OPTIMISM AND THE BRAIN: TRAIT OPTIMISM MEDIATES THE PROTECTIVE ROLE OF ORBITOFRONTAL CORTEX GRAY MATTER VOLUME AGAINST ANXIETY

BY

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THESIS

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ABSTRACT

Vast individual differences exist at both the personality level and the brain level that can influence anxiety as a general tendency. Trait optimism, characterized by the overall positive expectancy about the future, is positively correlated with emotional wellbeing and negatively correlated with anxiety. At the brain level, reduced volume in orbitofrontal cortex (OFC) has been linked to increased vulnerability to anxiety, whereas intact functioning of the same region seems to promote resilience and is associated with trait optimism. However, so far it is not clear whether these two factors, personality and OFC volume, are also linked to each other and how they together are related to anxiety. This issue was investigated in a sample of 61 healthy participants, who completed measures of trait optimism and anxiety and underwent structural scanning using magnetic resonance imaging. Results showed that OFC gray matter volume in the left hemisphere was positively correlated with optimism, which in turn was negatively correlated with anxiety. The volume of OFC was found to be negatively correlated with anxiety as well. Furthermore, trait optimism mediated the negative correlation between left OFC volume and anxiety, thus demonstrating that increased gray matter volume in this brain region predicts resilience against anxiety through increased optimism. These results contribute to the understanding of neural correlates involved in optimism and anxiety, and provide novel insights into the brain-personality relation in protecting against anxiety in healthy functioning. Such knowledge may facilitate future preventive and therapeutic interventions aimed at reducing susceptibility and increasing resilience to emotional disturbances.

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CHAPTER 1
INTRODUCTION

Anxiety disorders are the most prevalent class of mental illnesses in the United States. Each year, an estimated 40 million American adults are affected by anxiety disorders (Kessler, Chiu, Demler, & Walters, 2005), and almost 30% of the U.S. adult population will meet the criteria for a diagnosis of anxiety disorder at some point in life (Kessler, Berglund, et al., 2005). In addition to their high prevalence, anxiety disorders are also among the leading causes of burdens of disability in the United States (US Burden of Disease Collaborators, 2013) as well as worldwide (Global Health Observatory, 2014). Given the high prevalence and heavy personal and societal burden of anxiety disorders, there is an increased need to identify new psychological and biological markers for susceptibility to or resilience against anxiety (van der Werff, van den Berg, Pannekoek, Elzinga, & van der Wee, 2013; Wu et al., 2013).

Based on previous evidence linking trait optimism and the orbitofrontal cortex (OFC) to symptoms of anxiety (e.g., Talati, Pantazatos, Schneier, Weissman, & Hirsch, 2013; Zenger, Brix, Borowski, Stolzenburg, & Hinz, 2010), and identifying associations between OFC and optimism (Kringelbach, 2005), I adopted a comprehensive brain-personality-symptom approach to investigate the roles of gray matter volumes in OFC and of trait optimism in protecting against symptoms of anxiety in healthy participants. Furthermore, I also explored the potential mediating role of trait optimism in the relation between OFC gray matter volume and anxiety. Such multidimensional approaches are essential for the advancing our understanding of the neural and psychological factors providing protection against anxiety. This, in turn, will facilitate the development of evidence-based preventive and therapeutic interventions to enhance resilience against emotional dysregulation that characterizes affective disorders. The evidence justifying the rationale for this approach is discussed in detail below.

Trait Optimism Linked with Anxiety and OFC Function

Among the many personality factors, *trait optimism* has long been credited with promoting resilience against affective dysregulation in general, and against anxiety in particular (G. Andersson, 1996; Southwick & Charney, 2012; Wu et al., 2013). Defined as the *tendency for people to hold favorable expectancies about their future* (Carver, Scheier, & Segerstrom, 2010), trait optimism has been consistently regarded as a psychological asset that facilitates adaptive coping and subdues symptoms of affective dysregulation (Carver & Scheier, 2014; Carver et al., 2010; Nes & Segerstrom, 2006; Scheier, Carver, & Bridges, 1994). As a result, it has been linked to reduced anxiety symptoms in both healthy participants (Scheier et al., 1994; Siddique, LaSalle-Ricci, Glass, Arnkoff, & Diaz, 2006), in patients suffering through major health problems (Myhren, Ekeberg, Toien, Karlsson, & Stokland, 2010; Zenger et al., 2010), and in patients with affective disorders (Evans & Bullock, 2012; Peleg, Barak, Harel, Rochberg, & Hoofien, 2009).

On the other hand, there is evidence from functional magnetic resonance imaging (MRI) that trait optimism may be related to OFC. Specifically, OFC is shown to be involved in reward-related (Grabenhorst & Rolls, 2011; Kringelbach, 2005; Kringelbach & Berridge, 2009), and approach-oriented (Eddington, Dolcos, Cabeza, Krishnan, & Strauman, 2007) processing, such as the encoding of the value of rewards (Bray, Shimojo, & O'Doherty, 2010; Gottfried, O'Doherty, & Dolan, 2003). Although there has not been a direct test of the relation between OFC and trait optimism, it seems very likely that OFC would be involved in seeing the glass as half full, as optimistic individuals often do (Nes & Segerstrom, 2006; Scheier et al., 1994), which may in turn motivate adaptive emotion regulation and leads to reduced anxiety symptoms (Llewellyn, Dolcos, Iordan, Rudolph, & Dolcos, 2013; Nes & Segerstrom, 2006).

