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Neurophysiological correlates of habituation during exposure in spider phobia

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Abstract

Imaging studies using symptom-provocation paradigms in specific phobia have yielded contradictory results, possibly reflecting a failure to account for habituation processes. Given that a single session of exposure in vivo can result in significant improvement in specific phobia, we used prolonged exposure to phobic stimuli to identify CNS regions showing habituation. Eighteen subjects (12 with spider phobia, 6 healthy controls) underwent $H_2^{15}O$-positron emission tomography while being continuously presented with pictures of spiders or butterflies. Results showed main effects (spiders>butterflies) in the phobia group in the left fusiform gyrus (FG) and the right parahippocampal gyrus (PHG), with bilateral perirhinal cortex and right limbic areas approaching significance. Group×condition effects were found in the right amygdala and PHG. During spider scans, large habituation effects were observed in the anterior medial temporal lobe (MTL) bilaterally. Regression analyses demonstrated that state anxiety was correlated with activity in left amygdala, bilateral perirhinal cortex, right FG, and periaquaductal grey; by contrast, phobic fear was only associated with right-sided hippocampal activity. We conclude that prolonged exposure to phobic stimuli is associated with a significant decrease in bilateral anterior MTL regional cerebral blood flow. Right anterior MTL, identified when comparing phobic vs. neutral stimuli and habituation to phobic vs. neutral stimuli in the phobia group, implicates this region in phobic fear. Analyses of covariance suggest a further functional segregation with state anxiety being linked to enhanced activity in amygdala,

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perirhinal cortex, and tegmentum, and phobic fear with enhanced right hippocampal activity, suggesting a neuroanatomical differentiation between emotional-vegetative and cognitive aspects of (phobic) fear.

Keywords: Spider phobia; Positron emission tomography; Exposure; Habituation

1. Introduction

Specific phobia is a psychiatric disorder characterized by marked and persistent fear of circumscribed objects or situations, such as snakes, spiders, and being in a tunnel or elevator (American Psychiatric Association, 1994). Subjects with a specific phobia readily concede that their fears are exaggerated, but they nevertheless go to great lengths to avoid phobic stimuli. The etiology of specific phobias is unknown, although both constitutional and environmental factors may contribute to their pathogenesis (Fyer, 1998). Subtypes of specific phobias (animal, blood/injury, and situational phobias) tend to cluster in families (Skre et al., 2000; Kendler et al., 2002). In addition, previous traumatic experiences and/or vicarious learning may predispose to their onset (Lichtenstein and Annas, 2000). Exposure therapy, involving exposing patients to feared situations, is the gold standard for treatment of specific phobia. This treatment is based on the idea that anxiety subsides through a process of habituation. Habituation refers to a decline in fear responses, particularly physiological responses, with repeated exposures to fear-provoking stimuli. Several studies provide supportive evidence for the role of habituation in exposure therapy, with self-reported fear and physiological arousal showing a decline across exposure sessions, consistent with habituation (Emmelkamp, 2004).

Over the past decade, brain-imaging techniques, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), have been used to investigate the neuroanatomical substrate of specific phobias, particularly animal phobias. These studies typically involve exposing subjects to phobic objects such as snakes or spiders, either pictures or live animals, during scanning. To date, these studies have yielded conflicting results. Whereas Mountz et al. (1989) in an early PET study reported negative results, subsequent studies such as those of Wik et al. (1993) found increased regional cerebral blood flow (rCBF) in secondary visual cortex but decreased rCBF in hippocampus and orbitofrontal, prefrontal, temporopolar, and posterior cingulate cortex with exposure to phobic stimuli. In a follow-up study (Fredrikson et al., 1995), intravenous diazepam did not effect rCBF changes or influence subjective/physiological fear indices. Johanson et al. (1998), using ^{133}Xe-SPECT, reported decreased right lateral prefrontal flow during presentation of a spider video compared with a neutral video, particularly in near-panicking subjects. In contrast, Rauch et al. (1995), in their subjects with small animal phobia, found increased rCBF in left posterior orbitofrontal, left insular, and left somatosensory cortex, as well as in right anterior temporal and anterior cingulate cortex, but not in the amygdala complex during presentation of phobic objects compared with baseline. Similar findings were reported by Reiman (1997).

