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PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - ORIGINAL ARTICLE

Diagnostic classification of specific phobia subtypes using structural MRI data: a machine-learning approach

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Abstract While neuroimaging research has advanced our knowledge about fear circuitry dysfunctions in anxiety disorders, findings based on diagnostic groups do not translate into diagnostic value for the individual patient. Machine-learning generates predictive information that can be used for single subject classification. We applied Gaussian process classifiers to a sample of patients with specific phobia as a model disorder for pathological forms of anxiety to test for classification based on structural MRI data. Gray (GM) and white matter (WM) volumetric data were analyzed in 33 snake phobics (SP; animal subtype), 26 dental phobics (DP; blood–injection–injury subtype) and 37 healthy controls (HC). Results showed good accuracy rates for GM and WM data in predicting phobia subtypes (GM: 62 % phobics vs. HC, 86 % DP vs. HC, 89 % SP vs. HC, 89 % DP vs. SP; WM: 88 % phobics vs. HC, 89 % DP vs. HC, 79 % SP vs. HC, 79 % DP vs. HC). Regarding GM, classification improved when considering the subtype compared to overall phobia status. The discriminatory brain pattern was not solely based on fear circuitry structures but included widespread cortico-subcortical networks. Results demonstrate that multivariate pattern recognition represents a promising approach for the development of neuroimaging-based diagnostic markers that could support clinical decisions. Regarding the increasing number of fMRI studies on anxiety disorders, researchers are encouraged to use functional and structural data not only for studying phenotype characteristics on a group level, but also to evaluate their incremental value for diagnostic or prognostic purposes.

Keywords Machine learning · Gaussian process classifier · MRI · Specific phobia

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Introduction

Neuroimaging research has greatly advanced our understanding of the neurobiological underpinnings of fear and anxiety disorders (Etkin and Wager 2007; Shin and Liberzon 2010). In particular, specific phobia has served as a human model disorder to study the neurofunctional correlates of fear processing and pathological anxiety (reviewed in Linares et al. 2012). Yet, findings on fear circuitry dysfunctions do not translate into diagnostic value for the individual patient. Conventional mass-univariate group analyses are suitable to detect structural and functional differences related to the anxiety phenotype and underlying pathophysiology on a group level. These may be supplemented by multivariate pattern recognition employing machine-learning algorithms, which offer the advantage of single subject predictions necessary for individual

diagnostic classification. Supplementing functional neuroimaging data, acquisition and analysis of structural data is less time consuming, task independent and easy to apply, thus offering advantages for clinical application. Yet, besides a large body of functional neuroimaging studies (see Linares et al. 2012), surprisingly few studies have investigated structural abnormalities in specific phobia or its subtypes (Fisler et al. 2013; Rauch et al. 2004; Schienle et al. 2012).

Machine-learning approaches such as support vector machine (SVM) or Gaussian process classifier (GPC) are increasingly applied to functional and structural neuroimaging data to generate diagnostic and prognostic markers for neurodegenerative, and more recently, mental disorders (for a review see Orru et al. 2012). Pattern recognition is a field within the area of machine learning, which is concerned with automatic discovery of regularities in data through the use of computer algorithms. Using these regularities, it can classify data into different categories. In the context of neuroimaging, brain images are treated as spatial patterns and pattern recognition approaches are used to identify statistical properties of the data that discriminate between two or more groups of subjects. The multivariate pattern algorithm or discriminatory pattern is developed on a training set. Independent prediction of a single subject's classification is conveyed via a cross-validation approach. Leave-one-out cross-validation (LOO-CV) represents a frequently employed method encompassing the exclusion of a single subject from each group, while the classifier is trained on the remaining subjects. The excluded subjects are then used for testing the classifier; this procedure is iterated across subjects (Fu et al. 2008; Hahn et al. 2011, 2013; Mourao-Miranda et al. 2012; Rondina et al. 2014).

Applying GPC on gray matter (GM) volumetric data, Lim et al. (2013) reported disorder-specific classification of adolescents with attention deficit hyperactivity disorder (ADHD) compared to controls with an overall accuracy rate of 79 %. Of note, this classification was disorder specific for ADHD vs. autism disorder. Schnack et al. (2014) presented markers for the differential diagnosis of schizophrenic vs. bipolar patients using SVM on GM density images, successfully delineating both disorders with an accuracy of 88 %. Similarly, high accuracy rates could be obtained for classifying patients with a depressive disorder based on structural or functional MRI data (Costafreda et al. 2009; Gong et al. 2011). This body of evidence supports the assumption that multivariate pattern recognition in neuroimaging research could bridge the translational gap from basic research to clinical purposes and bring diagnostic markers into reach, thus supporting personalized medicine approaches. However, despite being the largest group of mental disorders (Wittchen et al. 2011) there is a remarkable lack of studies testing the potential of MRI data for (differential) diagnostic purposes in anxiety disorders.

In this proof-of-concept study, we aimed to use specific phobia as a model disorder to demonstrate the suitability of GPC to supply objective structural neuroimaging markers that may support traditional diagnostic procedures. Compared to previous studies on severe mental disorders such as schizophrenia, bipolar, autism and depressive disorders (Costafreda et al. 2009; Gong et al. 2011; Lim et al. 2013; Schnack et al. 2014), specific phobia exhibits less clinical impairment. Although there is a remarkable paucity of studies on structural abnormalities, the few available using mass-univariate testing showed only discrete effects on the structural integrity of the brain (Fisler et al. 2013; Rauch et al. 2004; Schienle et al. 2012). We will test whether GPC will be able to capture pattern features related to subtle morphological differences in this group of subjects. In addition, we will test whether GPC is able to differentiate between two subtypes of specific phobia with sufficient accuracy [snake phobics representing the animal subtype and dental phobics representing the blood–injection–injury (BII) subtype]. While all phobia subtypes share excessive, unreasonable and persistent fear of a particular situation or stimulus which is followed by pronounced avoidance behavior (American Psychiatric Association 2000), the animal and BII-subtype differ in regard to autonomic (Hamm et al. 1997; Thyer et al. 1985) and neural response patterns (Caseras et al. 2010; Hermann et al. 2007; Lueken et al. 2011, 2013; Schienle et al. 2003). Based on increasing evidence that phobia subtypes can be differentiated on multiple response levels, we hypothesized that considering the subtype information will improve the differential classification of phobic subtypes compared to the entire class of phobia.

