The phobic brain: morphometric features correctly classify individuals with small animal phobia

Alessandro Scarano[1], Ascensión Fumero[2], Teresa Baggio[1], Francisco Rivero[2], Rosario J. Marrero[2], Teresa Olivares[2], Wenceslao Peñate[2], Yolanda Álvarez-Pérez[2], Juan Manuel Bethencourt[2], Alessandro Grecucci[1,3]

[1]Department of Psychology and Cognitive Science, University of Trento, Italy

[2] Departamento de Psicología Clínica, Psicobiología y Metodología,
Facultad de Psicología, Universidad de La Laguna, 38200 La Laguna, Tenerife, Spain

[3]Center for Medical Sciences, University of Trento, Italy

Abstract

Specific phobia represents an anxiety disorder category characterized by intense fear generated by distinct stimuli or situational triggers. Among specific phobias, small animal phobia (SAP) denotes a particular condition that has been poorly investigated in the neuroscientific literature. Moreover, the few previous studies on this topic have mostly employed univariate analyses, with limited and unbalanced samples, often leading to inconsistent results. To overcome these limitations, and to characterize the neural underpinnings of SAP, this study aims to rely on a machine learning method known as Binary Support Vector Machine (BSVM), to develop a classification model of individuals with small animal phobia based on grey matter features. Moreover, the contribution of specific structural macro-networks, such as the Default Mode, the Salience, the Executive, and the Affective networks, in separating phobic subjects from controls was assessed. Thirty-two subjects with SAP and ninety matched healthy controls were tested to this aim. At a whole-brain level, we found a significant predictive model including brain structures related to emotional regulation, cognitive control, and sensory integration, such as the cerebellum, the temporal pole, the frontal cortex, temporal lobes, the amygdala and the thalamus. Instead, when considering macro-networks analysis, we found the Default Mode, the Affective, the Central Executive and the Sensorimotor networks to significantly outperform the other networks in classifying SAP individuals. In conclusion, this study expands knowledge about the neural basis of small animal phobia, proposing

new research directions and potential diagnostic strategies using advanced machine learning methods applied to neuroimaging data.

Keywords: animal phobia, affective neuroscience, support vector machine, machine learning, anxiety

Introduction

Anxiety disorders, encompassing a range of conditions such as generalized anxiety disorder, panic disorder, social anxiety disorder, and specific phobias, are among the most prevalent mental health issues (Santomauro et al., 2021). These disorders are characterized by excessive and persistent worries that significantly disrupt daily life, often resulting in profound avoidance behaviors, distress in social settings, and impaired occupational functioning (Craske et al., 2011; Mah et al., 2016; Olatunji, 2019; Santomauro et al., 2021). The prevalence of these conditions highlights the need for an in-depth understanding of their neural bases and development of effective treatments. Within the spectrum of anxiety disorders, specific phobias (SP) represent a category where distinct stimuli or situations trigger irrational and intense fears, having a high prevalence (10%) in the general population (Fyer, 1998). Among these, small animal phobia (SAP) stands out as a condition in which, despite the efforts various studies proposed to explore the brain circuits involved, the exact neural mechanisms underlying its condition remain elusive.

Functional neuroimaging studies have repeatedly identified activations in limbic and paralimbic structures in response to phobic stimuli, such as the insula, the amygdala, and the cingulate cortex (Del Casale et al., 2012; Peñate et al., 2017; Wright et al., 2003). Other brain regions outside the limbic area, such as the prefrontal cortex, the orbitofrontal cortex, and the cingulate cortex, have also shown different activation and volumes. Moreover, structural neuroimaging studies have found similar results when analyzing the differences between gray and white matter features between specific phobia and control individuals. For instance, one of the first studies on this topic showed significant increased cortical thickness in AP (animal phobia) versus healthy control individuals in the paralimbic cortex, specifically in the bilateral insular cortex, the bilateral pregenual anterior cingulate cortex, and the bilateral posterior cingulate cortex, as well as in the occipital and left occipitotemporal cortex (Rauch et al., 2004). Building on these findings, another study reported that SAP individuals had higher anxiety sensitivity (AS) with respect to healthy individuals and that higher AS predicted greater thickness and volume of the right anterior insular cortex in the SAP group, suggesting that the right anterior insula might be a key factor in mediating anxiety in those who are prone to excessive anxiety (Rosso et al., 2010). Another study

reported an increase of the 13% in the left amygdala volume (AMV) in 20 female individuals with spider phobia compared to 20 female control individuals (Fisler et al., 2013). Additionally, Hilbert and colleagues, analyzed data from individuals with different phobias such as dental phobia, snake phobia, and reported significantly increased gray matter volumes in several brain regions among the phobia groups compared to the control group, including the right subgenual ACC, left medial OFC, left precuneus, right calcarine sulcus, right fusiform gyrus, and right vermis (Hilbert et al., 2015). When the phobia subgroups were combined and compared to the control group, a significant volume increase was observed in the right OFC (Hilbert et al., 2015). Last but not least, a more recent study compared SAP individuals and healthy controls and found smaller GMV (gray matter volume) (in SAP individuals in the right and left insula, in the orbitofrontal cortex, in the left superior medial frontal, right superior frontal, and right anterior cingulate cortex (Rivero et al., 2023). SAP individuals also displayed larger GMV in the left putamen.

