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Co-activated yet disconnected—Neural correlates of eye closures when trying to stay awake

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ABSTRACT

Spontaneous eye-closures that herald sleep onset become more frequent when we are sleep deprived. Although these are typically associated with decreased responsiveness to external stimuli, it is less clear what occurs in the brain at these transitions to drowsiness and light sleep. To investigate this, task-free fMRI of sleep-deprived participants was acquired. BOLD activity associated with periods of spontaneously occurring eye closures were marked and analyzed. We observed concurrent and extensive hypnagogic co-activation of the extrastriate visual, auditory, and somatosensory cortices as well as the default mode network, consistent with internal sensory activity without external stimulation. Co-activation of fronto-parietal areas known to mediate attentional control could correspond with participants resisting sleep or additional engagement of mental imagery. This constellation of signal changes differed from those elicited by cued eye closures of similar duration and distribution in the same, rested participants. They also differ from signal changes associated with mind-wandering and consolidated light sleep. Concurrent with the observed event-related changes, eye closures elicited additional reduction in functional connectivity within nodes of the DMN and DAN, superposed on already reduced connectivity associated with sleep deprivation. There was concurrent deactivation of the thalamus during eye-closure during the sleep-deprived state but almost similar changes occurred in the well-rested state that may also be relevant. These findings highlight the dynamic shifts in brain activity and connectivity at border between wakefulness and sleep.

Introduction

Old aphorisms remind us that our eyes are the 'windows to our soul'. We close our eyes spontaneously when in agony or in the throes of ecstasy. More commonly, eye closures occur when we are fatigued or sleep deprived and at risk of behavioral lapses (Akerstedt and Kecklund, 2011; De Gennaro et al., 2005; Dinges et al., 1998). Such eye closures are accompanied by impaired auditory and visual perception, marking a withdrawal from the external environment and transition into sleep (Ong et al., 2013; Portas et al., 2000; Rechtschaffen et al., 1966). Paradoxically, vivid mental activity colorfully termed 'hypnagogic hallucinations' can occur at this time (Foulkes and Vogel, 1965; Kusse et al., 2012; Liberson and Liberson, 1965; Rowley et al., 1998; Schacter, 1976).

BOLD signal changes associated with longer duration eye closures of 0.5–24 s (cf. blinks) have been studied to characterize their effects on fMRI baseline signal (Marx et al., 2003, 2004) and resting state connectivity (Jao et al., 2013; Van Dijk et al., 2010). Of particular interest, these eye closures have been found to elicit varying degrees of somatosensory, auditory and/or visual cortical activation (Marx et al., 2003, 2004; Wiesmann et al., 2006) that have been attributed to a transition into an 'interoceptive state' while awake. Importantly, these studies did not report on factors that influence sleep propensity, such as eye closures, prior sleep history or the time of day.

As a third of participants in a large retrospective analysis of resting state fMRI scans showed imaging features of falling asleep (Tagliazucchi and Laufs, 2014), it is possible that the sensory co-activation previously attributed to an 'interoceptive state' while awake, may actually arise from behavioral microsleeps. The latter can elicit a divergent pattern of thalamus deactivation and sensory cortex activation (Poudel et al., 2014), similarly, to that observed during deep drowsiness (Olbrich et al., 2009).

Reconciling these varied observations, we posit that that hallucinatory or dream-like mentation occurring at sleep onset (Foulkes and Vogel, 1965; Liberson and Liberson, 1965; Rowley et al., 1998; Schacter, 1976) could be what underlies the multiple sensory cortex activation previously attributed to the act of eye closure alone. The vivid, autobiographical hallucinations that typify the hypnagogic state have been reported in between 75% and 95% of interviews conducted after awakening participants from this transition period (Foulkes and

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Vogel, 1965; Rowley et al., 1998) and occur in 70% of students surveyed (Schacter, 1976). Such mental activity (hallucinations) has been previously postulated to arise when asynchronous thalamo-cortical deactivation occurs during the descent into sleep (Magnin et al., 2010), allowing the neural correlates of visual imagery to be decoded from visual cortex (Horikawa et al., 2013). To test these predictions, we first enhanced the likelihood of observing eye closures associated with sleep onset by sleep depriving participants and then had them undergo task-free fMRI.

In sleep deprived persons, the BOLD signal changes evoked in association with eye closures might also be accompanied by alterations in functional connectivity similar to those occurring during the descent into light (Larson-Prior et al., 2009; Sämann et al., 2011) and deep sleep (Sämann et al., 2011). Sleep deprivation by itself can result in declines in functional connectivity within the Default Mode (DMN) and within the Dorsal Attention (DAN) networks (De Havas et al., 2012; Samann et al., 2010). These findings led us to wonder if eye-closure during sleep deprivation, would elicit *additional reductions* in functional connectivity relative to eyes-open epochs in this state, indicative of more pronounced decoupling of attentional and default-mode networks.

To test these predictions and to separate signal changes in the hypnagogic state that are related to sleep onset from those associated with the act of eye closure alone, we additionally tested an independent set of participants in both the rested and sleep deprived states, cueing eye closures in the rested state that were of a similar duration and temporal distribution to those in the sleep deprived state.

Materials and methods

Experiment 1

Twenty-nine healthy, young adults from the National University of Singapore were selected from respondents to a web-based questionnaire. They (1) were between 18 and 35 years of age, (2) were non-smokers, (3) had no history of psychiatric, neurological or sleep disorders, (4) consumed no more than two caffeinated drinks per day, (5) had good habitual sleep between 6.5 and 9 h daily (i.e. sleeping before 00:30 and getting up before 09:00) and (6) were not of an extreme chronotype as assessed on a reduced version of the Horne–Östberg Morningness–Eveningness questionnaire (Horne and Ostberg, 1976). All participants provided informed consent in compliance with a protocol approved by the National University of Singapore Institutional Review Board and were paid for their involvement. Sleep patterns of each participant were monitored throughout the entire duration of the study and only those whose actigraphy (Actiwatch, Philips Respironics, USA) data indicated habitual good sleep (i.e., sleeping no later than 12:30 AM and waking no later than 9:00 AM) were recruited following informed consent.

A total of 24 of 29 eligible participants successfully completed a paired set of resting-state scans in two sessions, once during rested wakefulness (RW) at around 08:00 AM and once following approximately 22 h of total sleep-deprivation (TSD) at around 06:00 AM. During functional imaging, an eye-tracking camera (Nordic Neurolab, Bergen, Norway) was used to monitor eyelid closures and to record these for offline analysis. The order of scanning sessions was counterbalanced across participants. Sessions were conducted a week apart to allow sufficient time for recovery—particularly in participants who completed the TSD session first. From this pool of 24 participants, five more were excluded due to problems with the eye-monitoring camera, and one because of excessively frequent eye closures (>70%). Data from 18 participants (9 male), aged 22 ± 2.0 years (mean ± SD), were analyzed.

