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Personality and local brain structure: Their shared genetic basis and reproducibility

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Abstract

Local cortical architecture is highly heritable and distinct genes are associated with specific cortical regions. Total surface area has been shown to be genetically correlated with complex cognitive capacities, suggesting cortical brain structure is a viable endophenotype linking genes to behavior. However, to what extent local brain structure has a genetic association with cognitive and emotional functioning is incompletely understood. Here, we study the

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Ethics statement

This study used publicly released HCP, GSP, and eNKI datasets. Reanalysis of the data from these cohort have been permitted through the local ethics committee of the university of Düsseldorf.

Declaration of competing interest

The authors declare no competing interests.

CRedit authorship contribution statement

Sofie L. Valk: Conceptualization, Formal analysis, Writing - original draft. **Felix Hoffstaedter:** Resources, Writing - original draft.

Julia A. Camilleri: Resources, Writing - original draft. **Peter Kochunov:** Software, Writing - original draft. **B.T. Thomas Yeo:** Resources, Writing - original draft. **Simon B. Eickhoff:** Conceptualization, Resources, Writing - original draft, Funding acquisition.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neuroimage.2020.117067>.

genetic correlation between personality traits and local cortical structure in a large-scale twin sample (Human Connectome Project, $n = 1102$, 22–37y) and we evaluated whether observed associations reflect generalizable relationships between personality and local brain structure two independent age-matched samples (Brain Genomics Superstructure Project: $n = 925$, age = 19–35y, enhanced Nathan Kline Institute dataset: $n = 209$, age: 19–39y). We found a genetic overlap between personality traits and local cortical structure in 10 of 18 observed phenotypic associations in predominantly frontal cortices. However, we only observed evidence in favor of replication for the negative association between surface area in medial prefrontal cortex and Neuroticism in both replication samples. Quantitative functional decoding indicated this region is implicated in emotional and socio-cognitive functional processes. In sum, our observations suggest that associations between local brain structure and personality are, in part, under genetic control. However, associations are weak and only the relation between frontal surface area and Neuroticism was consistently observed across three independent samples of young adults.

1. Introduction

The local macro-anatomical structure of the cerebral cortex is largely heritable, and has a highly polygenetic architecture (Grasby et al., 2020; Panizzon et al., 2009; Strike et al., 2019; Winkler et al., 2010). Recently, it has been shown that common genetic variants that influence surface area also affect various behavioral traits, suggesting that brain structure is an essential endophenotype linking genes and behavior (Grasby et al., 2020). However, to what extent the correlation between local cortical structure on the one hand and cognitive and emotional functioning on the other is driven by shared genetic factors is incompletely understood.

One of the most broadly used summaries of an individual's characteristic patterns of behavior, thought, and emotions is personality (Funder, 2001). Behavioral science establishes personality structure by parcellating the individual variability in goals, cognition, and emotion into independent components (Mischel, 2004). A widely used personality taxonomy is the Big Five Personality inventory (John and Srivastava, 1999; McCrae and Costa, 1997; Saucier and Srivastava, 2015). The Five-factor personality structure derives five orthogonal dimensions or traits of Agreeableness, Conscientiousness, Extraversion, Neuroticism, and Openness (John et al., 2008; Saucier and Srivastava, 2015). Personality traits have been related to the quality of social relationships (Asendorpf and Wilpers, 1998), job performance (Rothmann and Coetzer, 2003), risk for mental disorders (Miller et al., 2001; Trull, 2013), general health and wellbeing, and reproductive success (Alvergne et al., 2010; Strickhouser et al., 2017).

Personality has both stable and malleable features (Damian et al., 2019; Harris et al., 2016; Penke and Jokela, 2016) and has been found heritable with approximately 40% of the variance attributable to additive genetic factors (Bouchard, 1994; Bouchard and Loehlin, 2001; Bouchard and McGue, 2003; Jang et al., 1996; Loehlin et al., 1998; Vukasovic and Bratko, 2015). Evolutionary causes for variability in personality traits have been suggested to be due to balancing selection, where selection pressures in different directions affect the same traits enabling adaptation to changing environmental demands (Penke and Jokela,

2016). Indeed, genome-wide association studies (GWAS) have reported a large number of genetic variants associated with personality traits with each contributing to the heritability of personality (Genetics of Personality Consortium, 2015; de Moor et al., 2012; Lo et al., 2017; van den Berg et al., 2016; Verweij et al., 2012).

The biological basis of personality in humans has also been studied in relation to macroscale brain structure and function using magnetic resonance imaging (MRI) (Bjornebekk et al., 2013; DeYoung et al., 2010; Dubois et al., 2018; Ferschmann et al., 2018; Kong et al., 2019; Nostro et al., 2017; Riccelli et al., 2017; Wu et al., 2019). Various studies have reported a phenotypic relationship between local brain structure and personality traits (Bjornebekk et al., 2013; DeYoung et al., 2010; Gray et al., 2019; Nostro et al., 2017; Riccelli et al., 2017). Using the Human Connectome Project, young adult (HCP) sample, including monozygotic and dizygotic twins, Owens and colleagues (Owens et al., 2019) report significant phenotypic relationships between personality traits and various markers of cortical structure. For example, Owens and colleagues observed associations between Agreeableness, Conscientiousness, Neuroticism, and Openness with morphometry in prefrontal areas. However findings on the relationship between personality traits and local brain structure have been inconsistent, for instance, Avinun and colleagues failed to observe significant relations between personality and various markers of brain structure using the largest sample to date (Avinun et al. *bioRxiv*). In line with this report, Kharabian et al. have recently shown that, in general, relationships between local brain structure and psychometric variables are not robust and highly dependent on sample and effect size (Kharabian Masouleh et al. *bioRxiv*; Kharabian Masouleh, 2019). At the same time, it has recently been shown that traits such as neuroticism, general cognitive function, educational attainment, and depressive symptoms show a genetic correlation with total surface area, suggesting brain structure is a key phenotype reflecting individual differences in behavior (Grasby et al., 2020).

Taken together contemporary theory suggests that (a) individual variation in both local brain structure and personality can be, in part, attributed to genetic effects (b) brain structure is a viable endophenotype linking genes and behavior (c) personality relates to macro-scale brain structure and function, but local relationships are weak and vary as a function of sample and effect size. However, whether regional brain structure and personality have a shared genetic basis remains unclear. To answer our research question, we studied the relationship between the Big Five personality traits and local cortical thickness and surface area. We captured variations in brain morphometry using an atlas-based approach, dividing the cortex in 200 functionally-defined parcels (Eickhoff et al., 2018; Schaefer et al., 2018). We studied three independent samples of young adults, the HCP (n = 1102), Brain Genomics Superstructure Project (GSP, n = 925) and enhanced Nathan Kline Institute dataset (eNKI, n = 209). The HCP sample is unique in that it provided us with high quality neuroimaging and personality trait (NEO-FFI) data in a large number of twins, siblings, and unrelated individuals, enabling us to compute genetic correlation between personality and local brain structure. Analysis of heritability and genetic correlation was performed using maximum likelihood variance-decomposition methods using Sequential Oligogenic Linkage Analysis Routines (www.solar-eclipse-genetics.org; Solar Eclipse 8.4.0.). Second, to assess whether observed associations between personality and local brain structure in the HCP sample

reflect generalizable relationships between personality and local brain structure, we selected two samples (GSP (n = 925) and eNKI (n = 209)) of unrelated individuals between 18 and 40 years of age in which we studied whether personality-brain relationships observed in the HCP sample would replicate in two independent samples. Last, we performed functional decoding to further evaluate the functional mechanisms underlying brain regions robustly associated with personality.

2. Materials and methods

2.1. HCP sample

2.1.1. Participants and study design—For our analysis we used the publicly available data from the HCP S1200 release (<http://www.humanconnectome.org/>), which comprised data from 1206 individuals (656 females), 298 MZ twins, 188 DZ twins, and 720 singletons, with mean age 28.8 years (SD = 3.7, min-max = 22–37). We included individuals for whom the scans and data had been released ([humanconnectome.org](http://www.humanconnectome.org/)) after passing the HCP quality control and assurance standards (Marcus et al., 2013). The full set of inclusion and exclusion criteria are described elsewhere (Glasser et al., 2013; Van Essen et al., 2013). In short, the primary participant pool comes from healthy individuals born in Missouri to families that include twins, based on data from the Missouri Department of Health and Senior Services Bureau of Vital Records. Additional recruiting efforts were used to ensure participants broadly reflect ethnic and racial composition of the U.S. population. Healthy is broadly defined, in order to gain a sample generally representative of the population at large. Sibships with individuals having severe neurodevelopmental disorders (e.g., autism), documented neuropsychiatric disorders (e.g. schizophrenia or depression) or neurologic disorders (e.g. Parkinson’s disease) are excluded, as well as individuals with diabetes or high blood pressure. Twins born prior 34 weeks of gestation and non-twins born prior 37 weeks of gestation are excluded as well. After removing individuals with missing structural imaging, incorrect segmentations, or behavioral data our sample consisted of 1102 individuals (including 285 MZ-twins and 169 DZ-twins) with mean age of 28.8 years (SD = 3.7, min-max = 22–37). See further Table 1.

2.1.2. Structural imaging acquisition and processing—MRI protocols of the HCP are previously described (Glasser et al., 2013; Van Essen et al., 2013). The pipeline used to obtain the Freesurfer-segmentation is described in detail in a previous article (Glasser et al., 2013) and is recommended for the HCP-data. In short, the pre-processing steps included co-registration of T1 and T2 scans, B1 (bias field) correction, and segmentation and surface reconstruction to estimate cortical thickness. The HCP structural pipelines use Freesurfer 5.1 software (<http://surfer.nmr.mgh.harvard.edu/>) (Dale et al., 1999; Fischl, 2013; Fischl and Dale, 2000; Fischl et al., 1999) plus a series of customized steps that combine information from T_{1w} as well as T_{2w} scans for more accurate white and pial surfaces (Glasser et al., 2013). The HCP dataset contains high quality imaging data which has been pre-processed in FreeSurfer by independent researchers (Glasser et al., 2013; Marcus et al., 2013). To evaluate the quality of segmentations in our parcellation approach, S.L.V. visually inspected the parcel-values projected on the cortical surface for inaccuracies, and individuals whose

regional cortical thickness or surface area showed decreased correspondence ($r < 0.8$) to the mean pattern of the respective measure were excluded ($n = 4$).

2.1.3. Five factor model of personality—The Big Five personality traits were assessed using the NEO-Five-Factors-Inventory (NEO-FFI)(McCrae and Costa, 2004). The NEO-FFI is composed of a subset of 60-items extracted from the full-length 240-item NEO-PI-R. For each item, participants reported their level of agreement on a 5-point Likert scale, from strongly disagree to strongly agree. The NEO instruments have been previously validated in USA and several other countries (McCrae and Terracciano, 2005). See further Table 1.

As a proxy for IQ we used the NIH Toolbox Cognition (Weintraub et al., 2013), ‘total composite score’. The Cognitive Function Composite score is derived by averaging the normalized scores of each of the Fluid and Crystallized cognition measures, then deriving scale scores based on this new distribution. Higher scores indicate higher levels of cognitive functioning. Participant score is normed to those in the entire NIH Toolbox Normative Sample (18 and older), regardless of age or any other variable, where a score of 100 indicates performance that was at the national average and a score of 115 or 85, indicates performance 1 SD above or below the national average. See further Table 1.

2.2. GSP sample

2.2.1. Participants and study design—To evaluate the cross-sample reproducibility of observations we additionally investigated the association between personality and local cortical brain structure in the Brain Genomics Superstruct Project (GSP) (Holmes et al., 2015). In short, between 2008 and 2012 young adults (ages 18 to 35) with normal or corrected-to-normal vision were recruited from the Boston community to participate in the GSP. The 1570 individuals included in the data release (Holmes et al., 2015) were selected from a larger databased of individuals who participated in the ongoing GSP data collection initiative. Participants included well-educated individuals with relatively high IQs (many of the college age students are from local colleges). Participants provided written informed consent in accordance with guidelines established by the Partners Health Care Institutional Review Board and the Harvard University Committee on the Use of Human Subjects in Research (See Supplementary Appendix A in (Holmes et al., 2015)).

