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Persistent Default-Mode Network Connectivity During Light Sedation

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Abstract: The default-mode network (DMN) is a set of specific brain regions whose activity, predominant in the resting-state, is attenuated during cognitively demanding, externally-cued tasks. The cognitive correlates of this network have proven difficult to interrogate, but one hypothesis is that regions in the network process episodic memories and semantic knowledge integral to internally-generated mental activity. Here, we compare default-mode functional connectivity in the same group of subjects during rest and conscious sedation with midazolam, a state characterized by anterograde amnesia and a reduced level of consciousness. Although the DMN showed functional connectivity during both rest and conscious sedation, a direct comparison found that there was significantly reduced functional connectivity in the posterior cingulate cortex during conscious sedation. These results confirm that low-frequency oscillations in the DMN persist and remain highly correlated even at reduced levels of consciousness. We hypothesize that focal reductions in DMN connectivity, as shown here in the posterior cingulate cortex, may represent a stable correlate of reduced consciousness. *Hum Brain Mapp 29:839–847, 2008.*

Key words: consciousness; conscious sedation; default mode; episodic memory; posterior cingulate; resting-state

INTRODUCTION

The default mode hypothesis of brain function [Raichle et al., 2001] holds that there is a specific neural network whose activity predominates in the relaxed, resting state and decreases when one performs a demanding externally-cued task. This hypothesis is supported by fMRI studies of conscious rest [Beckmann et al., 2005; Fox et al., 2005; Fransson, 2005; Greicius et al., 2003; Laufs et al., 2003] and cognitively undemanding tasks [Greicius and Menon, 2004; Greicius et al., 2004] showing strong temporal coherence of low-frequency blood oxygen level-dependent (BOLD) signal oscillations among brain regions implicated in the network. Although evidence continues to mount

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supporting the existence of the default-mode network (DMN), its functional correlates remain uncertain. Given the prominence of the posterior cingulate cortex in the network and this region's role in episodic memory, our group and others [Buckner et al., 2005] have proposed that the network is involved in episodic memory processing. In support of such a role, the network includes the hippocampus in healthy subjects [Greicius and Menon, 2004; Greicius et al., 2004], is activated by tasks requiring retrieval of episodic memories [Buckner et al., 2005; Maddock et al., 2001; Maguire and Mummery, 1999] and is deficient in Alzheimer's Disease (AD) [Buckner et al., 2005; Greicius et al., 2004; Lustig et al., 2003; Rombouts et al., 2005], the preeminent disorder of episodic memory. Several attributes of the network—it appears to be integrally involved in episodic memory processing; its activity is ongoing during conscious rest; it is interrupted when subjects are asked to attend to a challenging, externally-cued task—have led our group and others [Binder et al., 1999; McKiernan et al., 2005] to suggest that it may represent the neural correlate of the stream of consciousness.

The connection between consciousness and low-frequency BOLD signal oscillations as measured in resting-state fMRI studies has recently been called into question. The study by Vincent et al. [2007] demonstrating DMN activity in macaques scanned under general anesthesia suggests that the presence of correlations in low-frequency BOLD signals across DMN regions may not, in and of itself, reflect conscious cognitive processing. One recent study has examined functional connectivity in wakefulness and the early stages of sleep and provides evidence that correlations in DMN activity persist in the early stages of sleep [Horovitz et al., 2007]. However, that study did not include a direct, quantitative comparison between DMN connectivity during wakefulness and sleep. The relationship between DMN connectivity and pharmacologic sedation has not been investigated, to date, in humans. Here, we test the hypothesis that low frequency oscillations in the DMN reflect ongoing stream-of-consciousness-like cognitive processing by directly comparing DMN connectivity in the same group of subjects at rest and during conscious sedation with midazolam.

MATERIALS AND METHODS

Subjects

Twelve healthy, nonsmoking, medical student volunteers were imaged on a 1.5 T GE Signa EchoSpeed MRI scanner (GE Medical Systems, Waukesha, WI) with a birdcage head coil (Medical Advances, Milwaukee, WI). Data from 9 subjects (aged 22–27, 5 females) were used in the analysis. Data from the three additional subjects were not included owing to reduced repetition time in one subject, reduced total scan time in a second subject, and faulty image reconstruction in the third subject. Written informed consent was obtained from the volunteers. The ethical committee of Oulu University Hospital approved the study.

