

RESEARCH ARTICLE

Depression mediates the association between insula-frontal functional connectivity and social interaction anxiety

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Abstract

High rates of comorbidity between depression and anxiety are frequently observed. However, few studies have investigated the relationship between depression and social interaction anxiety using a dimensional approach. The current study aimed to explore the associations between depression and social interaction anxiety with a multivariate approach in a comparably large dataset ($n = 194, 95$ males). All participants completed a structural and a resting-state functional magnetic resonance imaging (fMRI) scan and self-report measures of depression via Beck's Depression Inventory II and social interaction anxiety by social interaction anxiety scale. Voxel-based morphometry (VBM) results first identified grey matter volumes of insula were positively correlated with depression dimension scores. Next, whole brain seed-to-voxel analyses were conducted using a VBM-identified insula as a seed region to examine associations between depression/social anxiety and functional connectivity. The results suggested that a significant positive effect of depression/social anxiety was found on the connectivity between insula and dorsal lateral prefrontal cortex (dlPFC). Moreover, variations in depression mediated the association between insula-dlPFC connectivity and social interaction anxiety. Overall, the results indicate that individual differences in depression relate more to insula-dlPFC coupling compared to social interaction anxiety.

KEYWORDS

depression, functional connectivity, grey matter, resting state, social interaction anxiety

Weihua Zhao, Xiaolu Zhang, Feng Zhou, and Keith M. Kendrick contributed equally to this study.

1 | INTRODUCTION

Depression characterized by persistent feelings of sadness and loss of interest is regarded as the most burdensome disease in the world

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(World Health Organization, 2008). It was originally considered as a mood disorder of the middle-aged and the elderly; however, recently more and more teenagers and young adults are suffering from depression and seeking treatment (Mueller, 1989). A recent study showed the prevalence of depression among Chinese university students was 28.4% (95% CI: 25.7%–31.2%) (Gao et al., 2020). A large number of fMRI studies have shown that depressed individuals exhibit greater activity in the amygdala, dorsal anterior cingulate cortex, and insula compared to healthy participants (Hamilton et al., 2012). Some meta-analysis have also identified abnormal insula activity in depressive individuals (Fitzgerald et al., 2008). Moreover, hopelessness is one of the core features of depression, and insula activity is correlated with a higher level of hopelessness (Wiebking et al., 2014). The insula is regarded as a key component of the salience network (SN) and is suggested to provide both a structural and functional link between psychological and physiological processes of social affective experience and emotion regulation (Koban & Pourtois, 2014).

High rates of comorbidity (around 19.5%–74.5%; Zhao et al., 2020) have been found between depressive and social anxiety disorders (Keller, 2006), indicative of shared common symptoms/etiology, such as social function deficits (Saris et al., 2017), as well as vulnerabilities and emotion dysregulation (Ladouceur et al., 2005). Disruptions to emotion regulation contribute to both depression and anxiety disorders (Hofmann et al., 2012). On the other hand, some studies have suggested some distinct contributions with all four facets of extraversion/positive emotionality (sociability, tendency to experience positive emotions, ascendance, and fun-seeking) being more related to anxiety, whereas only low positive emotionality was more related to depression (Naragon-Gainey et al., 2009; Wang et al., 2012). Social anxiety disorder is characterized by a penetrating fear of social evaluation situations (Clark & Wells, 1995) and is defined as the fear and avoidance of meeting, interacting, and expressing oneself with others (Kashdan, 2004), which can be measured by the Social Interaction Anxiety Scale (SIAS) and social phobia scale (social interaction vs. situations involving observation by others) (Heimberg et al., 1992; Safren et al., 1998). Insula dysfunction is not only associated with severity of symptoms in major depression disorder (Wang et al., 2015) but also in anxiety (Paulus & Stein, 2006; Shin & Liberzon, 2010; Simmons et al., 2011). In addition, the executive control network (ECN), including dorsolateral prefrontal cortex (dlPFC), inferior parietal lobule (IPL), and dorsomedial prefrontal cortex (dmPFC), is altered in anxiety (Xu et al., 2019) and depression (Takamura et al., 2020; Tang et al., 2013; Yamamura et al., 2016). These ECN regions are mainly involved in top-down cognitive regulation (Power et al., 2011). In addition, patients with unipolar depression have significantly altered functional connectivity between the anterior insula and the ECN relative to control subjects (Ellard et al., 2018) and functional connectivity between insula and one of ECN regions (i.e., dlPFC) was associated with anxiety level (Zhang et al., 2019). Although the neural systems implicated in the interaction between anxiety and depression have been explored extensively, less is known about the neural interaction between depression and social anxiety using a dimensional approach. A dimensional approach is currently

widely used to provide quantitative indices of variance in symptoms (Hudziak et al., 2007). This method can help us to investigate the relationship between dimensional preclinical depressive and social interaction anxiety symptoms. In other words, it is currently unknown whether the insula or other regions play a role specifically in social anxiety, depression, or negative experience.

