BEHAVIORAL, ANATOMICAL AND GENETIC CONVERGENCE OF AFFECT AND COGNITION IN SUPERIOR FRONTAL CORTEX

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Abstract

Affective experience and cognition are key human traits that are proposed to be inherently coupled in the human brain. Here we studied shared genetic basis of cognitive and affective traits in behavior and brain structure in the twin-based Human Connectome Project sample (n=1087). Both affective and cognitive trait scores were highly heritable and showed significant phenotypic correlation on the behavioral level. We further evaluated the correlation of affect and cognition, respectively, with local brain structure (cortical thickness, subcortical volumes, and surface area). Cortical thickness in the left superior frontal cortex showed a phenotypic association with both affect and cognition, which was driven by shared genetic effects. Quantitative functional decoding of this region yielded associations with cognitive and emotional functioning. This study provides a multi-level approach to study the association between affect and cognition and suggests a convergence of both in superior frontal anatomy.

Introduction

The antagonistic relationship between cognition and emotion has been a topic of debate in philosophy and psychology for centuries. Classically considered to be distinct entities, recent theories emphasized the interplay and shared mechanisms of emotions and cognition in the human brain (Barrett, 2016; Pessoa, 2008). Emotions can both facilitate and impede cognitive function, depending on the context (Dolcos & Denkova, 2014; Okon-Singer et al., 2015). At the same time, cognitive processes are inherent in most aspects of emotional experience and regulation (Ochsner & Gross, 2005; Pessoa, 2008). This behavioral association is mirrored by the interplay of brain networks associated with the neurovisceral manifestation of emotions (Barrett, 2016; Khalsa et al., 2018) and cognitive control (Langner *et al.*, 2018; Pessoa, 2008). Thus, affective experience and cognitive abilities are inherently coupled in the human brain (Barrett, 2016; Pessoa, 2008). Moreover, affective and cognitive traits, as well as brain structure have been shown to underlie genetic effects (Davies et al., 2011; Okbay et al., 2016; Zheng et al., 2016), but the degree to which shared mechanisms of trait affect, cognition, and brain structure are genetically determined is incompletely understood.

Yet, most studies to date, have been investigating cognition and affect as separate constructs. Individual differences in cognition have been related to prefrontal and parietal thickness, though often with contradictory outcomes. Likely depending on study details (e.g. sample age and size, outcome measures), some studies found a positive correlation of cortical thickness and cognitive abilities (Karama *et al.*, 2009; Narr *et al.*, 2006; Shaw *et al.*, 2006, Bajaj et al., 2018, Hanford et al., 2019) while others found a negative correlation (Goh *et al.*, 2011; Salat *et al.*, 2002; Sowell *et al.*, 2001; Van Petten *et al.*, 2004). Cognitive abilities (Bartels et al., 2002; Davies et al., 2011; Kan et al., 2013; van Soelen et al., 2011; Wainwright et al., 2005), as well as brain volume, cortical surface and thickness are heritable (Brouwer et al., 2014;

Grasby et al., 2020; Panizzon et al., 2009; Winkler et al., 2009), demonstrating that associations between cognition and cortical thickness rely on shared genetic effects (Brans et al., 2010; Desrivières et al., 2015; Joshi et al., 2011; Shaw et al., 2006).

Conversely, trait affect can be sub-divided into positive and negative traits, which may correlate but are separable (Diener & Emmons, 1984; Russell & Carroll, 1999; Salsman et al., 2013; Watson & Tellegen, 1985). Positive affect is characterized by the experience of pleasant feelings, such as happiness, serenity and cognitive engagement (Diener & Emmons, 1984; Salsman et al., 2013, 2014). Negative affect comprises three principal negative emotions: anger, fear, and sadness (Pilkonis et al., 2013; Salsman et al., 2013). Emotions are conceptualized by states of affective experience that depend on habitual affective tendencies (E. Fox, 2002). State and trait emotional processes correlate with activity, connectivity and anatomy of the brain (Atkinson et al., 2007; Brierley et al., 2004; LaBar et al., 1995; Lindquist et al., 2012; Rohr et al., 2015; Tsuchiya et al., 2009). However, meta-analyses showed that positive and negative valence is not related to independent brain systems (Lindquist et al., 2016, 2012), suggesting that affect is represented by dynamic functional interactions between brain regions and networks rather than functional specializations of distinct localizations (Kragel & LaBar, 2016; Langner et al., 2018; Pessoa, 2008). Importantly, individual differences in trait affect are partly explained by genetic difference (Baker et al., 1992; Lykken & Tellegen, 1996). GWAS reported various loci associated with subjective well-being (Okbay et al., 2016). Notably, well-being is associated with enrichment of genes that are differentially expressed in the hippocampal subiculum and with enrichment for GABAergic interneurons, suggesting a genetic link between the brain and various measures of affective experience (Baselmans et al., 2019). Twin-based genetic studies found that trait negative affect is under genetic control, while trait positive affect is not heritable (Baker et al., 1992; Zheng et al., 2016). Similarly, neuroticism, a personality trait closely

linked to trait negative affect, has recently been associated with surface area in the right medial frontal cortex and this phenotypic association was driven by shared genetic effects (Valk et al., 2020).

In sum, 1) there is a complex interrelation between affect and cognition behaviorally and in brain structure and function; 2) cognitive abilities and their relation with brain structure are under genetic control; 3) affective experience is associated with brain function and structure and may also be driven by genetic factors. However, whether cognition and trait affect have a shared genetic relation to brain structure is not known to date. We studied the relationship of cognition and affect in behavior and local brain structure and evaluated whether cognitive abilities and trait affective self-reports have a shared genetic basis in both behavior and brain. First, we evaluated the relation of cognition and trait affect on the behavioral level by studying correlation, heritability, as well as genetic correlation in a large sample of healthy twins. Next, we assessed the relationship between cognition and affective traits in relation to cortical thickness, subcortical volumes and cortical surface area, to evaluate whether cognition and affect share phenotypic and genetic associations with local brain structure. We expected to observe that cognition and affect correlate behaviorally and with the brain, and that this correlation can be explained by shared genetic effects.

