Cortical surfaces mediate the relationship between polygenic scores for intelligence and general intelligence

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Abstract

Recent large-scale, genome-wide association studies (GWAS) have identified hundreds of genetic loci associated with general intelligence. The cumulative influence of these loci on brain structure is unknown. We examined if cortical morphology mediates the relationship between GWAS-derived polygenic scores for intelligence (PS_i) and *g*-factor. Using the effect sizes from one of the largest GWAS meta-analysis on general intelligence to date, PS_i were calculated among ten p-value thresholds. PS_i was assessed for the association with *g*-factor performance, cortical thickness (CT), and surface area (SA) in two large imaging-genetics samples (IMAGEN N=1,651; IntegraMooDS N=742). PS_i explained up to 5.1% of the variance of *g*-factor in IMAGEN ($F_{1,1640}$=12.2-94.3; P<0.005), and up to 3.0% in IntegraMooDS ($F_{1,725}$=10.0-21.0; P<0.005). The association between polygenic scores and *g*-factor was partially mediated by SA and CT in prefrontal, anterior cingulate, insula, and medial temporal cortices in both samples ($P_{FWER\text{-}corrected}$<0.005). The variance explained by mediation was up to 0.75% in IMAGEN and 0.77% in IntegraMooDS. Our results provide evidence that cumulative genetic load influences *g*-factor via cortical structure. The consistency of our results across samples suggests that cortex morphology could be a novel potential biomarker for neurocognitive dysfunction that are among the most intractable psychiatric symptoms.

Introduction

General intelligence (*g*-factor) is the primary component and predictor of performance on diverse psychometric tasks (Carroll 1993; Gray and Thompson 2004). These neurocognitive tasks are intercorrelated with one component consistently predicting approximately 40-45% of the variance (Carroll 1993; Jensen 1998a). Some life outcomes correlate with *g*-factor including physical and mental health, as well as job performance (Strenze 2007; Deary et al. 2018). Full-scale IQ measures and *g*-factor are distinct measures of intelligence in that IQ results from summation of standardized scores across several tests. These measures are generally highly correlated. However, *g*-factor is an important component of IQ, but IQ is a specific mixture of cognitive abilities and skills that may not be represented by *g*-factor (Colom et al. 2002).

Cortical brain volumes are associated with *g*-factor (Thompson et al. 2001; Posthuma et al. 2002; Haier et al. 2004; Mcdaniel 2005). Although global effects have been reported, *g*-factor performance is most commonly associated with the dorsolateral prefrontal cortex (DLPFC), medial temporal lobes, anterior and posterior cingulate, and inferior parietal lobes (Haier et al. 2004; Toga and Thompson 2005; Narr et al. 2006; Basten et al. 2015). The heritability observed in *g*-factor and IQ may be shared among volumetric measures of cortical structure (Posthuma et al. 2002; Davies et al. 2018a; Elliott, Sharp, et al. 2018; Savage et al. 2018), and potentially epigenetic variation (Kaminski et al. 2018). However, the association with cortical volume and *g*-factor may be more complex as cortical thickness (CT) and surface area (SA) have distinct genetic contributions and developmental trajectories (Panizzon et al. 2009; Winkler et al. 2010; Hogstrom et al. 2013; Jha et al. 2018). CT and SA also have been associated with intelligence throughout the lifespan (Narr et al. 2006; Karama et al. 2011; Schnack et al. 2015; Schmitt et al. 2019). In particular, changes in CT in frontotemporal and inferior parietal regions during development have been shown to mediate the heritability of IQ. The heritability of *g*-factor has also been associated

with brain volume differences in the same cortical regions, and these regions may partially share the genetic influences of neuropsychiatric disorders on brain structure (Toga and Thompson 2005).

The interindividual differences in *g*-factor performance have significant genetic and environmental contributions (Deary et al. 2009; Plomin et al. 2012). A conservative estimate for the heritability of *g*-factor is approximately 40% (Bouchard and McGue 1981; Deary et al. 2010; Haworth et al. 2010; Plomin and Deary 2015; Kaminski et al. 2018). Until recently, the contribution of common genetic variants accounting for this heritability was unclear. Several smaller GWAS identified tens of independent genetic loci associated with cognitive functioning (Davies et al. 2011, 2015, 2016; Benyamin et al. 2014; Kirkpatrick et al. 2014; Lencz et al. 2014; Lam et al. 2017; Sniekers et al. 2017; Trampush et al. 2017). More recently, a large genome-wide association meta-analysis uncovered 205 associated genomic loci and 1,016 genes that were statistically related to general intelligence in 269,867 participants (Savage et al. 2018). Another study with large sample overlap with Savage et al. (2018), identified 148 independent loci and 709 genes influencing general cognitive function in 300,486 individuals (Davies et al. 2018b). Polygenic scores based on the recent GWAS studies explained approximately 2.0-5.2% of the variance in general intelligence (Davies et al. 2018b; Savage et al. 2018). There was also a robust genetic correlation, but with small effect size (r_g~-0.20), of polygenic scores for intelligence with neuropsychiatric disorders with prominent cognitive symptoms including schizophrenia (SCZ) (Ohi et al. 2018; Savage et al. 2018). It has been reported that the genetic correlation with general cognitive function may be protective or mitigate the diagnosis of psychiatric disorders (Lam et al. 2017; Sniekers et al. 2017; Trampush et al. 2017; Davies et al. 2018b; Savage et al. 2018). These genetic findings represent an important step to further elucidating the architecture of human intelligence and potential neurobiological mechanisms underlying cognitive impairment in psychiatric disorders.

