Three distinct low-frequency (<4Hz) traveling wave types in volunteer propofol anaesthesia revealed by empirical mode decomposition

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Introduction

The human electroencephalogram (EEG) during propofol anaesthesia shows high delta-band (0.5-4Hz) activity accompanied by traveling slow waves (~1Hz)[1]. Slow-wave saturation (SWAS) has been proposed as an individualised endpoint for perception loss in anaesthesia[2,3]. In NREM sleep, traveling slow-waves have been proposed to be of two types with separate thalamocortical and cortico-cortical generation mechanisms[4,5]. Much remains unclear about the dynamics of anaesthetic slow-waves and their role in perception loss. In this advanced secondary analysis, we used a novel data-driven signal decomposition technique called iterated masked empirical mode decomposition[6–8] (EMD) to analyse dose-dependent behaviour of low-frequency waves.

Methods

Data for this analysis came from an ultra-slow target-controlled intravenous infusion of propofol up to 4 µg/ml in 16 healthy volunteers (8 female, age 28.6 ± 7 years, recruited by local advertising) as described in[2]. EEG was acquired using a 32-channel EEG cap sampled at 5kHz referenced to FCz. For this analysis, data was re-referenced to linked earlobes, down-sampled to 500Hz, and filtered with an 8th-order zero-phase Butterworth 0.1-30Hz bandpass filter. Masked EMD was performed using the open-source EMD Python toolbox (https://emd.readthedocs.io) on 46 continuous one-minute segments of data from induction of each subject. EMD was iterated 10 times, starting with an initial mask of [14, 7, 2.5, 0.5, 0.2]Hz. This mask was updated at each iteration as the amplitude-weighted mean of each mode's instantaneous frequency. This decomposition is robust to changes in the initial mask or number of modes. Cycles were identified from jumps in instantaneous phase on each channel calculated by the Hilbert transform. Cycles from intrinsic mode functions (IMFs) falling in 0.5-4Hz band were analysed further. Those with negative duration 0.125-1.5s, amplitude in the upper 50th percentile, and appearing on at least 5 channels within ±200ms of an arbitrary reference channel were accepted as traveling waves. Their wave density (waves detected per minute), frequency, globality (% of channels involved in slow wave), peak-to-peak amplitude, speed, and origin were calculated[9]. Subject-averaged IMF properties were compared using one-way ANOVA with Bonferroni correction for multiple comparisons. Significance was set at $P<0.05$.

Results

All 16 subjects were included in the analysis. In all subjects, iterated masked EMD decomposed the signal into five IMFs. The first intrinsic mode corresponded to alpha spindles (f = 11.85±0.48 Hz, grand mean± standard deviation across subjects). The next three modes captured low-frequency (<4Hz) activity (Figure 1). They had significantly different frequencies ($P<10^{-15}$) and are referred to

as *high delta* (IMF-2, f = 3.44±0.23 Hz), *low delta* (IMF-3, f = 1.44±0.09 Hz) and *slow* (IMF-4, f = 0.74±0.09 Hz). IMF-5 captured residual artefactual EEG drifts and was discarded.

Traveling waves identified from low-frequency modes had consistent between-subject morphological, dynamical, and topographical properties (Figures 2, 3). Slow waves (IMF-4) were fronto-central, decreased in globality with propofol concentration, had diffuse origins, and became saturated in wavenumber and amplitude. Low-delta waves (IMF-3) also saturated in amplitude and wavenumber but increased in globality with anaesthetic concentration unlike slow waves, had mostly lateral temporal origins, and were faster (v = 7.92±0.90 m/s vs v = 4.6±0.38 m/s for slow waves, $P<10^{-11}$). High-delta waves (IMF-4) were identified at high concentrations past SWAS. They had low globality, frontal origins, and were fastest (v = 13.9±1.1 m/s). All wave types decreased in frequency with increasing propofol concentration.

Conclusions

We identified three distinct types of low-frequency (<4Hz) traveling waves in propofol anaesthesia using a novel data-driven signal processing technique. These high delta, low delta, and slow waves were found in all subjects and with increasing propofol dose they had significant differences between their frequency, globality, origin, and speed. Our results show some similarities with Type I / II wave distinction proposed for sleep slow waves[4,5]. Type II waves (local, small amplitude) behave similarly to high delta, but type I (global, large amplitude) is comprised of two distinct types of waves, faster frontal low-delta and slower fronto-central slow waves. Similarly, slow-wave saturation results from an interplay between the low delta and slow wave modes as typically defined[3].The physiological origin of these types of waves remains to be investigated. We hypothesise these may reflect cortico-cortical and thalamocortical processes. The three wave types might thus have different functional significance and implications for optimal anaesthetic induction and maintenance.

References:

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Figure 1: (A) Example iterated masked EMD signal decomposition in 20 seconds of deep propofol anaesthesia EEG and (B) frequency of waves from IMFs in all 16 subjects. The **** marks significant differences at corrected $P<10^{-15}$.

