Altered functional connectivity of basal ganglia circuitry in dental phobia

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Abstract

Recent symptom provocation studies that compared patients suffering from dental phobia with healthy controls identified hyperactivation of basal ganglia structures, but none have assessed striatal functional connectivity. We reanalyzed data from a previous functional magnetic resonance imaging study on dental phobia. Patients (20 men, 25 women) and healthy controls (18 men, 23 women) had been exposed to pictures showing dental treatment, and neutral contents. We conducted connectivity analyses via psychophysiological interactions (PPI). Relative to nonphobic controls, the patients showed decreased connectivity between prefrontal and basal ganglia regions. Moreover, the clinical group was characterized by increased internal basal ganglia connectivity, which was more pronounced in female compared to male patients. This study provides first evidence for an altered information flow within a fronto-striatal network in dentophobic individuals during visual symptom provocation, which can be considered a neuromarker of this disorder.

Key words: dental phobia, psychophysiological interactions, connectivity, sex differences
1. Introduction

Our current knowledge about specific phobias has benefited greatly from functional neuroimaging approaches. Research has focused on animal phobias, whereas other subtypes such as dental phobia have been widely neglected (Schienle & Leutgeb, 2013). Dental phobia belongs to the blood-injection injury (BII) subtype of specific phobia. The disorder is characterized by extreme and uncontrollable fear of dentistry. The associated pronounced avoidance of seeking dental care has negative consequences for the oral health and the overall well-being of the afflicted patients (Armfield, 2008).

Two neuroimaging experiments (Lueken et al., 2011; Schienle et al., 2013) investigated neuronal responses during visual symptom provocation in dental phobia (pictures and videos of dental treatment). Whereas in one study, the patients did not differ in their activation from non-phobic controls (Lueken et al., 2011), in the other study the clinical group showed enhanced recruitment of several prefrontal regions (orbitofrontal cortex, anterior cingulate cortex, dorsolateral/ dorsomedial prefrontal cortex), the insula, the inferior parietal cortex as well as the basal ganglia (Schienle et al., 2013). Moreover, male and female dentophobics differed in their activation with greater recruitment of the dorsolateral prefrontal cortex (DLPFC) in male patients and greater recruitment of the caudate nucleus in female patients (Schienle et al., 2013). The authors proposed that this differential activation might mirror sex-specific cognitive strategies during exposure with male sufferers displaying more controlled visual attention to the phobic object (DLPFC), and women being more internally focused on the pain relevance of dental treatment (basal ganglia). The DLPFC recruitment of the male patients was negatively correlated with their experienced arousal implicating a positive functionality of their cognitive approach.
Although it is of great value to identify specialized hyperactive brain structures in specific phobia, this modularity approach is insufficient for the detection of dysfunctional brain mechanisms as it does not consider neuronal interactions. The analysis of coactivation patterns can provide additional information on the neuropathology of a particular disorder. Surprisingly, only a few investigations analyzed connectivity patterns in specific phobia. Ahs et al. (2009) studied animal phobics (spider, snake) and found increased functional coupling between the amygdala, the fusiform gyrus and the motor cortex during the presentation of disorder-relevant slides. Moreover, amygdalar-parahippocampal connectivity covaried with the recognition memory of phobia-related slides (Ahs et al., 2011).

To the best of our knowledge, connectivity patterns in dental phobia have not been studied thus far. For the present investigation we reanalyzed data from a previous fMRI study (Schienle et al., 2013) using psychophysiological interaction analyses (PPI, Friston et al., 1997). PPI analyses identify the functional coupling between brain regions of interest, and therefore provide data about the information flow across distributed neural networks. We chose the basal ganglia and the DLPFC as seed regions for the present analysis as phobics and controls as well as male and female patients had shown differential activation of these regions during exposure. We hypothesized that patients suffering from dental phobia, and especially female sufferers, would show enhanced functional connectivity of the basal ganglia with those brain regions that have been previously identified as crucial for the processing of disorder-relevant stimuli in dental phobia (e.g., insula, orbitofrontal cortex, anterior cingulate cortex; see Schienle et al., 2013). Also, we expected that men afflicted with dental phobia would show greater interaction between the DLPFC and phobia-relevant brain regions, such as the basal ganglia, compared to female patients.
2. Methods and Materials

2.1 Participants

A total of 86 individuals with a mean age of 30 years (SD = 9.8) participated in this study: 20 men and 25 women suffering from dental phobia according to DSM-IV-TR (American Psychiatric Association, 2000), and 18 male and 23 female non-phobic control subjects. The four groups did not differ in age ($F(4,81) = .33, p = .86$).

Male and female patients reported a similar disease duration ($M_{men} = 18.3$ years, $SD = 11.3$, $M_{women} = 15.4$ years, $SD = 10.3$, $t(40) = .88, p = .39$) and symptom severity on the Dental Anxiety Scale (DAS; Corah (1969); $M_{men} = 17.2$, $SD = 2.2$, $M_{women} = 16.8$, $SD = 2.5$, $t(43) = .43, p = .67$). Also, men and women of the control group did not differ in their DAS scores ($M_{men} = 6.3$, $SD = 1.5$, $M_{women} = 6.0$, $SD = 1.4$, $t(43) = .82, p = .42$).

