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ORIGINAL ARTICLE

Structure related to function: prefrontal surface area has an indirect effect on the relationship between amygdala volume and trait neuroticism

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Abstract

Trait neuroticism refers to individual differences in negative emotional response to threat, frustration, or loss, operationally defined by elevated levels of irritability, anger, sadness, anxiety, worry, hostility, self-consciousness, and vulnerability to mental and physical difficulties. While functional studies have been fairly consistent when identifying regions associated with neuroticism during emotional stimuli, structural imagining studies do not tend to find a relationship between amygdala volume and trait neuroticism. There is a great deal of functional evidence that frontoparietal areas are related to the amygdala, and to emotional reactivity more generally, as a function of their involvement in emotion regulation. Specifically, top–down emotion appraisal and expression appear to involve parts of the dorsolateral and dorsomedial prefrontal cortices, which operate at least in part via the indirect modulation of the amygdala. It was hypothesized that cortical surface area and cortical thickness in regions associated with emotion appraisal/expression and emotional attention (i.e., superior frontal and rostral middle frontal gyri, respectively) would have an indirect effect on the relationship between amygdala volume and self-reported neuroticism (respectively), potentially explaining the inconsistency in the structural literature. In sample of 1106 adults, superior frontal and rostral middle frontal gyri, as parcellated by Freesurfer, were examined as potentially restricting variance in a model of indirect effects, which may elucidate the overall relationship between cortical and subcortical gray matter volume and trait neuroticism. Results indicated that, despite no association between bilateral amygdala volume and trait neuroticism, when right superior frontal surface area was entered into the model of indirect effects, a significant relationship between amygdala volume and trait neuroticism emerged. Two of the three remaining models indicated that cortical surface area had an indirect effect on the relationship between amygdala volume and trait neuroticism. These findings highlight the relationship between structural and functional neuroimaging studies. Specifically, the results indicate that when volume is related to behavior, individual differences in higher-order cortical regions, particularly surface area, may help to better understand the relationship between emotion and subcortical gray matter volume.

Keywords Amygdala volume · Pre-frontal cortex · Emotion regulation · Neuroticism

Introduction

Personality traits are dimensional variations in typical responding to the environment that vary among individuals (Mischel 2004). Neuroticism refers to individual differences in negative emotional response to threat, frustration, or loss; operationally defined by elevated levels of irritability, anger, sadness, anxiety, worry, hostility, self-consciousness, and vulnerability that have been found to be substantially correlated with one another in factor analyses (Costa and McCrae 1992; Goldberg 1993). A number of longitudinal studies have controlled for shared items and concurrent depressive states and still found significant associations between the construct of neuroticism and measures of depression (Fergusson et al. 1989; Schmutte and Ryff 1997; Spijker et al. 2007). In addition, neuroticism is robustly linked to many mental disorders (i.e., major depressive disorder, generalized anxiety disorder, specific phobia, and social phobia, personality disorders, schizophrenia, eating disorders, somatoform disorders, externalizing disorders; see Kotov et al. 2010;

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Lahey 2009; Ormel et al. 2013a, b; Servaas et al. 2013), and to physical health problems that are not defined by symptoms that overlap with neuroticism items (see Lahey 2009). Indeed, there is also evidence that neuroticism predicts a wide range of physical health problems even when depression is controlled (Bouhuys et al. 2004; Lahey 2009; Russo et al. 1997).

A number of functional studies have been devoted to identifying regions associated with neuroticism during emotional stimuli during over fifteen different functional tasks (for a review see Servaas et al. 2013). For negative stimuli (when contrasted against neutral stimuli), neuroticism is fairly consistently found to be associated with increase activation in cortical areas consistently associated with emotion regulation (medial and lateral) dorsal prefrontal cortex (dmPFC, dlPFC; for a reviews see Kohn et al. 2014; Frank et al. 2014; Amting et al. 2010; Buhle et al. 2014; Etkin et al. 2011; Giustino and Maren 2015; Greening et al. 2013; Milad et al. 2007; Ochsner et al. 2009; Servaas et al. 2013; Wager et al. 2008). Specifically, the dlPFC is likely involved in cognitive processes related to attention/awareness of emotional stimuli (Kohn et al. 2014), whereas the dmPFC is important for the emotion expression and appraisal (Etkin et al. 2011; Milad et al. 2007). Subcortically, elevated neuroticism is often associated with increased amygdala activity (Brück et al. 2011; Chan et al. 2009; Cunningham et al. 2010; Haas et al. 2007; Harenski et al. 2009; Hooker et al. 2008). However, other studies using similar functional paradigms have not found such association with amygdala activity (Cremers et al. 2010; Drabant et al. 2009; Haas et al. 2008; Hyde et al. 2011). The majority of these studies, however, have been conducted in relatively small samples, which may account for these inconsistent findings (Yarkoni 2009).

