Changes in brain activation during sedation induced by dexmedetomidine

Won-Ho Kim[1],*, Dongrae Cho[2],*, Boreom Lee[2], Jae-Jin Song[3] and Teo Jeon Shin[4]

Abstract

Objective: Dexmedetomidine (DEX) has been widely used as a sedative, acting as an α2-adrenergic agonist on autoreceptors, presynaptic receptors and postsynaptic receptors without risk of respiratory depression. Although consciousness impairment is closely related to disturbances of brain function in different frequency bands, the time-varying DEX effects on cortical activity in specific frequency bands has not yet been studied.

Methods: We used electroencephalography (EEG) to analyse differences in cerebral cortex activity between the awake and sedated states, using electromagnetic tomography (standardized low resolution electromagnetic tomography (sLORETA)) to localize multiple channel scalp recordings of cerebral electric activity to specific brain regions.

Results: The results revealed increased activity in the cuneus at delta-band frequencies, and in the posterior cingulate cortex at theta frequencies, during awake and sedated states induced by DEX at specific frequency bands. Differences in standardized low resolution cingulate gyrus were found in beta1 frequencies (13–18 Hz), and in the cuneus at gamma frequencies.

Conclusion: Cerebral cortical activity was significantly altered in various brain areas during DEX sedation, including parts of the default mode network and common midline core in different frequency ranges. These alterations may elucidate the mechanisms underlying DEX sedation.

[1]Post-graduate student, School of Dentistry, Seoul National University, Seoul, Korea
[2]Department of Biomedical Science and Engineering, Institute of Integrated Technology, Gwangju Institute of Science and Technology (GIST), Gwangju, Korea
[3]Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Bundang Hospital, Seoul, Korea
[4]Department of Pediatric Dentistry and Dental Research Institute, School of Dentistry, Seoul National University, Seoul, Korea

*Won-Ho Kim and Dongrae Cho contributed equally to this work.

Corresponding authors:
Teo Jeon Shin and Boreom Lee, Department of Pediatric Dentistry and Dental Research Institute, Seoul National University School of Dentistry, 28 Yeongeon-dong Jongno-gu, Seoul 110-768, Republic of Korea; Department of Biomedical Science and Engineering, Institute of Integrated Technology, Gwangju Institute of Science and Technology (GIST), Republic of Korea.
Emails: snmc94@snu.ac.kr; leebr@gist.ac.kr

Introduction

Dexmedetomidine (DEX) is widely used as a sedative.[1] DEX has little effect on respiratory function, making it useful in situations for procedures performed within the airway, such as dental procedures. Unlike other sedatives, which act on gamma-aminobutyric acid (GABA) receptors, DEX acts as an α2-adrenergic agonist on autoreceptors, presynaptic receptors and postsynaptic receptors. DEX acts on α2 receptors in neurons that emanate from the locus coeruleus (LC),[2–3] producing a sedative effect resembling the electroencephalography (EEG) pattern of non rapid eye movement (NREM) sleep II.[4] The different site of action of DEX compared with other sedatives suggests that DEX may have a different anaesthetic mechanism. However, although DEX has been widely used to sedate patients, few studies have been performed to elucidate the mechanisms of DEX-induced sedation by examining changes in cortical activation.

Sedation can be considered as the state between consciousness and the loss of consciousness. According to information integration theory, consciousness requires the integration of scattered information processed in different brain areas.[5,6] As such, anaesthetic-induced impaired consciousness is likely to induce changes in cortical activity. Previous studies have shown that different levels of altered consciousness are associated with modulation of activity in multiple brain regions.[7,8] Understanding potential cortical differences during sedation may be useful for understanding the neural correlates of impaired consciousness. Functional neuroimaging studies have shown that DEX primarily disturbs long-range thalamocortical interactions.[4] However, time-varying DEX effects on cortical activity cannot be evaluated using neuroimaging methods that provide the highest spatial resolution, such as functional magnetic resonance imaging (fMRI). In addition, the brain modulates its functioning in specific frequency bands,[9] and consciousness impairment is closely related to disturbances in brain function in different frequency bands.[5] Even though interactions between distant brain areas are modulated in specific frequency bands, the cortical effects of DEX on comprehensive brain networks in various frequency bands has not yet been investigated.