The participants had been recruited via announcements in local newspapers and at the university campus. Written informed consent had been obtained from each subject prior to entry. All participants were non-medicated and right-handed. Exclusion criteria for the patients were substance dependence (except nicotine), psychotic disorder, bipolar disorder, obsessive-compulsive disorder, posttraumatic stress disorder, major depressive disorder, blood phobia with fainting symptoms as well as current use of psychotropic medication. Remaining comorbidities included the presence of an additional specific phobia (e.g. height phobia, small animal (pigeon) phobia) in seven female patients and in five male patients. A board-certified psychotherapist had verified the clinical diagnosis and had checked for comorbidities. If interested, the phobic participants were referred to psychotherapy. For healthy participants the presence of any mental disorder led to exclusion. The study had been approved by the ethics committees of the University Graz and Giessen.
2.2 Stimuli and Procedure
The paradigm included 120 pictures representing four different emotional categories: ‘Phobia’, ‘Fear’, ‘Disgust’ and ‘Neutral’ (Lang et al., 2008; Schienle et al., 2011). The phobia-related stimuli depicted scenes of dental treatment (e.g. physician holding a dental drill in his hand, patient with dental driller in his/her opened mouth, a patient sitting on a tilted back chair). Neutral picture consisted of household articles. The Disgust and Fear condition were not analyzed as this reanalysis focused on phobia-related connectivity patterns.

The symptom provocation was successful: the patients gave higher anxiety ratings (range: 1-9) for the phobic pictures (M = 5.82, SD = 2.1) relative to controls (M = 1.76, SD = 1.0; t(84) = 11.4, p < .001). Female patients reported marginally higher anxiety (p = .066) than male patients.

Full details for the procedure and affective ratings have been published previously (Schienle et al., 2013). The participants passively viewed the pictures in random order for 3000 ms each. The inter-stimulus intervals varied between 3000 and 6000 ms. The total fMRI experiment had a duration of 25 minutes.

2.3 PPI analysis
To investigate phobia-related functional connectivity, we conducted psychophysiological interaction (PPI) analyses (Friston et al., 1997) for each participant. PPIs assess the extent to which an experimental factor modulates the connectivity of one brain region with others, in terms of condition-specific covariation in residuals. Given a specific seed region (e.g. left/right caudate nucleus) PPI identifies voxels which covary differentially with the seed region as a function of an experimental factor. For each participant, a PPI analysis was performed by setting up a design matrix containing three columns of variables: the first regressor, the
physiological variable, represented the time series of activity taken from the seed region. The second regressor, the psychological variable, represented the condition type (e.g. the contrast Phobia > Neutral). The PPI variable (psychophysiological interaction term) represented the third regressor, which was computed as the element by element product of the deconvolved extracted time series of the selected seed region and a vector coding for the effect of task. Subject-specific interaction contrast images were then entered into a random-effects analysis (thresholded at p < .05, corrected for multiple comparisons (family-wise error)) in order to compare connectivity for the contrast: Phobia > Neutral between phobics and controls as well as between female and male phobics, and female and male controls. Based on our previous findings on disorder-related activation in dental phobia, we defined eight seed regions (caudate nucleus, pallidum, putamen, and the DLPFC; each region for the right and the left hemisphere), where patients (relative to controls) had shown greater activation during exposure and additionally sex-specific activation effects had been observed (Schienle et al., 2013).

Further we defined those regions as regions of interest (ROIs) for the PPI analyses, where patients had shown greater activation than controls when looking at phobic vs. neutral pictures: basal ganglia, insula, dorsomedial prefrontal cortex (DMPFC), dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and inferior parietal cortex (IPC). All ROIs were taken from the automatic anatomical labeling atlas (Tzourio-Mazoyer et al., 2002).

We conducted PPI analyses for ten contrasts (see Table 1 and supplementary Table 1), where we tested eight seed regions with regard to their ROI interactions. For three of these contrasts (phobics > controls; female phobics > male phobics; male phobics > female phobics) we had specific hypotheses. We expected that the patients (especially female patients) would show greater basal ganglia connectivity
and that male patients would display greater DLPFC connectivity with the seed regions.

3. Results

During exposure (contrast: Phobia > Neutral), the patient group was characterized by enhanced internal connectivity of basal ganglia structures (putamen, pallidum) relative to controls. The nonphobic participants displayed stronger functional coupling between basal ganglia regions (putamen, pallidum) and prefrontal regions (ACC, DLPFC) than the patients. Also, the control group showed greater connectivity between the DLPFC (seed) and the inferior parietal cortex (Table 1 and Figure 1).

We also investigated sex-specific connectivity patterns in dental phobia. Female patients showed increased internal basal ganglia connectivity relative to the other groups (male patients and female controls). Male phobics displayed a stronger coupling between the right putamen (seed) and the DMPFC compared to female phobics. Moreover, the male patients relative to male controls displayed increased connectivity between the left pallidum (seed), the OFC and the right pallidum (Table 1).

