# NEUROGENETIC BASIS OF PERSONALITY

Sofie L. Valk[1,2*]; Felix Hoffstaedter[1,2]; Julia Camilleri[1,2]; Peter Kochunov[3]; B.T. Thomas Yeo[4,5,6,7]; Simon B. Eickhoff[1,2]

*[1)] Institute of Neuroscience and Medicine (INM-7: Brain and Behaviour), Research Centre Jülich, 52425 Jülich, Germany*
*[2)] Institute of Systems Neuroscience, Heinrich Heine University Düsseldorf, 40225 Düsseldorf, Germany*
*[3)] Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, Maryland, USA.*
*[4)] Department of Electrical and Computer Engineering, Clinical Imaging Research Centre, Institute for Health and Memory Networks Program, National University of Singapore, Singapore, Singapore.*
*[5)] Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, USA.*
*[6)] Centre for Cognitive Neuroscience, Duke-NUS Medical School, Singapore, Singapore.*
*[7)] NUS Graduate School for Integrative Sciences and Engineering, National University of Singapore, Singapore, Singapore.*

*Corresponding author:
S.L.Valk: svalk@fz-juelich.de

**Summary**

Personality traits are influenced by genetic and environmental factors and are related to mental health. Previous neuroimaging studies have reported associations between personality and brain structure, while at the same time, studies on imaging genetics have repeatedly demonstrated heritability of brain structure. However, to date, it is unknown whether the association between personality and brain macrostructure can be explained by shared genetic factors. Here we report a large-scale twin study (Human Connectome Project), finding genetic correlation between personality traits and brain structure. Agreeableness was genetically correlated with the posterior-mid temporal, midcingulate, and dorsolateral frontal cortices, while extraversion showed a genetic relation to temporoparietal junction. Quantitative functional decoding indicated regions associated with personality are implicated in (socio-)cognitive and language processing. Last, assessment of genetic correlation of personality and adaptive behavior suggests overlapping neurogenetic substrates of personality and adaptive function and problems. Together, these observations provide first evidence of a direct genetic link between complex behavioral traits such as personality, local brain morphometry, and function of the respective brain regions.

Personality traits quantify individual differences in goals, cognition, and emotion, that lead to behavior[1]. It is a broad construct conceptualized in specific traits to quantify variability in human behaviors. The most prominent factor approach of personality is the Five-factor personality structure (NEO- Five-Factor-Inventory – NEO-FFI)[2,3], operationalizing personality into dimensions or traits of agreeableness (friendly/compassionate vs. challenging/detached), conscientiousness (efficient/organized vs. easy-going/careless), extraversion (outgoing/ energetic vs. solitary/reserved), neuroticism (sensitive/nervous vs. secure/confident), and openness (inventive/curious vs. consistent/cautious). These traits have been linked to the quality of social relationships[4], job performance[5], and risk for mental disorders[6,7]. For example, neuroticism has been related to a higher risk for psychiatric disorders such as depression, stress and anxiety[8-10], whereas ADHD has been related to extraversion[11]. At the same time, Big Five traits are five broad factors, combining more specific aspects of personality[12]. Personality facets, which decompose personality traits to more detailed descriptions of individual-difference[12], are used to further qualify inter-individual difference in personality. For example, extraversion entails both social as well as non-social components and can be subdivided in facets of sociability, positive affect, and activity, whereas openness relates to intellect, but also unconventionality[12].

Personality traits as well as facets are highly heritable with about 50% of the variance attributable to additive genetic factors[13-17 18]. In the last decade genome-wide association studies (GWAS) have also discovered several genetic variants associated with these traits[11,19,20]. Recent work has also identified genetic correlations between personality and psychiatric disorders. For example, extraversion was related to attention-deficit/hyperactivity disorder, neuroticism to internalizing behavior, and openness to schizophrenia[11]. In addition to developments in behavioral genetics, the relationship between personality and biology has also been investigated using magnetic resonance imaging (MRI)[21-24]. While most studies found some phenotypic relationship between brain structure and variations in personality

traits, the findings are inconsistent and often conflicting[21,23,24]. Possible causes for this variability could be small sample sizes, variability in gender effects, as well as methodological variations. Yet, despite often-conflicting reports, neurobehavioral correlates of personality are often reported in multi-modal regions of the frontal, cingulate, and temporo-parietal cortices implicated in higher cognitive processing. These regions have been found to greatly expand over the course of primate evolution, with complex connectivity patterns supporting cognitive flexibility[25]. Importantly, quantitative indices of brain structure are also heritable[26-30]. This raises the question whether shared variations in personality traits and brain structure are genetically driven, and if so, if the neurogenetic markers of personality traits are located within regions associated with higher-order processing.

Here, we investigate the genetic correlation of personality traits and brain morphology to probe the genetic basis of their relationship. We seek to answer the following three questions: (i) Can we replicate previous observations of heritability of personality traits as well as brain structure? (ii) Is the relationship between personality traits and brain structure driven by genetic processes? (iii) Is there a genetic link between personality traits and adaptive behavior at both the behavioral and brain level?

We assessed (co-)heritability of NEO-FFI personality traits and brain structure in a large, well-characterized sample of young participants drawn from the Human Connectome Project. This sample included monozygotic and dizygotic twins, siblings, and unrelated individuals aged 22-37 which enabled the analysis of shared genetic variance between personality and brain structure. We captured variations in brain morphometry using an atlas-based approach[31] leading to a more homogeneous and biological meaningful representation than common summary measures based on macro-anatomy[32]. Analysis of heritability and co-heritability was performed using maximum likelihood variance-decomposition methods using Sequential Oligogenic Linkage Analysis Routines (www.solar-eclipse-genetics.org; Solar Eclipse 8.4.0.) Heritability ($h^2$) is the total additive genetic variance and genetic ($\rho_g$)

correlations were estimated using bivariate polygenic analyses. To qualify the function of the brain regions observed genetically related to personality in terms of associated tasks and behavior, we performed quantitative function decoding based on the BrainMap database[33].

## Results

*Heritability and genetic correlation of NEO-FFI personality score (Figure 1)*

First, we assessed heritability and genetic correlations of personality traits using maximum likelihood variance-decomposition methods with Solar[34]. We observed all NEO-FFI scores to be heritable: agreeableness (h2=0.31, p<0.001), conscientiousness (h2=0.43, p<0.001), extraversion (h2=0.45, p<0.001), neuroticism (h2=0.35, p<0.001), and openness (h2=0.57, p<0.001). Openness and conscientiousness ($\rho_g$= -0.27, p<0.005) had significant negative genetic correlations. Extraversion showed positive genetic correlation with agreeableness ($\rho_g$ = 0.40, p<0.003. Personality facets, constructed based on previous literature [12], where all heritable and co-heritable with the NEO-FFI traits they were theorized to be subcomponents of (see further; Supplementary Figure 1).