Lower *g*-factor scores and IQ impairment have been reported among many neuropsychiatric disorders including SCZ (Heinrichs and Zakzanis 1998; Heaton et al. 2001), bipolar disorder (BPD) (Bora

and Pantelis 2015), major depressive disorder (MDD) (Rock et al. 2014), attention deficit hyperactivity disorder (Hill et al. 2016), and autism spectrum disorder (ASD) (Millan et al. 2012). The neurocognitive domains contributing to lower *g*-factor scores vary among individuals and clinical subpopulations of these diseases. Moreover, the causes of neurocognitive impairment may be different between these disorders. For instance, an MDD patient may have dysfunction due an acute depressive episode in contrast to persistent cognitive symptoms in some chronic schizophrenia patients. Among psychiatric patients, neurocognitive symptoms have a negative impact on quality of life, social functioning, and occupational functioning (Green 2006; McIntyre et al. 2013). Cognitive impairments are particularly severe in some patients with ASD and SCZ in which cognitive deficits are a core feature of the disorders that are highly prevalent, manifest early, are relatively stable over time, and correlate with overall symptom severity (Seidman 2006; Savilla et al. 2008; Hill et al. 2016). Impairment is also present in first-degree relatives of patients suggesting a genetic component that is not a downstream effect of the disease process (Clark et al. 2005; Snitz et al. 2006; Bora et al. 2009; Gau and Shang 2010; Rommelse et al. 2011). Therefore, *g*-factor has been argued to be an important endophenotype among psychiatric populations (e.g. Burdick et al. 2009).

In the present study, we used genome-wide, whole-brain neuroimaging, and neurocognitive performance data from two large independent samples: the naturalistic adolescent development cohort IMAGEN study (N=1,651), and the cross-psychiatric disorder IntegraMooDS sample (N=742) that includes healthy controls, as well as patients and first-degree relatives of patients with MDD, BPD, and SCZ. Our primary goal was to investigate the mechanistic relationship among the polygenic intelligence scores (PS_i), derived from the Savage et al. 2018 intelligence, wave 2 study (Savage et al. 2018), cortical structure, and *g*-factor performance which requires a number of intermediary steps. First, we aimed to validate the association between polygenic scores and *g*-factor. Second, we assessed the association of *g*-factor performance with vertex-wise measures of CT and SA. Third, we established which PS_i

(thresholds ranging from $P_T<5.0\times10^{-8}$ to $P_T=1.0$) were associated with CT and SA. Last, we aimed to use vertex-wise putative causal models to assess if the association between PS_i and *g*-factor performance was mediated by cortical brain structure in youths, adults, relatives of patients, and patients.

Materials and Methods

Subjects

We analyzed two independent samples with neuroimaging, neurocognitive and genome-wide genotype data. The first sample (IMAGEN; www.imagen-europe.com; N=1,651) is a large-scale, longitudinal European imaging genetics study. It is a community-based sample of adolescents with Caucasian origin that was collected at eight different sites in Europe: Berlin, Germany (N=214); Dresden, Germany (N=239); Dublin, Ireland (N=154); Hamburg, Germany (N=215); London, England (N=186); Mannheim, Germany (N=192); Nottingham, England (N=257); and Paris, France (N=194). The average age was 13.9 ± 0.45 including 817 males and 834 females. A detailed description of the IMAGEN sample has been provided in earlier publications (Schumann et al. 2010; Kaminski et al. 2018). The ethics committees approved the study among clinical sites. Legal guardians of participants provided written informed consent prior to commencement of the study.

The newly completed, cross-psychiatric disorder IntegraMooDS sample (N=742) consists of healthy controls (N=339), first degree relatives of MDD (rel-MDD; N=91), BPD (rel-BPD; N=69) and SCZ (rel-SCZ; N=67), and independent subgroups of patients with MDD (pat-MDD; N=67), BPD (pat-BPD; N=60), and SCZ (pat-SCZ; N=50; Table S1). The Structured Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) Axis-I Disorders (SCID-I) (First and Spitzer 2002) was used to confirm diagnosis of patients and to ensure that relatives and controls never suffered from a psychiatric disorder. Symptom severity was assessed using the SCL-90-R (Derogatis 1979) (Table S1). All participants reported having grandparents of European origin. Medication

information is listed in Table S2. Data of IntegraMooDS participants was collected across three different German research institutions: Central Institute of Mental Health at the University of Heidelberg, Mannheim; Department of Psychiatry and Psychotherapy, University of Bonn, Bonn; and the Department of Psychiatry and Psychotherapy at Charité-Universitätsmedizin Berlin. The ethics committees of the participating centers approved the study and all participants provided written informed consent prior to commencement of the study. IMAGEN and IntegraMooDS were both conducted in accordance with the Declaration of Helsinki.

General Intelligence

Using standard methods (Spearman 1904; Mackintosh 2011; Davies et al. 2016; Savage et al. 2018), *g*-factor was defined as the first principal component among psychometric neurocognitive batteries encompassing multiple dimensions of cognitive functioning. Since IMAGEN and IntegraMooDS have different neurocognitive batteries, we conducted a principal component analysis (PCA) of the different cognitive tests available and selected the first unrotated component independently in each sample. In IMAGEN, *g*-factor was calculated from the WISC-IV (Feis 2010) including: matrix reasoning, block design, digit span backward and forward, similarities and vocabulary. In IntegraMooDS, we conducted PCA from the Hamburg-Wechsler Adult Intelligence Scale (HAWIE-R) (Wechsler 2008) subtests digit span memory test (forwards and backwards), matrix reasoning, digit symbol and additional neurocognitive tests including verbal fluency (Aschenbrenner et al. 2000), verbal intelligence (Lehrl 1993), verbal learning and memory (Helmstaedter 2001), trail making test version a and b (Giovagnoli et al. 1996), and d2 concentration performance (Brickenkamp and Zillmer 1998). In both samples, the factor loadings of individual neurocognitive tests followed a typical pattern (Deary et al. 2010) and correlated highly with the extracted *g*-factor (all $r>0.47$; Figure S1). In general, *g*-factor scores are relatively stable even when calculated from a variety of cognitive tests (Jensen 1998b). For instance, *g*-factor scores

obtained from different domains of cognitive tests correlate highly (Johnson et al. 2004, >0.98; 2008). In previous studies, *g*-factor generally accounts for 40% or more of the variance across different cognitive domains (Carroll and B. 1993; Deary et al. 2010). A detailed description of the different neuropsychological tests used in both samples is shown in the intelligence measures section of the Supplementary Material.