Materials and methods

Participants

Structural MRI scans from phobic subjects and healthy controls (HC) stem from a series of studies (Hilbert et al. 2014; Lueken et al. 2011, 2013) conducted at the Institute of Clinical Psychology and Psychotherapy, Dresden between 2008 and 2013 on the neurofunctional substrates of specific phobia subtypes, namely, snake (SP) and dental phobics (DP). In order to avoid confounding by comorbid other mental disorders, subjects were recruited from a student population and were preselected by an online screening on snake and dental phobia using established cut-offs for the Snake Questionnaire (SNAQ; 20 points indicating clinically relevant snake phobia; Hamm 2008) and

the Dental Fear Survey (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 were screened using a standardized clinical diagnostic assessment [composite international diagnostic interview (CIDI); Wittchen and Pfister 1997]; severe mental disorders such as psychotic, bipolar, obsessive–compulsive disorders, posttraumatic stress disorder, severe depressive disorders and substance dependence (except nicotine) were followed by exclusion. Also, comorbid snake and dental phobia as indicated by the above cut-offs was excluded. Subjects did not exhibit MRI-related exclusion criteria, did not use psychotropic medication within the last 4 weeks and did not report any lifetime neurological disease. 33 SP, 26 DP and 37 HC were entered into the present analysis. The studies had been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, and were approved by the local ethics committee (EK23022008).

MRI data acquisition and preprocessing

MRI images were acquired on a 3-Tesla Trio-Tim MRI whole body scanner (Siemens, Erlangen, Germany). A magnetization-prepared rapid gradient-echo imaging sequence was used to acquire a structural reference image (176 sagittal slices, slice thickness = 1 mm, TE = 2.26 ms, TR = 1,900 ms, flip angle = 9°, FOV = 256 × 256 mm, matrix = 256 × 256). A standard 12-channel head coil and standard headphones were applied. For preprocessing of the structural data, the VBM8 toolbox for SPM8 (http://dbm.neuro.uni-jena.de/vbm/download/) was used. As a first step, structural images were segmented into GM, white matter (WM) and cerebrospinal fluid using the new segmentation routine implemented in the toolbox. Images were modulated to allow for an interpretation of regional tissue volume differences while accounting for individual total tissue volume. Afterwards, images were normalized to MNI space via the high-dimensional DARTEL algorithm (Ashburner 2007) using the standard template included in the toolbox. Following DARTEL default settings, scanning resolution was slightly downsampled to 1.5 × 1.5 × 1.5 mm. Finally, the images were smoothed by an 8-mm full-width half-maximum Gaussian kernel. All resulting images were checked for normalization artifacts, and their covariance matrices were inspected for outliers before inclusion in the following statistical analysis.

Pattern recognition using Gaussian process classifier

A classifier based on pattern recognition is trained by providing examples of the form <x,c>, where x represents a spatial pattern and c is the class label. Each spatial pattern (e.g., whole brain image) corresponds to a point in the input space, and each voxel in the brain image represents one dimension of this space. During the training phase, the pattern recognition algorithm finds a decision function that separates the examples in the input space according to the class label. Once the decision function is determined from the training data, it can be used to predict the class label of a new test example. There are different approaches to determine the decision function depending on the learning method used. It is important to have a decision function that not only classifies the training data correctly, but also does the same for the test data, i.e., one needs to find a classifier which is able to generalize well for new examples. The LOO-CV done to predict a subject's probability to belong to a certain classification (pGP) and to assess generalizability was conducted as follows: in each leave-one-out run, we used data from all but one subject (S-1 of the *S* subjects) to train the classifier. Subsequently, the pGP of the remaining subject, which was so far unseen by the algorithm, was calculated. This procedure was repeated *S* times, each time leaving out a different subject, yielding each subject's pGP for each condition.

GPC is one example of a pattern recognition algorithm, which gives probabilistic outputs. GP are based on Bayesian theory, therefore are guaranteed to handle probability distributions correctly. GPs are most easily understood as a distribution over functions, and GP inference consists of applying Bayes' rule to find the (posterior) function distribution that best approximates the training data. GP classification is actually an extension of the GP regression model, and data are classified by applying a latent regression model, which is then constrained to the unit interval to produce probabilistic predictions.

In this work, GP classification was performed using a customized version of the Gaussian processes for machine-learning (GPML) toolbox for Matlab (http://www.gaussianprocess.org/gpml). We used a linear covariance function and estimated hyperparameters controlling bias and regularization using an empirical Bayesian approach.

