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Dynamic functional connectivity and its behavioral correlates beyond vigilance

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ABSTRACT

Fluctuations in resting-state functional connectivity and global signal have been found to correspond with vigilance fluctuations, but their associations with other behavioral measures are unclear. We evaluated 52 healthy adolescents after a week of adequate sleep followed by five nights of sleep restriction to unmask inter-individual differences in cognition and mood. Resting state scans obtained at baseline only, analyzed using sliding window analysis, consistently yielded two polar dynamic functional connectivity states (DCSs) corresponding to previously reported '*low arousal*' and '*high arousal*' states. We found that the relative temporal preponderance of two dynamic connectivity states (DCS) in well-rested participants, indexed by a median split of participants, based on the relative time spent in these DCS, revealed highly significant group differences in vigilance at baseline and its decline following multiple nights of sleep restriction. Group differences in processing speed and working memory following manipulation but not at baseline suggest utility of DCS in predicting cognitive vulnerabilities unmasked by a stressor like sleep restriction. DCS temporal predominance was uninformative about mood and sleepiness speaking to specificity in its behavioral predictions. Global signal fluctuation provided information confined to vigilance. This appears to be related to head motion, which increases during periods of low arousal.

Introduction

Temporal correlations in fluctuations of blood oxygenation level dependent (BOLD) signals across spatially separate but functionally related brain regions have given rise to studies on resting state functional connectivity that have enlarged our understanding of brain organization (Biswal et al., 2010; Fox et al., 2005; van den Heuvel and Hulshoff Pol, 2010). While earlier work was based on characterization of stationary connectivity patterns throughout the duration of the fMRI scan, it is now clear that the fluctuating patterns of correlation over shorter timescales, in the order of seconds to minutes might additionally inform about brain organization and its relation to behavior.

Evaluating dynamic functional connectivity (DFC) most commonly utilizes sliding temporal windows (Allen et al., 2014) whereby the correlation structure of BOLD signals in multiple brain regions is estimated over successive time points. Multiple transient patterns of correlation are then clustered into sets of recurring patterns - dynamic connectivity states (DCS). The neurobehavioral significance of these 'brain states' remains somewhat contentious. Some fluctuations in functional connectivity (FC) have been attributed to episodes of random synchrony (Handwerker et al., 2012), head motion (Laumann et al., 2017) and physiological noise (Chang et al., 2013b), but converging evidence indicates that other fluctuations have neurobehavioral significance (Allen et al., 2014; Chang et al., 2013a, 2016; Haimovici et al., 2017; Hutchison et al., 2013; Rosenberg et al., 2016; Wang et al., 2016), particularly in relation to shifts in attention or arousal, including falling asleep (Chang et al., 2013a, 2016; Haimovici et al., 2017; Thompson et al., 2013; Wang et al., 2016).

Do DFC states index behavior in cognitive domains other than arousal or state of attentiveness? This possibility is suggested by observations of a richer repertoire of DCS during wakefulness relative to that observed under anesthesia (Barttfeld et al., 2015). However, the behavioral significance of DCS in healthy persons apart from falling asleep or increased head motion, has been recently refuted by simulation and review of prior empirical studies (Laumann et al., 2017).

Here, informed by prior work (Thompson et al., 2013; Wang et al., 2016; Yeo et al., 2015) we examined whether DCS derived from sliding window analysis obtained in well rested persons, can predict performance in cognitive domains other than vigilance, at baseline and after multiple nights of partial sleep deprivation (SD). An attractive feature of SD as a conditional manipulation is its reversible nature and its property of accentuating inter-individual differences in cognitive performance

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that are not apparent when observing behavior in well-rested individuals. This extends the range of observable behavior over which DCS-behavior correlations can be evaluated. Critically, SD affects performance variably across different cognitive domains (Lim and Dinges, 2010) in a trait like manner (Lim et al., 2007; Rupp et al., 2012; Van Dongen et al., 2004), with some subjects being vulnerable to sleep deprivation while others remaining resilient, making it attractive for evaluating the robustness of cognitive-behavioral associations.

In setting up our experiment to address the behavioral relevance of different DFC states, we had an opportunity to explore a procedural issue in functional connectivity studies: whether or not to perform global signal regression (Liu et al., 2017; Murphy et al., 2009; Murphy and Fox, 2017). While it has been argued that doing so introduces artefactual anti-correlations (Murphy et al., 2009) into connectivity analyses, it is becoming apparent that physiologically meaningful alterations in global signal fluctuation accompany periods of lowered arousal (Olbrich et al., 2009; Wong et al., 2013) and neuropsychiatric disorders (Yang et al., 2014) and that removing global signal in these contexts omits useful network information originating from neuronal sources (Liu et al., 2017). The extent to which global signal contributes to the prediction of behavior following sleep restriction is of interest and may clarify the utility its elucidation while studying behavior-FC associations.

To answer these questions, we obtained resting state fMRI in adolescents who were 'sleep saturated' prior to scanning to generate an ideal condition for upholding vigilance performance. We analyzed the imaging data using sliding window dynamic functional connectivity analysis performed with global signal regression. Global signal fluctuation itself was also assessed independent from this analytic pipeline. Participating adolescents then underwent 5 consecutive nights of sleep restriction under close supervision as well as nocturnal EEG monitoring to degrade cognitive performance and mood as well as to enhance inter-individual differences in these, in a reversible manner. We then related how differences in temporal occupancy (dwell time) of different DCS states *prior to sleep restriction*, informed about behavioral alterations in different cognitive domains *after sleep restriction*. We also examined the independent contribution of global signal to these behavioral predictions.

Materials and methods

Participants and recruitment criteria

A total of 80 participants (40 females, age = 15–19y) from three quasi-laboratory studies conducted in a student dormitory contributed data to this report. The recruitment criteria were identical across all studies. Participants were screened based on the following criteria: between 15 and 19 y of age, had no history of any chronic medical condition, psychiatric illness, or sleep disorder, had a body mass index (BMI) of $\leq$30; were not habitual short sleepers (i.e. had an actigraphically-assessed average TIB of >6 h and no sign of sleep extension on weekends); had to consume fewer than five cups of caffeinated beverages a day[1]; and must not have travelled across more than two time zones 1 month prior to the experiment. The studies were approved by the Institutional Review Board of the National University of Singapore. Participants were recruited through sleep education talks and recruitment campaigns in four high-ranking schools, advertisements on the laboratory and social networking websites, as well as by word of mouth. All interested participants and their legal guardians were invited to attend a briefing session, during which written informed consent was obtained from both the participant and their legal guardian.