Methods

Participants

The Human Connectome Project (HCP, www.humanconnectome.org) is a publicly available data base. In this study, the Young Adult Pool was used, which comprised 1206 healthy individuals (656 women, mean age = 28.8 years, standard deviation (SD) = 3.7, range = 22-37 years). In total, there were 298 monozygotic (MZ) twins, 188 dizygotic (DZ) twins, and 720 singletons. After exclusion of individuals without brain structural or behavioral data relevant to this study, the sample comprised 1087 individuals, of which 587 were females. The sample used in this study comprised 282 MZ twins, 165 DZ twins, and 641 singletons. The mean age, its standard deviation and range remained the same as for the total HCP sample.

Behavioral markers

Cognitive and affective scores were selected in the data base of the HCP. The behavioral measures used in this study were derived from the National Institute of Health (NIH) toolbox for Assessment of Neurological and Behavioral Function® (neuroscienceblueprint.nih.gov). Normalized composite scores from the cognition and emotion categories were used, while one category comprised several sub-domains (Table 1).

Cognition

The cognitive function composite (total cognitive) score was assessed by averaging the normalized scores of fluid cognition composite (fluid cognition) score and crystallized cognition composite (crystallized cognition) score. As illustrated in Table 1, the fluid cognition score was obtained by averaging the normalized scores of the Dimensional Change Card Sort Test, Flanker, Picture Sequence Memory, List Sorting, and Pattern Comparison measures. That is, fluid cognition is the combination of scores of executive function, inhibition and

attention, episodic memory, working memory, and processing speed (Akshoomoff et al., 2013). The crystallized cognition score was obtained by averaging the normalized scores of Picture Vocabulary and Oral Reading Recognition measures. That is, crystallized cognition consists of language in the sense of translation of thought into symbols and deriving meaning from text, as a reflection of past learning experiences (Akshoomoff *et al.*, 2013; Gershon *et al.*, 2013).

As cognition can be both conceived as a general factor (G), but at the same time crystallized and fluid cognition are differentiable, we investigated both general cognitive score (total cognition) as well as fluid and crystallized cognition.

Affect

To examine affective behavior in this study, a composite measure of general affect was used, consisting of both positive and negative affect. Emotional domains were obtained using the NIH toolbox with a written self-report (Pilkonis et al., 2013; Salsman et al., 2013, 2014).

The construct of positive affect, also known as psychological well-being, was composed by averaging the scores from the sub-domains of life satisfaction, meaning and purpose, and positive affect. The construct of negative affect was composed by the average of anger (anger-affect, hostility), sadness, fear-affect, and perceived stress (Table 1). As the positive and negative affect scores used in this study showed high intercorrelations (R = -0.6, see Figure 1C and Supplementary Figure 1), we created a composite score of mean affect by reversing the negative affect score and averaging it with the positive affect score. This enabled us to investigate positive and negative affect as separate entities, on the one hand, as well as a general estimate of mean affect that integrates both negative and positive emotions, on the other hand. All affect scores were normalized.

Table 1. Behavioral scores. Overview of composition of behavioral variables.

Category	*Domain*	*Sub-domain*	*Test*
Cognition	Fluid cognition	Executive function – cognitive flexibility	Dimensional Change Card Sorting (DCCS)
		Executive function – Inhibition and attention	Flanker
		Episodic memory	Picture Sequence Memory
		Processing speed	Pattern Comparison
		Working memory	List Sorting
	Crystallized cognition	Language	Picture Vocabulary
			Reading Recognition
Emotion	Positive affect/ psychological well-being	Life satisfaction	Self-report
		Meaning and purpose	
		Positive affect	
	Negative affect	Anger-affect	Self-report
		Anger-hostility	
		Fear-affect	
		Perceived stress	
		Sadness	

Table 2. Behavioral variables. Mean, standard deviation, as well as min and max of each variable included in our analyses. All data were used (no outlier removal).

Variables	*Mean*	*SD*	*Min*	*Max*
Total Cognition	121.9	14.6	84.6	153.4
Fluid Cognition	115.1	11.6	84.5	145.2
Crystallized Cognition	117.7	9.9	90.4	154.0
Positive Affect	52.1	7.2	27.1	72.6
Negative Affect	48.7	6.8	30.9	78.8
Mean Affect	1.7	6.2	-19.6	20.8

Structural imaging processing

MRI protocols of HCP were previously described in detail (Glasser et al., 2013; Van Essen et al., 2013). In short, MRI data used in the study was acquired on the HCP's custom 3T Siemens Skyra equipped with a 32-channel head coil. Two T1-weighted (T1w) images with identical parameters were acquired using a 3D-MPRAGE sequence (0.7 mm isotropic voxels, matrix = 320 × 320, 256 sagittal slices, TR = 2,400 ms, TE = 2.14 ms, TI = 1,000 ms, flip angle = 8°; iPAT = 2). Two T2w images were acquired using a 3D T2-SPACE sequence with identical geometry (TR = 3,200 ms, TE = 565 ms, variable flip angle; iPAT = 2). T1w and T2w scans were acquired on the same day. The pipeline used to obtain the FreeSurfer-

segmentation (Fischl, 2012) is described in detail in a previous article (Glasser et al., 2013) and is recommended for the HCP-data. The pre-processing steps included co-registration of T1- and T2-weighted scans, B1 (bias field) correction, and segmentation and surface reconstruction using FreeSurfer version 5.3-HCP to estimate brain volumes, cortical thickness and surface area.

