Published in final edited form as:

Neurosci Lett. 2014 February 21; 561: 18–23. doi:10.1016/j.neulet.2013.12.047.

Increased precuneus connectivity during propofol sedation

Xiaolin Liu^a, Shi-Jiang Li^a, and Anthony G. Hudetz^{b,*}

^aDepartment of Biophysics, Medical College of Wisconsin, Milwaukee, WI, USA

^bDepartment of Anesthesiology, Medical College of Wisconsin, Milwaukee, WI, USA

Abstract

Using functional magnetic resonance imaging in human participants, we show that sedation by propofol to the point of lost overt responsiveness during the performance of an auditory verbal memory task unexpectedly increases functional connectivity of the precuneus with cortical regions, particularly the dorsal prefrontal and visual cortices. After recovery of consciousness, functional connectivity returns to a pattern similar to that observed during the wakeful baseline. In the context of a recent proposal that highlights the uncoupling of consciousness, connectedness, and responsiveness in general anesthesia, the increased precuneus functional connectivity under propofol sedation may reflect disconnected endogenous mentation or dreaming that continues at a reduced level of metabolic activity.

Keywords

Precuneus connectivity; Anesthesia; Propofol sedation; Auditory verbal memory task; Functional magnetic resonance imaging

1. Introduction

The precuneus, along with adjacent posteromedial parietal neural structures, including the posterior cingulate and retrosplenial cortices, is among the most metabolically active regions of the parietal default mode network (DMN) of the brain in the conscious resting state [1–3]. Although the biological and functional significances of the DMN is still under debate [4], the involvement of the precuneus and associated posteromedial parietal structures in memory and consciousness has been supported by a variety of studies [5–7]. The precuneus itself has been proposed to function as a well-connected, important small-world network hub that links the frontal and parietal regions [8]. Regional cerebral blood flow (rCBF) and cerebral metabolic rate in the precuneus increase during internally directed, self-related mentation but decrease in non-self-directed cognitive tasks [2,9]. In particular, the metabolic rate of the precuneus is significantly reduced in states of suppressed or altered consciousness, such as sleep, vegetative state, anesthesia, epilepsy, Alzheimer's disease, and schizophrenia [6].

Despite the current evidence suggesting a role for the precuneus in supporting the state of consciousness, there has been a lack of understanding of how its functional interaction with

© 2013 Elsevier Ireland Ltd. All rights reserved.

Corresponding author at: Department of Anesthesiology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA. Tel.: +1 414 955 5622; fax: +1 414 955 6507. ahudetz@mcw.edu (A.G. Hudetz).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.neulet.2013.12.047>.

other brain regions may be modified in reduced states of consciousness, in particular, during anesthetic sedation. In this study, we intended to test the hypothesis that during sedation with propofol, precuneus connectivity with the rest of the cortex would be suppressed, reflecting a reduced level of cortical information integration associated with reduced awareness about the environment and self. We report that, contrary to our initial expectation, during propofol sedation titrated to the point just beyond the loss of responsiveness to verbal commands, functional connectivity of the precuneus increases prominently, particularly in the dorsal prefrontal and visual cortices. These results prompt us to reevaluate the functional role of the precuneus in modulating the state of consciousness. The implications of the findings are discussed in the context of a recent proposal for the uncoupling of consciousness, connectedness, and responsiveness in general anesthesia [10].

2. Methods

2.1. Data acquisition

Data analyzed here were obtained previously as described in two former publications [11,12]. Briefly, eight healthy human volunteers (four men and four women; ages 24–42; body mass index < 25) underwent propofol sedation during functional magnetic resonance imaging (fMRI). While being scanned, the participants performed a verbal memory task during each of the three 6-min-long runs in wakeful baseline, propofol-induced sedation, and recovery, with 15 min of separation between the runs. Blood oxygen level-dependent (BOLD) signals were collected at 1.5 T (repetition time [TR], 2s; in-plane resolution, 3.75 mm × 3.75 mm; thickness, 6 mm). Every participant had two intravenous catheters, one for propofol administration and another for the withdrawal of blood samples for measuring propofol plasma concentration. However, due to a problem of red blood cell lysis, the actually plasma propofol concentrations could not be determined in this study. Each imaging scan was initiated once the desired sedative state was achieved. During the scan, the sedation level was maintained by computer-controlled infusion with the preset plasma concentration. At the target plasma concentration of 2 µg/ml, participants no longer responded to verbal commands. After completing the scan under sedation, propofol administration was stopped. Upon confirmation that participants had recovered responsiveness to verbal commands, the last scanning session defined as “recovery” was initiated. The memory task conducted during each of the three states of consciousness involved listening to and encoding a distinct set of 40 high-frequency English words (nouns) presented with random time intervals during each of the scanning runs. As reported before [11,12], post-scan memory tests showed that subjects were able to freely recall significant percentages of the words heard in the scanner during wakeful baseline and recovery, but not during deep sedation.

