

# Investigating EEG Markers of Responsiveness to Surgical Noxious Stimuli under Propofol Anaesthesia

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## Research Article

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# Abstract

## Background:

While general anaesthesia typically induces unconsciousness, some patients retain the capacity to respond behaviourally to noxious stimulation. Reduction in frontal alpha power has been proposed as a marker of arousal, but its clinical reliability is inconsistent. This exploratory study aimed to identify multichannel EEG spectral and connectivity markers associated with intraoperative behavioural responsiveness around noxious stimulation.

## Methods:

Sixty-four-channel EEG was recorded intraoperatively from seven patients undergoing microlaryngoscopy under propofol anaesthesia accompanied by analgesia. Responsiveness was determined by reactions to verbal commands. Alpha-band spectral features of responders and non-responders were compared pre- and post-noxious stimulation using descriptive statistics.

The relationship between spectral power of individual channels and the factors of noxious stimulation and responsiveness was investigated using a linear mixed model (LMM). Event-related synchronization/desynchronization (ERS/ERD) and weighted Symbolic Mutual Information (wSMI) were computed across frequency bands and response categories, with correction for multiple comparisons.

## Results:

Alpha power and global coherence showed minimal changes after stimulation in both responders ( $n = 3$ ) and non-responders ( $n = 4$ ).

In contrast, volitional (or cognitive) responses to noxious stimulation were reliably associated with increased high-beta and gamma power in sensory-motor and auditory cortices. These responses showed event-related synchronisation in left-central channels, whereas reflexive movements were marked by desynchronisation in same areas. Theta-band activity also differentiated response types: cognitive responses showed suppression, while reflexive responses showed enhancement, particularly over the same regions. Connectivity analysis further revealed that cognitive responses were associated with increased global whole-brain integration, especially in the theta-band linking motor, auditory, and premotor cortices. Reflexive responses, by contrast, were associated with reductions in global brain connectivity.

## Conclusions:

Frontal alpha EEG markers did not reliably index intraoperative responsiveness. Instead, localized high-frequency power increases and enhanced theta-band connectivity more robustly reflected 'connected consciousness', a state in which patients remain capable of perceiving and processing sensory inputs despite anaesthesia. Despite the limitations behind small sample size and variability in anaesthetic and patient factors, the surgical setting of the study strengthens the clinical relevance of these multichannel EEG features for guiding intraoperative monitoring and analgesic management before noxious stimulation.

# Introduction

General anaesthesia induces a reversible state characterized by unconsciousness, amnesia, analgesia, and immobility while preserving autonomic and motor stability(1). Anaesthetized individuals lack the conscious experience of pain and direct indicators of nociception are lacking. Autonomic reactions including tachycardia and hypertension are often considered signs of insufficient analgesia(2, 3). Clinical endpoints like responsiveness to verbal commands or painful stimuli are limited by neuromuscular blockade, inter-individual variability and confounding factors. Thus, objective observations of patient responses to noxious stimuli remain critical in evaluating analgesic adequacy during general anaesthesia(2).

Electroencephalography (EEG) can detect rapid changes in brain states(4) and is increasingly harnessed to study drug-induced perturbations. Leveraging EEG to investigate neural correlates of noxious stimulation under anaesthesia could aid in developing more sensitive monitors of responsiveness. Frontal alpha (8–12 Hz) power typically increases during anaesthetic-induced unconsciousness, and a transient reduction in this activity (alpha dropout), has been proposed as a marker of arousal(5, 6). However, these hypotheses remain largely unvalidated in clinical settings using high-density EEG.

EEG time-frequency analyses in the alpha band have shown promise in predicting categorical responses to nail bed compression and gag reflexes after endoscope insertion under general anaesthesia(7, 8). In contrary, evidence has shown that conventional frontal EEG markers did not reliably distinguish connected consciousness (a state in which patients retain sensory and cognitive processing capabilities under anaesthesia without explicit recall(9)) from unresponsiveness(9, 10). The limited frontal electrode montages in these studies limit clinical interpretability since: (1) Cortical regions involved in sensory, motor, and cognitive regions remain unmonitored; and (2) sparse channel configuration restricts connectivity analyses which may offer insights into the network-level dynamics of consciousness.

To address this gap, we investigated whether behavioural responses to noxious stimulation are accompanied by neurophysiological changes as assessed via multichannel EEG activity. We hypothesized that noxious stimulation would alter alpha spectral power and global coherence in responsive patients, reflecting a transient re-emergence of conscious processing. We further explored spatially localized EEG responses across

frequency bands, comparing patterns associated with different cognitive, reflexive, and absent responses. This secondary exploratory analysis extended beyond conventional alpha-band features to identify alternative neural markers that may more accurately reflect residual consciousness under anaesthesia.

## Methods

### Study design

The study received approval by New Zealand Southern Health and Disability Ethics Committee in September 2016 (6/STH/134). Written informed consent was obtained from all participants, and the study was conducted according to the principles of the Declaration of Helsinki. Inclusion criteria were adult (> 18 years) surgical patients undergoing microlaryngoscopy requiring a spontaneously breathing anaesthetic technique. Exclusion criteria included inability to provide informed consent or patient refusal.

The data comprised of segments of multichannel EEG recordings, videos depicting the drug infusion process, and a written log of measures of responsiveness and the surgical event timeline, for seven surgical patients. Figure 1A summarizes the study paradigm.

The surgery involved a slow induction of anaesthesia to maintain spontaneous respiration. The anaesthetic agents of propofol and remifentanyl were administered as intravenous infusions via effect-site target-controlled infusion (TCI). The target concentration was slowly increased to induce unconsciousness whilst maintaining spontaneous respiration, which is required for open airway surgery to allow full surgical access to the larynx, thereby titrating individually to clinical endpoints. Drug concentrations were logged at 5s intervals using synchronized video recordings of the surgical procedure. The insertion of the operating laryngoscope was considered as the primary painful stimulus.

