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Neuroanatomical prediction of individual anxiety problems level using machine learning models: A population-based cohort study of young adults

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ABSTRACT

Anxiety, a mental state in healthy individuals, is characterized by apprehension of potential future threats. Though the neurobiological basis of anxiety has been investigated widely in the clinical populations, the underly mechanism of neuroanatomical correlates with anxiety level in healthy young adults is still unclear. In this study, 1080 young adults were enrolled from the Human Connectome Project Young Adult dataset, and machine learning-based elastic net regression models with cross validation, together with linear mix effects (LME) models were adopted to investigate whether the neuroanatomical profiles of structural magnetic resonance imaging indicators associated with anxiety level in healthy young adults. We found multi-region neuroanatomical profiles predicted anxiety problems level and it was still robust in an out-of-sample. The neuroanatomical profiles had widespread brain nodes, including the dorsal lateral prefrontal cortex, supramarginal gyrus, and entorhinal cortex, which implicated in the default mode network and frontoparietal network. This finding was further supported by LME models, which showed significant univariate associations between brain nodes with anxiety. In sum, it's a large sample size study with multivariate analysis methodology to provide evidence that individual anxiety problems level can be predicted by machine learning-based models in healthy young adults. The neuroanatomical signature including hub nodes involved theoretically relevant brain networks robustly predicts anxiety, which could aid the assessment of potential high-risk of anxiety individuals.

1. Introduction

Anxiety, a mental state in healthy individuals, is characterized by apprehension of future threats, together with worrying, difficulty to relax, and increased vigilance and passive avoidance (Barlow, 2000). Anxiety has valuable adaptive benefits, such as adapting behaviours to resolve potential dangers, while excessive and unmotivated, it can become dysfunctional, increasing the risk of developing anxiety disorders (Saviola et al., 2020). In essence, excessive anxiety has been implicated in not only mental disorders, but also several medical and neurological conditions (Robinson et al., 2019). Furthermore, anxiety disorder is recognised as one of the most common mental disorders, with ~14% prevalence (Penninx et al., 2021). They have been found to occur more frequently among women than men, and both cognitive behavioral therapy and drugs were needed for the treat, accompanying by a high financial cost (Penninx et al., 2021). Consequently, there is a clear need to identify neurobiological signature signaling anxiety problems level in healthy adults which could aid the assessment of potential high-risk individuals.

Functional magnetic resonance imaging (MRI) has been widely used to investigate the underlying mechanism of anxiety. It has been suggested that the children with generalized anxiety disorder showed abnormal amygdala functional connectivity with insula as well as ventrolateral prefrontal cortex (PFC) (Monk et al., 2008). Though the direction of the effect varies by the type of task presented, altered activation in both ventral PFC and dorsomedial PFC have been observed

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in childhood anxiety disorders (Bakker et al., 2011). Similarly, youth with anxiety exhibited heightened amygdala and ventral PFC activation during a cognitive reappraisal task, and amygdala functional connectivity with ventral PFC during emotion regulation differentially related to anxiety (Padgaonkar et al., 2021). Furthermore, anterior cingulate cortex and medial PFC activation was impacted by trait anxiety during decision-making tasks (Paulus et al., 2004). It has found that during a Stroop task, high-anxious individuals exhibited abnormal activation of the above regions, which suggested that attentional control impairment might lead to altered neural processing efficiency in individuals with anxiety (Basten et al., 2011). However, only functional MRI was adopted in these studies with small sample sizes, which has limited the sensitivity for true effects and increased risk for false positives (Button et al., 2013). Additionally, these studies mainly focused on the clinical populations, and the underly mechanism of neuroanatomical correlates with anxiety level in healthy adults is still unclear.

However, structural MRI (sMRI) has also been used to examine the neuroanatomical profiles of anxiety. Previous research has found that trait anxiety is associated with abnormal gray matter volume (GMV) in amygdala, and para-hippocampal gyrus (Hu et al., 2017), and altered cortical thickness (CT) in amygdala and cingulate regions (Potvin et al., 2015). Furthermore, there have also been reports finding that adolescents with generalized anxiety disorder exhibited lower GMV in orbitofrontal cortex, inferior frontal gyrus, and dorsolateral PFC (Hilbert et al., 2014; Strawn et al., 2013, 2015). Similarly, lower GMV within middle frontal gyrus and dorsolateral PFC has been found in adults with generalized anxiety disorder (Molent et al., 2018; Moon et al., 2017). However, these studies mainly investigated single neuroanatomical indictor, such as GMV or CT. It has been found that cortical GMV can be decomposed into CT and cortical surface area (CSA), with distinct morphological features and distinct developmental trajectories (Tadayon et al., 2020; Storsve et al., 2014). This implies that CSA and CT should be considered together to investigate their associations with anxiety.

