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Altered thalamocortical and intra-thalamic functional connectivity during light sleep compared with wake

Joanne R. Hale[1], Thomas P. White[1], Stephen D. Mayhew[1], Rebecca S. Wilson[1], David T. Rollings[1,2], Sakhvinder Khalsa[1,3], Theodoros N. Arvanitis[4], Andrew P. Bagshaw[1]

[1]*School of Psychology, University of Birmingham, Birmingham, United Kingdom*
[2]*Department of Neurophysiology, Queen Elizabeth Hospital, Birmingham, United Kingdom.*
[3]*Department of Neuropsychiatry, The Barberry National Centre for Mental Health, Birmingham, United Kingdom*
[4]*Institute of Digital Healthcare, WMG, University of Warwick, Coventry, United Kingdom*

Corresponding author:
Dr. Joanne Hale,
School of Psychology
University of Birmingham
Birmingham, B15 2TT
Tel : 0044 121 4143878
Fax : 0044 121 414 4897
Email : j.hale.1@bham.ac.uk

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Abstract

The transition from wakefulness into sleep is accompanied by modified activity in the brain's thalamocortical network. Sleep-related decreases in thalamocortical functional connectivity (FC) have previously been reported, but the extent to which these changes differ between thalamocortical pathways, and patterns of intra-thalamic FC during sleep remain untested. To non-invasively investigate thalamocortical and intra-thalamic FC as a function of sleep stage we recorded simultaneous EEG-fMRI data in 13 healthy participants during their descent into light sleep. Visual scoring of EEG data permitted sleep staging. We derived a functional thalamic parcellation during wakefulness by computing seed-based FC, measured between thalamic voxels and a set of pre-defined cortical regions. Sleep differentially affected FC between these distinct thalamic subdivisions and their associated cortical projections, with significant increases in FC during sleep restricted to sensorimotor connections. In contrast, intra-thalamic FC, both within and between functional thalamic subdivisions, showed significant increases with advancement into sleep. This work demonstrates the complexity and **state-specific** nature of functional thalamic relationships - both with the cortex and internally - over the sleep/wake cycle, and further highlights the importance of a thalamocortical focus in the study of sleep mechanisms.

Keywords: EEG-fMRI, fMRI, functional connectivity, sleep, thalamocortical, thalamus

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1. Introduction

The thalamus receives primary afferents from peripheral sense organs and selectively filters related incoming information before relaying it to functionally-specialised cortical regions (Steriade et al., 1993; Sherman and Guillery, 2002; Saalmann, 2014). However, the majority of its inputs are modulatory, feedback connections originating in widespread structures including neighbouring thalamic nuclei and cortex (Sherman and Guillery, 1996; Sherman, 2007). As such, both intra-thalamic and thalamocortical pathways fundamentally underlie information flow within the brain (Saalmann and Kastner, 2011). Dramatic differences in integration of information across the thalamocortical network are associated with changes in the state of consciousness (Alkire et al., 2008; Coenen, 2010; Llinas, 2003; Tononi and Massimini, 2008), which can be most readily investigated in the healthy brain in relation to sleep. The thalamus plays a crucial role in diverse sleep-related physiological phenomena. These include: attenuation of occipital alpha (Iber et al., 2007), generation and maintenance of sleep spindles (Contreras et al., 1997; Steriade, 1997) and propagation of K-complexes (Jahnke et al., 2012). However, despite their fundamental involvement, the intricacies of thalamocortical and intra-thalamic interactions in the sleeping human brain are yet to be definitively established.

Simultaneous acquisition of electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) data has provided non-invasive insight into the functional architecture of the human brain across the sleep-wake cycle (Duyn, 2012). Typically, EEG data is used to identify individual sleep stages or the electrophysiological discharges of sleep (Schabus et al., 2007; Dang-Vu et al., 2011), whilst temporal correlation between Blood Oxygenation-Level Dependent (BOLD) fMRI timecourses provides a measure of functional connectivity (FC) in these stages. To date only a handful of studies have investigated the influence of sleep on human cortical circuits. Evidence broadly suggests that cortical FC is preserved during light sleep (Horovitz et al., 2008; Larson-Prior et al., 2009; Sämann et al., 2011; Spoormaker et al., 2011). Furthermore, Spoormaker and colleagues (2010) reported widespread elevations in cortico-cortical FC during early stages of sleep compared

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with wakefulness. By contrast, the transition into N2 and slow wave sleep (SWS) has been shown to be accompanied by an uncoupling of intra-network relationships (Larson-Prior et al., 2011; Spoormaker et al., 2010; Wilson et al., 2015), including dissociation between anterior and posterior subdivisions of the default mode network (DMN) (Horovitz et al., 2009; Koike et al., 2011; Sämann et al., 2011).

Direct evidence of changes in human thalamocortical coupling in association with sleep is scarce. Laufs and colleagues (2007) investigated the FC of a thalamic seed activated by sleep spindles in a single subject, but reported no significant change in thalamocortical connectivity in relation to sleep stage. Subsequent group studies have, however, identified sleep-related decreases in thalamocortical FC (Picchioni et al., 2014; Spoormaker et al., 2010). Spoormaker et al. (2010) found bilateral thalamus was unique in displaying significantly reduced FC with extensive cortical regions in sleep compared with wake. This decrease was most pronounced during non-REM stage 1 (N1). Indeed, during N2 and SWS thalamocortical FC was seen to increase to similar levels as observed during wakefulness, with this re-synchronisation perhaps an effect of thalamically-generated discharges such as sleep spindles. Meanwhile, Picchioni et al. (2014) reported significant decreases in FC between the centromedial thalamic nucleus (CMN) and widespread heteromodal cortical areas, including the precuneus, cingulate gyrus and medial frontal gyrus, during N2 and SWS compared with wake. These studies have either considered the thalamus as a whole (Spoormaker et al., 2010) or have focused on FC measured from a single thalamic region (Laufs et al., 2007; Picchioni et al., 2014). However, the thalamus is comprised of anatomically distinct nuclei which project to specific cortical areas, forming a topographically organised thalamocortical network (Herrero et al., 2002; Mumford, 1998; Sherman and Guillery, 2013). The supplementary results of Picchioni and colleagues (2014), which, in contrast to their findings for the CMN, showed no differences in FC between the lateral geniculate nucleus (LGN) and calcarine cortex during SWS and wake, are suggestive of regional variation in the effect of sleep on thalamocortical FC. Clearer understanding of the role of the thalamus and thalamocortical interactions in sleep, and of the differential effects of

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sleep on specific parts of the thalamocortical system, therefore rests upon a more fine-grained, functionally-motivated partitioning of the thalamus.

Much of what is known about thalamic structure has been derived from work in animals (Jones, 1998, 2007; Nieuwenhuys, 1988; Webster et al., 1995) and histological studies (Morel et al., 1997). The feasibility of using waking resting-state fMRI data to non-invasively segment the human thalamus into functionally specific subdivisions has been demonstrated (Zhang et al., 2008), with similar functional parcellations being reported in subsequent fMRI studies (Fair et al., 2010; Hale et al., 2015; Kim et al., 2013; Woodward et al., 2012). Functionally-derived thalamic subdivisions also largely match those from previous tract-tracing studies as well as anatomical thalamic segmentations evaluated using diffusion tensor imaging (DTI) (Behrens et al., 2003a; Johansen-Berg et al., 2005; Unrath et al., 2008; Wiegell et al., 2003; Zhang et al., 2010).

