Neuroanatomical Correlates of Extraversion and Neuroticism

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Introversion/extraversion and neuroticism are 2 important and frequently studied dimensions of human personality. These dimensions describe individual differences in emotional responding across a range of situations and may contribute to a predisposition for psychiatric disorders. Recent neuroimaging research has begun to provide evidence that neuroticism and introversion/extraversion have specific functional and structural neural correlates. Previous studies in healthy adults have reported an association between neuroticism, introversion/extraversion, and the activity of the prefrontal cortex and amygdala. Studies of individuals with psychopathological states have also indicated that anatomic variations in these brain areas may relate to extraversion and neuroticism. The purpose of the present study was to examine selected structural correlates of neuroticism and extraversion in healthy subjects ($n = 28$) using neuroanatomic measures of the cerebral cortex and amygdala. We observed that the thickness of specific prefrontal cortex regions correlates with measures of extraversion and neuroticism. In contrast, no such correlations were observed for the volume of the amygdala. The results suggest that specific aspects of regional prefrontal anatomy are associated with specific personality traits.

Keywords: amygdala, emotion, human, magnetic resonance imaging, personality, prefrontal cortex

Introduction

Personality characteristics describe distinctive and recurrent patterns of thoughts, feelings, and actions that occur in response to particular situational demands (Mischel 2004). The Five-Factor Model (FFM) is perhaps the most influential model of human personality, reflecting over 4 decades of research by academic psychologists (Eysenck 1967; Gray 1970; John 1990; McCrae and Costa 1990; McCrae and John 1992; Costa and McCrae 2000). This model describes personality along the dimensions of extraversion, neuroticism, conscientiousness, agreeableness, and openness to experience. Each of these terms defines a dimension that is anchored by an opposite pole (e.g. the opposite pole of extraversion is introversion; the opposite of neuroticism is emotional stability). The FFM provides a convenient method for summarizing a wide range of human behaviors. Two of the dimensions, introversion/extraversion and neuroticism, are of particular interest because their brain bases might contribute to a predisposition toward mood and anxiety disorders (Rosenbaum and others 1991; Watson and Clark 1992; Costa and McCrae 1996; Biederman and others 2001; Khan and others 2005).

The introversion/extraversion dimension captures the social dimension of personality. Extraverts have a preference for seeking and engaging in social interactions, whereas introverts prefer to avoid social situations and tend to be reserved or socially awkward. Extraversion may also been characterized as a sensitivity to positive or pleasure cues in the environment (e.g., Larsen and Ketelaar 1991; McCrae and Costa 1991; Costa and McCrae 1992; Watson and Clark 1992; Izard and others 1993; Barrett and Pietromonaco 1997; Lucas and others 2000). Further, individuals who are high in extraversion are differentially sensitive to reward cues (Pickering and Gray 2001) and may have a propensity to experience positive affect (Lucas and others 2000; Lucas and Diener 2001).

Neuroticism is characterized as a pervasive sensitivity to negative or punishment cues in the environment (e.g., McCrae and Costa 1991; Wallace and others 1991; Costa and McCrae 1992; Watson and Clark 1992; Izard and others 1993). Individuals high in neuroticism automatically orient to novel situational cues (for reviews see Wallace and others 1991; Wallace and Newman 1997, 1998). They evaluate those cues for their personal significance, and display a sensitivity to punishment cues (Pickering and Gray 2001) like those present in negative social situations (Bolger and Schilling 1991; Bolger and Zuckerman 1995). Individuals who characterize themselves as high in neuroticism more readily assess situations as threatening than those who are low in neuroticism (Schneider 2004).

With the advent of modern functional neuroimaging techniques, increasing attention has been given to mapping the specific human brain regions associated with extraversion and neuroticism. In particular, functional neuroimaging studies indicate associations between extraversion and neuroticism in healthy individuals and the activities of the prefrontal cortex (PFC) and amygdala. For example, a positron emission tomography (PET) study assessing resting regional cerebral blood flow (rCBF) indicated that specific regions of the PFC were related to the extraversion/introversion dimension (Johnson and others 1999), with the lateral PFC having greater rCBF in individuals who describe themselves as introverts (i.e., low in extraversion), whereas the medial PFC (including the anterior cingulate) and amygdala had greater rCBF in those who described themselves as high in extraversion (i.e., extraverts). More recently, functional magnetic resonance imaging (fMRI) experiments have demonstrated that regions of the PFC and the amygdala exhibit differential responses to emotional stimuli in individuals who describe themselves as highly extraverted or neurotic (Canli and others 2001, 2002, 2004). In those studies, extraversion was

positively correlated with the activity of the lateral and medial PFC (including the cingulate gyrus) and the amygdala in response to viewing positive (vs. negative) stimuli. Neuroticism, in contrast, was positively correlated with the activity in the PFC when viewing negative (vs. positive) stimuli. Also of note, several studies examining other personality measures related to extraversion and neuroticism have found correlations with the activity of the lateral and ventromedial regions of the PFC (Zald and others 2002; Gusnard and others 2003; Gray and others 2005) and amygdala (Schwartz and others 2003).

There is some evidence that extraversion and neuroticism are associated with structural/anatomic variations in the PFC and amygdala in patient populations. Early studies of patients with gross brain lesions demonstrated that the structural integrity of the PFC and medial temporal lobe (including the amygdala) is important for the expression of personality to the extent that such lesions were observed to alter premorbid personality characteristics (e.g., Harlow 1848; Bingley 1958; O'Callaghan and Carroll 1982; Lhermitte 1986; Lhermitte and others 1986). More recently, anatomic methods used to study neurodegenerative disorders have demonstrated relationships between specific personality characteristics, such as neuroticism, and temporal lobe structures, including the amygdala (Gorno-Tempini and others 2004). Likewise, in disease states characterized by extreme variants of personality where gross brain structure is intact (e.g., borderline personality disorder), anatomic studies have demonstrated diminished PFC and amygdala volumes (Schmahl and others 2003; Tebartz van Elst and others 2003) that may correlate with clinical symptoms (Schmahl and others 2003).