Genetics

Quality control, imputation and analysis of the genetic data for both the IMAGEN and IntegraMooDS samples was performed according to the standards of the Psychiatric Genomics Consortium (PGC; http://www.med.unc.edu/pgc; for further details see Supplementary Material, Genetics section). IMAGEN was a minor contribution to the original study conducted by Savage et al. (2018). To avoid bias, we were provided with the summary statistics by the authors excluding IMAGEN. This resulted in 268,524 individuals from the original GWAS with 9,270,275 SNPs instead of the 269,867 individuals included in the publication. Polygenic scores are used to summarize genome-wide effects among sets of genetic variants that may not achieve significance alone in large-scale association studies (Dudbridge 2013). Among genetically complex phenotypes, in which thousands of genetic polymorphisms may be contributing to the trait, these aggregated polygenic scores increase the predictive power that would not be achievable by a single variant alone (Dudbridge 2013). We used the latest general intelligence meta-analysis conducted by Savage et al. (2018) to calculate PS_i for each individuals in both samples as the weighted sum of the alleles associated with lower general intelligence. For each individual, we calculated ten PS_i deciles at p-value thresholds ranging from p=1 to $p<0.5x10^{-8}$. Our thresholds, and the method in general, are standard among PGC publications (For further details, Supplementary Material, Genetics section) (Ripke et al. 2014; Cross-Disorder Group of the PGC 2013; Purcell et al. 2009). Genetic

population stratification was assessed among the first four genetic principal components (IMAGEN: Figure S3; IntegraMooDS: Figure S4).

Image Acquisition

In IMAGEN, the image acquisition parameters and preprocessing steps have been described in detail in a prior publication (Schumann et al. 2010), and they are summarized in the image acquisition section of the Supplementary Material. In IntegraMooDS, scans were acquired using three Siemens Trio 3T MR (Siemens, Erlangen, Germany) scanners at Charité Universitätsmedizin Berlin, at the Life and Brain Center of the University of Bonn, and at the Zentralinstitut für seelische Gesundheit, Mannheim. Image acquisition parameters and processing of structural images are described in detail in prior publications (Lett et al. 2017; Vogel et al. 2018), and in the methods section of the Supplementary Material.

Statistical Analysis

Our statistical models were different in IMAGEN and IntegraMooDS. In IMAGEN, we included sex, age, site and the top four principal components (PCs) from the population stratification analysis as covariates. In IntegraMooDS, we additionally included the subgroups (healthy controls, rel-MDD, rel-BPD, rel-SCZ, pat-MDD, pat-BPD, and pat-SCZ) as covariates along with sex, age, site, and the top four PCs from the population stratification analysis. In follow-up analyses, we determined if we should be including the cross-diagnostic subgroups in IntegraMooDS as an interacting variable with each PS_i for both the main effects (i.e. PS_i on cortical structure), as well as the mediation effects (i.e. PS_i on *g*-factor via cortical structure). In both samples, linear regression was applied to investigate the association between PS_i and general intelligence. In IntegraMooDS, we followed-up this analysis examining PS_i by subgroup interactions.

Neuroimaging analysis

For vertex-wise analyses of cortical surfaces, the TFCE_mediation toolbox (Lett et al. 2017) was used (https://github.com/trislett/TFCE_mediation). The toolbox performs threshold-free cluster enhancement (TFCE) transformation on vertex-wise statistic images (Smith and Nichols, 2009). Significance of the TFCE transformed statistic image is assessed via permutation testing after correcting for family-wise error rate ($P_{FWER\text{-}corrected}$). The toolbox also allows for cortex-wise mediation analyses. For all neuroimaging analyses, significance was determined after 10,000 permutations at a $P_{FWER\text{-}corrected}<0.05$ and $P_{FWER\text{-}corrected}<0.005$ for analyses that included PS_i.

Cortex-wise mediation is explained in detail in the Supplementary Material, as well as in prior publications (Lett et al. 2016, 2017, 2018). This analysis allowed us to determine if the associations between PS_i and *g*-factor were independent of differences in SA and CT, or if SA and CT were mediating the effect. The mediation models in IMAGEN and IntegraMooDS were performed with PS_i as independent variable, vertex-wise SA or CT were the mediator variables, and *g*-factor was the dependent variable. At each vertex, the indirect effect was assessed using the Sobel Test Z-statistic (Sobel 1986). The Z-statistic images then underwent TFCE, and significance of cortex-wise mediation was determined after 10,000 permutations.

Post hoc estimation of effect sizes

To estimate the degree of partial mediation, we used the effect sizes (partial η^2) of the top cluster from the vertex-wise mediation analyses among all significant PS_i thresholds. We calculated the direct effect (PS_i on *g*-factor), the effect of PSi on the mean cluster values, the effect of the mean cluster values on *g*-factor, and the indirect effect of PS_i on *g*-factor including the top clusters as additional covariates. Furthermore, we calculated the percentage of the explainable variance (see formula below) in *g*-factor performance that is explained by the indirect effect (see Table S9). Neuroimaging *post hoc* effects estimations are inflated; however, this bias is reduced in larger sample sizes (Reddan et al. 2017; Geuter et al. 2018).

$$Percentage\ of\ explainable\ variance = \frac{partial\ \eta^2\ direct\ effect - partial\ \eta^2\ indirect\ effect}{partial\ \eta^2\ direct\ effect} \times 100$$

Results

General intelligence

In IMAGEN, *g*-factor explained 41.1% variance, and 41.7% of the variance in IntegraMooDS (Figure S1). In both samples, *g*-factor explained a similar amount of variance across various cognitive tests (Table S3; Figure S2). Within IntegraMooDS, *g*-factor was significantly different between subgroups ($F_{6,726}$=9.34, P=1.8x10^{-9}, Figure S5). Pairwise comparisons revealed that *g*-factor was significantly lower in rel-SCZ, pat-BPD and pat-SCZ compared to healthy controls, with the greatest difference in pat-SCZ compared to control subjects (Table S4).