Structural neuroimaging research have been somewhat consistent when examining the neural correlates of neuroticism. For example, while one research group found a negative relationship between left amygdala volume and neuroticism (Omura et al. 2005), there is a much larger literature suggesting that there is no relationship between the structural volume of the amygdala and trait neuroticism (Avinun et al. 2019; Cremers et al. 2010; Delaparte et al. 2019; Wright et al. 2007; Wright et al. 2006). It is possible that there may not be a direct relationship between amygdala volume and trait neuroticism, but rather it is related to neuroticism through cortical areas related to emotion regulation (Anderson and Phelps 2000; Anderson and Sobel 2003; Buhle et al. 2014; Amting et al. 2010; Buhle et al. 2014; Etkin et al. 2011; Giustino and Maren 2015; Greening et al. 2013; Kim et al. 2010; Milad et al. 2007; Ochsner et al. 2009; Servaas et al. 2013; Wager et al. 2008). The majority of the functional literature has found a relationship between amygdala activity and neuroticism (Brück et al. 2011; Chan et al. 2009; Cunningham et al. 2010; Haas et al. 2007; Harenski et al. 2009; Hooker et al. 2008), as well as during affective tasks (e.g., Canli et al. 2000; Adolphs et al. 1994; Goldin et al. 2008; Ochsner et al. 2004; Shin et al. 2006). Moreover, neuroticism has not been found to be significantly associated with the magnitude of amygdala activation or amygdala habituation, but only amygdala–medial prefrontal cortex connectivity. Overall, these results suggest that trait neuroticism may represent a failure of higher-order cortical, rather than overactive emotion generation processes per se (Silverman et al. 2019). Missing from structural studies are measures of top–down frontoparietal areas associated with emotion regulation. Given this functional relationship between frontoparietal regions and the amygdala, we may also expect a corresponding structural relationship between them as well (Cruikshank and Weinberger 1996; Honey et al. 2009).

Further evidence for this explanation includes literature suggesting that the amygdala participates in emotion-related processes as one element in a number of subcortical and cortical circuits that work independently and in concert that gives rise to the ability to self-report subjective feelings (i.e., trait neuroticism; see LeDoux and Brown 2017; LeDoux and Pine 2016). Specifically, the two-system framework of emotion (LeDoux and Pine 2016) and theory of emotional consciousness (LeDoux and Brown 2017) collectively posit that the processing of threat information by the amygdala (among other subcortical regions) is dissociable from the conscious awareness of threat, which requires a higher-order cortical interpretation (i.e., by areas of the PFC). Importantly, it also suggests that conscious awareness of threats occur in the same higher-order structures that may explain why amygdala activation alone is not found to elicit self-reported fear. For instance, it has been repeatedly demonstrated that subliminal threats elicit amygdala activity and trigger physiological and behavioral responses, but not feelings of fear (Baars and Franklin 2003; Dehaene 2014; Hariri et al. 2002; Jacobs and Silvanto 2015; Kihlstrom 1987; Morris et al. 1999; Overgaard and Sandberg 2014). Finally, literature on patients with blind spots also support the two-system framework, where they exhibit amygdala activation to threat, defensive behaviors, and changes in physiology, despite not having conscious awareness of the threatening stimuli (Lau and Passingham 2006; Persaud et al. 2011).

Cortical surface area, cortical thickness, and trait neuroticism

Given the a priori interest in gray matter volumes that have been found to be related to emotion appraisal and expression (i.e., dmPFC) and attention to emotional stimuli (i.e., dlPFC), surface-based morphometric (SBM) methods were utilized via Freesurfer. Briefly, aberrant cortical surface area and gray matter thickness

are commonly observed in psychopathology associated with emotion dysregulation, including schizophrenia (Rapoport et al. 2012; Rimol et al. 2012), attention deficit hyperactivity disorder (Shaw et al. 2012; Shaw et al. 2007), depression (Foland-Ross et al. 2015; Lim et al. 2013; Peng et al. 2015), bipolar disorder (Hanford et al. 2016; Hartberg et al. 2011) and wide range of anxiety disorders (Bas-Hoogendam et al. 2018).

Expectedly, neuroticism is typically found to be negatively associated with PFC gray matter thickness and surface area (Bjørnebekk et al. 2013; Blankstein et al. 2009; Wright et al. 2006, 2007). Given the limited literature, little is known on how both SBMs (i.e., cortical surface area and cortical thickness) relate to trait neuroticism with models including amygdala volume. The computationally intensive surface-based techniques provide distinct cortical surface area and thickness measures that are shown to be both genetically and phenotypically independent (Panizzon et al. 2009, Winkler et al. 2010). While both thickness and surface area have been found to influence volume measurements of cortical gray matter, volume has been found to be more closely related to surface area than cortical thickness using SBM (Winkler et al. 2010). In sum, there is literature which suggests that surface area and cortical thickness measurements should be considered separately (Panizzon et al. 2009, Winkler et al. 2010), but the surface area of the PFC may be more related to gray matter amygdala volume (Winkler et al. 2010).