In the current study we employed seed-based FC analysis similar to that applied previously to resting state fMRI data (Fair et al., 2010; Hale et al., 2015; Woodward et al., 2012; Zhang et al., 2008) enabling us to investigate the impact of nocturnal sleep (in non sleep deprived individuals) on specific functional thalamocortical relationships. In accordance with previous studies (Picchioni et al., 2014; Spoormaker et al., 2010) we hypothesised that thalamocortical FC would alter progressively with sleep stage, most likely showing decreased FC during early stages of sleep compared with wake. We further hypothesized that sleep-related differences in FC across the thalamocortical network would be dissociable, in the sense that they would vary according to the thalamic and cortical regions being investigated. In addition to considering FC between the thalamus and cortex, we studied intra-thalamic FC. Despite their importance in mediating the transfer of information to and between areas of cortex (Sherman and Guillery, 1996), very few electrophysiological studies have focused on intra-thalamic pathways (Crabtree, 1999; Crabtree et al., 1998). The shortage of research in this area and the proposal that intra-thalamic mechanisms underlie the production of sleep spindles (Contreras et al., 1997), motivated our study of intra-thalamic FC, which we predicted would be altered by the sleep/wake cycle.

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2. Materials and Methods

2.1. Participants

21 healthy volunteers (10 male, 25 ± 3 years) (mean ± standard deviation) participated in the study. Written informed consent was obtained from all participants, and the study was approved by the Research Ethics Board of the University of Birmingham. **The volunteers, who were all accustomed to the MR environment,** had no personal history of neurological, psychiatric or sleep disorder. Participants' habitual sleep patterns were monitored through sleep diaries and wrist actigraphy (Actiwatch2, Philips, Respironics®) for 2 weeks prior to scanning. The actiwatch records wrist movement, which is logged as a summed activity count for each 1 minute interval. Intervals in which the total activity count exceeded 40 were defined as wake. Average total sleep time (TST) over this period was computed by off-line analysis of actigraphy data. TST defined from actigraphy was compared with sleep diary data for consistency. To assess levels of daytime sleepiness, levels of fatigue, insomnia and participants' sleep quality, participants also completed the Epworth Sleepiness Scale (ESS) (Johns, 1991), Fatigue Severity Scale (FSS) (Krupp et al., 1989), Insomnia Severity Index (ISI) (Bastien et al., 2001) and Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) questionnaires.

Participants that exhibited epochs of wake (W), non-REM stage 1 (N1) and non-REM stage 2 (N2) sleep (according to the sleep-staging procedure described in greater detail in section 2.3. below) were included in subsequent analysis. As such individuals that failed to sleep (n=3), did not enter N2 (n=2), or were exclusively asleep during data collection (n=1) were excluded. Data from another participant was excluded on account of a technical problem during EEG data acquisition. The final cohort consisted of 13 participants (9 male, 26 ± 4 years) (mean ± standard deviation) who completed all elements of the study.

2.2. EEG-fMRI data acquisition

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Simultaneous EEG-fMRI data were acquired using a 3 Tesla Philips Achieva MR scanner (Philips, Netherlands) with a 32 channel SENSE receive head coil and 64-channel EEG system with MR-plus amplifiers (Brain Products, Germany).

Throughout the scan session participants were asked not to resist sleep **and to signal when they were no longer able to sleep, at which point scans were terminated**. In order to promote sleep, scanning sessions took place at each participant's usual bedtime (between 22:00 and 00:00). Whole-brain gradient echo EPI data (TE = 35 ms; spatial resolution = 3 x 3 x 4 mm^3; field of view = 240 x 128 x 240 mm; flip angle = 80^0; SENSE factor 2; TR = 2 s with 32 slices) were acquired in consecutive runs of 1250 **volumes (scan duration ~41.7 minutes)**. Respiratory and cardiac fluctuations were recorded, using a pneumatic belt around the upper abdomen and a vectorcardiogram (VCG) respectively each acquired at sampling rate of 500 Hz. To facilitate coregistration to MNI space, high resolution (1mm isotropic) T1-weighted, anatomical images were also acquired. **Considerable foam padding was positioned around the head to reduce movement and improve participant comfort during scanning.**

EEG data were acquired from 62 Ag/AgCl MR-compatible scalp electrodes positioned according to the international 10-20 system, with an extra channel to record the electrocardiogram (ECG) (EasyCap, Brain Products, Germany). Electrode impedances were maintained below 20 kΩ. EEG data were acquired using Brain Vision Recorder (Brain Products, Germany) at a sampling rate of 5 kHz with hardware filters of 0.016–250 Hz. EEG data acquisition was synchronised with the MR scanner clock (Syncbox, Brain Products, Germany) (Mandelkow et al., 2006; Mullinger et al., 2008).

2.3. EEG pre-processing and sleep staging

Gradient and pulse artifacts were removed using average artifact correction (based on 21 local averages) (Allen et al., 2000; Allen et al., 1998) implemented in Brain Vision Analyzer2 (Brain Products, Germany). R-peak markers derived from the VCG were aligned with the EEG data and subsequently used **in the average artifact subtraction procedure** for pulse artifact correction (Mullinger et al., 2008). Sleep staging was performed in non-overlapping, consecutive 30-s epochs according to the American Association of Sleep Medicine criteria (Iber et al., 2007) by an experienced neurophysiologist (DTR) using a standard sleep montage.

2.4. fMRI pre-processing

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Pre-processing of fMRI data was performed using FSL (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl, Smith et al., 2004) and custom written software in Matlab (MathWorks, Natick, USA). Data were motion corrected using MCFLIRT, corrected for physiological noise using RETROICOR (Glover et al., 2000), spatially smoothed (using a 4mm Gaussian kernel) and temporally high-pass filtered (>0.01 Hz). White matter and ventricular signals, the global brain signal and the six parameters of head motion were removed from each voxel using linear regression. Motion parameters were assessed and maximal values found not to exceed the minimum voxel dimension (3 mm). **The average relative movement (assessed from outputted FLIRT movement parameters) was computed for each 30-s epoch of fMRI data, and epochs excluded if the average relative movement exceeded 0.5 mm.** Importantly, sleep stage was shown not to significantly affect the amount of relative movement (**p=0.238**, see supplementary information). fMRI data were co-registered to the standard 2 mm isotropic MNI space using FLIRT in FSL, via an intermediate coregistration step to the high-resolution anatomical data.

2.5. Cortical ROI definition

We parcellated the cortex into five homologous regions of interest, which have been previously shown to connect to distinct areas of the thalamus (Behrens et al., 2003a; Zhang et al., 2008; Zhang et al., 2010; Hale et al., 2015). Cortical ROIs were defined in standard MNI space by combining masks from the Harvard-Oxford cortical atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) in FSL and are equivalent to those used in Hale et al. (2015). These masks covered Occipital and Parietal cortices, Motor and Premotor cortices, Somatosensory cortex, Prefrontal cortex and Temporal cortex. Further details of mask regions are included in supplementary information. The Oxford thalamic connectivity atlas (Behrens et al., 2003a; Behrens et al., 2003b) thresholded at a probability of 25% (chosen to ensure that the whole thalamus was included, Serra et al., 2013) was used as the thalamus ROI. Figure 1A shows the cortical ROIs and whole thalamus mask overlaid on the MNI template.

