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Increased insula coactivation with salience networks in insomnia

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ABSTRACT

Insomnia is among the most prevalent and costly of all sleep-related disorders. To characterize the neural mechanisms underlying subjective dysfunction in insomnia, we examined brain activity in 17 female insomniacs and 17 female healthy controls using simultaneous functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) while they were resting and while they were trying to fall asleep. In examining the dynamic regional activity within intrinsic brain networks, we found that, compared with controls, insomniacs had greater involvement of the anterior insula with salience networks, as well as insula BOLD correlation with EEG gamma frequency power during rest in insomniacs. This increased involvement of the anterior insula was associated with negative affect in insomniacs. Aberrant activation of the insula, which integrates temporal and bodily states, in arousal networks may underlie the misperception of sleep quality and subjective distress in insomnia.

1. Introduction

Insomnia is a disorder of all-day impairment from sleep-related distress that involves a perceived difficulty falling asleep, staying asleep, or obtaining refreshing sleep. Afflicting up to 10% of the population (Ohayon, 2002), insomnia may persist for months or years and predicts the development of other disorders, such as Major Depressive Disorder (Ford & Kamerow, 1989). Researchers have proposed multiple psychological and biological explanations for the symptoms of insomnia (Harvey & Tang, 2012), including dysfunction in neural circuitry like the brainstem systems controlling sleep-wake (Lu, Sherman, Devor, & Saper, 2006), faulty sleep drive (Krystal & Edinger, 2010), psychological factors, or multiple causes (Riemann et al., 2009).

An important framework for understanding insomnia is 'hyperarousal,' or the posited heightened activity of neural, metabolic, electrophysiological, and neuroendocrine systems in insomniacs (Bonnet & Arand, 2010). Importantly, however, a key aspect of insomnia is the subjective reporting of more sleep dysfunction, such as increased sleep latency, than is recorded by 'objective' measures such as polysomnography. Thus, the diagnosis of insomnia is based on the subjective report of psychological distress, particularly during the sleep-to-wake transition. This suggests a limitation of polysomnography for capturing a neural phenotype of insomnia. Alternative imaging methods may elucidate the neural basis of hyperarousal, and one of the few studies to examine neural activity in individuals diagnosed with insomnia reported anomalies in both wakefulness-promoting regions and regions that underlie the neural response to stress (Nofzinger et al., 2004). Using positron emission tomography, these investigators found that insomniacs failed to reduce activation in limbic system structures, particularly in the medial temporal cortex, amygdala, insula, and anterior cingulate cortex. Notably, there were no differences between insomniacs and healthy controls in EEG measures of sleep, including sleep onset latency, sleep efficiency, and spectral characteristics of sleep.

Psychological states during the sleep-to-wake transition are challenging to assess, as are the brain systems underlying these states. Task-based functional magnetic resonance imaging (fMRI), in which participants respond to external cues or process information, is counterproductive to the quiescent process of sleep onset that is disrupted in insomnia. In contrast, intrinsic network imaging, which does not require a specific task or even participant engagement or alertness, is particularly well suited to provide novel insights concerning dynamic brain functions underlying psychological processes in insomnia. This method can provide a dynamic

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portrait of brain networks even in the absence of a guided task (Raichle et al., 2001). In intrinsic network imaging, the blood-oxygen level dependent (BOLD) signal in the brain is organized into networks of regions with coherent activity. Although the study of these networks and their relation to cognitive and affective states is nascent, these intrinsic network analyses are promising methods for determining regions with aberrant coactivation with canonical networks in neurological and psychiatric disorders (Sheline, Price, Yan, & Mintun, 2010). Regions with aberrant coactivation may elucidate the underlying neural basis for neurological and psychiatric disorders.

Intrinsic network imaging offers a powerful tool to investigate brain regions and networks involved in insomnia without disrupting an individual's current mental state with more intrusive or invasive methods. This method also enables targeting of specific networks putatively involved in arousal and insomnia. In the present study, we examined late-night, intrinsic network fMRI in 17 female adults diagnosed with insomnia and 17 female healthy-sleeping controls. To assess sleep-onset dysfunction in insomniacs, we imaged participants in two conditions: resting-state and 'fall asleep,' in which participants were asked to let themselves fall asleep. We focused specifically on the role of affective regions within resting-state networks that include arousal-promoting structures that have been implicated in insomnia (Nofzinger et al., 2004).

