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

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Abstract

Specific phobia represents an anxiety disorder category characterized by intense fear generated by specific stimuli. 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, leading to inconsistent results. To overcome these limitations, and to characterize the neural underpinnings of SAP, this study aims to develop a classification model of individuals with SAP based on gray matter features, by using a machine learning method known as the binary support vector machine. 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 90 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, the Affective, and partially 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 SAP, proposing new research directions and potential diagnostic strategies.

KEYWORDS

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

1 | INTRODUCTION

Anxiety disorders are among the most prevalent mental health issues (COVID-19 Mental Disorders Collaborators, 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), or phobias of insects, spiders, reptiles, rats, 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 response to phobic stimuli in regions 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 such as the prefrontal and the orbitofrontal cortex (OFC), have also shown different activations. Moreover, structural neuroimaging studies have found similar results. For instance, one of the first studies on this topic showed significant increased cortical thickness in AP 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 occipitotemporal cortex (Rauch et al., 2004). Building on these findings, another study reported that SAP individuals had higher anxiety sensitivity with respect to healthy individuals and that this 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 in 20 human female individuals with spider phobia compared to 20 female control individuals (Fisler et al., 2013). Additionally, Hilbert et al. (2015), analyzed data from human 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 Anterior cingulate cortex (ACC), left medial orbito-frontal cortex (OFC), left precuneus, and others. Lastly, a recent study found reduced gray matter volume (GMV) in human individuals with SAP in the right and left insula, OFC, left superior medial frontal gyrus, right superior frontal gyrus, and right anterior cingulate cortex (Rivero et al., 2023). Additionally, SAP individuals exhibited increased 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), but nevertheless can cause biases in the neural findings. Furthermore, and more importantly, previous studies relied on mass univariate analysis, focusing on individual voxels separately, without acknowledging the statistical interdependencies between them (Grecucci et al., 2022, 2023; Sorella et al., 2019). In some studies, analyses were confined to predefined regions of interest (ROI) rather than employing a comprehensive whole-brain methodology, thus limiting the findings to a few a priori selected to areas (Gentili et al., 2019). 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 sometimes led to unclear findings, particularly in studies of SAP, indicating the need for a broader analytical approach. For example, although the neural bases of fear conditioning are well known (Tovote et al., 2015), their involvement in individuals with SAP, is not clear. The OFC and the amygdala known to be responsible for fear conditioning may also be involved in SAP (Tovote et al., 2015). However, they are not consistently found in the SAP literature (Rivero et al., 2023). Also, although some authors reported areas included in the default mode network (DMN) to be altered in phobias, the proof of its involvement in SAP, as in other anxiety disorders (Baggio, Grecucci, Crivello, et al., 2023; Baggio, Grecucci, Meconi, et al., 2023), is missing.

Rather than relying on traditional univariate statistical methods, a new class of multivariate statistical techniques known as multivoxel pattern analysis (MVPA), or machine learning (ML) methods, has been increasingly utilized in neuroscience. These approaches offer greater accuracy and sensitivity in detecting complex latent patterns in brain signals, enabling them to classify

new cases with high precision (Norman et al., 2006). Recently, these methodologies have been successfully applied to disorders such as schizophrenia, borderline personality disorder (Grecucci et al., 2022, 2023; Sorella et al., 2019), narcissistic personality disorder (Jornkokgoud et al., 2023), and social anxiety disorder (Baggio, Grecucci, Crivello, et al., 2023; Baggio, Grecucci, Meconi, et al., 2023; Frick et al., 2014; Mwangi et al., 2012; Squarcina et al., 2017).

By capitalizing on such methods, one pioneering study by Lueken et al. (2015) applied Gaussian process classifier to classify spider and dental phobias versus healthy controls based on the structural MRI. For what concerns spider phobic individuals, authors reached an accuracy of 89%. The OFC, as well as the cingulate, the insula, the hippocampus, the temporal lobe and other structures, was responsible for such accuracy. In a more recent attempt to apply ML methods in a functional MRI experiment, Böhnlein et al. (2021) found that spider phobic individuals could be correctly classified with 73% balanced accuracy (BA) from their neural responses to supraliminal emotional faces in a large sample of participants. The regions involved were mainly the inferior parietal cortex, the fusiform gyrus, the middle cingulate, the postcentral cortex, and insula. Despite the merits, these studies only focused on spider phobic individuals, leaving unexplored the neural bases of general SAP.

In light of the limitations of previous studies, the aim of the present study is to apply a ML approach to classify SAP individuals versus matched controls. To accomplish this aim, a ML method known as binary support vector machine (BSVM) will be adopted. This method uses a multivariate statistical approach to interpret and discover complex patterns in brain imaging data (Frick et al., 2014; Mwangi et al., 2012; Norman et al., 2006; Squarcina et al., 2017), and extracting a predictive model, 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). The algorithm aims to identify the optimal decision boundary, or hyperplane, that divides the data points of different classes (Hastie et al., n.d.). BSVM is effective in a high-dimensional space such as the brain which contains circa 10^5 voxels; can handle nonlinear data by relying on kernel method, and is resistant to overfitting (Hastie et al., n.d.; Pisner & Schnyer, 2020). Thus, the primary objective of our study is to exploit the potential of BSVM, to classify SAP individuals.

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 OFC, 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 matched control individuals (CTRLs).

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, such as Borderline personality disorders (Grecucci et al., 2022, 2023; Langerbeck et al., 2023), Narcissistic personality disorder (Jornkokgoud et al., 2023, 2024), and anxiety disorders (Baggio, Grecucci, Crivello, et al., 2023; Baggio, Grecucci, Meconi, 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 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. We hypothesize that abnormalities in these networks, particularly the DMN, SN, and CEN, may be predictive of SAP. We further postulate that among these networks, the DMN might be the most significant in differentiating SAP individuals from CTRL ones. Our study aims to explore their relevance in the context of SAP. We also expect that, DMN-based classification will outperform the whole brain analysis. I.

Although a limbic network (sometimes called affective network, AN) has not been yet included in most of the resting state macro networks classifications now available (see Damoiseaux et al., 2006 and Uddin et al., 2019), and the possibility to detect an emotion related macro-network has been questioned (Barrett & Satpute, 2013, but see Yeo et al., 2011 for opposite results), we wanted to test the possibility that an affective related network might be relevant when classifying SAP individuals. This AN encompasses brain regions underscored in the existing literature for their pivotal roles in emotional processing and affective responses, including the amygdala, the cingulum, the pallidum, the hippocampus, the insula, the OFC, 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 is similar to the "limbic network" proposed (Enatsu

et al., 2015; Yeo et al., 2011), that usually includes the hypothalamus, the hippocampus, the mammillary body, the thalamus, the cingulate gyrus, the para-hippocampal gyrus and the entorhinal cortex. However, this network relies only on subcortical structures, while other findings have now widely and undoubtedly associated other cortical areas such as the OFC 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). Similarly, Janes et al. (2012) when testing for an emotion related network, mainly considered subcortical regions without any cortical contribution (Janes et al., 2012). The AN used in this study has also similarities with the AN used by Dörfel et al. (2020), for the consideration of the amygdala, the insula, and of regions of the prefrontal cortex (including the inferior frontal, middle frontal, superior frontal, medial frontal and orbital gyri, the cingulate gyri). However, in this network many subcortical regions (such as for example the basal ganglia) were not included. Additionally, Ahmadi Ghomroudi et al. (2024) described an AN related to emotion regulation abilities but this time mainly focused on the amygdala, and frontal and temporal regions, but neglecting the role of the other subcortical structures. To overcome the limitations of the previous limbic and AN, we decided to build a more inclusive AN. 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. Alternatively, 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 SAP. By using integrating advanced ML techniques with structural 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.

