Journal of Affective Disorders 152-154 (2014) 454–461

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

The neural representation of emotionally neutral faces and places in patients with panic disorder with agoraphobia

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ARTICLE INFO

Article history:
Received 8 May 2013
Received in revised form
7 October 2013
Accepted 8 October 2013
Available online 16 October 2013

Keywords:
fMRI
Panic disorder with agoraphobia
Emotional processing
Neutral stimuli

ABSTRACT

Background: Panic disorder with agoraphobia (PD-A) has been associated with abnormal neural activity for threat-related stimuli (faces, places). Recent findings suggest a disturbed neural processing of emotionally neutral stimuli at a more general level.
Methods: Using functional magnetic resonance imaging (fMRI) we investigated the neural processing of emotionally neutral faces and places in PD-A. Fifteen patients with PD-A and fifteen healthy subjects participated in the study.
Results: When they perceived neutral faces and places, the patients with PD-A showed significantly less brain activity in the fusiform gyrus, the inferior occipital gyrus, the calcarine gyrus, the cerebellum, and the cuneus compared with the healthy controls. However, the patients with PD-A showed significantly more brain activity in the precuneus compared with controls subjects.
Limitations: It was not possible to distinguish the agoraphobia-associated effects from possible contributions due to general anxiety induced by fMRI. For future investigations, an additional clinical control group with patients suffering from panic disorder without agoraphobia would be of interest. In addition, the psychopathology concerning the agoraphobic symptoms needs to be investigated in more detail.
Conclusions: The findings suggest altered neural processing of emotionally neutral faces and places in patients with PD-A. Reduced neural activity in different brain regions may indicate difficulties in recognizing the emotional content in face and place stimuli due to anxiety-related hyper-arousal.

1. Introduction

A large number of studies have focused on the neurobiology of panic attacks (Gorman et al., 2000) or the processing of emotional stimuli in panic disorder (Pillay et al., 2006, 2007). The neuroanatomical model of panic disorder with agoraphobia (PD-A) postulates a dysfunctional coordination between prefrontal cortical and limbic structures. This leads to an abnormally sensitive fear network which includes the cingulate and the medial prefrontal cortex, the insula, the thalamus, and the amygdala as well as projections to the brainstem and the hypothalamus (Gorman et al., 2000). The amygdala plays a key role in this neuroanatomical model of fear as it evaluates incoming sensory stimuli with regard to potential threat (Larson et al., 2006; LeDoux, 2000). The precise neurobiological mechanisms underlying PD-A have rarely been studied, and the results are inconclusive, even though the symptoms are highly impairing (Wittchen et al., 2008).

For panic disorder, the few existing studies applying functional brain imaging techniques differ in their included patients (panic disorder patients with and without agoraphobia) and used different paradigms such as an exposure paradigm in patients with PD-A (Bystritsky et al., 2001; Wittmann et al., 2011). In patients with panic disorder without agoraphobia (PD) a cognitive paradigm (Van den Heuvel et al., 2005) and visual facial stimuli (Pillay et al., 2006, 2007) have been investigated. All paradigms focused on the emotional processing that was proposed to be affected at a more general level in PD with or without agoraphobia (Roy-Byrne et al., 2006). Concerning emotional processing, the dysfunctional coordination between the prefrontal cortex and the limbic structures in the neuroanatomical model of PD-A was hypothesized to be the underlying mechanism for an attention shift towards fearful stimuli. In addition, the dysfunctional network also leads to an overproportional anxiety triggered by even non-fearful stimuli (Bouton et al., 2001;Chechko et al., 2009). The empirical results on

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0165-0327/$ - see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.jad.2013.10.016

the attentional bias in PD-A are inconsistent. On remitted PD-A an attentional bias was observed by Chechko et al. (2009), which could not be replicated on acute PD by De Cort et al. (2008). Concerning distractibility the results are contrasting as well. A larger distractibility was accompanied by a stronger limbic response in PD-A patients (Van den Heuvel et al., 2005), which could not be replicated by Dresler et al. (2013) in panic disorder patients with and without agoraphobia.

The frequently used method for probing neurobiological responses to emotional perception involves the use of faces (Ekman and Friesen, 1976). During general face- processing, healthy individuals showed greater neural activity in the middle fusiform gyrus and the inferior occipital gyrus (Rossion et al., 2003). Since highly anxious healthy subjects showed a reduced ability to process the emotional content of faces, including happy faces (Rossignol et al., 2005), face processing was investigated for PD with agoraphobia (PD-A). Hereby, patients exclusively diagnosed with PD without agoraphobia (PD) showed significant differences in the neural activation for neutral, happy, and fearful faces compared to healthy individuals (Pillay et al., 2006, 2007). For neutral faces, patients with PD demonstrated a significantly increased activation of the cingulate cortex, but not of the amygdala, compared to healthy controls (Pillay et al., 2006). In another study, the presentation of neutral faces was associated with a slightly increased activation of the left amygdala (Pillay et al., 2007). For happy faces, the PD patients revealed a significantly increased activation of the anterior cingulate cortex (ACC) (Pillay et al., 2007). However, it was still unclear whether these results were also applicable to PD-A since PD-A is the more prevalent group compared to PD (Kessler et al., 2001). In addition, the effect of the history of lifetime Major Depression (MD) as comorbidity and current psychotropic drug-treatment should be focused on in more detail.