Self-reported sleep timing, duration, and quality were assessed using the Pittsburgh Sleep Quality Index (Buysse et al., 1989), while morningness-eveningness preference was measured by the Morningness-Eveningness Questionnaire (Horne and Ostberg, 1976). Nonverbal intelligence was evaluated using the Raven's Advanced Progressive Matrices (Raven and Court, 1998). Participants also completed the Chronic Sleep Reduction Questionnaire (Meijer, 2008) to evaluate their symptoms of chronic sleep restriction. The levels of daytime sleepiness were quantified using the Epworth Sleepiness Scale (Johns, 1991), and obstructive sleep apnea was screened for using the Berlin Questionnaire (Chung et al., 2008). Anxiety and depression were evaluated using the Beck Anxiety Inventory (Steer and Beck, 1997) and the Beck Depression Inventory (Beck et al., 1996) respectively.

Study protocol

To minimize the possible effect of habitual school night sleep curtailment on sleep physiology and cognitive performance, participants were required to adhere to a strict 9 h nocturnal sleep opportunity (23:00 to 08:00) one week prior to the study. This served to 'sleep saturate' the participants to provide ideal conditions for testing vigilance performance, and was verified using actigraphy (Actiwatch 2, Philips Respironics, Inc., Pittsburgh, PA). Study 1 and study 3 lasted 14-days, with the first three nights being the baseline nights (B0 to B2), where all subjects received 9-h TIB (23:00 to 08:00), followed by 7 manipulation nights (M1 to M7), wherein the sleep restriction group received 5-h TIB (01:00 to 06:00) and the control group continued to receive 9-h TIB. The study ended with 3 recovery nights (R1 to R3), with all subjects receiving 9-h TIB again. Study-2 was a 15-day protocol made up of 5 components. The first 2 nights were baseline nights (B1-B2), with all subjects receiving 9-h TIB (23:00 to 08:00). This was followed by the 1st cycle of sleep restriction (M1-M5), wherein all subjects slept 5-h TIB (01:00 to 06:00). All studies were conducted in the same dormitory environment. Participants underwent the same manipulation from B1 till M5 (Fig. 1). Additional details of these studies have been reported elsewhere (Lo et al., 2016a, 2016b).

Cognitive performance test battery

Each subject underwent three sets of computerized cognitive test batteries every day, at 10:00AM, 03:00PM and 8:00PM respectively. The test batteries were administered on identical laptop computers (Acer Aspire E11, Acer Inc., Taipei, Taiwan). Each test battery comprised of six tasks presented to measure five different aspects of cognition:

Subjective sleepiness: 9-point Karolinska Sleepiness Scale (KSS) (Akerstedt and Gillberg, 1990),
Sustained attention: Psychomotor Vigilance Test (PVT) (Dinges and Powell, 1985),
Working memory and executive functions: verbal 1- and 3-back tasks (Lo et al., 2012),
Speed of processing: Symbol Digit Modalities Test (SDMT) (Smith, 1991) and Mental Arithmetic Test (MAT) (Klein et al., 1976).
Mood: Positive and Negative Affect Scale (PANAS) (Watson et al., 1988).

In the KSS, subjects rated their subjective sleepiness on a 9-point Likert scale (from 1: very alert to 9: very sleepy, great effort to keep awake). In the PVT, subjects responded as quickly as possible to a counter that appeared randomly at intervals varying uniformly between 2 and 10 s. If the subjects did not respond to a stimulus within 10 s, a loud high-pitched beep was presented. The primary outcome of the PVT was number of lapses (responses with reaction time exceeding 500 msec). In the verbal 1 and 3-back tasks, letters were presented sequentially for 1 s with a 3 s inter-trial interval (ITI). Participants were asked to decide whether the current stimulus matched the one shown one (1-back) or three (3-back) items ago. The ratio of match to mismatch was 8:24. Performance was quantified by sensitivity (*A'*) calculated using methods described by Pollack and Norman (1964) modified for an error correction

[1] Out of the 80 subjects, 70 consumed one or less cups of caffeinated drink/day, and the rest consumed 3 or less cups/day.

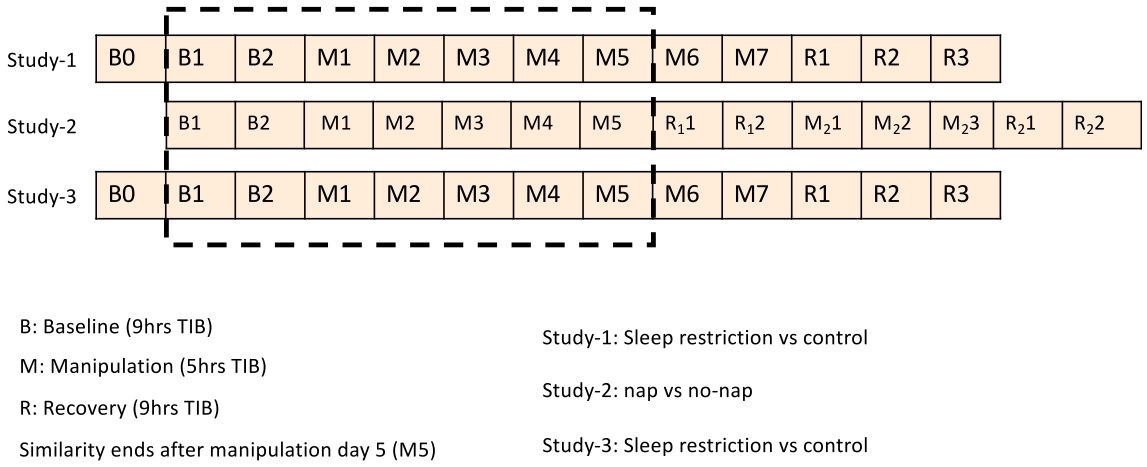

Fig. 1. The three experimental protocols. In study-1 and 3, subjects were randomly assigned to sleep restriction or control groups. The sleep restriction group received 5-h time in bed (TIB) during manipulation while the control group received 9-h TIB throughout the protocol. In study-2, subjects were randomly assigned to nap or no-nap groups. Both groups received 5-h TIB during manipulation with the nap group receiving additional 1-h of day-time sleep at a fixed time each afternoon. For this analysis, the sleep restriction groups from study-1 and study-3 and no-nap group from study-2 were combined and analyzed between B1 and M5 (black dotted box).

(Zhang and Mueller, 2005).

In the SDMT, participants were shown a key displaying 9 pairs of digits and symbols. On each trial, a symbol appeared below the key, and participants were required to respond by entering its corresponding digit (ranging from 1 to 9 on the keyboard) as quickly as possible. If participants did not respond within 15s, a high-pitched beep was presented. This task lasted for 2 min. The total number of correct trials was used as a measure of accuracy. In the MAT, a pair of 2-digit numbers was shown on the screen. Participants were asked to add the numbers as quickly as possible. If the participants did not respond within 15 s, a high-pitched sound was presented. The task lasted 4-mins. The number of correct trials in this 4 min was taken as the outcome.