Thus, we aimed to investigate the structural and functional connectivity of neural substrates underlying how depression interacts with social interaction anxiety. Neural anatomy associations were conducted using voxel-based morphometry (VBM), which is a reliable method to detect differences in individual personality traits and anatomical changes (Ashburner & Friston, 2000), and altered functional coupling was investigated using an fMRI resting-state approach (Gili et al., 2011; Liao et al., 2011). Furthermore, a mediation analysis was performed to further confirm the brain pathway, which regulate the relationship between depression and social interaction anxiety. Considering that some regions including insula and ECN regions are involved in the detection of emotional salience and integration of sensory, emotional, and cognitive information (Menon, 2011; Phillips et al., 2003; Power et al., 2011), we hypothesized that individual variations in depression would be related to differences in structure and functional connectivity of these emotion regulation regions. In addition, social anxiety is a risk factor for depression and plays an important role in predicting the occurrence and development of individual depression (Eng et al., 2001; Nordahl et al., 2018), so we further hypothesized that some of these differences would be mediated by social interaction anxiety.

2 | MATERIALS AND METHODS

2.1 | Participants

Two hundred volunteers were recruited (Zhou et al., 2021) and six participants were excluded due to the technique issues of questionnaires, which resulted in a final sample of 194 participants (95 males; age ranged from 18 to 26 years old, mean \pm SD: 21.43 \pm 2.16 years; see Table 1) for further analyses. All participants were right-handed and were free of any history of neurological or psychiatric disease. All participants provided informed consent before participating in the current experiment and were paid for their participation. The present study had full approval from the local ethics committee at the University of Electronic Science and Technology of China and the procedure was conducted according to the latest revision of the declaration of Helsinki.

2.2 | Questionnaire measurements

Prior to MRI scanning, depression levels were assessed using the Beck's Depression Inventory—2nd Edition (BDI-II; Beck et al., 1996) and social interaction anxiety using the SIAS, which reflects the levels of social anxiety during the initiation and maintenance of social

	Total sample	Female	Male	Statistics/ <i>p</i>
Subjects	194	99	95	
Age (years)	21.43 ± 2.16	21.35 ± 2.03	21.52 ± 2.28	0.521/.603 ^a
BDI-II	7.11 ± 6.29	7.35 ± 6.43	6.85 ± 6.14	-0.482/.630 ^b
SIAS	53.26 ± 12.97	53.93 ± 12.71	52.57 ± 13.20	-0.933/.351 ^b

Abbreviations: BDI-II, Beck's Depression Inventory - 2nd Edition; SIAS, Social Interaction Anxiety Scale.

^aIndependent *t* test.

^bMann Whitney test.

interaction behaviors (i.e., talking to a stranger or maintaining friendship) (Peters et al., 2012). Higher scores were associated with greater symptoms of social interaction anxiety (Brown et al., 1997). Cronbach's alpha measures in the present study showed good internal consistency (BDI: 0.90; SIAS: 0.896).

2.3 | Brain imaging data acquisition

Imaging data were collected using a 3.0 T GE Discovery MR750 system (General Electric Medical System, Milwaukee, WI) with an eight-channel-phased array head coil. OptoActive MRI headphones (<http://www.optoacoustics.com/>) were used to reduce acoustic noise exposure during MRI acquisition (Roozen et al., 2008). High-resolution T1-weighted anatomical images were acquired with a spoiled gradient echo pulse sequence: echo time (TE) = minimum, flip angle = 9°, repetition time (TR) = 5.9 ms, field of view (FOV) = 256 × 256 mm, acquisition matrix = 256 × 256, thickness = 1 mm, number of slices = 156. Seven-minute resting-state fMRI data were collected using a T2*-weighted echo planar imaging (EPI) sequence (TR = 2000 ms, TE = 30 ms, FOV = 240 × 240, image matrix = 64 × 64, flip angle = 90°, thickness = 3.4 mm, gap = 0.6 mm, number of slices = 39 [interleaved ascending order]). Participants were required to focus on a white cross with a black background and keep awake during scanning, and none of them reported being asleep in post-MRI follow-up.

2.4 | Data analyses

2.4.1 | Data analysis of brain structural data

The VBM analysis was preprocessed using CAT12 (r1720) (<http://www.neuro.uni-jena.de/cat/>) implemented in SPM12 v7219 (Wellcome Department of Cognitive Neurology, London, UK, <https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). Briefly, T1-weighted images were bias-corrected and were further segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF); GM images were spatially normalized to Montreal Neurological Institute (MNI) space with voxel size 2 × 2 × 2 mm and were spatially smoothed with 8 mm Gaussian kernels at full-width at half maximum (FWHM). The total grey matter volume was used as a covariate at the second level for regression.

TABLE 1 Demographics information

Subsequently, a multiple regression analysis was performed to identify the association between specific anatomical regions (GM images) and interindividual difference in depression scores using SnPM13 toolbox (Statistical NonParametric Mapping). In this model, we included age, gender, total GM as covariates of no interest. The absolute threshold was set to 0.2 and a gray matter mask from Data Processing & Analysis for Brain Imaging toolbox (DPABI, <http://rfmri.org/dpabi>; Yan & Zang, 2010) templates was used as an explicit mask.