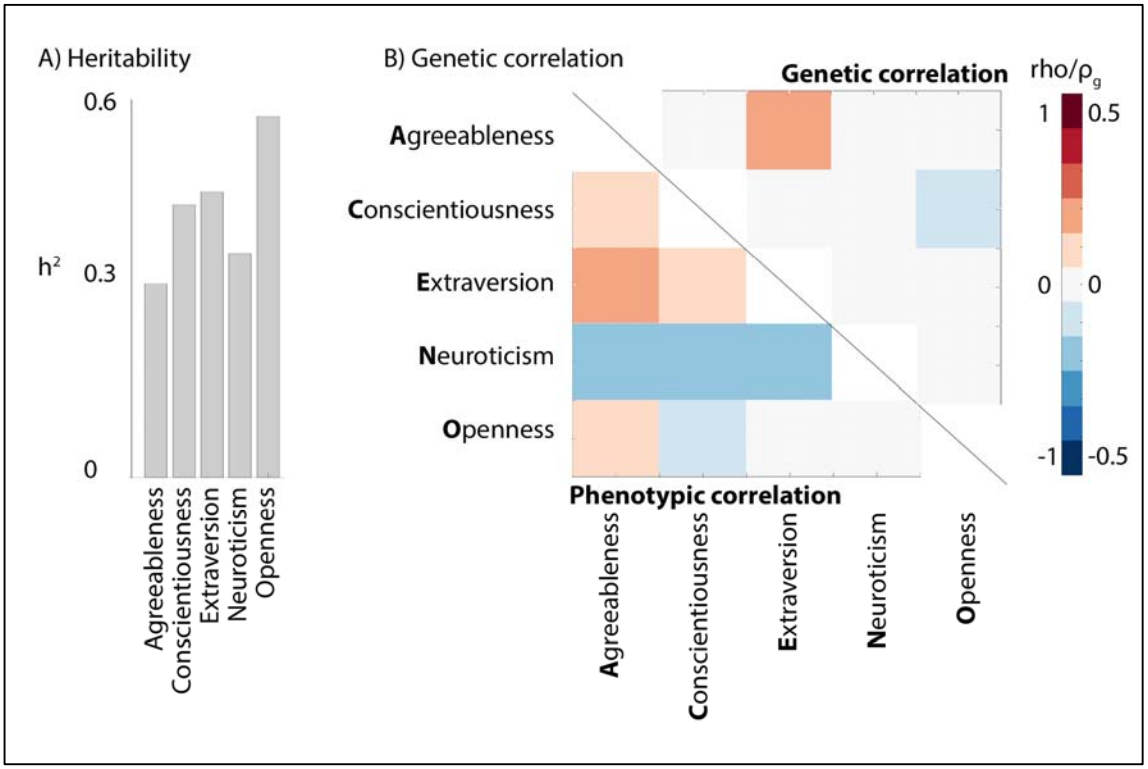


**FIGURE 1. INTER-INDIVIDUAL DIFFERENCES IN PERSONALITY ARE UNDER GENETIC CONTROL.** A). Heritability of personality scores; B). Phenotypic and genetic correlation of personality traits. Only findings that survive Bonferroni correction are reported.

*Genetic correlation of personality traits and brain structure (Figure 2)*

As all personality traits were significantly heritable in our current sample, we next confirmed cortical thickness to be heritable in our parcel-based approach (Supplementary Figure 2). This enabled us to perform genetic correlation analyses between personality traits and cortical structure. Agreeableness showed genetic correlation (FDR $p<0.05$) with cortical thickness in left posterior superior/mid temporal sulcus (rho=0.03; $\rho_g$ = 0.60, $p<0.0005$; $\rho_e$ = -0.15, $p<0.01$), right superior frontal cortex extending to mid cingulate (rho=-0.04; $\rho_g$ = -0.55, $p<0.0004$; $\rho_e$ =0.18, $p<0.005$), and right dorsolateral frontal cortex (rho=-0.02; $\rho_g$ = -0.51, $p<0.0006$; $\rho_e$ =0.21, $p<0.0004$). In a post-hoc analysis, we verified our observations at the level of agreeable facets, to investigate which personality facets genetic correlations at the level of personality traits were driven by specific personality facets (Supplementary Figure 3). This follow-up analysis revealed that the right superior frontal cortex related both to pro-sociality and non-antagonistic traits, whereas left posterior superior/mid temporal sulcus and right dorsolateral frontal cortex showed genetic correlation with non-antagonistic traits only. Second, we observed a genetic correlation (FDR $p<0.01$) between extraversion and left TPJ thickness (rho=0.1, $p<0.001$; $\rho_g$ = 0.49 $p<0.00005$; $\rho_e$ = -0.11, $p<0.05$). Follow up analysis of the relationship between facets of extraversion and left TPJ thickness also showed significant genetic correlation with 'sociability' facet of extraversion (see supplementary Figure 3). Observations of genetic correlations remained after controlling for general cognitive ability (Supplementary figure 4). We did not observe significant genetic correlations between cortical thickness and Conscientiousness, Neuroticism and Openness. Last, we performed a post-hoc analysis on the clusters that showed a significant phenotypic correlation between brain structure and personality traits to assess whether these phenotypical correlations were driven by genetic correlations. For agreeableness, we observed significant genetic correlation between left superior dorsolateral frontal cortex ($\rho_g$ = -0.35 $p<0.0038$; $\rho_e$ = 0.01, p=ns). Other

clusters of agreeableness, as well as neuroticism and openness only showed genetic correlations at trend levels (see further Supplementary Figure 5).