2 | METHODS

2.1 | Participants

The sample of the present study includes participants previously collected in the study of 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). All participants were adult, right-handed, and none had any visual problems. The phobia had to be the primary psychological disorder that could not be explained by another health condition. 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 SAP, and 90 healthy controls matched for age and gender (59 F, mean age: 31.95 ± 10.25). No significant differences were found for age ($t = 1.330$, $p = .186$) and gender ($t = 1.317$, $p = .190$) between groups. See Table 1. Phobic and controls had similar total intracranial volume.

TABLE 1 Table presenting demographic and diagnostic information about the participants, including their number, gender distribution, mean age, and inclusion criteria.

	SAP ($n = 32$)	CTRL ($n = 90$)	*p*-Value
Sex	7M, 25F	31M,59F	.19
Age	Mean age = 34.4 (SD ± 11.07)	Mean age = 31.95 (SD ± 10.25)	.18
Inclusion criteria	Smal animal phobia diagnosis, right-handedness, no contraindications for MRI scanning	No history of psichiatric or neurological disorder, Right-handedness, no contraindications for MRI scanning	

Abbreviations: CTRL, controls; F, females; M, males; SAP, small animal phobia individuals.

2.2 | MRI data acquisition

The MRI sessions for the original sample were conducted using a 3 T 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 3 T 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 × 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.

2.3 | 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 ($t(1,120) = 4.191$, $p < .001$). 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 the ML analyses, see Section 2.4) 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.

2.4 | Data analysis

ML analyses were performed using the binary support vector machine (BSVM) method within the Pattern Recognition for Neuroimaging Toolbox (Schrouff et al., 2013). The aim was to train and test the model to correctly classify individuals with SAP from matched controls, based on gray matter features. 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. In the first step (Enter data and design), the preprocessed gray matter images of both groups were entered into two separate classes. The denoising mask created to mitigate the difference of the scanning equipment described above, was entered as 1st level mask for both whole-brain analyses and specific network investigations to eliminate eventual residual noise. In the second step (Feature set) the values of the gray matter density of each voxel of each subject were extracted and reorganized into a $N_{samples} \times N_{features}$ data matrix, containing the values of selected features for each sample. This matrix was used to compute a "similarity matrix", or kernel (Hofmann et al., 2008), of size $N_{samples} \times N_{samples}$, which was then input into the classification algorithm. In the third step (Model specification and estimation), the BSVM was selected as training algorithm, and all 32 subjects with SAP were entered as one group, and all the 90 CTRLs subjects were entered as the second group. The soft-margin hyper-parameters (C) were optimized following PRONTO developers suggestions with the following values: 0.0001, 0.01, 1, 10, 100, and 1000

(Claesen & De Moor, 2015), in a nested cross-validation scheme. Two loops in the cross-validation scheme were created. The inner loop was used to optimize the hyperparameters, and the outer loop was used to assess the model's performance. The data was divided into training and testing sets according to a k-folds CV on subjects per group method with 5 folds as cross-validation scheme in both the inner and outer loops. This cross-validation technique enhances the model's reliability and securing that the data are not overfitted by the model. All participants were divided 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. The parameter that yielded the highest performance (measured by BA for a classification task) in the inner/nested loop was then applied in the outer loop. For each fold in the outer loop, the model was trained using this optimal hyperparameter value and tested on the excluded data (which was not used for parameter tuning). The accuracy for each class was determined by averaging the results from all the folds of the cross-validation process. Given the different number of participants between SAP and CTRLs we relied on the BA estimation as a more reliable method to assess the goodness of the model. Additional metrics were calculated to thoroughly evaluate the performance of the ML models across macro-networks in the classification tasks. These comprehensive metrics, including the F1-score, sensitivity (recall), and 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.

To ascertain the statistical robustness of our classification results, we conducted 5000 permutation testing on each model. Permutation testing allows to obtain meaningful confidence intervals and *p*-values. The model was estimated with permuted labels/targets, to produce a *p*-value for performance statistics. 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 (DMN, SN, CEN, sensory network, and visual network), derived from CAREN macro networks atlas (see Doucet et al., 2019 for a list of areas included in each mask), the reward mask (including the pallidum, the putamen, and the caudate) coherently with what reported by Haber and Knutson (2010), and the AN mask. To compensate for the fact that different regions contain different numbers of voxels, and as such different kernels may contain different number of features, we normalized the features and applied also a mean centering. Once the models were generated, to allow the interpretation of the models' parameters (weights) and to estimate the contribution of each brain region to the statistical model, a weight map was computed. The weight map is a spatial representation of the decision function and allows to understand the main brain regions allowing the classification. The whole brain weight map was then plotted as a 3D mesh in SurfICE. For the networks exploration, we plotted the original masks of the CAREN atlas as 3D meshes. See Figure 1.

2.5 | Whole brain results

The BSVM analyzing whole-brain gray matter features returned BA stood at 79.48 ($p = .0002$) 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 cerebellum, 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 SAP. See Table 2 and Figures 2 and 3.

2.6 | Macro-networks results

Our 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 ($p < .006$ threshold). The DMN showed the highest BA (BA: 80.49%, *p*-value: .0002, AUC: 0.92), indicating its strong discriminatory power, and overcoming even the whole brain results. The AN also demonstrated substantial classification capability (BA: 75.03%, *p*-value: .0002, AUC: 0.88). The CEN (BA: 72.12%, *p*-value: .0002, AUC: 0.88) and the sensorimotor network (BA: 70.90%, *p*-value: .0002, AUC: 0.83) followed in performance, both yielding statistically significant results. The other networks such as the salience (BA:

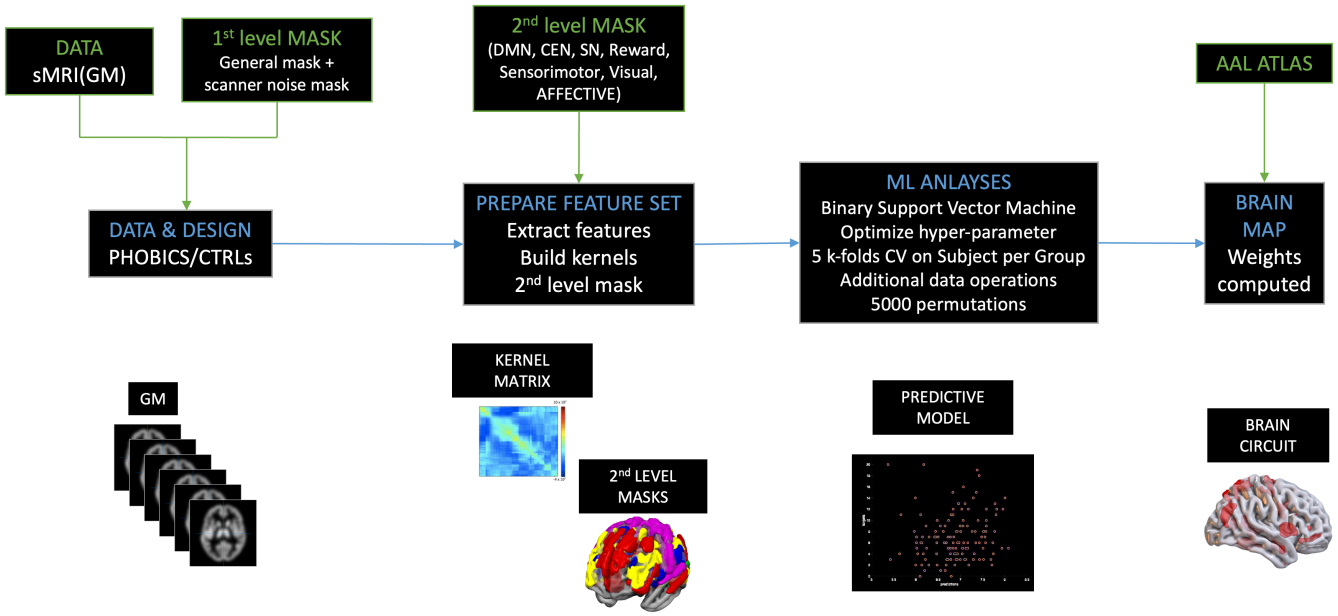

FIGURE 1 Graphical representation of the main steps of the ML analyses. AAL, automated anatomical labelling atlas; CEN, central-executive network; DMN, default mode network; GM, gray matter images; sMRI, structural magnetic resonance imaging; SN, salience network.

61.77%, *p*-value: .0134, AUC: 0.70), visual (BA: 61.22%, *p*-value: .0148, AUC: 0.68), and reward networks (BA: 52.19%, *p*-value: .2352, AUC = .67) displayed lower classification accuracies and did not survive the Bonferroni corrected threshold. See Table 3, and Figures 2 and 3. Of note, although the metrics were similar and good for all the significant networks, the precision of the CEN and of the Sensorimotor indicate lower reliability (performance around 50%) of these two networks. See also Table S1 for the BA of each fold in the cross-validation procedure.

3 | DISCUSSION

This investigation of neurobiological distinctions between individuals with 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 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 DMN, 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.

3.1 | 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; Olson et al., 2007; Schmahmann, 2019; Sherman, 2007; Squire et al., 2004). The cerebellum, often linked to motor control, has 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 concerns 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 OFC and medial frontal regions, is crucial for emotional regulation

TABLE 2 Table detailing the contributions of brain regions to the classification of SAP and CTRL individuals, listing ROIs, their weight in the classification model, and their size measured in voxels.

Whole brain results			
ROI label	**Region name**	**ROI weight (%)**	**ROI size (vox)**
Vermis_3	Vermis	2.2408	522
Vermis_1_2	Vermis	2.1067	109
Cerebelum_3_L	Left cerebellum	1.8075	314
Temporal_Pole_Mid_R	Right middle temporal pole	1.5780	2014
Temporal_Pole_Sup_R	Right superior temporal pole	1.5216	2284
Vermis_4_5	Vermis	1.5173	1175
Frontal_Mid_Orb_R	Right middle orbito-frontal gyrus	1.4257	1503
Frontal_Mid_Orb_L	Left middle orbito-frontal gyrus	1.3633	1396
Putamen_L	Left putamen	1.3230	1963
Putamen_R	Right putamen	1.3082	1824
Temporal_Inf_L	Left inferior temporal gyrus	1.2349	4125
Temporal_Inf_R	Right inferior temporal gyrus	1.2305	5574
Temporal_Pole_Sup_L	Left superior temporal pole	1.1857	2785
Lingual_L	Left lingual	1.1721	3873
Frontal_Inf_Orb_L	Left inferior orbito-frontal gyrus	1.1655	2721
Amygdala_R	Right amygdala	1.1380	392
Pallidum_R	Right pallidum	1.1268	608
Cingulum_Post_L	Left posterior cingulate	1.1121	720
Caudate_L	Left caudate	1.0841	1939
Frontal_Inf_Orb_R	Right inferior orbito-frontal gyrus	1.0821	2492
Vermis_8	Vermis	1.0769	528
Temporal_Mid_L	Left middle temporal gyrus	1.0658	8786
Angular_L	Left angular gyrus	1.0591	1873
Cerebelum_8_R	Right cerebellum	1.0522	2566
Frontal_Sup_Orb_R	Right superior orbito-frontal gyrus	1.0519	643
Thalamus_L	Left thalamus	1.0402	2420
Precuneus_L	Left precuneus	1.0361	5765
Vermis_9	Vermis	1.0186	274
Temporal_Pole_Mid_L	Left middle temporal pole	1.0165	1579
Temporal_Sup_L	Left superior temporal gyrus	1.0150	4430
Cerebelum_8_L	Left cerebellum	1.0071	2524
Frontal_Sup_Medial_L	Left superior medial frontal gyrus	1.0014	4905

Note: Please note that only the regions with more than 1% have been reported.

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' function in relaying sensory and motor

