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Sex-specific associations between grey matter volume and phobic symptoms in dental phobia

Albert Wabnegger, Wilfried Scharmüller, Anne Schienle*

Department of Clinical Psychology, BioTechMed Graz, University of Graz, Universitätsplatz 2/III, A-8010 Graz, Austria

HIGHLIGHTS

- Voxel-based morphometry study on dental phobia.
- Reduced DLPFC and DMPFC grey matter volume (GMV) in patients.
- Sex-specific correlations between dental anxiety/pain and GMV.

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ABSTRACT

The knowledge about brain structure and function in men and women suffering from dental phobia is still limited. We compared grey matter volume (GMV) data from 36 patients suffering from dental phobia and 36 non-phobic controls via voxel-based morphometry. Half of the subjects were male, the other half female. Scores on different dental anxiety and pain questionnaires were correlated with GMV. Relative to controls, the patients had a smaller volume of the dorsomedial and dorsolateral prefrontal cortex (DMPFC/DLPFC). Within the phobic group, personal pain experience during dental treatment was negatively correlated with DLPFC volume. Sex-specific correlations were found for the amygdala and the hippocampus. Whereas in female patients GMV of both structures was positively correlated with self-reported dental anxiety, for male patients experienced dental pain was negatively associated with hippocampus volume. Our findings show that memory as well as anticipation of dental pain is associated with amygdala-hippocampal structure in men and women afflicted by dental phobia.

1. Introduction

Patients suffering from dental phobia (DP) experience excessive and uncontrollable fear of dental treatment and exhibit pronounced avoidance behavior [1]. Fear of pain is the most common reason for avoiding the dentist, and some authors suggested that DP can be conceptualized as pain phobia [2].

Unlike other types of specific phobia, DP has a less skewed sex distribution. Oosterink et al. [3] reported a prevalence of 4.6% in females compared to 2.7% in males. Despite the considerable amount of male and female individuals afflicted by this disorder, sex differences in dentophobic symptoms and associated problems have hardly been investigated. The majority of studies on gender influences focused on dental fear (in nonclinical samples) instead of phobia. Several questionnaire studies revealed that women report to be more affected by dental pain and experience a lower level of pain control and acceptance than men. Interestingly, there were no sex differences in the number of painful experiences associated with dental treatment (e.g. [4]).

In the same vein, sex-specific neural correlates of dental phobia have hardly been analyzed thus far. To the best of our knowledge, there is only one magnetic resonance imaging (MRI) study that compared male and female dentophobics and controls during visual symptom provocation [5]. The authors showed that male and female patients responded differently to the presented dental treatment scenes. Women showed greater activation of the caudate nucleus, whereas men exhibited enhanced dorsolateral prefrontal cortex (DLPFC) involvement, which was negatively correlated with their experienced arousal. Both areas belong to a pain-modulatory network [6]. The basal ganglia integrate many aspects of pain, such as motor, emotional, autonomic, and cognitive responses to noxious stimulation. The elevated activation of the basal ganglia in female patients might mirror their greater tendency to rehearse pain-related thoughts [5]. The DLPFC is considered a classical area

* Corresponding author at: University of Graz, Department of Psychology, Universitätsplatz 2/III, A-8010 Graz, Austria. Tel.: +43 316 380 5086; fax: +43 316 380 9808.
E-mail address: anne.schienle@uni-graz.at (A. Schienle).

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involved in emotion regulation (e.g. [7]). Men possibly were more actively engaged in cognitive control attempts than females leading to an enhanced DLPFC recruitment. It has to be noted that this study [5] only revealed small sex differences, and male and female phobics displayed similar activation in several limbic regions (e.g., amygdala, hippocampus, putamen).

Moreover, dentophobic women were characterized by a greater caudate volume relative to phobic males as revealed by a voxel-based morphometry (VBM) analysis [5]. Thus there was converging functional and structural evidence for a fronto-striatal circuit involved in the processing of phobogenic stimuli. This is also in line with other MRI investigations on dental phobia (e.g. [8]).

The present VBM study attempted to replicate and extend findings on brain-morphological features of dental phobia. We expected that the grey matter volume (GMV) of specific brain regions relevant for pain processing, modulation and anticipation (e.g. DLPFC, caudate nucleus, amygdala, hippocampus), would be greater in patients, especially in female patients, relative to nonphobic controls. We also conducted exploratory regression analyses in order to detect (sex-specific) associations between different aspects of dental anxiety and GMV.

2. Methods

2.1. Sample

The sample consisted of 36 patients suffering from dental phobia according to DSM-5 and 36 non-phobic controls. Each group consisted of 18 men and 18 women. The participants had been recruited via announcements in local newspapers and at the university campus.