Current study

It was first hypothesized that amygdala volume would not be related to trait neuroticism, which is in line with the larger literature (e.g., Cremers et al. 2010; Wright et al. 2006; 2007). In contrast, it was posited that cortical surface and cortical thickness, in the superior frontal gyrus (SF) and rostral middle frontal gyrus (RMF), would be negatively related to neuroticism (Bjørnebekk et al. 2013; Blankstein et al. 2009; Wright et al. 2006, 2007). These gyri were selected a priori as they capture aspects of the dlPFC, dmPFC (as well as other areas of the PFC), as parcellated by Freesurfer (see Fig. 1). This decision was made given the vast amount of past structural literature that utilizes Freesurfer masks, and their importance in different aspects of emotion regulation (e.g., Kohn et al. 2014; Frank et al. 2014). The primary hypothesis was informed by research, which has generally found that there is no relationship between amygdala volume and neuroticism, despite literature noting the robust relationship between alterations in brain connectivity [using fMRI (Cremers et al. 2010), resting-state fMRI (Adelstein et al. 2011) and diffusion tensor imaging (DTI) (Bjørnebekk et al. 2013; Xu and Potenza 2012)] and trait neuroticism.

Specifically, it was hypothesized that cortical surface area and cortical thickness in regions associated with emotion regulation would have an indirect effect on the relationship between amygdala volume and self-reported neuroticism (respectively). An indirect effect of cortical surface area/thickness was posited as these regions appear to work as a third variable that leads to emotional experience, and therefore, the ability to self-report these

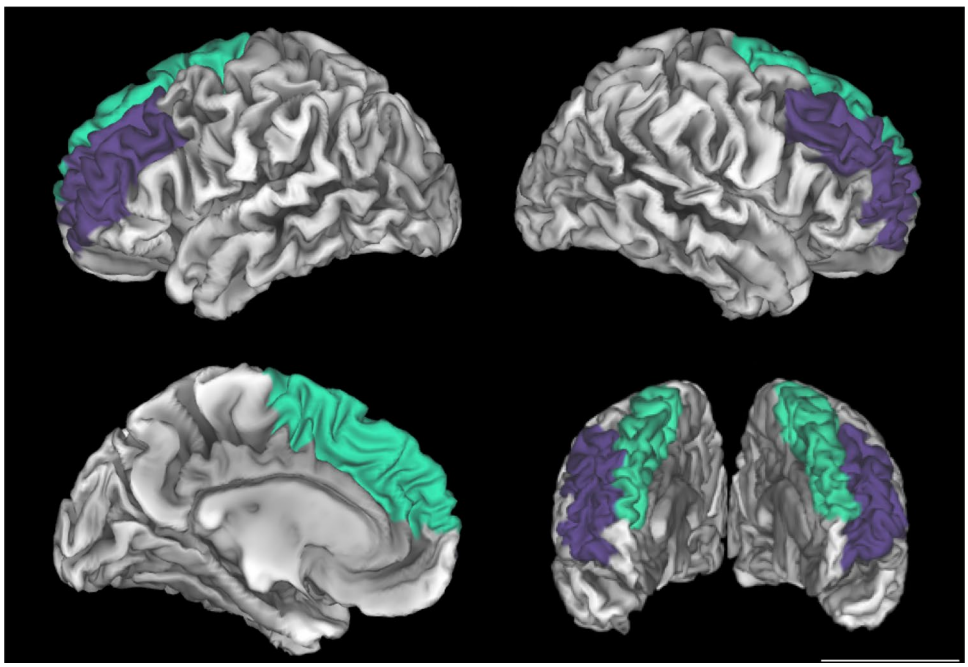

Fig. 1 Right/left superior frontal gyri (teal) and right/left rostral middle frontal gyri (purple) cortical thickness and surface area estimated from the structural magnetic resonance images using FreeSurfer

symptoms (e.g., LeDoux and Brown 2017; LeDoux and Pine 2016). This hypothesis is further informed by evidence that the specific regions examined in the study are likely to be related to top–down emotional expression/appraisal and emotion to attention to emotional stimuli (e.g., Etkin et al. 2011; Kohn et al. 2014) and research that individuals with bilateral amygdala damage continue to experience fear/anxiety (e.g., Anderson and Phelps 2000; Anderson and Sobel 2003). Put differently, this hypothesis is based on the notion that is central to the framework of emotion (LeDoux and Pine 2016) and theory of emotional consciousness (LeDoux and Brown 2017), where it is posited that the amygdala does not "create" an individuals' level of neuroticism (i.e., awareness of negative affect; see Anderson and Phelps 2000; Anderson and Sobel 2003), but rather the interpretation of its input by higher-order structures are needed to create the conscious experience of neurotic symptoms (see LeDoux and Brown 2017; LeDoux and Pine 2016).

Consistent with the larger literature, it was posited that amygdala volume would not be directly related to neuroticism; however, it was also hypothesized that the surface area and cortical thickness of the RMF and SF would restrict variance in the model, allowing for the amygdala's independent association with trait neuroticism to potentially become a significant predictor of trait neuroticism. Finally, follow-up moderation analyses were conducted. These were conducted to examine if the relationship between amygdala and trait neuroticism is strengthened (or weakened) by these areas of the PFC. Given the aforementioned literature, non-significant models were hypothesized, which would provide evidence that the trait neuroticism is not predicted by the interaction between cortical and subcortical volumes.