The rationale for the selected test times has been described in prior publications (Kong et al., 2014) and is intended to evaluate participants at times that are maximally unfavorable to the sleep deprived session (Doran et al., 2001; Graw et al., 2004). Mainly, the 'TSD' effect represents a *combination* of circadian and homeostatic effects. This interaction is critical to appreciate as it means 24 h of sustained wakefulness can have worse effects on behavioral performance than 40 h (Abe et al., 2014).

Participants were instructed not to consume alcohol and caffeinated beverages 24 h prior to the start of either RW or TSD session. For the TSD session, they reported to the laboratory at 19:00 and were kept awake overnight under the constant supervision of a research assistant. During this period, they were allowed to engage in light activities such as reading or watching movies. For the RW session, participants stayed in the sleep laboratory the night before their scan to provide them with an 8-h sleep opportunity. Polysomnographic signals were recorded using six EEG (F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, O2-A1) channels, left and right electrooculogram (EOG) and submental electromyographic (EMG) electrodes to objectively verify that participants had sufficient sleep. Sleep staging was performed according to American Academy of Sleep Medicine criteria (Iber et al., 2007). Prior to each RW and TSD scan session, subjective sleepiness was assessed with the Karolinska Sleepiness Scale (KSS) (Akerstedt and Gillberg, 1990).

Two TSD resting state scans were acquired: once before and once after an auditory vigilance task that was used to study the behavioral effects of eye closure (Ong et al., 2013). During each 6-min scan, participants were required to keep their eyes open in darkness. Pre-recorded wake-up calls (e.g. "Open your eyes", "Please keep your eyes open") were delivered whenever participants closed their eyes for more than 10 s. No more than 10 reminders per run were allowed in order to reduce disruption of 'resting-state' connectivity. Episodes of falling asleep are the principal reason why the sleep deprived state is of interest to study.

Functional images were acquired on a 3 T Tim Trio scanner (Siemens, Erlangen, Germany). A gradient echo-planar imaging (EPI) sequence (TR: 2000 ms; TE: 30 ms; FA: 90°; FOV: 192 × 192 mm; matrix size: 64 × 64; voxel size: 3.0 × 3.0 × 3.0 mm) was used. Thirty-six oblique axial slices (slice thickness: 3 mm) parallel to the AC-PC line were obtained. In total 180 volumes (6 min) were collected for each resting-state run (total 12 min), and 300 volumes in each of six auditory vigilance runs (total 60 min).

Structural images for co-registration and normalization were acquired using a T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (TR: 2300 ms; TI: 900 ms; FA: 9; BW: 240 Hz/pixel; FOV 256 × 240 mm; matrix size: 256 × 256; voxel size: 1.0 × 1.0 × 1.0 mm).

The functional imaging data underwent the following preprocessing steps: 1) slice-time correction with SPM2 (http://www.fil.ion.ucl.ac.uk/spm/) Wellcome Department of Cognitive Neurology, London, UK), and 2) motion correction using rigid body translation and rotation parameters (FSL; Jenkinson et al., 2002; Smith et al., 2004). Individual participants' T1 scans were then reconstructed into surface representations using FreeSurfer (http://surfer.nmr.mgh.harvard.edu). Functional data were registered to structural images using the reconstructed cortical surfaces (Greve and Fischl, 2009; http://surfer.nmr.mgh.harvard.edu/fswiki/FsFast). The structural images were in turn nonlinearly registered to the MNI152 space (Buckner et al., 2011; Yeo et al., 2011). The resulting nonlinear deformations were used to warp the functional data into MNI152 space and smoothed with a 6-mm FWHM smoothing kernel. Visualization was performed in BrainVoyager QX v2.3 (Brain Innovations, Maastricht, The Netherlands).

Four-second video clips (30 frames/s) for both resting state runs were extracted and rated by a trained observer in a similar manner to the behavior-only work previously published (Ong et al., 2013). Each segment was given an *Eyescore* (ES) value between 1 (eyes fully closed) and 9 (eyes fully open). In order to ensure that there was no systematic bias in detection of time-on-task effects on eye closure events, the video segments of each subject were randomly shuffled during the review process such that the rater had no idea when the event that was being viewed occurred. A total of 3240 events were scored using this procedure.

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To identify BOLD activation patterns associated with episodes of drowsiness, these 4 s segments were further collapsed into two categories. Segments with ES values of 1–2 were labeled as 'eyes closed' (EC) epochs, and those with ES values of 3–9 were labeled as 'eyes open' (EO) epochs. Two discrete levels were selected to obtain a proportionate amount of trials and increase detection sensitivity as our earlier work (Ong et al., 2013) revealed a clear non-linear association between auditory lapses and eyelid closure with an approximate cutoff at ES 2. Analyses of BOLD activity during EC compared with EO epochs were performed using a general linear model (GLM) with 1 main and 18 nuisance regressors. The main regressor was constructed using a boxcar function with duration equal to the length of each eye closure convolved with a canonical hemodynamic response function (HRF). To reduce variance estimates, nuisance regressors were also inserted: a boxcar regressor modelling the length of each pre-recorded wake-up call (0.5–1 s) convolved with a canonical HRF, a drift regressor to remove low frequency phenomena of no interest, 6 parameters obtained by rigid body head motion correction as well as ventricular and white matter signals (and their first order derivatives). To illustrate the effect of eye closure duration on BOLD signal changes, eye-closure events were binned into three categories: EC 0.5-4 s, EC 4-8 s and EC 8-12 s. The onset of these different time-courses was used for event-related averaging in selected regions of interest (ROIs) identified in Fig. 2.

Analyses were performed using BrainVoyager QX v2.4. A voxel-level threshold of $p < 0.0001$ (uncorrected) for t-maps was applied. To control for Type I errors, the remaining voxels were then processed using an iterative cluster size thresholding procedure (Goebel et al., 2006) that considered the spatial smoothness of functional imaging data when generating activation maps based on a corrected cluster threshold ($p < 0.05$).

