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Resting-state theta band connectivity and graph analysis in generalized social anxiety disorder

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ABSTRACT

Background: Functional magnetic resonance imaging (fMRI) resting-state studies show generalized social anxiety disorder (gSAD) is associated with disturbances in networks involved in emotion regulation, emotion processing, and perceptual functions, suggesting a network framework is integral to elucidating the pathophysiology of gSAD. However, fMRI does not measure the fast dynamic interconnections of functional networks. Therefore, we examined whole-brain functional connectomics with electroencephalogram (EEG) during resting-state.
Methods: Resting-state EEG data was recorded for 32 patients with gSAD and 32 demographically-matched healthy controls (HC). Sensor-level connectivity analysis was applied on EEG data by using Weighted Phase Lag Index (WPLI) and graph analysis based on WPLI was used to determine clustering coefficient and characteristic path length to estimate local integration and global segregation of networks.
Results: WPLI results showed increased oscillatory midline coherence in the theta frequency band indicating higher connectivity in the gSAD relative to HC group during rest. Additionally, WPLI values positively correlated with state anxiety levels within the gSAD group but not the HC group. Our graph theory based connectomics analysis demonstrated increased clustering coefficient and decreased characteristic path length in theta-based whole brain functional organization in subjects with gSAD compared to HC.
Conclusions: Theta-dependent interconnectivity was associated with state anxiety in gSAD and an increase in information processing efficiency in gSAD (compared to controls). Results may represent enhanced baseline self-focused attention, which is consistent with cognitive models of gSAD and fMRI studies implicating emotion dysregulation and disturbances in task negative networks (e.g., default mode network) in gSAD.

1. Introduction

Generalized social anxiety disorder (gSAD) is a common psychiatric illness characterized by inappropriate fears in a range of situations that involve potential scrutiny by others (Kessler et al., 2005; Stein and Stein, 2008). Cognitive models emphasize preferential processing of internal and external threat signals (e.g., negative thoughts, attentional bias to aversive faces; (Bögels and Mansell, 2004) as key to the development and maintenance of the gSAD (Clark and Wells, 1995; Hope et al., 1989). Accumulating data from task-based functional magnetic resonance imaging (fMRI) studies over the past decade involving negative stimuli indicate such bias is the result of frontolimbic disturbances resulting in limbic/paralimbic hyper-reactivity in emotion processing areas (e.g., amygdala, insula) and aberrant activation (hyper- or hypo-activity) in regions that regulate emotional response (e.g., anterior cingulate cortex, dorsolateral prefrontal cortex) (for review see Brühl et al., 2014).

The neurobiology of gSAD has also been informed with resting-state fMRI studies, which permit examination of intrinsic (spontaneous, task-independent) networks. Various studies have shown anomalous associations between spatially distant regions in gSAD suggesting the disorder involves baseline disruptions in distributed neural systems. For example, there is evidence of decreased frontolimbic functional connectivity and aberrant effective connectivity in gSAD relative to healthy controls (Ding et al., 2011; Hahn et al., 2011; Manning et al., 2015; Prater et al., 2013; Liao et al., 2010; Qiu et al., 2011; Zhang et al., 2015). Similarly, widespread alterations in task positive and negative systems (e.g.,

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dorsal attention network, default mode network, visual network) have been shown in gSAD (Anteraper et al., 2014; Liao et al., 2010; Liu et al., 2015a; Liu et al., 2015b). Taken together, fMRI findings indicate aberrant resting-state activity may underlie a threat-sensitive system in gSAD.

However, inferences of brain organization related to intrinsic activity are limited in fMRI due to its poor temporal resolution. That is, the millisecond to second time scales that reflect considerable information processing at rest are not captured with fMRI. A more appropriate technique is electroencephalogram (EEG), which assesses the fast and lagged spontaneous brain activity in time and frequency enabling the characterization of intrinsic neurocognitive networks (Koenig et al., 2005). Thus far, there has been little application of EEG in the study of gSAD at rest through limited research suggests electrophysiological patterns in gSAD differ from healthy controls. Using traditional power analysis, Sachs et al. (2004) reported a decrease in absolute and relative power in slow frequency bands (i.e., theta and delta) but higher intermediate beta absolute and average power in individuals with gSAD compared to healthy participants (Sachs et al., 2004). Evidence frequency-related vigilance effects (participants were aroused by auditory stimuli if drowsiness was detected) did not diminish at rest suggests gSAD is associated with hyperarousal (Sachs et al., 2004).

To date, there has been no EEG-based resting-state connectivity study in gSAD. Such a study is warranted as abnormal neurophysiological connectivity has been observed in internalizing conditions that share neurobiological features with gSAD (Etkin and Wager, 2007; Hamilton et al., 2015b). For example, individuals with major depressive disorder exhibit higher coherence (e.g., coupling) at rest relative to controls in delta, theta, alpha, and beta frequencies (Leuchter et al., 2012b). Similarly, posttraumatic stress disorder is associated with extensive increased theta and alpha connectivity at rest (Imperatori et al., 2014). Findings are proposed to reflect a loss of selectivity in functional networks, which may underlie symptomatology (e.g., cognitive impairment, emotion dysregulation, memory deficiencies) (Imperatori et al., 2014; Leuchter et al., 2012).