Polygenic intelligence score

In both samples, PS_1 to PS_{10} correlated positively with each other after correction for multiple testing indicating a relatively high degree of collinearity among PS_i (IMAGEN: r=0.23-0.99, P<1.2x10^{-20}; IntegraMooDS: r=0.30-0.99, P<8.5x10^{-17}; Figure S6). In IntegraMooDS, the PS_1 to PS_{10} did not differ significantly between subgroups ($F_{6,727}$=0.33-1.86, P>0.05).

Association of polygenic scores with general intelligence

In the IMAGEN sample, PS_1 to PS_{10} were associated with *g*-factor with PS_6 to PS_8 explaining approximately 5.1% of the variance ($F_{1,1640}$=12.23-94.30; P<0.005; Figure 1). In the IntegraMooDS sample, PS_2 to PS_{10} were associated with *g*-factor with PS_5 explaining 3.0% of the variance ($F_{1,725}$= 9.99-20.98; P<0.005; Figure 1). In follow-up analyses, we included the interaction between PS_i and IntegraMooDS subgroups. There were no significant subgroup by PS_i interactions on *g*-factor at all PS_i thresholds ($F_{6,720}$=0.31-1.03, P>0.05).

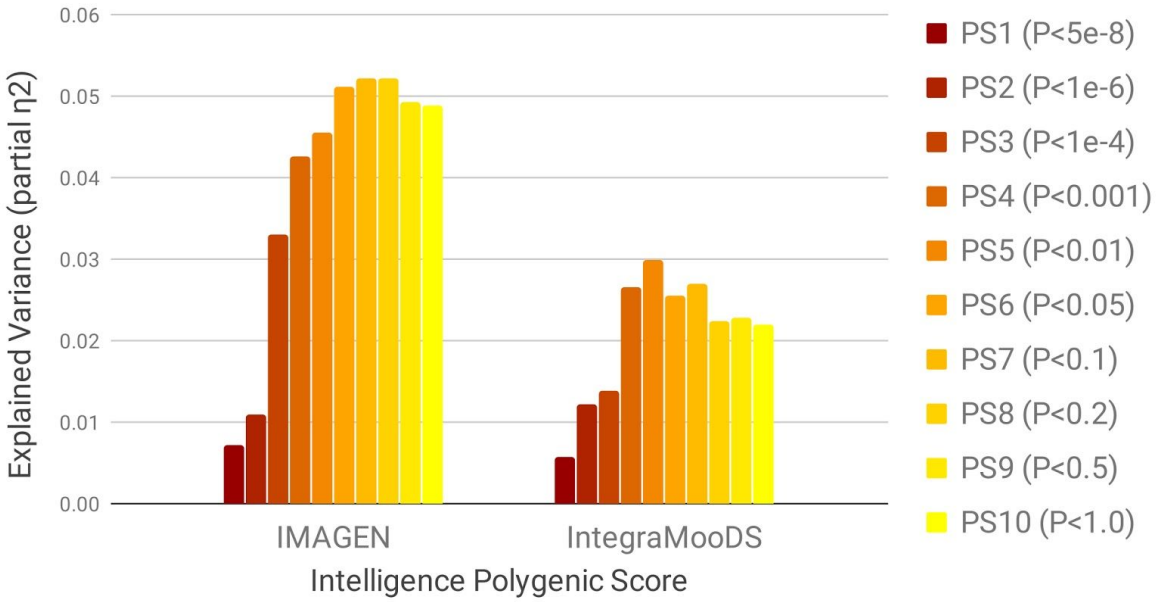

Figure 1. Effect sizes (partial eta squared) of associations between polygenic scores for general intelligence ranging from PS_1 to PS_{10} and *g*-factor performance. All polygenic scores were significantly associated with *g*-factor after Bonferroni correction for ten multiple comparisons (IMAGEN: $F_{1,1640}$= 12.23-94.30; IntegraMooDS: $F_{1,725}$= 9.99-20.98; all $P_{corrected} < 0.05$) except PS_1, which was nominally associated with *g*-factor in IntegraMooDS ($F_{1,725}$= 5.09; $P < 0.05$).

Association among *g*-factor, cortical thickness and surface area

In IMAGEN, vertex-wise analysis of CT and SA revealed a positive association with *g*-factor throughout the cortex ($P_{FWER\text{-}corrected}$<0.05; Figure S7). This global effect was also observed in IntegraMooDS where increased CT and SA were associated with *g*-factor performance ($P_{FWER\text{-}corrected}$<0.05; Figure S7).

Association of polygenic scores and brain structure

Cortical Thickness

Within IMAGEN, PS_3 to PS_8 ($P_T<1.0x10^{-4}$ to $P_T<0.2$) were associated with higher CT ($P_{FWER\text{-}corrected}<0.005$; Table 1, Table S5) in the prefrontal cortices, anterior cingulate, insula, medial temporal cortex, and inferior parietal cortex (Figure S8 for PS_4). Within the IntegraMooDS sample, PS_2, PS_4, and PS_5 were associated with higher CT in similar regions as in IMAGEN (bilateral prefrontal cortex, anterior cingulate, insula, temporal cortex and inferior parietal cortex; $P_{FWER\text{-}corrected}<0.005$; Table 1, Table S5, Figure S8 for PS_4 vertex-wise results). Vertex-wise results for PS_i scores at $P_{FWER\text{-}corrected}<0.05$ and $P_{FWER\text{-}corrected}<0.005$ are available in the Supplementary Material under Online Vertex-wise Results. In follow-up analysis, there was no significant PS_i by subgroup interaction in the IntegraMooDS sample ($P_{FWER\text{-}corrected}>0.05$).