In the PANAS task, participants were shown 20 adjectives with 10 describing positive mood and 10 describing negative mood. Participants needed to respond using a 5-point Likert scale (1 – very slightly, 5 – extremely). The sum of all responses for the positive and negative affect separately were taken as the outcome of the task.

Statistical analysis of behavioral data

Statistical analysis was performed using SPSS (version 24, Armonk, NY: IBM Corp). Differences in screening data between the two groups were compared using a one-way ANCOVA with study (study-1/2/3) as a confound. A general linear mixed-effects model (MIXED) procedure with first order heterogeneous auto-regressive (AR-1) covariance structure for repeated measures was used to investigate the effects of group, night and group × night interactions on cognitive measures. The covariance structure was chosen based on Bayesian information criterion. Differences of least square means were used to determine significant differences between the two groups and across nights at $P < 0.05$. The study (study-1/2/3) was included in the analysis as a confound. Contingency tables were analyzed using χ^2 test.

RS-fMRI scans

Scans were collected on a 3-Tesla Prisma system (Siemens, Erlangen, Germany). Two runs of a 6-min resting state scan were acquired using a gradient echo-planar imaging sequence (TR = 2000 ms, TE = 30 ms, FA = 90^0, FoV = 192 × 192 mm, voxel size = 3 × 3 × 3 mm). High resolution structural images were collected using MPRAGE sequence (TR = 2300 ms, TI = 900 ms, FA = 8^0, voxel dimension = 1 × 1 × 1 mm, FOV = 256 × 240 mm). Images were preprocessed following our previously described procedure in (Yeo et al., 2015). Preprocessing steps include 1) discarding the first four frames of each run, 2) correcting for slice acquisition-dependent time shifts in each volume with SPM-8 (Wellcome Department of Cognitive Neurology, London, UK) 3) correcting for head motion using 3 rigid body translations and 3 rotation parameters. 4) Linear trends over each run were removed and a low-pass temporal filter retained frequencies below 0.08 Hz. 5) 6-parameter head motion and their derivatives along with white and ventricular signals were regressed out and 6) Functional data of individual subjects were then projected to MNI152 space, downsampled to 2 mm voxels and then smoothed with a 6-mm full width half maximum kernel. To compute global signal, we created a whole brain mask and derived the average percent change in the signal time course across the mask. The standard deviation of this signal (Wong et al., 2013), constituted 'global signal power' (GS). Volumes having frame wise displacement (FD) > 0.2 mm or DVARS (Power et al., 2012) > 5% were marked as high motion. One volume before and two volumes after each high motion volume were also marked. If the number of volumes marked as high motion was greater than 50% of total volumes, the subject was excluded from the analysis. Global signal regression (GSR) was carried out as a part of the preprocessing pipeline as prior work has shown strong association between arousal and global signal (Wong et al., 2013; Yeo et al., 2015).

DFC analysis

DFC was computed using a sliding window approach following (Allen et al., 2014). Specifically, average BOLD time series from the 122 ROIs were first de-spiked and de-meaned. A tapered window was constructed by convolving a rectangular window (20 TRs) and a Gaussian function ($\sigma = 3$ TRs). Covariance among all possible ROIs pairs within the tapered window were estimated using the regularized precision matrix. The graphical LASSO method (Friedman et al., 2008) with L1 norm penalty (regularization parameter $\lambda = 0.1$) was applied to promote sparsity. This process was repeated by shifting the tapered window by 1 TR. For each functional run, we obtained 156 covariance matrices, each with 7381 (122 × 121/2) unique correlation values.

Covariance matrices from 52 subjects were concatenated together and k-means clustering was performed to classify each DFC matrix using L1 distance as the cost function. Occurrence of each DCS was computed as the proportion of total number of windows classified as that state for each functional run. The occurrence of each DCS was averaged across run for every subject. A study regressor (study-1/2/3) was used to account for study differences. Occurrence of each DCS was then compared between

the high and low arousal index subjects using independent samples t-tests (see section 2.7). This process was repeated for a range of clusters $k = 3$ to 7. A cluster hierarchy was formed by connecting clusters obtained at level k with the nearest cluster (based on L1 distance) at level k-1, to determine the stability and consistency of the clusters at different values of k. Irrespective of the value of k, two DCSs, appeared consistently and closely resembled the high arousal state (HAS) and low arousal state (LAS) previously reported (Wang et al., 2016) (see Results) representing the polar states of arousal. Therefore, the DCS obtained at $k = 3$ were used as representative HAS, LAS and intermediate state (IS). Clusters obtained at higher ks, were compared with the representative states based on their relative distances from the representative states.

Grouping of subjects based on arousal index

Given the consistency of the two polar states (Fig. 2), computation of an arousal index was carried out for $k = 3$ to maximize the contribution of each polar state while still allowing for an intermediate state. We combined dwell time in HAS and LAS into a single *arousal index* (AI) by subtracting proportion of time in LAS (t_l) from proportion of time spent in HAS (t_h). Specifically, AI was computed as:

$$AI = 1 + t_h - t_l$$

As most subjects spent more time in LAS, 1 was added to the AI equation to make the measure positive. Subjects who spent more time in