EEG data were acquired using a 64-channel wireless cap (g.Nautilus, g.tec medical engineering GmbH, Schiedlberg, Austria) with a sampling rate of 250 Hz, employing a standard 10–10 electrode montage. Each patient underwent a minimum of three EEG recordings: (1) a two-minute pre-operative recording, (2) an intraoperative recording, and (3) a postoperative recording.

Responsiveness was assessed with a set of verbal commands of increasing complexity. Responses were considered positive if they occurred by the end of the command: (1) squeeze my hand once, (2) squeeze my hand twice, (3) show two fingers. Commands were administered at critical moments or in response to signs of awareness. Each subsequent command was delivered only if the preceding command elicited a correct response. Additionally, spontaneous movements such as finger wriggling, were logged. Responses were logged by a single rater with experience from similar prior studies.

Response events were defined as follows:

- 1) cognitive response: clear response to verbal instruction,
- 2) reflex response: any movement independent of verbal instructions (e.g. leg twitching),
- 3) no response: absence of any detectable response.

### Statistical Analysis

MATLAB and the open-source toolboxes of EEGLAB(11) and FieldTrip(12) were used for pre-processing and all statistical analyses. We initially explored the effect of the noxious stimulus on key spectral measures previously reported to vary across different anaesthetic states: alpha-power and global coherence within and between predefined regions of interest. Due to the limitations in sample size, descriptive statistics were employed to compare pre- vs. post-stimulation measures within each group of responders and non-responders.

To further investigate spatial brain activations associated with positive patient responses to verbal commands around noxious stimulation, we applied linear mixed models (LMMs) relating spectral power to responsiveness and stimulation. Channels showing significant effects were further analysed for event-related spectral power changes, with events classified as cognitive, reflexive, or absent responses. Connectivity changes were assessed using Weighted Symbolic Mutual Information (wSMI)(13).

All statistical tests were conducted at a 5% confidence level, with correction for multiple comparisons using the Benjamini–Hochberg method where applicable.

### Pre-processing pipeline

Initial five seconds of each segment were excluded due to significant noise and absence of events. Laplacian referencing was applied, where the EEG is locally referenced to an average of EEG recorded at neighbouring electrodes. This approach removes the potential common to all nearby electrodes and eliminates the reference electrode distortion of coherence estimates(14). This was followed by manual demeaning to strictly remove any DC bias. Bandpass filtering included the application of a butterworth filter of order six, which ensured a moderately high roll off rate. The

frequency band of 1–47 Hz was used to capture the key frequency bands necessary for analysis. The artifact rejection algorithm was devised based on the deviation and correlation criteria, adapted from the PREP pipeline(15), and applied on five seconds windows of the signal. Accordingly, windows of a robust deviation exceeding five and/or of a correlation criterion less than 0.4 were marked for interpolation. This differs from the approach of the PREP pipeline in which a defected window would imply that all data of the corresponding channel would be interpolated. Thereafter, all five seconds segments identified by the above criteria were interpolated via spherical interpolation(16), a form of spatial interpolation. This approach estimates the potential of a channel based on the assumptions that this potential could be expressed as a combination of potentials of neighbouring channels; and that the head is modelled as a sphere. Finally, Independent Component Analysis was applied to the interpolated EEG data, resulting in 64 components. ICLABEL(17), an automated component identification algorithm, was used to identify and exclude non-brain components predicted with an accuracy exceeding 90%.

## Effect of Noxious Stimulus on Spectral Features

Time-frequency analysis was performed on pre-operative and intra-operative EEG using multitaper frequency transformation (3s window, 50% overlap, 1 Hz resolution). Decibel baseline correction was applied using the pre-operative eyes-closed segment to normalize individual variability and improve the visibility of the event-related power. The time-varying power within the alpha-band relative to the total power was averaged within pre-defined regions of interest: pre-frontal (FP1, FPZ, FP2), occipital (O1, OZ, O2) and parietooccipital regions (PO7, PO3, POZ, PO4, PO8).

Secondly, the global coherence (GC) between the EEG channel signals is a form of spatiotemporal analysis of anaesthetic states of the brain and is computed based on the cross-spectral matrix at a defined time and frequency(6, 18) (see Appendix). A global coherence closer to one signifies that the leading eigenvalue is significant compared to the remaining eigenvalues and, therefore implies a highly coordinated spatial activity across the channel signals.

Computations incorporated the Chronux(19) toolbox applying the following parameters(6): time-bandwidth product of 2, number of tapers of 3, and a spectral resolution of 2 Hz. The pairwise global coherence between the channel pairs in the frontal (e.g. FP1-FP2), occipital (e.g. O1-O2) and frontal-occipital (e.g. FP1-O1) regions were averaged within the regions.

To investigate the hypothesised alpha dropout associated with increased awareness in response to noxious stimulus, spectral features were analysed within 30-second segments before and after the perturbation. The relative power and GC, both within the alpha-band in the predefined scalp regions were averaged within the time segment, generating six measures: frontal power, parietooccipital power, occipital power, frontal GC, occipital GC and frontal-occipital GC. Participants were categorised into two groups: responders (n = 3; ML002, ML003, ML006), who exhibited either a behavioural response to verbal commands or spontaneous movement following the perturbation, and non-responders (n = 4; ML001, ML004, ML005, ML007), who did not.

## Analysis of Band Power Correlates of Responsiveness and Noxious Stimulation

A 200-second time segment centred on the stimulus was extracted for each participant. For participant ML006, broadband noise appeared 28 seconds post-stimulus; 15 seconds were removed, leaving 150 and 50 seconds of pre- and post-stimulus data. Based on previous findings on event-related changes in alpha, high-beta, and gamma power during motor activity limb movements(20, 21), spectral power was computed in the bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), low-beta (13–19 Hz), mid-beta (19–25 Hz), high-beta (25–30 Hz) and gamma (30–47 Hz).