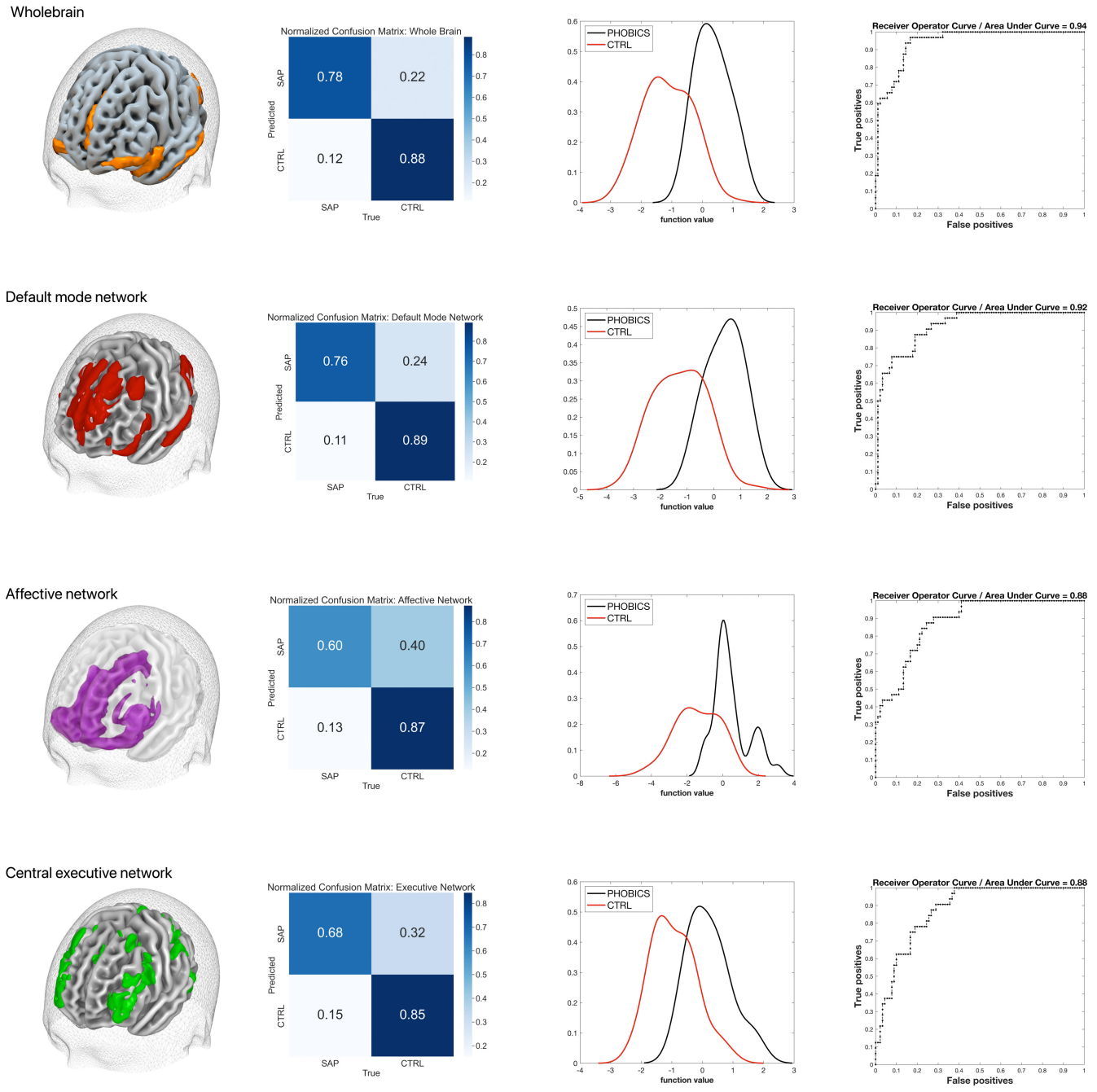

FIGURE 2 Brain plots, histogram plots and ROC curves of the whole brain, the DMN, the AN and the CEN. AN, affective network; CEN, central-executive network; DMN, default mode network; ROC, receiver operating characteristic.

signals to the cerebral cortex (Sherman, 2007). These regions might underpin the heightened fear response and sensory processing of phobic stimuli in SAP individuals. The amygdala has been shown to be relevant for anxiety disorders in general (Grupe and Nitschke, 2013; Tovote et al., 2015), and indeed, some studies have reported differences in amygdala volumes in various anxiety disorders, suggesting a potential structural basis for enhanced emotional responsiveness (Etkin & Wager, 2007; Schienle et al., 2011; Shin & Liberzon, 2010). However, some studies on anxiety failed to report the amygdala. This may be due to problems in the experimental design such as small sample size (see Shin & Liberzon, 2010, for a discussion of discordant findings in anxiety disorders).

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 &

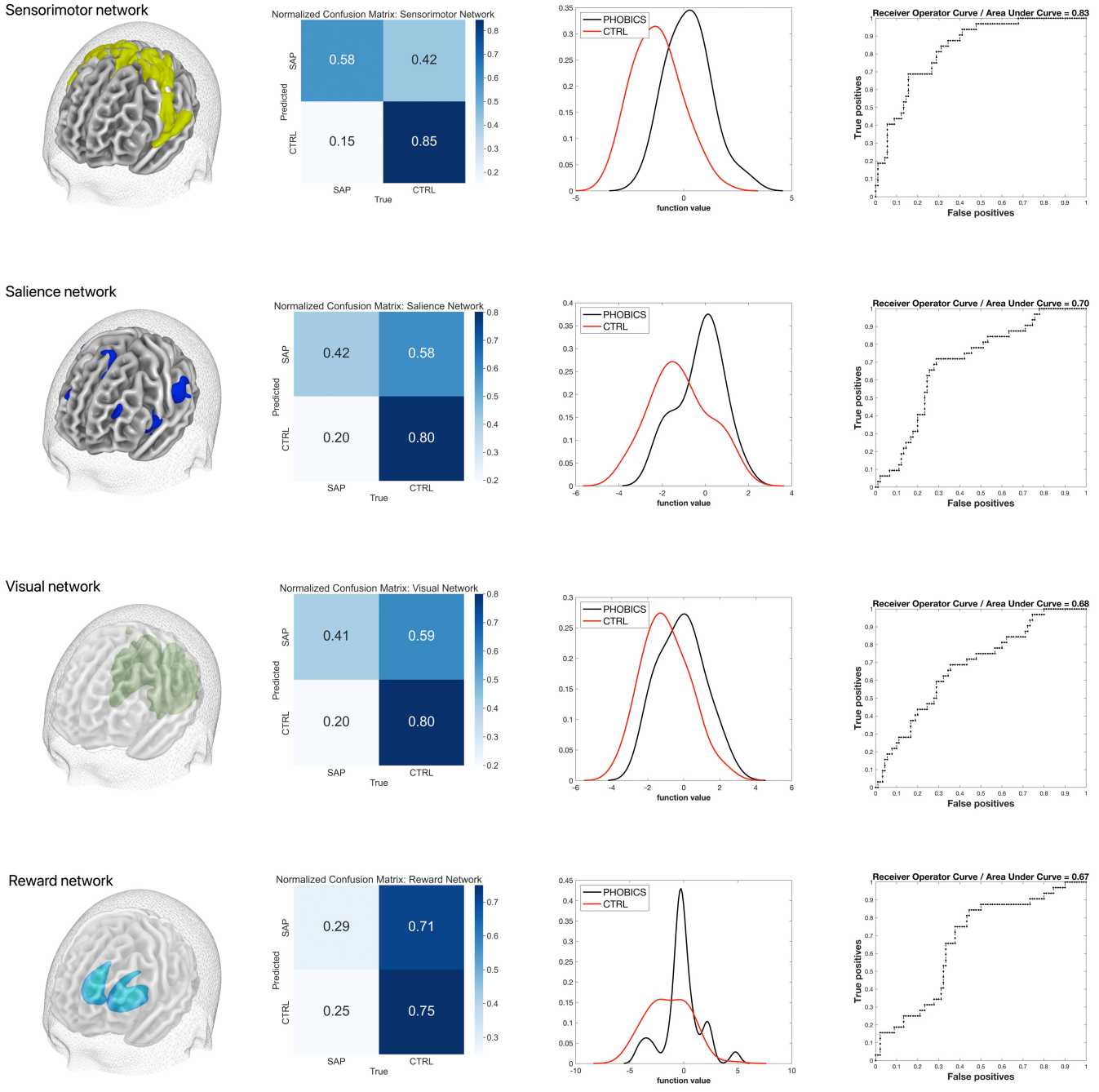

FIGURE 3 Brain plots, histogram plots and ROC curves of the sensorimotor network, the SN the visual network and the reward network. ROC, receiver operating characteristic; SN, salience network.