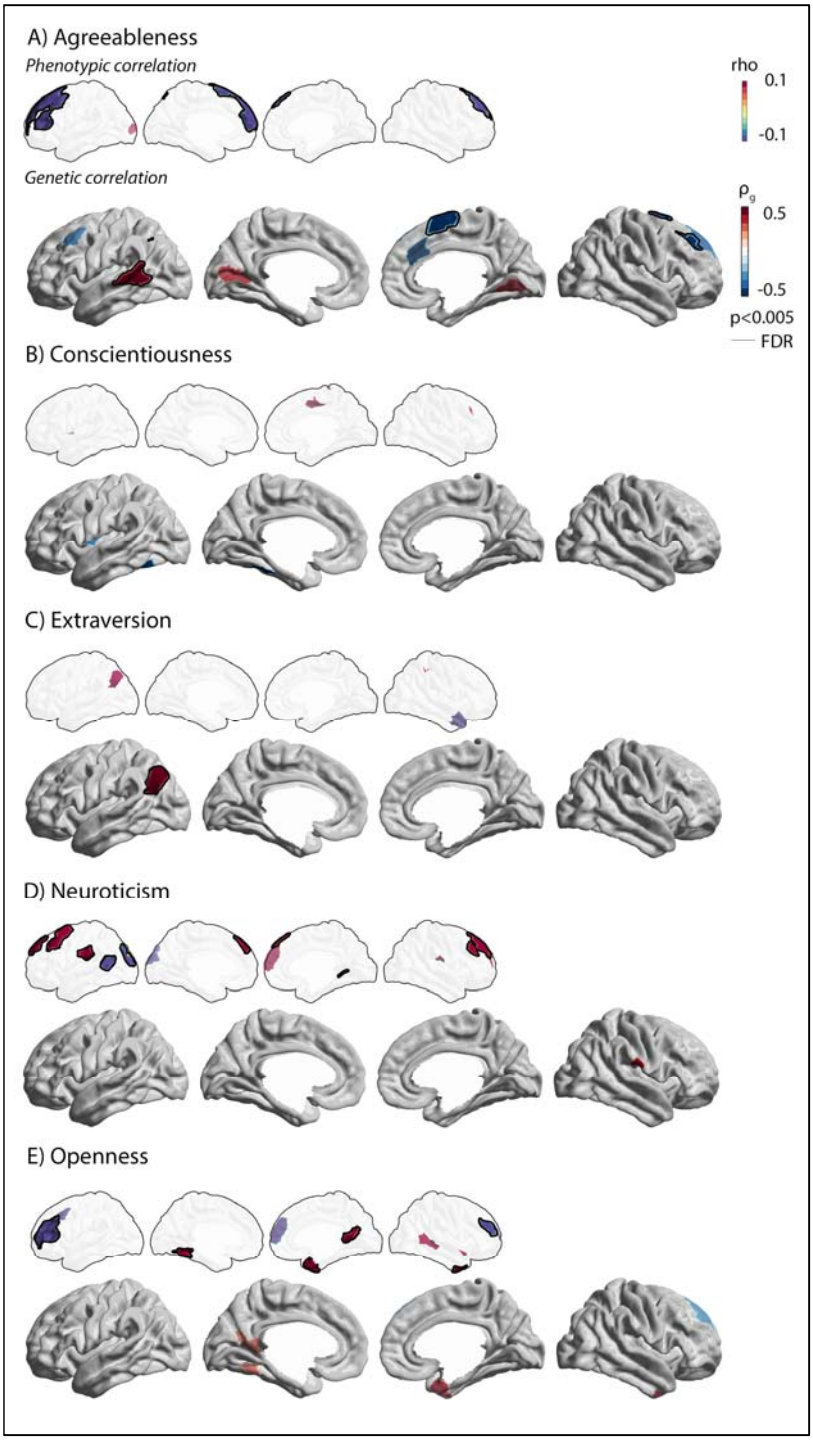


**FIGURE 2. SHARED GENETIC BASIS FOR PERSONALITY TRAITS AND BRAIN STRUCTURE.** A-E). Upper cortical surface display: phenotypic correlation as reference for genetic correlation analysis. Lower cortical surface display: Genetic correlation of personality trait and cortical thickness.

FDR-corrected findings have a black outline, uncorrected findings ($p<0.005$) are shown semi-transparent. For our both phenotypic and genetic correlation analysis between NEO-FFI traits and brain structure, we performed whole brain analysis.

*Functional decoding of neurogenetic correlates of personality traits (Figure 3)*

To enable inference about processes that are sustained by the regions showing significant genetic correlation with personality traits, we performed quantitative functional decoding using the BrainMap database[35]. Here we observed TPJ, implicated in extraversion, to be activated above chance by (socio-) cognitive tasks and hence should be implicated in cognitive and social cognitive processing ($p<0.05$). Next to socio-cognitive processing, the TPJ, was implicated in cognition related to reasoning and language. Of the parcels related to agreeableness, the left posterior superior-mid temporal sulcus was related to various forms of language processing, such as phonology, syntax, speech, and semantics ($p<0.05$), whereas the left superior frontal / mid cingulate parcel was related to action imagination and execution, as well as cognition and perception, and the dorsolateral prefrontal cortex was found implicated in cognitive tasks involving memory and reasoning.

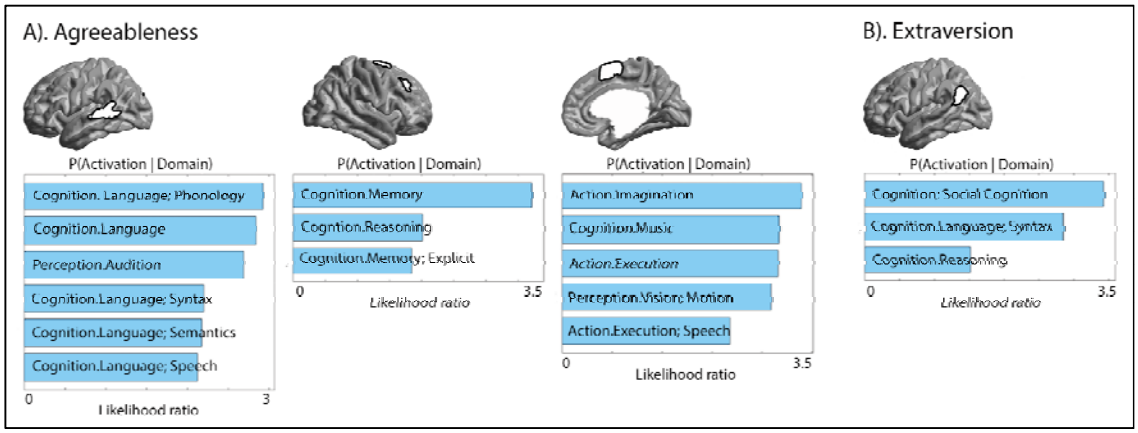


**FIGURE 3. NEUROGENETIC CORRELATES OF PERSONALITY TRAITS FUNCTIONALLY RELATE TO (SOCIO-) COGNITIVE AND LANGUAGE PROCESSING.** Quantitative functional decomposition of neurogenetic markers of personality based on the FDR-corrected clusters of phenotypical relationships of Figure 2.

*Neurogenetic overlap between personality traits and adaptive behavior (Figure 4)*

Last, based on previous behavioral reports of genetic correlation between personality and mental health, we sought to explore whether we could observe a neurogenetic overlap between personality traits and mental health. As a proxy of mental health, we used self-report data on adaptive function and problems, scored according to DSM-oriented scales. First, we performed phenotypical and genetic correlation analyses between personality traits and sub-clinical DSM-oriented markers of adaptive functions and problems at the behavioral level. Following we explored whether regions that showed a genetic correlation with personality traits also related to adaptive function and problems.

In our behavioral analysis, we observed considerable genetic correlation between personality traits and markers of adaptive behavior. Agreeableness related negatively to anti-social problems. Conscientiousness showed negative genetic correlation with AD/H, depressive, and inattention problems, whereas extraversion related negatively to avoidant behavior. Neuroticism showed a positive genetic correlation to a broad range of adaptive functions including AD/H problems, anxiety, avoidant, depressive, hyperactive, and inattention problems (see Further Supplementary table 1). Follow up analysis of personality facets in relation to adaptive function and problems followed these patterns (Supplementary Figure 6).

Genetic correlations between adaptive behavior and regions associated with personality traits followed behavioral patterns, with TPJ showing genetic correlation with AD/H (rho=0.04; $\rho_g$ = 0.23, $p<0.05$; $\rho_e$ = -0.06, p<n.s.) as well as avoidant problems (rho=-0.08; $\rho_g$ = -0.23, $p<0.05$; $\rho_e$ = 0.04, p<n.s.) and right dorsolateral frontal cortex relating to hyperactivity problems (rho=0.02; $\rho_g$ = 0.25, $p<0.05$; $\rho_e$ =-0.09, p<n.s.).