2.6. Thalamocortical FC analysis

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Simultaneously acquiring EEG-fMRI data allowed us to assign each 30-s epoch of fMRI data to a particular stage of sleep. Thalamocortical connectivity maps for each sleep stage were then generated by averaging fMRI FC measures across epochs. Previous fMRI studies employing 30-s analysis windows report mean connectivity in the DMN (Kucyi and Davis, 2014; Wilson et al., 2015) comparable to that obtained over 15 minutes (Wilson et al., 2015). To compute FC between the cortex and thalamus, average BOLD timecourses from each of the five cortical ROIs and timecourses from every voxel in the thalamus were first divided into non-overlapping 30-s epochs. The Pearson correlation coefficient was then computed between each cortical seed timecourse and all thalamic target voxels for all epochs, yielding 5 thalamocortical connectivity maps per epoch for each participant. Each thalamocortical connectivity map was then assigned to a sleep stage as determined from the corresponding 30-s epoch of EEG data. For each cortical ROI, thalamocortical correlation maps for a particular sleep stage were then averaged across epochs. **Note that in the present work we assessed FC using Pearson correlation, an approach that has been used previously to investigate changes in thalamocortical FC (Woodward et al., 2012; Fair et al., 2010) with consistent FC patterns observed across participants (Fair et al., 2010). This is in contrast to the procedure employed by Zhang and colleagues (2008) and Hale et al., (2015) in which FC was assessed via partial correlation analysis. The need to assess FC over 30-s epochs motivated our choice to employ Pearson correlations in the current work, since defining FC over short data epochs can cause the data covariance matrix to approach singularity, rendering partial correlation estimates inaccurate.**

Pearson correlation maps for each cortical ROI and sleep stage were converted to Z-maps using Fisher's transform with the degrees of freedom corrected using the Bartlett correction factor (BCF; Fox et al., 2005; Zhang et al., 2008; Hale et al., 2015) to account for autocorrelation (BCF=1.65 ± 0.03 mean ± standard error across participants). To ensure that the same amount of data was used for all fMRI runs for all participants the Bartlett correction factor was computed using the first 95 **volumes (~3.2 minutes)** of the fMRI timeseries. Individual Z-score maps for each cortical ROI and each sleep stage were combined across participants using a random-effects analysis. Since the interpretation of

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negative correlation coefficients is complicated by the regression of the whole brain signal (Fox et al., 2009; Murphy et al., 2009; Weissenbacher et al., 2009), here, in-line with previous work, (Fair et al., 2010; Hale et al., 2015; Woodward et al., 2012; Zhang et al., 2008) we focus on positive correlations.

To further consider the effect of sleep stage on thalamocortical FC, 5 binary thalamic ROI masks (corresponding to the subdivisions of the thalamus robustly connected to each of the 5 cortical ROIs) were generated by separately thresholding (at $p<0.001$) each of the group-level thalamocortical FC maps calculated (as described above) during wake epochs. This created a bilateral mask for each functional thalamic subdivision, hereafter referred to as OCC, MOT, SOM, PRE and TEM. For each participant and each thalamic ROI mask the mean FC strength for each sleep stage was calculated by averaging across Z-scores for all voxels in the mask.

2.7. Intra-thalamic FC analysis

2.7.1. Inter-hemispheric thalamic FC analysis

Firstly, we assessed the influence of sleep stage on inter-hemispheric intra-thalamic FC. The 5 thalamic subregion masks defined from the thalamocortical FC were split into left and right hemisphere masks. The average BOLD timecourse across voxels was then calculated for each lateralised mask and divided into non-overlapping 30-s epochs. The Pearson correlation was then computed for each epoch and converted to Z-scores using Fisher's transform and employing BCF. Based on the EEG sleep staging, each FC window was assigned to a sleep stage and inter-hemispheric correlation coefficients were averaged across all windows assigned to a particular stage. For each participant this yielded average inter-hemispheric FC values for each thalamic subregion for all sleep stages.

2.7.2. Intra-hemispheric thalamic FC analysis

As well as considering inter-hemispheric thalamic FC, we also investigated lateralised intra-thalamic FC, measured between different functional thalamic subregions within each hemisphere. Separately for each hemisphere BOLD timecourses were extracted from each of the 5 lateralised thalamic

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subregion ROI masks, averaged across voxels in each mask and divided into 30-s epochs. Separately for each hemisphere, in every epoch the Pearson correlation was then computed for all possible pair-wise combinations of thalamic subregion ROIs (10 in total). Fisher's r-to-z transform was then used to convert correlation coefficients to Z-scores, again employing BCF to correct the number of effective degrees of freedom. Each FC epoch was assigned to a sleep stage according to the corresponding epoch of EEG data, and correlation coefficients were averaged across all epochs allocated to the same stage. For each of the 10 pairs of thalamic subregion ROIs the left and right hemisphere FC was averaged to create one summary FC measure per ROI per sleep stage.

2.8. Statistical analysis

To investigate the effect of the within-subject factors of sleep stage (3 levels: W, N1, N2) and thalamic subdivision (5 levels: OCC, MOT, SOM, PRE, TEM) on thalamocortical FC strength a two-way repeated-measures ANOVA was performed using the mean Z-scored FC measurements within each thalamic subregion mask.

Another two-way repeated-measures ANOVA was conducted to investigate the within-subject effects of the same sleep stages and thalamic subdivisions on inter-hemispheric intra-thalamic connectivity. A final two-way repeated-measures ANOVA was performed to ascertain the effects of within-subject factors of sleep stage and intra-hemispheric connection (pair-wise across all thalamic subregion ROIs making 10 levels) on Z-scored intra-thalamic FC strength. Exploratory post-hoc paired t-tests were run to ascertain the direction of significant effects. Cohen's *d* was additionally calculated to provide effect-size estimates (Cohen, 1988). Statistical tests were performed using SPSS (version 20, IBM Inc., USA).

To reduce Type 1 error the conventional α threshold of 0.05 was Bonferroni corrected to 0.017 to reflect the number of ANOVAs performed.

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3. Results

Sleep questionnaire, actigraphy data, **sleep diary data** and the total and average number of epochs for each sleep stage from the final sample of 13 participants are summarised in Table 1. Participants were found to have normal levels of daytime sleepiness and fatigue, no evidence of insomnia, and sleep quality and habitual sleep times were representative of normal sleepers. **There was no significant difference between sleep duration estimated by actigraphy and sleep diary (T(12)=2.00, p=0.069). The trend towards increased sleep duration in the self-report as compared with the actigraphy data is not unexpected in light of previous work (Lauderdale et al., 2008), and these two measures of TST were significantly correlated (R(12)=0.626, p=0.022). Together, these findings suggest both measures were sensitive to variation in sleep duration but that individuals in this sample had a tendency to over-estimate sleep duration.** Across the included participants a total of **705** epochs of wake data were **analysed**, **944** epochs of N1 sleep and 414 epochs of N2 sleep. **Further details of the characteristics of data acquired in sleep stage are presented in Supplementary Table 1.**

Table 1

3.1. Thalamocortical FC

Figure 1B depicts the thalamic regions significantly connected with each cortical ROI during wake epochs, and demonstrates the selective pattern of FC between cortex and thalamus. The Occipital and Parietal cortical ROI FC map overlapped with the lateral geniculate nuclei and parts of the pulvinar with some extension into the medial geniculate nuclei. The Motor-Premotor and Somatosensory cortical ROIs were functionally connected to ventral posterior and ventral lateral regions of the thalamus, with the SOM FC map occupying a slightly more posterior area of the thalamus. FC with the Prefrontal cortical ROI was found to overlap with mediodorsal and ventral anterior portions of the thalamus. Whilst, the Temporal ROI connected most highly with medial geniculate nuclei.