Cortical morphological measures

We used a parcellation scheme (Schaefer et al., 2018) based on the combination of local gradient and global similarity approaches using a gradient-weighted Markov Random Field model. Using compressed features of structural MRI has been suggested to both improve signal-to-noise of brain measures (cf. Eickhoff et al., 2018; Genon et al., 2018) and optimize analysis scalability. The Schaefer parcellation has been extensively evaluated with regards to stability and convergence with histological mapping and alternative parcellations (Schaefer et al., 2018). In the context of the current study, we focused on the granularity of 200 parcels from the 7-network solution, as averaging will improve signal-to-noise ratio. In order to improve signal-to-noise ratio and analysis speed, we opted to average unsmoothed structural data within each parcel. Thus, cortical thickness of each ROI was estimated as the trimmed mean (10 percent trim) and parcel-wise surface area was computed as the sum of vertex-wise area per parcel.

Phenotypic analyses

Phenotypic analyses between cognitive and affective traits and local brain structure were carried out per parcel, using a 200 parcel-parcellation scheme (Schaefer et al., 2018) on surface area and cortical thickness. As in previous work (Bernhardt et al., 2014; Valk, Bernhardt, Böckler, Kanske, et al., 2016; Valk, Bernhardt, Böckler, Trautwein, et al., 2016), we used SurfStat for Matlab [R2020a, The Mathworks, Natick, MA] (Worsley et al., 2009)

for the linear models. In addition, we investigated volumes of subcortical structures. We controlled for age, sex, age × sex interaction, age^2, age^2 × sex interaction, as well as global thickness effects when investigating cortical thickness and intracranial volume (ICV) when assessing surface area and subcortical volumes. Behavioral correlations were assessed in a similar fashion, controlling for age, sex and their interaction. Results were corrected for multiple comparisons using Benjamini-Hochberg false discovery rate (FDRq<0.05) (Benjamini & Hochberg, 1995). We displayed significant findings on the brain surface.

Heritability and genetic correlation analyses

The heritability and genetic correlation of behavioral and brain structural phenotypic traits were assessed by twin-based heritability analyses. These were performed using the Sequential Oligogenic Linkage Analysis Routines (SOLAR; solar-eclipse-genetics.org, Solar-Eclipse 8.4.0) software. SOLAR is particularly suitable for imaging genetics, as well as pedigrees of arbitrary size and complexity (Kochunov *et al.*, 2019). SOLAR allows a homogenization of the data, which involves consistent regression of all distorted covariates and normalization of trait data by means of inverse Gaussian transformation (Kochunov *et al.*, 2019). This homogenization was performed prior to any heritability or genetic correlation analysis. Further correlation analyses in SOLAR were performed using Pearson's correlation corrected for non-independence of the subjects.

To determine the proportion of genetic and environmental influences on a phenotype, SOLAR uses maximum likelihood variance decomposition methods by modeling the genetic proximity by covariance between family members. The narrow-sense heritability h^2 is the ratio of the phenotypic variance σ_p^2 that is explained by the total genetic variance, $h^2 = \sigma_g^2/\sigma_p^2$ (Kochunov *et al.*, 2019). Therefore, h^2 is the estimation of how much a trait is influenced solely by genes. If a phenotypic covariance of genetically more similar individuals is higher compared to genetically less similar ones, it is expected to be more heritable.

Therefore, considering genetic proximity, the variance parameters are estimated comparing the observed phenotypic covariance matrix with the predicted covariance matrix within a trait (Kochunov *et al.*, 2019). The analyses were controlled for age, sex, age × sex, in addition to age^2, age^2 × sex interaction and global thickness for heritability of cortical thickness, as well as ICV for heritability of surface area and subcortical volumes. The heritability estimates were corrected for multiple comparisons by Benjamini-Hochberg FDRq<0.05 (Benjamini & Hochberg, 1995).

To assess if the variance of behavioral traits and brain structure is driven by a shared genetic influence, genetic correlation analyses were performed. The phenotypic variance σ_p^2 of a trait can be decomposed into $\sigma_p^2 = \sigma_g^2 + \sigma_e^2$, where σ_g^2 is the genetic variance, and σ_e^2 is the environmental variance (Griffiths *et al.*, 2000). With SOLAR bivariate polygenetic analyses were performed, based on the phenotypic correlation between the behavioral traits, or between a given trait and the mean cortical thickness / summed surface area in a parcel or the subcortical volume, by examining the deviation from zero in the additive genetic covariance matrix. Then, creating a restricted model by setting the shared residual additive genetic influence ρ_g or the shared residual additive environmental influence ρ_e to zero, the log likelihood of the restricted model was compared to an estimated model, in order to assess the significance (Almasy *et al.*, 1997). Here again, we controlled for age, sex, age × sex and additionally for age^2, age^2 × sex interaction and global cortical thickness (for cortical thickness analyses) or total intracranial volume (for surface area and subcortical volume analyses) when investigating the brain. The covariance analysis for the genetic basis of brain and behavior manifestation were controlled for multiple comparisons using Benjamini-Hochberg FDR (FDRq<0.05) (Benjamini & Hochberg, 1995).

Functional decoding

Parcels that were significantly correlated with both cognition and affect and shared genetic variance, were functionally characterized using the Behavioral Domain meta-data from the BrainMap database (http://www.brainmap.org, Laird et al., 2011, 2009). To do so, volumetric counterparts, delineating the surface-based parcels in volume space, as provided by Schaefer et al., were used (Schaefer et al., 2018, https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/Schaefer2018_LocalGlobal/Parcellations). In particular, we identified those meta-data labels (describing the computed contrast [behavioral domain as well as paradigm]) that were significantly more likely than chance to result in activation of a given parcel (P. T. Fox et al., 2014; Genon et al., 2018; Nostro et al., 2017). That is, functions were attributed to the parcels by quantitatively determining which types of experiments are associated with activation in the respective parcel region. Significance was established using a binomial test ($q<0.05$, corrected for multiple comparisons using FDR) and we report results of both forward and reverse inference analyses.