2. Methods

2.1. Participants

We recruited females, ages 18–40, who self-reported insomnia or healthy sleep. Participants were excluded for any past or present DSM-IV Axis I disorder, any past or present sleep disorder except insomnia, current use of prescription psychotropic or hypnotic medication, BMI greater than 30, and any exclusionary criteria for the MRI environment. We recruited only females because they have a higher prevalence of insomnia than do males (Ohayon, 2002), as well as to increase the homogeneity of the sample and the power of this study.

Eligible participants were administered the Structured Clinical Interview for Diagnosis of DSM-IV-TR Axis I disorders (First, Gibbon, Spitzer, & Williams, 1997) and the Duke Structured Interview for Sleep Disorders (Edinger, Wohlgemuth, Radtke, Marsh, & Quillian, 2001; Stepanski et al., 2004). No participant met any criteria for any DSM-IV-TR Axis I disorder or any sleep disorder, other than insomnia in insomniacs: DSM-IV-TR insomnia, ICSD-2 psychophysiological insomnia, or ICSD-2 idiopathic insomnia. Insomniacs had to retrospectively report at least 30 total minutes of sleep difficulty at least 3 times a week for at least 2 months, along with subjective distress. These criteria were selected to balance DSM-IV-TR and ICSD-2 criteria (Ohayon & Reynolds, 2009), while reflecting evolving nosologies of insomnia (Edinger et al., 2011). Participants then completed demographic information, the Beck Depression Inventory II (BDI-II) (Beck, Steer, & Brown, 1996), Beck Anxiety Inventory (BAI) (Beck, Epstein, Brown, & Steer, 1988), the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), the Dysfunctional Beliefs and Attitudes about Sleep scale (DBAS-16) (Morin, Vallières, & Ivers, 2007), the Insomnia Severity Index (ISI) (Bastien, Vallières, & Morin, 2001), the Ford Insomnia Response to Stress scale (FIRST) (Drake, Richardson, Roehrs, Scofield, & Roth, 2004), the Fatigue Severity Scale (FSS) (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989), and specific information about current (within the last month) and past (past six months) sleep.

Several factors suggest that this is a viable clinical group. Differences between the two groups in scores on the insomnia severity index (ISI), Ford Insomnia Response to Stress scale (FIRST), and Pittsburgh Sleep Quality Index (PSQI) clearly indicate that the insomnia group experiences greater subjective sleep distress than does the control group. Indeed, all but one of the insomnia group participants had at least subthreshold insomnia based on the ISI (Bastien et al., 2001); interestingly, this is not the same individual who reported less than 30 min of sleep latency. More than half (8 of 17) of the insomnia participants reported at least clinically severe levels of insomnia, based on the ISI.

2.2. fMRI acquisition

Eligible participants were instructed to abstain from using over-the-counter medications that may affect sleep for a week prior to the scan and to limit the consumption of caffeinated beverages on the day of the scan. At midnight, participants completed a high-resolution SPGR anatomical scan and two 20-min spiral-in/out scans: a resting-state scan, with the instruction to "rest quietly with your eyes closed," and a 'fall asleep' scan, with the instruction to "rest quietly with your eyes closed and let yourself fall asleep." Following each scan, participants rated using a button box both their alertness during the previous scan and their post-scan alertness on a modified version of the Karolinska sleepiness scale (Kaida et al., 2006); ratings on this scale ranged from 1 to 9, with 1 corresponding to "wide awake," and 9 corresponding to "in deep sleep." High-resolution anatomical scans were obtained with an SPGR sequence with a resolution of 0.859 mm × 0.859 mm × 1 mm. Resting-state and 'fall asleep' scans were whole-brain spiral-in/out scans (Glover & Law, 2001), with 30 oblique axial slices with a thickness of 4 mm (1 mm skip) and an in-plane voxel size of 3.4375 mm × 3.4375 mm (TE = 30 ms, FOV = 22 cm, flip angle = 80°, and TR = 2.04 s) and 600 time frames for each scan for a total time per scan of 20 min, 24 s. Before and after the session, participants completed the PANAS (Watson, Clark, & Tellegen, 1988).

