European Neuropsychopharmacology 83 (2024) 19–26

Contents lists available at ScienceDirect

European Neuropsychopharmacology

journal homepage: www.sciencedirect.com/journal/european-neuropsychopharmacology

Trait anxiety is associated with attentional brain networks

Víctor De la Peña-Arteaga [a,b,c,1], Pamela Chavarría-Elizondo [1,a,d,e], Asier Juaneda-Seguí [a,d], Ignacio Martínez-Zalacaín [a,d], Pedro Morgado [c,f,g], José Manuel Menchón [a,d,e], Maria Picó-Pérez [c,f,h], Miquel A. Fullana [e,i,j,*], Carles Soriano-Mas [a,e,k,**]

[a] Psychiatry and Mental Health Group, Neuroscience Program, Institut d'Investigació Biomèdica de Bellvitge - IDIBELL, L'Hospitalet de Llobregat, Spain
[b] Sant Pau Mental Health Research Group, Institut de Recerca Sant Pau (IR SANT PAU), Barcelona, Spain
[c] Life and Health Sciences Research Institute (ICVS), School of Medicine, Universidade do Minho, Braga, Portugal
[d] Department of Clinical Sciences, School of Medicine, Universitat de Barcelona - UB, L'Hospitalet de Llobregat, Spain
[e] Network Center for Biomedical Research on Mental Health (CIBERSAM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain
[f] ICVS/3B's, PT Government Associate Laboratory, Braga/Guimarães, Portugal
[g] 2CA-Clinical Academic Center, Braga, Portugal
[h] Departamento de Psicología Básica, Clínica y Psicobiología, Universitat Jaume I, Castelló de la Plana, Spain
[i] Adult Psychiatry and Psychology Department, Institute of Neurosciences, Hospital Clínic, Barcelona, Spain
[j] Imaging of Mood- and Anxiety-Related Disorders (IMARD) Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Department of Psychiatry, Hospital Clínic, Barcelona 140, 08036, Spain
[k] Department of Social Psychology and Quantitative Psychology, Institute of Neurosciences, Universitat de Barcelona - UB, Barcelona, Spain

ARTICLE INFO

Keywords:
Neuroimaging
fMRI
State trait anxiety inventory
Attention
Personality traits

ABSTRACT

Trait anxiety is a well-established risk factor for anxiety and depressive disorders, yet its neural correlates are not clearly understood. In this study, we investigated the neural correlates of trait anxiety in a large sample ($n = 179$) of individuals who completed the trait and state versions of the State-Trait Anxiety Inventory and underwent resting-state functional magnetic resonance imaging. We used independent component analysis to characterize individual resting-state networks (RSNs), and multiple regression analyses to assess the relationship between trait anxiety and intrinsic connectivity. Trait anxiety was significantly associated with intrinsic connectivity in different regions of three RSNs (dorsal attention network, default mode network, and auditory network) when controlling for state anxiety. These RSNs primarily support attentional processes. Notably, when state anxiety was not controlled for, a different pattern of results emerged, highlighting the importance of considering this factor in assessing the neural correlates of trait anxiety. Our findings suggest that trait anxiety is uniquely associated with resting-state brain connectivity in networks mainly supporting attentional processes. Moreover, controlling for state anxiety is crucial when assessing the neural correlates of trait anxiety. These insights may help refine current neurobiological models of anxiety and identify potential targets for neurobiologically-based interventions.

1. Introduction

A central focus of psychopathology research revolves around the exploration of anxiety as a multidimensional construct, characterized by two well-established dimensions: "state anxiety," which denotes a transitory emotional state to adverse events, and "trait anxiety," a more enduring feature, defined as the predisposition to appraise stimuli as threatening and respond with anxiety (Vagg et al., 1980). Individuals with high trait anxiety are more likely to develop anxiety-related and depressive disorders (Shackman et al., 2016; Weger and Sandi, 2018). Understanding the neural correlates of trait anxiety would help refine neurobiologically-based models of anxiety and could lead to more

* Corresponding author at: Department of Psychiatry, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, Rosselló 140, 08036, Barcelona, Spain.
** Corresponding author at: Department of Psychiatry, Bellvitge Biomedical Research Institute-IDIBELL, FeixaLlarga s/n, Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona 08907, Spain.
E-mail addresses: mafullana@clinic.cat (M.A. Fullana), carles.soriano.mas@ub.edu (C. Soriano-Mas).
[1] Víctor De la Peña-Arteaga and Pamela Chavarría-Elizondo shared first authorship.

https://doi.org/10.1016/j.euroneuro.2024.02.013
Received 27 September 2023; Received in revised form 20 February 2024; Accepted 22 February 2024
Available online 16 March 2024

effective prevention and treatment strategies for such disorders.

Early neurobiological accounts of trait anxiety focused on threat detection processes and subcortical brain regions (i.e., amygdala). More recent models have emphasized top-down regulatory mechanisms and prefrontal cortical areas (Bishop, 2009). For instance, several task-based functional magnetic resonance imaging (fMRI) studies have demonstrated that individuals with high trait anxiety struggle to engage prefrontal brain regions in response to conflict, resulting in a poor ability to maintain attention and process goal-relevant information (Basten et al., 2011; Bishop, 2009; Geng et al., 2016). Although valuable, these studies do not provide information about the neural correlates of trait anxiety at rest (i.e., not task-related) or at the system (i.e., network) level.

In recent years, resting-state functional connectivity (RSFC) has become the gold standard tool to study spontaneous brain function at the system level. Several studies have investigated the association between trait anxiety and RSFC, although most have followed seed-based strategies, i.e., focused on isolated brain regions (Baur et al., 2013; Cermaková et al., 2020; Geng et al., 2016; Martynova et al., 2020; Zhang et al., 2020). To accelerate progress in this area, a transition to network-based approaches, allowing for characterizing regional activity at the system level in terms of coordinated patterns of activity, seems warranted (Shackman et al., 2016).

To our knowledge, only two studies have assessed the neural correlates of trait anxiety at the brain network level. Modi et al. (2015) showed that individuals with high trait anxiety, compared to those with low trait anxiety, exhibit reduced RSFC in the default mode network (DMN), several perceptual networks, and a network involving temporal, parieto-occipital and frontal regions. However, this study had a small sample size ($n = 15$ per group) and did not control for current (i.e., state) anxiety. Therefore, the unique correlates of trait anxiety independent of state anxiety could not be determined. This is important because, despite being highly correlated at the psychometric level (Watson and Clark, 1984), trait and state anxiety could have different neural correlates (Bishop, 2008).