Surface Area

In IMAGEN, higher PS_3 to PS_5 were associated with larger SA ($P_{FWER\text{-}corrected}<0.005$; Table 1). The positive association between PS_i and SA was prominently observed in the frontal cortices, including bilateral DLPFC, as well as the anterior cingulate, insula, medial temporal cortex, and the inferior parietal cortex (Figure S8 for PS_4 vertex-wise results). In IntegraMooDS, higher PS_2, PS_4, PS_5, and PS_8 were associated with larger SA in similar regions as in IMAGEN (prefrontal cortices, anterior cingulate, insula, temporal cortex and inferior parietal cortex) ($P_{FWER\text{-}corrected}<0.005$; Table 1; Table S6). Vertex-wise results for PS_i scores at $P_{FWER\text{-}corrected}<0.05$ and $P_{FWER\text{-}corrected}<0.005$ are available in the Supplementary Material under Online Vertex-wise Results. Follow-up analysis revealed that there were no significant PS_i by subgroup interactions in the IntegraMooDS sample ($P_{FWER\text{-}corrected}>0.05$).

	Cortical Thickness		Surface Area	
Main Effect	IMAGEN	IntegraMooDS	IMAGEN	IntegraMooDS
PS_1 ($P_T < 5.0 \times 10^{-8}$)	-	*	-	-
PS_2 ($P_T < 1.0 \times 10^{-6}$)	*	***	*	***
PS_3 ($P_T < 1.0 \times 10^{-4}$)	***	*	***	*
PS_4 ($P_T < 0.001$)	***	***	***	***

PS_5 ($P_T < 0.01$)	***	***	***	***
PS_6 ($P_T < 0.05$)	***	*	***	*
PS_7 ($P_T < 0.1$)	***	*	*	*
PS_8 ($P_T < 0.2$)	***	*	*	***
PS_9 ($P_T < 0.5$)	*	*	*	*
PS_{10} ($P_T < 1.0$)	*	*	-	*
Indirect Effect	IMAGEN	IntegraMooDS	IMAGEN	IntegraMooDS
PS_1 ($P_T < 5.0 \times 10^{-8}$)	-	***	-	-
PS_2 ($P_T < 1.0 \times 10^{-6}$)	*	***	*	***
PS_3 ($P_T < 1.0 \times 10^{-4}$)	***	***	***	***
PS_4 ($P_T < 0.001$)	***	***	***	***
PS_5 ($P_T < 0.01$)	***	***	***	***
PS_6 ($P_T < 0.05$)	***	*	***	*
PS_7 ($P_T < 0.1$)	***	*	***	***
PS_8 ($P_T < 0.2$)	***	*	***	***
PS_9 ($P_T < 0.5$)	*	*	*	***
PS_{10} ($P_T < 1.0$)	*	*	-	***

Table 1. Associations of polygenic scores for general intelligence and surface area as well as cortical thickness in IMAGEN and IntegraMooDS at two different thresholds, separately for main effects and mediation analyses (indirect effect). *, represents the familywise error rate corrected significance threshold ($P_{FWER\text{-}corrected} < 0.05$). ***, represents significant p values after correcting for ten multiple comparisons as well as familywise error rate ($P_{FWER\text{-}corrected} < 0.005$). P_T, polygenic score threshold.

Cortex-wise mediation analyses

Cortical Thickness

In IMAGEN, CT partially mediated the relationship between PS_3 to PS_8 and *g*-factor ($P_{FWER\text{-}corrected}<0.005$; Table 1; Table S7). The mediation was primarily in the prefrontal cortices, anterior cingulate, insula, medial temporal cortex, and inferior parietal cortex (Figure 2 for PS_4). Within the IntegraMooDS sample, CT mediated the relationship between PS_2 to PS_5 and *g*-factor in similar regions as IMAGEN ($P_{FWER\text{-}corrected}<0.005$; Table 1; Table S7; Figure 2 for PS_4). Vertex-wise results for PS_i scores at $P_{FWER\text{-}corrected}<0.05$ and $P_{FWER\text{-}corrected}<0.005$ are available in the Supplementary Material under Online

Vertex-wise Results. We did not include IntegraMooDS subgroup as an interacting variable in the mediation model because there was no significant PS_i by subgroup interaction on CT ($P_{FWER\text{-}corrected}$>0.05).