In the current study, we analysed differences in cerebral cortex activity between awake and sedated states induced by DEX, using standardized low resolution electromagnetic tomography (sLORETA). sLORETA localizes cerebral electric activity obtained through EEG recordings from multiple channels to specific brain regions, as a functional brain imaging method.[10,11] sLORETA has been used to investigate the neurophysiological correlates of various diseases. However, few attempts have been made to investigate the neural correlates of sedation using this technique.

Thus, in the current study, we aimed to investigate changes in cortical activity during DEX sedation, to examine the potential neural correlates of DEX-induced consciousness impairment.

Materials and methods

Participant recruitment

A sample of 20 healthy participants ranging in age from 20–40 years were enrolled in this

study. All participants provided written informed consent, and approval was given by the Institutional Review Board of the College of Dentistry at Seoul National University. Each participant was instructed to fast for at least 8 hours prior to the experiment. Participants with significant medical diseases or laboratory abnormalities were excluded from the study.

EEG recording and dexmedetomidine infusion

Participants were acclimated to a room shielded against sound and electric fields, where EEG was recorded. Thirty-two electrodes were attached in the standard 10-20 international placement after fitting an appropriate EEG cap that best matched the head circumference of the participant. EEG recording was referenced to an average EEG, while keeping the impedance of all electrodes below 5 kΩ. Data were stored on a PC at a sampling rate of 2048 Hz during the entire experiment. After obtaining EEG recordings for 5 min with eyes closed, DEX was administered with a 0.5 mcg/kg loading bolus over 10 min, followed by a 0.5 mcg/kg/hr infusion until unconsciousness was reached. During the DEX infusion, cuff blood pressure, electrocardiogram, pulse-oximetry, and capnography were monitored. The bispectral index (BIS) was also monitored for objective evaluation of sedation depth. We instructed participants to keep their eyes closed during the entire experiment, and defined loss of consciousness as the loss of response to a verbal request to grasp the hand every 30 seconds. We stopped DEX administration when participants reached unconsciousness. Recovery of consciousness after discontinuing DEX infusion was evaluated as a positive response to verbal requests to grasp the hand, or spontaneous eye opening. EEG was continuously recorded until the participant regained full consciousness evaluated by either the return

to baseline BIS value or a positive response to the question "Are you feeling the same as before, when you were sitting in the dental chair?"

EEG preprocessing

Three 1-minute epochs of EEG data were selected for analysis from all participants in two conditions, awake and sedated. During DEX injection, we selected the 3 minutes of EEG recording 30 seconds before the loss of consciousness. All episodic artefacts were carefully removed from the EEG signal by manual inspection. The data were preprocessed by down-sampling to 256 Hz with a 0.5 Hz high-pass filter, a 70 Hz low-pass filter (fast Fourier transform filter applying a Hanning window) and a 60 Hz notch filter (64th-order finite impulse response [FIR] notch filters). EEG data pairs were baseline corrected to the average reference. In addition, independent component analysis (ICA) was performed to minimize artefacts from micro muscle movement, blinking, electrical noise and pulses from the carotid artery.

Source localization analysis

Standardized low-resolution brain electromagnetic tomography (sLORETA),[10] a functional imaging method using certain electrophysiological and neuroanatomical constraints, was conducted to estimate sources in the brain from electrical activity at the scalp in each of the following six frequency bands: delta (1.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta1 (sigma) (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz), and gamma (30–44 Hz).[12]

sLORETA gives a single linear solution to the inverse problem of functional cortical localization based on extracranial measurements[12] and generates images of standardized current density with no localization bias.[10] The localization accuracy of sLORETA has

been repeatedly validated by combining it with other localization methods, such as structural magnetic resonance imaging (MRI),[13] fMRI[14,15] and positron emission tomography.[16,17]

Statistical analyses

To identify potential differences between the awake and sedated states induced by DEX infusion, voxel-by-voxel analysis using sLORETA was performed for the six frequency bands, with between-condition comparisons of the current density distribution. Statistical nonparametric mapping (SPM) of sLORETA images was performed for each contrast using sLORETA's built-in voxel-wise randomization tests (5000 permutations) and employing a log-F ratio statistic for independent groups with a threshold $P < 0.05$.

