Spring 5-2016

Rostral Middle Frontal Gyrus Thickness is Associated with Perceived Stress and Depressive Symptomatology

Lindsay J. Michalski
Washington University in St. Louis

WASHINGTON UNIVERSITY IN ST. LOUIS

Department of Psychological and Brain Sciences

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by

Lindsay Michalski

A thesis presented to the
Graduate School of Arts & Sciences
of Washington University in
partial fulfillment of the
requirements for the
degree of Master of Arts

May 2016
St. Louis, Missouri

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Acknowledgments

I would like to extend thanks to the Graduate School of Arts and Sciences, the Department of Psychological and Brain Sciences, and Dr. Ryan Bogdan's Behavioral Research and Imaging Neurogenetics (BRAIN) Laboratory at Washington University in St. Louis. I would also like to acknowledge the Human Connectome Project for providing an open-source dataset from which to work. While conducting this research, I was funded by the Interface of Psychology, Neuroscience, and Genetics (IPNG) training grant (NIGMS: T32 GM081739).

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May 2016

Abstract of the Thesis

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Master of Arts in Psychological and Brain Sciences

Washington University in St. Louis, 2016

Dr. Deanna Barch, Chair

Elevated stress perception and depression commonly co-occur and have shared genetic and environmental influences, suggesting they may rest upon a common underlying neurobiology. The rostral middle frontal gyrus (RMFG), part of the dorsolateral prefrontal cortex, is critical for executive function, including emotion regulation and working memory. Variability in RMFG cortical thickness has been associated with both depression and stress-related phenotypes, although the directionality of these associations has been inconsistent thus far. The current study examined healthy participants (n=879) who completed the ongoing family-based Human Connectome Project were included in analyses. RMFG cortical thickness was computed from structural magnetic resonance imaging (MRI) scans using FreeSurfer. Depression symptoms, positive affect, personality traits, and perceived stress were assessed using self-report questionnaires: the PROMIS depression scale, the PANAS-X, and the PSS, respectively. After accounting for effects of sex, age, ethnicity, average whole-brain cortical thickness, twin status, and familial structure, as well as correcting for multiple tests, bilateral RMFG thickness was associated with increased perceived stress (left RMFG: p=.0017; right RMFG: p=.0013). Moreover, left RMFG cortical thickness was significantly positively associated with depressive symptoms (p=.0053) and negatively associated

with positive affect at levels approaching significance after correcting for multiple testing (p=.0196). Follow-up simultaneous linear models revealed unique associations between bilateral RMFG cortical thickness and perceived stress when accounting for associations with positive affect and depressive symptoms. Heritability analyses showed that bilateral RMFG thickness, depressive symptoms, and perceived stress were all significantly heritable. After decomposing variability between the constructs, shared genetic and environmental contributions to variability were observed among self-reported sadness, positive affect, and perceived stress, as well as between right and left RMFG cortical thickness. Collectively, these findings suggest that increased RMFG cortical thickness is associated with depressive symptoms and linked to the subjective perception of stress. More broadly, these results suggest that stress perception and depressive symptoms share a common underlying biology. What remains unclear from this cross-sectional study is the origin of individual differences in RMFG cortical thickness: it is possible that stress exposure and/or the presence of depressive symptoms may give rise to differences in brain structure, or it may be the case that increased RMFG thickness contributes to stress-related cognitive biases that promote vulnerability to depression

Introduction

Convergent evidence suggests that stress plays a prominent etiologic role in major depressive disorder (MDD). Both prospective and retrospective studies have shown that stressful life events often precede the development of MDD (Kendler, Karkowski, & Prescott, 1999), and non-human animal models have demonstrated that stress induces depressive-like behavior (Lee et al., 2013; Zhu, Shi, Wang, Wang, & Li, 2014). Importantly, however, there is vast variability in how individuals respond to stressors, with evidence that perceptions of low stressor controllability and inadequate coping resources contribute to the depressogenic effects of stress exposure (Morris, Kouros, Fox, Rao, & Garber, 2014). Twin studies indicate that the association between perceived stress and depressive symptoms is influenced by shared genetic and environmental factors (Bogdan & Pizzagalli, 2006; Kendler et al., 1995), which suggests that stress perception and depression also share a common neural underpinning.

