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Perceived stress is associated with increased rostral middle frontal gyrus cortical thickness: a family-based and discordant-sibling investigation

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Elevated stress perception and depression commonly co-occur, suggesting that they share a common neurobiology. Cortical thickness of the rostral middle frontal gyrus (RMFG), a region critical for executive function, has been associated with depression- and stress-related phenotypes. Here, we examined whether RMFG cortical thickness is associated with these phenotypes in a large family-based community sample. RMFG cortical thickness was estimated using FreeSurfer among participants ($n = 879$) who completed the ongoing Human Connectome Project. Depression-related phenotypes (i.e. sadness, positive affect) and perceived stress were assessed via self-report. After accounting for sex, age, ethnicity, average whole-brain cortical thickness, twin status and familial structure, RMFG thickness was positively associated with perceived stress and sadness and negatively associated with positive affect at small effect sizes (accounting for 0.2–2.4% of variance; p-fdr: 0.0051–0.1900). Perceived stress was uniquely associated with RMFG thickness after accounting for depression-related phenotypes. Further, among siblings discordant for perceived stress, those reporting higher perceived stress had increased RMFG thickness ($P = 4 \times 10^{-7}$). Lastly, RMFG thickness, perceived stress, depressive symptoms, and positive affect were all significantly heritable, with evidence of shared genetic and environmental contributions between self-report measures. Stress perception and depression share common genetic, environmental, and neural correlates. Variability in RMFG cortical thickness may play a role in stress-related depression, although effects may be small in magnitude. Prospective studies are required to examine whether variability in RMFG thickness may function as a risk factor for stress exposure and/or perception, and/or arises as a consequence of these phenotypes.

Keywords: rostral middle frontal gyrus, prefrontal cortical thickness, perceived stress, depression, discordant twins, heritability, etiology, SOLAR, positive affect, neurobiology

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Convergent evidence suggests that stress plays a prominent etiologic role in depression. Both prospective and retrospective studies have shown that stressful life events often precede depression (Hammen 2005; Kendler *et al.* 1999), and non-human animal models have showed that stress induces depressive-like behavior (Lee *et al.* 2013). Importantly, however, there is vast variability in how individuals respond to stressors. For instance, perceived stress - or the extent that one perceives situations in their life to be stressful, unpredictable, uncontrollable and unmanageable - is associated with the development of depressive symptoms, including elevations in negative affect and reductions in positive affect following stress exposure (Morris *et al.* 2014; Oni *et al.* 2012; Dunkley *et al.* 2017). Further, consistent with converging evidence that stress may induce anhedonia (Pizzagalli 2014; Bogdan & Pizzagalli 2006), perceived stress is also coupled with reduced behavioral reward learning and positive affect, as well as elevated anhedonia (Pizzagalli *et al.* 2008; Bogdan et al., 2012; Dunkley *et al.* 2017).

Twin studies showing that the association between stress perception and depression is primarily attributable to shared genetic and individual-specific environmental factors suggest that perceived stress and depression may share a common neurobiological basis (Bogdan & Pizzagalli 2009; Rietschel *et al.* 2014). In addition to well-documented associations between 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.* 2015; Whalen *et al.* 2002), recent work has linked rostral middle frontal gyrus (RMFG) cortical thickness to both depression and stress. Specifically, when compared with healthy controls, depressed adolescents and adults with remitted depression have increased cortical thickness within the RMFG (Phillips *et al.* 2015; Reynolds *et al.* 2014). However, both thicker (Qiu *et al.* 2014)

Table 1: Bivariate variance decomposition

	Left RMFG thickness			Sadness			Perceived stress		
	β	ρ_e (SE)	ρ_g (SE)	β	ρ_e (SE)	ρ_g (SE)	β	ρ_e (SE)	ρ_g (SE)
Right RMFG thickness	0.832	0.4390 (0.0626)	0.9971 (0.0164)	0.083	-	-	0.114	-	-
Positive affect	0.082	-	-	−0.468	−0.3804 (0.0583)	−0.7526 (0.1486)	−0.484	−0.4655 (0.0561)	−0.5398 (0.1411)
Sadness	0.098	-	-	-	-	-	0.565	0.4564 (0.0566)	0.8639 (0.1130)
Perceived stress	0.112	-	-	0.565	-	-	-	-	-

Variance decomposition analyses were conducted for bivariate pairs that were phenotypically correlated at $\beta > |0.20|$. Significant ρ_g and ρ_e estimates (all Ps < 0.0065) are listed above with SE values in parentheses.

