during baseline session in encoding epoch showing peaks that were used to determine stimulation frequency (dotted gray lines) in P2 and P3. (C) 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.

2.4. Statistics

All statistical analyses were performed using R. Linear mixed effects models were fitted using the lmertest package (Kuznetsova et al., 2017) 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.

2.5. Extraction of electrode location from neuroimaging data

3D Slicer (Fedorov et al., 2012) 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 (Fonov et al., 2009). Skull stripping was performed using ROBEX (Iglesias et al., 2011), and the gray matter and white matter were then segmented using ITK-Snap (Yushkevich et al., 2006). 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 (Fonov et al., 2011), recomputing electrode locations in the MNI space, transforming these locations to Talairach space, and using the Talairach Client (Lancaster et al., 2000) to obtain the label of the gray matter nearest to the coordinate representing electrode location.

3. 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 (Fig. 1A). The participants performed a Sternberg verbal working memory task that has been previously used in ECoG research (Meltzer et al., 2008; Raghavachari et al., 2001) (Fig. 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).

Oscillations in the theta (3–8 Hz) and alpha (8–12 Hz) bands have been shown to be modulated during working memory tasks (Jensen et al., 2002; Jensen and Tesche, 2002; Raghavachari et al., 2001). 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 Fig. 2A. Further analysis of data from electrodes over lSFG revealed that power modulation during the encoding epoch was influenced by list length (Fig. 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 suggest that the oscillations may reflect task relevant processing and specifically contribute to encoding.

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 s in duration (Fig. 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 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 Fig. 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 ± 111 ms; P2: 1188 ± 93 ms vs 954 ± 54 ms; P3: 841 ± 48 ms vs 727 ± 27 ms; Fig. 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 (Fig. 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 (Fig. 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 the list, with stimulation inducing a decrease in modulation indices (Linear mixed model factor condition $F(1305 = 27.742$;