Neuroimaging and non-human animal research suggests that stress and depression both are associated with individual differences in brain structure. In addition to well-documented changes in amygdala and hippocampal structure among both individuals exposed to stressful life events (Corbo et al., 2014; Morey et al., 2012; Tottenham & Sheridan, 2009) and those with depressive symptoms (Campbell & MacQueen, 2004; Rosso et al., 2005; Treadway et al., 2014; Whalen, Shin, Somerville, McLean, & Kim, 2002), recent work has also implicated structural differences in the dorsolateral prefrontal cortex (DLPFC) in the context of stress and depression. The DLPFC is critical for higher-order executive functions related to stress perception and appraisal, including attention, working memory, planning, executive cognition, and emotion regulation (Koenigs & Grafman, 2009; Miller & Cohen, 2001). In particular, evidence suggests that depression and stress exposure are both characterized by individual differences in cortical thickness within the rostral middle frontal gyrus (RMFG), a sub-region of the DLPFC. When compared to healthy controls,

adolescents with MDD have increased cortical thickness in the RMFG (Reynolds et al., 2014), while both increases (Qiu et al., 2014) and decreases (Peng et al., 2015) in thickness have been observed among adults experiencing their first depressive episode. The relationship between stress and prefrontal cortical thickness, particularly within the RMFG, has not yet been well-explored – although there is some evidence that stress exposure, posttraumatic stress disorder, and elevated cortisol levels are associated with individual differences in DLPFC cortical thickness (Arnsten, 2009; Lyoo et al., 2011) – and the directionality of associations have been inconsistent, with evidence of both relative thicker and thinner cortex (Eijndhoven et al., 2013; Qiu et al., 2014; Reynolds et al., 2014).

The current study examined whether RMFG cortical thickness is associated with depressive symptoms and perceived stress within a non-clinical sample of individuals who completed the ongoing Human Connectome Project (n=879). Because depression and stress-related phenotypes have been associated with both increased and decreased cortical thickness and associations with perceived stress have been unexplored, we expected these constructs to be related to RMFG cortical thickness, but we had no directional hypotheses. We further examined whether RMFG, perceived stress, and depression were heritable, and we explored whether genetic and environmental sources of variation were shared or unique across these constructs (when the strength of phenotypic correlations permitted).

Methods

Participants

Participants were drawn from the December 2015 public release (900 Subjects Release) of data from the Human Connectome Project (HCP; total n=970), which is an ongoing family-based study

(2-6 siblings per family, most including a twin pair; projected final N=1,200) designed to explore individual differences in brain circuits and their relation to behavior and genetic background. All participants were 22-37 years of age and free of the following exclusionary criteria: preterm birth, neurodevelopmental, neuropsychiatric, or neurologic disorders; a full list of exclusions is available in a prior publication (Van Essen et al., 2012). Participants were also excluded from analyses in the present study for poor-quality structural MRI data (n=73), missing questionnaire data (n=1), half-sibling status (n=11), or missing parent identity (n=6). This resulted in a final sample of 879 participants [mean age: 28.82 ± 3.68 years; 393 (43.9%) female; 597 (67.4%) Caucasian, 143 (16.2%) African/African-American, 44 (5.0%) Asian/Asian-American, and 73 (8.2%) Hispanic], with 107 monozygotic twin pairs, 116 dizygotic twin pairs, and 61 singletons.