Figure 2 presents mean thalamocortical FC for each thalamic subdivision as a function of sleep stage.

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We observed a significant main effect of thalamic subdivision ($F(4,48)=4.040$, $p=0.007$) on these connectivity values. Whilst the main effect of sleep stage was not significant ($F(1.379,16.552)=2.434$, $p=0.131$), there was a significant interaction between these factors ($F(3.038,36.454)=4.048$, $p=0.014$), suggesting that the relationship between FC and the different stages of sleep differed between thalamic subdivisions. T-tests revealed a significant increase ($p<0.05$) in FC between wake and N2 for the MOT and SOM thalamic subregions (Table 2). The MOT thalamic subregion also showed a significant increase in FC between N1 and N2. In addition, there was a trend towards reduced FC in N1 compared to wake for the PRE subregion.

Table 2

3.2. Intra-thalamic FC

3.2.1. Inter-hemispheric thalamic FC

Inter-hemispheric thalamic FC differed significantly with both sleep stage ($F(2,24)=16.233$, $p=3.48\times10^{-5}$) and thalamic subdivision ($F(1.273,15.280)=78.860$, $p=6.70\times10^{-8}$). The interaction of sleep stage with thalamic subdivision was not significant ($F(2.469,29.625)=1.960$, $p=0.151$). The variation in inter-hemispheric thalamic FC with sleep stage across thalamic subdivisions is shown in Figure 3. For all thalamic subdivisions FC increased in a step-wise fashion with sleep depth, increasing from wake to N1 and then rising further from N1 to N2. Increases in FC with sleep depth were found to be greatest between the SOM thalamic ROIs and between the MOT thalamic ROIs. Paired t-tests revealed highly significant ($p<0.05$) increases in connectivity during sleep compared with wakefulness for all thalamic ROIs, except for the comparison between N1 and wake for the OCC thalamic subdivision (Table 3).

Table 3

3.2.2. *Intra-hemispheric thalamic FC*

Finally we investigated the FC between pairs of non-homologous functional thalamic subregions within the same hemisphere. This revealed significant main effects of both sleep stage ($F(2,24)=20.418$, $p=6.62\times10^{-6}$) and thalamic connection ($F(3.248,41.135)=352.784$, $p=3.04\times10^{-30}$). The

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interaction between sleep stage and intra-hemispheric thalamic connection was not significant ($F(3.559,42.716)=1.942$, $p=0.128$). In general, FC was found to increase in N1 compared to wake; and for all thalamic ROI pairs, a significant, larger increase was observed from N1 to N2 sleep (Figure 4, Table 4). Considered across all sleep stages, the strongest FC was observed between the MOT and SOM thalamic subdivisions, whilst intra-hemispheric thalamic ROI pairs involving the PRE subdivision displayed the smallest average FC strength.

Table 4

4. Discussion

By integrating techniques for identifying functionally specific thalamocortical relationships this work provides novel insights into the effect of sleep on both thalamocortical and intra-thalamic network activity. We have demonstrated altered thalamocortical FC during light sleep (in non sleep deprived individuals) compared with wakefulness, which is in line with previous work (Picchioni et al., 2014; Spoormaker et al., 2010). Importantly, sleep was also shown to differentially influence functional thalamocortical pathways. In addition, the current study presents the first detailed investigation into human intra-thalamic FC. We observed that both intra- and inter-hemispheric thalamic connectivity measured from functionally defined thalamic subdivisions strengthened during the progression into sleep, with the largest increases seen during N2 sleep. Together, these observations suggest that FC analysis of fMRI time series data is sensitive to diverse changes in thalamocortical function relating to sleep. Most notable perhaps is the transition of the thalamus to a more functionally homogeneous structure, in association with the sleep stages characteristically representative of it changing from an external to an internal mode of function.

We employed seed-based FC analysis to derive functional thalamic segmentations during wake (Figure 1B and Hale et al., 2015). Group-level thalamocortical FC maps showed each cortical ROI connecting to discrete regions of the thalamus, consistent with the predictions of anatomical and electrophysiological studies (Jones, 1998, 2007; Morel et al., 1997; Nieuwenhuys, 1988; Webster et al., 1995), non-invasive human structural imaging (Behrens et al., 2003a; Johansen-Berg et al., 2005; Zhang et al., 2010) and resting state fMRI FC (Zhang et al., 2008., Hale et al., 2015; Fair et al., 2010;

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Woodward et al., 2012). Averaging FC within these disparate functional thalamic subdivions, we showed that changes in thalamocortical FC associated with the transition and progression into sleep differed according to thalamic subregion. Sensorimotor thalamocortical interactions revealed the largest sleep-related changes, with significant increases in FC reported between wake and N2 (and between N1 and N2 for MOT) (Figure 2, Table 2). Meanwhile, FC of other thalamic subdivisions trended towards a decrease in strength during sleep compared to wakefulness (PRE and TEM). The regional variability in thalamocortical interactions we observed during sleep is in agreement with previous work showing that during resting wakefulness, in comparison with other thalamic ROIs and the whole thalamus, the pulvinar displays a distinct pattern of FC with the visual cortex (Zou et al., 2009). Our findings highlight the importance and relevance of investigating specific functional relationships of the thalamocortical network.

The prominent increases in thalamocortical FC from wake to N2 in sensorimotor cortices might be driven by the effects of the electrophysiological hallmarks of N2, sleep spindles and K-complexes**, as hypothesised by Spoormaker et al. (2010)**. Both of these events are generated by thalamocortical interactions (Colrain, 2005; Contreras et al., 1997; Pace-Schott, 2009; Steriade, 1997), and although no studies have yet directly addressed their relationship with FC as measured with fMRI, it would seem reasonable to suppose that the appearance of these events would be associated with, or even reliant upon, increased thalamocortical FC. **This premise** is supported by studies that have attempted to determine the cortical and sub-cortical generators of these discharges. In particular, the increased FC we found in MOT and SOM may imply the involvement of fast spindles (~14Hz) which are most prominent over central and parietal EEG electrodes (De Gennaro and Ferrara, 2003) and which preferentially activate sensorimotor cortex compared to slow spindles (Schabus et al., 2007). The importance of sleep spindles to the consolidation of motor learning has also been widely demonstrated (Fogel and Smith, 2006; Morin et al., 2008; Nishida and Walker, 2007), and our observations may represent the underlying reinforcement of movement-related thalamocortical subnetworks elicited by spindle activity. K-complexes have also been associated with sensorimotor

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cortex activation using EEG-fMRI (Caporro et al., 2012; Jahnke et al., 2012), although there is also evidence that they are predominately generated in superior frontal cortex (Wennberg, 2010), which might lead to the expectation that prominent increases in FC would be found during N2 for the PRE thalamic subdivision (our data demonstrated a trend in this direction). This may suggest that, if these links between our observations and sleep transients of N2 are true, the mechanisms of sleep spindles contribute more to the current findings than those associated with K-complexes. This remains to be investigated further in future studies.