Interestingly, previous research has also emphasized valence-related hemispheric lateralization in the prefrontal cortex in processing emotional information and with regards to motivational and temperamental tendencies (Davidson & Irwin, 1999; Spielberg et al., 2011; Spielberg et al., 2012; but see Miller, Crocker, Spielberg, Infantolino, & Heller, 2013; Wager, Phan, Liberzon, & Taylor, 2003 for different views on this matter). Specifically, the left hemisphere has been associated with positive affect and approach tendencies, whereas the right hemisphere has been associated with negative affect and avoidance tendencies (Dolcos, LaBar, & Cabeza, 2004; Eddington et al., 2007). Given that trait optimism is associated with a cognitive bias toward positive expectations and approach-oriented regulation strategies (Nes & Segerstrom, 2006), a left-lateralization pattern might also exist at the structural level in the OFC.

OFC and Anxiety

Abnormality of OFC structure has been identified as a vulnerability factor in the development of psychological and behavioral symptoms in anxiety disorders (Aupperle & Paulus, 2010; Grupe & Nitschke, 2013; Milad & Rauch, 2007; Shin & Liberzon, 2010). Structural neuroimaging research has consistently reported volume reduction in the OFC in patients with anxiety disorders (Jackowski et al., 2012; Na et al., 2013; Talati et al., 2013; van der Werff et al., 2013). In healthy subjects, smaller regional volume of gray matter in the orbitofrontal area has been linked to anxiety-related traits (Kuhn, Schubert, & Gallinat, 2011; Montag, Reuter, Jurkiewicz, Markett, & Panksepp, 2013) and the experience of both cumulative adversity and recent stressful life events (Ansell, Rando, Tuit, Guarnaccia, & Sinha, 2012). Interestingly, in a well-timed study, Sekiguchi and colleagues (Sekiguchi et al., 2013) had the rare opportunity to follow the structural changes in the brain in the same group of subjects in response to same stressful event: the Great East Japan Earthquake in 2011. Comparisons between MRI scans taken before and after the natural disaster revealed a decrease in the regional gray matter volume in the OFC four months after the Earthquake. Importantly, this decrease was related to the presence of symptoms of Post-Traumatic Stress Disorder (Sekiguchi et al., 2013). These findings not only added to the extant evidence that OFC is particularly sensitive to acute anxiety-inducing events in the environment, but further demonstrated that volumetric changes in OFC could index anxiety levels as people go through real life traumatic events.

The findings on the link between OFC and anxiety at the structure level are echoed by functional neuroimaging research and animal studies. Meta-analysis of emotional processing in anxiety disorders identified a reduced response in the OFC along with hyperactivation in amygdala and insula (Etkin & Wager, 2007), possibly reflecting diminished top-down control and thus a deficit in emotion regulation. While the impaired regulatory function of OFC may be a vulnerability factor to anxiety, the healthy-functioning OFC may on the other hand foster resilience. Animal studies have shown that intact OFC is necessary in fear extinction and the acquisition of resilience over negative experiences (Franklin, Saab, & Mansuy, 2012; van der Werff et al., 2013; Wu et al., 2013).

Converging evidence from structural and functional neuroimaging research has indicated that OFC anomaly, especially volumetric reduction in this region, is closely related to anxiety. In light of this, the present study took a volumetric approach to investigate the relation between OFC, trait optimism, and anxiety in healthy individuals. It has also been argued that using volumetric measures of brain regions is seemingly advantageous in the study of personality, as stable individual differences may be more clearly manifested in structural changes of relevant regions than in task-related activations identified in functional neuroimaging research (DeYoung et al., 2010).

Trait Optimism as the Mediator in the OFC-Anxiety Relation

Together, the evidence reviewed above provides support for a three-way brain-personality-behavior relation among the OFC, trait optimism, and anxiety symptoms, in that the OFC volume and trait optimism are possibly positively related and both of them are negatively related to anxiety. Although the directionality of these relations is difficult to determine because of the correlational nature of the volumetric approach, there has been some arguments in favor of the idea of a causal influence coming from the brain (Montag et al., 2013; Powell, Lewis, Roberts, Garcia-Finana, & Dunbar, 2012), supported by neuroimaging studies showing that individual differences at perceptual, cognitive, and personality levels can be predicted from the variations in the regional gray matter in the brain (e.g., Gilaie-Dotan et al., 2014; Kanai & Rees, 2011). In line with this view, I constructed mediation models to predict personality-level and behavioral/symptom-level variables from the brain volumes (i.e., OFC gray matter volume). Although both trait optimism and anxiety index individual differences, they tap into different aspects of personality. Trait optimism primarily involves a cognitive orientation toward positive expectancies of future outcomes (Carver & Scheier, 2014), and has been considered to contribute to the process through which resilience to adversity develops (Wu et al., 2013). By contrast, trait anxiety has been related to the consequences of failing to regulate emotion properly in anxiety-provoking situations (Grupe & Nitschke, 2013). Therefore, in formulating the mediation hypothesis, the present study adopted the view that optimistic individuals would have lower anxiety levels due to a positive bias in their general cognitive expectancy. However, it should be noted that in the absence of longitudinal studies, assertions of causality in premature, and this model configuration needs to be explored carefully in empirical tests.

Using the brain-personality-symptom approach described above, I examined neural and psychological factors influencing resilience against anxiety in healthy participants.

Specifically, I first examined the existence of two-by-two relations among trait optimism, the OFC volume, and anxiety, and then used a mediation analysis approach to examine the potential mediating role of optimism in the relationship between the OFC gray matter volume and anxiety. I had the following two predictions: 1) Trait optimism would be positively associated with the gray matter volume in the OFC and negatively associated with anxiety; 2) OFC volumes would be negatively associated with anxiety; 3) trait optimism would mediate the relationship between the OFC volume and anxiety.