The purpose of this investigation is to examine whether extraversion and neuroticism are associated with anatomic variations in the PFC and amygdala in healthy young individuals. For these experiments, we employed 2 quantitative techniques to analyze high-resolution MRI data for anatomic correlates of extraversion and neuroticism. PFC thickness was studied using the relatively new technique of cortical surface analysis (Fischl and Dale 2000; Rosas and others 2002; Kuperberg and others 2003; Rauch and others 2004; Salat and others 2004), and amygdala volume was measured using manual anatomic methods (Wedig and others 2005; Wright and others 2006). Neuroticism has previously been found to correlate inversely with the ratio of total brain volume to intracranial volume (Knutson and others 2001), and measures of the tendency to psychopathology in healthy adults have been related to diminished total frontal lobe volume, particularly of the white matter (Matsui and others 2000). However, the present study examines the detailed structural correlates of personality derived from the FFM in specific regions of the cerebral cortex and in the amygdala of healthy young subjects. Understanding anatomic variations as they relate to extraversion and neuroticism may help put the functional findings in context and pave the way for studying microstructural influences (e.g. neuronal, interneuronal, glial and neuropil) on personality.

Materials and Methods

Subjects

Twenty-eight right-handed subjects (17 female, 11 male) were studied (age in years: mean = 24.0, SD = 2.9, range = 20–34). All subjects underwent cortical thickness analyses and a subset of these (n = 20; 12 females, 8 males; age mean = 24.0, SD = 2.1, range = 21–27) also underwent anatomic region of interest (ROI) analysis of the amygdala (see description later). Subjects were recruited from the local area using advertisements. Written informed consent was obtained from each subject. The study was approved and conducted in accordance with guidelines established by the Partners Human Research Committee. Routine screening assessments were used to rule out the presence of neurological, medical, psychiatric conditions (including personality disorders), and contraindications to MRI. All subjects also underwent the Structured Clinical Interview for DSM-IV (American Psychiatric Association 1994) to confirm the absence of DSM-IV Axis I diagnoses (First and others 1995), and were required to be free of psychoactive medications.

All subjects completed the NEO Five-Factor Inventory (FFI) (Costa and McCrae 1992) from which extraversion and neuroticism T-scores were calculated from gender-specific normative data to control for effects of gender on the T-score. These T-scores were used as the main variable of interest: 1) to control for the known effects of gender on the NEO measures by normalizing males to the male population data mean and female to the female population mean, 2) to facilitate an assessment of the extent to which the sample in question deviates from the normative population sample, and 3) to enhance the ability to generalize the results relative to the normative population data. We also calculated T-scores for openness, agreeableness, and conscientiousness and used these as well as raw scores in some analyses as described later.

As the FFM has been used to assess for personality disorders and has good agreement with DSM-IV and International Classification of Diseases, 10th ed., personality disorder criteria (Brieger and others 2000; Lynam and Widiger 2001; Miller and others 2001, 2005), we examined our NEO FFI data for any patterns suggestive of personality disorders. The factors most closely related to personality disorder are high neuroticism, low agreeableness, and high or low extraversion. None of our subjects had neuroticism scores that were more than 1.5 SD above or below the mean, extraversion scores that were more than 1.7 SD below the mean, or agreeableness scores that were more than 1.8 SD below the mean. This suggests a low likelihood of personality disorder (including paranoid, schizotypal, schizoid, antisocial, histrionic, narcissistic, obsessive-compulsive, borderline, avoidant, or dependent) in this sample. One subject had an extraversion score that was = 2.4 SD above the mean (T-score = 74). High extraversion is a criterion for histrionic personality disorders, but this subject had a low neuroticism score (T-score = 35, 1.3 SD below the mean). Because high neuroticism is also a criterion for histrionic personality disorder, this reduces the likelihood that such a disorder was present in this subject. Nevertheless, we assessed the effects of excluding this subject from the analyses. Because these analyses demonstrated no difference in the overall significance of our findings in the cortex or amygdala, the subject was included in the analyses described later.

Imaging

All subjects underwent structural brain imaging using a Sonata 1.5 T whole-body imaging device (Siemens Medical Systems, Iselin, NJ) with a 3-axis gradient head coil. Head movement was restricted using expandable foam cushions. After an automated scout image was acquired, 2 high-resolution 3-D MPRAGE sequences (time repetition/ echo time/flip angle = 7.25 ms/3 ms/7°) with an in-plane resolution of 1.3 mm and 1 mm slice thickness were collected. The acquisition parameters were empirically optimized to increase gray/white and gray/cerebrospinal fluid contrast.

Cortical Thickness Measurement

These methods have been previously described in detail (Rauch and others 2004; see also Rosas and others 2002; Kuperberg and others 2003; Salat and others 2004). The 2 high-resolution structural scans for each participant were motion corrected and averaged to create a single volume with a high signal-to-noise ratio. The resulting averaged volume was used to segment cerebral white matter (Dale and others 1999) and to estimate the gray/white interface. Topological defects in the gray/ white estimate were corrected (Fischl and others 2001), and this gray/ white estimate was used as the starting point for a deformable surface algorithm designed to find the pial surface with submillimeter precision (Fischl and Dale 2000). The entire cortical surface in each individual subject was then visually inspected and any inaccuracies in segmentation were manually corrected.

Cortical thickness measurements were obtained by reconstructing representations of the gray/white matter boundary (Dale and others 1999) and the cortical surface and then calculating the distance between those surfaces at each of approximately 160 000 points (per hemisphere) across the cortical mantle (software and complete documentation is available at http://www.nmr.mgh.harvard.edu/freesurfer). For each subject, thickness measures across the cortex were computed by finding the point on the gray-white boundary surface that was closest to a given point on the estimated pial surface (and vice versa) and averaging between these 2 values (Fischl and Dale 2000). The accuracy of the thickness measures derived from this technique has been previously validated by direct comparisons with manual measures on postmortem brains (Rosas and others 2002) and on MRI data (Kuperberg and others 2003).