Recently, predictive models have been conducted to investigate the neural correlates of anxiety. One previous study (N = 76) conducted connectome-based predictive modeling (CPM), and found that individual anxiety can be predicted successfully based on whole-brain resting state function connectivity, especially function connectivity between limbic areas and prefrontal cortex (Wang et al., 2021). Another study (N = 148) performed CPM using whole-brain structural connectivity and found that networks predictive of trait anxiety differed across age groups (Yoo et al., 2022). However, in these studies, CPM is based on linear relationships typically with a slope and an intercept, which may not be optimal for exploring complex, non-linear correlations between brain and behavior (Shen et al., 2017). However, the machine learning approach together with cross-validation (CV) can reduce the overfitting risk and result in more generalizable findings. One study (N = 116) has used resting-state fMRI indictors to train machine learning models with CV, and found that the orbitofrontal cortex and degree centrality contributed mostly to the prediction of social anxiety level (Kim et al., 2022), while another study (N = 557) failed to predict anxiety within the holdout sample using both brain functional and structural features (Boeke et al., 2020). These inconsistent findings may be due to the small sample size and machine learning-based models with limitations. However, machine learning-based elastic net regression (ENR) model, has been proposed to be ideal for prediction using inter-correlated predictors (Zou et al., 2005). Furthermore, ENR with CV exhibited better performance than other machine learning models at different range of effect sizes (Jollans et al., 2019).

To address these limitations, this study adopted machine learning-based ENR models with CV to predict anxiety problems level from various sMRI indictors including CSA, CT, and GMV. Then, linear mixed effects (LME) model was conducted to confirm the relationships between anxiety problems level and the neuroanatomical profiles which contributed to ENR models. Adopting machine learning-based models, this study aimed to explore whether anxiety problems level can be effectively predicted in an out-of-sample and to identify specific brain critical to the prediction of anxiety in healthy young adults.

2. Methods

2.1. Participants

This study used the data from the Human Connectome Project (HCP) Young Adult dataset. All participants from HCP were recruited between August 2012 and October 2015 (Van Essen et al., 2012). More details of inclusion and exclusion criteria are provided in previous research (Van Essen et al., 2012, 2013). Due to demographic or anxiety problems level data missing, and failing MRI quality control, some participants were excluded. Therefore, this study enrolled 1080 participants for the final analysis. More details about participants were listed in Table 1 and the supplementary materials. All procedures of this study were approved by the local institutional review board and in accordance with the Helsinki Declaration. Written informed consent were provided by all participants.

2.2. Anxiety problems level

In HCP, the anxiety problems level was assessed by the Anxiety Problems subscale of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, based on the Achenbach Adult Self-Report for ages 18–59, and all 7 items in the subscale were listed in Table S1 (Achenbach et al., 2005). All Items are rated on a 3-point Likert scale (from 0 = "not true" to 2 = "very true or often true"), and the total score ranges from 0 to 14. It has been proved to exhibit excellent test-retest reliability and internal consistency (Achenbach et al., 2003).

2.3. MRI acquisition and preprocessing

For HCP dataset, a 3 T Siemens Skyra scanner from one single center at Washington University in St. Louis was used to collect T1-weighted structural images with scanning parameters listed in the supplementary materials. A modified version of the FreeSurfer pipeline was adopted to reconstruct and preprocess all sMRI data (Fischl et al., 2004; Fischl, 2012). More details of preprocessing of sMRI data and sMRI data quality were provided in previous studies (Van Essen et al., 2012; Glasser et al., 2013; Marcus et al., 2013). Finally, the Desikan atlas was

Table 1
Demographic characteristics of sample (N = 1080).

