How specific is specific phobia? Different neural response patterns in two subtypes of specific phobia

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Abstract

Specific phobia of the animal subtype has been employed as a model disorder exploring the neurocircuitry of anxiety disorders, but evidence is lacking whether the detected neural response pattern accounts for all animal subtypes, nor across other phobia subtypes. The present study aimed at directly comparing two subtypes of specific phobia: snake phobia (SP) representing the animal, and dental phobia (DP) representing the blood-injection-injury subtype. Using functional magnetic resonance imaging (fMRI), brain activation and skin conductance was measured during phobogenic video stimulation in 12 DP, 12 SP, and 17 healthy controls. For SP, the previously described activation of fear circuitry structures encompassing the insula, anterior cingulate cortex and thalamus could be replicated and was furthermore associated with autonomic arousal. In contrast, DP showed circumscribed activation of the prefrontal and orbitofrontal cortex (PFC/OFC) when directly compared to SP, being dissociated from autonomic arousal. Results provide preliminary evidence for the idea that snake and dental phobia are characterized by distinct underlying neural systems during sustained emotional processing with evaluation processes in DP being controlled by orbitofrontal areas, whereas phobogenic reactions in SP are primarily guided by limbic and paralimbic structures. Findings support the current diagnostic classification conventions, separating distinct subtypes in DSM-IV-TR. They highlight that caution might be warranted though for generalizing findings derived from animal phobia to other phobic and anxiety disorders. If replicated, results could contribute to a better understanding of underlying neurobiological mechanisms of specific phobia and their respective classification.

Keywords: Animal phobia, Blood-injection-injury phobia, Dental phobia, fMRI, Anxiety, Insula, Anterior cingulate cortex

Introduction

Neuroimaging research has successfully employed specific phobia as a model disorder exploring the neurocircuitry of anxiety disorders. Research has predominantly been conducted on the animal subtype, and, more specifically, on spider phobics as an example of animal phobia. Recent reviews point towards a consistent response pattern in animal phobia encompassing hyperactivation of the amygdala, the insula and the dorsal anterior cingulate cortex (dACC; Etkin and Wager, 2007; Shin and Liberzon, 2010). Moreover, neurofunctional commonalities across different anxiety disorders reconstituted as "stress-induced and fear

circuitry disorders" (including posttraumatic stress disorder, panic disorder, specific phobia and social anxiety disorder) have been reported (Rauch and Drevets, 2009).

According to DSM-IV-TR (APA, 2000) five different phobia subtypes (blood-injection-injury (BII), animal, situational, natural environment, other) can be distinguished which show common, but also distinct clinical features (Lebeau et al., 2010). For example, all phobias share excessive, unreasonable and persistent fear of the phobogenic stimulus, followed by pronounced avoidance behavior. While the animal subtype is characterized by a sympathetically dominated autonomic response profile (Globisch et al., 1999; Hamm et al., 1997), the BII subtype does not exhibit exaggerated sympathetic arousal reactions, for example indicated by elevated skin conductance (SC) reactivity during symptom provocation (Hamm et al., 1997; Klorman et al., 1977). Instead, a diphasic vasovagal response pattern is observed during prolonged exposure that can result in a vasovagal syncope, followed by fainting (Lebeau et al., 2010; Ost et al., 1984; Thyer et al., 1985).

In contrast to functional magnetic resonance imaging (fMRI) studies on spider phobia, only few data exist on other phobia subtypes. Recent investigations on hemodynamic response patterns during sustained emotional processing in BII phobia (Caseras et al., 2010a; Hermann et al., 2007; Schienle et al., 2003) were not able to replicate the typical neural response pattern of spider phobia (including the amygdala, insula and ACC) for BII phobia when subjects were presented generally disgusting (Schienle et al., 2003) or phobogenic stimuli (Caseras et al., 2010a; Hermann et al., 2007). Instead, studies reported relatively unspecific activation of the thalamus and visual/attention areas (Caseras et al., 2010a), the right cuneus and lingual gyrus (Schienle et al., 2003), and decreased medial PFC activation (Hermann et al., 2007). Of particular interest are results from Caseras et al. (2010a,b) who reported similar response patterns during immediate reactions towards threat, but differences under sustained processing pointing towards the pivotal role of emotional regulation in the differentiation of these phobia subtypes.

Although evidence is accumulating indicating substantial overlaps in the functional neuroanatomy of various anxiety disorders as well as normal fear (Etkin and Wager, 2007; Rauch and Drevets, 2009), interpretation of findings regarding the specificity for phobia is limited. First, the vast majority of studies are lacking a phobic control group, so it remains unclear which differences in neural activation can be ascribed to phobogenic behavior or to general anxiety proneness which appears to be associated with activity in similar brain regions (Simmons et al., 2006; Stein et al., 2007). Second, owing to the relatively high availability in the general population, studies were predominantly conducted on the animal phobia subtype, particularly spider phobia. Since comparative studies employing more than one phobia subtype are rare (but see Caseras et al., 2010a,b), evidence is lacking whether the previously described neural response pattern accounts for all animal subtypes, nor across phobia subtypes.

The aim of the present study was to directly compare neural activation patterns during sustained symptom provocation in two phobia subtypes and a healthy control group. Supplementing other studies we intended to test if findings on spider phobia could also be detected in snake phobics. Regarding the second phobia group we confined our analysis to a homogenous subsample of BII phobics, dental phobics, who share the same anxiety focus but who have not yet been studied using fMRI before. Although they may not completely overlap, recent reports support the notion that dental phobia shares more similarities than differences with BII phobia (Lebeau et al., 2010) and is classified within the same phobia subgroup. A healthy control group as well as an analogue phobic control group was employed to control

for phobia-unspecific features such as heightened anxiety sensitivity. Autonomic arousal was recorded online in order to supplement analysis of hemodynamic response patterns. A video-based paradigm for symptom provocation was used (Lueken et al., 2011), employing the two anxiety conditions (snake and dental) as a respective non-phobic anxiety control condition for each subtype. Videos were chosen instead of static pictures to design ecologically valid scenarios of first-person encounters with the feared situation, including dynamic features of the feared stimulus.

We hypothesized that snake phobics would exhibit heightened activation of fear circuitry structures such as the thalamus, amygdala, insula and anterior cingulate cortex towards their phobogenic stimulus material when compared to healthy controls as well as to a phobic control group. Based on previous findings (Caseras et al., 2010a; Hermann et al., 2007) we did not assume to detect typical fear circuit activation patterns in dental phobics; instead, modulation of phobogenic responses by orbitofrontal areas was expected. In a first step, we investigated the specificity of neural activations in phobics, comparing them to both a healthy and an analogue phobic control group. Second, we conducted a direct comparison between the functional activation patterns of snake phobia vs. dental phobia. Finally, a positive relationship between neural activation and autonomic arousal in snake phobics was expected.