Integration of regional predictive probabilities

Using the GM and WM maps from the VBM analysis for GM and WM, respectively, whole brain data from 55 regions drawn from the Harvard–Oxford Brain Atlas as described in Carter et al. (2012) were extracted for each subject. Since WM information may be better mapped by a WM atlas, we conducted a second analysis of WM data using the ICBM-DTI-81 white matter label atlas containing 48 WM-tract labels (Oishi et al. 2008). This data was analyzed using GP classification in accordance with Marquand et al. (2010). We predicted a subject's probability

(pGP) to belong to a respective diagnostic class independently for each region based on all voxels within the respective region LOO-CV. A second GPC with the same specifications used for the local classifiers was applied to integrate the predictive classification probabilities obtained from the local leave-one-out GPC. We used GP classification probabilities as predictors based on which the algorithm determined the classification of a subject. In order to calculate the overall prediction accuracy of this approach, a leave-one-out procedure was implemented in analogy to the one used to determine the accuracy of the regional GP classifiers. Note that we used the same LOO-CV structure in the single classifiers and in this multi-region approach, which ensured that at each CV fold, the test set was completely independent of the training set. We evaluated the performance of the classifier by converting the predictive probabilities to categorical predictions, applying a threshold which categorized a subject as phobic (snake or dental) or control subject, if his/her pGP was larger than 0.5 (smaller than 0.5). Accuracies were calculated as the ratio of correct predictions to number of cases for each GPC. We calibrated classification accuracies in all analyses, since the number of subjects per group was not the same (for details see Hahn et al. 2013). To test the significance of the whole brain classifier's prediction accuracy, we computed the accuracy of the whole brain GPC based on the predictive probabilities derived with randomly permuted labels. Doing this 1,000 times provided a distribution of whole brain GPC accuracy under permutation. We then counted the number of permutations, which achieved higher accuracy than the one observed with the true labels. The p value was calculated by dividing this number by 1,000. To compare the classification accuracies for the three groups (DP vs. HC; SP vs. HC; DP vs. SP), we integrated over the binomial distribution between 0 and 1 in steps of 0.001 to obtain the p value of the respective difference in accuracy.

Regional multivariate mapping

Determining those brain regions, which contributed most to classification, weight maps were derived from the GPC models as described in Marquand et al. (2010) and averaged over all cross-validation folds. While this provides a multivariate estimate of the contribution of each region to classifier performance, one should be aware that the maps describe a non-linear multivariate pattern. Generally, importance scores for each of the regions should be interpreted in the context of the entire multivariate pattern.

Results

Sample characteristics are given in Table 1. Subjects were predominantly right-handed (with the exception of one SP and one DP) and female. Smoking status differed significantly between groups with SP encompassing non-smokers only. Significant differences also arose in phobic fear and anxiety sensitivity with phobics reporting higher scores on the anxiety sensitivity index (Reiss et al., 1986).

Integration of regional predictive probabilities based on gray matter data

Integrating the descriptive probabilities from all regional GP classifiers using an interregional GPC led to an accuracy of 62 % (sensitivity = 57 %; specificity = 67 %; $p = 0.021$) for the classification of patients (SP and DP combined) versus healthy controls based on GM data. Distinguishing between healthy controls and each of the phobia groups separately, however, yielded an increase of 24 % for DP subjects ($p < 0.001$) and an increase of 27 % for SP subjects ($p < 0.001$) compared to considering both phobia groups together, supporting the view that these represent two separate diagnostic entities. Specifically, DP

Table 1 Sample characteristics. Means (sd) except where noted

	Controls ($n = 37$)	DP ($n = 26$)	SP ($n = 33$)	Chi or F (df)	p
Female gender [n (%)]	28 (75.70)	20 (76.92)	25 (75.76)	0.015 (2)	0.992
Right handed [n (%)]	37 (100.00)	25 (96.15)	32 (96.97)	1.328 (2)	0.515
Smoking [n (%)]	7 (18.92)	4 (15.39)	0 (0.00)	6.696 (2)	0.035
Age (years)	22.76 (3.88)	25.27 (5.17)	22.91 (4.69)	2.755 (2)	0.069
DFS	28.68 (7.47)	80.54 (3.65)	47.58 (14.87)	203.573 (2)	<0.001[a]
SNAQ	4.27 (2.63)	9.31 (5.73)	22.73 (1.88)	243.902 (2)	<0.001[b]
ASI	13.65 (6.61)	20.27 (10.81)	19.33 (8.75)	5.745 (2)	0.004[c]

DP dental phobics, *SP* snake phobics, *DFS* dental fear survey, *SNAQ* snake questionnaire, *ASI* anxiety sensitivity index

[a] DP > SP > controls, $p < 0.001$

[b] SP > DP > controls, $p < 0.001$

[c] SP, DP > controls, $p < 0.05$ (all p's Bonferroni-corrected)

subjects could be distinguished from HC with an accuracy of 86 % (sensitivity = 90 %; specificity = 82 %; $p < 0.001$). Likewise, SP subjects were classified with an accuracy of 89 % (sensitivity = 87 %; specificity = 91 %; $p < 0.001$). In addition, we were also able to distinguish DP from SP subjects with excellent accuracy (accuracy = 89 %; sensitivity = 88 %; specificity = 91 %; $p < 0.001$). Regional multivariate mapping indicated that all 55 regions of the Harvard–Oxford Brain Atlas contributed to the discriminatory pattern differentiating phobics from controls (phobics vs. HC, SP vs. HC; DP vs. HC) and from the respective phobic group. Regions ranked according to GPC weights are displayed in Table 2. Although contributing to the predictive value of the GPC within the multivariate pattern, fear circuitry structures such as the amygdala, insular cortex, ACC, or pre-/orbitofrontal regions were not predominantly among the highest-ranking regions. Spearman rank correlations indicated that the order of regions contributing to the overall phobia vs. HC classification was negatively correlated with the DP vs. HC ranking ($r = -0.28$, $p = 0.037$), while being positively correlated with the SP vs. HC ranking ($r = 0.36$, $p = 0.007$).