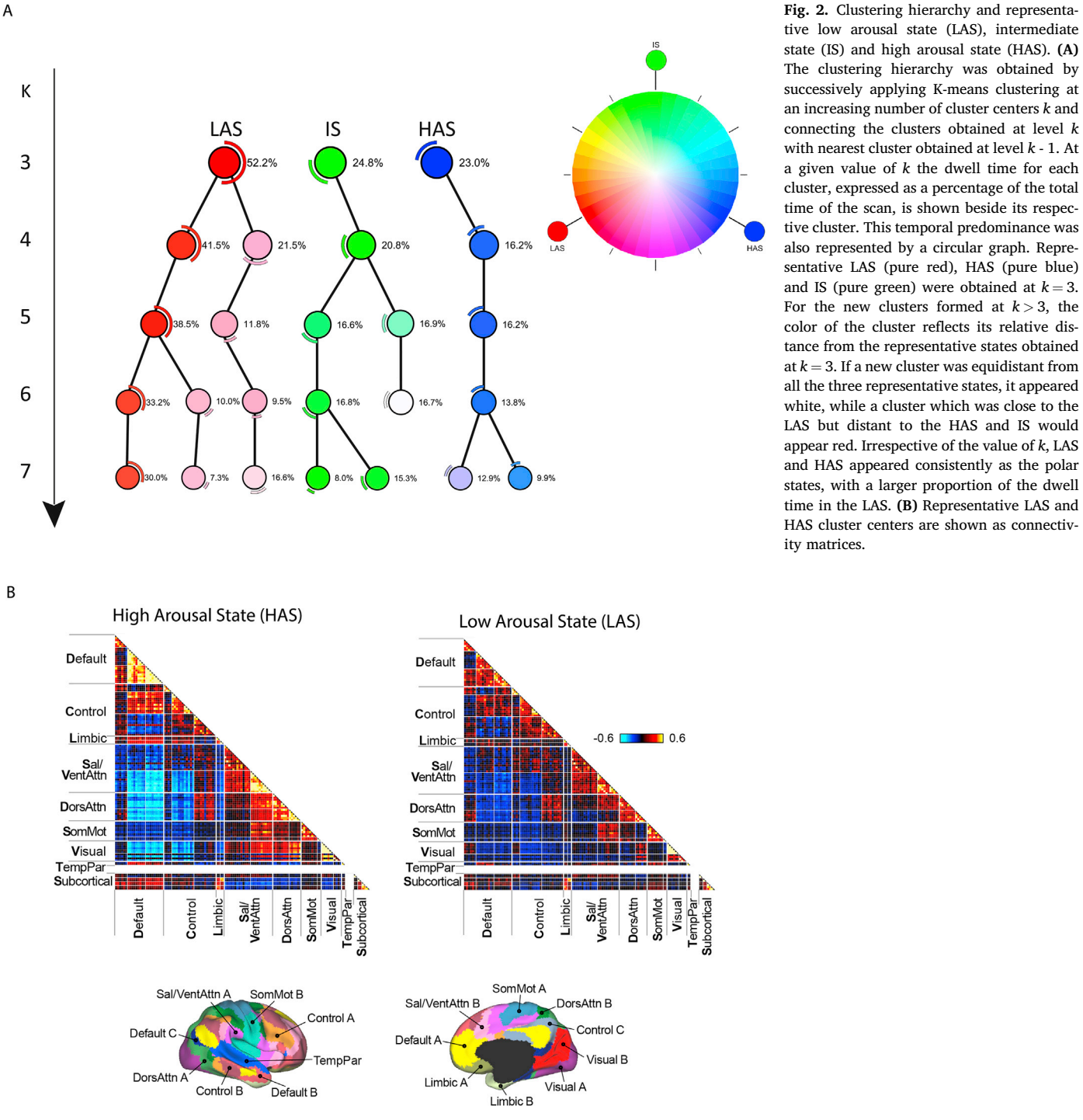

Fig. 2. Clustering hierarchy and representative low arousal state (LAS), intermediate state (IS) and high arousal state (HAS). **(A)** The clustering hierarchy was obtained by successively applying K-means clustering at an increasing number of cluster centers k and connecting the clusters obtained at level k with nearest cluster obtained at level k - 1. At a given value of k the dwell time for each cluster, expressed as a percentage of the total time of the scan, is shown beside its respective cluster. This temporal predominance was also represented by a circular graph. Representative LAS (pure red), HAS (pure blue) and IS (pure green) were obtained at $k = 3$. For the new clusters formed at $k > 3$, the color of the cluster reflects its relative distance from the representative states obtained at $k = 3$. If a new cluster was equidistant from all the three representative states, it appeared white, while a cluster which was close to the LAS but distant to the HAS and IS would appear red. Irrespective of the value of k, LAS and HAS appeared consistently as the polar states, with a larger proportion of the dwell time in the LAS. **(B)** Representative LAS and HAS cluster centers are shown as connectivity matrices.

HAS and less time in LAS were provisionally labeled as having 'higher arousal'. Conversely, subjects who spent less time in HAS and more time in LAS were labeled as having 'lower arousal'. Participants were subsequently median-split into two groups: a low arousal index (LAI) group and a high arousal index (HAI) group (HAI: AI $>$ 0.715, LAI: AI $\leq$ 0.715). This resulted in 26 subjects in each group.

Analysis of graph theoretic measures

To obtain subject specific clusters, the covariance matrices associated with a given DCS (HAS/LAS/IS obtained @k = 3) were averaged for each individual subject. This resulted in three subject level clusters corresponding to group level representative HAS, LAS and IS. Four subjects, who had either no HAS or IS (2 with no HAS and 2 with no IS) were removed from the analysis. The resulting mean covariance matrices were treated as undirected weighted graphs, with both positive and negative covariance being treated as equal. Graph theoretic network measures were then obtained for HAS, LAS and IS clusters for every individual. Global and local efficiency (Latora and Marchiori, 2001) which measure the efficiency of information exchange at global and local (node level) scales in a network, and network cost (Achard and Bullmore, 2007) which measures the energy cost associated with a network were computed. The network measures across the three clusters were compared using a one-way repeated measures ANOVA using SPSS (version 24, Armonk, NY: IBM Corp). Post-hoc comparisons with Sidak correction were carried out for measures showing significant difference across the three clusters.

Results

Two dynamic connectivity states (DCS) nominally related to 'arousal' were consistently observed

The cluster hierarchy obtained by repeatedly applying k-means clustering is shown in Fig. 2A. Irrespective of the value of *k*, two DCSs, appeared consistently and closely resembled the HAS and LAS previously reported (Wang et al., 2016). Compared to the 'low arousal' DCS (LAS), the 'high arousal' DCS (HAS; Fig. 2B) displayed higher within-network connectivity involving DMN, control network, ventral attention/salience network (SN) and DAN. Higher between-network connectivity was also observed between DMN and control network as well as between SN and DAN. High arousal (HAS) was accompanied by greater anti-correlation between the DMN and DAN/SN as well as between DMN and visual networks. In contrast, the low arousal DCS featured decoupling (lower correlation) between the visual network and higher-order cognitive networks including DMN, control and DAN. Even though new states appeared as the number of clusters was increased (see Figs. S1–S5 for the cluster centers obtained at $k = 3$ to 7 respectively and Fig. S6 for direct comparison of HAS and LAS clusters obtained at $k = 3$ with those obtained in Wang et al. (2016)), two polar states were consistently present across different values of *k* and the new states appeared to branch off from them (see Fig. 2A and Figs. S1–S5). The representative LAS and HAS network for $k = 3$ is shown in Fig. 2B and Fig. S1. The raw covariance matrices of the representative LAS, IS and HAS DCS are made available online (https://github.com/cnldukenus/Low-and-Hight-Arousal-DFC-states).

