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Looking at the self in front of others: Neural correlates of attentional bias in social anxiety

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In social anxiety disorder (SAD), anxiety reactions are triggered by attentional bias to social threats that automatically appear in social situations. The present study aimed to investigate the neural basis and underlying resting-state pathology of attentional bias toward internal and external social threats as a core element of SAD. Twenty-two patients with SAD and 20 control subjects scanned functional magnetic resonance imaging during resting-state and while performing the visual search task. During the task, participants were exposed to internal threat (hearing participants' own pulse-sounds) and external threat (crowds in facial matrices). Patients showed activations in the lateral orbitofrontal cortex, rostral anterior cingulate cortex and insula in response to internal threat and activations in the posterior cingulate cortex and middle temporal gyrus in response to external threat. In patients, neural activity related to combined internal and external threats in the posterior cingulate cortex was inversely correlated with the functional connectivity strengths with the default mode network during resting-state. These findings suggest that attentional bias may stem from limbic and paralimbic pathology, and the interactive process of internally- and externally-focused attentional bias in SAD is associated with the self-referential function of resting-state.

1. Introduction

Social anxiety disorder (SAD) is characterized by fear and avoidance of social situations (Stein and Stein, 2008). The roles of emotional hyper-reactivity and emotional dysregulation in response to threat stimuli have been highlighted in SAD (Etkin and Wager, 2007; Freitas-Ferrari et al., 2010). Social anxiety-provoking situations have shown to be related to increased activity in limbic and paralimbic regions, including the amygdala, insula and anterior cingulate cortex (ACC) (Freitas-Ferrari et al., 2010), and reduced cognitive reappraisal-related neural activation in the dorsolateral prefrontal cortex (DLPFC) and dorsal ACC in SAD (Goldin et al., 2009). However, neural correlates of cognitive distortion, another key feature of SAD (Clark and McManus, 2002; Rapee and Heimberg, 1997), have not been studied.

Attentional bias to social threats, as an initiator of cognitive distortion, is central to social fear (Clark and Wells, 1995; Heeren et al., 2015b; Rapee and Heimberg, 1997). The role of attentional bias to threat has been implicated in the development, maintenance, and remediation of anxiety pathology (Dudeney et al., 2015). Furthermore, a growing body of research has accumulated on the clinical capability of attentional bias modification in SAD (Heeren et al., 2015c). Patients with SAD often pay attention to how they come across to audiences through self-monitoring of inner threat cues, such as interoceptive information, self-imagery and negative thoughts, and if sufficient attentional resources are allocated to this self-monitoring, social performance is impaired (Schultz and Heimberg, 2008). One of the critical attentional processes in social situations is an "internal focus" on these inner cues, and the other is an "external focus" on environmental threats, such as negative evaluations of others (Schultz and Heimberg, 2008). Contrary to the relatively consistent findings for the excessive internal focus in SAD (Hackmann et al., 2000; Hirsch et al., 2003; Ingram, 1990; Mansell et al., 2003; McEwan and Devins, 1983), mixed results including attention towards or away from external

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threats have been reported for the external focus (Chen et al., 2002; Mansell et al., 2003; Mogg and Bradley, 2002; Mogg et al., 2004; Pineles and Mineka, 2005; Spector et al., 2003). Internal and external focuses have been explored in relative isolation, providing little opportunity for the examination of the potential interactive relationship. Besides, the corresponding neuronal mechanisms underlying these attentional biases in SAD remain unknown. Neurocognitive model of selective attention to threat suggests that the amygdala has a role in strengthening a threat-detection and the lateral prefrontal cortex and rostral ACC involve in attentional control to focus target stimuli rather than threat-related distractor (Bishop, 2008). Thus, it is expected that these regions would contribute to attentional biases in SAD.

When it comes to the global brain dynamics, frontoparietal control network and dorsal attention network have shown a contrary action to the default mode network (DMN) (Hellyer et al., 2014). The DMN is a group of regions including the midline structures that are more active at rest than during attention-based tasks (Raichle et al., 2001). Since this intrinsically organized network is responsible for a processing of introspective thoughts during resting-state (Mason et al., 2007), the DMN would have a pivotal role in the first step of allocation of attentional process when facing social threats. A simultaneous task- and resting-state study showed a dynamic change in the relationship between frontoparietal control and default networks during social working memory as social load increased from resting-state (Xin and Lei, 2015). Resting-state connectivity between the DMN and task-positive network also predicted behavioral performance in working memory (Sala Llonch et al., 2012). Therefore, resting-state connectivity between the DMN and regions related to attentional bias may reflect a pathological precondition of SAD.