A binary response series was constructed per participant (1 = response, 0 = no response), including both reflex movements and verbal responses. Due to variable inter-response intervals, a manual correction was performed by setting the response value to 0 within  $\pm 10$  seconds of each positive response. The series was then linearly interpolated at 1.5-second intervals to match the temporal resolution of the band power signals.

The relationship between spectral power at individual EEG channels and the factors of noxious stimulation and behavioural responsiveness was examined using linear mixed-effects models (LMMs). Separate models were fitted independently to each channel within each frequency band, avoiding multicollinearity across bands and ensuring that random slopes were estimated within, rather than across, frequency ranges.

Fixed effects included responsiveness, noxious stimulation, and their interaction, which tested whether responsiveness exerted an additional effect on spectral power specifically during noxious stimulation. Subject-specific random slopes were included for responsiveness and noxious stimulation, capturing individual variability in channel-level power changes associated with these factors. In addition, the random intercept accounted for inter-subject differences in baseline power levels.

## Power ~ Response \* Noxious stimulation + (1 + Response+ Noxious stimulation | Subject) (1)

Statistically significant channels were identified via correction for multiple comparison.

# Investigating event-related power and connectivity across response categories

The event-related power of channels showing significant response-related effects in the LMMs (e.g., C3) and their contralateral counterparts (e.g., C4) was computed. Power changes within the peri-stimulus interval were computed to investigate the event-related synchronization and desynchronization (ERS/ERD) relative to a pre-event baseline.

To investigate inter-channel information transfer during specific response events, we applied the wSMI, a non-directed measure of global information sharing previously shown to outperform other metrics such as Phase Lag Index (PLI) in discriminating altered states of consciousness(13, 22). It quantifies the joint probability between pairs of EEG channels transformed into discrete symbols of predefined time samples (see Appendix). We computed the median wSMI of each channel with all other channels separately for each response category. To assess whether these values differed significantly across response types, we conducted Mann-Whitney U tests at a 5% significance level, with correction for multiple comparisons. In addition, we examined inter-region differences in mutual information by comparing wSMI values between predefined pairs of frontal, parietal, and occipital regions across response categories.

## Results

This study involved 7 surgical patients undergoing variations of microlaryngoscopy at Waikato Hospital. Three patients responded – ML003 was the only participant who responded to auditory commands following stimulation, whereas ML002 and ML006 exhibited only reflexive movements. Table 1 summarizes patient demographics, surgical details, comorbidities and medications. Figure 1B illustrates group-level analysis of the propofol effect-site concentration (Ce), aligned to noxious stimulation. Considerable variability in Ce was observed during the maintenance phase, reflecting individual titration to clinical endpoints. Two patients (ML002, ML007) were not administered remifentanyl.

Table 1  
Summary of dataset patient information. The ASA physical status indicates the physical fitness of a patient prior to surgery ranging from a rating of 1 (healthy person) to 3 (severe systemic disease).

| ID    | Age | Gender | Ethnicity      | ASA <sup>1</sup><br>physical<br>status | Height | Weight | Surgery                                             | Comorbidities                                                                                             | Medications                                                                                                              | Betablocker |
|-------|-----|--------|----------------|----------------------------------------|--------|--------|-----------------------------------------------------|-----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|-------------|
| ML001 | 69  | M      | NZ<br>European | 3                                      | 179    | 87     | Laryngoscopy and<br>bilateral injection             | IHD ExSmoker<br>Type2DM<br>Pancreatic<br>lesion                                                           | Aspirin<br>Simvastatin<br>Metformin                                                                                      | 0           |
| ML002 | 71  | M      | NZ<br>European | 3                                      | 170    | 110    | Microlaryngoscopy<br>and laser tracheal<br>stenosis | MI VF arrest,<br>Short term<br>Memory<br>Impairment,<br>Hypertension,<br>Impaired<br>Glucose<br>Tolerance | Aspirin<br>Atorvastatin<br>Citalopram<br>Metoprolol<br>Candesartan<br>Amlodipine<br>Frusemide<br>Omeprazole<br>Doxazosin | 1           |
| ML003 | 21  | F      | NZ<br>European | 1                                      | 169    | 63.2   | Microlaryngoscopy<br>and Vocal Cord<br>Biopsy       | Nil                                                                                                       | Oral<br>Contraceptive<br>Pill                                                                                            | 0           |
| ML004 | 67  | F      | NZ<br>European | 2                                      | 154    | 53.4   | Microlaryngoscopy                                   | Hypothyroidism                                                                                            | Thyroxine                                                                                                                | 0           |
| ML005 | 40  | F      | NZ Maori       | 2                                      | 177    | 99     | Microlaryngoscopy                                   | Nil                                                                                                       | Nil                                                                                                                      | 0           |
| ML006 | 28  | M      | NZ<br>European | 2                                      | 194    | 114    | Microlaryngoscopy                                   | Lower Back<br>Pain, Reflux                                                                                | Omeprazole                                                                                                               | 0           |
| ML007 | 63  | M      | NZ<br>European | 2                                      | 171    | 107    | Microlaryngoscopy<br>and Vocal Cord<br>Biopsy       | Polymyalgia<br>GORD                                                                                       | Prednisone<br>Omeprazole                                                                                                 | 0           |

1. Abbreviations: ASA, American Society of Anaesthesiologists.

## Effect of Noxious Stimulus on Spectral Features

Median values of spectral measures before and after noxious stimulation remained numerically similar within responders and non-responders (Table 2). Standardized mean differences were mostly small in magnitude (IHedges’ gl < 0.4) across all measures. Occipital alpha GC increased in responders post stimulation with a moderate effect size of -0.565. However, given the limited sample size, these effect size estimates should be interpreted cautiously. Overall, these results suggest that the derived EEG features did not change notably in responders or non-responders around the time of noxious stimulus.

