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ORIGINAL ARTICLE

Heritable Variations in Gray Matter Concentration as a Potential Endophenotype for Psychopathic Traits

Fruhling V. Rijsdijsk, PhD; Essi Viding, PhD; Stéphane De Brito, PhD; Matteo Forgiarini, BSc; Andrea Mechelli, PhD; Alice P. Jones, PhD; Eamon McCrory, DClinPsych, PhD

Context: Genetic vulnerability to psychopathic traits is likely to also manifest at the neural level. We have recently reported increased gray matter concentration in several brain areas in boys with psychopathic traits.

Objective: To explore whether these gray matter concentration differences can be regarded as endophenotypes for psychopathic traits by (1) assessing their heritability and (2) examining the etiology of the cooccurrence of psychopathic traits and increased gray matter concentration.

Design: Community twin sample.

Setting: On-campus neuroimaging facility.

Patients or Other Participants: One hundred twenty-three male twins (56 monozygotic and 67 dizygotic individuals; mean age 11.55 years; range, 10-13 years).

Main Outcome Measures: We analyzed structural magnetic resonance imaging scans. Voxel-based morphometry analyses were used to obtain gray matter concentration values that were analyzed in a biometrical genetic twin model.

Results: Left posterior cingulate and right dorsal anterior cingulate gray matter concentrations were found to be the strongest endophenotype markers, with heritability estimates of 46% and 37%, respectively, and common genes explaining the phenotypic relationship between these regions and psychopathic traits. No significant heritabilities were found for several regions, including the right orbitofrontal cortex and insula.

Conclusions: These findings suggest that structural endophenotypes, in the form of variations in gray matter concentration, reflect genetic vulnerability for psychopathic traits. Specifically, gray matter concentration in the left posterior cingulate and right dorsal anterior cingulate, brain areas implicated in empathy, moral processing, and introspection, are potential candidate endophenotypes for psychopathic traits.

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A SUBGROUP OF CHILDREN with antisocial behavior also exhibit psychopathic traits, including lack of empathy and remorse, and are thought to be at risk for developing adult psychopathy.[1] Psychopathic traits show moderate to strong heritability[2] and antisocial behavior in combination with psychopathic traits is strongly heritable in childhood.[3,4] This genetic vulnerability is likely to be reflected at the neural level and we have recently demonstrated increased gray matter concentration (GMC), potentially reflecting delayed maturation, in several brain areas in boys with psychopathic traits.[5] The key regions where group differences were observed in our previous study included the left and right dorsal anterior cingulate cortex (dACC), left rostral anterior cingulate cortex, right orbitofrontal cortex, left cerebellum, left and right superior temporal gyrus, left parahippocampal gyrus (PHG), right insula, left posterior cingulate cortex (PCC), and left inferior temporal gyrus. These areas have been implicated in social cognition and moral processing and have also been shown to index psychopathy-related group differences in adult samples.[6,7]

Structural differences in select brain areas may represent potential endophenotype markers for psychopathic traits. The term *endophenotype* refers to a quantitative trait (or pathophysiological marker) that is proposed to reflect the pathway leading from genetic predisposition to psychiatric disorder.[8] Crucially, to establish whether variation in a specific brain structure can be regarded as a can-

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didate endophenotype, at least 3 requirements should be met: first, the endophenotype should be heritable; second, it should be reliably related to the disorder status; and third, it must share genetic variance with the disorder.[9]

Previous twin structural magnetic resonance imaging (sMRI) studies have, for the most part, focused on the heritability of more global indexes of gray matter, eg, gray matter volumes of different lobes.[10] One recent article by Schmitt and colleagues[11] has also analyzed the heritability of cortical thickness (an index closely related to GMC[12]) in several specific brain areas, including those implicated in psychopathy. Schmitt and colleagues reported modest to moderate heritability for cortical thickness in most brain areas. Despite these advances in understanding the relative importance of heritable and environmental influences on brain structure, little is known about the etiological relationship between brain morphology and specific disorders. Of particular interest here is whether common genetic influences can explain the association between psychopathic traits that we know are highly heritable and the observed differences in GMC associated with these traits.

The primary objective of this twin sMRI study is to investigate whether a set of brain regions, previously associated with psychopathic traits, meet the criteria as candidate endophenotypes for psychopathy. It is necessary to determine the relative importance of heritable and environmental influences on the GMC in these specific brain areas. Given that these regions have been implicated in the brain's social-cognitive and "moral" networks, an investigation of their GMC heritability is of considerable interest in its own right. Most importantly, it is necessary to formally quantify the extent of genetic overlap or the extent to which common genes drive the phenotypic relationship between psychopathic traits and those specific brain areas where the GMC appears heritable. To our knowledge, no previous twin multivariate model–fitting study has conducted such an analysis. By establishing heritability for regional GMC increases previously associated with psychopathic traits and quantifying the extent of common genetic influences, it will be possible to evaluate the degree to which these structural brain differences qualify as candidate endophenotypes for psychopathic traits.

