

Multimodal characterization of biological substrates of personality traits

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I ZUSAMMENFASSUNG

Die zwei Studien der vorliegenden Dissertation zielen darauf ab die Gehirnregionen und Netzwerke bezogen auf Persönlichkeit aufzudecken. Während die Debatte darüber *wie* Personen sich voneinander unterscheiden ziemlich überholt ist, haben nur wenige bildgebende Techniken geholfen der Frage nachzukommen *warum* sich Individuen bezüglich ihrer Persönlichkeit unterscheiden wie beispielsweise welche neuronalen Mechanismen mit interindividuellen Persönlichkeitsunterschieden assoziiert sind. Das Fünf-Faktoren Modell (FFM) bietet einen verständlichen Zugang zur Persönlichkeit, welche als Kombination von fünf Hauptdomänen: Offenheit für Erfahrungen, Gewissenhaftigkeit, Extraversion, Verträglichkeit und Neurotizismus definiert ist. Obwohl schon einige Studien die strukturellen und funktionellen Korrelate dieser fünf Persönlichkeit-Traits untersuchten, ist es dennoch schwierig ein klares Bild über die neurobiologischen Ursprünge des FFM aufzuzeigen. Haupteinschränkungen stellen kleine Stichprobengrößen, das Fehlen von non-parametrischer Statistik, die Heterogenität in der Vorverarbeitung und der Einbezug vom Geschlecht als nicht interessierende Kovariate. Trotz des enormen Wissens zu Geschlechtereffekten auf die Gehirnorganisation und auf selbstberichtete Persönlichkeits-Scores, wird es in den meisten Studien im Bereich der Persönlichkeit-Neurowissenschaft nicht zur neuronalen Untermauerung der Persönlichkeit berücksichtigt. In Studie 1 wurde die Voxel-basierte Morphometrie verwendet, welche geschlechterabhängige Veränderungen im Volumen der grauen Substanz aufzeigte. In der statistischen Analyse wurden über die gesamte Stichprobe keine signifikanten Korrelationen zwischen irgendeinem Trait und dem Volumen der grauen Substanz gefunden. Hingegen zeigten sich einige Effekte in der geschlechterspezifischen Stichprobe (nur Männer). Im Vergleich dazu trat in Studie 2 der Einfluss des Geschlechts auf die (funktionelle) Gehirn-Persönlichkeit Beziehung auf; während die funktionelle Resting-State-Konnektivität in meta-analytischen abgeleiteten Netzwerken, welche soziale, affektive, exekutive und mnemonische Funktionen sowie das gesamte Konnektom abdeckten, untersucht wurden. Die Relevance Vector Machine (RVM) erlaubte die Generalisierung der Ergebnisse zu testen, welche in den meisten Fällen, bei der Zusammenführung von Männern und Frauen zu einer Stichprobe, keine signifikante Vorhersageleistung ergab. Jedoch konnten Persönlichkeitseigenschaften entweder in Männern oder in Frauen signifikant vorhergesagt werden. Die Verwendung der beiden bildgebender

Techniken (VBM und RSFC) erlaubte eine detailliertere Charakterisierung vom männlichen und weiblichen Gehirn hinsichtlich der Persönlichkeit. Nach diesen beiden Studien konnten die weiblichen Gehirne während der Verwendung der Konnektivitätsmessung besser charakterisiert werden. Ovariale Hormone könnten dies verursacht haben und möglicherweise zu einer Fluktuation in der Persönlichkeit und in der funktionellen Konnektivität geführt haben sowie die interhemisphärische Konnektivität und Dezentralisierung begünstigt haben, welches jedoch nicht für das lokale Gehirnvolumen gilt. Daher untermauert die Kombination von Studie 1 und 2 den Gedanken der neuralen Grundlage der fünf Domänen. Noch wichtiger ist jedoch, dass die strukturellen und funktionellen Veränderungen unterstützen, dass sich wahrscheinlich jedes Trait zwischen männlichen und weiblichen Gehirn unterscheiden lässt.

II ABSTRACT

The two studies presented in this dissertation aimed to elucidate the brain regions and networks related to personality traits. While the debate on *how* each person differs from each other is quite dated, only recently neuroimaging techniques have helped investigating *why* individuals differ in terms of their personality, i.e. studying which neural mechanisms can be associated with interindividual differences in personality. The Five-Factor Model (FFM) provides a comprehensive assessment of personality, defined as the combination of five major domains: Openness to Experience, Conscientiousness, Extraversion, Agreeableness and Neuroticism. Although several studies have already investigated structural and functional correlates of these five traits, it is still difficult to delineate a clear picture on the neurobiological correlates of the FFM. Major limitations can be found in the rather small sample size, lack of non-parametric statistics, heterogeneity in preprocessing pipelines and considering gender as covariate of no interest. Indeed, despite the vast knowledge of the effect of gender on both the brain organization and on the self-reported personality scores, most of the studies in the field of personality neuroscience did not consider it in the neural underpinnings of personality. In Study 1, whole-brain Voxel-based Morphometry (VBM) was carried out revealing changes in grey matter volume (GMV) as highly dependent on gender: in the statistical analysis across the entire sample no significant correlations between any personality trait and GMV were detected. In contrast, several effects emerged in the gender-specific sample (men only). Comparably, Study 2 revealed

gender influence in the (functional) brain-personality relationships, while investigating resting-state functional connectivity (RSFC) in meta-analytically derived networks, covering social, affective, executive and mnemonic functions, as well as the entire connectome. The Relevance Vector Machine (RVM) allowed to test the generalization of the findings, revealing in most of the case no significant prediction performance when men and women were pooled in one sample. Conversely, personality traits could be significantly predicted in either men or women.

The implementation of two different neuroimaging techniques, as VBM and RSFC, allowed a more detailed characterization of male and female brain in terms of personality, as from these two studies it emerged that female brains could be better characterized while using connectivity measurements. This might be caused by ovarian hormones, possibly leading to fluctuations in personality and functional connectivity, such as promoting interhemispheric connectivity and decentralization, but not on local brain volume.

The combination of Study 1 and 2, therefore, corroborates the notion of a neural foundation for the Big Five, but, most importantly, that structural and functional changes supporting each trait might differ between male and female brains.

III GENERAL INTRODUCTION

My dissertation project will focus on examining the biological correlates of personality traits, using a combination of high-quality structural and functional MRI and personality, described by the Five-Factor Model (FFM, McCrae and Costa 2004). This project will also explore how brain-personality relationships vary upon gender, a crucial factor in the self-reported personality questionnaires as well as in brain measurements. This project therefore aims to answer at least two questions: first, how are individual differences in brain structure and function associated with individual differences in the five-major human personality trait dimensions; second, can we generalize these associations across men and women or can they only be found in either one or the other group? Knowing which area of the brain can be linked to the differences in personality and whether these associations are gender-specific can thus provide new information in the recently born field of personality neuroscience and new insights into the biological bases of personality disorders (e.g. phobias, depression, eating disorders), which, in fact, also express a gender-specific predominance.

3.1 Personality psychology: 2500 years of history

While the term “personality” is easy to grasp in the daily life and immediately relates to the concept of “what makes yourself unique”, in the psychology research it has been often debated. Several theories, systems and classifications have been developed about the best way to describe it. The most antique can be traced back to the ancient Greece, with Hippocrates hypothesizing two poles on which temperament could vary (hot/cold and moist/dry). This idea results in four possible combinations (hot/moist, hot/dry, cold/moist, cold/dry) called “humors” that were thought to be the key factors in both health issues and personality characteristics.

Since then, the study of personality has seen a growing abundance of theoretical traditions. The major theories include the psychodynamic perspective (Freud 1993) which proposed an influence of unconscious mind and childhood experience on personality. The humanistic view (Maslow 1968) emphasized the free will in determining how people behave (i.e. subjective experiences as opposed to forced, definitive factors that determine behavior). The behaviorist theory, of which Ivan Pavlov was a notable influencer (Pavlov 1927), explained personality in

terms of the effects external stimuli have on behavior. A modification of the behaviorist is the social learning perspective (Bandura 1989), which added to the theory two concepts: first, the existence of mediating processes between stimuli and responses. Second, the learning of behavior comes from the environment through the process of observational learning.

Beside them, one important branch, known as dispositional perspective, or trait theory, was initiated by Gordon Allport in 1936, by showing that more than 4000 words in an English language dictionary described personality traits and thus laying the foundation for the modern personality neuroscience. Here, each trait is conceptualized on a spectrum instead of as dichotomous variables and are defined as a statistical generalization that can better predict the average behavior rather than individual's behavior in any specific situation.

3.1.1 The Five-Factor Model and the reconciliation in the personality taxonomy

This multitude of personality factors taxonomy was eased by an increasing consensus among the trait psychologists on the use of the Five-Factor Model (FFM, Costa and McCrae 1992). It got vastly support as showing high internal consistency and validity. Additionally, these five factors (also known as Big Five) could be sufficient to account for the variance in the extended lists of adjectives in both self and peer ratings of personality (John 1990; Goldberg and Rosolack 1994). Indeed, the model was constructed on the so-called “lexical hypothesis” which assumes that basic individual differences are represented in the natural language by trait adjectives (Goldberg 1981; Digman 1990). Evidences supporting the FFM over the other theories of personality showed that no recurrent and important dimensions beyond these five could be recovered when factoring the items of several major personality questionnaires (Costa and McCrae 1992a). Moreover, the model acquired the attribute of “universal”, by showing remarkable consistence across age and culture (McCrae and Costa 1997; McCrae 2004). Genetic studies proved the “universality” of the Big Five by localizing homogenous set of genetic influences, which led the traits to be grounded in the human genome (Yamagata et al. 2006).

The five factors, Neuroticism (N), Extraversion (E), Openness to Experience (O), Agreeableness (A), and Conscientiousness (C) of the FFM can be measured by the Revised NEO Personality Inventory (NEO-PI-R, Costa and McCrae 1992) . Each domain is indexed by the sum of responses on six subscales or facets. Neuroticism's facets are Anxiety, Hostility, Depression,

Self-consciousness, Impulsiveness, Vulnerability to Stress. Extraversion's facets include Warmth, Gregariousness, Assertiveness, Activity, Excitement Seeking and Positive Emotion. Openness to experience/ Intellect is composed by the facets of Fantasy, Aesthetics, Feelings, Actions, Ideas and Values. For Agreeableness, the facets count Trust, Straightforwardness, Altruism, Compliance, Modesty, Tendermindedness. Lastly Conscientiousness's facet are Competence, Order, Dutifulness, Achievement Striving, Self-Discipline and Deliberation. DeYoung and colleagues grouped them in two-aspect solutions appropriate for each trait (DeYoung et al. 2007), which resulted in the "aspects" for Neuroticism of Volatility and Withdrawal, for Extroversion Enthusiasm and Assertiveness, for Openness/Intellect Openness and Intellect, for Agreeableness Compassion and Politeness, and for Conscientiousness Industriousness and Orderliness.

The Big Five not only can be sub-divided in narrow facets/aspects, but can also be grouped "superordinate factors" or meta-traits, forming in such a way a pyramidal hierarchy. The two higher-order solutions (Alpha and Beta factors) represented the concepts of Stability and Plasticity respectively (DeYoung et al. 2002): Alpha refers to a combination of Agreeableness, Conscientiousness and Emotional Stability (reversed for Neuroticism), while Beta is a combination of Extraversion and Openness. Scoring high in Stability (i.e. showing high level of A and C and low level of N) could be interpreted as the general ability to maintain stable relationships, motivation, and emotional states. On the other hand, the factor of Plasticity (high scores of both E and O), indicated the tendency in generating new goals, new interpretations of the present state, and new strategies to pursue existing goals, and more in general to the "cognitive flexibility".

The NEO-PI-R, which consisted of 240 items, was then revised as a shorter form (NEO-FFI; McCrae and Costa 2004), constituted of 60 questions, for a total of 12 item for each scale, which is nowadays the most widely used operationalization for the model.

3.2 Personality neuroscience: the biological bases of personality

A first link between personality traits and the brain was seen in the 19th century, with the neuroanatomist F. Gall. He promoted a science (or pseudo-science in the opinion of most) called *Phrenology*, where physical properties of different areas of the brain (such as size, shape, and

density) were associated to opinions, attitudes, and behaviors. Whereas Gall's science never took off, in the same century, Phineas Gage's accident, whose personality massively changed after an iron rod pierced his brain, showed some foundation in Gall's intuition: personality was rooted in the brain.

The first proper model on the biological bases of personality traits was proposed by Eysenck (Eysenck 1963), in which he assigned two "super-factors" to the dimensions of Extraversion (E) and Neuroticism (N) and later added a third, known as Psychoticism (P) (EPQ, Eysenck and Eysenck 1975). The three-factor model relied heavily on the functions of the brain's ascending reticular activating system. Accordingly, E would be related with the reticulo-cortical circuit and N with the reticulo-limbic circuit. Eysenck hypothesized that extraverts, by having a higher threshold for cortical arousal than introverts, would choose more stimulating activities through which they would reach a preferred level of arousal. On the other hand, neurotics would be more easily aroused by emotion-inducing stimuli than emotionally stable people. Eysenck did not develop as well-specified biological model of P, but at different times he hypothesized that it was negatively associated with serotonergic function (Eysenck 1992) and positively associated with dopaminergic function (Eysenck 1997) (cf. Chapman 2011).

Adding extensive animal research on Eysenck's theory, his student J.A. Gray formulated a new biopsychological model known as "Reinforcement Sensitivity Theory" (RST, Gray 1982; Gray and McNaughton 2000), in which two motivational systems were subserving the behavior. The first, the Behavioral Inhibition System (BIS), was sensitive to cues of threat, punishment and conflicts in general. It activated responses of inhibition and avoidance via noradrenergic and serotonergic activity under the control of the septo-hippocampal system and amygdala (Gray 1982; Depue and Iacono 1989; McNaughton and Corr 2004). The second opposite system was named Behavioral Activation System (BAS), sensitive to cues of reward via dopaminergic activity in the mesolimbic system (Gray 1994; Depue and Collins 1999). A more fine-grained division in aversion motivation can also distinguish BIS from a third system, the Fight-Flight-Freeze System (FFFS). While the BIS was theorized as sensitive to conditioned aversive stimuli, mediating therefore the emotion of anxiety, the FFFS would respond to unconditioned aversive stimuli, and thus mediating the emotion of fear. As can be seen in Figure 1, Gray's modification on Eysenck's theory was not only made on the neural bases of the emergent behaviors supported by these three systems (BIS, BAS, FFFS), but also on their location in the factor space: he

proposed a 30° rotation of the E and N scales so to create a more efficient reward and punishment sensitivity axes. Therefore, the emergent traits would be Anxiety (Neuroticism-Introversion axis), and Impulsivity (Emotional Stability – Extraversion axis). In fact, highly impulsive individuals would be, in Gray’s theory, most sensitive to signals of reward, relative to their low impulsive counterparts; on the other hand, highly anxious individuals would be most sensitive to signals of punishment, relative to low anxiety counterparts. Accordingly, Eysenck’s E and N dimensions are secondary factors of these more fundamental traits/processes. This new factor-space location allowed Gray also to explain why introverts were, generally, more cortically aroused: since punishment is more arousing than reward, introverts, by being more sensitive to first, usually display higher level of arousal. Conversely, extraverts, more sensitive to the second, are accordingly less aroused.

Figure 1

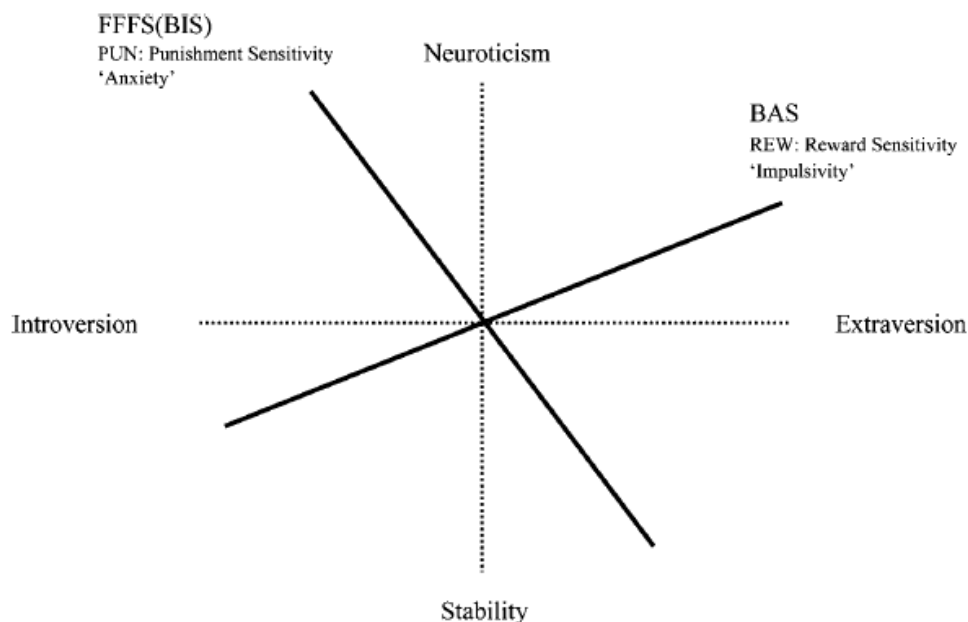


Figure 1. Position in factor space of the fundamental punishment sensitivity and reward sensitivity (unbroken lines) and the emergent surface expressions of these sensitivities, i.e., E and N (broken lines). Reprinted from *The Cambridge Handbook of Personality Psychology* (p. 356), by AL. Chapman, 2011.

In 1993, C.R. Cloninger formulated a personality model also built in the biological context. His Temperament and Character Inventory (TCI) (Cloninger et al. 1993) was particularly oriented in providing a tool for diagnosis of personality disorders and the latest and final version consisted of three characters, (Self-Transcendence (ST), Self-Directness (SD), Cooperativeness (Coop)),

and four temperaments (Novelty Seeking (NS), Reward Dependence (RD), Persistence (P) and Harm Avoidance (HA)). The main distinction between a character and a temperament consisted in the fact that the first would reflect personality development in the context of insight learning and environmental experiences, whereas temperament mostly refers to automatic responses in information processing and learning, presumed to be heritable. However, the temperaments could only distinguish among subtypes of personality disorders, but did not consistently differentiate individuals with personality disorders or poor social adjustment from other well-adapted individuals with extreme personality profiles. Therefore, he later added the three characters ST, SF and Coop. On the biological level, the temperaments of NS, HA, RD were described as results of different functioning in the dopaminergic, serotonergic and noradrenergic systems respectively. However, genetic analyses not always supported these associations to be homogenous, i.e. not reflecting the influence of one specific gene, but rather a common set of genes (i.e. genetically heterogeneous) (Schinka et al. 2002).