Table 2  
Descriptive statistics for spectral measures of responder and non-responder groups during pre- and post-noxious stimulus intervals. Effect sizes are expressed as Hedges' g and represent standardized mean differences between responders and non-responders. (NOX: Noxious stimulus, GC: Global Coherence)

|                              | Responders |          |             | Non-responders |          |             |
|------------------------------|------------|----------|-------------|----------------|----------|-------------|
| Measure                      | Median     |          | Effect size | Median         |          | Effect size |
|                              | Pre-NOX    | Post-NOX |             | Pre-NOX        | Post-NOX |             |
| Frontal alpha power          | 0.259      | 0.262    | 0.0345      | 0.187          | 0.177    | 0.0148      |
| Parietooccipital alpha power | 0.0466     | 0.0500   | 0.180       | 0.0607         | 0.0538   | 0.449       |
| Occipital alpha power        | 0.0775     | 0.0723   | 0.189       | 0.0836         | 0.0624   | 0.330       |
| Frontal alpha GC             | 0.874      | 0.853    | 0.121       | 0.883          | 0.896    | -0.0139     |
| Occipital alpha GC           | 0.844      | 0.857    | -0.565      | 0.828          | 0.822    | 0.221       |
| Frontal-occipital alpha GC   | 0.827      | 0.843    | -0.0813     | 0.864          | 0.866    | -0.0491     |

## Analysis of Band Power Correlates of Responsiveness and Noxious Stimulation

Extending the analysis to additional frequency bands spanning 1–47 Hz using separate LMM's, we observed that the population response effect ( $\beta$ ) was predominantly positive in the lower frequency bands (delta and theta), with electrodes showing effects  $> 0.1$  (Figure S1). In the delta band, several of these effects survived correction for multiple comparisons. In contrast, higher frequency bands (mid-beta to gamma) showed minor negative effects ( $< -0.05$ ), suggesting that behavioural response resulted in reductions in power in these bands across patients.

At the single-subject level, patient ML003 exhibited a consistent positive response effect in mid-beta to gamma frequencies over channels corresponding to the left somatosensory and auditory cortices (Fig. 2). Notably, this was the only patient who demonstrated cognitively meaningful responsiveness to auditory commands. Interestingly, patient ML004, who did not display any behavioural responsiveness, also showed a positive response effect in the gamma band. However, these effects did not reach significance.

Patient ML002, who exhibited reflexive movements, showed strong negative response effects in frontal channels in the higher frequency bands, alongside robust positive effects in delta frequencies over the right motor and motor planning regions. These delta effects ( $> 0.1$ ) were stronger than those observed in most other patients. However, this pattern was not replicated in patient ML006, who also demonstrated reflexive movements. This variability highlights that reflexive behaviours may not reliably align with the same electrophysiological signatures as cognitively meaningful responses.

Considering the population noxious stimulation effect, none of the channels were significant across frequency bands. Patient ML002 showed negative effects in frontal regions within the gamma band, suggesting a reduction in spectral power in response to painful stimulation (Figure S2). In contrast, patient ML003, who demonstrated purposeful responsiveness, exhibited increased gamma-band power in the left motor and frontal regions. A similar but less pronounced increase was also observed in patient ML004, although this effect did not reach the same level of significance. Overall, the effects of noxious stimulation were weaker than those associated with the response.

## Event-related power and connectivity across response categories

Event-related synchronization and desynchronization (ERS/ERD) for the selected channels are presented in Fig. 3, along with the statistics in Table S1. Focusing on the high-beta and gamma bands which were previously identified as relevant; cognitive responses were associated with a statistically significant increase in power over the left somatosensory and auditory cortices, distinguishing them from other response types.

Differences between response categories were also prominent in the theta band. Channels C5 and TP7 exhibited statistically significant contrasts: cognitive responses were characterized by ERD, while reflex responses showed ERS, even after correction for multiple comparisons.

At the whole-brain level, the median wSMI across channel pairs was higher during cognitive responses compared to reflex or no response (Fig. 4), suggesting enhanced global information sharing with cognition. The most pronounced differences across response categories were observed at a temporal resolution of  $\tau = 8$ , as indicated by the number of channels showing statistically significant differences. Increases were particularly evident in regions associated with motor execution, auditory processing, and premotor planning in the left hemisphere. Analysis of the top 95% strongest wSMI connections between all channels at  $\tau = 8$  revealed that interhemispheric connectivity was most prominent during responses (Figure S3). However, strong frontal-parietal coupling which is typically associated with decision-making and executive function was not observed. Supporting this, the mean wSMI between frontal and occipital or parietal regions was comparable between cognitive and reflexive responses (Table S2).

Interestingly, frontal-parietal connectivity was significantly lower ( $p < 0.05$ ) during reflex responses compared to no-response events. Moreover, reflex responses exhibited an overall reduction in whole-brain connectivity relative to the no-response events, as evidenced in Fig. 4.

## Discussion

Using predominantly within-subject analysis, this study aimed to identify neurophysiological signatures of responsiveness under general anaesthesia in the clinic, hypothesizing that noxious stimulation would evoke changes in alpha band spectral power and global coherence in cognitively responsive patients. Contrary to this hypothesis, these conventional EEG markers failed to capture responsiveness where anaesthesia appeared to preserve some residual consciousness. Using high-density (64-channel) EEG revealed localized increases in high-frequency power within task-relevant cortical regions, and enhanced theta-band connectivity, as possible markers of connected consciousness that would not have been accessible with conventional single-channel or frontal EEG monitoring.