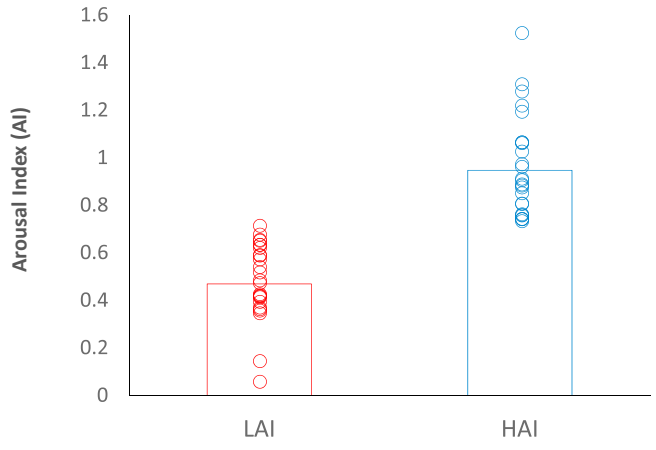

Fig. 3. Distribution of baseline arousal index values. Subjects were split in-to two groups: the low arousal index (LAI) and the high arousal index (HAI) group based on a median split in arousal index. Both individual arousal index at baseline as well as group averages are shown.

Dwell time within LAS and HAS: temporal preponderance

The dwell time in each state for the range of *k* is shown in Fig. 2A. Irrespective of the value of *k*, subjects spent about twice as long in LAS (average ≈52% @ k = 3) compared to HAS (average ≈23% @ k = 3) while intermittently transitioning to the intermediate state. Subjects showed large inter-individual differences in relative temporal predominance (dwell time) in HAS and LAS. We observed a large inter-individual difference in AI across subjects (range: 0.05 to 1.51). The distribution of AI across the two groups is shown in Fig. 3. The two groups did not differ in terms of age, gender, non-verbal IQ as assessed by the Raven's Progressive Matrices, sleepiness or sleep quality (Table 1).

HAS network shows higher information transfer efficiency but at the expense of higher network cost

The HAS, LAS and IS networks differed significantly from each other in terms of both global ($F_{2,94} = 92.4$, $P < 0.001$) and local ($F_{2,94} = 120.6$, $P < 0.001$) network efficiency and cost ($F_{2,94} = 115.8$, $P < 0.001$, see Fig. 4). Post-hoc comparisons revealed that both HAS and IS (with similar global efficiency ($P > 0.1$)) had higher global efficiency compared to LAS ($P < 0.001$). The HAS network had higher local efficiency as compared to IS network which in turn had higher local efficiency as compared to LAS network (all *Ps* < 0.001). A similar pattern was also observed in terms of network cost, with HAS network being most costly followed by IS and LAS respectively (all *Ps* < 0.001).

HAI and LAI groups showed baseline differences in vigilance

The LAI group had significantly higher lapses (reaction time $>$ 500 ms) compared to HAI group (4 lapses/session vs 1.87 lapses/session, $F_{1,49} = 12.4$, $P < 0.001$, Fig. 5). There was a significant negative correlation (after accounting for study differences) between baseline PVT lapses and arousal index ($r = -0.460$, $P < 0.001$, Fig. 5). There was no

Table 1
Subject characteristics. PSQI, Pittsburgh Sleep Quality Index. Mean ± SD are shown.

	LAI (mean ± SD)	HAI (mean ± SD)	P
n	26	26	
Age (years)	16.84 ± 1.09	16.70 ± 1.06	0.651
Sex (%males)	42.31	57.69	0.405
Body mass index	21.30 ± 2.55	20.77 ± 2.88	0.490
Raven's Advanced Progressive Metrics score	9.35 ± 2.08	9.65 ± 1.89	0.579
Epworth Sleepiness Scale score	7.77 ± 3.59	6.65 ± 2.67	0.210
Chronic Sleep Reduction Questionnaire			
Total score	35.50 ± 5.42	33.69 ± 4.77	0.201
Shortness of sleep	12.69 ± 2.20	12.23 ± 2.20	0.453
Irritation	7.08 ± 1.98	6.46 ± 1.30	0.191
Loss of Energy	7.92 ± 1.96	7.46 ± 1.98	0.403
Sleepiness	7.81 ± 1.41	7.53 ± 1.65	0.531
PSQI	5.61 ± 2.53	5.11 ± 1.90	0.424

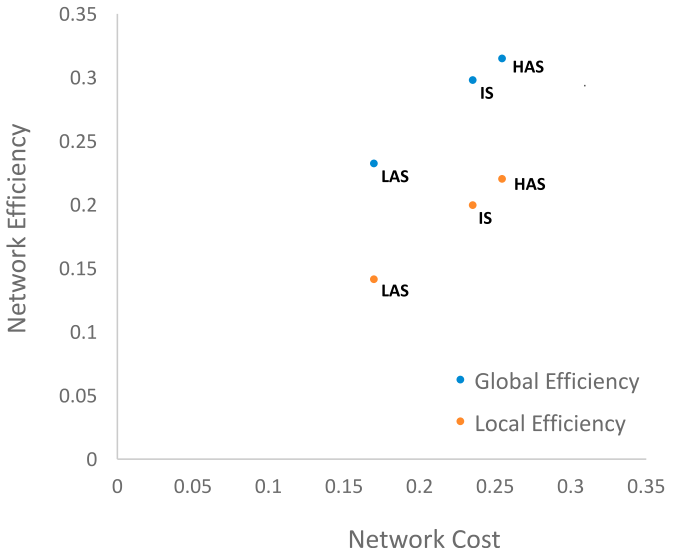

Fig. 4. Network efficiency vs. cost. The mean global and local network efficiency for the high arousal state (HAS), low arousal state (LAS) and intermediate state (IS) were plotted against their respective mean network cost. Except for global efficiency between HAS and IS, all other pairwise comparisons for global efficiency, local efficiency and cost were statistically significantly different across the three dynamic connectivity states ($P < 0.001$).

significant baseline difference in speed of processing, working memory and executive control, subjective sleepiness or mood.

Baseline DCS predicted unmasking of cognitive vulnerability by multiple nights of sleep restriction

Sleep restriction significantly affected most behavioral measures except for negative affect, as indicated by the main effect of day (Fig. 6): decline in vigilance as assessed by PVT lapses ($F_{5,95} = 15.23$, $P < 0.001$), speed of processing as measured by MAT ($F_{5,182} = 7.05$, $P < 0.001$), working memory as indicated by 1-back ($F_{5,76} = 4.13$, $P < 0.01$) and 3-back ($F_{5,105} = 2.30$, $P = 0.05$) and positive affect as indicated by PANAS positive score ($F_{5,201} = 5.85$, $P < 0.001$) together with an increase in subjective sleepiness as indicated by KSS ($F_{5,66} = 11.88$, $P < 0.001$).