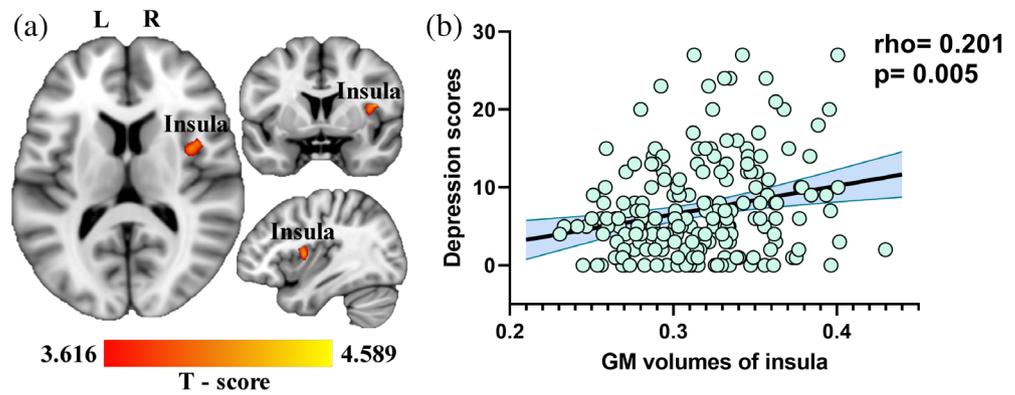
2.4.2 | Data analysis of resting-state functional connectivity

Resting-state functional time-series were preprocessed using DPABI v6.0 (<http://rfmri.org/dpabi>; Yan & Zang, 2010). The first 10 volumes were discarded to allow MRI T1 equilibration and active noise canceling by the headphones. Then the remaining functional images were slice-timing corrected and realigned to the first image to correct for head motion. Then these images were co-registered and segmented into GM, WM, and CSF. All realigned images were normalized to Montreal Neurological Institute (MNI) standard space and interpolated to 3 × 3 × 3 mm voxel size. Next, six head movement parameters and their derivatives, quadratic terms and squares of derivatives along with the nuisance covariates including white matter, CSF, global signal were regressed out (Yan et al., 2013). Finally, the influences of low-frequency drift and high-frequency noise were restricted by a band-pass filter (0.01–0.08 Hz). Resting data of all subjects are included since head movements were <2 mm and 2° in all cases.

We aimed to examine whether depression dimensions were associated with functional connectivity using the identified structural region as seed region. The whole brain seed-to-voxel or seed-to-network connectivity analyses were performed using DPABI. The 8-mm spheres centered at the peak coordinates of the VBM-identified region served as the seed region of interest (ROI) based on the current result of VBM analyses. Pearson's correlation between the average BOLD signal time course from the seed region and the other brain voxels was computed in the first-level analysis and resulted in Fisher's *r* transformed to *z* maps. Consistent with our brain structural analyses, a multiple regression in the group analysis was applied to *z*-FC maps to investigate which functional coupling was significantly associated with depression scores. Age, gender, and grey matter were included as covariates and mean-centered.

FIGURE 1 VBM results.

(a) Depression score was significantly positively correlated with the total GM volumes in the insula (PFWE < 0.05, peak-level, MNI center coordinates: 42, 7, 15; cluster size = 185 voxels, $T = 4.59$). (b) Scatter plot between GM volumes in the insula and depression scores ($\rho = 0.201$, $p = .005$)



2.5 | Mediation analysis

In order to clarify the role of functional connectivity in the relationship between depression and social interaction anxiety dimensions, we utilized the PROCESS v35 plug-in of SPSS 25.0 statistics software (Hayes, 2009) to employ a mediation analysis, with bootstrap-based significance testing (5000 replacements, Hayes, 2017). In this mediation model, path a is the association between X and M, path b represents the association between M and Y and the indirect effect is the product of path a times path b. Path c represents the total effect of the relationship between X and Y ignoring the mediator (path $c = \text{indirect effect} + \text{direct effect}$). Path c' as the direct effect represents the effect of X on the proposed mediator. An estimation of the proportion mediated (PM) is reported, which indicates how much of the total effect operates through the mediator (Ananth, 2019).

3 | RESULTS

3.1 | Behavioral results

Social interaction anxiety scores (ranged from 20 to 89) were normally distributed in our sample (Shapiro–Wilk $z = 0.990$, $p = .206$), but depression scores (ranged from 0 to 27) were not (Shapiro–Wilk $z = 0.893$, $p < .001$) (Whisman & Richardson, 2015). Thus, we conducted a non-parametric permutation correlation test (10,000 permutations) to identify the relationship between social interaction anxiety and depression. The results indicated that depression was significant positively correlated with social interaction anxiety ($\rho = 0.3391$, $p < .001$). No significant correlations were found between age and depression ($\rho = -0.042$, $p = .564$) or age and social interaction anxiety ($\rho = -0.058$, $p = .423$). In addition, Mann Whitney test suggested there were no significant sex differences in depression ($z = -0.482$, $p = .630$) or in social interaction anxiety ($z = -0.933$, $p = .351$, see Table 1).