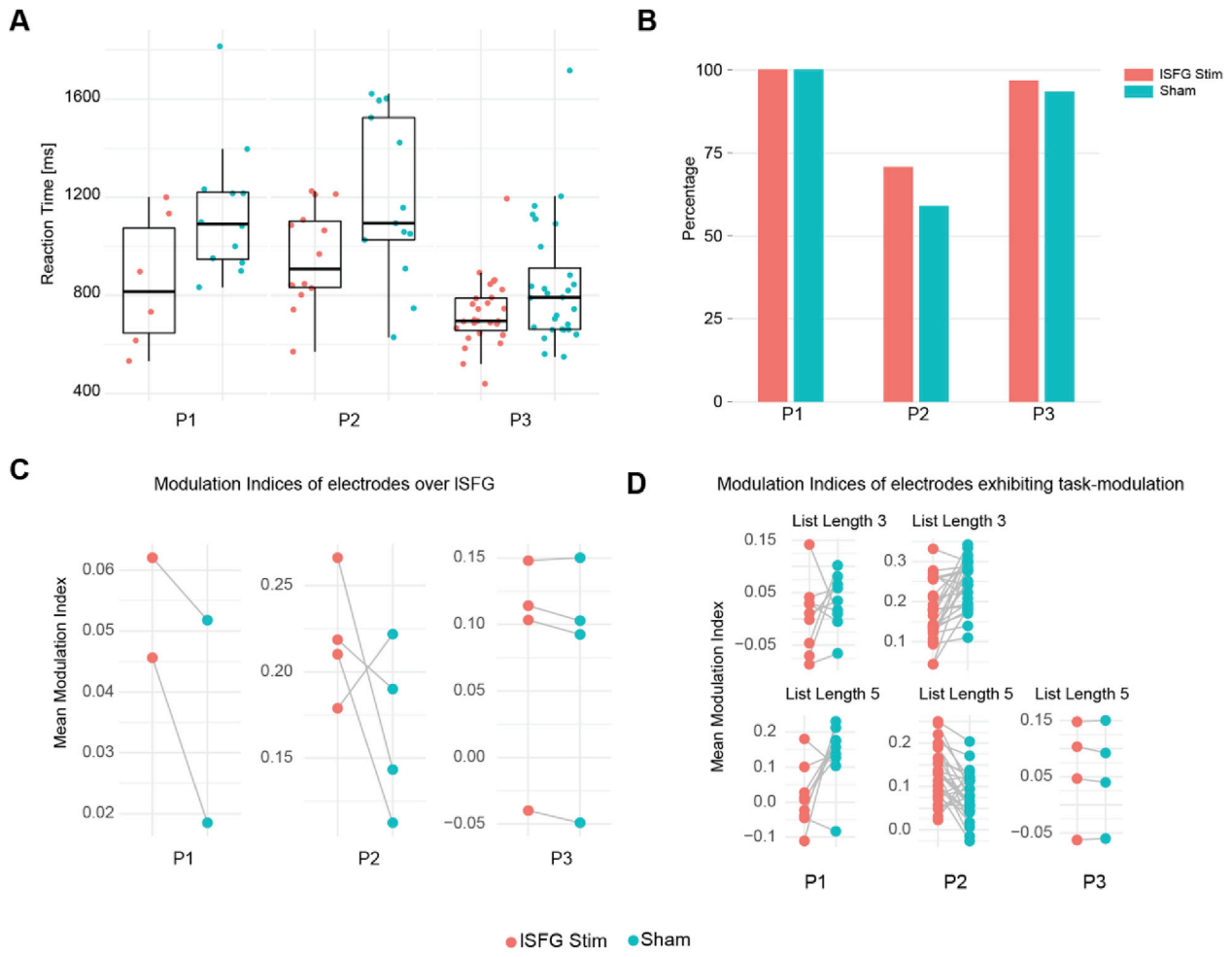

Fig. 3. (A) Reaction times in trials with 5 items showing a decrease with stimulation. (B) Accuracy was not affected by stimulation (C) Stimulation did not result in any changes in modulation indices of spectral power in electrodes over lSFG. (D) Differential effect of stimulation on modulation indices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

$p < 0.001$). 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 $F(1,215) = 0.005$; $p = 0.946$).

4. 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 at frequency close to the peak frequency of the endogenous oscillations led to an enhancement in working memory performance in 2 of the 3 participants. 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.

We were able to perturb lSFG with enhanced spatial resolution compared to other brain stimulation techniques resulting in improvement of working memory performance. To the best of our knowledge, we are the first to demonstrate the effect of stimulation of SFG on working memory performance. While direct cortical stimulation has been successfully used to map brain function from the days of Wilder Penfield, the strength of our approach lies in the ability to sufficiently recover ECoG activity during stimulation with post-hoc processing, allowing us to study the effect of stimulation on neurophysiology. Although our results on the effect of stimulation on oscillation strength have been inconclusive due to many factors, this approach can provide valuable information in studies with sufficient sample sizes.

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 (Curtis and D'Esposito, 2003; D'Esposito and Postle, 2015; Owen et al., 2005; Wager and Smith, 2003), the role of SFG is not clear. There have been a few neuroimaging studies that suggest SFG may be involved in working memory (Awh et al., 1995; Braver et al., 1997; Cornette et al., 2001; Rypma et al., 1999). SFG gray matter volume has been linked to working memory activation in intra-parietal sulcus (Harms et al., 2013). The strongest evidence for the role of SFG in working memory has come from a lesion study (du Boisgueheneuc et al., 2006) 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 (Li et al., 2013). As both networks are essential to working memory processes (Cole and Schneider, 2007; Engle and Kane, 2004; Harding et al., 2015), 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 (Jensen and Lisman, 1998; Raghavachari et al., 2001; Sauseng et al., 2009) and the strength of oscillations to reflect working memory load (Jensen et al., 2002; Jensen and Tesche, 2002; Meltzer et al., 2008). Frontal midline theta (FMT) is a commonly observed oscillatory signature in EEG studies of working memory (Hsieh and Ranganath, 2014) typically in Fz and neighboring electrodes in the 10–20 electrode system. The sources of FMT are thought to include lateral PFC and ACC (Mitchell et al., 2008). 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 (Curtis and D'Esposito, 2003).