Methods

Participants

Student volunteers from the Technische Universitaet Dresden (Germany) participated in an online-screening for preselection of snake and dental phobics using the Snake Questionnaire (SNAQ; Hamm, 2008) and the Dental Fear Survey (DFS; Tönnies et al., 2002). In order to avoid confounding by comorbid other mental disorders, subjects were recruited from a student population, applying established clinical cut-offs for the SNAQ (20 points indicating clinically relevant snake phobia; Hamm, 2008) and DFS (76 points indicating severe dental phobia; Tönnies et al., 2002). Subjects scoring in the lower quartiles of both questionnaires were selected as healthy controls. After obtaining written informed consent, subjects completed a standardized clinical diagnostic assessment (Composite International Diagnostic Interview: CIDI; Wittchen and Pfister, 1997) to control for psychiatric exclusion criteria, supplemented by questionnaires assessing symptom severity (SNAQ and DFS) and anxiety sensitivity (Anxiety Sensitivity Index: ASI; Reiss et al., 1986). Exclusion criteria encompassed any comorbidity within the last 12 months between dental and snake phobia, substance dependence (except nicotine), psychotic disorder, bipolar disorder, obsessive-compulsive disorder, posttraumatic stress disorder, severe major depressive disorder, fMRI-related exclusion criteria, current use of psychotropic medication (b four weeks prior to the assessment), and any lifetime neurological disease. One subject was classified as lefthander, but excluding this data set from the analysis did not alter results. A total of 47 subjects were recruited for the study; n=6 subjects had to be excluded due to comorbid disorders (severemajor depressive disorder: n=2, substance abuse: n=1; bipolar disorder: n=1) and excessive movements (n=2). The remaining 41 subjects (snake phobics SP: n=12; dental phobics DP: n=12; healthy controls: n=17) were entered into the data analysis. All subjects received either course credit or were paid 25€ for participation. The study protocol was approved by the local ethics committee.[1]

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[1] Ethics Committee of the Medical Faculty Carl Gustav Carus, Technische Universität Dresden (Germany): EK 23022008 (13.05.2008).

Experimental procedure

The symptom provocation paradigm consisted of 40 videos of 15 s each that were separated by a variable intertrial interval (fixation cross; 11–19 s). We used video sequences to design ecologically valid scenarios of first-person encounters with the feared situation, for example a dental treatment. Stimuli encompassed four conditions with 10 sequences each (snake-anxiety: SA; snake-neutral: SN; dental-anxiety: DA; dental-neutral: DN). The order of stimuli was pseudo-randomized for each subject. In order to avoid generalization effects, each neutral condition preceded the respective anxiety condition. Video pairs were not shown directly after one another to avoid carry-over effects (e.g., DN-1 and DA-1). Stimuli were taken from a pool containing 84 videos (for a detailed description of the stimulus material see Lueken et al., 2011).[2] Briefly, we used publicly available video material to assemble SA videos of living snakes. The respective neutral conditions (SN) were custom-fit videotaped and matched for environmental textures (e.g., stones, trees, or leaves) and timing of cuts within the sequences, thus providing an optimal baseline in order to control for non-anxiety specific processes. DA videos covered typical dentist actions that exhibit anxiety provoking stimulus characteristics as previously reported (Oosterink et al., 2008). Again, matched DN scripts were developed. For example, in the anxiety condition a dentist puts on a latex glove in order to prepare for the treatment, while in the neutral condition a different person in another context (no dental cues) puts on a white wool glove. All scenes were videotaped from a first-person perspective (i.e., sitting in the dentist chair). Persons appearing in the scenes were played by two different actors (dentist and control scenes). Based on pilot data from a student sample that was stratified on the DFS score using a median split procedure (Lueken et al., 2011) those 10 videos scoring highest in anxious subjects (classified as moderate, but not severe dental phobia as in the present sample)were selected for the scanner paradigm. Subjects were instructed to look attentively at the stimuli. After completion of the scanner session subjects rated each video on a nine-point Likert scale regarding valence ("The video was: negative/neutral/positive"), arousal ("The video made me nervous: not at all/very"), anxiety ("The video made me anxious: not at all/very"), disgust ("The video was disgusting: not at all/very") and pain ("The video made me feel/remember pain: not at all/very"). The paradigm was programmed using Presentation 12.0 (Neurobehavioral Systems, Albany, CA, USA) and presented on video goggles (VisuaStim Digital, Northridge, CA, USA).

SC was recorded from the second phalanx of the second and third index finger of the non-dominant hand, using Ag/AgCl electrodes (MES Medizintechnik, Munich, Germany) and isotonic electrode paste as contact medium (Synapse, Kustomer Kinetics, Arcadia, CA, USA). Recordings were carried out using Brain Vision hard- and software (Brain Vision ExG Amplifier and Brain Vision Recorder; Brain Products, Munich, Germany). Data were filtered using a low cut-off (10 s) and a high cut-off Filter (250 Hz). Initial sampling rate was 1000 Hz; SC data were subsequently downsampled on 10 Hz. SC data were analyzed using a Matlab (The MathWorks, Natick, MA, USA) based application (Ledalab Version 3.06; Benedek and Kaernbach, 2010) from which we used the decomposition analysis data. For each video, the number (NS.SCR) and sum amplitude (AMP.NS.SCR; response criterion 0.02 µS) of non stimulus-specific SC reactions were calculated. All SC parameters were range-corrected according to the method introduced by Lykken (1972). For both subjective ratings and autonomic markers difference scores were calculated between the anxiety and neutral control condition (e.g., SA minus SN; DA minus DN), thus paralleling individual t-contrasts from functional data that were entered in the second-level full factorial model.

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[2] Videos available upon request.

fMRI data acquisition and analysis

MRI images were acquired on a 3-Tesla Trio-Tim MRI whole-body scanner (Siemens, Erlangen, Germany). For functional images, 487 volumes were obtained using a T2* weighted gradient echo planar images (EPI) sequence covering the whole brain (repetition time TR 2500 ms, echo time TE 25 ms, field of view 192×192 mm, matrix 64×64). Each volume comprised 43 axial slices (slice thickness 3.5 mm, interleaved acquisition, no gap, in-plane resolution 3×3 mm) which were acquired using a tilted angle to reduce susceptibility artifacts in inferior brain areas (Deichmann et al., 2003). The first four scans were discarded to account for T1 equilibration effects. Structural images were obtained using a Magnetization Prepared Rapid Gradient Echo Imaging (MPRAGE) sequence (repetition time TR 1900 ms, echo time TE 2.26 ms). A standard 12 channel head coil and standard headphones were applied. fMRI Data were analyzed using SPM5 (Welcome Trust Centre for Neuroimaging, UCL, London, UK). Functional images were realigned and unwarped to correct for movement artifacts. Structural images were coregistered to the functional scans and all volumes were normalized to the MNI (Montreal Neurological Institute, Quebec, Canada) reference brain. Functional images were subsampled to a voxel size of 3×3×3 mm and smoothed with a Gaussian kernel of 8 mm full-with half-maximum.

