

Connectivity Between Scalp EEG and Intracranial Recordings During 40 Hz Visual Stimulation

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ABSTRACT: We investigated whether rhythmic visual stimulation at 40 Hz reveals connectivity-based relationships between scalp EEG and intracranial recordings. Two epilepsy patients with simultaneous EEG, ECoG, and SEEG recordings participated in regular, oddball, and irregular stimulation conditions. Connectivity was quantified using coherence and weighted phase lag index (wPLI). Rhythmic stimulation produced robust coupling between scalp and invasive electrodes, whereas irregular stimulation did not. These findings suggest that scalp EEG can reflect neural activity recorded in cortical and deeper brain structures during rhythmic stimulation.

INTRODUCTION

Scalp electroencephalography (EEG) provides a non-invasive measure of large-scale brain dynamics and is widely used to study rhythmic neural activity in humans. However, the extent to which EEG reflects activity originating from deeper brain structures remains debated [1]. Neural electric fields propagate through conductive tissue before reaching the scalp and are attenuated by distance as well as by the spatial organization of the underlying neuronal sources. The greater physical distance between deep neural generators and scalp electrodes further attenuates their measurable contributions to scalp recordings [2] and in particular, subcortical structures often exhibit distinct neuronal architectures that can generate weaker extracranial signals compared to cortical sources [3–5]

Despite these limitations, identifying signatures of deep neural activity in scalp EEG is of considerable interest for both clinical and research applications. One important example arises in the development of brain-computer interfaces (BCIs) based on implanted electrocorticography (ECoG) electrodes. For such systems, it would be highly valuable to determine before surgery whether a given individual is likely to generate neural signals that can support reliable BCI control [6]. Ideally, such a pre-implantation assessment would rely on non-invasive

recordings. Measurements obtained from scalp EEG could provide a rapid and practical approach for evaluating neural signal quality prior to implantation [6].

The ability to detect activity originating from deeper brain structures is also relevant for neurological disorders in which subcortical regions play a central role. For example, structures within the medial temporal lobe, including the hippocampus and amygdala, are some of the first regions to be affected by AD [7]. Because early stages of AD represent a potential window for intervention, identifying non-invasive biomarkers reflecting activity in these regions is of particular interest [8]. However, whether scalp EEG can reliably predict the presence of informative neural activity recorded intracranially remains an open question [9].

One approach to addressing the detectability of deep activity in scalp EEG is to induce a strong and well-defined oscillatory response and evaluate whether this activity can be observed simultaneously across recording modalities. In particular, visual stimulation around 40 Hz is known to produce robust gamma-band steady-state responses in the human brain [10]. If cortical and subcortical structures exhibit reliable 40 Hz activity during such stimulation, it becomes possible to evaluate whether corresponding signatures can be detected in scalp EEG.

Interpreting coupling between recording modes requires careful consideration of the mechanisms underlying correlated signals. Similar activity observed across electrodes may arise from two fundamentally different processes. In one case, passive spread of electrical potentials through conductive tissue leads to the same source being detected at multiple locations [11]. Under the quasi-static approximation of Maxwell's equations, such field spread results in signals that appear nearly simultaneous across sensors, producing relationships centered around zero phase difference [12]. In the other case, neural transmission between distinct neuronal populations generates a temporally structured activation sequence characterized by a consistent phase offset between signals [13].

In the present study, we investigated whether rhythmic visual stimulation at 40 Hz can reveal relationships be-

tween scalp EEG and intracranial recordings obtained simultaneously from cortical surface electrodes and depth electrodes. By combining coherence and phase-based connectivity measures, we examined whether activity observed at the scalp reflects signals recorded in cortical and subcortical regions, including hippocampal and other deep structures. Through this approach, we aim to assess the feasibility of detecting intracranial rhythmic activity from non-invasive scalp recordings and to characterize the nature of the coupling observed across recording modalities.