The surface representing the gray-white border was "inflated" (Fischl, Sereno and Dale 1999), differences among individuals in the depth of gyri–sulci were normalized, and each subject's reconstructed brain was then morphed and registered to an average spherical surface representation that optimally aligned sulcal and gyral features across subjects (Fischl, Sereno and Dale 1999; Fischl, Sereno, and others 1999). This spherical morphing procedure was used to construct the cortical thickness correlation brain maps. Thickness measures were then mapped on the inflated surface of each participant's reconstructed brain (Fischl, Sereno and Dale 1999). This procedure allows visualization of data across the entire cortical surface (i.e., both the gyri and sulci) without interference from cortical folding. The data were smoothed on the surface tessellation using an iterative nearest-neighbor averaging procedure. One hundred iterations were applied, which is equivalent to applying a 2-dimensional Gaussian smoothing kernel along the cortical surface with a full-width/half-maximum of 18.4 mm. Data were then resampled for participants into a common spherical coordinate system (Fischl, Sereno, and others 1999). The procedure provides accurate matching of morphologically homologous cortical locations among participants on the basis of each individual's anatomy, while minimizing geometric distortion, resulting in a mean measure of cortical thickness for each group at each point on the reconstructed surface. The data were also linearly transformed so that approximate Talairach coordinates could be derived at each point on the surface (Fischl and others 2002). In this study, Talairach coordinates (Talairach and Tournoux 1988) are included to allow comparisons with other studies, although the localization of significant correlations were based principally on the regional anatomy as displayed on the cortical surface in the spherical coordinate system.

Statistical Analysis

Statistical surface maps were generated by computing 2 separate general linear models for the effects of neuroticism or extraversion T-scores on cortical thickness at each point. Similar maps were also generated for openness, agreeableness, and conscientiousness T-scores. For the initial analyses only the effects of T-scores on cortical thickness were assessed. For covariate analyses, gender and age were used entered in the model as external regressors to control for their effects. Parallel analyses were performed for raw scores as well. Our a priori hypothesis was that differences would be observed within the PFC. Given their approximate surface area (average of male and female for both PFC combined = 5×10^4 mm^2; Pakkenberg and Gundersen 1997) and the degree of surface smoothing applied (yielding a resolution element of 337 mm^2), we selected a threshold of $P < 0.00031$ (2 tailed). This corresponds to a threshold of $P < 0.05$, Bonferroni corrected for the number of multiple comparisons within the entire PFC (L + R). For all areas outside the PFC a threshold of $P < 0.00013$ was used, reflecting a Bonferonni correction for the number of comparisons on this surface area (1.25×10^5 mm^2; Pakkenberg and Gundersen 1997). For our analyses of the other 3 personality factors (openness, agreeableness, and conscientiousness), we did not have specific a priori hypotheses and therefore our corrected threshold of significance was $P < 0.00003$ based on the entire cortical surface and on examination of 3 factors.

Once sites with significant effects were identified as described above, a ROI-based approach was used. For these analyses, thickness measures for each subject were obtained at the location corresponding to the coordinates of the peak P value on the group maps (see Figs. 1–3). These

thickness measures were then plotted against individual subject T-scores on a scattergram and fitted with a linear regression line. Pearson's product moment correlation coefficients (r values) and associated P values (via a correlation Z-test) were then calculated. This ROI-based approach was used primarily to display the individual subject data and obtain correlation coefficients. To test for significant differences in the laterality of our findings, a similar ROI-based approach was used, whereby matching points in the left and right hemisphere were compared by calculating the r values at each site, using a Fisher r-to-Z transformation and then examining for significant hemispheric differences using the test of differences (Cohen J and Cohen P 1983).

In addition, to our main whole-brain analyses as described above, we performed separate whole-cortical thickness analysis using gender and age as covariates in our general linear model. The effects of using raw extraversion and neuroticism scores were also assessed. Where notable differences between the statistical maps were found, further analyses (whole brain and ROI based) were performed to investigate the sources of these differences. Finally, for completeness, we also present the results for openness, agreeableness, conscientiousness and neuroticism T-scores.

Amygdala Volumetric Analysis and Correlations

The amygdala was manually traced on each individual subjects' motion corrected, averaged high-resolution 3-D image (e.g. see Fig. 4A,B). Tracings were performed by a technician who was blind to the results of the individual personality measures. As in earlier studies (Wedig and others 2005; Wright and others 2006), boundaries of the amygdala were defined using the Watson criteria, with the modifications suggested by Brierley and others (2002). The point at which lateral sulcus closes to form the endorhinal sulcus was used to define the anterior border of the amygdala. The posterior portion of the mamillary bodies was used to define the posterior-most border of the amygdala. The alveus and temporal horn of the lateral ventricle served to distinguish the amygdala from the hippocampus along its anterior–posterior extent. The optic tract and the white matter of the temporal lobe served as the medial boundaries. Measurements of the medial amygdala included the uncus, but the entorhinal cortex inferior to the uncal notch was excluded. The inferior horn of the lateral ventricle and adjacent white matter, including that of the temporal stem, were used to define the lateral and inferior boundaries. The superior boundary was defined by the line between the endorhinal sulcus (anteriorly) or optic tract (posteriorly) and the inferior portion of the circular sulcus of the insula. Amygdala volumes and the 2 personality measures were plotted on scattergrams with a regression line, and correlation r and P values were calculated. To assess the reliability of the procedure a second trained technician (E.F.) traced a random sample of 10 amygdala volumes and these results were compared with those traced by the primary rater (M.M.W.). We then calculated the intraclass correlation and reliability coefficients using a one-way random effects model. The single-rater intraclass coefficient (ICC) was 0.89 ($F = 17.0$, $P = 0.0001$), placing our tracing procedure in the highly reliable range (i.e., ICC $\geq$ 0.81; see Shrout and Fleiss 1979; Goncharova and others 2001).

For our amygdala volume–extraversion and neuroticism correlations, a statistical threshold of $P < 0.025$ (2 tailed) was used as a Bonferroni correction to examine the right and left amygdala. Males and females were also analyzed separately as were the effects using raw extraversion and neuroticism scores. The effects of openness, agreeableness, and conscientiousness were also evaluated, and as these 3 factors were not a priori contrasts additional multiple comparison corrects were made, yielding a threshold of $P < 0.0083$.