2.2.2. Structural imaging acquisition and processing—All imaging data were collected on matched 3T Tim Trio scanners (Siemens Healthcare, Erlangen, Germany) at Harvard University and Massachusetts General Hospital using the vendor-supplied 12-channel phased-array head coil. Structural data included a high-resolution (1.2 mm isotropic) multi-echo T1-weighted magnetization-prepared gradient-echo image (multi-echo MPRAGE, see further (Holmes et al., 2015):). The low participant burden resulting from the use of multi-echo MPRAGE anatomical scans makes this sequence well suited for high-throughput studies. The morphometric features derived through conventional 6-min 1 mm MPRAGE and the 2-min 1.2 mm multi-echo MPRAGE are highly consistent ($r^2 > 0.9$ for most structures) suggesting that rapid acquisition multi-echo MPRAGE can be used for many purposes in place of longer anatomical scans without degradation of the quantitative

morphometric estimates. All T1 scans pre-processed using the Freesurfer software library (<http://surfer.nmr.mgh.harvard.edu/>) version 6.0.0 (Dale et al., 1999; Fischl, 2013; Fischl and Dale, 2000; Fischl et al., 1999). Next, the individual cortical thickness and surface area maps were standardized to fsaverage5 for further analysis. Images in the GSP were screened for artifacts, acquisition problems, processing errors and excessive motion before the open release (Holmes et al., 2015) and participants were processed in FreeSurfer 6.0.0. in a full automated matter. S.L.V. visually inspected z-scored parcel-values projected on the cortical surface for inaccuracies to evaluate the quality of segmentations of our parcellation approach, and individuals whose regional cortical thickness or surface area showed a decreased correspondence ($r < 0.8$) to the mean pattern of the respective measure were excluded ($n = 1$).

2.2.3. Five factor model of personality—The Big Five personality traits were assessed using the full-length 240-item Revised NEO Personality Inventory NEO-Five-Factors-Inventory (NEO-PI-R)(Costa and McCrae, 1992), the full-length 240-item NEO-PI-R. For each item, participants reported their level of agreement on a 5-point Likert scale, from strongly disagree to strongly agree. The NEO instruments have been previously validated in USA and several other countries (McCrae and Terracciano, 2005). As a proxy for IQ we used the estimated IQ derived through the Oklahoma Premorbid Intelligence Estimate–3 (OPIE3) formula (Schoenberg et al., 2002). Reported values are in integers and binned. It is of note that distribution of IQ values is positively skewed relative to the general population and that many personality traits, including negative affect and Neuroticism were observed to have distribution that would be expected of a clinically-screened population-based sample (Holmes et al., 2015). See further Table 2.

2.3. eNKI sample

2.3.1. Participants and study design—To evaluate the cross-sample reproducibility of observations we additionally investigated correspondence between personality and cortical brain structure in the eNKI where we selected adults between 18 and 40 years of age to match the age-range of the HCP and GSP samples. The sample was made available by the Nathan-Kline Institute (NKI, NY, USA), as part of the ‘*enhanced NKI-Rockland sample*’ (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3472598/>). In short, eNKI was designed to yield a community-ascertained, lifespan sample in which age, ethnicity, and socioeconomic status are representative of Rockland County, New York, U.S.A. ZIP-code based recruitment and enrollments efforts were being used to avoid over-representation of any portion of the community. Participants below 6 years were excluded to balance data losses with scientific yield, as well as participants above the age of 85, as chronic illness was observed to dramatically increase after this age. All approvals regarding human subjects’ studies were sought following NKI procedures. Scans were acquired from the International Neuroimaging Data Sharing Initiative (INDI) online database http://fcon_1000.projects.nitrc.org/indi/enhanced/studies.html. For our phenotypic analyses, we selected individuals with complete personality and imaging data within the age-range of 18–40 years to match the age-range of the HCP and GSP samples. Our sample consisted of 209 (121 females) individuals with mean age of 26.0 years ($SD = 6.1$, min-max = 18–39). Please see Table 3 for demographic characteristics.

2.3.2. Structural imaging acquisition and processing—3D magnetization-prepared rapid gradient-echo imaging (3D MPRAGE) structural scans (Mugler and Brookeman, 1990) were acquired using a 3.0 T S Trio scanner with TR = 2500 ms, TE = 3.5 ms, Bandwidth = 190 Hz/Px, field of view = 256 × 256 mm, flip angle = 8°, voxel size = 1.0 × 1.0 × 1.0 mm. More details on image acquisition are available at http://fcon_1000.projects.nitrc.org/indi/enhanced/studies.html. All T1 scans were pre-processed using the FreeSurfer software library (<http://surfer.nmr.mgh.harvard.edu/>) version 6.0.0 (Dale et al., 1999; Fischl, 2013; Fischl and Dale, 2000; Fischl et al., 1999) to compute cortical thickness and surface area. Next, the individual cortical thickness and surface area maps were standardized to fsaverage5 for further analysis. We used a subsample of young adults who had with FreeSurfer segmentations available. S.L.V. visually inspected z-scored parcel-values projected on the cortical surface for inaccuracies to evaluate the quality of segmentations of our parcellation approach. Individuals whose regional cortical thickness or surface area showed a decreased correspondence ($r < 0.8$) to the mean pattern of the respective measure were excluded ($n = 1$).

2.3.3. Five factor model of personality—The Big Five personality traits were assessed using the NEOFFI3 (McCrae and Costa, 2004; McCrae and Terracciano, 2005).

For an assessment of intelligence we used the Wechsler Abbreviated Scale of Intelligence (WASI-II) (Wechsler, 1999), full scale IQ. The WASI is a general intelligence, or IQ test designed to assess specific and overall cognitive capabilities and is individually administered to children, adolescents and adults (ages 6–89). It is a battery of four subtests: Vocabulary (31-item), Block Design (13-item), Similarities (24-item) and Matrix Reasoning (30-item). In addition to assessing general, or Full Scale, intelligence, the WASI is also designed to provide estimates of Verbal and Performance intelligence consistent with other Wechsler tests. Specifically, the four subtests comprise the full scale and yield the Full Scale IQ (FSIQ-4), see further Table 3.

2.3.4. Parcellation approach—In all three samples, we used a parcellation scheme (Schaefer et al., 2018) based on the combination of a local gradient approach and a global similarity approach using gradient-weighted Markov Random models. The parcellation has been extensively evaluated with regards to stability and convergence with histological mapping and alternative parcellations. In the context of the current study, we focus on the granularity of 200 parcels, as averaging will improve signal-to-noise ratio. In order to improve signal-to-noise ratio and to accelerate analysis speed, we opted to average unsmoothed structural data within each parcel. Thus, cortical thickness of each ROI was estimated as the trimmed mean (10 percent trim) and surface area as the sum of area within an ROI.

2.3.5. Phenotypic correlation analysis—As in previous structural MRI analyses (Bernhardt et al., 2014; Valk et al., 2016a, 2017), we used SurfStat for Matlab [R2017a, The Mathworks, Natick, MA] (Worsley et al., 2009b). Phenotypic correlation analyses between personality traits and local brain structure were carried out per parcel, using a 200 parcel-parcellation scheme (Schaefer et al., 2018) on surface area and cortical thickness. We controlled for age, sex, age × sex interaction, age², age² × sex interaction,

as well as global thickness effects when investigating cortical thickness and intracranial volume when assessing surface area in order to evaluate associations between personality and local structure independent from global factors and make thickness estimates more comparable across sites and FreeSurfer versions (Kharabian Masouleh et al., 2020). Results were corrected for multiple comparisons using Benjamini-Hochberg FDR (Benjamini and Hochberg, 1995) at whole-brain analysis, where we corrected for number of analysis within the current step and report FDR thresholds. When investigating personality or in post-hoc brain analysis, we corrected for number of analysis \times ROIs. Post-hoc we also controlled for a proxy for intelligence, total cognitive score (Weintraub et al., 2013). We displayed significant ($FDRq < 0.05$) findings on the brain surface.

2.3.6. Heritability and genetic correlation analysis—To investigate the heritability and genetic correlation of brain structure and personality traits, we analyzed 200 parcels of cortical thickness and surface area, as well as personality trait score of each subject in a twin-based heritability analysis. As in previous studies (Glahn et al., 2010), the quantitative genetic analyses were conducted using Sequential Oligogenic Linkage Analysis Routines (SOLAR) (Almasy and Blangero, 1998). SOLAR uses maximum likelihood variance-decomposition methods to determine the relative importance of familial and environmental influences on a phenotype by modeling the covariance among family members as a function of genetic proximity. This approach can handle pedigrees of arbitrary size and complexity and thus, is optimally efficient with regard to extracting maximal genetic information. To ensure that our traits, behavioral as well as of brain structure, were conform to the assumptions of normality, an inverse normal transformation was applied for all behavioral and neuroimaging traits (Glahn et al., 2010).

Heritability (h^2) represents the portion of the phenotypic variance (σ_p^2) accounted for by the total additive genetic variance (σ_g^2), i.e., $h^2 = \sigma_g^2 / \sigma_p^2$. Phenotypes exhibiting stronger covariances between genetically more similar individuals than between genetically less similar individuals have higher heritability. Heritability analyses were conducted with simultaneous estimation for the effects of potential covariates. For heritability and genetic correlation analysis we included the same covariates as in our phenotypic correlation analysis including age, sex, age \times sex interaction, age², age² \times sex interaction. Post-hoc we also controlled for a proxy for intelligence, total cognitive score (Weintraub et al., 2013). When investigating cortical thickness, we additionally controlled for global thickness effects (mean cortical thickness) and in case of surface area we controlled for intracranial volume.

To determine if variations in personality and brain structure were influenced by the same genetic factors, genetic correlation analyses were conducted. More formally, bivariate polygenic analyses were performed to estimate genetic (ρ_g) and environmental (ρ_e) correlations, based on the phenotypic correlation (ρ_p), between brain structure and personality with the following formula: $\rho_p = \rho_g (h^2_1 h^2_2) + \rho_e [(1 - h^2_1)(1 - h^2_2)]$, where h^2_1 and h^2_2 are heritability's of the parcel-based cortical thickness and the various behavioral traits. The significance of these correlations was tested by comparing the log likelihood for two restricted models (with either ρ_g or ρ_e constrained to be equal to 0) against the log likelihood for the model in which these parameters were estimated. A significant genetic correlation (corrected for multiple comparisons using Benjamin-

Hochberg FDR (Benjamini and Hochberg, 1995)) is evidence suggesting that (a proportion of) both phenotypes are influenced by a gene or set of genes (Almasy et al., 1997).

To compute the contribution of genetic effects relative to the phenotypic correlation, we computed the contribution of the genetic path to the phenotypic correlation ($h^2_1 \times \rho_g \times h^2_2$)(ρ_{phg}) divided by the phenotypic correlation. For the relative contribution of environmental correlation to the phenotypic correlation we computed ($1-h^2_1 \times \rho_e \times 1-h^2_2$)(ρ_{phe}) divided by the phenotypic correlation (Zheng et al., 2019).

2.3.7. Bayes factors of replication—To compare the evidence that the personality-local brain structure could be replicated in two independent samples (H1, replication, and H0, no replication), we additionally quantified personality-brain associations within each ROI, using Bayes factors (Verhagen and Wagenmakers, 2014). In line with previous work of our group (Kharabian Masouleh et al. bioRxiv; Kharabian Masouleh, 2019) Bayes factors (BF) were summarized into four categories. These categories are used to simplify the interpretation and comparison of replication rates. For example, a BF_{01} lower than 1/3 shows that the data is three times or more likely to have happened under H1 than H0. “Successful” replication is defined as a replication lower than 1 in both replication samples.

2.3.8. Functional decoding—Parcel that were significantly replicated in at least one sample were functionally characterized using the Behavioral Domain meta-data from the BrainMap database (<http://www.brainmap.org> (Laird et al., 2011; Laird et al., 2009)). To do so, volumetric counterparts, delineating the surface-based parcels in volume space, as provided by Schaefer (Schaefer et al., 2018) (https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/Schaefer2018_LocalGlobal/Parcellations), were used. In particular, we identified those meta-data labels (describing the computed contrast [behavioral domain as well as paradigm]) that were significantly more likely than chance to result in activation of a given parcel (Fox et al., 2014; Genon et al., 2018; Nostro et al., 2017). That is, functions were attributed to the parcels by quantitatively determining which types of experiments are associated with activation in the respective parcellation region. Significance was established using a binomial test ($q < 0.05$, corrected for multiple comparisons using false discovery rate, FDR).