3.2 | Structural basis associated with depression

To investigate the structural basis underlying depression, we performed a multiple regression analysis to identify the correlation

between GM volumes and depression, including age, gender, GM as covariates. VBM results indicated that GM volumes in the right insula (MNI center coordinates: 42, 7, 15; cluster size = 185 voxels; peak-level $P_{FWE} < 0.05$, $T = 4.59$) were significant positively associated with depression scores (see Figure 1).

3.3 | Functional connectivity results

Based on our VBM results, we conducted functional connectivity analyses between the VBM-identified insula seed ROI and other brain regions at a whole brain level. The results showed that depression scores were significant positively associated with the functional connectivity between insula and dorsal lateral prefrontal cortex (dlPFC; MNI center coordinates: $-30, 48, 6$; cluster size = 41 voxels; $P_{FWE} < 0.005$, cluster-level, $T = 4.71$). Furthermore, insula-dlPFC functional connectivity was also significant positively correlated with social interaction anxiety ($r = .181$, $p = .011$).

3.4 | Mediation results

Mediation analysis showed that depression score mediated the relationship between the insula-dlPFC functional connectivity and social interaction anxiety (path a = 0.339, $p < .001$; path b = 0.309, $p < .001$; path c = 0.181, $p = .011$; path $c' = 0.077$, $p = 0.30$; indirect effect = 0.105; PM = 58%; see Figure 2) with 5000 bootstrap samples.

4 | DISCUSSION

The present study employed a dimensional approach in a large healthy sample to determine the relationship between trait depression and brain volumetric changes, as well as the interaction between depression and social interaction anxiety in terms of resting state functional connectivity between the anatomy-identified insula and dorsal lateral prefrontal cortex. A positive correlation was found between depression scores and insula GM volume suggesting that higher levels of depression were associated with greater insula volume. In addition, the functional connectivity between the anatomy identified insula