2.2. Data preprocessing

Imaging data analysis was conducted in the environments of the Analysis of Functional NeuroImages (AFNI, <http://afni.nimh.nih.gov/afni>) and the Matlab (The MathWorks, Natick, MA). Data preparation included transformation of high-resolution anatomical images into standard Talairach space, followed by co-registration of the functional data with resampling to 2-mm cubic voxels. Subsequent data preprocessing included despiking, detrending and motion correction. Physiological noise was estimated using the average BOLD time series from the regions of the white matter and the cerebrospinal fluid, which were manually identified in each individual's anatomical images. The voxelwise BOLD time series from each scanning run was then analyzed with a general linear regression model (*3dDeconvolve* in AFNI) using the eight regressors representing noise artifacts from the motion parameters, white matter, and cerebrospinal fluid, respectively. The residual signals of the regression analysis were considered representative of the voxelwise BOLD time

series. The subsequent connectivity analysis was conducted using the averaged voxel time courses of the precuneus seeds to obtain voxelwise Pearson cross-correlation ($3dfim+$ in AFNI) of the whole brain. The Fisher transformation, $m = 0.5 * \ln(1 + r)/(1 - r)$, was applied to the obtained correlation coefficients (r) to normalize the output. Spatial smoothing of the m -values was performed using a 3.5-mm full-width half-maximum Gaussian kernel filter to compensate for intersubject variability.

2.3. Precuneus seed definition

A recent study identified three subdivisions of the human precuneus using the resting-state functional connectivity technique [13]. The three subdivisions include the sensorimotor anterior region, cognitive/associative central region, and visual posterior regions, respectively. Accordingly, we manually defined three precuneus seeds based on the separating landmarks of the cingulate gyrus, precuneal sulcus, and parietooccipital fissure in each participant's medial sagittal anatomical images, with average 2052, 1806, and 1838 voxels (2-mm cubic) across participants at the centers of mass of $[-0.54, 48.5, 56.1]$, $[-0.38, 65.4, 42.7]$ and $[-0.4, 68.4, 34.8]$ in the Talairach coordinates for the three precuneus seeds 1 to 3. For a comparison with the well-described DMN functional connectivity, we used an additional nearby seed region in the posterior cingulate cortex (PCC) (average 980 voxels, center of mass in the Talairach coordinates at $[-0.36, 41.2, 26.4]$). Precuneus connectivity maps in each of the states of consciousness were derived using one-sample t -test, with results considered significant at $P < 0.05$ after correction for multiple comparisons using the *AlphaSim* method in AFNI (a minimum cluster threshold of 179 voxels of 2-mm cubic in the Talairach space).

3. Results

3.1. Changes of precuneus connectivity across the states of propofol sedation

Compared with wakeful baseline, deep sedation at the point of unresponsiveness (with auditory stimuli continuously supplied) was marked by a general increase of precuneus connectivity, particularly in the dorsal medial prefrontal and visual cortices, as indicated by white arrows (Fig. 1). The increase in precuneus connectivity was reversed after recovery (return of responsiveness after termination of propofol infusion), reestablishing a connectivity pattern similar to that observed at the wakeful baseline. The whole-brain connectivity map of precuneus seed-1 was displayed in Fig. 1, with connectivity maps of the other two precuneus seeds included in the Supplemental Information. For the purpose of demonstration, the sum of voxelwise correlations strength in the medial superior frontal and visual cortex areas (where precuneus connectivity showed significant effects in the three states of consciousness) were computed with its mean and standard deviation (SD) across the participants (Fig. 2). At wakeful baseline, the connectivity maps of the three precuneus seeds were similar, except that seed-1 had additional connections with the supplemental motor cortex, while seed-2 and seed-3 had more connections in the bilateral inferior frontal and parietal cortices. Additionally, seed-3 appeared to have more connections in the visual cortex. These subtle differences partially reflect the functional subdivision of the precuneus found earlier in the resting state [13], namely, the sensorimotor anterior region, cognitive/associative central region, and visual posterior regions, as intendedly represented by the three precuneus seeds 1–3 in the present study. However, an absence of exact correspondence between our results and those of others in the resting state [13,14] may be due to the presence of the auditory and mnemonic task in our study and potential differences in data acquisition. For example, because of the task-dependent selective deactivation [2], the auditory verbal memory task might suppress precuneus connectivity with the visual cortex at wakeful baseline, which however was resumed during propofol sedation and then reduced again in recovery.