CHAPTER 2

METHODS

Subjects

Structural MRI scans and personality assessments were collected from a sample of 61 healthy young (18-34 years of age, average = 23.23, SD = 4.00) adults (37 females). None of the subjects had been previously diagnosed with neurological, psychiatric, or personality disorders, and there were no significant age differences between the female and male participants [$t(59) = -0.16$, $p > 0.5$, two-tailed]. All participants provided written consent, and were compensated with either course credit or money.

Imaging Protocol and MRI Data Processing

Structural scanning was conducted on a 1.5-T Siemens Sonata scanner. After the sagittal localizer, 3-D MPRAGE anatomical images were obtained using the following parameters: TR = 1,600 ms; TE = 3.82 ms; FOV = 256 mm × 256 mm. This resulted in anatomical volumes with 112 axial slices and voxel size of $1 \times 1 \times 1$ mm^3. Cortical reconstruction was performed with the Freesurfer image analysis suite (Version 5.3.0; Fischl, 2012), which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). A semi-automatic workflow was adopted to ensure quality control at the following stages: Talairach registration, skull stripping, white matter surface reconstruction, and pial surface reconstruction. The outputs at each stage were manually inspected and corrected if necessary before the next stage was implemented. Anatomical ROIs of the bilateral medial OFC (mOFC) and lateral OFC (lOFC) were defined based on the Desikan-Killiany atlas (Desikan et al., 2006). According to this atlas, the mOFC and lOFC are defined relative to the midpoint of the medial orbital sulcus (mMOS). The mOFC, the portion of the OFC medial to the mMOS, is described as a region within the rostral and caudal extent of the medial orbitofrontal gyrus/gyrus rectus that borders the cingulate cortex and the medial bank of the superior frontal gyrus at the medial aspect. Note that this ROI partially overlaps with the ventromedial prefrontal cortex that is referenced in some literature (Kringelbach, 2005). The lOFC, the portion of the OFC lateral to the mMOS, is described as a region within the rostral and caudal extent of the lateral orbitofrontal gyrus, bordering the lateral bank of the lateral orbital sulcus and/or the circular insular sulcus at the lateral aspect. The anatomical regions of interest (ROIs) of OFC identified on a representative subject are shown in Figure 1.

For each subject, the gray matter volumes (GMVs) of these anatomical ROIs and the intracranial volume (ICV) were extracted from the parcellation results, and an index of the adjusted volume was obtained for each ROI by dividing the raw volumes by the ICV, and then multiplying them by 100. The resulting adjusted volumetric indices were used for group-level statistical analyses.

Personality Measures

Subjects completed personality measures that included scales assessing trait optimism and trait anxiety.

Trait Optimism. Trait optimism was assessed using the revised Life Orientation Test (LOT; Scheier et al., 1994), on which subjects are asked to indicate their agreement with each of the 10 statements on the test using a 0-4 Likert scale (0 = strongly disagree, 4 = strongly agree). Examples of the LOT statements are *"In uncertain times, I usually expect the best"* or *"If something can go wrong for me, it will."* A total score is calculated for each subject based on six statements, with three of them being reversed coded. The largest possible range of this scale is from 0 to 24. Higher scores on this scale indicate a higher level of trait optimism. The LOT has been shown to have high test-retest reliability and good discriminant validity for distinguishing optimism from other conceptually related constructs (Scheier et al., 1994). The Cronbach's alpha for LOT in our sample was 0.708.

Trait Anxiety. Trait anxiety was assessed using the State-Trait Anxiety Inventory-Trait (STAI-T; Spielberger, Gorsuch, & Lushene, 1970). STAI is commonly used to investigate anxious characteristics in non-clinical samples, and it was used here for sensitivity as a marker of risk for anxiety disorders (Grupe & Nitschke, 2013). Participants are required to indicate how they generally feel about 20 statements, such as *"I worry too much over something that really doesn't matter,"* using a 1-4 Likert scale (1 = not at all, 4 = very much so). Ratings of individual statements are summed to obtain a total score for each subject (ranging from 20 to 80). Higher total scores are considered to reflect a general vulnerability factor for anxiety disorders, and lower total scores as potentially indexing lower vulnerability, and hence potential markers for resilience against anxiety. The STAI-T has shown high internal consistency, test-retest reliability, and good construct and concurrent validity (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). The Cronbach's alpha for STAI-T in our sample was 0.875.

Statistical Analyses

Zero-order correlations were first used to assess the two-by-two relations between the OFC volumes, trait optimism, and trait anxiety scores; partial correlations were also performed to account for the potential effects of age and sex. Standardized scores were calculated for the personality and volumetric measures to detect outliers, using a criterion of 2.5 standard deviations (Stevens, 2009). In total, three subjects were identified as outliers on four of the variables except for the STAI-T and the left mOFC (see Table 1); one of the outlying subjects had extreme values on more than one variable. Outliers were excluded list-wise.