Experiment 2

This experiment was conducted on an independent sample to evaluate if the pattern of spontaneous eye-closure related BOLD signal changes observed during TSD is distinguishable from cue-directed eye-closures of similar distribution and temporal spacing in the well-rested (RW) state during which spontaneous eye closures rarely occur. Twenty young adult participants were selected and studied in a similar manner (both RW and TSD sessions) to that described in the resting-state session of Experiment 1 except for the critical manipulation where participants were instructed to close and open their eyes according to auditory cues 'CLOSE' or 'OPEN' lasting 500 ms in the RW session. The frequency and duration of cued eye-closure epochs were determined using the temporal characteristics of eye closures corresponding to the median subject from Experiment 1. This amounted to a grand average of 20 eyelid closures totaling 206 s (approximately 28.6% of the duration of the total resting scan). From this pool of 20 participants, five were excluded from the final analysis as they had too few (<10) long duration eye closures in the TSD state. As a result, only data from 15 participants (8 male), aged 22 ± 3.1 years (mean ± SD), were considered.

For the construction of GLM regressors in Experiment 2, EC epochs for the TSD session were derived in an identical manner to Experiment 1. In the RW session however, EC epochs were derived from periods of auditorily cued eye closure. An additional stick function regressor was added to the GLM to model variance due to the auditory cues. Wake-up calls, drift regressors, motion correction parameters as well as ventricular and white matter regressors were also added as in Experiment 1.

Connectivity analyses

For resting-state connectivity analyses, the data underwent both slice-time correction and motion correction procedures as detailed above. In addition, constant offset and linear trends over each run were removed and low pass filtering was performed to retain frequencies below 0.08 Hz. Sources of spurious variance (e.g. respiration-induced signal fluctuations; Van Dijk et al., 2010) were additionally removed by regressing out the six parameters obtained by rigid body head motion correction as well as the whole brain, ventricular and white matter signals (and their derivatives). Additional details about this methodology have been previously published (Buckner et al., 2011; Yeo et al., 2011). Whole brain signal regression was performed as prior work conducted at our laboratory indicated a widespread increase in whole brain signal across the entire brain following total sleep deprivation that could mask the conceptually important, albeit smaller, relative fluctuations in fMRI signals (Yeo et al., 2015). However, analyses without whole brain signal regression were also conducted as a comparison.

Experiment 1

TSD EO and TSD EC epochs of the resting state scan were then extracted for computation of separate connectivity maps. The RW resting state scan was also included as a baseline measure but no segregation by eye closure was performed, as eye closures were rare (<1%). Based on prior work examining cued eye closure (Van Dijk et al., 2010) and connectivity changes after total sleep deprivation (De Havas et al., 2012), we selected nodes in the DMN and DAN networks for computation of functional connectivity measures. These nodes were identified from a surface-based parcellation (Yeo et al., 2011) projected into the MNI152 space (Fig. 3a). Within each node, voxel time courses were averaged and correlation coefficient maps both within and between the DMN and DAN nodes were computed using Pearson's product moment correlation. The correlation scores were then converted into z-maps using Fisher's r-to-z transform to improve normality (Van Dijk et al., 2010) and averaged within each network. Finally paired sample t-tests were performed on these scores for RW vs. TSD regardless of eye closures, and TSD EO vs. TSD EC conditions to assess differences in connectivity strength across the different states.

Experiment 2

In Experiment 2 (Cued vs. Spontaneous Eye Closure), connectivity analyses for the TSD state were performed as per Experiment 1. However, in the RW state, epochs were additionally separated into eyes open (EO) and eyes closed (EC) epochs. Data were analyzed using two-way repeated measures ANOVA for each network pair: DMN-DMN, DAN-DAN and DMN-DAN, with state (RW/TSD) and eye closure (EC/EO) as within-subject factors. Where there were significant interaction effects, post-hoc analysis was performed using paired-sample t-tests. All tests were two-tailed.

Results

Experiment 1

Participants had significantly higher self-rated sleepiness scores in the TSD session compared with the RW session (Karolinska Sleepiness Scale; Akerstedt and Gillberg, 1990); 8.1 ± 1 versus 3.6 ± 1.4, $t_{21} = 12.14$, $p < 0.005$). Total sleep time (TST) for the night prior to the RW session as assessed by polysomnography was 7.9 ± 0.5 h (mean ± SD). On average, the number of eye closures recorded in the TSD state was 18 ± 7 events lasting 13 ± 8.6 s each (mean ± SD). In the RW state, this number was negligible (<1% of scan time). Wake-up calls in the TSD state were played an average of 1.8 ± 2.3 times (mean ± SD) per run, which totaled 1.2 ± 1.7 s (mean ± SD) per 6-min run. Critically, on-average, wake up calls constituted only ~10% of EC events per participant. They are thus not expected to have a major impact on the imaging findings. A large number of longer duration eye closures were

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associated with spontaneous eye-opening/wakening. The remaining EC events were brief enough not to warrant waking the participant up.

I) BOLD activation and deactivation during periods of eye closure (TSD only)

Compared to eyes-open epochs, eyes-closed epochs in resting state scans showed significant activation and deactivation in multiple brain regions (Fig. 1; Table 1). Significantly elevated BOLD signal was observed in sensory, motor and limbic areas: extrastriate visual cortex (EVC), auditory (A1), somatosensory, primary motor (M1), supplementary motor (SMA) cortices as well as in the hippocampal (HF) and parahippocampal regions (PHG). Additionally, higher signal was observed in 'task-positive': intraparietal sulcus (IPS) and frontal eye fields (FEF) as well as 'task-negative' (Default Mode; DMN) regions: ventromedial prefrontal (vmPFC), angular gyrus (AG) and retrosplenial cortex (Rsp). Regions showing significant deactivation during eye closure included the thalamus (Thal), anterior cingulate cortex (ACC) and brainstem.

To further illustrate this point, time courses corresponding to the onset of each eye closure event (0.5–4 s, 4–8 s and 8–12 s) were extracted in selected activated/deactivated ROIs. Longer duration eye closures elicited peak BOLD signals with higher amplitude and delayed peak latency (Fig. 2).

II) Functional connectivity during periods of eye closure (TSD and RW)

Functional connectivity results for Experiment 1 are given in Fig. 3b. Comparing all TSD and RW epochs, sleep deprivation was associated with reduced functional connectivity within the DMN ($t_{17} = 3.90$, $p < 0.005$) and within the dorsal attention network (DAN; $t_{17} = 2.89$, $p < 0.05$), and reduced anti-correlation between the DMN and DAN networks ($t_{17} = 3.23$, $p < 0.005$). In addition, within the TSD epochs, EC vs. EO epochs were associated with reduced functional connectivity within both the DMN ($t_{17} = 2.57$, $p < 0.05$) and DAN networks ($t_{17} = 5.04$, $p < 0.005$). Intriguingly, no additional reduction in DMN–DAN anti-correlation was observed ($p = 0.2$). Results without whole brain signal regression for the TSD EO and TSD EC epochs are also included in the Supplementary Material, (Fig. S1).