Integration of regional predictive probabilities based on white matter data

Integrating the descriptive probabilities from all regional GP classifiers using an interregional GPC led to an accuracy of 88 % (sensitivity = 87 %; specificity = 89 %; $p < 0.001$) for the classification of patients (SP and DP combined) versus HC based on WM data. DP subjects could be distinguished from HC with an accuracy of 89 % (sensitivity = 84 %; specificity = 94 %; $p < 0.001$). Likewise, SP subjects were classified with an accuracy of 79 % (sensitivity = 77 %; specificity = 80 %; $p < 0.001$). Thus, in contrast to the results based on the GM data, no improvement was observed when considering the phobia groups separately (all $p > 0.59$). Again, we were able to distinguish DP from SP subjects with high accuracy (accuracy = 79 %; sensitivity = 77 %; specificity = 80 %; $p < 0.001$). Similarly to GM results, all 55 regions of the Harvard–Oxford Brain Atlas contributed to the discriminatory pattern differentiating the respective groups as indicated in Table 3. Spearman rank correlations indicated that the order of regions contributing to the overall phobia vs. HC classification was positively correlated with the SP vs. HC ranking ($r = 0.43$, $p = 0.001$), while no significant correlation was observed with DP vs. HC ranking ($r = -0.22$, $p = 0.105$).

Analyses with the alternative white matter labels atlas yielded comparable results that did not differ significantly (all p's > 0.20) from those obtained using the Harvard–Oxford Brain Atlas (accuracy, sensitivity, specificity: phobics vs. HC: 82, 90, 74 %; DP vs. HC: 79, 84, 75 %; SP vs. HC: 69, 71, 67 %; DP vs. SP: 68, 73, 63 %).

Likewise, integrating GM and WM information by combining the two data sources did not result in improved prediction accuracies, but rather yielded lower rates (accuracy, sensitivity, specificity: phobics vs. HC: 67, 66, 68 %; DP vs. HC: 65, 64, 66 %; SP vs. HC: 80, 77, 83 %; DP vs. SP: 69, 65, 74 %).

Discussion

Multivariate pattern recognition and machine-learning approaches offer new ways to generate predictive information from neuroimaging data that can be used for single subject classificatory or prognostic purposes. As such, they complement conventional mass-univariate analyses that focus on phenotype differences on a group level. In the present study, we applied GPC to a sample of specific phobia subtypes (snake and dental phobics) to test the suitability of GPC for classifying these groups based on structural MRI data. As a proof-of-concept on this model disorder of pathological anxiety, we showed good accuracy rates for both GM and WM data in predicting the phobia subtype. Regarding GM, classification was significantly improved when considering the particular subtype. Combining both data sources did not improve prediction rates. Regional multivariate mapping showed that the discriminatory pattern was not restricted to selected fear circuitry structures, but included widespread cortico-subcortical networks.

Previous studies using machine learning on structural MRI data for patient classification reported accuracy rates for neurodegenerative disorders such as Alzheimer's disease or proposed precursor states such as mild cognitive impairment ranging between 80 and 100 % (summarized in Orru et al. 2012). Regarding mental disease, accuracy rates range between 53 and 90 % depending on patient group and data type (GM, WM). Present findings indicate comparable accuracy rates in a relatively homogenous and mildly affected sample on subtypes of a particular disorder (e.g., specific phobia). Using GM information, we were able to classify 86 % of DP and 89 % of SP compared to healthy controls and also 89 % of DP when compared to their phobic control group. WM information yielded comparable, slightly lower accuracy rates (DP vs. HC: 89 %; SP vs. HC: 79 %; DP vs. SP: 79 %). Using the JHU DTI-based white matter atlas did not improve results for WM information. At this point, we can only speculate on the reasons such as the highly distributed discriminatory pattern that may have been equally mapped by both atlases. Future methodological studies are

Table 2 Regional multivariate mapping and predictive probabilities based on gray matter data

Phobics vs. HC		DP vs. HC		SP vs. HC		DP vs. SP	
Region	Abs	Region	Abs	Region	Abs	Region	Abs
Parahippocampal gyrus (posterior division)	0.1028	Planum polare	0.0653	Frontal orbital cortex	0.0113	Planum polare	0.0006
Thalamus	0.1017	Lingual gyrus	0.0615	Accumbens	0.0110	Angular gyrus	0.0277
Superior temporal gyrus (posterior division)	0.0994	Temporal pole	0.0381	Cingulate gyrus (posterior division)	0.0104	Superior temporal gyrus (posterior division)	0.0994
Supramarginal gyrus (anterior division)	0.0993	Precentral gyrus	0.0315	Heschl's gyrus includes (H1 and H2)	0.0090	Supracalcarine cortex	0.0839
Pallidum	0.0961	Pallidum	0.0314	Frontal medial cortex	0.0087	Occipital fusiform gyrus	0.0519
Temporal fusiform cortex (anterior division)	0.0952	Supramarginal gyrus (anterior division)	0.0309	Postcentral gyrus	0.0084	Temporal fusiform cortex (anterior division)	0.0952
Accumbens	0.0912	Frontal orbital cortex	0.0306	Temporal pole	0.0082	Lateral occipital cortex (inferior division)	0.0138
Planum temporale	0.0906	Inferior frontal gyrus (pars opercularis)	0.0304	Planum temporale	0.0076	Central opercular cortex	0.0140
Cingulate gyrus (posterior division)	0.0895	Angular gyrus	0.0303	Temporal fusiform cortex (anterior division)	0.0075	Supramarginal gyrus (posterior division)	0.0455
Paracingulate gyrus	0.0853	Parietal operculum cortex	0.0293	Lateral occipital cortex (superior division)	0.0067	Inferior frontal gyrus (pars opercularis)	0.0495
Middle temporal gyrus (anterior division)	0.0852	Parahippocampal gyrus (anterior division)	0.0287	Subcallosal cortex	0.0060	Inferior temporal gyrus (temporooccipital part)	0.0473
Inferior frontal gyrus (pars triangularis)	0.0840	Cingulate gyrus (anterior division)	0.0273	Supramarginal gyrus (anterior division)	0.0058	Lingual gyrus	0.0344
Supracalcarine cortex	0.0839	Parahippocampal gyrus (posterior division)	0.0271	Pallidum	0.0057	Middle temporal gyrus (posterior division)	0.0139
Lateral occipital cortex (superior division)	0.0823	Inferior frontal gyrus (pars triangularis)	0.0260	Inferior temporal gyrus (temporooccipital part)	0.0055	Planum temporale	0.0906
Temporal fusiform cortex (posterior division)	0.0811	Superior parietal lobule	0.0252	Thalamus	0.0054	Temporal fusiform cortex (posterior division)	0.0811
Intracalcarine cortex	0.0795	Middle temporal gyrus (posterior division)	0.0252	Middle temporal gyrus (anterior division)	0.0054	Superior frontal gyrus	0.0372
Heschl's gyrus includes (H1 and H2)	0.0766	Putamen	0.0250	Superior temporal gyrus (posterior division)	0.0053	Pallidum	0.0961
Caudate	0.0744	Middle frontal gyrus	0.0242	Cingulate gyrus (anterior division)	0.0050	Frontal orbital cortex	0.0709
Precentral gyrus	0.0737	Frontal pole	0.0233	Putamen	0.0048	Parahippocampal gyrus (anterior division)	0.0077
Precuneus cortex	0.0721	Inferior temporal gyrus (posterior division)	0.0228	Parietal operculum cortex	0.0048	Lateral occipital cortex (superior division)	0.0823
Frontal orbital cortex	0.0709	Lateral occipital cortex (inferior division)	0.0223	Inferior temporal gyrus (posterior division)	0.0047	Postcentral gyrus	0.0048
Superior temporal gyrus (anterior division)	0.0670	Occipital pole	0.0210	Frontal pole	0.0046	Inferior temporal gyrus (anterior division)	0.0423
Parietal operculum cortex	0.0654	Middle temporal gyrus (anterior division)	0.0194	Temporal occipital fusiform cortex	0.0046	Temporal occipital fusiform cortex	0.0096
Cuneal cortex	0.0537	Temporal occipital fusiform cortex	0.0183	Lingual gyrus	0.0043	Occipital pole	0.0290
Subcallosal cortex	0.0537	Accumbens	0.0182	Insular cortex	0.0043	Superior parietal lobule	0.0115
Occipital fusiform gyrus	0.0519	Amygdala	0.0174	Frontal operculum cortex	0.0040	Putamen	0.0445

