Discovering the shared biology of cognitive traits determined by genetic overlap

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\textbf{ABSTRACT}

Investigating the contribution of biology to human cognition has assumed a bottom-up causal cascade where genes influence brain systems that activate, communicate, and ultimately drive behavior. Yet few studies have directly tested whether cognitive traits with overlapping genetic underpinnings also rely on overlapping brain systems. Here, we report a step-wise exploratory analysis of genetic and functional imaging overlaps among cognitive traits. We used twin-based genetic analyses in the human connectome project (HCP) dataset (N=486), in which we quantified the heritability of measures of cognitive functions, and tested whether they were driven by common genetic factors using pairwise genetic correlations. Subsequently, we derived activation maps associated with cognitive tasks via functional imaging meta-analysis in BrainMap (N=4484), and tested whether cognitive traits that shared genetic variation also exhibited overlapping brain activation. Our genetic analysis determined that six cognitive measures (cognitive flexibility, no-go continuous performance, fluid intelligence, processing speed, reading decoding and vocabulary comprehension) were heritable (0.3 < h\textsuperscript{2} < 0.5), and genetically correlated with at least one other heritable cognitive measure (0.2 < \rho_g < 0.35). The meta-analysis showed that two genetically-correlated traits, cognitive flexibility and fluid intelligence (\rho_g = 0.24), also had a significant brain activation overlap (\rho_{perm} = 0.29). These findings indicate that fluid intelligence and cognitive flexibility rely on overlapping biological features, both at the neural systems level and at the molecular level. The cross-disciplinary approach we introduce provides a concrete framework for data-driven quantification of biological convergence between genetics, brain function, and behavior in health and disease.

1. Introduction

The current biological understanding of cognition relies on an assumption of a bottom-up cascade of genetic variants, that affect cell functions, brain activation and connectivity, and ultimately converge onto behavior (Insel, 2014; Morris and Cuthbert, 2012; Meyer-Lindenberg and Weinberger, 2006; Klein et al., 2017). Data resources available worldwide have enabled us to expand our view of cognition and neurobiology in health and disease, by looking at their transcriptomic (Richiardi et al., 2015; Arnatkevičiūtė et al., 2019; Romme et al., 2017) and genomic underpinnings (Elliott et al., 2018; Heck et al., 2014). As big data and meta-analytic resources become increasingly available, new opportunities arise to understand how different domains of human biology converge and lead to interindividual differences in cognitive ability. Still, few studies to date have directly investigated the correspondence across three levels of biological complexity, integrating cognitive constructs, brain function, and their genetic underpinnings.

Cognition is an umbrella term for a range of higher-order functions, whose genetic underpinnings have been investigated by means of family studies in general, and twin studies in particular (Posthuma et al., 2001;...
Rijsdijk and Sham, 2002). Structural equation modeling (SEM) of twin-pair relationships (i.e. twin modeling) has consistently shown that cognitive measures, such as verbal and non-verbal intelligence, perceptual speed, working memory, reading, and math skills are significantly heritable, i.e. driven by additive and non-additive genetic variation (Posthuma et al., 2001; Hart et al., 2009; Calvin et al., 2012; Lee et al., 2012). Furthermore, twin studies have shown that cognitive measures correlate genetically, that is they share some of their genetic underpinnings, and that a proportion of their phenotypic correlations is significantly mediated by shared genetic variation. These shared genetic underpinnings across specific cognitive traits intuitively suggest that these traits rely on overlapping neurobiological systems (i.e. “circuits”).

Using functional magnetic resonance imaging (fMRI), cognitive tasks are routinely found associated with the activation of specific brain regions, generally organized within networks (Fox et al., 2005a; Smith et al., 2009; Poldrack et al., 2011). Regions within and across these networks are consistently found to be co-activated during the execution of specific tasks, as well as during rest (Greicius et al., 2003; Fox et al., 2005b). Functional MRI activation patterns during performance of different cognitive tasks have been found to overlap to some degree (Hirsch et al., 2000; McNab et al., 2008; Burgess et al., 2011; Ebisch et al., 2012; Yeo et al., 2015; Alexander-Bloch et al., 2018), but systematic quantification of this is limited to date. Activation and connectivity of brain networks were shown to be heritable (Glahn et al., 2010; Ge et al., 2017; Polderman et al., 2015), and, more recently, activation was found to be genetically correlated with cognitive measures (Guen et al., 2018). However, the degree to which cognition and brain function are genetically dependent on each other is unknown. Concretely, given a multi-level biological ontology of cognitive constructs and domains, one would expect that cognitive processes with shared genetic determinants also show a high degree of correspondence, both in their fMRI activation and co-activation patterns (Smith et al., 2009).

In this study, we investigated cognition in terms of genetic, circuits, and behavioral performance levels, with the goal of finding evidence for biological convergence across these biological levels. In the comprehensively phenotyped Human Connectome Project (HCP) cohort (http://humanconnectome.org), firstly, we used twin-based univariate genetic analysis to estimate the heritability of different measures of human cognition available for HCP participants (demographics displayed in Table 1). For heritable constructs we subsequently tested in a bivariate manner, sharing of genetic variation as quantified by genetic correlations. We then performed functional imaging meta-analysis in order to estimate spatial maps of brain activation associated with each cognitive trait using BrainMap (Laird et al., 2005), and tested whether there was spatial overlap in cognitive task-associated circuits of traits with shared genetic factors. Finally, we inferred whether each pair of cognitive traits biologically converged based on a fixed-effects meta-analysis, which combined the significances estimated for their respective genetic and circuit overlaps. With that, we demonstrate that current publicly-available resources are suitable for addressing biological convergence relevant for cognition. A general description of our methods is represented in Fig. 1; more details of our procedure can be found in Methods & Materials.