METHODS

The study and recruitment procedure were approved by the Institute of Psychiatry and Maudsley Research Ethics Committee. Written informed consent was obtained from the parents and written assent was obtained from the children.

PARTICIPANT SCREENING AND RECRUITMENT

All twins were recruited from the Twins Early Development Study (TEDS), a community-based study of twins in England and Wales. All twins were free from official medical, neurological, or diagnosed psychiatric problems as reported by parents. The participants were included in the study based on behavioral ratings collected at 9 years of age. Combined parent and teacher ratings on the Strengths and Difficulties Questionnaire conduct problems[13] and the Antisocial Process Screening Device callous-unemotional[14] subscales were used to index conduct problems and core psychopathic features, respectively (the scores for conduct problems ranged from 0-8 and for callous-unemotional traits, from 1-11, for the entire scanning sample). The highest rating given by parent or teacher for each question was recorded in line with standard practice used for multiple raters in previous studies of psychopathic traits in children.[15] In line with our previous work,[3,4] children were rated as having elevated levels of psychopathic traits if they scored within the top 10% of the TEDS sample for both conduct problems (mean [SD] score, 4.88 [1.47]) and callous-unemotional traits (mean [SD] score, 7.77 [1.20]). The mean (SD) scores for the children scoring in the top 10% for both callous-unemotional traits and conduct problems in the entire TEDS sample were slightly higher (conduct problems: 5.87 [1.54]; callous-unemotional traits: 8.65 [1.08]). However, the scores of the children with psychopathic traits who took part in this study were beyond the abnormal cutoff for conduct problems and by definition (in the top 10%) were elevated for callous-unemotional traits. More importantly, we have already demonstrated structural brain differences in this group of children in a previous study.[5] The control children scored within the normal range (within 1 SD of the TEDS mean) for both conduct problems and callous-unemotional traits (mean [SD], conduct problems, 0.91 [0.95]; callous-unemotional traits, 3.49 [1.26]). Further sample details are provided in the "Use of Residualized Gray Matter Concentration Scores" section in the eSupplement (http://www.archgenpsychiatry.com).

One hundred thirty-eight male twins attended the scanning facility for this study. Only 130 underwent sMRI, and of these, 125 had sMRI scans of sufficient quality to be included in the analyses. The analyzed sample consisted of 6 monozygotic (MZ) pairs concordant for psychopathic traits, 11 MZ pairs discordant for psychopathic traits, 2 dizygotic (DZ) pairs concordant for psychopathic traits, 17 DZ pairs discordant for psychopathic traits, 14 MZ control pairs, and 16 DZ control pairs. Discordance was assigned when only 1 twin reached the top 10% criteria for both callous-unemotional traits and conduct problems. For callous-unemotional traits, concordant pairs had a mean (SD) difference score of 0.61 (0.49) and discordant pairs had a mean (SD) difference score of 2.58 (1.55) ($t_{66}=5.00$; $P<.001$). For conduct problems, concordant pairs had a mean (SD) difference score of 0.63 (1.02) and discordant pairs had a mean (SD) difference score of 2.64 (1.51) ($t_{66}=5.01$; $P<.001$). Zygosity was assigned using DNA testing in 80% of the sample. For those twin pairs who did not provide DNA samples, parental ratings of physical similarity were used to determine the zygosity. This method assigns zygosity with more than 95% accuracy as validated by genotyping.[16]

sMRI ACQUISITION PARAMETERS

Structural brain images were acquired using a General Electric Signa 3.0-T Excite II MRI scanner (GE Medical Systems, Milwaukee, Wisconsin) at the Centre for Neuroimaging Science, Institute of Psychiatry, London, England. A high-resolution, 3-dimensional T1-weighted data set was acquired using an inversion recovery prepared spoiled gradient echo sequence. Imaging parameters were repetition time = 8 milliseconds; echo time = 2.9 milliseconds; inversion time = 450 milliseconds; and excitation flip angle = 20°. The in-plane matrix size was 256 × 192 over a 280 × 210 mm field of view, reconstructed to 256 × 256 over 280 × 280 mm. In-plane pixel size was thus 1.09375 × 1.09375 mm. Two hundred through-plane partitions (each 1.1 mm thick) were collected, with 2 partitions being discarded at each end of the imaging volume to minimize wraparound artifacts. Partial k-