Sedation

Conscious sedation is an anesthetic state characterized by anterograde amnesia and a diminished level of consciousness [Veselis et al., 2001]. Subjects under conscious sedation are able to breathe on their own and can respond to voice or gentle tactile prompts. It is used during moderately invasive procedures like gastric endoscopy or bronchoscopy, so that patients will be sufficiently conscious not to require mechanical ventilation but sufficiently sedated to be relaxed and, afterwards, amnestic for the procedure. Anterograde amnesia under conscious sedation has been confirmed explicitly in placebo-controlled trials by showing reduced episodic memory performance after exposure to midazolam but not placebo [Bulach et al., 2005; Merritt et al., 2005].

The sedation was performed and monitored by the attending anesthesiologist from the scanner side (VV, SA). The anesthesiologist verified the sedation level with tactile stimulus to the hand and verbal communication (saying the subject's name and asking "Do you hear me?"). At the level of Ramsay 3 sedation, the subject was barely awake, responding only to loud voice or having their hand shaken [Ramsay et al., 1974]. Before the procedure, the anesthesiologist opened an intravenous line on the back of the right hand. A heparinized saline bolus of 5–10 ml was introduced to test the intravenous line. The bolus served as a reference for the sedative drug administration. After the initial awake, 2.5 min resting-state scan the attending anesthesiologist administered the midazolam with 1 mg intravenous boluses at 3–5 min intervals until Ramsay sedation score of 3 was achieved. Once Ramsay 3 sedation was achieved the anesthesiologist signaled to the control room to start the scan. Subjects were not assessed during the 2.5 min scan. All subjects were noted by the anesthesiologist to be sedated still at the end of the 2.5 min scan.

The average midazolam dose needed to reach a Ramsay score of 3 was 4.1 mg (standard deviation 0.9 mg) for the 9 subjects whose data were included in this study. A dedicated MRI compatible anesthesia monitor (Magnetic Equipment Corporation, M9500, Bay Shore, NY) was used to monitor the heart and respiratory rates and peripheral oxygen saturation. After the imaging, the subjects were monitored for 30–45 min until they had completely recovered.

IMAGE ACQUISTION, PROCESSING, AND ANALYSIS

Six oblique axial gradient recalled echo planar (EPI) images (7 mm slice thickness) were acquired with the following parameters: repetition time 2,000 ms, echo time 60 ms, flip angle 90°, field of view 24 cm, 128 × 128 matrix.

