Clinical Neurophysiology 161 (2024) 222–230

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

The effect of propofol on effective brain networks

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HIGHLIGHTS

- The number of corticocortical evoked potentials decreases under anesthesia compared to the awake state.
- The N1-peak latency is increased under propofol-anesthesia.
- The topology of effective networks in awake patients is preserved under anesthesia.

ARTICLE INFO

Article history:
Accepted 24 January 2024
Available online 8 March 2024

Keywords:
Electrocorticography
Single pulse electrical stimulation
Propofol
Network topology
Intra-operative
N1-peak-latency
N1-peak-amplitude

ABSTRACT

Objective: We compared the effective networks derived from Single Pulse Electrical Stimulation (SPES) in intracranial electrocorticography (ECoG) of awake epilepsy patients and while under general propofol-anesthesia to investigate the effect of propofol on these brain networks.
Methods: We included nine patients who underwent ECoG for epilepsy surgery evaluation. We performed SPES when the patient was awake (SPES-clinical) and repeated this under propofol-anesthesia during the surgery in which the ECoG grids were removed (SPES-propofol). We detected the corticocortical evoked potentials (CCEPs) with an automatic detector. We constructed two effective networks derived from SPES-clinical and SPES-propofol. We compared three network measures (indegree, outdegree and betweenness centrality), the N1-peak-latency and amplitude of CCEPs between the two effective networks.
Results: Fewer CCEPs were observed during SPES-propofol (median: 6.0, range: 0–29) compared to SPES-clinical (median: 10.0, range: 0–36). We found a significant correlation for the indegree, outdegree and betweenness centrality between SPES-clinical and SPES-propofol (respectively r_s = 0.77, r_s = 0.70, r_s = 0.55, $p < 0.001$). The median N1-peak-latency increased from 22.0 ms during SPES-clinical to 26.4 ms during SPES-propofol.
Conclusions: Our findings suggest that the number of effective network connections decreases, but network measures are only marginally affected.
Significance: The primary network topology is preserved under propofol.

1. Introduction

Propofol is an intravenous agent used for induction and maintenance of general anesthesia during surgery and in the intensive care unit. Propofol inhibits, among other mechanisms of action, the γ-aminobutyric acid ($GABA_A$)-receptor by slowing the channel closing time of the receptor, with an inhibitory effect on neurotransmission (MacIver, 2014; Rudolph and Antkowiak, 2004; Sahinovic et al., 2018; Yip et al., 2013). In the EEG, slowing of brain signals and reduction of epileptic activity is observed (Hindriks and van Putten, 2012; Kuruvilla and Flink, 2003; San-Juan et al., 2010), as well as suppression of motor evoked potentials in a dose-dependent manner (Ohtaki et al., 2016).

Analyzing the difference between brain networks while awake or while under anesthesia may give us additional and complementary insight in the effects of anesthesia at a network level. Brain

Abbreviations: CCEP, corticocortical evoked potentials; ECoG, electrocorticography; PRIOS study, **Pr**opofol **I**ntra-**O**perative **S**PES study; SPES, single pulse electrical stimulation.

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https://doi.org/10.1016/j.clinph.2024.01.012
1388-2457/

networks can be categorized as structural, functional or effective networks (Yaffe et al., 2015). Structural networks are based on the anatomical connections between brain regions (typically corresponding to white matter fiber tracts). Functional networks are based on the temporal dependency between neural activities of different brain regions, usually estimated in fMRI or (intracranial) EEG data. Analysis of functional brain networks in human subjects has informed us that there is a balance between local segregation and global integration in the awake state, which means that lower-level information can be processed locally and modularly, whereas higher-level information is distributed efficiently over the brain because of global integration (Liu et al., 2022). This balance between local segregation and global integration is disturbed in anesthesia-induced loss of responsiveness (Zhang et al., 2019).

Effective networks describe the interaction between brain regions caused by perturbation in one brain region that leads to responses in other brain regions (van Blooijs et al., 2018). Single Pulse Electrical Stimulation (SPES) is one of the techniques that can be used to study effective brain connectivity by using direct electrical stimulation and recording of intracranial electrodes on the brain (Matsumoto et al., 2004). With SPES, we stimulate two adjacent electrodes and analyze the cortico-cortical evoked potentials (CCEPs) in all other electrodes (van Blooijs et al., 2018). CCEPs have a sharp negative deflection (N1) that occur between 9 and 100 ms after the stimulation artefact. A CCEP exposes an effective network connection between the stimulation site and the recording electrode. This has provided insight into eloquent brain networks such as language, cognitive and motor networks (Matsumoto et al., 2004, 2007, 2012).

The complex network structure of the brain can be characterized by a set of topological network measures, such as the indegree, outdegree and betweenness centrality (Haneef and Chiang, 2014; Keller et al., 2014; Olmi et al., 2019; Rubinov and Sporns, 2010; van Blooijs et al., 2018; van Mierlo et al., 2013; Wilke et al., 2011). The indegree is a measure describing the number of incoming connections towards an electrode of interest. In an effective network, this is the number of CCEPs evoked in the electrode of interest after stimulating other electrode pairs. The outdegree describes the number of outgoing connections from an electrode of interest. In an effective network, this is the number of CCEPs evoked elsewhere after stimulating the electrode of interest. The betweenness centrality is the fraction of all shortest paths in the network that pass through an electrode of interest (Rubinov and Sporns, 2010). Electrodes with a high betweenness centrality are assumed to be important controllers of a network (Joyce et al., 2010). These measures characterize the topological network and enable us to compare the network in an awake state to a network under anesthesia.

We analyzed whether propofol alters the effective network connections by investigating the number of CCEPs, the indegree, outdegree, betweenness centrality, the N1-peak-latency and the N1-peak-amplitude. To the best of our knowledge, this is the first study that compares effective brain networks in the same subjects in the awake state and under general propofol-anesthesia.

2. Material and methods

2.1. Subjects and data recording

Between 2020 and 2022, patients who underwent electrocorticography (ECoG) recordings for epilepsy surgery evaluation were asked to give consent to participate in this study (PRIOS: **Pr**opofol **I**ntra-**O**perative **S**PES). The study complied with the Dutch law on Medical Research in Humans and was approved by the medical research ethics committee of the University Medical Centre Utrecht. The ECoG implant strategy was determined solely by clinicians and not influenced by this study. ECoG data was recorded with a sample frequency of 2048 Hz.

