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Neurostructural correlates of two subtypes of specific phobia: A voxel-based morphometry study

Kevin Hilbert [a,b,c,*], Ricarda Evens [a,b], Nina Isabel Maslowski [a,b], Hans-Ulrich Wittchen [a,b], Ulrike Lueken [a,b]

[a] Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Dresden, Germany
[b] Neuroimaging Center, Technische Universität Dresden, Dresden, Germany
[c] Behavioral Epidemiology, Technische Universität Dresden, Dresden, Germany

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ABSTRACT

The animal and blood-injection-injury (BII) subtypes of specific phobia are both characterized by subjective fear but distinct autonomic reactions to threat. Previous functional neuroimaging studies have related these characteristic responses to shared and non-shared neural underpinnings. However, no comparative structural data are available. This study aims to fill this gap by comparing the two subtypes and also comparing them with a non-phobic control group. Gray and white matter data of 33 snake phobia subjects (SP), 26 dental phobia subjects (DP), and 37 healthy control (HC) subjects were analyzed with voxel-based morphometry. Especially DP differed from HC and SP by showing significantly increased grey matter volumes in widespread areas including the right subgenual anterior cingulate gyrus, left insula, left orbitofrontal and left prefrontal (PFC) cortices. In addition, white matter volume was significantly increased in the left PFC in DP compared with SP. These results are in line with functional changes observed in dental phobia and point toward those brain circuits associated with emotional processing and regulation. Future studies should aim to further delineate functional and structural connectivity alterations in specific phobia.

1. Introduction

Specific phobia is one of the most common mental disorders (Wittchen et al., 2011) and characterized by marked and disproportionate fear and anxiety or frequent avoidance of a phobic object or situation, causing significant distress or impairment (American Psychiatric Association, 2000, 2013). As such, specific phobia has also been used as a model disorder to investigate the neural processing of fear and fear circuitry dysfunctions (Linares et al., 2012; Ipser et al., 2013). Although past research presented accumulating data on the neurofunctional correlates of specific phobia and its subtypes, studies investigating alterations in structural brain anatomy are still scarce. But as structural alterations may underlie the disorder-related functional changes, deeper knowledge of these neurostructural correlates is of high importance for better understanding of the neurobiology of specific phobia, including the related pathogenic mechanisms.

Past studies investigated the neural alterations underlying specific phobia, with the majority of studies focusing on the animal subtype, particularly spider phobia subjects. This body of evidence consistently showed hyperactivation in fear-relevant structures, including the amygdala, dorsal anterior cingulate cortex (ACC), thalamus and insula (e.g., Dilger et al., 2003; Straube et al., 2004, 2006, 2007; Schienle et al., 2005.; Goossens et al., 2007; Hermann et al., 2009; Caseras et al., 2010a; Lueken et al., 2011). Beyond these, some reports also replicated hyperactivation in parts of the prefrontal cortex (Straube et al., 2004, 2006; Schienle et al., 2005; Caseras et al., 2010a), the hippocampus (Lueken et al., 2011, 2013) and the fusiform gyrus (Dilger et al., 2003; Schienle et al., 2005; Goossens et al., 2007; Straube et al., 2007). Compared with the large number of functional magnetic resonance imaging (fMRI) studies, relatively few studies examined structural alterations. These studies reported increased cortical thickness in the insula, both increased and decreased cortical thickness in the ACC, and decreased volume in the amygdala for animal phobia subjects compared with controls (Rauch et al., 2004; Fisler et al., 2013; Linares et al., 2014). None of these results have been successfully replicated so far, and no studies using whole brain morphometry are available.

Compared with studies on the animal subtype, less research has been conducted on other specific phobia subtypes such as the blood-injection-injury (BII) subtype, including dental phobia. Differential activation patterns were reported for an array of areas, but in comparison to animal phobia the results are less consistent

* Corresponding author at: Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Dresden, Germany. Tel.: +49 351 46342589; fax: +49 351 46336984.
E-mail address: Kevin.Hilbert@tu-dresden.de (K. Hilbert).