As amygdala volumes are known to vary with head size, we also performed our analyses using an amygdala volume corrected for estimated intracranial volume. To calculate estimated total intracranial volume (eTIV), we used an automated atlas-based method that has been validated against manual intracranial volume measures (Buckner and others 2004). The template atlas consisted of a combined young-and-old target previously generated from a representative sample of young ($n = 10$), middle-aged ($n = 10$), older ($n = 10$), and demented ($n = 10$) adults (data kindly provided by Dr Randy L. Buckner). By performing a linear registration between each subject's data and the atlas (Fischl and others 2002), a scaling factor was derived and then used to calculate
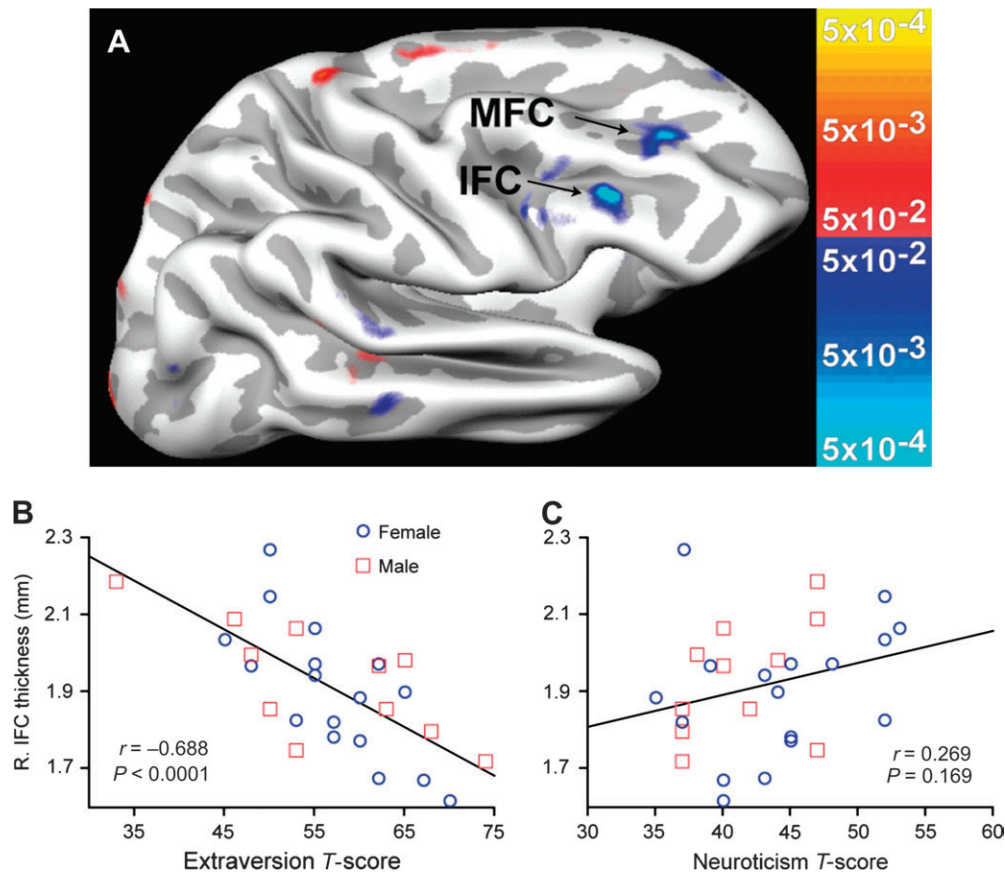
Figure 1. Significant correlations of cortical thickness and extraversion in the lateral prefrontal cortex. (*A*) Colorized statistical map superimposed upon a partially inflated group average cortical surface. The lateral aspect the right hemisphere is shown. Significant inverse correlations of cortical thickness with extraversion were found in the IFC. A similar trend effect was present in the middle frontal cortex (MFC). Dark gray regions are sulci, and light gray regions are gyri. Colorized scale bars show the *P* value for positive (red-yellow) and negative (blue) correlations. (*B*) Scatter plot and regression line demonstrating a significant inverse correlation between IFC thickness and extraversion. These values were extracted from the peak surface point of the IFG shown in *A*. (*C*) Scatter plot and regression line from the same IFG site in *A*. No significant correlation between IFC thickness and neuroticism is present.

eTIV. For correction of the effects of head size, amygdala volumes were divided by eTIV and then multiplied by 100%. These corrected volumes were then examined for correlations with extraversion, neuroticism, and the other personality measures.

Results

Personality Self-Report Characteristics

The descriptive statistics for this sample (n = 28) of FFM *T*-scores was as follows: extraversion: mean = 56.6, SD = 8.9, range, 33–74; neuroticism: mean = 43.1, SD = 5.3, range, 35–53; openness: mean = 62.9, SD = 7.8, range, 48–75; agreeableness: mean = 49.0, SD = 9.1, range, 35–65; conscientiousness: mean = 45.9, SD = 10.4, range, 27–67. Of note, extraversion was inversely correlated with neuroticism ($r = -0.401$, $P = 0.034$) and positively correlated with openness ($r = 0.368$, $P = 0.054$) and agreeableness ($r = 0.330$, $P = 0.086$) at trend statistical levels. There were no other significant correlations between the measures (all $|r| < 0.3$, $P > 0.2$).

Correlations with Extraversion and Cerebral Cortex Thickness

Whole brain surface–based analyses revealed a significant (peak *P* value = 0.000052) inverse correlation between cortical thickness and extraversion *T*-scores in the right inferior frontal cortex (IFC, approximate Brodmann area [BA] 45 and Talairach coordinates: $x = 44$, $y = 23$, $z = 20$). Adjacent to the right IFC locus, a separate peak in the middle frontal cortex (approximate BA 9 and Talairach coordinates: $x = 27$, $y = 36$, $z = 27$) exhibited a similar relationship between extraversion and cortical thickness but was just above the significance threshold (peak *P* value = 0.00063). Scatter plots based on ROI analysis at the right IFC peak confirmed the highly significant inverse relationship between cortical thickness and extraversion (Fig. 1*B*). Neuroticism scores were not significantly correlated with cortical thickness at this site (Fig. 1*C*). Further, when we compared the results from the right IFC with those from the corresponding point in the left IFC, there was a statistically significant hemispheric difference between the correlations (right vs. left IFC: $r = -0.688$ vs. $r = -0.013$, $Z = 2.94$, $P = 0.0033$).