3.2. PCC connectivity across the states of propofol sedation

Connectivity analysis of the PCC seed region showed the typical pattern of DMN connectivity at the wakeful baseline, with minimal changes in deep sedation and recovery as observed by visual inspection (Fig. 3). Particularly, there was no significant difference in the sum of voxelwise correlation strength in the medial superior frontal cortex between the wakeful baseline and deep sedation (Fig. 2, the rightmost panel). There was a minor increase of PCC seed connectivity with the visual cortex in deep sedation, which then decreased in recovery, accompanied by an increase of connectivity in the prefrontal cortex. The different connectivity pattern changes of seed regions in the PCC and precuneus across the states of propofol sedation suggest that the PCC and precuneus, which have traditionally been considered as one functional unit in the posteromedial parietal region, may have different functional attributes as expressed by their connectivity patterns and changes across specific cognitive states of the brain.

4. Discussion

The main goal of this investigation was to determine the effect of propofol sedation on functional connectivity of the precuneus. The precuneus has been implicated in memory, consciousness and internally directed thought [1,6], accompanied by distinctively high activity and metabolic rate in the resting state [2]. If the precuneus played a significant role in conscious mentation, a reduction of its function connectivity with other brain regions in the state of diminished consciousness was plausible. In fact, previous investigations found that in resting propofol-sedated subjects, rCBF was preferentially decreased in the precuneus and nearby regions, including the posterior cingulate cortex and cuneus [15–17]. In addition, a reduction of functional interaction in the frontoparietal networks [18,19] and neurophysiological communication between frontal and parietal cortical regions [20,21] has been found to accompany loss of consciousness under anesthesia. Given these findings, the observed increase of precuneus functional connectivity during propofol sedation in the present study was unexpected. However, these observations are not necessarily contradictory for several reasons. First, the changes in baseline neuronal/metabolic activity and functional connectivity are not necessarily correlated with each other. For instance, during slow-wave sleep, significant reductions in electrocortical activity of subcortical networks including the hypothalamus are accompanied by increased functional connectivity of the hypothalamus with frontal and parietal cortical areas [22]. Such increases in functional connectivity, based on the correlation of BOLD signals between remote brain regions, are consistent with an increase in global synchrony of the EEG typical to slow-wave sleep and anesthetic sedation. A more widespread connectivity of the precuneus serving endogenous mental processes may have continued at a lower rate of metabolic activity [15–17]. Second, the design of the experiments was different in that it involved an auditory verbal memory task during the fMRI scan. As a result, the stronger connectivity of the precuneus with frontal and visual cortices during sedation may have been due to disinhibition, by other information processing streams. For example, the dynamic anticorrelation between task-positive and task-negative processing networks is well known [23]. Accordingly, during wakefulness, the precuneus may have been partially inhibited by the heightened activity of the auditory verbal memory network. As sedation suppressed the auditory memory network [12], the balance could have been shifted to a disinhibition of the precuneus connectivity.

Relevant to the above possibilities is the proposition of Sanders et al. to differentiate the states of consciousness, connectedness, and responsiveness during general anesthesia [10]. These authors suggest that, during general anesthesia, internally directed consciousness may persist in the state of absent responsiveness and disconnection from the environment. We speculate that the observed increases in precuneus connectivity during propofol-induced

unresponsiveness may be associated with internally directed mentation or dreaming [24]. Dreaming is common in both anesthesia and REM sleep, in particular during propofol sedation [25,26]. Chow et al. observed, in REM sleep widespread, that temporally dynamic interaction among brain networks with the executive and high-order cognitive areas became more synchronous and the unimodal sensory and heteromodal cortices became more dissociated [27]. Using an fMRI-guided connectivity analysis of the same dataset, we previously found similar sensory disconnection during propofol sedation, while high-order cortical networks remained internally connected [12]. The findings revealed the detailed manner in which cognitive unbinding, as a proposed mechanism of anesthetic suppression of consciousness [28], occurs across different levels of the cognitive hierarchy in the sedated brain. Thus, the increase in precuneus connectivity may be a reflection of disconnected endogenous mental activity.