More recently, advances in analytic approaches have enabled the mapping of systems through which the brain is interconnected (i.e., connectomics), thereby increasing our understanding of the topological properties and oscillatory activity in different brain regions and whole-brain functional networks. Therefore, the main aim of the current study was to explore resting-state functional (dys)connectivity in gSAD with Weighted Phase Lag Index (WPLI). WPLI has been shown to circumvent sources of noise that may artificially induce functional connectivity such as volume conduction and reference electrode effects) (Guevara et al., 2005; Nunez et al., 1997) providing a more reliable index of phase synchronization (i.e., phase coupling)(Vinck et al., 2011). Specifically, WPLI measures the distribution of phase angle differences of two channels (i.e., electrodes) across frequency bands in different brain areas. If two channels' functional coupling is strong, the resulting connectivity index will be high in a given frequency domain (Cohen, 2013), which has pathophysiological significance. Phase-coupled activity is an important mechanism in the functional communication between brain regions (Fries, 2005; Gross et al., 2001; Power et al., 2012); thus, an essential aspect of the WPLI is the delineation of reliable estimators to determine the phase relationship between two signals. Given these properties, we applied graph theoretical measures to characterize complex networks (Bullmore, 2012; Bullmore et al., 2009) based on WPLI.

Accordingly, we examined Clustering Coefficient and Characteristic Path Length to identify the local integration and global segregation of networks where information processing efficiency is characterized by high local connectivity along with few long-range connections (Bullmore and Sporns, 2009). Additionally, we explored whether significant WPLI values or indices of global segregation and local integration network results correlated with anxiety measures in gSAD. A secondary aim was to assess whether regionally-based power across different frequency bands differed between individuals with gSAD and healthy controls.

2. Methods

2.1. Participants

All participants provided written informed consent as approved by the local Institutional Review Board at the University of Illinois at Chicago (UIC) and all procedures complied with the Helsinki Declaration. Diagnosis was based on the Structured Clinical Interview for DSM-IV ("SCID-IV"; First et al., 1995) and the clinician-administered Liebowitz Social Anxiety Scale ("LSAS"; Liebowitz, 1987) determined symptom severity. The self-reported Spielberger State-Trait Anxiety Inventory (Spielberger, 1983) and Beck Depression Inventory (Beck et al., 1996) were used to evaluate state anxiety, general anxiety, and depression levels, respectively. Participants were monetarily compensated for their time. Participants were between 18 and 55 years of age, free of major medical or neurologic illness as confirmed by a Board Certified physician. GSAD was required to be the primary diagnosis; however, comorbidity was permitted. All participants were free of psychotropic medications and none was engaged in psychotherapy. Healthy control (HC) participants were required to not have an Axis I disorder. Exclusion criteria for all participants were current substance abuse or dependence (within 6 months of study) or history of major psychiatric illness (e.g., bipolar disorder, psychotic disorder, pervasive developmental disorder).

2.2. EEG task

All participants underwent an 8-minute resting state recording session. Specifically, participants viewed a fixation cross on a blank background and were instructed to try not to think of anything in particular for the duration of the scan. All EEG data were recorded using the Biosemi system (Biosemi, Amsterdam, Netherlands) equipped with an elastic cap with 34 scalp channels.

2.3. EEG data processing

EEG data were preprocessed by the software *Brain Vision Analyzer* (Brain Products, Gilching Germany) and connectivity matrices were generated with the *MATLAB* toolbox *Fieldtrip* (Donders Centre for Cognitive Neuroimaging, Nijmegen, Netherlands). To evaluate phase lag synchronization (i.e., phase coupling) among electrode pairs, resting-state data was segmented into 7 second 'trials.' The minimum number was 15 segments (105 s), which is in the range of other resting-state studies (González et al., 2016; Hardmeier et al., 2014; Yu et al., 2016). All time points and segments were averaged accordingly to standard frequency bands: alpha (8–14 Hz), beta (13–30 Hz), theta (4–8 Hz) and delta (1 Hz–3 Hz).

2.4. Weighted phase lag index

Each index of weighted phased lag is characterized by the distribution of phase angle differences. The instantaneous phase lag and magnitude can be acquired through cross power density spectrums. The cross power density is defined as:

$$S_{xy}(\omega) = \lim_{T\to\infty} \frac{1}{T} E\{Y_x^*(\omega) Y_y(\omega)\} \quad (1)$$

where S_{xy} is the cross spectral density function between signals $y_y(t)$ and $y_x(t)$. $Y_x(\omega)$ in the finite Fourier transform of signal $y_x(t)$ at frequency ω, $Y_x^*(\omega)$ is the complex conjugate of $Y_x(\omega)$, and $E\{\}$ is the expectation. The cross power density is applied within each segment with the frequency of interest (i.e., 1 Hz–50 Hz).