In order to investigate the neural basis of attentional bias toward internal and external social threats in SAD, the present study was designed to combine activation and resting-state studies using functional magnetic resonance imaging (fMRI). As facial crowds of emotion are linked to fears of socially anxious individuals, a face-in-the-crowd-effect task (Gilboa-Schechtman et al., 2005; Pinkham et al., 2010) for detecting a target face among distracter faces was used as a social anxiety-provoking paradigm during fMRI. During the task, participants' own pulse-sounds and the crowdedness of the faces were used as internal and external focuses, respectively. We hypothesized that the provocation of attentional bias would be related to activations in attention modulation-related and limbic regions, including the lateral prefrontal and cingulate cortices, amygdala, and insula. In addition, these activations would have specific associations with intrinsic DMN activity. We also predicted that neural activations during attentional bias would contribute to clinical manifestation, including cognitive/emotional distress and functional disability, as well as social anxiety symptom.

2. Materials and methods

2.1. Participants and measurements

Participants (22 patients with SAD and 20 healthy controls) were recruited from the community through an advertisement on the internet message board of the local universities and the internet board for part-time job which is popular for undergraduate students. They were screened using self-report questionnaires, including the Social Interaction Anxiety Scale (SIAS) and Social Phobia Scale (SPS) (Mattick and Clarke, 1998), Brief version of the Fear of Negative Evaluation scale (B-FNE) (Leary, 1983), and Beck Depression Inventory (BDI) (Beck et al., 1961). SIAS is a 20-item questionnaire measuring the level of anxiety in interpersonal interactions with cutoffs of 34 or more indicative of SAD. SPS consists of 20 items that measure performance anxiety with cutoffs of 24 indicative of SAD. FNE was developed to measure apprehension about negative evaluation (Watson and Friend, 1969), and we used cutoffs of 48 on a 12-item of its brief version to exclude social anxiety trait in healthy controls. Twenty-one-item BDI was employed to exclude depressive disorder in any participant, and a cutoff score of 21 was proposed for Korean population (Hahn et al., 1986). The inclusion scores were SIAS $\geq$34 and/or SPS $\geq$24 in patients; SIAS <34, SPS <24, and B-FNE <48 in controls; and BDI <21 and years of education $\geq$12 in both groups. The exclusion criteria for both groups included any past or present history of medical or neurological or psychiatric illness (other than SAD). Patients were diagnosed using DSM-IV-TR criteria (First et al., 1997), and controls were given a clinical assessment to confirm absence of psychiatric illnesses by a clinical interview with a psychiatrist (Choi SH). Psychopathological symptoms were assessed using the Liebowitz Social Anxiety Scale (LSAS; a 24-item measure on fear and avoidance of a range of social interaction and performance situations) (Liebowitz, 1987) and Hamilton Anxiety Scale (HAS, a 14-item scale for psychic and physical anxiety) (Hamilton, 1959). Functional disability and intelligence were measured using the Global Assessment of Functioning (American Psychiatric Association, 2000) and Raven's Progressive Matrices (Raven et al., 1988), respectively. Socioeconomic status of participants and their parents were collected using a 5-level scale (Class I = highest level, Class V = lowest level). All participants were medication-naïve and right-handed. As presented in Table 1, demographic variables including age, sex, education, ratio of undergraduate students, socioeconomic status, and intelligence level were not statistically different between the two groups. Patients showed higher scores on HAS and BDI as well as social anxiety scores than controls. This study was approved by the institutional review board of Severance Hospital, and written informed consent was obtained from all participants.

2.2. The behavioral task during fMRI

Before scanning, all participants completed the Subjective Units of Disturbance Scale (Wolpe, 1969) to assess subjective distress, and their baseline pulse rates were measured. At first, resting-state fMRI was scanned for 5 min, in which participants were instructed to take a rest and allow thoughts to come and go freely with their eyes fixed on a cross-hair on the screen. Then, task fMRI was scanned during the face-in-the-crowd-effect task (Fig. 1). Participants' responses were to press a left or right button, depending on whether they detected the target or not during a 2.5-s presentation of facial crowds. A 0.5-s visual feedback followed after each trial. The target was a contemptuous face over the entire period of the task because it was previously shown to be a salient emotional cue in SAD (Goldin et al., 2009; Stein et al., 2002). Given that patients with SAD have enhanced vigilance and strong neural responses to angry faces relative to happy faces (Goldin et al., 2009; Mogg et al., 2004; Phan et al., 2006), the angry- and happy-facial crowds were used as the experimental and control conditions of distracters, respectively. The angry-versus happy-crowd contrast was used for the single-subject first-level analyses to obtain estimated parameter weights for the next step. This contrast is needed because task fMRI only provides information about changes in activation over time. The angry-versus happy-crowd contrast used to obtain linear contrasts distinguished the brain's response to aversive stimuli (angry faces) and its response to non-aversive stimuli (happy faces) while controlling for other physical features and cognitive processes (e.g., Phan et al., 2006). Although this contrast can yield neural responses that originate from the difference in attentional capture by angry crowds as well as in vigilance to angry faces (Pinkham et al., 2010), both would be suitable for the present study