2.3. fMRI preprocessing

For the two spiral-in/out scans, we used modified NITRC (NITRC.org) and custom-designed scripts to preprocess data. RETROICOR (Glover, Li, & Ress, 2000) was used to remove time-locked cardiac and respiratory artifacts, and RVHRCOR (Chang, Cunningham, & Glover, 2009) was used to remove low-frequency heart rate and respiratory volume artifacts. We discarded the first 6 TRs because of T1 equilibrium effects. We then applied slice timing correction, motion correction, skull-stripping, and linear and quadratic detrending. Functional scans were registered to the MNI152 average brain template (Mazziotta, Toga, Evans, Fox, & Lancaster, 1995). Motion files were used to 'censor' (remove) TRs in which the derivative value of any of six motion parameters (*x*-shift, *y*-shift, *z*-shift, rotation, pitch, yaw) exceeded a Euclidean norm of 1.2. Insomniacs and healthy controls did not differ in the number of TRs removed during the rest scan, $t(32) = 0.397$, or the 'fall asleep' scan, $t(32) = 1.792$, both $p > 0.05$.

Nuisance signal timecourses in spiral-in/out volumes arising from white-matter, and CSF were calculated from segmented anatomical scans and were regressed from spiral-in/out volumes along with the 6 motion parameters. The demeaned residuals were then subjected to Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) using FSL. We initially used the Laplace approximation to the Bayesian evidence of the model order to determine the number of components, but the length and resolution of the scans produced hundreds of components that proved impractical for analysis, as noted previously (Yourganov et al., 2011). Consequently, we selected 25 components for resting and 'fall asleep' scans based on previous dual regression studies (Filippini et al., 2009).

Visually identified components corresponding to known noise and artifacts resulting from scanner noise, movement, residual white matter or CSF signal, or residual physiological noise were filtered from the resulting volumes (Kelly et al., 2010). Given the size of the volumes and lengths of the scan, multiple noise components persisted after filtering; consequently, this procedure was repeated a total of three times on each scan session. The MELODIC component of dual-regression requires equivalent length data, thus excluding the use of motion-censored data blocks. Subsequent analyses that were later conducted on the original non-de-noised datasets indicated that the statistical contrasts did not differ from analyses conducted on de-noised datasets. Insomniacs and healthy controls did not differ in the number of noise components removed, $t(32) = 1.44$, $p > 0.05$.

2.4. fMRI analyses

All individual de-noised datasets from each scan were concatenated and decomposed into 25 spatiotemporal components for each of the two scan types. Components of interest were analyzed by dual regression (Filippini et al., 2009; Zuo et al., 2010). Briefly, the spatial maps derived from the temporal concatenation ICA were used to produce a timeseries for each component for each individual. Next, these timeseries were used to produce spatial maps of the corresponding component for each individual. A *z*-statistic of this resulting spatial map was subjected to non-parametric permutation testing, with 5000 permutations and a variance smoothing equal to the FWHM. The result of the permutation analysis is a test of between-group differences in each of the 25 component maps. Thresholding of group statistics was based on threshold-free cluster enhancement. Results are presented for clusters that reach a family-wise error corrected value of $p < 0.05$; uncorrected values of $p < 0.001$ are also shown for illustrative purposes.

2.5. EEG acquisition and preprocessing

EEG was acquired using a MRI-compatibile EGI HydroCel 256-electrode dense-array Geodesic Sensor Net at a sampling rate of 250 Hz. No signal quality decline was observed during the scan session. Using NetStation, the TR marker was used to filter out the MR artifact using a moving average of 5 TRs. Bad channels were visually identified and replaced with a spline interpolation. The resulting file was imported into the EEGlab toolbox in Matlab (R2011b). The first 6 and last 5 TRs, which remain contaminated with MR-related artifacts, were censored. The first three harmonics of the slice frequency (14.6 Hz, 29.3 Hz, 44.0 Hz) were removed using a finite impulse response (FIR) notch filter in Matlab. Using PPG markers, the ballistocardiographic artifact was removed using a principal components method (Niazy, Beckmann, Iannetti, Brady, & Smith, 2005), with an optimal basis set of 4 components. The resulting file was resampled to 125 Hz, re-referenced to average,