To assess the contributions of variance due to age and gender we performed additional whole-brain analyses treating these variables as covariates. These results were of lower significance but also met our corrected statistical significance threshold (peak *P* value = 0.00018; IFC, BA 45; Talairach coordinates: $x = 44$, $y = 23$, $z = 20$), indicating that age and gender did not account for the relationship between cortical thickness and introversion/extraversion. A similar result was also obtained when age and gender were used as covariates for the analyses
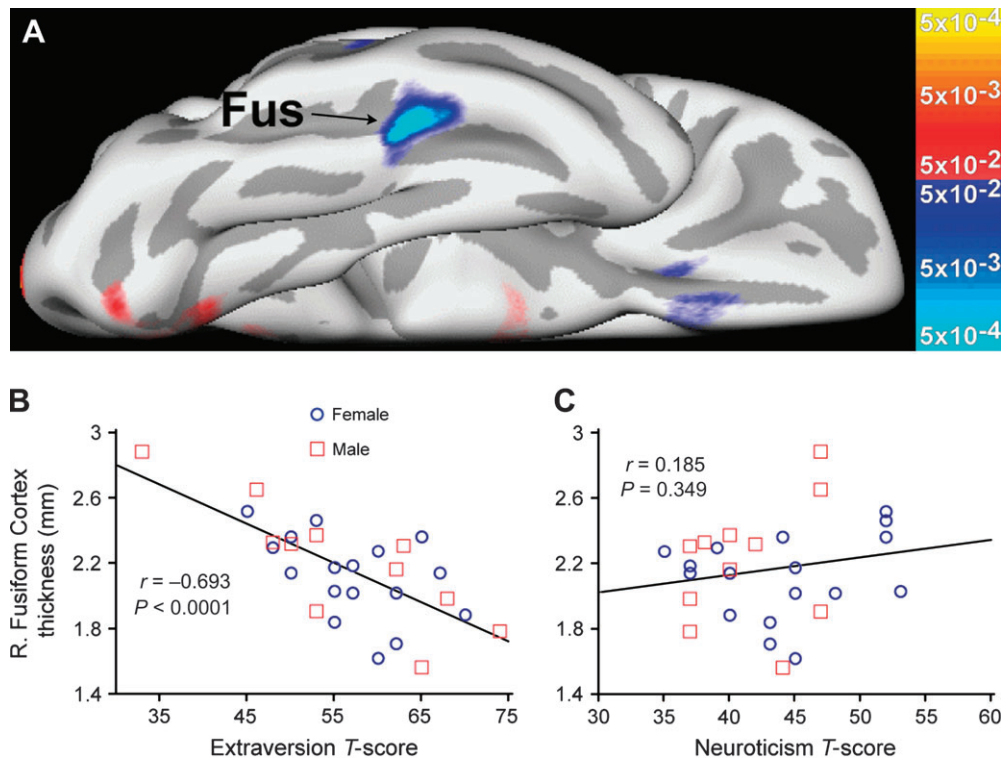
Figure 2. Significant correlations of cortical thickness and extraversion in the fusiform cortex. (*A*) Colorized statistical map superimposed upon a partially inflated group average cortical surface. The inferior aspect of the right hemisphere is shown. Significant inverse correlations of cortical thickness with extraversion were found in the fusiform cortex (Fus). Dark gray regions are sulci, and light gray regions are gyri. Colorized scale bars show the *P* value for positive (red-yellow) and negative (blue) correlations. (*B*) Scatter plot and regression line demonstrating a significant inverse correlation between fusiform thickness and extraversion. These values were extracted from the peak surface point of the fusiform cortex shown in *A*. (*C*) Scatter plot and regression line from the same fusiform site in *A*. No significant correlation between fusiform thickness and neuroticism is present.

examining the relation between cortical thickness and extraversion raw scores. The same peak localization in the IFC was found, and both analyses yielded a similar pattern of statistically significant results (without covariates, *P* = 0.000048; with covariates, *P* = 0.00018). Only one region outside the PFC (our a priori ROI) met the corrected statistical threshold for the remaining cerebral cortex, showing a significant relationship with extraversion. Specifically, individuals high in extraversion demonstrated less cortical thickness in the right fusiform cortex (approximate BA 20 and Talairach coordinates: x = 45, y = −20, z = −26). Whole brain surface–based analyses revealed a significant (peak *P* value = 0.000044) inverse correlation between right fusiform thickness and extraversion *T*-scores (Fig. 2*B*). Neuroticism scores were not significantly correlated with cortical thickness at this site (Fig. 2*C*). When the correlations from the right and left fusiform were compared, a statistically significant difference between hemispheres was present (right vs. left fusiform: *r* = −0.693 vs. *r* = −0.168, *Z* = 2.42, *P* = 0.016).

The link between extraversion *T*-scores and thickness of the right fusiform cortex was maintained even after controlling for age and gender as covariates (peak *P* = 0.00016; BA 20; Talairach coordinates: x = 45, y = −20, z = −26), indicating again that age and gender did not account for the relationship between introversion/extraversion and the thickness of the right fusiform cortex. When the raw scores were analyzed, similar and significant results were obtained at the same peak coordinates (without covariates, *P* = 0.000041; with covariates, *P* = 0.00018).

Correlations with Neuroticism and Cerebral Cortex Thickness

Whole brain surface–based analyses indicated significant inverse correlation (peak *P* value = 0.00019) between cortical thickness and neuroticism *T*-scores in the anterior portions of the left orbitofrontal cortex (OFC, approximate BA 10/11, Talairach coordinates x = −12, y = 66, z = 0), with extension into the most anterior parts of the medial frontal cortex (Fig. 3*A*). Scatter plots confirmed the significant negative correlation between thickness of the OFC and neuroticism (Fig. 3*B*) but demonstrated no such relationship with extraversion (Fig. 3*C*). When the correlations at identical points in the left and right OFC were compared, a statistically significant difference between hemispheres was present (left vs. right OFC: *r* = −0.648 vs. *r* = 0.185, *Z* = 3.39, *P* = 0.0007).

No other regions of the right or left hemisphere demonstrated significant correlations between cortical thickness and neuroticism.

Whole-brain analyses treating age and gender as covariates also yielded a generally similar pattern in terms of the direction and localization of the effect in the left OFC (BA 10/11, Talairach coordinates x = −12, y = 66, z = 0). However, the result became a statistically nonsignificant trend (*P* = 0.0011) based on the corrected threshold (*P* < 0.00031), suggesting influences of age or gender at this anatomic locus. Analyses of raw scores confirmed this effect (without covariates, *P* = 0.00013; with covariates, *P* = 0.0012).