3.2.1 Neurobiological substrates of the Five-Factor Model

In the personality neuroscience literature, many attempts have been made to functionally and structurally characterizing the Big Five. Classical statistical analyses showed various correlations between either structural (as GMV, cortical thickness, structural connectivity) or functional (activations or connectivity) properties of the brain and the five scores. From here, often, the traits have been associated to psychological functions when regions correlating with a trait were also known to subserve a specific function. More specifically, Neuroticism has been associated with sensitivity to punishment, via functional or morphometric correlations to affective regions like amygdala, hippocampus, cingulate cortex, medial prefrontal cortex (Kumari 2004; Cremers et al. 2010; DeYoung et al. 2010; Tzschoppe et al. 2014; Madsen et al. 2015; Pang et al. 2016), all previously linked to respond to threat and punishment. Extraversion with sensitivity to reward due to associations with reward-related stimuli as nucleus accumbens, striatum, amygdala and orbitofrontal cortex (DeYoung et al. 2010; Adelstein et al. 2011; Lei et al. 2015; Pang et al. 2016). Agreeableness associated to regions involved in the processing of social information, such as temporo-parietal junction, superior temporal gyrus and posterior cingulate cortex (Hooker et al. 2008; DeYoung et al. 2010; Adelstein et al. 2011). Conscientiousness and Openness to

executive functions and specifically to the lateral PFC, due to its role in planning, following complex rule and voluntarily control of behavior for Conscientiousness cortex (Asahi et al. 2004; Passamonti et al. 2006; DeYoung et al. 2010; Kunisato et al. 2011), while to its role in attention, working memory and cognitive flexibility for Openness (DeYoung et al. 2010; Kunisato et al. 2011).

However, this approach might be problematic for at least two reasons: i) brain regions can support many different mental functions (Laird et al. 2009) ii) many mental functions can contribute to a single trait (DeYoung 2015). Indeed, there are evidences in the personality neuroscience literature that support the “many-to-many” rather than the above “one-to-one” mapping among personality traits/ psychological functions/ brain. For example, a trait like Neuroticism, very often associated to affective regions, has been also linked to regions exerting cognitive functions, e.g. dlPFC (Kunisato et al. 2011; Pang et al. 2016), or behavioural performances probing attention (MacLean and Arnell 2010), working memory (Studer-Luethi et al. 2012), verbal fluency (Sutin et al. 2011) and explicit memory (Pearman 2009; Denkova et al. 2012). It is therefore possible that these systems (mnemonic, affective and executive) all contribute in explaining variance in Neuroticism.

Additionally, another recurrent methodological problem in the field is the low statistical power, which together with non-parametric statistics, recurrently led to Type I (false positive) or Type II (false negative) error rates, thus increasing the confusion and the inconsistent findings in the structural correlates of personality (Yarkoni 2009; Hu et al. 2011; Scarpazza et al. 2016).

Following up the issue of inconsistent and heterogeneous, Study 1 will show that there were no consistent locations in the brain where GMV correlated with any of the Big Five in a gender-mix group. This null result represents therefore a strong warning toward previous findings, which conversely showed several regions positively or negatively correlated with the personality scores, but with much smaller sample sizes. The fact that the only correlations could be detected in the gender-split groups further demonstrated an important role of gender, often disregarded in previous studies. Similarly, Study 2 also supports the notion of a crucial role of gender, revealing more and higher predictability power in the gender-split groups compared to the gender-mix group. Additionally, it also demonstrates that besides the most common associations between mental functions and personality traits (e.g. Neuroticism and emotional processing), other

functions appear to be also involved (e.g. Openness and pain processing), thus supporting the “many-to-many” mapping.

3.3 From personality psychology to personality neuroscience

A shift of focus from the *how* (how people differ from each other) to the *why* (why they differ from each other) is the main difference in the research question of personality psychology and neuroscience. The main goal of personality neuroscience is therefore the investigation at the neural level of the differences in processes like cognition, emotion and motivation, associated in differences in personality traits, making the brain a “proximal source” of personality characteristics (cf. DeYoung and Gray 2009).

Nowadays there are at least two reasons supporting this shift of attention: i) the reconciliation in the taxonomy has allowed the field to move toward the investigation of the causes and the consequences of these individual differences, ii) the tools for investigating the biological underpinning of personality have enormously improved with the rise of neuroimaging techniques (EEG and MRI, PET) and molecular genetics. Since my two projects have been carried out within the first framework (Study 1 using structural MRI and Study 2 using functional MRI), an introduction to the MRI techniques will follow.

3.3.1 Neuroimaging techniques: structural MRI

Magnetic resonance imaging (MRI) is often divided into structural and functional MRI. Structural MRI (sMRI) identifies differences among tissues of the brain and further measures the density of each tissue (Symms et al. 2004). This thus provides information to quantitatively describe the size and integrity of (mainly) grey matter structures in the brain. Broadly speaking, MRI signal varies across tissue types because gray matter contains more cell bodies (e.g., neurons and glial cells) than white matter, which is primarily composed of long-range nerve fibers (myelinated axons), along with supporting glial cells. Voxel based morphometry (VBM) is one of the most commonly used methods to measure grey matter volume (GMV) (Good et al. 2001). Here the aim is associating brain structural differences to inter-individual differences in some phenotypical aspects, such as personality traits. Structural brain images are spatially

normalized, to match a brain template, classified into grey and white segments and smoothed so that each voxel reflects the average percentage of grey matter within itself and the surrounding voxels (Ashburner and Friston 2000). Please note that a detailed explanation of the VBM procedure can be found in **Material and Methods** of Study 1.

3.3.2 Neuroimaging techniques: functional MRI

With an even larger sample size, Study 2 targeted the functional bases of the Big Five, by investigating fluctuation of the blood-oxygen-level-dependent (BOLD) signal at rest. fMRI is based on the idea that blood carrying oxygen from the lungs behaves differently in a magnetic field than blood that has already released its oxygen to the cells. As a result, oxygen-rich blood and oxygen-poor blood have a different magnetic resonance. Since more active areas of the brain receive more oxygenated blood, the fMRI picks up this increased blood flow to pinpoint greater activity. Functional connectivity (FC) is defined as the statistical association or dependency among two or more anatomically distinct time-series (Friston 2011), thus reflecting the level of functional communication between regions (cf. van den Heuvel and Hulshoff Pol 2010). Several methods are used to mapping connectivity using fMRI time series data. A major distinction can be made between “model-free”, as principal component analysis (PCA, Friston et al. 1993) or independent component analysis (ICA, Beckmann et al. 2005), and “model-dependent” methods, as seed-based analysis (Biswal et al. 1997). In the former, the aim is to decompose the whole-brain data covariance matrix in eigenvariates, each one including regions that may constitute a functionally connected network. The seed-based approach, instead, examines the functional connections of a particular brain region against the time-series of all other regions in the whole-brain, thus producing a functional connectivity map defining the functional connections of the predefined brain region (Biswal et al. 1997; Jiang et al. 2004). A variation of this approach is constituted by the network-based analysis, where FC is computed among all the nodes of a given network. A more detailed description of this method can be found in **Material and Methods** of Study 2.

Importantly, since 1995, it was shown that functional activity and connectivity was not only present while subjects are performing a certain task, but that it was possible detecting low BOLD frequencies also while participants were just lying in the scanner, resting (Biswal et al. 1995).

Afterwards, it has been demonstrated that the pattern of this intrinsic oscillatory behavior between regions mimics patterns of co-activation during task-based fMRI studies. Specifically, regions that work in concert during the performance of tasks seem to fluctuate together during resting-state (RS) scans (Smith et al. 2009; Cole et al. 2014). As a result of this, together with the easier acquisition of RS compared to task-based scans (i.e. fast acquisition of the data, logistically simpler, more standardize across studies and sites, independent of specific paradigms/designs) a gaining ground technique is the acquisition of functional scans at rest, i.e. subjects are not performing an explicit task.

Study 2 also employed RSFC to capture patters of connectivity which could be associated to variations in personality level. Importantly, FC was computed in meta-analytically derived networks as proxy for specific mental functions. Indeed, networks revealed by a meta-analysis across tasks probing a specific mental function should be primarily reflecting that particular function. This approach is, so far, the best way to tackle the problem of experimental and analytical flexibility. In particular, the spatial convergence of activation across all available neuroimaging experiments testing a specific mental function should reflect those regions that are consistently recruited by this process. Conversely, other regions that are more specific to particular paradigms, implementations, data processing and analysis strategies should not reveal any convergence (Eickhoff et al. 2009; Laird et al. 2009; Fox et al. 2014).

3.3.3 Statistical approaches

Unlike the other previous studies investigating personality in the functional brain, in Study 2, a multivariate pattern analysis (MVPA) was implemented in order to overcome some limitations of the univariate pattern analysis (UVPA). First, UVPA infers on identical information from several single voxels (Gonsalves and Cohen 2010) and thus fails to explicate patterns based on integrated information from multiple voxels, even when the voxels share non identical variance. On the contrary, MVPA approach uses a weighted average of responses, treating each voxel as a distinct source of information (Lewis-Peacock and Norman 2013). In such a way, the entire pattern within each single functional brain is used to seek for personality-related information. Second, traditional univariate pattern analyses make use of “within-sample correlations”, while multivariate approaches use an “out-of-sample” prediction to evaluate the accuracy of the model.

This can therefore account for a highest generalizability and lower over-fitting of the results (Yarkoni and Westfall 2017). The combination of such approaches allowed, therefore, to relate with greater confidence a specific trait to a particular mental function in terms of the network that subserves them in previously unseen individuals, rather than relating a personality trait to a particular function only because a brain region correlates with both. Please refer to **Material and Methods** of Study 2 for more detailed description of RSFC and the MVPA algorithm (Relevance Vector Machine, RVM (Tipping 2001)).

3.4 The influence of gender

Study 1 and 2 jointly pointed to a crucial role of gender in the investigation of brain-personality relationships. Here it follows a description of the major lines of researches focusing on personality, brain and why this factor should be included in the investigation of the neural correlates of personality.

3.4.1 The influence of gender on personality

Personality traits have been demonstrated to be stable over time, across situation (Mischel 2004), and across culture (McCrae 2002). However, they were proved to differ depending on males and females (Feingold 1994; Budaev 1999; Costa et al. 2001; Weisberg et al. 2011; De Bolle et al. 2015). It has been argued that these differences might arise as a result of either evolution, or social forces. According to the former, gender differences in personality can be explained through biologic factors such as genes, prenatal and postnatal exposure to sex hormones, and sex differences in neural development and brain structure – all ultimately molded by biologic evolution (Budaev 1999; Lippa 2010). Being the evolutionary reproductive success the main goal of the species, men and women would have developed differences in personality mostly in relation to reproduction. In men, therefore, higher levels of aggressiveness, risk-taking, and status-seeking presumably evolved as sexually selected traits that reached dominance and mates attraction. Higher female levels of nurturance, tender-mindedness, and people orientation evolved as sexually selected traits that fostered a successful raising of children. On the other hand, social-environmental theories on gender differences in personality, propose a cascade of

social influences to be responsible for them, such that women and men are expected to serve different roles in society and are therefore socialized to behave differently from one another (Wood and Eagly 2002).

As a result of the evolution, social factors, or the combination of the two, many researchers found consistent gender differences in personality operationalized by the Big Five: women significantly score higher than men in the traits of Agreeableness and Neuroticism (Chapman et al. 2007; Weisberg et al. 2011). However, subtler differences can be explored narrowing the factors to the aspects or even the lowest facets (DeYoung et al. 2007). For example, N which is usually scored higher from women at the trait level, but facets like Anger is usually scored higher in men (Costa et al. 2001). Extraversion, usually scored similarly across genders, shows opposite patterns when considering its facets: while Warmth, Gregariousness and Positive Emotions are higher in women, Assertiveness and Excitement Seeking are higher in men (Feingold 1994; Costa et al. 2001). Similarly, Openness to experience at the trait level does not show a consistent gender difference, which is instead present in its facets, where women typically score higher in Esthetics and Feelings while men in Ideas (Feingold 1994; Costa et al. 2001). No consistent (i.e. across culture) gender difference was found neither at the trait nor at the facets level for C; lastly, women scored higher in both the trait and facets for A (Feingold 1994; Costa et al. 2001). It is important to note that these differences do not preclude men to be nurturing or women to be aggressive, but that the *average* response from one gender is usually higher or lower than the other (Weisberg et al. 2011).

3.4.2 The influence of gender on brain and behavior

Men and women do not only differ in psychological traits (Costa et al. 2001; Levant et al. 2009; Lippa 2010; Van de Velde et al. 2010), they were also shown to differ in their cognitive performances (cf. Miller and Halpern 2014) and neuroanatomy (cf. Cahill 2006).

Especially three cognitive abilities (verbal, quantitative and visual-spatial abilities) were first identified by Maccoby and Jacklin (1974) as the loci of gender differences. Since then more studies investigated gender differences using neuropsychological batteries, either confirming or discrediting the originally proposed gender differences. Male advantages were consistently found in tasks encompassing visual-spatial working memory (Voyer et al. 2017), mathematical abilities

(Zhu 2007) and motor speed processing (Gur et al. 2012). On the other hand, it was often attributed to women an advantage in language, emotional and social tasks (for example verbal memory, non-verbal reasoning, emotion identification, empathy; Saykin et al. 1995; Zaidi 2010; Satterthwaite et al. 2015). Yet, a meta-analysis on more than 150 studies investigating verbal abilities yielded no evidence of substantial gender differences in any aspects of language processing (Hyde and Linn 1988). Quantitative and qualitative comprehensive analyses on cognitive empathy (Kirkland et al. 2013) and emotional processing (Kret and De Gelder 2012) agreed on a slight advantage displayed by women in such abilities. However, Kret and De Gelder highlighted the fact that performances on emotional discrimination might strongly depend on the type of emotion used in the paradigm: in case of facial expressions of fear and sadness, women were found to be better at their recognition (Mandal and Palchoudhury 1985; Nowicki and Hartigan 1988), while anger was better discriminated by men (Mandal and Palchoudhury 1985; Wagner et al. 1986; Rotter and Rotter 1988).

On a neural level, gender influences on brain anatomy, chemistry and function have been intensively investigated (cf. Cahill 2006). The first more prominent difference is brain size: women have smaller brain volume compared to men (average brain volume excluding cerebral spinal fluid and non-brain tissues, 1130 cm³ for women against 1260 cm³ of men; Cosgrove et al. 2007). However, when correcting for the intracranial volume, height and weight, women display a higher percentage of GMV. On the contrary, men display a higher percentage of white matter volume (WMV) and cerebrospinal fluid (CFS) (Gur et al. 1999; Luders et al. 2009). Also surface measurements, like cortical thickness (CT), supported this gender difference, as larger CT across the entire cortex of both hemispheres was detected in women compared to men (Im et al. 2006). As grey matter contains somatodendritic tissues of neurons and neuropil and white matter is formed by myelinated connecting axons, Gur and colleagues suggested that women could rely on more “computational” tissue rather than “transfer” tissue of information across different regions (Gur et al. 1999).

Gender differences at the behavioral level have been explained with differences in morphometric measurements. For example, regions with larger brain volume in women encompass the surroundings of the Sylvian fissure, engaged in language processing, as well as in limbic regions and orbito-frontal gyrus, subserving emotional processing (Gur et al. 2002). Conversely, there are evidences for a higher volume of grey matter in men in the parietal lobe along with best

performances on a mental rotation test (Koscik et al. 2009; Salinas et al. 2012). Also evidences on structural connectivity highlighted differences in the patterns of male and female brains: while in the first, connectivity was mostly intra-hemispheric, in the latter was mostly inter-hemispheric (Ingallhalikar et al. 2014). Accordingly, men's brain is more asymmetric than women's, who instead have a more bilateral organization. It has been argued that the size and shape of the corpus callosum, larger in women, may indeed provide a better communication between the hemispheres, such reducing the specialization and asymmetry (Luders et al. 2006; Grabowska 2017).

In fact, also brain function was shown to differ between genders. For example it has been suggested that the advantage for men in performing mathematical reasoning is due to a higher activation (rather than volume) in regions forming the ventral (para-hippocampal gyrus and lingual gyrus) and dorsal (intraparietal sulcus and angular gyrus) visual stream (Keller and Menon 2009). A meta-analysis on working memory task-based fMRI also demonstrated gender-specific networks whereby females consistently activate more limbic (e.g., amygdala and hippocampus) and prefrontal structures (e.g., right inferior frontal gyrus), and males activate a distributed network inclusive of more parietal regions (Hill et al. 2014). Also while performing decision-making tasks, men and women showed different pattern of activations, thus revealing that different brain mechanisms can be differently engaged by men and women for the same task (Bolla et al. 2004).

Functional gender differences were also found using resting state data (Biswal et al. 2010; Tian et al. 2011; Filippi et al. 2013; Hjelmervik et al. 2014; but see Weissman-Fogel et al. 2010). A study from Satterthwaite and colleagues (2014) for the first time showed using MVPA that RSFC could be efficiently employed to classify male and female brains with the 71% of accuracy (Satterthwaite et al. 2015). Tomasi and Volkow (Tomasi and Volkow 2012) identified in women 14% higher of local functional connectivity density in posterior cingulate/ ventral precuneus compared to men; Hjelmervik and colleagues (Hjelmervik et al. 2014) showed sex differences in two fronto-parietal networks (right dorsal and anterior) with women exhibiting higher functional connectivity. Conversely, another study showed increased RS connectivity in men in parietal and occipital networks, while women showed increased RS connectivity in frontal and temporal regions (Filippi et al. 2013). Allen et al. (2011) discovered no gender difference in the fronto-parietal network at all, but stronger RS connectivity within the DMN in

women.

Despite some inconsistencies on the location of gender differences, there are strong evidences for functional and structural dimorphisms between male and female brains, which ultimately is reflected in behavior and personality traits.

3.4.3 The influence of gender on personality and brain

Even though there are strong evidences for gender effects on both personality and brain parameters, many researchers investigating the neural underpinnings of personality did not consider gender as a separate factor in their studies. On the contrary, gender has been often treated as covariate of no interest in both structural (Omura et al. 2005; Gardini et al. 2009; DeYoung et al. 2010; Cremers et al. 2011; Kapogiannis et al. 2013) and functional (Adelstein et al. 2011; Aghajani et al. 2013; Coutinho et al. 2013; Koelsch et al. 2013; Deris et al. 2017) studies of personality, assuming therefore same neuronal mechanisms across all who express a specific level of a trait.