Self-Report Scales

Perceived Stress

Perceived stress was assessed using the 10-item Perceived Stress Scale (PSS) from the NIH toolbox. The PSS is a well-validated measure of stress perception that is heritable (Federenko et al., 2006) and has been associated with stress hormones, illness, and physiological responses (Cohen & Janicki-Deverts, 2012; Cohen, Tyrrell, & Smith, 1993; Cohen & Williamson, 1988; Ebrecht et al., 2004).*Depressive Symptoms*

Depressive symptoms were assessed using two distinct measures: sadness and positive affect. Sadness was assessed using the NIH toolbox Sadness Survey, which is comprised of 27 items from a depression item bank within the Patient Reported Outcome Measurement Information System (PROMIS). The PROMIS depression scale probes cognitive and affective indicators of depression (Pilkonis et al., 2011) and shows strong convergent validity with other measures of depression

(Pilkonis et al., 2014), including the Center for Epidemiological Studies Depression scale [CESD; (Radloff, 1977)] and the Patient Health Questionnaire [PHQ-9; (Kroenke & Spitzer, 2002)]. Positive affect was assessed via 34 items from the Positive and Negative Affect Schedule – Expanded Form [PANAS-X; (Crawford & Henry, 2004)], which measures higher-order positive and negative affect, as well as more specific affective states (Watson & Clark, 1994).

Magnetic Resonance Imaging: Acquisition and Processing

High resolution (0.7mm isotropic voxels) anatomical images were acquired using a customized Siemens Skyra 3T with a 32-channel head coil. HCP acquisition and preprocessing details have been described in previously described in detail (Glasser et al., 2013). Briefly, relevant steps for this study from the HCP processing pipeline within Freesurfer v5.3.0 included: 1) spline-based down-sampling of the 0.7mm T1 image to 1 mm; 2) intensity normalization and Talairach transformation; 3) skull registration; 4) FreeSurfer skull stripping; 5) FreeSurfer subcortical segmentation and extraction of cortical thickness estimates for our regions of interest.

Statistical Analyses

Sequential Oligogenetic Linkage Analysis Routines (SOLAR) software (http://www.sfbr.org/sfbr/public/software/solar) was used to conduct phenotypic association, heritability, and bivariate quantitative genetic analyses, while accounting for familial structure (Blangero & Almasy, 1996). More specifically, an individual's bivariate phenotypic association (e.g., between perceived stress and RMFG cortical thickness) was modeled as a linear function of the individual's measures and the kinship matrix coefficients for relationships among all pairs of individuals in their pedigree to account for the non-independence of these measures. To account

for multiple testing (6 total tests; i.e., right and left RMFG associations with positive affect, depressive symptoms, and perceived stress), we used matrix decomposition [Matrix Spectral Decomposition (MatSpD) software; http://gump.qimr.edu.au/general/daleN/matSpD/] to estimate the number of independent variables in our correlation matrix (Nyholt, 2004), then applied Bonferroni correction for the number of independent tests (i.e., 4.35), resulting in a corrected p value of 0.0115. Lastly, following significant associations between RMFG and depressive symptoms, positive affect, and perceived stress (see Results), we evaluated whether any independent associations remained when these variables were entered simultaneous into our regression model predicting RMFG cortical thickness.

Univariate heritability (h^2) analyses were performed on bilateral RMFG thickness estimates, perceived stress, and depressive symptoms. Any bivariate phenotypic associations that were stronger than r>.15 were examined for evidence of overlapping genetic (ρ_g) or individual-specific environmental (ρ_e) factors.

All analyses accounted for effects of sex, age, ethnicity (i.e., dummy coded for White, Black, Asian, and Hispanic), and zygosity (i.e., MZ/not MZ; DZ/not DZ). Analyses of rostral middle frontal gyrus thickness also accounted for whole-brain cortical thickness.

Results

Sample Characteristics

There were no significant associations between demographic variables (i.e., age, sex, zygosity, ethnicity) and bilateral RMFG thickness, depressive symptoms, or perceived stress (all p's>0.3460).