First-level statistical analysis was done for all subjects applying the general linear model (GLM). Using an fMRI block design, the expected blood oxygen level-dependent (BOLD) signal change was modeled by a canonical hemodynamic response function for the four regressors of interest (SA, SN; DA, DN); the six movement parameters of the rigid body transformation applied to the realignment procedure were further introduced as covariates into the model. BOLD responses for each regressor were extracted using peri-stimulus time histograms (rfxplot; Glascher, 2009) that were calculated from non-threshold data (sphere of 5 mm diameter) around a search volume of interest. Data are provided in seven time bins (corresponding to a TR of 2500 ms) for a time window of 15 s. Response peaks (maximum values) and latencies (time bin of maximum value) were calculated. For group inference, t-contrasts ((SA>SN) and (DA>DN)) were calculated for each subject. Using the neutral conditions (DN and SN) as tailored baselines, the individual contrast images for the two contrasts SA>SN and DA>DN from the first level analysis were used in a second-level random effects analysis employing a full factorial design with the two factors "group" (SP, DP and controls) and "video content" (snake and dental). Differences in functional activation patterns when comparing phobics with a healthy control group vs. a phobic control group were tested using the following contrasts: (SP>controls/SA>SN), (SP>DP/SA>SN), (DP>controls/DA>DN), and (DP>SP/DA>DN). Analyses were first conducted on a whole brain level; in a second step we used a region of interest (ROI) approach in order to keep the brain regions to be compared as constant as possible. Anatomical ROI's were applied using the WFU Pickatlas (Maldjian et al., 2003) for regions that have previously been associated with processing of phobogenic material (e.g., amygdala, insula, ACC, thalamus, hippocampus, OFC, inferior PFC, middle PFC and superior PFC). Differences in functional activation patterns of the respective phobia subtype were tested using the following contrasts: (SP (SA>SN)>DP (DA>DN)) and (DP (DA>DN)>SP (SA>SN)). Due to the high complexity of the stimuli we assumed that snake and dental videos may also differ in anxiety-unspecific features. We therefore used the respective contrast for healthy controls (e.g. (controls (SA>SN)>(DA>DN)) and vice versa) as an exclusive mask (p<0.05 uncorrected) for the former two contrasts, thus masking all activation clusters that were significant also in healthy controls. Estimated beta values from the GLM were extracted from the peak voxel for correlational analyses. Results are reported at p<0.05, corrected for multiple comparisons

using the false discovery rate (FDR; Genovese et al., 2002). Minimum cluster size was set at 15 (whole brain analysis) and 5 (ROI) contiguous voxels.

Statistical analysis on demographic data and behavioral responses

Demographic and clinical data were tested using chi2 tests and analyses of variance (ANOVA's). Subjective ratings and SC data were tested employing separate two-factorial ANOVAS with the between-subjects factor "group" (SP, DP; controls) and the within-subjects factor "video content" (snake and dental), followed by pairwise comparisons. Differences in BOLD response peaks and latencies for two regions of interest (right amygdala and insula) were tested using one-factorial ANOVA's with the between-factor "group". Pearson's correlations were computed between estimated beta values from fMRI data, subjective anxiety and autonomic markers (AMP.NS.SCR). Bonferroni-corrections were applied to multiple comparisons. The level of significance was set at pb0.05. Analyses were carried out using PASW 17 (SPSS, Chicago, IL, USA).

Results

Behavioral data

Subgroups were comparable regarding demographic characteristics (see Table 1 for details). As expected, DP exhibited highest scores on the DFS and SP on the SNAQ. A non-significant trend (p=0.054) emerged for anxiety sensitivity being higher in the two phobia subgroups compared to controls.

As seen in Fig. 1, SP rated snake videos as significantly more aversive than dental videos (except for pain), while the opposite effect was observed for DP (except for disgust). No differences between both video contents were seen in healthy controls (interaction effect video content*group: valence: $F_{(2, 38)}=18.25$; arousal: $F_{(2, 38)}=35.96$; anxiety: $F_{(2, 38)}=35.43$; disgust: $F_{(2, 38)}=20.97$; pain: $F_{(2, 38)}=13.00$; all p's<0.001). While snake and dental videos were comparable regarding overall valence and arousal, snake videos were generally rated as provoking higher anxiety and disgust levels than dental videos, and dental videos induced stronger feelings of pain (main effect for video content: valence: $F_{(1, 38)}=0.696$, p=0.409; arousal: $F_{(1, 38)}=1.190$, p=0.282; anxiety: $F_{(1, 38)}=4.95$, p=0.032; disgust: $F_{(1, 38)}=44.01$, p<0.001; pain: $F_{(1, 38)}=14.259$, p=0.001). Healthy controls rated both video contents combined generally lower than SP and DP, while the phobic subgroups' ratings were comparable (main effect of group: valence: $F_{(2, 38)}=14.63$; arousal: $F_{(2, 38)}=17.75$; anxiety: $F_{(2, 38)}=25.67$; disgust: $F_{(2, 38)}=13.73$; pain: $F_{(2, 38)}=14.76$; all p's<0.001).

SP reacted with higher SC amplitudes towards their respective stimulus material (e.g. higher amplitudes during snake compared to dental videos), while no such effect was observed in DP (interaction effect video content*group: $F_{(2, 38)}=5.86$, p=0.006; see Fig. 1 for details). Both healthy controls and DP showed lower amplitudes during the entire experiment than SP (main effect group: $F_{(2, 38)}=7.08$, p=0.002); mean amplitudes were higher for snake compared to dental videos in the entire group (main effect video content: $F_{(1, 38)}=7.52$, p=0.009). Nomain or interaction effects were observed for the number of SC reactions.