and thinner (Peng *et al.* 2015) RMFG[1] have been observed among adults experiencing their first depressive episode. Consistent with these mixed findings, stress-related phenotypes, including post-traumatic stress disorder (PTSD) and circulating cortisol, have also been linked to both relatively thicker (Lyoo *et al.* 2011; Qiu *et al.* 2014; Reynolds *et al.* 2014) and thinner (Van Eijndhoven *et al.* 2013) RMFG. Because the RMFG 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; Phillips *et al.* 2003), it may confer vulnerability to depression and negative stress-related outcomes, in part through associations with perceived stress.

This study examined whether RMFG cortical thickness is associated with depression-related phenotypes (i.e. sadness, positive affect) and perceived stress within a non-clinical sample of individuals who completed the ongoing family-based Human Connectome Project (HCP; $n = 879$). We examined cortical thickness, as opposed to surface area and gray-matter volume, due to evidence that these phenotypes have separable genetic influence (Winkler *et al.* 2010), as well as emergent literature linking indices of RMFG cortical thickness to depression and stress-related phenotypes. Because both depression and stress-related phenotypes have been associated with increased (Lyoo *et al.* 2011; Qiu *et al.* 2014; Reynolds *et al.* 2014) and decreased (Peterson *et al.* 2009; Mackin *et al.* 2013) RMFG thickness, and associations with perceived stress have been unexplored, we made no directional hypotheses. We further examined whether associations between RMFG cortical thickness and stress perception remain after accounting for depression-related phenotypes and whether differences in RMFG cortical thickness are present among siblings discordant for perceived stress. These analyses can be used to evaluate support for potential sibling-shared predisposition (i.e. discordant siblings who do not differ) or causal (i.e. discordant siblings differing) effects underlying associations. Additionally, to probe regional specificity, we evaluated whether cortical thickness in other prefrontal regions previously linked to depression [i.e., anterior cingulate (Reynolds *et al.* 2014; van Eijndhoven 2013)] are associated with depression-related phenotypes and perceived stress. Lastly, we estimated the heritability of RMFG cortical thickness, depression-related phenotypes, and perceived stress, as well as shared genetic and environmental covariation across these phenotypes when phenotypic correlations permitted. Understanding associations between depression and stress perception with RMFG cortical thickness may inform why these behavioral constructs co-occur and contribute to our etiologic understanding of depression to ultimately inform nosology and treatment.

Methods

Participants

Participants were drawn from the December 2015 public release of the HCP (total $n = 970$). The HCP is an ongoing, family-based study (2–6 siblings per family, with most families including a twin pair; projected final $n = 1200$) designed to explore individual differences in brain circuits and their relation to behavior and genetic background (Barch *et al.* 2013; Pagliaccio *et al.* 2014; Van Essen *et al.* 2013). All participants were 22–37 years of age and free of the following exclusionary criteria: preterm birth, neurodevelopmental, neuropsychiatric or neurologic disorders; a complete 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 missing or poor-quality structural magnetic resonance imaging 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%) European-American, 143 (16.2%) African-American, 44 (5.0%) Asian-American, and 73 (8.2%) Hispanic]. Of these participants, there were 107 monozygotic (MZ) twin pairs, 116 dizygotic (DZ) twin pairs, 276 non-twin siblings (87 families with 2 siblings, 20 families with 3 siblings, 8 families with 4 siblings, and 2 families with 5 siblings; none of these are twins, but there may be twin pairs in their family structure), and 157 individuals who were the only member of their family to provide usable data prior to this data release. There was an average of 2.00 ± 0.94 with a maximum of 6 siblings per family. Mean age difference between siblings within families (twin and non-twin siblings) was 2.81 ± 2.56 years for families with 2 siblings; 2.91 ± 2.59 years for families with 3 siblings; 3.00 ± 2.59 years for families with 4 siblings; 3.01 ± 2.58 years for

1 For prior studies that report results in the dorsolateral prefrontal cortex (DLPFC), but not in the RMFG specifically, we probed coordinates associated with the reported DLPFC region-of-interest (ROI) to be certain that they were within the Desikan-atlas-defined RMFG.

