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Altered brain functional connectivity in relation to perception of scrutiny in social anxiety disorder

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ABSTRACT

Although the fear of being scrutinized by others in a social context is a key symptom in social anxiety disorder (SAD), the neural processes underlying the perception of scrutiny have not previously been studied by functional magnetic resonance imaging (fMRI). We used fMRI to map brain activation during a perception-of-scrutiny task in 20 SAD patients and 20 controls. A multi-dimensional analytic approach was used. Scrutiny perception was mediated by activation of the medial frontal cortex, insula–operculum region and cerebellum, and the additional recruitment of visual areas and the thalamus in patients. Between-group comparison demonstrated significantly enhanced brain activation in patients in the primary visual cortex and cerebellum. Functional connectivity mapping demonstrated an abnormal connectivity between regions underlying general arousal and attention. SAD patients showed significantly greater task-induced functional connectivity in the thalamo-cortical and the fronto-striatal circuits. A statistically significant increase in task-induced functional connectivity between the anterior cingulate cortex and scrutiny-perception-related regions was observed in the SAD patients, suggesting the existence of enhanced behavior-inhibitory control. The presented data indicate that scrutiny perception in SAD enhances brain activity in arousal–attention systems, suggesting that fMRI may be a useful tool to explore such a behavioral dimension.

1. Introduction

Social anxiety disorder (SAD) is a prevalent and disabling psychiatric illness (Stein, 2006) characterized by heightened fear and avoidance of social situations, such as speaking in public, meeting people or attending gatherings. Typically, SAD patients demonstrate anxious behavior when faced with the prospect of becoming the focus of attention and being evaluated by other people. Specifically, the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 2000) defines SAD as a "marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others".

However, SAD patients often report a sense of uneasiness and anxiety arising from their concern as to how others will perceive them, even in non-performance situations, and merely on the basis of having their physical appearance judged by other individuals (Leary and Kowalski, 1995). Such concern, dubbed as public self-consciousness (Theron et al., 1991), may be generated in certain situations, such as being in a waiting room with people, where no performance is required and it is merely the person's physical self that is exposed to judgment by others. In this sense, the SAD population reports lower self-physical attractiveness than in the ratings made by observers (Rapee and Abbott, 2006). Other studies in SAD (beyond functional magnetic resonance imaging (fMRI)) involving scrutiny perception situations with no required performance demonstrate high levels of fear and avoidance behavior merely upon eye contact (Schneier et al., 2011) or even in virtual situations where there

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is no real, direct contact with another person (Wieser et al., 2010). Virtual reality exposure has been widely used in the treatment of social phobia, to reproduce such situations (for a recent review, see de Carvalho et al., 2010).

Consistent with the clinical definition, activity in fear-related brain circuits has been assessed by functional imaging during performance or exposure to socially relevant stimuli, such as public speaking (Tillfors et al., 2001), speech anticipatory anxiety (Tillfors et al., 2001; Lorberbaum et al., 2004), language-based criticism stimuli (Blair et al., 2008a), and responses to facial expressions, as relevant elements of social interaction (Straube et al., 2004a; Amir et al., 2005; Phan et al., 2006; Campbell et al., 2007; Stein et al., 2007; Blair et al., 2008b; Evans et al., 2008; Pujol et al., 2009a). The research has revealed enhanced neural activity in neuronal systems related to the amygdala, whose responsivity suggests a biased processing of social information possibly related to the disorder (Cooney et al., 2006; Kober et al., 2008). Recent advances in neuroimaging coincide in their reports of alterations in limbic and paralimbic regions in SAD, as well as in prefrontal and striatal regions, thus highlighting the complexity of the pathology, and the cortico-subcortical pathways still constitute a wide field to be researched within the framework of SAD (for a review, see Freitas-Ferrari et al., 2010).

Although static images of negative facial expressions are indeed a relevant social cue to reveal a person's disapproval of others, they capture a partial aspect of the fear-related systems in SAD samples in a social context. Despite some shared key features, the perception of being publicly scrutinized triggers an exaggerated fear when the individual is confronted with an external audience, and constitutes a common day-to-day situation that SAD patients attempt to avoid. In such a context, the goal of the present study was to directly examine brain activity by fMRI under real exposure to scrutiny by other people in SAD.

When confronting unfamiliar and/or feared settings, the socially phobic individual demonstrates increased reactivity, self-reporting an enhanced physical arousal (Edelmann and Baker, 2002); however, the essential feature of SAD (the fear of being scrutinized) has not been directly investigated using fMRI. Therefore, we developed a novel fMRI paradigm primarily to examine whether the mere perception of being scrutinized is associated with alterations in the attention and arousal thalamo-related networks in SAD patients. In a very recent study of general emotion processing in SAD, the perceptual-attention domain comprising the thalamus was found to be altered (Brühl et al., 2011).