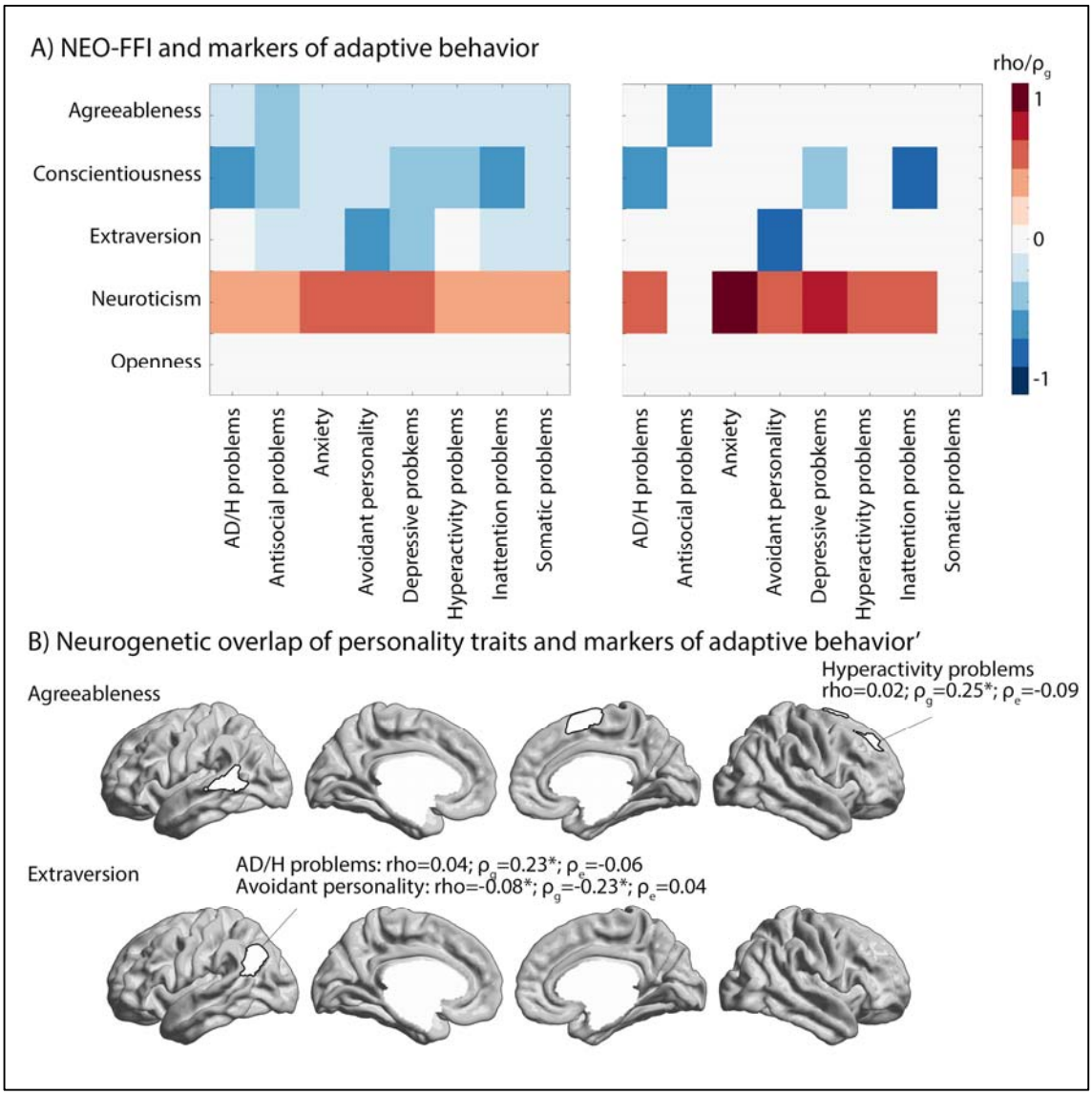


**FIGURE 4. NEO-FFI PERSONALITY TRAITS AND ADAPTIVE BEHAVIOR SHOW GENETIC CORRELATION IN BEHAVIORAL AND BRAIN.** A). Phenotypic and genetic correlation between NEO-FFI personality traits and ASR, DSM oriented scale[36], only correlations that survive Bonferroni corrections are displayed; B). Post-hoc relation of adaptive behavior to brain regions significantly associated with personality traits, * indicates a phenotypic/genetic correlation below 0.05.

## Discussion

Personality is an individuals' characteristic set of cognitive, emotional and behavioral patterns. Previous work has shown that personality is heritable and correlates with variation in brain structure [11,17,21-24]. Here, we examined the neurogenetic basis of personality and brain structure using large-scale structural imaging and pedigree structure of the HCP. Our analysis showed that brain-behavior relationships in personality are in part driven by shared genetic effects. We observed genetic correlations of agreeableness with cortical thickness in posterior superior/mid temporal sulcus, superior frontal/mid cingulate, and dorsolateral frontal cortex and of extraversion with cortical thickness in the TPJ. Structural regions that had a genetic link with personality traits were observed implicated in (socio-) cognitive, emotion, and language processing as revealed by quantitative functional decoding using the BrainMap database. Together our results provide evidence that the correlation between brain structure and personality traits is, in part, driven by shared genetic processes anchored in regions involved in (socio-)cognitive and language processes. Our observations suggest a direct genetic link between variations in local brain morphometry, function of the respective brain regions, and complex behavioral traits such as personality.

In the current study focused on the relationship between individual differences in personality traits and local anatomy, using compressed surface-based MRI data based on the parcellation scheme of Schaefer et al. Using compressed features of structural MRI has been suggested to both to improve signal-to-noise of brain measures, assuming the cortex can be subdivided in cortical areas that bridge different features such as connectivity and structure (cf. Eickhoff et al.[32] and Genon et al.[33]), as well as to optimize analysis scalability in our genetic analyses. The Schaefer parcellation is derived using functional MRI data from ~1500 subjects, by integrating local approaches that detect abrupt transitions in functional connectivity patterns and global approaches that cluster similar functional connectivity patterns[31]. Previous

research found that the Schaefer parcellation showed convergence with partitions based on structure alone[37]. 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[38]. Therefore, a parcellation approach that considers both local and global connectivity benefits structural image analysis, as it reduces signal-to-noise both within individual as across individuals and make control for multiple comparisons more straightforward[33]. Based on the findings in our study we suggest our approach might be a fruitful first exploratory step to further investigate the shared genetic basis of brain and behavior, and locate neural mechanisms of interest. Future studies can then verify these results by exploring more specific genetic mechanisms, as well as neuroanatomical features. For example, there is converging evidence that inter-individual differences in topological integrative features of multi-modal areas are more important for higher-order cognitive functions, such as intelligence, than local features only[39].