Considering the thalamus as a whole, Spoormaker and colleagues (2010) showed a steep reduction in widespread thalamocortical FC in the transition from wake to N1 accompanied by a rebound during N2 sleep. In contrast, employing our finer-grained thalamic parcellation we found that this reduction in FC specific to N1 was not widespread over the thalamus. **However, it is noted (with caution appropriate for a statistical trend) that the PRE thalamic subdivision showed a tendency towards the pattern of thalamocortical FC reported by Spoormaker and colleagues (2010).** The transition into sleep has been shown to be accompanied by globally decreased activity in prefrontal cortex (Muzur et al., 2002). Furthermore, given the involvement of prefrontal cortex in goal-directed behaviour (Donoso et al., 2014; Koechlin and Hyafil, 2007; Ridderinkhof et al., 2004), the trend towards decreased FC between thalamus and prefrontal cortex may reflect reduced prefrontal influence over thalamic output as a consequence of the lack of task-related behaviour during sleep. The presence of slower (~12 Hz) frontal spindles (De Gennaro and Ferrara, 2003; Gardner et al., 2013) and K-complexes (Wennberg, 2010) in N2 may underlie the restoration of PRE FC we report. **Whilst differences in thalamic parcellation may partly explain the divergence between our results and those of Spoormaker et al. (2010), variation in preprocessing strategy may also have contributed. More specifically, global signal regression was included here but omitted by Spoormaker et al. (2010). This procedure improves spatial specificity, particularly in conditions where a shift in global signal between experimental contexts can be expected (Yeo et al., 2015).**

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Previous EEG-fMRI studies assessing cortico-cortical (Horovitz et al., 2009; Koike et al., 2011; Larson-Prior et al., 2009) and thalamocortical (**Larson-Prior et al., 2011;** Picchioni et al., 2014**; Spoormaker et al., 2010**) interactions during sleep have largely focused on variations in connectivity between wake and N2 or SWS, since the latter are associated with the largest decreases in arousal and/or awareness. On account of the noisy and disruptive MR environment only two of the participants spent more than a minute in N3, which motivated our focus on N1 and N2 sleep. N1 is sometimes overlooked in sleep studies. It has been suggested that it should not be classified as a sleep stage (Johnson et al., 1976; Ogilvie, 2001; Ogilvie et al., 1991), but is better described as a 'sleep onset period' (Ogilvie and Wilkinson, 1984) marking the transition between wakefulness and sleep. The intricacy and complexity of electrophysiological interactions during N1 is exemplified by the Hori sleep staging criteria (Hori et al., 1994), which subdivides classically defined N1 into 6 substages using scoring windows of 5 s duration. Incorporation of these different substages may be of benefit to further investigate the trend towards reduced thalamocortical FC we observed in the PRE thalamic subregion during N1 in comparison with wake, and certainly the processes that occur during N1 deserve further attention.

Picchioni and colleagues (2014) reported reduced FC between the CMN and multiple heteromodal cortical areas during N2 (and SWS) compared with wakefulness. In addition, in supplementary analyses they found no sleep related differences in FC between the LGN and calcarine cortex. We similarly observed no significant changes in FC for our OCC thalamic subregion. However, a direct comparison between our findings and those of Picchioni et al. is somewhat complicated on account of their primary focus on a nonspecific nucleus, which is known to connect to widespread areas of cortex. In contrast, in our analyses we sought to uncover specific functional thalamocortical relationships, identifying largely spatially distinct thalamic subdivisions based on their unique pattern of FC with a single cortical ROI. In our previous work we found that defining a thalamic parcellation in this way did not show a direct one-to-one mapping with histologically defined thalamic nuclei (Hale et al., 2015), suggesting that future work is required to elucidate the

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association between cytoarchitecturally- and MR-defined thalamic regions (see section 4.1, 'Link with electrophysiology').

As well as investigating thalamocortical FC, we also examined the variation in intra-thalamic connectivity associated with the advancement from wake into light sleep. There is virtually no existing literature on the functional or structural connectivity of thalamic subregions, and only a handful of studies have considered interactions between simultaneous intra-cranial recordings in non-human animals (Contreras et al., 1997; Crabtree, 1999; Crabtree et al., 1998), despite the fundamental importance of thalamic nuclei in promoting sensory information transfer as well as providing cortico-cortical connections. To investigate this question, we computed intra-thalamic FC in two ways: 1) within thalamic subregions between the left and right hemispheres; and 2) between all thalamic ROI pairs within a hemisphere. In both cases intra-thalamic FC was found to significantly increase with progression into sleep, with FC strongest during N2 sleep (Figures 3 and 4, Tables 3 and 4). This monotonic increase in FC with sleep depth contrasts sharply with the results discussed above for thalamocortical FC, indicating the differential effect of sleep depth on internal and external thalamic connections. The inter-hemispheric analysis revealed that the thalamic ROIs which functionally connected to sensory cortical ROIs (OCC, MOT and SOM) displayed the lowest intra-thalamic FC values during wake, but underwent the largest incremental increases in FC from wake to N1 (MOT and SOM) and then N1 to N2 (OCC). Considering connectivity between thalamic ROIs, for multiple ROI pairs the increase in FC strength from N1 to N2 was most pronounced. These results imply strengthened connectivity both between and within functional thalamic subdivisions during sleep, especially in N2. This observation echoes findings from invasive electrophysiology in cats, which demonstrated intra-thalamic synchrony coexistent with spindle activity (Contreras et al., 1997). Alternatively increased intra-thalamic connectivity during N2 sleep may be explained by a universal reduction in thalamic output in this sleep stage (Livingstone and Hubel, 1981), which results in a more unified activity profile across thalamic nuclei. **The mechanisms responsible for the observed enhancements in intra-thalamic connectivity during sleep remain unclear. It appears**

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that the thalamic burst mode activity common in sleep is associated with step-shaped firing profiles (Sherman, 2001), which in turn act to diminish thalamic outputs for all but the most salient stimuli. Furthermore, bursting is more prevalent in higher-order than first-order nuclei (Ramcharan et al., 2005). Given the control directly exerted by higher-order nuclei on first-order nuclei, as well as the importance of higher-order nuclei for cortico-cortical information transfer and the related potential for cortex to provide feedback control on first-order nuclei and to propagate these putative synchronised signals, it is feasible that higher-order thalamic nuclei play a key role in this widespread thalamic coordination. However, the spatial constraints of the current study preclude direct investigation of this hypothesis (see section 4.1. 'Link with electrophysiology'). Promising results from this initial exploration of human intra-thalamic FC demonstrate the feasibility and importance of studying these overlooked relationships to enable a better understanding of the effect of sleep on the brain's functional networks. As well as replicating these findings in alternative cohorts of healthy participants, future work investigating neurological and neuropsychiatric disorders, which are known to affect thalamocortical connectivity (e.g., Schizophrenia: Andreasen, 1997; Welsh et al., 2010; Woodward et al., 2012, Autism: Nair et al., 2013, Epilepsy: Kim et al., 2014; Norden and Blumenfeld, 2002), could benefit from also considering variations in intra-thalamic FC.