Results

Heritability, phenotypic and genetic correlation of cognition and affect (Figure 1)

First, we evaluated the phenotypic associations between cognitive test scores and affective self-report scores (**Figure 1, Supplementary Figure 1**). Both composite scores (total cognition and mean affect), as well as their sub-domains (fluid cognition, crystallized cognition, positive affect, and negative affect), were normally distributed (**Figure 1A**). We observed high phenotypic interrelationships between the respective sub-tests of both cognitive and affective domains (**Supplementary Figure 1**), supporting the use of the composite scores total cognition and mean affect as proxies for the constructs of cognition and affect, respectively. As expected, cognitive scores were all positively associated among each other, while positive affect correlated positively, and negative affect correlated negatively to mean affect. We observed that mean affect had a positive phenotypic relationship with total cognition ($\beta = 0.09$, FDRq < 0.05). Similarly, positive affect was positively associated with total ($\beta = 0.09$) and fluid ($\beta = 0.11$) cognitive abilities, whereas negative affect was negatively associated with total ($\beta = -0.08$) and fluid ($\beta = -0.10$) cognitive abilities (all FDRq < 0.05; **Figure 1C**, lower triangle).

The heritability analysis revealed that all observed construct scores were heritable: total cognition ($h^2 = 0.75$, $p < 0.001$), which is a combination of fluid ($h^2 = 0.58$, $p < 0.001$) and crystallized ($h^2 = 0.83$, $p < 0.001$) cognition, as well as mean affect ($h^2 = 0.32$, $p < 0.001$), which is the signed average of positive ($h^2 = 0.27$, $p < 0.001$) and negative ($h^2 = 0.36$, $p < 0.001$) affect (**Figure 1B**). Next, we evaluated the genetic correlation between cognitive and affective scores. A strong positive genetic correlation between fluid and crystallized cognition ($\rho_g = 0.48$, FDRq<0.05) and a negative genetic correlation between positive and negative affect ($\rho_g = -0.63$, FDRq<0.05) was found (**Figure 1C**, upper triangle), suggesting that both sub-domain-sets reflect partly overlapping genetic mechanisms. We did not observe

a significant genetic correlation between total cognition and mean affect (FDRq > 0.05). At trend level, we did observe a genetic relationship between fluid cognition and mean affect ($\rho_g = 0.23$, $p<0.05$), and a genetic correlation between positive affect and fluid cognition ($\rho_g = 0.28$, $p<0.02$). In the following, we focus on reporting the results for the composite scores of total cognition and mean affect which sufficiently capture phenotypic and genetic variance of the constructs of cognition and affect. To additionally allow for more detailed assessment, we report associations with the sub-domain measures in the supplementary materials.

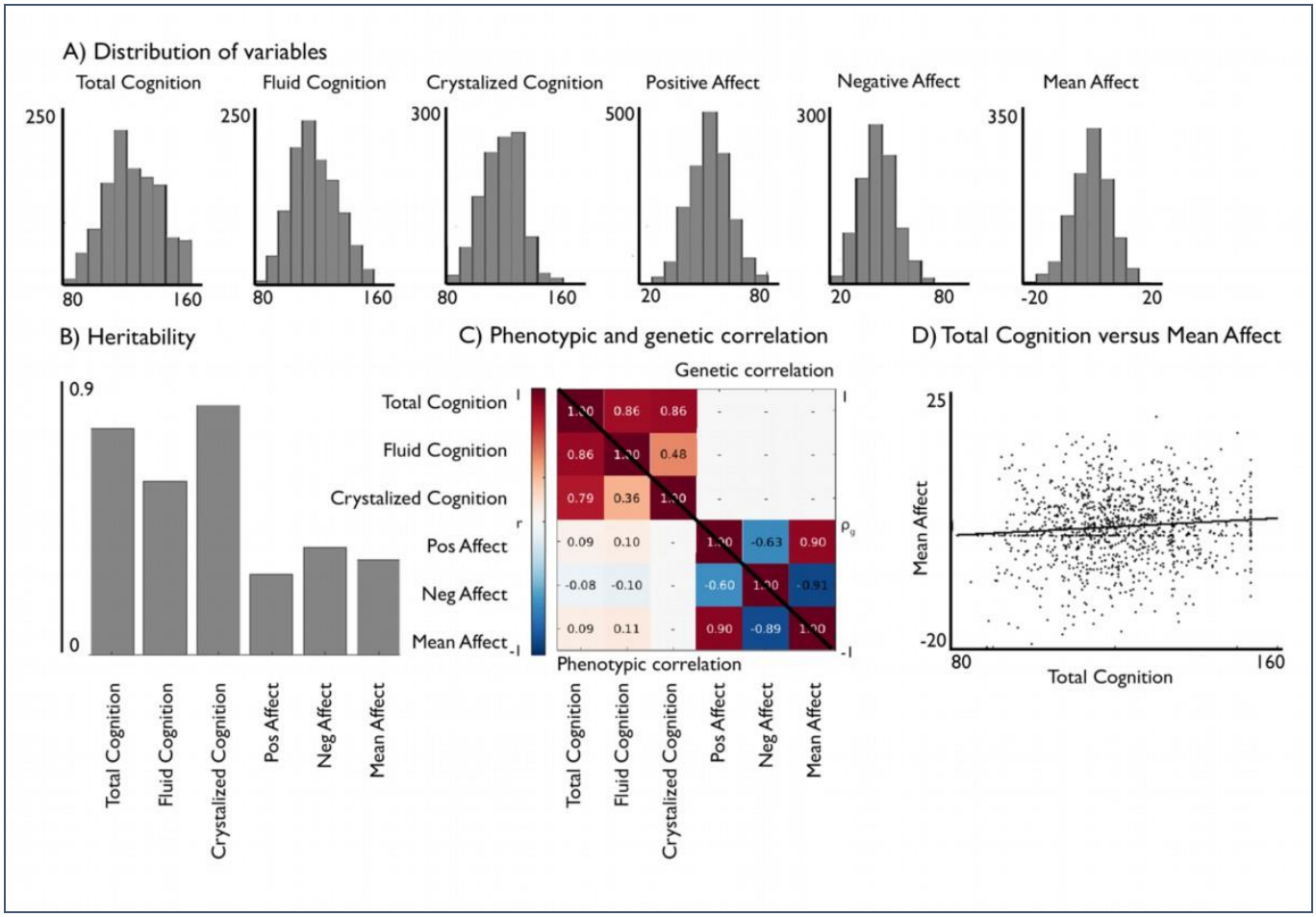

Figure 1. Phenotypic and genetic relation of cognition and affect. A) Distribution of variables; B) Heritability; C) bottom triangle: behavioral correlation (FDRq<0.05) and upper triangle: genetic correlation of the cognitive and affective scores (FDRq <0.05).