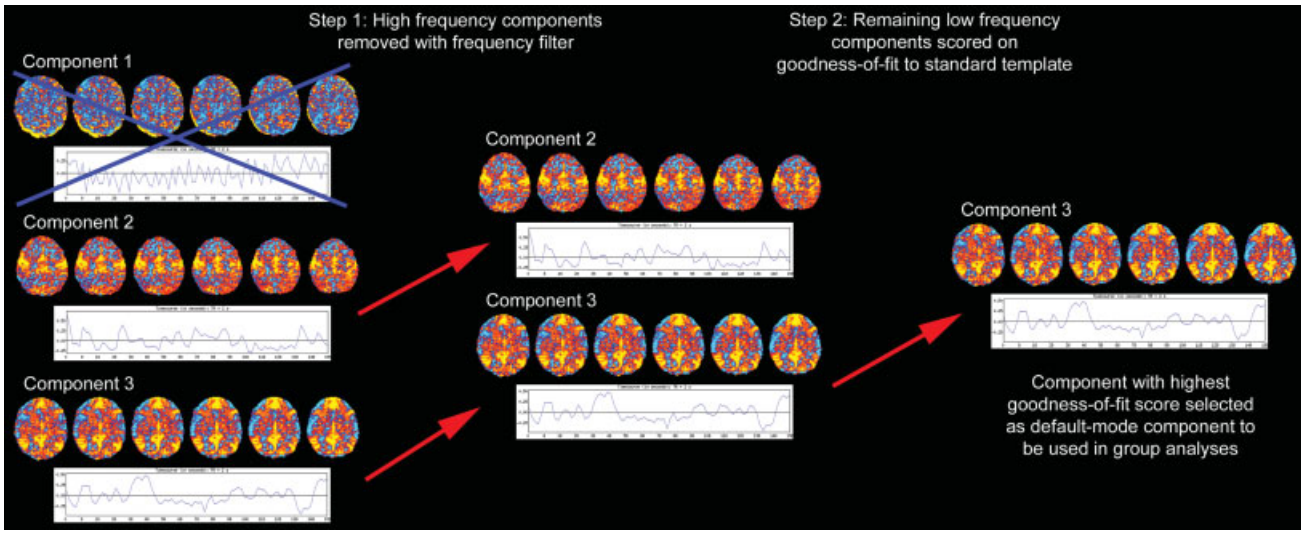

Figure 1.

Automated selection of the default-mode component. Each subject's default-mode component is selected from among their several independent components (shown here with only three components) based on the two-step process outlined earlier. Each component consists of a spatial map (colored axial images) and its corresponding time series shown beneath it. The color scale indicates the degree to which a given voxel's time series is correlated with the overall time series of that component (with yellow–red colors indicating a positive correlation and blue colors indicating a negative correlation). First, because resting-state neural networks are driven by low-frequency oscillations, all high-frequency components (component 1 in this example) are removed using a frequency filter. The remaining low-frequency components are scored based on their spatial goodness-of-fit to a standard template of the DMN derived from a separate dataset (template not shown). The component with the highest goodness-of-fit score (component 3 here) is then entered into the group analyses. Note that all voxels of the selected component have z-scores, not just those voxels that fall within the regions defined by the standard template. An identical technique is used to select the sensory-motor network (component 2 in this example) except that the standard template is changed from the DMN to the sensory-motor network.

The six slices covered an area of the brain extending roughly from the inferior aspect of the thalamus to within 1–2 cm of the vertex. Eighty-two n-frames were acquired. Images were preprocessed, normalized, and smoothed with SPM2. Images were corrected for movement using least square minimization without higher-order corrections for spin history and then normalized using a non-affine transformation that optimizes both global and local fit with the MNI template. As the Gaussian random field analysis, used to determine significant clusters, requires that voxels be isotropic, a 4th degree B-spline was used for interpolation with resampling every 2 mm. The resulting images were smoothed using a Gaussian kernel with 4 mm FWHM. After discarding the first two n-frames to allow for stabilization of the magnetic field, the smoothed images were concatenated across time into a single 4D image. The 4D image was then subjected to independent component analysis (ICA) with FSL melodic ICA software (www.fmrib.ox.ac.uk/fsl/melodic2/index.html). We allowed the software to estimate the optimal number of components for each scan (which ranged from 13 to 29 components).

The best-fit components for the DMN and the sensory-motor network were selected in an automated two-step process as in our previous studies [Greicius et al., 2004]. This process is illustrated in Figure 1. First, because resting-state connectivity is detected in the very low-frequency range [Cordes et al., 2001], a frequency filter was applied to remove any components in which high-frequency signal (>0.1 Hz) constituted 50% or more of the power in the Fourier spectrum. Next, standard templates of the DMN and the sensory-motor network were used to select the "best-fit" of the remaining low-frequency components in each subject. To do this, we used a template-matching procedure that involves taking the average *z*-score of voxels falling within the template minus the average *z*-score of voxels outside the template and selecting the component in which this difference (the goodness-of-fit) was the greatest. *z*-scores here reflect the degree to which a given voxel's time series correlates with the time series corresponding to the specific ICA component, scaled by the standard deviation of the error term. The *z*-score used here is, therefore, a measure of how many standard deviations the signal is from the background noise. As the standard template for the DMN we used, the map of the DMN derived from a separate group of 14 healthy controls (Fig. 1B in our previous study) [Greicius et al., 2004]. The standard