fMRI data: comparisons between phobics and healthy controls vs. phobic controls

For the contrast DP>controls/DA>DN and DP>SP/DA>DN we observed neither differences between DP and healthy controls nor DP and SP (as a phobic control group) in the whole brain analysis. This null result did not change when applying a less conservative ROI approach. In contrast, the whole brain analysis for the contrast SP>controls/SA>SN yielded elevated brain activation encompassing the inferior frontal operculum, middle temporal gyrus, middle cingulate gyrus, the pallidum, and the cerebellum. Employing DP as a phobic control group (contrast SP>DP/SA>SN), results yielded an even more pronounced activation pattern comprising the middle cingulate gyrus, superior temporal pole, middle frontal gyrus, insula/claustrum, supramarginal gyrus, precuneus, cuneus, postcentral gyrus, pallidum, thalamus, and the cerebellum. We applied an anatomical ROI approach in order to use identical brain areas for the comparison of differences between SP and healthy controls vs. phobic controls. Both comparisons exhibited substantial overlaps encompassing significant hemodynamic responses in the (dorsal) anterior cingulate gyrus, insula, middle frontal gyrus, and thalamus (see Table 2 and Fig. 2 for details). Peri-stimulus time histograms (Fig. 3) of the right amydala revealed initial BOLD responses in SP towards their phobogenic videos with an early decrease after the first half of the video, while DP showed initial, but lower magnitude responses. No significant differences in peak or latency values were observed between groups in the right amygdala (SA peak: $F_{(2, 40)}=1.09$, $p=0.346$; SA latency: $F_{(2, 40)}=2.23$, $p=0.122$; DA peak: $F_{(2, 40)}=1.52$, $p=0.232$; DA latency: $F_{(2, 40)}$ 0.92, $p=0.406$). In contrast, sustained BOLD responses in the right insula were observed in SP, but not in DP towards their respective stimulus material. Insula peak values for SA videos differed significantly between SP and controls (SA peak: $F_{(2, 40)}=3.43$, $p=0.043$; SA latency: $F_{(2, 40)}=0.95$, $p=0.395$; DA peak: $F_{(2, 40)}=0.079$, $p=0.924$; DA latency: $F_{(2. 40)}=0.21$, $p=0.816$).

fMRI data: comparisons between phobia subtypes

We tested phobia-specific BOLD responses between the two phobia subtypes. In order to control for unspecific effects in the complex stimulus material, contrasts were masked by significant activation patterns that also occurred in healthy controls during these contrasts (controls (DA>DN)>(SA>SN): activation clusters within the cerebellum, primary visual cortex, inferior parietal cortex, right posterior insula, middle frontal gyrus and parahippocampal gyrus; controls (SA>SN)>(DA>DN): activation clusters within the temporal lobe, inferior parietal cortex, precentral gyrus, inferior frontal operculum and inferior OFC). As can be seen in Table 3 and Fig. 4, DP (contrast DP (DA>DN)>SP (SA>SN)) showed elevated activation in the middle and inferior (lateral) orbitofrontal gyrus, inferior, middle, superior frontal gyrus, the occipito-parietal cortex (supramarginal and angular gyrus) and the cerebellum which was specific for their phobogenic material. SP (contrast SP (SA>SN)>DP (DA>DN)) showed elevated BOLD responses in the insula, thalamus, anterior and middle cingulate gyrus, supplemental motor area, superior frontal gyrus, parietal cortex (supramarginal and superior parietal gyrus), superior temporal gyrus and the cerebellum.

Relationship between neural responses, subjective ratings and autonomic reactivity

Estimated beta values from peak voxels within the insula, thalamus and ACC correlated positively with subjective ratings towards the snake stimuli across all emotional dimensions (anxiety: ranging from $r=0.69$ to $r=0.58$, p'sb0.001; disgust: $r=0.48$ to $r=0.58$; p's<0.001; pain: $r=0.41$ to $r=0.62$, p'sb0.01; arousal: $r=0.49$ to $r=0.60$, p's<0.001; valence: $r=-0.40$ to $r=-0.54$, p's<0.01). Likewise, neural activation positively correlated with SC amplitudes (Fig. 4).

Regarding dental stimuli, neural activation in clusters of the OFC and inferior frontal gyrus also correlated with subjective ratings, but with the exception of disgust (anxiety: ranging from r=0.35 to r=0.44, p's<0.05; disgust: r=0.22 to r=0.23; ns; pain: r=0.32 to r=0.33, p's<0.05; arousal: r=0.37 to r=0.41, p's<0.05; valence: r=−0.35 to r=−0.38, p'sb0.01). Beta values from prefrontal/orbitofrontal areas were not related to SC amplitudes (see Fig. 4).

Discussion

In this sample of specific phobia of the animal (snake phobia; SP) and BII subtype (dental phobia; DP) considerable differences were found between the phobia subtypes: first, present results confirm that the previously reported neural activation pattern encompassing the fear circuit in animal phobia does not only apply to spider, but also to snake phobics. Employing an analogue phobic control group (DP) it could be shown that activation patterns were specific to phobic anxiety and not to general anxiety proneness which was comparable between phobic groups. Second, this response pattern could not be demonstrated for the BII subtype. Instead, we observed a dissociation between subjective anxiety and autonomic and neural reactivity: while DP rated the dental videos equally aversive as SP their respective phobogenic stimuli, a marked non-responsiveness was observed on physiological response levels in DP when compared to healthy controls, including autonomic and hemodynamic responses. Third, employing a comparative design, we were able to directly compare neural substrates of snake and dental phobia. For DP, results again confirmed the absence of activation in structures within the fear circuit. While SP exhibited elevated neural activation in anxiety-related brain regions, DP instead activated prefrontal and lateral orbitofrontal areas only. Autonomic reactivity was associated with elevated responses in limbic and paralimbic regions, but not in the PFC and OFC. Assuming the validity of our paradigm, these findings seem to indicate different neural and psychophysiological processes in the two specific phobia subtypes studied.

While subjective ratings confirmed the validity of the paradigm, results on autonomic reactivity indicated a dissociation between subjective anxiety and autonomic responses in DP, but not SP, mirroring previous findings on absent sympathetically dominated defensive reactions in BII phobics (Hamm et al., 1997; Klorman et al., 1977). This lack of responsiveness was also observed on a neural level. It could be argued that DP might differ from SP in terms of severity of phobic fear, but subjects were selected according to well-established cut-offs. Although significant phobogenic reactions were obtained in both groups, DP appeared to exhibit slightly lower response magnitudes, which could have in turn affected the magnitude of neural responses. But even when applying a less conservative region of interest approach, null results for the DP group were obtained. Since differences in symptom severity are not likely to account for the observed effects, present findings could be interpreted as a dissociation of subjective and physiological fear reactions, extending to the neural level of phobic anxiety. A dissociation between subjective and biological (e.g. hypothalamic- pituitary-adrenal (HPA) axis activation) outcome measures of fear has been recently reported for spider phobia and for panic disorder as well (van Duinen et al., 2010; Petrowski et al., 2010). The diphasic vasovagal response pattern and fainting phenomena observed in BII phobia could influence cerebral blood flow (Thyer et al., 1985), and, in turn, hemodynamic responses. A comprehensive evaluation of vagal regulation and fainting phenomona is however lacking for the present sample, remaining this hypothesis speculative and requiring further testing. Assuming that drops in blood pressure should affect the BOLD response in the whole brain, we compared the magnitude of parameter estimates in the occipital cortex during the presentation of the dental-anxiety videos. Identical contrast estimates clearly deviating from zero in all three groups argue against this hypothesis. Lack of

