Effect of Closed-Loop Direct Electrical Stimulation during Sleep Spindles in Humans

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***Abstract*— Sleep spindles are transient oscillations in the brain related to sleep consolidation and memory. We investigated if brief, localized electrical pulses could perturb spindles on five human patients with intracerebral electrodes implanted for clinical purpose. We used a closed-loop setup to specifically detect spindles and stimulate in real-time during these events. Stimulation latency was 200-400 ms following spindle onset. Analyzing the intracranial electro-encephalographic (iEEG) data both locally and globally, we found, in two of the patients, that single pulse stimulation could stop the spindles locally. Spindles were shorter than those without stimulation and a decrease in power at the same frequency as spindles was observed following stimulation.**

***Clinical Relevance*— This study shows that brief and precise electrical stimulation may be used to modulate oscillatory behavior of the human brain. Applied to sleep spindles, further studies may establish that single pulses applied in a closed-loop manner could be used to modulate memory and could help understand effect of neuromodulation in sleep disruption.**

I. Introduction

Sleep is essential for the development and maintenance of cognition and memory [1,2]. As we sleep, the interactions between different brain networks change, modifying the electrical activity compared to wakefulness. In particular, 0.5–2 s long transient bursts of oscillatory activity between 10 and 16 Hz (sigma band) are observed in electro-encephalographic (EEG) recordings every 3 to 6 seconds: the so-called sleep spindles. Sleep spindles occur throughout the cortex and are involved in memory consolidation [3] and alterations in spindle density seem related to autism [4], schizophrenia [5], sleep disorders [6], and neurodegenerative diseases [7].

Sleep neuromodulation is becoming a growing field of research. Marshall et al. showed that transcranial electrical stimulation at 0.75 Hz during sleep enhanced sleep-specific slow-wave and spindles activity and boosted declarative memory [8]. Several groups have further confirmed these results using non-invasive stimulation techniques targeting slow-wave oscillations and specific memory tasks [9,10]. Beyond slow-wave activity, sleep spindles have also been targeted to improve memory. In particular, a study developed a feedback-controlled system to detect spindles in real time and stimulate with transcranial alternating current stimulation. With their protocol, the authors reported enhancement of both spindle activity and memory [11]. Several recent studies, however, challenged these previous results, reporting that increasing sleep oscillations may not always be sufficient to enhance memory performance [12,13].

Following the growing interest in sleep neuromodulation, we set out to determine if intracranial electrical stimulation could impact some of sleep graphoelements, and sleep-spindles specifically. Altering sleep-spindle duration and characteristics in a controlled, informed fashion may provide a powerful tool in enhancing memory consolidation (e.g. for Alzheimer's disease) or disrupting memory (e.g. for PTSD). Moreover, estimating the effects of electrical stimulation is becoming crucial since there is an ever increasing number of deep brain stimulation and other intracranial systems being developed to treat brain disorders. In the present work, we studied how closed-loop single pulse electrical stimulation (SPES) applied in near real-time alters spindles.

II. METHODS

A. Participants

Five patients participated in the study who had semi-chronic intracerebral depth electrodes implanted as part of their treatment for drug-resistant epilepsy. The studies were led at Massachusetts General Hospital (MGH) or Brigham and Women's Hospital (BWH). Patients voluntarily participated to the study, after giving a fully informed consent according to NIH guidelines as monitored by Partners Institutional Review Board (IRB). Sleep stage was assessed online by visually identifying K-complex and spindles on the scalp EEG. In three patients with offline scalp EEG, N2 stage was later confirmed with a sleep staging algorithm [14]. Table I shows a summary of the closed-loop experiments for each participant.

B. Recording system

Depth electrodes were 8 to 16 platinum/iridium-contacts, 1-2.4mm long and 0.8-1.0 mm diameter (Ad-tech Medical, Racine WI, USA, or PMT, Chanhassen, MN, USA) that were stereotactically placed exclusively for clinical purposes. The intracranial EEG (iEEG) was acquired at 2 kHz sampling rate (Blackrock Microsystems, Salt Lake City, UT, USA), referenced to a scalp contact. Depending on the patient, a total of 100 to 200 channels recorded the brain activity in real-time.

