Response to the Reviewers

Reviewer #1

Lett and colleagues investigate two larger imaging-genetics samples to revisit the relationship between cortical thickness and IQ as measured by the g-factor. While the samples are large, and the conducted analyses laudable, this reviewer is mostly concerned with what kind of novelty the present results are really putting forward. If the authors succeeded in highlighting how this investigation extends the existing literature, the paper can be a nice contribution to the corpus of scientific in the brain-behavior associations of human intelligence.

We would like to thank the Reviewer for the positive and helpful comments. We have now better framed how our results extend the existing literature with directly highlighting the novelty of our findings. Please see our comments below.

Major

1. *Introduction: ...could be streamlined + the transition from general to clinical aspects smoothened.*

We have followed the recommendation of the reviewer to streamline the introduction. It has now been reordered to transition better between the different concepts, and we believe that it is now more clear and concise.

2. *Abstract: Please clarify/unpack "among ten thresholds were assessed for their association"*

For our genetic analyses, we followed a polygenic score method used by many of the Psychiatric Genomic Consortium publications in which ten p-value thresholds, or deciles, are used to calculate ten polygenic scores with increasing evidence for genetic association (Cross-Disorder Group of the PGC 2013; Ripke et al. 2014; Purcell et al. 2009). We have now rewritten the abstract to clarify this strategy for calculating polygenic scores.

"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)."

3. *Methods: Using the first PC from different cognitive batteries is an important aspect of the conducted analyses, please provide further insight and descriptive analyses of how these two types of g factor are similar or different in the two sample, such as by including the explained variance metrics (comparing to 2nd and 3rd PC), basic statistics of the distribution of g-factor loadings, as well as their comparison to the existing imaging and wider literature.*

We have now included additional details and insights regarding our *g*-factor calculation using principal component analysis, as well as its comparison to the existing literature. Please see the following additions below:

Methods and Material, General Intelligence:

"**In both samples, the factor loadings of individual neurocognitive tests followed a typical pattern** (Deary, Penke, and Johnson 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 1998)**. For instance, *g*-factor scores obtained from different domains of cognitive tests correlate highly** (>0.98; Johnson et al. 2004; Johnson, Nijenhuis, and Bouchard 2008)**."**

Results, General Intelligence:

"In both samples, *g*-factor explained a similar amount of variance across various cognitive tests as earlier research has suggested (Table S3; Figure S2). In earlier studies, *g*-factor virtually always accounts for 40% or more of the variance across different cognitive domains (Carroll and B. 1993; Deary, Penke, and Johnson 2010)**"**

Supplementary Table S3, Supplementary Figure S1 and S2:

	IMAGEN		IntegraMooDS	
PC	Eigenvalues	% of variance	Eigenvalues	% of variance
1	3.29	41.06	3.66	40.62
2	1.68	21.04	1.17	13.04
3	1.07	13.35	0.91	10.12

Table S3 Eigenvalues and percentage of variance explained for the first three unrotated principal components from different cognitive batteries, separately for IMAGEN and IntegraMooDS.

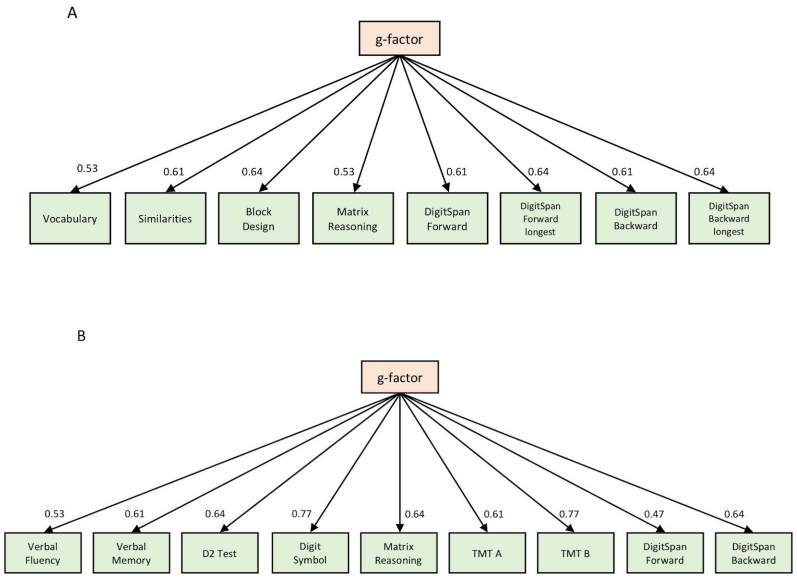

Figure S1. Factor loadings of individual neurocognitive tests on *g*-factor, separately for (**A**) IMAGEN and (**B**) IntegraMooDS. The *g*-factor explained 41.06 % of the variance across the different domains in IMAGEN and 41.72 % in IntegraMooDS.