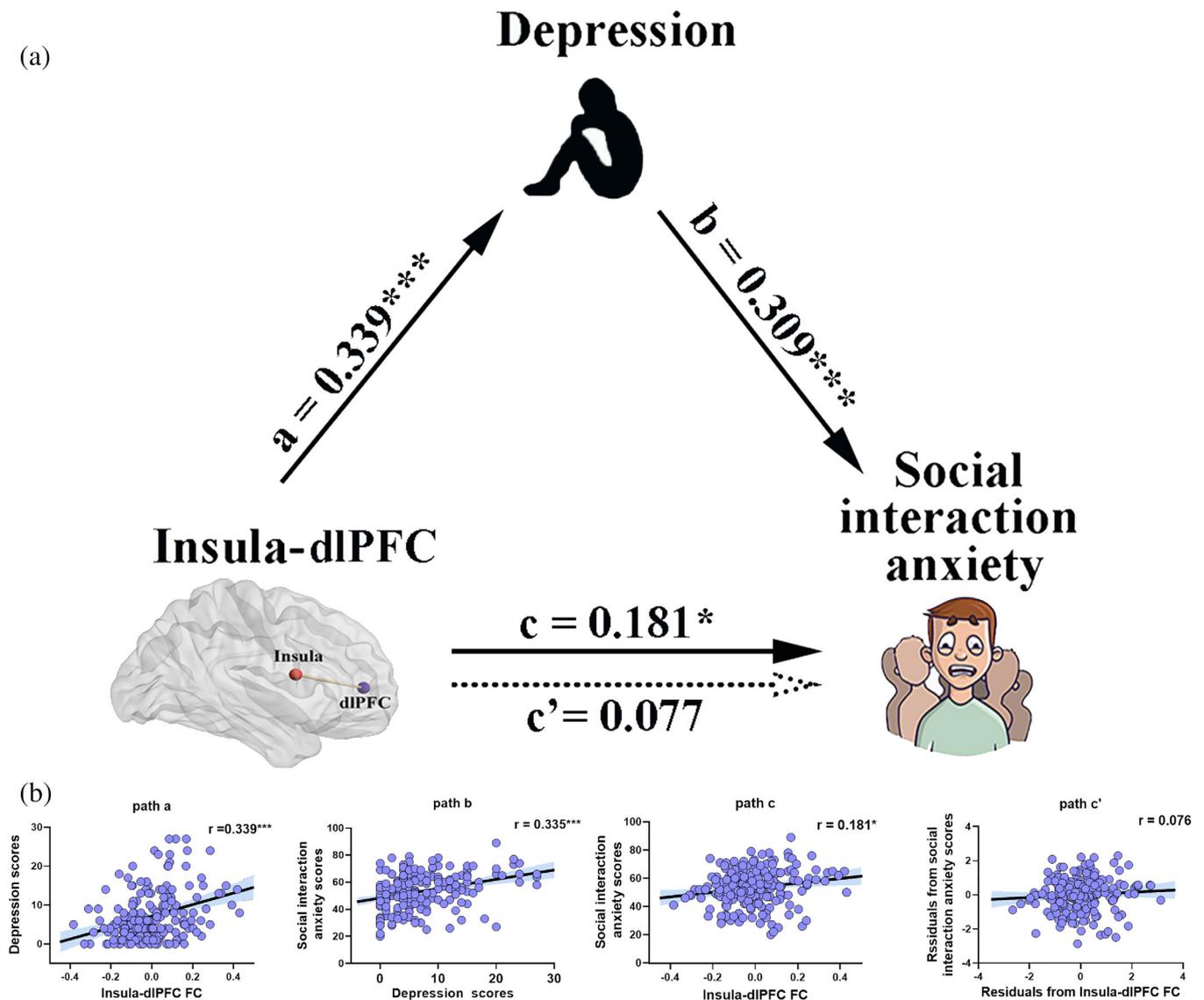


FIGURE 2 Mediation results. (a) The association between the functional connectivity between insula-dIPFC and social interaction anxiety was total mediated by depression scores ($*p < .05$, $***p < .001$). (b) Examples of each path in the mediation analysis. dIPFC, dorsal lateral prefrontal cortex

seed region and dIPFC was also positively associated with both depression and social interaction anxiety scores and depression mediated the relationship between social interaction anxiety and insula-dIPFC coupling. In summary, our findings suggest that insula-dIPFC connectivity contributed more to depression dimensions than to social interaction anxiety.

In the current study, we found a positive association between GM volumes in insula and depression scores. Our findings are in line with previous studies showing that depression disorders exhibit greater GM volumes as compared to healthy controls (Kong et al., 2014; Qi et al., 2014; Wang et al., 2017). In addition, positive correlations between translocator protein density in insula and depression severity in individuals with major depressive episode (Setiawan et al., 2015) and between anterior insula GM volume and psychiatric symptom severity (Hatton et al., 2012) were found, suggesting that larger GM volumes in insula are associated with more

severe psychiatric symptoms (i.e., depression). The insula has been implicated in information processing through cognitive control and attentional processes and in the switch between external and internal cognition (Craig & Craig, 2009; Menon & Uddin, 2010). Greater GM volume in insula may be involved in the early stage of major depressive disorder and is not likely to be the result of medication exposure (Kong et al., 2014). Although some studies have reported inconsistent results showing a negative correlation between insula GM volume and depression in older patients (Lai & Wu, 2014) or late-onset major depression (Hwang et al., 2010), or no associations (Takahashi et al., 2010), this may due to the longer illness durations or medication use (Serra-Blasco et al., 2013).

In our current study, functional connectivity between insula (key component of SN) and dIPFC was associated with both depression and social interaction anxiety, with hyper-connectivity found in individuals with higher depressive/anxiety symptoms. The dIPFC is

thought to play an essential role in top-down emotion regulation and so this may indicate an overattribution of affective salience to internal events, that is, negative depressive/anxious thinking during the resting-state condition. In addition, electroconvulsive therapy can normalize abnormal functional connectivity between the insula and dlPFC, which suggests that altered connectivity may be a biomarker for the antidepressant effects of the therapy (Wang et al., 2020).

A previous study conducted a mediation analysis showing that insula volume partially mediated the association between depression (or anxiety) and sleep quality separately, suggesting a key role for the insula in depression or anxiety and shared common symptoms (Yin et al., 2021). Considering this, our mediation analysis revealed that stronger insula-dlPFC functional connectivity was associated with higher scores in social interaction anxiety, but crucially also due to higher scores in depression, which further emphasizes the key role of insula-dlPFC functional connectivity in depression rather than in social interaction anxiety. In addition, hopelessness is one of the strong predictors of suicidal behaviors in major depression disorder (Sokero et al., 2003) and the scores are higher compared to generalized anxiety disorder and more highly correlated with depression than anxiety (Beck et al., 1988). Our findings therefore suggest that insula-dlPFC functional connectivity may be a specific biomarker for depression. However, we only focused on healthy participants in the current study and these findings need to be confirmed in clinical populations in the future.

Furthermore, depression mediates the relationship between insula-dlPFC functional connectivity and social interaction anxiety, indicating that depression contributed more than social interaction anxiety to this functional connectivity. Future clinical studies, especially in anxious relative to nonanxious depression, are needed to examine this functional connectivity and its relationship with symptom severity.

5 | CONCLUSIONS

Overall, the current study used a dimensional approach to investigate the neural basis of depression and its relationship with social interaction anxiety. Our results suggest that higher grey matter volume in the insula is associated with higher depression scores and that functional connectivity of the insula-dlPFC is positively correlated with both depression and social interaction anxiety. Furthermore, depression mediates the relationship between insula-dlPFC functional connectivity and social interaction anxiety, indicating that depression contributed more than social interaction anxiety to this functional connectivity. Future clinical studies, especially in anxious relative to nonanxious depression, are needed to examine this functional connectivity and its relationship with symptom severity.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

If anyone is interested in the data, just directly contact with the authors.