The use of age alone as a covariate did not significantly affect the results of the whole-brain analyses for neuroticism (as
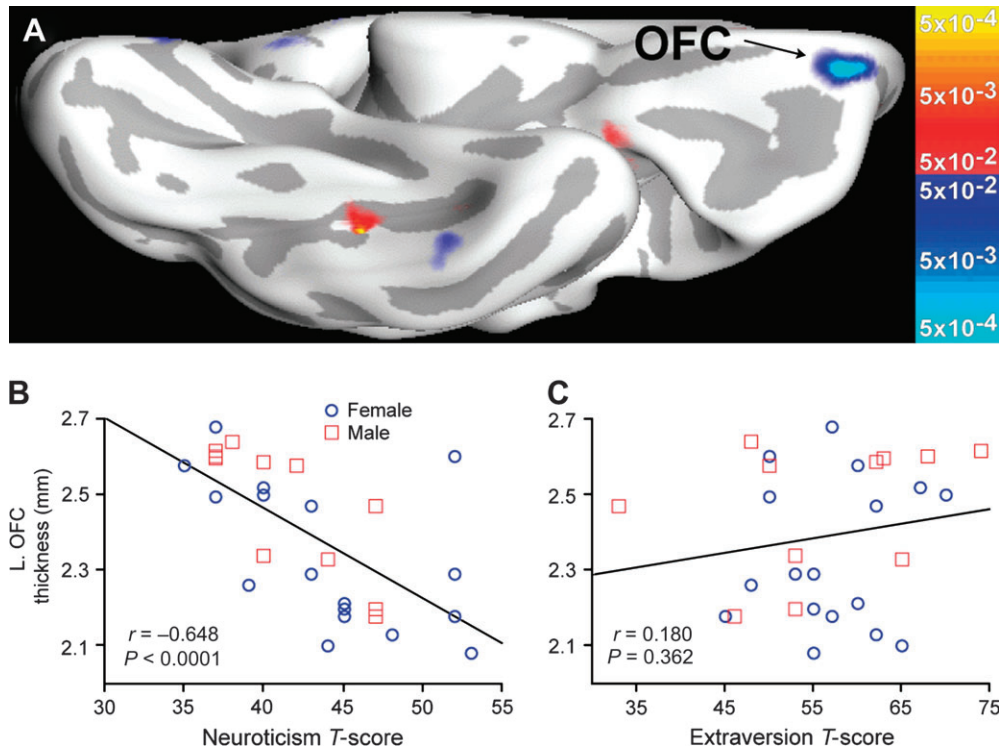
Figure 3. Significant correlations of cortical thickness and neuroticism in the orbitofrontal cortex. (*A*) Colorized statistical map superimposed upon a partially inflated group average cortical surface. The inferior aspect of the left hemisphere is shown. Significant inverse correlations of cortical thickness with neuroticism were found in the anterior OFC, with extension into the most anterior and inferior portion of the frontal lobe. Dark gray regions are sulci, and light gray regions are gyri. Colorized scale bars show the *P* value for positive (red-yellow) and negative (blue) correlations. A region of the left fusiform gyrus was positively correlated with neuroticism, but this did not reach statistical significance. (*B*) Scatter plot and regression line demonstrating a significant inverse correlation between OCF thickness and neuroticism. These values were extracted from the peak surface point of the OFC shown in *A*. (*C*) Scatter plot and regression line from the same OFC site in *A* demonstrating no significant correlation between OFC thickness and extraversion.

would be expected given the restricted age range of the subjects in this study). This indicated that the effect was primarily due to gender. We therefore assessed the contributions of gender with ROI-based analyses. For this purpose, thickness measures at the peak left OFC locus were used to calculate correlation coefficients for each group separately using their *T*-scores (see Fig. 3). These calculations indicated that the relationship between cortical thickness and neuroticism was stronger in males than females (male: $r = -0.796$, $P = 0.0021$; female: $r = -0.551$, $P = 0.02$). However, the difference between these correlations was not significant ($Z = 1.05$, $P = 0.29$). Although larger groups will be necessary to fully investigate the effects of gender, the moderating effects of the covariates analysis may be due to a relatively thinner OFC in females that is not fully accounted for by higher neuroticisms scores (Fig. 3*B*). Neither group demonstrated effects for extraversion at this locus (male: $r = 0.327$, $P = 0.37$; female: $r = 0.129$, $P = 0.63$).

Absence of Correlations with Extraversion, Neuroticism, and Amygdala Volume

No significant correlations between right or left amygdala volume and extraversion were found (Fig. 4*C,D*). Likewise there were no significant correlations with right or left amygdala volume and neuroticism (Fig. 4*E,F*). Similar results were obtained when males and females were analyzed separately, when the amygdala volumes were corrected for eTIVs and when raw personality scores were used (all $|r| < 0.4$, $P > 0.3$ with or without corrected amygdala volumes).

Anatomic Relationships of the Other NEO Factors: Openness, Agreeableness, and Conscientiousness

Although extraversion and neuroticism were the main factors of interest for this study, we examined the relationships between cortical thickness and amygdala volumes and the other 3 NEO factors (openness, agreeableness, and conscientiousness). No significant correlations were found between these 3 factors and cortical thickness or the eTIV-corrected right and left amygdala volumes.