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TABLE I. PARTICIPANTS AND TESTS INFORMATION

	Stim location	Amp (mA)	# DNoS	# DS	# RS	CCEP resp.	Spindle stop
P1	dlPFC	4	64	31	14	No	No
P2	dmPFC	4	25	48	51	Large	---
P3	dmPFC	2	21	30	17	Small	No
		4	21	25	20	Large	Yes
P4	lOFC	1	41	11	10	No	No
		2	41	32	20	Large	No
		4	41	6	4	Large	---
P5	vlPFC	4	57	18	19	Small	No
	dlPFC	4	59	24	22	Large	Yes
		2	57	21	12	No	No
		2	93	22	5	No	No
		6	96	22	12	Large	Yes
		4	93	22	19	Large	Yes

Characteristics of the experiment for the different participants and summary of results. Number of detected and stimulated spindles (DS), detected but not stimulated spindles (DNoS), and random stimulation (RS). Presence or absence of an evoked response to stimulation, i.e. cortico-cortical evoked potential (CCEP). Presence or absence of a spindle early stop as assessed by the computation of power and spindle duration. --- indicates that spindles finished earlier than stim or not enough spindles were detected. Amp: Stimulation amplitude; dlPFC: dorsolateral prefrontal cortex, dmPFC: dorsomedial prefrontal cortex, lOFC: left orbitofrontal cortex, vlPFC: ventrolateral prefrontal cortex.

C. Closed-loop system and spindle detection algorithm

We used a system developed in our lab to perform closed-loop stimulation [15]. Briefly, iEEG data was acquired, band-pass filtered, features were computed and fed into a decision algorithm. For spindle detection, iEEG from one detection channel was acquired, band-pass filtered (11-15 Hz, IIR Butterworth order 2), and power computed (50-100 ms smoothing window). If power exceeded a patient-specific threshold for more than a given duration (150-250 ms), a spindle was detected, and a stimulation pulse was sent. These parameters were patient specific and could be varied depending on real-time observation. Depending on the decision algorithm, stimulation may be triggered (*DetStim* event), or not (*DetNOStim* event, first control). The system also allowed for random interleaved stimulation (*RandomStim*, second control). Eventually, a spindle was detected around 300 to 400 ms after its onset.

The system could also be run offline, using previously acquired data. This setting was used to obtain more *DetNOStim* events with the exact same parameters on iEEG data recorded an hour before or after the tests.

D. Stimulation system and stimulation parameters

We used the Cerestim stimulation system (Blackrock Microsystems, Salt Lake City, UT). Stimulation was applied bipolarly, in two neighboring channels, adjacent to the detection channel. Charge-balanced biphasic pulses lasted 90 us with 53 us interphase interval and 4mA intensity. To understand the effect of stimulation amplitude on the spindles, we varied the intensity (TABLE I). To ensure independent trials, a 2-3 s long refractory period was chosen (i.e. minimal time between two consecutive SPESs).

E. Data pre-processing

Trials extraction: following the closed-loop test, iEEG data from each of the three types of events were extracted for all 100-200 channels. A trial was defined as the 4 seconds for which one *DetStim*, *DetNOStim*, or *RandomStim* event was found. As a convention, the time was set to zero at the time of detection or stimulation (i.e. a trial was in the range [-2 s, 2 s]).

Stimulation artifact removal: for the *DetStim* and *RandomStim* events, the stimulation artifact due to volume conduction (very sharp peaks corresponding to the stimulation occurring) was removed using a Tukey windowed median filter of order 38 [16]. Basically, a median filter was applied to the signal 40 ms around stimulation. Then, the signal in this time-window was replaced by a weighted average of the original signal and the median signal.

Evoked response removal: the signal evoked response contained a wide range of frequencies which could confound detecting the spindle event. To remove the SPES evoked response, the average of the evoked response over the *RandomStim* trials was computed, and it was subtracted from each *DetStim* and *RandomStim* trial.

1-30 Hz band pass filter: The signal was filtered with a bidirectional Butterworth band-pass filter of order 2. The lower frequency was set to 1 Hz to remove possible drifts in the signal. The higher frequency was set to 30 Hz as an intermediate value between the spindles frequency band and possible noise happening at higher frequencies (including 60 Hz noise).

