Amygdala activation and its functional connectivity during perception of emotional faces in social phobia and panic disorder

L.R. Demenescu [a,b,*], R. Kortekaas [b], H.R. Cremers [c,d], R.J. Renken [b], M.J. van Tol [b,e], N.J.A. van der Wee [f,g], D.J. Veltman [h], J.A. den Boer [i], K. Roelofs [c], A. Aleman [b,j]

[a] Department of Psychiatry, Psychotherapy and Psychosomatics, University Hospital Aachen, RWTH Aachen University, Germany
[b] Department of Neuroscience, Neuroimaging Center, University Medical Center Groningen, University of Groningen, The Netherlands
[c] Radboud University Nijmegen, Behavioural Science Institute (BSI), Nijmegen, The Netherlands
[d] Department of Psychiatry, The University of Chicago, Chicago, IL, USA
[e] Leibniz Institute for Neurobiology, Otto von Guericke University, Magdeburg, Germany
[f] Department of Psychiatry, Leiden University Medical Center, The Netherlands
[g] Leiden Institute for Brain and Cognition, Leiden University Medical Center, The Netherlands
[h] Department of Psychiatry, Amsterdam VU University Medical Center, The Netherlands
[i] Department of Psychiatry, University Medical Center Groningen, The Netherlands
[j] Department of Psychology, University of Groningen, The Netherlands

ARTICLE INFO

ABSTRACT

Social phobia (SP) and panic disorder (PD) have been associated with aberrant amygdala responses to threat-related stimuli. The aim of the present study was to examine amygdala function and its connectivity with medial prefrontal cortex (mPFC) during emotional face perception in PD and SP, and the role of illness severity. Blood oxygen level dependent responses while perceiving emotional facial expressions were compared in 14 patients with PD, 17 patients with SP, 8 patients with comorbid PD and SP, and 16 healthy controls. We found that PD, but not SP, was associated with amygdala and lingual gyrus hypoactivation during perception of angry, fearful, happy and neutral faces, compared to healthy participants. No significant effect of PD and SP diagnoses was found on amygdala−mPFC connectivity. A positive correlation of anxiety symptom severity was found on amygdala-dorsal anterior cingulate and dorsal mPFC connectivity during perception of fearful faces. Amygdala hypoactivation suggests reduced responsiveness to positive and negative emotional faces in PD. Symptom severity, but not the presence of PD and SP diagnosis per se, explains most of the abnormalities in amygdala−mPFC connectivity during perception of fearful faces.

1. Introduction

Social phobia (SP) has a prevalence of 12.1%, panic disorder (PD) of 4.7% (Kessler et al., 2005) and they frequently co-occur (Schneier et al., 1992). These anxiety disorders are characterized by an "alarm response [that normally occurs in response] to present or imminent danger" (Craske et al., 2009). However a clear distinction exists between SP and PD (Mannuzza et al., 1990). SP is characterized by extreme fear of negative evaluation and a resulting avoidance of social or performance situations. PD is characterized by recurrent, spontaneous panic attacks which are acute episodes of intense fear accompanied by physical as well as cognitive symptoms (American Psychiatric Association [DSM-IV], 2000). Moreover, given the low recovery rate of SP (Beard et al., 2010) and the favorable improvement rate, but frequent recurrence, for PD (Francis et al., 2007), understanding the neural networks associated with these disorders is of importance.

As a key brain structure involved in processing threat-related stimuli (LeDoux, 2000), the amygdala is likely to play a role in the aforementioned anxiety disorders. Neuroimaging studies in subjects with SP using faces reported amygdala hyperactivation in response to angry (Stein et al., 2002), fearful (Campbell et al., 2007), happy (Straube et al., 2005) and neutral (Cooney et al., 2006; Birbaumer et al., 1998) faces. With regard to PD, Kent and Rauch (2003) in their review hypothesized that PD might be

associated with abnormal amygdala function. In support of this hypothesis, amygdala hyperactivity has been reported during emotional conflict (Chechko et al., 2009) and during spontaneous panic attacks (Pfleiderer et al., 2007; Dresler et al., 2011) in PD. On the other hand, amygdala hypoactivation has been reported during anticipatory anxiety (Boshuisen et al., 2002) and in response to fearful faces (Pillay et al., 2006) in PD patients compared to healthy volunteers. The limited number of studies and the diversity of tasks make it difficult to draw a conclusion on the neural mechanism of emotional processing associated with PD. However, based on the existing literature it can be suggested that amygdala dysfunction is a key element of a shared mechanism involved in PD and SP.

Furthermore, abnormal neural responses in anxiety disorders have been reported in brain areas involved in attention and processing of facial features (prefrontal areas and fusiform gyrus [Gentili et al., 2008]), and emotional experience (insula [Straube et al., 2004; Etkin and Wager, 2007; Amir et al., 2005]). Anterior cingulate cortex (ACC) hyperactivation to disgusted faces has been reported in SP (Amir et al., 2005). In PD, aberrant ACC activation was reported in response to anticipatory anxiety, at rest (Boshuisen et al., 2002) and during an emotional conflict task (Chechko et al., 2009; van den Heuvel et al., 2005). From the above mentioned studies, we might conclude that not only the amygdala plays an important role in anxiety disorders, but that several other regions, including frontal areas, are also part of the neural mechanism associated with anxiety disorders.