activation within the fear circuitry in BII is further supported by previous studies (Caseras et al., 2010a; Hermann et al., 2007; Schienle et al., 2003). It should be noted, however, that those and present findings may be limited to sustained emotional responses in BII phobia, since different results have been obtained for rapid and transient fear reactions (Caseras et al., 2010b). Furthermore, directly comparing DP and SP indicated elevated neural activation in anxiety-related brain regions in SP, while DP predominantly activated prefrontal and lateral orbitofrontal areas. Regarding the specific role of the OFC in anxiety, two functional networks, the medial vs. lateral OFC, have been proposed (Milad and Rauch, 2007; Ongur et al., 2003; Ongur and Price, 2000). Following this model, negative affective states preferentially activate the lateral OFC, while the medial OFC is associated with the processing of positive affect (Milad and Rauch, 2007). In line with this, decreased left medial OFC activity in BII phobia was reported by Hermann et al. (2007) that normalized after cognitive-behavioral treatment (CBT), while present results indicated enhanced activation of the lateral OFC during phobogenic stimulus processing which was associated with subjective anxiety, but not autonomic arousal. Of particular note, disgust was the only emotional dimension not to be associated with OFC activation. As indicated by subjective ratings, a distinct phenomenological profile of dental phobia may be assumed with fear of pain, but not disgust being the primary trigger (Bradley et al., 2008). The OFC has furthermore been associated with the representation of rules reappraising emotional events (Ochsner et al., 2002). Thus, activation of the lateral OFC in DP may represent learned associations with aversive outcomes (e.g. dental situations). Following this interpretation DP may perceive their respective phobogenic stimuli based on evaluation processes controlled by orbitofrontal areas, whereas SP reactions towards phobogenic stimuli are primarily guided by areas of the anxiety circuit (i.e. amygdala, insula, and ACC).

Present findings on SP are well in line with previous studies on spider phobics that have reported hyperactivation of the amygdala (Dilger et al., 2003; Goossens et al., 2007; Schienle et al., 2005, 2007; Straube et al., 2006), insula (Dilger et al., 2003; Goossens et al., 2007; Schienle et al., 2005; Straube et al., 2006; Wendt et al., 2008), and (dorsal) ACC (Goossens et al., 2007; Schienle et al., 2005; Straube et al., 2006, 2007; Wendt et al., 2008). Based on negative findings regarding amygdala activation in the present study, we investigated BOLD response curves in more detail (Fig. 3). In accordance with other studies suggesting a crucial function of the amygdala in the initial processing of phobia-related threat (Larson et al., 2006), PSTH plots demonstrated early and short-lasting BOLD responses in the right amygdala that already decreased during the second half of the video. In line with this, Caseras et al. (2010b) reported reduced time-to-peak latencies of BOLD responses in the amygdala and insula for spider phobics. The choice of paradigm, in combination with a rather small sample size may hence have lead to subthreshold amygdala activation in this sample. Others have proposed a more restricted role of the amygdala with insular hyperreactivity being a key pathophysiological marker of animal phobia (Wendt et al., 2008; Wright et al., 2003). The insular cortex has been linked to the processing of (aversive) interoceptive stimuli and anxiety-proneness (Simmons et al., 2006; Stein et al., 2007). It has been suggested that the "limbic" sensory cortex of the insula is complemented by a limbic motor system of the ACC, (Craig, 2002). The ACC exerts strong projections to brainstem autonomic centers (Ongur and Price, 2000) and may, in concertation with the insula, be related to arousal components during phobogenic stimulus processing (Wendt et al., 2008), and to the emotion of disgust (Stark et al., 2007). Localizations of activation clusters in the insula and ACC for SP correspond well with recent findings from a meta-analysis on different anxiety disorders, including specific phobia (Etkin and Wager, 2007). The positive relationship between insular activation, subjective anxiety and autonomic reactivity further underlines the crucial role of the insula in animal phobia, thus conforming to findings from Caseras et al. (2010b). Although we did not

detect reduced response latencies, elevated BOLD amplitudes were observed for SP in the insula, but not the amygdala.

Results should be interpreted within the methodological limits of the study. Regarding the small sample size we have to acknowledge that the study generally was underpowered, resulting in difficulties to detect smaller scale effects. Although it is assumed that phobic anxiety exists upon a quantitative continuum, subjects were selected according to clinical cut-offs, but not DSM-IVTR diagnoses. It remains to be demonstrated if findings can be generalized to treatment-seeking samples. We utilized dental phobia as a subgroup of BII phobia; as neural correlates of dental phobia have not been studied yet and findings only partly overlap with previous results of BII phobia, it is to question whether dental phobia can be considered as a model disorder of BII phobia. Recent reports support the notion that dental phobia shares more similarities than differences with BII phobia (Lebeau et al., 2010). We do, however, strongly suggest a direct comparison of DP and other (non dental phobic) BII types to evaluate whether results can be generalized to the BII phobia category. Implementing a video approach required construction of different, tailored baselines. We cannot exclude the possibility that activation levels depend to a certain degree on the matching obtained between baseline and anxiety conditions (e.g., too close matching could induce anticipatory effects in the baseline condition). Subjective ratings however showed that positive differences between the two conditions were obtained for both phobia groups, while controls did not exhibit differences between anxiety and neutral conditions. A block design was used, which allows for maximum power to detect significant activations, but does not capture brief and short-time brain activations. Future studies should address the time course of fear responses, including anticipatory components, immediate threat reactions, as well as sustained emotional regulation to comprehensively characterize phobia subtypes on a neural level. Moreover, when directly comparing neural activation patterns of dental and snake phobic anxiety, a masking approach was used excluding those voxels that were significantly activated in healthy controls also. This approach appears to be rather strict, since brain regions that are present in controls, but stronger activated in phobics could have been excluded. Analyses without masking showed that predominantly multimodal sensory processing areas in the temporal and parietal cortices activated, corresponding to dorsal and ventral visual processing pathways. Notably, we also found significant activations in the right hippocampus for both phobic groups. It can thus be assumed that this structure had been masked due to significant activations also in controls, but should be taken in account when interpreting present findings for phobic reactions. Finally, although SC was recorded online as a physiological parameter, a thorough autonomic characterization including cardiovascular parameters is missing. Thus, we cannot provide closer information about the possible origin of the typically biphasic physiological response, as well as the fainting response in BII phobia in connection to the fMRI findings.