Metric	M(SD) or percent
Age	28.82 (3.68)
Sex	
Female	53.98%
Male	46.02%
Total family income	
<$10,000	7.13%
10K-19,999	7.96%
20K-29,999	12.50%
30K-39,999	12.13%
40K-49,999	10.28%
50K-74,999	20.93%
75K-99,999	13.43%
≥100,000	15.65%
Education level	
≤11 years	3.52%
12 years	13.89%
13 years	6.30%
14 years	12.50%
15 years	5.93%
16 years	42.31%
≥17 years	15.56%

Note. M: mean; SD: standard deviation.

used to define the cortical regions and mean value of CSA and CT for these cortical brain regions were derived (Desikan et al., 2006), and ASEG parcellation was adopted to define the subcortical regions, and mean value of GMV for these subcortical regions plus the intracranial volume (ICV) were derived (Fischl, 2012).

2.4. Data analyses

The Brain Predictability toolbox, a Python based machine learning library, was adopted to conduct ENR model analysis together with Scikit-Learn (Pedregosa et al., 2011; Hahn et al., 2021). LME model analysis was performed with the R-based lme 4 package. The schematic workflow of data analysis procedures was shown in Fig. 1.

2.4.1. ENR model analysis

In this study, 3 ENR models were constructed with anxiety score as the target. In Model 1, all regional sMRI indictors (Fig. 1A) were used as predictors (including CT and CSA per cortical ROI, GMV per subcortical ROI and total intracranial volume. This model was built to investigate whether pure neurobiological profiles could predict individual anxiety problems level in young adults. Model 2 with only demographic indictors (which were listed in Table 1) was conducted and aimed to check whether individual anxiety problems level could be predicted by only demographic variables. In Model 3, all sMRI and demographic indictors were included as predictors, and it aimed to ensure that pure neurobiological profiles of individual anxiety problems level from Model 1 were not affected entirely by the demographic indictors. In all models, prediction performance was evaluated by a modified coefficient of determination (R^2). Furthermore, ten times repetitions for each ENR model analysis were conducted to ensure finding stability across sample splits, and the results of the ENR models were averaged across 10 repetitions. Details about how to conduct machine learning-based ENR model are provided in the Supplemental Materials and previous research (Xu et al., 2023a, 2023b).

2.4.2. LME model analysis

To support the interpretation of findings from ENR models, a secondary analysis was conducted to use LME models to test the relationships between anxiety score with each sMRI indictors. In each LME model (Fig. 1C), each MRI variable and potentially confounding variables (including sex, age, education level, total family income, and intracranial volume) were included as fixed effects, with family ID (which indicted subjects who share at least one parent or were from a single family) included as a random effect, and anxiety score as a dependent variable. Significant correlations were indicted by $P < 0.05$ after Bonferroni correction. The sMRI predictors from machine learning-based ENR model were only regarded as neurobiological profiles of individual anxiety problems level if their relationships were further confirmed in this secondary LME model analysis. More details about LME model analysis were listed in the supplementary materials and previous research (Xu et al., 2023a, 2023b).

