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Brain functional connectivity differentiates dexmedetomidine from propofol and natural sleep

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Abstract

Background. We used functional connectivity measures from brain resting state functional magnetic resonance imaging to identify human neural correlates of sedation with dexmedetomidine or propofol and their similarities with natural sleep.
Methods. Connectivity within the resting state networks that are proposed to sustain consciousness generation was compared between deep non-rapid-eye-movement (N3) sleep, dexmedetomidine sedation, and propofol sedation in volunteers who became unresponsive to verbal command. A newly acquired dexmedetomidine dataset was compared with our previously published propofol and N3 sleep datasets.
Results. In all three unresponsive states (dexmedetomidine sedation, propofol sedation, and N3 sleep), within-network functional connectivity, including thalamic functional connectivity in the higher-order (default mode, executive control, and salience) networks, was significantly reduced as compared with the wake state. Thalamic functional connectivity was not reduced for unresponsive states within lower-order (auditory, sensorimotor, and visual) networks. Voxel-wise statistical comparisons between the different unresponsive states revealed that thalamic functional connectivity with the medial prefrontal/anterior cingulate cortex and with the mesopontine area was reduced least during dexmedetomidine-induced unresponsiveness and most during propofol-induced unresponsiveness. The reduction seen during N3 sleep was

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intermediate between those of dexmedetomidine and propofol.
Conclusions. Thalamic connectivity with key nodes of arousal and saliency detection networks was relatively preserved during N3 sleep and dexmedetomidine-induced unresponsiveness as compared to propofol. These network effects may explain the rapid recovery of oriented responsiveness to external stimulation seen under dexmedetomidine sedation.
Trial registry number. Committee number: 'Comité d'Ethique Hospitalo-Facultaire Universitaire de Liège' (707); EudraCT number: 2012-003562-40; internal reference: 20121/135; accepted on August 31, 2012; Chair: Prof G. Rorive. As it was considered a phase I clinical trial, this protocol does not appear on the EudraCT public website.

Key words: cerebrovascular circulation; magnetic resonance imaging; dexmedetomidine; propofol; sleep; slow-wave; anaesthesia

Editors key points

- Regional changes in neuronal activity can be detected by functional magnetic resonance imaging.
- Functional connectivity assesses the correlation between the neuronal activity of different regions and networks.
- Connectivity within the default mode network (DMN) is thought to be important for consciousness.
- The authors compared DMN connectivity during deep non-REM sleep and deep sedation with propofol and dexmedetomidine.

The mechanistic similarities or differences between physiological sleep and pharmacologically induced altered conscious states remain poorly understood. The α_2-adrenergic agonist sedative dexmedetomidine produces a behavioural state similar to sleep, with overlapping electroencephalogram (EEG) characteristics.[1] Moderate sedation with dexmedetomidine is known to produce EEG changes similar to those seen during stage 2 non–rapid eye movement (NREM) sleep (N2), namely slow-delta oscillations and spindles.[2] Spindles are composed of bursts of 9–15 Hz oscillations that last 1–2 s. Deeper unresponsive dexmedetomidine sedation produces strong slow-delta activity (0–4 Hz) without spindles, similar to stage 3 NREM sleep (N3).[2] This likely occurs through the promotion of endogenous sleep pathway activities.[3] Dexmedetomidine inhibits locus coeruleus–derived noradrenergic neurotransmission to the ventrolateral preoptic nucleus (VLPO), thus disinhibiting the VLPO and provoking an inhibition of cortical arousal nuclei. Hence we previously hypothesized that dexmedetomidine produces a restorative brain state similar to sleep, unlike the state produced by alternative sedatives.[4] Several studies have advocated that other sedatives, including propofol, also act through the promotion of subcortical sleep pathways.[5] However, human experimentation suggests the cortex is the primary target;[6] through augmenting the effects of γ-amino-butyric acid(GABA)-ergic inhibitory interneurons.[7] Hence it is possible that, while both dexmedetomidine and propofol modulate bottom-up pathways, propofol exerts more profound cortical effects, manifesting as changes in connectivity.

Dexmedetomidine has unique clinical properties compared with other sedative agents: it has been shown to reduce the burden of delirium in the critical care unit compared with benzodiazepine and propofol,[8] prevent delirium in elderly patients after non-cardiac major surgery,[9] and reduce agitation upon recovery in children.[10] It has been hypothesized that the mechanisms behind the relative protective effect of dexmedetomidine against delirium depends in part on its more natural restorative sleep–promoting actions.[4] A further important facet of dexmedetomidine sedation is that the patient can recover purposeful responsiveness after the application of a salient stimulus.[11] This distinguishes dexmedetomidine from other agents like propofol, which usually require cessation of administration to obtain sentient responsiveness.

To quantify the degree of neurobiological similarity between sleep, dexmedetomidine and propofol sedation and to identify the functional structures at the origin of patient rousability under dexmedetomidine sedation, a detailed functional comparison between these different brain states in humans is necessary.

In this study we used resting state functional magnetic resonance imaging (rs-fMRI) to examine differences in brain resting state functional connectivity (rs-FC) between dexmedetomidine sedation, propofol sedation, and N3 sleep. Previous studies have shown a disruption of resting state connectivity networks (RSNs) by anaesthetic agents and during sleep. The default mode network (DMN, associated with self-related mentation)[12] is altered during propofol-induced unresponsiveness[13] and N3 sleep.[14] DMN disruption may even be considered as a biomarker of altered consciousness.[15] Furthermore, the connectivity of other important RSNs, such as the executive control networks (left and right ECNs),[16] and the salience network[17] is also important to consciousness. The ECNs are associated with executive function and awareness of the environment,[16] while the salience network manages interaction with the environment and responses to relevant 'salient' sensory stimuli (such as being asked to respond to one's own name).[18] Within those networks we were specifically interested in whether connectivity involving the thalamus and the anterior cingulate cortex (ACC) was differentially modified by dexmedetomidine, propofol, or N3 sleep—notably because these regions are known to be part of the brain's arousal/salience system. In order to provide a comprehensive overview of the modified neural networks, we also analysed the auditory, sensorimotor, and visual RSNs. A methodological strength of this work is the simultaneous analysis of three datasets, using the same acquisition parameters and data analysis steps, allowing comparison of wakefulness with all three unresponsive states.

Materials and methods

Subjects

We used three datasets for our analysis. The dexmedetomidine dataset consisted of 11 healthy subjects (age range 19–29 years) and was acquired between November 11, 2012, and June 21, 2013. The propofol dataset has been published before[13 19 20] and consisted of 17 subjects (age range 18–31 years). The also previously published[21] N3 sleep dataset consisted of 12 subjects (age range 18–25 years). The studies were approved by the Ethics Committee of the Faculty of Medicine of the University of Liège,