2.2. Stimulation protocols

We applied two SPES protocols (Fig. 1): SPES-clinical and SPES-propofol. SPES-clinical was performed at least one day after subdural electrode grid implantation in the awake subject as part of clinical routine. Ten monophasic electrical pulses (0.2 Hz, 1 ms, 8 mA) were applied to each pair of adjacent electrodes in consecutive numbers across the implanted electrode grid (e.g. 1–2, 2–3, etc., Supplementary Fig. 1). We decreased the current intensity to 4 mA when electrodes were located on the pre- or post-central gyrus. After five stimuli, the anode and cathode were switched to reduce the stimulus artefact when averaging the responses to these stimuli.

SPES-propofol was performed under propofol-anesthesia at the start of the grid explantation surgery. We started with SPES-propofol at least five minutes after the initial administration of propofol, during preparations for grid explantation and often epilepsy surgery. We stimulated each adjacent electrode pair twice and switched anode and cathode after the first stimulus. If we finished the protocol in time and surgical preparations were still ongoing, additional stimuli were applied to some stimulus pairs. We considered all stimuli for analysis.

2.3. Signal processing

A clinical neurophysiologist (FL) annotated periods with burst suppression during SPES-propofol. We excluded epochs that were recorded during burst suppression, because CCEPs are suppressed during burst suppression (Suzuki et al., 2019).

We excluded data from noisy electrodes, and electrodes located on top of other electrode grids. ECoG recordings were converted to the Brain Imaging Data Structure (Demuru et al., 2022). For each electrode, epochs with a time window of 2 s pre-stimulus to 2 s post-stimulus, time-locked to the stimulus artefact, were re-referenced by subtracting the averaged signal of 10% of the electrodes with the lowest variance post-stimulation (Fig. 1B). For each electrode, epochs of all stimuli per stimulus pair were averaged (Fig. 1C).

2.4. N1-peak detection and visual check

The standard deviation (SD) was calculated in the pre-stimulus window (-2 s to −0.1 s). N1-peaks were detected (van Blooijs et al., 2018) in each averaged epoch per electrode when the evoked response exceeded 2.6 * SD (Fig. 1C). The detected N1-peaks of the CCEPs were visually checked by two observers (DvB and SB). When an incorrect N1-peak was selected by the detector, the correct N1-peak was selected manually.

For each subject and each SPES-protocol, an inter-observer agreement was calculated between the two observers with the unweighted Cohen's kappa. Subjects were excluded from further analyses when the inter-observer agreement of SPES-clinical or SPES-propofol was lower than 0.6. We only included N1-peaks for further analyses when these were visually confirmed by both observers. When both observers selected N1-peaks with more than five samples difference, these N1-peaks were visually checked (SB), and the correct N1-peak was selected (Fig. 1D). N1-peaks less than five samples apart were averaged.