Table 2 continued

Phobics vs. HC		DP vs. HC		SP vs. HC		DP vs. SP	
Region	Abs	Region	Abs	Region	Abs	Region	Abs
Frontal medial cortex	0.0518	Superior frontal gyrus	0.0171	Caudate	0.0040	Frontal operculum cortex	0.0414
Hippocampus	0.0498	Frontal medial cortex	0.0160	Superior frontal gyrus	0.0037	Intracalcarine cortex	0.0795
Inferior frontal gyrus (pars opercularis)	0.0495	Middle temporal gyrus (temporooccipital part)	0.0156	Intracalcarine cortex	0.0036	Middle temporal gyrus (anterior division)	0.0852
Cingulate gyrus (anterior division)	0.0488	Inferior temporal gyrus (anterior division)	0.0143	Paracingulate gyrus	0.0034	Cingulate gyrus (anterior division)	0.0488
Temporal pole	0.0476	Central opercular cortex	0.0132	Parahippocampal gyrus (posterior division)	0.0034	Supramarginal gyrus (anterior division)	0.0993
Inferior temporal gyrus (temporooccipital part)	0.0473	Temporal fusiform cortex (posterior division)	0.0127	Superior parietal lobule	0.0031	Cuneal cortex	0.0537
Middle temporal gyrus (temporooccipital part)	0.0460	Precuneus cortex	0.0124	Superior temporal gyrus (anterior division)	0.0030	Cingulate gyrus (posterior division)	0.0895
Supramarginal gyrus (posterior division)	0.0455	Juxtapositional lobule cortex	0.0124	Cuneal cortex	0.0029	Hippocampus	0.0498
Putamen	0.0445	Temporal fusiform cortex (anterior division)	0.0120	Occipital pole	0.0029	Precuneus cortex	0.0721
Middle frontal gyrus	0.0423	Postcentral gyrus	0.0120	Inferior temporal gyrus (anterior division)	0.0027	Parahippocampal gyrus (posterior division)	0.1028
Inferior temporal gyrus (anterior division)	0.0423	Inferior temporal gyrus (temporooccipital part)	0.0096	Supramarginal gyrus (posterior division)	0.0024	Inferior temporal gyrus (posterior division)	0.0141
Frontal operculum cortex	0.0414	Cuneal cortex	0.0095	Angular gyrus	0.0024	Frontal pole	0.0015
Insular cortex	0.0387	Superior temporal gyrus (anterior division)	0.0093	Supracalcarine cortex	0.0021	Middle temporal gyrus (temporooccipital part)	0.0460
Amygdala	0.0379	Superior temporal gyrus (posterior division)	0.0085	Central opercular cortex	0.0021	Middle frontal gyrus	0.0423
Superior Frontal gyrus	0.0372	Frontal Operculum Cortex	0.0083	Precentral gyrus	0.0016	Accumbens	0.0912
Lingual gyrus	0.0344	Caudate	0.0080	Middle temporal gyrus (posterior division)	0.0016	Juxtapositional lobule cortex	0.0001
Occipital pole	0.0290	Subcallosal cortex	0.0075	Juxtapositional lobule cortex	0.0015	Paracingulate gyrus	0.0853
Angular gyrus	0.0277	Heschl's gyrus includes (H1 and H2)	0.0069	Inferior frontal gyrus (pars opercularis)	0.0012	Insular cortex	0.0387
Inferior temporal gyrus (posterior division)	0.0141	Cingulate gyrus (posterior division)	0.0065	Middle frontal gyrus	0.0012	Heschl's gyrus includes (H1 and H2)	0.0766
Central opercular cortex	0.0140	Hippocampus	0.0064	Planum polare	0.0012	Inferior frontal gyrus (pars triangularis)	0.0840
Middle temporal gyrus (posterior division)	0.0139	Insular cortex	0.0063	Occipital fusiform gyrus	0.0009	Precentral gyrus	0.0737
Lateral occipital cortex (inferior division)	0.0138	Intracalcarine cortex	0.0059	Precuneus cortex	0.0009	Thalamus	0.1017
Superior parietal lobule	0.0115	Occipital fusiform gyrus	0.0051	Amygdala	0.0007	Frontal medial cortex	0.0518
Temporal occipital fusiform cortex	0.0096	Thalamus	0.0050	Lateral occipital cortex (inferior division)	0.0007	Temporal pole	0.0476
Parahippocampal gyrus (anterior division)	0.0077	Supramarginal gyrus (posterior division)	0.0033	Temporal fusiform cortex (posterior division)	0.0006	Superior temporal gyrus (anterior division)	0.0670
Postcentral Gyrus	0.0048	Planum Temporale	0.0021	Hippocampus	0.0005	Amygdala	0.0379