Although not many, there are studies showing exactly the opposite: men and women display different neural bases for the same trait. In the sMRI literature a VBM study from Blankstein et al. showed gender differences in the trait–brain relationship: in women, Extraversion correlated negatively with medial frontal gyrus GMV, and Neuroticism correlated positively with subgenual anterior cingulate cortex GMV. In men, the above correlations between GMV and personality showed exactly an opposite direction (Blankstein et al. 2009). Similarly, morphometry and functional connectivity analyses on the neural basis of Narcissism also enhanced the notion of a strong dependency on gender (Yang et al. 2015). In another VBM study, smaller right hippocampal volume was found to underlie the basis for higher anxiety-related traits to both genders, whereas anterior prefrontal volume contributed only in females (Yamasue et al. 2008). With regards to RSFC, Sutin and colleagues were able to show that Openness correlated positively with prefrontal activity in women, anterior cingulate activity in men, and orbitofrontal activity in both genders. Thus, while areas linked to reward and emotional processing could be engaged similarly by both genders, regions deputed to cognitive flexibility and monitoring processes underlie individual differences in Openness specifically for women and men respectively (Sutin et al. 2009).

A consideration on i) the well-known gender differences in brain structure and function (cf. Cosgrove et al. 2007; Zaidi 2010), ii) the effect of gender on the self-reported personality scores (Costa et al. 2001; Weisberg et al. 2011) and iii) the growing existing literature which started considering the two above together (Sutin et al. 2009; Yang et al. 2015), prompted the choice of carefully investigate the role of gender on the structural (Study 1) and functional (Study 2) correlates of the Big Five.

3.5 *Aim of the studies*

The main goal of my projects consisted in assessing gender-common or gender-specific neural correlates of the Big Five in a multi-modal approach. By the assumption that the brain is the “proximal” source of differences in each of the five scales (cf. DeYoung and Gray 2009), and that brain organization differs between men and women (cf. Cosgrove et al. 2007), variation of GMV (Study 1) and RSFC (Study 2) was used to investigate which neural regions could be associated with personality in men, in women or both.

Specifically, Study 1, by exploiting gross but robust anatomical index for morphometric changes such as VBM (Palaniyappan and Liddle 2012), could delineate regions in the whole-brain where GMV was correlating with personality traits in males and females. Functional decoding (using the BrainMap database) was then implemented so to identify which types of experiments were associated with activation in the respective regions. Next, mental processes were investigated in relation to the traits within a network perspective, i.e. using RSFC in meta-analytically derived networks presumably most engaged in a given mental process. MVPA substituted more traditional statistical analysis to ensure a data-driven learning of relevant information regarding each trait, based on the entire pattern of connectivity within each network, and higher generalizability. Again, brain-personality relationships were investigated by taking gender into account.

IV STUDY 1

Correlations Between Personality and Brain Structure:

A Crucial Role of Gender

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Total contribution 80%

Correlations between personality and brain structure: A crucial role of gender

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Abstract

Previous studies have shown that males and females differ in personality and gender differences have also been reported in brain structure. However, effects of gender on this “personality- brain” relationship are yet unknown. We therefore investigated if the neural correlates of personality differ between males and females. Whole brain voxel-based morphometry was used to investigate the influence of gender on associations between NEO FFI personality traits and grey matter volume (GMV) in a matched sample of 182 males and 182 females. In order to assess associations independent of and dependent on gender, personality-GMV relationships were tested across the entire sample and separately for males and females. There were no significant correlations between any personality scale and GMV in the analyses across the entire sample. In contrast significant associations with GMV were detected for neuroticism, extraversion and conscientiousness only in males. Interestingly, GMV in left precuneus/parieto-occipital sulcus correlated with all three traits. Thus, our results indicate brain structure-personality relationships are highly dependent on gender, which might be attributable to hormonal interplays or differences in brain organization between males and females. Our results thus provide possible neural substrates of personality-behavior relationships and underline the important role of gender in these associations.

1. Introduction

Personality is what makes every human unique, as it denotes individual differences in behaviors, cognition and emotion, which are stable over time and across situations (Mischel 2004). It has been shown that personality affects various domains in human life, such as job performance (Rothmann and Coetzer 2003), social and political attitude (Riemann et al. 1993), quality and stability of social relationships (Asendorpf and Wilpers 1998), as well as risk for mental disorders (Costa and McCrae 1992a; Miller et al. 2001). One of the most widely recognized personality models is the NEO Five Factor Inventory (NEO FFI; (Costa and McCrae 1992b)), consisting of the dimensions neuroticism, extraversion, openness, agreeableness and conscientiousness. Previous studies have indicated that there are gender differences in neuroticism and agreeableness, with women scoring higher on these two traits than men (Costa et al. 2001; Chapman et al. 2007; Weisberg et al. 2011).

Addressing the biological basis of personality, several voxel-based morphometry (VBM) studies have attempted to characterize the neural architecture of personality. For example, De Young (2010) suggested different brain systems might correlate with the traits of the NEO-FFI (DeYoung et al. 2010), but this view has been challenged by others (cf. (Hu et al. 2011; Koelsch et al. 2013)), illustrating the currently inconsistent and heterogeneous (with respect to both the associated regions and the direction of association) literature. Most importantly, the (generally rather low) sample size varies considerably between studies, and there is a substantial heterogeneity with regard to age and in particular gender distribution. For example, Barrós-Loscertales et al., 2006 (Barrós-Loscertales et al. 2006) only investigated males, Van Schuerbeek, 2011 (Van Schuerbeek et al., 2011) only females, while others investigated unbalanced samples of males and females (i.e. (Liu et al. 2013), (Yamasue et al. 2008)). It has, however, been shown that beyond mere brain size, males and females differ in brain structure. In particular, gender differences have been reported in grey matter volume (Luders et al. 2009), cortical thickness (Im et al. 2006), and structural connectivity

(Ingallhalikar et al. 2014). Given those gender differences in brain structure, as well as the fact that males and females differ also in traits such as the NEO-FFI (Costa et al. 2001; Chapman et al. 2007; Weisberg et al. 2011), it is likely that gender also has an influence on the neural correlates of personality. However, effects of gender on personality/brain relationships have rarely been investigated to date. Rather, most studies investigating personality in association to brain structure treated gender only as covariate of no interest (Omura et al. 2005; Gardini et al. 2009; Cremers et al. 2011; Kapogiannis et al. 2013; Lu et al. 2014).

The aim of the current study was thus to investigate brain regions associated with personality across both genders, as well as to assess a potential sexual dimorphism of the relationship between personality traits and local grey matter volume. Importantly, since personality traits in their extreme forms are considered as vulnerability factors of personality and mood disorders (Costa and McCrae 1992a), which show important differences in prevalence for males and females (Afifi 2007), a better knowledge of the underlying neural correlates of personality and of potential gender differences of these should also contribute to a better understanding of those clinical conditions.

2. Materials and methods

2.1 Subjects

Participants were selected from the data provided through the Human Connectome Project, WU-Minn Consortium, in the current “S500” release, (HCP, <http://www.humanconnectome.org> ((Van Essen et al. 2012), Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University.

Analyses of the HCP data were approved by the ethics committee of the Heinrich Heine University Düsseldorf.

The HCP sample is composed of monozygotic (MZ) and dizygotic (DZ) twins (at the moment of the selection of the subjects: 34 MZ males, 92 MZ females, 51 DZ males, 93 DZ females) and not-twins (132 males not-twins and 140 females not-twins). The category of the not-twins includes siblings of twins, just siblings and only-children (including those that have a not yet scanned sibling but not twin).

Given this structure, we paid particular attention to select a well-matched sample from this data that is as large as possible while at the same time controlling for possible effects of heritability, age and education. Evidently, we first selected all participants from the HCP sample for whom MRI images and personality data were available. Out of this sample, we then selected groups of males and females, respectively, which were closely matched with regard to their age and years of education. Importantly, we included only participants who met the following constraints to control for family structure and effects of premature birth (which is the norm in twins): only one subjects per monozygotic twin pair was selected due to the high genetic similarity to the co-twin and the same amount of monozygotics was chosen for males and females, while for dizygotic pairs both twins were included since they are genetically equal to siblings. Although it would have been more straightforward to use only unrelated individuals, this would have extremely reduced the sample size and, consequently, the statistical power.

Based on these criteria, a sample of 182 males (age 22-36 years, mean 29.0 ± 3.4 , education 14.7 ± 1.8) and 182 females (age 22-35 years, mean 29.2 ± 3.5 , mean of years of education 14.7 ± 1.9) were selected. The percentage of twins and non-twins participants did not differ by gender ($\chi^2_1 =$

2.2, n.s.). Moreover, no significant gender differences were detected for age ($t_{362} = -0.47$, ns.) and years of education ($t_{362} = -0.25$, ns.).

Figure 1 illustrates the distribution of siblings in the male and female sample. Specifically, 17 female-female dizygotic pairs and 27 females without the dizygotic twins were included in the female (for a total of 61 dizygotic females) and 15 pairs of male-male dizygotic twins and 17 dizygotic males without the dizygotic twin in the male sample (for a total of 47 dizygotic males). Furthermore, the sample consists of 19 monozygotic female individuals and 19 monozygotic male individuals as well as 102 non-twin females and 116 non-twin males. Therefore 80 individuals with a twin status and 102 individuals with a non-twin status formed the female group, while 66 individuals with a twin status and 116 individuals with a non-twin status formed the male group.

The 364 subjects belonged to a total of 200 different families, distributed as follows: 85 families were composed by just one individual, 75 families by 2 individuals, 31 families by 3 individuals, 8 families by 4 individuals and 1 family by 5 individuals. Thus, 85 subjects were unrelated (38 males and 47 females) while 279 had at least one other subject in the sample that was related to him/her (144 males and 135 females). 38 of the males and 47 of the females have no siblings; 67 of the males and 44 of the females have at least one male sibling, 47 of the males and 57 of the females have at least one female sibling; 30 of the males and 34 of the females have at least a male and a female sibling.

Fig. 1 about here please

2.2 Questionnaire

Subjects completed the English version of the NEO Five Factor Inventory (NEO FFI, (McCrae and Costa 2004)). The NEO FFI consists of 60 items in form of statements, 12 for each of the five factors (Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness).

2.3 MR imaging and pre-processing

3D structural T1w MRI scans were acquired (Glasser et al. 2013) on a Siemens Skyra 3T scanner using a 32-channel head coil and a 3D MPRAGE sequence (T1w MPR1, voxel size= 0.7x0.7x0.7 mm, FoV= 224x224 mm, matrix = 320, 256 sagittal slices in a single slab, TR= 2400 ms, echo time; TE= 2.14 ms, TI= 1000 ms, flip angle 8°).

Data preprocessing was performed with SPM8 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK, <http://www.fil.ion.ucl.ac.uk/spm/>) and the VBM8 toolbox (<http://www.neuro.uni-jena.de/vbm8>), running under Matlab R2014a (Mathworks, Natick, MA). Structural images were normalized using the DARTEL algorithm (Ashburner 2007) to the ICBM-152 template using both affine and non-linear spatial normalisation, bias-field corrected and segmented into grey matter, white matter and cerebrospinal fluid tissues. The normalized grey matter segments were then linearly and non-linearly modulated. Finally, images were smoothed with an isotropic Gaussian kernel (full-width-half-maximum = 8 mm).

2.4 VBM analyses: Relationships between GMV and personality

We performed multiple regression analysis in SPM8 using the voxel-wise grey matter volume (GMV) as dependent variable and the scores of the five factors of the NEO FFI as covariates of interest. Given the collinearity of the NEO FFI scores (**Table 1**), each factor was assessed by a separate GLM. For the analyses on the entire sample (364 participants) we included age, total brain volume (TBV) and gender as covariates of no interest. For the within-gender analyses only age and TBV were added. Inference was performed using threshold-free cluster enhancement (TFCE; (Smith and Nichols 2009)). The critical threshold to control the family-wise error at $p < 0.05$ was based on a non-parametric permutation framework (extend threshold of 50 voxels). In order to identify regions where GMV was correlated with more than one personality trait, conjunctions

were performed using the minimum statistic (Nichols et al. 2005) and multiple linear regression analyses were conducted to examine how their predictive power on the correlation to the GMV was shared among them. All activations are reported in MNI space and were anatomically localized by using the SPM anatomy toolbox 2.1 (Eickhoff et al. 2005, 2007).

We also calculated cortical thickness and cortical surface area in order to test whether the regions found in the VBM results were also detected in these other structural analyses. The description of method and results can be found in the supplement material.

2.5 Follow-up: Gender differences in volume-personality association

For regions where a significant correlation in either males or females was found, we further investigated if a significant difference in the correlation could be found between males and females. Therefore, Pearson correlations (r) between GMV and each personality score were calculated, separately for males and females, transformed into Fishers Z scores and compared between groups (Kenny 1987). For significant ($p < 0.05$) group differences we estimated the effect sizes by using the Cohen's q measure (Cohen 1988) ($q < 0.1$: no effect, $0.1 < q < 0.3$: small effect, $0.3 < q < 0.5$: intermediate effect, $q > 0.5$: large effect).

2.6 Follow-up: Functional Decoding

All significant clusters were in a last step functionally characterized using the Behavioral Domain meta-data from the BrainMap database (<http://www.brainmap.org>; (Fox and Lancaster 2002; Laird et al. 2009, 2011)). In particular, we identified those meta-data labels (describing the task that was performed [paradigm class] as well as the computed contrast [behavioral domain]) that were significantly more likely than chance to result in activation of a given cluster ((Henson 2005; Poldrack 2006)). That is, functions were attributed to the identified morphological effects by

quantitatively determining which types of experiments are associated with activation in the respective region.

3. Results

3.1. Gender differences and factors correlations in NEO-FFI scores

Comparison of the five personality scores between men and women (see **Fig. 2**) revealed a significant difference for neuroticism ($t_{362} = -3.02$; $p < 0.05$, $d = 0.31$) and conscientiousness ($t_{362} = -2.7$, $p < 0.05$, $d = 0.29$). For openness ($t_{362} = 1.63$, ns.), agreeableness ($t_{362} = -1.79$, ns) and extraversion ($t_{362} = 0.43$, ns) no significant gender differences were detected.

Correlations between factors were calculated separately for males and females and across the whole sample using SPSS 20 (IBM Corp. Released, 2011). Most of them were significant at $p < 0.05$ (Bonferroni-corrected) for both males and females and across the entire sample; however openness was found to be independent of most of the other factors, especially in the female sample (see **Table 1**). Furthermore, neuroticism was the only factor correlating negatively with most of the others: with agreeableness, conscientiousness and extraversion in men and in the mixed sample, in women also with openness.

Figure 2 and Table 1 about here please

3.2. Association to GMV

Across the entire sample, no significant correlation was found between any personality factor and GMV (controlling for age, TBV and gender). Likewise, our analyses revealed no significant relationships between any of the five personality factors and GMV in females (controlling for age and TBV). However, we found significant ($p < 0.05$, FWE corrected) correlations in males. Negative

correlations were found between neuroticism and GMV of bilateral parieto-occipital sulcus/cuneus (POS/Cun) extending into precuneus, left mid fusiform gyrus extending into cerebellum (lFFG/Cb), and right mid fusiform gyrus (rFFG). Positive correlations were found between extraversion and GMV of bilateral precuneus and parieto-occipital sulcus (Prc/POS), bilateral thalamus (Th), left mid FFG extending into the cerebellum (lFFG/Cb) and right cerebellum (rCb). Conscientiousness was positively correlated with GMV of left precuneus and parieto-occipital sulcus (Prc/POS) (**Table 2 and Fig. 3, 4, 5**).

Table 2 and Figure 3, 4, 5 about here please

Given that in the male sample, we found a significant relationship of GMV in the region of the left Prc/POS with conscientiousness, neuroticism and extraversion, we assessed a potential convergence between these effects by a minimum conjunction, confirming an association of a left Prc/POS with all three NEO FFI scores (**Table 3, Fig.6**). The multiple regression model with all three predictors produced $R^2 = 0.132$, $F(3, 178) = 9.0$, $p < 0.001$; specifically, conscientiousness was the only significant predictor of the model ($t_{178} = 2.3$, $p < 0.05$), while extraversion ($t_{178} = 1.8$, n.s.) and neuroticism ($t_{178} = -1.4$, n.s.), did not explain any additional variance.

Table 3 and Figure 6 about here please

Another minimum conjunction was computed between the whole brain VBM results of neuroticism and extraversion revealing a further overlap in left FFG and right cerebellum (**Table 4, Fig.7**).

Table 4 and Figure 7 about here please

3.3. Follow-up: Gender differences in GMV-personality association

All clusters that showed a significant association with one of the NEO FFI scores in males (cf. **Fig. 3.B, 4.B, 5.B**) also showed a significant gender-difference in the correlation between GMV and personality scores (**Table 5**).

Table 5 about here please

When comparing the GMV and NEO-FFI associations for the IPrc/POS, i.e., the core region identified in the three-way conjunction (relationship to conscientiousness, neuroticism and extraversion) between males and females, we also found a significant gender difference for all three scales (**Table 6, Fig. 6.B**). Likewise, assessing the clusters found in two-way conjunctions across NEO FFI scores (POS/Cun, left FFG and right cerebellum), also confirmed that the association between the GMV of these regions and the respective personality trait was significantly stronger in males (**Table 6, Fig. 7.B**).

Table 6 about here please

3.4. Follow-up: Functional characterization

Functional decoding of the regions which correlated separately with neuroticism, extraversion and conscientiousness is shown in **Fig. 3.C, Fig. 4.C** and **Fig. 5C**. The functional decoding of the IPrc/POS found in the three-way conjunction (**Fig.6.C**) revealed that this region was significantly associated with explicit memory and perception of visual motion as well as action inhibition ($p < 0.05$). The functional characterization of the clusters from the conjunction between neuroticism and extraversion (**Fig 7.C**), i.e., the only two-way conjunction yielding significant results outside the cluster already identified by the three-way conjunction, showed that the POS/Cun was associated with action observation, anxiety, olfactory and visual perception, as well as multiple

cognitive processes ($p < 0.05$). Finally, left FFG/Cb as well as right Cb were both associated to language processing, while the former was additionally related to emotion processing ($p < 0.05$).