Results

Among 20 subjects, EEGs obtained from two subjects were contaminated with excessive artefacts, which could not be removed even by applying sophisticated preprocessing techniques. Therefore, data from these participants were excluded from subsequent analyses.

The mean dose of DEX was 33.6 mcg. The mean baseline BIS was 93.2 during awake state and 77.3 during DEX induced sedation, respectively.

DEX-induced sedation was associated with cortical activity changes in different frequency bands. Compared with the baseline state, increased activity was found in the cuneus (BA 18) in the delta frequency band, the posterior cingulate cortex (BA 23) in the theta frequency, the cingulate gyrus (BA 24) in the sigma frequency band, and the cuneus (BA 18) in the gamma frequency bands, and was most prominent during DEX-induced sedation (Figures 1 (a), (b), (d), (e)). In contrast, relative to the awake state,

decreased activity was observed in the fusiform gyrus (BA 20) in the alpha frequency bands, and was most prominent during DEX-induced sedation, which was lateralized to the left. (Figure 1-c). Meanwhile, no significant differences were observed in the beta2 and beta3 frequency bands during DEX induced sedation. The cortical areas demonstrating significant changes during DEX-induced sedation for each frequency band are described in detail in Table 1.

Discussion

We found that DEX induced cortical activity changes during an impaired consciousness state. To the best our knowledge, this is the first study to investigate sedation-related cortical activity changes in each brain frequency band, with which the brain regulates its functioning.[9]