Filtering at the spindles' frequency band: To obtain the signal at the spindles' frequency band, a digital IIR Butterworth filter was used. The pass-band frequency range was 10-16 Hz, and the stop-band frequencies were 8 and 20 Hz respectively (30 dB attenuation). The filter thus exclusively kept the frequency band of interest (10-16 Hz).

F. Features calculation and statistical analysis

Features derived from voltage and power were calculated to assess the influence of SPES. The features were calculated both locally (a few channels around stimulation to assess the local effects) and globally (to observe the spread of the spindles and the global stimulation effects). Unless mentioned otherwise, the baseline period was defined as [-1.5 s to 1 s], far ahead of the event onset. The pre-stimulation period was defined as [-0.35 s to -0.1 s] and the post-stimulation period as [0.1 s to 0.35 s].

Voltage: Voltage was used to assess the presence of spindles. To this end, a very simple offline spindle detector was built using the signal filtered in the spindles' frequency band. For each channel and each trial, a baseline activity was computed in the time window [-1.25 s to -0.75 s] before the detected event. A spindle was defined as any signal with an amplitude higher than 2 standards deviations above the baseline activity (2% of the data, assuming normal distribution of amplitudes). A minimal duration for a spindle was set to 100 ms. Using this detector, we calculated the onsets, offsets, and durations of *DetNOStim* and *DetStim* events.

Power: We performed a time-frequency analysis of power with a Hanning taper, using the Fieldtrip toolbox [17]. The frequency range was [4 Hz 20 Hz] with steps of 1 Hz. To focus on the spindles' frequency band, the power was calculated by computing the square of the voltage amplitude in the sigma-band filtered signal. Power was normalized by the baseline power or by the maximum power across types of events.

Statistics: We used the nonparametric Wilcoxon rank-sum test to compare between stimulation trials and different conditions which does not assume normally distributed data. In the case of time-series related comparisons (power specifically), we used the false discovery rate (FDR) control to account for multiple comparisons [18].

III. RESULTS

For all patients, stimulation happened in the frontal lobe, either in the pre-frontal cortex or the lateral orbito-frontal cortex. For patients P3 and P5, SPES disrupted the spindles. For patients P1 and P4, no particular effect was found. For patient P2, stimulation happened as the spindles were terminating, preventing a reliable conclusion.

A. Local characteristics of spindles

Computing features on the detection channel, the spindles can be observed on the raw voltage, the sigma-band filtered data, and the time-frequency analysis of power (Figure 1). As expected, the spindles were captured in the *DetNOStim*, and *DetStim* events, but not in the *RandomStim* events. Therefore, the featurization was able to successfully capture the spindles which were reflected by an increase in the sigma-band power.