Saviola et al. (2020) recently attempted to disentangle the neural correlates of trait versus state anxiety by assessing RSFC and state anxiety, as well as trait anxiety, in 42 individuals. These authors reported that trait anxiety was positively associated with RSFC between the default mode network (DMN) and prefrontal areas like the superior frontal gyrus (SFG) and the middle frontal gyrus (MFG) but not with the salience network (SN). In this study, however, self-report measures of trait and state anxiety were not significantly correlated, which is at odds with the previous literature (Watson and Clark, 1984). Additionally, the sample size was limited for establishing brain-behavior correlations.

In this study, we aimed to investigate the neural underpinnings of trait anxiety by adopting a brain network perspective in a large sample size ($n = 179$) of individuals with varying levels of trait anxiety. Our primary objective was to identify distinct connectivity patterns within specific neural networks that exhibit unique associations with trait anxiety.

2. Experimental procedures

2.1. Sample

We recruited participants as part of a prospective longitudinal study investigating behavioral and neural predictors of anxiety. Initially, we screened 840 adults (age $\geq$ 18 years) using the Spanish version (Buela-Casal et al., 2016) of the State-Trait Anxiety Inventory–Trait (STAI-T) subscale via a secure web system. To ensure a diverse range of trait anxiety levels, we stratified STAI-T data into quartiles and selected individuals ($n = 361$) from each resulting stratum who met preliminary inclusion criteria.

During a telephone interview, a medical doctor administered the Spanish version of the Mini International Neuropsychiatric Interview (MINI), confirming that potential participants fulfilled the inclusion/exclusion criteria. Inclusion criteria were individuals aged 18 to 36 years, having a smartphone (due to smartphone-based assessments in the larger study), and expressing willingness to participate in a neuroimaging assessment. Exclusion criteria included self-reported current or previous severe medical disorders, current psychoactive medication, current or past mental disorders (except current anxiety disorder, see Section 3.1 *Socio-demographic and clinical characteristics*), or current substance use (except occasional use of alcohol and other recreational drugs or tobacco use), as per the MINI, and any contraindication to neuroimaging assessment.

Two hundred and six individuals meeting the inclusion/exclusion criteria provided written, informed consent, and participated in the current study. We excluded twenty-seven participants from MRI analysis (5 because of incidental findings and 22 due to in-scanner movement, see Section 2.4 *fMRI pre-processing*). The present study followed the latest version of the Declaration of Helsinki. The research and ethics committee at *Hospital de Bellvitge* (Barcelona, Spain) approved all procedures. We obtained signed informed consent from all participants.

2.2. Psychometric assessment

All participants completed the validated Spanish version of the STAI-T subscale during the recruitment phase. Due to practical constraints, the time elapsed between the STAI-T assessment and the MRI acquisition varied among participants (1–12 weeks). We assumed STAI-T scores would remain stable over time based on theoretical considerations (trait anxiety is stable by definition) and previous psychometric data demonstrating very high test-retest reliability of the STAI-T (>0.75) for intervals below 12 months (Barnes et al., 2002). On the day of the MRI session, participants completed the state subscale of the STAI (STAI-S) (Buela-Casal et al., 2016) before scanning.

2.3. MRI data acquisition

We scanned participants in a 3.0 Tesla Phillips Ingenia MRI scanner equipped with a 32-channel phased-array head coil. We measured changes in blood-oxygenation-level-dependent (BOLD) T2* signal using a gradient echo-planar imaging (EPI) sequence. During this sequence, participants actively stared at a fixation cross and were instructed to try "not think of anything". For each participant, we obtained a whole-brain acquisition with forty odd-even interleaved slices, totalling an 8-minute acquisition time [repetition time (TR) = 2000 ms, echo time (TE) = 25 ms, field of view (FOV) = 24 cm, 80×80 pixel matrix, flip angle = 90°, 3 × 3 × 3 mm isotropic voxel size with no gap, 240 vol]. In the same session, we acquired a high-resolution three-dimensional T1-weighted turbo-gradient-echo sequence of 6 min and 6 s (220 contiguous slices, TR = 10.5± ms, TE = 4.8± ms, flip angle = 8°, FOV = 24 cm, 320×320 pixel matrix, 0.75×0.75×0.75 mm voxel size) for anatomical reference.

2.4. fMRI pre-processing

We preprocessed the functional images using fMRIPrep 1.4.1. A full description of the anatomical and resting state pre-processing pipelines can be found in the **Supplementary Material**. After preprocessing, we performed denoising by regressing out 10 confounding factors. These factors included the mean signals from cerebrospinal fluid and white matter, DVARS (Derivative of root mean square VARiance over voxelS), the mean FD (framewise displacement), and the initial six principal components derived from aCompCor using fslregfilt. Subsequently, we used fslmaths to apply spatial smoothing (with a full-width at half maximum isotropic Gaussian kernel of 6 mm) and to band-pass filter the resulting time-series within the 0.01 to 0.08 Hz frequency range.

Regarding in-scanner movement, our exclusion criterion was a mean framewise displacement (FD) >0.25. Twenty-two participants surpassed this threshold, and were therefore, excluded (Power et al., 2013, 2015). Additionally, a visual inspection of fMRIPrep output reports was

performed to identify movement outliers and assess the accuracy of the coregistration. No participants were excluded because of this reason.

2.5. Resting-state independent component analysis (ICA)

Resting-state network (RSN) maps were voxel-wise analysed using a probabilistic independent component analysis (ICA) approach, as implemented in the Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC), distributed with FMRIB Software Library FSL (Beckmann and Smith, 2004). This approach enables the isolation of components based on the temporal correlation across brain areas while maximizing the spatial independence between components (Magalhães et al., 2021). Thirty-five independent components were selected based on the minimum description length criteria (Li et al., 2007). Afterwards, we conducted a dual-regression analysis following the approach outlined by Nickerson et al. (2017). In this phase, we used the group-average spatial maps derived from the MELODIC analysis to generate individualized versions of spatial maps and their corresponding timeseries for each subject. Initially, we regressed the group-average spatial maps onto each subject's 4D space-time dataset as spatial regressors in a multiple regression, yielding subject-specific timeseries associated with each group-level spatial map. Subsequently, we further regressed these timeseries into the same 4D dataset as temporal regressors in another multiple regression, resulting in a distinct set of subject-specific spatial maps corresponding to each group-level spatial map.