Regression Analyses

Bilateral RMFG cortical thickness was positively associated with perceived stress (right RMFG: β=0.1141, p=0.0013; left RMFG: β=0.1120, p=0.0017; **Figure 1a**). Left RMFG thickness was also negatively associated with self-reported positive affect (β=-0.0824, p=0.0053; **Figure 1b**) and positively associated with self-reported sadness at a trend level (β=0.0985, p=0.0196; **Figure 1c**), while right RMFG thickness was associated at a trend level with sadness (β=0.0832, p=0.0186) but not with positive affect (β=-0.0463, p=0.1900).

Next, we entered depression symptoms, positive affect, and perceived stress together in the regression to examine whether any of these variables were uniquely associated with variability in RMFG cortical thickness. Perceived stress continued to significantly predict right RMFG thickness (β=0.0828, p=0.0190); in the left RMFG, this association became a trend (β=0.0604, p=0.0868). Conversely, bilateral RMFG cortical thickness was no longer significantly associated with positive affect (right RMFG: β=0.0159, p=0.6519; left RMFG: β=-0.0219, p=0.5338) or sadness (right RMFG: β=0.0255, p=0.4579; left RMFG: β=0.0357, p=0.2983).

Sources of Variance and Covariance

Heritability analysis indicated that all traits were significantly heritable [left RMFG thickness: h^2=0.6156 (S.E.=0.0512), p=2.177^{e-22}; right RMFG thickness: h^2=0.7134 (S.E.=0.0402), p=2.940^{e-31}; positive affect: h^2=0.2396 (S.E.=0.0697), p=0.0002; sadness: h^2=0.2244 (S.E.=0.0814), p=0.0021; perceived stress: h^2=0.3385 (S.E.=0.0709), p=.0000; **Figure 2**]. Bivariate decomposition analyses revealed genetic and environmental correlations between perceived stress and both positive affect [ρ_g=-0.5398 (S.E.=0.1411), p=0.0062; ρ_e=-0.4655 (S.E.=0.0561), p=$5.9145e^{-13}$] and sadness [ρ_g=0.8639 (S.E.=0.1130), p=0.0001; ρ_e=0.4564 (S.E.=0.1129),

$p=7.7430e^{-12}$], as well as between sadness and positive affect [ρ_g=-0.7526 (S.E.=0.1486), p=0.0025; ρ_e=-0.3804 (S.E.=0.0583), $p=5.2222e^{-9}$], and between left and right RMFG thickness [ρ_g=0.9945 (S.E.=0.0179), $p=1.2949e^{-32}$; ρ_e=0.4584 (S.E.=0.0615), $p=7.6075e^{-13}$]. Because the strength of association between RMFG cortical thickness and depressive symptoms, positive affect, and perceived stress did not exceed r>.15, decomposition analyses were not conducted.

Discussion

Here, we examined associations among depressive symptoms, perceived stress, and RMFG cortical thickness. Three primary findings emerged. First, bilateral RMFG cortical thickness was positively associated with self-reported depressive symptoms and perceived stress and negatively associated with positive affect. Of these three related variables, only stress perception was uniquely associated with variance in RMFG cortical thickness. Second, RMFG cortical thickness, depressive symptoms, and stress perception were all significantly heritable. Third, evidence suggests that the correlation between self-report measures of depressive symptoms and perceived stress is due to shared genetic and environmental factors, while the correlation between cortical thickness estimates across hemispheres can be attributed primarily to shared genetic influence. Collectively, these data suggest individual differences in stress perception and depressive symptoms likely arise alongside differences in cognitive processes related to working memory, emotion regulation, and executive function that are, in part, dependent on the dorsolateral prefrontal cortex. As part of the DLPFC, the RMFG is involved in a host of executive functions, including mood and behavior regulation, that are impaired in depression (Pizzagalli, 2011). Recent studies have associated individual differences in RMFG cortical thickness to depression as well as

stress-related phenotypes. For instance, compared to healthy controls, depressed patients show differences in RMFG grey-matter volume (Abe et al., 2010) and cortical thickness (Peng et al., 2015; Qiu et al., 2014; Reynolds et al., 2014). The observed associations between increased RMFG cortical thickness, perceived stress, and depressive symptoms within this non-clinical sample align with what has been observed among depressed youth (Reynolds et al., 2014), adults experiencing their first depressive episode (Qiu et al., 2014), and trauma-exposed individuals (Lyoo et al., 2011).