4. Discussion

The current morphometric study investigated the neural correlates of personality traits assessed by the NEO-FFI and potential gender differences thereof. We found no significant correlations between any personality scales and GMV when investigating relationships across the entire sample. In contrast, when the sample was split by gender, significant associations were observed in males but not females. This sexual dimorphism was corroborated by the significant differences in GMV/personality correlations between males and females for the respective clusters. Together, these findings thus demonstrate that gender is a fundamental factor to consider when trying to understand the morphological underpinnings of inter-individual differences in personality traits.

4.1 Correlations among personality traits

Correlations among the five personality traits (**Table 1**) revealed similar patterns as reported in the literature (Egan et al. 2000; McCrae and Costa 2004; van der Linden et al. 2010), with mostly negative correlations between neuroticism and the other factors, and positive ones between extraversion, agreeableness and conscientiousness. Furthermore, also in line with previous reports (Egan et al. 2000; McCrae and Costa 2004; van der Linden et al. 2010) the lowest correlations were found between openness and the other factors, while the highest associations were observed for neuroticism with extraversion and neuroticism with conscientiousness (Egan et al. 2000; McCrae and Costa 2004; van der Linden et al. 2010). However, several correlation coefficients that were observed when performing separate analyses for males and females were somewhat higher than those observed in previous studies (e.g. extraversion and neuroticism in

males: -0.514; conscientiousness and extraversion in males: 0.449; conscientiousness and neuroticism in females: -0.428). It may be speculated that this may relate to the fact that some of our subjects were related to each other. However, when testing correlations only in a subsample of unrelated subjects, the higher than previously reported correlations persisted (**Supplement Table 1**). It is important to note that the meta-analytic intercorrelations reported in Van Der Linden et al. (2010) were based on different personality questionnaires and that previous studies investigating the NEO-FFI computed correlations in gender-mixed samples (Egan et al. 2000; McCrae and Costa 2004; van der Linden et al. 2010). Therefore, the higher values might be due to the fact that we did separate analyses for males and females, while correlations across the entire sample are comparable to previous reports. We would therefore argue that the discrepancy between our (gender-separated) correlations and those previously observed for gender-mixed samples (which we confirmed when analyzing males and females from our sample together) indicate that not only the mean NEO-scores but also their correlation structure shows a sexual dimorphism.

4.2 Gender differences in personality traits

Previous studies investigating gender differences in NEO-FFI have shown that women score higher in neuroticism and agreeableness, while conscientiousness, extraversion and openness did not show significant differences (Costa et al. 2001; Chapman et al. 2007; Weisberg et al. 2011). In line with these studies, we observed higher neuroticism-scores for women but no significant gender differences in openness and extraversion. However, in contrast to previous studies, we failed to find a significant gender difference in agreeableness, and found that women scored higher for conscientiousness than men. We would propose that these discrepancies may be attributable to the constitution of the cohort, most importantly the parenting experience. Indeed agreeableness has

been associated to motherhood and nurturance in females but not in males (Jokela et al. 2011) and this trait shows a significant increase around the age of 30 (Soto et al. 2011), when more often decisions about starting a family are taken. Since the HCP data consists of a young sample, we hypothesize that some women in our sample might not have had kids yet, resulting in a similar men's mean score. When looking at mean agreeableness scores in older (32-35 years old) and younger females (22-27 years old) there is, indeed, an indication of an increasing score with age (younger: mean 30.8; older: mean 32.6) while in males the means are similar (younger: 30.5; older: 30.7). On the other hand, our female sample scored significantly higher than males in conscientiousness. This might reflect a potential societal shift favoring (work-related) conscientiousness in young female cohorts and confirm the study from Jokela and colleagues (Jokela 2012), already demonstrating a birth-cohort effect on conscientiousness and agreeableness scores.

4.3 Association of NEO-FFI scores to GMV across the entire sample

The absence of any significant relationships between personality traits and regional GMV across the entire sample contradicts the biological model of the NEO-FFI suggested by De Young (2010) and other previous studies that supported such association (Omura et al. 2005; Gardini et al. 2009; Cremers et al. 2011; Kapogiannis et al. 2013; Lu et al. 2014). However, it may be noted that GMV-personality relationships are highly inconsistent over these previous studies in terms of location and direction. Part of this heterogeneity may be attributable to methodological differences and analytic variability between studies, including differences in personality questionnaires, whole-brain vs. regional analysis, differences in data preprocessing, variable types of statistical thresholds and (no) correction for multiple comparisons, different combinations of nuisance covariates (NCs,

specifically age, gender and total brain size; cf (Hu et al. 2011)). However, we would argue that probably the usually rather small sample size, leading to spurious associations, is the major culprit. In that context, it is interesting to note that our findings are in line with those by Liu and colleagues (Liu et al. 2013) who assessed a large sample (227 subjects) in a similar age range using a comparable approach and likewise found no significant associations between NEO-FFI personality items and GMV. However, it has to be noted that Liu and colleagues neither found any correlations when investigating relationships separately for males and females. However, considering that the male sample only consisted of 59 subjects, small and moderate effects, like those in our study, might thus have been missed.

Given that our study assessed a large and well-balanced sample, is by far the best powered to date, and capitalizes on the unprecedented data quality of the HCP project, the current negative result across both genders is particularly noteworthy given the backdrop of an inconsistent literature based on smaller samples. We would thus argue that the latter may have arisen from a combination of spurious associations in smaller samples (and/or liberal thresholding) and a publication bias towards positive findings (Wallentin 2009), a situation that may be a common problem in morphology/phenotype associations in basic and even more clinical neuroscience .

4.4 Association of NEO-FFI scores to GMV in the male sample

4.4.1 Convergence of Neuroticism, Extraversion and Conscientiousness

It has already been reported that extraversion and conscientiousness scores correlate positively with each other and negatively with neuroticism (McCrae and Costa 2004). In our male subsample the neural correlates of all three traits overlap in the POS as well as in Prc (overlapping with cluster 1 of the connectivity-based parcellation of Bzdok (Bzdok et al. 2014)), where their correlations with

GMV resembled their correlation structure as higher extraversion and conscientious scores go along with higher GMV, whereas a lower amount of GMV is associated to higher neuroticism.

We furthermore showed that this region is activated by task-fMRI studies probing visual (motion) perception, memory and action inhibition. It may thus be speculated that neuroticism, extraversion and conscientiousness should, via the morphological substrate of the IPrc/POS, relate to inter-individual performance in these functions. It has for example been shown that higher conscientiousness is associated to better performance in tasks requiring cognitive control and action inhibition, such as the Stroop (Bannon et al. 2002) and anti-saccade (Kelly et al. 2015) tasks. Similarly, higher extraversion goes along with an enhanced ability to ignore task-irrelevant information in a verbal Stroop task (Prabhakaran et al. 2012). Conversely, neuroticism is associated with a decreased ability to ignore irrelevant information (Prabhakaran et al. 2012). The latter has been related to a “*hypervigilance of threats*” (Mogg and Bradley 1998; Richards et al. 2014), i.e., an adaptive behavior to perceive a potential risk faster, which comes at the cost of specificity and, consequently, less successful inhibition of irrelevant stimuli and response sets. While the association of personality traits to visual processing have received less attention, the positive relation between conscientiousness and (anti-) saccade task performance corroborates the above picture, as does the role of extraversion as a positive predictor of attentional control in visual classification or change detection tasks (Stenberg 1994). There have also been several reports linking higher extraversion, as well as lower neuroticism, to better (long-term) memory performance (Nakamura et al. 1979; Ashby et al. 1999; Allen et al. 2011). Finally, conscientiousness was shown to correlate positively with subjective memory (Pearman 2009), which in turn might reflect performance in objective mnemonic tasks (Zimprich and Kurtz 2015).

In summary, we would thus argue that the observed convergence of morphometric substrates for neuroticism, extraversion and conscientiousness in the IPrC/POS may provide the structural correlate of the association between these personality traits and inter-individual performance-differences in the domains of action inhibition, visual perception and memory.

4.4.2 Convergence of Neuroticism and Extraversion

For the male subsample, additional convergence in the morphometric substrate for extraversion and neuroticism was found in the IFFG/Cb and rCb, regions associated to language and, in the case of IFFG/Cb, emotion, face and reward processing. This suggests a link between these personality traits and inter-individual performance difference in language tasks, which is supported, e.g., by previous work showing a positively association with extraversion, and a negative one with neuroticism for verbal fluency tasks (Sutin et al. 2011). Regarding the specific effects in the fusiform face region and the relation to emotion, we would speculate that individuals with higher extraversion spend more time with others resulting in use-dependent plasticity in face-selective regions. Alternatively, however, already higher GMV in face selective regions might lead to a stronger tendency to spend more time with others and hence even predispose towards an extraverted personality.

In contrast, hypervigilance in high neuroticism might favor the detection of threats (Richards et al. 2014), and concurrently impair the processing of the neutral faces and other emotions (Andric et al. 2015). With regard to reward sensitivity, there is evidence of an opposite role of approach (associated to extraversion) and avoidance (associated to neuroticism) on the anticipatory role of reward: approach relies on a higher sensitivity to social (Wilkowski and Ferguson 2014) and

monetary (Ostaszewski 1996) rewards, while avoidance is associated with reduced responsiveness to incentives (Bress et al. 2013).

4.5 Gender differences in brain structure-personality relationships

Our analyses revealed not only several personality “hotspots” in males, but strikingly also failed to find any relationship in the female subgroup. This absence of localized morphology/personality relationships may well relate to observations that female brains are more decentralized (Zaidi 2010) and feature stronger interhemispheric structural connectivity (Ingallhalikar et al. 2014); i.e., are potentially ‘hard-wired’ towards multitasking (Zaidi 2010). In particular, such more distributed and integrated architecture may reduce the explanatory power of any local morphological effect.

Another factor that likely plays a major role in the observed dimorphism is the effect of sex hormones, given their influence on personality (Daendee et al. 2013) and brain structure (De Vries 2004). Both estrogens and progesterone, for example, influence neuroticism via antagonistic modulation of GABA receptors (Maggi and Perez 1986; Daendee et al. 2013), and have been hypothesized to play a crucial role in generating the higher neuroticism scores (Seeman 1997) that have been observed for females in several studies, including ours. These hormones also influence neuropsychological features related to personality obtained through the functional profile; for instance, estrogens positively modulate saccadic eye velocity (Wihlbäck et al. 2005), long-term memory (Barros et al. 2015) and self-regulation/inhibitory control (Hosseini-Kamkar and Morton 2014), while progesterone negatively modulates saccadic eye velocity (van Broekhoven et al. 2006), memory (Barros et al. 2015) and self-regulation (Hosseini-Kamkar and Morton 2014). Furthermore, their fluctuation over the menstrual cycle has been connected to neural changes, on both structural and functional level in different brain regions (Witte et al. 2010; Rasgon et al. 2014; Lisofsky et al. 2015).

The influence of sex hormones on personality features and neurobiology, combined with their massive changes over the menstrual cycle in women and relative stability in men, may well explain the lack of significant results in the female sample. In particular, since we could not control for menstrual cycle in our sample, we must assume that female participants were scanned randomly in all phases of a natural menstrual cycle or under contraceptive medication, i.e., synthetic hormones. Given the ensuing variations in estrogens and progesterone levels, the female group should be substantially more heterogeneous than the male sample, which in turn should make it more difficult to detect associations between morphometric features and personality scores, if the increase in variance is not isomorphic between the phenotypical scores and (local) brain volume changes. In addition to the effects of female sex hormones, the higher levels of testosterone in males (Torjesen and Sandnes 2004) and its stable concentration across the life span (Liu et al. 2015) may also contribute to the differential findings. For example, testosterone is involved in regulating approach behavior and social status-seeking (Eisenegger et al. 2011) and therefore associated with extraversion (Smeets-janssen et al. 2015), but has also been shown to influence cortical thickness in cuneus and other visual areas (Bramen et al. 2012). Consequently, the above-discussed associations in males may reflect a common causal factor (i.e., testosterone) driving both morphometric features, personality and neuropsychological performance in various tasks.

4.6 Clinical implications

Personality traits may become themselves clinically relevant in their extreme forms as personality disorders (Miller et al. 2001). Rather and more importantly, they also seem to predispose towards multiple Axis-I disorders. For example, high neuroticism and low extraversion are associated with social, agoraphobia and specific phobias (Bienvenu et al. 2007), high neuroticism, low extraversion and conscientiousness with depression (Weiss et al. 2009), low extraversion and high agreeableness

with eating disorders (Tasca et al. 2009), high neuroticism and extraversion with substance abuse (Dubey et al. 2010). This strong link between personality traits and Axis-I disorders is corroborated by gender differences in prevalence. For example, mood, anxiety, social and eating disorders are more frequently found in females (McLean and Hofmann 2011; Viana and Andrade 2012; Seney and Sibille 2014) c.f. (Afifi 2007), while substance abuse is more common in males (Compton et al. 2007; Viana and Andrade 2012).

This convergence extends to the neurobiological level. For instance, depressed patients feature reduced GMV in the Prc/Cun (Grieve et al. 2013), which resonates well with its reduced volume in high neuroticism. Finally, in line with our result of decreased GMV in lPrc/POS going along with low extraversion, persistent GMV reduction of the precuneus has been demonstrated in anorexia (Joos et al. 2011). While more indirect evidence, it is also interesting to note that various Axis-I disorders also feature cognitive impairments in those domains that we found to be associated with the Prc/POS, i.e., the convergent structural substrate for multiple personality dimensions. In particular, it has been shown that patients with social anxiety demonstrate a lack of attentional control and difficulties in focusing on task-relevant stimuli (Derakshan et al. 2009; Wieser et al. 2009) and that patients with depression show impairments involving visual attention, cognitive flexibility (Hoffstaedter et al. 2012; Dose-Grünefeld et al. 2015) and control (De Lissnyder et al. 2012) as well as memory (Roca et al. 2015).

In summary, our results in combination with previous findings suggest the Prc/POS as a key structure in the close relationship between personality traits, gender, major psychiatric disorders and changes in brain structure as well as neuropsychological profiles. Moreover, they also highlight the importance of assessing potential sexual dimorphisms of these relationships.

4.7 Limitations

It has to be acknowledged that our sample partially consists of related subjects, which might have influenced the present findings. Therefore, in order to test if the association of personality with GMV in POS, IFFG and rCB could be replicated in an unrelated (though substantially lower powered) sample, we reran our analysis again in a more restricted sample, consisting of 150 unrelated subjects, with men and women matched for their zygoty, age and years of education. Also in this smaller group, we found a cluster located in the lPrc/POS, which GMV in males was positively associated to extraversion and negatively associated to neuroticism scores. However, correlations between IFFG and rCb with extraversion and neuroticism, as well as between lPrc/POS with conscientiousness could not be reproduced. These effects may thus have arisen from the family structure, although we would strongly argue that their absence could very likely be related to the much lower power in the now substantially smaller sample. In conclusion, the correlation between lPrc/POS and extraversion and neuroticism can be considered as stable and independent from genetic influences, while the associations with IFFG/Cb and rCb should be interpreted with caution, and should be replicated in a larger unrelated sample.

Furthermore, the presented neuroanatomical changes associated with personality were found in males, who have generally larger brains than females (Ruigrok et al. 2014). It has previously been shown that volume of specific brain regions as well as inter- and intra-hemispheric connectivity differences between males and females may be related to brain size ((Hänggi et al. 2014; Pintzka et al. 2015) but compare (Im et al. 2006; Luders et al. 2009)). Therefore the question arises whether the effects of the current study, which are only observed in men, can be fully attributed to gender, or are (partially) also driven by brain size. While we controlled for total brain volume by using it

as a covariate of no interest in our statistical models, we would still refrain from claiming that our results are purely attributable to gender.

Lastly, we performed a surface-based analysis of cortical thickness and area in order to explore whether the correlations we found in VBM analysis could also be found in these more specialized measures of cortical morphometry. Results revealed a positive association in males between conscientiousness and cortical thickness of the IPOS at an uncorrected level ($p < .001$, uncorrected), while no correlations were observed with the traits of extraversion and neuroticism neither for the IPOS nor for IFFG. Thus, based on our results, we would argue that, though on an uncorrected level ($p < 0.001$), the association between volume of IPOS and conscientiousness may be more related to changes in cortical thickness than surface area. However, given that the surface-based analyses yielded largely null-results it seems that grey matter volume is more sensitive in detection brain structure-personality relationships than either of its two constituents, i.e., cortical thickness or surface area. These results support the notion of GMV as a gross but robust anatomical index for morphometric changes, providing a mixed measure of regional grey matter properties including cortical surface area, thickness and potentially folding. Consequently, the more specialized SBM measures might fail to detect changes driven by interactions of multiple surface-based features and, consequently, when used in isolation, significant associations with performances might not be revealed (Smolker et al. 2015).

4.8 Summary and Conclusion

Our study challenges existing notions on morphological substrates for personality traits, by yielding a negative result in a well-powered analysis of high-quality data in a balanced sample. Additionally, it demonstrates that relationships between personality traits and brain structure are highly dependent on gender. This observation is corroborated by converging neuropsychological

and clinical evidence supporting a similar sexual dimorphism. We also identified the left precuneus as a convergent substrate for neuroticism, extraversion and conscientiousness in males. This region was functionally implicated by our analysis in cognitive control, visual perception and memory, i.e., mental functions that show robust relationships to the aforementioned personality traits. Extraversion and neuroticism converged also in the left fusiform gyrus and right cerebellum, regions related to emotion processing and language skills that are likewise related to personality.

Taken together, our study provides a critical view on previous links between brain structure and personality traits, revealing the precuneus as a key region linking personality, gender, mental functions and psychiatric disorders, and highlighting the need to account for sexual dimorphisms when trying to unravel the complex relationships between these aspects.