Despite these findings, prior studies investigating the neurological basis of anxiety disorders have faced considerable challenges that limit the depth and applicability of their findings. For example, previous studies frequently relied on limited sample sizes (Rauch et al., 2004; Rivero et al., 2023; Straube et al., 2006; Wright et al., 2003). Some of them exhibited an imbalance in participant gender distribution, with a preponderance of female subjects, leading to a possible bias in the neural findings. This imbalance is reflected also in the observed higher incidence of animal phobias among women compared to men, with estimates suggesting a ratio approaching 3:1 (Kendler et al., 2001). Furthermore, and more importantly, previous studies relied on mass univariate analysis, focusing on individual voxels separately, without acknowledging the statistical interdependencies between them (Sorella et al., 2019; Grecucci et al., 2022, 2023). In some studies, analyses were confined to pre-defined regions of interest (ROI) rather than employing a comprehensive whole-brain methodology, thus limiting the findings to a few a priori selected to areas. Additionally, the generalizability of this findings was not assessed and the applicability of these findings in terms of potential biomarker to diagnose new unobserved individuals was not evaluated (Pappaianni et al., 2019; Sorella et al., 2019). These limitations have often led to inconsistent and inconclusive findings, particularly in studies of SAP, indicating the need for a broader analytical approach.

Instead of the standard univariate statistical approaches, a new class of multivariate statistical approaches has been increasingly used in neuroscience. These approaches are known as Multi-voxel Pattern analysis, or Machine learning methods. These methods display higher accuracy and sensitivity in finding complex latent patterns in the brain signal able to correctly classify and predict new cases (Norman et al., 2006). The application of machine learning involves, among

others, classification algorithms trained to differentiate between two data classes using comprehensive, whole-brain pattern-based information. These methodologies have played a crucial role in the correct classification of subjects based on brain imaging data across diverse psychiatric and neurological conditions, with notable success rates ranging from 60 to 90% in disorders like depression, schizophrenia, borderline personality (Sorella et al., 2019; Grecucci et al., 2022, 2023) , narcissistic personality (Jornkokgoud et al., 2023) and social anxiety disorder (Baggio, Grecucci, Crivello, et al., 2023; Baggio, Grecucci, Meconi, et al., 2023; Frick et al., 2014; Grecucci et al., 2023; Mwangi et al., 2012; Squarcina et al., 2017).

In light of the limitations of previous studies on SAP, the aim of the present study is to apply a machine learning approach to classify a large sample of SAP individuals and matched controls. To accomplish this aim, a machine learning method known as binary support vector machine (SVM) will be adopted. This method represents a significant shift from traditional approaches, as it uses a multivariate statistical approach to interpret and discover complex patterns in brain imaging data, taking into account the signal from all voxels at once (Frick et al., 2014; Mwangi et al., 2012; Norman et al., 2006; Squarcina et al., 2017), and extracting a predictive model (unlike standard statistical approaches), that can be used to diagnose new unobserved individuals (Baggio, Grecucci, Crivello, et al., 2023; Baggio, Grecucci, Meconi, et al., 2023; Grecucci et al., 2023; Jornkokgoud et al., 2023). Thus, the primary objective of our study is to explore the potential of Binary Support Vector Machines (BSVM), to develop a classification model of individuals with small animal phobia (SAP). To our knowledge, this marks the first attempt of applying such a technique in this context. We hypothesize that specific brain structures, previously identified in separate studies as crucial in emotional regulation and the fear response mechanism — such as the orbitofrontal cortex, amygdala, and basal ganglia — can effectively differentiate these two groups (Mourao-Miranda et al., 2012; Rivero et al., 2023; Rondina et al., 2018; Vai et al., 2020). By employing BSVM, we can precisely quantify the contribution of each brain region to our classification models, identifying the most critical areas, assigning a weight to each, and highlighting the neurobiological distinctions between SAP individuals and CTRL ones (control individuals).

Expanding beyond whole-brain analyses, the second aim of the present study is to investigate whether specific brain macro-networks, previously associated with various psychiatric conditions (Langerbeck et al., 2023) , encode enough information to classify individuals with SAP compared to CTRLs. Recent research has suggested that patients with certain psychological conditions demonstrate functional impairments in the so called “triple network” brain networks like the default mode network (DMN), salience network (SN), and central executive network (CEN) (Doll et al., 2013; Langerbeck et al., 2023). These networks are present both at a functional and

structural level (Baggio, Grecucci, Meconi, et al., 2023; Grecucci et al., 2022; Meier et al., 2016), and have been linked to various psychiatric diseases. Our second objective, therefore, is to develop a predictive classification model based on these macro-networks. We hypothesize that abnormalities in these networks, particularly the DMN, SN, and Executive network, may be predictive of small animal phobia. We further postulate that among these networks, the DMN might be the most significant in differentiating SAP individuals from CTRL ones. This last hypothesis stems from the established role of these networks in a wide array of psychiatric conditions (Langerbeck et al., 2023), and our study aims to explore their relevance in the context of small animal phobia. We also expect that, DMN based classification will outperform the whole brain analysis. If this is true that means that the DMN is notably compromised in SAP individuals. We also expanded our investigation including an 'Affective Network', that we present here for the first time. This network encompasses brain regions underscored in existing literature for their pivotal roles in emotional processing and affective responses, including the amygdala, the cingulum, the pallidum, the hippocampus, the insula, the orbitofrontal cortex, the medial frontal cortex, the putamen and the caudate. All these regions have implicated in subserving emotion related process (Murphy et al., 2003; Vytal & Hamann, 2010). This network may resemble the 'limbic network' (Enatsu et al., 2015), that usually includes the hypothalamus, the hippocampus, the mammillary body, the thalamus, the cingulate gyrus, the para-hippocampal gyrus (PHG) and the entorhinal cortex. However, this network relies only on subcortical structure, while recent findings have now widely and undoubtedly associated other cortical areas such as the orbitofrontal cortex and the medial frontal cortex to an essential role in emotions expression and regulation (Del Casale et al., 2012; Hilbert et al., 2015; Peñate et al., 2017; Rauch et al., 2004; Straube et al., 2006). To overcome the limitations of the limbic network we decided to build a more general affective network. We hypothesize that this network may display a good classification accuracy, possibly outperforming the whole brain results, and similar to the DMN results. One possibility is that the AN outperforms the DMN. Alternatevely, the DMN may outperform the AN, suggesting again a prominent role in psychological disorders. Additionally, we intend to test as control networks also the visual, the sensorimotor and the reward networks. We expect these networks to not allow a correct classification of SAP individuals.