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 (Suthana et al., 2012). Concurrently there was an increase in theta-phase resetting. In another study, stimulation with very weak sinusoidal currents (0.01 mA) produced trend level effects in memory performance although no improvement compared to sham was seen (Fell et al., 2013). 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 (Lacruz et al., 2010). In another study, stimulation at 50 Hz impaired recognition of specific stimuli depending on whether left or right hippocampus was stimulated (Coleshill et al., 2004). More recently, stimulation of entorhinal/hippocampal and medial temporal regions was shown to affect both verbal and spatial memory (Jacobs et al., 2016; Kucewicz et al., 2018). 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 (Koubeissi et al., 2013). 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 (Miller et al., 2015). 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 (Bagherzadeh et al., 2016; Blumenfeld et al., 2014; Esslinger et al., 2014; Guse et al., 2013; Hoy et al., 2016; Luber et al., 2007; Yamanaka et al., 2010, 2014). It must also be noted that many studies report impairments of working memory and episodic memory by TMS as well (Gagnon et al., 2010; Mottaghy, 2006; Osaka et al., 2007; Postle et al., 2006). Transcranial alternating current stimulation, which likely produces more global subthreshold effects, has been shown to increase performance by targeting dlPFC and PPC (Polania et al., 2012; Vosskuhl et al., 2015). The neurophysiological underpinnings of the effects in these studies are often unclear (Violante et al., 2017; Yamanaka et al., 2010). Recently, rTMS applied at theta frequency to left intraparietal sulcus was shown to entrain theta oscillations with a concurrent improvement in auditory working memory (Albouy et al., 2017).

One of the advances we put forth in this study is the artifact removal process that allowed us to examine the effect of stimulation on oscillations during stimulation. The use of ICA for artifact removal while already established in EEG studies (Albouy et al., 2017) has not been, to our knowledge, used in studies with intracranial electrical pulse stimulation. The effectiveness of this approach is aided by the experimental setup and stimulation modality used. The setups used in the study had switching (Grass) and buffer circuits (Cerestim96) which ensured the current applied was routed to the electrodes and not to the amplifier. The amplifiers had sufficient input range that no saturation occurred. Also, the current flow in the case of direct cortical stimulation is between two local electrodes with little leakage. Hence the amplitudes of the artifacts are much less than observed in EEG/MEG studies. In addition, we ran ICA on each individual trial in contrast to the whole dataset which allowed better decomposition of artifacts into separate components. All of these factors contributed to the successful artifact removal. However, the approach may also lead to overcorrection of the data leading to underestimation of the effect of stimulation on neurophysiology. It is hard to estimate the extent to which such overcorrection may occur as ground truth is not available. Further experiments using phantoms and analyses of waveform shape in time domain and spectral analysis in frequency domain are needed to fully explain the performance of the algorithm.

We initially hypothesized that stimulation matched in frequency to the frequency of ongoing oscillations should strengthen the oscillations, i.e., increase the spectral power of the oscillations. Previous studies using computational models and noninvasive brain stimulation have suggested the effect of stimulation is maximized when frequency of imposed perturbation is matched to the endogenous frequency (Ali et al., 2013; Vossen et al., 2015). However, we did not find any consistent effect of stimulation modulation index across the three participants. In participant P1, stimulation of lSFG resulted in a decrease of modulation index while in P2, stimulation of lSFG resulted in an increase of modulation index in those electrodes that exhibited task-related modulation. This apparent contradictory result could be partially due to the differences in the anatomical location of the electrodes that are included in the analysis. In P1, electrodes that were modulated (apart from SFG) were mostly over posterior regions like motor cortex, posterior temporal lobe, and posterior parietal lobe while in P2, electrodes that were modulated were over anterior regions like middle frontal gyrus and anterior temporal cortex. In P3 electrodes that were modulated were mostly over SFG except for one electrode which was over motor area. While we observed an increase in mean modulation index in 8 out of the 10 electrodes over lSFG across the 3 participants, statistical analysis did not yield conclusive results, suggesting that the effect of stimulation may be subtler and may require larger samples. An alternate explanation could be that stimulation resulted in activation of regions that are functionally connected to SFG like the middle frontal gyrus that lead to the observed behavioral effect. However, the lack of sufficient coverage over these adjacent regions did not allow us to verify the effect.