4.1. Link with electrophysiology

Whilst we have further demonstrated the potential of using seed-based FC to non-invasively delineate functional subdivisions of the thalamus, one important limitation of our analyses relates to the distinction between first-order and higher-order thalamic nuclei (Sherman and Guillery, 2002, 2011, 2013). First-order nuclei are those which are involved in routing information from the periphery to the cortex, and are considered to connect primarily, although possibly not exclusively (Saalmann and Kastner, 2011), to a single cortical region (e.g., LGN). Higher-order nuclei (e.g., pulvinar) provide trans-thalamic cortico-cortical connections and would be expected to have wider cortical connectivity patterns (Guillery, 1995). The thalamic subregions we have investigated likely

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represent a mix of these two types of nuclei, which we are not able to distinguish with currently available methodologies. Furthermore, it would be expected that even when a thalamic nucleus is primarily connected to a single cortical region, these connections would consist of both feed-forward and feed-back loops, which with FC analysis of fMRI data we are not able to distinguish. Our results therefore represent a relatively coarse level of detail with respect to what is available with invasive recordings, but have the advantage of providing whole brain analysis of both cortical and sub-cortical regions, as well as a direct link with human behaviour, in our case sleep.

While the cortical ROIs employed currently were consistent with those used previously (Behrens et al., 2003a; Zhang et al., 2008) - thus aiding comparisons of our findings with the existing literature - they varied in the extent to which they mapped homogeneous cortical populations, for example Occipital, Prefrontal and Temporal cortical ROIs encompass nodes from diverse functional networks (Yeo et al., 2011; Power et al., 2011). Given the heterogeneity of prefrontal function, in particular, it will be valuable for future work to investigate thalamic connectivity in sleep using a more fine-grained parcellation scheme. Coupling this approach with an extensive pair-wise investigation of thalamocortical interactions would enable greater insight into the complex thalamocortical network and may help distinguish first-order and higher-order nuclei.

4.2. Methodological considerations

Simultaneous EEG-fMRI is currently the best and most widely-used technique for gaining non-invasive insights into human sleep; the temporal resolution afforded by EEG facilitates classification of sleep stages whilst the high spatial resolution of fMRI permits concurrent investigation of extensive cortical and subcortical networks. However, since the acoustic noise produced by standard fMRI sequences is the major factor limiting participants' propensity for sleep, future EEG-fMRI studies may profit from the application of multiband fMRI which accelerates data collection via simultaneous acquisition of multiple 2D image slices. This acceleration can be translated into quieter fMRI scans, increasing the chance of capturing sleep inside the scanner or much shorter TRs (e.g. 720 ms, Glasser et al., 2013) than conventional fMRI recordings. Considerably improving the temporal

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resolution of fMRI would allow prospective works to conduct a detailed dynamic evaluation of FC associated with sleep discharges, e.g. spindles, which our findings suggest could underlie alterations to both thalamocortical and intra-thalamic interactions. However, the feasibility and safety of simultaneously acquiring EEG data with multiband fMRI is yet to be established.

Future sleep studies should also consider using magnetoencephalography (MEG) to study neuronal network activity more directly (Brookes et al., 2011a; Brookes et al., 2011b; de Pasquale et al., 2010; de Pasquale et al., 2012; Hipp et al., 2012). Whilst sleep signatures are detectable with MEG (Dehghani et al., 2011) informing classical sleep stages from MEG data is non-trivial due to inherent differences in the sensitivities of EEG and MEG signals.

Sleep deprivation offers insight into the effects of perturbing brain mechanisms relating to sleep such as those identified in the current work. It has been diversely shown that sleep deprivation reduces functional network integrity (De Havas et al., 2012; Sämann et al., 2010). Most relevant to the current work is the recent report that sleep deprivation additionally diminishes thalamocortical FC and interestingly in light of the current observations that networks other than those relating to somatosensory and motor function are affected (Yeo et al., 2015). Future work investigating the effect of sleep deprivation on thalamocortical and intra-thalamic networks during wakefulness and sleep therefore has the potential to further our understanding of these phenomena.

The current study employed bivariate correlation analyses despite the advantages in parsing specific signal components offered by partial correlation, because partial correlation estimates become inaccurate when judged over small datasets since covariance matrices approach singularity. Selecting 30-s epochs for sleep staging and a 2-s TR permitted evaluation of sleep stage in line with clinical convention and enabled us to create an imaging environment in which participants were for the most part able to sleep, but their combination precluded use of partial correlation in this study. Despite attempting to ameliorate the issue of potential losses of specificity by using global signal regression (Fox et al., 2009), an alternative explanation for the

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similarities in modulation of thalamocortical connectivity between the MOT and SOM parcels and for the global consistencies in the intra-thalamic analyses could be that the current procedure was insufficiently powered to differentiate FC changes across regions. Future work re-investigating the reported phenomena using fMRI data collected at a higher temporal resolution thus permitting partial correlation over 30-s time windows would allow judgement of the extent to which this issue affected the current findings.

5. Conclusion

This study, the first to our knowledge to investigate FC during sleep across multiple thalamic ROIs, demonstrates significant modulations of both thalamocortical and intra-thalamic networks in sleep. In line with previous work, during wakefulness cortical ROIs were found to be functionally connected to distinct thalamic regions. Our finer-grained functional thalamic parcellation, compared with other studies, allowed us to observe differential effects of sleep across the thalamocortical network. This has implications for future work, stressing the value of considering the topological arrangement of the thalamocortical system, and emphasising the role of specific thalamic nodes in the whole-brain network. This approach also permitted us to examine internal thalamic relationships; we observed altered intra-thalamic connectivity, characterised by significantly increased FC both within and between functional thalamic subdivisions with advancement into sleep. Taken together, our findings highlight the utility of fMRI FC analysis to quantitatively describe the connectivity of the thalamus, both internally and to the cortex, in the transition to sleep. Uncovering the role of specific thalamic subregions in sleep onset and maintenance allows future studies to investigate questions which previously have only been amenable to invasive techniques. This approach is also likely to prove valuable in developing our understanding of consciousness states generally, as well neurological and neuropsychiatric disorders of consciousness (Bagshaw and Khalsa, 2013).