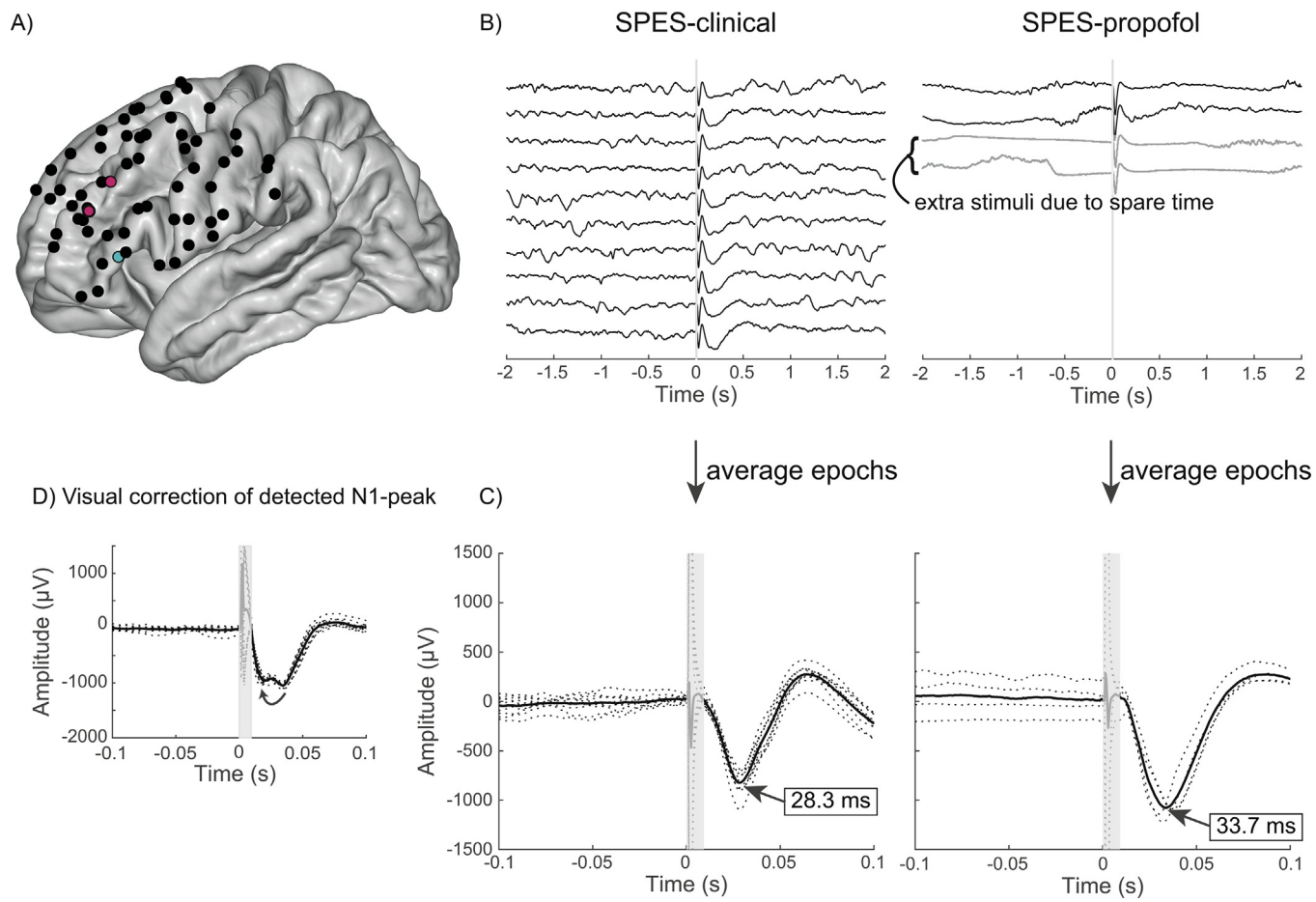

Fig. 1. Example of the two SPES (Single Pulse Electrical Stimulation)-protocols in PRIOS03. We performed two SPES protocols: SPES-clinical and SPES-propofol. A) Rendering of a standardized brain with electrode positions of PRIOS03 in MNI305 coordinates. The pink electrodes are stimulated. The responses to these stimuli in the blue electrode are shown in B). B) The responses to stimulation for SPES-clinical (left) and SPES-propofol (right). We were able to apply four stimuli to this stimulus pair during SPES-propofol due to spare time and visualized the four responses to these stimuli. C) We averaged the ten (in SPES-clinical) and four (in SPES-propofol) responses to stimuli visualized in B. The individual responses are displayed with dotted lines, the averaged response is displayed with a continuous line. The grey area corresponds to the interval in which no physiological response could be measured due to the stimulation artefact. The peak at 28.3 ms and 33.7 ms was the N1-peak of the CCEP (cortico-cortical evoked potential). D) Example of visual correction. When two small peaks were visible during the N1-waveform, the first N1-peak was selected in the averaged CCEP response.

2.5. Analysis

We first analyzed with a chi-square test whether stimulation of a given electrode pair would evoke a CCEP in similar electrodes in both SPES-protocols. We then used the Wilcoxon Signed Rank-test to compare the number of evoked CCEPs for each stimulus pair between SPES-clinical and SPES-propofol.

For the analysis of the network measures, we defined the electrodes as nodes and therefore, we needed to make the assumption that when stimulation in a stimulus pair would evoke a CCEP in another electrode, both electrodes in this stimulus pair contributed to this evoked CCEP. From this assumption, it follows that we include a connection in the network from both stimulation electrodes to the response electrode. For each electrode, we calculated the indegree, outdegree and betweenness centrality during SPES-clinical and SPES-propofol. We normalized these network measures by considering the number of possible connections (given the number of grid electrodes that was implanted) to enable comparison between subjects (van Blooijs et al., 2018). We used the Spearman rank correlation to correlate the indegree, outdegree and betweenness centrality between SPES-clinical and SPES-propofol.

For the analysis of the differences in N1-peak-latencies and N1-peak-amplitudes, we only included the N1-peak-latencies and amplitudes of CCEPs that were present during both SPES-clinical and SPES-propofol. We used the Wilcoxon Signed Rank-test to compare the N1-peak-latency and amplitude of the CCEPs evoked during SPES-clinical and SPES-propofol. All statistical analyses were corrected for multiple testing with FDR correction ($p < 0.05$).

2.6. Code and data availability

We performed all analyses and generated all figures using Matlab R2022b. The code is available on https://github.com/UMCU-EpiLAB/umcuEpi_PRIOS. The data is available on https://openneuro.org/datasets/ds004370.

3. Results

3.1. Patient characteristics

We included nine subjects (four females) with a median age of 27 years (range 13–53 years) (Table 1). All subjects were fully

informed of the nature of this study and gave informed consent. The electrode grids and strips consisted of platinum circular electrodes embedded in silicone with a 4.2 mm^2 contact surface and an inter-electrode distance of 1 cm (Ad-Tech, Racine, WI). PRIOS01 and PRIOS09 had an additional depth-lead with 6 electrodes implanted in the presumed epileptogenic region (DIXI Medical, Chaudefontaine, Marne, France).

Two subjects (PRIOS07 and PRIOS08) were excluded, because we were not able to perform SPES-propofol due to technical problems. One subject (PRIOS06) was excluded from further analysis because the interobserver agreement was lower than 0.6 (Table 1).

3.2. Numbers of evoked CCEPs

In all subjects, we found a large overlap in the electrodes in which a CCEP was evoked after stimulating a stimulus pair in both SPES-protocols (Fig. 2). Only a small number of electrodes showed a CCEP after stimulating a stimulus pair during SPES-propofol that did not show a CCEP after stimulating the same stimulus pair during SPES-clinical. There are a number of electrodes in which a CCEP was evoked during SPES-clinical without a correlate in SPES-propofol. In all subjects, we found that fewer CCEPs were evoked during SPES-propofol compared to SPES-clinical (Fig. 3). Fig. 3 also shows that in most stimulus pairs, the relative number of evoked CCEPs, and therefore the ranking, remained the same under anesthesia.

3.3. Network measures: indegree, outdegree and betweenness centrality

The indegree, outdegree and betweenness centrality showed high correlation strengths (Spearman's correlation, r_s > 0.5) between SPES-clinical and SPES-propofol (Fig. 4). All network measures showed around twice as high values for all electrodes during SPES-clinical compared to the values during SPES-propofol.

3.4. N1-peak-latencies and amplitudes

When we analyzed N1-peak-latencies in each individual subject, we found an increase in N1-peak-latency in SPES-propofol in three subjects (PRIOS02, PRIOS03 and PRIOS04: respectively 29.3 ms → 32.2 ms, 22.0 ms → 26.9 ms, 12.7 ms → 13.2 ms) (Fig. 5 A-B). We found a decrease in N1-peak-latency in one subject (PRIOS09: 35.6 ms → 31.2 ms). When combining all N1-peaks of all subjects, the N1-peak-latency increased from 22.0 ms during SPES-clinical to 26.4 ms during SPES-propofol.

When analyzing the N1-peak-amplitudes in each individual subject, we found a more negative N1-peak-amplitude in SPES-propofol in two subjects (PRIOS02, PRIOS03: respectively −392 μV → -399 μV, −592 μV → -701 μV) and a less negative N1-peak-amplitude in three subjects (PRIOS01, PRIOS04, PRIOS05: respectively −424 μV → -312 μV, −822 μV → -535 μV, −421 μV → -349 μV) (Fig. 5C). When combining all N1-peaks of all subjects, the N1-peak-amplitude was less negative during SPES-propofol (-499 μV → -466 μV).