Inconsistencies in previous findings may reflect methodological differences such as imaging modality, stimulus paradigms (eyes open or closed, visual stimuli vs. touch), and data-analytic techniques (region of interest vs. voxel by voxel methods). In addition, few studies have controlled for decrements in subjects' responses in time, due to habituation after repeated exposure to phobic stimuli. Reiman (1997) attempted to reduce habituation effects by placing the snake closer to the subject with successive scans. To our knowledge, only a preliminary report by Drevets et al. (1995) addressed the effects of repeated stimulation (using 'live' animals) on patterns of CNS activation in subjects with small animal phobia, where increased activity during habituation in left posterior orbitofrontal cortex alone was found. In normal volunteers, several studies have shown that responses to fearful stimuli, particularly in anterior medial temporal cortex, may decrease rapidly over time (Breiter et al., 1996; Buchel et al., 1999; Thomas

et al., 2001; Wright et al., 2001). This finding has been put forward as an explanation for the failure to demonstrate increased activity in the amygdala complex in the above-reviewed studies on specific phobias (Fischer et al., 2000), in spite of the hypothesized key role of this region in fear responses (LeDoux, 1998).

Two issues are, however, important when using functional neuroimaging as a tool to investigate habituation processes. First, habituation of responses in phobia patients during repeated stimulation, even in the anterior medial temporal lobe, may reflect not only diminished fear of phobic objects, but also decreased novelty effects or anticipatory anxiety (e.g., Boshuisen et al., 2002). In the latter case, habituation effects for fear-associated stimuli would be similar to those for neutral stimuli, as reported by Fischer et al. (2000). Second, although exposure is the preferred treatment for phobia, and significant improvement may occur after a single session (Ost, 1989), responses to phobic stimuli may be more resistant to extinction than those to fearful stimuli in normal volunteers. Therefore, brief presentations (1–2 min for each scan, as is customary for ^{15}O-PET) may not be sufficient to achieve a reduction of phobic fear.

In the present study, $H_2^{15}O$-PET was used to investigate the neurophysiological correlates of habituation during prolonged exposure in spider phobia patients. To this end, visual stimuli were presented not only during each scanning period, but continuously in order to mimic an exposure therapy session as closely as possible. In addition, ratings of both actual distress and phobic fear were obtained with the aim of differentiating between non-specific, fluctuating state anxiety and specific, enduring phobic fear. Based on results of previous functional magnetic resonance imaging (fMRI) studies in normal volunteers, it was expected that habituation would be associated with decreased regional blood flow in bilateral anterior medial temporal lobe (MTL), as would also be predicted by the model proposed by LeDoux (1998).

2. Methods

2.1. Subjects

Eighteen subjects (12 spider phobia patients and 6 control subjects) participated in the study. Twelve subjects (11 females, 1 male, mean age=32.1±S.D. 14.0 years) were diagnosed as spider phobics based on their scores on the Fear of Spiders Questionnaire (FSQ) and the Spider Phobia Questionnaire (SPQ) (Muris and Merckelbach, 1996). Scores on the FSQ and SPQ for phobic subjects were 77.4±21.4 and 19.5±9.5, respectively, in agreement with scores reported by Muris and Merckelbach (89.1±19.6 and 23.2±2.9 for their phobic subjects). Six age-matched control subjects were also included (4 females, 2 males; mean age=30.5±S.D., 10.6 years; FSQ score=7.2±10.9, SPQ score=2.8±3.8). Subjects with neurological and psychiatric disorders were excluded. In addition, pregnancy, inadequate contraception, and use of psychoactive substances were exclusion criteria. The study was approved by the Ethics Committee of the Vrije Universiteit Medical Center. Informed consent was obtained from all participants.