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Table 1: Intercorrelations (Pearson's r) among the five personality factors in males (n=182), females (n=182) and across the overall sample (n=364)

		Neuroticism	Extraversion	Openness	Conscientiousness	Agreeableness
Neuroticism	Males	-	-0.5140*/	0.1001/	0.3996*/	-0.3260*/
	Females		-0.3190*/	-0.0204/	-0.4287*/	-0.3565*/
	Overall		-0.416*	0.028	-0.383*	-0.320*
Extraversion	Males	-	-	0.0319/	0.4490*/	0.3398*/
	Females			0.0741/	0.2624*/	0.2378*/
	Overall			0.055	0.351*	0.285*
Openness	Males	-	-	-	-0.1888*/	0.2009*/
	Females				-0.0557/	0.1299/
	Overall				-0.136*	0.157*
Conscientiousness	Males	-	-	-	-	0.2802*/
	Females					0.1414/
	Overall					0.225*
Agreeableness		-	-	-	-	-

* marks significance at $p < 0.05$

Table 2: Regions where GMV was found to be correlated with Neuroticism, Extraversion and Conscientiousness in the male sample

Regions	X	Y	Z	Cytoarchitectonic Assignments
(size in voxels)				
Neuroticism				
<u>Parieto-occipital sulcus/</u> <u>Cuneus</u> (6053 voxels)	0	-78	13	left hOc1 (left hOc3d; right hOc1; left hOc1)
<u>Left fusiform gyrus/</u> <u>cerebellum</u> (1027 voxels)	-46	-49	-28	left lobule VIIa Crus I (left FG2; left lobule VIIa crus II; left lobule VI)
<u>Right fusiform gyrus</u> (297 voxels)	42	-48	-25	right FG2 (right lobule VI; right lobule VIIa crus I)
Extraversion				
<u>Precuneus/parieto-</u> <u>occipital sulcus</u> (11.001 voxels)	-1	-69	33	left hOc1 (right hOc1; right Area 5L; left hOc3d)
<u>Thalamus</u> (621 voxels)	9	-31	0	right Th-temporal (right Th-Parietal; left Th-Prefrontal; right Subiculum)
<u>Left fusiform gyrus/</u> <u>Cerebellum</u> (213 voxels)	-46	-48	-28	left lobule VIIa crus I (left FG2; left lobule VI)
<u>Right cerebellum</u> (444 voxels)	13	-81	-21	right lobule VIIa crus I (right lobule VI; right hOc4v; right hOc3v)
Conscientiousness				
<u>Left precuneus/parieto-</u> <u>occipital sulcus</u> (491 voxels)	-9	-73	30	left hOc4d (left hOc3d; left Area 7P; left Area 7M)

x, y and z coordinates denote the center of gravity in MNI space.

Reference for probabilistic cytoarchitectonic mapping of: hOc1 (Amunts et al. 2000); hOc3d, hOc4d (Kujovic et al. 2013); lobule VIIa crus I and lobule VI (Diedrichsen et al. 2009); FG2 (Caspers et al. 2013); Area 5L, 7P, 7M (Schepers et al. 2008); hOc3v and hOc4v (Rottschy et al. 2007); Th-temporal, Th-parietal, Th-prefrontal and Subiculum (Behrens et al. 2003)

Table 3: Results of the three-way conjunction across the analyses of Neuroticism, Extraversion and Conscientiousness in the male sample

Regions (size in voxels)	X	Y	Z	Cytoarchitectonic Assignments
Neuroticism, Extraversion and Conscientiousness				
<u>Left precuneus/parieto-occipital sulcus</u> (477 voxels)	-9	-73	30	left hOc4d (left hOc3d)

x, y and z coordinates denote the center of gravity in MNI space.

Reference for probabilistic cytoarchitectonic mapping of: hOc4d (Kujovic et al. 2013)

Table 4: Results of the two-way conjunction across the GMV results of Neuroticism and Extraversion

Regions (size in voxels)	X	Y	Z	Cytoarchitectonic Assignments
Neuroticism and extraversion				
<u>Parieto-occipital sulcus/Cuneus</u> (4082 voxels)	-2	-76	19	left hOc1 (right hOc1, left hOc3d left hOc2)
<u>Left fusiform gyrus/cerebellum</u> (189 voxels)	-46	-49	-27	left lobule VIIa crus I (left FG2, left lobule VI)
<u>Right cerebellum</u> (166 voxels)	16	-78	-19	right lobule VI (right hOc4v, right lobule VIIa crus I, in right hOc3v)

x, y and z coordinates denote the center of gravity in MNI space.

Reference for probabilistic cytoarchitectonic mapping of: hOc1 and hOc2 (Amunts et al. 2000); hOc3d (Kujovic et al. 2013); lobule VIIa crusI and lobule VI (Diedrichsen et al. 2009); FG2 (Caspers et al. 2013); hOc3v and hOc4v (Rottschy et al. 2007)

Table 5: Gender differences in GMV-Personality associations in regions individually correlating with neuroticism (POS/Cun, IFFG/Cb, rFFG), with extraversion (Prc/POS, Th, IFFG/Cb, rCb) and with conscientiousness (lPrc/POS)

	r_{males}	r_{females}	Z value of gender comparison of r: (Z_{males}-Z_{females})/σ(Z_{males}-Z_{females})	Cohen's q of gender difference
Neuroticism				
POS/Cun	-0.27 *	0.01	-2.7*	0.31
IFFG/Cb	-0.36*	0.15	-4.8*	0.53
rFFG	-0.38*	0.07	-4.4*	0.38
Extraversion				
Prc/POS	0.29*	-0.05	3.3*	0.35
Th	0.32*	-0.07	3.8*	0.4
IFFG/Cb	0.46*	-0.11	5.7*	0.6
rCb	0.31*	-0.01	3.1*	0.3
Conscientiousness				
lPrc/POS	0.3*	0.05	2.9*	0.3

* marks a significant correlation coefficient or gender difference.

Table 6: Gender differences in GMV-Personality associations of the regions found in the three-way conjunction region (lPrc/POS) and in the two-way conjunction (POS/Cun, IFFG/Cb, rCb)

	r_{males}	r_{females}	Z value of gender comparison of r: (Z_{males}-Z_{females})/σ(Z_{males}-Z_{females})	Cohen's q of gender difference
lPrc/POS				
Neuroticism	-0.27*	0.04	-2.24*	0.31
Extraversion	0.29*	0.07	2.16*	0.20
Conscientiousness	0.30*	0.04	2.54*	0.27
POS/Cun				
Neuroticism	-0.3*	0.0	-2.9*	0.31

Extraversion	0.29 *	-0.07	3.5*	0.37
IFFG/Cb				
Neuroticism	-0.33*	0.11	-4.7*	0.45
Extraversion	0.33*	-0.1	4.2*	0.35
rCb				
Neuroticism	-0.28*	0.0	-2.7*	0.28
Extraversion	0.31*	0.02	3.2*	0.3

*** marks a significant correlation coefficient or gender difference.**

Figure Legends

Fig.1 Distribution of siblings in the male and female sample with their relative zygosity (Not Twin, Dizygotic, Monozygotic). **Groups' abbreviations:** m (males with no siblings); f (females with no siblings); m:m (males who have at least another male sibling); f:f (females with at least another female sibling); m:f (males with at least a female sibling); f:m (females with at least a male sibling); m:f+m (males with at least a male and a female sibling); f:m+f (females with at least a male and a female sibling).

Fig.2 Mean scores of the five NEO FFI personality scales (neuroticism, extraversion, openness, conscientiousness and agreeableness) separately for males (orange) and females (violet); error bars represent standard errors. Significant differences between males and females, marked by a star, were found for neuroticism and conscientiousness.

Fig.3 Neural correlates of neuroticism in males. (A): Whole brain VBM results revealing negative relationships between neuroticism and GMV of POS/Cun, IFFG/Cb and rFFG in males. (B): Correlations between neuroticism and GMV in POS/Cun, IFFG/Cb and rFFG separately for males and females, with negative correlations in males but no correlation in females. (C): Functional decoding of the regions POS/Cun, IFFG/Cb and rFFG; behavioral domains at $p < 0.05$ uncorrected for multiple comparison

Fig.4 Neural correlates of extraversion in males. (A): Whole brain VBM results revealing positive relationships between extraversion and GMV of Prc/POS, Th, IFFG/Cb and rCb in males. (B): Correlations between extraversion and GMV in Prc/POS, Th, IFFG/Cb and rCb separately for males and females, with positive correlations in males but no correlation in females. (C): Functional decoding of the regions Prc/POS, Th, IFFG/Cb and rCb; behavioral domains at $p < 0.05$ uncorrected for multiple comparison.

Fig.5 Neural correlates of conscientiousness in males. (A): Whole brain VBM results revealing positive relationships between conscientiousness and GMV of Prc/POS in males. (B): Correlations between extraversion and GMV in Prc/POS separately for males and females, with positive correlations in males but no correlation in females. (C): Functional decoding of the regions Prc/POS; behavioral domains at $p < 0.05$ uncorrected for multiple comparison.

Fig.6 Three-way conjunction across the results of neuroticism, extraversion and conscientiousness. (A): Results of the minimum conjunction analysis across the three traits revealing a cluster in lPrc/POS where GMV significantly correlated with all 3 personality scores in the male but not female sample. (B): Individual correlations between neuroticism, extraversion and conscientiousness and GMV in lPrc/POS separately for males and females, with negative correlations in males but no correlation in females. (C): Behavioral characterization of lPrc/POS at $p < 0.05$, uncorrected for multiple comparison.

Fig.7 Two-way conjunction across the results of neuroticism and extraversion. (A): Results of the minimum conjunction analysis between these two traits revealing bilateral POS/Cun, lFFG and rCb. (B): Individual correlations between neuroticism and extraversion and GMV in POS/Cun, lFFG/Cb and rCb separately for males and females, with negative correlations in males but no correlation in females. (C): Behavioral domains significantly associated with POS/Cun, lFFG/Cb and rCb at $p < 0.05$ uncorrected for multiple comparison.

Supplementary Material

Gender differences in questionnaire results

Homogeneity of variances between groups was not violated for any factor, as assessed by Levene's Test for Equality of Variances, and therefore independent-samples two-tailed t-tests were run on SPSS 20 to determine if there were differences in personality traits between males and females. Results were regarded as significant at $p < 0.05$ (Bonferroni-corrected). In case of significant group differences, effect sizes (Cohen's d) were calculated to quantify effect sizes.

Females described themselves as being more neurotic ($\bar{x} = 17.8$, $s = 7.2$) and more conscientious ($\bar{x} = 35.2$, $s = 5.6$) compared to males (N: $\bar{x} = 15.5$, $s = 7.6$; C: $\bar{x} = 33.5$, $s = 6.2$), resulting in a significant difference (N: $t_{362} = -3.02$; $p < 0.05$, $d = 0.31$; C: $t_{362} = -2.7$, $p < 0.05$, $d = 0.29$). For openness ($t_{362} = 1.63$, ns. males: $\bar{x} = 28.8$, $s = 6.4$; females $\bar{x} = 27.7$, $s = 6.2$), agreeableness ($t_{362} = -1.79$, ns; males: $\bar{x} = 31$, $s = 5$ and females: $\bar{x} = 31.9$, $s = 4.9$) and extraversion ($t_{362} = 0.43$, ns; males: $\bar{x} = 30$, $s = 6.1$ and females: $\bar{x} = 29.8$, $s = 6.2$) no significant gender differences were detected.

Cortical thickness and surface area analyses

In this follow-up analysis we tested whether brain structure-personality relationships in Prc/POS or FFG, as observed in the VBM analysis, could also be found when specifically assessing cortical thickness or surface area.

Methods

We used individual surface-based data obtained by the preprocessing pipelines of the Human Connectome Project (Glasser et al. 2013). Preprocessing was carried out using a modified Freesurfer implementation, a detailed description of which is available at

http://www.humanconnectome.org/documentation/S500/HCP_S500_Release_Reference_Manual.pdf, in order to align individual surface models across subjects and perform a group analysis.

Statistical analysis was implemented via the SurfStat Matlab toolbox (<http://www.math.mcgill.ca/keith/surfstat>). Multiple regression analysis was conducted using the same statistical models as were tested in the VBM study; i.e., for the analyses on the entire sample (364 participants) we included age, total brain volume (TBV), and gender as covariates of no interest. For the within-gender analyses only age and TBV were added.

Results

The cortical thickness (CT) analysis revealed no significant associations of CT with extraversion, neuroticism and conscientiousness in the regions indicated by the VBM when correcting for multiple comparisons, neither across the whole sample, nor in males or females separately. Nevertheless, on an uncorrected level ($p < 0.001$), we were able to identify a positive significant association in males between the thickness of the left parieto-occipital sulcus (IPOS) and conscientiousness.

The analysis of the cortical surface area revealed no significant associations with the three traits neither when correcting for multiple comparisons, nor at $p < 0.001$ uncorrected.

VBM analyses on sample of unrelated subjects

The aim of this supplementary analysis was to test, whether we still find correlations between GMV of Prc/POS, IFFG, rCB with personality when restricting the analyses to unrelated subjects only.

Unrelated subjects sub-sample

Participants were selected from the initial sample of 364 individuals but, this time, we included only one individual per family. Males and females were matched with regard to zygosity (not twin, dizygotic and monozygotic) as well as age and years of education. This resulted in an unrelated sample of 75 men (58 not twins, 11 dizygotics and 6 monozygotics; mean age 28.64 ± 3.36 , education 14.92 ± 1.68) and 75 women (58 not twins, 11 dizygotics and 6 monozygotics; mean age 28.75 ± 3.31 , education 14.93 ± 1.76).

Correlations among factors

Supplementary Table 1: Correlations (Pearson's r) among the five personality factors in an unrelated subsample of males (n=75), females (n=75).

		Neuroticism	Extraversion	Openness	Conscientiousness	Agreeableness
Neuroticism	Males	-	-0.525*/	0.244*/	-0.447*/	-0.303*/
	Females		-0.365*/	-0.099/	-0.471*/	-0.518*/
	Overall		-0.445*	0.071	-0.433*	-0.412*
Extraversion	Males	-	-	0.045/	0.501*/	0.361*/
	Females			0.119/	0.307*/	0.310*/
	Overall			0.040	0.405*	0.333*
Openness	Males	-	-	-	-0.220/	0.316*/
	Females				-0.047/	0.213/
	Overall				-0.142	0.260*
Conscientiousness	Males	-	-	-	-	0.286*/
	Females					0.215/
	Overall					0.240*

Agreeableness	-	-	-	-	-
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Association to GMV

Across the entire sample, no significant correlation was found between any personality factors and GMV (controlling for age, TBV and gender). Likewise, our analyses revealed no significant relationships between any of the five personality factors and GMV in females (controlling for age and TBV). However, in males, a negative correlation with neuroticism and a positive correlation with extraversion were found for GMV of IPrc/POS.

References

Glasser MF, Sotiropoulos SN, Wilson JA, Coalson TS, Fischl B, Andersson JL, Xu J, Jbabdi S, Webster M, Polimeni JR, Van Essen DC, Jenkinson M. 2013. The minimal preprocessing pipelines for the Human Connectome Project. *Neuroimage*. 80:105–124.

Fig.1

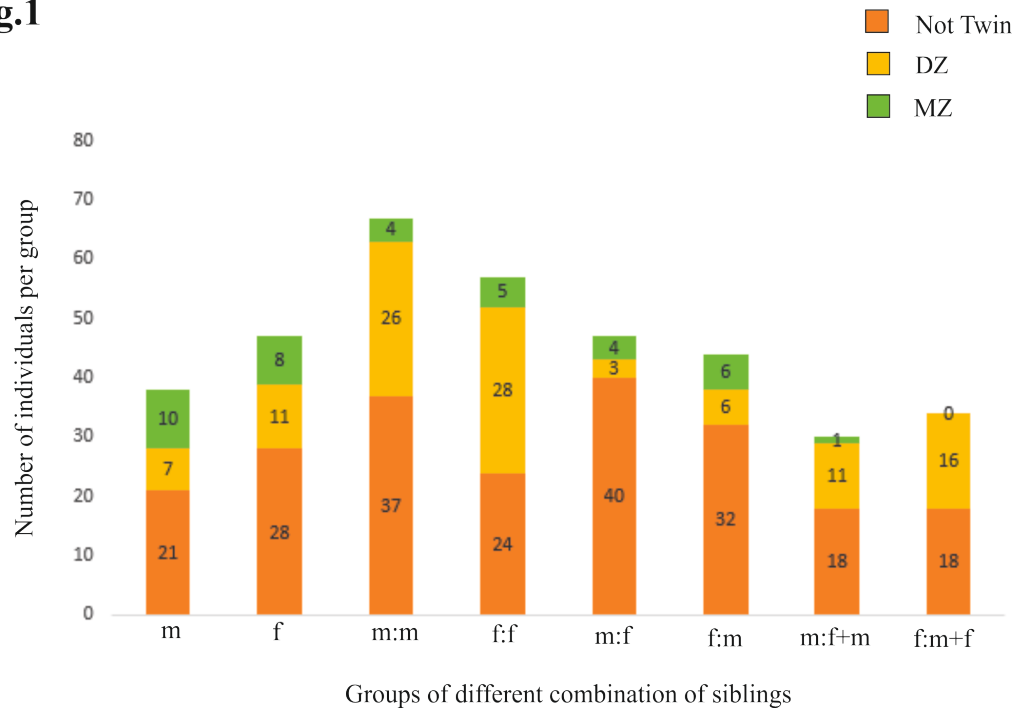


Fig.2

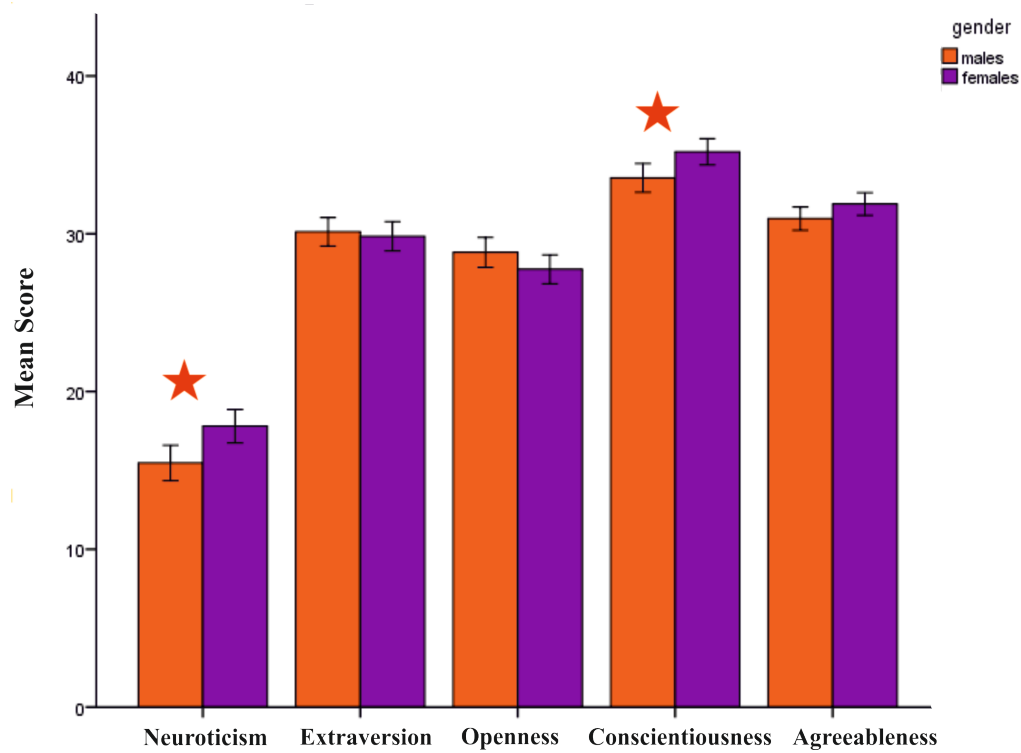
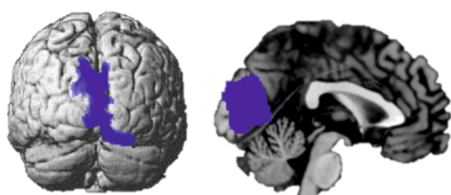


