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Phenotypic and Genetic Correlation of Cognition, Affect, and Brain Morphometry

Master Thesis

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List of Abbreviations

ρ_g	shared residual additive genetic influence
ACC	Anterior cingulate cortex
Crystallized cognition score	Crystallized cognition composite score
CT	Cortical thickness
DZ	Dizygotic
FDR	False discovery rate
Fluid cognition score	Fluid cognition composite score
fMRI	Functional magnetic resonance imaging
H^2	Broad-sense heritability
h^2	Narrow-sense heritability
HCP	Human Connectome Project
iEEG	Intracranial electroencephalography
LH	Left hemisphere
MR(I/T)	Magnetic resonance (imaging/tomography)
MZ	Monozygotic
NA	Negative affect
NIH	National Institute of Health
PA	Positive affect
PET	Positron emission tomography
RH	Right hemisphere
ROI(s)	Region(s) of interest
SOLAR	Sequential Oligogenic Linkage Analysis Routines
T1w	T1-weighted
T2w	T2-weighted
VBM	Voxel based morphometry

Anatomic abbreviations

d	dorsal
IFG	Inferior frontal gyrus
l	lateral
m	medial
M	middle
MFG	Middle frontal gyrus
MTG	Middle temporal gyrus
p	posterior
PFC	Prefrontal cortex
SFG	Superior frontal gyrus
STG	Superior temporal gyrus
TPJ	Temporo-parietal junction

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Abstract

Background: Cognition is marked by complex cognitive processes and can be quantified using intelligence constructs. On the other hand, affect is an indistinct construct, seemingly happening subconsciously and difficult to quantify (Newell & Shanks, 2014; Tamietto & de Gelder, 2010). A large body of evidence has shown that cognition is heritable and relates to brain structure (Devlin *et al.*, 1997; Krapohl *et al.*, 2014). Indeed, studies have shown that co-variation of cognition and brain structure is driven by shared additive genetic effects (Toga & Thompson, 2005). Contrary to this, little is known about the genetic basis of affective behavior. The current study investigates how cognition has a phenotypic and genetic correlation with emotion processing, and positive and negative affect, and whether these aptitudes relate to similar brain regions.

Methods: Using a large sample of healthy individuals based on the open access twin-design of the Human Connectome Project, phenotypic correlation and heritability and co-heritability of cognitive abilities, emotion processing, and positive and negative affect were tested using SOLAR-Eclipse. Following, these aptitudes were correlated to cortical thickness, using a 200 parcel-based approach (Schaefer *et al.*, 2018) to summarize individual differences in grey-matter structure in the cortex. Last, the genetic correlation between total cognitive score, emotion processing, and positive and negative affect on one hand, and cortical thickness on the other was assessed.

Results: Behaviorally, a positive phenotypic correlation of cognitive abilities with both successful emotion processing and positive affect was observed. The positive correlation between cognitive abilities and emotion processing was shown to be driven by additive genetic effects. At the brain level, phenotypic and genetic correlation between cognition and affect was strongest in the dorsolateral prefrontal cortex. Positive affect additionally showed phenotypic correlation in occipital and parietal lobe. In sum, this study points toward a shared genetic basis of cognition and affect, anchored in the dorsolateral prefrontal cortex.

Introduction

"It takes something more than intelligence to act intelligently." - Dostoevsky, 1866.

Intelligence, or cognition, and affect have been subject of research for a long time. And despite the common notion, that humans need both cognitive abilities and affective behavior to function properly (see quote), for long they were viewed as substantially different. Which is why they were investigated as something separate.

Cognition

The systematic research about cognition goes back into the early nineteen hundreds, where Spearman elaborated the "general ability factor g" (Spearman, 1904). This was further developed by several researchers, including Cattell, who introduced the theory that the general ability factor g is composed of two factors that work together: fluid and crystallized general ability; amongst other theories about the subcomponents of cognition. Fluid ability is needed in tasks that require adaptation to new circumstances to solve the tasks. Crystallized cognition, in contrast, accounts for the ability to retrieve knowledge previously learned (Cattell, 1963; Craik & Bialystok, 2006; Hunt, 2001).

Fluid cognitive abilities are a measure for problem solving that does not require pre-existing knowledge. It is the ability of an individual to solve problems that cannot be solved with previously acquired knowledge. It needs quick, novel and abstract reasoning. This includes logical thinking, pattern recognition, solving puzzles, hence solving problems of mathematical or spatial nature. These tasks are mostly non-verbal. The ability to solve novel problems includes the ability to manage multiple things at once, as well as the ability to manage an amount of information needed to solve this problem (Craik & Bialystok, 2006). This ability is also known as working memory (Hunt, 2001). Fluid cognitive abilities are the aspect of general cognitive abilities, that reach a maximum at early adulthood and then quite rapidly decline over lifespan (Baltes *et al.*, 1999; Craik & Bialystok, 2006; Jones & Conrad, 1933).

Crystallized cognitive abilities are different to fluid cognitive abilities, as they require the recognition and application of solutions an individual has acquired through education and past experiences. This includes verbal abilities, such as reading comprehension and grammar, and social knowledge. As "knowledge builds on knowledge" crystallized

cognitive abilities are – other than fluid cognition- growing over lifespan, with a peak in adult life and a slow decline until the age of 70 (Hunt, 2001; Jones & Conrad, 1933; Kaufman *et al.*, 1996).

Fluid and crystallized cognitive abilities cannot be seen as absolutely separate phenomenon, as during development both need to work efficiently together. If an individual is not able to grasp a problem in a creative and flexible manner (fluid cognition), it may not understand and learn from the problem to rely on in the future (crystallized cognition). This interrelation is decreasing after the age of 25 (Baltes *et al.*, 1999; Jones & Conrad, 1933).

Though the assessment of intelligence or cognitive ability is under constant study and development, current measurements of intelligence are reliable and broadly used. All intelligence measures have in common that they include a spectrum of methods to account for the different natures of cognitive abilities. For fluid cognition tests are developed to cover the sub-domains of executive function, processing speed, episodic memory, and working memory (Akshoomoff *et al.*, 2013; Carlozzi *et al.*, 2013; Tulsky *et al.*, 2013). These tests often include the reaction time as an influencing factor. As fluid cognition does not depend on previously acquired knowledge, measurement is to some extent universal. Quite in contrast to crystallized cognition. As here the scope of knowledge is underlain by education and practice, and is highly influenced by expertise (Hunt, 2001). A somewhat common denominator is found in language. Here, often vocabulary tests and reading recognition serve as measures (Akshoomoff *et al.*, 2013; Gershon *et al.*, 2013).

Affect

Affect, or emotion, is the "something" in Dostoevskys quote that is so difficult to put in words. Ever since 1884, as Dixon states, modern psychology is trying to give a comprehensive meaning to that word (Dixon, 2012). The issue with affect lies in the many meanings of it (Izard, 2010). It is so individual and bodily (Nummenmaa *et al.*, 2014), that finding universal measurement techniques remains an obstacle. Measurement approaches range from self-reports, to physiological response measures – such as heart rate, eye blinking, and skin conductance- or behavioral reaction to stimuli (Bradley & Lang, 2002). Moreover, the definitions of "emotion" and "affect" are indistinct and until

the present day subject of big debates within psychology. Defining either a strong separation or clear overlap between those two is not within the scope of this study. “Emotion” and “affect” will therefore be used analogously, as it is done frequently (Bradley & Lang, 2002; Diener & Iran-Nejad, 1986; Pessoa, 2008; Salsman *et al.*, 2013). Just on one note, in psychology “affect” is generally used to describe anything that is “emotional” (Lindquist *et al.*, 2012).

Despite the difficulty of putting a frame around affect and measuring it, psychology classifies affect into positive and negative constructs. Once more, there are a broad range of theories on how to correctly name and classify these states (Diener & Iran-Nejad, 1986). But still, positive and negative affect are seen as separate states, rather than opposing extremes of the same continuum, as in how an individual is able to experience either state over a period of time (Diener & Emmons, 1984; Salsman *et al.*, 2013).

Positive affect usually comprises happiness, joy, contentment, enthusiasm, and excitement, and is expanded to psychological well-being, which further includes life satisfaction, and meaning and purpose. Consequently, the positive evaluation of one’s own life, and the extent of how much one likes life and finds it meaningful, respectively, means higher positive affect. This covers the hedonic, as well as the eudaimonic aspect; that is, the experiential, as well as the cognitive evaluative – human flourishing- nature (Salsman *et al.*, 2013, 2014).

Negative affect comprises anger, fear, and sadness. Anger includes aggression and hostility, as well as an affective spectrum including irritation, frustration, and resentment. Fear includes the bodily perception of threat and symptoms of anxiety. Sadness is best described by low levels of positive affect. It includes the affective spectrum, such as loneliness, unhappiness, or helplessness, as well as the cognitive evaluation of one’s life being purposeless, or meaningless, i.e. signs of depressive symptoms (Pilkonis *et al.*, 2013; Salsman *et al.*, 2013).

As both positive and negative affect are highly personal and inherently private the assessment via self-report has been proven to be a coherent measure (Pilkonis *et al.*, 2013; Salsman *et al.*, 2013, 2014). Furthermore, measuring affect with e.g. physiological responses would imply, that there are clear cut emotions that always evoke the same physiological response, which is, as mentioned above, not the present consensus.

Cognition and Affect

Even within this short overview about cognition and affect, the overlap is inevitable. The feeling of emotions go together with thinking about them and evaluating them. We can easily remember our birthday two years ago, but can hardly recall what we have done two weeks ago. We know exactly it is anxiousness, when we are sitting in the hospitals waiting room, waiting for results. We clearly feel excitement when we set out on a long-awaited journey, but do not feel anything while spreading butter on our morning toast.

Despite these exemplary situations everyone has experienced in some form, research has treated cognition and affect for a long time separately (Storbeck & Clore, 2007). To name only a few examples, the reason for that lays in a) stimuli processing in nonhuman animals. As it was seen, some stimuli go directly into the amygdala and only then undergo cortical processing. This phenomenon can be used in fear conditioning, as that stimuli elicits a fear response, before reaching the cortex (Quirk *et al.*, 1997). Further, b) the affective primacy hypothesis addresses the affective reaction due to mere exposure. It describes the reaction to a stimuli without the subjective conscious processing, due to short exposure to stimuli (Zajonc, 1968). And lastly, c) the affective automaticity hypothesis tries to explain how we can decide to think about a subject, but feelings simply arise (Shiffrin & Schneider, 1977). In the last two decades, some voices advocating for an interrelation of cognition and affect are getting louder (Storbeck & Clore, 2007).

The relation between cognition and emotion is of such interest, that the journal "Current Opinion in Behavioral Sciences" has dedicated a whole issue themed "Emotion-cognition interactions" (Mather & Fanselow, 2018). This emphasizes the complexity and also inconsistency regarding this topic until the present day. As counterweight to the above mentioned hypotheses advocating for a separation of cognition and affect, it is to say, that a) the fear conditioning in nonhuman animals, is apparently not translatable to the human, as findings suggest, emotion processing requires integration in the cortex (Storbeck & Clore, 2007; Storbeck *et al.*, 2006). Opposing to the affective primacy hypothesis b) speaks that other observations proved, that e.g. the visual cortex can identify stimuli without conscious awareness, due to low firing rate but consistent pattern at sub-conscious exposure compared to longer exposure (Rolls *et al.*, 1994; Storbeck & Clore, 2007). And lastly, the affective automaticity hypothesis c) probably poses the most difficult obstacle for advocates of cognition and affect conjunction. A thorough assessment would be out of the scope of this study. As an impulse might serve the thought, that yes,

we have to consciously think about a subject and feelings simply arise, but these feelings can be further modulated by thought (Storbeck & Clore, 2007).

A representative of this intertwining of cognition and affect is emotion recognition, or emotion processing. Just like the affective behaviors mentioned above, emotion processing is hard to put a frame around. The name already implies the cognitive processing of something emotional or affective. This would not be possible, if cognition and affect are strictly separated (Langner *et al.*, 2018; Pessoa, 2008). In many studies emotion processing is measured by face recognition showing different emotions. Psychosis-prone and schizophrenic patients show deficits in emotion recognition (Germine & Hooker, 2011; R. E. Gur *et al.*, 2007), and general intelligence was found to correlate positively with emotion processing (Mathersul *et al.*, 2009). This implies the engrained connection of affective behavior and cognitive abilities.

Moreover, the inability to equilibrate cognition and affect is a consequence of some mental health disorders. Conduct disorder for example is characterized by repetitive aggressiveness and antisocial behavior, pronounced in emotional shallowness, impaired perception of emotion in oneself and others, and cruel disregard for others (Sterzer *et al.*, 2005). Attention deficit hyperactive disorder is marked by the inability to inhibit impulses, which leads to emotional bursts, excessive behavior and easy frustration (Walcott & Landau, 2004). Schizophrenia, schizoaffective disorder or bipolar disorder comes along with irritability, mood disturbance, and apathy which often subsequently results in psychosis (Livingstone *et al.*, 2009). Therefore, the functioning integration of cognition and affect is fundamental for a successful and normal course of life, for both the affected and its environment.

The Brain

In everyday life, someone smart is sometimes synonymously called “a brain”, the fresh lovers are feeling butterflies in their stomach, and the youngster longing to explore the world has itchy feet. In linguistic usage, the separative attribution of cognition to the brain and affect to the rest of the body is clear. But how about the integration of cognition and affect in the brain? Some mentioned aspects already imply the connection of both within the brain.

Cognition and the brain

Despite cognition being complex and multifaceted, the research community has boiled down some specific brain regions for cognition. Especially lesion patients laid the basis for the knowledge about crucial brain regions (Damasio *et al.*, 1996; Rosenbaum *et al.*, 2005; famous patient H.M.: Scoville & Milner, 1957; Stuss *et al.*, 2001). Then, from functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies, activation in healthy brains corroborate prefrontal and parietal regions as hubs for cognition. Tasks specifically demanding fluid cognition additionally engage occipital regions and in crystallized cognition temporal regions are further associated (Cabeza & Nyberg, 2000). A possible correlation with cortical thickness in these areas is therefore expected. And indeed, a correlation of cognition and cortical thickness in the mentioned regions is seen, though often with contradictory outcomes. Some studies found a positive correlation of cortical thickness and cognition (Karama *et al.*, 2009a; Narr *et al.*, 2006; Shaw *et al.*, 2006) while others found a negative correlation (Goh *et al.*, 2011; Salat *et al.*, 2002; Sowell *et al.*, 2001; Van Petten *et al.*, 2004). But nevertheless, it is clear to say, that cognition and cortical thickness show a high correlation in prefrontal and temporal regions.

Emotion and the brain

Intuitively, when thinking of affect in the brain, one thinks of subcortical, "primitive" structures in the brain, such as the amygdala (Davis & Whalen, 2001), the nucleus accumbens (Sabatinelli *et al.*, 2007), and the hypothalamus (Lane et al., 1997). The amygdala gained fame through its strong link to fear, which is an emotion that is fairly easy to evoke (Davis & Whalen, 2001; Quirk *et al.*, 1997). Cortical structures like the orbitofrontal cortex, the anterior cingulate cortex, and the ventromedial prefrontal cortex are only subsequently associated in the discourse of affective neuroscience (Pessoa, 2008). As Pessoa states, Papez was in 1937 the first to describe a network theory of emotion that is until the present day referred to as the limbic system, even though some structures included are not considered exclusively emotional anymore, such as the hippocampus. And conversely, many regions disregarded in the Papez' circuit are seen as essential for emotion today (Pessoa, 2008). Pessoa advocates for emotion to be found not

in local brain macro structure, but in networks: “the network itself is the unit, not the brain region” (Pessoa, 2018).

Nevertheless, lesion studies or atrophy of the amygdala revealed decreased fear in subjects, as well as impaired perceiving of fear in others. The damaged or affected anterior insula was reported to go along with decreased disgust, and was further shown to be involved in the awareness of bodily sensations (Lindquist *et al.*, 2012). Functional studies revealed the lateral prefrontal cortex (lPFC) to be involved in tasks encompassing affective stimuli and cognitive processing (Beauregard *et al.*, 2001; Pessoa, 2008; Staudinger *et al.*, 2011), and the dorsolateral PFC (dlPFC) is associated with discreet emotion experience and perception. Structural changes in orbitofrontal cortex are associated with increased aggression. The regulation of sadness was found to be located in the anterior cingulate cortex (ACC), and depression comes along with structural and functional changes in the ACC. Though, it is important to note, that only few regions associated with emotion survive a meta-analytic approach (Lindquist *et al.*, 2012). The current direction of affective neuroscience goes into the direction of a multivariate network approach (Kragel & LaBar, 2016; Langner et al., 2018; Pessoa, 2008).

Cognition and affect, and the brain

As mentioned above, behaviorally it is difficult to separate cognition and affect. This stays true for the relationship of both within the brain. All given regions associated with either cognitive abilities or affective behavior are under closer inspection also involved in the contrary instance. The strongly with fear associated amygdala is revealed to be further involved in attention (Pessoa, 2008). The dlPFC and the ACC were shown to be involved in cognitive control such as inhibition (Stephan *et al.*, 2003), as well as in emotion processing (Pessoa, 2008), and positive and negative affect (Lindquist *et al.*, 2016).

Langner and colleagues assessed in a thorough meta-analysis the commonalities between emotion and action regulation, coming to the conclusion that the control of both is to some extent distinct, but shares a common core network. These core regions are restricted to cortical areas (Langner *et al.*, 2018). A thorough understanding of the connection of cognition and affect in the brain is of importance to understand mental health disorders and the subsequent treatment.

Brain morphometry

Brain morphometry is a term encompassing a variety of methodologies for brain measurement. Voxel-based morphometry (VBM), as well as deformation-based, diffusion-weighted, and structure-based morphometry are being used.

In VBM, each voxel is attributed a value that represents the proportion of a particular matter, more precisely, a distance-weighted estimate of the tissue in its vicinity. This tissue is classified in advance and is usually limited to gray and white matter, and cerebrospinal fluid (Karama *et al.*, 2009b; Winkler *et al.*, 2010). Though, for example the cortical folding or misalignment of gyri, among other factors, can lead to a distortion of these concentration maps (Karama *et al.*, 2009b).

This, and further the negligence of the biological substrate, lead to the development of MRI-based quantification of cortical thickness. Here the folding pattern of the individual gyri is followed and used to tesselate white and gray matter surface. Subsequently, the distance between white and gray matter is measured in millimeters (Karama *et al.*, 2009b). Further, it was shown, that cortical surface area and cortical thickness are developing independent of each other (Winkler *et al.*, 2009). As both surface and thickness come with their own variance, it cannot be tracked back where the variance in grey matter volume comes from, which results in an uncertainty, that can easily be avoided by focusing on one parameter alone. In this study, the focus will lie on cortical thickness, as it was also associated as an indicator for healthy brain development (Sowell *et al.*, 2004) and was associated with behavioral phenotypes, such as cognitive skills (Fjell *et al.*, 2006; Goh *et al.*, 2011; Karama *et al.*, 2009b; Menary *et al.*, 2013; Narr *et al.*, 2006) and affective behavior (Churchwell & Yurgelun-Todd, 2013; Mather, 2012; Reynolds *et al.*, 2014; Valk *et al.*, 2016; Wilde *et al.*, 2012).

Genetics

Every trait is influenced by nature and nurture. Therefore, every attribute is to some extent influenced by the genetic heritage or by the environment that is surrounding and shaping the individual. Trivial characteristics such as an individual's height are determined by its parents, but it is further influenced by the nutrition received throughout development. This holds true for any trait, but the extent to which it is determined by genes or influenced by environment differs. The assessment of the genetic

influence helps to understand the biological basis and possible influences, that allow an appropriate functioning within a society.

The variance (V) of a phenotype (P) within a population is composed of genotypic (G) and environmental (E) variance. Narrow-sense heritability (h^2) is the proportion of V(G)/V(P). It therefore explains the fraction of phenotypic variance within a population that is due to the genetic variation (Bruell, 1970). Further, h^2 explains the additive genetic influence, hence the effects of multiple individual loci that combine additively. Broad-sense heritability (H^2) comprises h^2 and non-additive genetic influence, i.e. the interaction between alleles (Nes & Roysamb, 2015; Rettew *et al.*, 2008).

There are several approaches to assessing the genetic influence. In nonhuman animals, targeted breeding is a successful approach to disentangle nature and nurture. In order to estimate the genetic influence in humans there is the comparison of close relatives or genome-wide association studies. Best suited for this kind of analysis are twins and their siblings, as well as more complex family structures. In order to further identify genetic variants – or polymorphisms- associated with a given trait a hypothesis-free genome-wide association study or a hypothesis-bound candidate gene study can be performed (Scult & Hariri, 2018).

The basis of twin studies lies in the fact, that siblings, and therefore also fraternal – or dizygotic- twins (DT), share about 50 %, while identical – or monozygotic- twins (MT) share 100 % of their genes. Additionally, MT and DT share the same environment in the womb, and in development, which can serve as a proxy for controlled shared environment. Consequently, if identical twins share a trait that is not shared by fraternal twins, a genetic association can be assumed. If MT and DT share a trait that is not shared by their siblings, a strong environmental influence can be assumed (Sahu & Prasuna, 2016). Though, the environmental influence is difficult to extrapolate if no detailed information about the household and life style is given. Further, twin studies have revealed a fluctuation of genetic influence with age (Fraga *et al.*, 2005; Talens *et al.*, 2012), which implies, that a possible external intervention may have a different outcome depending on the time applied.