In sum, in the present study, we aim to enrich the existing body of knowledge on the neural basis of anxiety disorders, specifically related to small animal phobia. By using a larger sample with respect to previous studies, and by integrating advanced machine learning techniques with neuroimaging data, we aim to provide new light on the intricate neural networks that underpin specific phobias, paving the way for new research directions and potential therapeutic strategies.

Methods

Participants

The sample of the present study includes participants previously collected in the study of Rivero and colleagues (Rivero et al., 2023), with additional control subjects from the UCLA Consortium for Neuropsychiatric Phenomics dataset to balance gender and age discrimination. The Neuropsychiatric Phenomics dataset was derived from the Openneuro database (Gorgolewski et al., 2017), under the accession number ds000030, version 00016. Control subjects from the UCLA Consortium for Neuropsychiatric Phenomics dataset were recruited through a comprehensive approach involving community advertisements, outreach to local clinics, and online portals. Eligibility for participation for both samples was contingent upon having at least 8 years of formal education and proficiency in English or Spanish. Within our whole sample, individuals in the SAP group received a specific phobia diagnosis using the Composite International Diagnostic Interview (CIDI), Version 2.1 (Kessler & Üstün, 2004). Meanwhile, all control participants, including those from the previous study and additional ones from the UCLA dataset, had no psychiatric or neurological disorders. Our final sample consisted of 32 individuals (25 F, mean age: 34.4 ± 11.07) with small animal phobia, and 90 healthy controls matched for age and gender (59 F, mean age: 31.95 ± 10.25). No significant differences were found for age [t=1.330, p=0.186] and gender [t=1.317, p=0.190] between groups. See table 1.

Table 1

	SAP (n=32)	CTRL (=90)	p-value
n	32	90	
Sex	7M, 25F	31M,59F	p=0.19
Age	34.4 (±11,07)	31.95 (±10,25)	p=0.18
Inclusion criteria	Smal animal phobia diagnosis, Right-	No history of psichiatric or neurological	

	handedness, no contraindications for MRI scanning	disorder, Right-handedness, no contraindications for MRI scanning	

Figure 1.

Table presenting demographic and diagnostic information about the participants, including their number, gender distribution, mean age, and inclusion criteria.

MRI data Acquisition

The MRI sessions for the original sample were conducted using a 3T MR scanner (GE 3T Sigma Excite HD) with a 12-channel head coil. During the scans, participants were instructed to keep their eyes closed, relax but not fall asleep, and remain as still as possible. High-resolution three-dimensional T1-weighted images were acquired with specific parameters (TR/TE = 8852 ms/1756 ms, flip angle = 10°, 172 sagittal slices, slice thickness = 1 mm, FOV = 256 mm^2, data matrix = 256 × 256 × 172, voxel size = 1 × 1 × 1 mm, and TI = 650 ms). An experienced neuroradiologist reviewed each scan to ensure there were no visible movement artifacts or gross structural abnormalities. The scans on the additional CTRL individuals were performed on a 3T Siemens Trio scanner. A T1-weighted high-resolution anatomical scan (MPRAGE) was collected with parameters including a slice thickness of 1 mm, 176 slices, TR of 1.9 s, TE of 2.26 ms, matrix size of 256 x 256, and a FOV of 250 mm^2. Diffusion-weighted imaging data were collected with parameters such as a slice thickness of 2 mm, 64 directions, TR/TE of 9000/93 ms, flip angle of 90°, and a matrix size of 96 × 96, axial slices, and a b-value of 1000 s/mm^2. All participants provided written informed consent, in compliance with the ethical guidelines set by the consortium.

Preprocessing

Before initiating any analyses, and following a rigorous quality check to eliminate artifacts, all data underwent a standardized preprocessing routine. This process utilized the Computational Anatomy Toolbox (CAT12, available at http://www.neuro.uni-jena.de/cat/), which operates within the SPM12 software framework (accessible at http://www.fil.ion.ucl.ac.uk/spm/software) in MATLAB. This step involved the segmentation of gray matter, white matter, and cerebrospinal fluid. We opted for the modulated normalized writing method during this phase. For registration, we employed the Diffeomorphic Anatomical Registration through Exponential Lie algebra (DARTEL) approach, a robust whole-brain technique that presents as an effective alternative to the

conventional registration methods used in SPM (Grecucci et al., 2016; Pappaianni et al., 2018; Yassa & Stark, 2009). Subsequently, the DARTEL images were normalized to the MNI space and underwent spatial smoothing, applying a Gaussian smoothing kernel with a full width at half maximum of 12 mm in all dimensions, following suggestion from (Monté-Rubio et al., 2018) for MVPA approaches to structural studies.