4. Discussion

We studied whether the effective network derived from SPES-clinical was altered due to propofol. We found a large overlap between the electrodes in which a CCEP was evoked during SPES-clinical and SPES-propofol. The number of evoked CCEPs during SPES-propofol was lower than the number of evoked CCEPs during SPES-clinical. This decrease might be caused by the inhibitory effect of propofol on neurotransmission (MacIver, 2014; Rudolph and Antkowiak, 2004; Sahinovic et al., 2018; Yip et al., 2013). Although the lower number of evoked CCEPs during SPES-propofol could result in an altered network topology because of missing connections, the ranking of electrodes for values of network measures (indegree, outdegree, betweenness centrality) did not change: e.g. an electrode with a high indegree during SPES-clinical also had a high indegree during SPES-propofol. This means that the topology of the effective network was not altered during SPES-propofol. This was supported by the observation that the stimulus pair with the highest number of evoked CCEPs was the same for both SPES-clinical and SPES-propofol in two subjects (PRIOS02 and PRIOS03) (Supplementary Fig. 3 and Supplementary Table 1). In three subjects (PRIOS01, PRIOS04, PRIOS05), the location of the stimulus pair with the highest number of evoked CCEPs during SPES-propofol was localized near the stimulus pair with the highest number of evoked CCEPs during SPES-clinical. Furthermore, we observed that the electrode with maximal N1-peak-amplitude was the same for both SPES-clinical and SPES-propofol in nine situations, or these electrodes were located next to each other in three situations (Supplementary appendix and Supplementary Fig. 4). This was in agreement with a study (Yamao et al., 2021) in which they compared the location of the maximal N1-peak-amplitude in the awake state and under general anesthesia in the dorsal language white matter pathway. Interestingly, other studies show that activity of brain areas within a network becomes more independent from one another and the exchange and distribution of information are reduced during deep sedation (Schrouff et al., 2011; Wang et al., 2020). The number of local connections was significantly decreased during anesthesia (Wang et al., 2020). This is in agreement with our findings. With ECoG, we only sample a part of the brain, which might give an explanation why we only found a decrease in the number of connections during SPES-propofol and no changes in network topology.

Table 1
Characteristics of subjects included in the PRIOS study. Subjects PRIOS06, PRIOS07 and PRIOS08 were excluded from further analysis. M = male, F = female, NA = not applicable, SPES-clinical = Single Pulse Electrical Stimulation protocol after subdural electrode grid implantation in the awake subject as part of clinical routine, SPES-propofol = Single Pulse Electrical Stimulation protocol performed under propofol-anesthesia at the start of the grid explantation surgery.

Subject	Age (years)	Sex	Location of grid	Number of implanted electrodes / stimulus pairs	Cohen's Kappa SPES-clinical	Cohen's Kappa SPES-propofol
PRIOS01	22	M	Left, temporal	48 / 35	0.74	0.80
PRIOS02	53	F	Left, fronto-temporal	80 / 54	0.72	0.76
PRIOS03	37	M	Left, frontal	64 / 52	0.86	0.88
PRIOS04	24	M	Left, frontal, interhemispheric, parietal	56 / 48	0.76	0.61
PRIOS05	51	F	Right, pre-and post-central gyrus, interhemispheric	64 / 53	0.74	0.72
PRIOS06	13	F	Right, pre- and post-central gyrus, parietal		0.30	0.47
PRIOS07	44	M	Left, fronto-temporal, interhemispheric		NA	NA
PRIOS08	15	F	Left, temporo-occipital		NA	NA
PRIOS09	27	M	Left, temporal	56 / 44	0.89	0.81

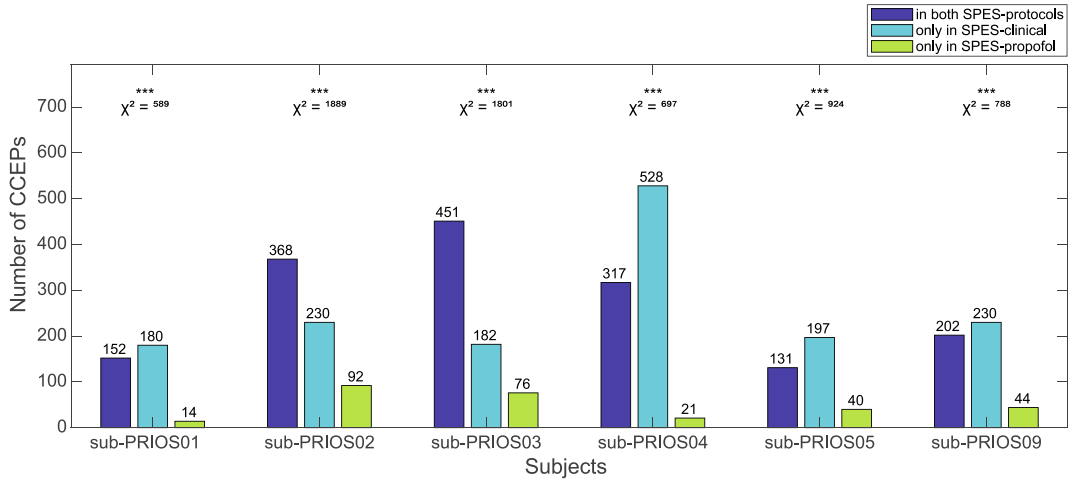

Fig. 2. Schematic overview of the number of cortico-cortical evoked potentials (CCEPs) during the two SPES (Single Pulse Electrical Stimulation)-protocols. For each subject, the numbers of evoked CCEPs are displayed in both SPES-clinical and SPES-propofol (purple), only during SPES-clinical (blue) and only during SPES-propofol (green). In all subjects, there is a high association between SPES-clinical and SPES-propofol which means that when a CCEP was evoked after stimulating a certain stimulus pair in one of the SPES-protocols, it would be evoked after stimulating a certain stimulus pair in the other SPES-protocol as well. ***p < 0.001, FDR corrected.