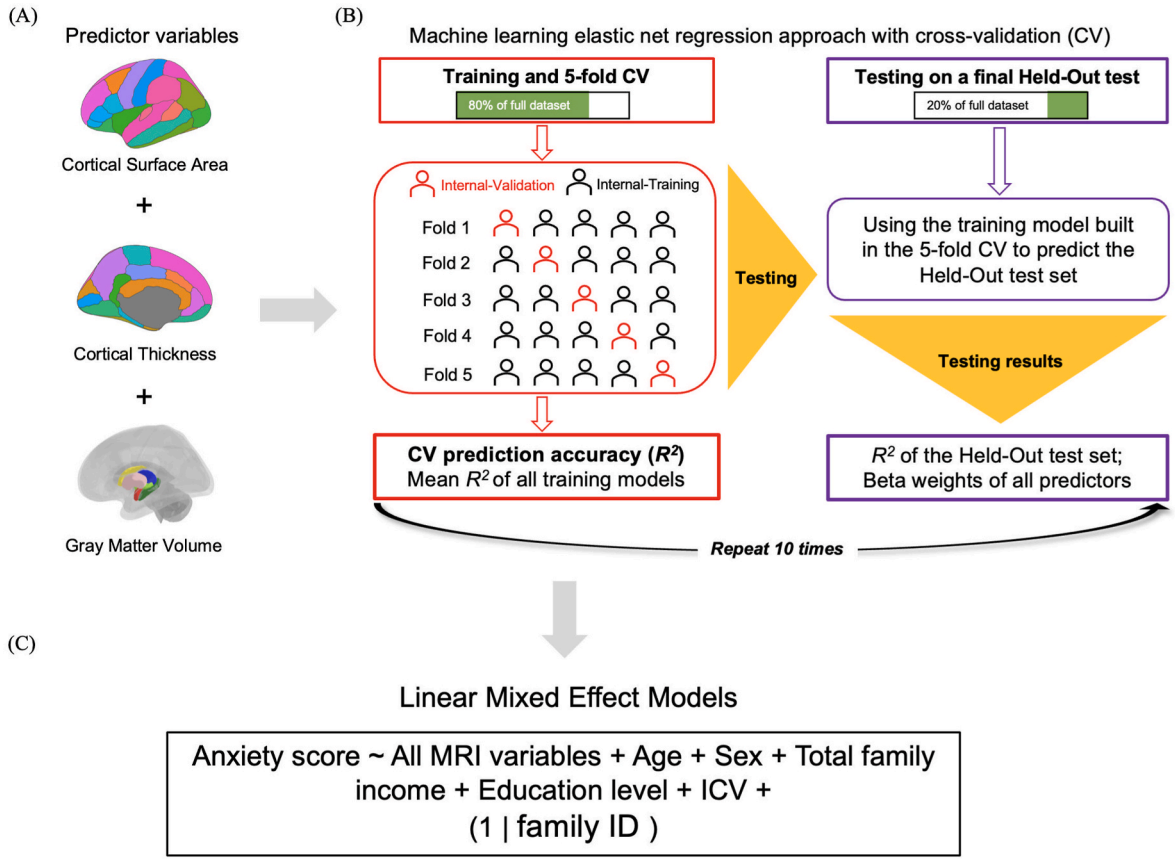

Fig. 1. Schematic workflow of data analyses procedures in this study. (1) All sMRI variables were included as predictors including cortical surface area, cortical thickness, and subcortical gray matter volume. (B) Machine learning elastic net regression models with CV were constructed to investigate how MRI features can predict anxiety problems level in a large sample of young adults. (C) A traditional univariate approach (linear mixed effects models) was conducted to confirm the univariate relationship between anxiety problems level and MRI features contributing to the elastic net regression models. CV, cross validation; MRI, magnetic resonance imaging; sMRI, structural MRI; ICV, intracranial volume.

3. Results

3.1. ENR model results

In Model 1, the mean R^2 within the 5-fold CV was 1.41% with the R^2 = 1.87% in an out-of-sample (Fig. 2 and Table S2). The neuroanatomical profiles identified as contributing to predict anxiety included widespread brain regions, including lateral orbitofrontal cortex, superior frontal gyrus, and anterior cingulate cortex (Fig. 3A and Table S3).

In Model 2, the mean R^2 within the 5-fold CV was 1.74% with the R^2 = 1.76% in an out-of-sample (Fig. 2, Table S2 and Table S4).

In Model 3, we found that the mean R^2 within the 5-fold cross-validation was 3.16% with the R^2 = 3.79% in an out-of-sample (Fig. 2, Table S2 and Table S5). Model 3 showed similar pattern of neuroanatomical profiles as that in Model 1 (Fig. 3B).

3.2. LME model results

The LME model results of significant associations were reported in Table 2. The LME model analysis found that there were significant relationships between anxiety problems level and widespread brain regions including CSA of superior frontal cortex and entorhinal cortex, and CT of lateral orbitofrontal cortex, rostral middle frontal cortex, caudal middle frontal cortex, and pars orbitalis ($p < 0.05$, FDR corrected, Table 2). Additionally, the overlapped brain cortical regions observed in both ENR models 1 and 3, and LME models are shown in Fig. 4.