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Tables

Table 1

Data from sleep questionnaires, actigraphy and sleep scoring

A) Sleep questionnaire data	Mean ± standard error
Epworth Sleepiness Scale	7.3 ± 1.0
Fatigue Severity Scale	22.5 ± 2.0
Insomnia Severity Scale	4.5 ± 0.8
Pittsburgh Sleep Quality Index	4.5 ± 0.6
B) Sleep data	
i) Prior to scan	
Total sleep time from actigraphy data (hours)	6.7 ± 0.2
Total sleep time from sleep diary data (hours)	**7.1 ± 0.2**
ii) During scan	
Number of W epochs	55.0 ± 8.1
Number of N1 epochs	72.7 ± 14.8
Number of N2 epochs	31.8 ± 10.2

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Table 2

Thalamocortical FC paired t-test results. For all analyses there were 12 degrees of freedom. * denotes significance at p<0.05. Superscripts following Cohen's *d* values indicate magnitude of the effect size (small(S)0.2-0.49; medium (M): 0.5-0.79; large(L): ≥0.8)

		t	p	Cohen's *d*
W vs. N1	OCC	-0.275	0.788	
	MOT	0.572	0.578	
	SOM	-1.333	0.207	
	PRE	2.097	0.058	
	TEM	-0.431	0.674	
W vs. N2	OCC	-1.503	0.159	
	MOT	-2.339	0.037*	0.797^{M}
	SOM	-2.203	0.048*	0.740^{M}
	PRE	0.740	0.473	
	TEM	0.016	0.330	
N1 vs. N2	OCC	-1.699	0.115	
	MOT	-2.769	0.017*	0.858^{L}
	SOM	-1.699	0.115	
	PRE	-1.668	0.121	
	TEM	1.318	0.212	

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Table 3.

Intra-thalamic inter-hemispheric FC paired t-test results. For all analyses there were 12 degrees of freedom. * denotes significance at p<0.05 and ** denotes significance corresponding to p<0.001. Superscripts following Cohen's *d* values indicate magnitude of the effect size (small(S): 0.2-0.49; medium (M): 0.5-0.79; large(L): ≥0.8)

		t	p	Cohen's *d*
W vs. N1	OCC	-1.357	0.20	
	MOT	-5.625	1.12×10^{-4}**	0.85^{L}
	SOM	-5.947	6.7×10^{-5}**	1.03^{L}
	PRE	-3.386	0.0054*	0.56^{M}
	TEM	-3.022	0.011*	0.48^{S}
W vs. N2	OCC	-4.410	8.5×10^{-4}**	1.01^{L}
	MOT	-4.904	3.63×10^{-4}**	1.26^{L}
	SOM	-5.040	2.89×10^{-4}**	1.47^{L}
	PRE	-3.209	0.0075*	0.80^{L}
	TEM	-3.559	0.0039*	0.80^{L}
N1 vs. N2	OCC	-3.285	0.0065*	0.78^{M}
	MOT	-2.123	0.055	
	SOM	-2.333	0.035*	0.52^{M}
	PRE	-1.658	0.123	
	TEM	-2.132	0.054	

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Table 4.

Intra-thalamic within hemisphere FC paired t-test results. For all analyses there were 12 degrees of freedom. * denotes significance at p<0.05 and ** denotes significance corresponding to p<0.001. Superscripts following Cohen's *d* values indicate magnitude of the effect size (small(S): 0.2-0.49; medium (M): 0.5-0.79; large(L): ≥0.8)

	W vs. N1			**W vs. N2**			**N1 vs. N2**		
	t	p	Cohen's *d*	t	p	Cohen's *d*	t	p	Cohen's *d*
OCC-MOT	-3.099	0.0092*	0.54^{M}	-6.389	3.5×10^{-5}**	1.45^{L}	-3.059	0.010*	0.79^{M}
OCC-SOM	-3.386	0.0054*	0.47^{S}	-4.877	3.8×10^{-4}**	1.05^{L}	-2.658	0.021*	0.56^{M}
OCC-PRE	-0.843	0.416		-3.333	0.0060*	1.01^{L}	-3.084	0.0095*	0.81^{L}
OCC-TEM	-2.951	0.012*	0.44^{S}	-3.808	0.0025*	0.99^{L}	-3.304	0.0063*	0.63^{M}
MOT-SOM	-4.705	5.1×10^{-4}**	0.39^{S}	-4.377	9.0×10^{-4}**	1.10^{L}	-3.350	0.0058*	0.73^{M}
MOT-PRE	-0.921	0.375		-3.108	0.0091*	0.82^{L}	-3.146	0.0084*	0.61^{M}
MOT-TEM	-0.343	0.737		-5.602	1.2×10^{-4}**	1.34^{L}	-4.423	8.3×10^{-4}**	1.16^{L}
SOM-PRE	-0.790	0.445		-4.522	7.0×10^{-4}**	1.07^{L}	-3.792	0.0026*	0.88^{L}
SOM-TEM	-0.512	0.618		-5.233	2.1×10^{-4}**	1.05^{L}	-4.462	7.8×10^{-4}**	0.89^{L}
PRE-TEM	0.162	0.872		-3.744	0.0028*	1.12^{L}	-3.440	0.0049*	0.13^{L}

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Figure captions

Figure 1. A) Five cortical ROI masks (left panel) and thalamus mask (right panel) shown overlaid on the standard MNI brain. B) Group-level thalamocortical FC maps for each cortical seed ROI during wake (top row), N1 (middle row) and N2 (bottom row). Height and extent thresholds for all images correspond to p <0.001. Images are shown overlaid on the standard MNI brain and displayed according to radiological convention.

Figure 2. Mean thalamocortical FC as a function of sleep stage across all thalamic subregion ROIs. Error bars represent standard error across participants.

Figure 3. The effect of sleep stage on inter-hemispheric thalamic FC across all thalamic ROIs. Results show mean ± standard error across participants.

Figure 4. Variability in intra-hemispheric thalamic connectivity, computed for all possible pair-wise combinations of thalamic ROI subregions. Results show mean ± standard error across participants.