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. Any mental disorder diagnosis led to exclusion of control subjects. Inclusion and exclusion criteria had been checked by a board-certified clinical psychologist based on a standardized clinical interview [9] and additional disorder-specific questions. Male and female patients reported a similar disease duration, and suffered on average 24 years (SD = 11) from their symptoms. The majority of the patients had developed dental fear in childhood, mostly associated with a painful experience at the dentist's office (e.g., tooth drilling/extraction without sufficient pain medication). After completion of the study, all patients were invited to participate in a psychoeducation program, where they were informed about the origin, typical symptoms and treatment options for dental phobia.

The conducted ANOVA for the mean age indicated a significant main effect for group ($F(1,72) = 8.1$, $p = .006$). The patients had a higher mean age ($M = 32.9$ years, SD = 10.3) than the control group ($M = 26.7$ years, SD = 8.3). Main effects for Sex and the interaction Sex × Group were nonsignificant (all p's > .20). The groups did not differ in years of education (all p's > .21).

Written informed consent had been obtained from each subject prior to entry. The study had been approved by the ethics committee of the University of Graz.

2.2. Questionnaires

The participants answered the following questionnaires:

(1) the Dental Anxiety Scale (DAS [11]; Cronbach's alpha = .84; in the present sample: .67) consists of four questions targeting experienced anxiety during anticipated and actual dental treatment (e.g., 'If you had to go to the dentist tomorrow, how would you feel about it?'). The questions are answered on five-point scales ranging from 1 = 'relaxed' to 5 = 'so anxious that I sometimes break out in a sweat or almost feel physically sick'. The resulting sum scores range from 4 to 20.

(2) The Dental Cognitions Questionnaire (DCQ [12]) describes 38 negative cognitions about dental treatment, which have to be answered with 'yes' or 'no' (Cronbach's alpha = .89; in the present sample: .90). The first section contains a list of 14 negative beliefs with regard to dentistry in general (e.g., 'Dentists don't care when it hurts'), and to the patient (e.g., 'I can't stand pain'). The second section consists of 24 negative self-statements that pertain to thoughts during the treatment (e.g., 'Everything goes wrong'). Possible total scores range between 0 and 38.

(3) The Fear of Dental Pain Questionnaire (FDP [13]; Cronbach's alpha = .93; in the present sample .80) consists of 18 items with the following instruction: 'Please look at each item and think about how FEARFUL you are of experiencing the PAIN associated with each item' (e.g., 'Having a tooth pulled', 'Receiving an anesthetic in the mouth', 'Being drilled in the jawbone'). The items are rated on 5-point scales (1 = 'no fear'; 5 = 'extreme fear'). Possible sum scores for the FDP_fear range between 18 and 90. Additionally, all items are extended with the question whether the subject ever experienced the pain personally (FDP_experience: yes/no; possible sum score: 0–18).

2.3. Analysis

Brain structural data were analyzed with the VBM8 toolbox (revision 343, http://dbm.neuro.uni-jena.de/vbm) for voxel-based morphometry. Individual anatomical scans were segmented into grey matter, white matter and cerebrospinal fluid partitions. An optimized blockwise nonlocal means de-noising filter, a Hidden Markov Random Field approach, partial volume estimates and normalization to MNI space by high-dimensional warping with a standard template included in the VBM8-toolbox were used for preprocessing (final resolution: 1.5 × 1.5 × 1.5 mm). In order to preserve brain volume and to correct for individual head sizes already in the pre-processing steps of the data, Jacobian modulation was applied to tissue class segments for non-linear normalization only. Finally, segments were smoothed by a Gaussian kernel (10 mm FWHM).

Afterwards, statistical analyses (voxel intensity tests) were carried out using random effect models. An analysis of variance with a full factorial design was computed with the factors Group (patients, controls) and Sex (men, women). Significant effects were followed up by means of simple t-contrasts. Regression analyses were used to correlate self-report measures of dental anxiety and pain (DCQ, FDP_fear, FDP_experience) with GMV. Due to insufficient reliability, the DAS was not considered anymore. The regression analyses were computed separately for both genders of the patient and control group.

For all random effect analyses, modulated grey matter images were thresholded at the absolute voxel value of >2. Only voxels at which all images exceeded the threshold were included. We conducted region of interest analyses (ROI) for such brain areas that were activated during symptom provocation and showed volume differences between dental phobics and nonphobic controls [5]. These ROIs were: basal ganglia (putamen, pallidum, caudate nucleus), DLPFC, DMPFC, amygdala, and hippocampus. The ROI masks were created using the WFU Pickatlas (v2.4; Wake Forest University School of Medicine) based on the automated anatomical labeling (AAL) template and from the Harvard-Oxford Cortical