The present results indicate a genetic correlation between complex behavioral traits and brain structure. The strength of genetic correlations is strongly dependent on the heritability of each of the correlated markers. In our sample, between 30% and 60% (on average 42%) of variance in personality traits was explained by additive genetic factors, with similar heritability estimates for meta-traits and facets. This is in line with previous studies using twin and family samples[15] as well as genome-wide approaches[11]. A recent meta-analysis[17] confirmed that an average 40% of the variance in personality traits is of genetic origin. Also, conform previous studies[28,40-43], we observe high (h2>0.4) heritability of cortical thickness, with highest values in primary sensory areas. The heritability patterns highlight high heritability of cortical thickness in unimodal cortices, whereas variance in association cortices is on average less influenced by genetic factors [28,30,40-42,44,45].

Genetic correlation analyses between brain morphometry and personality traits revealed a genetic link of agreeableness and extraversion to brain structure. Here, we observed a genetic correlation between agreeableness and cortical thickness in posterior superior-mid temporal sulcus, superior frontal/mid cingulate, and dorsolateral frontal cortex. Agreeableness is the ability to trust others, be cooperative, and is linked to prosocial behavior[46,47] as well as to non-antagonistic traits. Posterior superior-mid temporal areas, including Wernicke's area, are consistently implicated in language processing[48], as also shown by our functional decoding analysis, and are part of the default mode network[31,49]. Superior frontal/mid cingulate areas, are associated by functional decoding with imagination and execution of action[50], whereas dorsolateral region is associated by functional decoding with reasoning and memory[51]. Both cingulate as well as dorsolateral regions are involved in higher-order reasoning, meta-cognition, and cognitive control[52-54]. Indeed, the genetic relationship between agreeableness and regions involved in higher-order reasoning is in line with theoretical accounts that the ability to reflect on ones actions is essential for being able to be cooperative and prosocial[52]. At the same time, we observed a moderate relationship of dorsolateral regions with hyperactivity behaviors. Previous meta-analyses in patient populations have linked abnormalities in dorsolateral prefrontal functioning to Ad/H[55]. Overall, neurogenetic overlap between behavioral functions such as trust and cooperation, as well as problems of hyperactive behavior, and brain systems involved in communication and reasoning highlight functional specificity of genetic control over brain and behavior.

In case of extraversion we observed similar functional specificity. Extraversion was genetically associated with thickness of the TPJ. Regions in the temporo-parietal junction have repeatedly been associated with both social cognition and language[56-59]. Indeed, this was confirmed by our functional decoding analysis, which showed that these areas were predominantly related to tasks that involved (social-)cognitive processing. In line with these findings, the sociability, but not positive affect, facet of the extraversion trait had a significant

genetic relation to TPJ. At the same time, we observed negative genetic correlation of avoidance and hyperactivity with TPJ structure. In line with extraversions facets, extraversion does not only entail sociability but also 'action' components. Though only at trend level, also action facets of extraversion related to TPJ structure. Indeed, functionally and anatomically the TPJ is placed at a nexus. Its reconciling role combining attention, language, memory, and social cognitive processing also relates to the simulation of action in self and others[60]. Abnormal structure might result in impaired functional processing which in turn results in avoidance behavior or hyperactivity. Importantly, previous work has been able to identify sub-components of in the TPJ [61,62], and further studies on the genetic differentiability of these sub-regions will clarify its relation to social and non-social behavioral processes.

The functional specificity of neurogenetic correlates of personality traits suggests a direct genetic link between variations in local brain morphometry, function of the respective brain regions, and complex behavioral traits such as personality. The observed genetic correlation possibly reflects a persistent effect of genetic factors on specific brain structures, which gives rise to specific behaviors. On the other hand, however, it could also be that genetic predispositions shape behavioral traits in other ways than through brain morphometry and thus modulate brain structure of these regions only indirectly through use-dependent plasticity, e.g., by parental influences[63] or other mechanisms that cannot be seen in MRI. Interestingly, whole brain genetic correlations showed inverse effects of genetic and environmental correlations, suggesting complex interactions between genes and environmental are at play in the context of brain – behavior relationships. Environmental factors can modulate genetic predisposion in various ways[64], including enhancement, sensitivity, as well as (negative) interactions. Indeed, though the genetic overlap between participants in our sample should already have maximized genetic influence on phenotypical correlations between personality and brain, phenotypic correlations were not driven by

genetic processes alone, but rather a combination of both genetic and environmental effects. Importantly, we found little consistency in the patterns of environmental influences on brain morphometry and personality traits. This might be due to methodological limitations, since we had insufficient data to test for household effects, and thus environmental correlation in the current study results from unmeasured aspects of the environment or correlated measurement errors[65]. Given the twin set-up as well as age range of the HCP sample, other designs with broader age ranges and kinship relations might help to further understand environmental contributions to brain-behavior relationships.

Nevertheless, previous studies have shown that environment plays an important role in shaping brain-behavior relationships in the context of higher-cognitive and social skills. For example, various studies have shown how social-environmental factors such as city-living impact regulation of negative emotion and stress by mediation of genetic predispositions[66,67]. Also, improvement in socio-cognitive abilities following mental training have been shown to result in structural changes of the TPJ[68].

In sum, we demonstrate a shared genetic basis of variance in brain structure and personality traits. Functional decoding analysis indicated that regions genetically linked to personality traits were functionally involved in to (socio-) cognitive and language processes, supporting previous research on the biological basis of personality. Studying the genetic correlation between brain and personality might help to better describe and understand the neural endophenotype of personality traits, as well as the contribution of genetic and environmental factors to inter-individual difference. Ultimately genetic neuroimaging endophenotypes of personality traits can further help understand genetic predisposition and risk factors for mental illness.

## Methods

*Participants and study design*

For our analysis we used the publicly available data from the Human Connectome Project (HCP; 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, range = 22–37). We included for whom the scans and data had been released (humanconnectome.org) after passing the HCP quality control and assurance standards [69]. The full set of inclusion and exclusion criteria are described elsewhere[70,71].

After removing individuals with missing structural imaging or behavioral data our sample consisted of 1085 individuals (283 MZ-twins, 167 DZ-twins, and 579 non-twin siblings and 57 singles) with mean age of 28.8 years (SD =3.7, range =22-37).

*Structural imaging processing*

MRI protocols of the HCP are previously described in[70,71]. The pipeline used to obtain the Freesurfer-segmentation is described in detail in a previous article [70] and is recommended for the HCP-data. The pre-processing steps included co-registration of T1 and T2 scans, B1 (bias field) correction, and segmentation and surface reconstruction using FreeSurfer version 5.3-HCP to estimate cortical thickness.

We used a parcellation scheme[31] based on the combination of a local gradient approach and a global similarity approach using a 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. 200 parcels are close to granularity used in Enigma (Desikan-atlas, 68 parcels) while at the same time providing more anatomical detail in functionally heterogeneous regions such as parietal and frontal cortex. In order to improve signal-to-noise and improve 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).