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REFERENCES

- Ananth, C. V. (2019). Proportion mediated in a causal mediation analysis: How useful is this measure? *BJOG: An International Journal of Obstetrics & Gynaecology*, 126, 983.
- Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry—The methods. *NeuroImage*, 11, 805–821.
- Beck, A., Steer, R., Ball, R., & Ranieri, W. (1996). Comparison of Beck Depression 1 in Psychiatric Inpatients -1A and - outpatients. *Journal of Personality Assessment*, 67, 588–597.
- Beck, A. T., Riskind, J. H., Brown, G., & Steer, R. A. (1988). Levels of hopelessness in DSM-III disorders: A partial test of content specificity in depression. *Cognitive Therapy and Research*, 12, 459–469.
- Brown, E. J., Turovsky, J., Heimberg, R. G., Juster, H. R., Brown, T. A., & Barlow, D. H. (1997). Validation of the Social Interaction Anxiety Scale and the Social Phobia Scale across the anxiety disorders. *Psychological Assessment*, 9, 21–27.
- Clark, D. M., & Wells, A. (1995). A cognitive model of social phobia. In R. G. Heimberg, M. R. Liebowitz, & D. A. H. v. ark (Eds.), *Social phobia: Diagnosis, assessment, and treatment*. The Guilford Press.
- Craig, A. D., & Craig, A. D. (2009). How do you feel—now? The anterior insula and human awareness. *Nature Reviews Neuroscience*, 10, 59–70.
- Ellard, K. K., Zimmerman, J. P., Kaur, N., Van Dijk, K. R. A., Roffman, J. L., Nierenberg, A. A., Dougherty, D. D., Deckersbach, T., & Camprodon, J. A. (2018). Functional connectivity between anterior insula and key nodes of frontoparietal executive control and salience networks distinguish bipolar depression from unipolar depression and healthy control subjects. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 3, 473–484.
- Eng, W., Heimberg, R. G., Hart, T. A., Schneier, F. R., & Liebowitz, M. R. (2001). Attachment in individuals with social anxiety disorder: The relationship among adult attachment styles, social anxiety, and depression. *Emotion*, 1, 365–380.
- Fitzgerald, P. B., Laird, A. R., Maller, J., & Daskalakis, Z. J. (2008). A meta-analytic study of changes in brain activation in depression. *Human Brain Mapping*, 29, 683–695.
- Gao, L., Xie, Y., Jia, C., & Wang, W. (2020). Prevalence of depression among Chinese university students: A systematic review and meta-analysis. *Scientific Reports*, 10, 1–11.
- Gili, T., Cercignani, M., Serra, L., Perri, R., Giove, F., Maraviglia, B., Caltagirone, C., & Bozzali, M. (2011). Regional brain atrophy and