2.2. Exposure paradigm

Each subject was presented with nine 9.5-min series of 95 pictures of either spiders or butterflies, each of which was shown for 6 s without a break. A session contained six series of spider pictures and three series of butterfly pictures, suitably randomised across subjects. Butterflies were included to control for non-specific habituation effects, as they are visually similar to spiders. During each series, a 90-s PET scan was performed after 5–6 min of exposure. Stimuli were drawn from two sets (spiders and butterflies) of approximately 200 colour pictures each. Subjects therefore saw each picture two to four times. Care was taken, however, that only new pictures were presented during each scan. Using a personal computer, pictures were presented on a flat screen positioned in front of each subject, at a distance of about 0.5 m from the eyes. Subjects were instructed to concentrate on the task and watch each item carefully. After each series of pictures, subjects were asked to rate subjective distress (Subjective Units of Distress Scale; SUD-S) and fear for spiders on a 100-point scale. Blood pressure (RR) and heart rate (HR) were automatically recorded every 2.5 min using a cuff around the left upper arm (RR) and a sensor on the right middle or index finger (HR).

2.3. Scanning details

PET scanning was performed using a Siemens ECAT EXACT HR+(CTI/Siemens, Knoxville, TN) with an axial field of view of 15 cm. Before each scanning session, a cannula was inserted into the left antecubital vein and normal saline was infused. After a transmission scan was performed, for each of the nine emission scans, 10–15 ml normal saline containing 370–400 MBq of $H_2^{15}O$ was administered as a bolus injection using a MedRad infusion pump. Data acquisition lasted 90 s, and the interval between successive $H_2^{15}O$ injections was 10 min to allow for radioactive decay. Image reconstruction was done using an ordered subset-expectation maximisation (OSEM) method, with four iterations and 16 subsets (Boellaard et al., 2001; Mesina et al., 2002), followed by motion-corrected attenuation correction (Boellaard et al., 2002), with the aim of increasing the signal-to-noise ratio and of controlling for motion-related reconstruction artifacts. A T1-weighted magnetic resonance image (MRI) was acquired from each subject with a 1.5-T Sonata (Siemens, Erlangen) MR scanner [magnetisation prepared-rapid acquisition gradient echo (MP-RAGE); inversion time: 300 ms, TR=15 ms, TE=7 ms, flip angle=8°, voxel size 1×1×1.5 mm].

2.4. Statistical analysis

Psychometric and physiological data were analyzed using a standard statistical package. Imaging data were analyzed with SPM99 software (http://www.fil.ion.ucl.ac.uk). After reconstruction, PET images were realigned, and each subject's structural MRI was coregistered to the mean PET image. Next, PET images were transformed to approximate Talairach (Talairach and Tournoux, 1988) anatomical standard space, as defined by the SPM99 T1 template, using the transformation matrix obtained from warping each subject's coregistered T1 image. PET images were resampled to 3×3×3 mm voxels and smoothed using a 10-mm full-width/half-maximum (FWHM) Gaussian filter. Following spatial preprocessing, PET data were analyzed using a linear regression model, and weighted contrasts were computed for condition and time effects for each group, and for group×condition interactions. Additional regression analyses were performed to assess correlations between imaging data and psychometric and physiological measurements. Results are reported at $P<0.05$, corrected for multiple comparisons using the False Detection Rate (FDR) method (Genovese et al., 2002), unless indicated otherwise.

3. Results

3.1. Psychometric and physiological data

One subject (from the phobia group) complained of sleepiness during the scanning session; these data were excluded from the analysis. In the remaining 11