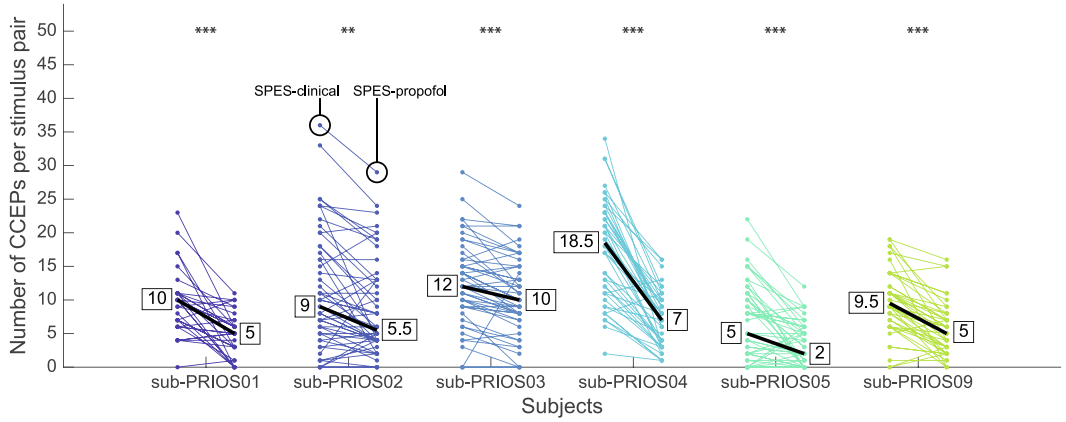

Fig. 3. The number of cortico-cortical evoked potentials (CCEPs) per stimulus pair. Each dot represents the number of CCEPs in one stimulus pair. The left dots represent the numbers of CCEPs evoked during SPES-clinical (Single Pulse Electrical Stimulation protocol after subdural electrode grid implantation in the awake subject as part of clinical routine). The right dots represent the numbers of CCEPs evoked during SPES-propofol (Single Pulse Electrical Stimulation protocol performed under propofol-anesthesia at the start of the grid explantation surgery). Dots of the same stimulus pair are connected by a line to visualize the differences in numbers of evoked CCEPs between the two SPES protocols. The median number of CCEPs evoked per stimulus pair are visualized with the numbers in the boxes and connected with a black line. **p < 0.01, ***p < 0.001, FDR corrected.

Median N1-peak-latency during SPES-propofol (26.4 ms) increased by 4.4 ms compared to SPES-clinical (22.0 ms). PRIOS09 showed the opposite effect: N1-peak-latency decreased during SPES-propofol. This difference in change in latency might be due to heterogeneity in underlying pathologies or might also be influenced by the fact that the subjects included in this study used various anti-seizure medication to suppress seizure activity. The timing of N1-peak-latencies is in agreement with several other studies. In awake patients, an N1-peak-latency of 27.9 ms (range 22–36 ms) was found in the arcuate fasciculus (Matsumoto et al., 2004). Under general anesthesia, an N1-peak-latency of 23 ± 3 ms (Giampiccolo et al., 2021) and during awake craniotomy, an N1-peak-latency of 28 ± 4 ms (Yamao et al., 2017) was found. Although these N1-peak-latencies were all measured in the arcuate fasciculus, it is difficult to compare these N1-peak-latencies from different subjects across these studies, since age, and probably other factors, might affect N1-peak-latencies (van Blooijs et al., 2023). A study that compared the N1-peak-latency in the arcuate fasciculus within subjects both under general anesthesia and during awake craniotomy found N1-peak-latencies of 26.6 ± 9.1 ms under general anesthesia and 23.2 ± 8.3 ms in the awake state (Suzuki et al., 2019). These N1-peak-latencies are comparable to the N1-peak-latencies we found in this study with four subjects who had coverage of the frontal and temporal endpoints of the arcuate fasciculus (Yeh et al., 2018) by subdural electrodes (Supplementary Fig. 2).

N1-peak-amplitudes were more negative in two subjects, and less negative in three subjects during SPES-propofol. This indicates that there was no clear effect of propofol on N1-peak-amplitude. Yamao et al. (Yamao et al., 2021) concluded that the N1-peak-amplitude had a tendency to increase in the awake state when investigating the dorsal language white matter pathway. Differences with our findings might be caused by the significant effect of number of trials on N1-peak-amplitude (Supplementary Fig. 5).

Unique in our study is that we applied SPES in all electrodes and not only in electrodes located on the endpoints of the arcuate fasciculus to analyze the effect of propofol on effective networks in general. We took as gold standard the awake state at least one