There was a main effect of group on performance such that the LAI group performed significantly poorer on the PVT, 3-back ($F_{1,59} = 4.78$, $P < 0.05$) and the SDMT tasks ($F_{1,51} = 7.67$, $P < 0.01$). Post-hoc tests showed that unlike the case of vigilance, group differences in working memory and speed of processing were significant only after sleep restriction (Fig. 6C and D). Despite the profound group difference in vigilance performance, there was no difference in subjective sleepiness (Fig. 6B), underscoring the well-known dissociation between objective and subjective measures of sleep loss (Leproult et al., 2003).

Only vigilance showed a significant group by day interaction ($F_{5,95} = 2.84$, $P < 0.05$); with the LAI group showing a significantly larger increase in lapses with ongoing sleep restriction. To further characterize this vigilance shift, the difference in lapse count (*ΔPVT lapses*) following sleep manipulation nights M1 to M5 and baseline night B2 was computed for both groups (Fig. 7A). There was a significant group by day interaction ($F_{4,86} = 3.05$, $P < 0.05$) with the difference between the two groups reaching statistical significance after the third night (M3). Vigilance decrement, measured as the difference in lapses between M5 and B2, correlated with the AI obtained at baseline (Spearman's $\rho = -0.421$, $P < 0.01$, Fig. 7B). No group by day interaction was observed in any other cognitive

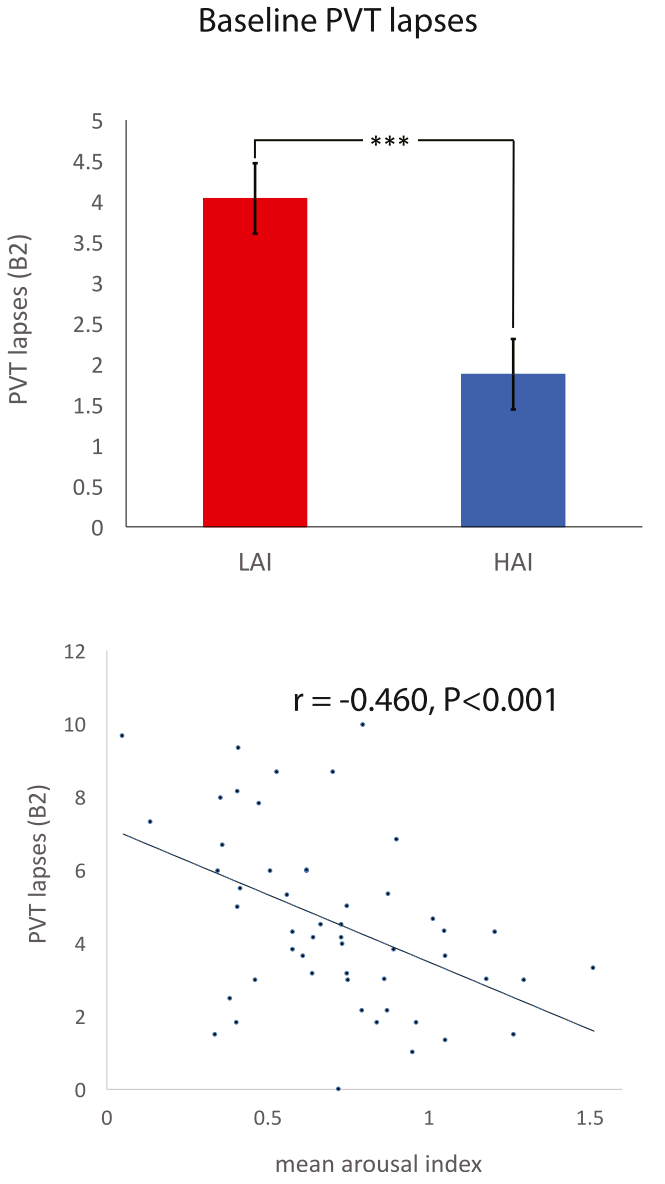

Fig. 5. Baseline performance differences between low arousal index (LAI) and high arousal index (HAI) groups. LAI subjects had significantly more number of PVT lapses following baseline night (B2) compared to HAI subjects. In addition, PVT performance at baseline was negatively correlated with mean arousal index. Mean ± SEM are shown. ***P < 0.001.

domain. The LAI group therefore were more vulnerable to the effects of partial sleep restriction in the domain of vigilance as compared to the HAI group.

AI and global signal capture non-overlapping aspects of vigilance

Considering the association between AI and vigilance, it is important to ascertain the extent to which global signal and AI make independent contributions to predicting vigilance decline following sleep restriction. GS was significantly higher in LAI subjects compared to HAI subjects (0.39% vs 0.28%, $F_{1,49} = 10.23$, $P < 0.01$). As motion contributes to GS we also performed an analysis that included DVARS (Power et al., 2012) as a covariate. Although reduced with this added step, the group difference in GS was still significant ($P < 0.05$).

GS and AI showed significant correlation with each other ($r = -0.344$, $P < 0.05$). To quantify the contribution of GS and AI to-