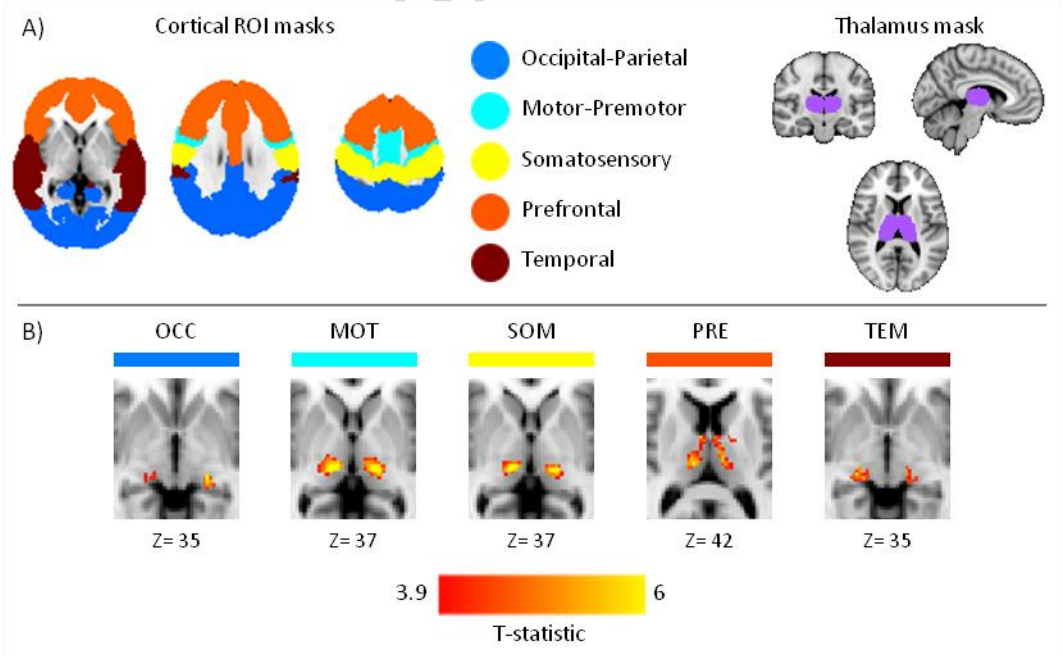


Fig. 1

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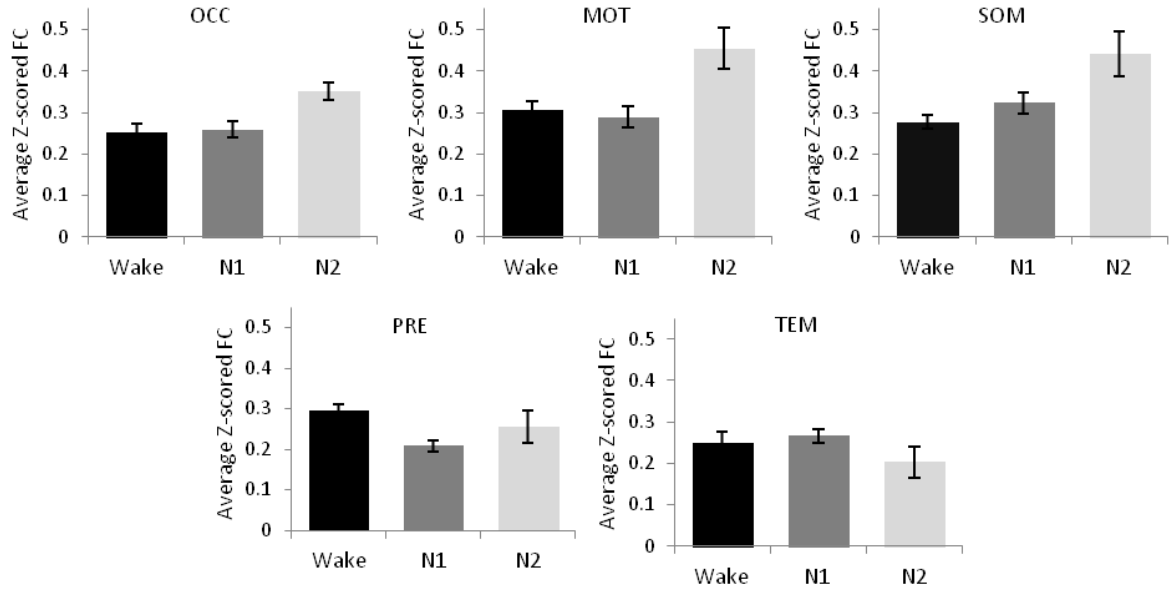


Fig. 2

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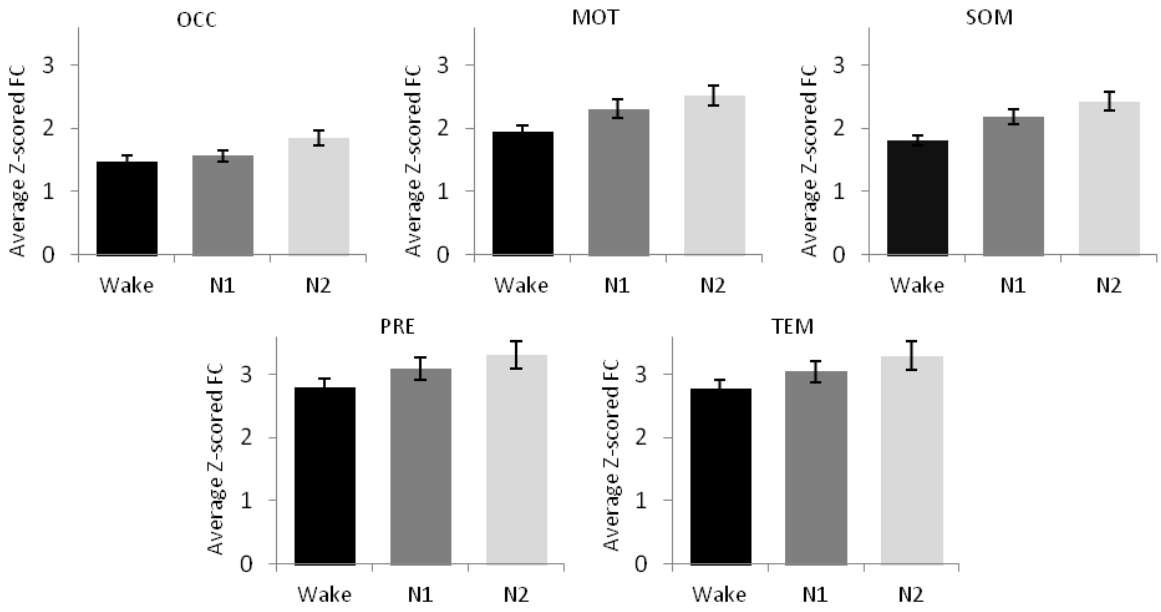


Fig. 3

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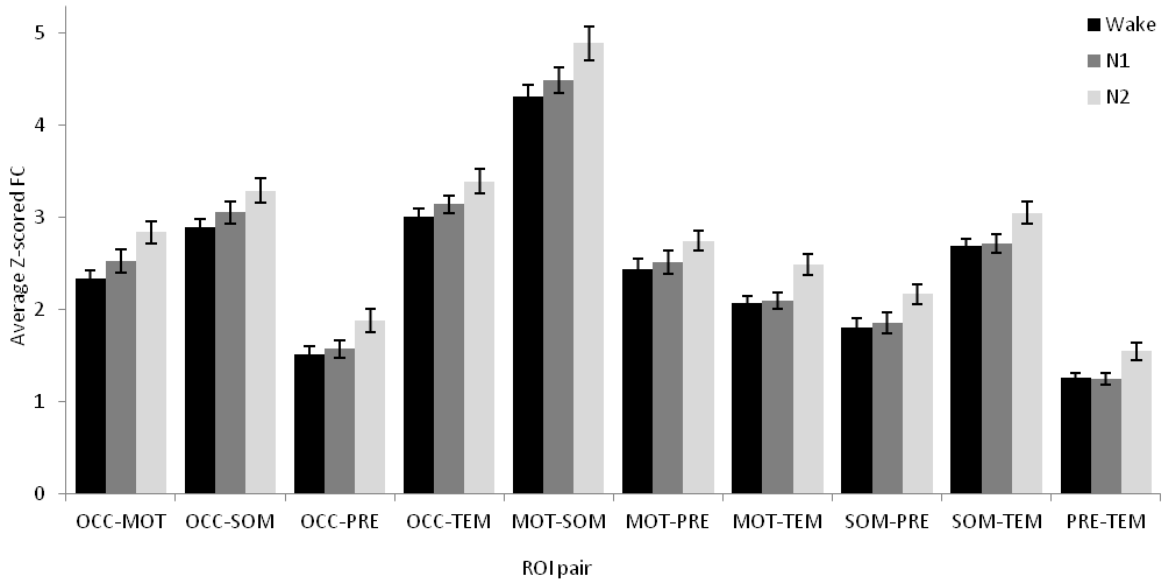


Fig 4

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