TABLE I. Significant clusters in the average sensory-motor network map

Connected regions	Brodmann's area (BA)	Cluster size (voxels)	Maximal *z*-score primary peak	Primary peak location
Mid-cingulate/SMA	BA 23/24	2,244	4.93	−2, −12, 44
PoCG/PCG/SMG	BA 3/4/2/40	3,311	4.68	−52, −24, 50
PCG/PoCG/SMG	BA 4/3/2/40	2,673	4.38	64, −18, 34
Cuneus/PCu	BA 18/31	162	4.2	−2, −72, 24
IFG	BA 45	195	3.98	56, 28, 20
MFG	BA 46	239	3.93	−36, 42, 30
ANG/IPC	BA 40	169	3.79	30, −46, 34
MOG	BA 19	97	3.63	36, −80, 12
MOG	BA 19	119	3.4	−40, −82, 20

Coordinates are in MNI space. SMA, supplementary motor area; PoCG, post-central gyrus; PCG, pre-central gyrus; SMG, supramarginal gyrus; PCu, precuneus; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; ANG, angular gyrus; IPC, inferior parietal cortex; MOG, middle occipital gyrus.

template for the sensory-motor network was also derived from this group of 14 healthy controls. To make the sensory-motor template, we visually selected the low-frequency component that showed the most activity over the bilateral sensory-motor cortices as has been done previously [Kiviniemi et al., 2003]. A group map of the sensory-motor network was computed from these 14 sensory-motor components and thresholded, like the default-mode template, at $P < 0.001$ height and extent. The final template for the sensory-motor network consisted of the bilateral sensory-motor cortex regions on this group map (i.e. other clusters such as those in the mid-cingulate were not included in the template).

For the sensory-motor network and DMN maps two one-sample *t*-tests combining each subject's best-fit component were computed in SPM2. This was done in each condition yielding sensory-motor network maps at rest and under conscious sedation and DMN maps at rest and under conscious sedation. Average maps of the sensory-motor network and the DMN over both conditions were also computed. For the average maps, each subject had a mean image made from their rest and conscious sedation images and these mean images were then used to compute the average group maps with one-sample *t*-tests. Finally, paired *t*-tests were computed comparing the functional connectivity in each network during rest versus conscious sedation. The images used in the paired *t*-tests were the same images used in the one-sample *t*-tests so that subject 1's resting default-mode image was contrasted with subject 1's sedated default-mode image, subject 2's resting default-mode image with subject 2's sedated default-mode image, etc... These paired *t*-tests were restricted (masked) to voxels in the average maps. The average maps were smoothed using a 4 mm full-width half-maximum kernel prior to being used as a mask for the paired *t*-tests. For all maps, significant clusters of activation were determined using the joint expected probability distribution with height ($P < 0.01$) and extent ($P < 0.05$) thresholds, corrected at the level of the whole imaged volume and a minimum cluster size of 50 voxels [Poline et al., 1997]. All functional images were overlayed on the normalized, group-averaged structural image from the group of healthy young controls used to make the functional templates [Greicius et al., 2004]. Coordinates cited in the results section refer to the standard space of the Montreal Neurological Institute (MNI) template used by SPM2 for normalization.

RESULTS

Applying ICA to fMRI data [Greicius et al., 2004], we examined DMN functional connectivity in a group of 9 subjects scanned at rest and during conscious sedation with midazolam. As a control, we also examined functional connectivity in a well-described resting-state sensory-motor network [Beckmann et al., 2005; Biswal et al., 1995; Xiong et al., 1999].

Sensory-Motor Network

During both the rest and conscious sedation scans, a well-defined sensory-motor network was detected (Fig. 2). The clusters for the average map (one-sample *t*-test of the nine mean images of each subject's rest and conscious sedation scan) are detailed in Table I. In addition to the bilateral sensory-motor cortices, the connectivity map includes midline clusters encompassing the mid-cingulate and supplementary motor areas as has been shown previously [Beckmann et al., 2005; Xiong et al., 1999]. Consistent with recent work showing that midazolam tends to increase functional connectivity parameters in primary sensory and sensory-motor neural networks [Kiviniemi et al., 2005], functional connectivity in the sensory-motor network showed focal increases with induction of conscious sedation (Fig. 2c). This focal increase was seen in a 102-voxel cluster in the mid-cingulate centered at (0, −10, 38). This focal increase in connectivity is emphasized in Figure 4.

