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Research paper

The left middle temporal gyrus in the middle of an impaired social-affective communication network in social anxiety disorder

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ABSTRACT

Background: Previous studies on patients diagnosed with social anxiety disorder (SAD) reported changed patterns of the resting-state functional connectivity network (rs-FCN) between the prefrontal cortices and other prefrontal, amygdalar or striatal regions. Using a graph theory approach, this study explored the modularity-based community profile and patterns of inter-/intra-modular communication for the rs-FCN in SAD.
Methods: In total, for 28 SAD patients and 27 healthy controls (HC), functional magnetic resonance imaging (fMRI) data were acquired in resting-state and subjected to a graph theory analysis.
Results: The within-module degree z-score for a hub region [out of a total of 10 hub regions ranked using the participation coefficient] named left middle temporal gyrus was impaired in SAD compared to HC, proportional to the severity of clinician-scored and patient-reported functional impairment in SAD.
Limitations: Most of participants included in this study were undergraduate students in their early-to-mid 20's.
Conclusions: This study showed the importance of functional communication from the left middle temporal gyrus with other opercular-insular-subcortical regions for better objective functioning and lesser subjective disability in SAD.

1. Introduction

Social anxiety disorder (SAD) is a common mental disorder with a point prevalence of 4.4% and lifetime prevalence of 6.1% (Ohayon and Schatzberg, 2010; Stein and Stein, 2008). Patients diagnosed with SAD suffer primarily from a notable fear and avoidance of most social or performance situations; repeated experiences of anxiety and fear against social threat such as scrutiny by others, even in seemingly harmless situations, interferes substantially with occupational performance as well as social relationship, and impairs quality of life in SAD (Stein and Kean, 2000; Stein and Stein, 2008). What is worse, typical compensatory maneuvers by SAD patients such as conducting attentive self-monitoring or repeating ruminative self-reflection on their own behavior often result in amplified perception of interpersonal stress and increased expression of negative emotions in response to stressful social events (Farmer and Kashdan, 2015; Hackmann et al., 2000). Furthermore, standard treatments for SAD using cognitive behavioral therapy (CBT) and pharmacotherapy improve clinical symptoms only to a moderate degree and a large proportion of SAD patients continue to suffer (Blanco et al., 2010; Davidson et al., 2004; Heimberg et al., 1998). Therefore, advanced treatment approaches based on a more integrated understanding of the neural underpinning of SAD symptomatology are in great need.

Prior studies of functional connectivity network in SAD have been focused on the imbalanced communication between the limbic region of the amygdala versus other cortical regions (Hattingh et al., 2012) during the emotional decoding of angry or contemptuous facial stimuli (Prater et al., 2013; Stein et al., 2002), classical conditioning for socially threatening stimuli (Pejic et al., 2013), and emotional regulation in preparation for public speech (Cremers et al., 2015). Moreover, inefficient prefrontal control of attentional focus by non-threatening distractor (Bishop, 2009) as well as insular hyper-activation toward

Abbreviations: HC, healthy controls; MTG, middle temporal gyrus; rs-FCN, resting state functional connectivity network; SAD, social anxiety disorder

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inner-threatening cue [pulse-sound] in front of social situation [faces of crowd] (Choi et al., 2016) implied neural mechanism for the subjective misinterpretation of social situations in SAD underpinned the heightened awareness of fear-related interoceptive arousal and negative affective status despite effortful inner attempts at executive control (Diekhof et al., 2011; Yoon et al., 2016). However, a resting-state functional connectivity network (rs-FCN) approach, which reflects intrinsic functional brain organization in the lower-frequency [< 0.1 Hz] range during a task-free state (Biswal et al., 1995), demonstrated changed profile of functional crosstalk among broader brain regions in SAD (Fouche et al., 2013) encompassing the default mode network, salience and executive control networks, visual and sensorimotor networks, affective and reward networks (Liu et al., 2015b; Manning et al., 2015; Pannekoek et al., 2013; Peterson et al., 2014). Of note, altered strength of functional communication between the orbitofrontal cortex versus amygdala or executive control network components distinctively characterized SAD compared to HC (Geiger et al., 2016; Liu et al., 2015a). Furthermore, strength of the rs-FCN between amygdala and the anterior cingulate cortex was related to the intensity of social inhibition in general population (Blackford et al., 2014) as well as to the degree of symptom improvement in SAD after CBT or intranasal application of oxytocin (Dodhia et al., 2014; Klumpp et al., 2014; Whitfield-Gabrieli et al., 2015).