Cognition and genetics

The genetic basis of cognition is subject of interest for a long time already, going back to the 1860s (Galton, 1869). Hence, the findings in this regard are manifold. Longitudinal twin studies show, that the heritability of cognitive abilities increase strongly with age (Bartels *et al.*, 2002; van Soelen *et al.*, 2011; Wainwright *et al.*, 2005). Ever since the theory about fluid and crystalized cognition was stated, the heritability of the different components was tried to unscramble. Cattell proposed a theory that was until recently scientific consensus: as fluid cognition is needed to build knowledge, i.e. crystallized cognition, the determining factor of acquiring knowledge needs to be fluid cognition. Therefore, the heritability of crystallized cognition will be lower than of fluid cognition (Cattell, 1980; Kan *et al.*, 2013). But as sample sizes are growing and heritability analyses are being refined, different outcomes were yielded. So, a recent large meta-analysis by Kan *et al.* assessed a higher heritability of crystallized cognition (Kan *et al.*, 2013). This underlines both the further research needed within this field, but also the actual separation between fluid and crystallized cognition, while further underlining the strong genetic influence on cognition.

Affect and genetics

And again, while the findings for cognition and the genetic influence are quite delineated, the same cannot be said about affect and genetics in the human. A thorough twin study by Baker *et al.* revealed a strong narrow-sense heritability h^2 for negative affect, but none for positive affect (Baker *et al.*, 1992). Another twin study found a relatively high broad-sense heritability H^2 for well-being (Lykken & Tellegen, 1996).

The systematic assessment of the genetic influence of affect in the human remains an obstacle until the present day. But there were quite some findings made in nonhuman animals: selective breeding of “emotional” or sensitive rats and “non emotional” rats revealed a genetic basis of “emotional” behavior, just like for “shy” versus “curious” rats (Bruell, 1970). Shyness was also found to be to some extent heritable in rhesus monkeys. Findings in higher order animals, such as monkeys, prove the genetic influence to increase with age (Rockville, 1996).

The brain and genetics

As mentioned above, both cognition and affect are intrinsically rooted in the brain. As both are shown to be heritable to some extent, then aspects of the brain should also be heritable. And indeed as research has shown, brain volume, cortical surface, cortical thickness (Brouwer *et al.*, 2014; Panizzon *et al.*, 2009; Winkler *et al.*, 2009), and even functional connectivity (Sinclair *et al.*, 2015) was shown to be heritable. As mentioned above, since brain volume is composed of two factors, which each come with their variance, and were further shown to be independently heritable, the genetic analysis with brain volume is not suggested (Winkler *et al.*, 2010, 2009). As both, the genetic determination and the environmental influence are of critical interest, and in order to paint a clear picture, this study will investigate the coheritability of cortical thickness and cognition and affect. A thorough understanding of the connection of cognition and affect in the brain, and further their genetic influence is of importance to understand the biological basis of mental health disorders and the subsequent treatment.

Open Science

The ever-growing sample sizes, data and results, and easy and efficient access to them in the "digital world" is an enormous advantage for scientist and the society. Sharing of expansive data leads to decreased costs and increased knowledge in the long run and open access enables a quality assurance incomparable with that of only a few selected readers. Further, reproducibility plays an important role in the vast amount of results. To enable this, comprehensive and detailed methods and raw data should be provided with any study.

The current work is based on the open-access young adult sample of the "Human Connectome Project" (HCP). The HCP dataset comprises extensive behavioral assessment, as well as different brain scanning modalities of healthy young adults. The aim of the HCP is to "map the human brain" and to "connect its structure to function and behavior" (HCP web site: humanconnectome.org).

In order to enable reproduction of the here found results, all necessary information, such as methods and statistics, but also subject IDs are provided.

Aim and Objectives

Humans experience feelings, have thoughts and integrate both constantly. In various situations it is of importance to be able to control and properly assess both cognition and affect. A functioning equilibration of thoughts and feelings is crucial for a normal course of life. If this integration fails and cognition and emotion overbalance, as it is seen in mental health disorders in both directions, problems for the individual as well as their proximity may arise. The influence of genes on both cognition and affect is further important in order to broaden and refine the knowledge about influences on the balanced cognition-emotion-interaction in the brain. A thorough knowledge may ultimately lead to development of biological markers.

The aim of this study is to assess whether cognitive and affective behavioral variation is dissociable at the neuroanatomic and genetic level. First, the relation of cognition and affect will be assessed on the behavioral level by studying phenotypic correlation, heritability as well as genetic correlation in a large sample of healthy twins.

Next, the relationship between cognitive function and affective behavior, and macroscale grey matter anatomy will be assessed to understand which brain regions play a role behaviorally and which regions are co-heritable.

Then, the relation of brain morphometry and co-heritability of cognitive abilities will be assessed, so that the relation between cognitive abilities and affective behavior can be evaluated based on the gained insight.

Based on the current literature, the hypothesis is that cognition and affect will show a relation both phenotypically and in brain morphometry, while the heritability for the cognitive scores is stronger than for the affective scores.

Methods

Human Connectome Project

The Human Connectome Project (HCP, www.humanconnectome.org) is a publicly available data base. In this study the Young Adult Pool was used, which comprises 1206 healthy individuals (656 females). The mean age is 28.8 years (range = 22-37), with a standard deviation of 3.7. In total it comprises 298 MZ twins, 188 DZ twins, and 720 singletons. After exclusion of individuals without structural or chosen behavioral data, the sample comprised 1087 individuals, of which 587 were females. The sample used in this study comprised 282 MZ twins, 165 DZ twins, and 640 singletons. The exact subject IDs of the individuals used in this study can be found in the appendix (see "Supplement", **Error! Bookmark not defined.**). The mean age, range and standard deviation remained the same.

HCP- Structural image acquisition

All MRIs within the HCP were acquired on a Siemens Skyra 3 Tesla scanner (Glasser *et al.*, 2013). A high spatial resolution was aimed to achieve by balancing matrix size, field-of-view, and slice thickness. Additionally, to ensure accurate cortical thickness delineation, the flip angle, inversion time (for T1-weighted; T1w), and echo time (for T2-weighted; T2w) were adjusted as parameters for higher contrast (Glasser *et al.*, 2013). The accurate imaging of myelination in each subject is crucial for cortical surface analysis. A sharp transition in myelin content is the basis for a correct delineation of cortical area borders, as well as high spatial resolution. To ensure this in the HCP, T1w and T2w structural images (0.7 mm isotropic) were acquired, then a ratio of T1w/T2w is used (Glasser & Van Essen, 2011). The T1w/T2w signal intensity ratio is used to make myelin maps by contrasting heavily and lightly myelinated areas. More specifically, to improve intracortical contrast for myelin detection echo time is prolonged in T2w images, and flip angle and inversion time is prolonged in T1w scans. Further, to be able to correct readout distortions and intensity inhomogeneity in T1w and T2w retrospectively, B1- and B1+ maps were additionally acquired, so that correction is possible by modeling B1- receive and B1+ transmit fields (Glasser *et al.*, 2013).

HCP- Structural image processing

The data used in this study, was processed by the preprocessing pipeline of the HCP, to ensure comparable results, through enabling cross-subject comparison and multi-modal analysis of the brain (Glasser *et al.*, 2013).

The pipeline is divided into 3 steps, all steps are performed with the publicly available software FreeSurfer (version 5.3). The first step "PreFreeSurfer" is the correction for gradient nonlinearity distortion (Jovicich *et al.*, 2006), alignment and averaging T1w and T2w images (Jenkinson *et al.*, 2002), the alignment and registration to the Montreal Neurological Institute template, removal of readout distortion (Greve & Fischl, 2009), and then intensity inhomogeneity correction and B1- and B1+ bias correction (Jenkinson *et al.*, 2002). The second step "FreeSurfer" is based on FreeSurfer version 5.2 and uses the output of "PreFreeSurfer". It includes segmentation of the T1w volume (Fischl et al., 2002), tessellation and topology correction of white matter surface (Dale *et al.*, 1999), which is then used for fine-tuned T2w to T1w registration (Greve & Fischl, 2009). Further, recon-all from FreeSurfer is performed, which includes spherical inflation of the cortical surface (Fischl, Sereno, & Dale, 1999) and registration to the fsaverage template. This template is based on a 2-D sheet-like surface-based coordinate system (Fischl, Sereno, Tootell, et al., 1999). Then, for accurate removal of dura and blood vessels, which are clearly visible on a T2w image, but close to isointense to gray matter in a T1w image, these images are extrapolated to define the gray matter ribbon, and to reconstruct white and pial cortical surfaces. Lastly, surface and volume is anatomically parcellated and morphometrically measured. The third step "PostFreeSurfer" performs surface registration, and creation of myelin maps. More specifically, based on the distance between white and pial surface, the voxels are mapped to a volume segmentation of the cortical ribbon, i.e. gray matter (Glasser *et al.*, 2013; Glasser & Van Essen, 2011).

After the image processing, the extracted vertices are assigned to the Schaefer parcellation. The Schaefer atlas is based on the fMRI atlas by Yeo *et al.*, which assessed 7 and 17 networks obtained by co-activation within the brain (Yeo *et al.*, 2011). This was further refined taking into account local gradient approach (Schaefer *et al.*, 2018). The parcels used in this study are divided into 200 regions (7 networks solution). This atlas and granularity was chosen, as it considers neurobiologically meaningful features of brain

organization through a combination of local gradient approach and global similarity approach (Schaefer *et al.*, 2018), especially by differentiating functionally heterogeneous regions such as the frontal and parietal cortex, as well as a good signal to noise ratio. The assigned vertices within a parcel are averaged unsmoothed by a 10 percent trimmed mean, which further improves signal-to-noise ratio as well as processing speed (Valk *et al.*, 2019).

Behavioral data

To identify indices of cognitive and affective behavior, cognitive and affective scores were selected in the data base of the HCP. Except for "emotion recognition", the behavioral measures used in this study all derive from the National Institute of Health (NIH) toolbox for Assessment of Neurological and Behavioral Function® (neuroscienceblueprint.nih.gov). Scores from the cognition and emotion category were used, while one category comprises several domains. The cognitive function composite (total cognitive) score is yielded by summation of fluid cognition composite (fluid cognition) score and crystallized cognition composite (crystallized cognition) score. As illustrated in Table 1 (p. 24), the fluid cognition score is yielded by combination of scores from Dimensional Change Card Sort Test, Flanker, Picture Sequence Memory, List Sorting, and Pattern Comparison measures. That is, the fluid cognition is a combination of executive function, inhibition and attention, episodic memory, working memory, and processing speed. The crystallized cognition score in contrast, is yielded by the combination of scores from 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).

In order to examine affective behavior in this study, both positive and negative affect, as well as emotion recognition were used. Positive and negative affective behavior were obtained using the NIH toolbox with a written self-report (Pilkonis *et al.*, 2013; Salsman *et al.*, 2013, 2014). Positive affect is composed of scores from the sub-domain of life satisfaction, meaning and purpose, and positive affect. Negative affect is composed of anger, fear, and sadness, whereas anger is subdivided into affective anger, aggression, and hostility. Fear is subdivided into affective and somatic fear (see Table 1, on page 24). As

the positive and negative affect scores used in this study showed high intercorrelations at the single behavior level (see Supplementary Figure 2, Supplementary *Figure 3* and Supplementary *Figure 4*) and the questionnaire was designed to cover the whole range of negative affect (Pilkonis *et al.*, 2013; Salsman *et al.*, 2013), constructs were made by z-scoring the sub-domains and combining them by summating and diving by the number of sub-domains.

Table 1) Behavioral scores

Category	*Domain*	*Sub-domain*	*Test*
Cognition	Fluid cognition	Executive function – cognitive flexibility	DCCS
		Executive function – Inhibition and attention	Flanker
		Episodic memory	Picture Sequence Memory
		Processing speed	Pattern Comparison
		Working memory	List Sorting
	Crystal 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 aggression	
		Anger hostility	
		Fear affect	
		Fear somatic	
		Sadness	
	Emotion processing		Penn ER40, correct response time

DCCS: Dimensional change card sorting, ER40: Emotion recognition 40 faces.

Other than the previous scores, "emotion recognition" was tested with the Penn Emotion Recognition Test (R. C. Gur *et al.*, 2010, 2002). Here, the individual is shown 40 faces with

4 different emotions (happy, sad, anger, fear), the correct responses are counted. Due to the low Cronbach alpha (Cronbach, 1951) of the total emotion recognition correct responses score in this sample, it was decided to omit that score, but use the emotion recognition correct response time, as a proxy for emotion processing (Mathersul *et al.*, 2009). The selected scores were controlled: the variance was assessed by box plots (see Supplementary Figure 10) and the normality distribution by analyzation of quantile-quantile plots (QQ plots, see Supplementary Figure 9). (For further data control see Supplementary Table 1.)

Statistical analyses

Behavior-behavior correlations

To assess the correlations between selected behavioral markers, Spearman's rank correlation was used, in order to counter the skewed variance and normality in some of the selected scores. The behavior-behavior correlations were corrected for significance by Bonferroni correction.

Brain-behavior correlation

To assess the correlations between selected behavioral markers and cortical thickness partial Spearman's rank correlation was performed, controlling for age, sex, age*sex, age^2 and global cortical thickness. The brain-behavior correlations are controlled for multiple comparisons using Benjamini-Hochberg false discovery rate (FDR; Benjamini & Hochberg, 1995). The parcels indicating significant brain-behavior-correlation after FDR-correction in total, fluid, and crystallized cognition scores were used for analysis of the affective scores.

Heritability analysis and genetic correlation

The heritability and genetic correlation 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 with Pearson's correlation.

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 (Valk *et al.*, 2019).

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. Hence, how much variation remains, given that the environment is equal to all individuals (Griffiths *et al.*, 2000). 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, taking into account 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 heritability analysis was controlled for age, age^2, sex, age*sex, and age^2*sex interaction. The heritability estimates are corrected for multiple comparison by Bonferroni correction.

To assess if the variance of traits and the brain structure is driven by the same genetic influence, genetic correlation analysis 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 a bivariate polygenetic analysis was performed, based on the phenotypic correlation between the traits, or between a given trait and the mean cortical thickness in a parcel, 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 is compared to an estimated model, in order to assess the significance (Almasy *et al.*, 1997; Valk *et al.*, 2019). Here, it was as well controlled for age, age^2, sex, age*sex, and age^2*sex interaction and additionally for global cortical thickness when investigating the brain. Post-hoc, in the analysis of fluid cognition scores with cortical thickness it was further controlled for crystallized cognition scores and vice versa. The covariance analysis for the

genetic basis of brain and behavior manifestation are controlled for multiple comparisons using Benjamini-Hochberg FDR (Benjamini & Hochberg, 1995). The parcels indicating significant coheritability after FDR-correction in total, fluid, and crystallized cognitive abilities were used for co-heritability analysis of the affective scores.

Results

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

The assessment of the behavioral correlations (Figure 1A, on page 29, below diagonal) indicates a consistency in the observed scores: the cognitive scores all correlate positively, and positive and negative affect go into opposite directions, with a strong anticorrelation (see also Supplementary Figure 5). On an explorative level ($p < 0.05$; see Supplementary Figure 1) slow emotion processing correlates negatively with all cognitive scores, and positive affect behavior correlates positively with total and fluid cognitive abilities. Crystallized cognition is stable throughout the scores, with a positive correlation with positive and negative affect scores, and a negative correlation with low emotion processing scores. Total and fluid cognition scores on the other hand correlate positively with positive affective behavior and negatively with negative affective behavior.

The next step was to evaluate the narrow-sense heritability h^2 and genetic correlations between the scores. The heritability analysis revealed, as visible in Figure 1B, that all observed scores are heritable. Total cognition ($h^2 = 0.51$, $p < 0.001$), which is a combination of fluid ($h^2 = 0.35$, $p < 0.001$) and crystallized ($h^2 = 0.75$, $p < 0.001$) cognition. What is noticeable, the affective scores are less heritable compared to cognition: emotion recognition ($h^2 = 0.23$, $p < 0.001$), positive ($h^2 = 0.27$, $p < 0.001$) and negative ($h^2 = 0.32$, $p < 0.001$) affect. Hence, analysis of heritability revealed, that all selected cognitive and affective scores are heritable, though cognitive scores display a higher heritability within this sample.

Then, the phenotypic genetic correlation was analyzed (Figure 1A, above diagonal). There is a strong positive genetic correlation (Figure 1A, above diagonal) between the cognitive tasks: total and fluid cognition ($\rho_g = 0.87$, $p < 0.001$), total and crystal cognition ($\rho_g = 0.90$, $p < 0.001$), fluid and crystal cognition ($\rho_g = 0.52$, $p < 0.001$). As well as a negative genetic correlation between positive and negative affect ($\rho_g = -0.64$, $p < 0.005$). A negative genetic correlation between total cognition and emotion processing ($\rho_g = -0.51$, $p < 0.001$) was observed, driven by its fluid cognition subcomponent (fluid cognition and emotion processing: $\rho_g = -0.78$, $p < 0.001$).

As, in general, genetic correlations are driving the phenotypic correlations (Chevroud's conjecture; Cheverud, 1988; Sodini *et al.*, 2018), the pattern of both phenotypic (Figure 1A, below diagonal) and genetic (Figure 1A, above diagonal) correlation is expectedly

similar. The phenotypic correlations are in contrast less strong. In the phenotypic correlation is additionally a positive correlation between fluid cognition and positive affect ($r = 0.11$, $p < 0.005$; figure 1B, below diagonal). Hence, no correlation between cognition and positive and negative affect on the genetic level was observed, while emotion processing builds the bridge between cognitive and affective scores. Phenotypically there is additionally an overlap between positive affect and fluid cognition scores.

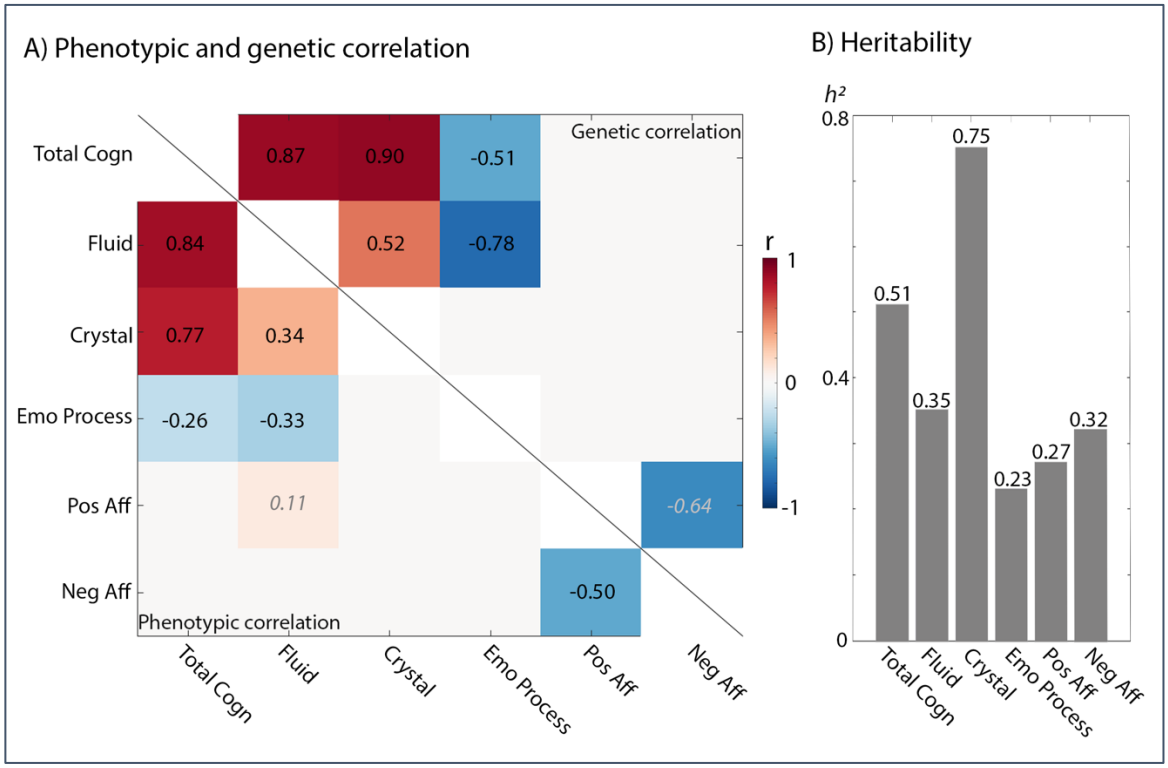

Figure 1) Behavioral relation of cognition and affect. A) Below diagonal: behavioral correlation and above diagonal: co-heritability of the cognitive and affective scores. Black values: $p < 0.001$, grey values: $p < 0.005$, Bonferroni corrected. B) Narrow-sense heritability h^2 of the cognitive and affective scores. $p < 0.001$.