We utilized an inverse modelling technique to determine which areas in specific frequency ranges were disturbed in the brain during DEX sedation. This inverse modelling method (sLORETA) is based on the notion that individual neurons are synchronized with adjacent neurons, and this enables electrical source localization.[11,18] Through localizing the sources of electric activity, sLORETA statistically computes the difference in cerebral electrical activity between two states, and visualizes statistical results in a three dimensional distribution. This three dimensional distribution of statistical differences is displayed as a current density distribution in the solution space, allowing for the detection of changes in brain activity more easily.[11,18] However, few studies have attempted to investigate the mechanisms underlying impaired consciousness using sLORETA, despite its advantages, such as its simplicity and graphical representation of brain activity differences between two conditions. To our knowledge, this is the first study to investigate the
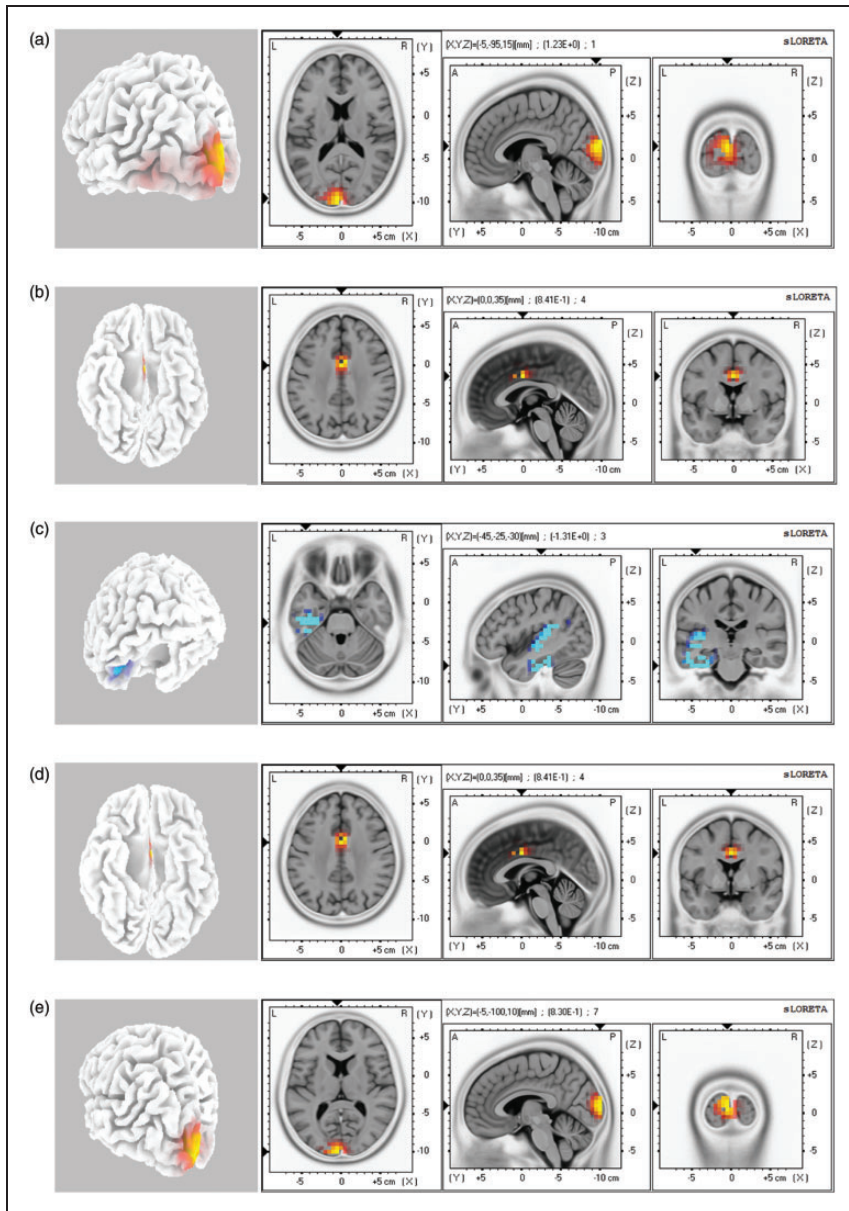
Figure 1. Statistical nonparametric mapping (SnPM) of sLORETA images for each band (a) delta (b) theta (c) alpha (d) sigma (e) gamma.

mechanisms underlying DEX sedation using the sLORETA technique.

The default mode network (DMN) has been investigated as an anatomical and functional mechanism for maintaining attention and consciousness.[19] In addition, the common midline core (CMC), which includes the midline precuneus/cuneus, prefrontal cortex, and other brain areas, is commonly targeted by general anaesthetic,

Table 1. Cortical areas demonstrating significant changes during DEX-induced sedation for each frequency band.

Frequency band	MNI coordinates (x y z)			Voxel value	Brodmann area	Structure
Delta						
	−5	−95	15	1.23	18	Cuneus
	−5	−100	20	1.23	18	Cuneus
	−5	−100	15	1.23	18	Cuneus
	−5	−95	10	1.23	18	Cuneus
	−5	−100	10	1.23	18	Middle occipital gyrus
Theta						
	0	−50	25	1.06	23	Posterior cingulate
	5	−50	25	1.06	23	Posterior cingulate
	−10	−50	30	1.06	31	Precuneus
	−5	−50	30	1.05	31	Precuneus
	−10	−55	30	1.05	31	Precuneus
Alpha						
	−45	−25	−30	−1.31	20	Fusiform gyrus
	−50	−25	−30	−1.31	20	Fusiform gyrus
	−50	−25	−25	−1.31	20	Inferior temporal gyrus
	−40	−25	−20	−1.31	20	Fusiform gyrus
	−40	−45	20	−1.31	13	Insula
Beta 1						
	0	0	35	0.84	24	Cingulate gyrus
	5	5	35	0.84	24	Cingulate gyrus
	5	0	35	0.83	24	Cingulate gyrus
	0	0	40	0.83	24	Cingulate gyrus
	0	10	35	0.83	24	Cingulate gyrus
Gamma						
	−5	−100	10	0.83	18	Middle occipital gyrus
	−5	−100	5	0.83	18	Cuneus
	−5	−100	15	0.82	18	Cuneus
	−10	−100	15	0.82	18	Cuneus
	−5	−95	10	0.82	18	Cuneus