4. Discussion

This study aimed to use machine-learning models to explore neuroanatomical profiles of individual anxiety problems level in healthy young adults. Our finding revealed multi-region neuroanatomical profiles predicted anxiety problems level, including the dorsal lateral prefrontal cortex (DLPFC), supramarginal gyrus (SMG), and entorhinal cortex (EC). These widespread brain regions are hubs of brain classical functional networks including the default mode network (DMN) and frontoparietal network (FPN). Furthermore, the relationships of the neurobiological profiles with anxiety problems level were further supported by traditional univariate LME models. These findings suggested individual anxiety problems level can be predicted by multi-region-related neuroanatomical profiles involved in different brain functional networks in healthy young adults.

In this study, the DLPFC was identified as significant neuroanatomical predictors of anxiety problems level in healthy adults. As acted as a vital role in emotion regulation and attention control, DLPFC has been found to be involved in the regulation for dispositional anxiety (Bishop, 2009). It has been found the activation strength of DLPFC under anxiety induction condition was negatively associated with anxiety in healthy participants, which speculated weak DLPFC activation may be linked to less anxiety downregulation (Balderston et al., 2017a). While the activation of DLPFC aimed to bear task goals in mind, it would suppress emotional interference and alleviates anxiety, which furtherly suggested that the DLPFC is a hub node for emotion functioning (Vytal et al., 2012). Additionally, individuals with psychiatric disorders featuring anxiety exhibited DLPFC hypoactivation during cognitive tasks

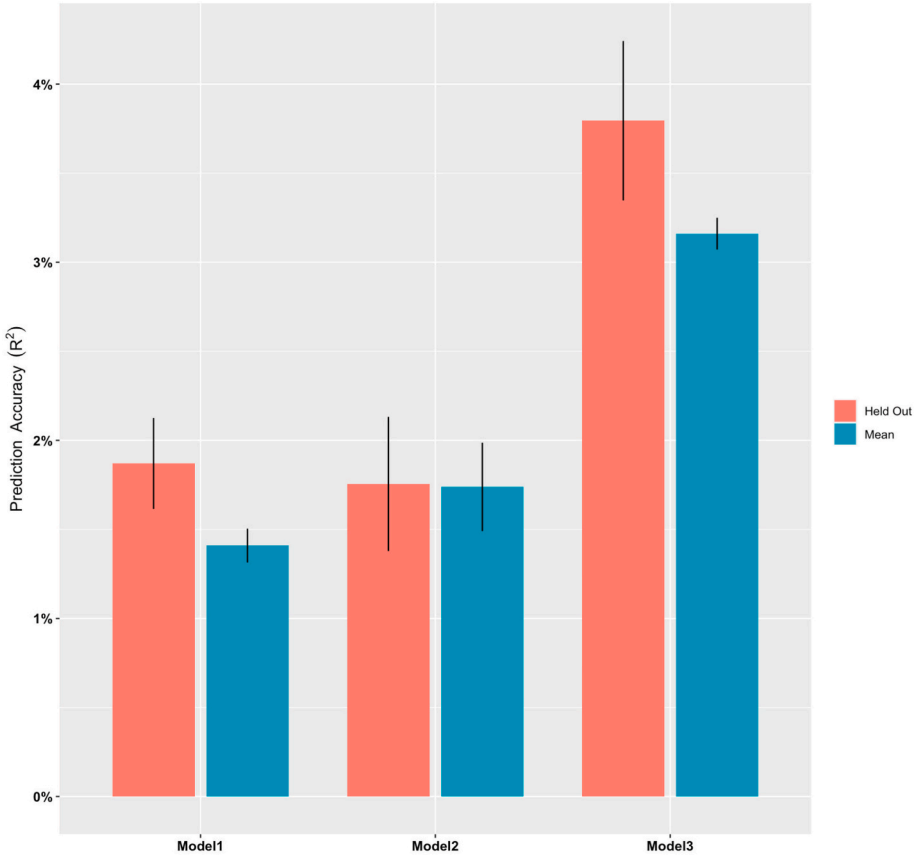

Fig. 2. Prediction Accuracy (R^2) for elastic net regression models to predict anxiety problems. In Model 1, regional sMRI variables (i.e., the CT and CSA of each cortical region, the GMV of each subcortical region and brain stem) were predictors. In Model 2, demographic variables (i.e., age, sex, total family income, and education level) were only used as predictors. In Model 3, both sMRI variables and demographic variables were used as predictors. "Mean" indicate the mean R^2 of all models built in the training phase. "Held Out" indicates the all R^2 of all models from the training phase being tested on the held-out test set. Error bars stand for standard error of mean. CSA, cortical surface area; CT, cortical thickness; GMV, gray matter volume.