Methods

Participants and procedure

The sample comprised of 1106 healthy participants (550 males, 656 females) aged 22–57 years (20.5% between 22 and 25; 43.7% between 26 and 30; 34.7% between 31 and 35; 1.2% over 36 years of age) and had no prior history of neurological disorders. Anatomical imaging for the purposes of this study revealed no structural abnormalities in any of the subjects. The participants were instructed to keep their eyes closed, relax their minds, and remain as motionless as possible during the echo-planar imaging (EPI) data acquisition. A capsule of vitamin E was taped to the subject's right temple in every scan session to enable definitive determination of the right side in the image data.

Measure

NEO Personality Inventory-Revised (NEO PI-R; Costa and McCrae 1992). The NEO PI-R is a standard measure of the Five Factor Model of personality, providing a systematic assessment of personality traits. The NEO PI-R is a measure used to assesses five major domains of personality (i.e., Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness), as well as the six traits or facets that define each domain. The current study utilized the trait Neuroticism subscale, which requires the participants to rate how much they agree with each item statement on a 5-point scale. Item responses are scored from 1 to 5, with higher scores more indicative of the trait. Previous studies have provided support for the scale's internal consistency (Cronbach's coefficient = .89) and test–retest reliability (6-month test–retest correlation = 0.93; Wilson et al. 2007).

Imaging acquisition

Publicly available MRI data were acquired as part of the Consortium of the Human Connectome Project (HCP) (http://www.humanconnectome.org) and supported by the WU-Minn HCP Consortium were used for all structural and behavioral analyses (van Essen et al. 2013). All participants in the HCP data provided informed consent for the study, in compliance with the ethics committee of Washington University in St. Louis and the University of Minnesota. Pulse sequences and acquisition protocols for the HCP dataset are detailed extensively elsewhere (Barch et al. 2013; Sotiropoulos et al. 2013; van Essen et al. 2013). Briefly, subjects underwent a scan in a custom Siemens Connectome Skyra MRI scanner (Siemens, Erlangen, Germany) located at Washington University in St. Louis. High-resolution (i.e., 0.7-mm isotropic voxel size) T1-weighted (T1w) images from a Siemens 3T Siemens Connectome Skyra MRI scanner platform (32-channel head coil) and Siemens product sequences were utilized. The WU-Minn Human Connectome HCP protocol uses 0.7-mm isotropic structural acquisitions. The 3D T1w images were acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence [time repetition (TR)/time echo (TE) = 2400/2.14 ms, inversion time (IT) = 1000 ms, flip angle (FA) = 8°, field of view (FOV) = 224 × 224 mm^2, BW (Hz/Px) = 210]. The scan lasted seven min and 40 s and were used for spatial normalization and group-specific template generation.

Structural preprocessing

Data were downloaded in preprocessed form from the HCP database. The images had undergone the minimal preprocessing pipeline (i.e., V. 3.1) as described elsewhere (Glasser et al. 2013). The structural images first went through the

PreFreeSurfer pipeline which performed gradient distortion correction, alignment and averaging of the two sets of T1w and T2w scans, brain extraction, readout distortion correction, bias field correction, then registration to MNI space (Fischl 2012; Jenkinson et al. 2002, 2012; Milchenko and Marcus 2013). The FreeSurfer pipeline consisted of a custom version of FreeSurfer version 5.3 designed to perform a more robust brain extraction and more accurate mapping of the white and pial surfaces.

Cortical reconstruction and calculation of surface area and cortical thickness

Cortical thickness and surface area were estimated from the structural magnetic resonance images using FreeSurfer software (http://surfer.nmr.mgh.harvard.edu, Dale et al. 1999), a set of automated tools for reconstruction of brain cortical surface (Fischl and Dale 2000; Greve and Fischl 2009). First, the T1-weighted images were used to segment cerebral white matter and to estimate the gray–white matter interface. This gray–white matter estimate was used as the starting point of a deformable surface algorithm searching for the pial surface. The whole cortex of each individual subject was visually inspected for inaccuracies in segmentation and manually corrected if necessary. Local cortical area was measured based on the difference between the position of equivalent vertices in the pial and gray–white matter surfaces. The surface of the gray–white matter border was inflated and differences between subjects in the depth of gyri and sulci were normalized. Each subject's reconstructed brain was morphed and registered to an average spherical surface. To obtain cortical area and cortical thickenss, difference maps of the data were smoothed on the surface using Gaussian smoothing kernal with a full-width half maximum of 10 mm.

Statistical analyses

First, Pearson's correlations among amygdala volume, two PFC regions (i.e., their cortical surface area and thickness), and trait neuroticism were examined. The second step towards testing the primary hypothesis utilized eight independent multiple linear regressions to examine ipsilateral indirect effects SF and RMF (respectively) have on the relationship between amygdala volume and trait neuroticism. All models were conducted in the same manner, differing only in which of the eight PFC mediators were included. All analyses included sex as covariates given their statistically significant association with the outcome variable (i.e., trait neuroticism; see Weisberg et al. 2011). In addition, amygdala, and SF, RMF were divided by intercranial volume to control for differences in overall brain size, consistent with previous literature (e.g., Marqués-Iturria et al. 2013; Shad et al. 2004). Specifically, tests of indirect effects were run using the Preacher and Hayes model (2004). The two PFC regions (i.e., their respective cortical surface area and thickness; see Fig. 1; Fig. 2 for an example of one of the models), were evaluated for total effect of amygdala volume on trait neuroticism, which was divided into direct and indirect effects that vary as a function of the explanation of variance provided by the presence of the respective cortical thickness PFC clusters. A bootstrapping method with 10,000 iterations was used to test the 95% confidence intervals of the indirect effect (Palaniyappan et al. 2013). Analyses were conducted using R, SPSS 25, and Microsoft Excel.