*Behavioral assessment*

The NEO-FFI personality traits were assessed using the NEO-Five-Factors-Inventory (NEO-FFI)[72]. 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[73]. As conventional scoring of the NEO-FFI does not provide scores on more specific aspects of the broad-bandwidth factors, we also computed facets based on Saucier et al[12]. Here, 13 factor-analytically derived scales were found to replicate across halves of a sample of self-descriptions by adults (N = 732). The scales demonstrated reliability and factor structure comparable to that of the 30 facet scales of the NEO-PI-R.

For markers of adaptive behavior and problems, we used the Achenbach Adult Self-Report (ASR) for Ages 18-59[36]. The ASR is a self-administered test examining diverse aspects of adaptive functioning and problems. Scales are based on 2020 referred adults and normed on 1767 non-referred adults. The test-retest reliability of the ASR was supported by 1-week test-retest that were all above 0.71. The ASR also has good internal consistency (0.83). (https://aseba.org/wp-content/uploads/2019/01/ASEBA-Reliability-and-Validity-Adult.pdf).

As a proxy for IQ we used the NIH Toolbox Cognition[74], '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.

*Statistical analysis*

To investigate the heritability and genetic correlation of brain structure and personality traits, we analyzed 200 parcels of cortical thickness, as well as personality trait score of each subject in a twin-based heritability analysis. As in previous studies[65], the quantitative genetic analyses were conducted using Sequential Oligogenic Linkage Analysis Routines (SOLAR)[34]. 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 cortical thickness parcels, conform to the assumptions of normality, an inverse normal transformation was applied for all behavioral and neuroimaging traits[65].

Heritability ($h^2$) represents the portion of the phenotypic variance ($\sigma^2_p$) accounted for by the total additive genetic variance ($\sigma^2_g$), i.e., $h^2 = \sigma^2_g/\sigma^2_p$. Phenotypes exhibiting stronger covariances between genetically more similar individuals than between genetically less similar individuals have higher heritability. Within SOLAR, this is assessed by contrasting the observed covariance matrices for a neuroimaging measure with the structure of the covariance matrix predicted by kinship. Heritability analyses were conducted with simultaneous estimation for the effects of potential covariates. For this study, we included covariates including age, sex, age × sex interaction, age$^2$, age$^2$ × sex interaction. Post-hoc we also controlled for a proxy for intelligence, total cognitive score[74]. When investigating cortical thickness, we additionally controlled for global thickness effects (mean cortical thickness). Heritability estimates were corrected for multiple comparisons using Benjamin-Hochberg

FDR[75] at whole-brain analysis. Bonferroni correction was applied when investigating behavior or in post-hoc brain analysis, and corrections across number of analysis were applied.

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 ($\rho_g$) and environmental ($\rho_e$) correlations, based on the phenotypical correlation ($\rho_p$), between brain structure and personality with the following formula: $\rho_p = \rho_g\sqrt{(h^2_1 h^2_2)} + \rho_e\sqrt{[(1 - h^2_1)(1 - h^2_2)]}$, where $h^2_1$ and $h^2_2$ are the 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 $\rho_g$ or $\rho_e$ constrained to be equal to 0) against the log likelihood for the model in which these parameters were estimated. For our phenotypical analysis we performed Spearman correlation analysis, controlling for the same variables as in the genetic analysis, namely age, sex, age × sex interaction, age$^2$, age$^2$ × sex interaction, as well as global thickness effects when investigating brain structure. A significant genetic correlation (corrected for multiple comparisons using Benjamin-Hochberg FDR[75] in case of whole-brain analysis and Bonferroni correction when investigating behavior or in post-hoc brain analysis) is evidence suggesting that (a proportion of) both phenotypes are influenced by a gene or set of genes[76].

*Functional decoding*

All significant parcels were in a last step functionally characterized using the Behavioral Domain meta-data from the BrainMap database using forward inference (http://www.brainmap.org[77,78]). To do so, volumetric counterparts of the surface-based parcels were identified. In particular, we identified those meta-data labels (describing the computed contrast [behavioral domain]) that were significantly more likely than chance to result in

activation of a given parcel[22,33,35]. That is, functions were attributed to the identified neurogenetic effects by quantitatively determining which types of experiments are associated with activation in the respective parcellation region. Significance was established using a binomial test ($p < 0.05$, corrected for multiple comparisons using false discovery rate (FDR)).

## References


1 Mischel, W. Toward an integrative science of the person. *Annu Rev Psychol* **55**, 1-22, doi:10.1146/annurev.psych.55.042902.130709 (2004).

2 McCrae, R. R. & Costa, P. T., Jr. Updating Norman's "Adequate Taxonomy": intelligence and personality dimensions in natural language and in questionnaires. *J Pers Soc Psychol* **49**, 710-721 (1985).

3 McCrae, R. R. & Costa, P. T., Jr. Validation of the five-factor model of personality across instruments and observers. *J Pers Soc Psychol* **52**, 81-90 (1987).

4 Asendorpf, J. B. & Wilpers, S. Personality effects on social relationships. *Journal of Personality and Social Psychology* **74**, 1531-1544 (1998).

5 Rothmann, S. & Coetzer, E. P. The big five personality dimensions and job performance. *SA Journal of Industrial Psychology* **29** (2003).

6 Miller, J. D., Lynam, D. R., Widiger, T. A. & Leukefeld, C. Personality disorders as extreme variants of common personality dimensions: can the Five-Factor Model adequately represent psychopathy? *J Pers* **69**, 253-276 (2001).

7 Trull, T. J. Dimensional models of personality: the five-factor model and the DSM-5. *Dialogues Clin Neurosci* **15**, 135-146 (2013).

8 Roelofs, J., Huibers, M., Peeters, F., Arntz, A. & van Os, J. Rumination and worrying as possible mediators in the relation between neuroticism and symptoms of depression and anxiety in clinically depressed individuals. *Behav Res Ther* **46**, 1283-1289, doi:10.1016/j.brat.2008.10.002 (2008).

9 Brainstorm, C. *et al.* Analysis of shared heritability in common disorders of the brain. *Science* **360**, doi:10.1126/science.aap8757 (2018).

10 Gunthert, K. C., Cohen, L. H. & Armeli, S. The role of neuroticism in daily stress and coping. *J Pers Soc Psychol* **77**, 1087-1100 (1999).

11 Lo, M. T. *et al.* Genome-wide analyses for personality traits identify six genomic loci and show correlations with psychiatric disorders. *Nat Genet* **49**, 152-156, doi:10.1038/ng.3736 (2017).

12 Saucier, G. Replicable Item-Cluster Subcomponents in the NEO Five-Factor Inventory. *Journal of Personality Assessment* **70**, 263-276 (1998).

13 Bouchard, T. J., Jr. Genes, environment, and personality. *Science* **264**, 1700-1701 (1994).

14 Bouchard, T. J., Jr. & McGue, M. Genetic and environmental influences on human psychological differences. *J Neurobiol* **54**, 4-45, doi:10.1002/neu.10160 (2003).

15 Jang, K. L., Livesley, W. J. & Vernon, P. A. Heritability of the big five personality dimensions and their facets: a twin study. *J Pers* **64**, 577-591 (1996).