In summary, we provide preliminary evidence for the idea that snake and dental phobia are characterized by distinct underlying neural systems during sustained stimulus processing: a cognitive evaluation system (PFC/OFC) in DP vs. a direct fear-reaction system in SP. In DP this higher-order cognitive evaluation system appeared to be dissociated from physiological components of a defensive fear reaction. The origin of this altered response pattern remains however speculative and should be targeted by future studies. As emphasized by the research agenda for DSM-V it is crucial to incorporate findings from clinical neuroscience in order to complement psychiatric classification (Kupfer et al., 2002). Our findings can be seen as indirect support for the need of differentiating specific phobia subtypes. They however also raise the question of how similar fear circuitry processes might be across phobic disorders or anxiety disorders in a broader sense, emphasizing the need of coherent comprehensive studies

implying subjects with various anxiety disorders (Rauch and Drevets, 2009). If replicated, present results could contribute to a better understanding of underlying neurobiological mechanisms of specific phobia and their respective classification.
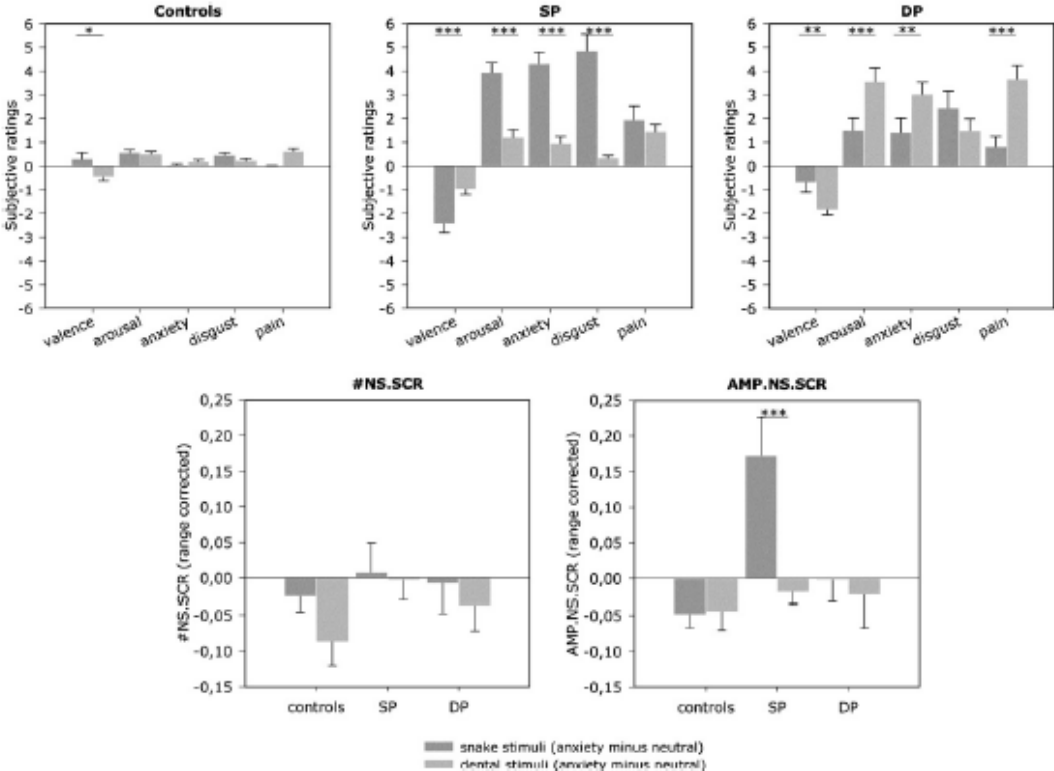

Fig. 1. Behavioral data for validation of the symptom provocation task. Upper line: subjective ratings; lower line: skin conductance data. Difference scores (snake-anxiety minus snake-neutral; dental-anxiety minus dental-neutral) were used for all analyses, error bars indicate the standard error of mean (SEM). SP: snake phobics; DP: dental phobics; #NS.SCR: mean number of non-stimulus specific skin conductance reactions; AMP.NS.SCR: mean sum amplitude of non-stimulus specific skin conductance reactions. *p<0.05; **p<0.01; and *** p<0.001 (Bonforroni-corrected).
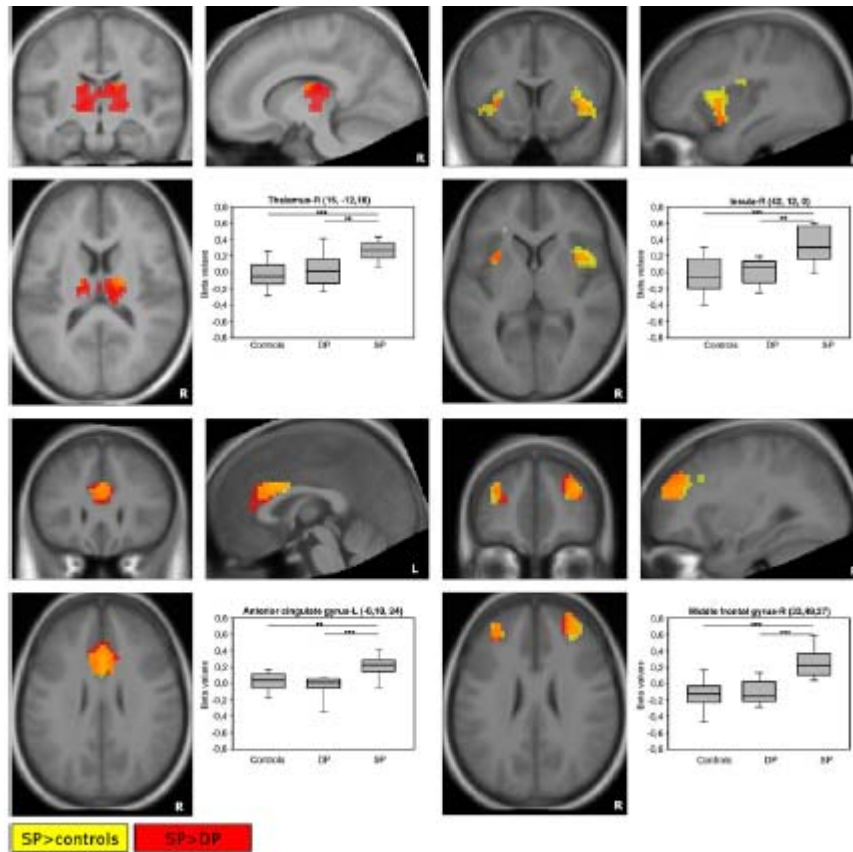
Fig. 2. Comparison of two control groups for the contrast snake-anxiety>snake-neutral. SP: snake phobics; DP: dental phobics. Yellow: SP (snake-anxiety>snake-neutral)>controls (snake-anxiety>snake-neutral); red: SP (snake-anxiety>snake-neutral)>DP (snake-anxiety>snake-neutral). We applied a region of interest approach in order to obtain identical brain regions for both comparisons (p<0.05, FDR correction; max. cluster size 5 contiguous voxels). l: left; R: right. ** p<0.01; and *** p<0.001 (Bonferroni-corrected).
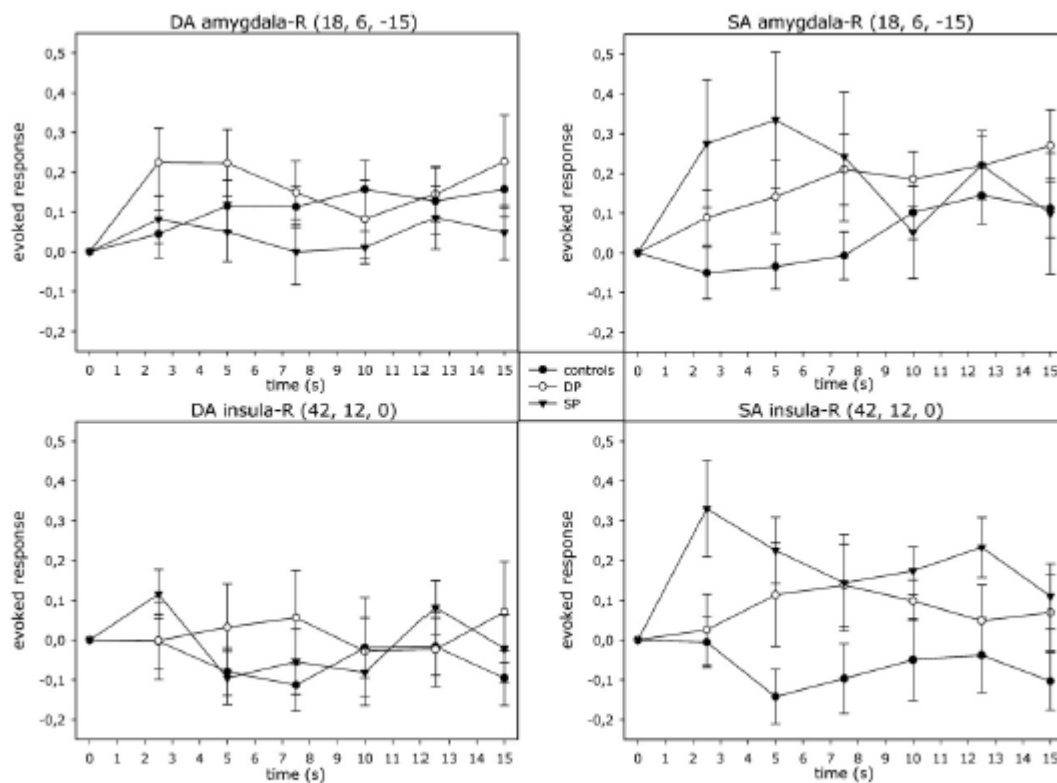