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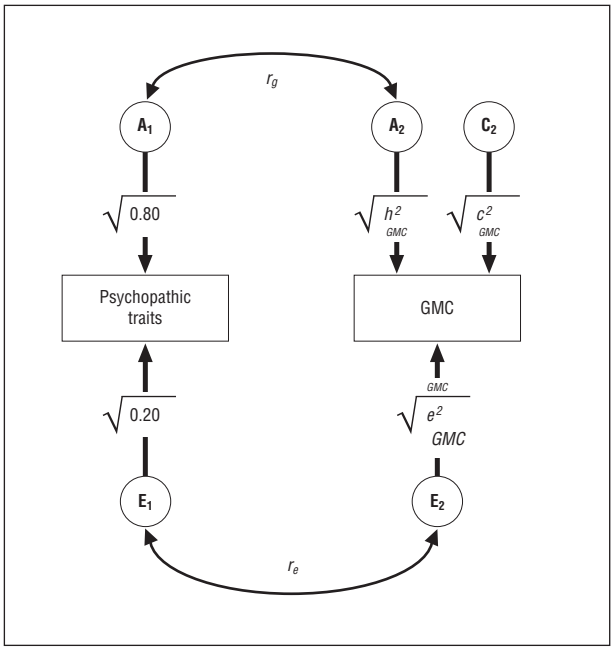

Figure 1. The correlated-factors solution of the bivariate genetic model. The additive genetic (A_1 and A_2) and nonshared environmental (E_1 and E_2) factors on psychopathic traits and gray matter concentration (GMC) are correlated (r_g, r_e). The paths from A_1 to psychopathic traits and A_2 to GMC are the square roots of their heritabilities (only estimated for GMC). Part of the phenotypic correlation (r_{ph}) due to genetic effects is calculated by $\sqrt{0.80} \times r_g \times \sqrt{h^2_{GMC}}$ and that due to environmental effects, by $\sqrt{0.20} \times r_e \times \sqrt{e^2_{GMC}}$. The C_1 factor is omitted since c^2 for psychopathic traits is fixed to zero (in line with Viding et al[3]).

space coverage (0.75 number of excitations) was used. The scanning time was 6 minutes.

IMAGE PROCESSING AND ANALYSIS

Structural images were preprocessed using optimized voxel-based morphometry implemented with Statistical Parametric Mapping software (SPM 5; Wellcome Trust Centre for Neuroimaging, London, England) running under MATLAB 7.0 (The MathWorks, Natick, Massachusetts). Voxel-based morphometry is a whole-brain, unbiased, semiautomated technique for characterizing regional cerebral differences in structural magnetic resonance images.[17,18] In voxel-based morphometry, concentration analyses of gray matter compare the proportion of gray matter with all tissue types within a specific region.[18] To ensure appropriate processing of the input images, we first proceeded to construct custom reference data for segmentation and spatial normalization.[19] The creation of the customized probability maps generally followed the approach taken by Good et al[19] and is described in detail in our prior work[5,18] (eSupplement, "Creation of the Customized Probability Maps" section). The normalization step was implemented without modulation to assess GMC. All images were written out to $1 \times 1 \times 1$-mm isotropic voxel in standard anatomical space (Montreal Neurological Institute, http://www.bic.mni.mcgill.ca/brainweb). The resulting gray matter images were convolved with an 8-mm full-width-at-half-maximum gaussian kernel. Smoothing is required to compensate for the inexact nature of spatial normalization and to maximize the chance that regional effects are expressed at a spatial scale where homologies in structural anatomy exist over subjects. After smoothing, each voxel represents the local average amount of gray or white matter in the region, the size of which is defined by the smoothing kernel.

Regional densities were extracted from 10 "primary" regions of interest (ROIs) in each subject using a sphere with a 3-mm radius centered on the group-difference maxima between boys with psychopathic traits and control boys from De Brito et al.[5] These were the left dACC (x=−7, y=2, z=40), right dACC (x=10, y=29, z=22), right orbitofrontal cortex (x=3, y=20, z=−19), left cerebellum (x=−2, y=−69, z=−26), left superior temporal gyrus (x=−22, y=1, z=−39), right superior temporal gyrus (x=27, y=15, z=−34; x=58, y=−24, z=−1), left PHG (x=−16, y=−34, z=−9), right insula (x=44, y=−8, z=12), left PCC (x=−8, y=−59, z=8), and left inferior temporal gyrus (x=−47, y=−10, z=−37). An additional constraint stipulated that a chosen ROI had to be implicated in at least 1 previous sMRI study of adult psychopathy.[6,7] All coordinates were anatomically validated using the standard T1-weighted template in Montreal Neurological Institute stereotactic space.

Further, "secondary" ROIs included areas that had been implicated in our previous study,[5] but not in adult studies of psychopathy, potentially representing developmentally specific endophenotypes. These were the left inferior parietal lobule (x=−40, y=−38, z=46), left PCC (x=−1, y=−25, z=39), left precuneus (x=−19, y=−66, z=45), left posterior hippocampus (x=−28, y=−38, z=−4), left PHG (x=−21, y=−38, z=−22), left rostral anterior cingulate cortex (x=−3, y=42, z=12), left superior parietal lobule (x=−29, y=−53, z=59; x=−38, y=−64, z=59), right calcarine sulcus (x=1, y=−76, z=−1), right cuneus (x=3, y=−84, z=25), right intraparietal sulcus (x=27, y=−63, z=43), right PCG (x=49, y=−8, z=23), right superior frontal gyrus (x=17, y=16, z=45), and right uncus (x=17, y=−3, z=−29).