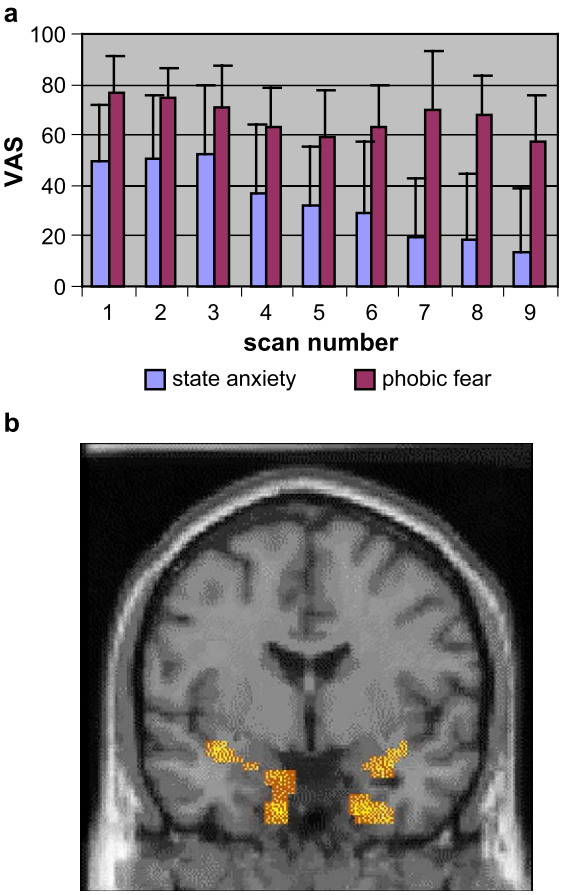

Fig. 1. (a) State anxiety (SUD-S) and phobic fear ratings during spider scans (1–6) and butterfly scans (7–9) in phobic subjects (n=11). (b) Habituation (signal decrease over time) during spider scans in the phobia group (n=11).

subjects in the phobia group, state anxiety (as measured with the SUD-S) during exposure to spider pictures decreased from 49.6±22.4 to 29.6±22.7 (Fig. 1a). Paired comparisons showed that the main decrease in SUD-S occurred between the third and fourth spider scan (t=4.6, P<0.001). Fear of spiders decreased from 76.4±15.2 to 62.7±17.1, also with the only significant change occurring between the third and fourth spider scan (t=2.6, P<0.05). Surprisingly, pairs of ratings (SUD-S and fear of spiders) for each scan did not show statistically significant correlations, with r's ranging between −0.18 and +0.38.

Mean state anxiety in the phobia group was higher than in controls during the spider scans (41.9±23.9 vs. 13.6±9.1, P<0.01) but not during butterfly scans (17.0±24.5 vs. 13.5±9.3, n.s.). In contrast, fear of spiders was higher in the phobia group both during spider scans (68.1±13.9 vs. 15.4±10.4, P<0.0001) and butterfly scans (65.4±17.7 vs. 16±10.8, P<0.0001). In the control group, neither the decrease in SUD scores (15.8±9.1 to 12.5±9.6) nor the decrease in ratings of fear of spiders (18.7±11.1 to 13.3±10.8) was statistically significant.

Mean arterial blood pressure in the two groups was similar during spider scans (86.3±7.0 vs. 86.6±6.9, n.s) and control scans (86.0±6.4 vs. 86.3±6.2, n.s). Differences in heart rate between the two groups were also not observed (spider scans: 65.0±6.8 vs. 60.3±6.4, n.s.; butterfly scans: 63.0±4.8 vs. 59.8±6.4, n.s.).

Table 1
Main effects (phobia group, N=11) for spider pictures vs. butterfly pictures

Spiders>butterflies					
Region	Coordinates			BA	Z-score
R lateral prefrontal cortex	51	9	27	44	3.5*
R posterior insula	39	−3	−3		3.5*
L temporal					
Perirhinal cortex	−33	−12	−39	38/20	3.8*
	−24	−6	−45	38/20	3.4*
R temporal					
Amygdala	15	0	−21		3.3*
Perirhinal cortex	33	−6	−42	38/20	3.8*
Parahippocampal gyrus	36	−33	−24	36	4.2
L fusiform gyrus	−36	−42	−24	20	4.6
	−45	−69	−9	37	4.2
Thalamus	18	−21	−6		3.6*

BA=Brodmann area.
* P<0.1 corrected for multiple comparisons.

