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ScienceDirect
Psychiatry Research: Neuroimaging 155 (2007) 113–120
PSYCHIATRY RESEARCH NEUROIMAGING
www.elsevier.com/locate/psychresns

Visual presentation of phobic stimuli: Amygdala activation via an extrageniculostriate pathway?

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Received 1 June 2006; received in revised form 6 October 2006; accepted 6 December 2006

Abstract

In the present study, event-related functional magnetic resonance imaging (fMRI) was used to examine the neural correlates of phobic fear by exposing spider phobic subjects to a visual presentation of spiders. In contrast to control subjects, spider phobics showed significantly increased activation in the amygdala and the pulvinar nucleus of the thalamus on the basis of region of interest (ROI) analysis. Furthermore, voxelwise analysis revealed increased activation related to phobia-specific pictures bilaterally in the anterior cingulate cortex, the left insular cortex and bilaterally in the supplementary motor area. These findings confirm the involvement of the amygdala in the processing of phobia-relevant stimuli as found earlier in a recent study. Moreover, the thalamus findings support the involvement of an extrageniculostriate pathway in the process of phobic fear.

Keywords: Event-related functional magnetic resonance imaging; Spider phobia; Fear

1. Introduction

Fear can be seen as an automatic response to danger that is essential for survival, a natural reaction seen in everyday life. When this reaction becomes more pronounced than acceptable in a given situation, or when it arises in an inappropriate situation, it becomes a fear or anxiety disorder (Marks, 1987; Öhman, 1992).

The amygdala is very often referred to in studies on fear (Davis and Whalen, 2001; Zald, 2003). Activation of the amygdala occurs in healthy individuals processing faces expressing fear compared with neutral faces, as well as other potentially threatening material. Fear-conditioning studies also point to the importance of the amygdala in the acquisition of fear. Furthermore, previous studies with social phobic patients (Birbaumer et al., 1998) and individuals suffering from posttraumatic stress disorder (PTSD) (Gilboa et al., 2004) implicate the amygdala in symptom-provocation paradigms.

Activation of the amygdala has been said to be mediated by a subcortical pathway passing through the pulvinar nucleus of the thalamus (LeDoux, 1996). This route bypasses the primary sensory cortices. Inputs from the thalamus to the amygdala would facilitate transmission of rough, but rapid, signals about fear-related stimuli, thus enabling one to respond reflexively and rapidly to danger. Evidence in favor of such a pathway comes from behavioral and functional studies of patients with selective brain lesions (Morris et al., 2001a; Ward et al., 2005). For example, 'blindsight' patients with

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doi:10.1016/j.pscychresns.2006.12.005

striate lesions who are unable to consciously perceive visual stimuli still show activity in the pulvinar region in response to fear-related stimuli (Morris et al., 2001b).

Despite the widely accepted central role of the amygdala in the cascade of fear processing, people suffering from specific phobia, known to typically display exaggerated fear towards a specific stimulus or even a picture of that stimulus (Cuthbert et al., 2003), fail to show amygdala activation in most of the imaging studies conducted to date (Fredrikson et al., 1993; Rauch et al., 1995; Johanson et al., 1998). Dilger et al. (2003) were the first to provide evidence of the involvement of the amygdala in phobic fear. By means of event-related functional magnetic resonance imaging (fMRI), they demonstrated increased amygdala activation in phobic subjects confronted with a picture of their feared object. It has been suggested that the negative outcomes from previous studies were due to the presentation of stimuli in blocks of a certain amount of time. This sustained presentation may have caused habituation of the rapid amygdala responses (see Breiter et al., 1996; Buchel et al., 1998).

The present study seeks to replicate and provide further evidence for the involvement of the amygdala in phobic fear. Moreover, since the reaction of phobics to their feared stimulus has also been described as reflexive (LeDoux, 1996), it is conceivable that in such an automatic fear reaction the amygdala will be rapidly activated via the subcortical pathway, in parallel to the classic route via the primary visual cortex. If this is true, we hypothesize that there will also be increased thalamic activation during phobia-relevant picture processing.

2. Methods

2.1. Subjects

Participants were 13 female and 2 male subjects with spider phobia (mean age = 24 years, S.D. = 2) and 12 female and 2 male control subjects (mean age = 23 years, S.D. = 1), all recruited by public advertisement. Subjects received a small financial compensation (€15) for their participation.

Subjects were diagnosed as spider phobics before the experiment using a structured psychiatric interview [Mini International Neuropsychiatric Interview, MINI, (Sheehan et al., 1998)]. In addition, we used the self-administered Spider Phobia Questionnaire [SPQ (Klorman et al., 1974)] (mean = 21, S.D. = 2). All spider phobic subjects were untreated. Control subjects did not reveal any signs of phobia (SPQ mean = 2, S.D. = 1). All subjects were free of additional psychopathology according to the MINI, including specific phobia for snakes. Right-handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). Written informed consent was obtained from each participant before the experiment. The study was approved by the local ethics committee.

2.2. Design

We adopted a paradigm previously described by Dilger et al. (2003). Subjects were exposed to a series of spider (phobia-relevant), snake (potentially fear-relevant), and neutral stimuli taken from the International Affective Picture System, and a fixation cross as a null event (27 pictures from each category). The snakes were introduced to control for possible hyperreactivity to threat-related stimuli in general. All stimuli were equated for visual content.

Pictures were presented in a random order for 1 s each with a variable inter-stimulus interval of 2.25 s to 9 s between succeeding stimulus. The pictures were viewed

Table 1
Significant activation to Spider vs Neutral pictures for Phobics > Controls

Spiders > Neutral						
Brain area	L/R	P_{FDR}	*t*-value	Talairach coordinates		
				x	*y*	*z*
Voxelwise						
Thalamus, pulvinar	R	0.000	7.91	2	−29	1
Thalamus,medial dorsal nucleus	L	0.000	5.51	−4	−15	10
Thalamus, ventral anterior nucleus	R	0.002	4.69	14	− 1	11
Posterior cingulate cortex	L	0.006	4.01	−2	−40	20
Anterior cingulate gyrus	R	0.000	6.66	6	23	25
Anterior cingulate gyrus	L	0.000	5.86	−4	26	24
Superior frontal gyrus (SMA)	L	0.001	4.95	−6	0	70
Superior frontal gyrus (SMA)	R	0.002	4.48	12	9	66
Fusiform gyrus	R	0.000	6.38	40	−67	−15
Lingual gyrus	R	0.001	5.30	2	−86	−11
Fusiform gyrus	L	0.001	5.02	−18	−77	−16
Lingual gyrus	L	0.001	4.96	−16	−90	−14
Superior temporal gyrus	R	0.001	5.02	59	13	−7
Insula	L	0.005	4.04	−40	13	−4
Parahippocampal gyrus	L	0.008	3.86	−18	1	−12
Precuneus	L	0.031	3.18	−6	−57	64
ROI						
Amygdala	L	0.013	3.71	−18	−1	−14
Thalamus, pulvinar	R	0.000	7.18	6	−29	3
Thalamus, pulvinar	L	0.004	3.53	−6	−29	5

SMA, supplementary motor cortex; L, left; R, right; Talairach coordinates of maximally activated voxel (activation threshold: $P_{FDR\ corrected} < 0.05$).