Table 2 continued

Phobics vs. HC		DP vs. HC		SP vs. HC		DP vs. SP	
Region	Abs	Region	Abs	Region	Abs	Region	Abs
Frontal pole	0.0015	Paracingulate gyrus	0.0009	Inferior frontal gyrus (pars triangularis)	0.0002	Subcallosal Cortex	0.0537
Planum polare	0.0006	Lateral occipital cortex (superior division)	0.0008	Parahippocampal gyrus (anterior division)	0.0001	Caudate	0.0744
Juxtapositional lobule cortex	0.0001	Supracalcarine cortex	0.0006	Middle temporal gyrus (temporooccipital part)	0.0001	Parietal operculum cortex	0.0654

Regions are derived from the Harvard–Oxford Brain Atlas which contains 55 distinct brain regions. For each group classification, regions are ranked according to GPC weights

Abs absolute whole brain GPC weights based on gray matter data, *HC* healthy controls, *DP* dental phobic subjects, *SP* snake phobic subjects

needed to address comparisons of multiple white matter atlases in detail.

When classifying the overall group status including both DP and SP differences arose between GM and WM information: using GM, only 62 % of phobic subjects were classified correctly, compared to 88 % using WM information. This finding indicates that subgroup information improves classification accuracy from GM, but not WM information. Recent evidence from fMRI studies (focusing indirectly on GM information associated with brain activation) indicates differential neural activation in the animal and BII-subtype, including DP, under symptom provocation (Caseras et al. 2010; Lueken et al. 2011). Present findings on a superior capacity of structural GM data to differentiate the subtype may reflect these functional differences in neural activation patterns. Also, findings could imply that in these subtypes particularly GM volume is altered, while not affecting WM tissue in such a differential way. As a further indirect line of evidence, the GM ranking of regions contributing most to the global classification of phobics vs. controls was positively correlated with the ranking that classified SP, but inversely to the ranking specific for DP. These results emphasize the assumption that neurofunctional substrates may differ between dental vs. snake phobia, further supporting the notion of separate diagnostic entities. However, we have to acknowledge that due to the paucity of structural studies in specific phobia, this interpretation warrants validation in future studies directly addressing this issue.

We further tested the incremental value of combining both data sources in increasing the accuracy of prediction. This approach did however not yield superior, but rather lower accuracy rates. The absent gain and descriptive decrease in performance could be due to the increase in dimensionality, while simultaneously the amount of non-redundant information did not increase. Regarding other disorders, comparison on GM and WM information used for classificatory purposes is limited, since the majority of studies used GM information only. Those analyzing both GM and WM reported varying findings with superior GM classification of autism disorder (Ecker et al. 2010), but better results from WM in non-refractory when compared to refractory depression (Gong et al. 2011).

Albeit constituting one of the most frequently investigated anxiety disorders in fMRI research, there is a lack of studies on structural abnormalities (including both GM and WM) in specific phobia. Thus, assumptions on the etiopathogenetic relevance of GM and WM differences for phobia subtypes lack direct support from structural neuroimaging studies. In one of the first studies, Rauch et al. (2004) investigated cortical structural alterations and reported increased thickness in the bilateral insular, bilateral pregenual anterior cingulate cortex (ACC), and bilateral posterior cingulate cortex as well as left visual cortical regions in a sample of ten animal phobics. Using a region-of-interest approach, Fisler et al. (2013) observed decreased left amygdalar volumes in spider phobics. Being the only study on structural alterations in dental phobics so far, Schienle et al. (2012) reported sex differences between male and female DP affecting the GM volume of the caudate nucleus. However, no information was available on the main effect of phobia. Whole brain analyses on GM and WM volumes in specific phobia and its subtypes are missing so far, limiting the integration of our results. Present findings underline that also regions beyond the so-called "fear circuit" (encompassing the amygdala, insula, ACC and pre-/orbitofrontal regions; Etkin and Wager 2007; Linares et al. 2012; Shin and Liberzon 2010) may contribute to the classification and differential diagnosis of specific phobia. Due to their system approach, multivariate pattern analyses consider the interrelation between brain regions, thus being particularly suitable and sensitive to detect network alterations. Moreover, they exhibit increased statistical power and are superior to mass-univariate tests in detecting distributed patterns of morphological differences. These methodological considerations

Table 3 Regional multivariate mapping and predictive probabilities based on white matter data