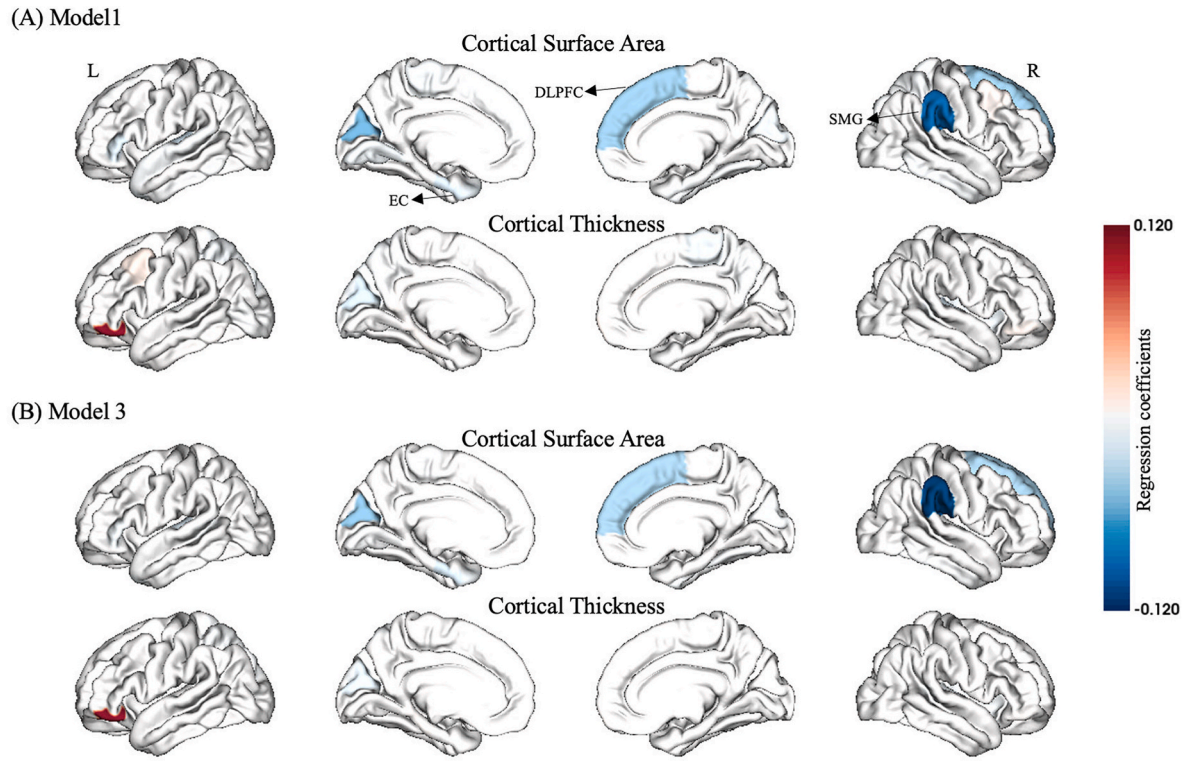

Fig. 3. Similar neuroanatomical patterns derived from elastic net regression models predicted anxiety problems for **(A)** Model 1, and **(B)** Model 3. The color bar of brain regions represented regression coefficients. L, left; R, right; DLPFC, dorsal lateral prefrontal cortex; SMG, supramarginal gyrus; EC, entorhinal cortex. Brain mapping was conducted by ENIGMA toolbox.

Table 2
Significant sMRI correlates of anxiety problems level in linear mixed effect analyses.