16 Loehlin, J. C., McCrae, R. R., Costa, P. T. & John, O. P. Heritabilities of Common and Measure-Specific Components of the Big Five Personality Factors. *Journal of Research in Personality* **32**, 431-453 (1998).

17 Vukasovic, T. & Bratko, D. Heritability of personality: A meta-analysis of behavior genetic studies. *Psychol Bull* **141**, 769-785, doi:10.1037/bul0000017 (2015).

18 Bouchard, T. J., Jr. & Loehlin, J. C. Genes, evolution, and personality. *Behav Genet* **31**, 243-273 (2001).

19 de Moor, M. H. *et al.* Meta-analysis of genome-wide association studies for personality. *Molecular psychiatry* **17**, 337-349, doi:10.1038/mp.2010.128 (2012).

20 van den Berg, S. M. *et al.* Meta-analysis of Genome-Wide Association Studies for Extraversion: Findings from the Genetics of Personality Consortium. *Behav Genet* **46**, 170-182, doi:10.1007/s10519-015-9735-5 (2016).

21 DeYoung, C. G. *et al.* Testing predictions from personality neuroscience. Brain structure and the big five. *Psychol Sci* **21**, 820-828, doi:10.1177/0956797610370159 (2010).

22 Nostro, A. D., Muller, V. I., Reid, A. T. & Eickhoff, S. B. Correlations Between Personality and Brain Structure: A Crucial Role of Gender. *Cereb Cortex* **27**, 3698-3712, doi:10.1093/cercor/bhw191 (2017).

23 Riccelli, R., Toschi, N., Nigro, S., Terracciano, A. & Passamonti, L. Surface-based morphometry reveals the neuroanatomical basis of the five-factor model of personality. *Soc Cogn Affect Neurosci* **12**, 671-684, doi:10.1093/scan/nsw175 (2017).

24 Bjornebekk, A. *et al.* Neuronal correlates of the five factor model (FFM) of human personality: Multimodal imaging in a large healthy sample. *Neuroimage* **65**, 194-208, doi:10.1016/j.neuroimage.2012.10.009 (2013).

25 Sneve, M. H. *et al.* High-Expanding Regions in Primate Cortical Brain Evolution Support Supramodal Cognitive Flexibility. *Cereb Cortex*, doi:10.1093/cercor/bhy268 (2018).

26 Baare, W. F. *et al.* Quantitative genetic modeling of variation in human brain morphology. *Cereb Cortex* **11**, 816-824 (2001).

27 Glahn, D. C., Thompson, P. M. & Blangero, J. Neuroimaging endophenotypes: strategies for finding genes influencing brain structure and function. *Hum Brain Mapp* **28**, 488-501, doi:10.1002/hbm.20401 (2007).

28 Strike, L. T. *et al.* Genetic Complexity of Cortical Structure: Differences in Genetic and Environmental Factors Influencing Cortical Surface Area and Thickness. *Cereb Cortex*, doi:10.1093/cercor/bhy002 (2018).

29 Thompson, P. M. *et al.* Genetic influences on brain structure. *Nat Neurosci* **4**, 1253-1258, doi:10.1038/nn758 (2001).

30 Teeuw, J. *et al.* Genetic Influences on the Development of Cerebral Cortical Thickness During Childhood and Adolescence in a Dutch Longitudinal Twin Sample: The Brainscale Study. *Cereb Cortex*, doi:10.1093/cercor/bhy005 (2018).

31 Schaefer, A. *et al.* Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. *Cereb Cortex* **28**, 3095-3114, doi:10.1093/cercor/bhx179 (2018).

32 Eickhoff, S. B., Constable, R. T. & Yeo, B. T. T. Topographic organization of the cerebral cortex and brain cartography. *Neuroimage* **170**, 332-347, doi:10.1016/j.neuroimage.2017.02.018 (2018).

33 Genon, S., Reid, A., Langner, R., Amunts, K. & Eickhoff, S. B. How to Characterize the Function of a Brain Region. *Trends Cogn Sci* **22**, 350-364, doi:10.1016/j.tics.2018.01.010 (2018).

34 Almasy, L. & Blangero, J. Multipoint quantitative-trait linkage analysis in general pedigrees. *Am J Hum Genet* **62**, 1198-1211, doi:10.1086/301844 (1998).

35 Fox, P. T., Lancaster, J. L., Laird, A. R. & Eickhoff, S. B. Meta-analysis in human neuroimaging: computational modeling of large-scale databases. *Annu Rev Neurosci* **37**, 409-434, doi:10.1146/annurev-neuro-062012-170320 (2014).

36 Achenbach, T. M. & Rescorla, L. A. (ed Youth and Families Research center for Children) (University of Vermont, Burlington, VT, USA, 2003).

37 Varikuti, D. P. *et al.* Evaluation of non-negative matrix factorization of grey matter in age prediction. *Neuroimage* **173**, 394-410, doi:10.1016/j.neuroimage.2018.03.007 (2018).

38 Van Essen, D. C. & Glasser, M. F. Parcellating Cerebral Cortex: How Invasive Animal Studies Inform Noninvasive Mapmaking in Humans. *Neuron* **99**, 640-663, doi:10.1016/j.neuron.2018.07.002 (2018).

39 Seidlitz, J. *et al.* Morphometric Similarity Networks Detect Microscale Cortical Organization and Predict Inter-Individual Cognitive Variation. *Neuron* **97**, 231-247 e237, doi:10.1016/j.neuron.2017.11.039 (2018).
40 Kremen, W. S. *et al.* Genetic and environmental influences on the size of specific brain regions in midlife: the VETSA MRI study. *Neuroimage* **49**, 1213-1223, doi:10.1016/j.neuroimage.2009.09.043 (2010).
41 Eyler, L. T. *et al.* 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, doi:10.1017/thg.2012.3 (2012).
42 Panizzon, M. S. *et al.* Distinct genetic influences on cortical surface area and cortical thickness. *Cereb Cortex* **19**, 2728-2735, doi:10.1093/cercor/bhp026 (2009).
43 Winkler, A. M. *et al.* Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *Neuroimage* **53**, 1135-1146, doi:10.1016/j.neuroimage.2009.12.028 (2010).
44 Hofer, E. & al., e. Genetic Determinants of Cortical Structure (Thickness, Surface Area and Volumes) among Disease Free Adults in the CHARGE Consortium. *bioRxiv preprint first posted online Sep. 9, 2018; doi: http://dx.doi.org/10.1101/409649.* (2018).
45 Fjell, A. M. *et al.* Development and aging of cortical thickness correspond to genetic organization patterns. *Proc Natl Acad Sci U S A* **112**, 15462-15467, doi:10.1073/pnas.1508831112 (2015).
46 Martin-Raugh, M. P., Kell, H. J. & Motowidlo, S. J. Prosocial knowledge mediates effects of agreeableness and emotional intelligence on prosocial behavior. *Pers Individ Dif.* **90**, 41-49 (2016).
47 Hilbig, B. E., Glockner, A. & Zettler, I. Personality and prosocial behavior: linking basic traits and social value orientations. *J Pers Soc Psychol* **107**, 529-539, doi:10.1037/a0036074 (2014).
48 Binder, J. R. The Wernicke area: Modern evidence and a reinterpretation. *Neurology* **85**, 2170-2175, doi:10.1212/WNL.0000000000002219 (2015).
49 Yeo, B. T. *et al.* The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol* **106**, 1125-1165, doi:10.1152/jn.00338.2011 (2011).
50 Nachev, P., Wydell, H., O'Neill, K., Husain, M. & Kennard, C. The role of the pre-supplementary motor area in the control of action. *Neuroimage* **36 Suppl 2**, T155-163, doi:10.1016/j.neuroimage.2007.03.034 (2007).
51 Mars, R. B. & Grol, M. J. Dorsolateral prefrontal cortex, working memory, and prospective coding for action. *J Neurosci* **27**, 1801-1802 (2007).
52 Frith, C. D. The role of metacognition in human social interactions. *Philos Trans R Soc Lond B Biol Sci* **367**, 2213-2223, doi:10.1098/rstb.2012.0123 (2012).
53 Cole, M. W., Yarkoni, T., Repovs, G., Anticevic, A. & Braver, T. S. Global connectivity of prefrontal cortex predicts cognitive control and intelligence. *J Neurosci* **32**, 8988-8999 (2012).
54 MacDonald, A. W., 3rd, Cohen, J. D., Stenger, V. A. & Carter, C. S. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science* **288**, 1835-1838 (2000).
55 Hart, H., Radua, J., Nakao, T., Mataix-Cols, D. & Rubia, K. Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. *JAMA Psychiatry* **70**, 185-198, doi:10.1001/jamapsychiatry.2013.277 (2013).