The observed increase in precuneus connectivity contrasts with the relative preservation of PCC connectivity under propofol sedation. Such dissociation may suggest region-specific drug effect, an effect of network interaction, or adaptive reconfiguration of different functional systems of the brain [29]. The PCC of course is another important region of the DMN that has been found relatively resistant to propofol sedation in its connectivity, although the changes appeared to be dose-dependent. Light-to-moderate sedation with propofol (0.27 and 0.67 $\mu\text{g/mL}$ plasma concentration) produced an increase in PCC connectivity with the anterior cingulate cortex, somatosensory, and motor cortex [30]. In deep propofol sedation (3.20 $\mu\text{g/mL}$ plasma concentration), functional connectivity of the DMN, including that of the PCC with various prefrontal, parahippocampal and temporoparietal cortical areas, were partially preserved [18]. These findings generally parallel those in NREM sleep suggesting the preservation of the DMN and PCC connectivity [31–33]. Nevertheless, the pattern of DMN changes may be different with different anesthetics. Greicius et al. found increased sensory-motor network connectivity and persistent DMN connectivity with a focal decrease in the posterior cingulate area (limited to a 111-voxel cluster) under sedation with midazolam [34]. In contrast, Martuzzi et al. found an increase in DMN connectivity at 1% (0.5 MAC) sevoflurane anesthesia which is at the threshold for loss of consciousness [35]. Obviously, the differing pharmacological characteristics of the anesthetic agents may have been in part responsible for the variance in the results. Because we did not measure the plasma concentration of propofol, we do not know how exactly our results compare to those of the other propofol studies at the same plasma concentration. Nevertheless, based on the behavioral criteria of lost responsiveness, our level of sedation appears consistent with the relatively unchanged DMN connectivity.

A few methodological concerns need to be addressed. In this study, precuneus functional connectivity was evaluated under the task condition. Although most functional connectivity analyses have been performed in the resting-state, there is no a priori reason for excluding the derivation of functional connectivity from BOLD time series acquired during stimulus presentation or task. Sensory stimulation or cognitive task can serve to preferentially augment specific processing systems in a particular modality while modulating functional connectivity in other sensory, motor and integrative systems. From this point of view, functional connectivity analysis under a task condition is a justified approach to probe the coordination and integration of spatially distinct brain regions subserving a specific neurocognitive state of the brain. In fact, functional connectivity changes during sensory stimulation in sedated participants were recently investigated [36]. We previously compared thalamocortical functional connectivity with and without regressing out the auditory stimulus from the BOLD time course and the obtained connectivity results were similar in the two cases. Future investigations may compare the effect of sedation on precuneus connectivity with and without the auditory task. In addition, most previous studies of resting-state functional connectivity utilized band-pass filtering in the low-frequency range,

generally at 0.01–0.1 Hz. Because our experiments included task that may entail relatively fast BOLD changes, low-pass filtering was not applied to the present data. Recent studies suggest that there may be important contributions from the BOLD signal at frequencies higher than the usual 0.1 Hz cutoff to resting state connectivity [37–39]. By bypassing the filtering step, we hoped to preserve as much task-related information as possible in the BOLD time series. To facilitate a comparison with conventional resting-state functional connectivity studies, we also conducted an additional set of precuneus connectivity analysis using BOLD signal with task effect regressed out and band-pass filtering at 0.01–0.1 Hz. As indicated in Supplemental Figs. 3–6, the resulting connectivity maps and their changes across the three states of consciousness with each of the four seed regions were similar to those obtained under the task condition without the band-pass filtering.