Overall cognition and the brain (Figure 2)

In order to assess correlations of total cognition scores and cortical thickness spearman correlation was used, then controlling for multiple comparisons using Benjamini-Hochberg FDR (Benjamini & Hochberg, 1995). As shown in figure 2A, a strong correlation with bilateral prefrontal cortex was found: the superior (LH: $r = -0.08/-0.09$, $p < 0.01/0.005$; RH: $r = -0.11$ to -0.15, $p < 0.005$, see also 2nd and 4th scatter in Figure 2A,

on page 31) and middle (LH: r = -0.11 to -0.19, $p < 0.005$; RH: r = -0.08/-0.11, $p < 0.01/0.005$) frontal gyrus, stretching into the inferior frontal gyrus (LH: r = -0.08, $p < 0.01$; RH: r = -0.08, $p < 0.01$) and medial frontal gyrus (LH: r = -0.11, $p < 0.005$; RH: r = -0.08/-0.13, $p < 0.01/0.005$). Additionally, the left superior medial frontal gyrus (r = -0.11, $p < 0.005$) is engaged. The correlation between total cognition score and cortical thickness within the frontal cortex is strongly negative. On the parietal cortex a positive correlation was found in the central sulcus up to the postcentral gyrus (LH: r = 0.15, $p < 0.001$, see also 1st scatter in Figure 2A, on page 31; RH: r = 0.10 to 0.11, $p < 0.005$). Further, a positive correlation between cortical thickness and total cognition score was found in bilateral posterior middle temporal gyrus (LH: r = 0.08, $p < 0.01$; RH: r = 0.09, $p < 0.01$), stretching on the left hemisphere to the posterior superior temporal gyrus (r = 0.10, $p < 0.005$), over to the temporo-parietal junction (r = 0.10, $p < 0.01$), and on the right hemisphere into the middle occipital gyrus (r = 0.09, $p < 0.01$) and to the middle superior temporal gyrus (r = 0.09, $p < 0.01$). In addition, a positive correlation in the left occipital pole (r = 0.10, $p < 0.01$) and right temporal pole (r = 0.10, $p < 0.01$), bilateral cuneus (LH: r = 0.10, $p < 0.01$; RH: r = 0.11, $p < 0.01$), posterior cingulate gyrus (LH: r = 0.11, $p < 0.005$; RH: r = 0.13, $p < 0.001$, see also 3rd scatter in Figure 2A, on page 31), and left posterior lingual gyrus (r = 0.08/0.11; $p < 0.01/0.005$) was found. Bilaterally the anterior (LH: r = 0.09/0.12, $p < 0.01/0.005$; RH: r = 0.11, $p < 0.01$), and posterior insula (LH: r = 0.11, $p < 0.005$; RH: r = 0.09, $p < 0.01$) revealed positive correlations with cortical thickness and total cognitive score (see Table 2). When observing the scatters (exemplary scatters are shown in Figure 2A, on page 31, all other scatters of significant regions can be found in “Supplement - Scatter plots”, on page 70ff) it can be seen, that there is a “roof” at total cognitive score of 155. Some scatter plots reveal a few outliers, especially in the lower cortical thickness. These outliers are not extreme, and the use of Spearman’s rank correlation leverages that. In a nutshell, regions from throughout the cortex are phenotypically correlated with total cognition, including the frontal regions, where the correlation with total cognitive score is negatively correlated.

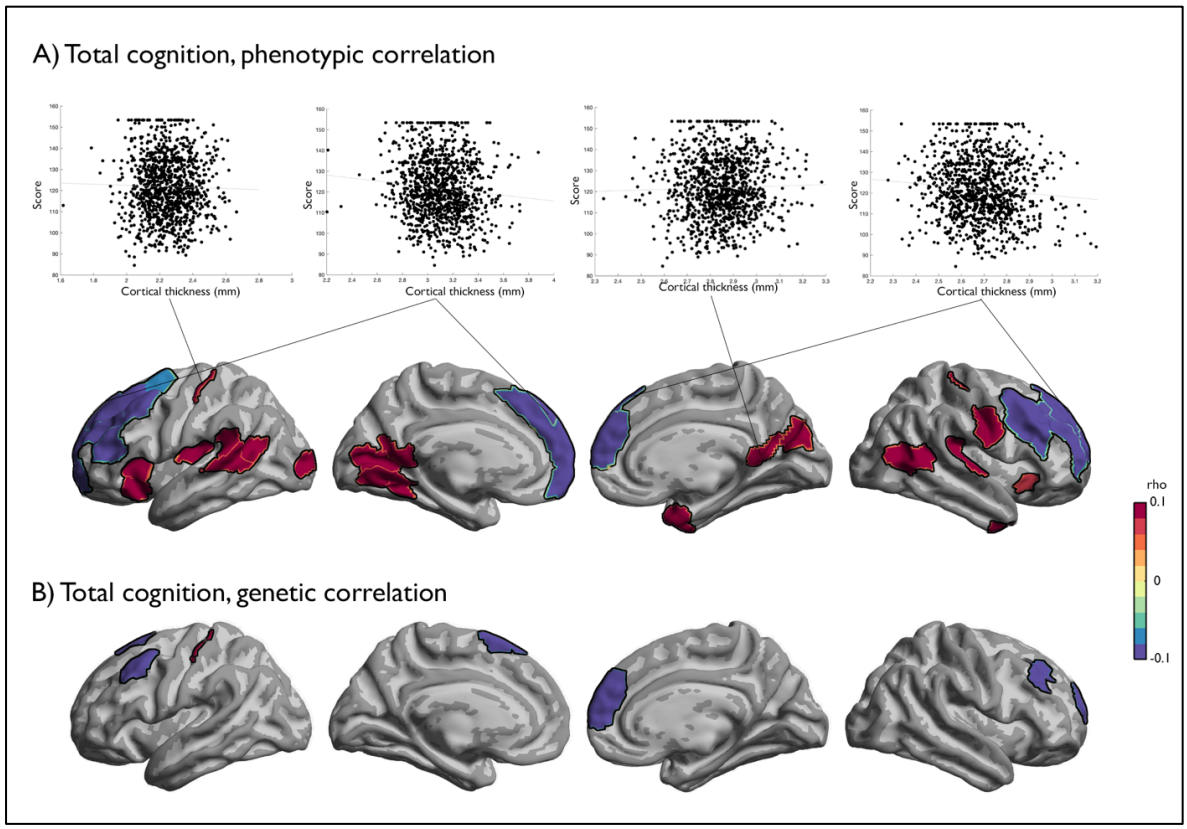

Figure 2) Total cognition and cortical thickness. FDR corrected, p < 0.05. A) Selected scatter plots of total cognition score and cortical thickness (in mm) in indicated region; phenotypic correlation of total cognition and cortical thickness. B) Genetic correlation of total cognition and cortical thickness.

Table 2) Phenotypic correlations of total cognition and cortical thickness in significant parcels

	LH			*RH*		
Brain region	*Parcel no.*	*p*	*rho*	*Parcel no.*	*p*	*rho*
SFG	43	0.0093	-0.0787	196	0.0000	-0.1503
	92	0.0028	-0.0903	197	0.0003	-0.1097
	95	0.0026	-0.0909			
MFG	94	0.0000	-0.1891	175	0.0008	-0.1018
	52	0.0003	-0.1105	176	0.0057	-0.0837
				177	0.0005	-0.1048
mSFG	93	0.0003	-0.1106			
mFG	90	0.0003	-0.1096	172	0.0070	-0.0815
	87	0.0004	-0.1068	195	0.0000	-0.1265
IFG	69	0.0080	-0.0802	174	0.0071	-0.0814

Postcentral s.	25	0.0000	0.1531			
Postcentral g.				123	0.0003	0.1104
				128	0.0013	0.0973
pCingulate	97	0.0003	0.1099	199	0.0000	0.1320
M Occipital g.				137	0.0037	0.0878
Occipital pole	10	0.0010	0.0992			
Cuneus	11	0.0015	0.0961	114	0.0004	0.1075
TPJ	45	0.0011	0.0986			
(p/m) STG	79	0.0003	0.1088	117	0.0031	0.0894
pMTG	80	0.0063	0.0826	149	0.0031	0.0894
aInsula	49	0.0029	0.0899	170	0.0086	0.0795
	84	0.0001	0.1178			
pInsula	18	0.0003	0.1090	120	0.0046	0.0858
Temporal pole				163	0.0013	0.0970
pLingual g.	2	0.0062	0.0827			
	5	0.0003	0.1090			

LH: left hemisphere, RH: right hemisphere; SFG: superior frontal gyrus, MFG: middle frontal gyrus, mFG: medial frontal gyrus, IFG: inferior frontal gyrus, TPJ: temporo-parietal junction, STG: superior temporal gyrus, MTG: middle temporal gyrus; a: anterior, g: gyrus, m: medial, M: middle, p: posterior, s: sulcus.

To assess if the variance of total cognition and the brain structure is driven by the same genetic influence, genetic correlation analysis were performed through a bivariate polygenetic analysis, controlling for multiple comparison using Benjamini-Hochberg FDR (Benjamini & Hochberg, 1995). As shown in figure 2B, the genetic correlation shows overlap in regions that revealed also significant in the phenotypic analysis (figure 2A), while being focused to fewer regions and showing stronger correlations. The left postcentral sulcus is the only region that is positively correlated ($r = 0.24$, $p < 0.005$). Further, the prefrontal cortex shows negative genetic correlation: bilateral superior frontal gyrus (LH: $r = -0.25$, $p < 0.005$; RH: $r = -0.29$, $p < 0.005$) and middle frontal gyrus (LH: $r = -0.28$, $p < 0.005$; RH: $r = -0.32$, $p < 0.005$), as well as right medial frontal gyrus ($r = -0.23$, $p < 0.005$; see Table 3). The findings in the genetic correlation analysis of total cognition and cortical thickness are mirrored by the behavioral correlations (Figure 1A, on page 29). The co-heritability is stronger and more focused than the phenotypic

correlation. Fewer regions, mainly the prefrontal cortex, were shown to be co-heritable with total cognition.

Table 3) Genetic correlations of total cognition and cortical thickness in significant parcels

	LH			*RH*		
Brain region	*Parcel no.*	*p*	*rho*	*Parcel no.*	*p*	*rho*
SFG	96	0.0011	-0.2470	197	0.0006	-0.2845
MFG	94	0.0005	-0.2818	176	0.0002	-0.3150
mFG				195	0.0010	-0.2322
Postcentral s.	25	0.0010	0.2404			

LH: left hemisphere, RH: right hemisphere; SFG: superior frontal gyrus, MFG: middle frontal gyrus, mFG: medial frontal gyrus, s: sulcus.

Subcomponents of cognition (Figure 3)

The next step was to further understand cognition by investigating fluid and crystallized cognition. The correlations with fluid and crystallized cognition scores and cortical thickness were assessed with Spearman's rank correlation and controlled for multiple comparisons using Benjamini-Hochberg FDR (Benjamini & Hochberg, 1995).

Fluid cognition shows significant correlation with cortical thickness in two regions (Figure 3A, on page 36), which drives the overlap with total cognition (fig. 2A): a positive correlation in the left occipital pole ($r = 0.11$, $p < 0.005$) and a negative correlations with the superior frontal gyrus ($r = -0.11$, $p < 0.005$; see Table 4). Exploratively, (no FDR-correction, $p < 0.005$; Figure 3A, transparent regions) the balance of the pattern between frontal and parietal and occipital regions, lies in fluid cognition more on the latter, compared to total cognition. The scatters of the significant regions are shown, visualizing the differences between frontal and occipital region: the superior frontal gyrus (Figure 3A, right scatter) shows higher variability than the occipital pole (Figure 3A, left scatter). In the correlation between fluid cognition score and cortical thickness remain two distinct regions: frontal and occipital, with negative and positive correlation, and higher and lower variability, respectively.

Table 4) Phenotypic correlations of fluid cognition and cortical thickness in significant parcels

	LH			*RH*		
Brain region	*Parcel no.*	*p*	*rho*	*Parcel no.*	*p*	*rho*
SFG				196	0.0005	-0.1053
Occipital pole	10	0.0004	0.1077			

LH: left hemisphere, RH: right hemisphere; SFG: superior frontal gyrus.

The phenotypic correlation of the crystallized cognition score and cortical thickness is more diversified than in fluid cognition and resembles total cognition. There is a negative correlation of bilateral middle (LH: r = -0.13, p < 0.001, see also 1st scatter in Figure 3C; RH: r = -0.11, p < 0.005), and inferior frontal gyrus (LH: r = -0.11, p < 0.005; RH: r = -0.09, p < 0.005, see also 4th scatter in Figure 3C), and left medial frontal gyrus (r = -0.09/-0.11, p < 0.005). Further revealing the influence on total cognition is the positive correlation of the left postcentral sulcus (r = -0.10, p < 0.005), and middle temporal gyrus/superior temporal sulcus (r = 0.09/0.11, p < 0.005), as well as the posterior (r = 0.11, p < 0.005, see also 2nd scatter in Figure 3C) and anterior insula (r = 0.10, p < 0.005), and the posterior cingulate gyrus (r = 0.10, p < 0.005). In the phenotypic correlation of crystallized cognition and cortical thickness, the lingual gyrus is bilaterally significant (LH: r = 0.13/0.09, p < 0.001/0.005; RH: r = 0.11, p < 0.005, see also 3rd scatter in Figure 3C; in total cognition only left lingual gyrus, compare Figure 2A). Further, in crystallized cognition, the parietal lobe is engaged: the left superior parietal gyrus (r = 0.09, p < 0.005) and angular gyrus (r = 0.09, p < 0.005) and the right middle occipital gyrus (r = 0.09, p < 0.005; see Table 5). Crystallized cognition shows overlap with correlation of total cognition and cortical thickness in a bit more than half of the regions. Some of the regions that are unique to crystallized cognition are close to regions that are also remain significant in total cognition. For example, as an extension of the inferior frontal gyrus or the middle temporal gyrus. But interestingly, the regions that are not an extension in crystallized cognition, are located in the parietal lobe. These regions are also not driven by extreme outliers (compare "Supplement, Scatter plots", on page 76ff, especially the plots "Crystallized Cognition – 39" and "– 83"). To sum up, the correlations of crystallized cognition and brain morphometry shows a typical pattern with significant regions in the frontal and temporal lobe, but also in the parietal lobe.

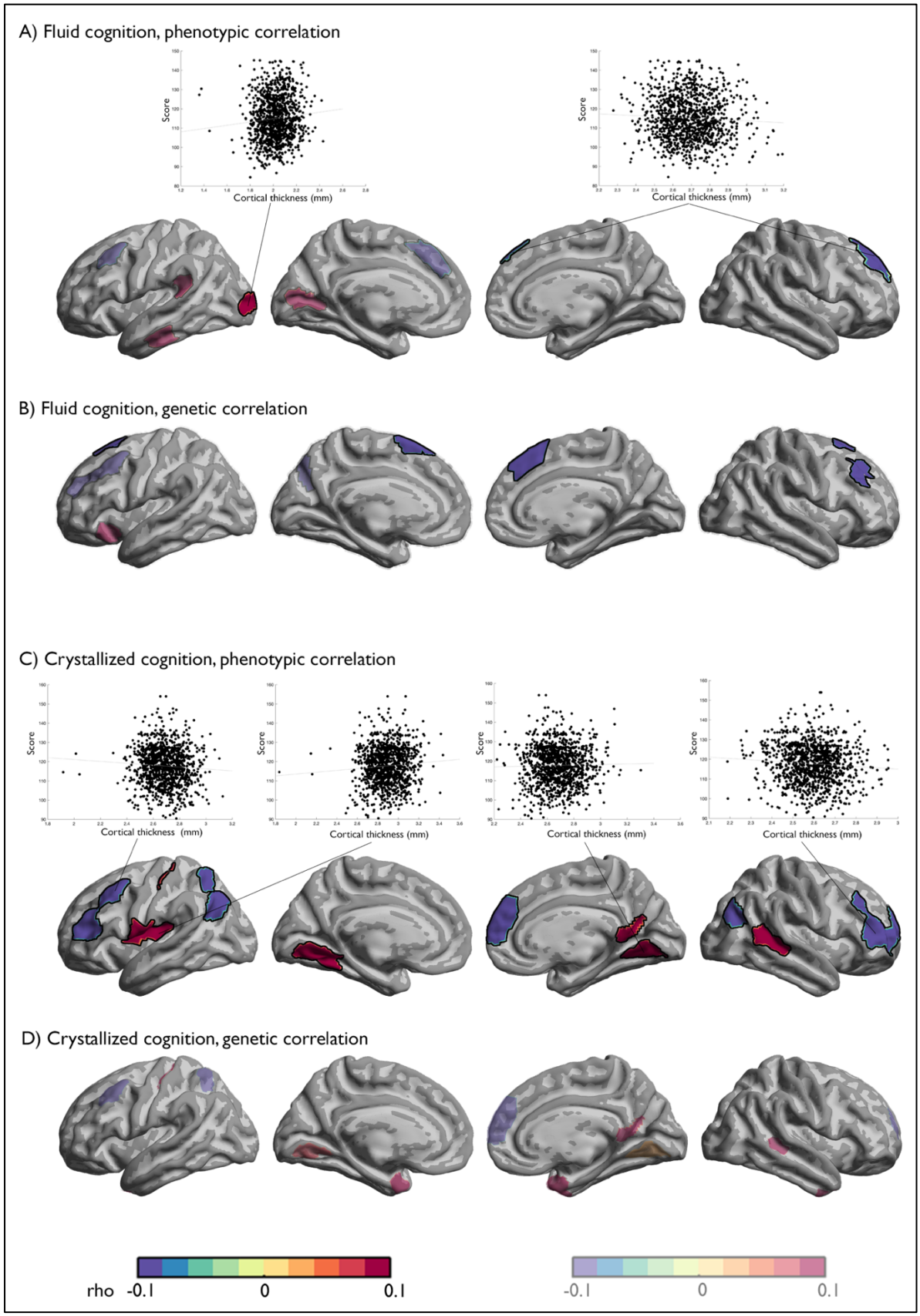
A) Fluid cognition, phenotypic correlation
Score
Cortical thickness (mm)
Score
Cortical thickness (mm)
B) Fluid cognition, genetic correlation
C) Crystallized cognition, phenotypic correlation
Score
Cortical thickness (mm)
Score
Cortical thickness (mm)
Score
Cortical thickness (mm)
Score
Cortical thickness (mm)
D) Crystallized cognition, genetic correlation
rho -0.1 0 0.1
-0.1 0 0.1

Figure 3) Subcomponents of cognition, and cortical thickness. Black-bordered regions FDR corrected, $p < 0.05$; transparent regions explorative ($p < 0.005$). Phenotypic correlation of fluid (A) and crystallized (C) cognition with cortical thickness. Selected scatter plots of cognition score and cortical thickness (in mm) in indicated region. Genetic correlation of fluid (B) and crystallized (D) cognition and cortical thickness. B) Prefrontal regions in genetic correlation of fluid cognition and cortical thickness significant. D) exploratively, regions in genetic correlation of crystallized cognition are mirrored by phenotypic correlation.

Table 5) Phenotypic correlations of crystallized cognition and cortical thickness in significant parcels

	LH			*RH*		
Brain region	*Parcel no.*	*p*	*rho*	*Parcel no.*	*p*	*rho*
MFG	94	0.0000	-0.1263	176	0.0004	-0.1070
mFG				172	0.0039	-0.0874
				195	0.0002	-0.1128
IFG	69	0.0004	-0.1069	173*	0.0033	-0.0888
iPrecentral g.	19*	0.0007	0.1023			
Postcentral s.	25	0.0016	0.0952			
SPL	39*	0.0033	-0.0890			
Angular g.	83*	0.0027	-0.0907			
pCingulate				199	0.0008	0.1013
M Occipital g.				183*	0.0018	-0.0943
MTG				149	0.0045	0.0860
				190*	0.0002	0.1109
aInsula	50*	0.0012	0.0983			
pInsula	18	0.0005	0.1052			
Lingual g. (LH: p)	2	0.0000	0.1285	105*	0.0002	0.1124
	5	0.0029	0.0902			

LH: left hemisphere, RH: right hemisphere; MFG: middle frontal gyrus, mFG: medial frontal gyrus, IFG: inferior frontal gyrus, SPL: Superior parietal lobule; g: gyrus, m: medial, M: middle, p: posterior, s: sulcus. Parcels marked with an asterisk are unique to crystallized cognition.

While the phenotypic and genetic correlations of total cognition, resemble each other, a different picture is drawn in the subcomponents of cognition. In the genetic correlation analysis by bivariate polygenetic analysis in fluid cognition (Figure 3B), regions are

significant that are not in the phenotypic analysis: bilateral superior medial frontal gyrus is strongly negative (LH: r = -0. 25, p < 0.005; RH: r = -0.31, p < 0.005), as well as the right middle frontal gyrus (r = -0.36, p < 0.005; see Table 6). In crystallized cognition no region survives FDR correction. The trend (p < 0.005; see Figure 3D, transparent regions) indicates a similar pattern as in the phenotypic analysis. Hence, in the subcomponents of cognition, there are only few frontal regions in fluid cognition scores significant, and none in crystalized cognition scores, where the variance can be explained by the same genetic influence.

Table 6) Genetic correlations of fluid cognition and cortical thickness in significant parcels

	LH			*RH*		
Brain region	*Parcel no.*	*p*	*rho*	*Parcel no.*	*p*	*rho*
SFG	96	0.0011	-0.2470			
MFG				176	0.0006	-0.3564
				197	0.0004	-0.3583
mFG				182	0.0006	-0.3088

LH: left hemisphere, RH: right hemisphere; SFG: superior frontal gyrus, MFG: middle frontal gyrus, mFG: medial frontal gyrus.

Cognition and affect (Figures 4 and 5)

To assess how cognition and affect are related, both phenotypically and genetically on the brain level, the correlation of affective scores and cortical thickness was analyzed in post-hoc regions of interest (ROIs). These ROIs were obtained in the previous steps: the phenotypic correlation of the three cognitive scores with cortical thickness were assessed with spearman correlation, and the genetic correlation analysis were performed through a bivariate polygenetic analysis, both controlled for multiple comparisons using Benjamini-Hochberg FDR (Benjamini & Hochberg, 1995). The parcels surviving the FDR correction were used as ROIs (for parcels within the ROIs, see the table indicated). Within these three ROIs for the phenotypic analysis (total (Table 2), fluid (Table 4), crystallized (Table 5) cognition) and two ROIs for the genetic analysis (total (Table 3), and fluid (Table 6) cognition) all three affective scores (emotion processing, positive (PA), and negative affect (NA)) were analyzed. The ROIs are visualized in Figure 4 (on page 38) and Figure 5 (on page 40) as white areas with black borders.