For the control group, the contrasts revealed stronger connectivity of the right caudate nucleus (seed) and the putamen in women compared to men. The male control group relative to the female control group showed no stronger functional connectivity of the selected seed regions (Table 1).

- Insert Table 1/ Figure 1 about here –
4. Discussion

The present PPI analyses demonstrated that individuals suffering from dental phobia not only display hyperactivation in distinct brain areas, but also altered neuronal connectivity when they are exposed to disorder-relevant material.

The patient group was characterized by enhanced internal basal ganglia connectivity. This type of enhanced coupling constitutes a possible mechanism of how hyperactivation is realized during symptom provocation. Both regions reciprocally stimulate each other. This leads to increased striatal activation, which has been previously observed in patients suffering from dentophobia during symptom provocation (Schienle et al., 2013).

The internal basal ganglia connectivity was most pronounced in female patients relative to the other studied groups (male patients, female controls). Previous research on sex-specific neuronal interactions has provided evidence that men and women differ within this parameter. Tomasi and Volkov (2012) used resting-state data from a large sample of 561 healthy subjects and detected a generally higher functional connectivity density in women compared to men. This finding corresponds with findings on structural MRI data that implicated a greater overall anatomical connectivity in the female brain (Gong et al., 2009). Our observed enhanced intra-striatal coupling in female patients however does not simply mirror this overall effect of gender as it was stronger in female patients compared to healthy women. Therefore, a disorder-related interpretation seems legitimate. The enhanced intra-striatal connectivity can be considered a neuromarker of this disorder.

Sex differences in dental phobia have repeatedly been identified on the self-report level. Women indicated to remember more painful experiences after dental treatment (e.g., Eli et al., 2000), displayed more avoidance behavior, and perceived greater loss of (internal) control during the treatment (Sartory et al., 2006, Schienle et
As striatal regions belong to a pain modulatory system (e.g., Borsook et al., 2010), it seems promising to specifically investigate whether the observed altered striatal (co)activation indeed is connected with pain processing in dental phobia. This could be achieved in an experiment by instructing the patients to imagine or to remember painful experiences at the dentist’s office.

Contrary to our predictions, the clinical group (male and female patients) displayed reduced functional connectivity of the basal ganglia relative to the controls. In their meta-analysis on basal ganglia functional connectivity Postuma and Dagher (2005) showed that coactivation patterns of striatal nuclei in healthy individuals are widespread and comprise the prefrontal cortex (including the ACC), the insula and the parietal cortex. For the control group of our experiment, we identified this network. In contrast, the patients were characterized by reduced coactivation implicating an altered balance of facilitatory and inhibitory influences between the basal ganglia and the frontal cortex.

Because male relative to female patients had displayed greater DLPFC activation during exposure (Schienle et al., 2013), we investigated the functional connectivity of this seed region. However, we did not find gender-specific results for the DLPFC. Instead, the whole control group was characterized by a greater DLPFC-putamen coupling than the whole patient group. Thus, enhanced DLPFC activation together with its enhanced basal ganglia connectivity might mirror a positive strategy to deal with exposure to dental treatment scenes.

As a limitation of the present study it has to be noted that the disorder specificity of the observed connectivity pattern cannot be evaluated. Abnormal fronto-striatal coupling has been described in several mental disorders, including anxiety disorders and affective disorders (e.g., Furman et al., 2011; Gimenez et al., 2012, Lorberbaum et al. 2004; Sareen et al. 2007, Maltby et al. 2005; Nakao et al. 2005;
Woolley et al. 2008). For example, Furman et al. (2011) identified attenuated functional connectivity between the striatum and the ventromedial prefrontal cortex as well as the ACC in patients suffering from major depression. Abnormalities concerning striatal connectivity have also been detected in social phobia (Lorberbaum et al. 2004; Sareen et al. 2007), and in obsessive-compulsive disorder (Maltby et al. 2005; Nakao et al. 2005; Woolley et al. 2008). Therefore, a direct comparison of connectivity during individualized symptom provocation might elucidate those neuronal interactions which are crucial for a particular disorder.

Finally, the influence of psychotherapy on connectivity would be of great interest. It can be assumed that a successful reduction of dentophobic symptoms should be accompanied by changes of intra-basal ganglia connections as well as by functional changes of the prefrontal-basal ganglia loop.
Conflict of interest

The authors declare that they have no conflict of interest.
5. References


Highlights

- Dentophobic patients showed reduced frontostriatal coupling.
- They displayed enhanced internal basal ganglia connectivity.
- This intrastriatal coupling was more pronounced in female relative to male patients.
Table 1: Functional connectivity for the contrast Phobia > Neutral

<table>
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<th>REGION</th>
<th>H</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>T</th>
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SEED = seed region for PPI Analysis; H = hemisphere; X, Y, Z, = MNI (Montreal Neurological Institute) coordinates; T = t-value; P(FWE) = p value, family wise-error corrected.
Fig. 1 Increased functional coupling for the contrast Phobia > Neutral
323x252mm (120 x 120 DPI)