resulting in anesthesia.[20] The DMN is reported to be activated in situations where attention to external environments is not necessary. The DMN consists of multiple interacting subsystems within the brain. Although the precise function of the DMN remains unclear, it is thought to play a critical role in internally-directed cognition. The DMN is activated during non-stressful resting states, such as autobiographical memory and planning for the future. DMN disturbance is also associated with the development of neuropsychiatric diseases, such as Alzheimer's disease, schizophrenia, autism, depression and attention deficit hyperactivity disorder.[21] In the DMN, the posterior cingulate cortex (PCC) acts as a hub, and is functionally connected to other brain areas.[22] The current results revealed that cortical activity

changes associated with DEX sedation involved significant alterations in PCC, which acts as a hub within the DMN. DEX also caused changes in brain activity in other areas of the DMN (precuneus, angular gyrus), although these changes did not reach statistical significance (data not shown). Considering the roles of the DMN and CMC in regulating consciousness and mental states, DEX may be likely to induce changes in both DMN and CMC activity, leading to impaired consciousness.

In accord with this hypothesis, DEX-induced sedation was associated with significant changes in cortical activity in the PCC, an area that acts as a hub among DMN and CMC structures. However, cortical activity in this area was augmented rather than suppressed, contrary to our expectation. These results appear to contradict those of previous studies demonstrating impaired activity in these brain areas during general anesthesia.[20,23] It remains unclear why DEX sedation was associated with increased cortical activation in these areas. However, a recent study may provide an explanation for increased brain-specific activity appearing somewhat contradictory in a DEX-induced sedative state, as discussed below.

In line with the current results, a previous study reported that functional connectivity of the PCC to other brain area increases during propofol sedation.[24] In the awake state, the arousal center in the brainstem inhibits PCC function.[24] During sedation, as the connection from the arousal center to the PCC weakens, the PCC paradoxically increases functional connectivity to other brain areas. The PCC acts as a hub within the DMN brain network[22] and connects to other brain areas, such as the cuneus and anterior cingulate cortex, in which increased activation during sedation was observed in the current study. Taken together, these findings suggest that the increased activity we observed in these regions may

have resulted from disinhibition during sedation, making robust connections more prominent. From the perspective of information integration, the synchronized brain network may impair the efficiency of information processing.[25] In clinical practice, impaired responses to external stimuli, such as verbal, auditory, and visual stimuli are commonly observed under sedation. Increased activation during sedation may be related to impaired and delayed responses to stimuli during sedation.

In the alpha frequency bands, we observed decreased cortical activity in the auditory cortex (AC) and the fusiform gyrus, where significant cortical activity alterations were observed during sedation. The fusiform gyrus is involved in processing word recognition and visual information,[26] while AC activation is associated with auditory stimulation. The PCC plays an important role in auditory perception.[27] Perceived auditory stimulation is a prerequisite for word recognition,[28] and one study reported that event-related potentials during auditory stimulation are significantly affected in the alpha frequency range.[29] The present study demonstrated deactivation in temporal brain areas in the alpha frequency bands which may explain the delayed response to verbal stimuli. In the current study, all subjects showed a delayed response to verbal stimuli that were presented to evaluate the level of consciousness before unconsciousness was exhibited. Considering the importance of the fusiform gyrus in regulating visual perception, DEX may also impair the efficiency of visual stimulus processing, leading to blurred or double vision[30] during sedation, even though the subjects in the present experiment were instructed to close their eyes.

Interestingly, the deactivation in the alpha frequency band was lateralized to the left. Alpha oscillation is involved in higher cognitive processes, such as memory and consciousness.[31] A left-lateralized neural system distributed in the frontal, parietal,

and temporal lobes is thought to be involved in language and memory processing.[32–34] Therefore, the DEX induced left-lateralized deactivation we observed in the alpha frequency band may suggest that the neural network required for high-level verbal and memory processing can be separated during deep DEX sedation.