3. Results

3.1. Association between personality traits and cortical brain structure

To assess the association between personality and macroscale cortical brain structure we first evaluated distribution of behavioral measures. Using the Kolmogorov-Smirnov test we found that all personality traits in the HCP sample ($n = 1102$ including 285 MZ-twins and 169 DZ-twins) were conform to normal distributions (KS-score between 0.97 and 1) (Fig. 1). We observed significant phenotypic correlation between all personality traits, with the exception of Openness and Neuroticism ($r = 0.01$) (Fig. 1, Supplementary Table 1).

Next, we assessed phenotypic correlation between personality traits and cortical structure, specifically cortical thickness and surface area. Distribution of cortical thickness values

summarized in 200 functionally informed parcels (Schaefer et al., 2018) showed highest thickness in anterior insula, and relatively low values in occipital regions (Fig. 2A).

At the regional level, we observed correlations between Agreeableness, Neuroticism, and Openness and local cortical thickness (Fig. 2B). Specifically, Agreeableness related negatively to variations in thickness in left lateral and bilateral medial prefrontal cortex ($FDRq < 0.05$). Neuroticism related positively to thickness in dorsolateral frontal areas and left posterior operculum, and negatively to thickness in left posterior occipital regions ($FDRq < 0.05$). Openness related negatively to thickness in left ventrolateral cortex, and positively to right temporal pole ($FDRq < 0.05$). We did not observe significant associations between mean cortical thickness and personality scores (Table 4).

Total surface area had a negative relation with conscientiousness ($t = -2.45$, $p < 0.005$) and a positive association with openness ($t = 2.68$, $p < 0.002$) (Table 4). Regionally, we found a negative relation between Neuroticism and local surface area in bilateral medial frontal cortex, left inferior frontal gyrus, left posterior insula, and right temporal pole ($FDRq < 0.05$).

To test stability of our findings we additionally evaluated the robustness of phenotypic associations between personality and global and local brain structure while controlling for total cognitive score and the other personality traits (Supplementary Materials, Supplementary Tables 2 and 3). While all local associations remained significant at $p < 0.01$, strength of associations was generally reduced and few regions reached $FDRq < 0.05$ significance levels.

3.2. Genetic relationship between personality traits and cortical brain structure

Subsequently, we sought to evaluate whether the phenotypic correlations observed in the twin-sample were due to shared genetic or environmental effects on grey matter brain structure and personality traits. All personality traits were significantly heritable in our current sample (Fig. 3C, Supplementary Table 4), as were mean cortical thickness ($h^2 = 0.85$) and total surface area ($h^2 = 0.93$), and we confirmed also local cortical thickness (h^2 : mean \pm std: 0.34 ± 0.10) and surface area (h^2 : \pm mean \pm std: 0.41 ± 0.13) to be heritable in our parcel-based approach (Fig. 3A–B, Supplementary Table 5 and 11).

Following, we assessed genetic correlation between personality traits and cortical structure. We did not observe genetic or environmental associations between personality and global thickness (Table 5), however, the phenotypic association between total surface area and conscientiousness was observed to be driven by shared genetic effects ($\rho_g = -0.12$, $p < 0.05$) whereas the association between openness and total surface area was driven by environmental effects ($\rho_e = 0.18$, $p < 0.03$).

Last, we evaluated the genetic correlation of regions that showed phenotypic correlations between personality and local brain structure. We observed that 10 out of 18 phenotypic correlations showed a genetic correlation ($p < 0.05$), and 3 out of 18 phenotypic correlates related to an environmental correlation ($p < 0.05$) (Table 6). More specifically, we found a negative genetic correlation between Agreeableness and bilateral superior frontal thickness ($p < 0.05$), a positive genetic correlation between Neuroticism and right superior and lateral

frontal cortex thickness ($p < 0.05$) and a positive genetic correlation between right temporal pole thickness and Openness ($p < 0.01$). Neuroticism had a negative genetic correlation between local surface area in left posterior insula, and bilateral superior frontal cortex, and right medial frontal regions ($p < 0.05$). See Supplementary Tables (6–10 and 12–16) for genetic and environmental correlations between personality traits and all parcels.

3.3. Cross-sample reproducibility of the association between personality trait and local brain structure

In the previous analysis steps, we could show that a) there is a significant relationship between local cortical structure and personality traits in a large-scale twin sample (HCP) and that b) this relationship can be, in part, attributed to shared genetic factors. Following, to study whether associations between local brain structure and personality traits are generalizable, we evaluate the phenotypic correlation between personality traits and cortical phenotypes observed in the HCP sample are reproducible in two age-matched samples of young adults (GSP and eNKI). To formalize the level of reproducibility, we computed Bayes Factors (BF) summarizing the evidence of a successful reproduction across samples (Verhagen and Wagenmakers, 2014).

We found moderate to anecdotal evidence of replication for only one personality-brain association in both samples; the relationship between local surface area in right medial frontal cortex and Neuroticism (GSP: $t = -1.55$, $p < 0.07$; BF = 0.82; and eNKI: $t = -1.97$, $p < 0.025$; BF = 0.17). Various associations between local cortical thickness and personality traits could be reproduced in one of both replication samples (Table 7). Specifically, in GSP, the association between thickness in right superior frontal cortex and Agreeableness ($t = -1.79$, $p < 0.05$; BF = 0.48), and between thickness of right dorsal lateral PFC and Neuroticism ($t = 2.08$, $p < 0.02$; BF = 0.25). In the eNKI sample we observed some evidence of successful replication of the association between left visual cortex and Neuroticism ($t = -1.76$, $p < 0.05$; BF = 0.25), left dorsolateral prefrontal thickness Openness ($t = -0.97$, $p > 0.1$, BF = 0.76), surface area of left sensory-motor cortex ($t = -1.11$, $p > 0.1$, BF = 0.60) and left prefrontal cortex ($t = -1.05$, $p > 0.1$, BF = 0.64) Neuroticism. Global of cortical and thickness and surface area did not replicate out of sample, only in case of the positive association between total surface area and Openness we observed anecdotal evidence of successful replication in the eNKI sample ($t = 1.51$, $p < 0.1$, BF 0.34) (Supplementary Table 17).

3.4. Quantitative functional decoding

Last, we performed quantitative functional mapping of the personality – brain relationships for which we observed a) phenotypic and genetic correlation in the HCP sample b) an association ($p < 0.05$) in combination with a BF of < 1 in at least one additional sample.

The right medial frontal cortex, where we observed a robust association between surface area and Neuroticism, was functionally involved in various emotional domains, social cognition, and memory, and active in paradigms involving self-reflection, Theory of Mind, and emotion induction ($FDRq < 0.05$) (Fig. 4).

4. Discussion

Both local brain structure and personality are heritable. Moreover, a large body of evidence has suggested a relationship between personality and local brain structure. However, effects are weak and vary as a function of sample and effect size. In the current study, we used the large scale and openly available HCP dataset which included monozygotic and dizygotic twins to study whether there is a genetic correlation between local brain structure and personality traits. Second, we evaluated the robustness of personality-brain relationships in two additional age-matched samples.

First, we identified phenotypic associations between personality traits and local cortical structure. Associations between personality on the one hand and cortical thickness and surface area on the other were predominantly observed in frontal cortices. Performing genetic correlation analysis, we found that 10 of 18 phenotypic associations could be explained by shared genetic effects. To evaluate whether observed relationship between personality traits and local brain structure were generalizable to other samples, we additionally studied phenotypic correlations between personality traits and brain structure in two independent age-matched samples of unrelated individuals (GSP and eNKI). Here, we found that surface area in right medial prefrontal cortex was robustly associated with Neuroticism across all three samples. In sum, our findings suggest that part of phenotypic associations between personality and local brain structure can be attributed to shared genetic effects in a large-scale twin sample. However, associations were weak and only the association between surface area in right medial prefrontal cortex and Neuroticism replicated in two independent samples.

We assessed the genetic basis of the association between personality and cortical thickness using compressed surface-based MRI data based on the parcellation scheme of Schaefer et al. (2018). Using compressed features of structural MRI has been suggested to both improve signal-to-noise ratio of brain measures (cf. (Eickhoff et al., 2018) and (Genon et al., 2018)), and optimize analysis scalability. The Schaefer parcellation is derived using functional MRI data from ~1500 subjects and integrates local approaches detecting abrupt transitions in functional connectivity patterns and global approaches that cluster similar functional connectivity patterns (Schaefer et al., 2018). Indeed, a combination of within-area micro circuitry, proxied by brain morphometry, and between-area connectivity enables each area to perform a unique set of computations (Van Essen and Glasser, 2018). Therefore, a parcellation approach that considers both local and global connectivity might benefit structural image analysis, as it reduces signal-to-noise both within and across individuals and makes control for multiple comparisons more straightforward (Genon et al., 2018). Based on the findings in our study, we suggest our approach might be a fruitful first exploratory step to investigate the genetic relation between brain structure and behavior, and locate mechanisms of interest. Future studies can subsequently verify these results by exploring more specific genetic mechanisms, as well as neuroanatomical features.

Though we could establish phenotypic correlations between personality traits and local cortical thickness, associations were weak and phenotypic associations ranged between t -values of 3.5 and -3.5 . In the HCP dataset phenotypic correlations between predominantly

frontal regions and personality traits of Agreeableness, Neuroticism, and Openness have been previously reported using a non-parcel-based method by Owens and colleagues (Owens et al., 2019). Frontal cortices are functionally involved in a number of tasks involving higher cognitive functioning, such as executive functioning, memory, metacognition and social cognition (Amodio and Frith, 2006; Baird et al., 2013; Bludau et al., 2014; Buckner et al., 2008; Fleming and Dolan, 2012; Valk et al., 2016a). We additionally observed various relationships between global measures of surface area and cortical thickness on the one hand and personality traits on the other. Indeed, we could replicate a recently reported association between total surface area and Neuroticism in phenotypic correlation analysis (Grasby et al., 2020). However, associations between global measures of cortical structure and personality were not consistent across samples.

We extend previously reported phenotypic observations by showing that these phenotypic relationships between personality and local cortical structure are driven, in part, by shared additive genetic effects rather than environmental factors alone. The contribution of genetic effects on phenotypic correlations is dependent on the heritability of each of the correlated markers. In our sample, between 30% and 57% (on average 42%) of variance in personality traits was explained by additive genetic factors. This is in line with previous studies using twin and family samples (Jang et al., 1996) as well as genome-wide approaches (Lo et al., 2017). A recent meta-analysis (Vukasovic and Bratko, 2015) confirmed that on average 40% of the variance in personality traits is of genetic origin. Also, conform with previous studies (Eyler et al., 2012; Kremen et al., 2010; Panizzon et al., 2009; Strike et al., 2019; Winkler et al., 2010), we observe heritability of local cortical thickness, with highest values in primary sensory areas. Heritability patterns followed previously described patterns with relatively strong genetic influence on cortical thickness in unimodal cortices, whereas variance in association cortices is on average less influenced by genetic factors (Eyler et al., 2012; Grasby et al., 2020; Hofer et al., 2018; Kremen et al., 2010; Panizzon et al., 2009; Strike et al., 2019; Winkler et al., 2010). Also, local surface area was heritable, with lowest heritability values in dorsolateral PFC and temporal-parietal regions (Eyler et al., 2012; Grasby et al., 2020; Hofer et al., 2018; Kremen et al., 2010; Panizzon et al., 2009; Strike et al., 2019; Winkler et al., 2010).

Performing genetic correlation analysis, we observed that the phenotypic correlation between personality and local brain structure in 10 out of 18 regions was driven by genetic factors. These regions were predominantly located in frontal areas, suggesting a genetic link between local structure in frontal cortices and personality. Indeed, various studies have suggested a relationship between personality and the frontal lobe in humans (DeYoung et al., 2010; Owens et al., 2019; Riccelli et al., 2017) and in chimpanzees (Latzman et al., 2015). There are various ways in which a genetic process would affect the relationship between personality and cortical macrostructure and it is likely the observed genetic correlations between local cortical structure and personality traits in the HCP sample are due to mediated pleiotropy (a gene affects A which affects B). On the one hand, it could be a genetic factor affects grey matter macrostructure and associated function and, as a consequence, personality. On the other hand, it could be that genetic variation affects brain function which in turn modulates both macroscale structure as well as personality, or a genetic mechanism affects an unknown biological factor which in turn affects personality

and brain structure. Recent work using GWAS and genetic correlation in a large sample of individuals could find a genetic association between cortical brain structure and various markers of behavior, providing first evidence of a direct link of genes and behavior via cortical brain structure (Grasby et al., 2020). Here, Grasby et al. found evidence that genetic regulatory elements influencing local surface area and local cortical thickness stem from different developmental mechanisms. Whereas surface area is associated with genetic variants active during fetal development, cortical thickness may reflect genetic processes underlying myelination, branching and pruning. Such differential mechanistic timing effects on cortical structure might contribute to the understanding of which biological mechanisms underlie personality, and further dissociate factors that shape personality across the life-span.