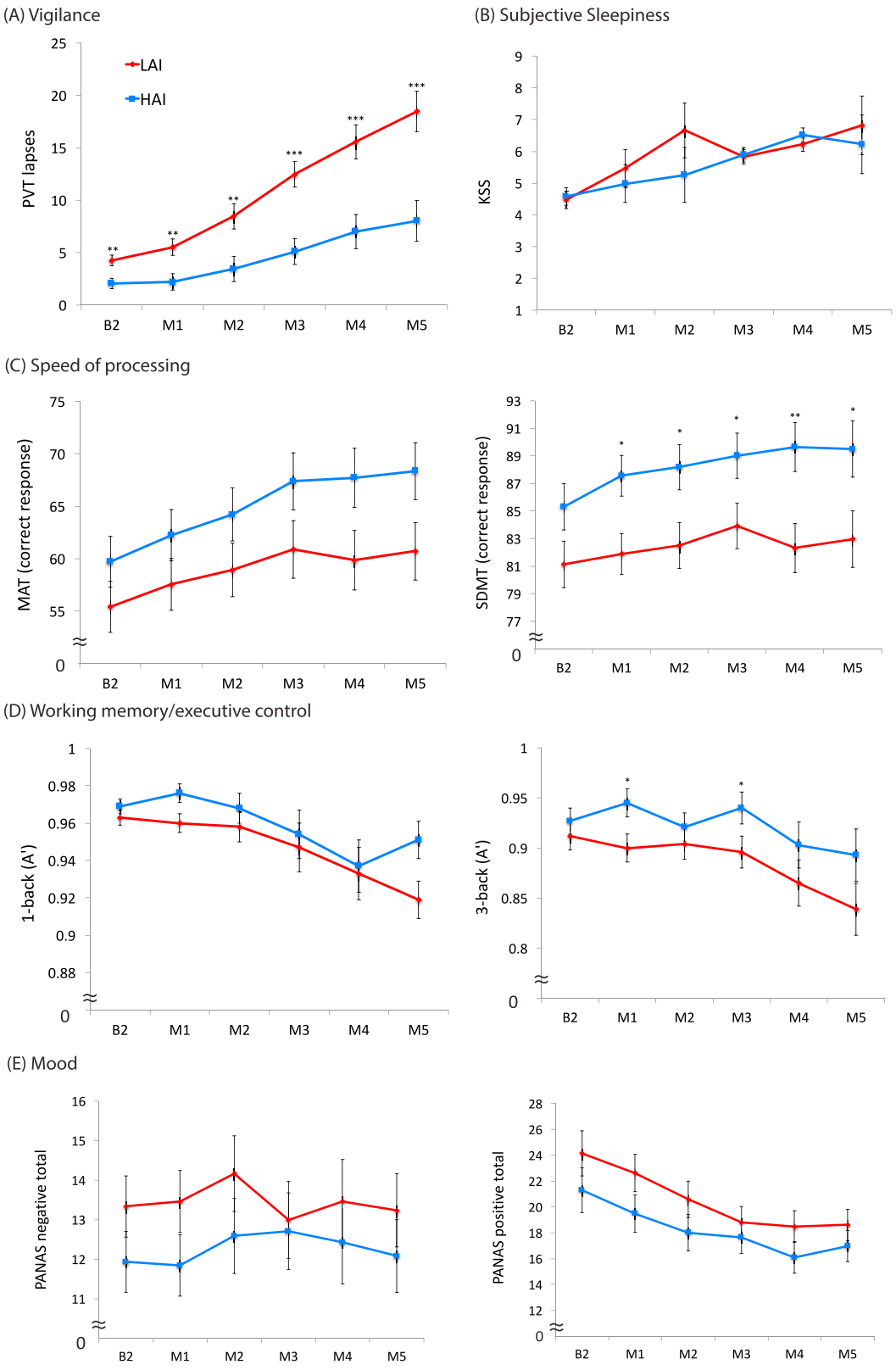

Fig. 6. Effects of consecutive nights of partial sleep deprivation on cognitive performance, subjective sleepiness and mood. Least squared means and standard errors from the linear mixed effects model for low arousal index (LAI: red) and high arousal index (HAI: blue) subjects were shown for: **(A)** vigilance, measured by Psychomotor Vigilance Task (PVT) lapses, **(B)** subjective sleepiness, indicated by the score on the Karolinska Sleepiness Scale (KSS), **(C)** working memory and executive function, indicated by sensitivity A′ in the verbal 1 and 3 back task, **(D)** speed of processing, measured by the number of correct responses on the Mental Arithmetic Task (MAT) and the Symbol Digit Modalities Test (SDMT) and **(E)** mood, indicated by the score on the Positive and Negative Affect Scale (PANAS). *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

wards predicting lapses in vigilance, both were simultaneously introduced into a multivariate linear regression model. Additionally, a variance inflation factor (VIF) was computed for each independent variable to ensure that the models did not suffer from multicollinearity. At the baseline scan performed in well-rested conditions, only AI predicted lapses in a statistically significant manner (standardized $\beta = -0.418$, $P < 0.01$). Both AI and GS predicted lapses (standardized $\beta = -0.313$, $P < 0.05$ and standardized $\beta = 0.342$, $P < 0.05$ respectively) after multiple nights of sleep restriction at M5.

When head motion, indexed using DVARS, was introduced as a covariate, AI continued to predict lapses both at baseline (standardized $\beta = -0.400$, $P < 0.01$) and following M5 (standardized $\beta = -0.287$, $P < 0.05$). However, with motion factored in this fashion, GS was no longer predictive at either time point in any domain (all $P > 0.05$). The results remained when frame wise displacement (FD) was substituted for DVARS; i.e., AI predicted lapses both at baseline (standardized $\beta = -0.409$, $P < 0.01$) and following M5 (standardized $\beta = -0.279$, $P < 0.05$), but GS was not predictive at either time point (all $P > 0.05$). Estimated VIF remained within 2.6, suggesting that none of the regression models had a problem of multicollinearity.

Discussion

We studied dynamic functional connectivity states (DCS) and global signal in sleep saturated adolescents and examined how these might inform about behavioral performance when the same participants underwent 5 nights of sleep restriction to unmask inter-individual differences in cognition and mood. Inter-individual differences in decline of speed of processing (SOP) and working memory (WM) appeared after sleep restriction. The relative temporal preponderance of two dynamic connectivity states (DCS) in well-rested participants, predicted inter-individual differences in vigilance at baseline and further divergence in vigilance performance following multiple nights of sleep restriction. In contrast, there was a clear but relatively consistent separation in prediction of SOP and WM performance after multi-night sleep restriction. Sleepiness and mood shifts from baseline also followed this pattern. Global signal by itself could also inform about deterioration in vigilance with continued sleep restriction, but did not associate with deterioration in any other cognitive domains. Polar DCS states are thus most informative about vigilance but also carry some predictive information about speed of processing and working memory. In contrast, global signal fluctuations inform about vigilance only. Their increase during periods of low arousal relates to increased head motion.

Polar dynamic connectivity states: relation to arousal

The two polar DCS in the present study derived from well rested adolescent participants resembled those discovered when evaluating young adults in the sleep deprived state. The 'high arousal' DCS was characterized by greater between network segregation in networks that are typically anti-correlated at rest (default mode network vs. ventral and dorsal attention networks as well as the visual network) and greater within network integration in default mode and attention networks. Three variations from our original DCS study which reported DCS generated from sleep deprived participants (Wang et al., 2016) might be the result of pre-scan sleep saturation that reduced drowsiness/sleep during scanning (Tagliazucchi and Laufs, 2014). First, the anti-correlations between default mode and ventral attention/salience as well as dorsal attention networks in the 'high arousal' state were more pronounced in the current dataset, resembling a previous report on static connectivity in well-rested young adults (Yeo et al., 2015). Secondly, anti-correlation between visual and DMN areas was clearer in the present data than in the sleep deprived dataset. This greater anti-correlation was present in the comparison between less vulnerable and more vulnerable participants when using static FC to predict vigilance decline following TSD from data obtained from rested young adults (Yeo et al., 2015).