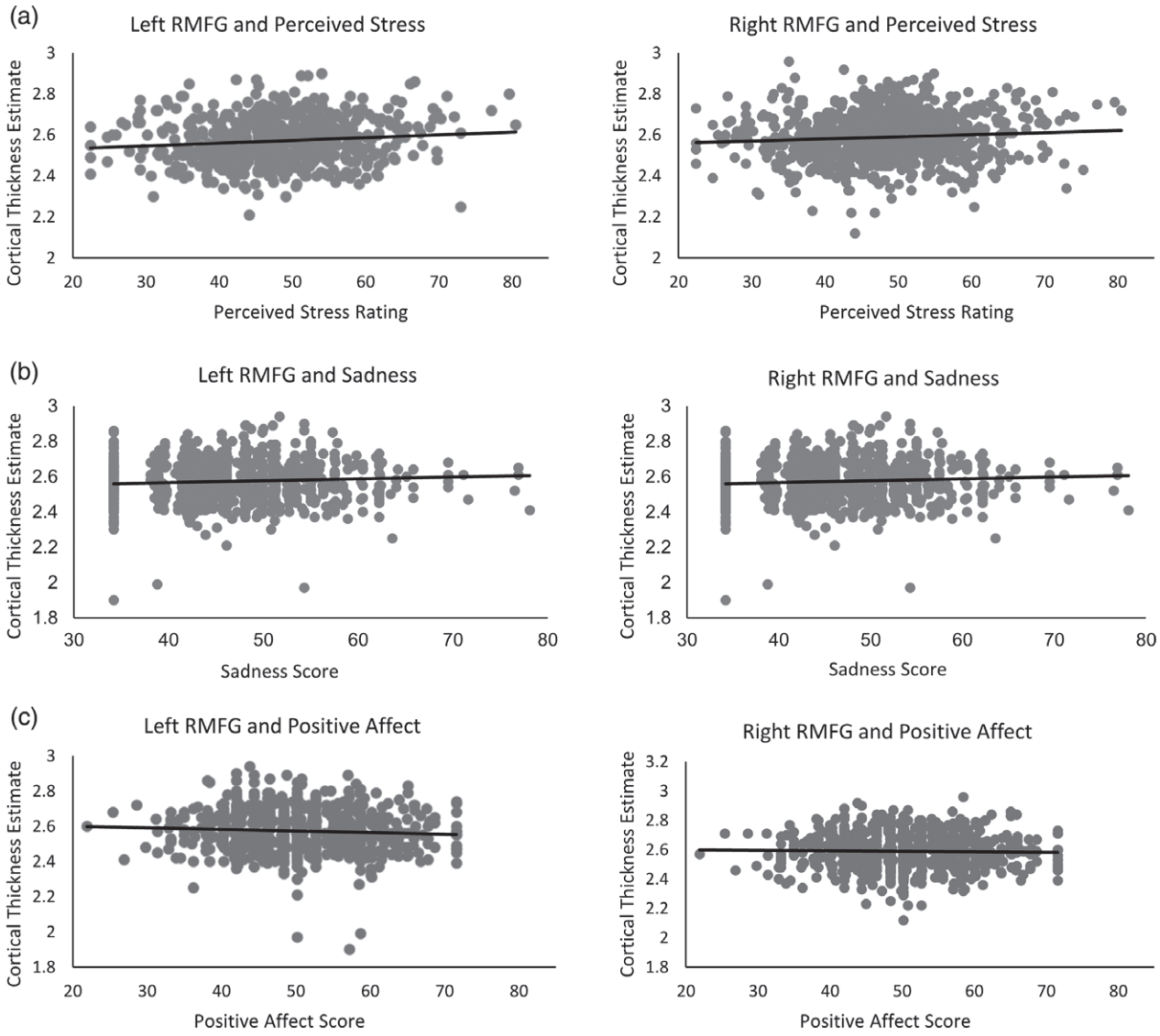

Figure 1: Bilateral RMFG thickness is associated with perceived stress, positive affect, and sadness. Graphs depict winsorized data points but do not represent covariate adjustment.

families with 5 siblings; and 3.02 ± 2.57 years for families with 6 siblings. Each participant provided informed written consent prior to participation in accord with the guidelines of the Washington University in St Louis Institutional Review Board and received $400 remuneration, as well as additional winnings ($5) and travel expenses. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Self-report scales