Importantly, because the ICA approach may identify noisy components corresponding to non-biological signal, such as movement artifacts, independent components of interest were selected after visual inspection of their spatial distribution (Horowitz-Kraus et al., 2015). Specifically, components that were mainly present in regions that do not generate BOLD signal (white matter, ventricles, or outside the brain) were excluded from the analysis. In addition, to further refine the component selection, a correlation with the component templates distributed by the Stanford University Greicius Lab (https://greiciuslab.stanford.edu/resources) was performed using fslcc command. Finally, we obtained 15 RSN of interest (see Section 3.2 *Independent Component Analysis*), which were used in subsequent analyses.

2.6. Statistical analyses

We evaluated the relationship between trait anxiety (STAI-T scores) and the voxel-wise values from the individual RSNs using multiple regression analyses (one for network), controlling for sex, age, and state anxiety (STAI-S scores). The incorporation of sex and age as covariates is justified by their well-established influence on the clinical presentation, course, and neurobiological underpinnings of anxiety (Correa and Brown, 2019; Farhane-Medina et al., 2022; Gold et al., 2020; Lenze and Wetherell, 2011). Controlling for state anxiety was also deemed essential to unravel the specific correlates of trait anxiety, given the unresolved debate surrounding the correlation between these two anxiety measures (Saviola et al., 2020; Watson and Clark, 1984). Additionally, we conducted the same analyses without controlling for state anxiety.

Statistical significance was assessed using the nonparametric permutation procedure implemented in FSL's randomise tool (Winkler et al., 2014). Specifically, we used threshold-free cluster enhancement (TFCE) to detect significant correlations while controlling for the family-wise error rate (FWE-R). We set the significance threshold at $\alpha = 0.05$ and performed 5000 permutations.

3. Results

3.1. Socio-demographic and clinical characteristics

Table 1 shows the sociodemographic and clinical characteristics of the final sample ($n = 179$). Thirty-one participants displayed one or more current symptoms of anxiety disorders, with 27 exhibiting symptoms of generalized anxiety disorder, 7 showing symptoms of social anxiety disorder, 11 presenting panic disorder symptoms, and 2 displaying symptoms of agoraphobia, as indicated by the MINI interview. Following a dimensional approach, we did not exclude any participant (see **Supplementary Table S1**).

Table 1
Socio-demographic and clinical characteristics.

Sociodemographic characteristics	
Age, years: mean (SD) [range]	25.08 (4.51) [19–36]
Sex, male: n (%)	86 (48 %)
Race/ethnicity	
White: n (%)	129 (72.1 %)
Hispanic/Latin: n (%)	48 (26.8 %)
Asian: n (%)	2 (1.1 %)
Clinical characteristics	
STAI-T; mean (SD) [range]	20.53 (10.18) [1–45]
STAI-S; mean (SD) [range]	12.10 (7.17) [1–34]

Abbreviations: **STAI-T**: State-Trait Anxiety Inventory-Trait; **STAI-S**: State-Trait Anxiety Inventory-State; **SD:** Standard Deviation.

Participants' trait and state anxiety scores are comparable to published normative values from the general population (Guillén-Riquelme and Buela-Casal, 2011). Note that in the Spanish versions of the STAI-T and STAI-S, scores range from 0 to 60. As expected, and like previous work (Shackman et al., 2016), STAI-T and STAI-S scores were positively and significantly correlated ($r = 0.56$, $p < 0.0005$).

3.2. Independent component analysis (ICA)

Our ICA resulted in 35 components (RSNs), 20 of which were located in non-BOLD signal regions or showed no correlation with any recognizable RSN. Analyses were therefore performed with the remaining 15 RSNs (Fig. 1).

3.3. Neural correlates of trait anxiety

When we controlled for age, sex, and state anxiety, trait anxiety was positively and significantly associated with brain connectivity in the left angular gyrus/inferior parietal within the dorsal attentional network (DAN), in the right precuneus within the ventral Default Mode Network (vDMN), and the left superior temporal cortex (STC) and the left planum temporale within the auditory network (AN). These results are presented in Fig. 2 and Table 2. When we did not control for state anxiety, trait anxiety was positively and significantly associated with brain connectivity levels in four RSNs: at the level of a right posterior cingulate cortex (PCC) cluster within the dorsal Default Mode Network (dDMN), in two left angular gyrus/inferior parietal clusters and at the level of the left middle frontal cortex (MFC) within the left executive control network (LECN), in two right precuneus clusters within the vDMN, and a left inferior parietal cluster and a right PCC cluster from the precuneus network (PN). These results are presented in Fig. 3 and Table 2.

In a post-hoc analysis, we verified that the correlations between the ICA connectivity values of each voxel and STAI-T measures showed no significant differences between individuals experiencing current symptoms of anxiety disorders ($n = 31$) and those without these symptoms ($n = 148$). However, an exception emerged in the correlation between trait STAI scores and the connectivity of the precuneus within the vDMN (controlling for state anxiety), indicating a higher correlation in the subgroup with anxiety symptoms ($z = -2.28$, $p = 0.02$). Despite this divergence, the correlation values were positive and significant in both subgroups (with anxiety symptoms $r = 0.60$, $p < 0.001$; without anxiety symptoms $r = 0.22$, $p = 0.007$).