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. 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).

3.2 | Macro-network contributions

In our study we also investigating the possibility to classify SAP individuals via macro networks. Even if our study only used structural data, several previous studies have shown that resting state macro-networks are reflected also at a structural level (Baggio, Grecucci, Crivello, et al., 2023; Baggio, Grecucci, Meconi, et al., 2023; Grecucci et al., 2022; Jornkokgoud et al., 2024; Luo et al., 2020; Vanasse et al., 2021). Upon applying a Bonferroni correction for multiple comparisons, only four networks demonstrated robust

TABLE 3 Table ranking the brain networks by their effectiveness in classifying SAP and CTRL individuals, presenting BA, F1-score, sensitivity (recall), specificity, precision, and *p*-values for each network.

Model	Balanced accuracy	F1-score	Sensitivity	Specificity	Precision	AUC (area under the curve)	*p*-Values
Default Mode Network	80.49%	0.7213	0.7586	0.8925	0.6875	0.92	.0002
Whole Brain	79.48%	0.7119	0.7778	0.8842	0.6562	0.94	.0002
Affective Network	75.03%	0.6269	0.6000	0.8736	0.6562	0.88	.0002
Central Executive Network	72.12%	0.5965	0.6800	0.8454	0.5312	0.88	.0002
Sensorimotor Network	70.90%	0.5714	0.5806	0.8462	0.5625	0.83	.0002
Salience Network	61.77%	0.4412	0.4167	0.8023	0.4688	0.70	.0134
Visual Network	61.22%	0.4348	0.4054	0.8000	0.4688	0.68	.0148
Reward Network	52.19%	0.3143	0.2895	0.7500	0.3438	0.67	.2352

Note: Bonferroni-corrected threshold ($p < .006$ threshold) was considered.

classification capabilities: the DMN, the AN, and partially the CEN, 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 AN 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. Regions belonging to the DMN are known for mediating self-referential thoughts and mind-wandering at a functional level, processes often dysregulated in psychiatric conditions (Buckner et al., 2008; Langerbeck et al., 2023; Raichle et al., 2001), explaining the possible 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 at a functional level, 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 AN 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 OFC—this network elucidates the possible 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).

Although with a lower precision value, we also found evidence for the CEN and the Sensorimotor. 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).

The sensorimotor network although not included in our hypotheses, was significant but with a low precision value. The Sensorimotor 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 a lack of association of some macro-networks with SAP in line with our initial hypotheses. Although, the Reward network and

the Salience may have some implications with anxiety disorders, they may not be so relevant when considering SAP. Another possibility is that due to the relatively small sample size used in this paper, their role could not be clearly estimated.

4 | CONCLUSIONS AND LIMITATIONS

In our study, we were interested in developing a classification model of SAP individuals versus controls based on the 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' 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 ML model that can distinguish SAP and CTRL individuals based on the structural gray matter features.

Despite the merits, this study does not 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. Moreover, the direction of the gray matter was not considered in this study. Future studies, with other methods, are necessary to assess this aspect. A second limitation is represented by the relatively small SAP sample size. Although comparable or larger than some of 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. We found that although with different values of accuracy, four out of seven networks correctly classified SAP versus CTRLs. This may indicate a lack of precise localization of SAP brain anomalies. However, an alternative hypothesis is that SAP involves a widely distributed network that overlaps with different macro-networks. In support of this, previous studies showed that a triple network including the DMN, the CEN, and the SN, are all compromised in many psychiatric disorders (Doll et al., 2013; Langerbeck et al., 2023). This is also in line with a more widely distributed conception of brain abnormalities in psychiatric disorders. So, it does not come with surprise that even for SAP, different networks are involved. Of note the whole brain analyses returned many brain regions included in the other significant networks. Future studies may want to further explore this point. Of note, we could not control for socioeconomic status and other relevant demographic variables. Future studies may want to better control for these variables. Another limitation may be the fact that in this study we used only structural data. Future studies using resting state functional MRI data are needed to replicate our findings on the macro-networks contributions we found. Last but not least, the estimation of each region contribution (weights in the model) to the decision function of each model should be taken with cautions. Variations in the dataset (as induced by the cross-validation scheme) may lead to slightly different regional contribution estimation. Therefore, care should be taken when considering the regions found (Schrouff et al., 2013).

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.

AUTHOR CONTRIBUTIONS

Alessandro Scarano: Data curation; formal analysis; methodology; writing – original draft; writing – review and editing. **Ascensión Fumero:** Conceptualization; data curation; investigation; methodology; project administration; supervision; writing – review and editing. **Teresa Baggio:** Conceptualization; supervision; writing – original draft; writing – review and editing. **Francisco Rivero:** Conceptualization; data curation; investigation; methodology; project administration; writing – review and editing. **Rosario J. Marrero:** Conceptualization; investigation; project administration; writing – review and editing. **Teresa Olivares:** Conceptualization; investigation; writing – review and editing. **Wenceslao Peñate:** Conceptualization; investigation; project administration; writing – review and editing. **Yolanda Álvarez-Pérez:** Conceptualization; investigation; writing – review and

editing. **Juan Manuel Bethencourt:** Conceptualization; investigation; project administration; writing – review and editing. **Alessandro Grecucci:** Conceptualization; data curation; formal analysis; methodology; project administration; supervision; validation; visualization; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILBILITY STATEMENT

Data are available upon reasonable request.

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REFERENCES

Ahmadi Ghomroudi, P., Siugzdaite, R., Messina, I., & Grecucci, A. (2024). Decoding acceptance and reappraisal strategies from resting state macro networks. *Scientific Reports*, *14*, 19232 (2024). https://doi.org/10.1038/s41598-024-68490-9

Baggio, T., Grecucci, A., Crivello, F., Marc, J., & Tzourio, C. (2023). Fronto-parietal and cerebellar circuits characterise individuals with high trait anxiety: A parallel ICA and Random Forest approach. *Research Square*. https://doi.org/10.21203/rs.3.rs-3416641/v1

Baggio, T., Grecucci, A., Meconi, F., & Messina, I. (2023). Anxious brains: A combined data fusion machine learning approach to predict trait anxiety from morphometric features. *Sensors*, *23*(2), 610. https://doi.org/10.3390/s23020610

Barrett, L. F., & Satpute, A. B. (2013). Large-scale brain networks in affective and social neuroscience: Towards an integrative functional architecture of the brain. *Current Opinion in Neurobiology*, *23*(3), 361–372. https://doi.org/10.1016/j.conb.2012.12.012

Bechara, A., Damasio, H., Damasio, A. R., & Lee, G. P. (1999). Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *19*(13), 5473–5481. https://doi.org/10.1523/JNEUROSCI.19-13-05473.1999

Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1997). *Deciding advantageously before knowing the advantageous strategy* (Vol. *275*, pp. 1293–1295). https://doi.org/10.1126/science.275.5304.1293