56 Bzdok, D. *et al.* Left inferior parietal lobe engagement in social cognition and language. *Neurosci Biobehav Rev* **68**, 319-334, doi:10.1016/j.neubiorev.2016.02.024 (2016).
57 Mar, R. A. The neural bases of social cognition and story comprehension. *Annu Rev Psychol* **62**, 103-134, doi:10.1146/annurev-psych-120709-145406 (2011).
58 Kanske, P., Bockler, A., Trautwein, F. M. & Singer, T. Dissecting the social brain: Introducing the EmpaToM to reveal distinct neural networks and brain-behavior relations for empathy and Theory of Mind. *Neuroimage* **122**, 6-19, doi:10.1016/j.neuroimage.2015.07.082 (2015).
59 Valk, S. L. *et al.* Socio-Cognitive Phenotypes Differentially Modulate Large-Scale Structural Covariance Networks. *Cereb Cortex*, doi:10.1093/cercor/bhv319 (2016).
60 Carter, R. M. & Huettel, S. A. A nexus model of the temporal-parietal junction. *Trends Cogn Sci* **17**, 328-336, doi:10.1016/j.tics.2013.05.007 (2013).
61 Krall, S. C. *et al.* The role of the right temporoparietal junction in attention and social interaction as revealed by ALE meta-analysis. *Brain Struct Funct* **220**, 587-604, doi:10.1007/s00429-014-0803-z (2015).
62 Mars, R. B. *et al.* Connectivity-based subdivisions of the human right "temporoparietal junction area": evidence for different areas participating in different cortical networks. *Cereb Cortex* **22**, 1894-1903, doi:10.1093/cercor/bhr268 (2012).
63 Kong, A. *et al.* The nature of nurture: Effects of parental genotypes. *Science* **359**, 424-428, doi:10.1126/science.aan6877 (2018).
64 Reiss, D., Leve, L. D. & Neiderhiser, J. M. How genes and the social environment moderate each other. *Am J Public Health* **103 Suppl 1**, S111-121, doi:10.2105/AJPH.2013.301408 (2013).
65 Glahn, D. C. *et al.* Genetic control over the resting brain. *Proc Natl Acad Sci U S A* **107**, 1223-1228, doi:10.1073/pnas.0909969107 (2010).
66 Meyer-Lindenberg, A. & Tost, H. Neural mechanisms of social risk for psychiatric disorders. *Nat Neurosci* **15**, 663-668, doi:10.1038/nn.3083 (2012).
67 Tost, H., Champagne, F. A. & Meyer-Lindenberg, A. Environmental influence in the brain, human welfare and mental health. *Nat Neurosci* **18**, 1421-1431, doi:10.1038/nn.4108 (2015).
68 Valk, S. L. *et al.* Structural plasticity of the social brain: Differential change after socio-affective and cognitive mental training. *Sci Adv* **3**, e1700489, doi:10.1126/sciadv.1700489 (2017).
69 Marcus, D. S. *et al.* Human Connectome Project informatics: quality control, database services, and data visualization. *Neuroimage* **80**, 202-219, doi:10.1016/j.neuroimage.2013.05.077 (2013).
70 Glasser, M. F. *et al.* The minimal preprocessing pipelines for the Human Connectome Project. *Neuroimage* **80**, 105-124, doi:10.1016/j.neuroimage.2013.04.127 (2013).
71 Van Essen, D. C. *et al.* The WU-Minn Human Connectome Project: an overview. *Neuroimage* **80**, 62-79, doi:10.1016/j.neuroimage.2013.05.041 (2013).
72 McCrae, R. R. & Costa, P. T. A contemplated revision of the NEO Five-Factor Inventory. *Pers Individ Dif.* **36**, 587-596 (2004).
73 McCrae, R. R. & Terracciano, A. Personality profiles of cultures: aggregate personality traits. *J Pers Soc Psychol* **89**, 407-425, doi:10.1037/0022-3514.89.3.407 (2005).
74 Weintraub, S. *et al.* Cognition assessment using the NIH Toolbox. *Neurology* **80**, S54-64, doi:10.1212/WNL.0b013e3182872ded (2013).
75 Benjamini, Y. & Hochberg, Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society. Series B (Methodological)* **57**, 289-300 (1995).

76 Almasy, L., Dyer, T. D. & Blangero, J. Bivariate quantitative trait linkage analysis: pleiotropy versus co-incident linkages. *Genet Epidemiol* **14**, 953-958, doi:10.1002/(SICI)1098-2272(1997)14:6<953::AID-GEPI65>3.0.CO;2-K (1997).

77 Laird, A. R. *et al.* The BrainMap strategy for standardization, sharing, and meta-analysis of neuroimaging data. *BMC Res Notes* **4**, 349, doi:10.1186/1756-0500-4-349 (2011).

78 Laird, A. R. *et al.* ALE Meta-Analysis Workflows Via the Brainmap Database: Progress Towards A Probabilistic Functional Brain Atlas. *Front Neuroinform* **3**, 23, doi:10.3389/neuro.11.023.2009 (2009).

**Contributions**

S.L.V. and S.B.E. conceived this study. S.L.V. developed and implements the analysis, with input from F.H., B.T.T.Y. and P.K. J.C. implemented the Quantitative functional decoding analysis. S.L.V. wrote the paper, and S.L.V., F.E., J.C., B.T.T.Y, P.K., and S.B.E. were involved in interpreting results and editing the manuscript.