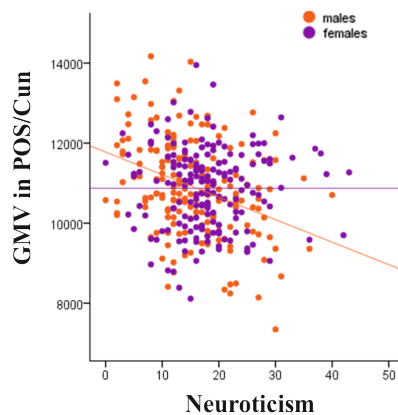
Fig.3

A

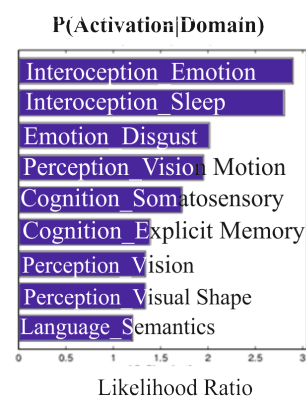
POS/Cun



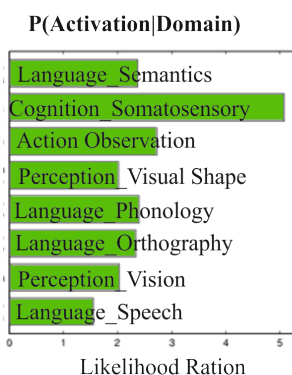
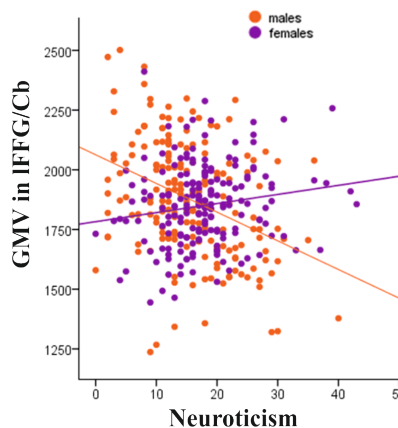
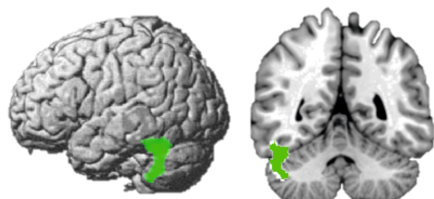
B



C



lFFG/Cb



rFFG

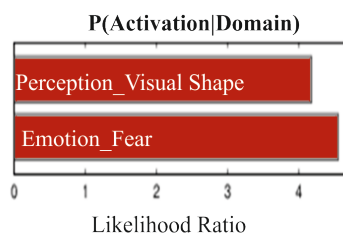
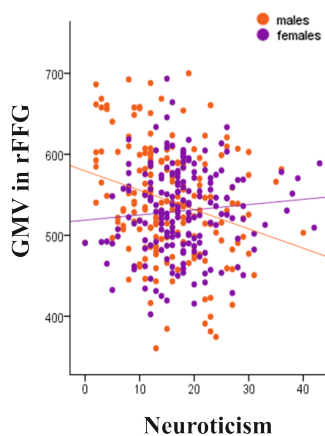
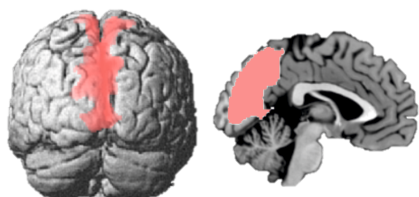


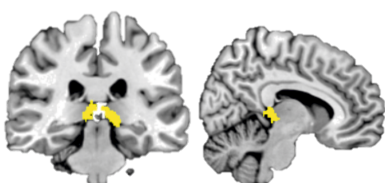
Fig.4

A

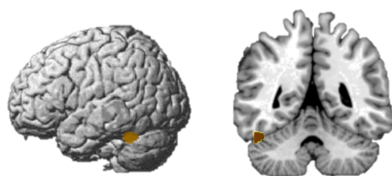
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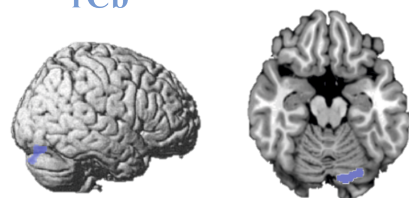
Th



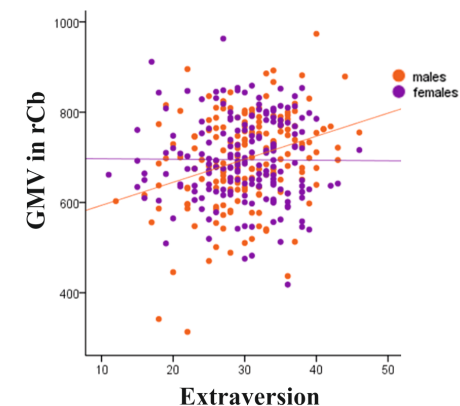
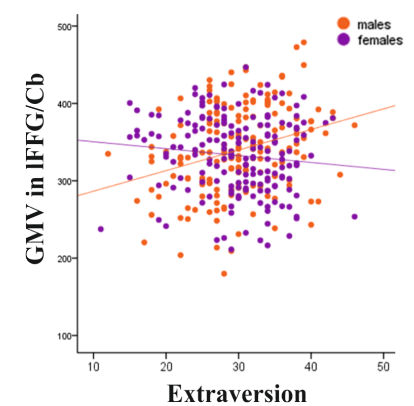
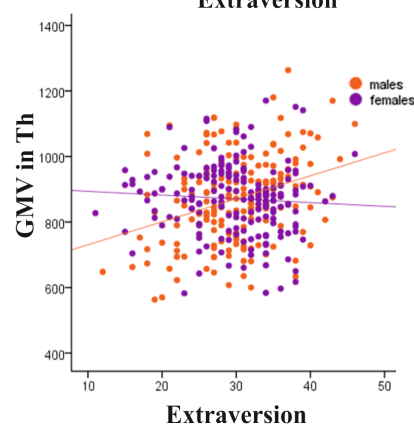
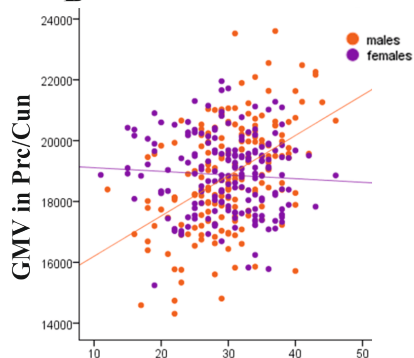
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rCb

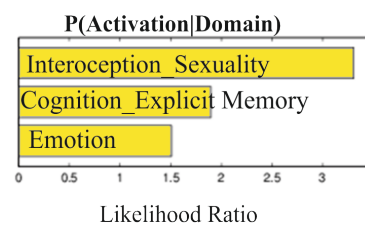
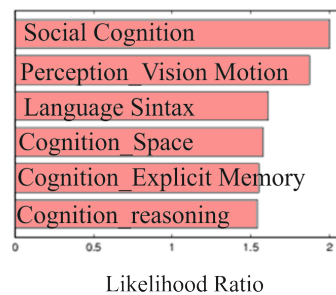


B

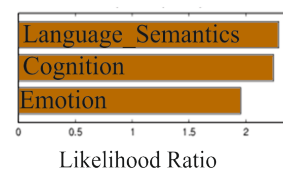


C

P(Activation|Domain)



P(Activation|Domain)



P(Activation|Domain)

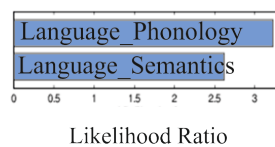


Fig.5

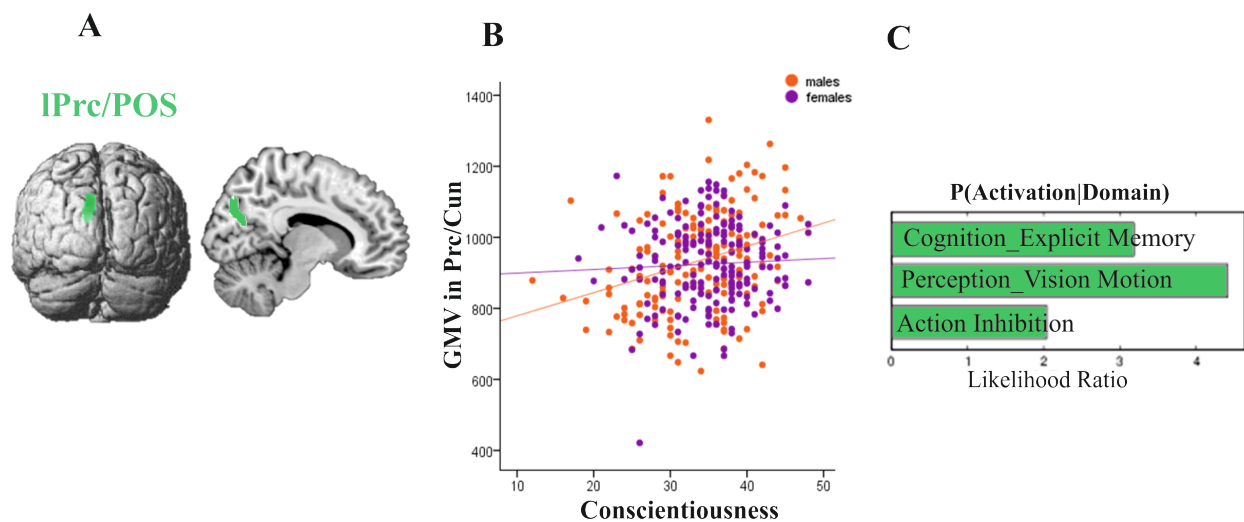


Fig.6

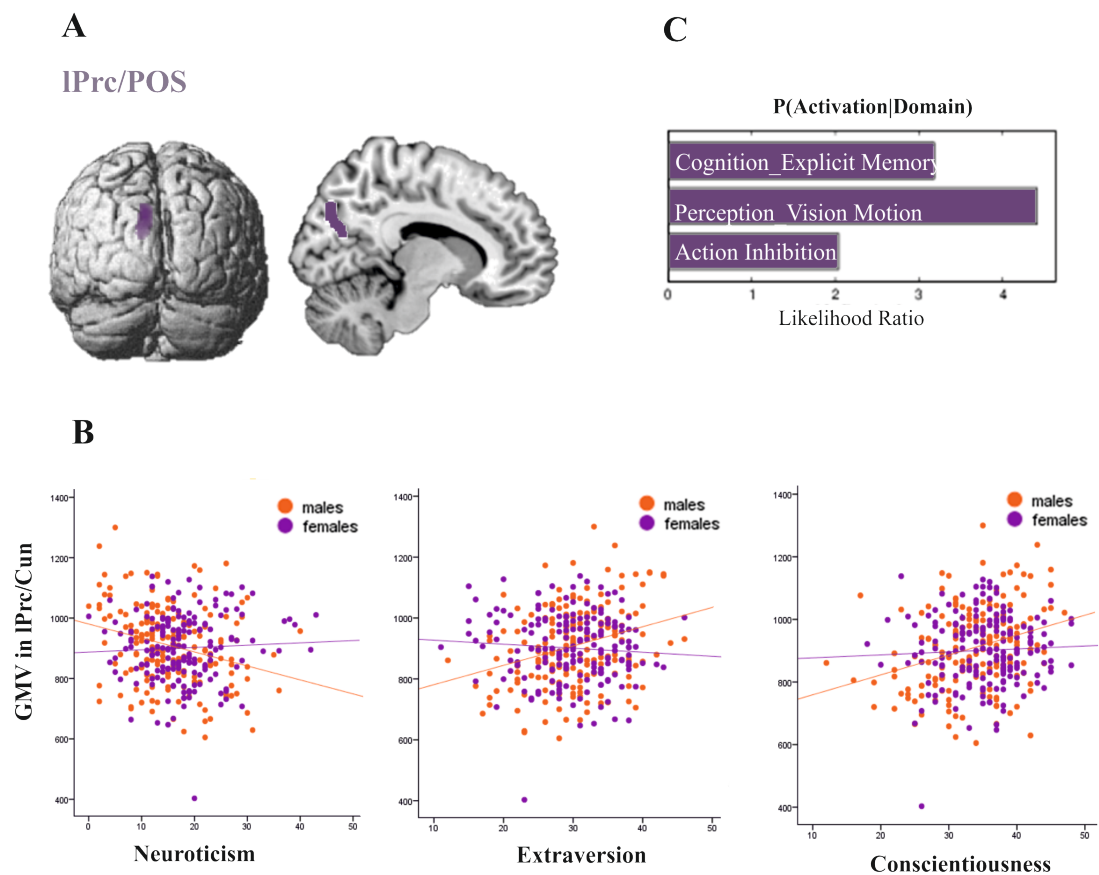
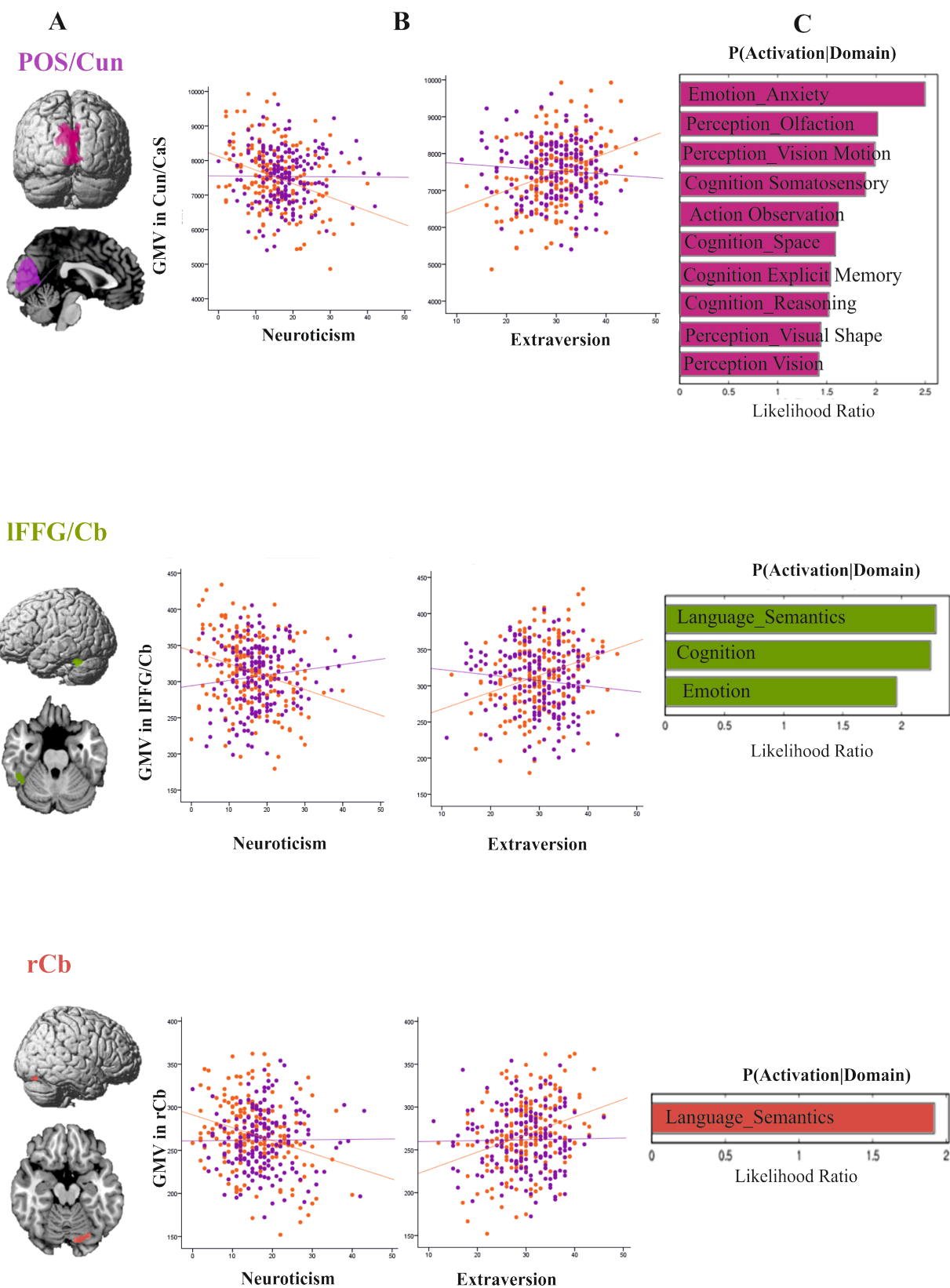


Fig.7



V STUDY 2

Predicting Personality from Network-based Resting-State

Functional Connectivity

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Own contributions:

Conception and design of experiment

Reviewing and adapting analysis code

Statistical data analysis

Interpretation of results

Preparing figures

Writing the paper

Total contribution 80%

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Predicting personality from network-based resting-state functional connectivity

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Abstract

Personality is associated with variation in all kinds of mental faculties, including affective, social, executive, and memory functioning. The intrinsic dynamics of neural networks underlying these mental functions are reflected in their functional connectivity at rest (RSFC). We, therefore, aimed to probe whether connectivity in functional networks allows predicting individual scores of the five-factor personality model and potential gender differences thereof. We assessed nine meta-analytically derived functional networks, representing social, affective, executive, and mnemonic systems. RSFC of all networks was computed in a sample of 210 males and 210 well-matched females and in a replication sample of 155 males and 155 females. Personality scores were predicted using relevance vector machine in both samples. Cross-validation prediction accuracy was defined as the correlation between true and predicted scores. RSFC within networks representing social, affective, mnemonic, and executive systems significantly predicted self-reported levels of Extraversion, Neuroticism, Agreeableness, and Openness. RSFC patterns of most networks, however, predicted personality traits only either in males or in females. Personality traits can be predicted by patterns of RSFC in specific functional brain networks, providing new insights into the neurobiology of personality. However, as most associations were gender-specific, RSFC–personality relations should not be considered independently of gender.