Because standard statistical parametric mapping (SPM) analysis of task-related activation only partially evaluates possible brain fMRI abnormal responses, a whole-brain functional connectivity analysis was also performed. Three specific objectives were considered: (a) to evaluate possible brain activation enhancement in the SAD group while under scrutiny; (b) to assess between-group differences in task-induced functional connectivity by means of psychophysiological interaction (PPI) analyses; and (c) to test for possible between-group differences in functional connectivity considering the whole fMRI run as a global "modulated resting-state" context. We hypothesize that the perception of being under scrutiny will affect brain activation and functional connectivity in neural systems associated with the management of emotionally aversive situations, including arousal systems, fear brain circuits and related cortico-subcortical neuronal networks engaged in the top-down regulation of emotional response (Goldin et al., 2008; Kober et al., 2008; Brühl et al., 2011).

On the basis of the context-dependent change in our current fMRI task (scrutiny on/off), a PPI analysis was included to ascertain whether the effect of a specific influencing region upon another depends on the experimental context. Interestingly, the PPI approach has proved to be very useful in assessing for the modulation of thalamo-cortical systems in response to fear signals (Das et al., 2005). Finally, in keeping with previous evidence that abnormal sustained emotion-related responses are longer than the stimulus duration in certain pathologies (Pujol et al., 2009b), we suspect that the sensation of being scrutinized may evoke brain responses extending beyond the scrutiny blocks, inducing both an abnormal, sustained anxious and arousal-related state for the whole assessment period. We therefore performed a seed-based correlation mapping analysis in order to capture the functional connectivity between different brain regions across the task as a whole "modulated resting-state" (interpreting the scanning as "steady-state" time series data). Thus, functional connectivity assessments may be complementary to conventional neuroimaging characterizing brain dysfunctions in SAD.

2. Methods

2.1. Subjects

A sample of 20 patients with generalized SAD was included. The patients' mean score on the Liebowitz Social Anxiety Scale (LSAS) (Liebowitz, 1987) was 80.7 points (S.D. = 16.2, range: 55–113). All subjects were right-handed.

Inclusion criteria were: (a) outpatients with a primary psychiatric diagnosis of SAD (American Psychiatric Association, 2000; DSM-IV-300.23) in conjunction with the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), (b) LSAS score ≥ 50, and (c) men or women aged between 18 and 60 years. Patients with relevant medical or neurological disorder, substance abuse or other psychiatric illness were not considered for inclusion. Specifically, subjects who meet DSM-IV criteria for diagnosis of any other Axis I disorder such as dysthymia, simple phobia, major depression, obsessive-compulsive disorder, body dysmorphic disorder, or panic disorder as a primary diagnosis currently or within 6 months prior to the screening visit were not included. Also, subjects receiving any current psychotherapy or pharmacologic treatment were not included.

A group of 20 reference healthy volunteers were matched by age and educational status, and comparable by gender, were evaluated under the same health restrictions. The mean score on the LSAS for controls was 11.8 points (S.D. = 8.5, range: 1–35). Subjects of both groups who scored ≥ 15 on the Hamilton Depression Scale (HamD-17) at screening were excluded. For a description of sample characteristics, see Table 1.

All participants were included into the study via public media advertisement. Subjects were instructed to refrain from tobacco, alcohol and caffeine 12 h before the fMRI session. Written informed consent was obtained from all the participants. The study was approved by the local Ethics Committee Clinical Research Ethical Committee-Institut Municipal d'Assistència Sanitària (CEIC-IMAS), Barcelona), and in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Behavioral assessments

2.2.1. Spielberger State-Trait Anxiety Inventory (STAI-S) pre fMRI

The Spielberger State-Trait Anxiety Inventory (STAI-S) (Spielberger et al., 1983) was administered before fMRI scanning to measure state-anxiety levels related to the immediate fMRI scanning situation.

Table 1
Characteristics of subject populations.

Variable	SAD group ($N = 20$)	Control group ($N = 20$)	p[a]
	M (S.D.)/N (%)	M (S.D.)/N (%)	
Age (years)	24.15 (5.22)	24.40 (5.59)	0.87
Gender (M/F)	5/15	6/14	0.72
Education level: Superior studies	20 (100%)	20 (100%)	n.a.
SAD age of onset (years)	9.72 (5.11)	–	n.a.
Illness duration (years)	14.61 (7.15)	–	n.a.
HamD-17	3.10 (2.17)	0.90 (1.67)	<0.0005
PHQ-15	5.05 (3.47)	–	n.a.
CGI-S			n.a.
Moderately ill	6 (30%)	–	
Markedly ill	9 (45%)	–	
Severely ill	5 (25%)	–	

Abbreviations: CGI-S: Clinical Global Impression-Severity Scale; HamD-17: 17-item Hamilton Rating Scale for Depression; PHQ: 15-item Patient Health Questionnaire. n.a.: not applicable.

[a] Mann–Whitney U and Chi-Square, 2-tailed, between SAD patients and healthy controls.