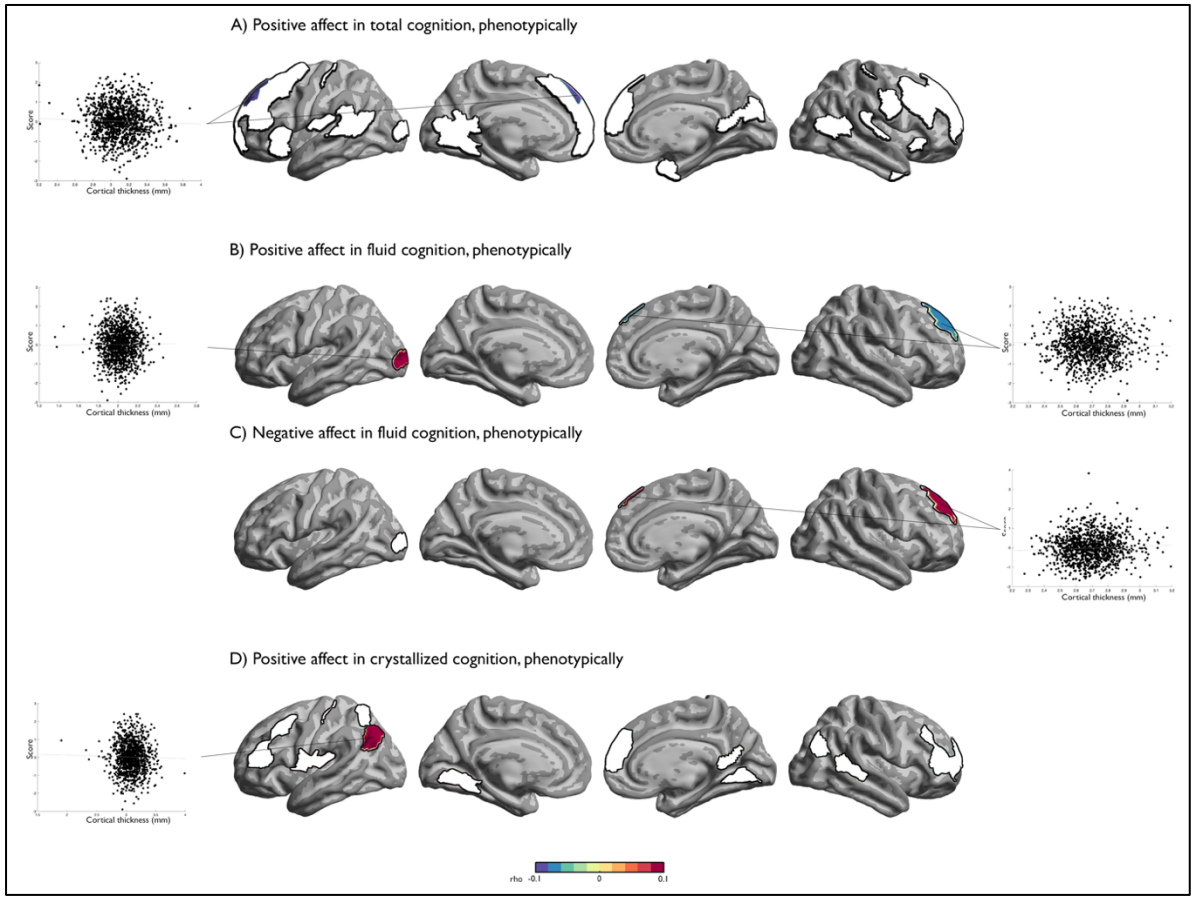

Figure 4) Behavioral relation of cognition and affect, and cortical thickness. Black-bordered, white surface: ROIs from cognitive phenotypic analyses. A) Phenotypic correlation of PA and cortical thickness in ROIs of total cognition. Negative correlation with left superior frontal gyrus, no overlap is seen in NA or emotion processing, and total cognition. PA (B) and NA (C) show overlap with fluid cognition in right superior frontal gyrus, PA additionally in occipital pole (B). PA is phenotypically positively correlated with left cuneus in the ROIs of crystallized cognition (D). Scatter plots of affective score and cortical thickness (in mm) in indicated region.

The phenotypic overlap of cortical thickness and affect, within the ROIs of total cognition is restricted to positive affect and one parcel in the left superior frontal gyrus ($r = -0.11$, $p < 0.001$, see Figure 4A and Table 7). In the ROIs of fluid cognition, both positive and negative affect show convergence. Positive affect has a negative correlation in the superior frontal gyrus ($r = -0.08$, $p < 0.05$) and a positive correlation in the occipital pole ($r = 0.09$, $p < 0.005$; see Figure 4B and Table 7), both correlations go into the same directions as in fluid cognition (to compare see Figure 3A). Negative affect, on the contrary, shows in the same parcel in the superior frontal gyrus a positive correlation ($r = 0.09$, $p < 0.005$, see Figure 4C and Table 7).

In the ROIs of crystallized cognition, just like with total cognition, only positive affect shows overlap in cortical thickness and cognition score. Positive affect is positively correlated with cortical thickness in the angular gyrus ($r = 0.10$, $p < 0.005$, Figure 4D and Table 7). Hence, the phenotypic overlap of cortical thickness and cognition and affect is restricted to very few regions, with emotion processing not showing any overlap.

Table 7) Phenotypic correlations of affect and cortical thickness in ROIs of cognition in significant parcels

		LH			*RH*		
Analysis	*Brain region*	*Parcel no.*	*p*	*rho*	*Parcel no.*	*p*	*rho*
Total							
PA	SFG	92	0.0001	-0.1143			
Fluid							
PA	SFG				196	0.0114	-0.0760
	Occipital pole	10	0.0026	0.0903			
NA	SFG				196	0.0025	0.0906
Crys							
PA	Angular g.	83	0.0007	0.1015			

LH: left hemisphere, RH: right hemisphere; PA: Positive affect; NA: Negative affect; SFG: superior frontal gyrus; g: gyrus.

The final step was to assess, if there is any overlap of shared genetic variance in the cortical thickness and affective scores in the above mentioned ROIs. As mentioned earlier, the genetic ROIs are more focused, than the phenotypic (see results “Overall cognition and the brain”, p. 29). Further, there were only significant regions in the genetic correlation of total and fluid correlation (compare results “Subcomponents of cognition”, p. 33). Hence, the regions showing overlap in this regard are few: in positive affect the superior frontal gyrus is in the ROIs of both total (see Figure 5A, on page 40) and fluid cognition (see Supplementary Figure 8) negatively correlated ($r = -0.40$, $p < 0.005$, see Table 8), again going into the same directions as in the cognitive scores (compare Figure 2B andFigure 3B). The same parcel is also engaged in negative affect, in ROIs of total (see Figure 5B) and fluid cognition: there is a positive correlation of cortical thickness and the superior frontal gyrus ($r = 0.29$, $p < 0.01$, see Table 8). Just like in the phenotypic correlation, while there

is no overlap with cognition and emotion processing, the genetic overlap of cognition and affect is limited to one parcel in the superior frontal gyrus.

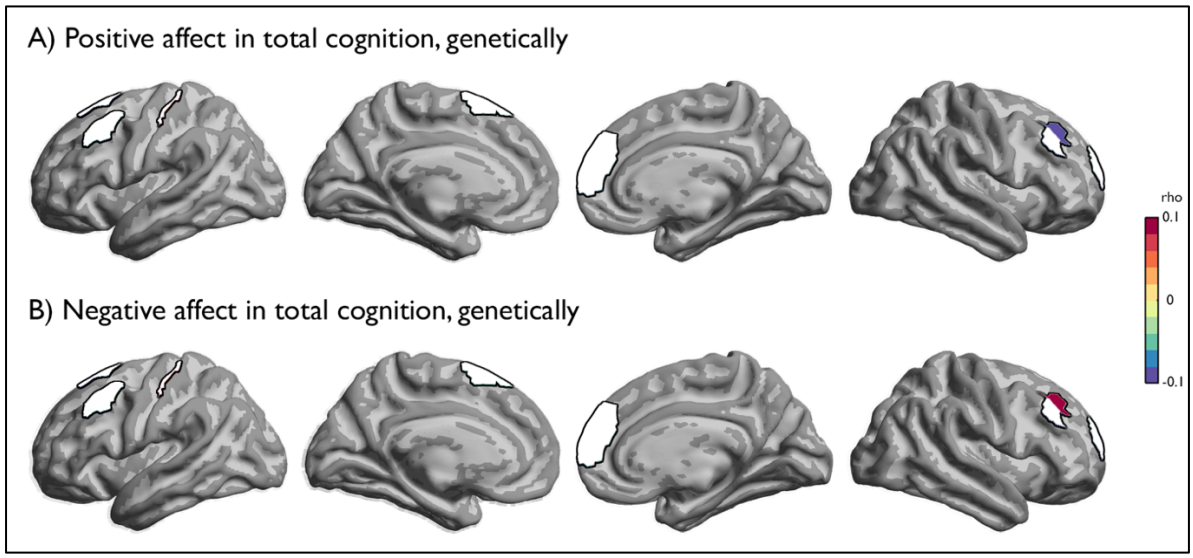

Figure 5) Genetic relation of cognition and affect, and cortical thickness. Black-bordered, white surface: ROIs from cognitive genetic analyses. Genetic correlation of PA (A) and NA (B) and cortical thickness in ROIs of total cognition. A) PA is negatively correlated with middle frontal gyrus (A), negative affect shows positive correlation in the same region (B).

Table 8) Genetic correlations of affect in ROIs of total and fluid cognition and cortical thickness in significant parcels

		RH		
Analysis	*Brain region*	*Parcel no.*	*p*	*rho*
Total				
PA	SFG	197	0.0005	-0.3995
NA	SFG	197	0.0068	0.2851
Fluid				
PA	SFG	197	0.0005	-0.3995
NA	SFG	197	0.0068	0.2851

LH: left hemisphere, RH: right hemisphere; PA: Positive affect; NA: Negative affect; SFG: superior frontal gyrus.

Discussion

The aim of this study was to assess whether cognitive and affective behavioral variation is dissociable at the neuroanatomic and genetic level. First, the relation of cognition and affect was assessed on the behavioral level by investigating the phenotypic correlation, heritability as well as genetic correlation. Then, the relationship between cognitive function and affective behavior, and macroscale grey matter anatomy was assessed to investigate which brain regions play a role behaviorally and which regions are co-heritable. Lastly, the relation of cortical thickness and co-heritability affective behavior was assessed in relation to cortical thickness and co-heritability of cognitive abilities. To understand the influence of genes on both cognition and affect is important to broaden and refine the knowledge about influences on the balanced cognition-emotion-interaction in the brain, especially in regard of mental health diseases.

Relation of cognition and affect - behaviorally

Boldly, it can be stated, that on the behavioral level cognition and affect do not relate (Figure 1A, below diagonal). However, emotion processing builds a bridge between cognition and affect, where a weak emotion processing correlates negatively with high cognition scores (total and fluid cognition). This may indicate a strong cognitive influence in emotion processing. Though, since the correct response time of emotion recognition was used as a proxy for emotion processing (see "Methods - Behavioral data", on page 23), the correlation between it and total and fluid cognition may indicate that the correct response time of emotion recognition is just another aspect of fluid cognition. Fluid cognition contains aspects of executive function – cognitive flexibility (dimensional change card sorting test), and inhibition and attention (Flanker test), and processing speed (pattern comparison; see Table 1 for comparison). These three out of five tests that add up to fluid cognition include the reaction time into their total scores (Carlozzi *et al.*, 2013; Zelazo *et al.*, 2013). Hence, the assumed proxy of emotion processing by correct response time of emotion recognition, may have been a stronger proxy for fluid cognition. The correct responses of emotion recognition were not used in this study, because the estimated reliability of this test (measured by Cronbach's alpha) was too weak. One conclusion from these findings is, that there is a need for a better measurement of emotion

processing or emotion recognition needed to verify if emotion processing builds the bridge between the otherwise behaviorally very separated cognition and affect.

As stated above, based on the Bonferroni corrected behavioral results, cognition and affect are distinct. Though, on an explorative level ($p < 0.05$, see Supplementary Figure 1) high cognition scores correlate positively with positive affect. What is striking, that except from crystallized cognition, all cognitive measures (total, fluid; emotion processing in retrospect) correlate positively with positive affect. Crystallized cognition is the odd one out, it does not correlate, neither significantly, nor exploratively with other scores than cognition. This may be due to the consistency, that is a hallmark of crystallized cognition. It neither varies greatly throughout lifespan (Craik & Bialystok, 2006; Horn & Cattell, 1967), nor daily condition (Brown *et al.*, 2011; Grossman *et al.*, 1994; Ismail & El-Naggar, 1981). Crystallized cognition was further shown to be more heritable than fluid cognition in this (see Figure 1B) as well as in a large meta-analysis (Kan *et al.*, 2013), which might emphasize the stability of crystallized cognition. This leads to conclude, that the cognition scores used in this study are consistent and in line with previous findings, and therefore valid measures.

The findings of the co-heritability analysis (see Figure 1A, above diagonal), to assess weather phenotypes are driven by the same genetic influence, mirror the behavioral correlations (Figure 1A, below diagonal). These results underline the behavioral separation of cognition and affect also on a genetic level, while assuring a strong genetic link within the two categories.

The heritability analysis in this study (Figure 1B) revealed a strong heritability for the cognitive scores. As mentioned above, the genetic basis of cognition is subject of interest for a long time already, going back to the 1860s (Galton, 1869). Hence, the findings in this regard are manifold. Longitudinal twin studies show, that the heritability of cognitive abilities increase with age. In young children between 20-30 % of the variance is explained by heritability, whereas in adolescence – depending on measurement and cohort- 70 to 80 % is estimated to account for by heritability (Bartels *et al.*, 2002; van Soelen *et al.*, 2011; Wainwright *et al.*, 2005). The sample of this project comprises young adolescents, hence the findings of 51 % of heritability of total cognition is partly lower, though still in line with previous findings. What is striking, that crystallized cognition is by far more heritable (75 %) in this sample than fluid cognition (35 %). Though the scientific community agreed by logic (Cattell, 1980; Kan *et al.*, 2013) for a long time, that

the reverse should be the case (van Soelen *et al.*, 2011). Nevertheless, the findings here are in line with a recent large meta-analysis by Kan *et al.* from 2013 (Kan *et al.*, 2013).

Since intelligence is a quite delineated concept with accepted measurement methods, conclusions drawn from it are decently robust. A different picture is drawn regarding affect. Affect is both not as tangible and stable and hence not as straightforward to measure, impeding large-scale results (Cloninger & Garcia, 2015). A thorough twin study by Baker *et al.* revealed a strong narrow-sense heritability h^2 for negative affect, but none for positive affect (Baker *et al.*, 1992). Another twin study by Lykken and Tellegen found a broad-sense heritability H^2 of 44 - 52 % for well-being (Lykken & Tellegen, 1996). While a recent study conducted in a similar fashion as this present study assessed no narrow-sense heritability h^2 for positive affect, but 38 % of non-additive effect (Stubbe *et al.*, 2005).

Narrow-sense heritability h^2 is explained by the additive genetic influence, hence the effects of multiple individual loci that combine additively. Broad-sense heritability H^2 comprises h^2 and non-additive genetic influence, i.e. the interaction between alleles (Nes & Roysamb, 2015; Rettew *et al.*, 2008). Based on this assessment about the ambiguous current findings on heritability of affect, it is clear to say that the research on both affect and heritability needs clearer measurement approaches and a gold-standard to allow comparation.

Cognition – in brain morphometry

To understand the overlap of cognition and affect, it is first needed to understand the separate phenomenon. In this subsection, the following questions will be addressed: Does cognitive ability covary with regional macrostructural variation? Which brain regions can be associated with cognitive function? Is this association genetically driven? The next subsection will address these questions regarding affect.

Does cognitive ability covary with regional macrostructural variation?

Despite cognition being complex and multifaceted, research has boiled down some specific brain regions for cognition. Lesion patients, fMRI, and PET studies in healthy and in diseased individuals revealed prefrontal and parietal regions as hubs for cognition

through activation. Tasks specifically demanding fluid cognition additionally engage occipital regions and in crystallized cognition temporal regions are further associated (Cabeza & Nyberg, 2000). A correlation of cognition and cortical thickness in the mentioned regions is seen, though often with contradictory outcomes. Some studies found a positive correlation of cortical thickness and cognition (Karama *et al.*, 2009a; Narr *et al.*, 2006; Shaw *et al.*, 2006) while others found a negative correlation (Goh *et al.*, 2011; Salat *et al.*, 2002; Sowell *et al.*, 2001; Van Petten *et al.*, 2004). The differences in outcome may have several reasons. It may be due to different approaches on methods on all steps: the acquisition of MR images, the analysis of differently weighted images – T1w or T2w-, the method to distinguish grey and white matter in the image – i.e. the software-, the cohort, the age range of the participants and ultimately also the sample size plays an important role in what kind of results are emphasized as significant. Here a consensus regarding methods is needed, also to improve comparability and enable large meta-analyses. Walhovd *et al.* for example proposed in a review about inconsistent results regarding cortical thickness the application of a T1w/T2w ratio for the assessment of the grey/white matter boundary (Walhovd *et al.*, 2017), which was used in this present study according to Glasser and Van Essen (Glasser & Van Essen, 2011). Another approach may be to not investigate the grey matter cortical thickness alone, but the ratio of white matter to grey matter thickness. However, the basis of the inconsistencies in research may be of biological cause as well. Depending on what time point of the development the study is looking at, different mechanisms may influence the cortical thickness. These mechanisms are still under debate when and to what extend they occur. There is pruning of neurons or intracortical myelination advocating for a thinner cortex, but also dendritic spines, dendritic arborization and axonal sprouting arguing for thicker cortex. Vascular development may contribute to both phenomenon (Huttenlocher, 1979; Huttenlocher & Dabholkar, 1997; Walhovd *et al.*, 2017). As Goh *et al.* point out, particular studies finding a positive correlation of cortical grey matter thickness and cognitive abilities – among other methodological differences – did not control for global brain volume (Goh *et al.*, 2011). Though, global brain volume is known to be associated with cognitive abilities (Narr *et al.*, 2006). A positive correlation of cortical thickness and cognition may hence be driven by the global volume (Goh *et al.*, 2011). These inconsistencies and nescience regarding cortical thickness open a wide range of questions, that needs further investigation through manifold approaches, that will be addressed in the subchapter "Outlook".

Which brain regions can be associated with cognitive function?

The present study investigated a large sample (n = 1087) and a decently wide age range, without being too wide to confound ageing effects (range = 22-37; mean age = 28.8). Additionally, accepted (pre-) processing measures were applied (see "Methods", on page 21f). Therefore, the results from this study have some validity within the spectrum it investigated. The results of the cognitive phenotypes to the cortical thickness in this study revealed a correlation of a thinner prefrontal cortex to higher cognition scores (see Figure 2, on page 31). As mentioned above, this finding 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.*, 2009a; Narr *et al.*, 2006). Despite all this, the authors of the above mentioned studies come to a rough congruency involving 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).

The prefrontal cortex is important for the temporal integration, (Courtney *et al.*, 1998; Miller & Cohen, 2001) working memory (Bechara *et al.*, 1998; Brzezicka *et al.*, 2019), preparatory set of action, and inhibitory control (Fuster, 2002). These sub-domains can be grouped into fluid intelligence, and hence it was in this study (see Table 1). Therefore, a strong correlation of the cortical thickness within the prefrontal cortex was expected rather in fluid, than in crystallized cognition. However, this study found a significant correlation of cortical thickness and fluid cognition only in one parcel of the right superior temporal gyrus and in the occipital pole. In contrast, in crystallized cognition, the prefrontal cortex bilaterally as well as the parietal and temporal lobe showed significant correlation. This surprising result may have different underlying reasons: One study revealed, that crystallized cognition showed higher correlation with structure than with function and the opposite emerged for fluid cognition (Choi *et al.*, 2008), implicating a dissociable pattern within the brain for fluid and crystallized cognition. Hence, the behavioral measure of the cognitive subcomponents may capture aspects of fluid and crystallized cognition, that are not embedded in cortical thickness. Additionally, it is noteworthy, that the construct of fluid cognition in this study is made of more compounds than the construct of crystallized cognition. This may lead to "blurring" in the results of fluid cognition. Another possibility of this finding may also lay within the characteristic of this sample: the analyzed young adults are overly educated (mean total cognition: 121

points, fluid: 115, crystallized: 117). Above average cognition may lead to more regions being involved in the process, rather than shaping and thickening one particular region. The detection of such particular region would be impeded in an above average intelligent sample of this sample size. Therefore, in order to validate these findings, this analysis would need to be repeated in another sample, preferably with average cognition score, to resemble the average population. Overall, based on this analysis it is clear to say that fluid and crystallized cognition are separable on the brain level and together illustrate the complexity of cognition, though, the common ground builds the prefrontal cortex, which is known to be involved in cognitive tasks.

Is the relation of cognition and brain morphometry genetically driven?

There is a strong genetic influence on the brain (Peper *et al.*, 2007; Thompson *et al.*, 2001), as well as on the cortical thickness (Brouwer *et al.*, 2014; Panizzon *et al.*, 2009). Also, cognition is behaviorally highly heritable (Devlin *et al.*, 1997; Kan *et al.*, 2013), which was also shown in this sample (see Figure 1B). The driving question in this study was, to what extend are the phenotypic correlations seen, driven by the same genetic influence?