Experiment 2

Participants had significantly higher self-rated sleepiness scores in the TSD session compared with the RW session (KSS; 5.8 ± 2.3 versus 3.1 ± 0.8, $t_{14} = 4.98$, $p < 0.005$). In the TSD state, participants averaged 16.9 ± 7.7 eye closures spanning 14.5 ± 12.8 s each (average participant total $= 230 \pm 164$ s). The frequency and duration of eye closures did not significantly differ from the average across all participants in Experiment 1 (two-sample t-test; frequency: $t_{31} = 0.50$; n.s.; duration: $t_{31} = 0.35$; n.s.) or from the median participant used for RW (cued) eye closure (one-sample t-test; frequency: $t_{14} = 1.60$; n.s.; duration: $t_{14} = 0.57$; n.s.).

I) BOLD activation and deactivation during periods of eye closure (TSD and RW)

Compared to EO epochs, spontaneous EC epochs in the TSD state elicited activation and deactivation patterns in multiple brain regions, similar to Experiment 1 (Fig. 4B and Table 1). However,

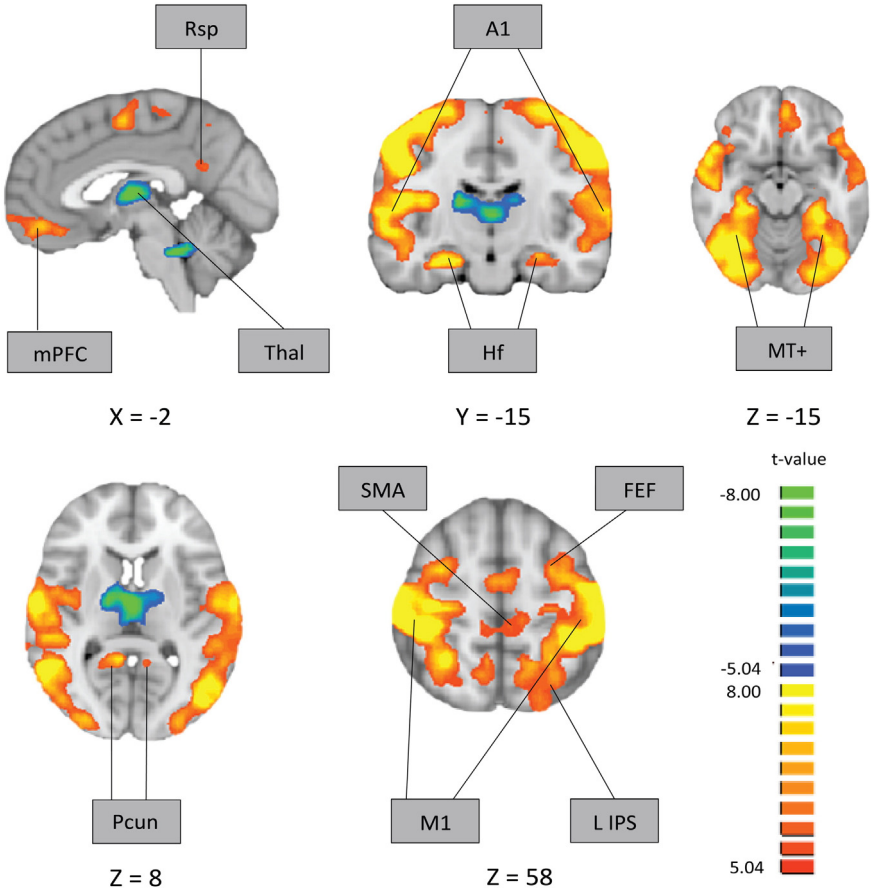

Fig. 1. Regions showing significant activation (red–yellow) and deactivation (blue–green) during eye closure when participants were sleep deprived ($N = 18$, $p < 0.001$, cluster-corrected $p < 0.05$). Legend: vmPFC, ventromedial prefrontal cortex; Thal, thalamus; Rsp, retrosplenial cortex; A1, primary auditory cortex; Hf, hippocampus; EVC, extrastriate visual cortex; Pcun, precuneus; M1, primary motor cortex; SMA, supplementary motor area; FEF, frontal eye fields; IPS, intra-parietal sulcus.

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Table 1
Regions exhibiting significant activation and deactivation in response to eye closure at rest in Experiments 1 and 2. MNI coordinates (mm) and statistical values correspond to peak voxels of significant BOLD activity ($p < 0.001$, cluster-corrected $p < 0.05$).

	Experiment I				Experiment II							
	TSD (spontaneous) eye closures (N = 18)				TSD (spontaneous) eye closures (N = 15)				RW (cued) eye closures (N = 15)			
Region	x	y	z	*t*-Value	x	y	z	*t*-Value	x	y	z	*t*-Value
Activations												
Sensorimotor												
Supplementary motor cortex	10	−23	49	6.55	4	−20	58	5.77				
R primary motor cortex	55	−17	49	19.47	49	−20	55	7.25				
L primary motor cortex	−59	−17	52	13.91	−53	−17	46	5.95				
R primary auditory cortex	61	−11	7	10.52	70	−26	13	6.21				
L primary auditory cortex	−67	−11	7	8.50	−59	1	1	5.76				
R extrastriate cortex	28	−66	−6	8.50	37	−77	−14	9.38	56	−54	−2	5.28
L extrastriate cortex	−20	−64	−6	10.78	−32	−68	−8	9.41				
R primary somatosensory cortex	40	−32	61	19.17	43	−34	67	7.30				
L primary somatosensory cortex	−35	−35	52	11.51	−38	−41	58	6.14				
Limbic												
R hippocampus	22	−11	−23	9.66	19	−5	−14	7.78				
L hippocampus	−29	−17	−17	7.65	−26	−6	−23	5.03				
R parahippocampal gyrus	28	−32	−17	9.68	39	−44	−23	8.32				
L parahippocampal gyrus	−29	−37	−14	9.51	−29	−32	−17	5.60				
R insula	48	−23	16	10.28	43	−14	16	5.94	40	4	−14	5.09
L insula	−44	−29	19	8.10	−44	−38	19	6.73				
Attention												
R intraparietal sulcus	25	−61	46	6.11	28	−64	52	5.94				
L intraparietal sulcus	−29	−51	52	6.34	−26	−66	50	5.35				
R superior parietal lobule	−17	−50	67	9.31	22	−59	70	7.38				
L superior parietal lobule	28	−47	58	9.02	−23	−75	55	6.18				
R frontal eye field	34	−5	64	8.27	31	3	59	9.24				
L frontal eye field	−26	−2	61	8.42	−29	−8	65	5.94				
Frontal pole	−11	64	31	5.87	−11	61	31	5.17				
Default-mode												
Retrosplenial cortex	−8	−53	18	6.58	−13	53	19	6.01				
Medial prefrontal cortex	−5	46	−11	8.48	−5	49	−14	6.10				
R angular gyrus	46	−62	25	8.80	46	−62	22	6.05				
L angular gyrus	−56	−65	18	10.58	−53	−68	13	6.37				
R supramarginal gyrus									64	−38	34	5.24
Deactivations												
R thalamus	18	−14	16	−9.02	6	−5	13	−7.13	10	−17	13	−6.17
L thalamus	−4	−17	7	−7.20	−17	−2	10	−8.77	−8	−14	7	−6.42
Brainstem	1	−38	−32	−8.70								
R precentral gyrus									−50	−2	55	−7.55
R primary visual cortex									7	−92	10	−16.28
L primary visual cortex									−3	−92	2	−14.00
Precuneus									−2	−70	1	−13.43
Dorsal anterior cingulate cortex									−14	49	−2	−6.31
Posterior cingulate cortex									−2	−32	31	−5.81