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and seem to be more dependent on stimulus modality and task effect (Hilbert et al., 2014). Fear circuit areas with the notable exception of the amygdala were reported as well in some (Caseras et al., 2010a; Schienle et al., 2013; Hilbert et al., 2014) but not all studies (e.g., Lueken et al., 2011, 2013). In addition, prefrontal (Straube et al., 2006; Hermann et al., 2007, 2013; Schienle et al., 2013; Hilbert et al., 2014), and orbitofrontal areas (Caseras et al., 2010b; Schienle et al., 2013), and also temporal and occipital structures (Caseras et al., 2010a; Schienle et al., 2013), seem to be relevant. However, there are almost no data available on corresponding structural alterations in dental phobia, with the only study on neurostructural changes in dental phobia finding no group differences in a sample of 45 dental phobic subjects and 41 control subjects (Schienle et al., 2013).

Taken together, these studies suggest partly overlapping, but also distinct neurofunctional correlates in fear circuitry structures. Specific phobia subtypes commonly present functional alterations in the PFC and in the ACC, insula and thalamus, although the activation pattern in the latter areas is more variable in dental phobia and considerably related to stimulus modality and possibly other task characteristics. Of these functional alterations, particularly the insula and ACC have been related to anticipatory anxiety, threat perception and evaluation of phobic stimuli (Straube et al., 2006, 2007), and may be activated in all subgroups during appropriate experimental stimulation. However, while subjective fear and anxiety are present in all specific phobia subtypes, some psychophysiological correlates may differ: in contrast to the animal subtype, the blood-injection-injury (BII) subtype is characterized by a biphasic vasovagal response that may eventually lead to fainting in some patients (Ost et al., 1984; Hamm et al., 1997). In line with this, prefrontal and particularly orbitofrontal areas seem to be more but not exclusively related to BII phobia (see also Del Casale et al., 2012), where they have been proposed to resemble the re-evaluation and the subsequent decrease in autonomic arousal observed in BII phobia (Lueken et al., 2011; Hermann et al., 2013; Schienle et al., 2013). On the other hand, the amygdala is clearly connected to animal phobia and is related to the increase in autonomic arousal observed (Ahs et al., 2011). Given the paucity of data on structural alterations, it remains unclear if results from functional studies can be generalized to make inferences on the corresponding brain anatomy. In addition, functional studies raise the question of whether the partly common, partly diverging clinical and physiological responses of specific phobia subtypes, as outlined above, can also be related to common and specific neurostructural alterations.

Therefore, the current study aimed to investigate the common and specific structural alterations in animal and BII phobia by directly comparing grey and white matter volumes in both phobia subtypes against each other and against healthy controls. Based on previous evidence from functional neuroimaging studies, altered grey matter volumes in both phobic groups compared with healthy controls were expected for the insula, ACC and thalamus. Altered grey matter volumes in the amygdala were expected specifically for the animal phobia group, while altered grey matter volumes in the PFC and particularly the orbitofrontal cortex (OFC) were expected predominantly for the BII phobia group. These specific volume changes were expected to correlate with symptom severity in the respective groups.

2. Methods

2.1. Subjects

Structural brain imaging data from 26 dental phobia subjects (DP), 33 snake phobia subjects (SP) and 37 healthy control subjects (HC) who participated in a range of studies from our workgroup between 2007 and 2009 (Lueken et al., 2011, 2013; Hilbert et al., 2014) were used. In these original studies, only functional alterations were reported. The structural data have been used before in a proof-of-concept work that demonstrated, how the diagnostic class of phobic subgroups can be successfully predicted using multivariate pattern analysis and machine learning approaches (Lueken et al., 2014). However, because this kind of analysis aims at deriving diagnostic markers for the individual patient, it is not suitable to describe phenotypic characteristics on a group level and thereby further define the pathophysiology of specific phobia types. The current study provides an analysis adequate to this task. Subjects were selected according to their scores in the Dental Fear Survey (DFS; Tönnies et al., 2002) and the Snake Questionnaire (SNAQ; Hamm, 2008). Subjects scoring 20 or more points in the SNAQ were selected as SP, as this cut-off indicates clinically relevant snake phobia (Hamm, 2008). Subjects scoring 76 or more points in the DFS were selected as DP, as this cut-off indicates severe dental phobia (Tönnies et al., 2002). Subjects scoring in the lower quartiles of both the SNAQ and the DFS served as the HC group. Subjects who scored above cut-offs for both the DFS and SNAQ were excluded. Additional exclusion criteria were either MRI-related or neurological diseases, psychotropic medication, a diagnosis according to DSM-IV-TR criteria of psychotic, bipolar, or obsessive–compulsive disorders, posttraumatic stress disorder, severe depressive disorders or substance dependence (except nicotine). The Composite International Diagnostic Interview (Wittchen and Pfister, 1997) was used to screen for psychiatric exclusion criteria. The Beck Depression Inventory II (BDI-II; Beck et al., 1996) and the Anxiety Sensitivity Index (ASI; Reiss et al., 1986) were used as additional measures. All subjects provided written informed consent. The study protocols of the original studies were approved by the local ethics committee, and all investigations were conducted in accordance with the principles laid down in the Declaration of Helsinki.