Perceived stress was assessed using the 10-item Perceived Stress Scale (PSS) from the National Institutes of Health (NIH) toolbox (NIH TB; www.nihtoolbox.org; Gershon *et al.* 2013). The PSS (Cohen & Williamson 1988) is a commonly used measure of stress perception that is heritable (Bogdan & Pizzagalli 2009; Federenko *et al.* 2006) and has been associated with stress hormones, illness and physiological responses (Cohen & Janicki-Deverts 2012; Cohen *et al.* 1993; Ebrecht *et al.* 2004). Sadness was assessed using the NIH TB Sadness Survey, which is comprised of 27 items from a depression item bank within the Patient Reported Outcome Measurement Information System (PROMIS) that shows strong convergent validity with other measures of depression (Pilkonis *et al.* 2014). Positive affect was assessed via 34 items from the Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Crawford & Henry 2004) measuring higher-order positive affect, or the extent to which an individual feels pleasurable engagement with the environment (Watson & Clark 1994). While positive affect is not a direct depressive symptom measure, low positive affect is similar to the concept of anhedonia (Crawford & Henry 2004) and has been reported to be specifically associated with depression (i.e. not anxiety; Jolly *et al.* 1994); furthermore, positive affect as measured by the PANAS is typically negatively correlated with measures of anheodnia (Tuohy & McVey 2008).

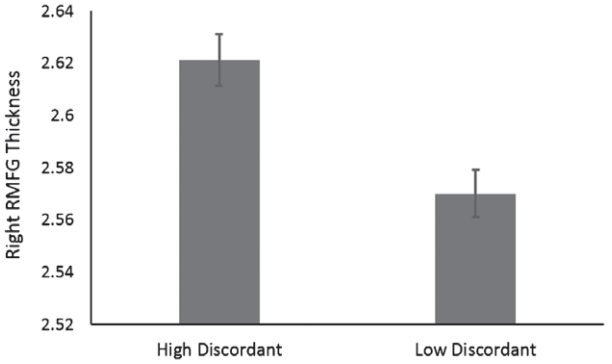

Figure 2: RMFG cortical thickness among siblings discordant for perceived stress. Among sibling pairs discordant for perceived stress, those who reported relatively high levels (≥ 0.5 SD units above the mean) had thicker right RMFG relative to those reporting relatively low levels (≤ 0.5 SD units below the mean; $P = 4 \times 10^{-7}$). Error bars depict SE of the mean.

Magnetic resonance imaging: acquisition and processing

High-resolution (0.7 mm isotropic voxels) 3D anatomical images, both T1-weighted (MPRAGE) and T2-weighted (T2-SPACE), were acquired using a customized Siemens 3 T scanner with a 32-channel head coil. The HCP acquisition and preprocessing details have been previously described in detail (Glasser *et al.* 2013; Van Essen *et al.* 2012). Briefly, relevant steps for this study from the HCP processing pipeline within Freesurfer v5.3.0 included: (1) spline-based down-sampling of the 0.7 mm T1 image to 1 mm; (2) intensity normalization and Talairach transformation; (3) skull registration; (4) skull stripping; (5) subcortical segmentation; (6) creation of white and pial surfaces and their refinement using the full (0.7 mm) resolution data; (7) refinement of the pial surface using the T2-SPACE scan to help exclude colony-stimulating factor and dura and (8) extraction of cortical thickness estimates for the RMFG from cortical parcellation that delineates subregions with high accuracy based on the Desikan atlas (see Fig. S1; Desikan *et al.* 2006).

Statistical analyses

Data were winsorized to ±3SD from the mean of each variable to minimize the influence of extreme outliers. Sequential Oligogenetic Linkage Analysis Routines (SOLAR; software version 7.6.4: 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, to account for the nonindependence of measures in related individuals, 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. In the *Results* section, Benjamini-Hochberg false discovery rate (FDR; Benjamini and Hochberg, 1995) corrected *P*-values are reported for each analysis to account for multiple testing of initial hypotheses (i.e. associations between both right and left RMFG cortical thickness with sadness, positive affect and perceived stress). We further entered depression-related phenotypes and perceived stress into a simultaneous regression to examine whether any of these constructs had unique associations with RMFG cortical thickness.