Phobics vs. HC		DP vs. HC		SP vs. HC		DP vs. SP	
Region	Abs	Region	Abs	Region	Abs	Region	Abs
Parahippocampal gyrus (anterior division)	0.0618	Precentral gyrus	0.1167	Lingual gyrus	0.0405	Inferior temporal gyrus (posterior division)	0.0359
Occipital pole	0.0610	Precuneus cortex	0.0959	Pallidum	0.0383	Frontal operculum cortex	0.0382
Middle temporal gyrus (anterior division)	0.0588	Frontal operculum cortex	0.0877	Subcallosal cortex	0.0330	Postcentral gyrus	0.0302
Cingulate gyrus (posterior division)	0.0585	Parietal operculum cortex	0.0815	Cingulate gyrus (posterior division)	0.0326	Middle frontal gyrus	0.0064
Cuneal cortex	0.0570	Frontal medial cortex	0.0716	Inferior temporal gyrus (posterior division)	0.0321	Inferior frontal gyrus (pars triangularis)	0.0109
Lingual gyrus	0.0534	Middle frontal gyrus	0.0653	Supracalcarine cortex	0.0315	Inferior temporal gyrus (anterior division)	0.0298
Pallidum	0.0501	Parahippocampal gyrus (anterior division)	0.0618	Frontal medial cortex	0.0281	Precuneus cortex	0.0192
Frontal medial cortex	0.0490	Inferior frontal gyrus (pars triangularis)	0.0600	Middle temporal gyrus (posterior division)	0.0275	Lingual gyrus	0.0534
Accumbens	0.0462	Inferior temporal gyrus (posterior division)	0.0595	Precentral gyrus	0.0275	Occipital pole	0.0610
Insular cortex	0.0440	Frontal orbital cortex	0.0580	Accumbens	0.0250	Hippocampus	0.0121
Subcallosal cortex	0.0412	Occipital pole	0.0568	Amygdala	0.0231	Precentral gyrus	0.0251
Amygdala	0.0402	Inferior temporal gyrus (temporooccipital part)	0.0565	Caudate	0.0228	Paracingulate gyrus	0.0191
Putamen	0.0394	Parahippocampal gyrus (posterior division)	0.0564	Superior parietal lobule	0.0225	Lateral occipital cortex (inferior division)	0.0114
Middle temporal gyrus (posterior division)	0.0394	Temporal occipital fusiform cortex	0.0532	Inferior temporal gyrus (temporooccipital part)	0.0216	Frontal medial cortex	0.0490
Thalamus	0.0392	Superior frontal gyrus	0.0511	Temporal occipital fusiform cortex	0.0208	Cuneal cortex	0.0570
Superior frontal gyrus	0.0391	Hippocampus	0.0473	Superior temporal gyrus (posterior division)	0.0193	Temporal fusiform cortex (anterior division)	0.0228
Frontal operculum cortex	0.0382	Central opercular cortex	0.0437	Occipital pole	0.0189	Intracalcarine cortex	0.0334
Temporal pole	0.0379	Insular cortex	0.0426	Middle temporal gyrus (anterior division)	0.0178	Parahippocampal gyrus (posterior division)	0.0127
Angular gyrus	0.0361	Supramarginal gyrus (posterior division)	0.0385	Angular gyrus	0.0175	Frontal orbital cortex	0.0009
Juxtapositional lobule cortex	0.0359	Temporal fusiform cortex (posterior division)	0.0367	Lateral occipital cortex (superior division)	0.0174	Pallidum	0.0501
Inferior temporal gyrus (posterior division)	0.0359	Temporal fusiform cortex (anterior division)	0.0358	Postcentral gyrus	0.0173	Frontal pole	0.0070
Caudate	0.0357	Postcentral gyrus	0.0354	Planum temporale	0.0161	Superior parietal lobule	0.0238
Parietal operculum cortex	0.0335	Frontal pole	0.0340	Inferior frontal gyrus (pars opercularis)	0.0160	Supracalcarine cortex	0.0287
Intracalcarine cortex	0.0334	Temporal pole	0.0337	Frontal orbital cortex	0.0152	Superior temporal gyrus (posterior division)	0.0231
Inferior frontal gyrus (pars opercularis)	0.0331	Lateral occipital cortex (inferior division)	0.0329	Juxtapositional lobule cortex	0.0144	Temporal fusiform cortex (posterior division)	0.0267
Inferior temporal gyrus (temporooccipital part)	0.0310	Supramarginal gyrus (anterior division)	0.0316	Parietal operculum cortex	0.0137	Cingulate gyrus (anterior division)	0.0231