2. Results

Univariate genetic analyses. With the data from HCP twin participants (demographics summarized in Table 1), we estimated the heritability of cognitive measures available in the dataset. Heritability estimates (h²), and associated statistics of our twin-based univariate analysis, are shown in Table 2. Heritability was significant in the cases of cognitive flexibility, no-go continuous performance, delay discounting for 200$ reward, inhibitory control and attention, fluid intelligence, picture sequence memory, processing speed, reading decoding and vocabulary comprehension (p ≤ 0.05). Heritability estimates were moderate in all cases, ranging from 0.3 to 0.5. Additionally, twin correlations of cognitive flexibility, no-go continuous performance, inhibitory control and attention, and processing speed indicated the presence of non-additive genetic effects (e.g. dizygotic twin correlation is less than half monozygotic twin correlation), which thus show that these cognitive traits have a broad-sense heritability representative of additive and non-additive genetic effects.

In Table S5, we show that genetic results obtained only with the largest ethnic group (European-descendents, who represent 83% of the total sample) were consistent with the results observed for the whole sample. Heritability of all the cognitive measures remained significant in this subset analyses, except for fluid intelligence and delay discounting (p < 0.05). Furthermore, we considered the confounding effects of socio-economic status, and report in Table S7 the heritability estimates produced by a univariate twin modeling approach that included total years of education and total household income as covariates. All heritability estimates reported in Table 2 remained significant when accounting for socio-economic status.

Bivariate genetic analyses: Twenty-nine out of 36 phenotypic correlations investigated among heritable cognitive measures were significant (p ≤ 0.05), whose coefficients are shown in Fig. S1. Of the 29 pairs of cognitive traits, 23 were successfully modeled in our twin-based bivariate analysis, which reported, without exception, positive phenotypic and genetic correlations for all the pairs (Table 3). The phenotypic correlation coefficients ranged between 0.13 and 0.66. Furthermore, six of these genetic correlations were found to be significant as the 95% confidence interval (CI), in which the lower boundary of the CI did not cross zero: cognitive flexibility with fluid intelligence, processing speed and reading decoding, and reading decoding with no-go continuous performance, fluid intelligence, and vocabulary comprehension. In Table S2, we report the genetic results with their correspondent p-values and FDR-corrected estimates.

In Tables S3 and S4, we report the remaining non-genetic components of phenotypic correlations that are explained by shared and non-shared environmental factors. Three correlations, involving delay discounting, inhibitory control and attention, reading decoding and vocabulary comprehension, were significantly explained by shared environmental factors, i.e. environmental factors shared between twin relatives. Another three correlations involving cognitive flexibility, processing speed, inhibitory control and attention, reading decoding and vocabulary comprehension were significantly driven by unique environmental factors, i.e. environmental factors not shared between twin relatives. Moreover, Table S6 reports the bivariate genetic results obtained only with the largest ethnic group (European-descendents, who represent 83% of the total sample), which were partly consistent with the results observed for the whole sample. From the six genetic correlations found to be significant in Table 3, only two reached significance (reading decoding with no-go continuous performance and vocabulary comprehension).

Functional imaging meta-analysis: We derived activation maps for five of the individual cognitive traits that we found to be genetically correlated (see Table 3). The five activation maps are displayed in Fig. 2,
already arranged in pairs according to their genetic associations. We could not perform a meta-analysis of processing speed due to the lack of functional imaging studies in the BrainMap database reporting an HCP-equivalent task performance. Main information regarding the meta-analysis conducted for each trait are presented in Table 4, whereas additional details are reported in Table S8. Moreover, the studies and respective activation contrasts collected for the meta-analyses of cognitive flexibility, no-go continuous performance, fluid intelligence, reading decoding, and vocabulary comprehension are listed separately for each cognitive trait in Tables S9–S13. Detailed information regarding the anatomical regions covered by these activation maps is reported in Tables S14–18.

The activation maps displayed in Fig. 2 were estimated via meta-analytic procedures that comprised task performance in health and disease, in an effort to represent the general population, and maximize the reliability of the BrainMap algorithm, which improves with additional contrasts. To assess to what extent the inclusion of first-level contrasts in patient samples may have influenced our results, we compared the activation maps with those of healthy individuals only (Fig. S2). We show in Table S24 that the healthy individuals-only activation maps of cognitive flexibility, no-go continuous performance, fluid intelligence, reading decoding, and vocabulary comprehension overlap considerably with the respective maps that included patient populations via the permuted correlation approach used throughout this study (0.69 < \( \rho_{perm} \)).