These analyses were used to support the primary hypothesis that structural literature typically does not find a relationship between amygdala volume and neuroticism because individual differences in regions important for top–down emotion appraisal, expression, and attention to emotional stimuli are not taken into consideration. Finally, follow-up mediation analyses were conducted in an exploratory nature to ensure mediation models were the best fit for the data. Moderation analyses between amygdala volume, SF and RMF (respectively) were utilized as predictors of trait neuroticism. Moderation models were all conducted in the same manner; the first step included the main effects of the SF or RMF, where the second step included the respective interaction term. Amygdala volume, SF, and RMF (controlled for intracranial volume) were centered prior to analyses. Sex was again utilized as a covariate (within the first step of the linear regressions).

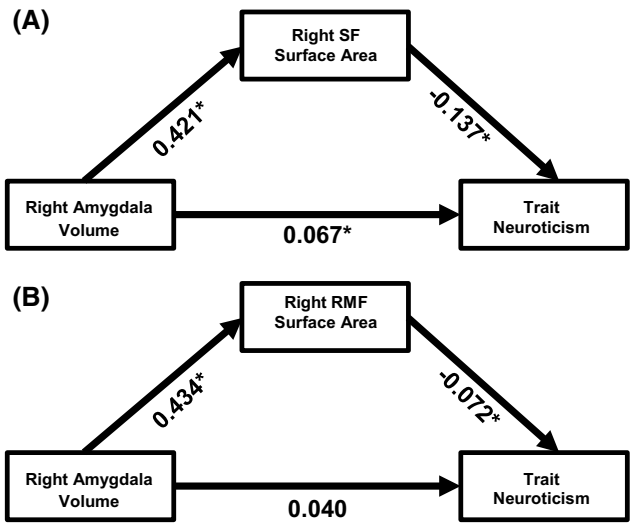

Fig. 2 **a** Right superior frontal gyri surface area's (SF) indirect effect on the relationship between right amygdala volume (controlled for intracranial volume) and trait neuroticism; $*p < .01$; standardized betas. Trait neuroticism as measured by the Revised NEO Personality Inventory T-score. **b** Right rostral middle frontal gyri surface area's (RMF) indirect effect on amygdala volume (controlled for intracranial volume) and trait neuroticism; $*p < .01$; standardized betas

Results

Correlations

Means, standard deviations, and Pearson correlations are presented in Table 1. As expected, SF cortical thickness and surface area were significantly related to one another, but not to a degree that would indicate problems with multicollinearity (i.e., $r > .70$; Tabachnik and Fidell 2007), with further support provided by variance inflation factor scores less than 4.0 in all models. Consistent with past literature, there was no association between right amygdala ($r = .015$, $p > .05$) or left amygdala ($r = -.010$, $p > .05$) and trait neuroticism.

The indirect effects right/left superior frontal and rostral middle frontal gyri cortical thickness have on the relationship between right amygdala volume and trait neuroticism

First, right/left SF and RMF gray matter cortical thickness were examined as possible mediators between right/left amygdala volume and self-reported trait neuroticism (respectively). Only models demonstrating significant fit were examined further ($p < .05$). Surprisingly, all four models examining the indirect effect of right/left SF and right/left RMF cortical thickness relationships were not significant mediators between right/left amygdala volume (respectively) and trait neuroticism. These results indicate that cortical thickness of the SF and RMF, regardless of hemisphere, may not be viable variables when examining the direct or indirect effect between amygdala volume and trait neuroticism.

The indirect effects right superior frontal and rostral middle frontal gyri surface area have on the relationship between right amygdala volume and trait neuroticism

Next, models were conducted in the same manner outlined above, except they included SF and RMF gray matter surface area as potential mediators (respectively; See Fig. 1). Right amygdala volume did not have a significant direct effect when predicting trait neuroticism within the first block [$t(1102) = .298$, $p > .05$]; however, when individual mean SF gray matter surface area was included as a mediator (block two), right amygdala volume demonstrated a significant positive effect when predicting trait neuroticism [$t(1102) = 2.036$, $p < .05$]. Further, SF gray matter surface area had both a significant, negative direct [$t(1102) = -4.187$, $p < .001$] and indirect effect on trait neuroticism, with a standardized coefficient of -0.0579 (SD=.0140), $p < .05$), 95% confidence limits from bootstrap test ($-.0836$ to $-.0319$). When examining the same model but with the inclusion of mean right RMF gray matter surface area as the mediator, it also demonstrated both a significant, negative direct [$t(1102) = -3.924$, $p < .001$] and indirect effects on trait neuroticism with a

Table 1 Means, standard deviations, and Pearson correlations of amygdala volume, bilateral RMF thickness, RMF surface area, SF thickness, SF surface area, and trait neuroticism