Although the current study revealed several neural correlates that may be associated with DEX-induced sedation, there are several limitations that should be addressed in future studies. First, we focused on changes in cortical activity during DEX sedation. However, a change in brain activity does not guarantee alterations in brain network properties. Even without changes in brain activity, functional connectivity between different brain areas may be altered.[24] It is therefore necessary to identify changes in the EEG dynamics associated with sedation induced by DEX. Further studies should be conducted to clarify this point in more depth. Second, changes in cortical activity, as shown in this study, may represent different patterns during different levels of sedation. Previous studies have shown that DEX induces changes in sleep-like EEG patterns and causes a slight increase in power in the theta, alpha and beta bands.[35–37] Indeed, we have shown that DEX changes the activity of the cerebral cortex in these frequency bands. However, the activation pattern of the cerebral cortex may vary with each frequency band depending on the depth. Investigating cortical activity during DEX infusion at a constant level of effect-site concentration may be helpful for elucidating the mechanisms underlying different levels of impaired consciousness. Furthermore, EEG changes between different levels of sedation should also be compared with better understand transitional changes from consciousness to unconsciousness.

In summary, the current results revealed changes in cortical activity in different frequency ranges during DEX sedation. These alterations may explain the mechanisms underlying DEX sedation, potentially enabling the tracking of changes in levels of consciousness as an objective marker during DEX administration.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

References

1. Chrysostomou C and Schmitt CG. Dexmedetomidine: sedation, analgesia and beyond. *Expert Opin Drug Metab Toxicol* 2008; 4: 619–627.
2. Correa-Sales C, Rabin BC and Maze M. A hypnotic response to dexmedetomidine, an alpha 2 agonist, is mediated in the locus coeruleus in rats. *Anesthesiology* 1992; 76: 948–952.
3. Mizobe T, Maghsoudi K, Sitwala K, et al. Antisense technology reveals the alpha2A adrenoceptor to be the subtype mediating the hypnotic response to the highly selective agonist, dexmedetomidine, in the locus coeruleus of the rat. *J Clin Invest* 1996; 98: 1076–1080.
4. Akeju O, Loggia ML, Catana C, et al. Disruption of thalamic functional connectivity is a neural correlate of dexmedetomidine-induced unconsciousness. *Elife* 2014; 3: e04499.
5. Soddu A, Vanhaudenhuyse A, Bahri MA, et al. Identifying the default-mode component in spatial IC analyses of patients with disorders of consciousness. *Hum Brain Mapp* 2012; 33: 778–796.

6. Cauda F, Micon B, Sacco K, et al. Disrupted intrinsic functional connectivity in the vegetative state. *J Neurol Neurosurg Psychiatry* 2009; 80: 429–431.

7. Quan X, Ye TH, Lin SF, et al. Propofol affects different human brain regions depending on depth of sedation. *Chin Med Sci J* 2015; 30: 135–142.

8. Fiset P, Plourde G and Backman SB. Brain imaging in research on anesthetic mechanisms: studies with propofol. *Prog Brain Res* 2005; 150: 245–250.

9. Lachaux J-P, Rodriguez E, Martinerie J, et al. Measuring phase synchrony in brain signals. *Hum Brain Mapp* 1999; 8: 194–208.

10. Pascual-Marqui RD. Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. *Methods Find Exp Clin Pharmacol* 2002; 24 Suppl D: 5–12.

11. Pascual-Marqui RD, Michel CM and Lehmann D. Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. *Int J Psychophysiol* 1994; 18: 49–65.

12. Marco-Pallares J, Grau C and Ruffini G. Combined ICA-LORETA analysis of mismatch negativity. *Neuroimage* 2005; 25: 471–477.

13. Worrell GA, Lagerlund TD, Sharbrough FW, et al. Localization of the epileptic focus by low-resolution electromagnetic tomography in patients with a lesion demonstrated by MRI. *Brain Topogr* 2000; 12: 273–282.