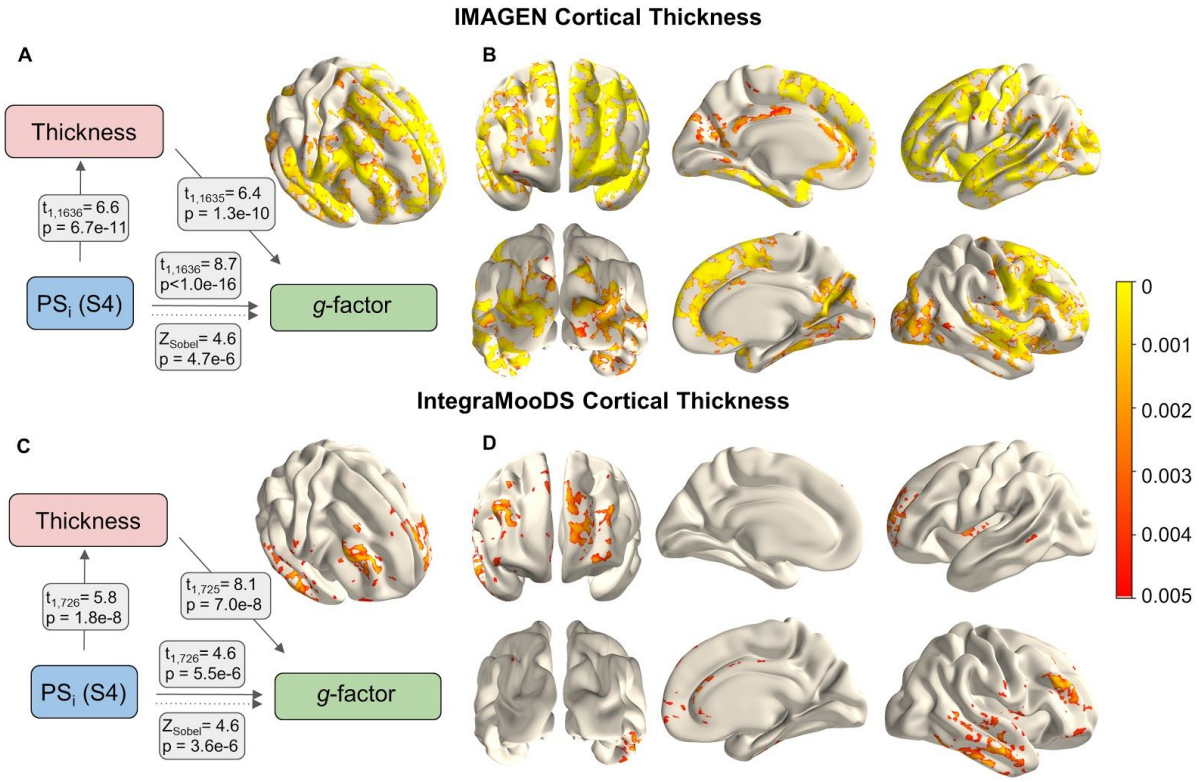

Figure 2. The association of PS_4 (P_T < 0.001) and *g*-factor is mediated by cortical thickness in key regions associated with general intelligence in IMAGEN (N = 1,651) and IntegraMooDS (N = 742). Significant vertices are shown ranging from $P_{FWER\text{-}corrected}$ < 0.005 (red) to $P_{FWER\text{-}corrected}$ < 0.001 (yellow). (**A**) Mediation model statistics from the largest significant cluster (Supplementary Table S7) for associations among PS_4, cortical thickness and *g*-factor in IMAGEN. Solid arrows represent direct effects, the dotted arrow represents the indirect effect of PS_4 on *g*-factor. (**B**) Brain orientation labels in clockwise direction: rostral, left, superior, inferior, right, caudal. (**C**) Mediation model statistics from the largest significant cluster (Supplementary Table S7) for associations among PS_4, cortical thickness and *g*-factor in IntegraMooDS.

Solid arrows represent direct effects, the dotted arrow represents the indirect effect of PS_4 on *g*-factor. (**D**) Brain orientation labels in clockwise direction: rostral, left, superior, inferior, right, caudal.

Surface Area

In IMAGEN, the association between PS_i and *g*-factor was partially mediated by SA, particularly in the prefrontal cortices, including bilateral DLPFC, as well as anterior cingulate, insula, medial temporal cortex, and inferior parietal cortex (Figure 3 for PS_4 vertex-wise results). SA mediated the relationship between PS_4 to PS_8 and *g*-factor ($P_{FWER\text{-}corrected}<0.005$; Table S8). Within the IntegraMooDS sample, SA mediated the relationship between PS_2 to PS_5 and PS_6 to PS_{10} and *g*-factor in similar regions as IMAGEN ($P_{FWER\text{-}corrected}<0.05$; Table 1; Table S8; Figure 3 for PS_4). Vertex-wise results for PS_i scores at $P_{FWER\text{-}corrected}<0.05$ and $P_{FWER\text{-}corrected}<0.005$ are available in the Supplementary Material under Online Vertex-wise Results. We did not include IntegraMooDS subgroup as an interacting variable in the mediation model because there was no significant PS_i by subgroup interaction on SA ($P_{FWER\text{-}corrected}>0.05$).