Variable	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	*M*	*SD*
1. Right Amygdala Volume	–										1636.84	217.59
2. Right RMF Gyri Thickness	.427	–									3.014	0.200
3. Right SF Thickness	.421	.981	–								2.873	0.127
4. Right RMF Gyri Area	.451	.383	.394	–							6238.10	819.03
5. Right SF Gyri Area	.437	.401	.379	.610	–						7208.25	900.78
6. Left Amygdala Volume	.751	.435	.434	.439	.446	–					1555.67	204.41
7. Left RMF Gyri Thickness	.428	.982	.976	.392	.402	.437	–				2.572	0.115
8. Left SF Gyri Thickness	.415	.973	.985	.383	.373	.429	.981	–			2.841	0.130
9. Left RMF Gyri Area	.435	.384	.390	.795	.644	.442	.380	.380	–		6006.56	785.80
10. Left SF Gyri Area	.432	.417	.402	.644	.800	.453	.416	.390	.620	–	7367.41	909.43
11. Trait Neuroticism	.015^{ns}	.080	.093	-.045^{ns}	-.096	-.010^{ns}	.088	.095	-.034^{ns}	-.078	16.80	7.39

Boxes indicate ipsilateral relationships between the right/left amygdala and the respective right/left RMF and SF thickness and area. Means are shown but all variables were mean centered and controlled for intracranial volume prior to analysis

Pearson correlations, means, and standard deviations of measured variables note. *ns* not significant correlation; all other correlations are significant at $< .01$, *RMF* rostral middle frontal gyri, *SF* superior frontal cortex, *trait neuroticism* neuroticism subscale of the NEO Personality Inventory-Revised (NEO PI-R)

standardized coefficient of − 0.0311 (SD=.0143), $p < .05$), 95% confidence limits from bootstrap test (− .0598 to − .0042). See Fig. 2.

The indirect effects left superior frontal and rostral middle frontal gyri surface area have on the relationship between left amygdala volume and trait neuroticism

When examining the left hemisphere, SF surface area had a significant, negative direct [$t(1102) = -3.277$, $p < .01$], and indirect effect, when predicting trait neuroticism. The completely standardized coefficient was − 0.0485 (SD=.0155), $p < .001$), 95% confidence limits from bootstrap test (− .0802 to − .0187). Mean left RMF gray matter surface area did not demonstrate a significant direct nor indirect effect when predicting trait neuroticism (completely standardized coefficient was − 0.020 (SD=.014), $p > .05$, 95% confidence limits from bootstrap test (− .0482 to .0073). With the exception of the latter, all surface area models demonstrated a similar effect, where right RMF and right/left SF had a significant indirect effect on trait neuroticism through amygdala volume. See Fig. 3.

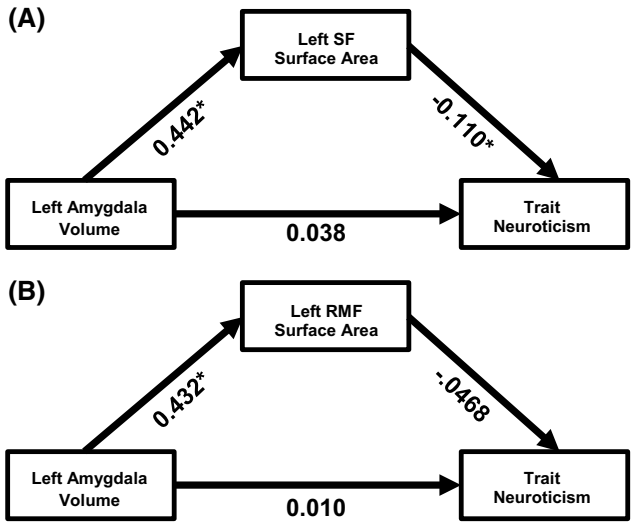

Fig. 3 **a** Left superior frontal gyri surface area's (SF) indirect effect on the relationship between left amygdala volume (controlled for intracranial volume) and trait neuroticism; *$p < .01$; standardized betas; trait neuroticism as measured by the Revised NEO Personality Inventory T-score. **b** Left rostral middle frontal gyri surface area's (RMF) nonsignificant indirect effect on the relationship between left amygdala volume (controlled for intracranial volume) and trait neuroticism; *$p < .01$; standardized betas

The interactions between right/left superior frontal, rostral middle frontal gyri, and right/left amygdala as predictors of trait neuroticism

Given the models examining cortical thickness did not demonstrate significant indirect effects on the relationship between right/left amygdala volume and trait neuroticism, only the interactions between right/left SF and RMF surface area and right/left amygdala volume (respectively) were examined as predictors of trait neuroticism. While the overall models of ipsilateral right hemisphere relationships were significant [SF: $R^2 = 0.029$; $F(4, 1101) = 8.293$, $p < .0001$; RMF: $R^2 = 0.018$; $F(4, 1101) = 4.946$, $p < .001$], the interaction between neither SF and amygdala volume [$\Delta R^2 = .001$; $F(1, 1101) = 1.017$, $p > .05$], nor RMF and amygdala volume [$\Delta R^2 = .0005$; $F(1, 1101) = .5138$, $p > .05$] significantly contributed to the model predicting trait neuroticism. Similarly, the two left hemisphere interaction models had a significant fit when predicting trait neuroticism [SF: $R^2 = 0.024$; $F(4, 1101) = 6.891$, $p < .001$; RMF: $R^2 = 0.015$; $F(4, 1101) = 4.149$, $p < .01$]. Again, the interaction between neither left SF and amygdala volume [$\Delta R^2 = .002$; $F(1, 1101) = 3.056$, $p > .05$], nor left RMF and amygdala volume [$\Delta R^2 = .000$; $F(1, 1101) = 0.001$, $p > .05$] significantly contributed to the model predicting trait neuroticism. These results indicate that SF/RMF surface area do not strengthen or weaken the relationship between amygdala volume and trait neuroticism.