14. Olbrich S, Mulert C, Karch S, et al. EEG-vigilance and BOLD effect during simultaneous EEG/fMRI measurement. *Neuroimage* 2009; 45: 319–332.

15. Vitacco D, Brandeis D, Pascual-Marqui R, et al. Correspondence of event-related potential tomography and functional magnetic resonance imaging during language processing. *Hum Brain Mapp* 2002; 17: 4–12.

16. Zumsteg D, Wennberg R, Treyer V, et al. H215O or 13NH3 PET and electromagnetic tomography (LORETA) during partial status epilepticus. *Neurology* 2005; 65: 1657–1660.

17. Pizzagalli D, Oakes T, Fox A, et al. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. *Mol Psychiatry* 2004; 9: 393–405.

18. Jung KY, Kim JM, Lee IK, et al. Cortical Representation to Odorant Stimulation: Statistical Non-parametric Mapping of Low Resolution Electro magnetic Tomography (LORETA). *J Korean Neurol Assoc* 2004; 22: 334–339.

19. Buckner RL, Andrews-Hanna JR and Schacter DL. The brain's default network. *Ann N Y Acad Sci* 2008; 1124: 1–38.

20. Xie G. Exploration of the mechanisms of unconsciousness induced by propofol with positron emission tomography (PET) functional brain imaging. Ph.D thesis 2006.

21. Leech R and Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. *Brain* 2014; 137: 12–32.

22. Fransson P and Marrelec G. The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. *Neuroimage* 2008; 42: 1178–1184.

23. Alkire MT, Hudetz AG and Tononi G. Consciousness and anesthesia. *Science* 2008; 322: 876–880.

24. Stamatakis EA, Adapa RM, Absalom AR, et al. Changes in resting neural connectivity during propofol sedation. *PLoS One* 2010; 5: e14224.

25. Tononi G. An information integration theory of consciousness. *BMC Neurosci* 2004; 5: 42.

26. McCandliss BD, Cohen L and Dehaene S. The visual word form area: expertise for reading in the fusiform gyrus. *Trends Cogn Sci* 2003; 7: 293–299.

27. Boly M, Faymonville M-E, Peigneux P, et al. Auditory processing in severely brain injured patients: differences between the minimally conscious state and the persistent vegetative state. *Arch Neurol* 2004; 61: 233–238.

28. Frost R and Katz L. Orthographic depth and the interaction of visual and auditory processing in word recognition. *Mem Cognit* 1989; 17: 302–310.

29. Krause CM, Lang HA, Laine M, et al. Event-related desynchronization evoked by auditory stimuli. *Brain Topogr* 1994; 7: 107–112.

30. Malamed SF. Sedation-a guide to patient management. 2010.

31. Başar E and Güntekin B. A short review of alpha activity in cognitive processes and in cognitive impairment. *Int J Psychophysiol* 2012; 86: 25–38.

32. Binder JR, Desai RH, Graves WW, et al. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb Cortex* 2009; 19: 2767–2796.

33. Curtis CE and D'Esposito M. Persistent activity in the prefrontal cortex during working memory. *Trends Cogn Sci* 2003; 7: 415–423.

34. Wagner AD, Shannon BJ, Kahn I, et al. Parietal lobe contributions to episodic memory retrieval. *Trends Cogn Sci* 2005; 9: 445–453.

35. Huupponen E, Maksimow A, Lapinlampi P, et al. Electroencephalogram spindle activity during dexmedetomidine sedation and physiological sleep. *Acta Anaesthesiol Scand* 2008; 52: 289–294.

36. Mason KP, O'Mahony E, Zurakowski D, et al. Effects of dexmedetomidine sedation on the EEG in children. *Paediatr Anaesth* 2009; 19: 1175–1183.

37. Maksimow A, Snapir A, Särkelä M, et al. Assessing the depth of dexmedetomidine-induced sedation with electroencephalogram (EEG)-based spectral entropy. *Acta Anaesthesiol Scand* 2007; 51: 22–30.