Default-Mode Network

Default-mode functional connectivity was readily detectable in both the rest (Fig. 3a) and conscious sedation scans

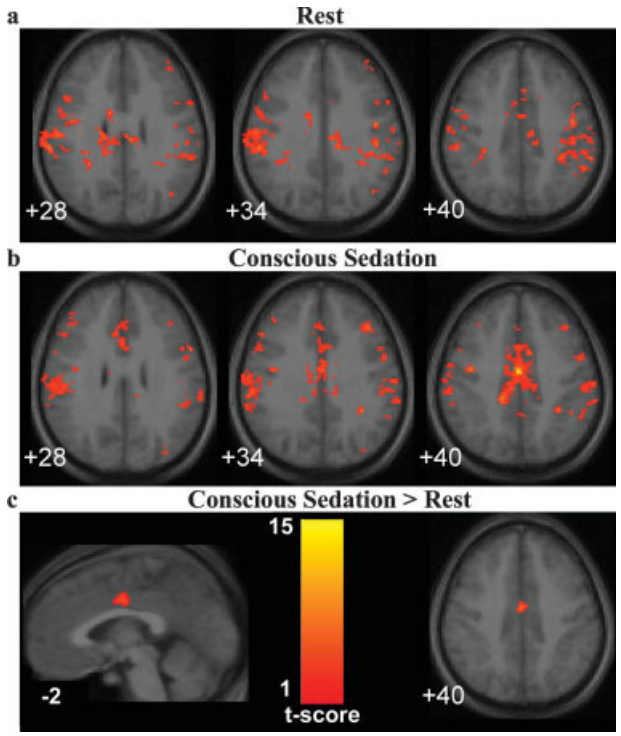

Figure 2.

Increased sensory-motor network functional connectivity during conscious sedation. The sensory-motor network is shown during rest (**a**) and during conscious sedation (**b**). A region in the mid-cingulate showed increased functional connectivity in the conscious sedation versus rest contrast (**c**). There were no regions showing significantly greater functional connectivity in the rest versus conscious sedation contrast. Numbers below the images refer to coordinates of the Montreal Neurological Institute template. For axial images, the left side of the image corresponds to the right side of the brain (radiologic convention). *T*-score bar for all three panels is shown in (c).

(Fig. 3b). The clusters for the average map (one-sample *t*-test of the nine mean images of each subject's rest and conscious sedation scan) are detailed in Table II. The four main regions included in the map, posterior cingulate, bilateral inferior parietal, and medial prefrontal cortices have been reported in numerous prior studies of the default-mode using both PET [Mazoyer et al., 2001; Shulman et al., 1997] and fMRI [Beckmann et al., 2005; Fox et al., 2005; Fransson, 2005; Greicius et al., 2003]. Hippocampal co-activation in the network, which we have reported previously [Greicius and Menon, 2004; Greicius et al., 2004], could not be detected here because the scan parameters did not allow for whole brain coverage. Sensory-motor network functional connectivity increased, whereas DMN functional connectivity showed focal decreases in the posterior cingulate cortex during conscious sedation (Fig. 3c). This focal decrease occurred in a 111-voxel cluster centered just to the right of the midline at (10, −56 18). This focal decrease in connectivity is emphasized in Figure 4.

DISCUSSION

This is the first human study to explore changes in DMN functional connectivity during sedation. The detection of robust connectivity in default-mode regions during conscious sedation, added to the recent report of DMN connectivity in monkeys sedated with isoflurane [Vincent et al., 2007] and the recent study demonstrating DMN connectivity during the early stages of sleep [Horovitz et al., 2007], confirms that there is not a binary, on–off relationship between low-frequency BOLD signal oscillations in the DMN and consciousness. That is, the presence of low-frequency BOLD signal oscillations temporally correlated across DMN regions does not allow one to predict if a subject is conscious, minimally conscious (as during conscious sedation with midazolam), or deeply unconscious