4. Discussion

We investigated resting-state brain networks associated with trait

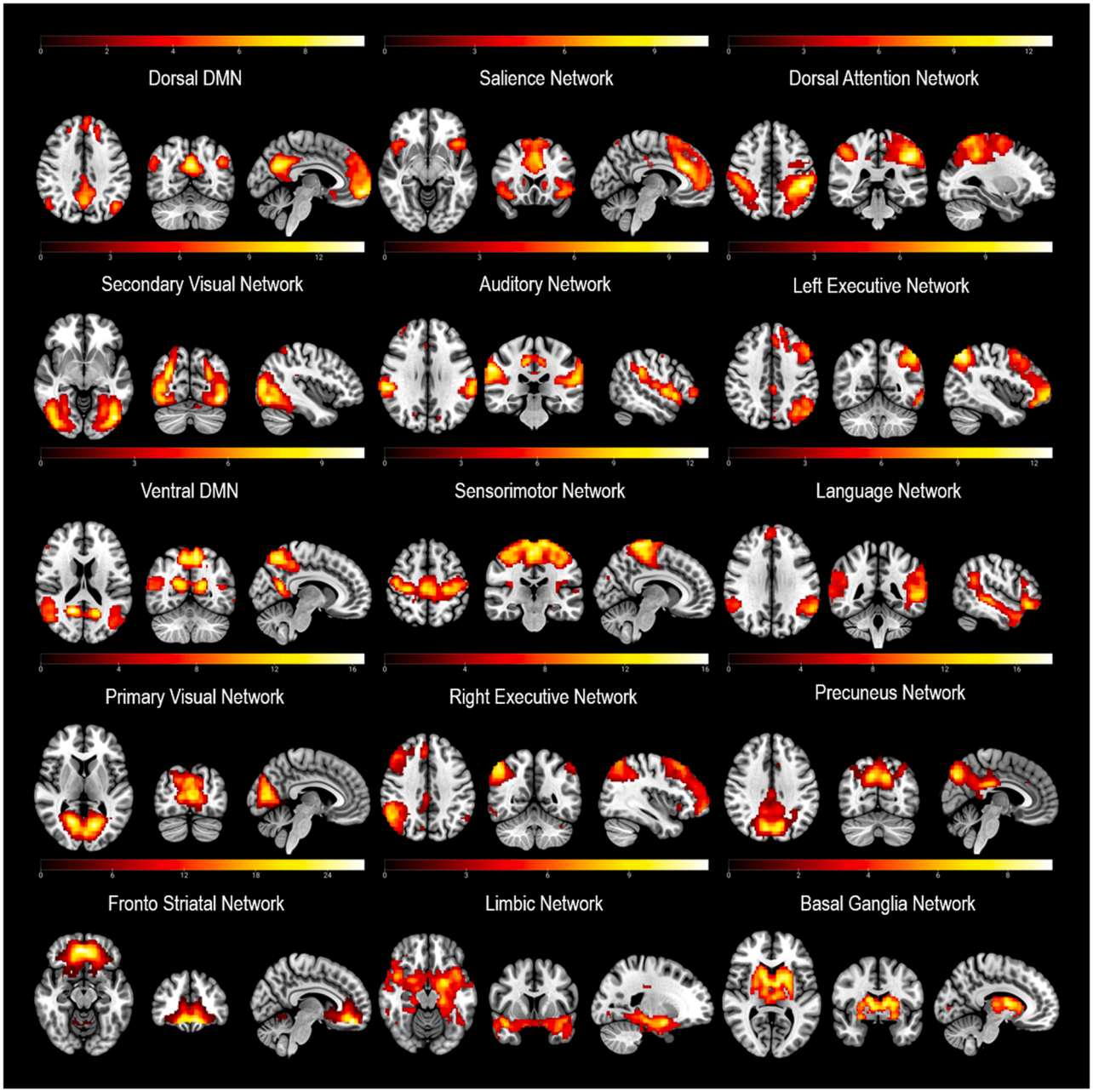

Fig. 1. Resting state networks assessed in the current study.

anxiety in a large sample of individuals with a wide range of scores in self-report measures of trait anxiety. In this study, trait anxiety uniquely correlated with intrinsic connectivity in posterior regions of three brain networks: the DAN, the ventral DMN, and the AN.

First, recent functional studies have revealed that various regions within the DAN play distinct roles in top-down attentional control (Rajan et al., 2021), and elevated connectivity across these DAN regions has been found to correlate with anxiety scores (Huang et al., 2022). Additionally, in clinical populations, disruptions in the lateral parietal regions of the DAN have been associated with compromised emotion regulation abilities, which can be conceived as a specific form of attentional control (Picó-Pérez et al., 2017). Our findings, establishing a connection between trait anxiety scores and intrinsic connectivity within the DAN, align with these prior investigations and can be therefore interpreted in terms of modulation of attention-related processes.

Our results are, however, at odds with a recent study associating resting-state connectivity in the precuneus (a "functional core" of the DMN; Utevsky et al., 2014) with state but not with trait anxiety (Saviola et al., 2020). In their investigation, the authors attributed their findings to the purported involvement of posterior DMN regions in behavioral adaptation to environmental changes and attentional control, as posited by other researchers (Cavanna and Trimble, 2006; Pearson et al., 2011). In contrast, we propose that heightened engagement of posterior DMN nodes may be associated with a trait-like predisposition to exhibit poor adaptation to changes rather than manifesting distress in response to actual uncertain scenarios. Further research is needed to elucidate the reasons for these contradictory findings. Notably, our study diverges significantly from Saviola and colleagues in terms of statistical power, the timing of state anxiety assessment (pre- vs. post-imaging assessment), and the control for the confounding effects of the complementary STAI scores.

Our suggestion that the resting-state neural correlates of trait anxiety mainly involve attentional networks fits well with previous

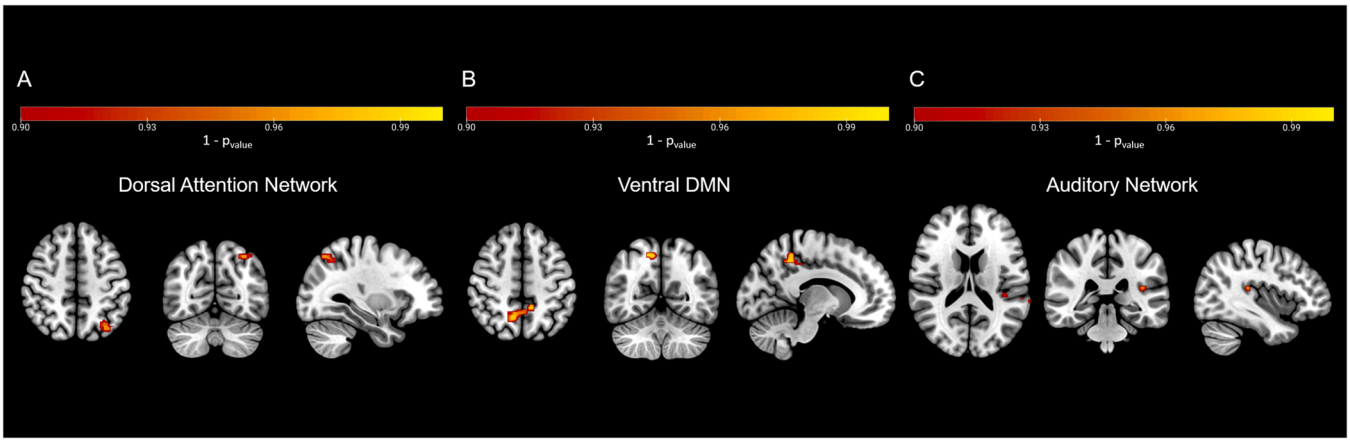

Fig. 2. Brain regions within resting-state networks significantly associated with trait anxiety after controlling for age, sex, and state anxiety ($n = 179$). For better visualization, results are thresholded at $p_{FWE\text{-}corr}<0.1$.