To test the mediation hypothesis, I conducted mediation analysis, with trait optimism as the mediator (M), the volumes of mOFC and lOFC as the predictor (X), and anxiety scores as the outcome variable (Y). Using standard conventions (Preacher & Hayes, 2004), the mediation analysis focused on testing the regression coefficients in the following relations: 1) Path *a*, representing the X to M relation, 2) path *b*, representing the M to Y relation controlling for X, 3) path *c*, representing the regression coefficient of the total effect from X to Y, and 4) path *c*', representing the regression coefficient of the direct effect from X to Y controlling for M. The magnitude of the mediation was measured by the indirect effect *ab*, representing the X to Y relation while taking M into account. This measure of the indirect effect was submitted to a bootstrapping procedure (number of samplings = 5000) to obtain 95% confidence intervals (CI), which is recommended for the present sample size (Preacher & Hayes, 2004). The product term *ab* has been shown to be equivalent to *c* - *c*' in most cases (Preacher & Hayes, 2004), and thus a CI that does not contain zero would indicate that the total effect from X to Y has been significantly reduced upon the addition of the mediator to the model. Index of mediation (standardized *ab*) was calculated as the effect size measure (Preacher & Kelley, 2011). The same mediation analysis was performed with the trait optimism as the predictor, OFC volumes as the mediator, and anxiety symptoms as the outcome as a test of the alternative hypothesis that brain volumes mediated the relation from personality to symptoms. All statistical analyses were performed using SPSS for Windows (Version 20.0; IBM, Released 2011).

CHAPTER 3
RESULTS

Increased Trait Optimism Linked to Increased OFC Volume and Decreased Anxiety

Confirming my first prediction, trait optimism was positively associated with the volumes of mOFC ($r = 0.31$, $p < 0.016$; Figure 2a) and lOFC ($r = 0.31$, $p < 0.021$; Figure 2b) in the left hemisphere, and negatively associated with anxiety ($r = –0.45$, $p < 0.001$; Figure 2c). Table 1 displays the zero-order correlation coefficients among all personality and volumetric variables. These results remained significant when controlling for age and sex.

Increased OFC Volumes Linked to Decreased Anxiety

Confirming my second prediction, the volumes of mOFC and lOFC in the left hemisphere were found to be negatively correlated with anxiety (for the left mOFC, $r = –0.25$, $p = 0.052$, marginally significant; for left lOFC, $r = –0.27$, $p = 0.038$). There was also a negative correlation between right lOFC volume and anxiety ($r = –0.28$, $p = 0.035$). After controlling for age and sex, these results remained the same (the trending correlation between left mOFC and anxiety remained marginally significant).

Trait Optimism Mediates the Relationship between OFC Volume and Anxiety

Confirming my second prediction, mediation analyses identified significant indirect negative effects of trait optimism on the relation between left OFC volumes and anxiety (Figure 3). Based on the correlation analyses that identified significant relations between optimism scores and gray matter volumes of left OFC, and between optimism and anxiety, two mediation models were constructed, with left medial OFC and lateral OFC as the predictors, trait optimism as the mediator, and anxiety as the outcome variable. For the left mOFC model (Figure 3a), the CI of indirect effect *ab* did not contain zero, indicating that the indirect effect was significant ($a = 15.281$, $p = 0.016$; $b = –0.881$, $p = 0.001$; $c = –24.601$, $p =$

0.064; *c'* = –11.138, not significant; *ab* = –13.463, bootstrapped 95% CI = [–26.085, –0.741]; N = 60; index of mediation = –0.132). A similar pattern was also identified for left lOFC (*a* = 13.163, *p* = 0.207; *b* = –0.802, *p* = 0.003; *c* = –24.731, *p* = 0.0365; *c'* = –14.175, *p* > 0.2; *ab* = –10.555, bootstrapped 95% CI = [–22.871, –0.175]; N = 59, index of mediation = –0.117). These two mediation models survived Bonferroni correction for laterality when tested using a more stringent threshold (for left lOFC, bootstrapped 97.5% CI = [–29.037, –0.776]; for left mOFC a × b = –13.463, bootstrapped 97.5% CI = [–32.239, –1.578]). The alternative model, placing trait optimism as the predictor and OFC volume as the mediator, was not significant.

CHAPTER 4

DISCUSSION

The present investigation yielded two main findings. First, OFC gray matter volume predicted increased optimism, which in turn predicted reduced anxiety. Second, trait optimism mediated the relationship between left OFC volumes and anxiety. These findings provide initial evidence identifying OFC as a neural marker of trait optimism, and demonstrate that the protective role of gray matter volume in this brain region against anxiety in healthy functioning is mediated by trait optimism. These findings will be discussed in turn below.

Increased Trait Optimism Linked to Increased OFC Volume and Decreased Anxiety

The association between optimism and OFC volume considerably advances previous research on trait optimism, which has primarily been investigated only in the behavioral domain for the past two decades (Carver & Scheier, 2014), by extending the investigation of this trait with structural neuroimaging tools. The present finding, based on volumetric assessments in healthy participants, clearly identifies OFC gray matter volume as a neural marker of trait optimism in healthy functioning. This finding complements evidence from functional brain imaging studies linking transient activation of OFC with approach-oriented coping strategies and processing (Eddington et al., 2007), suggesting that the approach-oriented aspects of OFC function may be related to individual characteristics of trait optimism. For instance, previous research has shown that the maintenance of optimistic bias is related to dopaminergic function in the brain (Sharot, Guitart-Masip, Korn, Chowdhury, & Dolan, 2012), and that individual differences in the responsivity of the dopaminergic system in ventromedial prefrontal cortex (partially overlapping with mOFC) are associated with the willingness to invest effort despite low probability of reward (Treadway et al., 2012). In addition, activation of OFC has also been consistently associated with the processing of positive affect, such as the encoding of reward, value, and pleasure (Grabenhorst & Rolls, 2011; Kringelbach & Berridge, 2009; Rangel & Hare, 2010), and maintaining positive evaluations of self even when threatened (Flagan & Beer, 2013). Since the hallmark characteristic of optimism is a robust positive regard toward self, life, and future, the present finding that trait optimism is directly related to OFC at the structural level further extends previous findings, in support of the idea that OFC contributes to the maintenance of positive expectancies in optimistic individuals. Finally, there is also evidence of OFC's sensitivity to environmental changes (Kringelbach, 2005), which might contribute to the flexibility in coping strategies observed in optimistic individuals when facing adversity (Nes & Segerstrom, 2006).