To minimize the impact of having participants acquired with two different scanners (see participants section), we applied Independent Component Analysis to detect and separate the noise derived from the scanners. Group-ICA using the GIFT toolbox (https://trendscenter.org/software/gift/) was used to this aim. The minimum description length (MDL) (Calhoun et al., 2009) estimated 13 components in the data. These 13 components were then estimated with Group-ICA. Of these components, only the IC13 significantly differed between scanner 1 and scanner 2 ($t(1,120)=4.191$, $p<0.001$). Thus, we removed the effect of this component from the data and subsequent analyses, by generating a mask with IC13. This mask was merged with the mask 'SPM_noeyes.nii' (used in Pronto for ML analyses, see the next section) to create a combined denoising mask. The mask was generated inside SPM12 (Statistical Parametric Mapping, https://www.fil.ion.ucl.ac.uk/) with the ImCalculator option.

Data analysis

Machine learning analyses were performed using the Binary Support Vector Machine (BSVM) method within the Pattern Recognition for Neuroimaging Toolbox (Schrouff et al., 2013). We focused on between-group analyses, classifying individuals into two categories: those with small animal phobia and non-phobic controls, based on preprocessed gray matter images. Binary Support Vector Machines (BSVM) methods are specifically designed for binary classification, offering a targeted approach, optimizing the decision boundary between two classes with a clear margin. This specialization allows for a more straightforward and focused application, enhancing interpretability and improving classification performance in neuroimaging studies where the distinction between conditions or groups is critical. The denoising mask created to mitigate the difference of the scanning equipment was adopted as 1st level mask both whole-brain analyses and specific network investigations and to eliminate features that are not important for the analysis. Data was mean centered. All models followed a training phase where the algorithm was trained to discern patterns in the data that correlate with the diagnostic labels - distinguishing between individuals with small animal phobia and healthy controls. Following the training, the algorithms were used for a test phase, predicting the classification outcomes based on the learned patterns in an

independent dataset. For the validation of our model, we utilized the k-folds CV on subjects per group method on Pronto with 5 folds. This cross-validation technique enhances the model's reliability and securing that the data are not overfitted by the model. The data into 5 subsets, where each subset is used once as a test set while the other 4 subsets collectively serve as the training set. This approach ensures that each subject is included in the test set exactly once, allowing for a more comprehensive assessment of the model's accuracy and generalizability, and more importantly, making the test set independent from the training set. We optimized the hyper-parameters according to the suggestions provided by the Pronto creators (0.0001, 0.01, 1, 10, 100, 1000) (Claesen & De Moor, 2015). The accuracy for each class was determined by averaging the results from all the folds of the cross-validation process. Given the unbalanced number of participants between SAP and CTRLs we relied on the balanced accuracy estimation. To ascertain the statistical robustness of our classification results, we conducted permutation testing on each model with 5,000 permutations. This procedure was identical for all analyses. For testing the relevance of macro-networks we used a second level masks, including the five major brain networks (Default mode network, Salience network, Central Executive network, Sensory network, and Visual network), derived from CAREN macro networks atlas (Doucet et al., 2019), the reward mask, and the additional Affective Network mask. See Figure 1.

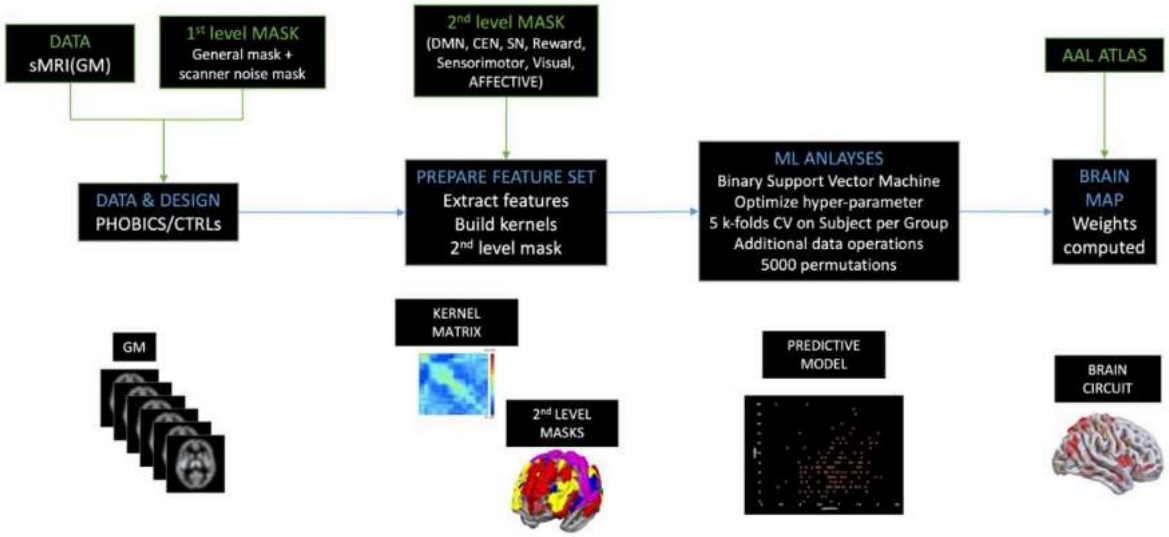

Figure 1.

Graphical representation of the main steps of the machine learning analyses.

Whole brain results

The Binary Support Vector Machine (BSVM) analyzing whole-brain gray matter features returned balanced accuracy (BA) stood at 79.48 (p=0.0002) validating the model's performance beyond chance. Such results confirm the BSVM model ability at discerning SAP and CTRL individuals. The model's robustness was further demonstrated in the receiver operating characteristic (ROC) curve analysis, which showed an area under the curve (AUC) of 0.94. This high AUC underscores the model's definitive capacity to separate the two groups distinctly and confidently. Upon examining the most significant regional contributors to this classification, it became evident that areas like the orbito-frontal cortex, the amygdala, the temporal pole, the cingulate, and the putamen were pivotal. Their substantial influence corresponds with their established involvement in emotional processing and fear response mechanisms, reinforcing their significance in small animal phobia. See Table 2 and Figure 2.