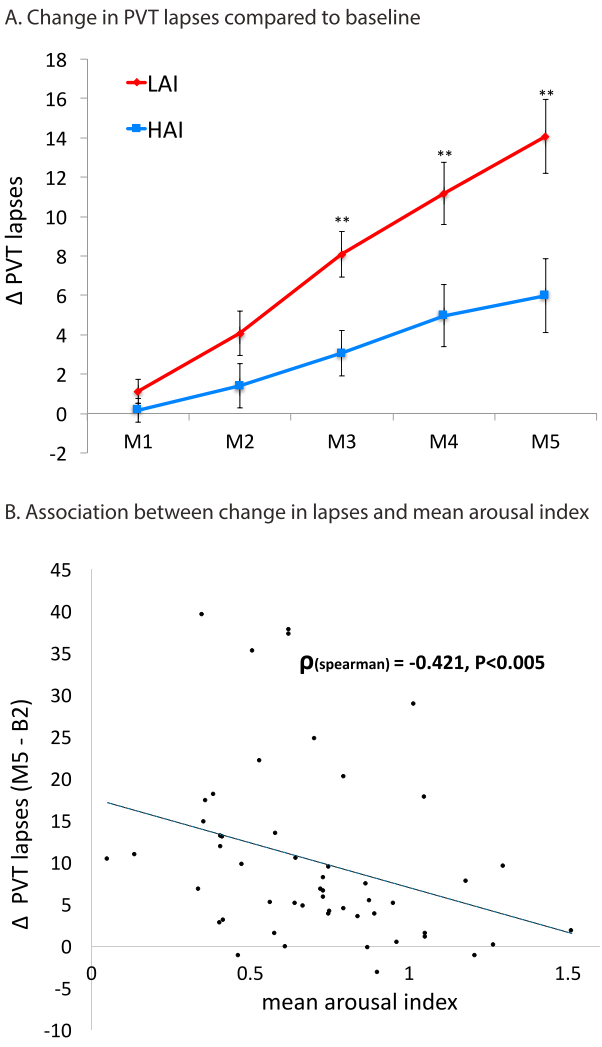

Fig. 7. Change in Psychomotor Vigilance Task (PVT) lapses across multiple nights of sleep deprivation. **(A)** With reference to baseline night B2, changes in PVT lapses across consecutive nights of sleep restriction (M1 to M5) are shown for the low arousal index (LAI) and high arousal index (HAI) groups. Decline in performance became significantly different between the two groups following the third night of sleep restriction (M3). **(B)** The overall decline in PVT lapses measured as a difference between lapses in M5 and B2 negatively correlated with the baseline mean arousal index.

Finally, there was higher within-network connectivity in the default as well as dorsal and ventral attention networks as well as higher between network connectivity between visual and attention networks. Being associated with fewer lapses (mean 2.24 lapses vs. 9.50 lapses in Wang et al., 2016; Fig. S6), the 'low arousal' DCS in the present study can be thought of as lying on a higher level on a continuum of arousal compared to our original study, accompanied by correspondingly higher levels of network segregation and integration.

The temporal predominance of the 'low arousal' DCS even in participants who were verified to have adequate sleep prior to scanning, is striking and suggests that there is energetic cost or penalty for remaining in the 'high arousal' state while not actively performing a task (Bullmore and Sporns, 2012). Persons with higher arousal indices, who spent more time in this state may have greater 'reserve' to deal with the effect of sleep restriction (Mu et al., 2005). We previously observed that baseline differences in static functional connectivity obtained in the rested state predict vigilance decline in the sleep deprived state (Yeo et al., 2015). These baseline differences only partially overlapped with changes

observed between well rested and sleep deprivation condition; the shifts in connectivity across state were largely similar across vulnerability. This suggests that group differences in vigilance decline under conditions of sleep deprivation/restriction are mostly captured in baseline physiological observations.

Utility of DCS in predicting behavior at baseline and following sleep restriction

Sleep restriction can be thought of as a 'cognitive stress test' akin to a treadmill stress test that serves to unmask cognitive vulnerabilities by amplifying subtle deviations in physiological or behavioral measures already present on baseline testing but which are still within acceptable bounds (Chua et al., 2014). Classified according to AI differences, participants from the present study showed significant baseline differences in vigilance as well as group differences in processing speed and working memory after nights of sleep restriction (for SDMT and 3-back tasks). As such, DCS, while most clearly speaking to differences in vigilance/arousal also inform about two cognitive domains that account for much of the variance in inter-individual cognitive ability (Van Dongen et al., 2004).

Previous work (Chua et al., 2014) suggests that sleep restriction resilient subjects show increased baseline arousal arising from greater ascending neuro-modulatory input compared to vulnerable subjects based on their having a higher baseline heart rate, lesser change in heart rate variability and lower theta activity in the waking EEG compared to vulnerable subjects. The greater temporal preponderance of the 'high arousal' state in participants who have better vigilance, speed of processing and working memory lends support to this argument. While more efficient, this network state is more 'costly' (Achard and Bullmore, 2007; Bullmore and Sporns, 2012) and may be switched to only when needed to facilitate task performance.

Resilient individuals may have brains that exhibit 'task ready' levels of functional connectivity more frequently, and are more likely to be higher functioning. This notion finds support in a recent study that showed, albeit using different methodology, that greater similarity between functional connectivity at rest and 'efficient connectivity' during task performance marks a higher level of general intelligence (Schultz and Cole, 2016). While leaders of organizations are often sleep deprived, intelligence does not appear to be associated with resilience to sleep deprivation. In the present sample, differences in vigilance decline were not associated with general intelligence as assessed by Ravens Progressive Matrices.

Global signal fluctuation relates to vigilance and head motion

In contrast to the DCS based arousal index (AI), global signal differences between participants only predicted vigilance after nights of sleep restriction but did not distinguish participants on baseline performance. GS, which represents the standard deviation of this signal over the entire time course of a resting state study, has been shown to relate to EEG-measured vigilance (Olbrich et al., 2009; Wong et al., 2013), and the transition to light sleep (Horovitz et al., 2008). More recently, the global signal has also been found to be induced by a characteristic electrophysiological event that occurs at state transitions and appears to be related to subcortical regions regulating arousal and vigilance (Liu et al., 2018). Future work should investigate how GS amplitude and DFC state occurrence influence temporal fluctuations in vigilance at the subject-level.

Functional imaging studies have noted a correlation between GS and head motion but have not directly linked this to decreases in vigilance. Increased head motion and decline in vigilance has been reported in behavioral (Van Den Berg, 2006) and driving studies (Vural et al., 2007). In agreement with these observations, we found that the association between global signal and vigilance became non-significant when motion was introduced as a co-variate in the analysis of global signal contributions to behavioral prediction. The present findings should thus encourage thinking of head motion not merely as a 'nuisance' but a factor that shows phenotypic variation that has neural (lower arousal) origins.

Conclusion

In sum, polar DCS states are most informative about vigilance but also carry predictive information about declines in speed of processing and working memory following sleep restriction. These DCS states do not predict increased sleepiness or decline in mood. In contrast, global signal fluctuations appear to only inform us about vigilance changes following sleep restriction. These findings clarify the cognitive associations between dynamic functional connectivity and behavior that are accentuated during sleep restriction.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2018.04.049.

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