## Effect of Noxious Stimulus on Spectral Features

Since frontal alpha power typically increases during anaesthesia, 'alpha dropout' has been proposed as a marker of arousal(5, 6). However, descriptive statistics showed negligible differences between pre vs post noxious stimulus measures of alpha band spectral power and global coherence in responsive patients.

The absence of strong noxious stimulation effects in the LMM suggests that anaesthetic agents dampened typical spectral responses. For example, patient ML003, who later showed cognitive responsiveness, exhibited no immediate spectral change at the stimulus but effects emerged seconds later, reflected in response-related LMM effects.

## Localized changes of spectral power and connectivity

Patient ML003 demonstrated volitional motor behaviour by following auditory commands post-stimulation, suggesting preserved auditory processing and motor planning to allow the hand squeeze response(23). In this patient, we observed significant response related effects in mid-beta to gamma band power in electrodes overlying left somatosensory and auditory cortices (e.g., C1, C3, C5, T7). Gamma enhancement over the left auditory cortex reflects verbal command processing, aligning with established left-hemisphere dominance in right-handed individuals for language comprehension(24). These changes were not seen in other patients, supporting their specificity for preserved perception and motor intent. Rigorous pre-processing reduced the likelihood that the observed gamma-band increases were driven by EMG artefacts.

These findings are consistent with prior evidence of event-related desynchronization (ERD) in contralateral sensorimotor areas during intention to move(20). An EEG study(21) showed a significant ERD in the contralateral sensorimotor cortex in the beta and gamma bands for limb movements and was consistent with prior outcomes in fMRI studies. While exact electrode locations of the primary motor cortex of the hand cannot be confirmed due to electrode placement variability, electrodes such as C3, C4(25) and C1, C2(26) are frequently associated with motor cortex activity in pain and movement studies.

In patient ML003, the presence of cortical activation despite stable frontal alpha power, an EEG marker typically linked to awareness, may suggest the occurrence of connected consciousness(9). Unlike general awareness, connected consciousness allows the perception of bodily or external inputs during anaesthesia, which could explain the stable alpha spectral measures despite observable responses to commands. A large-scale study has shown connected consciousness incidence of ~ 11% after tracheal intubation which exceeded that of explicit recall but did not report concurrent neurophysiological data(27). Other studies identified EEG markers distinguishing sensory connection versus disconnection under sedation, but connected consciousness was only assessed retrospectively, lacking real-time neural correlates of connected consciousness(28). Furthermore, a study preceding this work demonstrated the limited efficacy of frontal EEG markers in detecting connected consciousness(10). Contrary to prior work, we identified concurrent multichannel EEG markers, specifically, localized high-frequency power increases in task-relevant cortical regions occurring concurrently with behaviourally confirmed connected consciousness.

Interestingly, patient ML004, who lacked overt responses, showed similar response related effects to ML003, albeit with lower statistical strength. This may represent covert consciousness, where motor intention or sensory connection does not manifest behaviourally, highlighting that unresponsiveness does not necessarily equate to complete disconnectedness – referred to as cognitive motor dissociation(29, 30).

## Specific event-related analyses

Cognitive responses were associated with statistically significant increases in high-frequency power (beta and gamma bands) over the left sensorimotor and auditory cortices, while reflex and non-response events lacked such activations. Theta-band effects in channels like C5 and TP7 further distinguished categories: reflex responses showed event-related synchronization (ERS), while cognitive responses showed desynchronization (ERD), suggesting different mechanisms of cortical excitability.

Connectivity analyses revealed higher median wSMI during cognitive responses, reflecting increased information integration. Temporal resolution choices tuned wSMI to frequency ranges ( $\tau = 2$ : beta-gamma,  $\tau = 4$ : alpha-beta,  $\tau = 8$ : theta), with theta-sensitive settings showing the clearest discrimination. Theta-band coupling, particularly interhemispheric, dominated during cognitive responses, consistent with its proposed role in conscious processing and top-down control(31). However, we did not observe increased fronto-parietal connectivity, often implicated in executive function, suggesting localized cortical processing may be sufficient for simple motor responses under anaesthesia.

Reflex responses showed reduced whole-brain and frontal-parietal connectivity compared to non-response events. While the underlying mechanism remains unclear, this may reflect suppressed cortical communication during automatic, subcortical motor activity. This distinction between cognitive and reflex responses highlights the importance of distinguishing volitional activity from mere motor output when assessing awareness.

## Clinical Implications

Our findings challenge the reliability of alpha power or global coherence as sole markers of anaesthetic depth. While alpha dropout has been linked to nociceptive responses, it appears insufficient for detecting connected consciousness with complete reliability. Notably, the absence of connected consciousness and not full unconsciousness, has been suggested as an optimal anaesthetic target, given associations with reduced intraoperative awareness and postoperative delirium(9, 30). This underscores the need to distinguish between connectedness and awareness. High-frequency power changes in task-relevant cortical regions, coupled with increased information-sharing metrics such as wSMI, may offer more specific indicators of connected consciousness.

## Limitations and future work

Several factors limit the generalizability of the study's findings. The small sample size, with only one patient (ML003) with clear cognitive responses limits statistical power. Given this was a clinical cohort, anaesthetic depth, noxious stimulus intensity, and remifentanyl administration were not standardized, introducing potential confounds. The patient cohort spanned a wide age range, and prior work suggests higher connected consciousness incidence in younger patients(27).

Despite these constraints, the real-world surgical setting of the study enhances clinical relevance. Unlike controlled laboratory environments, surgical variability reflects actual practice. The EEG markers identified here may aid intraoperative monitoring, particularly in guiding analgesic administration before noxious stimulation. A larger patient cohort with standardized anaesthetic and analgesic drugs, controlled noxious stimuli and balanced demographics would help validate these outcomes.