Next, we examined whether same-sex twin and non-twin sibling pairs discordant for perceived stress differed from each other on RMFG cortical thickness. These analyses examined whether PSS was associated with RMFG cortical thickness after accounting for same-sex sibling-shared genetic background and experience. If siblings discordant for perceived stress do not differ from one another with respect to RMFG cortical thickness, this would provide support for potential sibling shared predisposition effects that contribute to the relationship between perceived stress and RMFG cortical thickness. If, however, perceived stress-discordant siblings do differ from one another on RMFG cortical thickness, this would provide evidence in support of a person-specific, and potentially causal, relationship (i.e., factors unique to each sibling, that are present after accounting for sibling-shared genetic and environment background) between perceived stress and RMFG cortical thickness. Siblings were considered discordant if one sibling was at least 0.5 SDs above the sample mean for perceived stress ('high discordant'; PSS: 55.95 ± 5.62) while another was at least 0.5 SDs below ('low discordant'; PSS: 39.61 ± 5.15; mean $\Delta SD_{\text{discordant pairs}} \pm SD = 1.22 \pm 0.98$). This resulted in 127 nonindependent discordant pairings from 55 families with 1 sibling pair meeting criteria, as well as 33 families with 2, 3, or 4 sibling pairs meeting criteria. Discordancy analyses were conducted using linear mixed models using the Psych (Revelle 2015) and lme4 (Bates *et al.* 2015) packages in R to account for the multiple-sibling structure within families.

Additionally, we examined whether cortical thickness in other prefrontal regions previously linked to depression [rostral and caudal anterior cingulate (Reynolds *et al.* 2014; van Eijndhoven *et al.* 2013)] were associated with depression-related phenotypes or perceived stress.

Lastly, univariate heritability (h^2) analyses were performed on bilateral RMFG thickness estimates, perceived stress, positive affect and sadness. We examined contributions of overlapping genetic (ρ_g) or individual-specific environmental (ρ_e) factors within bivariate phenotypic associations that were stronger than $\beta > |0.20|$, to ensure that effects were large enough to warrant variance decomposition within our relatively modest sample size.

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) and were run with and without extreme outliers (i.e., prior to and after winsorizing), which did not affect our results. Analyses of cortical thickness also accounted for whole-brain cortical thickness. Because left-handed participants were included in our dataset, we also ran analyses with handedness as an additional covariate; results, including what was and was not significant with FDR correction, were unchanged by the inclusion of handedness in our models.

Results

Sample characteristics

There were no significant zero-order associations between covariates (i.e. age, sex, zygosity, ethnicity) and bilateral RMFG thickness, depression-related phenotypes (i.e. positive affect, sadness), or perceived stress (all Ps > 0.3460), with the exception of whole brain cortical thickness, which was positively correlated with left ($r = 0.1998$, $P = 2 \times 10^{-8}$) and right ($r = 0.2590$, $P = 3 \times 10^{-13}$) RMFG cortical thickness. No variables showed evidence of significant skew (perceived stress: $m = 48.30 \pm 9.11$, skew = 0.12; positive affect: $m = 50.04 \pm 7.87$, skew = 0.10; sadness: $m = 46.42 \pm 8.02$, skew = 0.45; left RMFG thickness: $m = 2.57 \pm 0.12$, skew = −0.33; right RMFG thickness: $m = 2.59 \pm 0.11$, skew = 0.05).

RMFG, perceived stress and depression-related phenotypes

Bilateral RMFG cortical thickness was positively associated with perceived stress (*PSS*: left: $\beta = 0.1120$, $r^2 = 0.0125$, $P = 0.0017$, p-fdr = 0.0051; right: $\beta = 0.1141$, $r^2 = 0.0130$, $P = 0.0013$, p-fdr = 0.0051; Fig. 1a) as well as sadness (left:

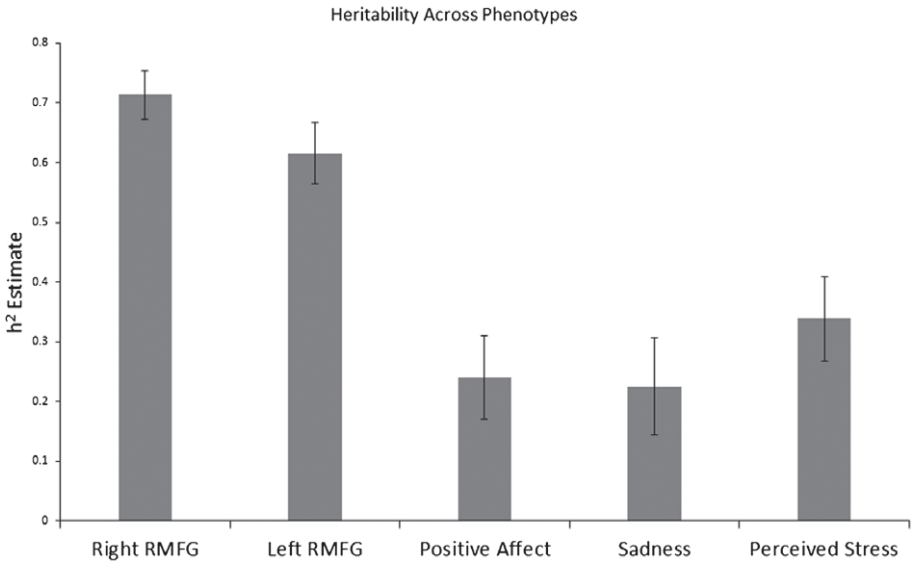

Figure 3: Heritability of phenotypes. Heritability estimates: right RMFG thickness = 71.34%, left RMFG thickness = 61.56%, positive affect = 23.96%, sadness = 22.44%, perceived stress = 33.85%. * = significant at $P < 0.05$. Household effects (i.e. living with the same biological mother) were used to test for shared/rearing environment and were found to be nonsignificant ($P > 0.05$ across all phenotypes). Thus, any remaining variance can be attributed to individual specific environmental factors or error.

$\beta = 0.0985$, $r^2 = 0.0097$, $P = 0.0196$, p-fdr = 0.0240; right: $\beta = 0.0832$, $r^2 = 0.0069$, $P = 0.0186$, p-fdr = 0.0240; Fig. 1b). Positive affect was negatively coupled with left RMFG thickness ($\beta = -0.0824$, $r^2 = 0.0070$, $P = 0.0053$, p-fdr = 0.0106) but was not significantly related to right RMFG cortical thickness ($\beta = -0.0463$, $r^2 = 0.0021$, $P = 0.1900$, p-fdr = 0.1900; Fig. 1c; see Table S1). A simultaneous regression examined whether our variables of interest (i.e. perceived stress, sadness, positive affect) are uniquely associated with variability in RMFG cortical thickness. In this model, perceived stress was uniquely associated with right RMFG cortical thickness (right: $\beta = 0.0828$, $\Delta r^2 = 0.0069$, $P = 0.0190$; left: $\beta = 0.0604$, $\Delta r^2 = 0.0036$, $P = 0.0868$), while associations with sadness and positive affect were not significant (all Ps > 0.3796; Table S2). Notably, other regions in which cortical thickness has been previously associated with depression (i.e. rostral and caudal anterior cingulate cortex) were not significantly associated with depression-related phenotypes or perceived stress (all Ps > 0.1180; Table S3).

Perceived stress discordancy

Because perceived stress remained a unique predictor of right RMFG cortical thickness, even after accounting for depression-related phenotypes, we examined whether same-sex siblings (including MZ and DZ twin pairs as well as non-twin sibling pairs) discordant for perceived stress (see *Methods* section) differed from one another on RMFG cortical thickness. These analyses showed that siblings who reported high perceived stress (i.e. PSS: 55.95 ± 5.62; see *Methods* section) had increased right RMFG cortical thickness (2.6214 ± 0.11) relative to their discordant (i.e. PSS: 39.61 ± 5.15; see *Methods* section) sibling who reported low perceived stress [RMFG: 2.5702 ± 0.10; 95% bootstrapped confidence interval (CI): 0.015–0.034; $P = 4 \times 10^{-7}$; Fig. 2]. Significant results are also obtained when examining left RMFG cortical thickness (95% CI: 0.021–0.042; $P = 7.9 \times 10^{-9}$).

Heritability and sources of variance and covariance

Heritability estimates ranged from 22.44% (for sadness) to 71.34% (for right RMFG thickness; Fig. 3). Briefly, bilateral RMFG cortical thickness, perceived stress, sadness and positive affect were all significantly heritable. Bivariate genetic analyses showed significant genetic and environmental correlations among self-report variables and between right and left RMFG cortical thickness (Table 1). In short, all bivariate relationships among self-report variables had significant shared genetic and environmental contributions, with shared genetic effects being largest. Because the strength of association between RMFG cortical thickness and self-report measures was small (i.e. $\beta < |0.20|$), decomposition analyses were not conducted among these variables.