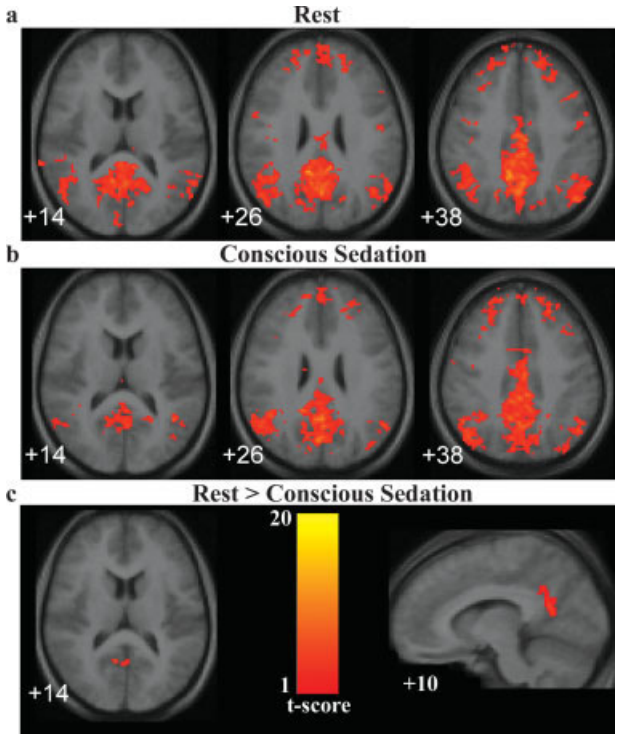

Figure 3.

Reduced DMN functional connectivity during conscious sedation. The DMN is shown during rest (**a**) and during conscious sedation (**b**). A 111-voxel cluster in the posterior cingulate cortex showed increased functional connectivity in the rest versus conscious sedation contrast (**c**). There were no regions showing significantly greater functional connectivity in the conscious sedation versus rest contrast. Other details per Figure 2.

TABLE II. Significant clusters in the average default-mode network map. Coordinates are in MNI space

Connected regions	Brodmann's area (BA)	Cluster size (voxels)	Maximal z-score primary peak	Primary peak location
PCC/PCu	BA 23/7/18	8,118	5.62	6, −42, 32
SFG/MFG	BA 9	2,903	4.98	32, 24, 36
ANG/MTG	BA 39/37	1,783	4.82	−44, −68, 32
ANG/MTG	BA 39/37	2,369	4.63	50, −68, 22
Caudate		100	4.26	−14, 2, 20
MFG	BA 8	263	3.75	−44, 20, 38
MTG	BA 22	97	3.68	68, −40, 6
PCG	BA 4	72	3.48	−38, −18, 40
SFG	BA 8	101	3.35	12, 28, 44

PCC, posterior cingulate cortex; PCu, precuneus; SFG, superior frontal gyrus; MFG, middle frontal gyrus; ANG, angular gyrus; MTG, middle temporal gyrus.

(as during sleep or under general anesthesia with isoflurane).

We did, however, detect regional differences in the DMN from rest to conscious sedation. Previous work applying a region-of-interest (ROI)-based analysis of fMRI acquired during conscious sedation [Kiviniemi et al., 2005] has shown increased synchrony of low-frequency BOLD signal oscillations within primary sensory and sensory-motor networks. Here using ICA, we report a similar finding of increased functional connectivity during conscious sedation compared to rest for a mid-cingulate region in the sensory-motor network. Despite this tendency for midazolam to increase BOLD signal synchrony within resting-state networks, the effect was reversed in the DMN where there was reduced functional connectivity in the posterior cingulate cortex in conscious sedation compared to rest. Thus, while a qualitative estimate of the presence or absence of DMN activity does not appear to correspond to the presence or absence of consciousness, it may still be the case that quantitative measures of reduced connectivity within the DMN do correlate with the level of consciousness. One additional study has reported increased amplitude of low-frequency BOLD signal oscillations in sensory networks of subjects who reported falling asleep during a long resting-state scan compared to subjects who reported being awake throughout the scan [Fukunaga et al., 2006]. However, that study has several limitations, including the lack of objective evidence for sleep, a between-groups