Table 2

ROI Label	ROI weight (%)	ROI size (vox)
Vermis_3	2.2408	522
Vermis_1_2	2.1067	109
Cerebelum_3_L	1.8075	314
Temporal_Pole_Mid_R	1.5780	2014
Temporal_Pole_Sup_R	1.5216	2284
Vermis_4_5	1.5173	1175
Frontal_Mid_Orb_R	1.4257	1503
Frontal_Mid_Orb_L	1.3633	1396
Putamen_L	1.3230	1963
Putamen_R	1.3082	1824
Temporal_Inf_L	1.2349	4125
Temporal_Inf_R	1.2305	5574
Temporal_Pole_Sup_L	1.1857	2785
Lingual_L	1.1721	3873
Frontal_Inf_Orb_L	1.1655	2721
Amygdala_R	1.1380	392
Pallidum_R	1.1268	608
Cingulum_Post_L	1.1121	720

Caudate_L	1.0841	1939
Frontal_Inf_Orb_R	1.0821	2492
Vermis_8	1.0769	528
Temporal_Mid_L	1.0658	8786
Angular_L	1.0591	1873
Cerebelum_8_R	1.0522	2566
Frontal_Sup_Orb_R	1.0519	643
Thalamus_L	1.0402	2420
Precuneus_L	1.0361	5765
Vermis_9	1.0186	274
Temporal_Pole_Mid_L	1.0165	1579
Temporal_Sup_L	1.0150	4430
Cerebelum_8_L	1.0071	2524
Frontal_Sup_Medial_L	1.0014	4905

Table 2.

Table detailing the contributions of brain regions to the classification of SAP and CTRL individuals, listing regions of interest (ROI), their weight in the classification model, and their size measured in voxels.

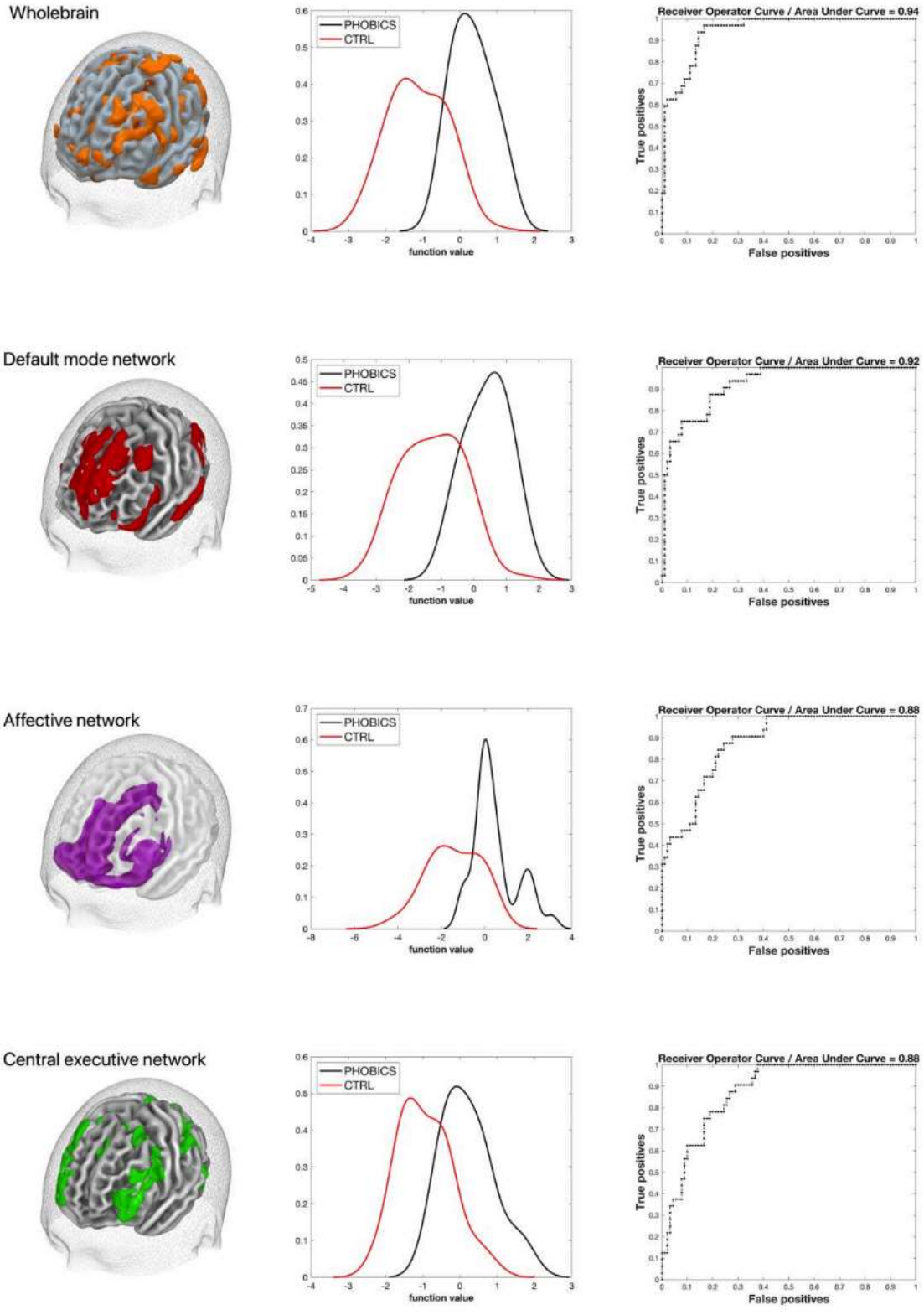

Figure 2.