Discussion

We examined associations among depression-related phentoypes (i.e., sadness, positive affect), perceived stress and RMFG cortical thickness. We found that bilateral RMFG cortical thickness was positively associated with sadness and perceived stress and that left RMFG thickness was negatively associated with positive affect, although at relatively small effect sizes. Further, among siblings discordant for perceived stress, those with relatively high levels had thicker RMFG cortex. This suggests that the association between RMFG thickness and perceived stress remains after accounting for sibling-shared genetic background and experience, providing support for potential causation. Consistent with prior literature, depression-related phenotypes (Sullivan et al., 2000) and stress perception (Bogdan & Pizzagalli 2009; Federenko *et al.* 2006) were significantly heritable, and much like heritability estimates of average cortical thickness across the entire brain (Panizzon *et al.* 2009), RMFG cortical thickness was highly heritable. Further, we found that the correlation between self-report measures of depression-related phenotypes (i.e. sadness and low positive affect) 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 that perceived stress and depression-related phenotypes share common genetic, environmental and neural correlates, and that relatively increased RMFG cortical thickness may contribute to stress-related depressive symptomology.

Our results linking increased RMFG cortical thickness with depression-related phenotypes and perceived stress in a nonclinical sample are consistent with observations among depressed youth (Reynolds *et al.* 2014), adults experiencing their first depressive episode (Qiu *et al.* 2014; but see also: Peng *et al.* 2015), and trauma-exposed individuals (Lyoo *et al.* 2011). As the RMFG is involved in a host of executive functions – including mood and behavior regulation (Koenigs & Grafman 2009; Miller & Cohen 2001) – that are impaired in depression (Murrough *et al.* 2011), our findings bolster the putative role of RMFG structure in depression-related phenotypes. However, these results contrast with reports that unaffected individuals at familial risk for depression (Peterson *et al.* 2009) and those experiencing depression in later life (Mackin *et al.* 2013) have relatively thinner RMFG. Importantly, however, controlling for illness duration seems to abolish some significant structural differences between early- and late-onset depressed patients (Truong *et al.* 2013). One possibility that may explain these discrepant results is that increased cortical thickness is associated with first or early episodes of depression as well as nonclinical levels of depression and stress perception, which may transition to decreases in cortical thickness over time alongside the expression of recurrent depressive symptoms and/or stress generation (Liu & Alloy, 2010; Kendler & Gardner 2016). Notably, cortical thickness in other prefrontal regions previously associated with depression and/or stress exposure (i.e. rostral and caudal anterior cingulate cortex) showed no nominally significant associations with depression-related phenotypes or perceived stress in our study (all Ps > 0.118). While the lack of significance here may reflect specific relationships between RMFG cortical thickness, depression, and perceived stress, it is also possible that our general population sample was underpowered to detect differences in these other regions.

Due to its cross-sectional nature, the current study cannot inform whether individual differences in stress perception and depressive symptoms may precede and/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 depression-related phenotypes, as well as increased RMFG cortical thickness. Consistent with this proposition, increased RMFG thickness has been observed among disaster survivors following trauma exposure (i.e. after 1.42 years); additionally, greater thickness here predicted better recovery from PTSD, and thickness normalized (i.e. decreased) to the extent that symptoms remitted by 5-year follow-up (Lyoo *et al.* 2011). These results suggest trauma-dependent increases in RMFG cortical thickness, which resolve alongside psychological recovery. It is plausible that, within our sample, increased cortical thickness may reflect stress exposure and unresolved recovery, resulting in greater perceptions of stress as well as expression of depression-related phenotypes.

Alternatively, RMFG cortical thickness may serve as a preexisting vulnerability factor that influences stress perception and/or confers vulnerability to depression. In support of this explanation, increased DLPFC (including a region within the Desikan-atlas-defined RMFG ROI) gray-matter volume, a different structural metric than cortical thickness which was evaluated in our study, has 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). The relatively high heritability estimates of RMFG cortical thickness that we observe (Right RMFG: 71.34%; left RMFG: 61.56%) are consistent with this notion. However, other findings contradict this interpretation. First, we observed relatively increased cortical thickness among those reporting elevated perceived stress relative to their discordant sibling. Thus, these data suggest that these differences arise from individual specific genetic and/or environmental effects, and that sibling shared genetic and environmental factors are not predisposing in this manner. Other evidence also contradicts this interpretation, as relatively decreased cortical thickness in the DLPFC (including within the RMFG) in adolescent females 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 *et al.* 2015).