Table 2
Condition (spider vs. butterfly pictures) by group [spider phobia (N=11) vs. controls (N=6)] interaction effects

Condition×group effects					
Region	Coordinates			BA	Z-score
Right temporal					
Amygdala	15	3	−18	–	3.4
Parahippocampal gyrus	33	−30	−21	36	3.3

BA=Brodmann area.

3.2. Imaging data

3.2.1. Main effects: spiders vs. butterflies

Table 1 presents the main effects for pictures of spiders (compared with butterflies) in the phobia group. At the chosen threshold (P<0.05, FDR-corrected, which was equivalent to Z>4.0 for this contrast), activations were found in left fusiform and right parahippocampal gyrus. At a slightly lower threshold of P<0.1 corrected (Z>3.4), we found activations in right lateral prefrontal cortex, bilateral perirhinal cortex, right pulvinar, right posterior insula, and right medial amygdalar region.

The reverse contrast did not show significant activations, nor did we observe significant main effects in the control group. Condition (spiders vs. butterflies)×group interactions showed specific effects in the phobia group in right amygdala and right parahippocampal gyrus (Table 2).

Table 3
Habituation effects (phobia group, N=11) for spider pictures

Habituation: spiders					
Region	Coordinates			BA	Z-score
Left temporal					
Anterior inferior	−24	6	−36	28	3.9
Amygdala	−24	0	−18	34	3.8
Perirhinal cortex	−12	−6	−39	36	4.3
Right temporal					
Anterior inferior	36	21	−27	38	4.8
Amygdala	24	0	−21		3.4
Perirhinal gyrus	24	−9	−42	36	4.1
Hypothalamus	6	−3	−9		3.7

BA=Brodmann area.

Table 4
Habituation×condition effects (phobia group, N=11) for spider vs. butterfly pictures

Habituation: spiders>butterflies					
Region	Coordinates			BA	Z-score
Prefrontal					
Anterior cingulate	4	34	18	24	3.7
Left temporal					
Anterior inferior	−24	6	−36	28	3.9
Amygdala	−22	0	−16		3.3
Perirhinal gyrus	−10	−6	−38	36	4.1
Right temporal					
Anterior inferior	38	20	−24	38	4.3
Amygdala					n.s.
Perirhinal gyrus	22	−8	−40	36	3.6
Hypothalamus	6	−2	−10	–	3.3

BA=Brodmann area.

3.2.2. Habituation/sensitization

In the phobia group, as expected, large habituation effects for spider stimuli (signal decrease as a linear function of time) were found bilaterally in the anterior medial temporal lobe, including the amygdala, extending bilaterally into posterior insular cortex, and hypothalamus (Table 3, Fig. 1b). Post hoc paired comparisons revealed that right amygdala activity decreased mainly between the first and second spider scans, whereas left amygdala activity showed a significant decline between the second and third spider scans. Sensitization effects for spider stimuli (signal increases as a linear function of time) were not found.

Habituation×condition (spiders vs. butterflies) interactions in the phobia group were found in bilateral perirhinal cortex, anterior cingulate cortex, left anterior temporal pole including the amygdala region, and right anterior pole extending into posterior insula (Table 4). In the control group, we did not find significant habituation×condition interactions.

3.2.3. Regression analyses

Additional regression analyses were performed to identify areas in which activity correlated with physiological or behavioral data. Scan-to-scan variability in heart rate and mean arterial blood pressure were both positively correlated with activity in periaquaductal grey matter, as well as with activity adjacent to lateral temporal poles, the latter presumably due to extracranial sources (Reiman et al., 1989; Drevets et al., 1992). State anxiety, as measured with the SUD-S, was associated with enhanced activity in left amygdala and bilateral perirhinal cortex, as well as right fusiform gyrus and periaquaductal grey matter. Fear of spiders (after regressing out state anxiety) was not correlated with rCBF changes, although at a slightly lower threshold (P<0.1, FDR corrected, or Z>4.3 for this contrast), a correlation with rCBF in the right hippocampus was found (Table 5).