The present finding of a negative association between trait optimism and anxiety symptoms in our sample of healthy young adults confirms previous evidence identifying trait optimism as a resilience factor in healthy (Scheier et al., 1994) and clinical (Evans & Bullock, 2012; Zenger et al., 2010) adults. Optimism has been consistently associated with positive outcomes, such as improved subjective well-being and physical health, as well as larger and more fulfilling social networks (M. A. Andersson, 2012). Moreover, optimism has been shown to motivate active and persistent coping behavior, which are particularly beneficial at times of adversity (Nes & Segerstrom, 2006). Overall, the present findings add to the extant evidence showing a selective bias toward positive information in optimistic individuals (Segerstrom, 2001), by identifying OFC volume as an important neural marker of this personality trait.

Increased OFC Volumes Linked to Decreased Anxiety

The finding that increased OFC volume was associated with attenuated anxiety symptoms is consistent with the previous research showing that intact OFC is required in the acquisition of resilience (e.g., Franklin et al., 2012), and that reduced gray matter volume in OFC is found in both affective disorders (e.g., Jackowski et al., 2012) and healthy adults in response to life events (Ansell et al., 2012; Sekiguchi et al., 2013). Insights from meta-analysis of functional neuroimaging results point to the possibility that the negative correlation between OFC and anxiety at the structural level may reflect the diminished top-down regulation of this region over basic emotion processing regions, such as amygdala (Etkin & Wager, 2007). Support for this interpretation comes from recent advances using Diffusion Tensor Imaging to evaluate the integrity of white matter fibers. For instance, the integrity of uncinate fasciculus, a white matter bundle connecting the anterior temporal lobe and the orbitofrontal region, has been found to be impaired in anxiety disorders (Baur et al., 2013; Phan et al., 2009; Tromp, Grupe, Oathes, & et al., 2012), and negatively correlated with anxiety symptoms in healthy adults (Baur, Hanggi, & Jancke, 2012), although results have not been consistent (Modi et al., 2013). Although it is beyond the scope of the present study, investigation into the structural connectivity between OFC and the lower level limbic regions will clearly help elucidate the mechanism underlying the negative association between OFC volume and anxiety, which will undoubtedly be an exciting avenue for future research.

Trait Optimism Mediates the Relations between OFC Volumes and Anxiety

Further extending my second finding, the present study demonstrated that the negative relation between OFC volume and anxiety was mediated by trait optimism. Furthermore, the finding that brain- but not personality- level factors predicted anxiety symptoms through optimism provides support for the idea of a causal link between brain structures and personality-level variables (Montag et al., 2013). The brain-to-personality relation identified in this study is also consistent with previous evidence linking structural neuroanatomical features of the human brain with individual cognitive and personality traits

(Gilaie-Dotan et al., 2014; Kanai & Rees, 2011). Alternatively, it is also possible that frequent engagement of processes tapping into OFC function may result in increased volume in this region. However, the lack of significance for the mediation models testing optimism as the predictor and OFC as the mediating variable is not consistent with such an interpretation regarding the role of trait optimism in predicting OFC volume.

It is noteworthy that, consistent with the view that the left hemisphere is more sensitive to the processing of approach-related and/or positive information (Davidson & Irwin, 1999; Hecht, 2013; Spielberg et al., 2011; Spielberg et al., 2012), our mediation effects were identified only in the left hemisphere. Previous evidence has shown that optimistic estimations of negative events activated left inferior frontal gyrus (IFG; Sharot, Korn, & Dolan, 2011), and temporary disruption to the activity in the left (but not right) IFG reduced individuals' tendency to maintain positive expectancies (Sharot, Kanai, et al., 2012). In addition, emotion regulation strategies aimed to enhance positive emotional states (e.g., reappraisal), which are likely to underlie trait optimism, were linked to the activity in the left hemisphere, specifically left medial OFC (Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner et al., 2004). However, it is also worth noting that the current literature has painted a more sophisticated picture regarding the valence-/motivation- related lateralization in the PFC (Miller et al., 2013), suggesting that the complexity of the functional specialization in the frontal lobes calls for more nuanced conceptualization beyond the traditional approach of simply regarding each hemisphere as a unit of analysis. Together, while this hypothesis awaits further confirmation, the current finding of a mediating effect of optimism in the left hemisphere is consistent with the lateralization account, and may reflect the correspondence between the preference for positive information in optimistic individuals and the left-lateralized tendency for processing positive information in these cortical regions.

Overall, the present mediation findings are important because they show promise that, by modifying brain- and/or personality-level factors, it is possible to change behavioral-level outcomes reflected in symptoms of anxiety, even in healthy functioning. OFC volume has been shown to respond to significant changes in life (Sekiguchi et al., 2013), and cognitive therapies designed to impart an optimistic attitude hold promise in alleviating symptoms of emotional dysregulation and disturbances (Meevissen, Peters, & Alberts, 2011). The malleability of brain structures and trait-level resilience factors reflects the dynamic interaction between the brain and behavior, and suggests the possibility that resilience and well-being can indeed be "learned" through training (Crocker et al., 2013; Davidson & McEwen, 2012). Hence, by identifying concrete brain (OFC volume) and personality (trait optimism) factors influencing resilience against anxiety symptoms, the present investigation provides specific targets for future therapeutic and preventive interventions.