2.2. Structural MRI data acquisition and analysis

Structural brain images were acquired by using a magnetization-prepared rapid gradient echo imaging sequence (MPRAGE; 176 sagittal slices, slice thickness = 1 mm, echo time = 2.26 ms, repetition time = 1900 ms, flip angle = 9°, field of view = 256 × 256 mm, matrix = 256 × 256) on a 3-Tesla Trio-Tim MRI whole-body scanner (Siemens, Erlangen, Germany) with a 12-channel head coil. For preprocessing and analysis of the data, Statistical Parametric Mapping-8 (SPM8; ⟨http://www.fil.ion.ucl.ac.uk/spm/software/spm8/⟩) and the VBM8 toolbox (⟨http://dbm.neuro.uni-jena.de/vbm/download/⟩) were used. Modulated images were used to account for individual total tissue volume while interpreting regional tissue volume differences. After segmentation into grey matter (GM), white matter (WM) and cerebrospinal fluid, the IXI550 template included in the toolbox was used for DARTEL-normalizing the images to Montreal Neurological Institute space. During preprocessing, the resolution was slightly down-sampled, from initially 1 × 1 × 1 mm to 1.5 × 1.5 × 1.5 mm. Both the GM and WM data were smoothed by an 8-mm full-width at half-maximum Gaussian kernel and visually checked for artifacts.

After preprocessing, two separate models were used for group comparisons of the WM and GM data. Age and sex were included as covariates, and an image threshold of 0.2 was used. As group differences in smoking behavior were observed during the analysis of demographic data, smoking status was included as a covariate as well. Contrasts were specified for both phobic groups combined and separately versus HC (Phobia groups combined > HC, HC > Phobia groups combined, SP > HC, HC > SP, DP > HC, HC > DP) and for SP versus DP (SP > DP, DP > SP). Whole-brain analyses were conducted and a cluster-size based threshold for significance was used, with each significant cluster including at least 60 consecutive voxels at $p < 0.001$ uncorrected. In addition, a region of interest (ROI) analysis was conducted on the amygdala with $p < 0.001$ uncorrected and a minimum number of 25 voxels per cluster.

2.3. Analysis of demographic and clinical data

Demographic and clinical data were examined via chi-square tests and one-way analyses of variance (ANOVAs). Post-hoc tests for pairwise comparisons were used when appropriate. Clinical data were correlated with GM volumes for significant clusters in the insula, ACC and OFC using Pearson's r in DP or both phobic groups combined, as these areas have previously been implicated in specific phobia psychopathology. GM volumes were extracted for the whole cluster as being significant in the group comparison via the first eigenvariate. If more than one significant cluster was found in one area, the volumes from the cluster yielding the highest t-score were taken. Correlations of these clusters with the BDI-II score were computed to check for an influence of depressive symptoms, as the DP group exhibited higher BDI-II scores. Bonferroni corrections were applied to adjust correlations for multiple testing. Analyses were conducted using SPSS 21 (IBM, New York, NY, USA) with the level of significance being set at $p < 0.05$.

3. Results

3.1. Demographic and clinical data

Sample characteristics are given in Table 1. No group differences were observed for most of the demographic data with the exception