Our present findings on precuneus connectivity should be interpreted in the context of the experimental protocol, the anesthetic regime, and the extent of analysis. It is possible, in fact very likely, that precuneus connectivity would be eventually suppressed at a sufficiently deep level of propofol anesthesia. As already indicated, other types of intravenous and volatile anesthetics may exert different effects on functional connectivity. The results may also be different in task-free, resting condition, as opposed to the memory task and auditory stimulation as applied here. Finally, possible changes in functional connectivity of the precuneus with major identified intrinsic functional networks of the brain [40], such as the sensory, executive, salience, and attention networks, could be investigated in the future. Given the paucity of imaging studies focusing on precuneus connectivity and its dependence on the state of consciousness to-date, the present findings represent one of the first steps toward a better understanding of the organization and functional role of the precuneus in mediating cognition and consciousness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research reported in this publication was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Number R01-GM103894 and by the W. M. Keck Foundation, Los Angeles, California. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors thank Carrie M. O'Connor, MA, Editorial Assistant, Department of Biophysics, Medical College of Wisconsin, for editorial assistance.

References

1. Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain*. 2006; 129:564–583. [PubMed: 16399806]
2. Gusnard DA, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. *Nat. Rev. Neurosci.* 2001; 2:685–694. [PubMed: 11584306]
3. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc. Natl. Acad. Sci. U. S. A.* 2001; 98:676–682. [PubMed: 11209064]
4. Morcom AM, Fletcher PC. Does the brain have a baseline? Why we should be resisting a rest. *Neuroimage*. 2007; 37:1073–1082.
5. Alkire MT, Hudetz AG, Tononi G. Consciousness and anesthesia. *Science*. 2008; 322:876–880. [PubMed: 18988836]
6. Cavanna AE. The precuneus and consciousness. *CNS Spectr.* 2007; 12:545–552. [PubMed: 17603406]
7. Hudetz AG. General anesthesia and human brain connectivity. *Brain Connect.* 2012; 2:291–302. [PubMed: 23153273]

8. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat. Rev. Neurosci.* 2009; 10:186–198. [PubMed: 19190637]
9. Raichle ME, Snyder AZ. A default mode of brain function: a brief history of an evolving idea. *Neuroimage.* 2007; 37:1083–1090. [PubMed: 17719799]
10. Sanders RD, Tononi G, Laureys S, Sleigh JW. Unresponsiveness not equal unconsciousness. *Anesthesiology.* 2012; 116:946–959. [PubMed: 22314293]
11. Liu X, Lauer KK, Ward BD, Li SJ, Hudetz AG. Differential effects of deep sedation with propofol on the specific and nonspecific thalamocortical systems: a functional magnetic resonance imaging study. *Anesthesiology.* 2013; 118:59–69. [PubMed: 23221862]
12. Liu X, Lauer KK, Ward BD, Rao SM, Li SJ, Hudetz AG. Propofol disrupts functional interactions between sensory and high-order processing of auditory verbal memory. *Hum. Brain Mapp.* 2012; 33:2487–2498. [PubMed: 21932265]
13. Margulies DS, Vincent JL, Kelly C, Lohmann G, Uddin LQ, Biswal BB, Villringer A, Castellanos FX, Milham MP, Petrides M. Precuneus shares intrinsic functional architecture in humans and monkeys. *Proc. Natl. Acad. Sci. U. S. A.* 2009; 106:20069–20074. [PubMed: 19903877]
14. Cauda F, Geminiani G, D'Agata F, Sacco K, Duca S, Bagshaw AP, Cavanna AE. Functional connectivity of the posteromedial cortex. *PLoS ONE.* 2010; 5:e13107. [PubMed: 20927345]
15. Kaisti KK, Langsjo JW, Aalto S, Oikonen V, Sipila H, Teras M, Hinkka S, Metsahonkala L, Scheinin H. Effects of sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow oxygen consumption, and blood volume in humans. *Anesthesiology.* 2003; 99:603–613. [PubMed: 12960544]
16. Fiset P, Paus T, Daloze T, Plourde G, Meuret P, Bonhomme V, Hajj-Ali N, Backman SB, Evans AC. Brain mechanisms of propofol-induced loss of consciousness in humans: a positron emission tomographic study. *J. Neurosci.* 1999; 19:5506–5513. [PubMed: 10377359]
17. Vogt BA, Laureys S. Posterior cingulate, precuneal and retrosplenial cortices: cytology and components of the neural network correlates of consciousness. *Prog. Brain Res.* 2005; 150:205–217. [PubMed: 16186025]
18. Boveroux P, Vanhaudenhuyse A, Bruno MA, Noirhomme Q, Lauwick S, Luxen A, Degueldre C, Plenevaux A, Schnakers C, Phillips C, Brichant JF, Bonhomme V, Maquet P, Greicius MD, Laureys S, Boly M. Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. *Anesthesiology.* 2010; 113:1038–1053. [PubMed: 20885292]
19. Schrouff J, Perlberg V, Boly M, Marrelec G, Boveroux P, Vanhaudenhuyse A, Bruno MA, Laureys S, Phillips C, Pelegri-Isaac M, Maquet P, Benali H. Brain functional integration decreases during propofol-induced loss of consciousness. *Neuroimage.* 2011; 57:198–205. [PubMed: 21524704]
20. Lee U, Ku S, Noh G, Baek S, Choi B, Mashour GA. Disruption of frontal-parietal communication by ketamine, propofol, and sevoflurane. *Anesthesiology.* 2013; 118:1264–1275. [PubMed: 23695090]
21. Imas OA, Ropella KM, Ward BD, Wood JD, Hudetz AG. Volatile anesthetics disrupt frontal-posterior recurrent information transfer at gamma frequencies in rat. *Neurosci. Lett.* 2005; 387:145–150. [PubMed: 16019145]
22. Kaufmann C, Wehrle R, Wetter TC, Holsboer F, Auer DP, Pollmacher T, Czigic M. Brain activation and hypothalamic functional connectivity during human non-rapid eye movement sleep: an EEG/fMRI study. *Brain.* 2006; 129:655–667. [PubMed: 16339798]
23. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc. Natl. Acad. Sci. U. S. A.* 2005; 102:9673–9678. [PubMed: 15976020]
24. Cabanis M, Pyka M, Mehl S, Muller BW, Loos-Jankowiak S, Winterer G, Wolwer W, Musso F, Klingberg S, Rapp AM, Langohr K, Wiedemann G, Herrlich J, Walter H, Wagner M, Schnell K, Vogeley K, Kockler H, Shah NJ, Stocker T, Thienel R, Pauly K, Kircher T. The precuneus and the insula in self-attributional processes. *Cogn. Affect. Behav. Neurosci.* 2013; 13:330–345. [PubMed: 23297009]