Discussion

Despite trait neuroticism being a transdiagnostic and robust risk factor for nearly all psychopathology, it is surprising that structural neuroimaging literature tends to find no relationship between amygdala volume and trait neuroticism (Avinun et al. 2019; Cremers et al. 2010; Delaparte et al. 2019; Omura et al. 2005; Wright et al. 2007; Wright et al. 2006). The goal of the current study was to build on previous literature by examining the relationship between prefrontal cortex (PFC) gray matter, subcortical amygdala volume, and self-reported neuroticism. The two regions were selected a priori [i.e., superior frontal gyrus (SF) and rostral middle frontal gyrus (RMF), as shown in Fig. 1] given the vast literature on their importance in emotion regulation and, more specifically, emotion expression/appraisal (e.g., Etkin et al. 2011; Milad et al. 2007) and attention to emotional stimuli (Kohn et al. 2014). First, the relationship between cortical surface area, cortical thickness, amygdala volume, and trait neuroticism was assessed. Consistent with the larger literature, as well as the hypotheses, neither right nor left amygdala volume was significantly associated with

trait neuroticism (Avinun et al. 2019; Cremers et al. 2010; Delaparte et al. 2019; Wright et al. 2006, 2007).

The current models of ipsilateral relationships between SF/RMF cortical surface area (but not cortical thickness) had an indirect effect on the relationship between amygdala volume and trait neuroticism, with one exception (i.e., left RMF and left amygdala volume). These results suggest that volumetric cortical and subcortical gray matter can be related to self-reported neuroticism through modeling their respective direct and indirect effects. These findings only partially support the overall hypothesis that past research may find no relationship between amygdala volume and trait neuroticism because regions of the PFC implicated in emotion regulation have not been taken into consideration. However, this notion was only supported when examining the association between right amygdala volume and trait neuroticism through the indirect effect of SF surface area. SF surface area restricted variance provided by individual differences in cortical regions that are found to be implicated in emotion expression and appraisal (Etkin et al. 2011; Milad et al. 2007), which led to a relationship between amygdala volume and trait neuroticism to emerge.

Overall, three of the four models of indirect effects were significant, where only the model including the left RMF did not demonstrate an indirect effect on the relationship between left amygdala volume and trait neuroticism. This hemispheric difference is consistent with a recent meta-analysis that indicated significant involvement of only the right dlPFC, which has a high degree of overlap with the RMF. The two remaining models suggest that bilateral SF had a significant indirect effect on the relationship between right/left amygdala volume and trait neuroticism (respectively). These results fit nicely with a quantitative meta-analysis of functional activation related to emotion regulation where this region was bilateral activated across the regulation of emotional states (Frank et al. 2014). Although the size of the effect was small, only the model including right SF and right amygdala provided support for the hypothesis that the restriction in variance of the PFC cortical surface area would result in the amygdala to become a significant predictor of trait neuroticism. Given the small effect, there should be some caution with its interpretation; however, this may highlight the importance of the dmPFC, largely overlapping with SF, that has been found to pertain to emotional expression and appraisal (i.e., Etkin et al. 2011; Milad et al. 2007).

The provide some support LeDoux and Brown (2017) and LeDoux and Pine's (2016) respective theories and frameworks, which suggest two independent systems of fear/anxiety. One aids in the incorporation of higher-order representations (i.e., involving cortical regions of the PFC) of the second, lower-order system providing subcortical information (i.e., involving individual differences in amygdala volume). While the amygdala is clearly involved in the emotional process, its structural examination should be considered in the light of regions involved in top–down regulation. Specifically, it is posited that the conscious awareness of fear/anxiety requires a higher-order cortical interpretation (i.e., by areas of the PFC). Importantly, the need for higher-order cortical structures for conscious awareness of threats may explain why amygdala activation alone is not found to elicit self-reported fear (e.g., Baars and Franklin 2003; Dehaene 2014; Hariri et al. 2002; Jacobs and Silvanto 2015; Kihlstrom 1987; Lau and Passingham 2006; Morris et al. 1999; Overgaard and Sandberg 2014; Persaud et al. 2011). Extendedly, the current study provides some evidence that this may be the same reason why studies, by in large, do not find a relationship between amygdala volume and trait neuroticism.