4. Discussion

In the present study, we used PET to investigate neurophysiological changes (habituation) during repeated exposures to phobic stimuli in spider phobia patients. To this end, a behavioral therapy paradigm (prolonged visual stimulation) was adapted by also including a neutral control condition (pictures of butterflies). Psychometric data showed that this

Table 5
Areas showing activity associated with state anxiety (SUD-S) in fear of spiders (phobia group)

Region	VAS state anxiety					VAS phobic fear				
	Coordinates			BA	Z-score	Coordinates			BA	Z-score
Left temporal										
Amygdala	−21	3	−18		4.0*					
Perirhinal gyrus	−12	−6	−36	36	3.8*					
Right temporal										
Perirhinal gyrus	24	0	−39	38	4.6					
Hippocampus						30	−15	−18		4.3*
Right fusiform gyrus	39	−36	−27	36	3.7*					
Periaquaductal grey	−3	−24	−15		4.3*					

BA=Brodmann area.
* P<0.1 corrected for multiple comparisons.

paradigm was successful in reducing not only state anxiety as measured with the SUD-S, but also phobic fear, albeit to a lesser extent. In the phobia group, phobic fear was similar during spider and neutral scans, as expected given that spider phobia is a trait characteristic; in contrast, state anxiety was significantly higher during the spider scans. The imaging data, on the other hand, showed a clear, if incomplete, dissociation between main effects for condition and habituation effects. Main effects for spider vs. butterfly pictures were found predominantly in fusiform/parahippocampal gyrus, but also in bilateral perirhinal cortex, right posterior lateral prefrontal cortex, and right medial amygdalar region. Habituation effects (decreases over time) were found exclusively in so-called limbic structures involving the bilateral anterior medial temporal lobe including the amygdala, as well as in the posterior insula, and hypothalamus.

Main effects for phobic vs. neutral stimuli in the present study are only partially in agreement with those of previous imaging studies in phobic subjects. In contrast to the studies of Fredrikson et al. (1995) and Johanson et al. (1998), no significant deactivations were found. Activity in insular and posterior thalamic regions was found in accordance with observations by Reiman (1997) and Rauch et al. (1995), although their finding of medial prefrontal activity was not replicated. In a recent fMRI study by Paquette et al. (2003), spider phobia subjects were scanned twice, before and after four sessions of cognitive behavior therapy. Before therapy, viewing film excerpts depicting spiders was associated with activity in anterior right dorsolateral prefrontal cortex, as well as in visual association areas and parahippocampal gyrus. In the present study, additional main effects were identified not only in bilateral fusiform gyrus, but also perirhinal cortex, and right inferior frontal gyrus. The fusiform gyrus has been reported earlier in imaging studies using anxiogenic stimuli in normal volunteers (Breiter et al., 1996; Morris et al., 1998; Williams et al., 2001), and this may reflect emotional modulation of visual processing systems. Perirhinal cortical activity has been found to predict successful encoding (e.g., Strange et al., 2002), possibly through association of higher-order sensory inputs with emotion-related inputs from the amygdala (Kajiwara et al., 2003). This effect, we suggest, reflects an automatic engagement of memory-related processes for a phobic object consequent upon emotional modulation. The right inferior frontal gyrus, on the other hand, previously implicated in declarative (fact) processing of fear (Williams et al., 2001), may reflect an obligatory retrieval of previous episodes of fear.

In the present study, extensive habituation in bilateral anterior MTL, including the amygdala, was found. This phenomenon has not previously been reported in phobia patients, but may account for the negative findings regarding the anterior MTL in earlier imaging studies, as suggested by Fischer et al. (2000). Habituation of amygdalar responses to anxiogenic stimuli (fearful faces) in normal volunteers has been described by several authors (Breiter et al., 1996; Morris et al., 1996; Fischer et al., 2000; Wright et al., 2001; Phillips et al., 2001). Most investigators have found habituation effects in the right amygdala, but not in the left, which has led to speculations that the right amygdala might be involved in rapid emotional stimulus detection, whereas the left amygdala might be associated with sustained stimulus evaluation. This hypothesis is, however, not supported by the present data. Possible explanations include differences in stimulus paradigm (spiders vs. angry faces), subject groups (phobic patients vs. normal controls) and, presumably most important, stimulus presentation duration (ca. 60 min vs. a maximum of 10 min). This period may be critical in view of the finding that left amygdalar activity decreased, mainly between the second and third spider scans (i.e., after 15–25 min of exposure). In contrast, right amygdalar activity showed a significant decline between the first and second spider scans (after 5–15 min of exposure). This finding suggests that left amygdalar habituation might have been missed in several earlier studies because the stimulation interval might was too short. It also indicates that diminished amygdalar activity may antedate a decrease in state anxiety and/or phobic fear, which occurred mainly between the third and fourth spider scan.