In total cognition the coheritability of cognition and cortical thickness is expressed in bilateral prefrontal regions, as well as in the left postcentral gyrus (see Figure 2B). In the subcomponents of cognition a similarly diverse picture as in the phenotypic correlation is drawn: in fluid cognition only prefrontal regions are coheritable with cortical thickness, while in crystallized cognition, no region reaches significance. Though, on an exploratory level ($p < 0.005$) the balance is shifted towards the temporal lobe (see Figure 3D). A striking aspect is that there are some parcels in fluid cognition indicating to be genetically driven, without phenotypically being associated with cortical thickness (compare Figure 3A and B). Genetic correlations, that are not observed in phenotypic correlations, indicate, that the environmental influence is strongly going into the opposite direction. This could be actual environmental influence (e.g. due to drug abuse; Momenan *et al.*, 2012) or noise going into the opposite direction as the genetic correlation. Nevertheless, the strong genetic influence onto the prefrontal cortex and specifically the superior and middle frontal gyrus (i.e. dorsolateral prefrontal cortex; dlPFC; Sanches *et al.*, 2009) is striking. Especially this region was found in lesion and fMRT, but also in intracranial electroencephalography (iEEG) studies to be associated with cognitive control (Miller &

Cohen, 2001), working memory (lesion patients: Bechara *et al.*, 1998; iEEG: Brzezicka *et al.*, 2019; fMRI: Courtney *et al.*, 1998) and value-based decision-making (Morris *et al.*, 2014). This present study therefore not only proves the importance of this region in cognition, but also the evidence, that within this sample the cortical thickness of the prefrontal cortex and the left postcentral gyrus is influenced by the same set of genes, that also influence cognition. Which is also in line with previous studies (Brouwer *et al.*, 2014; Toga & Thompson, 2005).

Affect – in brain morphometry

In the previous subchapter, the relation of cognition and cortical thickness and the genetic influence was analyzed. Now, the question was to understand the relation of cognition and affect. Therefore, the following questions will be addressed here: Does affective behavior covary with regional macrostructural variation? Which brain regions can be associated with affective behavior? Is this association genetically driven? Do affect and cognition overlap in brain morphometry? Is this relation of affect and cortical thickness genetically driven?

Does affective behavior covary with regional macrostructural variation?

An exploratory analysis of the correlation of positive and negative affect and cortical thickness – as a tool of brain morphometry- revealed no significant regions. Therefore, the short answer to this question is that affect, in contrast to cognition, does not show significant regions measured with cortical thickness. A possibility would be to investigate subcortical brain regions, though this was not within the scope of this study. The interest of this study was however, to understand the relation between affect and cognition in cortical thickness, as the overlap of cognition and affect was also shown in previous studies to be in the cortex (Langner et al., 2018). Therefore, the ROIs of the cognitive scores were used to investigate a possible relation.

Relation of cognition and affect – in brain morphometry

Do affective behavior and cognitive abilities overlap in brain morphometry? Based on the results, there is only a weak, but a quite coherent overlap of cognition and affect in cortical

thickness. Positive affect shows overlap within regions of all cognitive domains; the correlations with the cortical thickness always go into the same direction as within cognitive scores. Negative affect shows overlap only within regions of fluid cognition. The correlation of cortical thickness goes into the opposite direction as within fluid cognition (Figure 4). The overlap of cognition and affect in the brain is mirrored by the phenotypic correlation amongst them (see Supplementary Figure 1). This, and further the observation, that positive affect shows significant correlation in prefrontal cortex, parietal and occipital lobe opens the stage for speculation. It may be that positive affect is closer connected to cognition than negative affect. The scores of positive affect include "life satisfaction" and "meaning and purpose" which may involve aspects of conscious planning and control over an individual's life (see also Supplementary Figure 5). While negative affect includes "anger", "fear", "sadness", all of which includes helplessness and loss of control. Consequently, a stronger relation between cognition and positive affect may be explained by the psychological basis of cognition and the different affective characteristics. Importantly, the negative correlation of cortical thickness and positive affect in the dlPFC, and the reverse correlation of negative affect, was seen analogously in an fMRI study investigating positive and negative emotion reappraisal (Silvers, Wager, *et al.*, 2015), underlining the prefrontal cortex as an important hub for cognition and affect integration.

Is this relation of affect and cortical thickness genetically driven?

The neurogenetic approach on cognition and affect is only starting to evolve in a more systematic manner. Scult and Hariri have reviewed specific genes, that are associated with both cognitive and affective phenotypes (Scult & Hariri, 2018). They mention a specific gene known to influence the brain structure and cognitive function, that is further suspected to be involved in mood disorders (Chang *et al.*, 2018), as well as a polymorphism leading to depressive symptoms and altered attention and working memory (Scult & Hariri, 2018); amongst other examples for the entangled connection between cognition and affect on the genetic level.

An overlap of cognition and affect was seen in this regard in the superior frontal gyrus (i.e. dlPFC, Sanches et al., 2009), but in no other region within the ROIs of cognition (see Figure 5). Once more it was shown, that within cortical thickness the relation between

cognition and affect is restricted, but existent. Especially the dlPFC is intriguing, since it was shown to be involved in value-based decision-making (Morris *et al.*, 2014), attentional modulation (Grimm *et al.*, 2008; Staudinger *et al.*, 2011) as well as in (positive and negative) emotional self-regulation and modulation (Beauregard *et al.*, 2001; Lévesque *et al.*, 2003; Silvers, Weber, *et al.*, 2015). Hence, the cortical thickness of the dlPFC was shown to share variance with both cognition and emotion and vice versa. In both conditions, this correlation is genetically driven: the cortical thickness of the superior frontal gyrus is influenced by the same set of genes, that also influence affect. The variance within the superior frontal gyrus is also driven by the genetic influence of total cognition. A question remains to investigate which amount of variance of the cortical thickness is shared by affect and cognition.

Limitations

Despite the straightforward and congruent results this study yielded, some limitations have to be addressed. As mentioned above, the measurement techniques offer a spectrum of possible parameters to adjust and refine, which is a research topic of its own. This study therefore aimed to apply state-of-the-art techniques and high sample size, which also leads to concessions in e.g. behavioral data acquisition. Even though the self-report used for positive and negative affect was verified (Pilkonis *et al.*, 2013; Salsman *et al.*, 2013, 2014), the somewhat inconsistent findings, especially shown by heritability, lead to conclude, that this measure is not robust enough and would need refinement. This applies even more to the emotion recognition task used. Accepted, verified (R. C. Gur *et al.*, 2010, 2002) and used in many other studies, the estimated reliability of this test was too weak, even within this large sample, to be properly used.

The HCP data set chosen for this study offers a decently big sample size. Though, in regard to the number of twins within the sample and due to the complex behavioral traits assessed, a significantly larger sample size may have drawn a more precise picture regarding brain structure and genetic influence. Kharabian Masouleh *et al.* proved 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). Therefore, the association of complex behaviors to brain anatomy proves a challenge. Moreover, the cortical thickness is a rigid value to associate with

something as fluctuating as affect. But cortical thickness on the other hand is very heritable (Brouwer *et al.*, 2014; Panizzon *et al.*, 2009; Toga & Thompson, 2005), as is emotion (Baker *et al.*, 1992; Bruell, 1970; Chang *et al.*, 2018; Cloninger & Garcia, 2015; Stubbe *et al.*, 2005; Zheng *et al.*, 2016). This limitation therefore also serves as the strength of this study: to combine this knowledge from previous studies into new insights of the relation of cognition and affect and its genetic influence.

In general, the aim of this study was to investigate, to what extent cognition and emotion are interrelated. As mirrored by the current notion in the scientific community (Mather & Fanselow, 2018), the results within the different aspects show a multifaceted and straightforward, but by no means definite picture.

Outlook

This study, conducted in a large healthy sample of young well-educated young adults, led to conclude, that cognition and affect are to some extent separable on both behavioral, and cortical brain morphometry. In order to prove these results in the manner Kharabian Masouleh *et al.* suggested, a verification in an independent sample would be advantageous (Kharabian Masouleh *et al.*, 2019). The UK Biobank (www.ukbiobank.ac.uk) would serve as an excellent resource here. This data set comprises around 500 000 volunteers, part of which were scanned under different MRI modalities, and provided genetic sampling. Here, also a "genome wide association study" could be performed to investigate, not only the genetic influence as done with twin analyses, but to subsequently nail down specific genes influencing both cortical thickness, cognition and affect. This could further fortify our understanding about the findings made in this present study. This data set, in combination with younger participants, could additionally help to improve our knowledge about the development of the brain, which proves to still have some important question marks. Even today, an open question is the role of cortical thickness in the different parts of the brain and whether "bigger is better" or "small but mighty" applies. Though, for example Sowell *et al.* suggested, that the appearing thinner grey matter thickness in youth might be due to an increase of cortical myelination, which shifts the MR signal (Sowell *et al.*, 2004) and then blurs the grey/white matter boundary. In addition to that, myelination is heterogenous throughout the cortex, which makes delineating the grey/white matter boundary a challenge (Glasser & Van Essen, 2011). One approach to

further broaden the knowledge might be to study more healthy people to understand what is "normal", instead of deducing from diseased patients. Additionally, the assessment of cortical thickness and behavioral phenotypes is a rather young approach (Menary *et al.*, 2013), and while the results show a general overlap regarding cognition, a meta-analysis would be needed to assess whether these overlaps remain after a systemized analysis, while also improving statistical power. This offers a great contribution to refining structurally significant regions in the brain, both phenotypically and the genetic influence thereon. Kharabian Masouleh *et al.* have elaborated the advantages of meta-analyses thoroughly also pointing out the difficulty of heterogenous behavioral measures (Kharabian Masouleh *et al.*, 2019). As also stated in the introduction and in the limitations of this study, especially the measures of the affective phenotypes need improvement. Not only to compare them amongst several studies, but also to improve the classification of affect in the first place.

In the short run, it might be worth to run these analyses without the outliers, or even just without the very high scorers in the cognitive tasks, to see how this might influence the findings, despite the use of Spearman's rank correlation performed in this study. One immediate approach to corroborate the findings of this present study could be to compare them with functional MRI (fMRI), that is also available in the HCP data set. As mentioned above, Choi and colleagues revealed, that crystallized cognition showed higher correlation with structure than with function and the opposite emerged for fluid cognition (Choi *et al.*, 2008). The analysis of fMRI and structural data together would help to capture different aspects of the relation of cognition and affect within both modalities, but also further broaden the knowledge about the genetic influence on both function and cortical thickness.

Conclusion

This study, conducted in a large healthy sample of young well-educated young adults, led to conclude, that cognition and affect are to some extent separable on both behavioral, and brain level. Nevertheless, there is an undoubted intertwined connection of both, that is seen on a trend level behaviorally, but also significantly in the brain, this connection is driven by genetic influence. As a hub of cognition-affect-conjunction the dorsolateral

prefrontal cortex emerged. This finding may help to refine our knowledge about mental health diseases.

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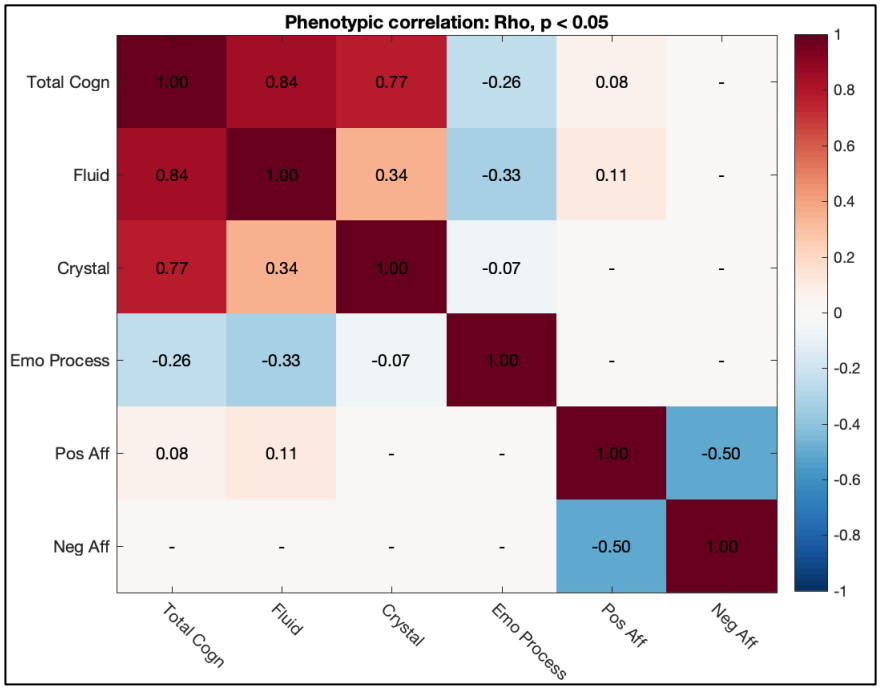
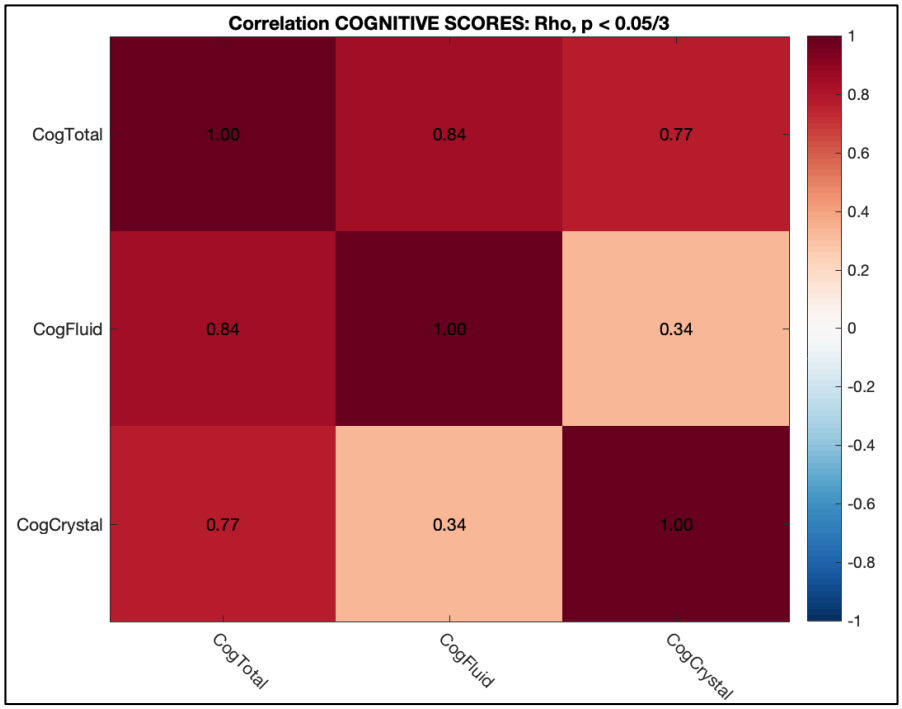
Supplementary data

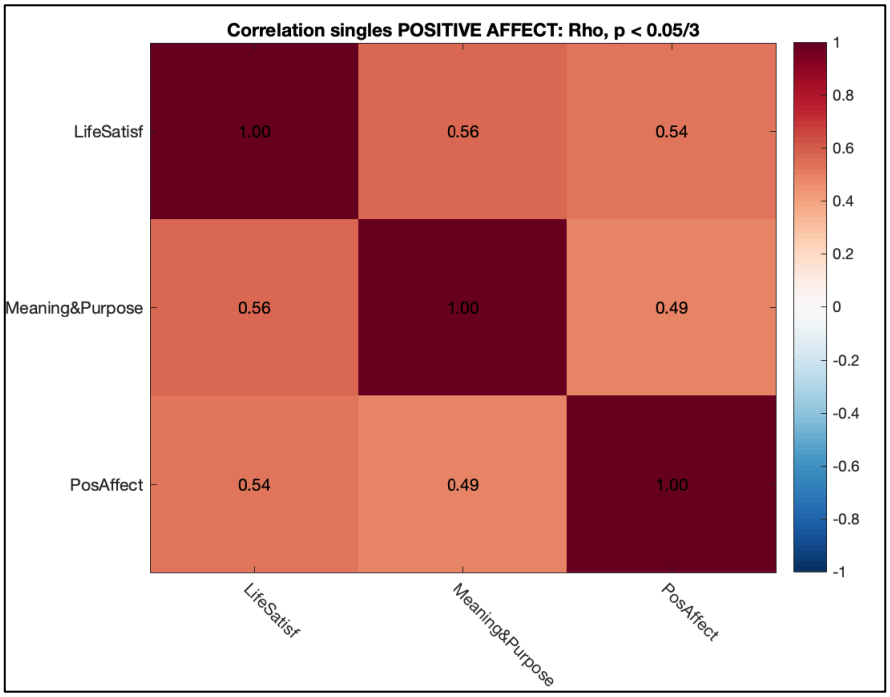
Phenotypic correlations



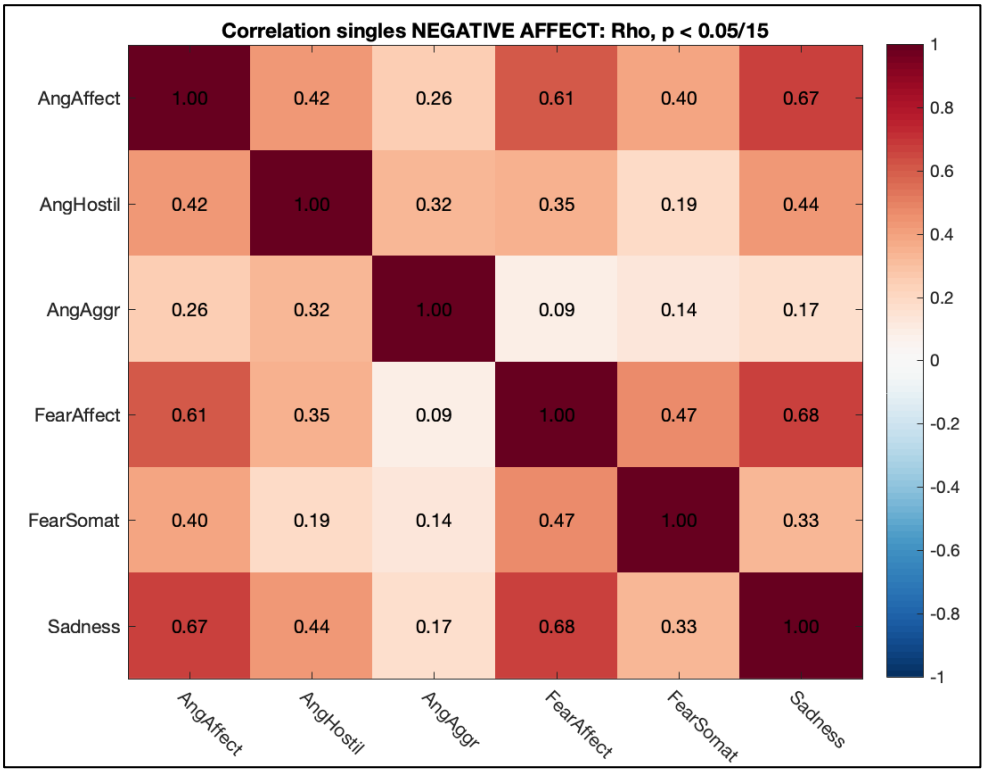
Supplementary Figure 1) Behavioral relation of cognition and affect – explorative



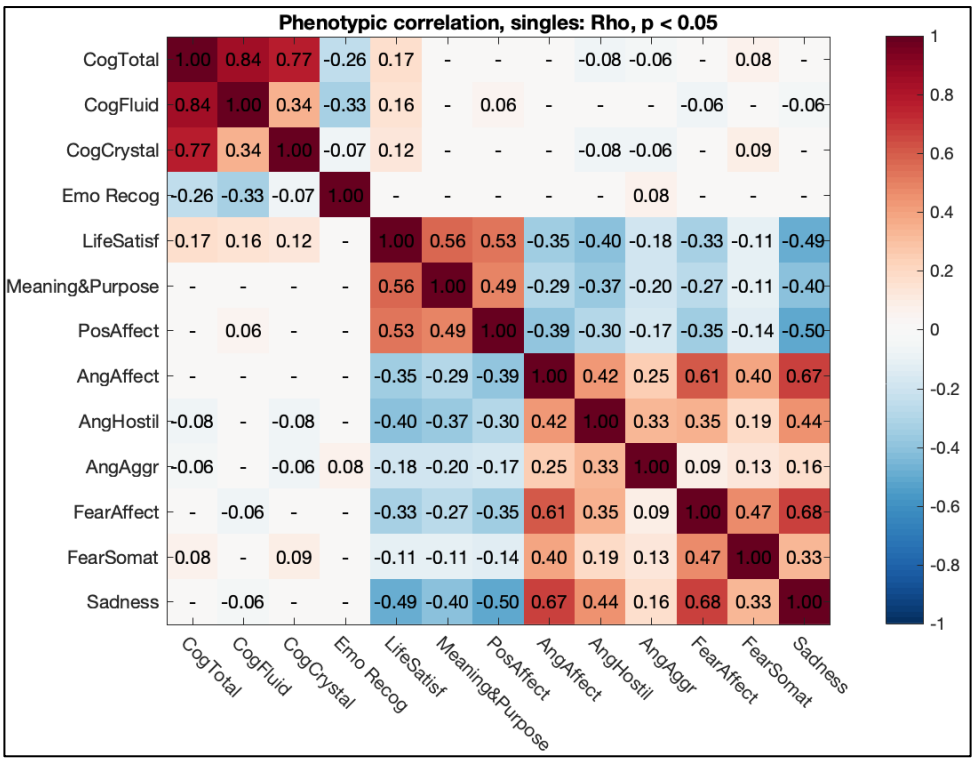
Supplementary Figure 2) Spearman correlation of single aspects of cognitive scores. Bonferroni corrected for multiple comparison.