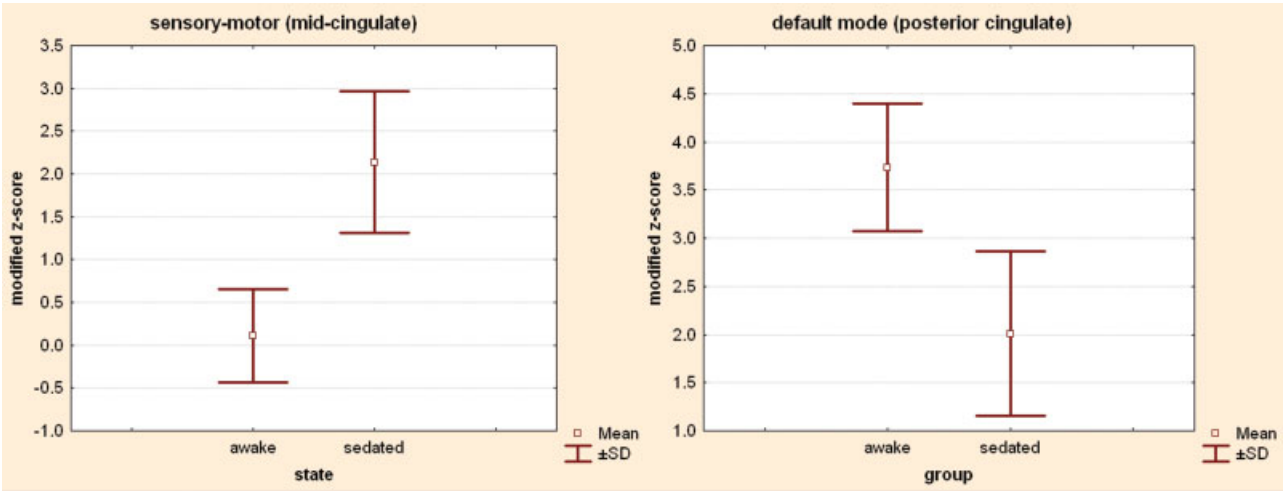

Figure 4.

Differential effects of sedation on connectivity in the sensory-motor and DMNs. The graph on the left shows the mean and standard deviation of the individual z-scores within the mid-cingulate cluster of the sensory-motor network that showed significantly increased connectivity in the sedated state (see Fig. 2c). The graph on the right shows the mean and standard deviation of the individual z-scores within the posterior cingulate cluster of the DMN that showed significantly decreased connectivity in the sedated state (see Fig. 3c).

design, and a focus on sensory networks rather than the DMN, which limits its applicability to the question of whether reduced DMN connectivity correlates with reduced consciousness. A more recent study by the same group does include an objective measure of sleep and demonstrates persistent DMN connectivity during the early stages of sleep [Horovitz, et al., 2007]. The study by Horovitz et al. [2007], however, did not include a direct statistical comparison of DMN connectivity between sleep and wakefulness relying instead on a qualitative comparison of DMN connectivity in the two states. To date, no other study has used a within-subjects design to directly compare DMN connectivity across differing levels of consciousness.

This study has several limitations including a small sample size, short scan times, and limited brain coverage. As such, while the one-sample *t*-test confirms the persistence of DMN connectivity during conscious sedation (Fig. 3B), the findings from the paired *t*-test (Fig. 3C) should be considered as preliminary. Given these limitations and the lack of evidence (in either direction) from other groups, whether there is a consistent difference in degree, but not kind, in DMN connectivity between conscious and unconscious states remains an open question for future studies to address. Further, we cannot be sure whether and how the effects described here would change if an alternate agent, such as propofol, were used to induce conscious sedation. Ideally, well-designed functional connectivity studies could elucidate the regional effects of commonly used (and incompletely understood) anesthetic agents.