Table 3 continued

Phobics vs. HC		DP vs. HC		SP vs. HC		DP vs. SP	
Region	Abs	Region	Abs	Region	Abs	Region	Abs
Planum temporale	0.0306	Juxtapositional lobule cortex	0.0293	Frontal pole	0.0135	Angular gyrus	0.0361
Postcentral gyrus	0.0302	Superior parietal lobule	0.0283	Cuneal cortex	0.0130	Putamen	0.0394
Inferior temporal gyrus (anterior division)	0.0298	Occipital fusiform gyrus	0.0269	Lateral occipital cortex (inferior division)	0.0118	Supramarginal gyrus (posterior division)	0.0110
Middle temporal gyrus (temporooccipital part)	0.0296	Superior temporal gyrus (posterior division)	0.0260	Insular cortex	0.0115	Thalamus	0.0392
Supracalcarine cortex	0.0287	Caudate	0.0255	Paracingulate gyrus	0.0113	Cingulate gyrus (posterior division)	0.0585
Lateral occipital cortex (superior division)	0.0276	Cuneal cortex	0.0246	Inferior temporal gyrus (anterior division)	0.0112	Planum temporale	0.0306
Heschl's gyrus includes (H1 and H2)	0.0271	Thalamus	0.0243	Cingulate gyrus (anterior division)	0.0109	Caudate	0.0357
Temporal fusiform cortex (posterior division)	0.0267	Inferior frontal gyrus (pars opercularis)	0.0222	Temporal fusiform cortex (anterior division)	0.0109	Heschl's gyrus includes (H1 and H2)	0.0271
Precentral gyrus	0.0251	Lingual gyrus	0.0208	Parahippocampal gyrus (anterior division)	0.0101	Middle temporal gyrus (temporooccipital part)	0.0296
Superior parietal lobule	0.0238	Cingulate gyrus (posterior division)	0.0189	Supramarginal gyrus (posterior division)	0.0092	Temporal occipital fusiform cortex	0.0111
Superior temporal gyrus (posterior division)	0.0231	Inferior temporal gyrus (anterior division)	0.0187	Heschl's gyrus includes (H1 and H2)	0.0086	Accumbens	0.0462
Cingulate gyrus (anterior division)	0.0231	Putamen	0.0180	Supramarginal gyrus (anterior division)	0.0075	Occipital fusiform gyrus	0.0152
Temporal fusiform cortex (anterior division)	0.0228	Lateral occipital cortex (superior division)	0.0160	Frontal operculum cortex	0.0067	Subcallosal cortex	0.0412
Planum polare	0.0222	Subcallosal cortex	0.0126	Parahippocampal gyrus (posterior division)	0.0063	Insular cortex	0.0440
Precuneus cortex	0.0192	Heschl's gyrus includes (H1 and H2)	0.0124	Superior frontal gyrus	0.0059	Lateral occipital cortex (superior division)	0.0276
Superior temporal gyrus (anterior division)	0.0191	Middle temporal gyrus (posterior division)	0.0117	Occipital fusiform gyrus	0.0058	Inferior frontal gyrus (pars opercularis)	0.0331
Paracingulate gyrus	0.0191	Supracalcarine cortex	0.0112	Central opercular cortex	0.0057	Superior temporal gyrus (anterior division)	0.0191
Occipital fusiform gyrus	0.0152	Amygdala	0.0090	Temporal fusiform cortex (posterior division)	0.0055	Parahippocampal gyrus (anterior division)	0.0618
Parahippocampal gyrus (posterior division)	0.0127	Cingulate gyrus (anterior division)	0.0087	Inferior frontal gyrus (pars triangularis)	0.0054	Juxtapositional lobule cortex	0.0359
Hippocampus	0.0121	Paracingulate gyrus	0.0076	Planum polare	0.0052	Middle temporal gyrus (anterior division)	0.0588
Lateral occipital cortex (inferior division)	0.0114	Middle temporal gyrus (temporooccipital part)	0.0044	Temporal pole	0.0045	Middle temporal gyrus (posterior division)	0.0394
Temporal occipital fusiform cortex	0.0111	Intracalcarine cortex	0.0041	Intracalcarine cortex	0.0044	Inferior temporal gyrus (temporooccipital part)	0.0310
Supramarginal gyrus (posterior division)	0.0110	Accumbens	0.0039	Middle frontal gyrus	0.0030	Supramarginal gyrus (anterior division)	0.0024
Inferior frontal gyrus (pars triangularis)	0.0109	Superior temporal gyrus (anterior division)	0.0034	Precuneus cortex	0.0027	Central opercular cortex	0.0040
Frontal pole	0.0070	Angular gyrus	0.0034	Thalamus	0.0022	Temporal pole	0.0379
Middle frontal gyrus	0.0064	Middle temporal gyrus (anterior division)	0.0020	Superior temporal gyrus (anterior division)	0.0017	Parietal operculum cortex	0.0335

Table 3 continued

Phobics vs. HC		DP vs. HC		SP vs. HC		DP vs. SP	
Region	Abs	Region	Abs	Region	Abs	Region	Abs
Central opercular cortex	0.0040	Planum temporale	0.0012	Middle temporal gyrus (temporooccipital part)	0.0012	Amygdala	0.0402
Supramarginal gyrus (anterior division)	0.0024	Planum polare	0.0001	Putamen	0.0006	Superior frontal gyrus	0.0391
Frontal orbital cortex	0.0009	Pallidum	0.0000	Hippocampus	0.0004	Planum polare	0.0222

Regions are derived from the Harvard–Oxford Brain Atlas which contains 55 distinct brain regions. For each group classification, regions are ranked according to GPC weights

Abs absolute whole brain GPC weights based on white matter data, *HC* healthy controls, *DP* dental phobic subjects, *SP* snake phobic subjects

might explain why widespread cortico-subcortical networks contributing to the discriminatory pattern were predominant in this study.

Findings should be reviewed in light of the study limitations. First, the diagnosis of specific phobia and its particular subtype can be carried out with sufficient sensitivity and specificity based on subjective report. However, our approach was to provide a proof-of-concept that MRI information can be used to predict diagnostic classification of a single subject. Present results should stimulate future research to test the utility of structural MRI data for the differential diagnosis in anxiety disorders for less clear-cut constellations such as comorbidity, identification of at-risk subjects or prediction of treatment response where distinct clinical markers may not be available. Second, smoking (and age also as a trend) was not equally distributed between groups, thus representing a potential confounder. However, high accuracy rates in DP (with an equal proportion of smokers compared to HC) speak against a strong bias. Finally, employing a cross-sectional design, we cannot differentiate if structural pattern abnormalities represent causes or consequences of phobia. Longitudinal designs targeting at-risk subjects and their transition to actual disease are needed. Finally, our results call for replication in an independent second dataset, using the classifier of the present study as a starting point.

In conclusion, we here demonstrate that multivariate pattern recognition represents a promising approach for the development of neuroimaging-based diagnostic markers that could support clinical decision processes. Using the example case of specific phobia, good accuracy rates in predicting a subjects' status could be obtained. Regarding the increasing number of fMRI studies on anxiety disorders, researchers are encouraged to use functional and structural data not only for studying phenotype characteristics on a group level, but to evaluate the incremental value of these data for generating diagnostic or predictive markers.

Conflict of interest The following authors report no conflict of interest: U. Lueken, K. Hilbert, T. Hahn. A. Reif participated in two non-interventional trials sponsored by Astra Zeneca. H.-U. Wittchen has served as a general consultant (non product-related) for Pfizer, Organon, Servier, Essex Pharma and has received grant funding for his institution from Sanofi Aventis, Pfizer, Lundbeck, Novartis, Essex Pharma, Servier and Whyet.

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