MATERIALS AND METHODS

Participants: For the current study, two epilepsy patients were recruited at Ghent University Hospital (UZ Gent) following approval from the Commission Medical Ethics of UZ Gent. All procedures were conducted in accordance with applicable ethical regulations for research involving human participants. Both patients were acutely implanted with subdural grids (ECoG) and/or depth electrodes (SEEG) as part of their clinical evaluation, while simultaneous scalp EEG recordings were obtained using surface electrodes. Prior to participation, they were informed about the study procedures, including data processing and storage, and provided written informed consent.

Experimental procedure and data acquisition: The experimental protocol comprised three stimulation conditions [14, 15]: Regular (40 Hz), Oddball (40 Hz with task), and Irregular. Each comprised a 1-minute baseline and two 2.5-minute stimulation blocks. Regular and Task conditions utilized 40 Hz square-waves (50% duty cycle), whereas the Irregular control featured single periods from random frequencies between 30–50 Hz. Participants maintained central fixation 55 cm from the LED panel. During the Task, participants mentally counted random 250 ms red LED flashes; behavioral data were not analyzed. LED luminance was 225–250 lumen. Simultaneous EEG, ECoG, and SEEG were acquired via an SD LTM 64 Express system (Micromed, Italy) at 256 Hz, referenced to average mastoids.

Electrode localization: For each participant, cortical reconstruction and volumetric segmentation were performed on the preimplantation MRI using the FreeSurfer image analysis suite (version 6.0) [16]. The post implantation CT scan was subsequently co-registered to the FreeSurfer-derived images using the Brainstorm toolbox with the SPM12 extension [17] [18]. Electrode coordinates were manually identified from CT artifacts and mapped onto the cortical surface. Cortical visualizations were generated using the Brainstorm toolbox.

Preprocessing: The preprocessing pipeline was implemented using the FieldTrip toolbox for MATLAB [19] and included re-referencing to minimize reference-dependent bias in subsequent connectivity analyses, band-pass filtering, and attenuation of 50 Hz line noise and its harmonics in the EEG, ECoG, and SEEG recordings.

For each participant, 5-minute stimulation epochs and a 1-minute baseline were extracted and aligned to stimulation onset. These were segmented into non-overlapping 5-second trials to enable artifact rejection while preserving temporal structure. Trials with variance exceeding the 80th percentile were excluded to minimize the influence of movement artifacts and non-physiological transients. The remaining artifact-reduced trials were retained for subsequent spectral and connectivity analyses.

Signal to noise ratio analysis: Given the heterogeneous electrode placement across participants, 40 Hz activation was evaluated at the level of individual electrodes. Power spectral density (PSD) was estimated for each 5-second trial and each channel using Welch's method with 1-second Hamming windows and 50% overlap [20]. To quantify entrainment, 40 Hz signal-to-noise ratio (SNR) was computed per electrode as $10\log_{10}(P_{\text{signal}}/P_{\text{noise}})$, using 40 Hz for signal and the mean of 38–39 Hz and 41–42 Hz for noise. Stimulation SNR distributions were compared against rest using one-sided nonparametric rank-based tests. Multiple comparisons were controlled via the Benjamini–Hochberg procedure ($\alpha = 0.05$), with effect sizes quantified as the area under the receiver operating characteristic curve (AUC).

Coherence: Coherence is a frequency-domain measure of synchronization between two signals and quantifies the consistency of their relative amplitude and phase relationship at a given frequency [21, 22]. When the phase difference between two signals remains stable across time, coherence approaches 1; when the relationship varies from moment to moment, coherence approaches 0. Thus, coherence reflects the strength of the linear relationship between two signals at a specific frequency [23].

Consider two signals $x(t)$ and $y(t)$. The magnitude-squared coherence (MSC) is defined as

$$C_{xy}^2(f) = \frac{|S_{xy}(f)|^2}{S_{xx}(f)S_{yy}(f)}, \quad (1)$$

where $S_{xy}(f)$ denotes the cross-spectrum between the signals and $S_{xx}(f)$ and $S_{yy}(f)$ denote their respective autospectra.