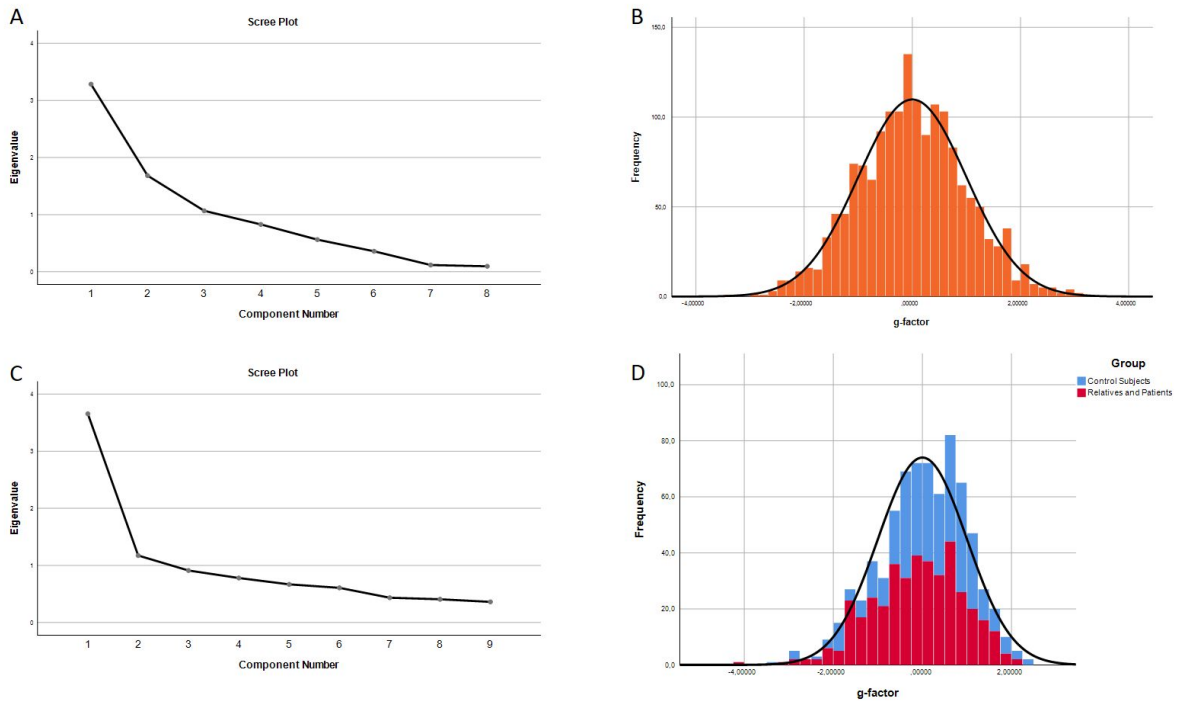

Figure S2 Basic statistics for the principal component analysis. (A) Scree plot for eight principal components from different cognitive batteries in IMAGEN. (B) Histogram for the first unrotated principal component (*g*-factor) in IMAGEN. (C) Scree plot for nine principal components from different cognitive batteries in IntegraMooDS. (D) Histogram for the first unrotated principal component (*g*-factor) in IntegraMooDS, separately for control subjects (blue) as well as relatives and patients (red).”

4. *Methods: Please provide a more detailed description of how the mediation analysis was implemented mathematically.*

We would like to thank the reviewer for this suggestion. Previously, we have published a comprehensive technical report on the TFCE_mediation software package in the journal Human Brain Mapping (Lett et al. 2017). We have now added a section of the calculations performed during cortex-wise mediation using TFCE_mediation to the cortex-wise mediation analysis of the Supplementary Material.