when these same participants were well-rested, cued eye closures elicited a pattern of activation distinct from those in the TSD state (Fig. 4A). Crucially, there was a pronounced deactivation of the early visual areas (V1) accompanied by thalamic deactivation and extrastriate cortex activation (the latter two also elicited in the TSD state). However, there was little or no activation in the sensory, DAN and DMN regions.

II) Functional connectivity during periods of cued and spontaneous eye closures

Functional connectivity results for Experiment 2 are shown in Fig. 5. Within nodes of the DMN, there was a significant main effect of state on connectivity ($F(1,14) = 22.93$, $p < 0.001$) where TSD resulted in reduced functional connectivity on average compared to RW. No significant main effect of eye closure or interaction effects were present (p's > 0.55). Within the DAN however, there was a significant interaction effect of state by eye closure ($F(1,14) = 16.25$, $p = 0.001$) where eye closure resulted in reduced connectivity only in the TSD state (post-hoc t-tests; RW: $t_{14} = 0.15$, $p = 0.89$; TSD: $t_{14} = 3.75$, $p < 0.005$). Finally, between DMN and DAN networks, there were significant main effects of both state and eye closure where TSD and eye closure independently contributed to reduced anti-correlation (state: $F(1,14) = 17.78$, $p = 0.001$, eye closure: $F(1,14) = 6.93$, $p < 0.05$, state × eye closure: $F(1,14) = 0.24$, $p = 0.63$).

Discussion

Eye-closures in TSD were associated with co-activation of multiple brain areas including parts of the default mode and dorsal attention networks, extrastriate visual, auditory, somatosensory and motor cortices in the absence of external stimulation or task performance. Longer eye closures elicited BOLD activation/deactivations of greater magnitude and delay than shorter duration eye closures. These changes observed in TSD differed markedly from those elicited by cue-driven eye closures of similar frequency and duration in well-rested participants. Eye closures during TSD further reduced functional connectivity within

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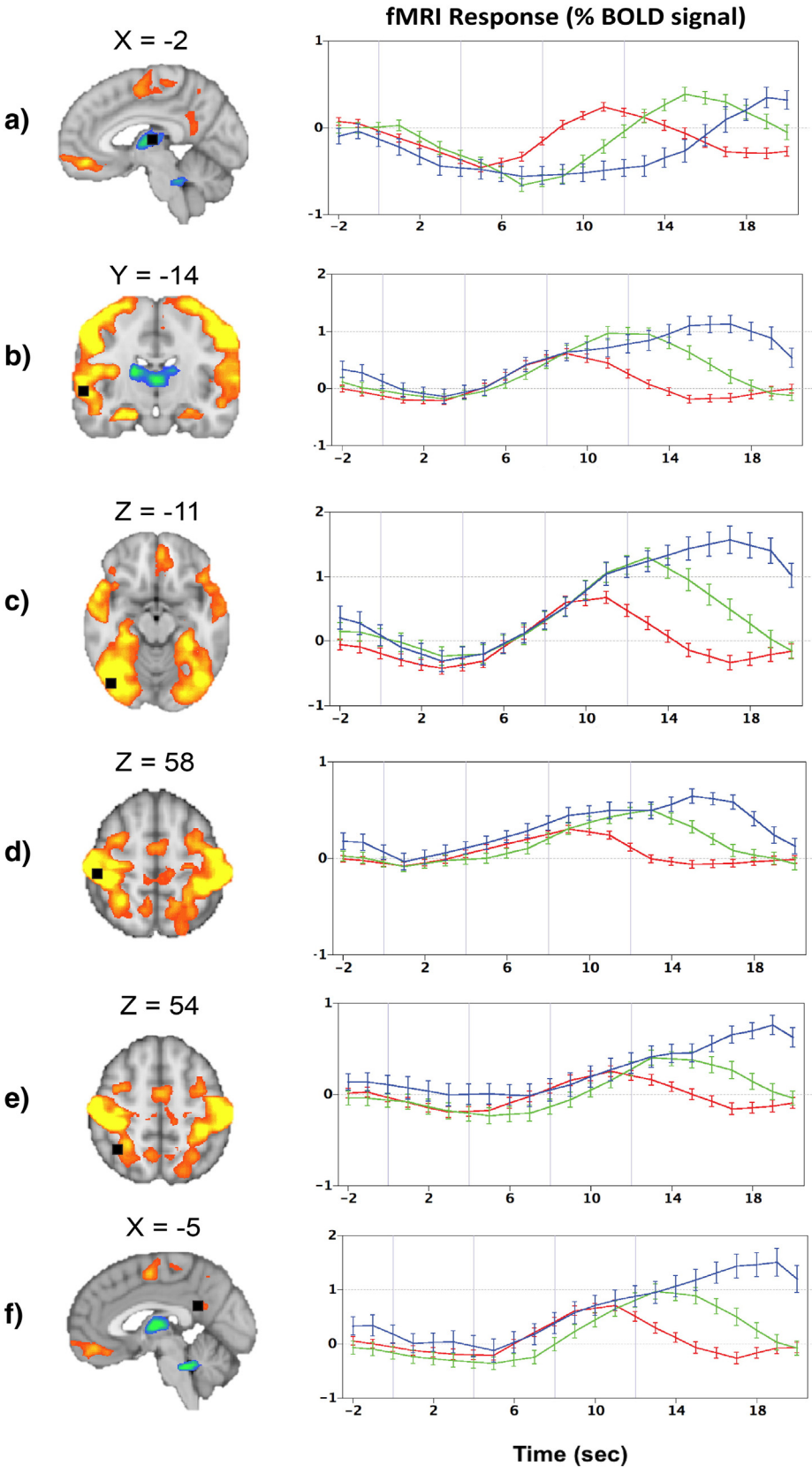