- functional disconnection across Alzheimer's disease evolution. *Journal of Neurology, Neurosurgery & Psychiatry*, 82, 58–66.
- Hamilton, J. P., Etkin, A., Furman, D. J., Lemus, M. G., Johnson, R. F., & Gotlib, I. H. (2012). Functional neuroimaging of major depressive disorder: A meta-analysis and new integration of baseline activation and neural response data. *American Journal of Psychiatry*, 169, 693–703.
- Hatton, S. N., Lagopoulos, J., Hermens, D. F., Naismith, S. L., Bennett, M. R., & Hickie, I. B. (2012). Correlating anterior insula gray matter volume changes in young people with clinical and neurocognitive outcomes: An MRI study. *BMC Psychiatry*, 12, 1–10.
- Hayes, A. F. (2009). Beyond Baron and Kenny: Statistical mediation analysis in the new millennium. *Communication Monographs*, 76, 408–420.
- Hayes, A. F. (2017). *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach*. Guilford Publications.
- Heimberg, R. G., Mueller, G. P., Holt, C. S., Hope, D. A., & Liebowitz, M. R. (1992). Assessment of anxiety in social interaction and being observed by others: The Social Interaction Anxiety Scale and the Social Phobia Scale. *Behavior Therapy*, 23, 53–73.
- Hofmann, S. G., Sawyer, A. T., Fang, A., & Asnaani, A. (2012). Emotion dysregulation model of mood and anxiety disorders. *Depression and Anxiety*, 29, 409–416.
- Hudziak, J. J., Achenbach, T. M., Althoff, R. R., & Pine, D. S. (2007). A dimensional approach to developmental psychopathology. *International Journal of Methods in Psychiatric Research*, 16, S16–S23.
- Hwang, J.-P., Lee, T.-W., Tsai, S.-J., Chen, T.-J., Yang, C.-H., Lirng, J.-F., & Tsai, C.-F. (2010). Cortical and subcortical abnormalities in late-onset depression with history of suicide attempts investigated with MRI and voxel-based morphometry. *Journal of Geriatric Psychiatry and Neurology*, 23, 171–184.
- Kashdan, T. B. (2004). The neglected relationship between social interaction anxiety and hedonic deficits: Differentiation from depressive symptoms. *Journal of Anxiety Disorders*, 18, 719–730.
- Keller, M. B. (2006). Social anxiety disorder clinical course and outcome: Review of Harvard/Brown anxiety research project (HARP) findings. *Journal of Clinical Psychiatry*, 67, 14–19.
- Koban, L., & Pourtois, G. (2014). Brain systems underlying the affective and social monitoring of actions: An integrative review. *Neuroscience & Biobehavioral Reviews*, 46, 71–84.
- Kong, L., Wu, F., Tang, Y., Ren, L., Kong, D., Liu, Y., Xu, K., & Wang, F. (2014). Frontal-subcortical volumetric deficits in single episode, medication-naïve depressed patients and the effects of 8 weeks fluoxetine treatment: A VBM-DARTEL study. *PLoS One*, 9, e79055.
- Ladouceur, C. D., Dahl, R. E., Williamson, D. E., Birmaher, B., Ryan, N. D., & Casey, B. J. (2005). Altered emotional processing in pediatric anxiety, depression, and comorbid anxiety-depression. *Journal of Abnormal Child Psychology*, 33, 165–177.
- Lai, C.-H., & Wu, Y.-T. (2014). Frontal-insula gray matter deficits in first-episode medication-naïve patients with major depressive disorder. *Journal of Affective Disorders*, 160, 74–79.
- Liao, W., Xu, Q., Mantini, D., Ding, J., Machado-de-Sousa, J. P., Hallak, J. E. C., Trzesniak, C., Qiu, C., Zeng, L., & Zhang, W. (2011). Altered gray matter morphometry and resting-state functional and structural connectivity in social anxiety disorder. *Brain Research*, 1388, 167–177.
- Menon, V. (2011). Large-scale brain networks and psychopathology: A unifying triple network model. *Trends in Cognitive Sciences*, 15, 483–506.
- Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: A network model of insula function. *Brain Structure and Function*, 214, 655–667.
- Mueller, P. S. (1989). Increasing rates of depression. *JAMA: The Journal of the American Medical Association*, 262, 899.
- Naragon-Gainey, K., Watson, D., & Markon, K. E. (2009). Differential relations of depression and social anxiety symptoms to the facets of extraversion/positive emotionality. *Journal of Abnormal Psychology*, 118, 299–310.
- Nordahl, H., Nordahl, H. M., Vogel, P. A., & Wells, A. (2018). Explaining depression symptoms in patients with social anxiety disorder: Do maladaptive metacognitive beliefs play a role? *Clinical Psychology & Psychotherapy*, 25, 457–464.
- Paulus, M. P., & Stein, M. B. (2006). An insular view of anxiety. *Biological Psychiatry*, 60, 383–387.
- Peters, L., Sunderland, M., Andrews, G., Rapee, R. M., & Mattick, R. P. (2012). Development of a short form Social Interaction Anxiety (SIAS) and Social Phobia Scale (SPS) using nonparametric item response theory: The SIAS-6 and the SPS-6. *Psychological Assessment*, 24, 66–76.
- Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003). Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biological Psychiatry*, 54, 504–514.
- Power, J. D., Cohen, A. L., Nelson, S. M., Wig, G. S., Barnes, K. A., Church, J. A., Vogel, A. C., Laumann, T. O., Miezin, F. M., & Schlaggar, B. L. (2011). Functional network organization of the human brain. *Neuron*, 72, 665–678.
- Qi, H., Ning, Y., Li, J., Guo, S., Chi, M., Gao, M., Guo, Y., Yang, Y., Peng, H., & Wu, K. (2014). Gray matter volume abnormalities in depressive patients with and without anxiety disorders. *Medicine*, 93, e345.
- Roozen, N. B., Koevoets, A. H., & den Hamer, A. J. (2008). Active vibration control of gradient coils to reduce acoustic noise of MRI systems. *IEEE/ASME Transactions on Mechatronics*, 13, 325–334.
- Safren, S. A., Turk, C. L., & Heimberg, R. G. (1998). Factor structure of the social interaction anxiety scale and the social phobia scale. *Behaviour Research and Therapy*, 36, 443–453.
- Saris, I. M. J., Aghajani, M., van der Werff, S. J. A., Van der Wee, N. J. A., & Penninx, B. (2017). Social functioning in patients with depressive and anxiety disorders. *Acta Psychiatrica Scandinavica*, 136, 352–361.
- Serra-Blasco, M., Portella, M. J., Gomez-Anson, B., de Diego-Adelino, J., Vives-Gilabert, Y., Puigdemont, D., Granel, E., Santos, A., Alvarez, E., & Perez, V. (2013). Effects of illness duration and treatment resistance on grey matter abnormalities in major depression. *The British Journal of Psychiatry*, 202, 434–440.
- Setiawan, E., Wilson, A. A., Mizrahi, R., Rusjan, P. M., Miler, L., Rajkowska, G., Suridjan, I., Kennedy, J. L., Rekkas, P. V., & Houle, S. (2015). Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. *JAMA Psychiatry*, 72, 268–275.
- Shin, L. M., & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology*, 35, 169–191.
- Simmons, A. N., Stein, M. B., Strigo, I. A., Arce, E., Hitchcock, C., & Paulus, M. P. (2011). Anxiety positive subjects show altered processing in the anterior insula during anticipation of negative stimuli. *Human Brain Mapping*, 32, 1836–1846.
- Sokero, T. P., Melartin, T. K., Rytsälä, H. J., Leskelä, U. S., & Isometsä, E. T. (2003). Suicidal ideation and attempts among psychiatric patients with major depressive disorder. *The Journal of Clinical Psychiatry*, 64, 20288.
- Takahashi, T., Yücel, M., Lorenzetti, V., Tanino, R., Whittle, S., Suzuki, M., Walterfang, M., Pantelis, C., & Allen, N. B. (2010). Volumetric MRI study of the insular cortex in individuals with current and past major depression. *Journal of Affective Disorders*, 121, 231–238.
- Takamura, M., Okamoto, Y., Shibasaki, C., Yoshino, A., Okada, G., Ichikawa, N., & Yamawaki, S. (2020). Antidepressive effect of left dorsolateral prefrontal cortex neurofeedback in patients with major depressive disorder: A preliminary report. *Journal of Affective Disorders*, 271, 224–227.
- Tang, Y., Zhang, X., Simmonite, M., Li, H., Zhang, T., Guo, Q., Li, C., Fang, Y., Xu, Y., & Wang, J. (2013). Hyperactivity within an extensive cortical distribution associated with excessive sensitivity in error processing in unmedicated depression: A combined event-related potential and sLORETA study. *International Journal of Psychophysiology*, 90, 282–289.