25. Eer AS, Padmanabhan U, Leslie K. Propofol dose and incidence of dreaming during sedation. *Eur. J. Anaesthesiol.* 2009; 26:833–836. [PubMed: 19528807]
26. Leslie K, Sleigh J, Paech MJ, Voss L, Lim CW, Sleigh C. Dreaming and electroencephalographic changes during anesthesia maintained with propofol or desflurane. *Anesthesiology.* 2009; 111:547–555. [PubMed: 19672164]
27. Chow HM, Horovitz SG, Carr WS, Picchioni D, Coddington N, Fukunaga M, Xu Y, Balkin TJ, Duyn JH, Braun AR. Rhythmic alternating patterns of brain activity distinguish rapid eye movement sleep from other states of consciousness. *Proc. Natl. Acad. Sci. U. S. A.* 2013; 110:10300–10305. [PubMed: 23733938]
28. Mashour GA. Integrating the science of consciousness and anesthesia. *Anesth. Analg.* 2006; 103:975–982. [PubMed: 17000815]
29. Lee U, Oh G, Kim S, Noh G, Choi B, Mashour GA. Brain networks maintain a scale-free organization across consciousness, anesthesia, and recovery: evidence for adaptive reconfiguration. *Anesthesiology.* 2010; 113:1081–1091. [PubMed: 20881595]
30. Stamatakis EA, Adapa RM, Absalom AR, Menon DK. Changes in resting neural connectivity during propofol sedation. *PLoS ONE.* 2010; 5:e14224. [PubMed: 21151992]
31. Samann PG, Wehrle R, Hoehn D, Spoormaker VI, Peters H, Tully C, Holsboer F, Czisch M. Development of the brain's default mode network from wakefulness to slow wave sleep. *Cereb. Cortex.* 2011; 21:2082–2093. [PubMed: 21330468]
32. Horovitz SG, Fukunaga M, de Zwart JA, van Gelderen P, Fulton SC, Balkin TJ, Duyn JH. Low frequency BOLD fluctuations during resting wakefulness and light sleep: a simultaneous EEG-fMRI study. *Hum. Brain Mapp.* 2008; 29:671–682. [PubMed: 17598166]
33. Horovitz SG, Braun AR, Carr WS, Picchioni D, Balkin TJ, Fukunaga M, Duyn JH. Decoupling of the brain's default mode network during deep sleep. *Proc. Natl. Acad. Sci. U. S. A.* 2009; 106:11376–11381. [PubMed: 19549821]
34. Greicius MD, Kiviniemi V, Tervonen O, Vainionpaa V, Alahuhta S, Reiss AL, Menon V. Persistent default-mode network connectivity during light sedation. *Hum. Brain Mapp.* 2008; 29:839–847. [PubMed: 18219620]
35. Martuzzi R, Ramani R, Qiu M, Rajeevan N, Constable RT. Functional connectivity and alterations in baseline brain state in humans. *Neuroimage.* 2010; 49:823–834. [PubMed: 19631277]
36. Mhuirheartaigh RN, Rosenorn-Lanng D, Wise R, Jbabdi S, Rogers R, Tracey I. Cortical and subcortical connectivity changes during decreasing levels of consciousness in humans: a functional magnetic resonance imaging study using propofol. *J. Neurosci.* 2010; 30:9095–9102. [PubMed: 20610743]
37. Boubela RN, Kalcher K, Huf W, Kronnerwetter C, Filzmoser P, Moser E. Beyond Noise, Using temporal ICA to extract meaningful information from high-frequency fMRI signal fluctuations during rest. *Front. Hum. Neurosci.* 2013; 7:168. [PubMed: 23641208]
38. Lee HL, Zahneisen B, Hugger T, LeVan P, Hennig J. Tracking dynamic resting-state networks at higher frequencies using MR-encephalography. *Neuroimage.* 2013; 65:216–222. [PubMed: 23069810]
39. Niazy RK, Xie J, Miller K, Beckmann CF, Smith SM. Spectral characteristics of resting state networks. *Prog. Brain Res.* 2011; 193:259–276. [PubMed: 21854968]
40. Raichle ME. The restless brain. *Brain Connect.* 2011; 1:3–12. [PubMed: 22432951]