Hemisphere	Region	B	SE	*t*	*p*	R^2
CT						
Left	Pars orbitalis	2.2451	0.5435	4.1311	0.0000	0.0572
Left	Lateral orbitofrontal cortex	1.7973	0.6759	2.6593	0.0080	0.0482
Right	Pars orbitalis	1.1881	0.5397	2.2015	0.0279	0.0464
Left	Rostral middle frontal cortex	1.5412	0.7283	2.1161	0.0346	0.0460
Left	Caudal middle frontal cortex	1.4290	0.6863	2.0823	0.0376	0.0460
Left	Pars triangularis	1.3435	0.6595	2.0372	0.0419	0.0457
CSA						
Right	Supramarginal gyrus	−0.0004	0.0002	−2.5577	0.0107	0.0482
Right	Superior frontal cortex	−0.0003	0.0001	−2.3494	0.0190	0.0474
Left	Cuneus	−0.0010	0.0004	−2.2536	0.0244	0.0471
Left	Entorhinal cortex	−0.0022	0.0011	−2.0665	0.0390	0.0462

Note. sMRI: structural magnetic resonance imaging; B: unstandardized regression coefficient; SE: standard error; CT: cortical thickness; CSA: cortical surface area.

including emotion regulation anxiety induction procedures (Balderston et al., 2017b; McTeague et al., 2017). An altered functional network including DLPFC has also been found in adults with generalized anxiety disorder (Etkin et al., 2009). Moreover, individuals with high trait anxiety exhibited lower DLPFC activation under a low cognitive load condition (Bishop, 2009). Taken together, these studies implied that as a key node of FPN, the observed deficit involvement of DLPFC may represent a regulation style that makes these individuals vulnerable to anxiety, perhaps through difficulties disengaging from irrelevant stimuli. Consistent with these studies, the morphometry of the DLPFC observed in this study was suggested to be a vital indicator of anxiety problems level, which might suggest the important role of DLPFC in anxiety regulation in healthy young adults.

In addition, SMG was identified as a neuroanatomical predictor of individual anxiety problems level in young adults. As a portion of the posterior parietal lobe, the SMG has been identified as a hub for bodily self-consciousness (Limanowski et al., 2015) and associated with monitoring peripersonal space (di Pellegrino et al., 2015), which is believed to be the "margin of safety" around the body especially when stressful or threatful events happened (Bogdanova et al., 2021; Serino, 2019). Previous research has found that the SMG is engaged in the processing of threatening, painful, and stressful stimuli in the peripersonal space network (de Borst et al., 2020; Grivaz et al., 2017). Furthermore, a meta-analysis of neuroimaging studies has identified the SMG as a key node activated during physiological stress (Kogler et al., 2015). Hence, our finding suggested the observed deficit involvement of SMG might make young adults experienced more stress, which in turn make them perceive high anxiety problems level when dealing with stressful events.

Previous research of a functional model has proposed the EC as a hub node of DMN (Andrews-Hanna et al., 2014). The EC was identified to be essential for potential future experiences imagination and construction (Andrews-Hanna et al., 2014; Schacter et al., 2012). This further proved that the relationship of anatomical nodes of DMN with anxiety problems