In the present study, regions specific for spider phobia habituation were found in bilateral perirhinal and posterior insular cortex, as well as right hypothalamus and right amygdala, but not left amygdala. This implies that the involvement of the left amygdala, in this paradigm at least, is not primarily associated with specific fears, but may also be due

to, e.g., anticipatory anxiety and/or novelty. This conclusion is supported by the finding that group by condition interactions specifically involved the right amygdala and parahippocampal gyrus, although these findings need to be interpreted with caution in view of the small control group. Interestingly, in the Paquette et al. (2003) study, pretreatment activity in parahippocampal gyrus disappeared after treatment, explained as due to deconditioning of contextual fear, similar to the present study.

Additional regression analyses showed that state anxiety was associated with activity in left amygdala and bilateral perirhinal cortex, as well as right fusiform gyrus, and periaquaductal grey matter, whereas phobic fear was associated with right hippocampal activity only. The latter finding again suggests that habituation to phobic stimuli in this paradigm is correlated with activity in right limbic structures. The association of amygdalar and tegmental activity with state anxiety and heart rate/arterial blood pressure is in line with earlier findings linking these structures to emotional and autonomic aspects of fear responding (Critchley et al., 2000).

Regarding the role of the hippocampus, Williams et al. (2001) reported that presentation of anxiogenic stimuli in normal volunteers led to amygdalar activation only if a concomitant change in skin conductance occurred. Anxiogenic stimuli that did not elicit skin conductance responses were associated with hippocampal activity. These findings were interpreted as implying a neuroanatomical dissociation between visceral experience and declarative fact processing of fear, as outlined by LeDoux (1998).

Although the present study was not designed to test this model, the data appear to be in agreement with such a 'dual system' hypothesis. Phobic fear was found to be correlated with right hippocampal activity only, after regressing out state anxiety, indicating that the right hippocampus is involved in cognitive aspects of (phobic) fear (Bechara et al., 1995). Moreover, exploratory analyses using regional blood flow data as covariates of interest indicated that right amygdala was functionally coupled with left amygdala, as well as bilateral perirhinal cortex, hypothalamus, and PAG, but not right hippocampus. In contrast, right hippocampus was functionally coupled with left hippocampus, right fusiform gyrus, and right posterior inferior lateral frontal cortex (data not shown). Whereas the former regions have been implicated in both visceral and emotional aspects of fear response, the latter subsystem is similar to the hippocampal–lateral prefrontal network identified by Williams et al. (2001) as being involved in 'fear without arousal'.

In summary, we found that prolonged exposure to phobic stimuli during $H_2^{15}O$-PET-scanning was associated with a significant decrease in bilateral anterior medial temporal lobe (MTL) perfusion. In addition, right anterior MTL was identified when comparing phobic vs. neutral stimuli between patients and control subjects, and when comparing habituation to phobic vs. neutral stimuli in the phobia group, implicating a specific role for this region in phobic fear. Additional regression analyses suggested a further functional segregation, since state anxiety was associated with activity in amygdala, perirhinal cortex, and tegmentum, whereas phobic fear was associated with right hippocampal activity only. Given the modest size of our experimental group and the limited spatial resolution of $H_2^{15}O$-PET, these findings clearly need replication; in addition, future research should further address the issue of anterior MTL functional lateralisation, e.g., by including familiar items to account for activity related to novelty.

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