As various studies have indicated relationships between local brain structure and psychometric variables are not robust (Avinun et al. *bioRxiv*; Kharabian Masouleh et al. *bioRxiv*; Kharabian Masouleh, 2019), we further evaluated the robustness of phenotypic associations between personality and local brain structure in two age-matched samples of unrelated individuals. Indeed, though most associations did not replicate across all three samples, the association between medial prefrontal surface area and Neuroticism was observed in all three samples. Functional decoding indicated that this region is functionally involved in (social)--cognitive and emotional processing. Additionally, we found anecdotal to moderate evidence for successful replication of various associations cortical thickness and personality in either GSP or eNKI sample. However, given the inconsistency across samples, these replications are challenging to interpret.

4.1. Limitations and outlook

Moving forward, there are various limitations and challenges in operationalizing personality that might have resulted in a lack of consistent findings across samples. For example, the sample size of the eNKI sample was small ($n = 209$), compared to the HCP and GSP sample, potentially resulting in a lower power to replicate associations between personality and cortical brain structure. Though our samples all were from WEIRD (Western, educated, industrialized, rich, and democratic) populations (Laajaj et al., 2019), it might be that personality traits probed are not comparable across samples due to challenges to reliably operationalize personality, and that confounding environmental and noise effects vary across samples. For example, it is possible inconsistent or lack of findings with regard to macroscale neuroanatomical associations of personality may be a function of the assessment of personality used (in this case, the NEO-FFI/NEO-PI-R) rather than a true null or unreliable finding (Avinun et al. *bioRxiv*). The five-factor personality model and the subsequent operationalizations in instruments such as the NEO are based on a lexical approach. Though such an approach might be able to dissociate various personality traits, it is debated whether lexical taxonomy has a direct relation to neurobiology (Perkins et al., 2020; Yarkoni, 2015). Future studies might benefit from using personality instruments developed in concordance with brain structure and function such as Hierarchical Taxonomy of Psychopathology (HiTOP) (Perkins et al., 2020).

Second, a review on the neurobiology of personality suggested that rather than focusing on a one-to-one mapping between personality and neurobiology, as done in the current

study, studies that seek to identify mechanisms contributing to particular clusters of behaviors might be a more fruitful approach to capture the neurobiological mechanisms underlying personality traits (Yarkoni, 2015). For example, though brain structure is a viable endophenotype of personality, correlation between personality and macro-scale cortical structure is weak. Thus, further study of the relationship between personality and functional activity and functional dynamics might further contribute to understanding the biological basis of personality and other complex traits (Dubois et al., 2018; Kebets et al., 2019; Kong et al., 2019; Wu et al., 2019).

Third, only 40% of personality variance in the current sample could be attributed to genetic effects. Environment, such as family environment, peer-groups, and stress have been reported to influence personality (Hopwood et al., 2011; Nakao et al., 2000), and also local cortical structure and associated behavior has been reported to change as a consequence of changing environments in adulthood (Valk et al., 2017). Though genetic and gene by environment effects are not to be excluded in this context, it is likely such environmental mechanisms further shape the relation between personality traits and brain structure, above and beyond direct additive genetic effects. Longitudinal designs might help to further understand the environmental relationship between personality and brain structure and function.

Taken together, in the current study we report evidence of a shared genetic basis of personality traits and local brain structure within the HCP sample, and a robust association of local surface area in medial prefrontal regions and Neuroticism across three independent samples. It is of note that our study on the shared genetic basis of personality and brain structure was made possible by the open HCP, GSP, and eNKI neuroimaging repositories. These initiatives offer cognitive neuroimaging communities an unparalleled access to large datasets for the investigation of the brain basis of individual difference. They have also enabled us to highlight variability across samples and validation experiments to verify stability of our observations. Notably, the use of multiple datasets enabled us to test robustness of our findings. Given that replicability is essential to understand and evaluate the robustness of brain-behavior associations, our study illustrates the advantages of open data to increase understanding of complex traits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data and code availability statement

All data, analyzed in this manuscript, were obtained from the open-access HCP young adult sample (<http://www.humanconnectome.org/>)(Van Essen et al., 2013) GSP sample, (Holmes et al., 2015), and enhanced NKI-Rockland sample (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3472598/>) (Nooner et al., 2012). Brain images were acquired from the International Neuroimaging Data Sharing Initiative (INDI) online database http://fcon_1000.projects.nitrc.org/indi/enhanced/studies.html. The raw data may not be shared by third parties due to ethics requirements, but can be downloaded directly via the above weblinks. Phenotypic analysis were performed using SurfStat for matlab, (Worsley et al., 2009a), (<https://github.com/MICA-MNI/micaopen/tree/master/surfstat>).

Genetic analyses were performed using solar eclipse 8.4.0 (<http://www.solar-eclipse-genetics.org>), and data on the pedigree analysis is available here: https://www.nitrc.org/projects/se_linux/ (Almasy and Blangero, 1998; Kochunov et al., 2019). BrainMap analysis were performed using <http://www.brainmap.org>(Laird et al., 2009, 2011).

References

- Almasy L, Blangero J, 1998. Multipoint quantitative-trait linkage analysis in general pedigrees. *Am. J. Hum. Genet* 62, 1198–1211. [PubMed: 9545414]
- Almasy L, Dyer TD, Blangero J, 1997. Bivariate quantitative trait linkage analysis: pleiotropy versus co-incident linkages. *Genet. Epidemiol* 14, 953–958. [PubMed: 9433606]
- Alvergne A, Jokela M, Lummaa V, 2010. Personality and reproductive success in a high-fertility human population. *Proc. Natl. Acad. Sci. U. S. A* 107, 11745–11750. [PubMed: 20538974]
- Amodio DM, Frith CD, 2006. Meeting of minds: the medial frontal cortex and social cognition. *Nat. Rev. Neurosci* 7, 268–277. [PubMed: 16552413]
- Asendorpf JB, Wilpers S, 1998. Personality effects on social relationships. *J. Pers. Soc. Psychol* 74, 1531–1544.
- Avinun R, Isreal S, Knodt AR, Hariri AR, biorXiv. No Evidence for Associations between Big Five Personality Traits and Variability in Brain Gray or White Matter
- Baird B, Smallwood J, Gorgolewski KJ, Margulies DS, 2013. Medial and lateral networks in anterior prefrontal cortex support metacognitive ability for memory and perception. *J. Neurosci* 33, 16657–16665. [PubMed: 24133268]
- Benjamini Y, Hochberg Y, 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. Roy. Stat. Soc. B* 57, 289–300.
- Bernhardt BC, Valk SL, Silani G, Bird G, Frith U, Singer T, 2014. Selective disruption of sociocognitive structural brain networks in autism and alexithymia. *Cerebr. Cortex* 24, 3258–3267.
- Bjornebekk A, Fjell AM, Walhovd KB, Grydeland H, Torgersen S, Westlye LT, 2013. Neuronal correlates of the five factor model (FFM) of human personality: multimodal imaging in a large healthy sample. *Neuroimage* 65, 194–208. [PubMed: 23063449]

- Bludau S, Eickhoff SB, Mohlberg H, Caspers S, Laird AR, Fox PT, Schleicher A, Zilles K, Amunts K, 2014. Cytoarchitecture, probability maps and functions of the human frontal pole. *Neuroimage* 93 Pt 2, 260–275. [PubMed: 23702412]
- Bouchard TJ Jr., 1994. Genes, environment, and personality. *Science* 264, 1700–1701. [PubMed: 8209250]
- Bouchard TJ Jr., Loehlin JC, 2001. Genes, evolution, and personality. *Behav. Genet* 31, 243–273. [PubMed: 11699599]
- Bouchard TJ Jr., McGue M, 2003. Genetic and environmental influences on human psychological differences. *J. Neurobiol* 54, 4–45. [PubMed: 12486697]
- Buckner RL, Andrews-Hanna JR, Schacter DL, 2008. The brain's default network: anatomy, function, and relevance to disease. *Ann. N. Y. Acad. Sci* 1124, 1–38. [PubMed: 18400922]
- Costa PT, McCrae RR, 1992. NEO PI-R Professional Manual Psychological Assessment Resources, Inc.
- Dale AM, Fischl B, Sereno MI, 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* 9, 179–194. [PubMed: 9931268]
- Damian RI, Spengler M, Sutu A, Roberts BW, 2019. Sixteen going on sixty-six: a longitudinal study of personality stability and change across 50 years. *J. Pers. Soc. Psychol* 117, 674–695. [PubMed: 30113194]
- de Moor MH, Costa PT, Terracciano A, Krueger RF, de Geus EJ, Toshiko T, Penninx BW, Esko T, Madden PA, Derringer J, Amin N, Willemsen G, Hottenga JJ, Distel MA, Uda M, Sanna S, Spinhoven P, Hartman CA, Sullivan P, Realo A, Allik J, Heath AC, Pergadia ML, Agrawal A, Lin P, Gruzca R, Nobile T, Ciullo M, Rujescu D, Giegling I, Konte B, Widen E, Cousminer DL, Eriksson JG, Palotie A, Peltonen L, Luciano M, Tenesa A, Davies G, Lopez LM, Hansell NK, Medland SE, Ferrucci L, Schlessinger D, Montgomery GW, Wright MJ, Aulchenko YS, Janssens AC, Oostra BA, Metspalu A, Abecasis GR, Deary IJ, Raikonen K, Bierut LJ, Martin NG, van Duijn CM, Boomsma DI, 2012. Meta-analysis of genome-wide association studies for personality. *Mol. Psychiatr* 17, 337–349.
- DeYoung CG, Hirsh JB, Shane MS, Papademetris X, Rajeevan N, Gray JR, 2010. Testing predictions from personality neuroscience. Brain structure and the big five. *Psychol. Sci* 21, 820–828. [PubMed: 20435951]
- Dubois J, Galdi P, Han Y, Paul LK, Adolphs R, 2018. Resting-state functional brain connectivity best predicts the personality dimension of openness to experience. *Personal Neurosci* 1.
- Eickhoff SB, Constable RT, Yeo BTT, 2018. Topographic organization of the cerebral cortex and brain cartography. *Neuroimage* 170, 332–347. [PubMed: 28219775]
- Eyler LT, Chen CH, Panizzon MS, Fennema-Notestine C, Neale MC, Jak A, Jernigan TL, Fischl B, Franz CE, Lyons MJ, Grant M, Prom-Wormley E, Seidman LJ, Tsuang MT, Fiecas MJ, Dale AM, Kremen WS, 2012. A comparison of heritability maps of cortical surface area and thickness and the influence of adjustment for whole brain measures: a magnetic resonance imaging twin study. *Twin Res. Hum. Genet* 15, 304–314. [PubMed: 22856366]
- Ferschmann L, Fjell AM, Vollrath ME, Grydeland H, Walhovd KB, Tamnes CK, 2018. Personality traits are associated with cortical development across adolescence: a longitudinal structural MRI study. *Child Dev* 89, 811–822. [PubMed: 29313947]
- Fischl B, 2013. FreeSurfer. *Neuroimage* 62, 774–781.
- Fischl B, Dale AM, 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc. Natl. Acad. Sci. U. S. A* 97, 11050–11055. [PubMed: 10984517]
- Fischl B, Sereno MI, Dale AM, 1999. Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. *Neuroimage* 9, 195–207. [PubMed: 9931269]
- Fleming SM, Dolan RJ, 2012. The neural basis of metacognitive ability. *Philos. Trans. R. Soc. Lond. B Biol. Sci* 367, 1338–1349. [PubMed: 22492751]
- Fox PT, Lancaster JL, Laird AR, Eickhoff SB, 2014. Meta-analysis in human neuroimaging: computational modeling of large-scale databases. *Annu. Rev. Neurosci* 37, 409–434. [PubMed: 25032500]
- Funder DC, 2001. Personality. *Annu. Rev. Psychol* 52, 197–221. [PubMed: 11148304]