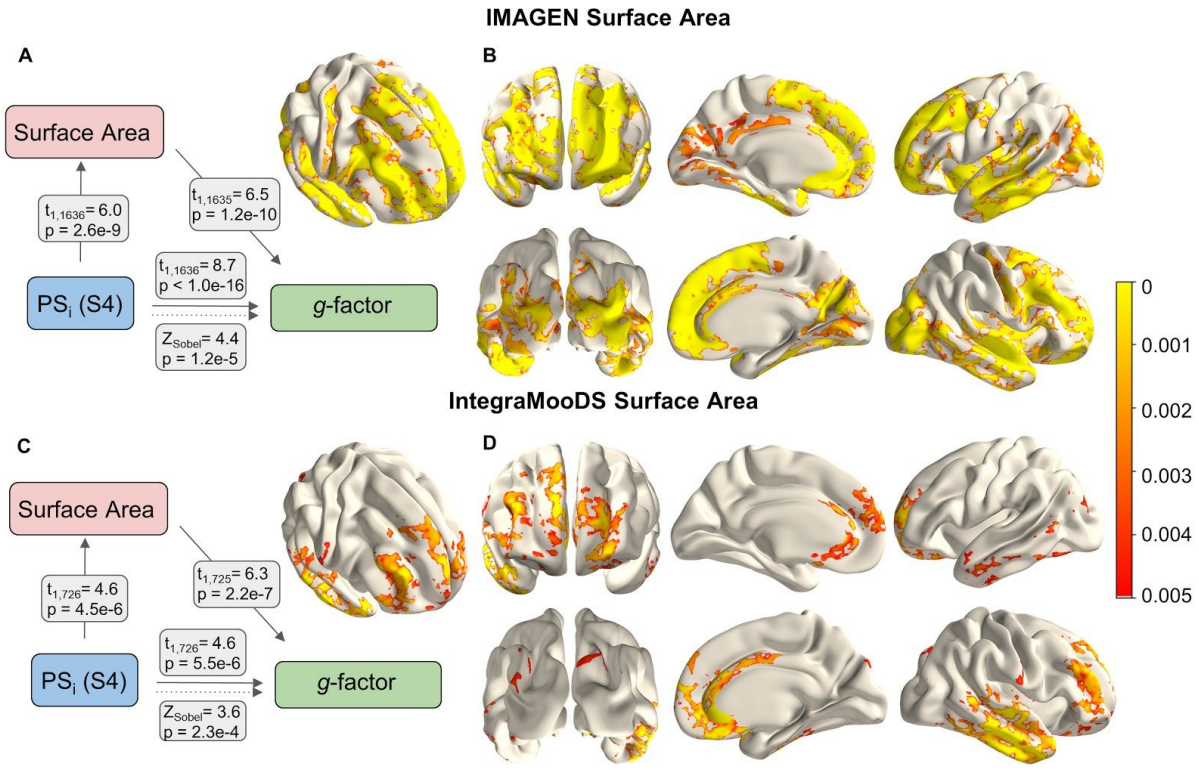

Figure 3. The association of PS_4 ($P_T < 0.001$) and *g*-factor is mediated by surface area in key regions associated with general intelligence in IMAGEN (N = 1,651) and IntegraMooDS (N = 742). Significant vertices are shown ranging from $P_{FWER\text{-}corrected} < 0.005$ (red) to $P_{FWER\text{-}corrected} < 0.001$ (yellow). (**A**) Mediation model statistics from the largest significant cluster (Supplementary Table S8) for associations among PS_4, surface area and *g*-factor in IMAGEN. Solid arrows represent direct effects, the dotted arrow represents the indirect effect of PS_4 on *g*-factor. (**B**) Brain orientation labels in clockwise direction: rostral, left, superior, inferior, right, caudal. (**C**) Mediation model statistics from the largest significant cluster (Supplementary Table S8) for associations among PS_4, surface area and *g*-factor in IntegraMooDS. Solid arrows represent direct effects, the dotted arrow represents the indirect effect of PS_4 on *g*-factor. (**D**) Brain orientation labels in clockwise direction: rostral, left, superior, inferior, right, caudal.

Post hoc estimation of the mediation effects

We estimated the *post hoc* effect sizes from the mean top cluster values of the vertex-wise mediation analyses (Table 1, Figures 2-3, and Tables S6-S8). For the direct effect, associations between PS_i and *g*-factor, the partial η^2 of the ranged from 0.007-0.054 in IMAGEN and 0.014-0.028 in IntegraMooDS (Figure 1, Table S9). The variance explained for PS_i, on CT ranged from partial η^2=0.009-0.017 in IMAGEN, and partial η^2=0.019-0.034 in IntegraMooDS, and the variance explained for PS_i on SA ranged from partial η^2=0.005-0.013 in IMAGEN, and partial η^2=0.012-0.023 in IntegraMooDS (Table S9).

The indirect effect of PS_i and *g*-factor via the top CT clusters ranged from partial η^2 = 0.0028 to 0.0075 in IMAGEN, and partial η^2=0.0019-0.0076 in IntegraMooDS (Table S9). Of the explainable variance in *g*-factor by PS_i, the indirect effect explained ranged between 10.7%-24.9% in IMAGEN, and 12.2%-41.0% in IntegraMooDS. The indirect effect of PS_i and *g*-factor via CT ranged from partial η^2=0.0021-0.0065 in IMAGEN, and partial η^2=0.0029-0.0062 in IntegraMooDS (Table S9). Of the explainable variance in *g*-factor, the indirect effect of the SA explained between 6.3%-18.9% in IMAGEN, and 17.7%-32.3% in IntegraMooDS (Table S9).

Discussion

It has been reported that the genetic contribution to general intelligence is partially shared with the genetics of cortical structure (Grasby et al. 2018; Savage et al. 2018). To the best of our knowledge, we provide first direct evidence that the genetic influence of common variants on general intelligence is partially mediated by its intermediate effect on CT and SA. Individuals with higher PS_i scores, particularly at the P_T<0.001 threshold (PS_4), had higher CT and SA in the frontotemporal, inferior parietal, and anterior cingulate regions that putatively led to better *g*-factor performance. These results were remarkably consistent among 14-year-old adolescents in the IMAGEN sample, as well as among the adult subgroups of the IntegraMooDS sample, suggesting that PS_i may be independent of the subject population. Moreover, we potentially validate the functional effect of our SNP-derived PS_i since the

cortical regions that mediate genetic effects on *g*-factor are similar to the regions associated with intelligence identified in twin-based heritability studies. All in all, we provide functional evidence that the cortical regions associated with the PS_i may be integral to inter-individual differences in *g*-factor performance.

Among the IMAGEN and IntegraMooDS samples, we found remarkably consistent associations among: (1) PS_i and *g*-factor, (2) PS_i and cortical structure, and (3) cortical structure and *g*-factor. We demonstrated consistent associations between PS_i and *g*-factor performance in IMAGEN and IntegraMooDS with variance explained maximizing around the $P_T<0.001$ threshold (PS_4). Importantly, it should be noted that we derived our PS_i from a subsample of the meta-analysis that excluded IMAGEN. We replicated the Savage et al. (2018) PS_i association with intelligence in the cross-disorder IntegraMooDS sample, and in both samples the maximum PS_i was around $P_T<0.001$ polygenic threshold (PS_4) (Savage et al. 2018). Importantly, PS_i was also robustly associated with CT and SA in prefrontal, medial temporal, anterior cingulate, parietal, and insular cortices in both samples even after correcting for ten PS_i thresholds and FWER across all vertices (approximately 3 million vertices in total). The topography of these associations is consistent with regions that have been heavily implicated by structural and functional neuroimaging studies in neurocognitive capacity (Deary et al. 2010; Basten et al. 2015; Pietschnig et al. 2015). The associated regions are also consistent to previously reported areas that have high heritability and are associated with general intelligence (Thompson et al. 2001; Gray and Thompson 2004; Toga and Thompson 2005; Narr et al. 2006). Within our samples, there were brain-wide positive correlations among CT and SA and *g*-factor performance. The unspecific effect of cortex morphology on *g*-factor performance is consistent with recent meta-analytic data demonstrating robust associations between general cognitive function and total brain volume (Elliott, Belsky, et al. 2018). This result is also consistent with general associations with most structural MRI phenotypes (Ritchie et al. 2015) and

intelligence including CT (Shaw et al. 2006; Karama et al. 2011) and SA (Lencz et al. 2014). Therefore, a natural question is if there is a latent association among these three correlations.