Phenotypic association between cognition and local brain anatomy (Figure 2)

To evaluate the phenotypic association of cognition and affect with brain anatomy, we first evaluated the correlation between cognition and local cortical thickness, while controlling for global thickness. We observed positive associations between total cognition and bilateral insula, bilateral cuneus, bilateral sensory-motor regions, left middle temporal gyrus, and right middle cingulate, whereas bilateral frontal regions showed a negative relation with total cognitive score (**Figure 2A**). Conversely, surface area showed only positive, but not negative, associations with cognitive scores. Total cognition was associated with local surface area in bilateral occipital areas, temporal poles, sensorimotor cortices, and lateral and orbital frontal cortices, as well as left anterior cingulate and right posterior-mid cingulate cortex (**Figure 2B**). With regards to subcortical volumes, we found a significant positive effect between total cognition and left hippocampal volume (**Figure 2C**). Fluid and crystallized cognition sub-scores showed similar associations with local brain structure and volume (**Supplementary Tables 1-3, 7-12**).

Phenotypic association between affect and local brain anatomy (Figure 2)

Next, we evaluated the association between affect and local brain structure. We found that affect measures showed significant associations with local cortical thickness and subcortical volumes, but not with local surface area. Mean affect was negatively associated with cortical thickness in left superior frontal cortex and positively associated with cortical thickness in left occipital cortex (**Figure 2A, Supplementary Table 4**). In addition, bilateral caudate volume was significantly associated with mean affect (**Supplementary Table 13**).

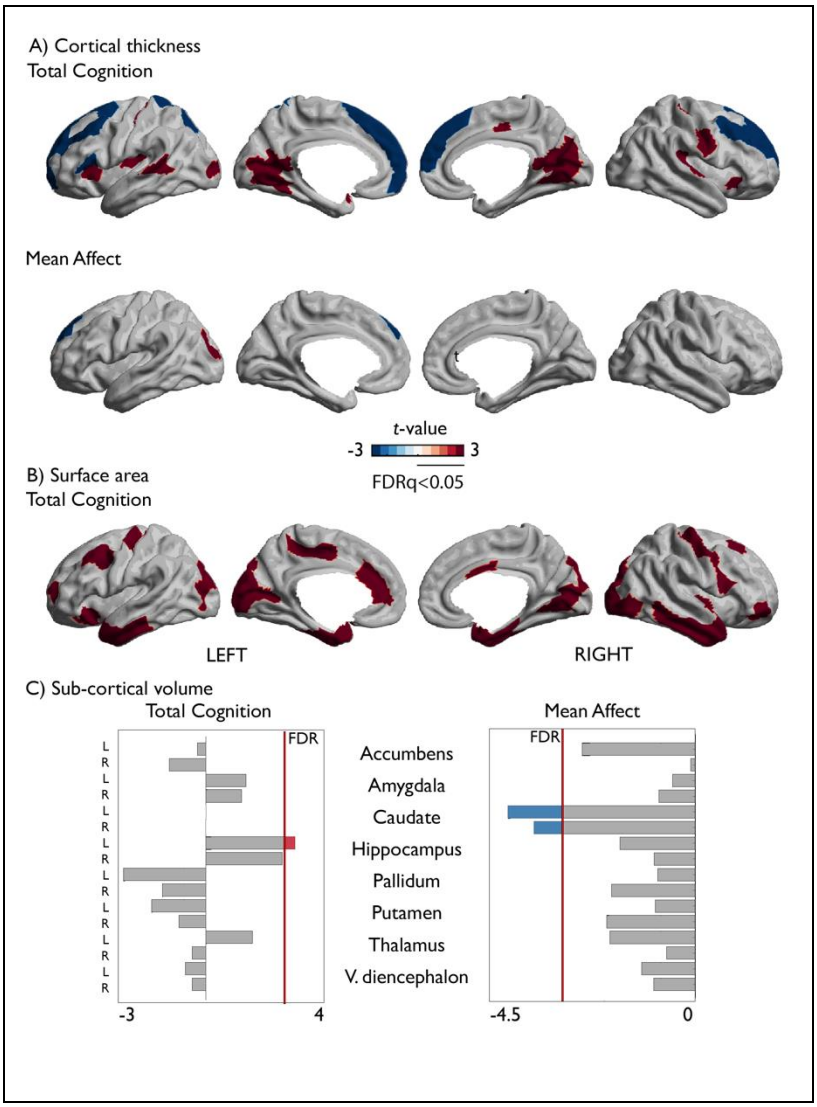

Figure 2. Associations between cognition, affect and local brain structure. A) Correlation between total cognition and local cortical thickness; Second row: Correlation between mean affect and local cortical thickness B) Correlation between total cognition and local surface area. C) Correlations between cognition / affect and sub-cortical regions volumes. Red indicates a positive association, and blue a negative association between cognition / affect and local brain structure. Only FDRq<0.05 corrected findings are reported.

Genetic correlation between cognition/affect and local brain structure (Figure 3)

To assess if the correlation between cognitive and affective traits on the one hand and local brain structure on the other is driven by shared genetic effects, genetic correlation analyses were performed through a bivariate polygenetic analysis. Both local thickness and surface area were heritable in our sample (cortical thickness h^2=mean±sd: 0.35±0.11 and surface area: h^2=0.42±0.13), as were subcortical volumes (h^2=0.68±0.11, **Supplementary Figure 4**, **Supplementary Tables 21-23**).