Fig. 1. Flow chart summarizing the analysis here implemented. Starting with a selection of cognitive measures evaluating performance among specific higher-order functions (a), we used twin-based univariate genetic analysis (b) to test whether they were driven by genetic variation, i.e. heritable (c). Among heritable cognitive measures (d), we addressed their phenotypic correlations (e), and tested further with a twin-based bivariate genetic analysis (f) whether phenotypic correlations were driven by genetic covariation, i.e. genetically correlated (g). Focusing on cognitive measures that were genetically correlated (h), we conducted for each a coordinate-based meta-analysis based on functional imaging studies available in the BrainMap database (i), retrieving activation maps representative of task performance related to these cognitive traits (j). Then, we tested whether these cognitive maps overlapped for traits with genetic correlations (k). Finally, we combined p-values retrieved by inferences of genetic correlation and spatial overlap between cognitive maps, and inferred via fixed-effects meta-analysis whether pairs of cognitive traits biologically converged based on their overlapping genetics and circuitry (l).
< 0.94; \( p_{\text{perm}} \leq 3.3E-5 \). A brief description of the permuted correlation method is reported in Methods and Materials: Brain Activation Overlap.

Additionally, we identified throughout our approach that the meta-analysis conducted for fluid intelligence relied on a heterogeneous set of problem solving and reasoning tasks. Therefore, we compared in Fig. S3 the fluid intelligence activation map with an activation map based on the activation contrast in which its HCP-equivalent cognitive task (i.e. the matrix reasoning task) was reported. In Table S25, we address their overlap quantitatively, which was found to be moderate and highly significant (\( \rho_{\text{perm}} = 0.31; p_{\text{perm}} = 6.3E-4 \)).

Brain activation overlap: For pairs of cognitive traits with activation maps estimated via meta-analysis, we inspected spatial overlap visually based on their surface projections (Fig. 2, Movies S1-S5), and by means of three quantitative measures (Table 5): number of voxels, which provides an absolute measure of volumetric overlap; DSC, a standard relative measure of volumetric overlap; Pearson’s correlations with permutation-based inference, an inference-based relative measure of surface overlap. The three measures showed consistent results showing a high degree of spatial overlap between cognitive flexibility and fluid intelligence, which was the only significant result according to the inference-based approach. The anatomical regions shared between the two traits are the left and right superior parietal lobules, right paracallosal gyrus, right insula, and right inferior frontal gyrus. In spite of not finding significant overlaps among the other trait pairs, we can observe in Fig. 2 that no-go continuous performance and reading decoding show a considerable overlap in the right hemisphere, in the juxta-possitional lobule cortex and precentral gyrus; and an overlap between reading decoding and vocabulary comprehension in the left hemisphere, in the temporal occipital fusiform cortex and superior temporal gyrus. Tables S19–S23 provide a detailed description in MNI space of the anatomical regions involved in all the five overlaps, whereas Movies S1-S5 show the overlaps activation maps in their original volumetric format.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.neuroimage.2019.116409.

Biological convergence between cognitive traits: We highlight in Table 6, for each pair of cognitive traits, the \( \rho \)-values retrieved by their genetic and circuit overlap inferences, respectively, and the results of their fixed-effects meta-analysis. Given we tested five pairs of cognitive traits in terms of their overlapping genetics and circuitry, the fixed-effects meta-analysis provided evidence for cognitive flexibility and fluid intelligence to show significant biological convergence in terms of their genetics, circuitry, and behavior (\( p \leq 0.01 \)).

### 3. Discussion

In this study, we investigated the biological convergence across genetics, circuits, and cognition, by means of twin data and meta-analytic resources that are publicly available. We report a significant biological convergence between cognitive flexibility and fluid intelligence in terms of their genetics, brain activation, and behavioral performance. Firstly, we showed using twin-based univariate genetic analysis that genetic effects explained performance in nine cognitive measures present in our dataset. Next, in a bivariate genetic analysis, we showed that six cognitive measures shared genetic factors that significantly explained a proportion of five of their phenotypic correlations. Then, we took into account the six genetically-correlated cognitive traits in a functional imaging meta-analysis with BrainMap. We conducted a coordinate-based meta-analysis for each cognitive trait, which successfully retrieved spatial maps of brain activation for five of the six genetically-correlated traits. Further, we found that cognitive flexibility and fluid intelligence were the only pair of cognitive traits with shared genetic factors that also exhibited a significant spatial overlap between their activation maps. We confirmed afterwards, via fixed-effects meta-analysis of \( \rho \)-values, that this cognitive trait pair was the only to biologically converge.

Our findings for the heritability of the nine cognitive traits are consistent with previous literature (Hart et al., 2009; Lee et al., 2012; Light et al., 1998; Wright et al., 2001; Anokhin et al., 2008, 2015; Owens et al., 2011a, 2011b; Godinez et al., 2012; de Zeeuw et al., 2016; Müller et al., 2017; Tosto et al., 2017). Our results on genetic correlations of cognitive flexibility with fluid intelligence, processing speed and reading decoding, and those of reading decoding with the no-go continuous performance, fluid intelligence, and vocabulary comprehension extend existing literature. Previous twin studies have shown that cognitive flexibility, as measured by the card sorting test, shares genetic factors with general cognitive ability (Lee et al., 2012), and with other, more specific, measures of cognition such as working memory. By taking a more data-driven approach, we showed that cognitive flexibility is also genetically correlated with fluid intelligence, processing speed and reading decoding. Regarding the other genetic correlations involving reading decoding, previous literature supports a genetic link with general markers of intelligence (Hart et al., 2009; Owens et al., 2011b; Greven et al., 2014), as well as specific aspects of intelligence, such as problem solving and reading comprehension (Light et al., 1998). Therefore, the fact that we found reading decoding to be genetically correlated with fluid intelligence and vocabulary comprehension strengthens the idea of a common genetic background between reading and general intelligence, as well as with the more specific cognitive domain of language. To our
knowledge, however, no previous studies have reported a genetic link of reading decoding with continuous performance. Still, this genetic correlation may relate to the idea that reading skills require sustained attention and to its shared genetics with inhibition problems (Ebejer et al., 2010; Greven et al., 2011), which are commonly captured using go/no-go experimental designs (Casey et al., 1997).