TWIN MODEL–FITTING ANALYSIS

The program Mx[20] was used to obtain maximum likelihood polychoric correlations as well as parameter estimates for the genetic model. Models were fitted directly to the GMC values extracted from our ROIs, which allowed incorporation of incomplete observations. The bivariate genetic model uses the data of MZ and DZ twin pairs ascertained on psychopathic traits to estimate (1) the heritability of the GMC at the ROIs and (2) the extent to which the overlap between psychopathic traits and GMC is due to genetic (eg, the same neurodevelopmental genes) and/or nonshared environmental effects (eg, obstetric complications, accidents). In this applied bivariate model, additive genetic (A), shared environmental (C), and nonshared (individual-specific) environmental (E) effects are specified such that factors A_1 and E_1 influence both psychopathic traits and GMC, inducing a familial covariance that is due to either A or E. Shared environmental effects for psychopathic traits were fixed at zero (see explanation later). Factors A_2, C_2, and E_2 are specific to the GMC in each ROI. The standardized solution of this model is the correlated-factors model (**Figure 1**). In this model, the paths from A_1 to psychopathic traits and A_2 to GMC are the square roots of their heritabilities. The correlation between A_1 and A_2 is the genetic correlation (r_g) between psychopathic traits and GMC, denoting the extent to which the same genetic factors influence the 2 measures. The part of the phenotypic correlation (r_{ph}) between psychopathic traits and GMC due to genetic effects is calculated by $(\sqrt{h^2_{\text{Psychopathic Traits}}} \times r_g \times \sqrt{h^2_{GMC}})$. Exactly the same estimates can be obtained for nonshared environment (E).

For the genetic models, a goodness-of-fit index (χ^2 value) was obtained by computing the difference in likelihoods (and *df*) between the genetic model and a saturated model (with maximum number of parameters). A χ^2 with a nonsignificant *P* value indicates a good fit. For the reported polychoric correlations (to enhance interpretability), a constrained model was used that produced 1 phenotypic correlation between each GMC and psy-

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chopathic traits; 1 MZ and 1 DZ twin correlation for the GMC, and 1 MZ and 1 DZ cross-trait cross-twin correlation (between psychopathic traits and the GMC).

ASCERTAINMENT CORRECTION

Selected samples are more efficient and can be more powerful when studying low-prevalence disorders,[21] but model-fitting analyses will usually require an ascertainment correction. However, since selection is through psychopathic traits and blind to GMC values, the required ascertainment correction will depend only on the model for psychopathic traits. The need for this ascertainment correction is, therefore, obviated by fixing the model parameters for psychopathic traits (variance components and prevalence) to constant values. We used the point estimates (h^2=0.80, c^2=0, e^2=0.20) from our earlier twin study[3] and fixed the prevalence to 0.7% in line with estimates from the literature.[22] The variance components for GMC as well as their relationship with psychopathic traits were free parameters to be estimated from the data. This model has been validated and successfully applied to schizophrenia and bipolar illness in analyses that included brain volumes[23]; event-related potential data[24,25]; and neuropsychological measures.[26] The genetic variance of the selection variable (psychopathic traits) is additive and fixed. Thus, to estimate a (broad-sense) genetic overlap with each GMC, their genetic variance was also modeled as additive effects (even if the twin correlations indicated dominance genetic effects, ie, DZ correlations, which are much smaller than half the MZ correlations).

Before model fitting, the effects of full-scale IQ, hyperactivity, and total gray matter were regressed out from the raw GMC scores and the residuals categorized in 5 equal classes to enable analyses with the dichotomous psychopathic traits variable (eTable 1).

RESULTS

To demonstrate GMC differences as a potential endophenotype for psychopathic traits, the following conditions had to be satisfied. First, the individual differences in GMC in each ROI had to be at least partly heritable, because GMC increases associated with psychopathic traits could also stem from entirely environmental sources. Second, although we had previously demonstrated group differences between typically developing children and children with psychopathic traits in the ROIs selected for the current analyses,[5] we required a reliable phenotypic relationship between GMC and psychopathic traits (coded categorically for absence or presence of such traits) across the whole sample to satisfy the criterion of a robust relationship between the endophenotype and phenotype measures. Finally, to qualify as a potential endophenotype, at least some of the covariance between GMC and psychopathic traits had to be driven by common genetic influences. All this information is derived from the constrained correlational models and the bivariate ACE models (additive genetic [A], shared environmental [C], and nonshared environmental [E] effects) (each GMC with psychopathy). With the exception of the left cerebellum, left PHG, and left PCC ($\Delta\chi^2_{11}$=20.5, 23.7, and 23.9; P=.04, .01, and .01, respectively), all bivariate models fitted the data well (ie, the data are consistent with the predictions of the model). We now present in turn the heritabilities of the GMCs and their genetic overlap with psychopathy.