Patients with PD-A did not show an extreme fear reaction triggered by other people's faces. Instead, the fear reaction was triggered by place stimuli, as they are emotionally more relevant for PD-A (American Psychiatric Association (ed.), DSM-IV-TR, 2004; Wittmann et al., 2011). To our knowledge, there is only one published study that investigated the emotional processing of an agoraphobic–specific picture-set using fMRI (Westphal-paradigm, Wittmann et al., 2011). Here patients with PD-A showed greater neural activity in the parahippocampal cortex, the precuneus, the insula, and the middle temporal gyrus when compared with neutral stimuli (IAPS, pictures, Lang et al., 1997). In addition, during the perception of agoraphobic stimuli, the patients showed a greater activation in the middle occipital gyrus, the superior occipital gyrus, the middle temporal gyrus, and the fusiform gyrus.

One possible underlying mechanism might be that patients with PD-A seem to allocate more attention to recognizing environmental features and scenes due to their higher arousal as shown in PD (Pillay et al., 2006). The hyper-arousal is due to the anticipatory anxiety which is one criterion for the disorder PD-A (American Psychiatric Association (ed.), DSM-IV-TR, 2004) and is accompanied with an increased activation of the amygdala and central areas of the fear circuit (Gorman et al., 2000; Schienle et al., 2009). Even healthy individuals, who expected unpleasant stimuli, showed anticipatory anxiety and similar neural activations (Herwig et al., 2007; Simmons et al., 2004; Ueda et al., 2003). Therefore, the hyper-arousal in PD-A might also be responsible for the increased activity in memory creation and recollection of visual scenes (Wittmann et al., 2011).

In Wittmann et al. (2011) neutral stimuli (IAPS, Lang et al., 1997) were tested without a control group. Therefore, the neural processing of emotionally neutral places in PD-A in contrast to healthy individuals is still under investigation. In healthy individuals, the neural networks underlying the perception of non-aversive place stimuli have been shown to consistently include the superior occipital cortex and the middle temporal gyrus (Sugiura et al., 2005). For the differentiation of neutral place and face stimuli, healthy individuals consistently showed activation in the para-hippocampal places area and the fusiform face area (O'Craven and Kanwisher, 2000).

At present, the neural processing of neutral places and faces in PD-A has not been investigated. This is surprising given that neutral pictures are often used as a control condition in PD-A studies. Therefore the aim of this study was to compare the neural activity displayed with neutral/non-aversive place and face images between patients with PD-A and healthy individuals in a sample without interfering variables.

In sum, when processing neutral faces healthy individuals show neural activation in the middle fusiform gyrus and inferior occipital gyrus (Rossion et al., 2003). Anxious healthy individuals show a reduced ability to process emotional content based on differences in a neural network of frontal and temporoparietal regions as well as limbic structures (Rossignol et al., 2005). In anxiety patients with PD neutral face processing was associated with increased activation of the cingulate cortex and the amygdala (Pillay et al., 2006, 2007). We therefore hypothesized (1) that PD-A patients when compared with healthy controls show greater neural activity in the middle fusiform gyrus and the inferior occipital gyrus when they perceive neutral faces.

When they perceive fearful places, patients with PD-A show greater neural activity in the occipital cortex, in the parahippocampal place area, the precuneus, and the fusiform gyrus when compared with neutral non-place-stimuli (Wittmann et al., 2011). With respect to the processing of emotionally neutral, non-aversive place stimuli, the anticipatory anxiety, which is one diagnostic criterion for the disorder (American Psychiatric Association (ed.), DSM-IV-TR, 2004), might affect the neural processing. Increased activation of the amygdala and central areas of the fear circuit has been demonstrated in healthy individuals (Herwig et al., 2007; Simmons et al., 2004; Ueda et al., 2003) as well as in patients with PD and phobic disorders (Gorman et al., 2000; Schienle et al., 2009). We therefore expect PD-A patients to pay increased attention on recognizing environmental features and scenes due to their anticipatory anxiety and higher arousal (Pillay et al., 2006). We hypothesize (2) that PD-A patients when compared with healthy individuals show greater neural activity in the occipital cortex, the parahippocampal place area, the precuneus, and the fusiform gyrus when they perceive neutral places.

2. Methods

2.1. Subjects

The patients for the study were recruited at the University Hospital of the Technical University Dresden, Germany from 2008 to 2010. The Structured Clinical Interview (SCID) (Spitzer et al., 1990; Wittchen et al., 1997) for the diagnostic and statistical manual of mental disorders (DSM-IV) was used to ascertain a diagnosis of panic disorder with agoraphobia (American Psychiatric Association (ed.), DSM-IV-TR, 2004). The healthy individuals responded to public advertisements. The patients were recruited in an outpatient unit of the clinic for psychosomatic medicine and psychotherapy (Technische Universität Dresden) specializing in the diagnostic of anxiety disorder.

Fifteen patients with a diagnosis of PD-A confirmed by the structured clinical interview and 15 healthy subjects (for details see Table 1) who were matched by age and gender participated in the study. The patients had not suffered from any other mental disease in their lifetime and were free of psychotropic drug treatment. For the evaluation of depressive symptomatology, the