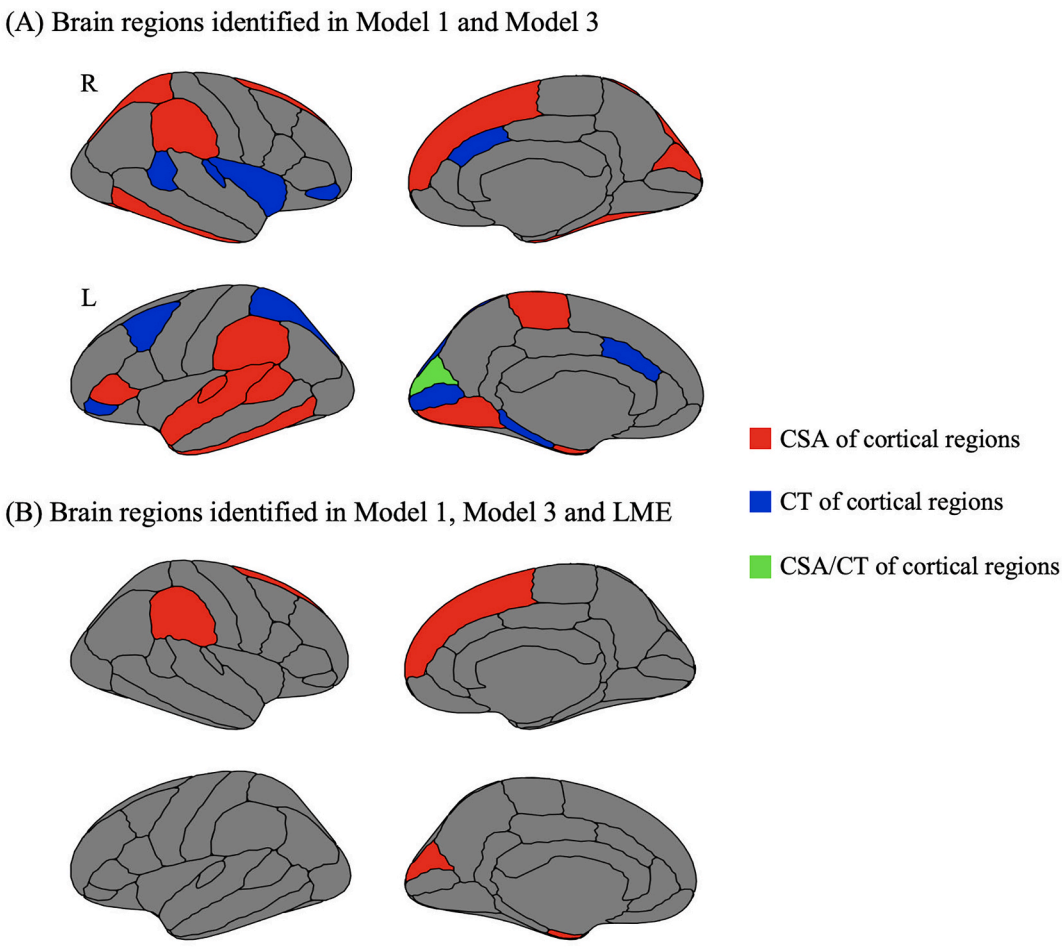

Fig. 4. Brain map for brain regions identified in both elastic net regression Model 1 and Model 3 (A), were also significantly associated with anxiety problems in linear mixed effects models (B). Red indicates cortical surface area (CSA) of cortical region, blue indicates cortical thickness (CT) of cortical region, and yellow indicates both CSA and CT of cortical region.

level emphasised its importance in the processing of anxiety. Furthermore, previous research supported the role of the EC proposed by the above theoretical model, and it revealed that significant hyperactivation of the EC was observed in youth with anxiety disorders (Ashworth et al., 2021). Moreover, EC functional connections with widespread cortical regions has been involved in emotion and reward processing (Navarro Schröder et al., 2015). Furthermore, it has been suggested that higher CT of EC may predispose to encoding enhancement of emotionally-salient memories, together with higher levels of irritability in youth at risk for bipolar disorder (Bertocci et al., 2019). Together with these findings, it is reasonable to argue that the morphometry of the EC observed in our study may also act a vital contributor to anxiety problems level in healthy young adults.

This study has some noteworthy strengths. It is a large sample size study to adopt machine learning-based models for the prediction of anxiety problems level using multiple sMRI indictors. The most vital brain regions observed by the ENR models were aided by traditional LME models. In addition, the findings of our study were consistent with previous research on neuroanatomical associations with anxiety, providing reliable evidence for the generalizability of our findings. However, there were still several limitations in this study. First, the causality of the observed relationships in this study can't be made due to its cross-sectional design. Future research should be conducted using longitudinal design. Second, only sMRI data was used in this study. Functional MRI data can be adopted in the future to further test the validity of the machine learning-based models with CV. Third, only machine learning-based ENR model analysis was conducted in this study. Future research can try to explore additional models, such as support vector machines and Gaussian process regression model.

5. Conclusions

To sum up, adopting machine learning-based ENR models with CV, neuroanatomical profiles of anxiety problems level were observed. The profiles including hub brain cortical regions enrolled in FPN and DMN. These findings shed light on understanding the neuroanatomical profiles of anxiety with machine learning approaches. These findings illuminate the structural neural correlates of anxiety problems level which were involved in anxiety circuit.

CRediT authorship contribution statement

Hui Xu: Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jing Xu:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis. **Dandong Li:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Ethics approval and consent to participate

This study was approved and consented by the Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. All participants provided written informed consent. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration.

Consent for publication

Not applicable.

Data and code availability statement

All data were provided by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University in St. Louis. The authors are grateful to the Human Connectome Project for open access to its data. The code that supports the analyses of this study is available on request from the corresponding authors.

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Declaration of competing interest

The authors report no biomedical financial interests or potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2024.100705.

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