HERITABILITIES OF GMCs

Table 1 shows the maximum likelihood correlations of the constrained correlational model of each primary GMC and psychopathic traits. Significant MZ correlations in the presence of lower DZ correlations indicate GMCs that show some heritable variance: right dACC, left cerebellum, left PHG, and left PCC. The heritability estimates for these ROIs are 0.37, 0.33, 0.23, and 0.46, respectively, with those for the left cerebellum and left PHG including zero, despite significant MZ correlations (Table 1). This is likely to reflect our sample size constraints necessitated by magnetic resonance imaging. Given the significant MZ correlations and previous data from other groups reporting significant heritability estimates for these regions,[11] we further concentrate on reporting these 4 ROIs in our bivariate analyses as the most promising endophenotypes. Significant nonshared environmental estimates, ranging from 0.54 (left PCC) to 0.98 (inferior temporal gyrus), were obtained for all ROIs. In line with other studies,[11] shared environmental influences were not observed for any GMCs.

GENETIC OVERLAP: PSYCHOPATHIC TRAITS AND GMCs

Table 1 further shows that, of the potential endophenotypes, only the right dACC, left PHG, and left PCC have a significant positive phenotypic correlation with psychopathic traits: 0.21, 0.17, and 0.22, respectively. We discuss the dACC, left PHG, and left PCC in the subsequent bivariate analyses because they all showed heritable influences and a relationship with psychopathic traits. The genetic and environmental overlap with psychopathic traits is indicated by examining the MZ and DZ ratio of the cross-twin cross-trait correlations (**Table 2**, columns 1 and 2). A ratio of 2:1 would indicate that the phenotypic correlation is determined by a substantial proportion of overlapping additive genetic variance, and a ratio of 1:1 would indicate shared environmental effects. For the left PCC and right dACC, cross-twin cross-trait correlations with psychopathic traits indicated shared environmental influences, but it was not possible to estimate these in our model because the psychopathic trait estimates were fixed not to include shared environment. For the left PCC, the model fitting provided estimates of moderate overlap of genetic influences between psychopathic traits and GMC (R_g=0.42) (Table 2). These common genes appeared to drive the relationship between psychopathic traits and GMC, because the strength of the genetic contribution to phenotypic variance ($r_{ph\text{-}a}$) was in line with the phenotypic correlation. If we ignore the nonsignificant negative nonshared environmental overlap between psychopathic traits and GMC in the left PCC, this means that 100% of the estimated correlation is due to a genetic overlap. There was also moderate genetic overlap between psychopathic traits and GMC in the right dACC (R_g=0.37) (Table 2). Again, most (estimated 95%) of the phenotypic relationship between psychopathic traits and the right dACC GMC was accounted for by these common genes. The nonshared environment nonsignificantly con-

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Table 1. GMC Variance Component Estimates and MZ and DZ Twin Correlations Within GMCs and the Correlations Between Psychopathic Traits and GMCs[a]

GMC (x, y, z)	Estimate (95% CI)					Phenotypic Correlation With Psychopathic Traits (95% CI)
	MZ	DZ	h^2	c^2	e^2	
Right OFC (3, 20, –19)	0.12 (–0.34 to 0.52)	0.12 (–0.29 to 0.48)	0.11 (0 to 0.50)	0.02 (0 to 0.40)	0.87 (0.50 to 1)	0.16 (0 to 0.33)
Right dACC (10, 29, 22)	0.46 (0.06 to 0.72)[b]	0.00 (–0.35 to 0.36)	0.37 (0.01 to 0.67)[b]	0 (0 to 0.37)	0.63 (0.34 to 0.98)	0.21 (0.05 to 0.36)
Left dACC (–7, 2, 40)	0.14 (–0.36 to 0.55)	0.27 (–0.08 to 0.55)	0.01 (0 to 0.58)	0.23 (0 to 0.49)	0.76 (0.42 to 1)	0.11 (–0.05 to 0.26)
Left cerebellum (–2, –69, –26)	0.44 (0.06 to 0.70)[b]	0.25 (–0.17 to 0.57)	0.33 (0 to 0.68)	0.07 (0 to 0.51)	0.60 (0.32 to 0.92)	0.14 (–0.02 to 0.30)
Left STG (–22, 1, –39)	0.28 (–0.12 to 0.59)	0.25 (–0.18 to 0.58)	0.15 (0 to 0.59)	0.15 (0 to 0.51)	0.70 (0.41 to 1)	0.09 (–0.08 to 0.24)
Right STG (27, 15, –34)	0.22 (–0.23 to 0.58)	0.27 (–0.10 to 0.57)	0.01 (0 to 0.59)	0.24 (0 to 0.50)	0.74 (0.41 to 1)	0.04 (–0.12 to 0.20)
Right STG (58, –24, –1)	–0.26 (–0.61 to 0.20)	0.19 (–0.18 to 0.51)	0.01 (0 to 0.29)	0 (0 to 0)	0.99 (0.71 to 1)	0.05 (–0.11 to 0.20)
Left PHG (–16, –34, –9)	0.59 (0.18 to 0.80)[b]	–0.34 (–0.59 to 0.02)	0.23 (0 to 0.64)	0 (0 to 0.24)	0.77 (0.36 to 1)	0.17 (0.01 to 0.32)[b]
Right insula (44, –8, 12)	0.13 (–0.30 to 0.50)	0.48 (0.13 to 0.72)[b]	0.05 (0 to 0.51)	0.29 (0 to 0.53)	0.66 (0.42 to 0.94)	0.13 (–0.03 to 0.29)
Left PCC (–8, –59, 8)	0.64 (0.25 to 0.84)[b]	–0.03 (–0.36 to 0.32)	0.46 (0.03 to 0.77)[b]	0 (0 to 0.32)	0.54 (0.23 to 0.95)	0.22 (0.06 to 0.38)[b]
Left ITG (–47, –10, –37)	0.14 (–0.29 to 0.51)	–0.18 (–0.51 to 0.20)	0.03 (0 to 0.38)	0 (0 to .24)	0.98 (0.62 to 1)	0.01 (–0.14 to 0.16)