Fig. 3. Peri-stimulus time histograms for selected regions of interest (upper line: right amygdala; lower line: right insula). BOLD response curves are shown for the two regressors dental-anxiety (DA) and snake-anxiety (SA), separately for dental phobics (DP), snake phobics (SP) and healthy controls. Error bars indicate the standard error of mean (SEM).

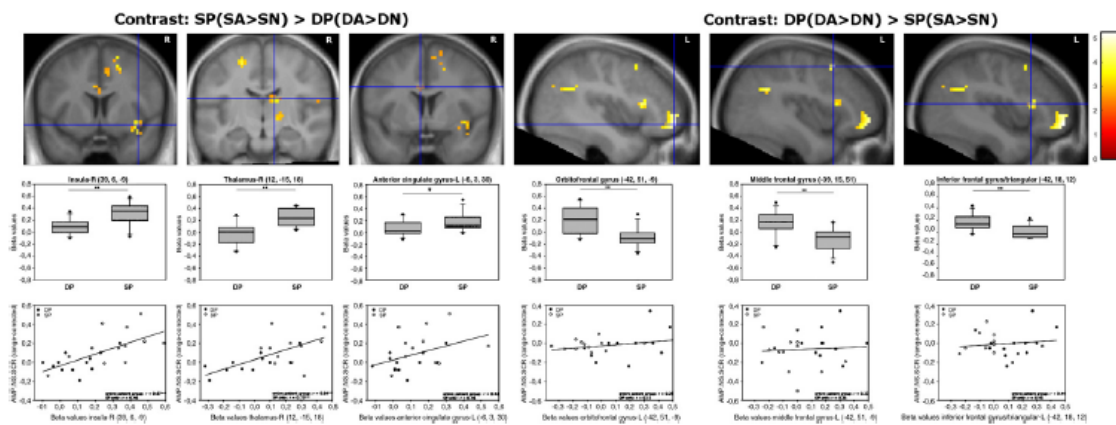**Contrast: SP(SA>SN) > DP(DA>DN)**   **Contrast: DP(DA>DN) > SP(SA>SN)**

Fig. 4. Direct comparison between the two phobia subtypes; results present neural activation patterns specific for dental phobics (DP) when compared to snake phobics (SP) and vice versa. Upper line: functional activation patterns; middle line: differences in beta values extracted from the peak voxels; lower line: scatterplot showing the relationship between neural activity and autonomic reactivity. Please note that an exclusive mask was applied for activation that was unspecific for phobia using the respective contrast in healthy controls (p<0.05, FDR correction; max. cluster size 15 contiguous voxels). L: left; R: right; and AMP.NS.SCR: mean sum amplitude of non-stimulus specific skin conductance reactions.

Table 1
Sample characteristics [means (sd) except where noted].

	Controls (n=17)		DP (n=12)		SP (n=12)		chi^2/F^a (df)	p
Female gender [n (%)]	12	(71.10)	9	(75.00)	9	(75.00)	0.99 (2)	ns
Smoking [n (%)]	6	(35.30)	2	(16.70)	0	(0.00)	5.67 (2)	ns
Age (years)	23.7	(4.44)	25.6	(7.54)	25.1	(7.03)	0.36 (40)	ns
DFS	31.8	(9.51)	80.7	(4.80)	51.5	(13.46)	80.53 (40)	<0.0001^b
SNAQ	5.1	(4.01)	9.2	(6.03)	22.8	(2.41)	60.58 (40)	<0.0001^c
ASI	14.9	(8.31)	22.1	(11.17)	22.0	(7.36)	3.15 (40)	0.054

DP: dental phobics; SP: snake phobics; DFS: Dental Fear Survey; SNAQ: Snake Questionnaire; ASI: Anxiety Sensitivity Index.

[a] Fisher's exact test when appropriate.

[b] Dental phobics>snake phobics>controls, p<0.001.

[c] Snake phobics>dental phobics, controls, p<0.001 (all p's Bonferroni-corrected).

Please note that questionnaire data relate to the date of screening that was used for study inclusion.

Table 2
Brain activation during the processing of phobic and neutral video sequences. Comparisons between phobics and controls and the two phobic subgroups are shown.

