BJA

British Journal of Anaesthesia, 121 (1): 303–313 (2018)

doi: 10.1016/j.bja.2018.04.031
Advance Access Publication Date: 25 May 2018
Research Article

Spectral and phase-amplitude coupling signatures in human deep brain oscillations during propofol-induced anaesthesia

Y. Huang[1], D. Wu[1], N. F. A. Bahuri[2], S. Wang[3], J. A. Hyam[1,2], S. Yarrow[4], J. J. FitzGerald[1], T. Z. Aziz[1] and A. L. Green[1,*]

[1]Nuffield Department of Surgical Sciences and University of Oxford, John Radcliffe Hospital, Oxford, UK, [2]Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK, [3]Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai, China and [4]Nuffield Department of Anaesthesia, University of Oxford, John Radcliffe Hospital, Oxford, UK

*Corresponding author. E-mail: alex.green@nds.ox.ac.uk

Abstract

Background: Both the cerebral cortex and subcortical structures play important roles in consciousness. Some evidence points to general anaesthesia-induced unconsciousness being associated with distinct patterns of superficial cortical electrophysiological oscillations, but how general anaesthetics influence deep brain neural oscillations and interactions between oscillations in humans is poorly understood.

Methods: Local field potentials were recorded in discrete deep brain regions, including anterior cingulate cortex, sensory thalamus, and periaqueductal grey, in humans with implanted deep brain electrodes during induction of unconsciousness with propofol. Power-frequency spectra, phase-amplitude coupling, coherence, and directed functional connectivity analysis were used to characterise local field potentials in the awake and unconscious states.

Results: An increase in alpha (7–13 Hz) power and decrease in gamma (30–90 Hz) power were observed in both deep cortical (ACC, anterior cingulate cortex) and subcortical (sensory thalamus, periaqueductal grey) areas during propofol-induced unconsciousness. Robust alpha-low gamma (30–60 Hz) phase-amplitude coupling induced by general anaesthesia was observed in the anterior cingulate cortex but not in other regions studied. Moreover, alpha oscillations during unconsciousness were highly coherent within the anterior cingulate cortex, and this rhythm exhibited a bidirectional information flow between left and right anterior cingulate cortex but stronger left-to-right flow.

Conclusion: Propofol increases alpha oscillations and attenuates gamma oscillations in both cortical and subcortical areas. The alpha-gamma phase-amplitude coupling and the functional connectivity of alpha oscillations in the anterior cingulate cortex could be specific markers for loss of consciousness.

Keywords: anaesthesia; anterior cingulate cortex; local field potential; periaqueductal grey; thalamus

Editorial decision: April 30, 2018; **Accepted:** April 30, 2018

Editor's key points

- Most studies of general anaesthetic effects on neuronal activity in humans use surface electroencephalography of superficial neuronal activity.
- The effects of propofol anaesthesia on deep brain neuronal oscillations were investigated in six patients receiving deep brain electrodes for treatment of chronic pain.
- Propofol increased alpha oscillations and attenuated gamma oscillations in both cortical and subcortical areas.
- Alpha-gamma phase-amplitude coupling and functional connectivity of alpha oscillations in the anterior cingulate cortex could be markers for propofol-induced loss of consciousness.

How general anaesthesia causes unconsciousness and alterations in brain networks remains elusive. Functional imaging studies have identified changes of activities within several regions such as the cerebral cortex, thalamus, and brainstem during the transition to loss of consciousness (LOC),[1–3] and the disruption of communication between these structures is thought to underlie LOC.[3,4] Electrophysiological techniques, especially scalp EEG, are feasible for monitoring dynamic brain states under general anaesthesia. EEG studies in humans show that propofol-induced LOC is accompanied by changes in EEG power across a broad range of frequencies, including an increase in global slow-wave (<1 Hz) power,[5,6] increase in frontal alpha (8–14 Hz) power,[6–8] and a decrease in occipital alpha power.[6] Similar patterns have been observed by using intracranial electrocorticography (ECoG) in humans during propofol-induced LOC.[9,10]

Different EEG frequency oscillations are thought to represent different neural sources, for instance, low frequency oscillations appear to represent large scale cortical–subcortical interactions (e.g. thalamocortical circuits[11,12]), whereas higher frequency oscillations are locally generated and more likely to reflect local cell assembly organisation.[13,14] EEG and ECoG studies have identified distinct characteristics in low and high frequency oscillations during general anaesthesia, suggesting both cortex and subcortical regions could play an important role in propofol-induced LOC. However, as neither EEG nor ECoG directly measures subcortical activity, any conclusions drawn using cortical recordings are by inference. Deep intracranial recordings in humans are required to investigate this fully. In addition, most oscillations studies to date have treated each rhythm independently, offering limited insight into the modulation of brain network activity as a whole. Critical characteristics for understanding brain states related to consciousness may be contained in patterns of interactions between different frequencies that could be detected by cross-frequency coupling.[15] Cross-frequency coupling, more specifically phase-amplitude coupling, is believed to reflect neural coding and information processing within microscale and macroscale neural ensembles of the brain and play a role in regulation of neural networks during learning, memory, attention, and sensory processing.[16–18] Recent studies have found a variety of phase-amplitude coupling characteristics related to anaesthesia.[6,9,15,19] The coupling between the delta phase and gamma amplitude in the cortex appears to strengthen with propofol-induced anaesthesia.[9] Different patterns of slow-wave (<1 Hz) phase-alpha amplitude coupling were observed during propofol-induced anaesthesia.[6,15] The influence of propofol on phase-amplitude coupling of neural activities in deep cortical and subcortical areas in humans has not been clearly established.

To characterise the neural activities in deep brain regions and their interaction during anaesthesia, we measured local field potentials (LFPs) directly recorded from various brain areas [i.e. anterior cingulate cortex (ACC), sensory thalamus, and periaqueductal grey (PAG)], while administering propofol to patients undergoing deep brain stimulation used as a treatment for chronic pain. We firstly investigated the spectral properties in LFPs during induction of general anaesthesia with propofol using power spectral and time-frequency analysis. Furthermore, to investigate the interactions between different frequencies, we analysed the phase-amplitude coupling characteristics in these regions. Moreover, we used coherence and directed transfer function analysis to assess the functional connectivity between areas for understanding the functional connection between different areas during anaesthesia.

Methods

Subjects

This study was conducted at the John Radcliffe Hospital, Oxford, UK and approved by the Local Ethics Committee. Informed written consent was obtained from all participants. Six patients undergoing deep brain stimulation for chronic pain participated. Of these patients, two underwent bilateral implantation of electrodes into the ACC, three underwent unilateral implantation electrodes into both the sensory

Table 1 Subject characteristics, aetiologies, positions of electrode implantation, and general anaesthesia induction time. ACC, anterior cingulate cortex; F, female; M, male; PAG, periaqueductal grey; S Thal, sensory thalamus

Subject	Age (yr)/sex	Aetiology	Electrode position	Induction time (s)
1	46/M	Brachial plexus injury	Bilateral ACC	100
2	63/M	Poststroke pain	Bilateral ACC	50
3	53/M	Brachial plexus injury	S Thal PAG	50
4	53/M	Phantom limb pain	S Thal PAG	40
5	39/F	Glossopharyngeal neuralgia	S Thal PAG	90
6	46/M	Phantom limb pain	S Thal	60