Contrary to these findings, however, unaffected individuals at familial risk for depression have relatively thinner DLPFC (Peterson et al., 2009). This is similar to what has been observed among depressed patients in later life (Mackin et al., 2013), though controlling for illness duration seems to abolish significant structural differences between early- and late-onset depressed patients (Truong et al., 2013). One previous study has proposed that increased cortical thickness is related to deficient neuronal pruning during brain development (Reynolds et al., 2014), our results may, in fact, suggest that this structural effect is conserved into adulthood and is related to depression independent of familial risk. Another possibility is that increased cortical thickness is associated with non-clinical levels of depression and stress perception that may transition to decreases in cortical thickness over time, alongside the expression of depressive symptoms or stress generation (Hammen, 1991).

As a cross-sectional study, this study cannot resolve whether individual differences in stress perception and depressive symptoms precede or follow the associated differences in RMFG anatomical variability. However, based on prior literature, we can make some speculations. It is possible that stress exposure leads to elevations in perceived stress and depressive symptoms as well as increased RMFG cortical thickness. Consistent with this proposition, increased DLPFC thickness has been observed among disaster survivors close to the time of trauma, and greater

thickness predicted better recovery from PTSD and normalized (i.e., decreased) over time to the extent that symptoms remitted (Lyoo et al., 2011). These results suggest trauma-dependent increases in DLPFC cortical thickness that resolve alongside psychological recovery. Thus, in our sample, increased cortical thickness may reflect stress exposure and unresolved recovery, which result in greater perceptions of stress and depressive symptoms.

Alternatively, though not mutually exclusive, RMFG cortical thickness may serve as a preexisting vulnerability factor that influences stress perception and, as such, confers vulnerability to depression. In support of this putative explanation, among healthy adults, increased DLPFC grey-matter volume has also been correlated with rumination, or the tendency to dwell repetitively on negative emotional experiences (Wang et al., 2015). Rumination is a key risk factor for depression that also mediates the relationship between chronic perceived stress and psychological health risk indicators (e.g., depressive symptoms and sleep quality; Zawadzki, 2015). However, other findings contradict this interpretation; in adolescents, relatively decreased cortical thickness in the DLPFC has been associated with decreased cognitive reappraisal, a form of emotion regulation (Vijayakumar et al., 2014), which has been correlated with reduced stress perception across stages of adulthood (Prakash, Hussain, & Schirda, 2015). Heritability analyses suggested that phenotypic variation in perceived stress, depressive symptoms, and bilateral RMFG cortical thickness is, in part, due to genetic variation among individuals. Relatively high heritability estimates of bilateral RMFG cortical thickness, in line with previous estimates of the heritability of average whole-brain cortical thickness (Panizzon et al., 2009), suggest that this neural phenotype likely contributes to familial transmission of depression risk. Furthermore, decomposition analyses suggest a contribution of both genetic and environmental factors in the proportion of variance shared between perceived stress and depressive symptoms, emphasizing

the intersecting role of biology and the external environment on cognitive and behavioral phenotypes related to depression.