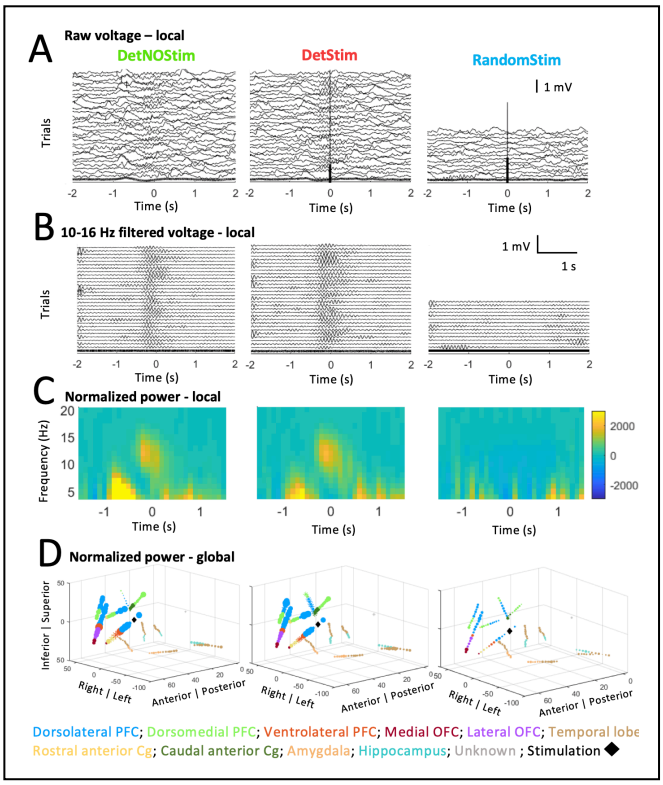

Figure 1. Local evidence of spindles for P1. The first column corresponds to *DetNOStim* events, the second to *DetStim* events, and the third to *RandomStim* events. **A**. Raw voltage on the detection channel. **B**. Filtered signal (10-16 Hz). Spindle activity was clear for *DetNOStim* and *DetStim* events in each trial. **C**. Time-frequency analysis of power normalized with respect to baseline. Power increase before t = 0 s in the 10 - 16 Hz range highlights occurrence of spindle. D. Normalized sigma-band power for each channel before stimulation. The size of the dots is proportional to power and the color is related to brain region. PFC: prefrontal cortex, OFC: orbitofrontal cortex, Cg: cingulate.

B. Global characteristics of spindles

The spread of the spindles in the brain was assessed using the power in the sigma band for all channels. Figure 1.D displays in a 3D plot the median power in all channels in the pre-stim period. Assuming that an increase in power in the sigma band was related to spindle activity, the electrodes with higher power highlight areas most implicated in spindle activity. The comparison with *RandomStim* events shows that the spindles mostly occurred in frontal areas of the cortex. Spindle activity was increased in both hemispheres, particularly in the prefrontal cortex (dlPFC, which was also where stimulation happened, dmPFC, vlPFC), in the orbitofrontal cortex (lOFC, mOFC) and in the cingulate cortex. Spindle activity did not increase in subcortical areas (hippocampus, amygdala) and in the temporal lobe. The local variations in power for given areas may be due to grey/white matter delimitation.

C. Local evidence of spindles early-termination

In patients P3 and P5, SPES induced early termination of the spindles. This effect depended on stimulation amplitude and location. Local evidence of this effect for P5 in the detection channels is shown in Figure 2. We found spindles early stop when stimulation was applied in the dlPFC for an amplitude higher than 4 mA (Fig 2) as observed in the raw voltage (Fig 2.B): the oscillations at the spindle frequency disappear in the evoked response to stimulation in the *DetStim* case. The power in *DetStim* case decreases faster than in the *DetNOStim* case and the difference was statistically significant (Fig. 2.C). Normalized power at 0.2s was higher for *DetNOStim* than for *DetStim* (P3: 0.17 [0.08 0.29] vs 0.07 [0.05 0.09]; p = 0.005. P5 0.60 [0.19 0.85] vs 0.08 [0.05 0.14]; p = 1e-5). Using the offline spindles detector, we found no difference in the spindle onset between *DetNOStim* and *DetStim* cases (P3: p = 0.8, P5: p = 0.3, Fig 2.D). The duration of the *DetNOStim* spindles was significantly longer for P5 (0.85 [0.6 1.1] vs 0.6 [0.45 0.75]; p = 0.009) (Fig 2.E), but not for P3 (in seconds, P3: 0.7 [0.34 1.28] vs 0.45 [0.39 0.66]; p = 0.1). These results suggest that the closed-loop system detected all the spindles events in the same manner, whether stimulation was applied or not, but SPES caused an early termination of the spindles. We repeated the experiment for different amplitudes and locations. Spindles were not stopped when using a lower stimulation amplitude (2 mA) in the same location. For P3, normalized power at 0.2s was *DetNOStim*: 0.16 [0.08 0.27]; *DetStim*: 0.13 [0.05 0.29] (p = 0.4). For P5, it was *DetNOStim*: 0.52 [0.22 0.96]; *DetStim*: 0.52 [0.12 0.96] (p = 0.7). For P5 with same stimulation amplitude but in a different location (4 mA in the vlPFC) spindles normalized power at 0.2 s was *DetNOStim*: 0.47 [0.29 0.83]; *DetStim*: 0.33 [0.19 0.46]; (p = 0.06). Two days after the first session, oscillations' early termination was seen again for P5 (4 mA, dlPFC). The effect of stimulation may be consistent over time.

IV. DISCUSSION

Our results demonstrate the ability to successfully detect and stimulate during spindles using our novel closed-loop setup [15]. Spindle occurrence was assessed at local and global scales, using voltage and power. In two of the five participants, we observed early termination of spindles, suggesting that brief and localized direct electrical stimulation was able to disrupt spindles.