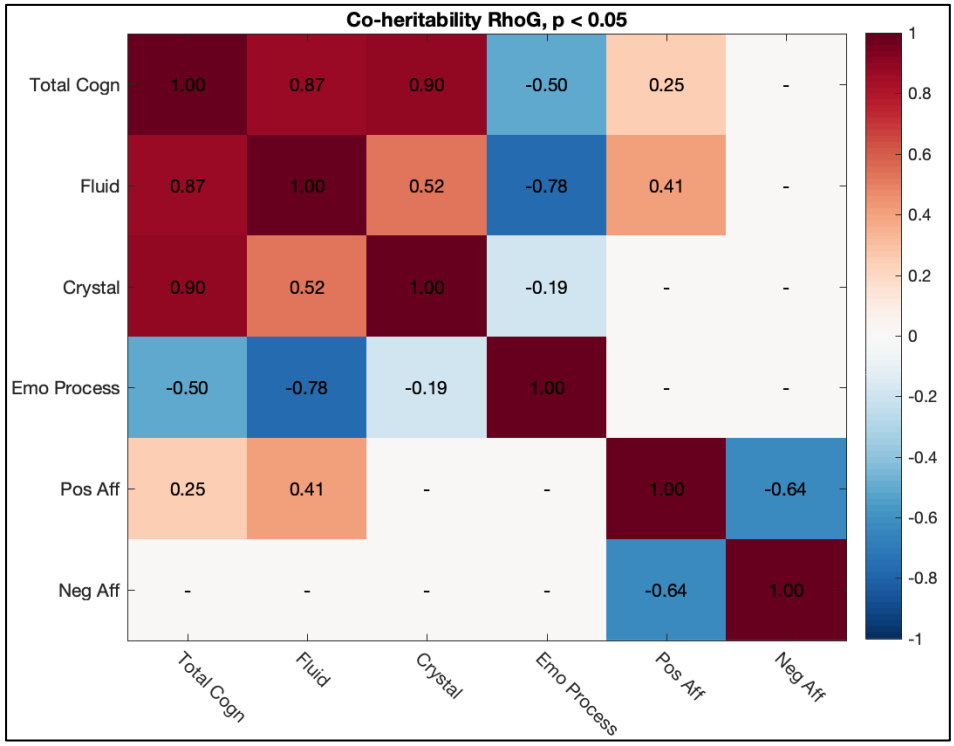
Supplementary Figure 3) Spearman correlation of single aspects of positive affect scores. Bonferroni corrected for multiple comparison.



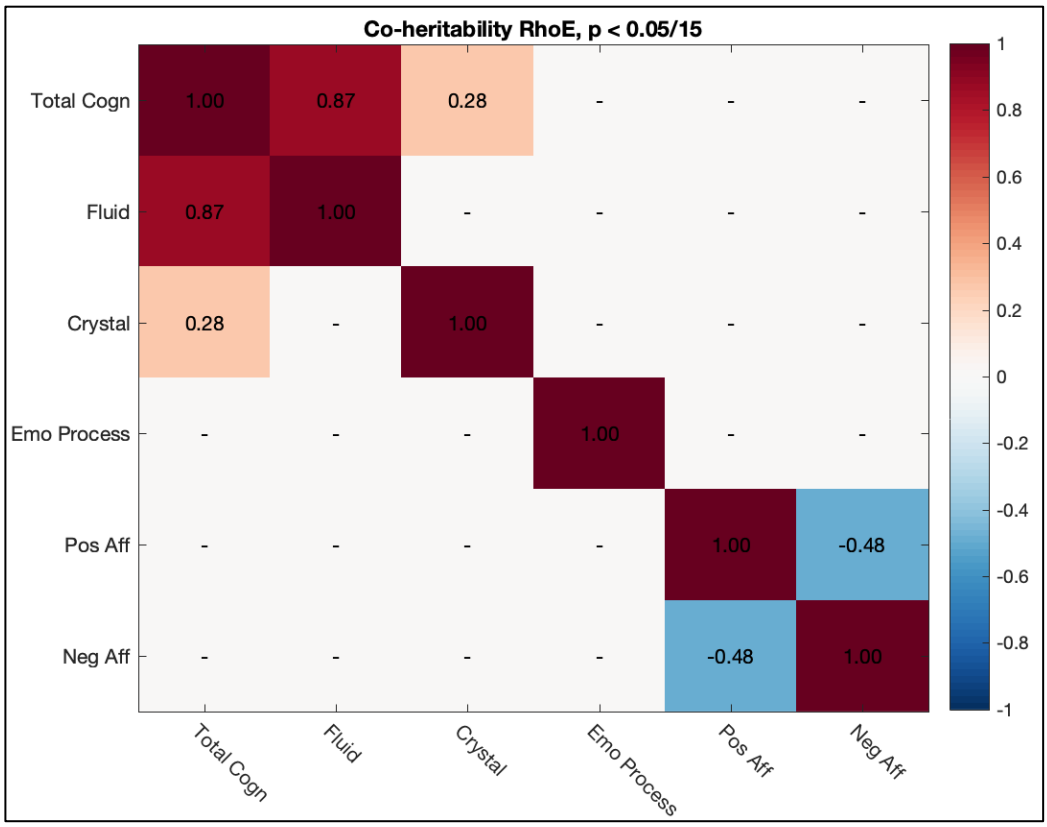
Supplementary Figure 4) Spearman correlation of single aspects of negative affect scores. Bonferroni corrected for multiple comparison.



Supplementary Figure 5) Behavioral relation of single aspects of cognition and affect - explorative

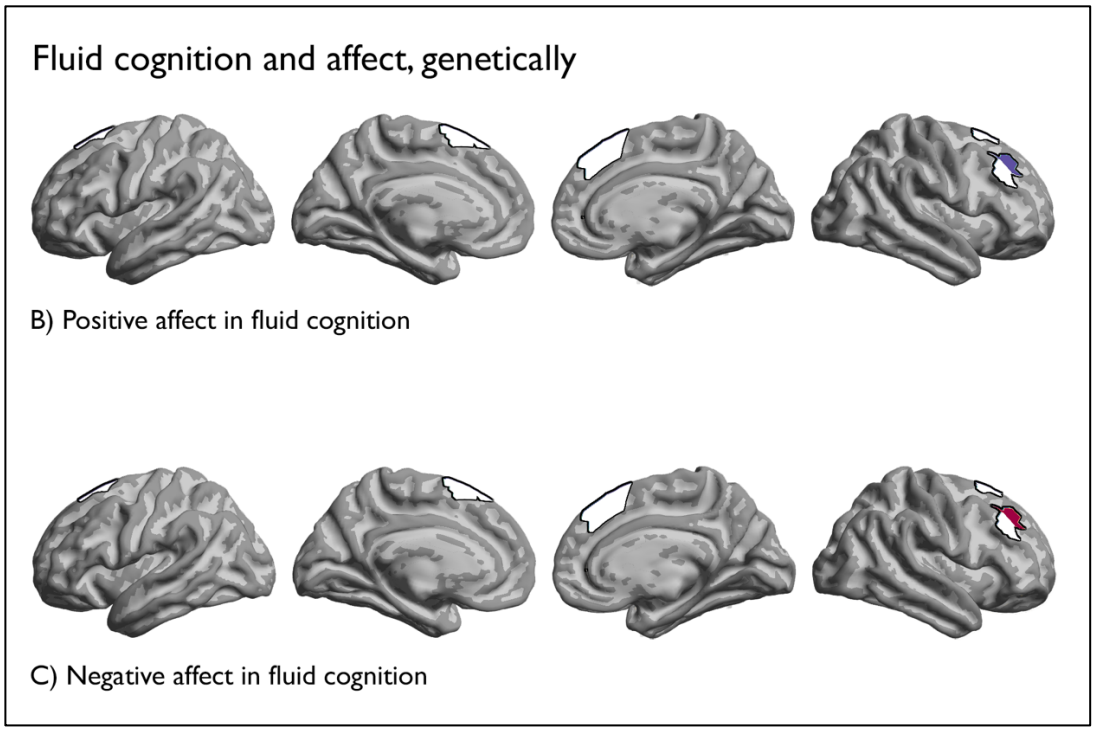


Supplementary Figure 6) Genetical relation of cognition and affect - explorative



Supplementary Figure 7) Relation of cognition and affect, environmental influence

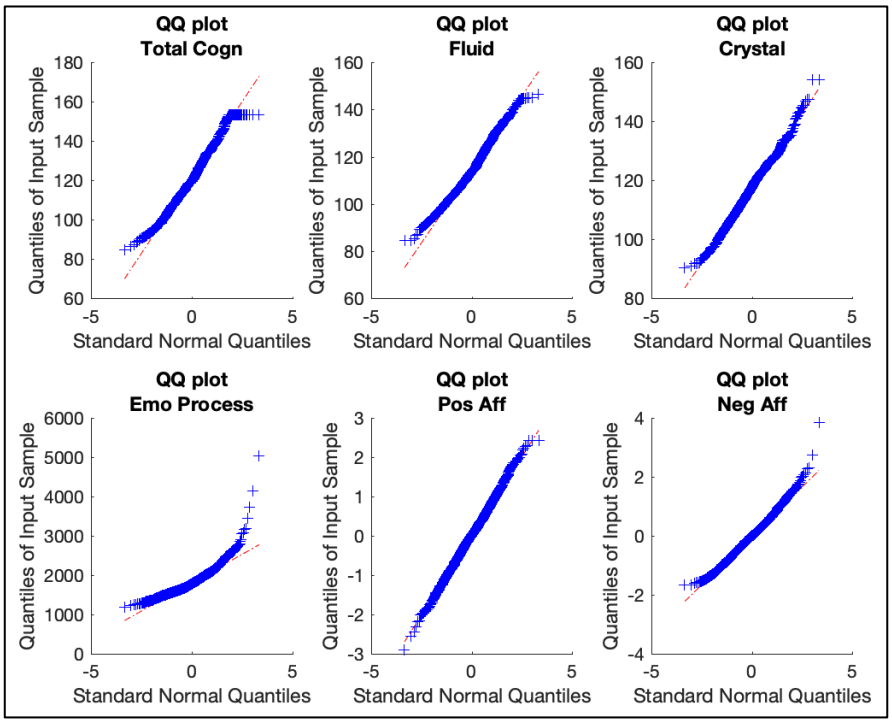
Genetic Correlation



Supplementary Figure 8) Genetic relation of fluid cognition and affect in brain morphometry

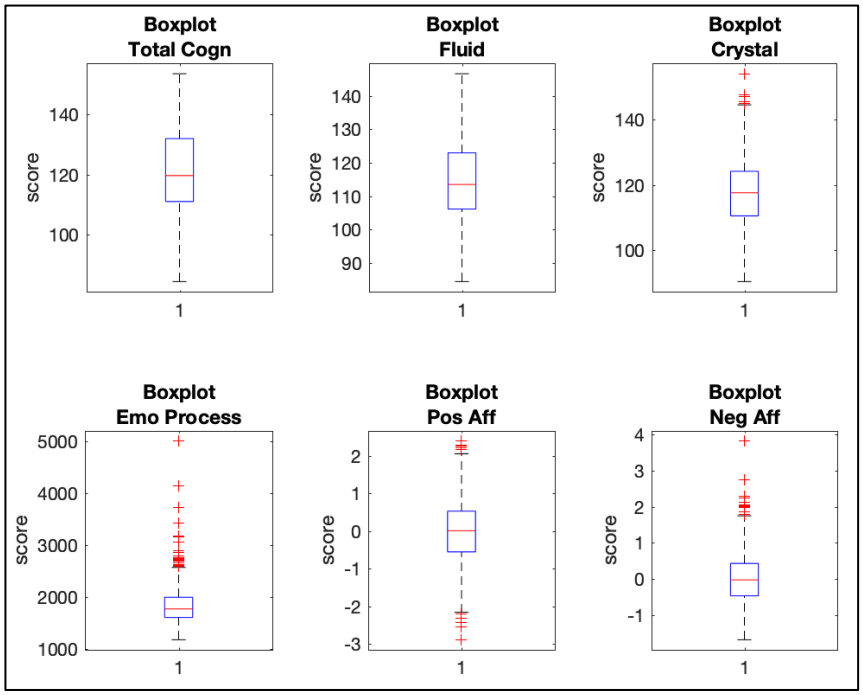
Statistics

The quantile-quantile (QQ) plots were analyzed to check the normality:



Supplementary Figure 9) QQ plots

The boxplots were analyzed to check the variance:



Supplementary Figure 10) Box plots

Descriptive summary of used data:

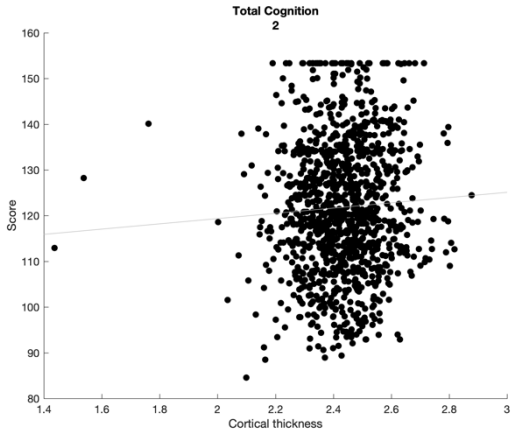
Supplementary Table 1) Descriptive summary of used data

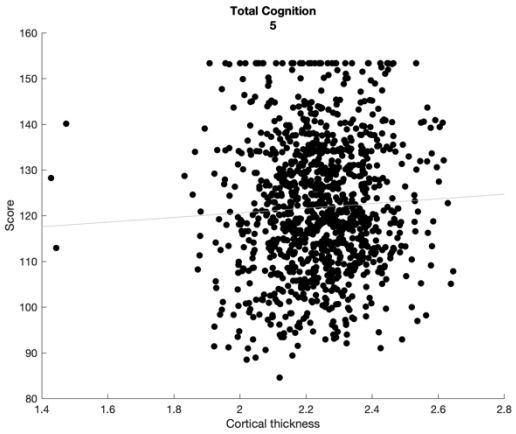
CogTotal 1206×1 double Values: Min 84.55 Median 119.66 Max 153.36 NumMissing: 19	**CogFluid:** 1206×1 double Values: Min 84.48 Median 113.53 Max 146.64 NumMissing: 18	**CogCrystal** 1206×1 double Values: Min 90.44 Median 117.57 Max 153.95 NumMissing: 10	**Emo Process:** 1206×1 double Values: Min 1180: Median 1774.2 Max 5020: NumMissing: 8
LifeSatisf_Unadj: 1206×1 double Values: Min 23.7 Median 55 Max 74.6 NumMissing: 1	**MeanPurp_Unadj:** 1206×1 double Values: Min 29.4 Median 50.6 Max 71.6 NumMissing: 1	**PosAffect_Unadj:** 1206×1 double Values: Min 21.9 Median 50.2 Max 71.6 NumMissing: 1	
AngAffect_Unadj: 1206×1 double Values: Min 28.6 Median 48.4 Max 85.4 NumMissing: 1	**AngHostil_Unadj:** 1206×1 double Values: Min 36.6 Median 51.1 Max 74 NumMissing: 1	**AngAggr_Unadj:** 1206×1 double Values: Min 43.4 Median 52.2 Max 83.1 NumMissing: 1	**FearAffect_Unadj:** 1206×1 double Values: Min 3 2.9 Median 51.2 Max 84.9 NumMissing: 1
FearSomat_Unadj: 1206×1 double Values: Min 40.1 Median 51.8 Max 87.5 NumMissing: 1	**Sadness_Unadj:** 1206×1 double Values: Min 34.2 Median 46.1 Max 78.1 NumMissing: 1		

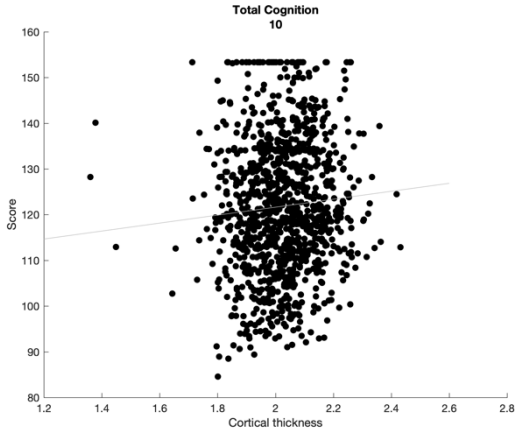
Scatter plots

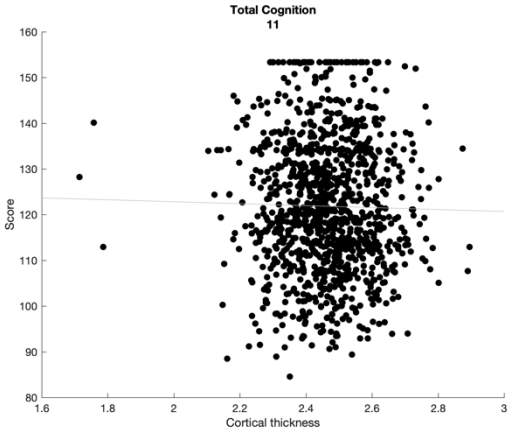
Behavioral scores and cortical thickness (in mm). Parcel number is indicated underneath the title.

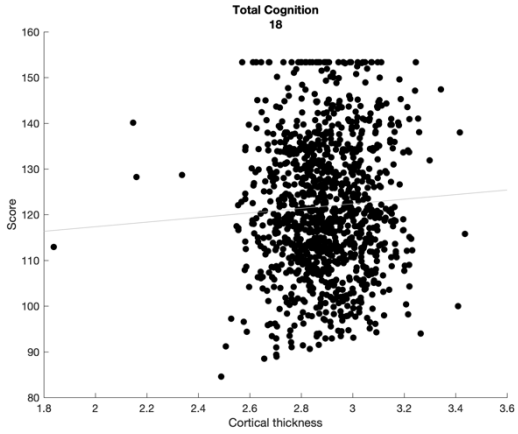
Phenotypic analysis: Spearman correlation total cognitive score and cortical thickness (in mm)


Total Cognition
2
Score
Cortical thickness


Total Cognition
5
Score
Cortical thickness


Total Cognition
10
Score
Cortical thickness


Total Cognition
11
Score
Cortical thickness


Total Cognition
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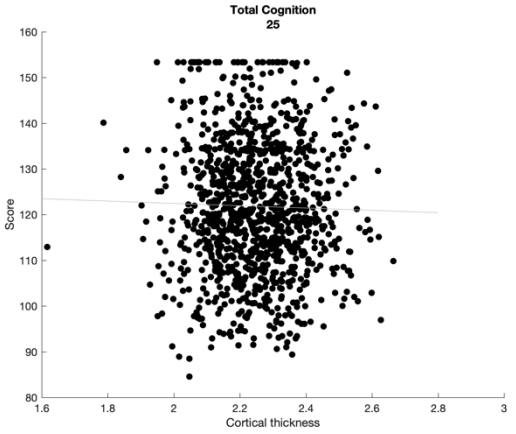
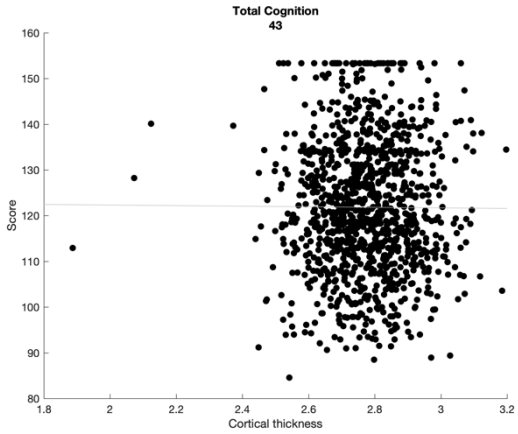
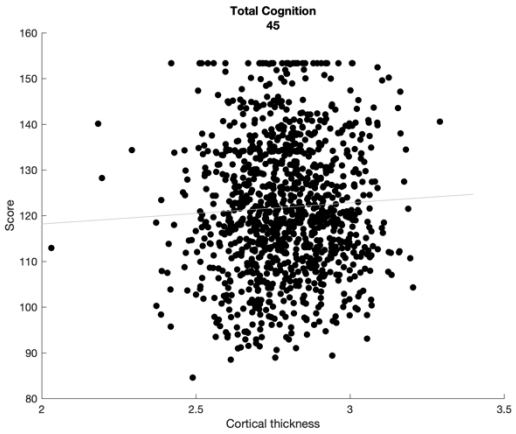
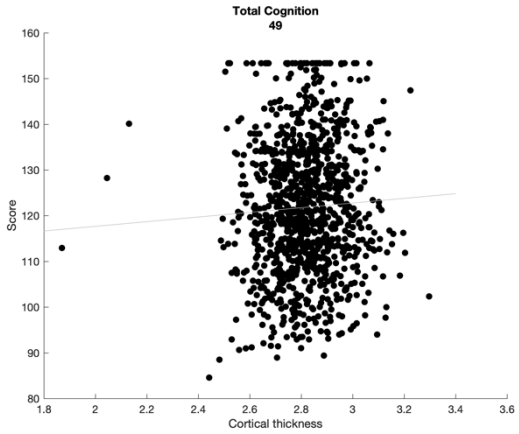
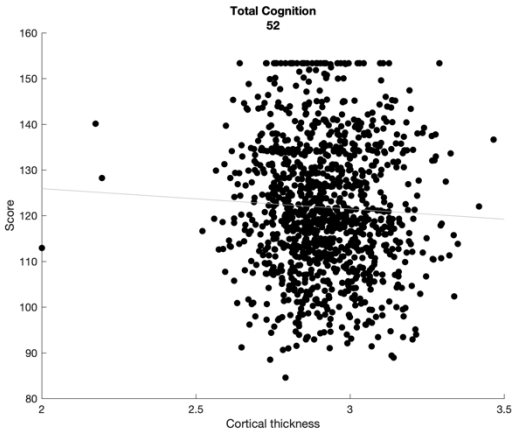
Score
Cortical thickness