It is important to consider study limitations when interpreting the present results. First, as mentioned above, the study is cross-sectional, leaving uncertain both the underlying temporal nature of associations and their etiologic plausibility. Further longitudinal work will be required in order to elucidate temporal effects, which would bolster confidence in the potential mechanisms underlying these associations (e.g., that perceived stress causes structural differences or, alternatively, that structural differences alter the perception of stress). Second, because this is a relatively healthy sample, it is unclear whether the results would generalize to clinical levels of depression and perceived stress. Indeed, such differences may underlie some conflicting directional associations within the literature between DLPFC cortical thickness and depression and stress-related phenotypes. Third, the modest correlations between RMFG cortical thickness and depressive symptoms did not allow us to deconstruct their sources of variance into shared and unique genetic and environmental contributors. These limitations notwithstanding, our study suggests that relatively increased RMFG cortical thickness is a common neural substrate of stress perception and depressive symptoms that may promote depression/stress vulnerability or result from such experience.

Figure 1. Left RMFG thickness is associated with (A) increased perceived stress, (B) decreased positive affect, and (C) increased sadness.

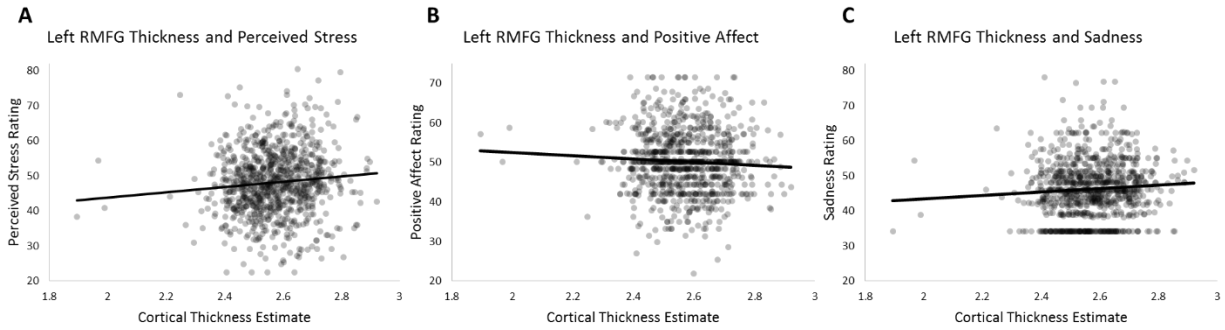
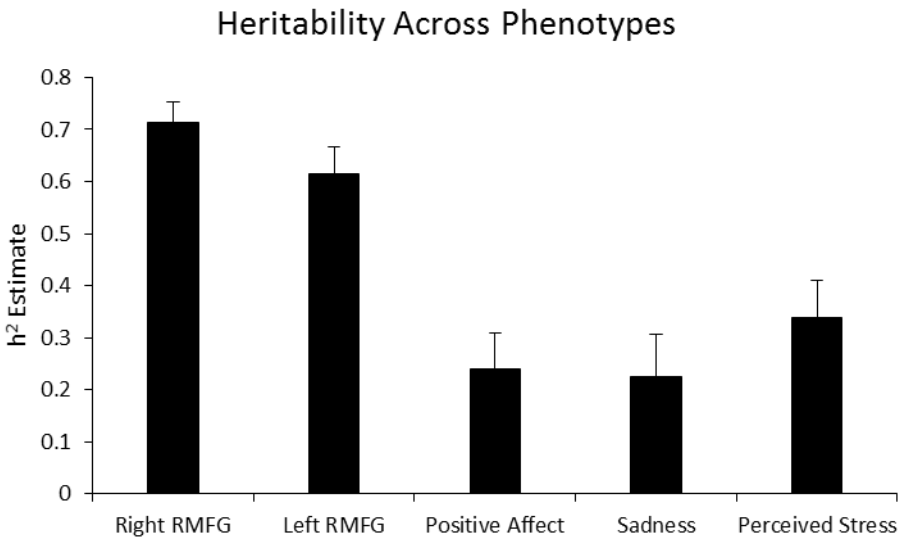


Figure 2. Bilateral RMFG thickness, depressive symptoms, and perceived stress were all significantly heritable.



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