Table 2
Anatomical locations within resting-state networks significantly associated with trait anxiety.

Analysis[†]	Anatomical location	MNI coordinates			Network	*k*	*t* value	*p* value[*]
		X	*Y*	*Z*				
Controlling for state anxiety	Angular Gyrus/Inferior Parietal Cortex (L)	−30	−66	48	DAN	38	3.9	0.036
	Superior Temporal Gyrus (L)	−66	−40	18	AudN	25	4.5	0.025
	Planum Temporale (L)	−38	−34	14	AudN	8	4.0	0.049
	Precuneus (R)	12	−58	50	vDMN	200	4.5	0.009
Not controlling for state anxiety	Posterior Cingulate Cortex (R)	4	−30	38	dDMN	39	4.0	0.036
	Angular Gyrus/Inferior Parietal Cortex (L)	−36	−64	44	LECN	65	3.8	0.031
	Angular Gyrus/Inferior Parietal Cortex (L)	−48	−76	42	LECN	29	3.6	0.041
	Middle Frontal Gyrus (L)	−44	48	12	LECN	25	3.9	0.038
	Precuneus (R)	12	−60	26	vDMN	46	3.9	0.034
	Precuneus (R)	12	−58	50	vDMN	32	3.8	0.035
	Inferior Parietal Gyrus (L)	−26	−48	38	PCuN	53	3.9	0.037
	Posterior Cingulate Cortex (R)	16	−42	36	PCuN	2	4.3	0.05

Abbreviations: *AudN*: Auditory Network, *DAN*: Dorsal Attention Network, *dDMN*: Dorsal Default Mode Network, *L*: Left, *LECN*: Left Executive Control Network, *MNI*: Montreal Neurological Institute, *PCuN:* Precuneus Network, *R*: Right, *vDMN*: Ventral Default Mode Network.

[†] Both analyses were controlled for age and sex.

[*] Family-wise error rate (FWE-R) corrected for multiple comparisons (i.e., threshold-free cluster enhancement).

experimental research linking increased trait anxiety with attentional impairment (Berggren and Derakshan, 2013, 2014). Likewise, our findings align with the Attentional Control Theory (Eysenck et al., 2007), which suggests that high trait anxiety is associated with disruptions in the capacity to inhibit task-irrelevant information and flexibly shift attention across different sources; proposals highlighting the dysregulation of attentional control as the hallmark of anxiety (Bishop, 2009); and general cognitive models that attribute anxiety to maladaptive information processing (see Valadez et al., 2022 for a recent review).

One relatively unexpected finding of our study was the association of trait anxiety with intrinsic connectivity in regions within the auditory network (e.g., superior temporal gyrus). However, this is consistent with previous resting-state studies on trait anxiety (Saviola et al., 2020) and clinical populations (Su et al., 2020; Wei et al., 2021). These changes in functional connectivity in sensory networks observed in association with anxiety scores have been suggested to stem from an altered ability to modulate attention to sensory stimuli (Albertina et al., 2022). These findings indicate potential novel approaches for treating anxiety conditions. While the results described in previous paragraphs seem to indicate that the modulation of attentional processes may be useful for the treatment of anxiety, the results involving the auditory network suggest that interventions at earlier stages of sensory processing on more basic perceptual processes could be also effective.

When we did not control for state anxiety in our analyses, trait anxiety was also significantly associated with intrinsic connectivity in frontal regions of the executive networks. This suggests that these neural correlates are common to both trait and state anxiety. Interestingly, previous reports have shown that, specifically in individuals with high anxiety levels, neural correlates of trait and state anxiety overlap in functionally connected networks encompassing ventral prefrontal regions (Takagi et al., 2018), and our findings were indeed located in the left ventro-lateral prefrontal cortex (middle frontal gyrus). Future research should disambiguate the role of prefrontal regions in trait and state anxiety. From a methodological perspective, our results highlight the importance of controlling for states (in this case, anxiety) when assessing the neural correlates of traits.

Our study has strengths and limitations. We assessed a large sample of individuals with different levels of trait anxiety, which allowed for a robust assessment of individual differences. Moreover, we used state-of-the-art methods to assess brain networks and validated self-report measures of trait and state anxiety. It is also important to highlight that our sample did not encounter confounding effects from medication, as participants were not using psychotropic drugs. This represents a notable strength of the present study, as this aspect is frequently overlooked in many clinical research studies (Ilzarbe and Vieta, 2023). We also acknowledge some limitations. We did not assess "true" brain activity but the correlation between regional time courses and the average time courses of their respective networks. This approach allowed for calculating the correlation between STAI scores and resting-state fMRI data. However, further research should investigate whether similar conclusions may be obtained during task-based fMRI, especially during