With our functional imaging meta-analysis, we derived activation maps for cognitive traits showing genetic overlap. By accessing the BrainMap database (Laird et al., 2005), one of the biggest available to conduct coordinate-based meta-analysis, we collected a minimally-required number of studies for having a sample representative of each trait, and thus a well-powered meta-analysis (Eickhoff et al., 2012), except for processing speed. Overall, we observed spatial maps that reliably captured activation reported across studies, showing regions of activation mostly located in the cortex. When testing whether cognitive traits sharing genetic factors also spatially overlapped in their meta-analytic activation maps, we found cognitive flexibility and fluid intelligence to show significant overlap covering the left and right superior parietal lobules, the right paracingulate gyrus, right insula, and right inferior frontal gyrus. On the other hand, the overlaps involving reading decoding with cognitive flexibility, no-go continuous performance, fluid intelligence, and vocabulary comprehension were not significant. Without addressing the genetics of cognitive traits, other studies had already reported common regions of activation between some of the cognitive traits tested here (McNab et al., 2008; Yeo et al., 2015; Bartley et al., 2018; Ekstrand et al., 2019), although that the results of these studies did not correspond to the activation overlaps we reported in our analysis. Still, Yeo et al. (2015) and Bartley et al. (2018) reported functional imaging meta-analysis of cognitive flexibility and fluid intelligence (Yeo et al., 2015; Bartley et al., 2018), respectively, showing that superior parietal cortex, insula, and prefrontal cortex are engaged in each of these cognitive domains, in agreement with our results.

By using a data-driven approach based on a genetically informed variable selection, we found that most genetically correlated traits did not show significant brain activation overlap. This does not immediately imply that they do not have a shared neurobiology, but rather that any neurobiology they may share is not generally and consistently reflected in, or captured by, fMRI studies. There are many biological levels...
intermediate between the genetic and brain mesoscopic level, and the biological convergence of these cognitive traits may be better reflected on a more microscopic scale of human neurobiology. Alternatively, biological convergence may still occur at the mesoscopic level, and be captured using other types of imaging modalities looking at different types of brain measurements, such as structure or electrophysiology-related measures. However, our negative results may also be interpreted as challenging the classic bottom-up view of genetic effects through the brain to behavior framework that is often implicitly accepted in the current literature. Contradicting this classic view, recent findings in gene-environment correlation and epigenetics indicate that genes and behavior are not linked by an unidirectional bottom-up effect, but rather by a more complex interplay in which biological effects may propagate back and forth between the environment and the brain, and down via methylation to gene expression (Trerotola et al., 2015; Kong et al., 2018).

Because the resources we used in our study are not appropriate to address this type of gene-environment interplay through the brain, we were not able to answer, whether they are the cause of the absence of shared neurobiology in cognitive traits that are genetically correlated. Still, the biological convergence between cognitive flexibility and fluid intelligence shows that in some cases we are able to capture how complex traits, such as cognition, interact across multiple levels of human biology.

Regarding the genetic methods employed here, we opted for using twin modeling, a standard approach in the field of psychiatric genetics. Our study shows, consistent with existing literature, that using twin modeling is a powerful and reliable tool to estimate the genetic and environmental factors influencing behavior and cognition (Posthuma et al., 2001; Hart et al., 2009; Calvin et al., 2012; Lee et al., 2012). However, we did not find significant heritability for cognitive traits such as spatial orientation, verbal episodic memory, or working memory, contrary to other twin studies (Lee et al., 2012; Ando et al., 2001; Kremen et al., 2007). These non-findings may be explained by our moderate sample size, and by the assumptions underlying twin modeling and its

### Table 4

<table>
<thead>
<tr>
<th>Cognition measure</th>
<th>Number of Studies</th>
<th>Number of Samples</th>
<th>Total number of individuals (number of healthy individuals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Flexibility</td>
<td>26</td>
<td>33</td>
<td>678 (591)</td>
</tr>
<tr>
<td>No-go Continuous Performance</td>
<td>64</td>
<td>98</td>
<td>1705 (1255)</td>
</tr>
<tr>
<td>Fluid Intelligence</td>
<td>18</td>
<td>29</td>
<td>417 (372)</td>
</tr>
<tr>
<td>Reading Decoding</td>
<td>28</td>
<td>33</td>
<td>385 (343)</td>
</tr>
<tr>
<td>Vocabulary Comprehension</td>
<td>78</td>
<td>97</td>
<td>1299 (1178)</td>
</tr>
</tbody>
</table>

For each trait reported in Table 3, we report the total number of studies found in the BrainMap database, the total number of samples reported across studies, and the total number of individuals across the samples.