- Wang, G.-Z., Belgard, T. G., Mao, D., Chen, L., Berto, S., Preuss, T. M., Lu, H., Geschwind, D. H., & Konopka, G. (2015). Correspondence between resting-state activity and brain gene expression. *Neuron*, *88*, 659–666.
- Wang, L., Wei, Q., Wang, C., Xu, J., Wang, K., Tian, Y., & Wang, J. (2020). Altered functional connectivity patterns of insular subregions in major depressive disorder after electroconvulsive therapy. *Brain Imaging and Behavior*, *14*, 753–761.
- Wang, W., Zhao, Y., Hu, X., Huang, X., Kuang, W., Lui, S., Kemp, G. J., & Gong, Q. (2017). Conjoint and dissociated structural and functional abnormalities in first-episode drug-naïve patients with major depressive disorder: A multimodal meta-analysis. *Scientific Reports*, *7*, 1–13.
- Wang, W.-T., Hsu, W.-Y., Chiu, Y.-C., & Liang, C.-W. (2012). The hierarchical model of social interaction anxiety and depression: The critical roles of fears of evaluation. *Journal of Anxiety Disorders*, *26*, 215–224.
- Whisman, M. A., & Richardson, E. D. (2015). Normative dData on the Beck Depression Inventory - Second Edition (BDI-II) in College Students. *Journal of Clinical Psychology*, *71*, 898–907.
- Wiebking, C., Duncan, N. W., Tiret, B., Hayes, D. J., Marjańska, M., Doyon, J., Bajbouj, M., & Northoff, G. (2014). GABA in the insula—A predictor of the neural response to interoceptive awareness. *NeuroImage*, *86*, 10–18.
- World Health Organization. (2008). *The global burden of disease: 2004 update*. World Health Organization.
- Xu, J., Van Dam, N. T., Feng, C., Luo, Y., Ai, H., Gu, R., & Xu, P. (2019). Anxious brain networks: A coordinate-based activation likelihood estimation meta-analysis of resting-state functional connectivity studies in anxiety. *Neuroscience & Biobehavioral Reviews*, *96*, 21–30.
- Yamamura, T., Okamoto, Y., Okada, G., Takaishi, Y., Takamura, M., Mantani, A., Kurata, A., Otagaki, Y., Yamashita, H., & Yamawaki, S. (2016). Association of thalamic hyperactivity with treatment-resistant depression and poor response in early treatment for major depression: A resting-state fMRI study using fractional amplitude of low-frequency fluctuations. *Translational Psychiatry*, *6*, e754.
- Yan, C., & Zang, Y. (2010). DPARSF: A MATLAB toolbox for "pipeline" data analysis of resting-state fMRI. *Frontiers in Systems Neuroscience*, *4*, 13.
- Yan, C.-G., Craddock, R. C., Zuo, X.-N., Zang, Y.-F., & Milham, M. P. (2013). Standardizing the intrinsic brain: Towards robust measurement of inter-individual variation in 1000 functional connectomes. *NeuroImage*, *80*, 246–262.
- Yin, H., Zhang, L., Li, D., Xiao, L., & Cheng, M. (2021). The gray matter volume of the right insula mediates the relationship between symptoms of depression/anxiety and sleep quality among college students. *Journal of Health Psychology*, *26*, 1073–1084.
- Zhang, X., Huettel, S. A., O'Dhaniel, A., Guo, H., & Wang, L. (2019). Exploring common changes after acute mental stress and acute tryptophan depletion: Resting-state fMRI studies. *Journal of Psychiatric Research*, *113*, 172–180.
- Zhao, Y., Niu, R., Lei, D., Shah, C., Xiao, Y., Zhang, W., Chen, Z., Lui, S., & Gong, Q. (2020). Aberrant gray matter networks in non-comorbid medication-naïve patients with major depressive disorder and those with social anxiety disorder. *Frontiers in Human Neuroscience*, *14*, 172.
- Zhou, X., Wu, R., Zeng, Y., Qi, Z., Ferraro, S., Yao, S., Kendrick, K. M., & Becker, B. (2021). Location, location, location—choice of voxel-based morphometry processing pipeline drives variability in the location of neuroanatomical brain markers. *bioRxiv*. <https://doi.org/10.1101/2021.03.09.434531>

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