Abbreviations: CI, confidence interval; dACC, dorsal anterior cingulate cortex; DZ, dizygotic; GMC, gray matter concentration; ITG, inferior temporal gyrus; MZ, monozygotic; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; PHG, parahippocampal gyrus; STG, superior temporal gyrus.

[a] Additive genetic (h^2), shared (c^2), and nonshared (e^2) environmental estimates for GMCs estimated from the full bivariate ACE (additive genetic [A], shared environmental [C], and nonshared environmental [E] effects) genetic models. Fixed genetic models for psychopathic traits used $h^2 = 0.80$, $c^2 = 0$, and $e^2 = 0.20$. Fixed correlations for psychopathic traits used MZ = 0.80, DZ = 0.40, and prevalence fixed to 0.7% (estimates based on Blair et al[22] and Viding et al[3]).

[b] Significant estimates. The contribution of e^2 is always significant since it includes measurement error.

tributed to the phenotypic relationship. Finally, no genetic or environmental overlap between psychopathic traits and the left PHG GMC could be established. However, there was a trend of overlapping child-specific (nonshared) environmental influences that accounted for most of the phenotypic relationship. **Figure 2** illustrates the phenotypic group difference maxima for these 3 candidate endophenotype areas together with graphs displaying the proportion of phenotypic correlation between psychopathic traits and GMC driven by common genetic factors.

None of the secondary ROIs fulfilled endophenotype criteria. Heritability and phenotypic correlation data from these areas are presented in eTable 2.

COMMENT

The primary objective of this twin sMRI study was to investigate whether a set of brain regions previously associated with psychopathic traits met our criteria for candidate endophenotypes. We first investigated the relative contribution of heritable and environmental influence on the GMC in several brain structures identified in our earlier analysis of psychopathic traits.[5] Some of these areas had also been implicated in adult studies of psychopathy.[6,7] Then, given that we are aware of no twin studies to date that have provided a validation of potential structural brain endophenotypes for psychopathic traits, we used a multivariate twin model–fitting approach to formally quantify the extent of genetic overlap between psychopathic traits and GMC in those specific brain areas where GMC appeared heritable. Furthermore, we were able to investigate the extent to which common genes drive the phenotypic relationship between psychopathic traits and GMC.

In line with 1 previous article analyzing the heritability of cortical thickness in several specific brain areas in children,[11] we report heritability estimates of GMC ranging from zero to moderate. Consistent with Schmitt and colleagues,[11] we report moderate heritability in 2 locations of the cingulate gyrus (PCC and anterior cingulate cortex). The remainder of our reported heritability findings of GMC are not in good agreement with the Schmitt and colleagues cortical thickness study. We report no heritability for the superior temporal gyrus or orbitofrontal cortex, while the cortical thickness in these areas shows moderate heritability in the Schmitt et al study. Similarly, we report no heritability for the insula, but Schmitt and colleagues report a modest heritability estimate for cortical thickness in this region (although their confidence interval for this region includes zero). Until more structural twin data using reasonable sample sizes become available, it is difficult to know whether the different findings are driven by different methods (GMC vs cortical thickness; differences in the confounds regressed out; use of 5 categories vs continuous measure

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Table 2. MZ and DZ Cross-twin Cross-trait Correlations Between Psychopathic Traits and GMC and the Genetic and Environmental Basis of Their Overlap[a]