## Abbreviations

- LMM  
Linear Mixed Model
- ERS  
Event-Related Synchronization
- ERD  
Event-Related Desynchronization
- wSMI  
weighted Symbolic Mutual Information
- EEG  
Electroencephalography
- IFT  
Isolated Forearm Test
- TCI  
Target-Controlled Infusion
- GC  
Global Coherence
- PLI  
Phase Lag Index
- Ce  
Effect-Site Concentration

## Declarations

### Ethics approval and consent to participate:

The study received approval by New Zealand Southern Health and Disability Ethics Committee in September 2016 (6/STH/134). Written informed consent was obtained from all participants, and the study was conducted according to the principles of the Declaration of Helsinki.

### Consent for publication:

Written informed consent was obtained from all participants.

### Availability of data and materials:

The data will be available upon request from the authors.

**Competing interests:**

None

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**Authors' contributions:**

Vidushani Dhanawansa: This author helped with study conceptualization, data analysis, interpretation and writing of the article.

Jamie Sleight MD: This author helped with study conceptualization, interpretation and finalization of the article.

Amy Gaskell: This author helped with data collection, study conceptualization, interpretation and finalization of the article.

Adeel Razi: This author helped with study conceptualization, interpretation and finalization of the article.

Levin Kuhlmann: This author helped with study conceptualization, data analysis, interpretation and finalization of the article.

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**Authors' information (optional):**

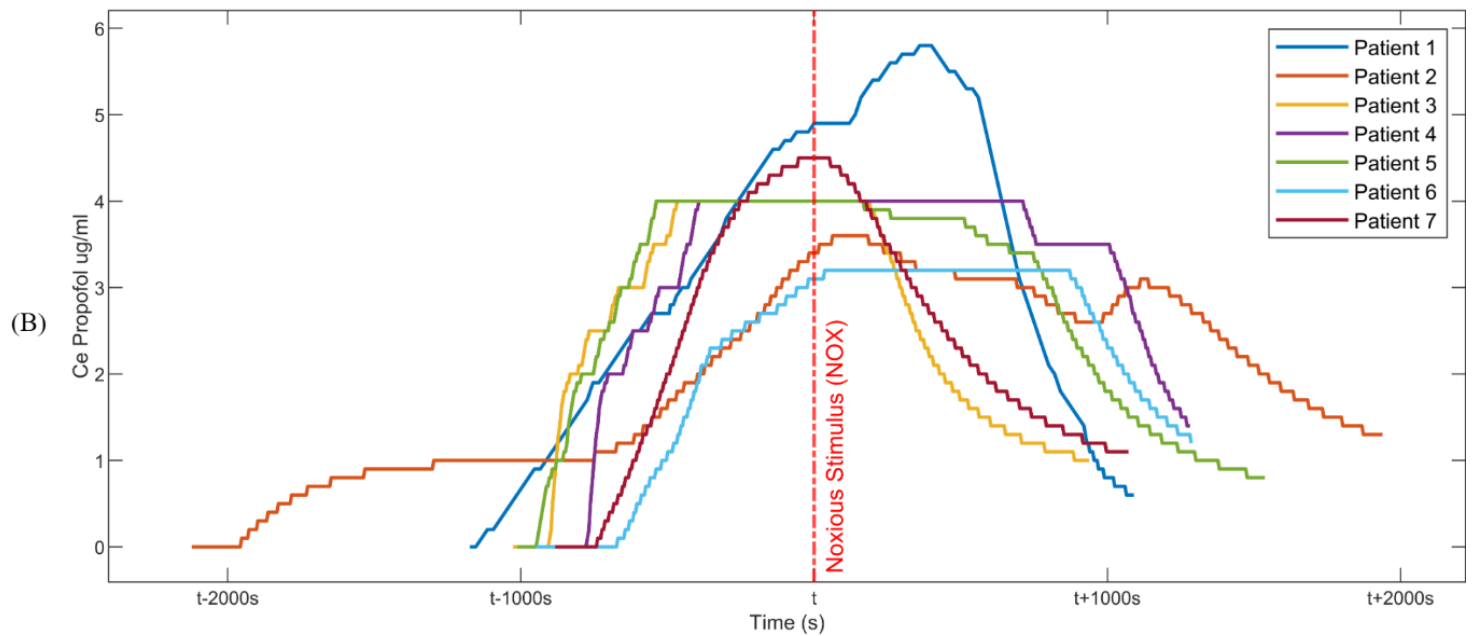
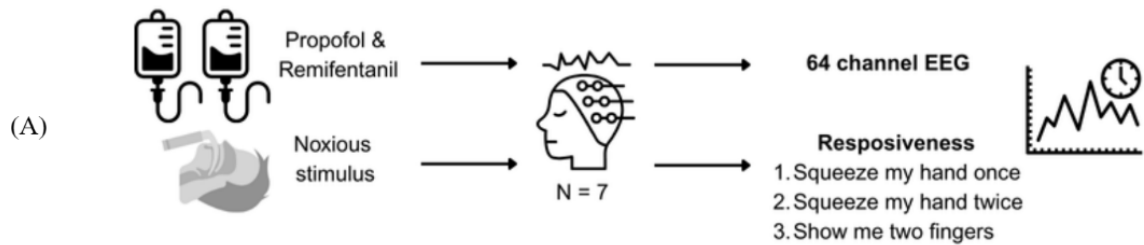
N/A

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## Figures



**Figure 1**

Summary of study. (A) Representation of the study design. 7 patients underwent microlaryngoscopy surgery, anaesthetised under propofol and remifentanyl. The insertion of the laryngoscope formed the painful or noxious stimulus. Intraoperative 64-channel EEG was recorded, along with responses to 3 verbal commands. (B) Group figure of effect site concentration (Ce) of Propofol aligned by the primary noxious stimulus (NOX).