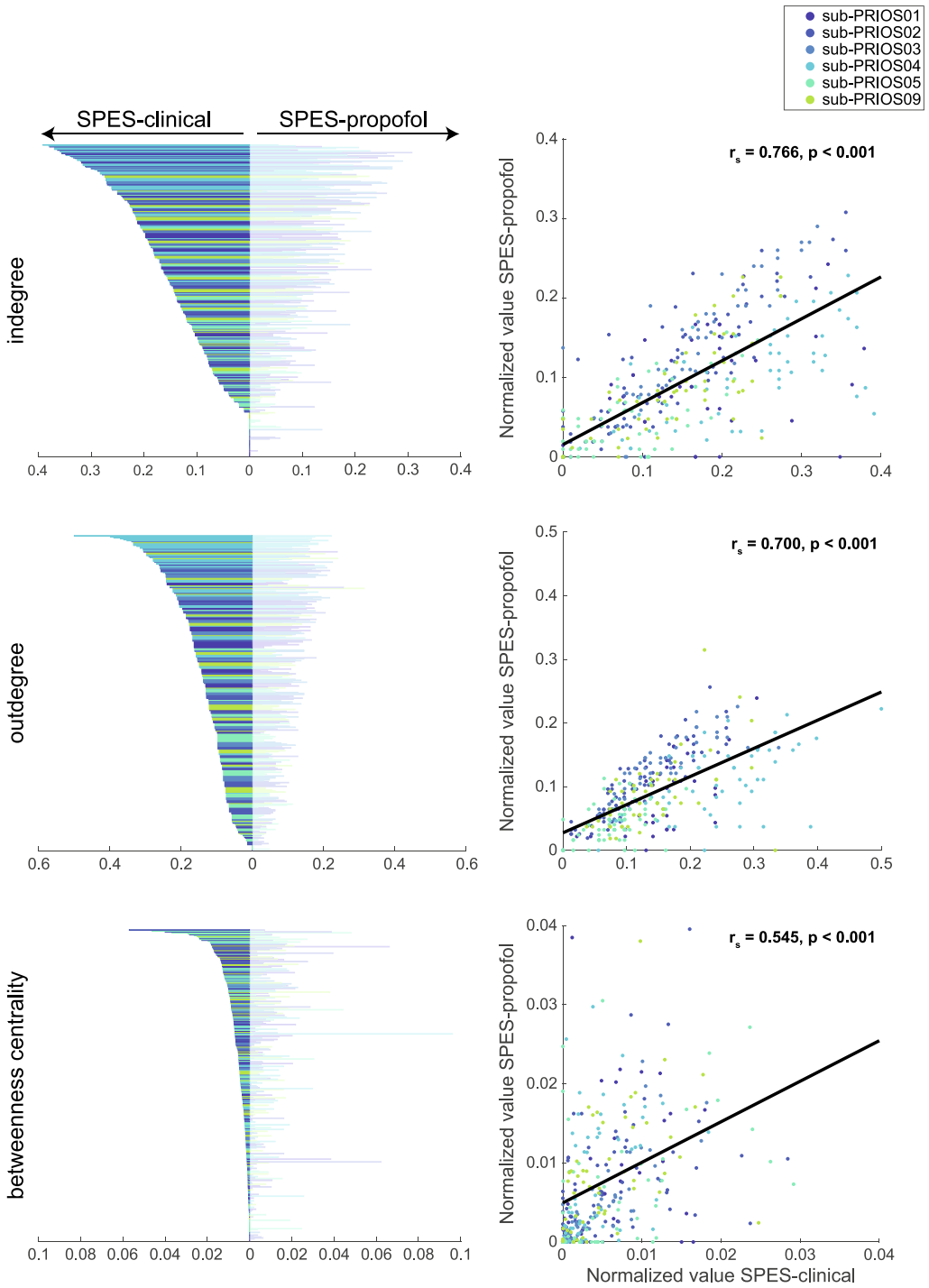

Fig. 4. Correlation of the indegree, outdegree and betweenness centrality between the two SPES (Single Pulse Electrical Stimulation)-protocols. On the left: horizontal bars of all subjects combined for the indegree (upper), outdegree (middle) and betweenness centrality (lower). Each horizontal bar represents the normalized value of a network measure per electrode. The values of the network measures of SPES-clinical are sorted in descending order (SPES-protocol after subdural electrode grid implantation in the awake subject as part of clinical routine, on the left side of the bar plot). The values of network measures during SPES-propofol (SPES-protocol performed under propofol-anesthesia at the start of the grid explantation surgery, on the right side of the bar plot) are sorted accordingly. On the right: scatter plots are displayed for the network measures indegree (upper), outdegree (middle) and betweenness centrality (lower). All three network characteristics showed significant correlations between SPES-clinical and SPES-propofol (Spearman's correlation, $p < 0.001$, FDR corrected). The strength of the correlation was expressed with the correlation coefficient (r_s). Both the horizontal bars and dots in the scatter plots have different colors for all individual subjects.

day after surgery (SPES-clinical), ensuring that the effect of propofol and other anesthesia used during implantation surgery have been eliminated.

One of the limitations of this study is the small number of participants (n = 6). With more included subjects, differences in effective connectivity across cortical regions could be investigated. Other studies found prominent changes in functional networks in the prefrontal cortex, which normally plays an important role in integrating and broadcasting distributed information (Lee et al., 2017; Schrouff et al., 2011). Another study found a decrease in

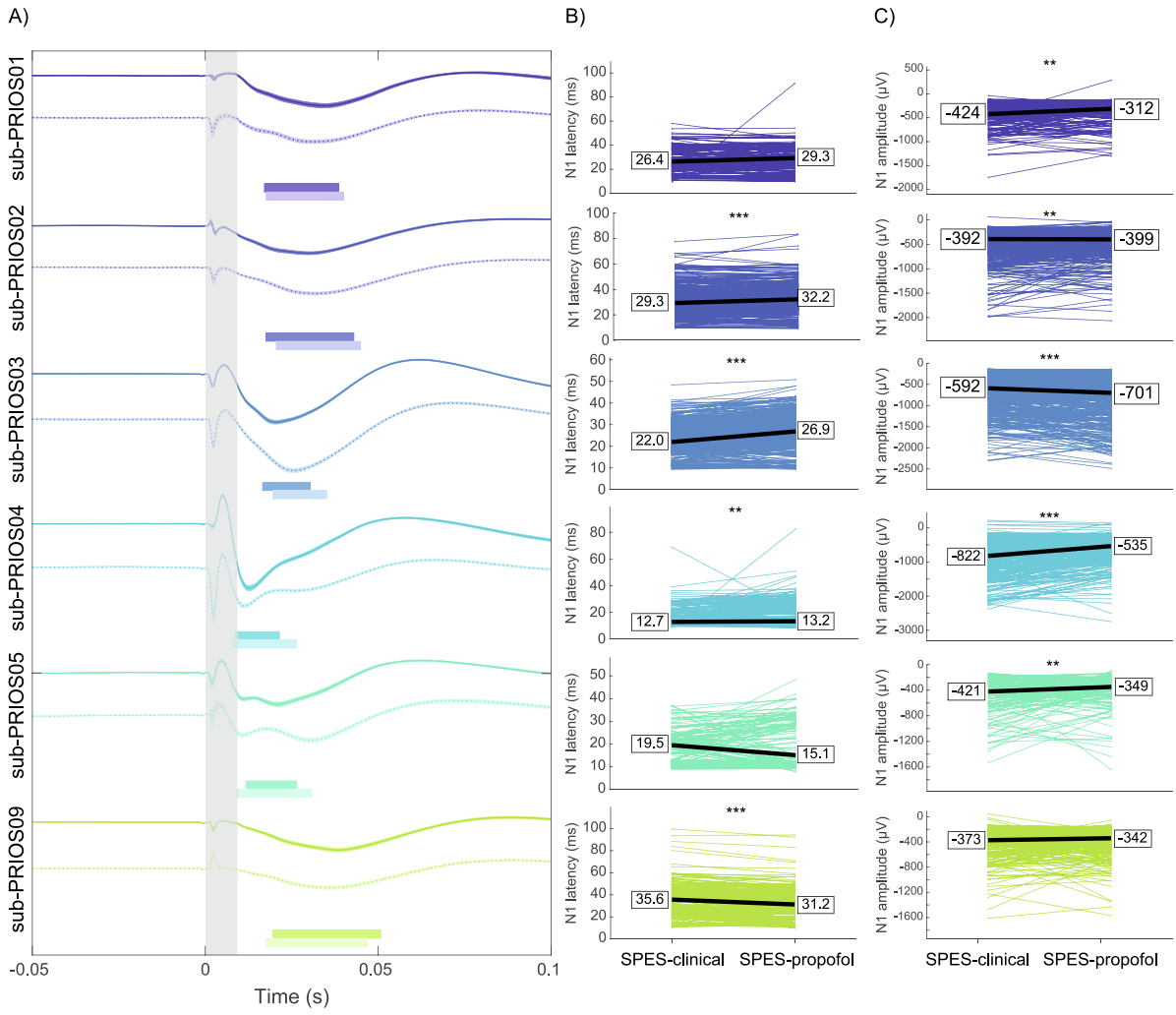

Fig. 5. Overview of the averaged cortico-cortical evoked potentials (CCEPs) for both SPES (Single Pulse Electrical Stimulation)-protocols. A) Six sets of CCEP-plots: the averaged CCEP ± Standard Error of the Mean (SEM) during SPES-clinical (SPES-protocol after subdural electrode grid implantation in the awake subject as part of clinical routine, upper) and during SPES-propofol (SPES-protocol performed under propofol-anesthesia at the start of the grid explantation surgery, lower) for each individual subject. Below each set of CCEP-plots, two horizontal bars are shown, indicating the mean ± SEM of the N1-peak-latencies in SPES-clinical (upper) and SPES-propofol (lower). B) The median latency of each N1-peak during SPES-clinical and SPES-propofol are represented by dots and connected by a line to indicate how the latency changes between the two protocols. The median latency is displayed by a thicker black line and the median values are displayed in boxes. C) The median amplitude of each N1-peak during SPES-clinical and SPES-propofol are represented by dots and connected by a line to indicate how the amplitude changes between the two protocols. The median amplitude is displayed by a thicker black line and the median values are displayed in boxes. $^{**}p < 0.01$, $^{***}p < 0.001$, FDR corrected.

functional integration within and between most brain networks, especially in the network between the frontal and parietal cortices (Schrouff et al., 2011) and other high-order cognitive networks (Wang et al., 2020).