There was a strong overlap between phenotypic correlations and genetic correlations. 36 out of 39 phenotypic correlations between total cognition and local cortical thickness could be attributed to genetic effects (FDRq<0.05, **Figure 3, Supplementary Table 16**) and genetic correlation patterns largely mirrored phenotypic associations between cognitive scores and local cortical thickness (see also **Supplementary Figure 5** and **Supplementary Table 18**). Similarly, the phenotypic associations between cognitive scores and subcortical volumes were genetically driven (**Supplementary Table 20**). Furthermore, the associations between local surface area and cognitive scores were largely driven by shared genetic factors. Here, 29 out of 43 phenotypic associations between total cognition and local surface area were driven by shared genetic factors (**Figure 3, Supplementary Table 17; Supplementary Figure 6** and **Supplementary Table 19** for sub-score results). Among the associations with mean affect score, thickness of left superior frontal cortex (ρ_g = -0.47, p=0.00, **Figure 3, Supplementary Table 16**) and bilateral caudate volumes (left: ρ_g = -0.25, p=0.00, right: ρ_g = -0.27, p=0.00, **Supplementary Table 20**) were also driven by shared genetic factors.

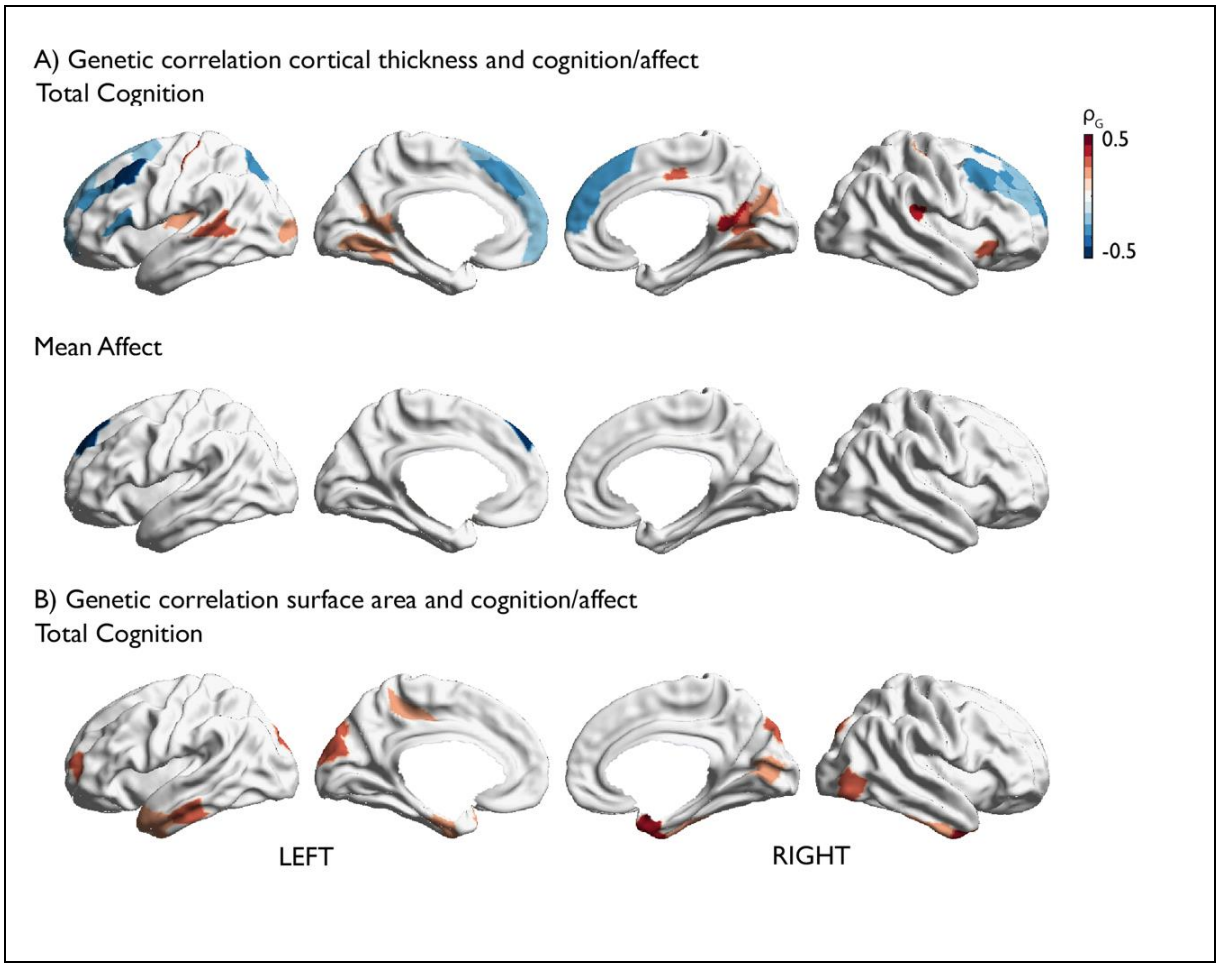

Figure 3. Whole-brain genetic correlation between local cortical structure and cognition or affect. A) Results for cortical thickness. B) Results for surface area. Positive correlation is depicted in red, negative in blue. Only FDRq<0.05 corrected findings are depicted

Shared brain basis between cognitive and affective tendencies (Figure 4)

Last, we evaluated whether cognitive and affective traits also showed an overlapping relationship to local brain structure. Both cognition and affect scores had an association (FDRq < 0.05) with thickness in the left superior frontal cortex. In both measures, these effects were driven by shared genetic factors (**Supplementary Tables 16-17**). We performed functional decoding to further quantify the functional processes associated with this region and we found this region to be involved in cognitive and socio-cognitive processes, as well as emotional processes (valence and negative emotions) and action inhibition (**Figure 4**).