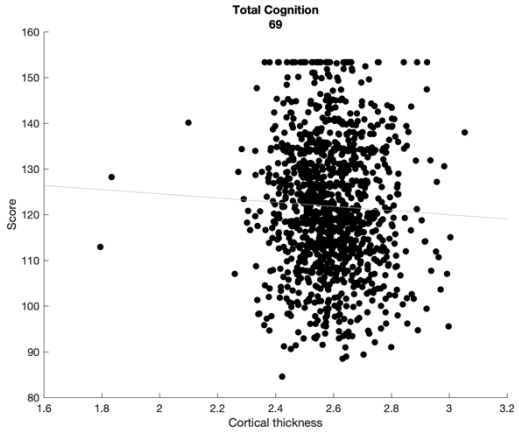

Total Cognition
25
Score
Cortical thickness

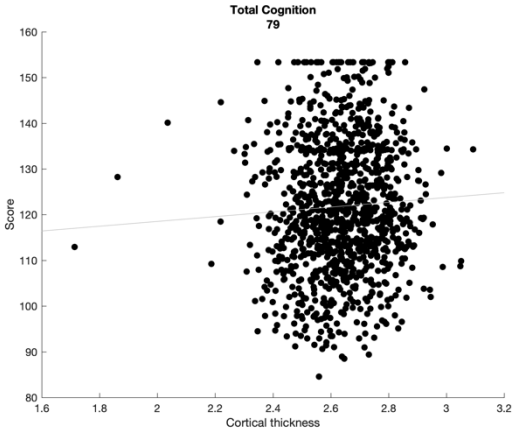

Total Cognition
43
Score
Cortical thickness

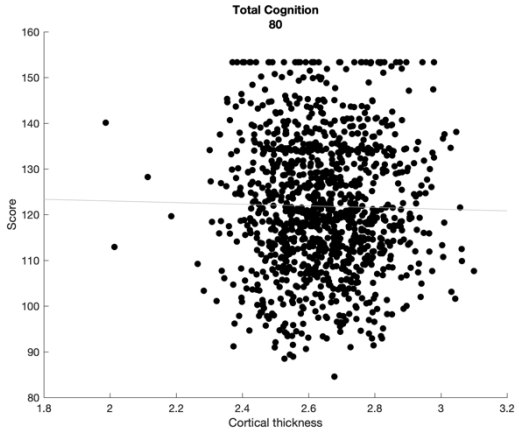

Total Cognition
45
Score
Cortical thickness

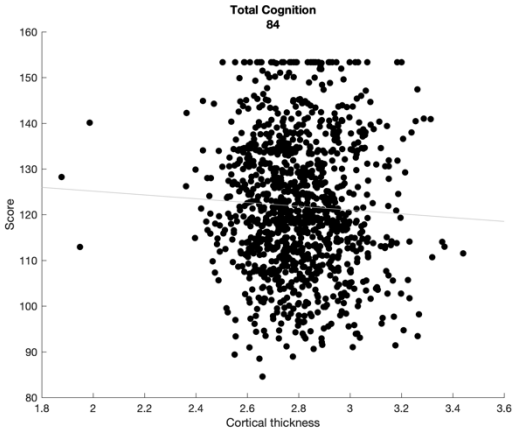

Total Cognition
49
Score
Cortical thickness

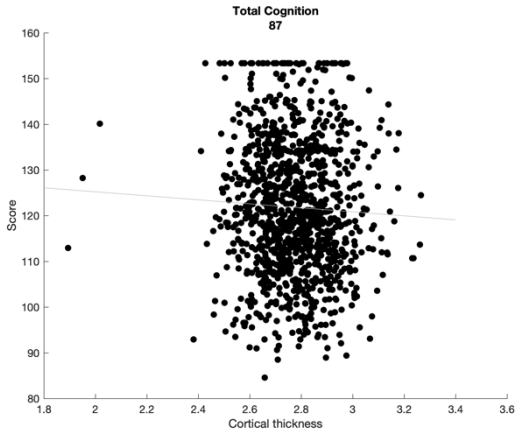

Total Cognition
52
Score
Cortical thickness

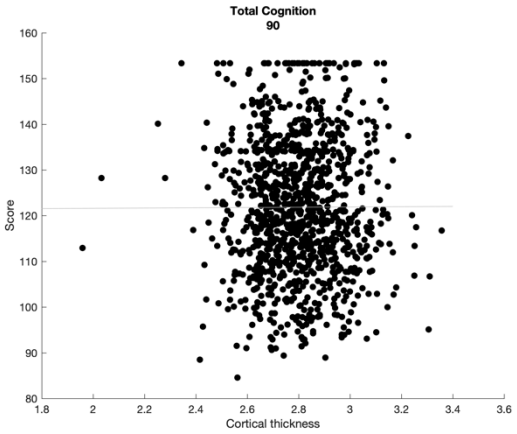

Total Cognition
69
Score
Cortical thickness

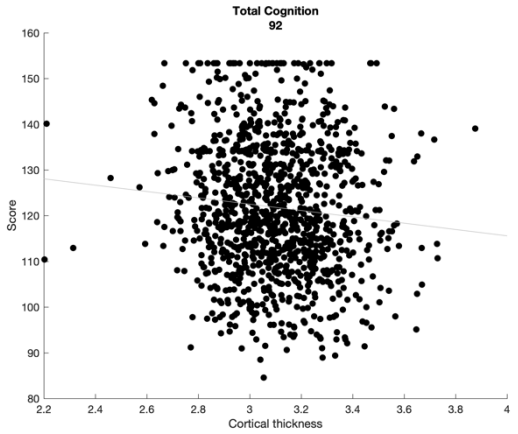

Total Cognition
79
Score
Cortical thickness

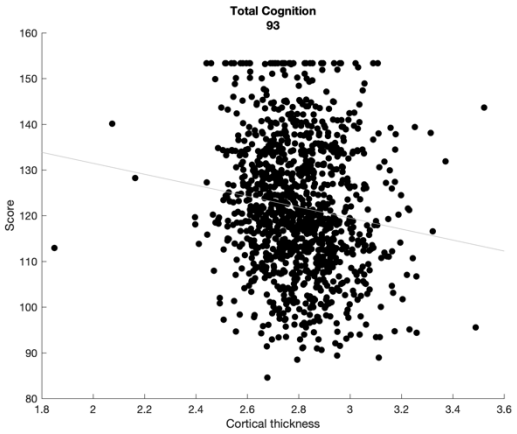

Total Cognition
80
Score
Cortical thickness

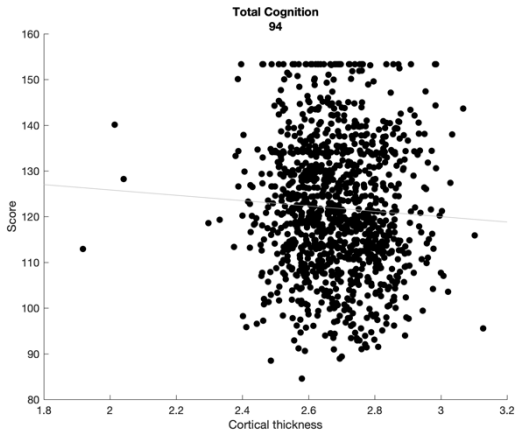

Total Cognition
84
Score
Cortical thickness

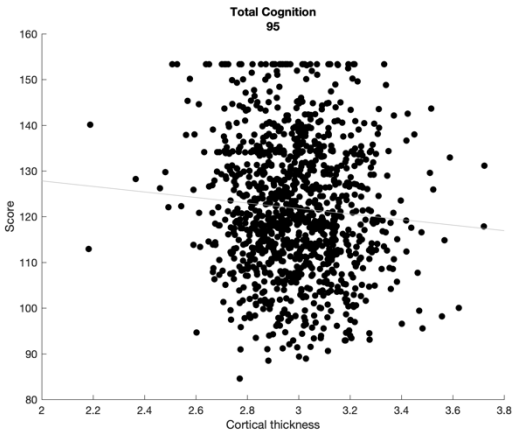

Total Cognition
87
Score
Cortical thickness

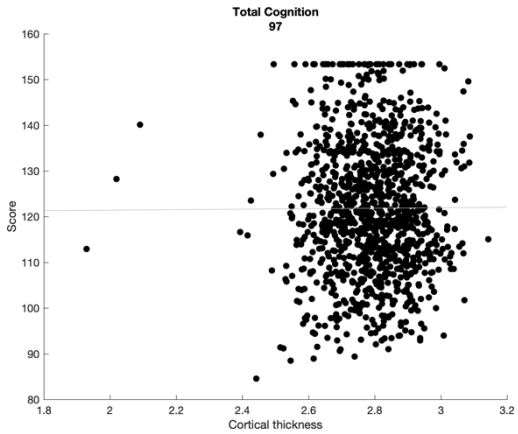

Total Cognition
90
Score
Cortical thickness

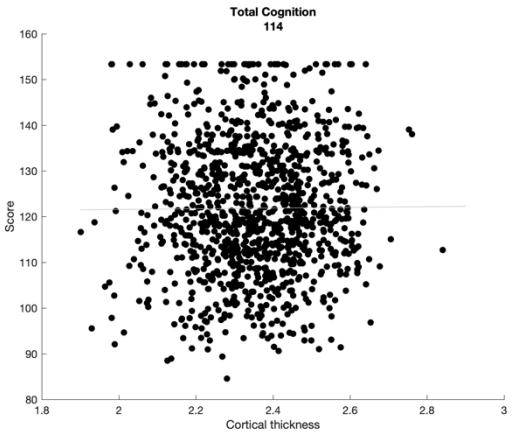

Total Cognition
92
Score
Cortical thickness

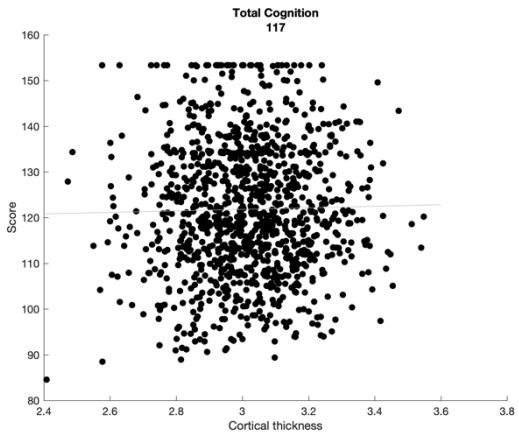

Total Cognition
93
Score
Cortical thickness

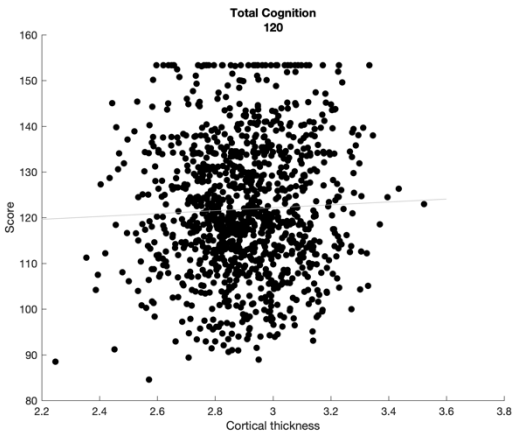

Total Cognition
94
Score
Cortical thickness

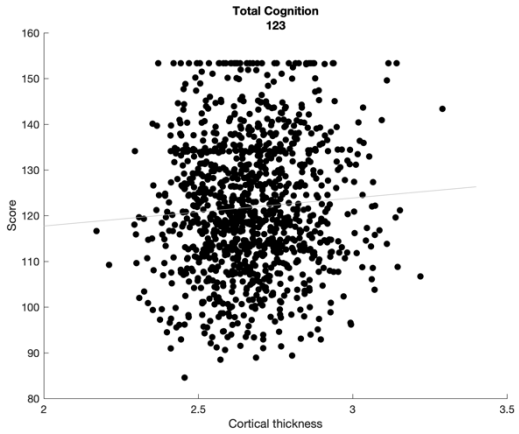

Total Cognition
95
Score
Cortical thickness

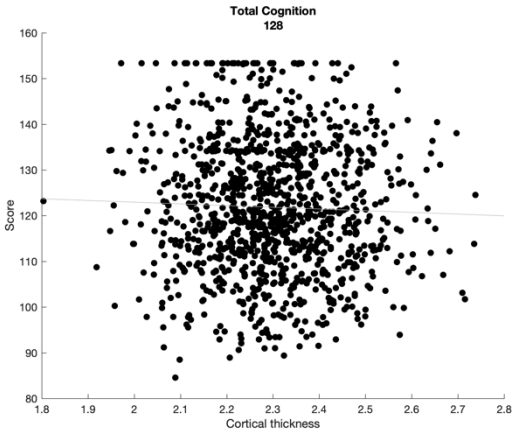

Total Cognition
97
Score
Cortical thickness

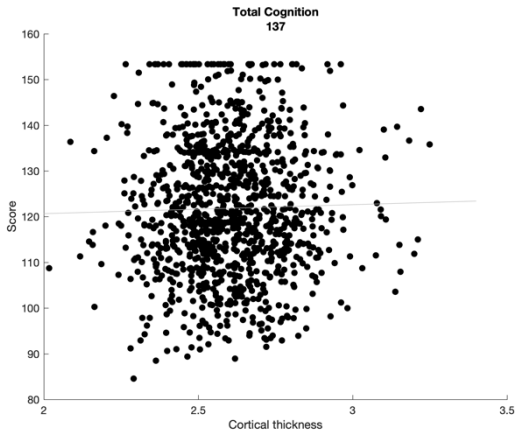

Total Cognition
114
Score
Cortical thickness

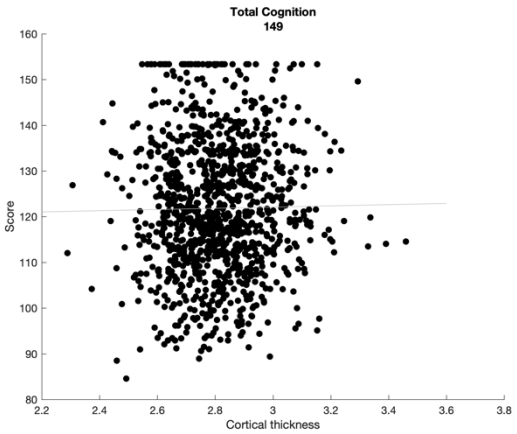

Total Cognition
117
Score
Cortical thickness

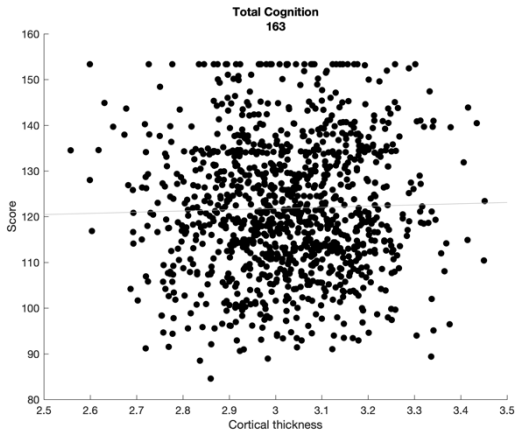

Total Cognition
120
Score
Cortical thickness

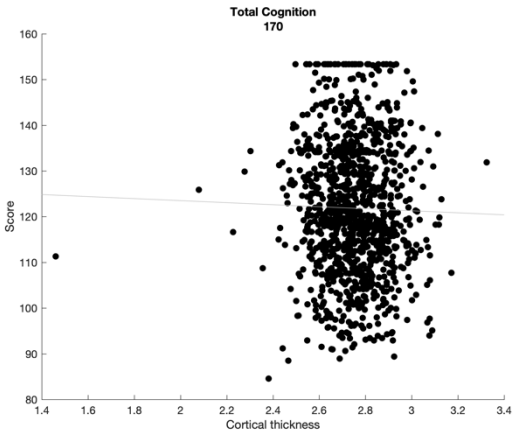

Total Cognition
123
Score
Cortical thickness

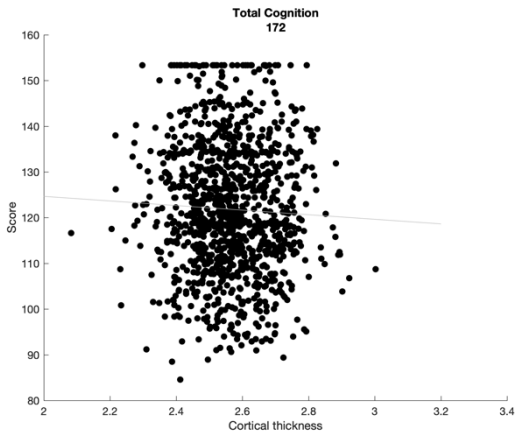

Total Cognition
128
Score
Cortical thickness

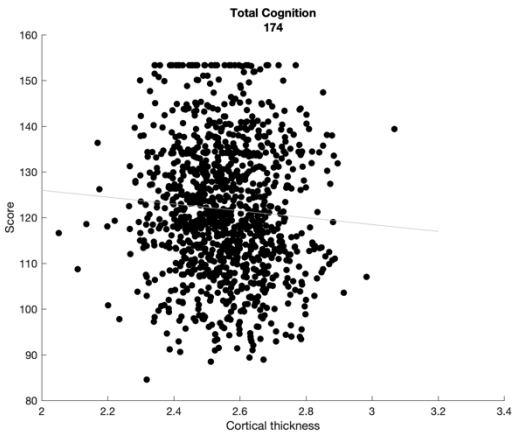

Total Cognition
137
Score
Cortical thickness

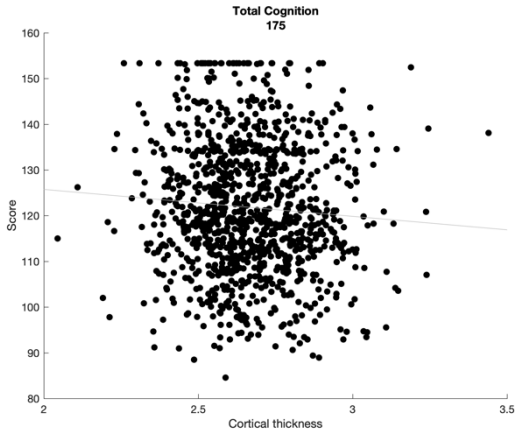

Total Cognition
149
Score
Cortical thickness

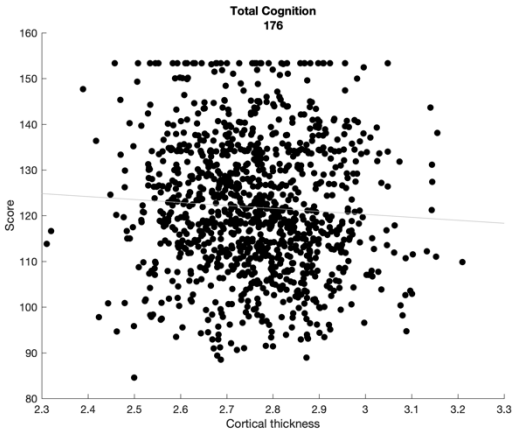

Total Cognition
163
Score
Cortical thickness

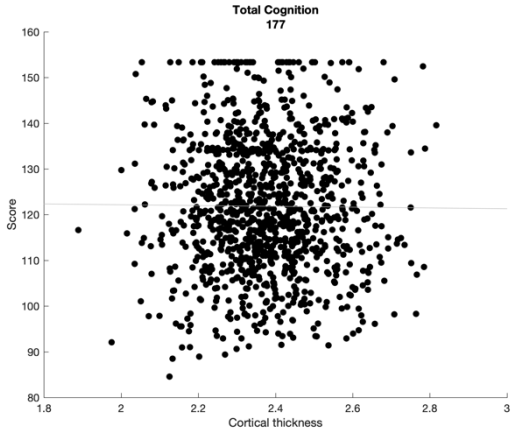

Total Cognition
170
Score
Cortical thickness

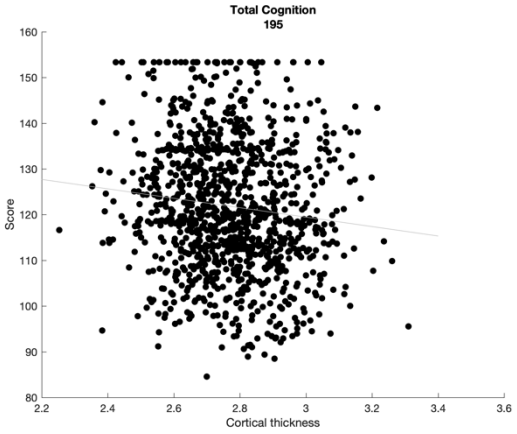

Total Cognition
172
Score
Cortical thickness

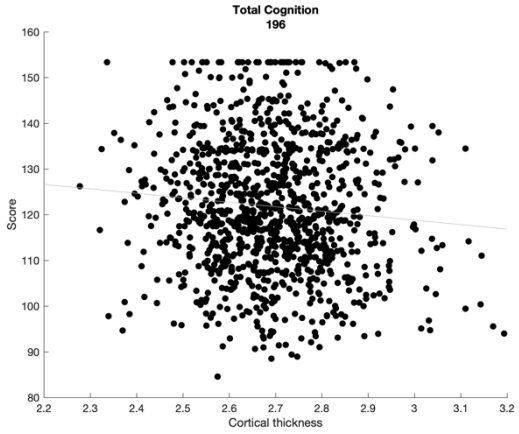

Total Cognition
174
Score
Cortical thickness

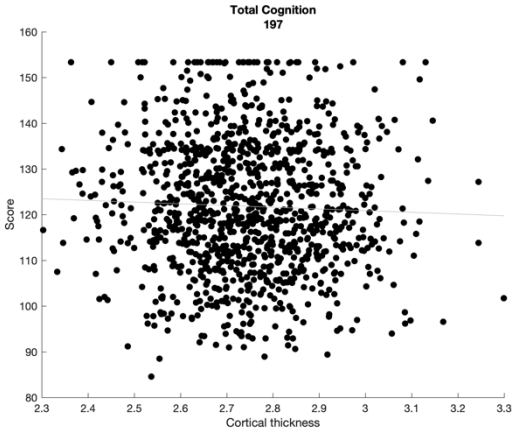

Total Cognition
175
Score
Cortical thickness

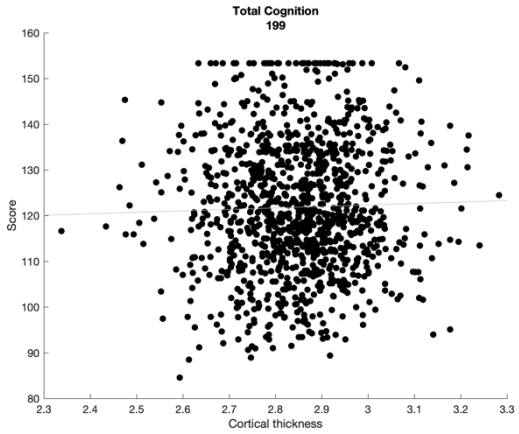

Total Cognition
176
Score
Cortical thickness


Total Cognition
177
Score