Fig. 2. Peak signal amplitude and time-to-peak increased with eye closure duration in Experiment 1 (N = 18). BOLD signal time courses were averaged across all participants grouped according to duration of eye closure (red curve: 0.5–4 s, green curve: 4–8 s, blue curve: 8–12 s). Time courses were averaged within cubes of edge 9 mm centered around the peak voxel (indicated by black squares) in the (a) thalamus (MNI coordinates: x = −2, y = −11, z = 7), (b) right auditory cortex (MNI coordinates: x = 55, y = −14, z = 10), (c) right extrastriate cortex (MNI coordinates: x = 25, y = −65, z = −11), (d) right motor cortex (MNI coordinates: x = 55, y = −15, z = 49), (e) right intraparietal sulcus (MNI coordinates: x = 16, y = −65, z = 54), (f) retrosplenial cortex (MNI coordinates: x = −5, y = −50, z = 13).

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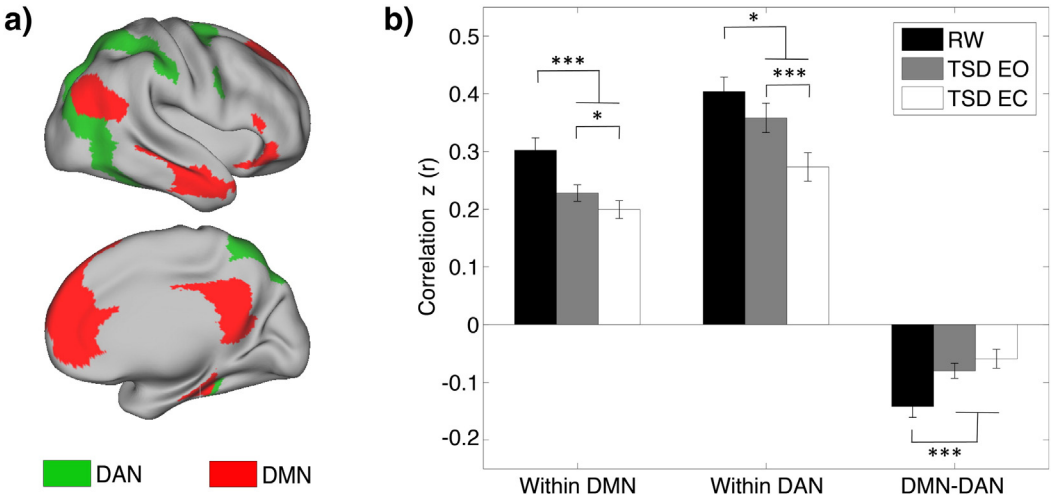

Fig. 3. (a) Surface map parcellation of DMN (red) and DAN (green) regions (Yeo et al., 2011). These regions were projected into MNI 152 volume space for connectivity analyses. (b) Functional connectivity strength within the DMN, DAN and between the DAN and DMN regions in Experiment 1 (N = 18). Connectivity strength within both networks was significantly reduced from rested wakefulness (RW) to total sleep deprivation (TSD), and during periods of eye closure (EC) compared to when the eyes were open (EO) in TSD. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.005$.

nodes of the DMN and DAN relative to eyes-open epochs in TSD which themselves were associated with reduced connectivity relative to the rested state.

Multisensory and motor cortex activation during eye-closures

Cue directed eye closures elevated BOLD signal in the somatosensory, auditory, extrastriate visual and gustatory cortex to varying degrees across several studies (Marx et al., 2003, 2004; Wiesmann et al., 2006). These previous findings have been attributed to the transition from an externally oriented to an 'interoceptive' state.

We hold that this explanation is unlikely to be correct. Firstly, although multisensory activation was attributed to the recall of sensory experiences (Marx et al., 2003), experimental studies have shown only activation of sensory cortex restricted to the modality of the imagined activity (Cohen et al., 1996; Kosslyn et al., 2001; Yoo et al., 2001). Secondly, activation of sensorimotor cortex (Dresler et al., 2011) and extrastriate visual cortex (Dresler et al., 2012) corresponding to lucid dreaming in REM sleep has been documented. Finally, we did not observe multiple sensory cortex activation when participants were scanned in the rested state (after a normal night's sleep), even when eye closures of similar duration to those in TSD were reproduced.

We thus propose that multi-sensory activation associated with eye closures mark sleep onset/deep drowsiness (Olbrich et al., 2009) and the hypnagogic mentation that accompanies it. Vivid mentation at sleep onset described as 'unrealistic' and 'leaping' (Kjaer et al., 2002) has been reported in a majority (upwards of 70%) of instances when participants were allowed to fall asleep and then woken up and asked to describe their subjective experiences (Foulkes and Vogel, 1965; Liberson and Liberson, 1965; Rowley et al., 1998).

Paralleling the activation of visual, auditory, somatosensory and motor cortices, participants in behavioral studies have reported features