Böhnlein, J., Leehr, E. J., Roesmann, K., Sappelt, T., Platte, O., Grotegerd, D., Sindermann, L., Repple, J., Opel, N., Meinert, S., Lemke, H., Borgers, T., Dohm, K., Enneking, V., Goltermann, J., Waltemate, L., Hülsmann, C., Thiel, K., Winter, N. R., … Dannlowski, U. (2021). Neural processing of emotional facial stimuli in specific phobia: An fMRI study. *Depression and Anxiety*, *38*(8), 846–859. https://doi.org/10.1002/da.23191

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: Anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences*, *1124*, 1–38. https://doi.org/10.1196/annals.1440.011

Calhoun, V. D., Liu, J., & Adali, T. (2009). A review of group ICA for fMRI data and ICA for joint inference of imaging, genetic, and ERP data. *NeuroImage*, *45*(1 Suppl), S163–S172. https://doi.org/10.1016/j.neuroimage.2008.10.057

Claesen, M., & De Moor, B. (2015). Hyperparameter search in machine learning (arXiv:1502.02127). *arXiv*. https://doi.org/10.48550/arXiv.1502.02127

COVID-19 Mental Disorders Collaborators. (2021). Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *The Lancet*, *398*(10312), 1700–1712. https://doi.org/10.1016/S0140-6736(21)02143-7

Craske, M. G., Rauch, S. L., Ursano, R., Prenoveau, J., Pine, D. S., & Zinbarg, R. E. (2011). What is an anxiety disorder? *Focus*, *9*(3), 369–388. https://doi.org/10.1176/foc.9.3.foc369

Damoiseaux, J. S., Rombouts, S. A., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences of the United States of America*, *103*, 13848–13853. https://doi.org/10.1073/pnas.0601417103

Del Casale, A., Ferracuti, S., Rapinesi, C., Serata, D., Piccirilli, M., Savoja, V., Kotzalidis, G. D., Manfredi, G., Angeletti, G., Tatarelli, R., & Girardi, P. (2012). Functional neuroimaging in specific phobia. *Psychiatry Research: Neuroimaging*, *202*(3), 181–197. https://doi.org/10.1016/j.pscychresns.2011.10.009

Doll, A., Sorg, C., Manoliu, A., Woller, A., Meng, C., Forstl, H., Zimmer, C., Wohlschlager, A. M., & Riedl, V. (2013). Shifted intrinsic connectivity of central executive and salience network in borderline personality disorder. *Frontiers in Human Neuroscience*, *7*, 727. https://doi.org/10.3389/fnhum.2013.00727

Dörfel, D., Gärtner, A., & Scheffel, C. (2020). Resting state cortico-limbic functional connectivity and dispositional use of emotion regulation strategies: A replication and extension study. *Frontiers in Behavioral Neuroscience*, *14*, 128. https://doi.org/10.3389/fnbeh.2020.00128

Doucet, G. E., Lee, W. H., & Frangou, S. (2019). Evaluation of the spatial variability in the major resting-state networks across human brain functional atlases. *Human Brain Mapping*, *40*(15), 4577–4587. https://doi.org/10.1002/hbm.24722

Enatsu, R., Gonzalez-Martinez, J., Bulacio, J., Kubota, Y., Mosher, J., Burgess, R. C., Najm, I., & Nair, D. R. (2015). Connections of the limbic network: A corticocortical evoked potentials study. *Cortex*, *62*, 20–33. https://doi.org/10.1016/j.cortex.2014.06.018

Etkin, A., & Wager, T. D. (2007). Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *The American Journal of Psychiatry*, *164*(10), 1476–1488. https://doi.org/10.1176/appi.ajp.2007.07030504

Fisler, M. S., Federspiel, A., Horn, H., Dierks, T., Schmitt, W., Wiest, R., de Quervain, D. J.-F., & Soravia, L. M. (2013). Spider phobia is associated with decreased left amygdala volume: A cross-sectional study. *BMC Psychiatry*, *13*(1), 70. https://doi.org/10.1186/1471-244X-13-70

Frick, A., Gingnell, M., Marquand, A. F., Howner, K., Fischer, H., & Kristiansson, M. (2014). Classifying social anxiety disorder using multivoxel pattern analyses of brain function and

structure. *Behavioural Brain Research*, *259*, 330–335. https://doi.org/10.1016/j.bbr.2013.11.003

Fyer, A. J. (1998). Current approaches to etiology and pathophysiology of specific phobia. *Biological Psychiatry*, *44*(12), 1295–1304. https://doi.org/10.1016/S0006-3223(98)00274-1

Gentili, C., Messerotti Benvenuti, S., Lettieri, G., Costa, C., & Cecchetti, L. (2019). ROI and phobias: The effect of ROI approach on an ALE meta-analysis of specific phobias. *Human Brain Mapping*, *40*(6), 1814–1828. https://doi.org/10.1002/hbm.24492

Gorgolewski, K. J., Durnez, J., & Poldrack, R. A. (2017). Preprocessed consortium for neuropsychiatric Phenomics dataset. *F1000Research*, *6*, 1262. https://doi.org/10.12688/f1000research.11964.2

Grahn, J. A., Parkinson, J. A., & Owen, A. M. (2008). The cognitive functions of the caudate nucleus. *Progress in Neurobiology*, *86*(3), 141–155. https://doi.org/10.1016/j.pneurobio.2008.09.004

Grecucci, A., Dadomo, H., Salvato, G., Lapomarda, G., Sorella, S., & Messina, I. (2023). Abnormal brain circuits characterize borderline personality and mediate the relationship between childhood traumas and symptoms: A mCCA+jICA and random forest approach, *23*, 2826.

Grecucci, A., Lapomarda, G., Messina, I., Monachesi, B., Sorella, S., & Siugzdaite, R. (2022). Structural features related to affective instability correctly classify patients with borderline personality disorder. A supervised machine learning approach. *Frontiers in Psychiatry*, *13*, 804440. https://doi.org/10.3389/fpsyt.2022.804440

Grecucci, A., Rubicondo, D., Siugzdaite, R., Surian, L., & Job, R. (2016). Uncovering the social deficits in the autistic brain. A source-based morphometric study. *Frontiers in Neuroscience*, *10*, 388. https://doi.org/10.3389/fnins.2016.00388

Grupe, D. W., & Nitschke, J. B. (2013). Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. *Nature Review Neuroscience*, *14*(7), 488–501. https://doi.org/10.1038/nrn3524

Haber, S. N., & Knutson, B. (2010). The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology*, *35*(1), 4–26.

Hastie, T., Tibshirani, R., & Friedman, J. (2009). *The elements of statistical learning* (2nd ed.). Springer.

Hilbert, K., Evens, R., Maslowski, N. I., Wittchen, H. U., & Lueken, U. (2015). Neurostructural correlates of two subtypes of specific phobia: A voxel-based morphometry study. *Psychiatry Research: Neuroimaging*, *231*, 168–175.

Hilbert, K., Lueken, U., & Beesdo-Baum, K. (2014). Neural structures, functioning and connectivity in generalized anxiety disorder and interaction with neuroendocrine systems: A systematic review. *Journal of Affective Disorders*, *158*, 114–126. https://doi.org/10.1016/j.jad.2014.01.022

Hofmann, T., Scholkopf, B., & Smola, A. J. (2008). Kernel methods in machine learning. *Annals of Statistics*, *36*(3), 1171–1220.