- Genetics of Personality Consortium, 2015. Meta-analysis of genome-wide association studies for neuroticism, and the polygenic association with major depressive disorder. *JAMA Psychiatry* 72 (7), 642–650. 10.1001/jamapsychiatry.2015.0554. [PubMed: 25993607]
- Genon S, Reid A, Langner R, Amunts K, Eickhoff SB, 2018. How to characterize the function of a brain region. *Trends Cognit. Sci* 22, 350–364. [PubMed: 29501326]
- Glahn DC, Winkler AM, Kochunov P, Almasy L, Duggirala R, Carless MA, Curran JC, Olvera RL, Laird AR, Smith SM, Beckmann CF, Fox PT, Blangero J, 2010. Genetic control over the resting brain. *Proc. Natl. Acad. Sci. U. S. A* 107, 1223–1228. [PubMed: 20133824]
- Glasser MF, Sotiropoulos SN, Wilson JA, Coalson TS, Fischl B, Andersson JL, Xu J, Jbabdi S, Webster M, Polimeni JR, Van Essen DC, Jenkinson M, Consortium, W.U.-M.H, 2013. The minimal preprocessing pipelines for the Human Connectome Project. *Neuroimage* 80, 105–124. [PubMed: 23668970]
- Grasby KL, Jahanshad N, Painter JN, Colodro-Conde L, Bralten J, Hibar DP, Lind PA, Pizzagalli F, Ching CRK, McMahon MAB, Shatikhina N, Zsembik LCP, Thomopoulos SI, Zhu AH, Strike LT, Agartz I, Alhusaini S, Almeida MAA, Alnaes D, Amlien IK, Andersson M, Ard T, Armstrong NJ, Ashley-Koch A, Atkins JR, Bernard M, Brouwer RM, Buimer EEL, Bulow R, Burger C, Cannon DM, Chakravarty M, Chen Q, Cheung JW, Couvy-Duchesne B, Dale AM, Dalvie S, de Araujo TK, de Zubicaray GI, de Zwart SMC, den Braber A, Doan NT, Dohm K, Ehrlich S, Engelbrecht HR, Erk S, Fan CC, Fedko IO, Foley SF, Ford JM, Fukunaga M, Garrett ME, Ge T, Giddaluru S, Goldman AL, Green MJ, Groenewold NA, Grotegerd D, Gurholt TP, Gutman BA, Hansell NK, Harris MA, Harrison MB, Haswell CC, Hauser M, Herms S, Heslenfeld DJ, Ho NF, Hoehn D, Hoffmann P, Holleran L, Hoogman M, Hottenga JJ, Ikeda M, Janowitz D, Jansen IE, Jia T, Jockwitz C, Kanai R, Karama S, Kasperaviciute D, Kaufmann T, Kelly S, Kikuchi M, Klein M, Knapp M, Knodt AR, Kramer B, Lam M, Lancaster TM, Lee PH, Lett TA, Lewis LB, Lopes-Cendes I, Luciano M, Macciardi F, Marquand AF, Mathias SR, Melzer TR, Milaneschi Y, Mirza-Schreiber N, Moreira JCV, Muhleisen TW, Muller-Myhsok B, Najt P, Nakahara S, Nho K, Olde Loohuis LM, Orfanos DP, Pearson JF, Pitcher TL, Putz B, Quide Y, Ragothaman A, Rashid FM, Reay WR, Redlich R, Reinbold CS, Reppele J, Richard G, Riedel BC, Risacher SL, Rocha CS, Mota NR, Salminen L, Saremi A, Saykin AJ, Schlag F, Schmaal L, Schofield PR, Secolin R, Shapland CY, Shen L, Shin J, Shumskaya E, Sonderby IE, Sprooten E, Tansey KE, Teumer A, Thalamuthu A, Tordesillas-Gutierrez D, Turner JA, Uhlmann A, Vallerga CL, van der Meer D, van Donkelaar MMJ, van Eijk L, van Erp TGM, van Haren NEM, van Rooij D, van Tol MJ, Veldink JH, Verhoef E, Walton E, Wang M, Wang Y, Wardlaw JM, Wen W, Westlye LT, Whelan CD, Witt SH, Wittfeld K, Wolf C, Wolfers T, Wu JQ, Yasuda CL, Zaremba D, Zhang Z, Zwiers MP, Artiges E, Assareh AA, Ayesa-Arriola R, Belger A, Brandt CL, Brown GG, Cichon S, Curran JE, Davies GE, Degenhardt F, Dennis MF, Dietsche B, Djurovic S, Doherty CP, Espiritu R, Garijo D, Gil Y, Gowland PA, Green RC, Hausler AN, Heindel W, Ho BC, Hoffmann WU, Holsboer F, Homuth G, Hosten N, Jack CR Jr., Jang M, Jansen A, Kimbrel NA, Kolskar K, Koops S, Krug A, Lim KO, Luykx JJ, Mathalon DH, Mather KA, Mattay VS, Matthews S, Mayoral Van Son J, McEwen SC, Melle I, Morris DW, Mueller BA, Nauck M, Nordvik JE, Nothen MM, O’Leary DS, Opel N, Martinot MP, Pike GB, Preda A, Quinlan EB, Rasser PE, Ratnakar V, Reppermund S, Steen VM, Tooney PA, Torres FR, Veltman DJ, Voyvodic JT, Whelan R, White T, Yamamori H, Adams HHH, Bis JC, Debette S, Decarli C, Fornage M, Gudnason V, Hofer E, Ikram MA, Launer L, Longstreth WT, Lopez OL, Mazoyer B, Mosley TH, Roshchupkin GV, Satizabal CL, Schmidt R, Seshadri S, Yang Q, , Alzheimer’s Disease Neuroimaging, I, Consortium, C, Consortium, E, Consortium, I, Consortium, S.Y.S, Parkinson’s Progression Markers, I, Alvim MKM, Ames D, Anderson TJ, Andreassen OA, Arias-Vasquez A, Bastin ME, Baune BT, Beckham JC, Blangero J, Boomsma DI, Brodaty H, Brunner HG, Buckner RL, Buitelaar JK, Bustillo JR, Cahn W, Cairns MJ, Calhoun V, Carr VJ, Caseras X, Caspers S, Cavalleri GL, Cendes F, Corvin A, Crespo-Facorro B, Dalrymple-Alford JC, Dannlowski U, de Geus EJC, Deary IJ, Delanty N, Depondt C, Desrivieres S, Donohoe G, Espeseth T, Fernandez G, Fisher SE, Flor H, Forstner AJ, Francks C, Franke B, Glahn DC, Gollub RL, Grabe HJ, Gruber O, Haberg AK, Hariri AR, Hartman CA, Hashimoto R, Heinz A, Henskens FA, Hillegers MHJ, Holmes AJ, Hong LE, Hopkins WD, Hulshoff Pol HE, Jernigan TL, Jonsson EG, Kahn RS, Kennedy MA, Kircher TTJ, Kochunov P, Kwok JBJ, Le Hellard S, Loughland CM, Martin NG, Martinot JL, McDonald C, McMahon KL, Meyer-Lindenberg A, Michie PT, Morey RA, Mowry B, Nyberg L, Oosterlaan J, Ophoff RA, Pantelis C, Paus T, Pausova Z, Penninx B, Polderman TJC, Posthuma D, Rietschel

M, Roffman JL, Rowland LM, Sachdev PS, Samann PG, Schall U, Schumann G, Scott RJ, Sim K, Sisodiya SM, Smoller JW, Sommer IE, St Pourcain B, Stein DJ, Toga AW, Trollor JN, Van der Wee NJA, van 't Ent D, Volzke H, Walter H, Weber B, Weinberger DR, Wright MJ, Zhou J, Stein JL, Thompson PM, Medland SE, Enhancing Neuroimaging Genetics through Meta-Analysis Consortium- Genetics working, g, 2020. The genetic architecture of the human cerebral cortex. *Science* 367.

- Gray JC, Owens MM, Hyatt CS, Miller JD, 2019. No Evidence for Morphometric Associations of the Amygdala and hippocampus with the Five-Factor Model Personality Traits. *psyarXiv*.
- Harris MA, Brett CE, Johnson W, Deary IJ, 2016. Personality stability from age 14 to age 77 years. *Psychol. Aging* 31, 862–874. [PubMed: 27929341]
- Hofer E, al, e., 2018. Genetic Determinants of Cortical Structure (Thickness, Surface Area and Volumes) Among Disease Free Adults in the CHARGE Consortium. *bioRxiv*. 10.1101/409649 preprint first posted online Sep. 9, 2018.
- Holmes AJ, Hollinshead MO, O'Keefe TM, Petrov VI, Fariello GR, Wald LL, Fischl B, Rosen BR, Mair RW, Roffman JL, Smoller JW, Buckner RL, 2015. Brain Genomics Superstruct Project initial data release with structural, functional, and behavioral measures. *Sci Data* 2, 150031. [PubMed: 26175908]
- Hopwood CJ, Donnellan MB, Blonigen DM, Krueger RF, McGue M, Iacono WG, Burt SA, 2011. Genetic and environmental influences on personality trait stability and growth during the transition to adulthood: a three-wave longitudinal study. *J. Pers. Soc. Psychol* 100, 545–556. [PubMed: 21244174]
- Jang KL, Livesley WJ, Vernon PA, 1996. Heritability of the big five personality dimensions and their facets: a twin study. *J. Pers* 64, 577–591. [PubMed: 8776880]
- John OP, Naumann LP, Soto CJ, 2008. *Paradigm Shift to the Integrative Big-Five Trait Taxonomy: History, Measurement, and Conceptual Issues*. Guilford Press, New York, NY.
- John OP, Srivastava S, 1999. The Big Five Trait taxonomy: history, measurement, and theoretical perspectives. In: Pervin LA, John OP (Eds.), *Handbook of Personality: Theory and Research*. Guilford Press, pp. 102–138.
- Kebets V, Holmes AJ, Orban C, Tang S, Li J, Sun N, Kong R, Poldrack RA, Yeo BTT, 2019. Somatosensory-motor dysconnectivity spans multiple transdiagnostic dimensions of Psychopathology. *Biol. Psychiatr* 86, 779–791.
- Kharabian Masouleh S, Eickhoff SB, Genon S, *bioRxiv*. Searching for Replicable Associations between Cortical Thickness and Psychometric Variables in Healthy Adults: Empirical Facts.
- Kharabian Masouleh S, 2019. Empirical examination of the replicability of associations between brain structure and psychological variables. *elife* 8, e43464. 10.7554/eLife.43464. [PubMed: 30864950]
- Kharabian Masouleh S, Eickhoff SB, Zeighami Y, Lewis LB, Dahnke R, Gaser C, Chouinard-Decorte F, Lepage C, Scholtens LH, Hoffstaedter F, Glahn DC, Blangero J, Evans AC, Genon S, Valk SL, 2020. Influence of processing pipeline on cortical thickness measurement. *Cerebr. Cortex*, bhaa097. 10.1093/cercor/bhaa097.
- Kochunov P, Donohue B, Mitchell BD, Ganjgahi H, Adhikari B, Ryan M, Medland SE, Jahanshad N, Thompson PM, Blangero J, Fieremans E, Novikov DS, Marcus D, Van Essen DC, Glahn DC, Elliot Hong L, Nichols TE, 2019. Genomic kinship construction to enhance genetic analyses in the human connectome project data. *Hum. Brain Mapp* 40, 1677–1688. [PubMed: 30496643]
- Kong R, Li J, Orban C, Sabuncu MR, Liu H, Schaefer A, Sun N, Zuo XN, Holmes AJ, Eickhoff SB, Yeo BTT, 2019. Spatial topography of individual-specific cortical networks predicts human cognition, personality, and emotion. *Cerebr. Cortex* 29, 2533–2551.
- Kremen WS, Prom-Wormley E, Panizzon MS, Eyer LT, Fischl B, Neale MC, Franz CE, Lyons MJ, Pacheco J, Perry ME, Stevens A, Schmitt JE, Grant MD, Seidman LJ, Thermenos HW, Tsuang MT, Eisen SA, Dale AM, Fennema-Notestine C, 2010. Genetic and environmental influences on the size of specific brain regions in midlife: the VETSA MRI study. *Neuroimage* 49, 1213–1223. [PubMed: 19786105]
- Laajaj R, Macours K, Pinzon Hernandez DA, Arias O, Gosling SD, Potter J, Rubio-Codina M, Vakis R, 2019. Challenges to capture the big five personality traits in non-WEIRD populations. *Science Advances* 5.