Recent intervention studies have shown promise using such a targeted approach. For instance, OFC was found to be responsive to a single session of cognitive-behavioral therapy in phobic patients, compared to a patient control group (Schienle, Schafer, Hermann, Rohrmann, & Vaitl, 2007), demonstrating training-induced plasticity in this region. Two recent studies (Scheinost et al., 2013; Scheinost et al., 2014) have shown that modulating OFC activity through real-time neurofeedback significantly improved anxiety symptoms in both healthy subjects and clinical (OCD) patients, and that baseline global connectivity between the OFC and the rest of the brain predicted greater improvement as the result of the intervention. Importantly, the beneficial effects of OFC training were seen days after the last training session, thus possibly reflecting more persistent neural changes in the OFC. Overall, these complementary lines of evidence emphasize that knowledge about the OFC can be used to identify individuals more likely to benefit from training, and that interventions targeting this region can effectively enhance control over anxiety, possibly leading to persistent anatomical reorganization of the OFC and its networks. Clearly, longitudinal studies are needed to establish the speculated long-term impact of interventions targeting OFC.

Limitations

The present study has taken a novel perspective on the relations among the brain (OFC), individual differences (trait optimism), and anxiety symptoms, and has provided insights into the neural basis of optimism as a prominent resilience factor. The study was led by clear hypotheses, and obtained unambiguous results showing that OFC volume statistically predicted anxiety level via trait optimism. Nevertheless, there are also some limitations. First, as has been mentioned above, the current study design is cross-sectional in nature, which is akin to a snapshot of the status of the involved variables at a single moment in time, and thus cannot reveal how these variables have developed to influence each other. Longitudinal studies are needed to further illustrate the mechanism of development and possible interactions among brain, personality, and symptoms variables. Second, STAI was chosen as the anxiety measure because it has been widely and commonly used as an index of anxiety symptoms, and is sensitive to subclinical symptoms in healthy populations (Grupe & Nitschke, 2013). However, there also have been reports showing that STAI may not be sensitive enough to the subtypes of anxiety (i.e., anxious apprehension and anxious arousal), which seem to be subserved by different neural mechanisms (Nitschke, Heller, Imig, McDonald, & Miller, 2001; Nitschke, Heller, Palmieri, & Miller, 1999), and that it is not distinguished enough from measures of depression (Bieling, Antony, & Swinson, 1998). To address this issue, other measures of anxiety can be incorporated to further investigate the relations among OFC, trait optimism, and anxiety subtypes.

Future Directions

The present study will greatly benefit from further investigations along several lines of research. First, expanding the scope of investigation to include other brain regions involved in emotional processing, particularly in positive affect, reward processing and emotion regulation will help clarify the exact contribution of OFC in its relation to trait optimism and anxiety. Second, the use of voxel-based morphometry will complement the current analysis by enabling the detection of gray matter variations on a finer scale. Progress on these two aspects will not only help us better understand the link between trait optimism and OFC, but will also provide insight into the larger network in which multiple brain regions interact with personality to establish a profile of resilience or vulnerability to anxiety. Third, as briefly discussed above, white matter tractography with diffusion tensor imaging will be particularly helpful to shed light on the mechanism underlying the current findings. Finally, future investigations can also employ other scales that more specifically target anxious apprehension and anxious arousal, such as the Penn State Worry Questionnaire (Meyer, Miller, Metzger, & Borkovec, 1990) and the Anxious Arousal scale of the Mood and Anxiety Symptom Questionnaire (Watson et al., 1995), to complement the current findings.

CHAPTER 5

CONCLUSION

In summary, the present study responds to the increasing need to identify new bio-psychological markers of resilience against emotional dysregulation, in general, and anxiety symptoms, in particular. Overall, the present findings identified OFC gray matter volume as a neural marker for trait optimism, and demonstrate the role of this personality trait in mediating a protective role of OFC against anxiety. These results provide initial evidence about the brain-personality mechanisms protecting against anxiety, and could inform the development of therapeutic and preventive interventions aimed at reducing susceptibility to and increasing resilience against symptoms of affective dysregulation and emotional disturbances in order to promote overall psychological well-being.

TABLE AND FIGURES

Table 1.
Averages, Standard Deviations (SDs), and Correlations between Personality and Volumetric Measures.

Variables	Mean	SD	Range	1	2	3	4	5	6
Personality Measures									
1. Optimism / LOT	16.63	3.92	[6, 23]	–					
N	60								
2. Anxiety / STAI-T	36.25	8.30	[23, 55]	-0.46***					
N	61			60	–				
CI				[-1.43, -0.47]					
Volume Statistics (%)									
3. Left mOFC	0.42	0.08	[0.24, 0.60]	0.31*	-0.25†				
N	61			60	61	–			
CI				[2.95, 27.61]	[-52.75, 0.25]				
4. Left lOFC	0.60	0.09	[0.36, 0.79]	0.30*	-0.27*	0.71***			
N	60			59	60	60	–		
CI				[2.08, 24.24]	[-48.82, -1.45]	[0.61, 1.03]			
5. Right mOFC	0.41	0.07	[0.23, 0.57]	0.20	-0.15	0.75***	0.73***		
N	60			59	60	60	60	–	
CI				[-3.49, 24.65]	[-46.74, 13.10]	[0.61, 0.98]	[0.67, 1.12]		
6. Right lOFC	0.61	0.09	[0.39, 0.83]	0.22	-0.28*	0.75***	0.86***	0.74***	
N	59			58	59	59	59	59	–
CI				[-1.82, 20.12]	[-50.93, -1.96]	[0.49, 0.79]	[0.69, 0.95]	[0.44, 0.72]	

Note. * $p < 0.05$. *** $p < 0.001$. † marginally significant at $p = 0.052$. *N* = number of participants; CI = Confidence Interval.
All correlations remained significant after controlling for age and sex, except for the trending relation between left mOFC and STAI-T, noted as an exception. LOT, Life Orientation Test (13); STAI-T, State-Trait Anxiety Inventory-Trait (40); mOFC, medial orbitofrontal cortex; lOFC, lateral orbitofrontal cortex.