Our study suffers from the low sample size limitation that is inherent in single-center studies involving invasive recordings in human. The sample size of three participants limits the ability to generalize across a wider population. In addition, we had to restrict the duration of the experiment. With longer durations of experiment, participants may get tired introducing additional confounds that we sought to avoid. This resulted in fewer trials per condition than that is typically the norm in cognitive tasks used in studies with healthy volunteers. This drawback is to be noted when the results of the study are interpreted. Moreover, owing to the unique nature of the participant sample, there were differences in the task design and stimulation frequencies. The differences in working memory load in baseline session, calibrated according to individual performance, across three participants makes direct comparison

difficult. However, the loads for the results of stimulation presented here were all maintained at 5 items across the three participants thereby reducing the uncertainty. The differences in stimulation frequencies preclude any interpretation of the exact process being modulated that resulted in working memory performance. Our study was motivated with the hypothesis that stimulation matched to the frequency of endogenous oscillations would be the most effective in enhancing oscillations with potential benefits in behavior. Therefore, we targeted functionally relevant oscillations irrespective of frequency. Alpha oscillations are thought to represent inhibition of task-irrelevant regions (Jensen and Mazaheri, 2010) while theta oscillations are thought to represent memory processes including maintenance of serial order (Hsieh and Ranganath, 2014; Roux and Uhlhaas, 2014). Given the evidence for individual differences in memorization strategies used in Sternberg task (Corbin and Marquer, 2009), the oscillations may also represent different strategies the participants used to perform the task. When participants use a rehearsal procedure during encoding and retention, theta oscillation may have been modulated as in participants P1 and P3 in this study. In contrast, participants who use an active maintenance of the verbal information may exhibit an increased alpha oscillation (Khader et al., 2010) as was observed in participant P2. Regardless of the strategy used, stimulation may have served to reinforce these processes resulting in an improvement in performance. Future studies where the strategy used by the participant is controlled for in experimental design will enable answering these questions at a deeper mechanistic level. Apart from this, the specificity of the effects to parameters of stimulation such as frequency and location cannot be determined from the current study as appropriate control frequency or control location was not included in the study design.

The experimental paradigm reported here was 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. Another 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 (Kim et al., 2016, 2018) or an adaptive approach using closed-loop stimulation based on the state of the network (Ezzyat et al., 2017, 2018).

In P1, 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 (Helfrich et al., 2014; Thut et al., 2011). 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 (Alagapan et al., 2016). When there is a strong ongoing oscillation, stimulation does not alter 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 (Li et al., 2017).

The results presented for P1 is from the sham trials as time constraints did not allow a separate baseline session. It is possible the behavior and neurophysiology may be influenced by stimulation trials that happened along with the sham trials. However, the effects of DCS are typically short-lived on the order of a few seconds (Alagapan et al., 2016) and longer stimulation durations are needed to observe longer-lasting effects (Keller et al., 2018). Therefore, we do not expect significant differences between the baseline and sham session.

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.

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Authorship statement

SA, HS, and FF designed the experiments; SA, EH, and HS performed the electrophysiological recordings; SA, CL analyzed the data; and SA, CL, EH, HS, and FF prepared the manuscript.

Conflicts of interest

FF is the lead inventor of IP filed on the topics of noninvasive brain stimulation by UNC. FF is the founder, CSO and majority owner of Pulvinar Neuro LLC. The other authors declare no competing interests.

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Appendix A. Supplementary data

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