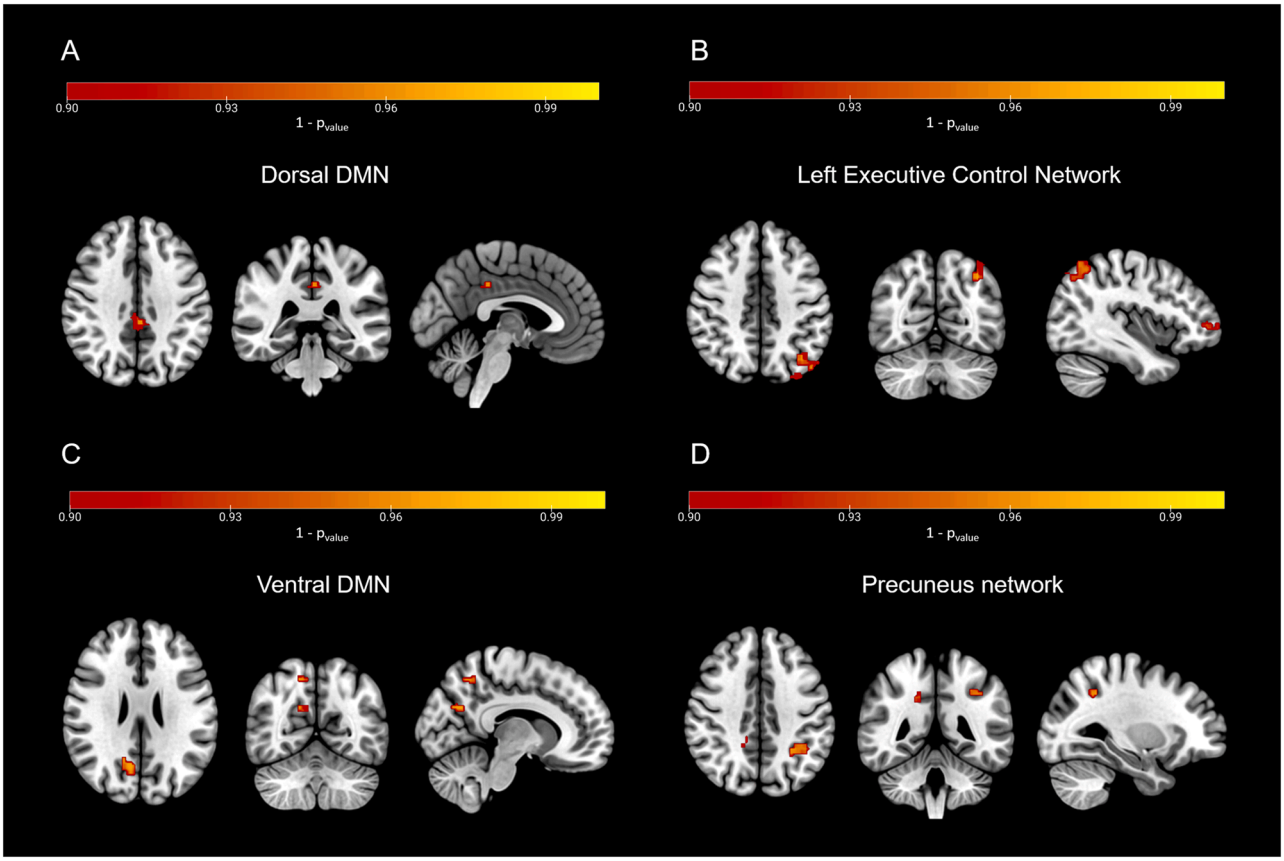

Fig. 3. Brain regions within resting-state networks significantly associated with trait anxiety after controlling for age and sex (not controlling for state anxiety) (n = 179). For better visualization, results are thresholded at $p_{\text{FWE-corr}}<0.1$.

the induction of anxiety states. Also, it is important to note that the networks identified by our ICA analysis were somewhat overlapping. Thus, regions such as the precuneus or the angular gyri may be ascribed to different networks. Another limitation of the study is that the final sample might underrepresent individuals with the highest anxiety values due to the presence of specific exclusion criteria in this subgroup. Despite this limitation, it's important to note that our study sample effectively encompasses a range of anxiety levels, aligning with our primary goal of capturing diversity in anxiety levels. Finally, we limited our anxiety assessment to a single self-report (the STAI) and two dimensions (state and trait anxiety). In contrast, other scales of similar constructs (neuroticism, negative affect, etc.) exist.

In summary, we have demonstrated that the neural correlates of trait anxiety are distributed across different brain networks and that trait anxiety is uniquely associated with intrinsic connectivity in posterior brain regions. Our findings may help refine neurobiological models of trait anxiety by highlighting the prominent role of parietal areas, and the alleged attentional processes supported by these regions. In addition, given the well-established role of trait anxiety as a risk factor for mental disorders, our results open the door to the development of risk biomarkers (Shackman et al., 2016), i.e., using the neural correlates of trait anxiety identified here to predict which individuals have more chances of developing full-blown disorders. Eventually, these biomarkers could inform intervention or prevention efforts. Indeed, from the perspective of precision psychiatry, the ultimate goal of integrating these biomarkers is to guide initiatives focused on early detection and prevention efforts (Fusar-Poli et al., 2022). For instance, if the role of attentional networks in trait anxiety is consistently observed, interventions could be tailored to 'retrain' attention in individuals at an increased risk (Liu et al., 2018). This may involve employing regulatory strategies in the context of cognitive-behavioral or mindfulness techniques. Additionally, strategic interventions for individuals with high trait anxiety may encompass pharmacological or neurostimulation methods (e.g., transcranial magnetic stimulation) targeting the specific areas identified in this study. Future research should also strive to unravel the functional distinctions among brain areas linked to trait anxiety and those more specifically associated with anxiety disorders, potentially through symptom provocation studies in clinical samples.

Data availability

The data that support the findings of this study and the brain maps of all analyses are available from the corresponding authors upon reasonable request.

Contributors

Authors CSM and MAF designed the study and wrote the protocol. Authors VDA, PCH, AJS and IMZ conducted the experiment and collected the data. Authors VDA and MPP undertook the statistical analysis, and authors VDA and PCH wrote the first draft of the manuscript. AJS, IMZ, PM, JMM, MPP, MAF and CSM revised the manuscript draft. All authors contributed to and have approved the final manuscript.

Role of the funding source

This work was supported by Instituto de Salud Carlos III (ISCIII) [PI16/00889, PI16/00144, PI19/01171, PI19/00272], FEDER funds/ European Regional Development Fund -a way to build Europe-, the Departament de Salut, Generalitat de Catalunya [PERIS SLT006/17/ 249], and the Agència de Gestió d'Ajuts Universitaris i de Recerca [2021

SGR 01017]. The study has also received funding from the European Union Horizon 2020 research and innovation programme under the Marie Sklowdowska Curie grant agreement No. 714673 and Fundación Bancaria “la Caixa”. VDA was supported by “la Caixa” Foundation [ID 100010434, fellowship code LCF/BQ/IN17/11620071] and by the Spanish Ministry of Science, Innovation and Universities, State Research Agency, and the European Union-NextGenerationEU/PRTR (JDC2022–048445-I). IMZ was supported by a P-FIS grant [FI17/00294]. MPP was supported by the Spanish Ministry of Universities, with funds from the European Union - NextGenerationEU [MAZ/2021/11]. The Institute of Neurosciences of the University of Barcelona is a María de Maeztu Unit of Excellence CEX2021-001159-M of the Ministry of Science and Innovation of Spain. Funding sources had no role in the study design.

Declaration of competing interest

PM has received in the past 3 years grants, CME-related honoraria, or consulting fees from Angelini, AstraZeneca, Bial Foundation, Biogen, DGS-Portugal, FCT, FLAD, Janssen-Cilag, Gulbenkian Foundation, Lundbeck, Springer Healthcare, Tecnimede and 2CA-Braga. Other authors declare that they have no competing interests.

Acknowledgments

We thank CERCA Programme/Generalitat de Catalunya for institutional support.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2024.02.013.