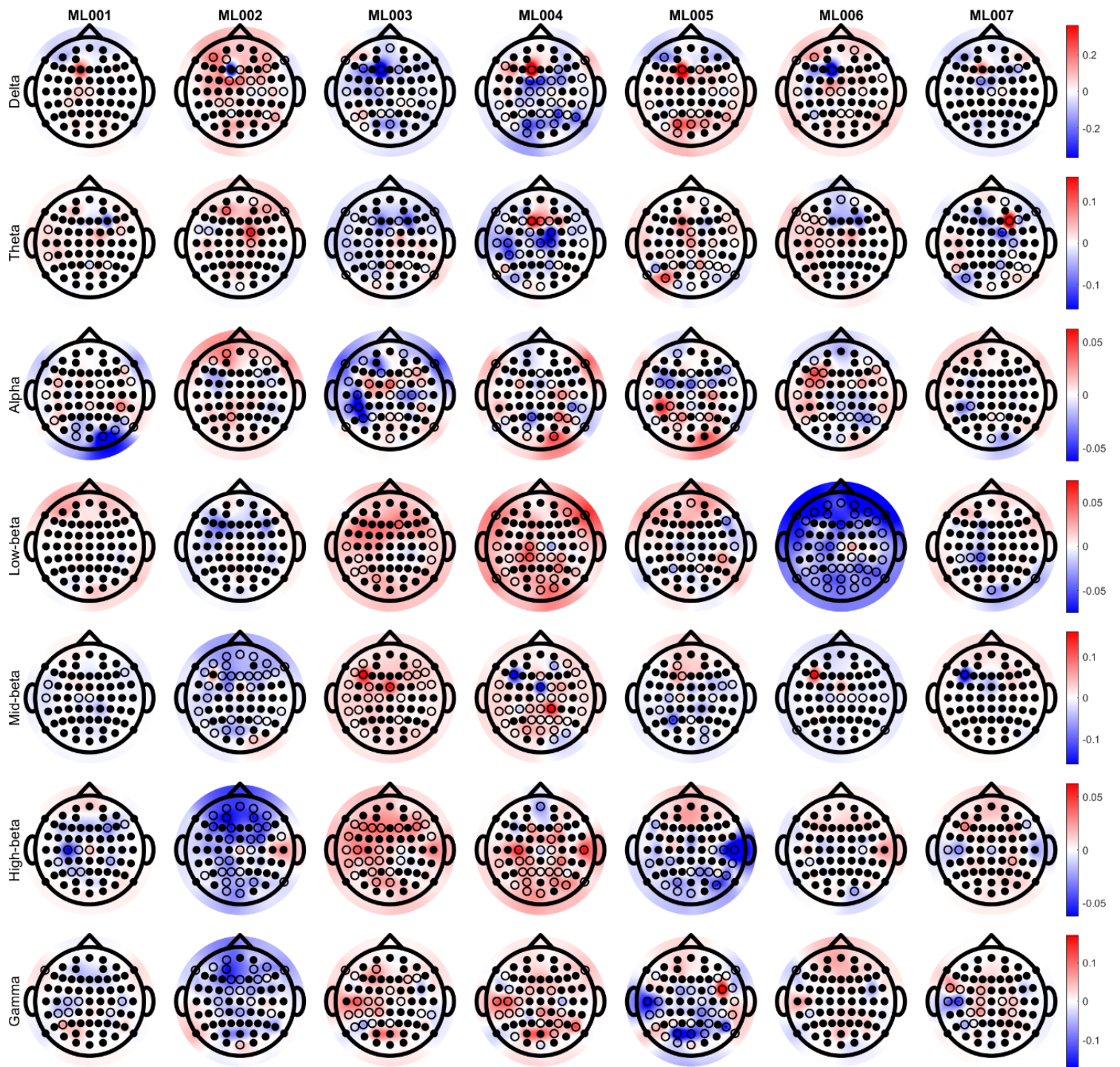
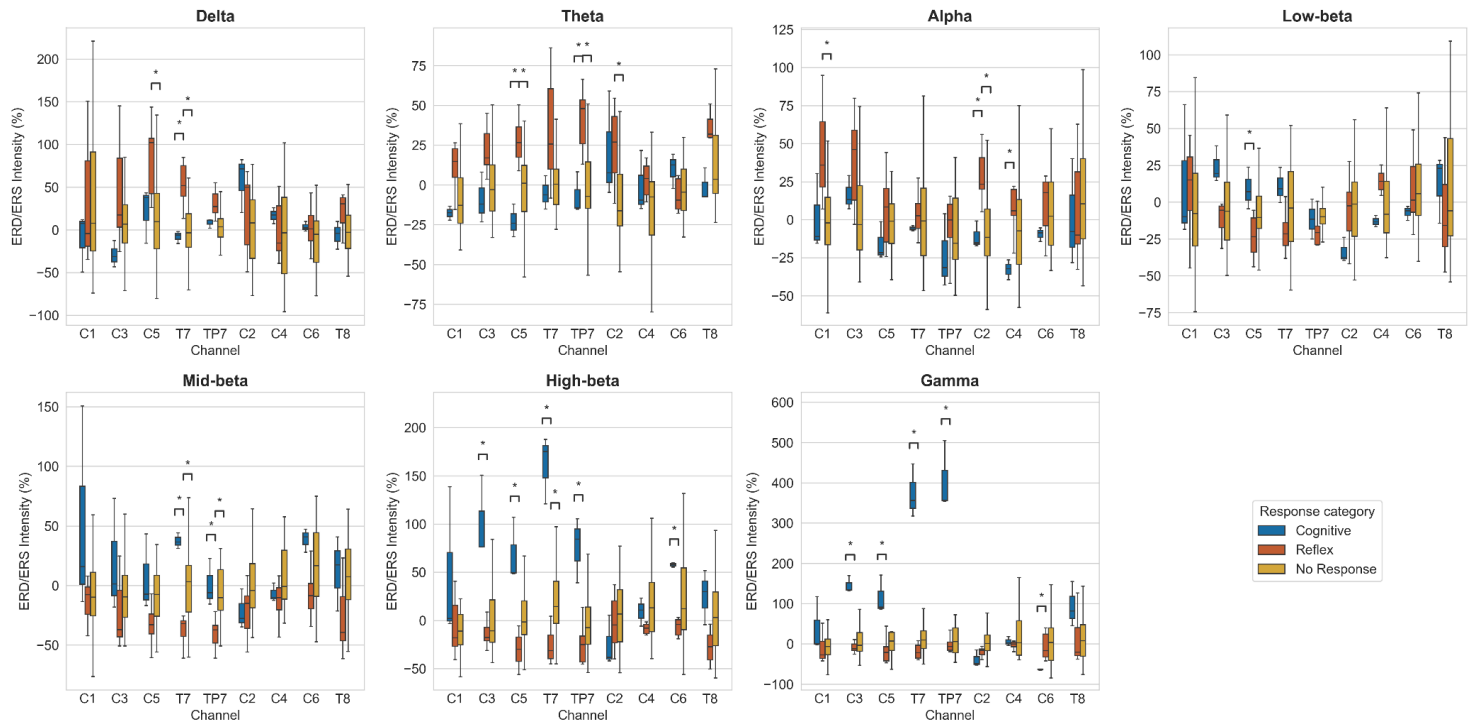