As a matter of fact, a recent pioneering study using the graph theory approach and modularity-based community detection successfully untangled the dynamic connectivity among cognitive and behavioral processes in SAD and demonstrated a primal role of orienting component of attention in the psychopathology of SAD by way of their influence toward the fear for and resultant avoidance of social situations (Heeren and McNally, 2016). However, there have been few studies on SAD to explore the graph theory-based global and regional rs-FCN network characteristics; the exact qualities of small-worldness reflecting the degree of balance between network integration [≈ lower average path length among the nodes in a network] versus functional segregation [≈ higher levels of triangular clustering constructed among the three neighboring nodes in a network] for rs-FCN network for SAD (Fornito et al., 2016) has not yet been clarified. Accordingly, this study aimed to explore the network characteristics of small-worldness and modularity-based community profile [in which each community was comprised of the non-overlapping groups of brain regions to maximize the number of within-group connection and minimizes the number of between-group connection in a network; a statistic term named modularity quantifies the degree to which a network could be subdivided into such clearly delineated communities] (Newman, 2006) for rs-FCN in SAD. In partcular, this study tried to elucidate a neural underpinning of functional impairment related to social anxiety symptoms in SAD, as reflected in the changed profile of inter- or intra-network functional communication between the hub brain regions versus other members of functional community.

2. Method

2.1. Participants

Using an internet-based advertisement targeting undergraduate students, we recruited a total of 28 patients diagnosed with SAD, and 27 HC who closely matched for age, sex, years of education with SAD. With clinical interview with a licensed psychiatrist, each participant was evaluated for diagnosis with SAD using DSM-IV-TR criteria [classified as SAD] or for confirmation of no prior history of/current morbidity with psychiatric disorders using DSM-IV-TR criteria [classified as HC]. Degree of psychopathology as well as for functional disability were also scored using various scales including the Liebowitz Social Anxiety Scale (LSAS) (Liebowitz, 1987), the Hamilton Anxiety Scale (HAM-A) (Bruss et al., 1994), and the Global Assessment of Functioning (GAF). In addition, a package of self-report questionnaires including the Social Interaction Anxiety Scale (SIAS), Social Phobia Scale (SPS), Brief Version of the Fear of Negative Evaluation Scale (B-FNE), Beck Depression Inventory (BDI), and Sheehan Disability Scale (SDS) were used to measure the degree of perceived anxiety for interpersonal interaction or social performance, degree of negative apprehension for negative evaluation from others, and severity of depressive symptomatology, and perceived severity of functional impairment in relation to the clinical symptoms of SAD, respectively (Beck et al., 1961; Leary, 1983; Mattick and Clarke, 1998; Park and Kim, 2010; Sheehan, 1983). No volunteer with a previous history or current diagnosis of a clinically meaningful medical or neurological diseases, years of education < 12 yrs, or a BDI total score ≥21 was included in this study (Hahn et al., 1986). This study was approved by the institutional review board of Gangnam Severance Hospital. Written informed consent was obtained from every participant after thorough information for this study was provided.

2.2. Functional magnetic resonance imaging (MRI) data acquisition and pre-processing

Using a whole-body 1.5-T MRI system (Signa Eclipse; GE Medical Systems, Milwaukee, WI, USA) with an echo-planar imaging sequence (64×64×30 matrix; TR/TE =2000/22 ms; FOV =240 mm; FA =90°), blood oxygen level-dependent (BOLD) signals during resting status functional MRI [rs-fMRI; participants were instructed to do nothing in particular and rest with both eyes closed] were acquired for a total of 5 min (a total of 150 slices) per participant. In addition, using the same MRI equipment, a high-resolution T1-weighted images using a fast spoiled gradient echo sequence (256×256×116 matrix; TR/TE =8.5/1.8 ms; FOV =240 mm; FA =12°) were also obtained.

We pre-processed the rs-fMRI data using Statistical Parametric Mapping 12 software (SPM12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). After initial exclusion of the first five slices, the remaining rs-fMRI image slices were corrected for slice timing, co-registered to the reference slice, realigned to Montreal Neurological Institute (MNI) anatomical space using a six-parameter rigid body affine transformation, normalized for signal intensity, and finally smoothed using a Gaussian kernel with 8-mm full-width-at-half-maximum (FWHM). Finally, using an in-house script running by way of Matlab R2014b (www.mathworks.com/products/matlab/), these preprocessed rs-fMRI data were band-pass filtered in terms of the temporal dimension [0.009–0.08 Hz], regressed out for the effects of head motion as well as for the nuisance signals from brain white matter, cerebrospinal fluid and global brain signal (Shin et al., 2014). Finally, regional time-series of processed BOLD signal for a total of 90 cerebral regions-of-interest (ROIs) comprising the Automated Anatomic Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) were extracted, to calculate the individual correlation matrix of resting state functional connectivity network consisting of Pearson's correlation coefficients [$r > 0$] between two different ROIs per participant.

2.3. Graph theory analyses

To examine the characteristics of rs-FCN for SADs and HCs in terms of small-world and modular organization, a total of five global network characteristics including (1) *gamma* [normalized characteristic path length; the number of processing steps between different brain regions along the routes of functional connectivity, normalized as a ratio to values calculated from 1000 randomly rewired null model] (Rubinov and Sporns, 2010; Maslov and Sneppen, 2002), (2) *lambda* [normalized clustering coefficient; the fraction of triangles comprised of the neighboring brain regions in local network, averaged across the whole brain and normalized as a ratio to values calculated from 1000 randomly rewired null model] (Watts and Strogatz, 1998; Maslov and Sneppen, 2002), (3) *sigma* (small-worldness = *gamma*/*lambda*), (4) *Eglob* [normalized global efficiency; the average of the inverse shortest

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