Weighted phase lag index (wPLI): While coherence provides an indication of consistent phase relationships between two signals, it does not distinguish the underlying nature of this relationship. The critical difference between volume conduction and functional connectivity lies in the phase lag between signals. Volume conduction induces near-zero phase differences across sensors, whereas genuine functional interactions are characterized by consistent non-zero phase lags [12, 13].

Let the cross-spectrum between signals x and y at frequency f be defined as

$$S_{xy}(f) = E\{X(f)Y^*(f)\}, \quad (2)$$

where $X(f)$ and $Y(f)$ are the Fourier transforms of the signals and $*$ denotes complex conjugation. The complex coherence is then

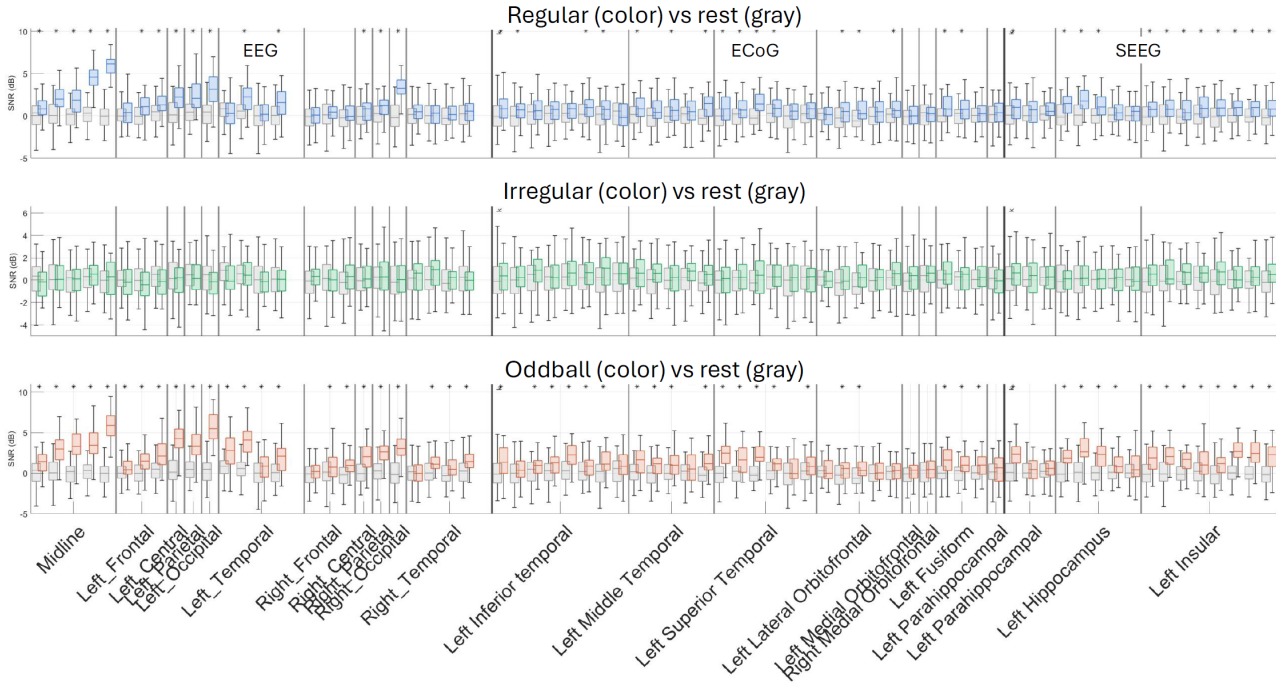


Figure 1: Electrode-wise 40 Hz signal-to-noise ratio (SNR) during regular stimulation relative to rest (gray) for Subject_01. Rhythmic stimulation produced strong electrophysiological responses detectable at the scalp level, with the strongest activity observed over central, parietal, and occipital electrodes. dots indicate significant differences between the stimulation and resting states.

$$\gamma_{xy}(f) = \frac{S_{xy}(f)}{\sqrt{S_{xx}(f)S_{yy}(f)}}. \quad (3)$$

Because the cross-spectrum is complex-valued, it can be written as

$$S_{xy}(f) = |S_{xy}(f)|e^{i\phi(f)}, \quad (4)$$

where $\phi(f)$ represents the phase difference between the signals. Volume conduction primarily contributes to the real part of $S_{xy}(f)$, corresponding to $\phi(f) \approx 0$.