- Laird AR, Eickhoff SB, Fox PM, Uecker AM, Ray KL, Saenz JJ Jr., McKay DR, Bzdok D, Laird RW, Robinson JL, Turner JA, Turkeltaub PE, Lancaster JL, Fox PT, 2011. The BrainMap strategy for standardization, sharing, and meta-analysis of neuroimaging data. *BMC Res. Notes* 4, 349. [PubMed: 21906305]
- Laird AR, Eickhoff SB, Kurth F, Fox PM, Uecker AM, Turner JA, Robinson JL, Lancaster JL, Fox PT, 2009. ALE meta-analysis workflows via the brainmap database: progress towards A probabilistic functional brain atlas. *Front. Neuroinf* 3, 23.
- Latzman RD, Hecht LK, Freeman HD, Schapiro SJ, Hopkins WD, 2015. Neuroanatomical correlates of personality in chimpanzees (*Pan troglodytes*): associations between personality and frontal cortex. *Neuroimage* 123, 63–71. [PubMed: 26311604]
- Lo MT, Hinds DA, Tung JY, Franz C, Fan CC, Wang Y, Smeland OB, Schork A, Holland D, Kauppi K, Sanyal N, Escott-Price V, Smith DJ, O'Donovan M, Stefansson H, Bjornsdottir G, Thorgeirsson TE, Stefansson K, McEvoy LK, Dale AM, Andreassen OA, Chen CH, 2017. Genome-wide analyses for personality traits identify six genomic loci and show correlations with psychiatric disorders. *Nat. Genet* 49, 152–156. [PubMed: 27918536]
- Loehlin JC, McCrae RR, Costa PT, John OP, 1998. Heritabilities of common and measure-specific components of the big five personality factors. *J. Res. Pers* 32, 431–453.
- Marcus DS, Harms MP, Snyder AZ, Jenkinson M, Wilson JA, Glasser MF, Barch DM, Archie KA, Burgess GC, Ramaratnam M, Hodge M, Horton W, Herrick R, Olsen T, McKay M, House M, Hileman M, Reid E, Harwell J, Coalson T, Schindler J, Elam JS, Curtiss SW, Van Essen DC, Consortium, W.U.-M.H., 2013. Human Connectome Project informatics: quality control, database services, and data visualization. *Neuroimage* 80, 202–219. [PubMed: 23707591]
- McCrae RR, Costa PT, 2004. A contemplated revision of the NEO Five-Factor Inventory. *Pers. Individ. Differ* 36, 587–596.
- McCrae RR, Costa PT Jr., 1997. Personality trait structure as a human universal. *Am. Psychol* 52, 509–516. [PubMed: 9145021]
- McCrae RR, Terracciano A, 2005. Personality profiles of cultures: aggregate personality traits. *J. Pers. Soc. Psychol* 89, 407–425. [PubMed: 16248722]
- Miller JD, Lynam DR, Widiger TA, Leukefeld C, 2001. Personality disorders as extreme variants of common personality dimensions: can the Five-Factor Model adequately represent psychopathy? *J. Pers* 69, 253–276. [PubMed: 11339798]
- Mischel W, 2004. Toward an integrative science of the person. *Annu. Rev. Psychol* 55, 1–22. [PubMed: 14744208]
- Mugler JP 3rd, Brookeman JR, 1990. Three-dimensional magnetization-prepared rapid gradient-echo imaging (3D MP RAGE). *Magn. Reson. Med* 15, 152–157. [PubMed: 2374495]
- Nakao K, Takaishi J, Tatsuta K, Katayama H, Iwase M, Yorifuji K, Takeda M, 2000. The influences of family environment on personality traits. *Psychiatr. Clin. Neurosci* 54, 91–95.
- Nooner KB, Colcombe SJ, Tobe RH, Mennes M, Benedict MM, Moreno AL, Panek LJ, Brown S, Zavitz ST, Li Q, Sikka S, Gutman D, Bangaru S, Schlachter RT, Kamiel SM, Anwar AR, Hinz CM, Kaplan MS, Rachlin AB, Adelsberg S, Cheung B, Khanuja R, Yan C, Craddock CC, Calhoun V, Courtney W, King M, Wood D, Cox CL, Kelly AM, Di Martino A, Petkova E, Reiss PT, Duan N, Thomsen D, Biswal B, Coffey B, Hoptman MJ, Javitt DC, Pomara N, Sidtis JJ, Koplewicz HS, Castellanos FX, Leventhal BL, Milham MP, 2012. The NKI-Rockland sample: a model for accelerating the pace of discovery science in psychiatry. *Front. Neurosci* 6, 152. [PubMed: 23087608]
- Nostro AD, Muller VI, Reid AT, Eickhoff SB, 2017. Correlations between personality and brain structure: a crucial role of gender. *Cerebr. Cortex* 27, 3698–3712.
- Owens MM, Hyatt CS, Gray JC, Carter NT, MacKillop J, Miller JD, Sweet LH, 2019. Cortical morphometry of the five-factor model of personality: findings from the Human Connectome Project full sample. *Soc. Cognit. Affect Neurosci* 14, 381–395. [PubMed: 30848280]
- Panizzon MS, Fennema-Notestine C, Eyer LT, Jernigan TL, Prom-Wormley E, Neale M, Jacobson K, Lyons MJ, Grant MD, Franz CE, Xian H, Tsuang M, Fischl B, Seidman L, Dale A, Kremen WS, 2009. Distinct genetic influences on cortical surface area and cortical thickness. *Cerebr. Cortex* 19, 2728–2735.

- Penke L, Jokela M, 2016. The evolutionary genetics of personality revisited. *Cur. Op, Psyc* 7, 104–109.
- Perkins ER, Lutzman RD, Patrick CJ, 2020. Interfacing neural constructs with the hierarchical taxonomy of Psychopathology: ‘why’ and ‘how. *Pers. Ment. Health* 14, 106–122.
- Riccelli R, Toschi N, Nigro S, Terracciano A, Passamonti L, 2017. Surface-based morphometry reveals the neuroanatomical basis of the five-factor model of personality. *Soc. Cognit. Affect Neurosci* 12, 671–684. [PubMed: 28122961]
- Rothmann S, Coetzer EP, 2003. The big five personality dimensions and job performance. *SA J. Ind. Psychol* 29.
- Saucier G, Srivastava S, 2015. What makes a good structural model of personality? Evaluating the big five and alternatives. In: Mikulincer M, Shaver PR (Eds.), *APA Handbook of Personality and Social Psychology: Vol 4. Personality Processes and Individual Differences*. American Psychological Association.
- Schaefer A, Kong R, Gordon EM, Laumann TO, Zuo XN, Holmes AJ, Eickhoff SB, Yeo BTT, 2018. Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI. *Cerebr. Cortex* 28, 3095–3114.
- Schoenberg MR, Scott JG, Duff K, Adams RL, 2002. Estimation of WAIS-III intelligence from combined performance and demographic variables: development of the OPIE-3. *Clin. Neuropsychol* 16, 426–437. [PubMed: 12822052]
- Strickhouser JE, Zell E, Krizan Z, 2017. Does personality predict health and wellbeing? A metasynthesis. *Health Psychol* 36, 797–810. [PubMed: 28277701]
- Strike LT, Hansell NK, Couvy-Duchesne B, Thompson PM, de Zubicaray GI, McMahon KL, Wright MJ, March 2019. Genetic complexity of cortical structure: differences in genetic and environmental factors influencing cortical surface area and thickness. *Cerebr. Cortex* 29 (3), 952–962. 10.1093/cercor/bhy002.
- Trull TJ, 2013. Dimensional models of personality: the five-factor model and the DSM-5. *Dialogues Clin. Neurosci* 15, 135–146. [PubMed: 24174888]
- Valk SL, Bernhardt BC, Bockler A, Kanske P, Singer T, 2016a. Substrates of metacognition on perception and metacognition on higher-order cognition relate to different subsystems of the mentalizing network. *Hum. Brain Mapp* 37, 3388–3399. [PubMed: 27151776]
- Valk SL, Bernhardt BC, Bockler A, Trautwein FM, Kanske P, Singer T, Feb 2017. Socio-cognitive phenotypes differentially modulate large-scale structural covariance networks. *Cerebr. Cortex* 27 (2), 1358–1368. 10.1093/cercor/bhy319.
- Valk SL, Bernhardt BC, Trautwein FM, Bockler A, Kanske P, Guizard N, Collins DL, Singer T, 2017. Structural plasticity of the social brain: differential change after socio-affective and cognitive mental training. *Sci Adv* 3, e1700489. [PubMed: 28983507]
- van den Berg SM, de Moor MH, Verweij KJ, Krueger RF, Luciano M, Arias Vasquez A, Matteson LK, Derringer J, Esko T, Amin N, Gordon SD, Hansell NK, Hart AB, Seppala I, Huffman JE, Konte B, Lahti J, Lee M, Miller M, Nutile T, Tanaka T, Teumer A, Viktorin A, Wedenoja J, Abdellaoui A, Abecasis GR, Adkins DE, Agrawal A, Allik J, Appel K, Bigdeli TB, Busonero F, Campbell H, Costa PT, Smith GD, Davies G, de Wit H, Ding J, Engelhardt BE, Eriksson JG, Fedko IO, Ferrucci L, Franke B, Giegling I, Grucza R, Hartmann AM, Heath AC, Heinonen K, Henders AK, Homuth G, Hottenga JJ, Iacono WG, Janzing J, Jokela M, Karlsson R, Kemp JP, Kirkpatrick MG, Latvala A, Lehtimaki T, Liewald DC, Madden PA, Magri C, Magnusson PK, Marten J, Maschio A, Mbarek H, Medland SE, Mihailov E, Milaneschi Y, Montgomery GW, Nauck M, Nivard MG, Ouwens KG, Palotie A, Pettersson E, Polasek O, Qian Y, Pulkki-Raback L, Raitakari OT, Realo A, Rose RJ, Ruggiero D, Schmidt CO, Slutske WS, Sorice R, Starr JM, St Pourcain B, Sutin AR, Timpson NJ, Trochet H, Vermeulen S, Vuoksima E, Widen E, Wouda J, Wright MJ, Zgaga L, Generation S, Porteous D, Minelli A, Palmer AA, Rujescu D, Ciullo M, Hayward C, Rudan I, Metspalu A, Kaprio J, Deary IJ, Raikonen K, Wilson JF, Keltikangas-Jarvinen L, Bierut LJ, Hetttema JM, Grabe HJ, Penninx BW, van Duijn CM, Evans DM, Schlessinger D, Pedersen NL, Terracciano A, McGue M, Martin NG, Boomsma DI, 2016. Meta-analysis of genome-wide association studies for extraversion: findings from the genetics of personality Consortium. *Behav. Genet* 46, 170–182. [PubMed: 26362575]
- Van Essen DC, Glasser MF, 2018. Parcellating cerebral cortex: how invasive animal studies inform noninvasive mapping in humans. *Neuron* 99, 640–663. [PubMed: 30138588]