Janes, A. C., Nickerson, L. D., Frederick, B., & Kaufman, M. J. (2012). Prefrontal and limbic resting state brain network functional connectivity differs between nicotine-dependent smokers and non-smoking controls. *Drug and Alcohol Dependence*, *125*(3), 252–259. https://doi.org/10.1016/j.drugalcdep.2012.02.020

Jornkokgoud, K., Baggio, T., Bakiaj, R., Wongupparaj, P., Job, R., & Grecucci, A. (2024). (2024). Narcissus reflected: Grey and white matter features joint contribution to the default mode network in predicting narcissistic personality traits. *The European Journal of Neuroscience*, *59*(12), 3273–3291. https://doi.org/10.1111/ejn.16345

Jornkokgoud, K., Baggio, T., Faysal, M., Bakiaj, R., Wongupparaj, P., Job, R., & Grecucci, A. (2023). Predicting narcissistic personality traits from brain and psychological features: A supervised machine learning approach. *Social Neuroscience*, *18*(5), 257–270. https://doi.org/10.1080/17470919.2023.2242094

Kendler, K. S., Myers, J., Prescott, C. A., & Neale, M. C. (2001). The genetic epidemiology of irrational fears and phobias in men. *Archives of General Psychiatry*, *58*(3), 257–265. https://doi.org/10.1001/archpsyc.58.3.257

Kessler, R. C., & Üstün, T. B. (2004). The world mental health (WMH) survey initiative version of the world health organization (WHO) composite international diagnostic interview (CIDI). *International Journal of Methods in Psychiatric Research*, *13*, 93–121.

Langerbeck, M., Baggio, T., Messina, I., Bhat, S., & Grecucci, A. (2023). Borderline shades: Morphometric features predict borderline personality traits but not histrionic traits. *NeuroImage: Clinical*, *40*, 103530. https://doi.org/10.1016/j.nicl.2023.103530

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience*, *23*, 155–184. https://doi.org/10.1146/annurev.neuro.23.1.155

Lueken, U., Hilbert, K., Wittchen, H.-U., Reif, A., & Hahn, T. (2015). Diagnostic classification of specific phobia subtypes using structural MRI data: A machine-learning approach. *Journal of Neural Transmission*, *122*(1), 123–134. https://doi.org/10.1007/s00702-014-1272-5

Luo, N., Sui, J., Abrol, A., Chen, J., Turner, J. A., Damaraju, E., Fu, Z., Fan, L., Lin, D., Zhuo, C., Xu, Y., Glahn, D. C., Rodrigue, A. L., Banich, M. T., Pearlson, G. D., & Calhoun, V. D. (2020). Structural brain architectures match intrinsic functional networks and vary across domains: A study from 15000+ individuals. *Cerebral Cortex*, *30*(10), 5460–5470. https://doi.org/10.1093/cercor/bhaa127

Mah, L., Szabuniewicz, C., & Fiocco, A. J. (2016). Can anxiety damage the brain? *Current Opinion in Psychiatry*, *29*, 56–63.

Meier, J., Tewarie, P., Hillebrand, A., Douw, L., van Dijk, B. W., Stufflebeam, S. M., & Van Mieghem, P. (2016). A mapping between structural and functional brain networks. *Brain Connectivity*, *6*(4), 298–311. https://doi.org/10.1089/brain.2015.0408

Milad, M. R., & Rauch, S. L. (2007). The role of the orbitofrontal cortex in anxiety disorders. *Annals of the New York Academy of Sciences*, *1121*, 546–561. https://doi.org/10.1196/annals.1401.006

Monté-Rubio, G. C., Falcón, C., Pomarol-Clotet, E., & Ashburner, J. (2018). A comparison of various MRI feature types for characterizing whole brain anatomical differences using linear pattern recognition methods. *NeuroImage*, *178*, 753–768. https://doi.org/10.1016/j.neuroimage.2018.05.065

Mourao-Miranda, J., Almeida, J., Hassel, S., Oliveira, L., Versace, A., & Marquand, A. (2012). Pattern recognition analyses of brain activation elicited by happy and neutral faces in unipolar and bipolar depression. *Bipolar Disorders*, *14*, 451–460. https://doi.org/10.1111/j.1399-5618.2012.01019.x

Murphy, F. C., Nimmo-Smith, I., & Lawrence, A. D. (2003). Functional neuroanatomy of emotions: A meta-analysis.

Cognitive, Affective, & Behavioral Neuroscience, *3*(3), 207–233. https://doi.org/10.3758/cabn.3.3.207

Mwangi, B., Ebmeier, K. P., Matthews, K., & Steele, J. D. (2012). Multi-centre diagnostic classification of individual structural neuroimaging scans from patients with major depressive disorder. *Brain: A Journal of Neurology*, *135*, 1508–1521. https://doi.org/10.1093/brain/aws084

Norman, K. A., Polyn, S. M., Detre, G. J., & Haxby, J. V. (2006). Beyond mind-reading: Multivoxel pattern analysis of fMRI data. *Trends in Cognitive Sciences*, *10*(9), 424–430. https://doi.org/10.1016/j.tics.2006.07.005

Olatunji, B. O. (Ed.). (2019). *The Cambridge handbook of anxiety and related disorders*. Cambridge University Press. https://doi.org/10.1017/9781108140416

Olson, I. R., Plotzker, A., & Ezzyat, Y. (2007). The enigmatic temporal pole: A review of findings on social and emotional processing. *Brain: A Journal of Neurology*, *130*(Pt 7), 1718–1731. https://doi.org/10.1093/brain/awm052

Packard, M. G., & Goodman, J. (2013). Factors that influence the relative use of multiple memory systems. *Hippocampus*, *23*(11), 1044–1052. https://doi.org/10.1002/hipo.22178

Pappaianni, E., Pisapia, N., Siugzdaite, R., Crescentini, C. A., & Job, R. (2019). Less is more: Psychological and morphometric differences between low vs. high reappraisers. *Cognitive, Affective & Behavioral Neuroscience*, *20*, 128–140. https://doi.org/10.3758/s13415-019-00757-5

Pappaianni, E., Siugzdaite, R., Vettori, S., Venuti, P., Job, R., & Grecucci, A. (2018). Three shades of grey: Detecting brain abnormalities in children with autism using source-, voxel- and surface-based morphometry. *The European Journal of Neuroscience*, *47*, 13704. https://doi.org/10.1111/ejn.13704

Paulus, M. P., & Stein, M. B. (2006). An insular view of anxiety. *Biological Psychiatry*, *60*(4), 383–387. https://doi.org/10.1016/j.biopsych.2006.03.042

Peñate, W., Fumero, A., Viña, C., Herrero, M., Marrero, R. J., & Rivero, F. (2017). A meta-analytic review of neuroimaging studies of specific phobia to small animals. *The European Journal of Psychiatry*, *31*(1), 23–36. https://doi.org/10.1016/j.ejpsy.2016.12.003

Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron*, *43*(6), 897–905. https://doi.org/10.1016/j.neuron.2004.08.042

Pisner, A., & Schnyer, D. M. (2020). Support vector machine. *Machine Learning*, *2020*, 101–121.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences*, *98*(2), 676–682. https://doi.org/10.1073/pnas.98.2.676