Brain plots, histogram plots and ROC curves of the whole brain, the default mode network, the affective network and the central executive network.

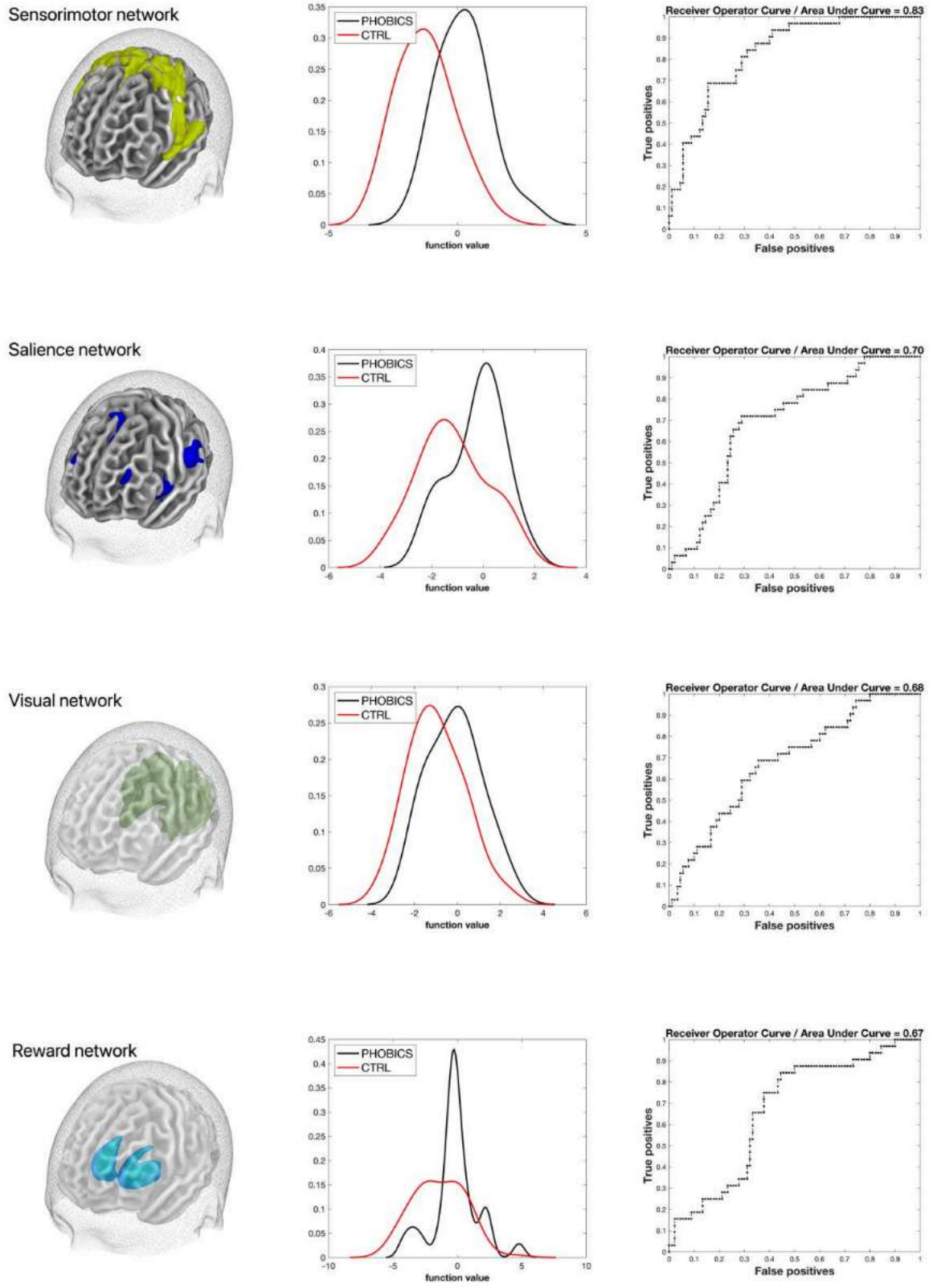

Figure 3.

Brain plots, histogram plots and ROC curves of the sensorimotor network, the salience network the visual network and the reward network.

Macro-networks results

Our Binary Support Vector Machine (BSVM) analysis across macro networks revealed varied performance in classifying SAP individuals from CTRL ones. Notably, only the default mode (DMN), the affective, the central executive, and the sensorimotor networks survived Bonferroni corrected threshold ($p<0.006$ threshold). The DMN showed the highest balanced accuracy (BA: 80.49%, p-value: 0.0002, AUC: 0.92), indicating its strong discriminatory power, and overcoming even the whole brain results. The affective network also demonstrated substantial classification capability (BA: 75.03%, p-value: 0.0002, AUC: 0.88). The central executive network (BA: 72.12%, p-value: 0.0002, AUC: 0.88) and the sensorimotor network (BA: 70.90%, p-value: 0.0002, AUC: 0.83) followed in performance, both yielding statistically significant results. The other networks such as the salience (BA: 61.77%, p-value: 0.0134), visual (BA: 61.22%, p-value: 0.0148), and reward networks (BA: 52.19%, p-value: 0.2352) displayed lower classification accuracies and did not survive the Bonferroni corrected threshold. See Table 3, and Figures 2 and 3.