- Van Essen DC, Smith SM, Barch DM, Behrens TE, Yacoub E, Ugurbil K, Consortium, W.U.-M.H., 2013. The Wu-minn human connectome project: an overview. *Neuroimage* 80, 62–79. [PubMed: 23684880]
- Verhagen J, Wagenmakers EJ, 2014. Bayesian tests to quantify the result of a replication attempt. *J. Exp. Psychol. Gen* 143, 1457–1475. [PubMed: 24867486]
- Verweij KJ, Yang J, Lahti J, Veijola J, Hintsanen M, Pulkki-Raback L, Heinonen K, Pouta A, Pesonen AK, Widen E, al, e., 2012. Maintenance of genetic variation in human personality: testing evolutionary models by estimating heritability due to common causal variants and investigating the effect of distant inbreeding. *Evolution* 66, 3288–3251.
- Vukasovic T, Bratko D, 2015. Heritability of personality: a meta-analysis of behavior genetic studies. *Psychol. Bull* 141, 769–785. [PubMed: 25961374]
- Wechsler D, 1999. Wechsler Abbreviated Scale of Intelligence. The Psychological Corporation., San Antonio, TX.
- Weintraub S, Dikmen SS, Heaton RK, Tulsky DS, Zelazo PD, Bauer PJ, Carlozzi NE, Slotkin J, Blitz D, Wallner-Allen K, Fox NA, Beaumont JL, Mungas D, Nowinski CJ, Richler J, Deocampo JA, Anderson JE, Manly JJ, Borosh B, Havlik R, Conway K, Edwards E, Freund L, King JW, Moy C, Witt E, Gershon RC, 2013. Cognition assessment using the NIH Toolbox. *Neurology* 80, S54–S64. [PubMed: 23479546]
- Winkler AM, Kochunov P, Blangero J, Almasy L, Zilles K, Fox PT, Duggirala R, Glahn DC, 2010. Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *Neuroimage* 53, 1135–1146. [PubMed: 20006715]
- Worsley K, Taylor JE, Carbonell F, Chung MK, Duerden E, Bernhardt BC, Lyttelton OC, Boucher M, Evans A, 2009a. SurfStat: a Matlab toolbox for the statistical analysis of univariate and multivariate surface and volumetric data using linear mixed effect models and random field theory. *Neuroimage* S102.
- Worsley K, Taylor JE, Carbonell F, Chung MK, Duerden E, Bernhardt BC, Lyttelton OC, Boucher M, Evans AC, 2009b. SurfStat: a Matlab toolbox for the statistical analysis of univariate and multivariate surface and volumetric data using linear mixed effects models and random field theory. *Neuroimage* 47.
- Wu X, He H, Shi L, Xia Y, Zuang K, Feng Q, Zhang Y, Ren Z, Wei D, Qiu J, 2019. Personality traits are related with dynamic functional connectivity in major depression disorder: a resting-state analysis. *J. Affect. Disord* 245, 1032–1042. [PubMed: 30699845]
- Yarkoni T, 2015. Neurobiological substrates of personality: a critical overview. In: M M, R SP, L CM, J LR (Eds.), *APA Handbooks in Psychology®. APA Handbook of Personality and Social Psychology*. American Psychological Association, pp. 61–83.
- Zheng D, Chen J, Wang X, Zhou Y, 2019. Genetic contribution to the phenotypic correlation between trait impulsivity and resting-state functional connectivity of the amygdala and its subregions. *Neuroimage* 201, 115997. [PubMed: 31284029]

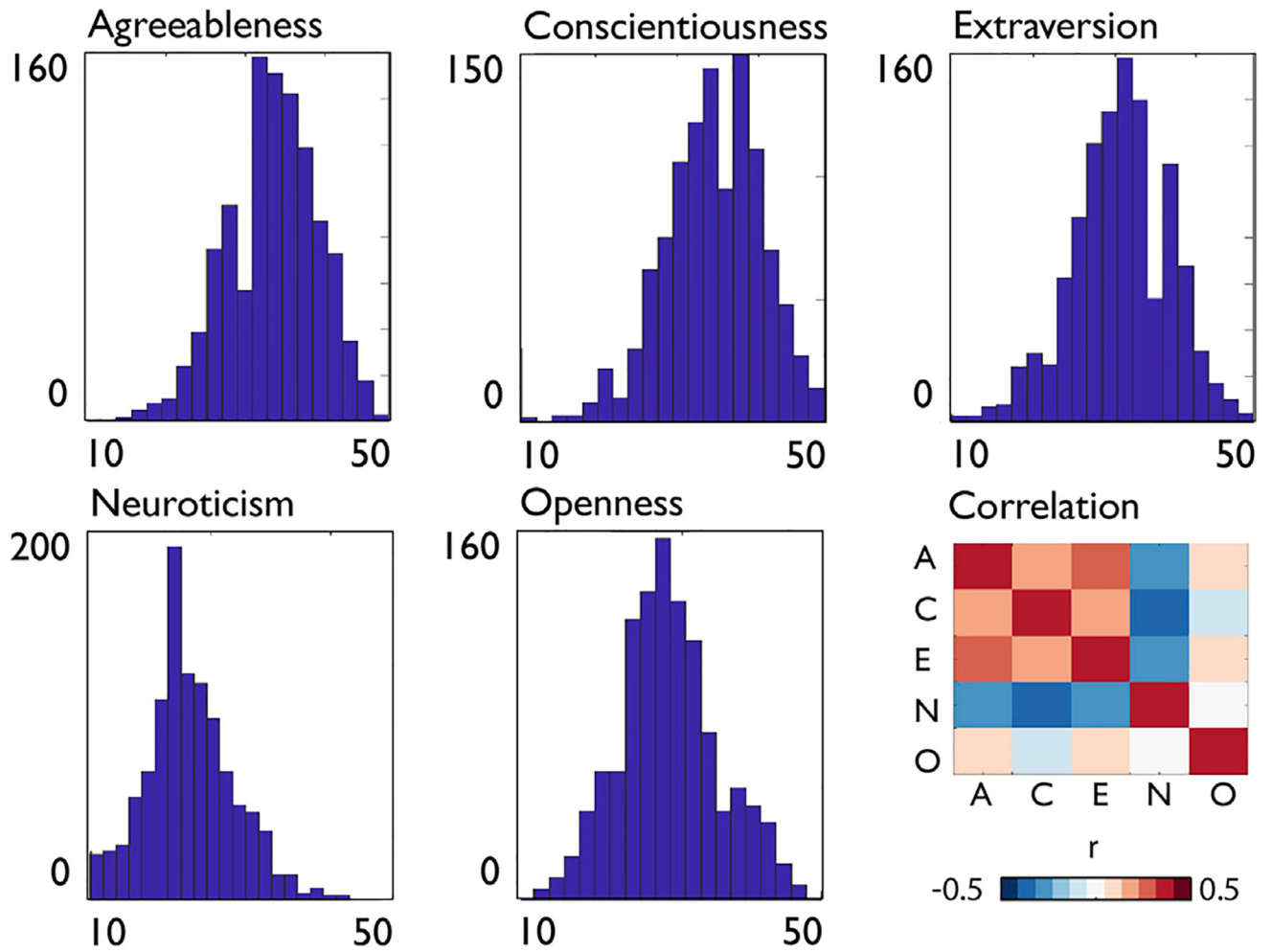


Fig. 1. Distribution of personality traits in the full HCP sample.

Distribution of NEO-FFI personality traits in the HCP dataset, score on x-axis, number of occurrences on the y-axis, as well as the correlation between NEO-FFI traits in the HCP sample (A = Agreeableness, C = Conscientiousness, E = Extraversion, N = Neuroticism, O = Openness).

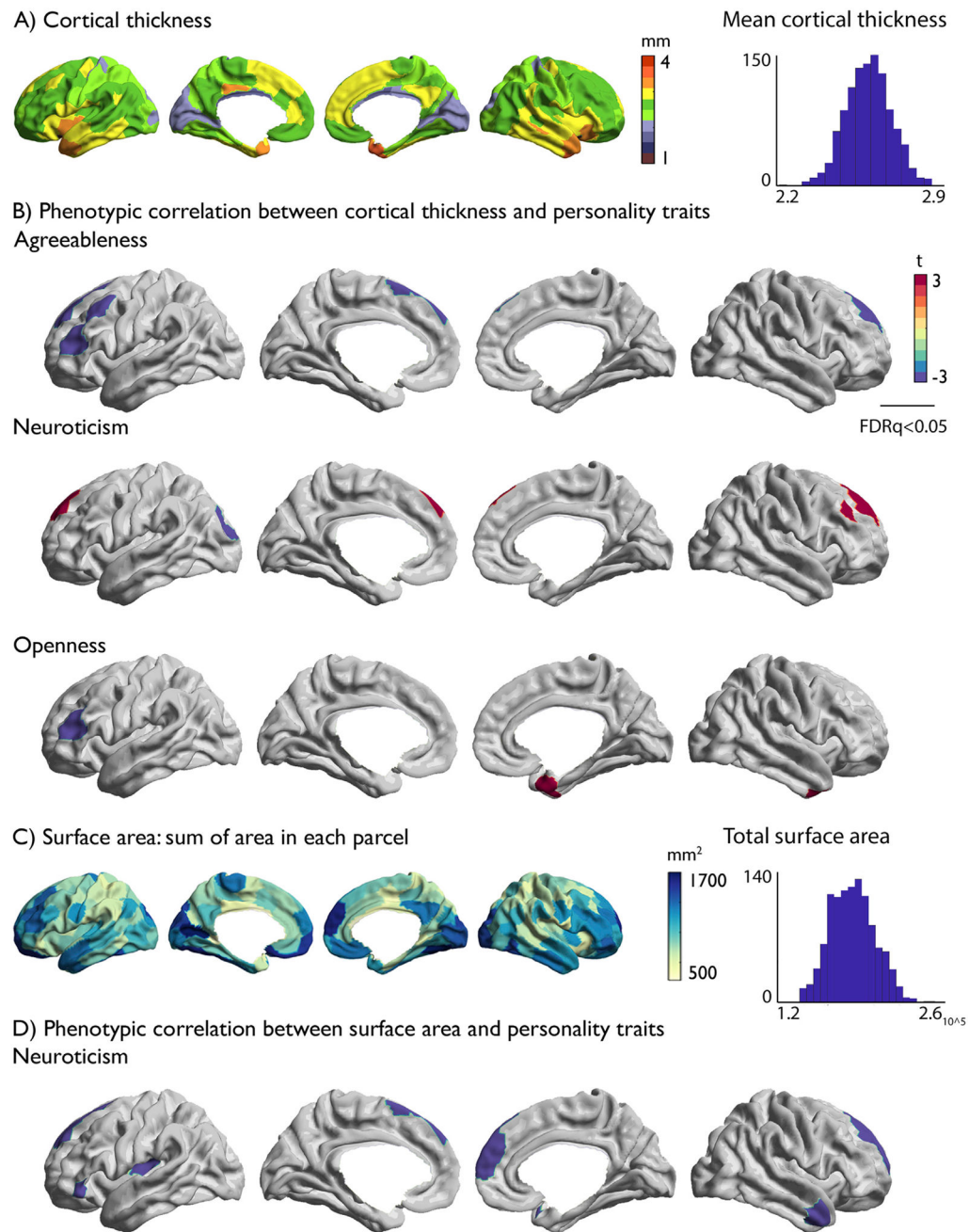
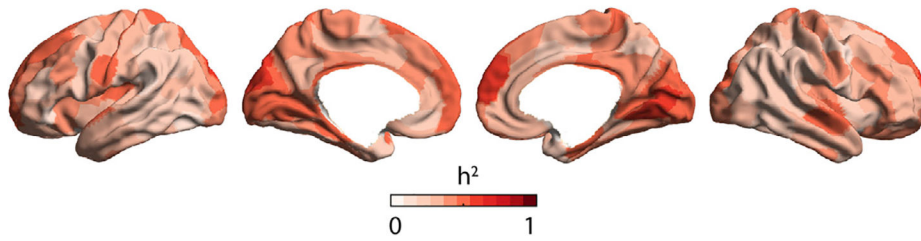
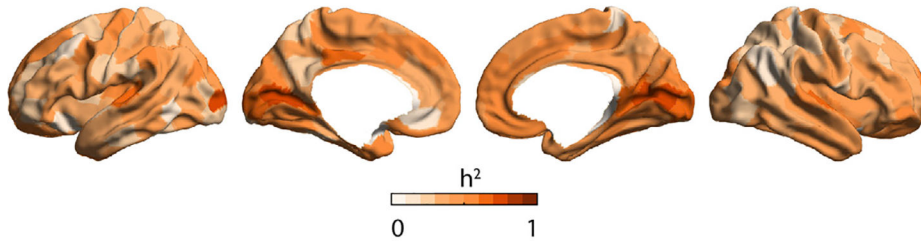


Fig. 2. Relation between personality traits and local brain structure in the full HCP sample. A) Mean cortical thickness of each parcel and the distribution of average cortical thickness across participants; B) Regional associations between personality traits and cortical thickness; C) Average surface area sum per parcel and the distribution of total surface area across participants; D) Regional associations between surface area and personality traits. Positive associations between local brain structure and each personality trait are displayed in red and negative associations displayed in blue. Multiple comparisons were accounted for by using FDR corrections at $q < 0.05$ correcting for the number of parcels (200) and only significant associations are displayed.

A) Heritability of cortical thickness



B). Heritability of surface area



C) Heritability of NEO-FFI

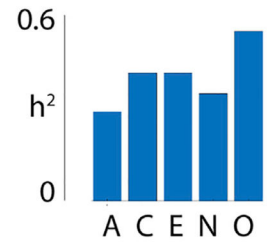


Fig. 3. Heritability of local cortical structure and personality traits.

A) Heritability of local cortical thickness; B) Heritability of surface area; C) Heritability of NEO-FFI: A = Agreeableness, C=Conscientiousness, E = Extraversion, N=Neuroticism, O=Openness.