From the total number of participants, we highlight for each trait the number of healthy individuals, from whom we collected the majority of the reported coordinates we used in further meta-analytic steps.

Fig. 2. Brain surface visualization of activation maps estimated for cognitive flexibility, no-go continuous performance, fluid intelligence, reading decoding, and vocabulary comprehension (colored in blue, pink, green, yellow and brown, respectively). Among these maps, five brain activation overlaps were addressed in result of our genetic correlation results (in Table 3), here sorted from top to bottom: cognitive flexibility with fluid intelligence and reading decoding; and reading decoding with no-go continuous performance, fluid intelligence, and vocabulary comprehension (overlapping regions highlighted in red).
We tested only brain activation overlaps between cognitive traits which were found to be genetically correlated (see Table 3).

Remainder overlaps that were not tested are signaled with a dash (“-”).

In the bottom matrix, we highlight in bold the brain activation overlaps found to be significant by the permutation-based inference.

Table 5
Correlation matrices showing results relative to spatial overlaps between activation maps estimated for cognitive flexibility, no-go continuous performance, fluid intelligence, reading decoding, and vocabulary comprehension.

<table>
<thead>
<tr>
<th>Number of Voxels</th>
<th>Cognitive Flexibility</th>
<th>No-go Continuous Performance</th>
<th>Fluid Intelligence</th>
<th>Reading Decoding</th>
<th>Vocabulary Comprehension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Flexibility</td>
<td>2920</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>No-go Continuous Performance</td>
<td>-</td>
<td>5354</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fluid Intelligence</td>
<td>606</td>
<td>1769</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reading Decoding</td>
<td>27</td>
<td>1</td>
<td>7</td>
<td>4044</td>
<td>-</td>
</tr>
<tr>
<td>Vocabulary Comprehension</td>
<td>-</td>
<td>-</td>
<td>224</td>
<td>5950</td>
<td>-</td>
</tr>
</tbody>
</table>

Dice Similarity Coefficient

<table>
<thead>
<tr>
<th>Dice Similarity Coefficient</th>
<th>Cognitive Flexibility</th>
<th>No-go Continuous Performance</th>
<th>Fluid Intelligence</th>
<th>Reading Decoding</th>
<th>Vocabulary Comprehension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Flexibility</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>No-go Continuous Performance</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fluid Intelligence</td>
<td>0.256</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reading Decoding</td>
<td>0.008</td>
<td>0.034</td>
<td>0.002</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Vocabulary Comprehension</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.045</td>
<td>1</td>
</tr>
</tbody>
</table>

Pearson’s Correlation (Permuted p-value)

<table>
<thead>
<tr>
<th>Pearson’s Correlation (Permuted p-value)</th>
<th>Cognitive Flexibility</th>
<th>No-go Continuous Performance</th>
<th>Fluid Intelligence</th>
<th>Reading Decoding</th>
<th>Vocabulary Comprehension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Flexibility</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>No-go Continuous Performance</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fluid Intelligence</td>
<td>0.286 (1.0E-3)</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reading Decoding</td>
<td>0.023 (0.86)</td>
<td>-0.007 (0.39)</td>
<td>0.019</td>
<td>0.59</td>
<td>-</td>
</tr>
<tr>
<td>Vocabulary Comprehension</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.006 (0.38)</td>
<td>1</td>
</tr>
</tbody>
</table>

Three correlation matrices are displayed from up downwards, each containing one of the three measures of spatial overlap we calculated: number of voxels between volumetric maps, dice similarity coefficient (DSC) between volumetric maps, and Pearson’s correlation with permutation inference between surface maps.

We tested only brain activation overlaps between cognitive traits which were found to be genetically correlated (see Table 3).

Remainder overlaps that were not tested are signaled with a dash (“-”).

In the bottom matrix, we highlight in bold the brain activation overlaps found to be significant by the permutation-based inference.

Table 6
Fixed-effects meta-analysis conducted on p-values retrieved by genetic correlation (P(ρg)), and brain activation overlap P(ρperm), estimated for pairs of cognitive traits that were tested in terms overlapping genetics and circuitry.

<table>
<thead>
<tr>
<th>Pairs of Cognitive Traits</th>
<th>P(ρg)</th>
<th>P(ρperm)</th>
<th>P(Fisher’s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Flexibility</td>
<td>0.041</td>
<td>0.001</td>
<td>4.5E-04</td>
</tr>
<tr>
<td>Fluid Intelligence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive Flexibility</td>
<td>0.053</td>
<td>0.86</td>
<td>0.19</td>
</tr>
<tr>
<td>Reading Decoding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-go Continuous Performance</td>
<td>0.032</td>
<td>0.39</td>
<td>0.066</td>
</tr>
<tr>
<td>Fluid Intelligence</td>
<td>0.087</td>
<td>0.59</td>
<td>0.20</td>
</tr>
<tr>
<td>Reading Decoding</td>
<td>0.042</td>
<td>0.38</td>
<td>0.082</td>
</tr>
<tr>
<td>Vocabulary Comprehension</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

We tested the following five pairs of cognitive traits: cognitive flexibility paired with fluid intelligence and reading decoding; and reading decoding with no-go continuous performance, fluid intelligence, and vocabulary comprehension.