Table 3

RANK	NETWORK	BALANCED ACCURACY	p-value
1	**Default mode network**	80,49%	p=0.0002
2	**Whole brain**	79,48%	p=0.0002
3	**Affective network**	75,03%	p=0.0002
4	**Central executive network**	72,12%	p=0.0002
5	**Sensorimotor network**	70,90%	p=0.0002
6	Salience network	61,77%	p=0.0134
7	Visual network	61,22%	p=0.0148
8	Reward network	52,19%	p=0.2352

Table 3.

Table ranking the brain networks by their effectiveness in classifying SAP and CTRL individuals, presenting the balanced accuracy and p-values for each network.

Additional metrics were calculated to thoroughly evaluate the performance of the machine-learning models across macro-networks in the classification tasks. These comprehensive metrics, including F1-Score, Sensitivity (Recall), Specificity, offer a complete view of each model's ability to classify individuals. F1-Score refers to a metric that balances the precision and recall by taking their harmonic mean, and it is advantageous when the class distribution is uneven. Sensitivity refers to a measure of the model's ability to correctly identify all actual positives. Finally, Specificity refers to the model's ability to identify all actual negatives. These indexes are summarized in table 4.

Table 4

Model	F1-Score	Sensitivity	Specificity	Precision
Default Mode Network	0.7213	0.7586	0.8925	0.6875
Whole Brain	0.7119	0.7778	0.8842	0.6562
Affective Network	0.6269	0.6000	0.8736	0.6562
Central Executive Network	0.5965	0.6800	0.8454	0.5312
Sensorimotor Network	0.5714	0.5806	0.8462	0.5625
Salience Network	0.4412	0.4167	0.8023	0.4688
Visual Network	0.4348	0.4054	0.8000	0.4688
Reward Network	0.3143	0.2895	0.7500	0.3438

Table 4.

Table ranking the brain networks by their effectiveness in classifying SAP and CTRL individuals, presenting the F1-Score, Sensitivity (Recall), Specificity, and Precision for each network.

Discussion

This investigation of neurobiological distinctions between individuals with small animal phobia (SAP) and controls holds the promise to elucidate the neural underpinnings of this anxiety disorder. The primary objective of this investigation was to use a multivariate, whole-brain machine learning method (BSVM) to differentiate SAP from CTRL. This was done to extract a predictive model able to recognize new SAP cases from structural brain features. Additionally, the study aimed to assess the predictive capability of specific brain networks, including a novel Affective Network, for SAP, challenging traditional neurobiological models of anxiety disorders and extending our comprehension of their complexity. Results showed that a whole brain circuit was able to correctly classify SAP individuals from controls above chance. Additionally, the Default mode network, the Affective, the Central Executive and the Sensorimotor were able to classify SAP individuals with different degrees of accuracy. In the next section we discuss our findings in more details.

The phobic network

Results for whole brain analyses showed a significant brain network able to correctly classify SAP from CTRL individuals. Key regions distinguishing SAP from CTRL individuals encompassed various cortical and subcortical brain regions such as the cerebellum, the temporal pole, the frontal cortex, temporal lobes, the amygdala and the thalamus. These regions are implicated in a wide range of functions, from emotional regulation and cognitive control to sensory integration and response to fear stimuli (Bechara et al., 1997; LeDoux, 2000; Squire et al., 2004; Olson et al., 2007; Sherman, 2007; Schmahmann, 2019). The cerebellum, often linked to motor control, has recently been implicated in emotional processing and fear conditioning (Schutter & van Honk, 2005). In SAP individuals this brain region might relate to the integration of sensory input and motor responses associated with phobic reactions. For what conerns the temporal pole and temporal lobes, their role in emotional processing, social cognition and memory is largely known (Olson et al., 2007). These regions may contribute to the heightened emotional responses and memory recall of phobic stimuli in individuals with SAP. On the other side the frontal cortex, including the orbitofrontal cortex (OFC) and medial frontal regions, is crucial for emotional regulation and decision-making in the context of fear (Bechara et al., 1999; Milad & Rauch, 2007). The involvement of this region may reflect alterations in the cognitive control over emotional responses to feared stimuli, aligning with findings of decreased volumes in anxiety disorder patients (Shin & Liberzon, 2010). Additionally, the amygdala and the thalamus are also important emotion-related processes' hubs, with the amygdala's key role in processing fear-related stimuli (LeDoux, 2000) and the thalamus's function in relaying sensory and motor signals to the cerebral cortex

(Sherman, 2007). These regions might underpin the heightened fear response and sensory processing of phobic stimuli in SAP individuals. Lastly, the putamen in SAP individuals, which is related to motor regulation and learning (Grahn et al., 2008), suggests a neurobiological basis for the avoidance behavior that characterize individuals with phobias. This aligns with the hypothesis that the putamen might be linked to heightened reactivity to threat cues or resistance to extinction, reflecting the reinforced avoidance behavior towards phobic stimuli (LeDoux, 2000; Packard & Goodman, 2013). Overall these findings align with previous research indicating structural brain differences in anxiety disorders (Hilbert et al., 2014; Strawn et al., 2015).