References

Albertina, E.A., Barch, D.M., Karcher, N.R., 2022. Internalizing symptoms & adverse childhood experiences associated with functional connectivity in a middle childhood sample. Biol. Psychiatry Cogn. Neurosci. Neuroimaging. https://doi.org/10.1016/j.bpsc.2022.04.001.

Barnes, L.L.B., Harp, D., Jung, W.S., 2002. Reliability generalization of scores on the spielberger state-trait anxiety inventory. Educ. Psychol. Meas. 62 (4), 603–618. https://doi.org/10.1177/0013164402062004005.

Basten, U., Stelzel, C., Fiebach, C.J., 2011. Trait anxiety modulates the neural efficiency of inhibitory control. J. Cogn. Neurosci. 23 (10), 3132–3145. https://doi.org/10.1162/jocn_a_00003.

Baur, V., Hänggi, J., Langer, N., Jäncke, L., 2013. Resting-state functional and structural connectivity within an insula-amygdala route specifically index state and trait anxiety. Biol. Psychiatry 73 (1), 85–92. https://doi.org/10.1016/j.biopsych.2012.06.003.

Beckmann, C.F., Smith, S.M., 2004. Probabilistic independent component analysis for functional magnetic resonance imaging. IEEe Trans. Med. ImAging 23 (2), 137–152. https://doi.org/10.1109/TMI.2003.822821.

Berggren, N., Derakshan, N., 2013. The role of consciousness in attentional control differences in trait anxiety. Cogn. Emot. 27 (5), 923–931. https://doi.org/10.1080/02699931.2012.750235.

Berggren, N., Derakshan, N., 2014. Inhibitory deficits in trait anxiety: increased stimulus-based or response-based interference? Psychon. Bull. Rev. 21 (5), 1339–1345. https://doi.org/10.3758/s13423-014-0611-8.

Bishop, S.J., 2008. Neural mechanisms underlying selective attention to threat. Ann. N. Y. Acad. Sci. 1129, 141–152. https://doi.org/10.1196/annals.1417.016.

Bishop, S.J., 2009. Trait anxiety and impoverished prefrontal control of attention. Nat. Neurosci. 12 (1), 92–98. https://doi.org/10.1038/nn.2242.

Buela-Casal, G., Guillén-Riquelme, A., Seisdedos Cubero, N., 2016. Cuestionario De Ansiedad Estado-Rasgo, 9th ed. TEA Ediciones.

Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain A J. Neurol. 129 (Pt 3), 564–583. https://doi.org/10.1093/brain/awl004.

Cermaková, P., Andrýsková, L., Brázdil, M., Marečková, K., 2020. Socioeconomic deprivation in early life and symptoms of depression and anxiety in young adulthood: mediating role of hippocampal connectivity. Psychol. Med. https://doi.org/10.1017/S0033291720004754. May.

Correa, J.K., Brown, T.A., 2019. Expression of generalized anxiety disorder across the lifespan. J. Psychopathol. Behav. Assess. 41 (1), 53–59. https://doi.org/10.1007/s10862-018-9697-z.

Eysenck, M.W., Derakshan, N., Santos, R., Calvo, M.G., 2007. Anxiety and cognitive performance: attentional control theory. Emotion. 7 (2), 336–353. https://doi.org/10.1037/1528-3542.7.2.336.

Farhane-Medina, N.Z., Luque, B., Tabernero, C., Castillo-Mayén, R., 2022. Factors associated with gender and sex differences in anxiety prevalence and comorbidity: a systematic review. Sci. Prog. 105 (4), 003685042211354 https://doi.org/10.1177/00368504221135469.

Fusar-Poli, P., Manchia, M., Koutsouleris, N., Leslie, D., Woopen, C., Calkins, M.E., Dunn, M., Tourneau, C.Le, Mannikko, M., Mollema, T., Oliver, D., Rietschel, M., Reininghaus, E.Z., Squassina, A., Valmaggia, L., Kessing, L.V., Vieta, E., Correll, C.U., Arango, C., Andreassen, O.A, 2022. Ethical considerations for precision psychiatry: a roadmap for research and clinical practice. Eur. Neuropsychopharmacol. 63, 17–34. https://doi.org/10.1016/j.euroneuro.2022.08.001.

Geng, H., Li, X., Chen, J., Li, X., Gu, R., 2016. Decreased intra- and inter-salience network functional connectivity is related to trait anxiety in adolescents. Front. Behav. Neurosci. 9 (January), 1–11. https://doi.org/10.3389/fnbeh.2015.00350.

Gold, A.L., Abend, R., Britton, J.C., Behrens, B., Farber, M., Ronkin, E., Chen, G., Leibenluft, E., Pine, D.S., 2020. Age differences in the neural correlates of anxiety disorders: an fmri study of response to learned threat. Am. J. Psychiatry 177 (5), 454–463. https://doi.org/10.1176/appi.ajp.2019.19060650.

Guillén-Riquelme, A., Buela-Casal, G., 2011. [Psychometric revision and differential item functioning in the State Trait Anxiety Inventory (STAI)]. Psicothema 23 (3), 510–515.

Horowitz-Kraus, T., DiFrancesco, M., Kay, B., Wang, Y., Holland, S.K., 2015. Increased resting-state functional connectivity of visual- and cognitive-control brain networks after training in children with reading difficulties. Neuroimage Clin. 8, 619–630. https://doi.org/10.1016/j.nicl.2015.06.010.

Huang, Q., Hou, L., Zhang, W., Zhou, R., 2022. The dysregulation of top-down control in individuals with high test anxiety: A resting state fMRI study. J. Psychiatr. Res. 151, 649–656. https://doi.org/10.1016/j.jpsychires.2022.05.023.

Ilzarbe, L., Vieta, E., 2023. The elephant in the room: medication as confounder. In: European Neuropsychopharmacology, 71. Elsevier B.V, pp. 6–8. https://doi.org/10.1016/j.euroneuro.2023.03.001.

Lenze, E.J., Wetherell, J.L., 2011. A lifespan view of anxiety disorders. Dialogues Clin. Neurosci. 13 (4), 381–399. https://doi.org/10.31887/DCNS.2011.13.4/elenze.

Li, Y.O., Adali, T., Calhoun, V.D., 2007. Estimating the number of independent components for functional magnetic resonance imaging data. Hum. Brain Mapp. 28 (11), 1251–1266. https://doi.org/10.1002/hbm.20359.