Rauch, S. L., Shin, L. M., & Wright, C. I. (2003). Neuroimaging studies of amygdala function in anxiety disorders. *Annals of the New York Academy of Sciences*, *985*, 389–410. https://doi.org/10.1111/j.1749-6632.2003.tb07096.x

Rauch, S. L., Wright, C. I., Martis, B., Busa, E., McMullin, K. G., Shin, L. M., Dale, A. M., & Fischl, B. (2004). A magnetic resonance imaging study of cortical thickness in animal phobia. *Biological Psychiatry*, *55*(9), 946–952. https://doi.org/10.1016/j.biopsych.2003.12.022

Rivero, F., Marrero, R. J., Olivares, T., Peñate, W., Álvarez-Pérez, Y., Bethencourt, J. M., & Fumero, A. (2023). A voxel-based morphometric study of gray matter in specific phobia. *Lifestyles*, *13*(1), 119. https://doi.org/10.3390/life13010119

Rondina, J. M., Ferreira, L. K., Souza Duran, F. L., Kubo, R., Ono, C. R., Leite, C. C., Smid, J., Nitrini, R., Buchpiguel, C. A., & Busatto, G. F. (2018). Selecting the most relevant brain regions to discriminate Alzheimer's disease patients from healthy controls using multiple kernel learning: A comparison across functional and structural imaging modalities and atlases. *NeuroImage: Clinical*, *17*, 628–641.

Rosso, I. M., Makris, N., Britton, J. C., Price, L. M., Gold, A. L., Zai, D., Bruyere, J., Deckersbach, T., Killgore, W. D. S., & Rauch, S. L. (2010). Anxiety sensitivity correlates with two indices of right anterior insula structure in specific animal phobia. *Depression and Anxiety*, *27*(12), 1104–1110. https://doi.org/10.1002/da.20765

Schienle, A., Ebner, F., & Schäfer, A. (2011). Localized gray matter volume abnormalities in generalized anxiety disorder. *European Archives of Psychiatry and Clinical Neuroscience*, *261*(4), 303–307. https://doi.org/10.1007/s00406-010-0147-5

Schmahmann, J. D. (2019). The cerebellum and cognition. *Neuroscience Letters*, *688*, 62–75. https://doi.org/10.1016/j.neulet.2018.07.005

Schrouff, J., Rosa, M. J., Rondina, J. M., Marquand, A. F., Chu, C., Ashburner, J., Phillips, C., Richiardi, J., & Mourão-Miranda, J. (2013). PRoNTo: Pattern recognition for neuroimaging toolbox. *Neuroinformatics*, *11*(3), 319–337. https://doi.org/10.1007/s12021-013-9178-1

Schutter, D. J. L. G., & van Honk, J. (2005). The cerebellum on the rise in human emotion. *Cerebellum (London, England)*, *4*(4), 290–294. https://doi.org/10.1080/14734220500348584

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A. L., & Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *27*(9), 2349–2356. https://doi.org/10.1523/JNEUROSCI.5587-06.2007

Sherman, S. M. (2007). The thalamus is more than just a relay. *Current Opinion in Neurobiology*, *17*(4), 417–422. https://doi.org/10.1016/j.conb.2007.07.003

Shin, L. M., & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *35*(1), 169–191. https://doi.org/10.1038/npp.2009.83

Sorella, S., Lapomarda, G., Messina, I., Frederickson, J. J., Siugzdaite, R., & Job, R. (2019). Testing the expanded continuum hypothesis of schizophrenia and bipolar disorder. Neural and psychological evidence for shared and distinct mechanisms. *NeuroImage*, *23*, 101854. https://doi.org/10.1016/j.nicl.2019.101854

Squarcina, L., Bellani, M., Rossetti, M. G., Perlini, C., Delvecchio, G., & Dusi, N. (2017). Similar white matter changes in schizophrenia and bipolar disorder: A tract-based spatial statistics study. *PLoS One*, *12*, 0178089. https://doi.org/10.1371/journal.pone.0178089

Squire, L. R., Stark, C. E. L., & Clark, R. E. (2004). The medial temporal lobe. *Annual Review of Neuroscience*, *27*, 279–306. https://doi.org/10.1146/annurev.neuro.27.070203.144130

Straube, T., Mentzel, H.-J., & Miltner, W. H. R. (2006). Neural mechanisms of automatic and direct processing of Phobogenic stimuli in specific phobia. *Biological Psychiatry*, *59*(2), 162–170. https://doi.org/10.1016/j.biopsych.2005.06.013

Strawn, J. R., Hamm, L., Fitzgerald, D. A., Fitzgerald, K. D., Monk, C. S., & Phan, K. L. (2015). Neurostructural abnormalities in pediatric anxiety disorders. *Journal of Anxiety Disorders*, *32*, 81–88. https://doi.org/10.1016/j.janxdis.2015.03.004

Tovote, P., Fadok, J. P., & Lüthi, A. (2015). Neuronal circuits for fear and anxiety. *Nature Reviews Neuroscience*, *16*(6), 317–331.

Uddin, L. Q., Yeo, B. T. T., & Spreng, R. N. (2019). Towards a universal taxonomy of macro-scale functional human brain networks. *Brain Topography*, *32*(6), 926–942. https://doi.org/10.1007/s10548-019-00744-6

Vai, B., Parenti, L., Bollettini, I., Cara, C., Verga, C., Melloni, E., Mazza, E., Poletti, S., Colombo, C., & Benedetti, F. (2020). Predicting differential diagnosis between bipolar and unipolar depression with multiple kernel learning on multimodal structural neuroimaging. *European Neuropsychopharmacology*, *34*, 28–38. https://doi.org/10.1016/j.euroneuro.2020.03.008

Vanasse, T. J., Fox, P. T., Fox, P. M., Cauda, F., Costa, T., Smith, S. M., Eickhoff, S. B. & Lancaster, J. L. Brain pathology recapitulates physiology: A network meta-analysis. *Communications Biology*, *4*(1), 301. https://doi.org/10.1038/s42003-021-01832-9

Vytal, K., & Hamann, S. (2010). Neuroimaging support for discrete neural correlates of basic emotions: A voxel-based meta-analysis. *Journal of Cognitive Neuroscience*, *22*(12), 2864–2885. https://doi.org/10.1162/jocn.2009.21366

Wright, C. I., Martis, B., McMullin, K., Shin, L. M., & Rauch, S. L. (2003). Amygdala and insular responses to emotionally valenced human faces in small animal specific phobia. *Biological Psychiatry*, *54*(10), 1067–1076. https://doi.org/10.1016/S0006-3223(03)00548-1

Yassa, M. A., & Stark, C. E. L. (2009). A quantitative evaluation of cross-participant registration techniques for MRI studies of the medial temporal lobe. *NeuroImage*, *44*, 319–327. https://doi.org/10.1016/j.neuroimage.2008.09.016

Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zöllei, L., Polimeni, J. R., Fischl, B., Liu, H., & Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*(3), 1125–1165. https://doi.org/10.1152/jn.00338.2011

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

TABLE S1. Folds performances.

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