We display the significances of overlap-infering tests, and the results of the respective fixed effects meta-analysis that was conducted on the two previously referred p-values, for each cognitive trait pair.

Fixed-effects meta-analysis was implemented using Fisher’s sum of logs method, which provides a p-value (P(Fisher’s)) indicating whether each trait pair biologically converged in terms of their genetics and circuitry (p ≤ 0.01). Significant p-values are highlighted in bold for P(Fisher’s) (p ≤ 0.01).

Classic view of multifactorial traits (Fisher, 1919). Twin modeling imposes constraints on the data to be analyzed, such as the need to have a trait measure that follows normal distribution; and conceptual constraints concerning equally shared environment and gene-environment interplay between monozygotic and dizygotic twin pairs. Given the existence of gene-environment correlations and epigenetics (Trerotola et al., 2015; Kong et al., 2018; Plomin et al., 1977; Plomin, 2014), we have to consider that heritable variance is not purely driven by additive genetic effects. With twin studies, we model a broad-sense heritability that accounts more comprehensively for the effects of genetic variants, including non-additive genetic effects and single nucleotide polymorphisms that are not genotyped/imputed in standard genome-wide association studies (Plomin et al., 2013; Davis et al., 2014). Another advantage of the twin design is, despite the assumptions, the better characterization of environmental factors by disentangling the effects driven by shared and unique environment. The environmental results obtained via univariate (Table 2) and bivariate twin modeling (Tables S3-S4) show that environmental factors have also a significant impact on cognitive traits and how they are correlated. Although environmental factors were not central to our goal to study the biology of cognition by looking at the convergence of genetic effects on the brain, we consider it relevant to share these supplementary findings with the scientific community, helping to increase our understanding of the factors that shape cognition in our society.

Strengths of our study are: the deep phenotyping of the HCP sample, with a comprehensive set of cognitive measures in a substantial sample size; and the use of twin modeling and functional imaging meta-analysis in a data-driven and step-wise approach, which allowed investigating unprecedented research questions in the fields of cognition, neuro-imaging, and genetics. Nonetheless, there are limitations that may be taken into account for future studies following this kind of approaches. One of them relates to the fact that twin modeling does not provide an optimal way to correct for ancestral differences in multi-ethnic samples. Still, we expected our heritability estimates not to be driven by these differences. Our supplementary analysis shows that modeling only the largest ethic group provided results pointing to the same conclusion as the main findings we obtained based on the whole sample (Tables S5-S6). Furthermore, we showed in supplementary analysis that controlling socio-economic status did not alter the significance of our heritability estimates (Table 57). Therefore, we speculate that there is a very unlikely influence of multi-ethnicity in our genetic results. Apart from that, we did not intend to investigate any association between our results and ethnicity. In our view, there are worldwide initiatives, with a wider ethnic representation within and across nations, that are better equipped to answer this kind of questions. We see these initiatives, along with the multi-ethnic sample provided by the HCP consortium, as the first step of many toward a better representation of the population we scientists aim to understand.

In our functional imaging meta-analysis, we intended to estimate activation maps that generally represented task performance in the
population, in health and disease. Therefore, we selected first-level contrasts capturing the performance of both patient and healthy individuals. To address the impact of including patient samples in our meta-analysis, we conducted an additional meta-analysis for each cognitive trait that was consisted of activation contrasts of healthy adult participants exclusively. We visualized in Fig. S2 considerable overlap between the activation maps including all participants and those including only healthy participants; Table S24 shows that all the overlaps are high and highly significant. With these supplementary results, we speculate that including first-level contrasts of patients not only increases the statistical power of the analysis, but also may provide additional information about task performance in the population.

Furthermore, the availability of studies in the BrainMap database also represented a constraint to our approach. For the meta-analytic activation maps to be reliable, it is recommended to provide a minimum of 20 activation contrasts (Turkeltaub et al., 2012). We had to balance that requirement with the need for a task-specific match to the behavioral protocols conducted by the HCP consortium. We achieved a close match for most of the traits, but needed to extend our criteria for fluid intelligence. In the HCP dataset, fluid intelligence is measured by a matrix reasoning task. In BrainMap we only found five contrasts reporting brain activation associated with matrix reasoning. Therefore, we adopted a broader selection of task protocols for fluid intelligence, including all tasks designed to look at (non-crystallized) problem solving and reasoning skills. We interpret the resulting activation maps as a general representation of the cognitive domains the HCP behavioral protocols are designed to capture, rather than activation signatures specific to individual behavioral tasks. To investigate to what extent this generalization may have influenced our results, we performed an exploratory meta-analysis comparing the fluid intelligence activation map, reported in Fig. 2, with a activation map representative of the matrix reasoning task performance only. In Fig. S3 we show the overlap between the more general fluid intelligence map and the specific matrix reasoning map, in which most clusters reporting activation in frontal regions overlap, and Table S25 reports that this overlap is moderate and highly significant.