These findings challenge traditional models by suggesting that phobias may be better explained by focusing on frontal areas' control rather than solely on the deactivation of limbic areas. This perspective is supported by the lack of significant differences in amygdala, which contrasts with the common emphasis on amygdala hyperactivity in anxiety disorders. Studies have shown that amygdala hyperactivity does not necessarily correlate with morphometric features. However, other research has reported differences in amygdala volumes in various anxiety disorders, suggesting a potential structural basis for enhanced emotional responsiveness (Etkin & Wager, 2007; Shin & Liberzon, 2010; Schienle et al., 2011). Additionally, the larger left putamen GMV, specific to phobias, underscores the role of complex motor regulation and learning in phobic responses, suggesting neurodevelopmental vulnerabilities or enhanced reactivity to threat cues (Rauch et al., 2003).

Macro-networks Contributions

In our study we also investigating the possibility to classify SAP individuals via macro networks. Upon applying a rigorous Bonferroni correction for multiple comparisons, only four networks demonstrated robust classification capabilities: the Default Mode network (DMN), the Affective network, the Central Executive network, and the Sensorimotor network. Of note these networks have regions partially included in the whole brain analyses. This may explain the fact that both whole brain and these macro networks are able to correctly classify SAP individuals.

The DMN emerged as the most potent discriminative network even when compared to the whole brain analysis. Following the DMN, the Affective network displayed significant classification performance, highlighting the relevance of its included brain regions in the neurobiological underpinnings of SAP. The Central Executive and Sensorimotor networks also showed noteworthy classification accuracies. The salience, visual, and reward networks did not meet the stringent Bonferroni correction criteria and, thus, were not considered statistically significant in our analyses.The DMN is known for mediating self-referential thoughts and mind-

wandering, processes often dysregulated in psychiatric conditions (Buckner et al., 2008; Langerbeck et al., 2023; Raichle et al., 2001), explaining the potential cognitive and emotional disruptions characteristic of SAP. The DMN's pronounced ability to discriminate between SAP and CTRL individuals could thus stem from its critical role in processing internal states, which may be perturbed by the heightened focus on phobic stimuli or maladaptive rumination associated with fear in SAP individuals. This underscores the deep cognitive undercurrents of anxiety disorders, pointing towards a complex interplay of internal cognitive and emotional processes.

The Affective Network marks a significant stride in understanding the emotional dimensions of SAP. Comprising regions integral to emotional processing—such as the amygdala, the insula, and the orbitofrontal cortex (OFC)—this network elucidates the heightened emotional reactivity and dysregulation at the heart of SAP. The involvement of the amygdala in fear and threat detection, coupled with the insula's role in integrating bodily sensations with emotional states, paints a detailed picture of the affective disturbances in SAP (Paulus & Stein, 2006; Phelps et al., 2004). The OFC's contribution to modulating these responses highlights a disruption in the top-down control mechanisms essential for emotional regulation in people living with phobia. This network's prominence in the classification process reinforces the centrality of emotional dysregulation in SAP and aligns with contemporary understandings of the brain's role in emotion regulation and the expression of phobias (Paulus & Stein, 2006; Phelps et al., 2004).

The CEN, is associated with high-level cognitive functions, including working memory and attentional control (Seeley et al., 2007). Its significant classification performance may reflect the cognitive-attentive aspects of anxiety disorders, where dysfunctions in attentional control and heightened vigilance towards threat-related stimuli are one of the main features (Etkin & Wager, 2007).

Last but not least, we found a significant role of the Sensorimotor network in classifying SAP individuals. This network was not included in our hypotheses but can be easily understood for its involvement in the physical manifestations of anxiety, such as heightened startle response and avoidance behavior seen in SAP individuals. This network's role in the classification underscores the integration of sensory inputs with motor outputs in response to phobic stimuli, possibly indicating a heightened readiness for fight-or-flight responses in SAP subjects (LeDoux, 2000). Other networks, such as the salience, visual, and reward networks, displayed lower classification accuracies and did not survive the Bonferroni corrected threshold. This outcome may indicate their broader engagement across various psychiatric and neurological conditions without a distinct profile for SAP.

Conclusions and limitations.

In our study we were interested in developing a classification model of SAP individuals vs controls based on structural MRI features. The whole-brain analysis revealed structural differences in the cerebellum, temporal pole, frontal cortex, temporal lobes, amygdala, and thalamus, highlighting the multifaceted nature of SAP. The whole-brain analysis's identification of structural differences in areas traditionally associated with fear and emotion regulation adds a structural dimension to the functional impairments observed in the macro networks. This comprehensive view suggests that SAP is characterized by network-specific dysfunctions and anatomical variations, offering a nuanced understanding of the disorder that transcends the limitations of focusing solely on either functional connectivity or structural abnormalities. These findings, complemented by the significant roles of the DMN, affective, CEN, and sensorimotor networks, suggest that SAP involves both discrete neural circuitries and widespread brain areas, implicating a broad spectrum of emotional, cognitive, and sensorimotor processes. As such, the present study provides the first attempt at creating a classification machine learning model that can distinguish SAP and CTRL individuals based on structural gray matter features.

Despite the merits, this study doesn't come without limitations. One limitation was utilizing only gray matter features for the model creation, as this may exclude the relevance of white matter and functional features as potential biomarkers for classifying SAP individuals. A second limitations is represented by the relatively small SAP sample size. Although larger compared to the previous studies, a bigger SAP sample size may have been useful to create a more generalizable model. Future studies may want to expand the sample size. This will guarantee a stronger generalizability of the findings.

To conclude, the findings from our study may pave the way for future research directions and potential therapeutic strategies that aim to modulate the implicated networks and address the identified structural differences. By offering a more effective treatment paradigm for SAP and related anxiety disorders, this study not only enriches the existing body of knowledge but also opens new avenues for personalized medicine approaches that target the intricate neural networks underpinning specific phobias.

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