Another limitation was the restricted time in which we had to execute SPES under anesthetics. We were able to apply at least two alternating pulses per stimulus pair instead of the ten pulses we applied in SPES-clinical. The effect of the number of trials on N1-peak-latency can be neglected (Supplementary Fig. 5). However, the effect of the number of trials on N1-peak-amplitude cannot be ignored and any conclusions on differences between N1-peak-amplitude in the awake state compared to the state under anesthetics should be taken carefully.

Subjects had epilepsy, which may have altered networks (van Blooijs et al., 2018). There is no consistent effect of epilepsy on the N1-peak-latency (van Blooijs et al., 2023), but the epileptogenic region is a densely connected region with high in- and outdegree values (Mouthaan et al., 2015; van Blooijs et al., 2018). Since we compare the N1-peak-latency, N1-peak-amplitude and network measures within a subject, we assume that a potential effect of epilepsy would be leveled out. Furthermore, on average, only 6% of the electrodes covered epileptogenic regions in our subjects, limiting the effect of epilepsy on our results.

In a study that investigated the depth of anesthesia, a negative correlation was found between the bispectral index and N1-peak-latency and a positive correlation between the bispectral index and N1-peak-amplitude in four patients indicating an increase in N1-peak-latency and a decrease in N1-peak-amplitude when the depth of anesthesia was stronger (Suzuki et al., 2019). In this study, we did not systematically monitor the depth of anesthesia during SPES-propofol. PRIOS03, PRIOS06 and PRIOS07 showed periods of burst suppression, which gradually disappeared, indicating that the level of propofol-anesthesia was not constant.

The amplitude of evoked potentials is decreased during anesthesia (Ohtaki et al., 2016; Yamao et al., 2017). This could have complicated the detection of the CCEPs during SPES-propofol. By excluding the burst suppression periods, we compensated for the varying levels of propofol-anesthesia and minimized the risk that CCEPs were missed due to smaller amplitudes of CCEPs. Future studies could give more insight in the working mechanisms of

anesthesia on brain networks if we continuously monitor dose-dependent effects of anesthesia on CCEPs and network characteristics. In a future prospective study, brain target-controlled infusion or Bispectral Index Monitoring could be used to estimate different states of consciousness and the depth of propofol anesthesia (Ozgoren et al., 2010).

In summary, our results show that the number of evoked CCEPs decreased, but this minimally affected the topology of the effective networks derived under propofol-anesthesia. The N1-peak-latency is increased when SPES is applied under propofol-anesthesia, but no clear effect was found on N1-peak-amplitude. More research investigating dose-dependent effects could expand our understanding of how propofol affects effective brain networks.

Disclosures

None of the authors have potential conflicts of interest to be disclosed.

CRediT authorship contribution statement

D. van Blooijs: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft. **S. Blok:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft. **G.J.M. Huiskamp:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. **P. van Eijsden:** Resources, Writing – review & editing. **H.G.E. Meijer:** Conceptualization, Methodology, Supervision, Writing – review & editing. **F.S.S. Leijten:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

Acknowledgements:

Research reported in this publication was supported by EpilepsieNL under Award Number NEF17-07 (DvB) and NEF19-12 (DvB, SB).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2024.01.012.

References

van Blooijs D, van den Boom MA, van der Aar JF, Huiskamp GM, Castegnaro G, Demuru M, et al. Developmental trajectory of transmission speed in the human brain. Nat Neurosci 2023. https://doi.org/10.1038/s41593-023-01272-0.

Demuru M, van Blooijs D, Zweiphenning W, Hermes D, Leijten F, Zijlmans M. A practical workflow for organizing clinical intraoperative and long-term iEEG Data in BIDS. Neuroinformatics 2022. https://doi.org/10.1007/s12021-022-09567-6 0123456789.

Giampiccolo D, Parmigiani S, Basaldella F, Russo S, Pigorini A, Rosanova M, et al. Recording cortico-cortical evoked potentials of the human arcuate fasciculus under general anaesthesia. Clin Neurophysiol 2021;132(8):1966–73. https://doi.org/10.1016/j.clinph.2021.03.044.

Haneef Z, Chiang S. Clinical correlates of graph theory findings in temporal lobe epilepsy. Seizure 2014;23(10):809–18. https://doi.org/10.1016/j.seizure.2014.07.004.

Hindriks R, van Putten MJAM. Meanfield modeling of propofol-induced changes in spontaneous EEG rhythms. Neuroimage 2012;60(4):2323–34. https://doi.org/10.1016/j.neuroimage.2012.02.042.

Joyce KE, Laurienti PJ, Burdette JH, Hayasaka S. A new measure of centrality for brain networks. PLoS One 2010;5(8). https://doi.org/10.1371/journal.pone.0012200.

Keller CJ, Honey CJ, Entz L, Bickel S, Groppe DM, Toth E, et al. Corticocortical evoked potentials reveal projectors and integrators in human brain networks. J Neurosci 2014;34(27):9152–63. https://doi.org/10.1523/JNEUROSCI.4289-13.2014.

Kuruvilla A, Flink R. Intraoperative electrocorticography in epilepsy surgery: useful or not? Seizure 2003;12(8):577–84. https://doi.org/10.1016/S1059-1311(03)00095-5.

Lee H, Noh G, Joo P, Choi B, Silverstein BH, Kim M, et al. Diversity of functional connectivity patterns is reduced in propofol-induced unconsciousness. Hum Brain Mapp 2017(June). https://doi.org/10.1093/biostatistics/manuscript-acf-y5.

Liu J, Dong K, Sun Y, Kakkos I, Huang F, Wang G, et al. Progress of brain network studies on anesthesia and consciousness: framework and clinical applications. Engineering 2022. https://doi.org/10.1016/j.eng.2021.11.013.