Interestingly, cortical thickness of the SF and RMF did not demonstrate an indirect effect between amygdala volume and trait neuroticism, despite having correlations of similar magnitude as SF/RMF surface area with trait neuroticism. However, this is consistent with previous research finding more robust correlations between cortical surface area and subcortical gray matter volume, when compared to cortical thickness (see Winkler et al. 2010). Future research should be mindful of the method by which they assess structural differences in cortical and subcortical regions, as there appears to be a growing literature on the independence of these methods of measurement. The current findings are also consistent with literature which has found that surface area and cortical thickness measurements should be considered separately, where the surface area of regions in the PFC may be more related to gray matter amygdala volume (Winkler et al. 2010). Given the limited past research on cortical surface area and cortical thickness' relationship with negative affect and subcorticalt gray matter, more research is needed to better understand this nuanced relationship.

Partial support was found for the hypothesis that cortical surface area and thickness in the SF and RMF, but not amygdala volume, would be significant predictors of trait neuroticism. Interestingly, bilateral RMF surface area was not associated with train neuroticism, whereas bilateral SF had a negative relationship with trait neuroticism. This is congruent with a large line of literature (Bjørnebekk et al. 2013; Blankstein et al. 2009; Wright et al. 2006, 2007), where trait neuroticism has been found to be related to widespread decrease in white matter microstructure and smaller frontotemporal surface area (Bjørnebekk et al. 2013). Overall, the SF includes aspects of the mPFC and dmPFC, which is consistent with the literature linking these areas with emotional expression and appraisal (i.e., Etkin et al. 2011; Milad et al. 2007). Additionally, the negative relationship between bilateral SF surface area and trait neuroticism is in line with research finding abnormalities in the mPFC in psychopathology associated with

emotion dysregulation, including schizophrenia (Rapoport et al. 2012; Rimol et al. 2012), attention deficit hyperactivity disorder (Shaw et al. 2007, 2012), depression (Foland-Ross et al. 2015; Lim et al. 2013; Peng et al. 2015), bipolar disorder (Hanford et al. 2016; Hartberg et al. 2011) and wide range of anxiety disorders (Bas-Hoogendam et al. 2018). Also, of interest is the finding that bilateral SF and RMF cortical thickness was positively related to trait neuroticism. This finding is less consistent with past research, and this dissociation in the direction of the relationship between surface area and cortical thickness of the SF/RMF and trait neuroticism may warrant follow-up. These correlations may partially explain why surface area, but not thickness, had an indirect effect between amygdala volume and neuroticism. The results are somewhat difficult to interpret; smaller surface areas of the SF/RMF are related to elevated neuroticism but reduced cortical thickness of the SF/RMF is associated with less neurotic symptoms. This finding is consistent with aforementioned notion that surface area and cortical thickness measurements should be considered separately as surface area of regions in the PFC may be more related to gray matter amygdala volume (Winkler et al. 2010). Future research should examine if these structural metrics (i.e., surface area and cortical thickness) extend to other regions, such as the vlPFC, vmPFC, and orbitofrontal cortex. Moreover, while we utilized SF and RMF as structural proxies for dlPFC and dmPFC, future research may wish to follow-up with more specific masks.

Interaction analyses

The results of the moderation analyses between amygdala volume and PFC cortical surface areas (respectively) were not found to be significant. This indicates that neither the (right/left) SF nor RMF interacts with amygdala volume (respectively) when predicting neuroticism. The nonsignificant interaction models suggest that it is unlikely that the amygdala volume's relationship with trait neuroticism does not become stronger or weaker as a function of individual differences in SF and RMF cortical surface area. It was posited that these analyses would not be significant as they have been theorized to be part of two independent systems, where the higher-order cortical structures are a third variable that gives rise to the conscious awareness of emotion (LeDoux and Brown 2017; LeDoux and Pine 2016). In contrast, as elaborated above, these areas of the PFC seem to only have an indirect effect on the relationship between amygdala and trait neuroticism. Overall, these results suggest that future research may benefit from examining alterations in structural cortical and subcortical gray matter with tests of indirect effects when examining their relationship with negative affect.

Limitations and future directions

As with all studies, the current study should be interpreted in the context of its weaknesses. First, large regions of the PFC (SF and RMF) were utilized, which are not direct proxies for the dlPFC and dmPFC. While this decision was made to increase the extension of the findings to other structural studies using Freesurfer parcellation, they only include some portions of the dlPFC and dmPFC (as well as other areas of the PFC). Nerveless, it may limit the findings when extending it to functional literature. It would be interesting for future studies to use a mask more specific to theseregions (i.e., dlPFC and dmPFC), as well as others (i.e., vlPFC, vmPFC, etc.). Second, it would have been appropriate to examine these questions while also incorporating diffusion weighted imaging (DTI). While this is an important next step, it was outside the scope of the current manuscript, where demonstrating that an indirect effect exists was seen as the overall goal and first step towards setting up research utilizing diffusion weighted imaging. With this first step established, follow-up studies focusing on using DTI to examine this question would be of great interest. In addition, we examined trait neuroticism, which is broadly defined. This trait includes anxiety, depression, hostility, vulnerability, self-conscientiousness, and impulsivity, which all warrant investigation in the same manner to explore whether the current study's findings extend to the components that comprise trait neuroticism and how various regions of the PFC potentially demonstrate differential relationships with these facets of neuroticism.

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Compliance with ethical standards

Conflict of interest The author declares that they he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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