To date, the majority of neuroimaging and genetics studies examining cognition have focused on pairwise relationships among genetics-cognition, genetics-brain, or brain-cognition. We performed vertex-wise mediation analysis of CT and SA among ten PS_i thresholds in two independent samples linking genetics, brain structure and general intelligence. Our cortex-wise mediation findings are in-line with the few studies that have examined genetics-brain-cognition relationships. We observed a consistent mediation particularly in frontal regions, such as the DLPFC, as well as the anterior cingulate cortex, posterior cingulate cortex, and medial temporal lobes, where cortical structure mediated the effect of PS_i on *g*-factor. Our results are spatially similar to twin-based heritability studies. In virtually identical regions, cortical grey matter volume mediated the association of the genetic influence on *g*-factor (Gray and Thompson 2004). More recently, frontotemporal cortical thickness, as well as change in cortical thickness during adolescence were also demonstrated to mediate the genetic association with full-scale IQ (Schmitt et al. 2019). Therefore, the genetic influence estimated by GWAS meta-analysis derived PS_i or twin-based heritability both support a shared associations of genetics and brain structure on intelligence. Furthermore, a meta-analysis across four independent samples found a weak but consistent mediation effect among polygenic scores derived from an education attainment GWAS (Davies et al. 2016), total brain volume, and cognitive performance (Elliott, Belsky, et al. 2018). These previous findings on total brain volume mediation are consistent with our results given the relatively strong, GWAS-derived, genetic correlation between intelligence and educational attainment (r_g~0.70) (Rietveld et al. 2013; Savage et al. 2018). Our mediation findings are also consistent with the association between intelligence and brain activation during cognitive demand in lateral prefrontal, insular, parietal, temporal, motor, as well as posterior and anterior cingulate regions (Basten et al. 2015; Hearne et al. 2016; Saxe et al. 2018).

Since we observed a more specific mediation effect in frontotemporal, and insular regions, it could be speculated that the relatively weak total brain volume mediation could be too general of a phenotype.

There are some important limitations to this study. Mediation analyses inherently imply causal inference; however, we are cautious of this implication. We had a strong *a priori* hypothesis of the direction of our mediation models: genetics likely determine brain structure (and not vice versa), and brain structure likely determines *g*-factor; however, in both IMAGEN and IntegraMooDS the PS_i only explained 3-5% of the variance in *g*-factor performance. We are only explaining a portion of the genetic contribution to intelligence (for example, the SNP-based heritability of general intelligence is approximately 20% (Marioni et al. 2014; Davies et al. 2018b; Savage et al. 2018)). Moreover, while we observed widespread and strongly significant associations among CT, SA and *g*-factor, these structures explained only 2-3% of the variance of *g*-factor after including PS_i as a covariate. Together these explain why the maximum amount of the variance mediated by CT and SA was only around 0.7%. However, it should be noted that 0.7% represents 20-40% of the initial PS_i association with *g*-factor in IMAGEN and IntegraMooDS, respectively. While in the context of imaging-genetics studies of behavior phenotypes this amount of explained variance is not trivial, we cannot infer direct conclusions explaining *g*-factor performance. Therefore, our results should not be viewed as a causal gene-brain-behavior mechanism, but rather as an insight to cortical regions that directly related to PS_i and *g*-factor performance that are more specific than either of these associations alone. Further, our subgroups were too small to make definitive conclusions about the patient groups. Within IntegraMooDS, our results were consistent across patient and relative subgroups suggesting the genetic association is independent from psychiatric diagnosis, nevertheless these results need to be confirmed in larger patient samples. Moreover, both our samples were of European descent; therefore, we are unable to assess the effect of PS_i in other ethnic subgroups. Last, there is a known interaction among age, surface area, cortical thickness and intelligence (Narr et al. 2006; Karama et al. 2014). We observed consistent genetic effects on cortical structure in adolescents and

adults. However, a sample designed to assess across-the-lifespan effects would be needed to assess any neurodevelopmental effects.

Our findings support a direction of effect in which GWAS-derived PS_i effects cortical structure, which in turn, correlates with *g*-factor performance. In particular, it supports an intermediate role of cortical morphology in the relationship between cumulative genetic load for general intelligence and *g*-factor performance. Although polygenic scores are unlikely to account for all of the genetically explained variance in *g*-factor performance, PS_i appears to be an interesting factor collectively influencing cortical structure and neurocognition.

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Conflicts of Interest

T.B. has served as an advisor or consultant to Bristol-Myers Squibb, Desitin Arzneimittel, Eli Lilly, Medice, Novartis, Pfizer, Shire, UCB, and Vifor Pharma; he has received conference attendance support, conference support, or speaking fees from Eli Lilly, Janssen McNeil, Medice, Novartis, Shire, and UCB; and he is involved in clinical trials conducted by Eli Lilly, Novartis, and Shire; the present work is unrelated to these relationships. M.M. has been a member of the scientific advisory boards for the Lundbeck Foundation and Robert-Bosch-Stiftung, is a member of the Medical-Scientific Editorial Office of Deutsches Ärzteblatt, has received travel support from Shire Deutschland GmbH, and receives a salary from and holds shares in Life and Brain GmbH. A.M-L. discloses speaker and/or advisor or authorship fees from Astra Zeneca, Servier, Bristol-Myers Squibb GmbH & Co.KGaA, Desitin Arzneimittel GmbH, Defined Health, F. Hoffmann-La Roche Ltd., Lilly Deutschland GmbH, Gerson Lehrmann Group (GLG), Pricespective, Elsevier, Alexza Pharmaceuticals Inc., Outcome Sciences Inc., Pfizer Pharma GmbH, Janssen-Cilag EMEA. H.W. received a speaker honorarium from Servier (2014). The other authors report no financial interest or potential conflicts of interest.

Online Supplementary Material

- Online Vertex-wise Results

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