A. Variability across patients

A strong variability was observed across patients. This may be due to differences in epileptic brain areas, previous resections, medications, sleep stages, or electrode locations. Secondly, variability was found in terms of spindles characteristics. While most patients displayed spindles spreading over the frontal lobe, P4 had very localized events, observed in a couple of channels neighboring the detection site. Variability in spindles characteristics has already been reported [19] and may be related to differences in detection location (lOFC as for P4, instead of dmPFC and dlPFC for all

other patients). As electrodes were implanted for clinical reasons, there was no control regarding their location. The variability between patients indicates that higher amounts of data and new patients will help refine the present analysis.

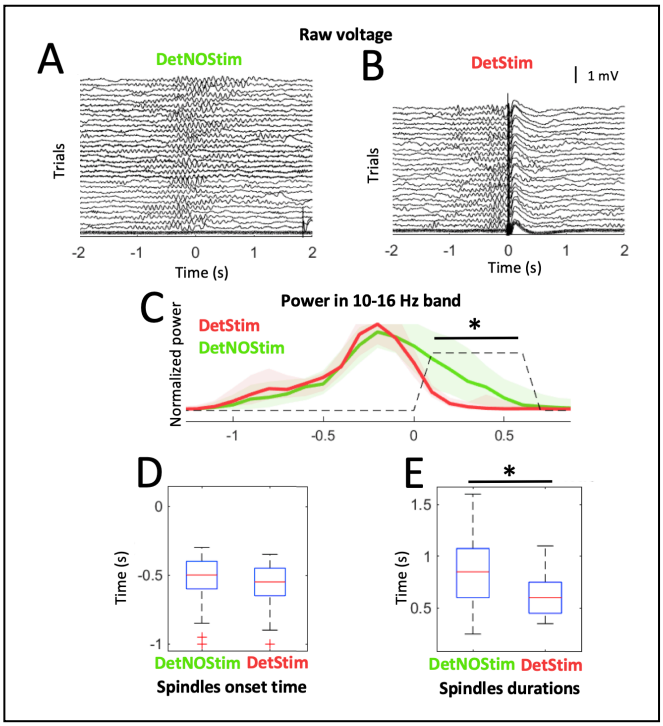

Figure 2. Local evidence of spindles early termination induced by SPES for P5. A and B. Raw voltage for *DetNOStim* and *DetStim* events. C. Comparing the power between the *DetNOStim* and *DetStim* cases, a statistically significant difference was found following stimulation: the power decreases faster for the *DetStim* events (Wilkoxon ranksum test with FDR correction, p = 1e-5). D. Distribution of the onset times of the spindles for *DetNOStim* and *DetStim* events. No difference was found, the spindles were equally detected by the closed-loop system. E. Distribution of the durations of the spindles for *DetNOStim* and *DetStim* events. *DetStim* events duration was shorter and statistically different to *DetNOStim* events duration (Wilkoxon ranksum test, p = 0.009). * indicates p < 0.05.

B. Methodological optimization

Experimentally, our methodology to target spindles may be further optimized. First, the order of the spindles' band-pass filter (order 2) in the closed-loop system may be too low, since non-spindles events were found in some trial sessions (not used in this study). While the low order was chosen for the sake of fast real-time computations, a more specific filter may limit the occurrence of false positives. Second, using replay data to increase the number of *DetNOStim* events may not be ideal, given the within-patients spindles variability. We selected the patient's sleep data closest to stimulation session (e.g. less than one hour away from the session), which is reasonable since the within-patient variability was found on time scales of days, perhaps due to changes in medication. However, obtaining all the *DetNOStim* data needed during the online session may remove a possible source of error.

C. Further steps

In this study, spindles early termination was assessed locally. The spatial extension of the spindles' disruption, its conditions of occurrence, and its consequences in terms of network connectivity should be further investigated.

V. Conclusion

We presented preliminary results of spindle disruption with SPES in the human brain using a closed-loop system. Larger cohorts are needed to validate these results, to study effect variability, and to better understand the effect of this disruption in memory consolidation and sleep maintenance.

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