Keywords Functional networks · Gender differences · Hormonal influence · Machine learning · NEO-FFI · Resting-state functional connectivity

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00429-018-1651-z>) contains supplementary material, which is available to authorized users.

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Introduction

Inter-individual differences in personality permeate all aspects of life, from affective and cognitive functioning to social relationships. One of the most comprehensive and most widely recognized models of personality is the Five-Factor Model (FFM; Costa and McCrae 1992), consisting of five broad dimensions: Openness to experience/Intellect, Extraversion, Neuroticism, Agreeableness, and Conscientiousness. Openness to experience/Intellect reflects the engagement with aesthetic/sensory and abstract/intellectual information, as well as the degree of appreciation and toleration for the unfamiliar (Nicholson et al. 2002; Fleischhauer et al. 2010; Fayn et al. 2015). Extraversion relates to approach behaviour of driving toward a goal that contains cues for reward, and tendency to experience positive emotions given by the actual attainment of that goal (Depue and Collins 1999; DeYoung 2015). Neuroticism relates to a person's emotional life and reflects the tendency

to heightened emotional reactivity to negative emotions (Goldberg and Rosolack 1994; Rusting and Larsen 1997; Gray and McNaughton 2000). Agreeableness relates to interpersonal behaviour and reflects the degree of avoidance of interpersonal conflicts (stability between individuals) (Graziano et al. 2007; Butrus and Witenberg 2013). Conscientiousness reflects the degree to which individuals perform tasks and organize their lives, exhibiting a tendency to show self-discipline, act dutifully, and aim for achievement (stability within individuals) (Ozer and Benet Martínez 2006; Roberts et al. 2009) (cf. for more details McCrae and Costa 2004; DeYoung and Gray 2009).

Since the FFM of personality is based on language descriptors of adjectives applied to human and human behaviour in English lexicon, rather than neurobiological features, many attempts have been made to explore the neural bases of these five factors. At first, each trait has been associated with its most crucial and characterizing psychological functions (e.g., Neuroticism and Extraversion to sensitivity to punishment and reward, respectively, Agreeableness to social processes, Conscientiousness to top-down control of behaviour and Openness cognitive flexibility), and hypotheses have been developed about the associations between brain systems supporting those psychological functions, and the respective trait, paving the way for a biology of personality traits (c.f. DeYoung and Gray 2009). It has, therefore, been suggested that Neuroticism is associated (functionally or structurally) to affective regions that had been linked to respond to threat and punishment like amygdala, hippocampus, cingulate cortex, and medial prefrontal cortex (Kumari 2004; Cremers et al. 2010; DeYoung et al. 2010; Tzschoppe et al. 2014; Madsen et al. 2015; Pang et al. 2016). Extraversion has been linked to regions responding to reward-related stimuli like nucleus accumbens, striatum, amygdala, and orbitofrontal cortex (DeYoung et al. 2010b; Adelstein et al. 2011; Pang et al. 2016, c.f.; Lei et al. 2015). Conscientiousness has been related to the lateral prefrontal cortex (Asahi et al. 2004; Passamonti et al. 2006; DeYoung et al. 2010; Kunisato et al. 2011), deputed to the planning, following complex rule and voluntarily control of behaviour. Similarly, Openness has also been associated with the functions of the lateral PFC (DeYoung et al. 2005; Kunisato et al. 2011), but, in contrast to Conscientiousness, more because of its role in attention, working memory, and cognitive flexibility. Finally, Agreeableness has been associated with regions involved in the processing of social information, such as temporo-parietal junction, superior temporal gyrus and posterior cingulate cortex (Hooker et al. 2008; DeYoung et al. 2010; Adelstein et al. 2011). However, the associations between brain systems underlying specific mental functions and personality traits might be more complex than such one-to-one mapping; instead, it is much

more plausible that the mapping between traits and brain systems is rather many-to-many (c.f. Yarkoni 2015; Allen and DeYoung 2016). One example is provided by Neuroticism, which has not only been associated to affective regions, but also to regions exerting cognitive functions, e.g., dlPFC (Kunisato et al. 2011; Pang et al. 2016), or behavioural performances probing attention (MacLean and Arnell 2010), working memory (Studer-Luethi et al. 2012), verbal fluency (Sutin et al. 2011), and explicit memory (Pearman 2009; Denkova et al. 2012). It is, therefore, possible that these systems (affective and executive) both contribute in explaining variance in Neuroticism. The potential contribution of other regions rather than the ones originally suggested also holds for other traits. For example, increasing evidence points to a link between Openness and the functional organization and global efficiency of the default mode network (DeYoung 2014; Sampaio et al. 2014; Beaty et al. 2016). Similarly, even if not directly investigating the trait of Agreeableness, there is evidence (Gazzola et al. 2006; c.f.; Iacoboni 2009) showing a possible association between one of its facet, empathy, with the mirror neuron system.

Furthermore, one of the major challenges of using functional studies for the association between personality traits and brain systems is the fact that the latter can only be based on specific implementations such as behavioural tests or paradigms used in experimental research. Moreover, there is a general consensus that mental functions arise from the coordinated activity within distributed networks rather than any individual brain region (Eickhoff and Grefkes 2011). Therefore, relating a personality trait to a particular function only because a brain region correlates with both is problematic. These considerations have prompted a network-centered perspective of brain organization (c.f. De Vico Fallani et al. 2014), highlighting the importance of functional integration for mental processes and their inter-individual differences. However, this approach, which requires a priori defined seeds, suffers from an important methodological limitation. That is, by choosing pre-defined nodes from a single task-based fMRI study, the findings might be biased toward that particular paradigm operationalization. Furthermore, task-based fMRI literature often suffers from low statistical power and low reproducibility, due to the small sample sizes typically used and considerable heterogeneity in the analysis pipeline (cf. Samartsidis et al. 2017). To solve the problem of a more objective definition of relevant nodes in a given functional network, quantitative meta-analyses of task-based neuroimaging studies aggregate the findings of many individual task-activation studies into a core network representing those locations that are reliably recruited by engaging in a given kind of mental process (cf. Fox et al. 2014). The investigation of RSFC in meta-analytically defined networks representing specific social, affective, executive, or memory

functions, therefore, provides a viable approach to capturing the complex intrinsic neural architecture underlying personality (Adelstein et al. 2011; Sampaio et al. 2014).

Given that network connectivity data are almost inevitably high-dimensional, consisting of many correlated features, univariate analyses of associations between connectivity measures and phenotypical traits such as personality may not represent an optimal strategy (Orrù et al. 2012). Moreover, univariate analyses will likely fail to elucidate associations that depend on the pattern of connectivity within a network rather than any specific individual connection. On the other hand, machine learning and multivariate pattern analysis (MVPA), suitable for analysing neuroimaging data (cf. Otkar and Otkar 2015; Gael; Varoquaux and Thirion 2014), provides an approach that overcomes these limitations by searching for patterns in the connectivity matrix that allow the prediction of a continuous target variable (Doyle et al. 2015). In this article, the term “prediction” refers to the out-of-sample evaluation of a statistical model’s ability to predict the personality score for previously unseen individuals based on their RSFC. The potential of such approaches to predict behavioural scores from resting-state connectivity data has already been demonstrated with respect to sustained attention (Rosenberg et al. 2016), autistic traits (Plitt et al. 2015), and impulsivity in economic decision-making (Li et al. 2013). Conversely, personality traits have been predicted from cyber records such as personal websites (Marcus et al. 2006) or social networks (Golbeck 2011; Golbeck et al. 2011; Bachrach et al. 2012) but not yet from neuroimaging data.

Bringing together the different aspects outlined above, the current study explored whether individual levels of five major personality traits can be predicted from RSFC profiles in a priori defined brain networks representing specific cognitive functions. The selection of the networks used a priori knowledge based on the associations reported in the literature between psychological functions (and deputed networks) with personality. Accordingly, we chose functional networks associated with affective (emotion processing, reward, and pain) functions given their main associations with both Extraversion and Neuroticism, social (empathy and face processing) functions in relation to Agreeableness, executive functions as linked to Conscientiousness and Openness (vigilant attention and working memory to represent, respectively, rigid control and flexibility), and memory (autobiographic and semantic) functions as many traits were also found to be associated with them. However, it is important to note that we refrained from having hypotheses about network—predicted traits associations, since we believe that multiple brain systems, among the selected ones, can contribute to explaining inter-individual variance in one trait (e.g., Openness being predicted from networks outside the executive domain). We additionally used a network with

whole-brain coverage consisting of 264 nodes (we here refer to it as **Connectome**; Power et al. 2011) to predict the five personality traits to test if personality can be better predicted by specific functional networks or a rather unspecific whole-brain network. In addition, in light of the previous findings of sexual dimorphism in the relationships between brain structure and personality traits (Nostro et al. 2016) as well as gender differences in RSFC (Allen et al. 2011; Filippi et al. 2013; Hjemmervik et al. 2014; Weis et al. 2017) and personality (Yang et al. 2015), these analyses were performed in a gender-mixed sample as well as separately in male and female subsamples.

Materials and methods

Participants

All data were obtained from the Human Connectome Project (HCP) WU-Minn Consortium as provided in the current “S1200” release (<http://www.humanconnectome.org>, Van Essen et al. 2013). The HCP was funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University. Our analyses of the HCP data were approved by the ethics committee of the Heinrich Heine University Düsseldorf.

The HCP sample is composed of monozygotic and dizygotic twins as well as not-twins, the latter including siblings of twins, just siblings, and only-children (including those that have an as-yet not scanned sibling but not twin). Given this structure of related and unrelated subjects, we paid particular attention to select a well-matched sample of males and females that was as large as possible, while, at the same time, controlling for possible effects of heritability by creating a sample of only unrelated subjects. Evidently, we first selected all participants from the HCP sample for whom resting-state fMRI volumes and personality data were available. Out of this sample, we then selected groups of unrelated males and females (i.e., only one representative of a given family), matched for age, years of education, and twin status. This last match (twin or not twin) was preferred over the match for zygosity (not twin, dizygotic or monozygotic) as it enabled us to select a higher number of participants while not introducing dependencies in the sample. In fact, Kolmogorov–Smirnov test showed that zygosity does not lead to any significant difference in the five scores distribution, cf. supplementary Table S1. Importantly, we created a first main sample (**Sample 1**), where we aimed for the highest number of participants according to the inclusion criteria, but, since a considerable number of individuals were left out from the first selection, we additionally created a “replication” sample, (**Sample 2**). **Sample 2** was thus created by

removing the subjects belonging to the **Sample 1** from the main release (S1200) and re-applying the selection criteria on the remaining participants.

The final selection procedure of **Sample 1** resulted in a total of 420 subjects: 205 males (119 non-twins, 91 twin subjects; aged $22\text{--}37$ years, mean: 28.3 ± 3.5 ; years of education: 14.9 ± 1.8) and 205 females (117 non-twins, 93 twin subjects; aged $22\text{--}36$ years, mean: 28.8 ± 3.5 ; years of education: 15.0 ± 1.8).

From the remaining subjects not selected for **Sample 1**, **Sample 2** was obtained resulting in a sample of 302 subjects: 151 males (75 non-twins, 76 twin subjects; aged $22\text{--}36$ years, mean: 28.2 ± 3.4 ; years of education: 14.8 ± 1.8) and 151 females (76 non-twins, 75 twin subjects; aged $22\text{--}35$ years, mean: 28.9 ± 3.5 ; years of education: 15.0 ± 1.8). For an overview on the samples selection, see Fig. 1.

In addition, **Sample 1** and **Sample 2** were combined to form the largest group of subjects available from the HCP data that are gender-balanced and matched for age and education (Sample 3). This allowed us to investigate the stability of the results discovered in the two unrelated samples (i.e., that did not contain related individuals) and screen for additional relationships. The latter, however, need to be taken with caution, as the pooled sample does systematically contain closely related individuals (siblings and twins). Please refer to the supplementary material for a more detailed overview of the sample and the results of this analysis.

Self-report data

Personality was assessed using the English-language version of the NEO Five-Factor Inventory (NEO-FFI; McCrae and Costa 2004). The NEO-FFI consists of 60 items in the form of statements describing behaviours that are characteristic for a given trait, 12 for each of the five factors (Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism). Each factor is assessed by aggregating individual responses given on five-point Likert-type ratings scales, yielding sum scores between 0 and 60 for each factor. Data were analyzed using SPSS 20 (IBM Corp. Released 2011); scores of males and females were compared via *t* tests ($p < 0.05$, Bonferroni-corrected for multiple comparisons) for each personality trait. In case of significant group differences, we estimated effect sizes using Cohen's *d* measure (Cohen 1988). Furthermore, correlations among factors were calculated and tested for significance (Bonferroni-corrected) separately for males and females (for details, see supplementary material). Importantly, as reported on the HCP listserv (<https://www.mail-archive.com/hcp-users@humanconnectome.org/msg05266.html>), the Agreeableness factor score in the HCP database was erroneously calculated due to item 59 not reversed. We addressed this issue by reversing it and using the correct score of Agreeableness.

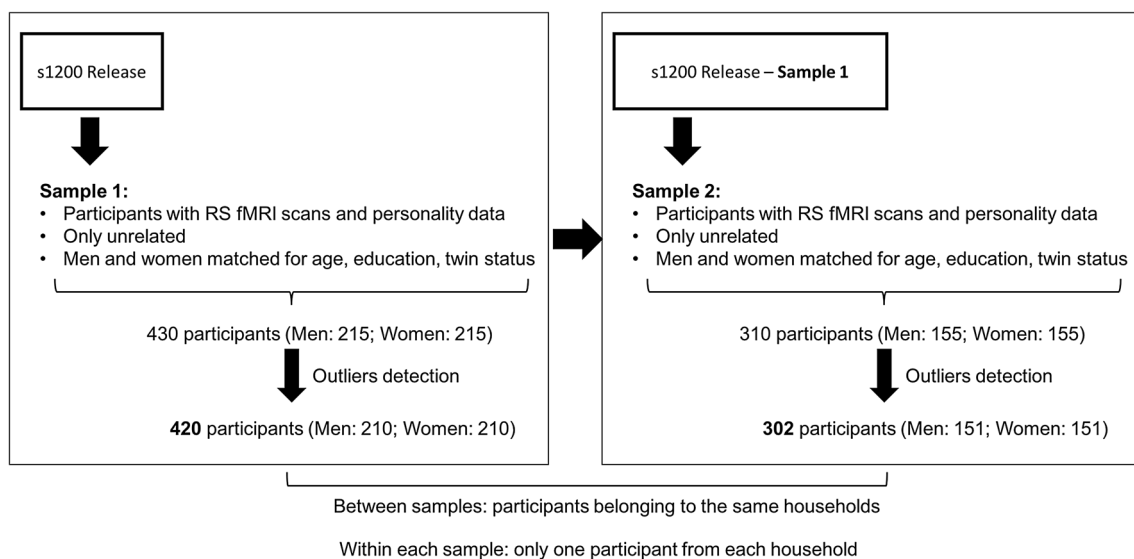


Fig. 1 Samples selection overview: first **Sample 1** (or “main” sample) was created aiming for the largest number of participants. Once 430 subjects were selected for this sample, the same procedure was applied on the remaining subjects of the HCP to generate **Sample 2**

(or “replication” sample). The two samples result in this was related to each other (as siblings of the subjects in **Sample 1** are present in **Sample 2**), but, within each sample, there are no subjects related to each other

Meta-analytically derived networks

Selection of networks

We selected nine meta-analytic networks representing regions consistently activated by various social, affective, executive, and memory functions. Specifically, we used two networks related to social cognition: empathy (*Emp*; Bzdok et al. 2012) and static face perception (*Face*; Grosbras et al. 2012); three networks related to affective processing: reward (*Rew*; Liu et al. 2011), physiological stress/pain (*Pain*; Kogler et al. 2015), and perception of emotional scenes and faces (*Emo*; Sabatinelli et al. 2011); two networks related to executive functions: working memory (*WM*; Rottschy et al. 2012) and vigilant attention (*VA*; Langner and Eickhoff 2013); two networks related to long-term memory: autobiographic memory (*AM*; Spreng et al. 2008) and semantic processing (*SM*; Binder et al. 2009).

Selection of coordinates

From each meta-analysis, we selected the reported coordinates of the networks to include in our analyses and modelled a 6-mm sphere around each coordinate. This ensured that all nodes were represented by region of interest of equal size (ROIs) within and across networks. Within each single network, we only selected peaks that either represented different anatomical regions, preventing multiple representations of a single region, or were at least 15 mm apart from each other [according to the SPM anatomy toolbox 2.1; (Eickhoff et al. 2005, 2007)]. In cases of multiple peaks within an anatomical region that were closer to each other, we included the peak showing the highest Z-score. Please note that these criteria were only applied for multiple regions within a single network, while we did not exclude any regions that were found also in another network. That is, even if different networks featured peaks at the same location, these presumably shared nodes were retained. Given that little is yet known about the effect of the networks' sizes on the outcome predictability, we also had to consider the size of the networks (i.e., number of nodes) to make sure that possible differences in their predictive power were not due to the number of nodes included. As a result, the size of the networks ranged between 16 (*VA*) and 24 (*Emo*) nodes. Further details on the meta-analytic networks can be found in Table 1, supplementary Table S3 and supplement Fig S1.

Connectome analysis

In addition, we employed a brain-wide network of 264 functional areas from Power and colleagues (*Connectome*; Power et al. 2011) to compare the predictive power of RSFC from the whole-brain and from meta-analytic networks. For

the coordinates of this *Connectome*, please refer to the supplementary Table S2 of Power et al.