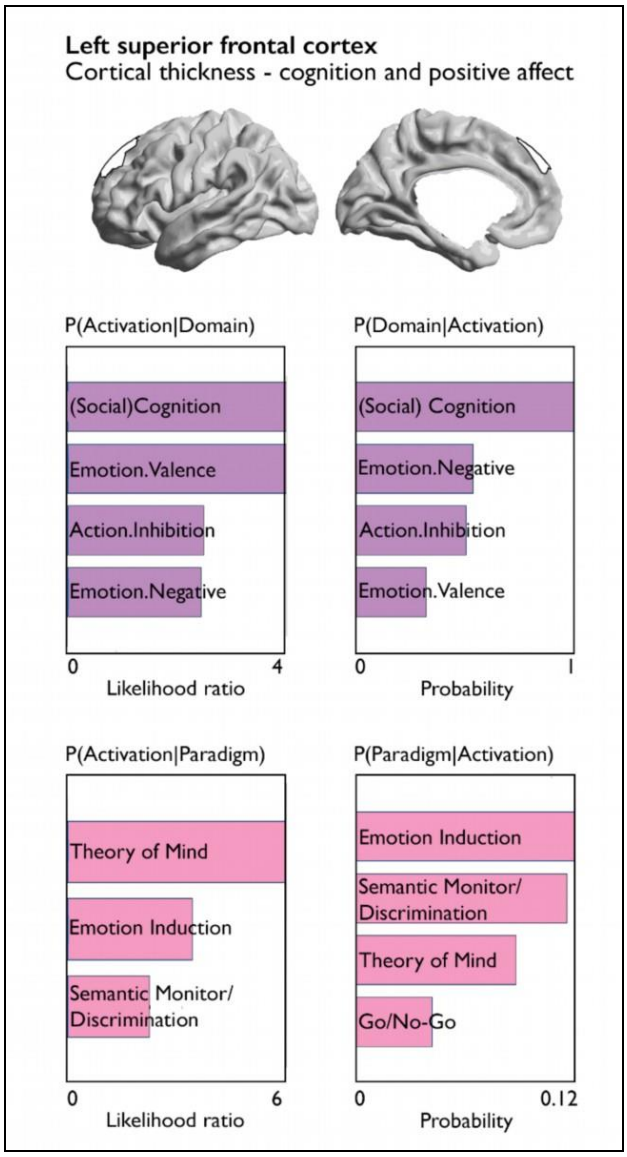

Figure 4. Quantitative functional decoding of region showing association with both cognition and affect. Both forward inference and reverse inference of activation-domain and paradigm-domain contrasts are reported for the left superior frontal cortex which showed evidence of shared phenotypic and genetic association for cognition and affect scores.

Discussion

We evaluated shared behavioral, genetic and brain structural factors of cognitive and affective traits. We found that both cognitive and affective traits were heritable and observed significant genetic correlation between fluid cognition and trait affect, but not between total cognition and trait affect. Following, we assessed the correlation between cognitive and affective traits on the one hand, and macroscale brain anatomy on the other. Whereas cognition had widespread associations with local cortical thickness and surface area, trait affect showed only sparse associations. We found that most phenotypic behavior-brain associations were driven by shared genetic effects. Finally, we evaluated whether total cognition and mean affect were embedded in a common brain structural correlate and found that both measures showed a shared phenotypic and genetic association with cortical thickness of left superior frontal cortex. Quantitative functional decoding indicated that this region is involved in both cognitive and emotional functioning.

Shared basis of cognition and affect in behavior, genetics and superior frontal cortex thickness

We combined behavioral and brain imaging approaches to study the association between trait affect and cognition. Scores for mean affect and total cognition showed a positive association at the behavioral level, highlighting the synergy of affective and cognitive traits. Previous work has suggested positive affect might have a motivating role in enhancing cognitive flexibility (Ashby et al., 1999; Fredrickson, 2001; Liu & Wang, 2014). In turn, cognitive control is a core feature of successful emotion regulation (Engen & Anderson, 2018; Ochsner & Gross, 2005) and contributes to psychological well-being over the lifespan (Mather & Carstensen, 2005).

Recent work indicated a shared genetic basis between local brain structure and complex behavioral traits (Grasby et al., 2020; Zhao et al., 2019). In line with this work, our study

demonstrated that mean trait affect and total cognition have a shared phenotypic and genetic relationship with local cortical thickness in left superior frontal cortex. This cortical ROI is situated on the left superior frontal gyrus. The region has been classically considered a core region for higher cognitive functions, including attention, working memory and cognitive control. Yet, a growing body of research has highlighted its involvement in emotional processes, such as motivated behavior and emotion regulation (Engen & Anderson, 2018; Hallam et al., 2015; Okon-Singer et al., 2015). On a network level, using the 7-networks parcellation by Yeo et al. (Schaefer et al., 2018), we found this region in the superior frontal cortex to be embedded in the default mode network and the frontoparietal control network, depending on the parcellation granularity, integrating its functions to broader associative, self-reflective processes, as well as controlling operations across the cortex. Our observation of an inter-relationship of cognition and affect in superior frontal cortex is in line with a previous meta-analysis, where interactions between emotion and cognition were associated with this region, next to medial prefrontal cortex and basal ganglia (Cromheeke & Mueller, 2014). In addition, the results we obtained from our functional decoding analysis agreed with the variety of cognitive and emotional functions that previous studies have allocated to this region, such as activation related to social cognition, emotional valence and action inhibition.