To overcome this limitation, the weighted phase lag index (wPLI) relies on the imaginary component of the cross-spectrum. The wPLI is defined as [12]

$$\text{wPLI}(f) = \frac{E \{ |\text{Im}(S_{xy}(f))| \text{sign}(\text{Im}(S_{xy}(f))) \}}{E \{ |\text{Im}(S_{xy}(f))| \}}. \quad (5)$$

By weighting the imaginary part of the cross-spectrum, wPLI emphasizes consistent non-zero phase differences while down-weighting contributions close to zero phase lag [12]. Because purely zero-lag interactions yield $\text{Im}(S_{xy}(f)) = 0$, wPLI collapses toward zero in the presence of volume conduction. Consequently, wPLI provides a more conservative estimate of functional connectivity by selectively capturing phase-lagged synchronization.

In the present study, wPLI was used to further characterize the nature of the interactions identified by coherence analysis. After identifying electrode pairs exhibit-

ing significant coherence, the corresponding wPLI values were evaluated to determine whether the observed coupling reflected phase-lagged interactions or near-zero-lag synchronization.

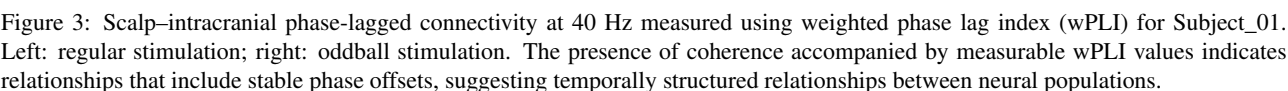
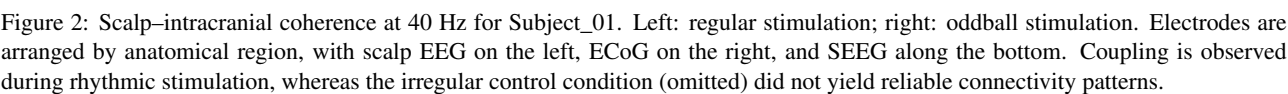
RESULTS

40 Hz signal-to-noise ratio: Regular 40 Hz stimulation produced clear increases in signal-to-noise ratio (SNR) relative to rest in both participants (Fig. 1). After FDR correction, 44 of 78 electrodes in Subject_01 and 43 of 58 electrodes in Subject_02 showed significantly higher SNR during the regular condition. Significant responses were present in both scalp and invasive recordings. Median SNR increased from 0.014 dB at rest to 0.753 dB in Subject_01 and from 0.190 dB to 1.762 dB in Subject_02. In contrast, irregular stimulation did not produce reliable entrainment. No electrodes survived FDR correction and median SNR values remained close to resting levels.

The oddball condition produced even stronger responses. After FDR correction, 59 of 78 electrodes in Subject_01 and 43 of 58 electrodes in Subject_02 showed significantly higher SNR than rest. In both participants, the median SNR increase was larger in scalp electrodes than in invasive recordings.

Overall, the results show a consistent condition-dependent pattern: regular and oddball stimulation produced robust 40 Hz entrainment across scalp and invasive electrodes, whereas irregular stimulation did not.

40 Hz coherence: Coherence analysis revealed syn-



Weighted phase lag index: Weighted phase lag index (wPLI) analysis revealed phase-lagged interactions dur-

The present analysis examined how rhythmic visual stimulation at 40 Hz is represented across scalp EEG and in-

tracranial recordings.

In both subjects, rhythmic stimulation produced strong electrophysiological responses detectable at the scalp level, with the strongest activity observed over posterior electrodes. This spatial distribution is consistent with the visual origin of the stimulation paradigm and aligns with previous work showing that visual flicker around 40 Hz produces strong gamma-band steady-state responses measurable in scalp EEG, particularly over occipital regions [10, 14]. These results indicate that rhythmic visual stimulation reliably induces large-scale oscillatory responses that can be detected using non-invasive recordings.