The DMN does not lend itself to simple, direct deduction of its functional correlates. By definition, the moment an investigator attempts to control behavior with a defined task, DMN activity is attenuated. As such, the standard functional imaging approaches tend to yield little information, with some notable exceptions. Whereas nearly any cognitively demanding functional task will induce deactivation in the DMN, tasks that require retrieval of episodic memories [Buckner et al., 2005; Maddock et al., 2001; Maguire and Mummery, 1999; Vincent et al., 2006] and those that involve self-evaluative judgments [Johnson et al., 2007; Kelley et al., 2002] tend to activate regions in the DMN. Such activation of default-mode regions appears to depend largely on the type of task used as a control condition. One study whose activation map has generated the best match to the DMN used a relatively challenging task (counting syllables) in the control condition [Maguire and Mummery, 1999]. Presumably, this syllable-counting task was challenging enough to deactivate the network, some during the control condition, to allow for a larger relative increase when compared with the experimental condition of retrieving episodic and semantic memories. Using rest or a simple motor task, where default-mode activity tends to be high, as a control condition would likely have blunted the relative BOLD signal increases in that study. A similar line of reasoning led Binder et al. [1999] to another method for gleaning insight into the functional correlates of the network: find tasks which, compared to rest, yield little to no deactivation. By using this approach they found that a semantic judgment task (press the button when you hear the name of an animal found in the United States and used by people) yielded almost no deactivation compared to rest and, when compared with a more challenging auditory perception task, yielded activation in a number of default-mode regions. Although this constitutes a null finding, the assumption in this case is that the lack of deactivation suggests that brain regions in the DMN are performing similar operations at rest and during the semantic task.

Another indirect approach to deducing the functional correlates of the DMN is to examine the degree to which tasks deactivate the network. By parametrically manipulating task difficulty, McKiernan et al. [2003] have demonstrated that the more difficult the task, the greater the degree of deactivation in default-mode regions . We have shown that at the group level, passive sensory paradigms tend not to deactivate the network. At the single subject level, however, the more subjects suppressed their default-mode activity during visual and auditory stimulus blocks, the greater the degree of activation in the respective sensory cortices [Greicius and Menon, 2004]. Most recently, in an event-related study of the anti-saccade task it has been shown that correct, but not incorrect, trials resulted in deactivation of default-mode regions [Polli et al., 2005]. In a similar vein, Weissman et al. [2006] have shown that momentary lapses of attention during a challenging cognitive task are associated with reduced deactivation in the DMN. Taken together, these studies strongly suggest that the DMN, like the stream-of-consciousness, is suppressed when sufficient attention is directed to an externally-cued task.

The final method that has been used to interrogate the functional correlates of this network involves comparing its activity between two samples or states that differ in some fundamental attribute. To date, default-mode activity in AD [Greicius et al., 2004; Lustig et al., 2003; Rombouts et al., 2005] and mild cognitive impairment (MCI) [Rombouts et al., 2005] has been compared to activity in healthy controls. All three studies have shown abnormal activity in the network of AD patients. The Rombouts study also found that activity in MCI patients was greater than activity in AD patients but lesser than activity in healthy controls suggesting that network activity might be a reasonable marker of progressive memory loss on the spectrum from healthy aging through MCI and into AD. This is the first study to directly compare DMN functional connectivity in the same subjects across different states. The findings reported here are consistent with the studies in AD and MCI in demonstrating that reduced episodic memory capacities, whether due to a disease or a medication, are reflected in reduced default-mode functional connectivity. While we did not test for it, conscious sedation at the level induced in our subjects is designed for and typically results in anterograde amnesia [Bulach et al., 2005]. Assuming that anterograde amnesia was achieved in our subjects,

it is not surprising that conscious sedation resulted in reduced functional connectivity (Fig. 3c) in a part of the DMN that has been linked to episodic memory processing: the posterior cingulate cortex [Maddock et al., 2001; Maguire and Mummery, 1999; Valenstein et al., 1987]. The fact that the posterior cingulate is specifically implicated in this study as well as in the previous three studies in AD/MCI suggests that it may be a central node in the DMN.

Our results demonstrate that DMN activity persists in the state of reduced consciousness induced by conscious sedation with midazolam. Taken together with the recent findings in sedated monkeys [Vincent et al., 2007] and humans in the early stages of sleep [Horovitz et al., 2007], our results strongly suggest that the presence of low-frequency oscillations in the DMN cannot be used as a correlate of consciousness. Further studies are needed to determine if focal reductions in DMN connectivity, as shown here in the posterior cingulate cortex, represent a stable correlate of reduced consciousness. Finally, the significant reduction in DMN connectivity during a state characterized by anterograde amnesia adds further evidence to the hypothesis that the DMN generally and the posterior cingulate more specifically are integral to episodic memory processing.

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