Cortical thickness

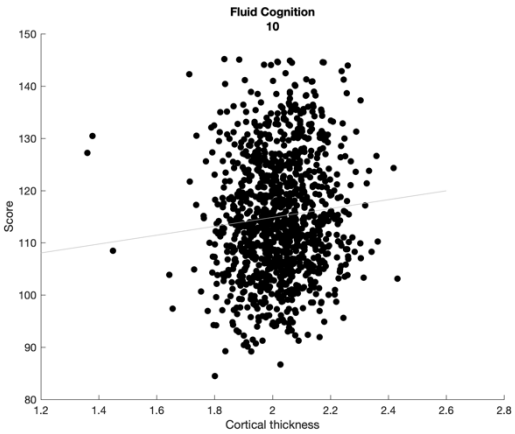

Total Cognition
195
Score
Cortical thickness

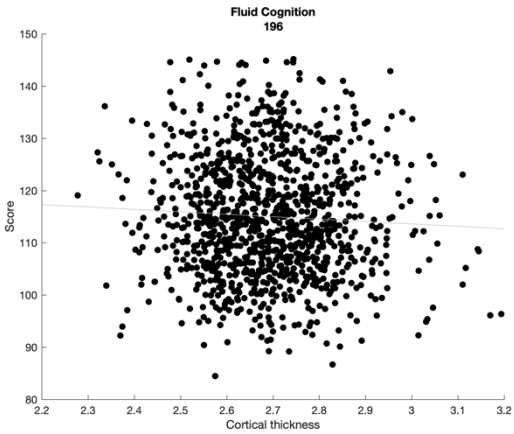

Total Cognition
196
Score
Cortical thickness


Total Cognition
197
Score
Cortical thickness

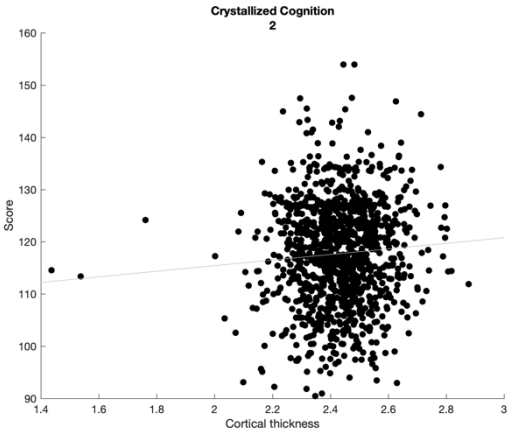

Total Cognition
199
Score
Cortical thickness

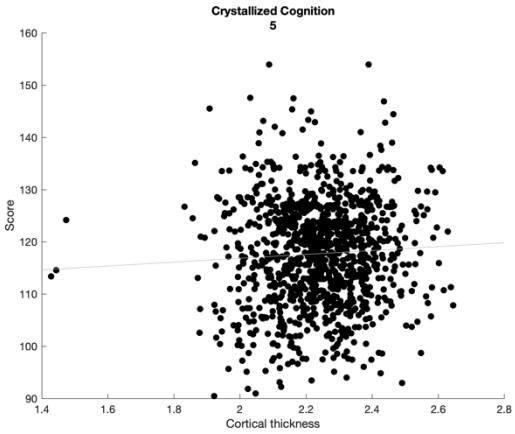
Phenotypic analysis: Spearman correlation fluid cognition score and cortical thickness (in mm)

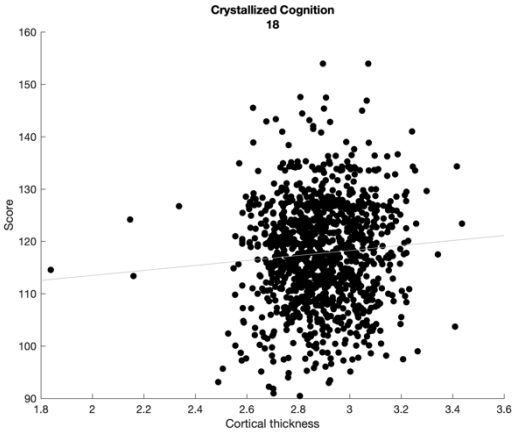


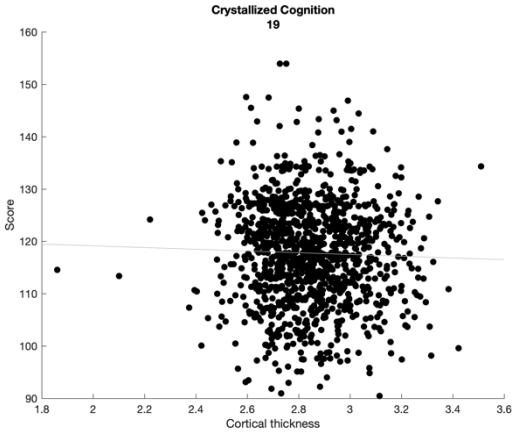


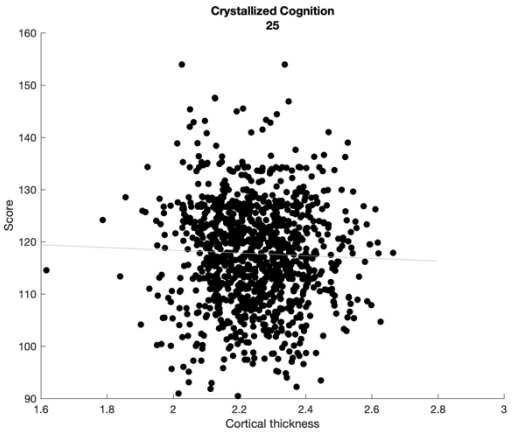
Phenotypic analysis: Spearman correlation crystallized cognition score and cortical thickness (in mm)

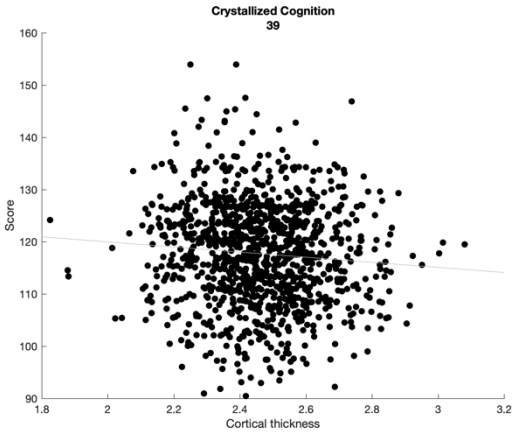


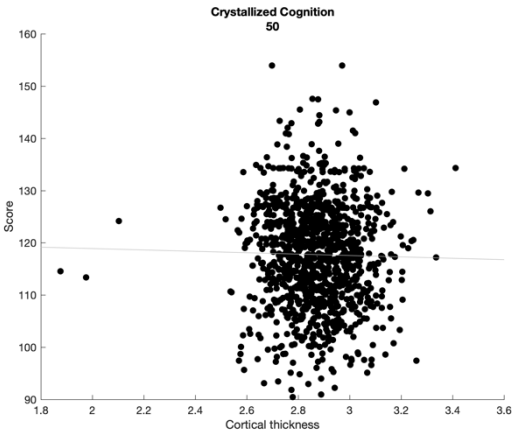


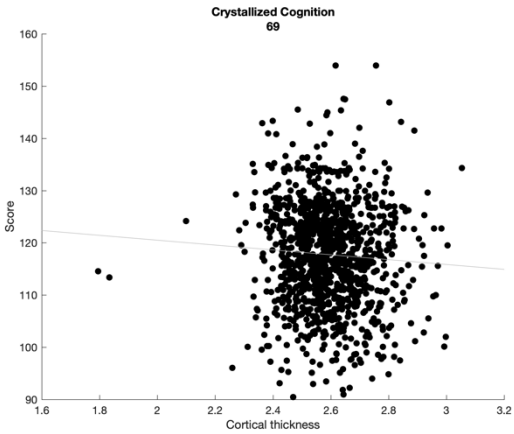


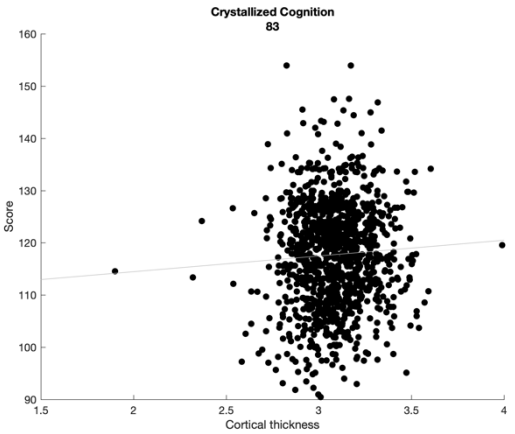


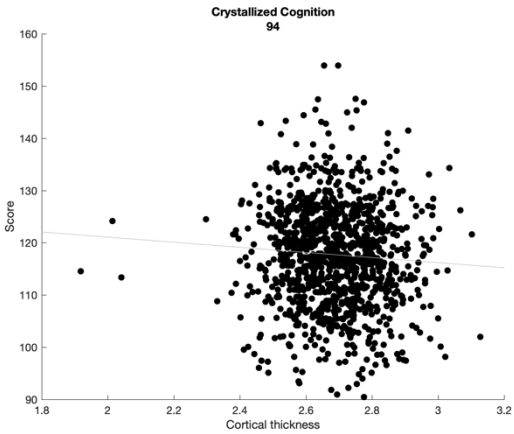

Crystallized Cognition
25
Score
Cortical thickness

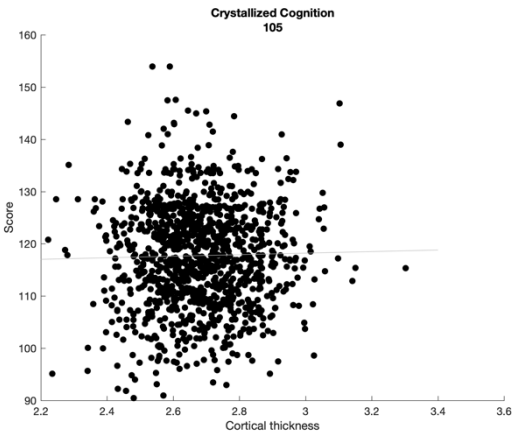

Crystallized Cognition
39
Score
Cortical thickness

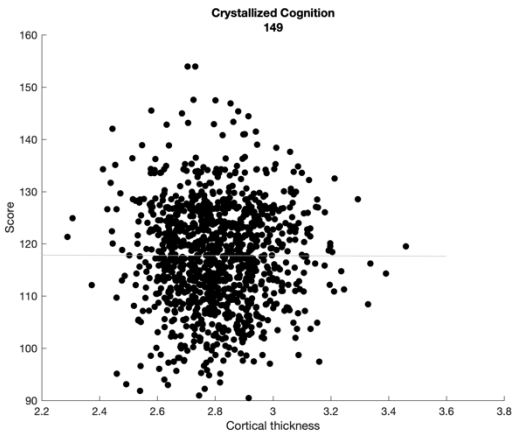

Crystallized Cognition
50
Score
Cortical thickness

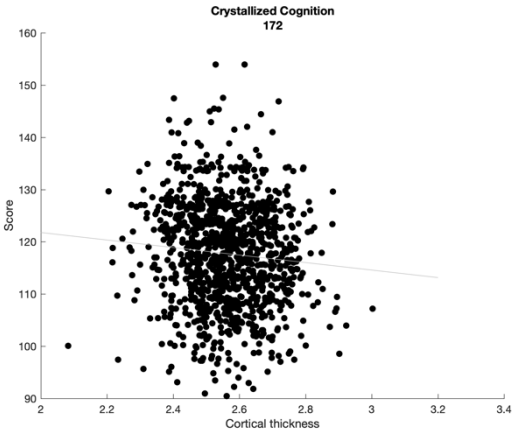

Crystallized Cognition
69
Score
Cortical thickness

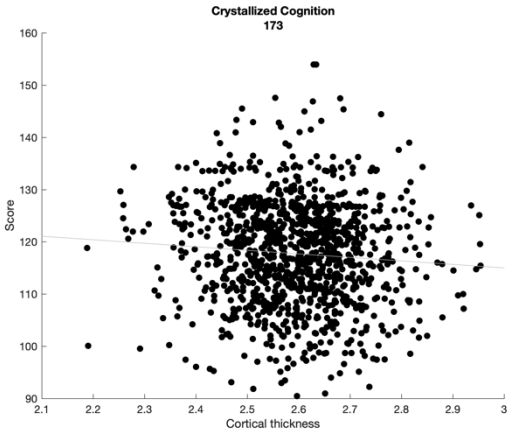

Crystallized Cognition
83
Score
Cortical thickness

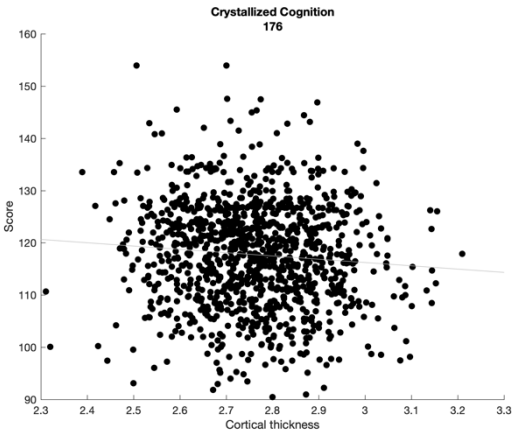

Crystallized Cognition
94
Score
Cortical thickness

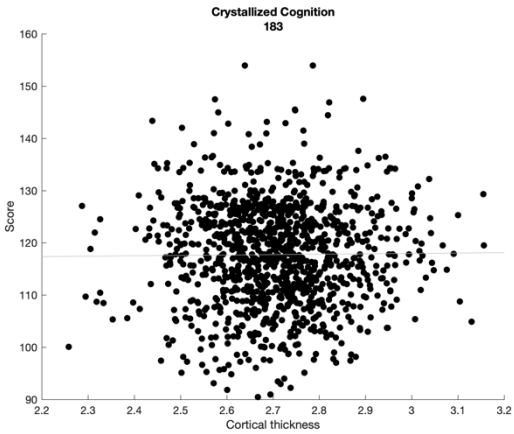

Crystallized Cognition
105
Score
Cortical thickness

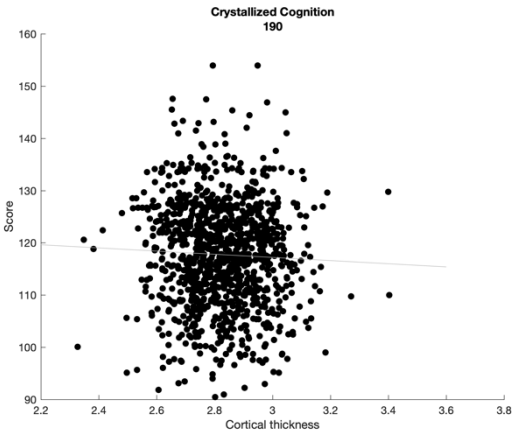

Crystallized Cognition
149
Score
Cortical thickness

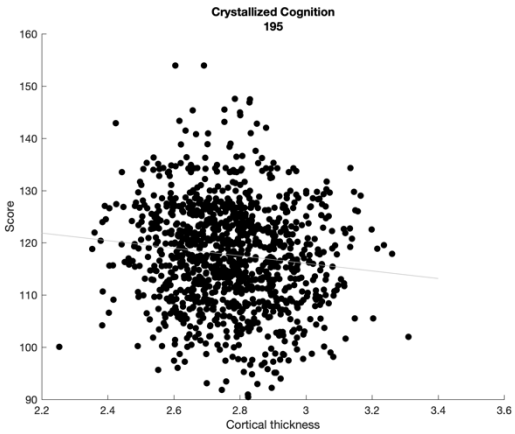

Crystallized Cognition
172
Score
Cortical thickness

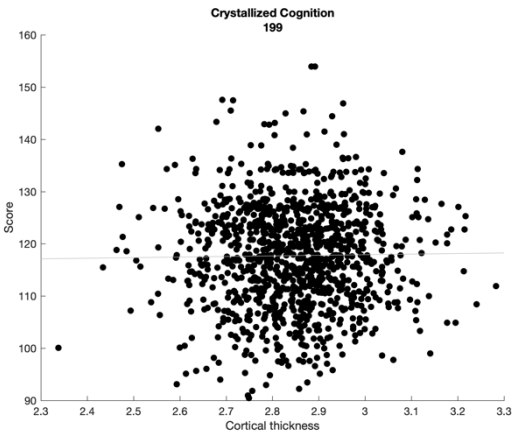

Crystallized Cognition
173
Score
Cortical thickness


Crystallized Cognition
176
Score
Cortical thickness


Crystallized Cognition
183
Score
Cortical thickness

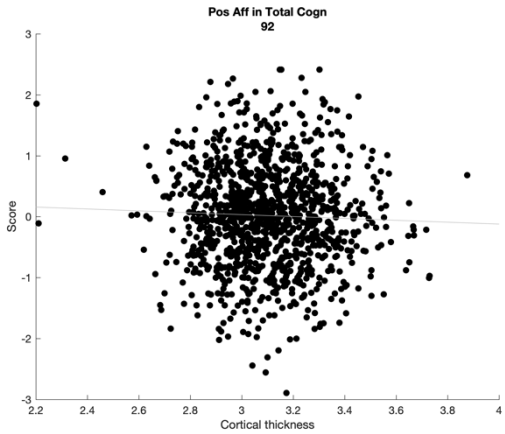

Crystallized Cognition
190
Score
Cortical thickness


Crystallized Cognition
195
Score
Cortical thickness


Crystallized Cognition
199
Score
Cortical thickness

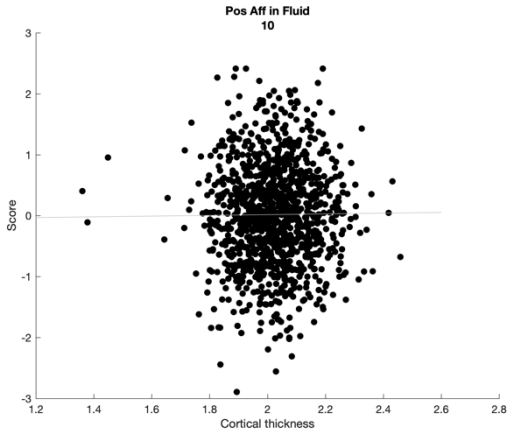
Phenotypic analysis: Spearman correlation positive affect and cortical thickness

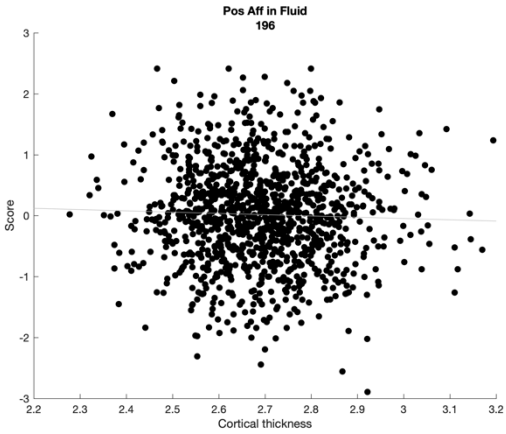
(in mm; in ROIs of total cognition)



Phenotypic analysis: Spearman correlation positive affect and cortical thickness

(in mm; in ROIs of fluid cognition)





Phenotypic analysis: Spearman correlation negative affect and cortical thickness

(in mm; in ROIs of fluid cognition)