	Correlation (95% CI)					
GMC	MZ	DZ	R_g	R_e	$r_{ph\text{-}a}$	$r_{ph\text{-}e}$
Left PCC	0.23 (0.04 to 0.42)[b]	0.20 (0 to 0.38)	0.42 (0.08 to 1)[b]	–0.16 (–0.57 to 0.31)	0.26 (0.05 to 0.45)[b]	–0.05 (–0.20 to 0.10)
Right dACC	0.17 (–0.03 to 0.35)	0.22 (0.03 to 0.40)[b]	0.37 (0.02 to 1)[b]	–0.02 (–0.45 to 0.44)	0.20 (0.01 to 0.38)[b]	–0.01 (–0.16 to 0.16)
Left PHG	0.03 (–0.15 to 0.21)	0.01 (–0.18 to 0.20)	0.07 (–1 to 1)	0.44 (–0.03 to 0.82)	0.03 (–0.16 to 0.23)	0.17 (–0.01 to 0.34)

Abbreviations: CI, confidence interval; dACC, dorsal anterior cingulate cortex; DZ, dizygotic; GMC, gray matter concentration; MZ, monozygotic; PCC, posterior cingulate cortex; PHG, parahippocampal gyrus; R_g and R_e, genetic and nonshared environmental correlations, ie, the correlation between $A_1 – A_2$ and $E_1 – E_2$. $r_{ph\text{-}a}$ and $r_{ph\text{-}e}$, phenotypic correlation due to additive genetic and specific environmental influence.

[a] The genetic (R_g) and environmental (R_e) correlations, and the decomposed source of the phenotypic correlation (r_{ph-a} and r_{ph-e}), estimated from the full bivariate ACE (additive genetic [A], shared environmental [C], and nonshared environmental [E] effects) models. Fixed genetic models for psychopathic traits used $h^2 = 0.80$, $c^2 = 0$, and $e^2 = 0.20$. Fixed correlations for psychopathic traits used MZ = 0.80, DZ = 0.40, and prevalence fixed to 0.7% (estimates based on Blair et al[22] and Viding et al[3]). Phenotypic correlations estimated from the genetic models were 0.21, 0.20, .and 0.20 for the left PCC, right dACC, and left PHG, respectively, corresponding closely with those values obtained from the constrained correlational model (Table 1).

[b] Significant estimates.

of gray matter), different age ranges (narrow in the present study vs wide in the Schmitt et al study), different exclusion/inclusion criteria (present study enriched with children with psychopathic traits), or power issues (the current sample is smaller than the Schmitt et al study sample). Also, where we report lower heritabilities than Schmitt and colleagues, these may in part stem from the focus on selected voxels that show group difference for psychopathic traits. While this approach is imperative for the study of endophenotypes, selection of group difference voxels does not maximize our ability to detect within–twin pair similarity in specific brain areas.

The primary objective of our study was to investigate whether those brain regions that showed heritability in the GMC differences associated with psychopathic traits would qualify as endophenotypes for psychopathic traits. We were particularly interested in this question because psychopathic antisocial behavior appears strongly heritable in children and the genetic vulnerability for this disorder is likely to manifest itself in the brain.[3,4] Because endophenotypes are proposed to reflect the pathway from genetic predisposition to psychiatric disorder, they need to, in addition to demonstrating heritability, be reliably related to and share genetic variance with "disorder status"[9] (or in this case a circumscribed set of personality traits). We had earlier demonstrated group differences in GMC in several ROIs between children with psychopathic traits and typically developing children.[5] However, in the interest of stringency and power, we only pursued those associations in the bivariate genetic analyses that were statistically significant across the whole sample (including midscorers). Of the brain areas that showed group differences and heritable influences, the left PCC, right dACC, and left PHG fulfilled these criteria. The strongest finding was observed for the left PCC, where nearly half of the genetic influences between psychopathic traits and GMC overlapped. These common genes appeared to drive the relationship between psychopathic traits and GMC. There was also moderate genetic overlap between psychopathic traits and GMC in the right dACC. Again, the common genes appeared to be responsible for the phenotypic relationship between psychopathic traits and the right dACC GMC. Finally, it was not possible to detect statistically significant genetic or nonshared environmental overlap between psychopathic traits and the left PHG GMC. The estimates suggested that any genetic overlap was extremely modest and common genes accounted for only a fraction of the observed phenotypic association. In contrast, most of the phenotypic association appeared to be driven by common nonshared (child-specific) environmental influences. These findings provide preliminary evidence that the left PCC and right dACC may constitute endophenotypes for psychopathy, but the left PHG is a much weaker candidate endophenotype. Both the left PCC and right dACC are involved in empathy for pain, moral judgments, and self-referential thinking (including judgments and obligations[27-30]) and as such represent logical endophenotype markers for psychopathy, a disorder characterized by impairments in social and moral cognition.[31,32] It is premature to speculate regarding the putative mechanism by which genes could increase GMC and in turn lead to increased psychopathic traits. However, future imaging genetic studies could investigate the role of neurodevelopmental genes. We have speculated that the GMC increases in children with psychopathic traits may reflect maturational delay.[5] The specific neurodevelopmental genes of interest could be specified following a genomewide association study of psychopathic traits.