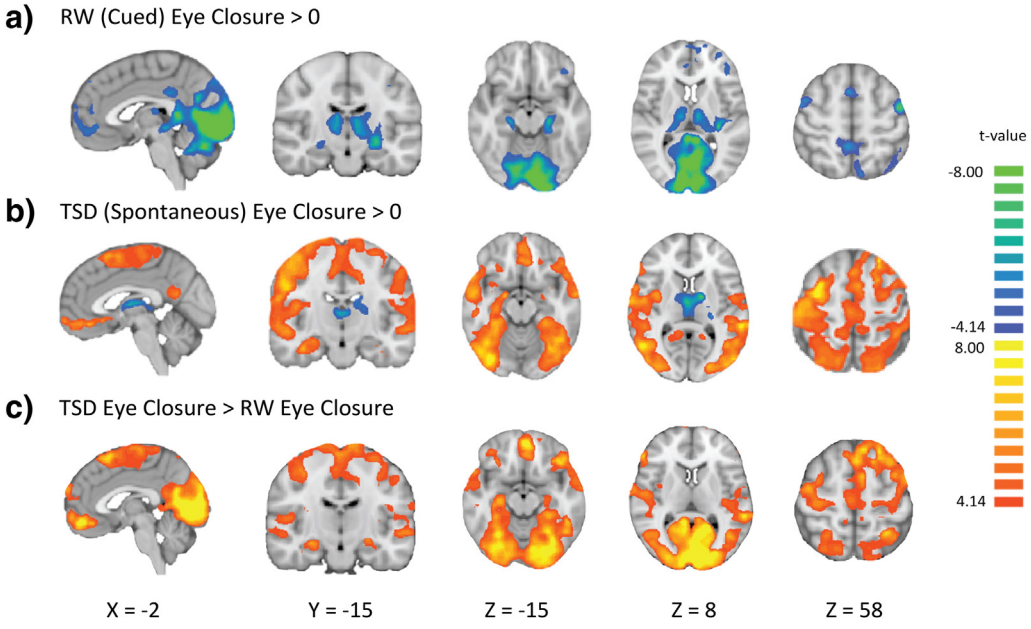

Fig. 4. Regions showing significant activation (red–yellow) and deactivation (blue–green) during RW (cued) and TSD (spontaneous) eye closure in Experiment 2 (N = 15, $p < 0.001$, cluster-corrected $p < 0.05$).

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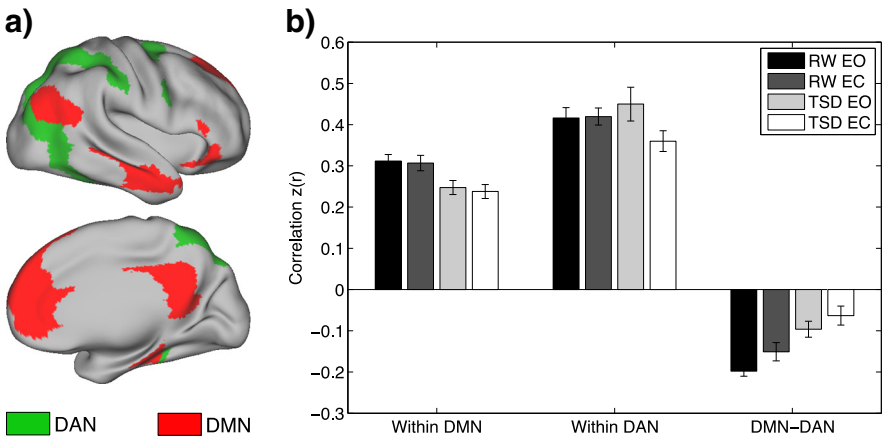

Fig. 5. (a) Surface map parcellation of DMN (red) and DAN (green) regions (Yeo et al., 2011). These regions were projected into MNI 152 volume space for connectivity analyses. (b) Functional connectivity strength within the DMN, DAN and between the DAN and DMN regions for RW (cued) and TSD (spontaneous) eye closure in Experiment 2 (N = 15).

in their mentation corresponding to these sensory modalities. The associated mental state has been likened to dreaming, but in the absence of REM sleep. Dream-like mentation outside REM sleep has been clearly documented (Oudiette et al., 2012) and its contents shortly after sleep onset have been decoded using fMRI (Horikawa et al., 2013). The incidence of imagery and autobiographical (vs. experiment related) content of such mentation increases with longer periods of sleep (Fosse et al., 2001; Rowley et al., 1998). For example, visual content increases to about 20% after 15 s of sleep (Rowley et al., 1998). Given that the propensity to sleep in our sleep-deprived participants was higher than in prior studies, one could expect that for a similar (or even shorter) duration of eye closure in our study, there would be more extensive activation as a result of a higher incidence of imagery with increasing sleep depth.

Changes observed during eye closures in TSD differ from 'mind wandering' observed in the rested state

Activation of the default mode network (DMN) regions observed here, occurs with mind wandering in participants asked to monitor their internal thoughts (Christoff et al., 2009). Intriguingly, although mind-wandering might be expected to elicit mental imagery, activation of sensory or motor areas *does not occur* as seen in experiments when a specific imagined activity is probed (Kosslyn et al., 2001). Imaging studies on eye-closure (Marx et al., 2003, 2004; Wiesmann et al., 2006) have also not previously referred to changes in DMN activation characteristic of the mind wandering state.

The retrosplenial, ventromedial prefrontal and hippocampal components of the DMN areas activated during eye closures in TSD have been reported to show activation that correlates with higher imagery ratings (Andrews-Hanna et al., 2010). They are strikingly congruent with areas engaged when *imagining events* in the past or future as opposed to merely recalling actual past events (Addis et al., 2009). The activation of these default mode regions may arise from the nature of hypnagogic mentation (Hori et al., 1994; Liberson and Liberson, 1965; Rowley et al., 1998) that may be more vivid and autobiographical compared to mental imagery invoked when responding to a set of instructions.

Thalamus deactivation and sensory disconnection

Somatosensory, visual and auditory information from the environment must pass through the thalamus before reaching the cerebral cortex and this speaks to its role in the control of sensory gating and analysis (McCormick and Bal, 1994). The thalamus shows decreased activity at sleep onset that can precede cortical deactivation by several minutes (Magnin et al., 2010). The spatially extensive deactivation observed in the present study suggests involvement of multiple thalamic nuclei beyond the mediodorsal and lateral geniculate nuclei previously observed to deactivate with eye closures in rested persons (Marx et al., 2003, 2004). Thalamic deactivation and preserved cortical activation may contribute to the genesis of the hypnagogic experiences (Magnin et al., 2010) in that there is a disconnection between a still active cortex and external sensory input gated by the thalamus.

Decreases in thalamic activation are also relevant to lapses of attention in sleep deprived persons performing tasks (Chee and Tan, 2010; Chee et al., 2008; Tomasi et al., 2009), deviations when performing a continuous visual tracking task (Poudel et al., 2014), periods of decreased vigilance (Olbrich et al., 2009) and transitions to sleep during eyes-closed rest (Kajimura et al., 1999; Van Dijk et al., 2010). Conversely thalamus activation is relatively preserved in those who are less affected by sleep deprivation (Chee and Tan, 2010; Tomasi et al., 2009).

Based on these previous findings, we predicted that more pronounced thalamic deactivation would occur during spontaneous compared to cued eye closures. In the present dataset however, differences between TSD and RW conditions fell short of traditional significance levels. Why pronounced deactivation in the rested state occurs is currently unclear and will be investigated in future studies.