Liu, P., Taber-Thomas, B.C., Fu, X., Pérez-Edgar, K.E., 2018. Biobehavioral markers of attention bias modification in temperamental risk for anxiety: a randomized control trial. J. Am. Acad. Child Adolesc. Psychiatry 57 (2), 103–110. https://doi.org/10.1016/j.jaac.2017.11.016.

Magalhães, R., Picó-Pérez, M., Esteves, M., Vieira, R., Castanho, T.C., Amorim, L., Sousa, M., Coelho, A., Fernandes, H.M., Cabral, J., Moreira, P.S., Sousa, N., 2021. Habitual coffee drinkers display a distinct pattern of brain functional connectivity. Mol. Psychiatry. https://doi.org/10.1038/s41380-021-01075-4.

Martynova, O., Tetereva, A., Balaev, V., Portnova, G., Ushakov, V., Ivanitsky, A., 2020. Longitudinal changes of resting-state functional connectivity of amygdala following fear learning and extinction. Int. J. Psychophysiol. 149, 15–24. https://doi.org/10.1016/j.ijpsycho.2020.01.002.

Modi, S., Kumar, M., Kumar, P., Khushu, S., 2015. Aberrant functional connectivity of resting state networks associated with trait anxiety. Psychiatry Res. Neuroimaging 234 (1), 25–34. https://doi.org/10.1016/j.pscychresns.2015.07.006.

Nickerson, L.D., Smith, S.M., Öngür, D., Beckmann, C.F., 2017. Using dual regression to investigate network shape and amplitude in functional connectivity analyses. Front. Neurosci. 11 (MAR) https://doi.org/10.3389/fnins.2017.00115.

Pearson, J.M., Heilbronner, S.R., Barack, D.L., Hayden, B.Y., Platt, M.L., 2011. Posterior cingulate cortex: adapting behavior to a changing world. Trends Cogn. Sci. 15 (4), 143–151. https://doi.org/10.1016/j.tics.2011.02.002 (Regul. Ed.).

Picó-Pérez, M., Radua, J., Steward, T., Menchón, J.M., Soriano-Mas, C., 2017. Emotion regulation in mood and anxiety disorders: a meta-analysis of fMRI cognitive reappraisal studies. Prog. Neuro Psychopharmacol. Biol. Psychiatry 79 (May), 96–104. https://doi.org/10.1016/j.pnpbp.2017.06.001.

Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2013. Steps toward optimizing motion artifact removal in functional connectivity MRI; a reply to Carp. Neuroimage 76, 439–441. https://doi.org/10.1016/j.neuroimage.2012.03.017.

Power, J.D., Schlaggar, B.L., Petersen, S.E., 2015. Recent progress and outstanding issues in motion correction in resting state fMRI. Neuroimage 105, 536–551. https://doi.org/10.1016/j.neuroimage.2014.10.044.

Rajan, A., Meyyappan, S., Liu, Y., Samuel, I.B.H., Nandi, B., Mangun, G.R., Ding, M., 2021. The Microstructure of Attentional Control in the Dorsal Attention Network. J. Cogn. Neurosci. 33 (6), 965–983. https://doi.org/10.1162/jocn_a_01710.

Saviola, F., Pappaianni, E., Monti, A., Grecucci, A., Jovicich, J., De Pisapia, N., 2020. Trait and state anxiety are mapped differently in the human brain. Sci. Rep. 10 (1), 11112.

Shackman, A.J., Tromp, D.P.M., Stockbridge, M.D., Kaplan, C.M., Tillman, R.M., Fox, A.S., 2016. Dispositional negativity: an integrative psychological and neurobiological perspective. Psychol. Bull. 142 (12), 1275–1314. https://doi.org/10.1037/bul0000073.

Su, Q., Yu, M., Liu, F., Li, Y., Li, D., Deng, M., Lu, J., Wu, C., Guo, W., 2020. Abnormal functional asymmetry in the salience and auditory networks in first-episode, drug-naive somatization disorder. Neuroscience 444, 1–8. https://doi.org/10.1016/j.neuroscience.2020.07.043.

Takagi, Y., Sakai, Y., Abe, Y., Nishida, S., Harrison, B.J., Martínez-Zalacaín, I., Soriano-Mas, C., Narumoto, J., Tanaka, S.C., 2018. A common brain network among state,

trait, and pathological anxiety from whole-brain functional connectivity. Neuroimage 172 (February), 506–516. https://doi.org/10.1016/j.neuroimage.2018.01.080.

Utevsky, A.V., Smith, D.V., Huettel, S.A., 2014. Precuneus is a functional core of the default-mode network. J. Neurosci. 34 (3), 932–940. https://doi.org/10.1523/JNEUROSCI.4227-13.2014. : The Official Journal of the Society for Neuroscience.

Vagg, P.R., Spielberger, C.D., O'Hearn, T.P, 1980. Is the state-trait anxiety inventory multidimensional? Pers. Individ. Differ. 1 (3), 207–214. https://doi.org/10.1016/0191-8869(80)90052-5.

Valadez, E.A., Pine, D.S., Fox, N.A., Bar-Haim, Y., 2022. Attentional biases in human anxiety. Neurosci. Biobehav. Rev. 142, 104917 https://doi.org/10.1016/j.neubiorev.2022.104917.

Watson, D., Clark, L.A., 1984. Negative affectivity: the disposition to experience aversive emotional states. Psychol. Bull. 96 (3), 465–490.

Weger, M., Sandi, C., 2018. High anxiety trait: a vulnerable phenotype for stress-induced depression. Neurosci. Biobehav. Rev. 87, 27–37. https://doi.org/10.1016/j.neubiorev.2018.01.012.

Wei, H.L., Chen, Y.C., Yu, Y.S., Guo, X., Zhou, G.P., Zhou, Q.Q., Qu, L.J., Yin, X., Li, J., Zhang, H., 2021. Aberrant activity within auditory network is associated with psychiatric comorbidities in interictal migraineurs without aura. Brain Imaging Behav. 15 (5), 2464–2471. https://doi.org/10.1007/s11682-020-00446-9.

Winkler, A.M., Ridgway, G.R., Webster, M.A., Smith, S.M., Nichols, T.E., 2014. Permutation inference for the general linear model. Neuroimage 92 (100), 381–397. https://doi.org/10.1016/j.neuroimage.2014.01.060.

Zhang, R., Chen, Z., Liu, P., Feng, T., 2020. The neural substrates responsible for how trait anxiety affects delay discounting: right hippocampal and cerebellar connectivity with bistable right inferior parietal lobule. Psychophysiology. 57 (3) https://doi.org/10.1111/psyp.13495.