Dissociations of affect and cognition in brain structure

Both individual differences in cognitive and affective traits could be linked to local brain structure. Total cognition was associated with lower thickness in frontal regions which is in line with some studies (Goh *et al.*, 2011; Salat *et al.*, 2002; Sowell *et al.*, 2001; Van Petten *et al.*, 2004), but contradicting others (Fjell et al., 2006; Karama et al., 2009; Narr et al., 2006). At the same time, there is some congruency with previous studies involving the location of regions critical for cognition, including mostly frontal and parietal regions (Jung & Haier, 2007), but also anterior and posterior temporal, and occipital regions (Goh *et al.*, 2011;

Menary *et al.*, 2013). Notably, we also observed associations between cognition and various regions within the insular cortices, functionally implicated in both cognitive, but also emotional processes (Kelly et al., 2012; Lindquist et al., 2012). In addition, we found wide-spread associations in temporal, frontal and occipital lobes between local surface area and cognitive ability, but not with affective traits. Mean affect was, however, phenotypically correlated with cortical thickness in left superior frontal cortex, left lateral occipital cortex and bilateral caudate volume. It is noteworthy that affective traits showed less strong and wide-spread associations to local thickness relative to cognitive scores. This observation is in line with reports suggesting inter-regional interactions, rather than local anatomy, may encode emotional experience (Kragel & LaBar, 2016; Langner et al., 2018; Pessoa, 2008). Dissociable patterns of cortical thickness and surface area in relation to behavior might also underlie genetic influences. As such, individual variation in surface area has been associated with genes expressed pre-birth, whereas cortical thickness has been related to adult-specific gene expression and emerging genetic associations with cognitive abilities throughout development (Brouwer et al., 2014; Grasby et al., 2020; Panizzon et al., 2009).

Heritability and genetic correlations of cognition and affect

Complementing previous studies on affect, cognition, and macroscale brain anatomy, we interrogated also the genetic basis of affect and cognition using twin-based genetic approaches. We observed a moderate to strong heritability of cognitive scores (h^2 = 0.6-0.8), which is in line with previous work: In childhood and adolescence – depending on measurement and cohort- 70 to 80 % of the variance in cognitive ability is estimated to be accounted for by genetic factors (Bartels *et al.*, 2002; van Soelen *et al.*, 2011; Wainwright *et al.*, 2005). Using GWAS of adult samples, Davies et al. (2011) observed that 40% of the variation in crystallized-type intelligence and 51% of the variation in fluid-type intelligence between individuals is accounted for by genetic variants. Notably, crystallized cognition was observed

to be more heritable than fluid cognition in the current sample. These findings are in line with a large meta-analysis by Kan *et al.* from 2013. Kan and colleagues assessed the heritability of cognitive traits based on their cultural load, where traits with higher cultural load were shown to be more heritable (Kan et al., 2013). Traits that we summarized as crystallized cognition were attributed a higher cultural load in Kan et al.'s study. This indicates that the known cultural and educational homogeneity of the HCP sample may have led to a high estimated heritability of crystallized cognition.

Conversely, our findings on the heritability of affective self-reports were less strong. Previous work in a twin sample by Baker *et al.* revealed a strong heritability for negative affect, but none for positive affect (Baker *et al.*, 1992), which was conceptually replicated by Zheng et al. (2016). In addition, angry temperament has been associated with genetic processes involved in memory and learning (Mick et al., 2014). Another twin study by Lykken and Tellegen (1996) found the heritability for subjective well-being to be 44-52%, which appears to be higher than the heritability scores we observed for affect measures. However, few studies to date have assessed the heritability of both cognitive and affective traits and our observations suggest that inter-individual variance in cognition is more robustly explained by genetic factors, possibly related to the challenge to quantify individual difference in affective traits with ecological validity using self-report data.

We observed shared genetic correlations between cognition and affect, respectively, on the one hand, and brain structure on the other. First, we replicated previous results that showed heritability of surface area and cortical thickness and indicated that both variance in cortical thickness and surface area are partly driven by largely non-overlapping genetic factors (Brouwer et al., 2014; Grasby et al., 2020; Panizzon et al., 2009; Winkler et al., 2009). Extending previous work, we also observed strong genetic correlations between total cognition and local cortical structure which indicates that the majority of phenotypic associations between total cognition and cortical thickness and surface area, respectively,

could be associated with shared genetic factors (Brouwer et al., 2014; Grasby et al., 2020; Toga & Thompson, 2005).

Affect was phenotypically correlated with superior frontal thickness and genetic correlation analyses yielded that this association was driven by shared genetic effects. Recent work has implicated various genetic loci to be involved in well-being and significant enrichment, as observed in GABAergic interneurons sampled from hippocampus and prefrontal cortex (Baselmans et al., 2019; Okbay et al., 2016). Relevant with respect to these findings, we also observed genetic associations between crystallized cognition and hippocampal volumes. Conversely, affect was genetically correlated with bilateral caudate volumes, emphasizing a shared genetic basis in neuropsychiatric health (Satizabal et al., 2019; Zhao et al., 2019).

Limitations and conclusions

We observed converging evidence for a shared biological basis of inter-individual differences in cognition and affect combining multi-level analysis within the HCP dataset and ad-hoc meta-analytical functional decoding. At the same time, we observed that correlations within each domain were generally stronger than between cognition and affect. Further research might benefit from studying task-based as well as physiological measures of cognitive and affective inter-individual variation to further evaluate the dynamic relation between cognitive aptitude and habitual and transient affective experience. The singular nature of the twin-based HCP sample impedes replication. Greater insight into the association between affect and cognition may be garnered by inspecting different samples, integrating more fine-grained genetic approaches with various indices of cortical anatomy. However, associations were weak, and it is of note that the combination of behavioral assessments and its association with brain structure has been recently challenged. For example, Kharabian Masouleh *et al.* showed in an extensive study that the association of psychological traits and brain structure is rarely statistically significant or even reproducible in independent samples (Kharabian Masouleh *et al.*, 2019).

Additionally, Hedge and colleagues pointed out, that commonly used measurements of behavior may not be optimal to determine underlying neural correlates, due to low between-participant variability within established paradigms (Hedge et al., 2018). Here we utilized different levels of analysis to capture the association between affect and cognition. Follow-up work on the biological basis of complex behaviors may take a similar approach and integrate behavioral assessments with neuroimaging, behavioral genetics, and functional decoding. To conclude, the current work provides evidence at three levels of enquiry that cognitive abilities and affective traits are linked to partially overlapping neurobiological processes. We anticipate that the increased availability of open datasets with rich phenotyping will enable to outline more specific biological mechanisms that help describe the relationship between thoughts and feelings.

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