Another limitation we encountered with our approach was associated with the lack of systematic measurement for quantifying spatial overlap among brain imaging maps. We chose the three measures that, according to our knowledge, were better design to estimate this quantity: number of voxels, DSC, and the recent method inferring Pearson’s correlations with permutation inference (Alexander-Bloch et al., 2018). The latter method is up to date, as far as we know, the only one that provides statistical inference of spatial overlaps among meta-driven activation maps. Validating methods that infer spatial overlap has been dependent on controversial and still on-going questions, such as the definition of a true null hypothesis for this particular test (Nichols et al., 2005; Friston et al., 2005). We raise awareness for debating and clarification of these limitations, and we see the permuted-correlation method we used as a significant progress toward the solution (Alexander-Bloch et al., 2018).

In conclusion, we find, by means of our data-driven and step-wise approach, evidence pointing to the biological convergence among genetics, brain function, and behavioral performance for selected measures of cognition. The idea of biological convergence, we portray in this study, emphasizes that a better understanding of cognition involves a deeper knowledge of its biological underpinnings and their respective associations. Furthermore, our demonstration of biological convergence has broader implications for the study of human behavior in health and disease, as it provides a concrete framework towards more precise selection and characterization of traits and their associated neural systems and biological pathways.

4. Methods & Materials

HCP sample. We used the S1200 sample released by the WU-Minn HCP consortium in March 2017 (Van Essen et al., 2013). The healthy individuals present in the HCP S1200 sample were recruited from the Missouri Family and Twin Registry. Our sample consisted of 149 monozygotic (MZ) and 93 dizygotic (DZ) twin pairs (from which 92 DZ twin pairs share the same sex), with an age range of 26–32 years old. Twin individuals were included if they had fifteen cognitive scores reflecting task accuracy among the twelve cognitive traits we used for further analysis: cognitive flexibility, go/no-go continuous performance, delay discounting (200$ and 40k$ reward), fluid intelligence, inhibitory control and attention, picture sequence memory, processing speed, reading decoding, spatial orientation (correct and wrong position), working memory, verbal episodic memory, and vocabulary comprehension. In Table S1, we provide a match between the cognitive terms here enumerated and the official HCP designations of these tasks, whereas the detailed description about these tasks is available in https://wiki.humanconnectome.org/. Demographics about the sample we analyzed is provided in Table 1.

Twin Modeling. We performed univariate and bivariate genetic analysis of HCP cognitive data by means of twin modeling. We conducted our twin modeling approach using R v3.3.3 (https://www.r-project.org/), and the software package OpenMx v2.8.3 (Neale et al., 2016).

Prior to modeling, cognitive measures that did not follow a normal distribution, as indicated by a significant Shapiro-Wilk test, were transformed. First, by excluding outliers (±3 standard deviations), and if necessary, via inverse-normal transformation. Where age and sex were significantly associated with the output variable (determined by linear regression), they were included as covariates in the twin model.

We applied twin models according to the standard ACE design. Based on the genetic and environmental relationships among twins, the ACE model quantifies the extent to which three latent factors drive the variance in a trait: additive genetic (A), shared environmental (C), and unique environmental (E) factors; for a detailed explanation, consult publication by Fruhling and Sham (Rijssijk and Sham, 2002). We first ran a univariate ACE model for each cognitive measure to quantify its heritability. The significance of the heritability estimates was estimated by comparing each ACE model with its respective CE model as a null-model (p ≤ 0.05). Next, heritable cognitive measures were further investigated in terms of their phenotypic and genetic correlations. We calculated phenotypic correlations in the whole sample, independent of zyosity, by computing the Pearson’s correlation coefficient and respective significance. For each trait pair with significant phenotypic correlation, we tested with a bivariate ACE model whether the phenotypic correlation was partly driven by shared genetic factors. The significance of the genetic correlation was determined via confidence intervals (CI = 95%). In spite of not carrying out multiple comparison correction to infer the genetic correlations, we estimated FDR-adjusted p-values for these correlations to be added as supplementary material. Furthermore, the same model also provided the proportions of phenotypic correlations mediated by shared and unique environmental factors.

In supplementary analyses, we addressed the effects of socioeconomic status by considering two representative demographic measures: total household income, and total years of education. If total household income or total years of education were significantly associated with the outcome variable when running a linear regression model, they were included as mean regressors in the supplementary univariate genetic analysis. Additionally, by taking into account that we used a multi-ethnic sample, we intended to show that our genetic results were representative of all the ethnicities here reported. Thus, we designed an extra univariate and bivariate genetic analysis exclusively with the largest ethnic group (European descendants, 85% of the total sample), in order to exclude the hypothesis that our genetic results were driven by ethnicity.

Functional Imaging Meta-Analysis. For cognitive traits with significant genetic correlations, we performed a coordinate-based meta-analysis to estimate activation maps that resembled task performance associated with each of these traits. We conducted our meta-analysis using the database and software tools provided by the BrainMap Initiative (Laird et al., 2005).

Firstly, we accessed the BrainMap database via Sleuth 2.4 to search
for studies whose procedure matched, according to the BrainMap taxonomy (Fox et al., 2005a), the HCP-equivalent cognitive task (last search conducted in September 26, 2018). Each study in the database reported one or more imaging contrasts of conditions (e.g. task versus rest), which yielded the coordinates of interest that we selected for our analysis. In this selection, we included first-level contrasts capturing the activation of both patients and healthy individuals, while excluding from the analysis second-level contrasts comparing patients against healthy individuals. Furthermore, we accounted for bias related to having different number of contrasts across studies (Turkeltaub et al., 2012), while guaranteeing that no study was repeated across taxonomies. Detailed description of the steps taken in this meta-analytic search is reported in SI Appendix, Methods: Detailed Description of Meta-Analytic Search.