Although these findings represent a promising advance in the study of genes-brain-behavior relationships in antisocial behavior and psychopathy, several limitations should be noted. First, the brain regions that emerged as potential endophenotypes in this study are unlikely to be the only structural brain endophenotypes for psychopathic traits. Our study, despite being large by neuroimaging standards, was probably underpowered to detect true endophenotype effects in several of our ROIs. Some ROIs may also be less robustly associated with psychopathic traits across a range of behavioral impairment, which would have led to difficulty in detecting a significant phenotypic association. Second, the correlations between the GMCs and psychopathic traits were modest. However, it is unlikely that structural differences in any single brain region would account for a large proportion of variance in psychopathy and in this con-

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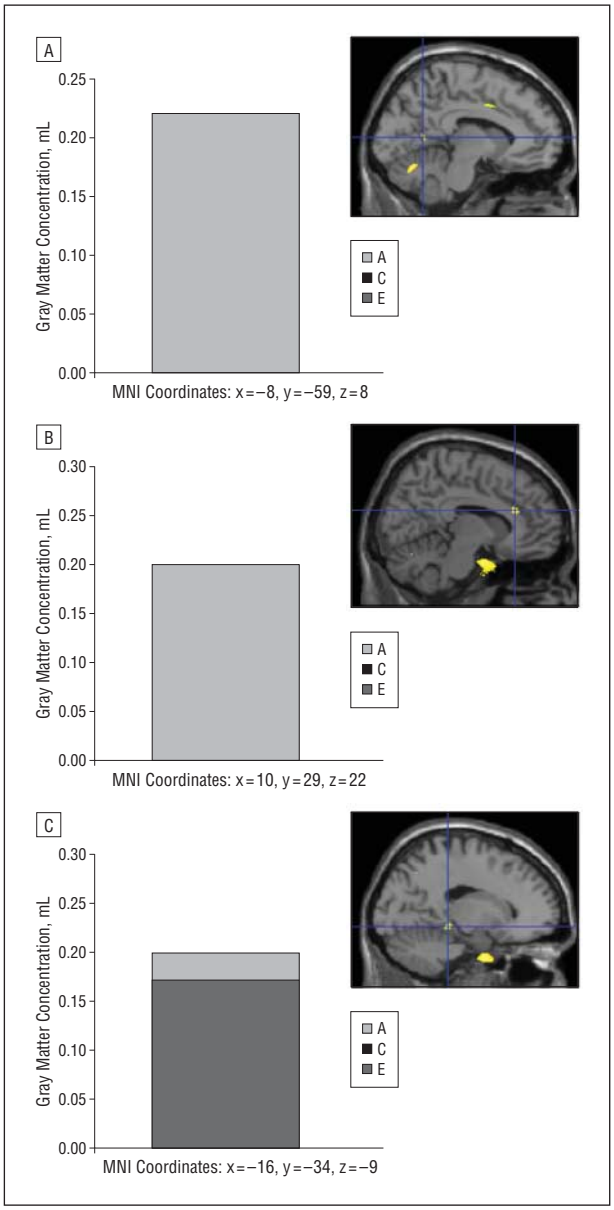

Figure 2. The proportion of phenotypic correlation between psychopathic traits and gray matter concentration (GMC) accounted for by common genetic (A), shared environmental (C), and nonshared environmental (E) factors for the left posterior cingulate cortex (part A); right dorsal anterior cingulate cortex (part B); and left parahippocampal gyrus (part C). Yellow indicates clusters of significant group difference in GMC between typically developing boys and boys with psychopathic traits as defined in our group-difference study.[5] MNI indicates Montreal Neurological Institute.

text, the modest, but statistically significant, correlations are interesting and what we would expect. Third, because of specification of the fixed genetic parameters of the selection variable in the models (psychopathic traits), dominance genetic effects were not modeled in the GMCs even if indicated by twin correlations. By specifying additive genetic effects for each GMC, we allowed, in a broad sense, estimation of the genetic overlap with psychopathic traits, which is a reasonable approach for these data. Fourth, since we did not specify any shared environmental variance for psychopathic traits in the fixed model, all familial overlap between the 2 traits was forced in the additive genetic component. This was necessary since we do not have any indication of significant C effects on psychopathic traits (as measured in a large population sample of twins[3,4]). Fifth, our sample consisted of undiagnosed children from the community who had elevated levels of conduct problems and callous-unemotional traits. These findings should be replicated with clinic samples if possible.

In conclusion, our findings suggest that structural endophenotypes, in the form of variations in GMC, reflect genetic vulnerability for psychopathic traits. Specifically, GMC in the left PCC and right dACC represent potential candidate endophenotypes for psychopathic traits. These brain areas have been implicated in empathy, moral processing, and introspection.[27-30] Future research into psychopathic traits should incorporate functional brain endophenotypes assessed with functional magnetic resonance imaging. Imaging genetic approaches with measured genotypes could also provide a promising area of new inquiry.

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