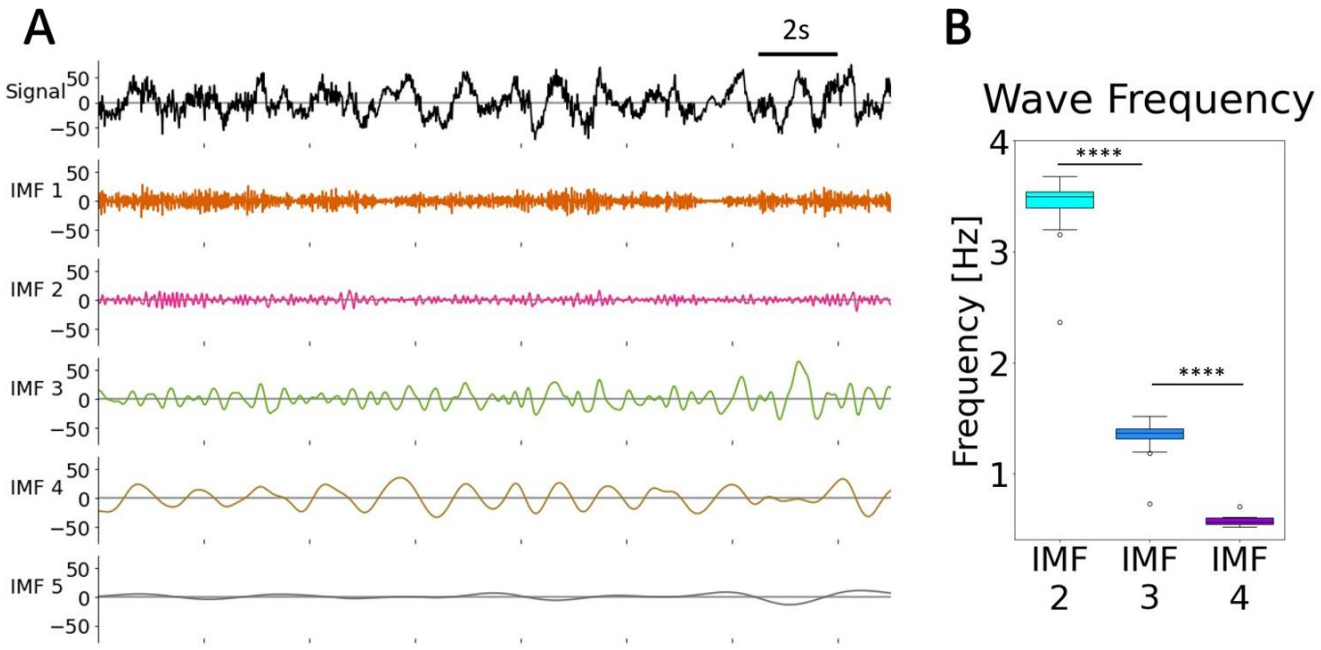

Figure 2: Changes observed with increasing propofol concentration in grand mean across subjects of the A) globality, B) wave density, C) frequency, and D) amplitude for the 3 low-frequency (<4Hz) wave types.

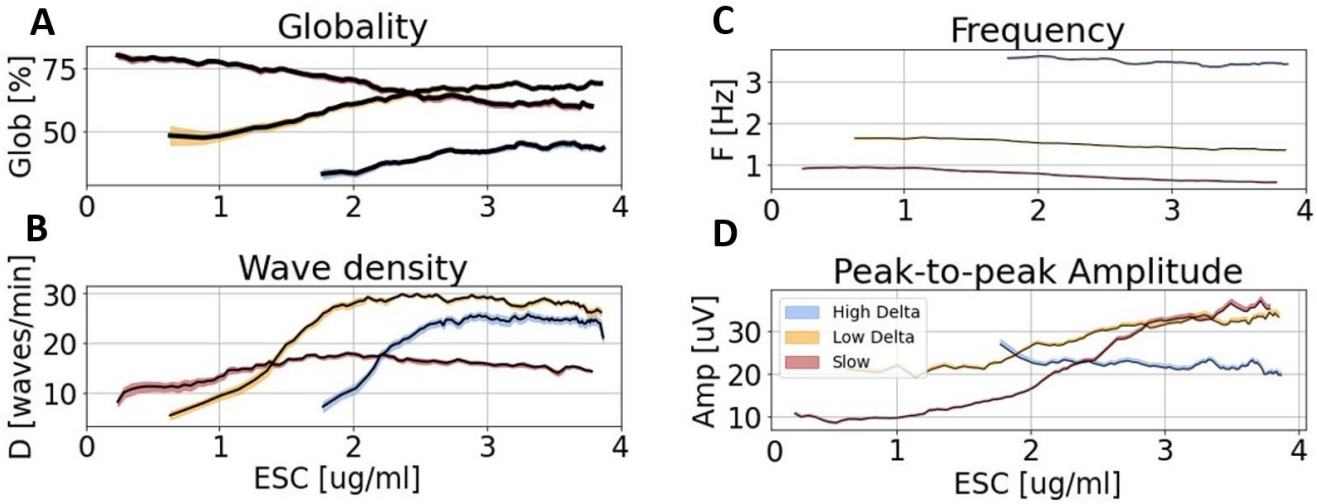

Figure 3: Changing topography of wave properties with increasing propofol concentration. (A) low concentrations near loss of behavioural response. (B) high concentrations near end of induction.