Contrast/region	Side	Voxels	x	y	z	t	p corr.
Whole brain analysis							
Dental anxiety > dental neutral							
DP(DA > DN) > controls (DA > DN)	No differential activation						
DP(DA > DN) > SP(DA > DN)	No differential activation						
Snake anxiety > snake neutral							
SP(SA > SN) > controls(SA > SN)							
Cerebellum	L	6469	−6	−63	−12	5.59	0.002
Cerebellum	L	20	−30	−54	−48	3.66	0.008
Cerebellum	L	16	−33	−60	−27	3.12	0.020
Inferior frontal operculum	L	141	−51	3	6	4.30	0.003
Middle temporal gyrus	R	15	51	−33	−15	3.67	0.008
Middle cingulate gyrus	R	100	12	−30	42	3.60	0.009
Pallidum	R	17	21	−3	−3	3.58	0.009
SP(SA > SN) > DP(SA > SN)							
Cerebellum	L	1004	−3	−63	−12	5.63	0.003
Middle cingulate gyrus	R	904	3	12	45	5.40	0.003
Middle cingulate gyrus	R	54	9	−33	45	4.05	0.009
Supramarginal gyrus	R	168	60	−27	27	4.74	0.004
Supramarginal gyrus	L	26	−66	−30	24	4.17	0.007
Middle frontal gyrus	R	115	30	48	27	4.67	0.004
Middle frontal gyrus	L	106	−36	42	24	3.73	0.014
Insula	R	115	42	12	0	3.62	0.016
Claustrum	L	33	−30	12	3	3.65	0.015
Precuneus	L	74	−12	−63	51	4.00	0.009
Cuneus	L	21	−9	−75	33	3.49	0.020
Postcentral gyrus	L	21	−27	−45	57	3.87	0.011
Pallidum	R	28	21	−6	0	3.87	0.011
Thalamus	L	85	−12	−9	0	3.84	0.012
Thalamus	R	49	12	−18	18	3.82	0.012
Superior temporal pole	L	16	−54	9	−3	3.56	0.017
Region of interest analysis							
Dental anxiety > dental neutral							
DP(DA > DN) > controls (DA > DN)	No differential activation						
DP(DA > DN) > SP(DA > DN)	No differential activation						
Snake anxiety > snake neutral							
SP(SA > SN) > controls(SA > SN)							
Amygdala	L/R	No differential activation					
Thalamus	R	18	15	−12	18	4.65	0.006
Thalamus	L	5	−15	−12	18	4.09	0.010
Insula	R	191	42	12	0	4.65	0.005
Insula	L	184	−30	−18	21	4.11	0.005
Anterior cingulate gyrus	L	161	0	15	30	4.17	0.007
Hippocampus	L/R	No differential activation					
Orbitofrontal gyrus	L/R	No differential activation					
Inferior frontal gyrus	L/R	No differential activation					
Middle frontal gyrus	R	188	33	48	27	5.17	0.001
Middle frontal gyrus	L	113	−30	42	30	3.65	0.006
Superior frontal gyrus	L/R	No differential activation					
SP(SA > SN) > DP(SA > SN)							
Amygdala	L/R	No differential activation					
Thalamus	L	403	−12	9	0	3.84	0.012
Insula	R	31	42	12	0	3.62	0.038
Claustrum	L	16	−30	12	3	3.65	0.038
Anterior cingulate gyrus	L	279	−6	18	24	4.68	0.002
Anterior cingulate gyrus	L	17	−15	48	0	3.42	0.005
Hippocampus	L/R	No differential activation					
Orbitofrontal gyrus	L/R	No differential activation					
Inferior frontal gyrus	L/R	No differential activation					
Middle frontal gyrus	R	158	30	48	27	4.67	0.004
Middle frontal gyrus	L	125	−36	42	24	3.73	0.009
Superior frontal gyrus	L/R	No differential activation					

L: left; R: right; DP: dental phobics; SP: snake phobics; voxel: number of voxels per cluster; x, y, z: MNI coordinates; exploratory analysis: minimum cluster size = 15; ROI analysis: minimum cluster size = 5; p corrected using the false discovery rate (FDR; p < 0.05).

Table 3
Comparison of brain activation between phobia types towards their respective phobic stimulus material.

Contrast/region	Side	Voxels	x	y	z	t	p corr.
Whole brain analysis							
DP(DA>DN)>SP(SA>SN)							
Orbitofrontal gyrus (middle)	L	59	−42	51	−9	5.16	>0.001
Orbitofrontal gyrus (inferior)	R	68	45	45	−12	4.72	0.001
Orbitofrontal gyrus (inferior)	L	17	−18	24	−18	3.64	0.011
Middle frontal gyrus	L	20	−39	15	51	4.65	0.001
Middle frontal gyrus	R	33	36	21	54	4.59	0.001
Angular gyrus	R	15	57	−51	33	4.64	0.001
Supramarginal gyrus	L	54	−48	−51	30	4.56	0.001
Inferior frontal gyrus (triangular)	L	30	−42	18	12	4.19	0.003
Superior frontal gyrus (medial)	L	55	−3	45	48	4.15	0.004
Superior frontal gyrus (medial)	L	53	0	45	24	3.72	0.010
Superior frontal gyrus (medial)	R	20	9	33	39	3.82	0.008
Cerebellum	R	17	21	−90	−30	3.23	0.026
SP(SA>SN)>DP(DA>DN)							
Superior temporal gyrus	R	71	57	−33	9	5.24	>0.001
Supramarginal gyrus	L	121	−66	−30	24	5.02	>0.001
Supramarginal gyrus	R	28	57	−33	33	3.90	0.002
Superior parietal gyrus	L	15	−21	−60	48	3.04	0.017
Superior frontal gyrus	L	75	−21	−12	57	5.00	<0.001
Superior frontal gyrus	R	97	21	9	57	3.75	0.003
Insula	R	29	39	6	−9	3.98	0.002
Thalamus	R	22	12	−15	18	3.66	0.004
Thalamus	L	26	12	−21	0	3.52	0.005
Anterior cingulate gyrus	L	16	−6	3	30	3.44	0.007
Middle cingulate gyrus	R	17	15	−24	42	3.20	0.012
Cerebellum	L	18	−6	−69	−18	3.39	0.007
Supplemental motor area	R	25	6	12	45	3.21	0.011

L: left; R: right; DP: dental phobics; SP: snake phobics; voxel: number of voxels per cluster; x, y, z: MNI coordinates; exploratory analysis: minimum cluster size = 15; p corrected using the false discovery rate (FDR; p<0.05). Please note that an exclusive mask for the respective contrast in healthy controls was used to control for nonspecific differences in neural responses towards the stimulus material.

Disclosure statement

Acknowledgments

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