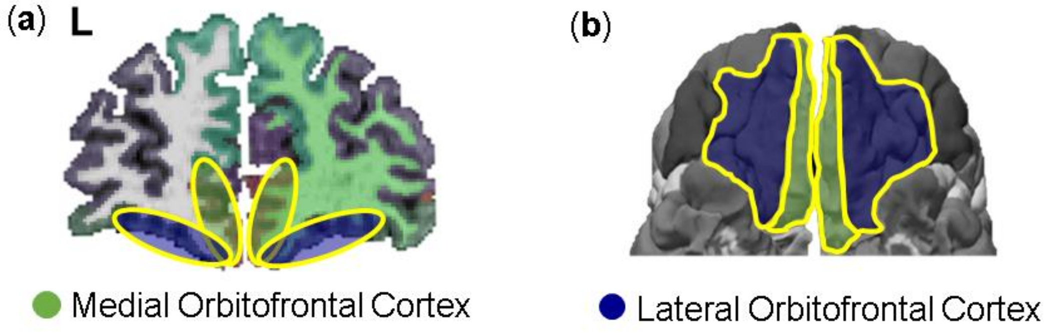

Figure 1. The anatomical regions of interest of the medial (green) and lateral (blue) orbitofrontal cortex identified by Freesurfer on a representative subject, as seen on a slice in the coronal view (Panel a) and on the cortical surface in the bottom-up axial view (Panel b). L, left.

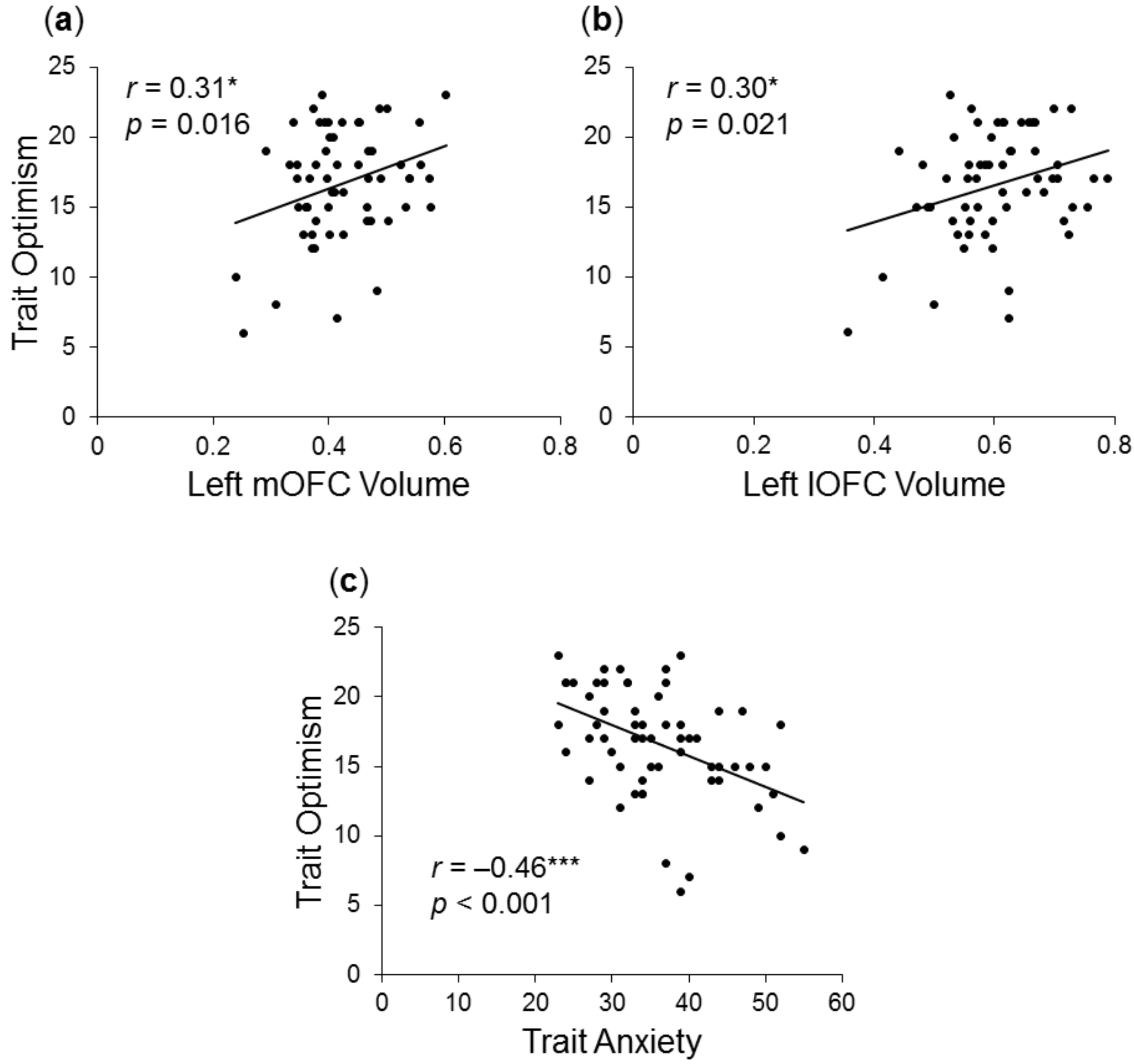

Figure 2. Increased trait optimism was linked to increased gray matter volumes in the left orbitofrontal cortex (OFC) and decreased anxiety scores. Presented here are scatterplots showing a significant positive correlation between trait optimism and gray matter volume of left medial orbitofrontal cortex (mOFC; Panel a) and left lateral orbitofrontal cortex (lOFC; Panel b). There was also a significant negative correlation between trait optimism and anxiety symptoms (Panel c). * $p < 0.05$. *** $p < 0.001$.