Invasive recordings confirmed that the 40 Hz response was not restricted to scalp measurements. Both subjects exhibited rhythmic activity across multiple intracranial electrodes. Although the precise anatomical distribution differed between subjects due to differences in electrode implantation, rhythmic responses were observed across several cortical and deeper brain regions sampled by the implanted electrodes. Previous intracranial studies have similarly demonstrated that rhythmic visual stimulation can entrain gamma-band activity across cortical regions and deeper structures including the hippocampus [15]. Together, these observations indicate that the scalp responses observed during rhythmic stimulation co-occur with activity recorded locally by intracranial electrodes.

Two factors motivated the focus on 40 Hz activity. First, the signal serves as a functional tracer, ensuring that the observed coupling is stimulus-driven rather than a random occurrence. Second, the continuous nature of this rhythmic activity provides the stationarity required for connectivity measures like coherence and wPLI to accurately estimate phase relationships—a task not possible with transient or random/resting state signals.

The irregular condition (30–50 Hz jitter) served as a stochastic control because its non-periodic nature prevents frequency-specific entrainment. It should be noted that irregular flickering differs from code-modulated (cVEP) paradigms, which use repeated m-sequences and would compromise their use as a stochastic control.

Connectivity analyses examined the relationship between scalp EEG and intracranial recordings during the stimulation conditions. Across both participants, coupling between scalp EEG and intracranial recordings was observed during the rhythmic stimulation conditions (Fig. 2), whereas the irregular control condition did not produce high-SNR scalp regions and therefore did not yield reliable connectivity patterns. This indicates that the interactions described below were specifically associated with the presence of rhythmic stimulation.

In Subject 01, interactions linked temporal scalp regions with temporal cortical recordings, including inferior temporal, middle temporal, and superior temporal cortex. Additional interactions connected frontal scalp regions with the lateral orbitofrontal cortex. In these region pairs, coherence occurred together with very low wPLI values, indicating relationships centered around zero phase dif-

ference between scalp and cortical signals.

Interactions between scalp EEG and SEEG contacts were also present in Subject 01, involving depth electrodes located within the insula, hippocampus, and parahippocampal region. For these region pairs, coherence was again accompanied by very low wPLI values, indicating relationships centered around zero phase difference between scalp activity and signals recorded in these deeper structures.

In Subject 02, interactions linked midline scalp regions with frontal cortical areas, including middle frontal, superior frontal, and precentral cortex. In these region pairs, coherence occurred together with very low wPLI values, indicating relationships centered around zero phase difference between scalp and cortical activity.

Interactions between scalp EEG and SEEG contacts were also observed in Subject 02, involving depth electrodes located within regions associated with focal cortical dysplasia (FCD). In these region pairs, coherence was accompanied by very low wPLI values, indicating relationships centered around zero phase difference between scalp signals and SEEG recordings.

Interactions characterized by coherence together with measurable wPLI values were also observed in the dataset, indicating relationships that include stable phase offsets between recording sites. Because wPLI emphasizes consistent non-zero phase differences, these interactions are less compatible with purely instantaneous field spread and instead suggest temporally structured relationships between neural populations.

Across both participants, the presence of significant coherence accompanied by very low wPLI values suggests a substantial contribution of volume conduction. Because volume conduction reflects the spread of electrical fields through brain tissue, skull, and scalp, this finding implies that scalp recordings may retain information about activity originating from deeper brain structures. Similar conclusions have been reported in previous studies using different methodological approaches [1, 9, 24]. Crucially, robust 40 Hz signals did not universally yield high connectivity. Multiple sites with high SNR displayed no significant coherence or wPLI with the scalp. This dissociation confirms that the observed coupling is not a trivial consequence of signal strength or volume conduction, but reflects specific functional interactions within an entrained neural circuit.

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