Further, based on these coordinates, we computed activation maps for each cognitive trait using GingerALE v2.3.6, the activation likelihood estimation (ALE) algorithm provided by BrainMap (Eickhoff et al., 2009, 2012; Turkeltaub et al., 2002). We used GingerALE to apply cluster-level inference (cluster-forming threshold = 0.001; 10,000 permutations for cluster-size null distribution; cluster-level threshold = 0.05), retrieving thresholded Z-score maps for each cognitive trait. The anatomical description of the activation maps and their respective overlaps in MNI space was retrieved using the standard automatic atlas query from FSL (FMRIB Software Library, www.fmrib.ox.ac.uk/fsl). For a detailed description of our ALE settings, consult SI Appendix, Methods: Settings of Activation Likelihood Estimation Analysis.

Throughout the meta-analysis, two factors may have influenced the output activation maps: the selection of first-level contrasts capturing the task-related activation in patients; and the resemblance between the specific tasks in the BrainMap database with the respective cognitive task in the HCP database. To evaluate the impact of the first factor, we conducted an additional meta-analysis for each trait, including activation contrasts reported by healthy adult participants exclusively. Regarding the second issue, in case the meta-analysis of a given trait relied on a heterogeneous selection of cognitive tasks, we carried out a supplementary meta-analysis of that trait, including only activation contrasts based on the specific HCP-equivalent cognitive task.

**Brain activation overlap:** Given the meta-analytic activation maps we obtained for each cognitive trait, we investigated spatial overlaps between cognitive maps, in order to find whether they had overlapping circuits.

This step in our pipeline was constrained by the current limitations in quantifying and inferring spatial overlaps between volumetric activation maps, with varying smoothness and spatial characteristics, and the lack of established standard methods to perform this type of analysis. An exception to current scenario is the recently reported permutation-based approach using Pearson’s correlation as a measure of spatial overlap (Alexander-Bloch et al., 2018); method is available online (https://www.github.com/spin-tes). Therefore, we opted for estimating three complementary measures of spatial overlap using Matlab v2018b (https://www.mathworks.com/): (a) the number of imaging voxels in the intersection of the two maps; (b) the Dice similarity coefficient (DSC); and (c) the Pearson’s correlation coefficients with permutation-based inference (30, 000 permutations).

With the volumetric Z-score maps retrieved by GingerALE, we counted the number of activated voxels in each map to obtain the total number of voxels per cognitive trait, whereas the minimum-statistic map among two cognitive-specific maps were used to estimate the number of overlapping voxels between the traits.

Afterwards, we calculated DSC between maps, given by the mathematical expression:

\[ DSC = \frac{2 |X \cap Y|}{|X| + |Y|} \]

where, \(|X|\) and \(|Y|\) represent the number of activated voxels in the maps X and Y, respectively, and \(|X \cap Y|\) the number of activated voxels common to both X and Y. We binarized the Z-maps retrieved by GingerALE (Z-score threshold = 2.3) and, for each cognitive trait pair, we calculated the DSC overlap between their maps (maps X and Y, according to the DSC expression (1)).

For the permuted correlation approach, we projected the thresholded Z-maps retrieved by GingerALE onto the FreeSurfer surface template by nearest neighbor interpolation (isaverage5, consisted of 10,242 vertices per hemisphere), because this permuted-correlation method does not support volumetric maps. Our cortical surface maps resulted of sampling and averaging across eleven equidistant surface projections in the cortical layer, from the white to the pia mater surfaces. After the volume-to-surface conversion, we built a null distribution by means of 30,000 rotational permutations, and further tested whether the correlation between two surface maps were significant according to the permuted null distribution (p ≤ 0.05).

**Relevance of step-wise pipeline.** Our exploratory analysis involved the performance of multiples tests. If all the tests we performed, across all the above steps, were conducted independently from each other, our analysis would be confounded by type I error inflation. Furthermore, not limiting the number of tests would have been particularly unfavorable for estimating genetic correlations, due to the decrease statistical power related to moving from univariate to bivariate genetic analysis. Thus, we used a step-wise approach, in which each analysis step served as a variable selection for the subsequent step. First, only heritable traits were included in the phenotypic correlation analysis. Of those, only trait-pairs that were significantly correlated were tested for genetic correlations. And from this, only traits showing significant genetic correlation, with at least one other trait, were further tested for brain activation overlap.

**Inference of biological convergence.** To address whether the pairs of cognitive traits tested throughout our step-wise pipeline biologically converged, we combined the p-values retrieved by testing genetic correlation and activation overlaps, for each cognitive trait pair, and performed fixed-effects meta-analysis of the two significant values by using the Fisher’s sum of logs method (p ≤ 0.05/number of cognitive trait pairs). In the end, cognitive trait pairs reporting a significant p-value via this fixed-effects meta-analysis were reported to be biologically converged across the domains of genetics, brain activation and behavior.

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