Right medial frontal cortex
Surface area - Neuroticism

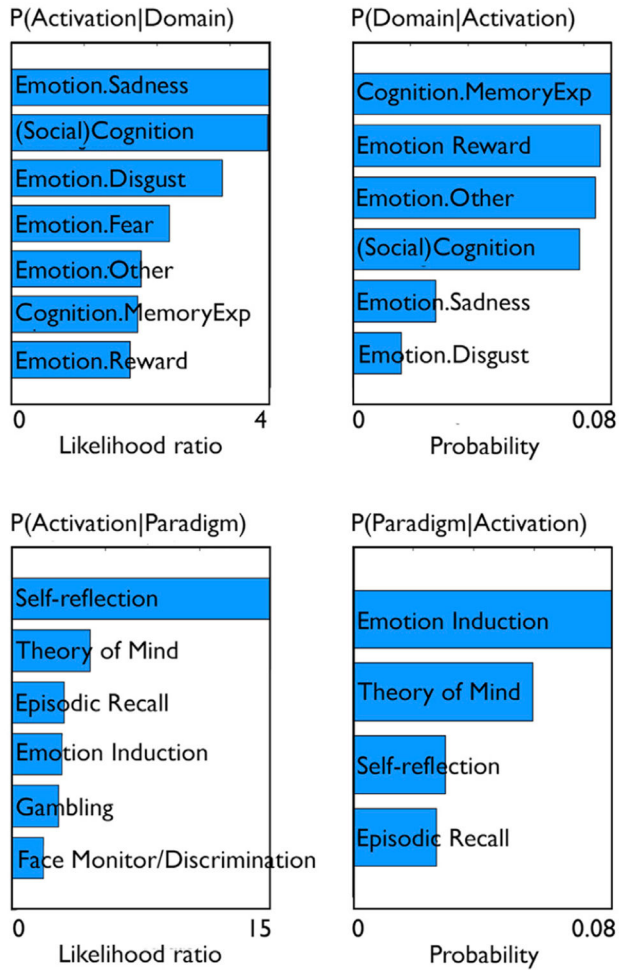
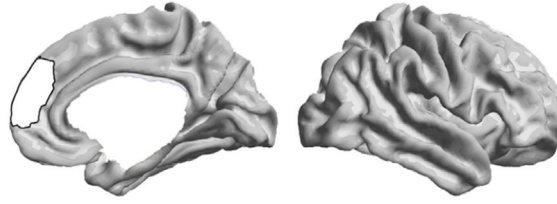


Fig. 4. Quantitative functional decoding of consistent associations between personality and local brain structure.

Both forward inference and reverse inference of activation-domain and paradigm-domain contrasts are reported for the right medial frontal cortex which showed evidence of successful replication in two samples.

Table 1

Behavioral characteristics of the HCP sample.

Measure	n	mean \pm SD (min-max)
<i>Males/Females</i>	504/598	–
<i>Age</i>	1102	28.8 \pm 3.7 (22–37)
<i>Intelligence (Composite score)</i>	1085	121.9 \pm 14.6 (84.6–153.4)
<i>Agreeableness</i>	1102	33.5 \pm 5.8 (10–48)
<i>Conscientiousness</i>	1102	34.5 \pm 5.9 (11–48)
<i>Extraversion</i>	1102	30.7 \pm 6 (10–47)
<i>Neuroticism</i>	1102	16.6 \pm 7.3 (0–43)
<i>Openness</i>	1102	28.3 \pm 6.2 (10–47)

Behavioral characteristics for gender, age, intelligence as well as the NEO-FFI scores in the HCP sample.

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Table 2

Behavioral characteristics of the GSP sample.

Measure	n	mean \pm SD (min-max)
<i>Males/Females</i>	535/390	–
<i>Age</i>	925	21.6 \pm 3.9 (19–35)
<i>Estimated IQ</i>	891	108.7 \pm 8.1 (77–129)
<i>Agreeableness</i>	925	32.0 \pm 6.6 (9–47)
<i>Conscientiousness</i>	925	31.7 \pm 7.2 (8–48)
<i>Extraversion</i>	925	30.7 \pm 6.5 (9–48)
<i>Neuroticism</i>	925	20.3 \pm 8.8 (0–48)
<i>Openness</i>	925	31.6 \pm 6.1 (14–47)

Behavioral characteristics for gender, age, intelligence as well as the NEO-FFI scores in the GSP sample.

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Table 3

Behavioral characteristics of the eNKI sample.

Measure	n	mean ± SD (min-max)
<i>Males/Females</i>	121/88	–
<i>Age</i>	209	26.0 ± 6.1 (18–39)
<i>Intelligence (WASI)</i>	209	100.3 ± 12.3 (69–135)
<i>Agreeableness</i>	209	33.6 ± 6.1 (18–48)
<i>Conscientiousness</i>	209	33.9 ± 7.3 (13–48)
<i>Extraversion</i>	209	30.5 ± 6.3 (7–44)
<i>Neuroticism</i>	209	19.7 ± 8.1(2–42)
<i>Openness</i>	209	33.0 ± 6.2 (12–48)

Behavioral characteristics for gender, age, intelligence as well as the NEO-FFI scores in the eNKI sample.

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Table 4

Association between personality traits and whole brain summaries of surface area and cortical thickness in the full HCP sample.

	Average cortical thickness	Total surface area
Agreeableness	0.13	0.97
Conscientiousness	0.49	-2.45 **
Extraversion	0.83	1.01
Neuroticism	1.95 *	-2.19 *
Openness	-1.21	2.68 **

T-values of the association between average cortical thickness and total surface area and personality traits.

** indicates FDR $q < 0.05$,

* indicates $p < 0.05$.

Table 5

Genetic and environmental correlation between personality traits and whole brain summaries of surface area and cortical thickness.

	Global thickness		Total surface area	
Agreeableness	$\rho_e = 0.07, p = \text{ns};$	$\rho_g = -0.04, p = \text{ns}$	$\rho_e = -0.07, p = \text{ns};$	$\rho_g = 0.08, p = \text{ns}$
Conscientiousness	$\rho_e = -0.02, p = \text{ns};$	$\rho_g = 0.04, p = \text{ns}$	$\rho_e = 0.04, p = \text{ns};$	$\rho_g = -0.12, p < 0.05$
Extraversion	$\rho_e = -0.01, p = \text{ns};$	$\rho_g = 0.06, p = \text{ns}$	$\rho_e = 0.03, p = \text{ns};$	$\rho_g = 0.03, p = \text{ns}$
Neuroticism	$\rho_e = 0.11, p = \text{ns};$	$\rho_g = 0.02, p = \text{ns}$	$\rho_e = -0.09, p = \text{ns};$	$\rho_g = -0.06, p = \text{ns}$
Openness	$\rho_e = -0.05, p = \text{ns};$	$\rho_g = -0.02, p = \text{ns}$	$\rho_e = 0.18, p < 0.03;$	$\rho_g = 0.08, p = \text{ns}$

Genetic and environmental correlations are computed in the HCP sample, and exact p-values are reported, associations that showed phenotypic correlation at $p < 0.05$ threshold are in bold.

Genetic and environmental correlation of personality brain associations in the full HCP sample.

Table 6

Cortical thickness	ROI	Environmental correlation	Genetic correlation	Genetic contribution to phenotypic correlation
Agreeableness	LH Cont_PFC_L4	$\rho_e -0.12, p < 0.05^*$	$\rho_g -0.09, p = ns$	22%
	LH Default_PFC_9	$\rho_e -0.05, p = ns$	$\rho_g -0.21, p < 0.1$	72%
	LH Default_PFC_L11	$\rho_e 0.01, p = ns$	$\rho_g -0.36, p < 0.005^{**}$	100%
	LH Default_PFC_L13	$\rho_e -0.03, p = ns$	$\rho_g -0.26, p < 0.05^*$	84%
Neuroticism	RH Default_PFCm_5	$\rho_e 0.03, p = ns$	$\rho_g -0.33, p < 0.01^{**}$	100%
	LH Vis_L14	$\rho_e -0.07, p = ns$	$\rho_g -0.20, p < 0.1$	64%
	LH Default_PFC_9	$\rho_e 0.07, p = ns$	$\rho_g 0.17, p = ns$	63%
	RH Cont_PFC_L6	$\rho_e 0.03, p = ns$	$\rho_g 0.27, p < 0.05^*$	82%
Openness	RH Default_PFCm_5	$\rho_e 0.03, p = ns$	$\rho_g 0.23, p < 0.05^*$	83%
	LH Cont_PFC_L4	$\rho_e -0.13, p < 0.05^*$	$\rho_g -0.14, p = ns$	43%
	RH Limbic_TempPole_1	$\rho_e 0.01, p = ns$	$\rho_g 0.34, p < 0.01^{**}$	95%
	LH SomMot_3	$\rho_e 0.03, p = ns$	$\rho_g -0.29, p < 0.02^*$	100%
Surface area Neuroticism	LH Default_PFC_3	$\rho_e -0.05, p = ns$	$\rho_g -0.17, p = ns$	71%
	LH Default_PFC_9	$\rho_e 0.13, p < 0.1$	$\rho_g -0.45, p = 0.0002^{**}$	100%
	LH Default_PFC_L13	$\rho_e -0.04, p = ns$	$\rho_g -0.21, p = ns$	75%
	RH Default_Temp_L1	$\rho_e -0.16, p < 0.02$	$\rho_g 0.00, p = ns$	1%
	RH Default_PFCm_4	$\rho_e 0.01, p = ns$	$\rho_g -0.25, p < 0.02^*$	100%
	RH Default_PFCm_5	$\rho_e -0.04, p = ns$	$\rho_g -0.30, p < 0.02^*$	81%

Genetic and environmental correlations are computed in the HCP sample, and exact p-values are reported.

^{**} denotes a significant genetic correlation at $FDRq < 0.05$, corrected for the number of ROIs associated with the respective personality trait within the structural marker.

^{*} indicated an association of $p < 0.05$. The genetic contribution of phenotypic correlation was computed using the respective heritability of the personality trait and the local parcel as well as their genetic and phenotypic correlation.

Table 7

Replication of personality brain associations.

Cortical thickness	ROI	GSP t-value (BF)	eNKI t-value (BF)
Agreeableness	LH Cont_PFC1_4	1.26 (>3)	<u>-0.01 (>2.5)</u>
	LH Default_PFC_9	<u>-0.35 (>3)</u>	0.39 (>3)
	LH Default_PFC_11	<u>-0.14 (>3)</u>	<u>-0.26 (>2.5)</u>
	LH Default_PFC_13	<u>-0.39 (>3)</u>	<u>-0.53 (>1)</u>
	LH Default_PFCm_5	<u>-1.79[*] (0.48)</u>	1.40 (>3)
Neuroticism	LH Vis_14	1.97 [*] (>3)	-1.76 [*] (0.25)
	LH Default_PFC_9	<u>0.94 (>3)</u>	<u>0.74 (>1)</u>
	RH Cont_PFC1_6	<u>2.08[*] (0.25)</u>	-1.79 [*] (>3)
	RH Default_PFCm_5	-0.14 (>3)	-0.53 (>3)
Openness	LH Cont_PFC1_4	0.72 (>3)	<u>-0.97 (0.76)</u>
	RH Limbic_TempPole_1	<u>0.63 (>3)</u>	<u>0.56 (>1)</u>
Surface area Neuroticism	LH SomMot_3	<u>-1.06 (>1.5)</u>	<u>-1.11 (0.60)</u>
	LH Default_PFC_3	2.30 [*] (>3)	0.36 (>3)
	LH Default_PFC_9	<u>-0.18 (>3)</u>	<u>-0.39 (>1.5)</u>
	LH Default_PFC_13	<u>-0.14 (>3)</u>	<u>-1.05 (0.64)</u>
	RH Default_Temp_1	1.21 (>3)	<u>-0.42 (>1)</u>
	RH Default_PFCm_4	<u>-1.55 (0.82)</u>	<u>-1.97[*] (0.17)</u>
	RH Default_PFCm_5	0.07 (>3)	<u>-0.40 (>2)</u>

Replication in the GSP and eNKI sample of significant associations between personality and local brain structure observed in the HCP sample, t-values as well as Bayes Factors (BF) are reported. If a BF₀₁ is between 0 and 1/3 there is a moderate/strong evidence for H1 (replication), between 1/3 and 1 anecdotal evidence for H1, between 1 and 3 anecdotal evidence for H0 (no replication) and >3 moderate to strong evidence of H0. We underlined replications with a correct sign.

** indicates a significant correlation at FDR_q<0.05,

* is p < 0.05.