“As described in Lett et al. (2017), in TFCE_mediation, sets of regression analyses are performed to assess the indirect (mediation) effect using the Aroian variant of the Sobel equation (Mackinnon, Warsi, and Dwyer 1995; Sobel 1982, 1986)**:**

$$Z\ value = \frac{a \times b}{\sqrt{b^2 \times S_a^2 + a^2 \times S_b^2 + S_a^2 \times S_b^2}}$$

For Path A, the independent variable (PS_i) is regressed on the mediator variable (brain structure). For Path B, the mediator variable (brain structure) is regressed on the dependent variable (*g*-factor) including the independent variable (PS_i) as a covariate. The unstandardized regression coefficients (betas: a and b) and the standard errors (S_a and S_b) are used to produce a z-value at each vertex of the cortical surface. The z-value then undergoes vertex-wise TFCE transformation, and significance is determined using permutation testing. For additional information please see our methods paper as well as recent publications using TFCE_mediation (Lett et al. 2017; Vogel et al. 2018; Lett et al.

2018)**. Moreover, the source code and further information are available on the website: https://github.com/trislett/TFCE_mediation"**

5. *Methods: the aim, implementation and possible outcomes of "Polygenic intelligence score" should be more introduced in the methods section*

We like to thank the reviewer for this suggestion. We have now added a description of the PS_i method, and its rational to better introduce the polygenic scores.

Materials and Methods, Genetics section:

"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)** (Purcell et al. 2009; Cross-Disorder Group of the PGC 2013; Ripke et al. 2014)**."**

6. *Discussion / "Moreover, to the best of knowledge, our study is the first to perform whole brain vertex-wise analysis (>300,000 vertices per subject) with permutation testing on large neuroimaging samples providing unprecedented level of regional specificity.": It should be clearly worked out what the primary contributions this study makes to the existing literature. The way it is present at this point suggests incremental progress, rather than a genuinely new finding.*

We would also like to thank the reviewer for this suggestion as we feel that the quoted text distracts from the novelty and importance of our results.

Our study is unique because: (1), it is the first evidence that the accrued genetics association for intelligence from thousands of genetics variants is associated with cortical surface area and cortical thickness in two relatively large independent samples, (2), our mediation analyses demonstrate a shared, as well as inferred causal, gene-brain-behavior relationship in which the effect of PS_i on *g*-factor is mediated by cortical structure, and (3), this relationship was spatially very similar in both samples. The latter is particularly important since the topography of our results is very similar to heritability results from previous studies. Therefore, our vertex-wise mediation analyses results support that the GWAS meta-analysis derived PS_i share some commonality to heritably results. Please see the following changes in the discussion.

Discussion, Paragraph 1:

"To the best of our knowledge, we provide first direct evidence that the genetic influence of common on general intelligence is partially mediated by its intermediate effect on CT and SA."

"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."

Discussion, Paragraph 3:

"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."**

7. *Semantics: "Cognition", "cognitive ability", and "IQ" are related but distinct concepts, please be carefully in not extending the IQ notion too much in the various places across the manuscript.*

The reviewer raises an important point that cognition, cognitive ability and IQ should not be used interchangeably even if they are related concepts. To reiterate, we have only analyzed *g*-factor as our measure of general intelligence in our study. We have now further clarified the difference between *g*-factor and IQ, as well as carefully edited the manuscript to specifically refer to the exact intelligence measure of interest. Please see the introduction, as well as specific examples below:

Introduction, First paragraph,

"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)**."**

Introduction, Fourth paragraph,

"The neurocognitive domains contributing to lower *g*-factor scores vary among individuals and clinical subpopulations of these diseases."

8. *Discussion: please provide a more detailed discussion of the *locations* that were most related to IQ as measured by cortical thickness in the brain, with some*

commonly discussed functional associations.

There was a widespread (i.e., regionally unspecific) association of *g*-factor with cortical thickness and cortical surface area. We now discuss these unspecific findings with respect to other structural evidence. However, since we did observe more specific effects from the mediation analyses, we have also expanded our discussion regarding the regional specificity of our mediation findings and their functional associations.

Discussion, Paragraph 2:

"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 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)**."**

Figure S7:

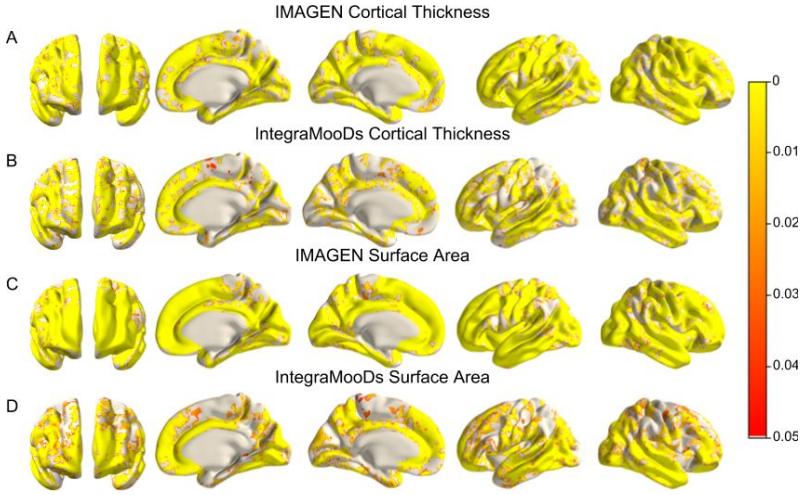

Figure S7. The association of *g*-factor with CT, as well as g-factor with SA throughout the cortex ranging from $P_{FWE\text{-}corrected} < 0.05$ (red) to $P_{FWE\text{-}corrected} < 0.001$ (yellow). Anatomical locations from left to right: rostral, left, superior, caudal, right, inferior. IMAGEN included sex, age, site and ethnicity as covariates. IntegraMooDS included subgroup, sex, age, site, and ethnicity as covariates. (**A**) The association of *g*-factor and CT in IMAGEN (N = 1651). (**B**) The association of *g*-factor and CT in IntegraMooDS (N=742). (**C**) The association of *g*-factor and SA in IMAGEN. (**D**) The association of *g*-factor and SA in IntegraMooDS. CT, cortical thickness; SA, surface area.

Discussion, paragraph three:

"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."

"The topography of these associations is consistent with regions that have been heavily implicated by structural and functional neuroimaging studies in neurocognitive capacity (Deary, Penke, and Johnson 2010; Basten, Hilger, and Fiebach 2015; Pietschnig et al. 2015)**."**

"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, Hilger, and Fiebach 2015; Saxe, Calderone, and Morales 2018; Hearne, Mattingley, and Cocchi 2016)**."**

Minor
Methods: please clarify "baseline data"

Our apologies, this was a typographical error that has now been removed from the manuscript.

Reviewer #2

In "Cortical surfaces mediate the relationship between polygenic scores for intelligence and general intelligence," Lett et al., present a series of interesting and rigorous analyses to assess the relationships between polygenic scores for intelligence (PSi) and g-factor performance; PSi and cortical morphology; and the potential mediation of the relationship between PSi and g-factor performance via cortical morphology characteristics in two large, independent samples. At multiple significance thresholds, they find that PSi is associated with g-factor performance, as well as surface area and cortical thickness in multiple regions previously implicated in neurocognitive performance (e.g., prefrontal cortex, anterior cingulate, medial temporal cortex). They also find that CT and SA partially mediate the relationship between PSi and g-factor performance in many of these same regions.

Overall, the analyses appear to be thoughtfully and competently carried out, the replication sample is a great strength of the study, and the results will be of interest to a broad readership. The authors are also careful to be moderate in their interpretation of the results throughout the discussion. I have only minor comments.

We would like to thank the Reviewer for the positive comments regarding the thoughtful and competent analyses of our manuscript, the interest to a broad readership, as well as the careful interpretation of the results.

1. *There are a number of typos throughout the paper (e.g., Page 13 line 38, should the word "In" at the beginning of the sentence be removed? Page 15 line 54 appears to be missing the word "that"). Please check and correct throughout the manuscript.*

We apologize and thank the reviewer for bringing theses typographical errors to our attention. We have now proofread and corrected the manuscript.

2. *In the introduction the authors note that they examine whether the association between PSi and g-factor performance is mediated by cortical brain structure in youths, adults, relatives of patients, and patient groups. In the results, they appear to find the relationships between PSi and g-factor performance and brain structure across the adolescent (IMAGEN) + adult samples (IntegraMooDS study), including without statistical evidence for interactions in these relationships by psychiatric subgroup in the IntegraMooDS study. However, it is unclear if interactions by psychiatric subgroup were also assessed for the mediation effect. If this was not tested, can the authors please clarify why not?*

This is an important comment raised by the reviewer. We did not include moderated mediation of cortical structure and our clinical subgroups in the IntegraMooDS sample because there was no significant PS_i*Group interaction for cortical thickness and surface area. Therefore, there was no opportunity for moderated mediation to occur. We have now specifically stated when moderated mediation was not included in the manuscript:

Results, Cortex-wise mediation analysis, Cortical Thickness:

“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).”

Results, Cortex-wise mediation analysis, Surface Area:

“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).”

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