Discussion

Earlier studies have demonstrated associations with neuroticism and the ratio of whole-brain volume to intracranial volume (Knutson and others 2001) and between the tendency to psychopathology and diminished total frontal lobe volume (Matsui and others 2000). Also, in the elderly, volume changes in temporal, parietal, and frontal cortices have been shown to relate to measures of self-transcendence (Kaasinen and others 2005). The present study demonstrates selective structural correlates of personality, using the FFM, in selective regions of the cerebral cortex of healthy young subjects. Specifically, the results show that individuals who described themselves as extraverted have a thinner cortical gray matter ribbon in regions of the right inferior PFC and fusiform gyrus, compared with those describing themselves as introverted. Individuals who described themselves as more neurotic have a thinner cortex mantle in anterior regions of the left OFC. The difference in hemispheric lateralization for all these cortical effects was
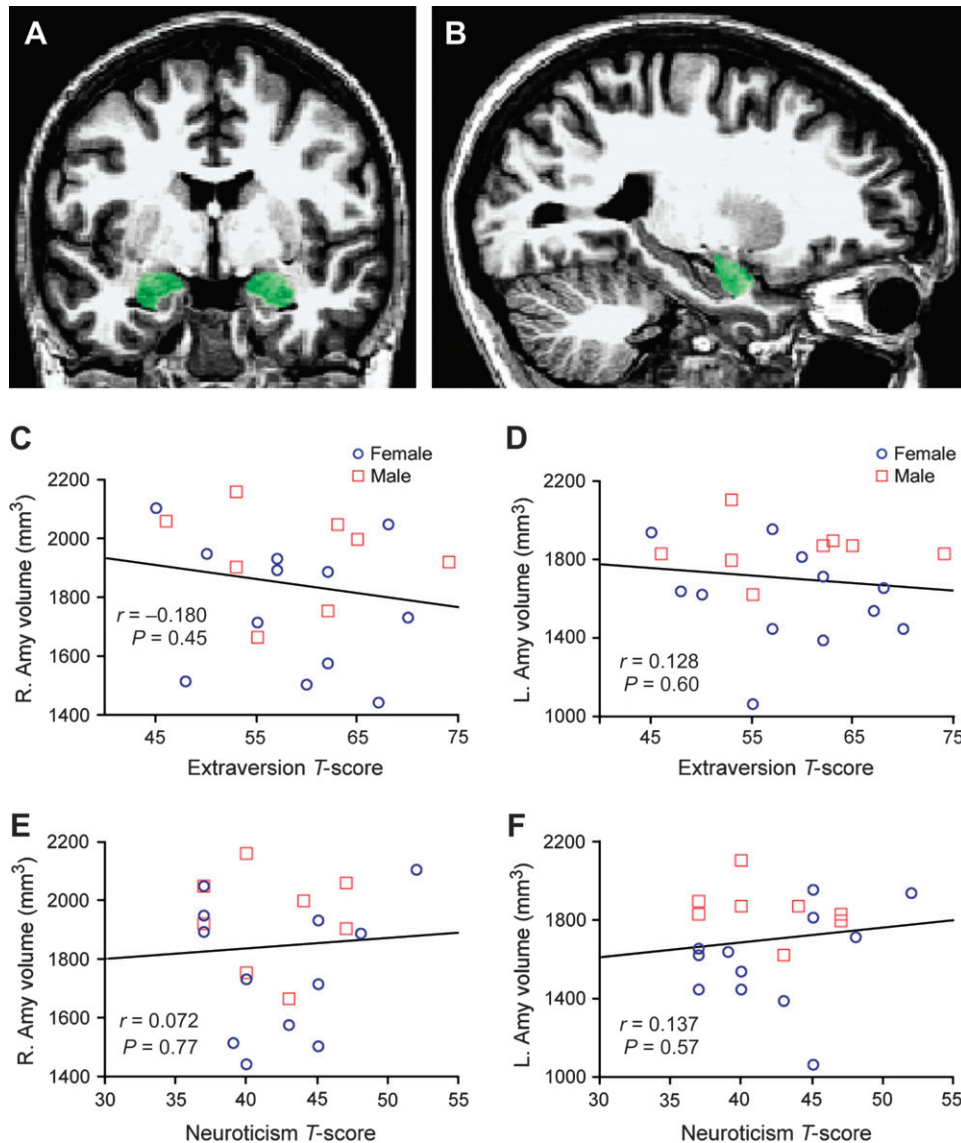
Figure 4. Absence of correlations between neuroticism and extraversion and amygdala volume. High-resolution coronal (*A*) and saggital (*B*) T_1-weighted image demonstrating right and left amygdala tracings in a 25-year-old female. Scatter plots and regression lines demonstrating the absence of a significant correlation between extraversion and right (*C*) or left (*D*) amygdala volumes, or neuroticism and right (*E*) or left (*F*) amygdala volumes.

significant. Neither extraversion nor neuroticism was associated with right or left amygdala volumes. These results held, regardless of whether normalized (*T*-scores) or raw personality scores were used in the analyses, and were replicated when age and gender were used at covariates in the general linear model, except for the OFC–neuroticism relationship, which became a statistically nonsignificant trend due to moderating effects of gender.

Possible Significance of Regional Thickness Cortical Correlations with Extraversion

Two core aspects of extraversion are positive affect and a tendency to seek out and participate in social situations (Lucas and Diener 2001; Lucas and Baird 2004). Both these aspects of extraversion are related to hemispheric asymmetries in the PFC, as greater left-sided versus right-sided anterior electrophysiological activity is associated with positive affect and approach behaviors (Tomarken and others 1990, 1992; Davidson 2004a, 2004b). Furthermore, individuals with the heritable introversion-related trait of inhibited temperament (Matheny 1990; Robinson and others 1992)—characterized by timidity with unfamiliar people, objects, and situations—have greater right versus left frontal electrophysiological activity (Davidson 1994, 2003; Fox and others 1995; Calkins and others 1996). Thus, the current cortical thickness findings may represent a structural correlate of these previously described personality-related electrophysiological asymmetries in the PFC. Such electrophysiological changes have been postulated to relate to decreased social inhibition and increased approach behavior in extraverts, as well as to social wariness and avoidance in introverts. The relative regional thinning in the left lateral PFC could represent a neural substrate for the diminished social inhibition found in extraversion, whereas thickening in the area may relate to the social avoidance seen in introverts. Likewise, these anatomic correlates may relate to the

disinhibition and sensation seeking that is associated with extraversion (Bone and Montgomery 1970; Paisey and Mangan 1980; Izard and others 1993).

To the extent that size may reflect metabolic activity, our finding that extraverts have thinner right IFC is also consistent with an earlier PET study demonstrating decreased resting blood flow in the lateral PFC of extraverts relative to introverts (Johnson and others 1999), and with a recent fMRI study showing that behavioral approach sensitivity is inversely related to the activity of the IFC during a working memory task (Gray and others 2005). Similarly, our findings are consistent with the 2 most influential biological models of personality, both of which hold that introverts have higher cortical activity than extraverts, especially in the frontal lobes (Eysenck 1967; Gray 1970).