Disrupted connectivity between amygdala and medial prefrontal cortex (mPFC) including ACC has been related to anxiety (Kim et al., 2011). Moreover, anxiety was associated with a negative amygdala–ventral mPFC connectivity, suggesting impaired emotion regulation, and a positive amygdala–dorsal mPFC connectivity, indicating hypervigilance to external stimuli (Straube et al., 2009). In addition, SP has been associated with a distinct right-sided abnormal functional connectivity between amygdala and superior temporal cortex, inferior parietal and middle PFC (Danti et al., 2010). In PD amygdala functional connectivity with brain areas involved in emotional processing is not clearly delineated. Gorman et al. (2000) in their review proposed that the "fear network", involving amygdala as a main center and its interaction with mPFC, is central to PD.

The present study takes a step forward in understanding the neural mechanism of emotional processing associated with SP and PD, by not only looking at the individual brain areas, but also at their interaction. In particular, the present study aims to examine the pattern of brain activation and the coupling of amygdala response to mPFC regions during emotional face perception as an effect of SP and PD diagnoses. Additionally, we examined the extent to which the abnormalities in the neural network involved in emotional processing are related to anxiety severity rather than diagnosis-related factors. Moreover, by including not only patients with a diagnosis of PD or SP only, but also patients with PD and SP comorbidity, we aimed to determine whether there is a diagnosis-independent neural mechanism of disturbed emotional processing across anxiety disorders. Based on the literature, we hypothesized elevated amygdala, ACC and insula activation in response to angry, fearful, happy and neutral faces in SP. In PD abnormal amygdala activation was hypothesized to be limited to perception of fearful faces. Additionally, we expected abnormal coupling of amygdala–mPFC including the ACC during perception of emotional faces to be a common factor in anxiety disorders. For patients, we hypothesized that anxiety symptom severity would modulate amygdala response and its functional connectivity during perception of negative emotional faces.

2. Materials and methods

2.1. Participants

Participants were selected from the database of the Netherlands Study of Depression and Anxiety (NESDA, Penninx et al., 2008). Three centers participated: University Medical Center Groningen (UMCG), Amsterdam Medical Center (AMC) and Leiden University Medical Center (LUMC). The Ethical Review Board of each center approved the study. Inclusion criteria were: 1) age range 18–57 years, 2) no history of seizures or brain injury, 3) no criteria for any DSM axis I disorders other than social phobia (SP) and panic disorder with or without Agoraphobia (PD) (generalized anxiety disorder [GAD] was not an exclusion criterion), 4) no substance abuse, 5) no physical limitations that prohibited them from undergoing an fMRI examination and 6) no use of antidepressant or anxiolytic medication. Although in the NESDA fMRI study the use of selective serotonin reuptake inhibitors and infrequent benzodiazepine use (three times a week or within 48 h before the scanning) was not an exclusion criterion, in the present analyses these patients were excluded ($n = 18$ patients), to exclude the confounding effects of medication. All subjects were native Dutch speakers. After receiving written information, each participant gave written informed consent.

Seventeen patients diagnosed with SP, fourteen patients diagnosed with PD and eight patients with a double diagnosis — SP + PD — were included in the present study. The diagnosis was established by trained clinical staff on the basis of the Composite International Diagnosis Interview (CIDI) — lifetime version 2.1 (Andrews and Peters, 1998) in accordance with DSM-IV criteria (American Psychiatric Association [DSM-IV], 2000). All patients met the criteria for primary SP and/or PD. Sixteen healthy controls (HC) were selected from 65 HC included in the whole NESDA MRI study (Demenescu et al., 2011; van Tol et al., 2011a,b) and this group was matched on sample size, age, educational level and gender. Healthy controls did not meet the criteria for any current Axis I disorder and had no history of psychiatric disorders.

Before the scanning session, all participants were evaluated by means of a battery of standardized questionnaires and structured interviews. Beck Anxiety Inventory (BAI, Beck et al., 1988), Fear Questionnaire (FQ, Marks and Mathews, 1979) and Montgomery–Åsberg Depression Rating Scale (MADRS, Montgomery and Åsberg, 1979) were administered to all participants.

2.2. Stimuli and paradigm

A detailed description of the paradigm has been published elsewhere (Demenescu et al., 2011). Briefly, the paradigm consisted of 120 color photographs of angry, fearful, sad, happy and neutral faces and 80 scrambled faces (control condition). The photographs were selected from the Karolinska Directed Emotional Faces System (Lundqvist et al., 1998). Twenty-four photographs were presented for each facial expression of emotion depicted by twelve female and twelve male actors. Photographs were presented pseudorandomly against a black screen for 2.5 s with an inter-stimulus (black screen) interval varying between 0.5 and 1.5 s (Wolfensberger et al., 2008). Participants were instructed to indicate the actor's gender. During the scrambled faces, participants had to press the corresponding button as indicated on the screen, i.e., an arrow pointing left or right. The faces paradigm was part of a larger MRI exam and was preceded by a planning (van Tol et al., 2011a) and a memory (van Tol et al., 2011b) paradigm.