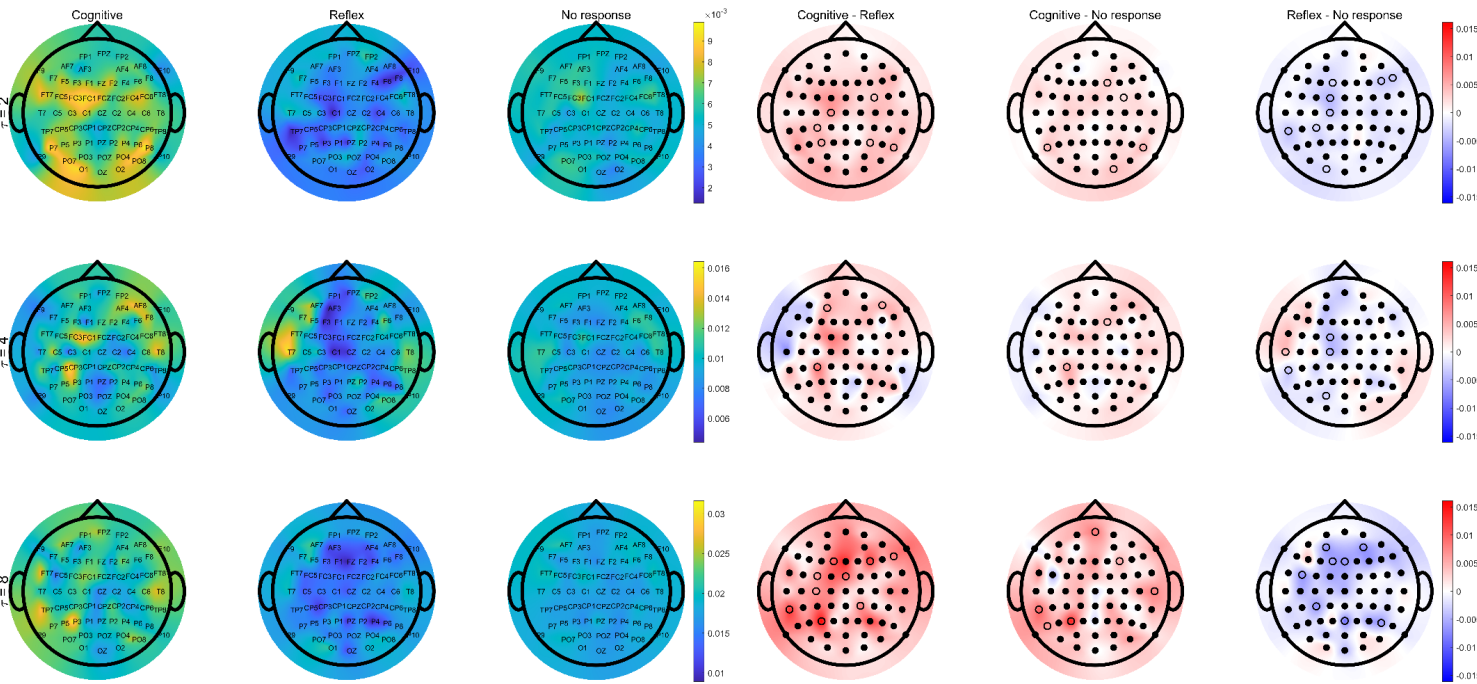
Figure 2

Topographic maps showing subject-specific response effect ( $\beta$ ) with individual colour scales for each frequency band. Frequency bands span across 1-47 Hz (unfilled channels:  $p < 0.05$ , corrected for multiple comparisons).



**Figure 3**

Group plot for event related desynchronization/ synchronization (ERD/ERS) of relative power of frequency bands for the identified response categories (\* $p < 0.05$  and survived multiple comparisons). Channel selection is based on channels of significant response related effects in the linear mixed model.



**Figure 4**

Weighted Symbolic Mutual Information (wSMI) of each channel with other channels for different response categories and temporal resolutions ( $\tau$ ). Columns 1-3 show the median wSMI of each channel with all other channels for each response category. Columns 4-6 depict the differences between the response categories (unfilled channels:  $p < 0.05$ , uncorrected for multiple comparisons).

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