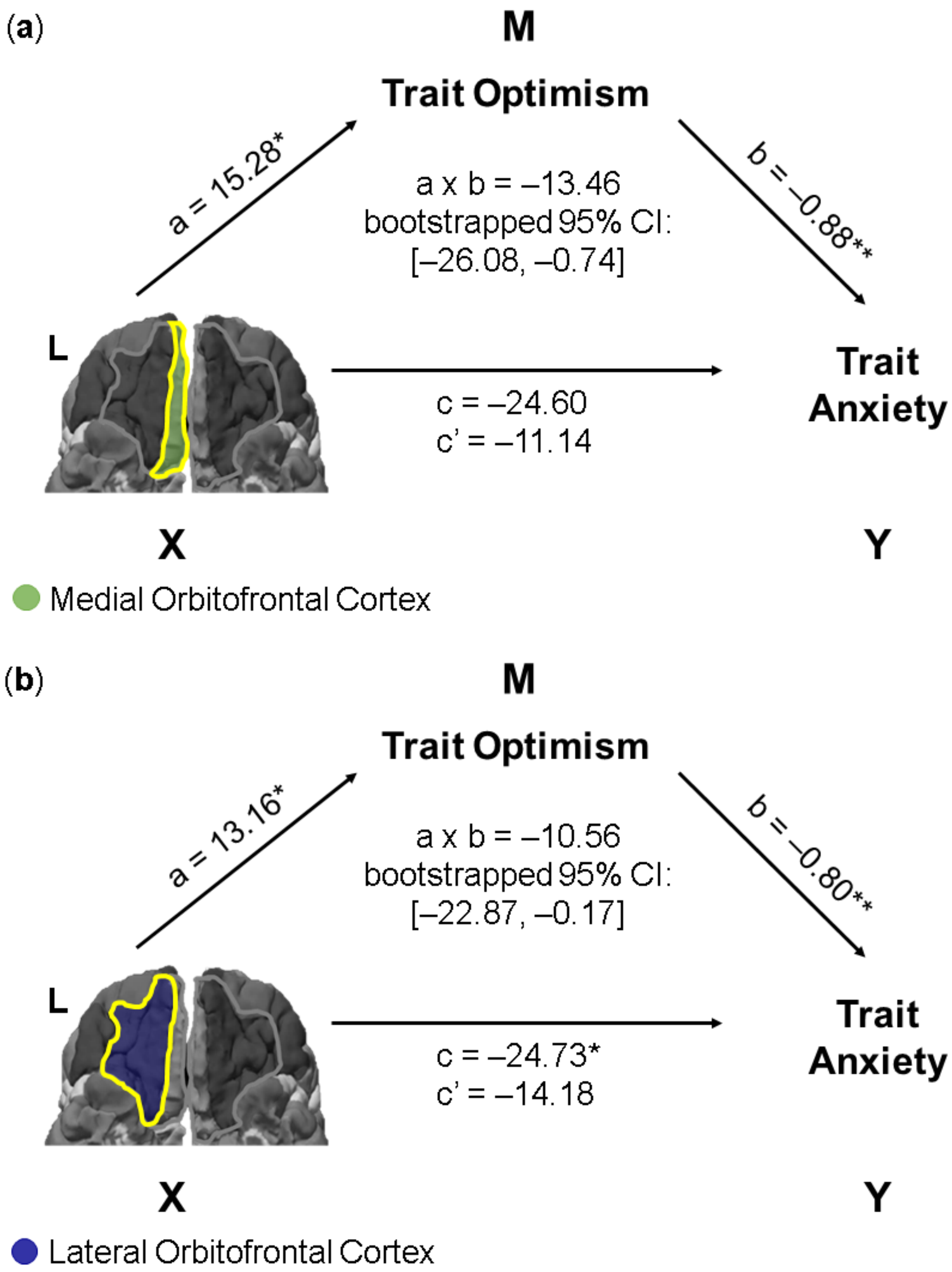

Figure 3. Trait optimism mediated the relationship between orbitofrontal cortex (OFC) volume and anxiety. Presented here are the mediation models showing the significant negative indirect effects of trait optimism on the relations of gray matter volumes in left medial orbitofrontal cortex (mOFC; Panel a) and left lateral orbitofrontal cortex (lOFC; Panel b) to anxiety. Path *a* refers to the relation from the predictor variable, X, to the mediator variable, M, and path *b* refers to the relation from M to the outcome variable, Y, while controlling for X. Path *c* refers to the total effect from X to Y, and path *c*' refers to the direct effect from X to Y controlling for M. The indirect effects were represented by the interaction term *ab*, and the significance of these effects were indicated by the bootstrapped 95% confidence intervals (CI) not including zero. Unstandardized regression coefficients are displayed. L, left hemisphere. * $p < 0.05$; ** $p < 0.01$.

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