We also found that extraversion was inversely related to the thickness in the right fusiform gyrus. This finding is at least partly consistent with the recent work of Onitsuka and others (2005), who reported a positive correlation between extraversion and fusiform volume schizophrenics but not control participants. Although not statistically significant in their healthy control cohort, the relationship between extraversion and the volume in the fusiform gyrus in this group was negative and therefore consistent with that observed in the present study. The resolution of our point-by-point thickness analysis may have allowed us to observe a statistically significant relation between fusiform structural measures and extraversion scores. The peak of our thickness–extraversion relationship corresponded to the most anterior portions of the "posterior fusiform" ROI of Onitsuka and others (2005). Their volume measurements may therefore have combined the portion of the fusiform volume containing the peak effect, as well as other regions of the fusiform where the effect was weaker, thereby resulting in an overall nonsignificant effect.

Possible Significance of Regional Cortical Thickness Correlations with Neuroticism

Although we initially found a statistically significant correlation between neuroticism and the thickness of the OFC across all subjects, these effects became nonsignificant trends when gender was included as a covariate. Therefore, the findings with respect to the relationship between neuroticism and OFC thickness must be considered tentative. One apparent reason for the gender effects relates to the observation that the females have lower mean cortical thickness in the OFC than males, but the presence of accordingly higher neuroticism scores in females—which would be expected if this relationship were explained purely by gender differences—was not found. The relatively reduced size of the OFC in women versus men has been previously described (Goldstein and others 2001). This may cause a floor effect or reduce variability in cortical thickness for the range of neuroticism scores in females decreasing the power to detect differences in females alone or in groups containing both genders.

Although the covariates analysis for neuroticism and cortical thickness did not meet our strict Bonferroni-corrected threshold, the correlation r values for both males and female are of moderate size and likely of biological relevance. Support for the biological plausibility of this finding includes observations that a core feature of neuroticism is excessive sensitivity to negative cues in the environment (Bolger and Schilling 1991; Mroczek

and Almeida 2004) and that the structural integrity of the OFC is important in for emotional reappraisal (Rolls and others 1994; Rolls 2004). Moreover, atrophy or thinning of the OFC is present in disease states with symptoms indicative of dysfunction of emotional processing and regulation (e.g., Sanfilipo and others 2000; Chemerinski and others 2002; Kuperberg and others 2003; Ballmaier and others 2004; Choi and others 2004; Kang and others 2004; Lacerda and others 2004; Pujol and others 2004). Future studies of larger cohorts of men and women will be necessary to better understand the effects of gender on the relationship between neuroticism and OFC thickness.

Neuroticism, Extraversion, and Amygdala Anatomy

Although the activity of the amygdala has been associated with measures of extraversion (Johnson and others 1999; Canli and others 2002), as well as with uninhibited and inhibited temperaments (Schwartz and others 2003), we did not find any significant relationship between amygdala volume and the 2 personality factors when we examined all subjects, or when males and females were separately assessed. There are several potential reasons for our failure to find a link between extraversion, neuroticism, and amygdala volumes. For example, whole amygdala volume measurements may obscure variations at the level of individual subnuclei, such as the central nucleus or basolateral complex, that seem to have dissociable roles in emotional processing (Parkinson and others 2000; Whalen and others 2001; Holland and Gallagher 2003; Corbit and Balleine 2005). Future studies examining the volume of specific amygdala subregions would be of interest in this regard, either via new anatomic boundary delineation protocols, very high resolution MRI, or with voxelwise techniques such as voxel-based morphometry, though this latter technique may not allow accurate comparisons in regions where individual variations in structural boundaries are present. Alternatively, it is possible that the differences in activation observed in previous studies may not directly relate to macroscopic structural differences.

Personality, Anatomy, and Directions of Effect

As discussed above, it may be that the cortical regions identified in this study play a specific role in determining some aspects of the complex behaviors associated with extraversion and neuroticism. Conversely, it is possible that the anatomic effects are secondary to the individual behavioral patterns that lead to the particular personality characterizations. In this case, the effects of being extraverted or neurotic might lead to specific alterations in regional brain anatomy via different lifetime experiences (i.e., more or less social contact, or more or less negative affect experienced) as has been previously described (Kolb and others 2003; Als and others 2004). Longitudinal studies on the effects of aging, development, and the predilection for psychopathology as they relate to the structural correlates of extraversion and neuroticism could help resolve such issues.

Functional Implications of Structural Differences and Other Caveats

The current findings suggest that variation in regional cortical thickness may have behavioral significance for the expression of the personality dimensions descriptively captured in extraversion and possibly neuroticism. It should be noted, however, that

decreased size (thickness or volume) is not necessarily related to diminished activation in a given structure. For example, the lateral PFC has been implicated as a neural correlate of extraversion in fMRI activation studies (Canli and others 2001, 2002), with greater activation to positive stimuli (vs. negative stimuli) in those with higher extraversion scores. It is currently uncertain how the current findings of decreased thickness and earlier reports of decreased rCBF (Johnson and others 1999) in extraverts relate to those fMRI activation studies. It may be that the lower resting baseline, perhaps associated with cortical thinning, allows for a greater differential response to extraversion-relevant (i.e., positive) stimuli. Alternatively, if the thinning was due to fewer inhibitory interneurons or dendritic pruning related to enhanced processing efficiency, a smaller or thinner cortex could lead to increased activity. To fully characterize the relationship between structure and function as it relates to these personality measures, noninvasive techniques are needed that can distinguish among the difference structural compartments of the gray matter (neurons, interneurons, glia, and neuropil) that contribute to these measures of size (thickness and volume). Changes in these elements could lead to a variety of different effects on brain activity as it relates to measures such as extraversion or neuroticism. Until studies are performed in which direct comparisons can be made between the different gray matter compartments, metrics of activation, and measures of personality or disposition, several possible explanations for the finding discussed above should be considered.

Finally, although we ruled out Axis I disorders using a structured clinical interview, and our subjects were free of such disorders, one additional caveat of our study is that we did not formally rule out personality disorders using a structured interview for Axis II disorders. We did assess for extreme variations in personality scores on the NEO FFI and did not find patterns supportive of personality disorders. Nevertheless, such analyses of personality inventories may not be adequate to fully exclude the presence of DSM-IV Axis II personality disorders (Shedler and Westen 2004). Therefore, although our cohort was thoroughly screened for DSM-IV Axis I disorders, this cohort may more be representative of the general community as regards the presence of Axis II personality disorders.

Notes

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