HIGHLIGHTS

- The precuneus is known to be involved in memory and consciousness functions.
- Precuneus connectivity unexpectedly increases in the dorsal prefrontal and visual cortices upon loss of response to verbal commands in propofol sedation.
- Changes of posterior cingulate cortex connectivity in sedation are minimal.
- Increased precuneus connectivity in propofol sedation may reflect disconnected endogenous mentation or dreaming that continues at a reduced level of metabolic activity.

Fig. 1.

Functional connectivity maps of the precuneus seed-1 in wakeful baseline, deep sedation, and recovery when eight participants performed an auditory verbal memory task during fMRI scanning. Compared with the wakeful baseline (A), functional connectivity of the seed-1 demonstrated a prominent increase in the deep sedation (B), particularly in the dorsal medial prefrontal and visual cortices (arrows). After recovery of consciousness (C), functional connectivity returns to a pattern similar to that observed during the wakeful baseline. The statistical results were computed using one-sample *t*-test followed by a transformation to Z score in AFNI and correction for multiple comparisons. The precuneus seed-1 contains average 2052 voxels of 2-mm cubic at the center of mass of $[-0.54, 48.5, 56.1]$ in the Talairach coordinates.

Fig. 2.

The sum of voxelwise correlation strength (after Fisher transformation) in brain areas showing significant effects of precuneus connectivity in the medial superior frontal (MSF, including both the left and right) gyrus and the visual cortex (including the left and right calcarine sulcus and cuneus) across the states of wakeful baseline, deep sedation, and recovery. The error bar represents standard deviation across the eight participants. Paired comparisons that show a main effect of difference are marked by asterisk.

Fig. 3.

Functional connectivity maps of the PCC seed in wakeful baseline, deep sedation, and recovery. In general, connectivity map at the wakeful baseline demonstrated the typical pattern of DMN connectivity and showed minimal changes across the other two states. Compared the wakeful baseline, there was no main effect of change in the medial prefrontal regions during the deep sedation. The PCC seed contains average 980 voxels at the center of mass of $[-0.36, 41.2, 26.4]$ in the Talairach coordinates.