Consistent with a large and established prior literature (Polderman *et al.* 2015), heritability analyses suggest that phenotypic variation in perceived stress, depression-related phenotypes, and bilateral RMFG cortical thickness is, in part, attributable to genetic factors. The relatively high heritability estimates of bilateral RMFG cortical thickness (i.e. 61.56–71.34%) are at the upper end of heritability estimates in psychiatric phenotypes (Polderman *et al.* 2015) and consistent with estimates of average whole-brain cortical thickness (Panizzon *et al.* 2009). These findings suggest that RMFG cortical thickness may contribute to familial transmission of stress perception and depression risk. Furthermore, decomposition analyses suggest that the association between perceived stress and depression-related phenotypes is attributable to common sources of environmental (e.g. potentially stress) and genetic variation (e.g. potentially brain structure; Bogdan & Pizzagalli 2009).

It is important to consider study limitations when interpreting the present results. First, the study is cross-sectional, leaving uncertain both the underlying temporal nature of associations and their etiologic plausibility. Longitudinal work is needed to elucidate temporal effects, which would bolster confidence in the potential mechanisms underlying these associations (e.g. that perceived stress causes structural differences and/or that structural differences alter the perception of stress). Second, it is important to consider the limitations of large-scale studies assessing multiple phenotypes such as the HCP. To facilitate broad phenotypic coverage and

large samples, such generalist studies are often unable to provide comprehensive within-phenotype assessment. For example, in our study, we were limited by the lack of an explicit anhedonia measure and relied on a correlated measure of positive affect. Similarly, because the HCP did not measure trauma or stressful-life-event exposure, we are unable to ascertain whether associations between RMFG cortical thickness and perceived stress are attributable to heightened subjective perceptions of stress and/or heightened stress exposure that may lead to increased perception. Third, because this is a relatively healthy sample, it is unclear whether the results might generalize to clinical levels of depression and perceived stress. Indeed, such differences in sample makeup may underlie conflicting directional associations within the literature between RMFG cortical thickness and depression- and stress-related phenotypes (Peng *et al.* 2015; Peterson *et al.* 2009; Reynolds *et al.* 2014).

Importantly, the association between RMFG cortical thickness and self-reported phenotypes – including depression-related phenotypes and perceived stress – were small in magnitude (0.2–2.4% of variance explained), which prohibited our ability to evaluate shared genetic and environmental covariation across these phenotypes. One reason for these small effects may be our use of a relatively healthy community sample. Given prior reports linking both increased and decreased RMFG cortical thickness to depression and stress-related phenotypes, it is possible that heterogeneous presentations or correlates of depression and stress perception may have oppositional associations with RMFG cortical thickness that reduced our observed effect size. The large effects observed in our discordant sibling analyses that account for unmeasured sibling shared factors support this speculation. Further, prior reports of larger associations (Reynolds *et al.* 2014) between RMFG cortical thickness and depression as well as stress-related phenotypes have been observed in smaller patient or trauma-exposed samples (Reynolds *et al.* 2014; Peng *et al.* 2015; Qiu *et al.* 2014; depressed patient n ranging from 16–46). Such small samples, when combined with publication bias, may result in imprecise and enlarged effect size estimates. For example, a recent meta-analysis including over 17 000 individuals with major depressive disorder found that the effect size of the association between hippocampal volume and depression is small (i.e. 0.5% of variance explained) and less than half of what was found in a prior meta-analysis drawn from fewer participants ($n = 351$ patients; Schmaal *et al.* 2015; Videbech and Ravnkilde 2004). While such observations suggest that small studies of patients may have led to overestimated effects between brain structure and illness, it is also important to consider that large meta-analyses may also result in more heterogeneous patient groupings that diminish effect sizes.

These limitations notwithstanding, our study suggests that relatively increased RMFG cortical thickness is a common neural substrate of stress perception and depression-related phenotypes that may promote depression/stress vulnerability and/or result from such experience. Although our results suggest that RMFG cortical thickness is positively coupled with both depression-related phenotypes and stress perception, the effect of this association is small and presently would not be informative on an individual level in isolation regarding treatment or risk assessment. Notably, however, our discordancy analyses of perceived stress suggest that this association cannot be attributed to sibling shared genetic factors and familial environment (and indeed becomes much larger when accounting for these factors), providing support for a potential causal relationship between RMFG cortical thickness and perceived stress, although the directionality of causation cannot be determined.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Figure S1. Desikan atlas ROIs. The rostral middle frontal gyrus ROI, as defined by the Desikan Atlas (image reproduced with modification from Desikan *et al.* 2006).

Appendix S1. Independent regression statistics.