MacIver MB. Anesthetic agent-specific effects on synaptic inhibition. Anesth Analg 2014;119(3):558–69. https://doi.org/10.1213/ANE.0000000000000321.

Matsumoto R, Nair DR, Ikeda A, Fumuro T, Lapresto E, Mikuni N, et al. Parieto-frontal network in humans studied by cortico-cortical evoked potential. Hum Brain Mapp 2012;33(12):2856–72. https://doi.org/10.1002/hbm.21407.

Matsumoto R, Nair DR, LaPresto E, Bingaman W, Shibasaki H, Luders HO. Functional connectivity in human cortical motor system: a cortico-cortical evoked potential study. Brain 2007;130(Pt 1):181–97. https://doi.org/10.1093/brain/awl257.

Matsumoto R, Nair DR, LaPresto E, Najm I, Bingaman W, Shibasaki H, et al. Functional connectivity in the human language system: a cortico-cortical evoked potential study. Brain 2004;127(10):2316–30. https://doi.org/10.1093/brain/awh246.

Mouthaan BE, van 't Klooster MA, Keizer D, Hebbink GJ, Leijten FSS, Ferrier CH, et al. Single pulse electrical stimulation to identify epileptogenic cortex: clinical information obtained from early evoked responses. Clin Neurophysiol 2015;127(2):1088–98. https://doi.org/10.1016/j.clinph.2015.07.031.

Ohtaki S, Akiyama Y, Kanno A, Noshiro S, Hayase T, Yamakage M, et al. The influence of anesthetic depth on motor evoked potential response during awake craniotomy. Sapporo Med J 2016;85(1–6):56–7. https://doi.org/10.3171/2015.11.JNS151291.260.

Olmi S, Petkoski S, Guye M, Bartolomei F, Jirsa V. Controlling seizure propagation in large-scale brain networks. PLoS Comput Biol 2019;15(2):1–23. https://doi.org/10.1371/journal.pcbi.1006805.

Ozgoren M, Bayazit O, Kocaaslan S, et al. Brain function assessment in different conscious states. Nonlinear Biomed Phys 2010;4(Suppl 1):S6. https://doi.org/10.1186/1753-4631-4-S1-S6.

Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. Neuroimage 2010;52(3):1059–69. https://doi.org/10.1016/j.neuroimage.2009.10.003.

Rudolph U, Antkowiak B. Molecular and neuronal substrates for general anaesthetics. Nat Rev Neurosci 2004;5(9):709–20. https://doi.org/10.1038/nrn1496.

Sahinovic MM, Struys MMRF, Absalom AR. Clinical pharmacokinetics and pharmacodynamics of propofol. Clin Pharmacokinet 2018;57(12):1539–58. https://doi.org/10.1007/s40262-018-0672-3.

San-Juan D, Chiappa KH, Cole AJ. Propofol and the electroencephalogram. Clin Neurophysiol 2010;121(7):998–1006. https://doi.org/10.1016/j.clinph.2009.12.016.

Schrouff J, Perlbarg V, Boly M, Marrelec G, Boveroux P, Vanhaudenhuyse A, et al. Brain functional integration decreases during propofol-induced loss of consciousness. Neuroimage 2011;57(1):198–205. https://doi.org/10.1016/j.neuroimage.2011.04.020.

Suzuki Y, Enatsu R, Kanno A, Yokoyama R, Suzuki H, Tachibana S, et al. The influence of anesthesia on corticocortical evoked potential monitoring network between frontal and temporoparietal cortices. World Neurosurg 2019;123:e685–92. https://doi.org/10.1016/j.wneu.2018.11.253.

van Blooijs D, Leijten FSS, van Rijen PC, Meijer HGE, Huiskamp GJM. Evoked directional network characteristics of epileptogenic tissue derived from single pulse electrical stimulation. Hum Brain Mapp 2018(February):1–12. https://doi.org/10.1002/hbm.24309.

van Mierlo P, Carrette E, Hallez H, Raedt R, Meurs A, Vandenberghe S, et al. Ictal-onset localization through connectivity analysis of intracranial EEG signals in patients with refractory epilepsy. Epilepsia 2013;54(8):1409–18. https://doi.org/10.1111/epi.12206.

Wang S, Li Y, Qiu S, Zhang C, Wang G, Xian J, et al. Reorganization of rich-clubs in functional brain networks during propofol-induced unconsciousness and natural sleep. NeuroImage: Clin 2020;25(December). https://doi.org/10.1016/j.nicl.2020.102188.

Wilke C, Worrell G, He B. Graph analysis of epileptogenic networks in human partial epilepsy. Epilepsia 2011;52(1):84–93. https://doi.org/10.1111/j.1528-1167.2010.02785.x.

Yaffe RB, Borger P, Megevand P, Groppe DM, Kramer MA, Chu CJ, et al. Physiology of functional and effective networks in epilepsy. Clin Neurophysiol 2015;126(2):227–36. https://doi.org/10.1016/j.clinph.2014.09.009.

Yamao Y, Matsumoto R, Kunieda T, Nakae T, Nishida S, Inano R, et al. Effects of propofol on cortico-cortical evoked potentials in the dorsal language white matter pathway. Clin Neurophysiol 2021;132(8):1919–26. https://doi.org/10.1016/j.clinph.2021.04.021.

Yamao Y, Suzuki K, Kunieda T, Matsumoto R, Arakawa Y, Nakae T, et al. Clinical impact of intraoperative CCEP monitoring in evaluating the dorsal language white matter pathway. Hum Brain Mapp 2017;38:1977–91. https://doi.org/10.1002/hbm.23498.

Yeh FC, Panesar S, Fernandes D, Meola A, Yoshino M, Fernandez-Miranda JC, et al. Population-averaged atlas of the macroscale human structural connectome and its network topology. Neuroimage 2018;178(April):57–68. https://doi.org/10.1016/j.neuroimage.2018.05.027.

Yip GMS, Chen ZW, Edge CJ, Smith EH, Dickinson R, Hohenester E, et al. A propofol binding site on mammalian GABA A receptors identified by photolabeling. Nat Chem Biol 2013;9(11):715–20. https://doi.org/10.1038/nchembio.1340.

Zhang Y, Wang C, Wang Y, Yan F, Wang Q, Huang L. Investigating dynamic functional network patterns after propofol-induced loss of consciousness. Clin Neurophysiol 2019;130(3):331–40. https://doi.org/10.1016/j.clinph.2018.11.028.