Nevertheless, this finding should not detract from our explanation of thalamic contribution to hypnagogic mentation although it does indicate thalamic deactivation alone may not be sufficient to do so. Thalamic deactivation associated with voluntary eye-closure was not accompanied by the same sensory cortical changes observed in fatigued (Poudel et al., 2014) or sleep deprived persons (present data). Neither was it accompanied by the additional changes in functional connectivity associated with eye-closures in the sleep-deprived state. How these additional changes in activation and connectivity interact with thalamic deactivation to contribute to hypnagogic mentation remains to be evaluated in future work.

Effects of eye closure duration and differences from functional changes associated with consolidated sleep

The magnitude of activation of multiple cortical areas increased from eye closures of 4 s duration to those of 12 s duration. This relationship was mirrored in the thalamus, where there was increased magnitude of deactivation for longer EC durations, replicating findings obtained when assessing the neural correlates of behavioral microsleeps of different durations during a continuous tracking task (Poudel et al., 2014).

The sole $H_2^{15}O$-PET study specifically examining blood flow changes at sleep onset to-date, found a regional increase in blood flow in visual extrastriate regions (Kjaer et al., 2002). However, when NREM sleep entered Stage 2, no areas showed an increase in blood flow relative to the

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baseline. Instead, from light to deep NREM sleep a progressive reduction in blood flow to polymodal fronto-parietal association cortices and no change in blood flow to sensory areas occurs (Kajimura et al., 1999; Kjaer et al., 2002), opposite to what was observed here. When measuring blood flow using Arterial Spin Labeling in sleep-deprived participants, one study showed blood flow *decreases* in fronto-parietal areas in drowsy participants but not non-drowsy participants (Poudel et al., 2012), while another did not show significant blood flow changes in these regions (Asplund and Chee, 2013).

As EC occupied approximately a third of the total duration of the two resting state scans in the present study, the detection of BOLD signal increases in response to EC necessitates that BOLD signal was either preserved or reduced during the rest of the scans that served as baseline. Over the entire TSD period (mixing eyes open and closed periods) a previous study found no significant resting state differences in blood flow between TSD and rested wakefulness apart from a small increase in primary visual cortex (Asplund and Chee, 2013). As such, the changes we describe here in relation to eye closure must have been transient, underscoring the dynamic nature of functional imaging signals in the wake–sleep transition. Indeed fMRI may uncover physiological differences during this period that are not evident from observing EEG (Picchioni et al., 2008).

Co-activation of fronto-parietal areas during eye-closures

During eye-closures, we observed co-activation of the FEF and superior parietal areas typically associated with attentional control. Activation of these latter areas has not been described in experiments where participants were either allowed to sleep (Olbrich et al., 2009) or not specifically discouraged from doing so (Marx et al., 2003, 2004; Wiesmann et al., 2006). In contrast, this pattern of signal change has been reported in the eyes-open condition rather than the eyes-closed condition in rested participants (Marx et al., 2003). Together with recent work showing seemingly paradoxical superior parietal activation during periods of tracking failure (Poudel et al., 2014), the present findings suggest that activation of fronto-parietal areas known to mediate the control of attention may signify resisting sleep. During sleep deprivation, elevated homeostatic drive for sleep can result in rapid and uncontrolled sleep initiation which subjects resist using increasingly greater compensatory effort. The latter could explain why persons less vulnerable to the effects of TSD recruit fronto-parietal areas mediating attention control during task performance to a greater degree than vulnerable participants (Chee and Tan, 2010).

An alternative explanation for activation of these areas is that they are involved in imagination of movement (see Yeo et al., in press) for a meta-analysis of studies involving mental rotation of objects.

Eye closure during TSD is associated with additional changes in 'resting state' functional connectivity not observed during cued eye closure in RW

Inter-individual and intra-individual differences in functional connectivity have been associated with variation in task performance and cognitive function (Fox et al., 2007; Seeley et al., 2007). Relevant to this work, weaker anti-correlation between DMN and DAN has been associated with neuropsychiatric disorders (Whitfield-Gabrieli and Ford, 2012) and lower cognitive performance in healthy subjects (Kelly et al., 2008).

Reduced DMN connectivity and anti-correlation between DMN and task-positive areas have been observed during partial and total sleep deprivation (Sämann et al., 2011; De Havas et al., 2012), periods of mind-wandering in the absence of meta-awareness (Christoff et al., 2009) and during eyes-closed rest compared to eyes-opened rest (Van Dijk et al., 2010). It has been proposed that "descent to sleep" is facilitated by reduced thalamocortical connectivity at sleep onset and a breakdown of general connectivity in slow-wave sleep, with both processes limiting the capacity of the brain to integrate information across functional modules (Horovitz et al., 2009; Sämann et al., 2011; Spoormaker et al., 2010; Tononi and Massimini, 2008). In this work, weaker functional connectivity within DMN and DAN networks was observed suggesting further decoupling of these networks.

It is conceivable that during brief transitions to and from periods of eye closure, evoked responses could contaminate neighboring EO epochs and vice-versa. However, this would mean an underestimation of connectivity differences between EC and EO epochs; the actual difference could be significantly greater.

This reduction of functional connectivity during spontaneous eye closure was replicated in a separate group of subjects in the TSD state (Experiment 2). However, there were no significant reductions within the DMN and DAN when participants cued to close their eyes in the RW state. These results indicate that at least within the DMN and DAN, voluntary eye closure should not significantly impact functional connectivity analyses if a person is sufficiently well-rested. This contradicts prior work which found lowered connectivity within the DMN and DAN in resting-state runs where participants were allowed to keep their eyes closed compared to when they were required to keep them open or fixated on a cross-hair (Van Dijk et al., 2010). One possible explanation for this could be that participants in the eyes-closed condition had fallen asleep as lying supine in a darkened in-scanner environment can be conducive to sleep, particularly if sleep propensity is high (Chee et al., 2006; Tagliazucchi and Laufs, 2014). In today's sleep-deprived society, this would be reasonable notion; thus prompting a need for future resting-state experiments to monitor sleep patterns, obtain subjective ratings of sleepiness and/or track eye-closure during the scan.

Conclusion

The present findings suggest that the dramatic changes in brain activation and connectivity associated with spontaneous eye closures in the sleep-deprived state are the neural correlates of sleep onset hypnagogic mentation. Our results underscore the importance of checking for the propensity to sleep, as well as for behavioral features suggesting sleep onset when collecting fMRI data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.03.085.

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