Resting-state fMRI data: acquisition, preprocessing, and functional connectivity analyses

As part of the HCP protocol (Glasser et al. 2013), images were acquired on a Siemens Skyra 3T Human Connectome scanner (<http://www.humanconnectome.org/about/project/MR-hardware.html>) using a 32-channel head coil. Resting-state (RS)-BOLD data (voxel size = $2 \times 2 \times 2$ mm³, FoV = 208×180 mm², matrix = 104×90 , 72 slices in a single slab, TR = 720 ms; TE = 33.1 ms, flip angle = 52°) were collected using a novel multi-band echo planar imaging pulse sequence that allows for the simultaneous acquisition of multiple slices (Xu et al. 2013). RS-fMRI data were then cleaned of structured noise through the Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) part of FSL toolbox (<http://www.fmrib.ox.ac.uk/fsl>). This process pairs independent component analysis with a more complex automated component classifier referred to as FIX (FMRIB's ICA-based X-noisifier) to automatically remove artefactual components (Salimi-Khorshidi et al. 2014).

The FIX-denoised RS-fMRI data were further preprocessed using SPM12 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK, <http://www.fil.ion.ucl.ac.uk/spm/>), running under Matlab R2016a (Mathworks, Natick, MA). For each participant, the first four EPI images were discarded prior to further analyses. Then, EPI images were corrected for head movement by affine registration using a two-pass procedure: in the first step, images were aligned to the first image, and in the second step to the mean of all volumes. Next, the mean EPI image was spatially normalized to the non-linear MNI152 template (Holmes et al. 1998) using the "unified segmentation" approach to account for inter-individual differences in brain morphology (Ashburner and Friston 2005). Finally, images were smoothed with an isotropic Gaussian kernel (full-width at half-maximum = 5 mm).

The activity time series of each voxel was further cleaned by excluding variance that could be explained by mean white-matter and cerebrospinal-fluid signal (Satterthwaite et al. 2013). Data were then band-pass filtered with cut-off frequencies of 0.01 and 0.08 Hz.

To identify participants with aberrant RSFC patterns, we computed each subject's entire connectome sampled on a 1-cm grid. We then computed the pairwise Euclidean distance between the subjects and identified the nearest neighbour for each subject. We excluded the subjects whose distance to their nearest neighbour was in the highest 2.5% and at least 3 SD away from the average distance. This procedure was done separately for men and women (**Sample**

Table 1 Description of the meta-analytic derived networks

Domain	Meta-analytic network	Abbreviation	Author, year	Reference of the network in the original paper	Number of included Nodes	Network description
Social	Empathy	Emp	Bzdok, 2012	Table n.1 (ALE meta-analysis of empathy)	22	Regions consistently activated during tasks referring to conscious and isomorphic experience of somebody else's affective state
Social	Static face perception	Face	Grosbras, 2012	Table n. 7 (Static face perception)	19	Convergence across tasks consisting in viewing photographs of faces or viewing objects/ scrambled images
Affective	Reward	Rew	Liu 2011	Table n. 1	23	Convergence across reward valence and decision stages contrasts
Affective	Physiological stress	Pain	Kogler, 2015	Table n.1 (Activation physiological)	18	Regions consistently activated during tasks referring to unpleasant sensoric, emotional and subjective experience that is associated with potential damage of body tissue and bodily threat
Affective	Perception of emotional scenes and faces	Emo	Sabatinelli, 2012	Table n.2 (emotional face > neutral face) and Table n.3 (emotional scenes > neutral scenes)	24	Regions consistently activated during tasks referring to discrimination of emotional faces > neutral faces contrast combined with emotional scenes > neutral scenes contrast
Executive	Working memory	WM	Rottschy, 2012	Table n. 2	22	Regions consistently activated during all WM contrasts/ experiments (mainly n-back, Stenberg, DMTS, delayed simple matching)
Executive	Vigilant attention	VA	Langner, 2012	Table n.1	16	Regions consistently activated during tasks posing only minimal cognitive demands on the selectivity and executive aspects of attention for more than 10 s
Memory	Autobiographic memory	AM	Spreng, 2008	Table n. 6	23	Convergence across tasks referring to autobiographical recall: episodic recollection of personal events from one's own life
Memory	Semantic memory	SM	Binder, 2009	On request to the author	23	Regions consistently activated during all SM contrasts/ experiments (mainly words vs. pseudowords, semantic vs. phonological task, high vs. low meaningfulness)
Whole-brain	Connectome	Connectome	Power, 2011	Supplement material	264	Meta-analytic ROIs and FC-mapping ROI merged to form a maximally-spanning collection of ROIs. Meta-analytic ROIs were given preference, and non-overlapping fc-mapping ROI were then added

1: 5 males, 5 females; **Sample 2:** 4 males, 4 females). No subjects were excluded due to outlier motion parameters (DVARs and FD both displaying zero-centered values) (Salimi-Khorshidi et al. 2014; Varikuti et al. 2016; Ciric et al. 2017). For RSFC analyses, the subject-specific time series for each node of each network were computed as the first eigenvariate of the activity time courses of all gray-matter voxels within 6 mm of the respective peak coordinate. We then computed pairwise Pearson correlations between the eigenvariates of all nodes in each network, which then were transformed using the Fischer's Z scores and adjusted (via linear regression) for the effects of age and movement.

RSFC-based prediction of personality traits by relevance vector machine learning

We examined if the RSFC patterns within each network predicted personality scores by means of statistical learning via the Relevance Vector Machine (RVM; Tipping 2001) as implemented in the *SparseBayes* package (<http://www.miketipping.com/index.htm>). The RVM is a machine learning technique that can learn to predict a continuous target value given explanatory variables (also called features). In our case, the features were the RSFC values between all nodes of a meta-analytic network, while the score of a specific personality factor scale was the target value.

Briefly, RVM is a multivariate approach that was developed from the Support Vector Machine (SVM) to induce sparseness in the model's parameters. The RVM, in contrast to SVM, implements a fully probabilistic Bayesian framework: for each possible value of the input vector (e.g., set of FC values), the RVM algorithm provides a probability distribution of the predicted target value (e.g., FFM personality score), unlike a point estimate obtained by the SVM:

$$\hat{y}(x, w) = w_0(0; \sigma_0) + \sum_{i=1}^n w_i(0; \sigma_i) K_{\sigma}(x_i, x).$$

In the RVM formulation above, the kernel K is a multivariate zero-centered Gaussian with standard deviation σ (estimated by the algorithm) and every parameter w_i , assigned to each subject x_i in the *training set*, is assumed to follow a Gaussian with mean zero and standard deviation σ_i . The standard deviations σ_i that describe the probability distribution of the parameters w_i are iteratively estimated from the training data to maximize the likelihood of the model. Sparseness is achieved by discharging parameters w_i converged to zero. Once σ_0 and σ_i have been estimated, the trained model can be used to predict the target value (e.g., FFM personality score) from a previously unseen input vector (RSFC data from participants that were not part of the training data) by computing the predictive distribution (for a more detailed description, see Tipping 2001).

In our study, we implemented the RVM algorithm with a 10-fold cross-validation. That is, the sample was randomly split into 10 equally sized groups of which 9 were used for training, while one was held back and used for assessing the performance of the prediction in previously unseen data. Holding out each of the 10 groups in turn then allowed computing the prediction performance across the entire data set. Importantly, this procedure was repeated 250 times using random initial splits of the data to obtain robust estimates of the RVM performance for predicting a given NEO-FFI score from a particular network's RSFC pattern. For each subject, the predicted values resulting from each cross-validation (i.e., one replication) were averaged over the 250 replications and ultimately correlated with the real score.

As we performed 250 replications of a 10-fold cross-validation, in total 2500 models were computed to predict each trait. We thus quantified the contribution of each connection by the fraction of these 2500 models in which the weight for the respective connection was non-zero. The connections that had a non-zero weight in at least 80% of all models were identified as the connections that were most robustly part of the predictive model. The brain networks were visualized with the BrainNet Viewer (<http://www.nitrc.org/projects/bnv/>) (Xia et al. 2013).

For both the “main” (**Sample 1**) and “replication” (**Sample 2**) samples, predictions were first carried out for all subjects with males and females combined (All_{Sample1}: $n=410$ All_{Sample2}: $n=302$), and then separately for the male (Men_{Sample1}: $n=210$; Men_{Sample2}: $n=151$) and female groups (Women_{Sample1}: $n=210$; Women_{Sample2}: $n=151$) to assess gender differences in predictability. Predictive power was assessed by computing Pearson correlations between real and predicted NEO-FFI scores and mean absolute error (MAE). Importantly, results were only regarded as significant when they were significant at a threshold of $p < 0.05$ in both samples (**Sample 1** and **Sample 2**). The p value was computed via permutation testing between real and predicted values with 10,000 runs. For each run, we shuffled the predicted scores across subjects in either the entire sample (for “All”) or in the gender groups (for “Men” and “Women”) without replacement. From here, the definition of the p value as the fraction of runs when the correlation between real and the shuffled predicted score was higher than the one obtained between the real and the original predicted value.

For all significant results in either “All”, “Men” or “Women”, we further tested for significant differences in prediction performance (i.e., correlation between real and predicted value) between males and females in the main sample. Pearson correlation coefficients (r) were transformed into Fisher's Z and the difference between Z_{Men} and Z_{Women} calculated and then 95% confidence intervals (CI) were computed based on these difference scores. The difference in correlation coefficients between males and females

were regarded as significant if the 95% confidence interval did not contain zero (Lane 2013).

Results

NEO-FFI scores

Subjects scored in the same range as reported by McCrae and Costa (McCrae and Costa 2004) in both the samples.

Correlations between factors were calculated separately for males and females and in the entire sample (see Supplementary Table S2 for more detailed information). Most of them were significant at $p < 0.05$ (Bonferroni-corrected) in both males and females and the entire sample. Openness, however, was found to be independent of most of the other factors, except for Agreeableness (in **Sample 1** for All, Men, and Women), and Conscientiousness (in All for both **Sample 1** and **Sample 2**). Furthermore, Neuroticism was the only factor correlating negatively with almost all the others (except for Openness in Men of **Sample 1** and in All, Men, and Women of **Sample 2**).

Comparison of the scores for the five personality traits between Men and Women revealed a significant difference for Agreeableness in both samples (**Sample 1**: $t_{407} = -4.95$; $p < 0.05$, $d = -0.49$; **Sample 2**: $t_{299} = -2.2$; $p < 0.05$, $d = -0.27$), with females scoring higher than males. For Neuroticism, Women significantly scored higher than Men in **Sample 1** ($t_{407} = -2.8$; $p < 0.05$, $d = -0.28$), while in **Sample 2**, this difference only showed a trend ($t_{299} = -1.93$; $p = 0.055$, $d = -0.2$). For Openness (**Sample 1**: $t_{407} = 0.1$; $p = 0.9$; **Sample 2**: $t_{299} = 1.64$; $p = 0.1$) and Extraversion (**Sample 1**:

$t_{407} = 1.1$; $p = 0.3$; **Sample 2**: $t_{299} = -0.68$; $p = 0.5$) no significant gender differences were found. For Conscientiousness, Women significantly scored higher than Men in **Sample 2** ($t_{299} = -2.11$; $p < 0.05$, $d = -0.245$), while in **Sample 1** Women scored higher than Men, but not significantly ($t_{407} = -0.41$; $p = 0.15$).

RVM: predicting personality traits based on RSFC

Results are only be reported if they were significant both in the main (**Sample 1**) and in the replication sample (**Sample 2**).

Predictions in the entire sample (balanced males and females)

In the entire sample, the RSFC pattern of four networks significantly predicted personality factors: **Pain** and **VA** predicted Openness, **AM** predicted Agreeableness and **Connectome** predicted Neuroticism (see Table 2; Fig. 2 for an overview of the results and Fig. 3 for the correlation plots).

Predictions of personality traits in the gender-split groups

In the gender-split groups, we also found a significant prediction of Openness scores based on FC patterns within the **Pain** network in Women as well as prediction of Neuroticism based on the **Connectome** FC in Men. In contrast, the **VA**- and **AM**-related networks did not significantly predict Openness and Agreeableness in either sub-group. However, in the gender-specific groups, additional significant predictions were observed: in males, Extraversion was predicted by the

Table 2 Results of the relevance vector machine

Predicted trait	Predicting network	Group	r (Sample 1)	p value (Sample 1)	r (Sample 2)	p value (Sample 2)
O	VA	All	0.12	0.006	0.17	0.001
O	Pain	All	0.1	0.018	0.2	0.0
O	Rew	Women	0.17	0.006	0.2	0.006
O	Pain	Women	0.12	0.048	0.29	0.0
E	Face	Men	0.18	0.005	0.14	0.04
E	Rew	Women	0.14	0.02	0.23	0.002
E	Connectome	Women	0.29	0.0	0.23	0.002
A	AM	All	0.1	0.018	0.18	0.001
N	Connectome	All	0.14	0.018	0.14	0.04
N	Connectome	Men	0.17	0.0	0.37	0.0
N	Emo	Men	0.2	0.002	0.42	0.0

Predicted trait: O openness, E extraversion, A agreeableness, N neuroticism

Predicting network: VA: vigilant attention; Pain: pain processing; Rew: reward; AM: autobiographic memory; Face: face perception; Connectome: whole-brain network; Emo: emotional processing

Correlation coefficients between real and predicted values which resulted significant at $p < 0.05$ in both samples in either across the entire sample ("All"), or in gender groups ("Men" or "Women")

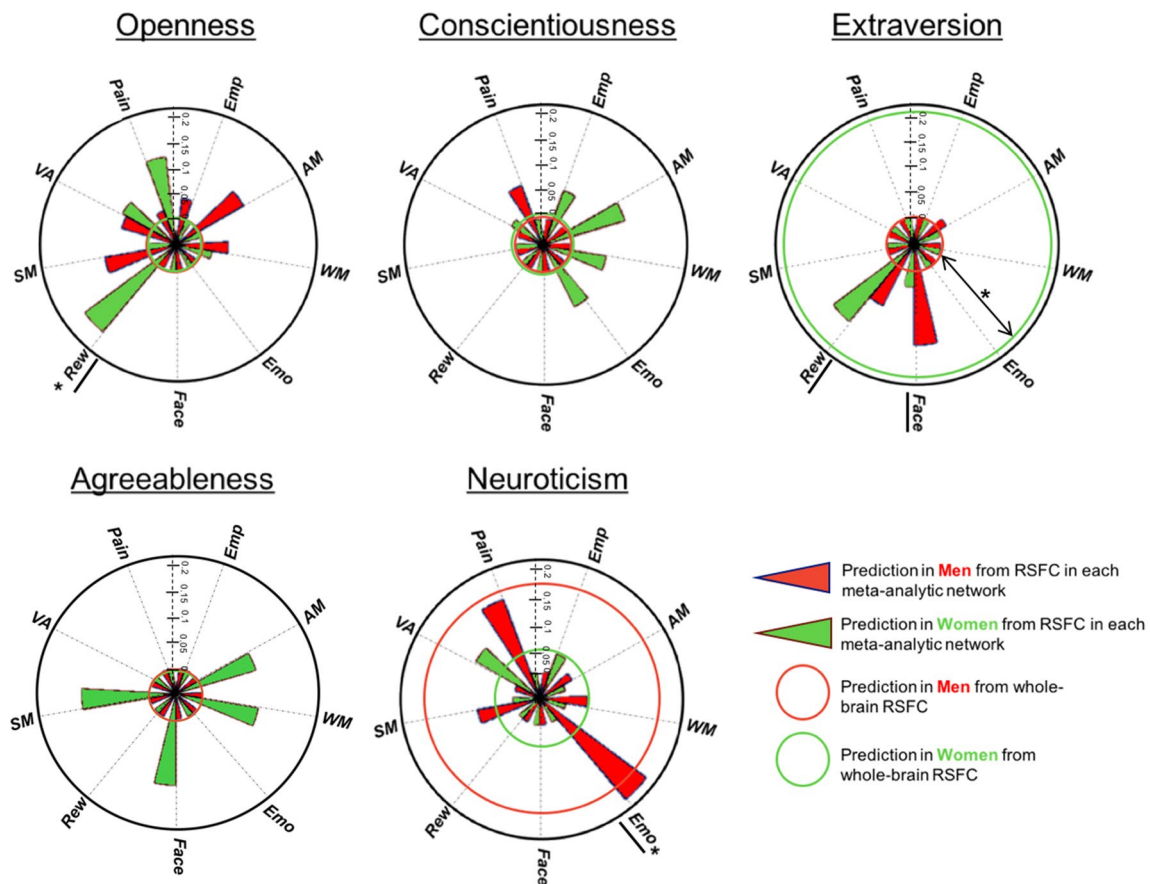


Fig. 2 *Emp*: empathy; *AM*: Autobiographic memory; *WM*: working memory; *Emo*: emotional processing; *Face*: face processing; *Rew*: reward; *SM*: semantic memory; *VA*: vigilant attention; *Pain*: pain processing. Summary of the networks for which FC patterns significantly predicted the five personality traits. For each network-trait combination in either Men or Women, and here, it is reported the conjunction between the correlation coefficients (i.e., minimum r

value). Only predictions with $r > 0.1$ are displayed. While the nine meta-analytic networks are represented as slices (triangles) of the five personality circles, the connectome is represented as well as a circle. Triangles and circles are scaled based on the r values of the predicting networks (r values reported in the axis). Meta-analytic networks are underlined if a significant prediction is detected in either Men or Women. Asterisks mark significant gender differences in **Sample 1**

RSFC patterns of *Face* and Neuroticism by *Emo* networks (Table 2; Figs. 2, 3). In females, Openness was predicted by *Rew* network. Furthermore, in females, Extraversion was predicted by *Rew* network and the *Connectome* (Table 2; Figs. 2, 3).

Gender differences in personality predictability

For all the predictions that were significant in at least one group (All/Males/Females), we tested if prediction performance was significantly different between the male and female sub-groups. Significantly better predictability in Men than Women was found for Neuroticism predicted from *Emo* network (Table 3, supplementary Fig S2). In Women compared with Men, Openness was significantly better predicted from *Rew* network and Extraversion from the entire *Connectome* (Table 3, supplementary Fig S2).

Notably, not all associations that were only found predictive in one sub-group showed significant differences in predictability between males and females. In particular, no gender differences were found in predicting Openness from *Pain*, and *VA* networks, Neuroticism from *Connectome*, Agreeableness from *AM*, and Extraversion from *Face* and *Rew* networks (Table 3, supplementary Fig S2).

Discussion

Here, we report associations between major dimensions of personality and RSFC in functional brain networks. In particular, individual scores of various personality traits of the Five-Factor Model (McCrae and Costa 2004) could be predicted from patterns of RSFC in specific meta-analytically defined networks as well as from the whole-brain FC pattern. In assessing the generalizability of our findings, we focused

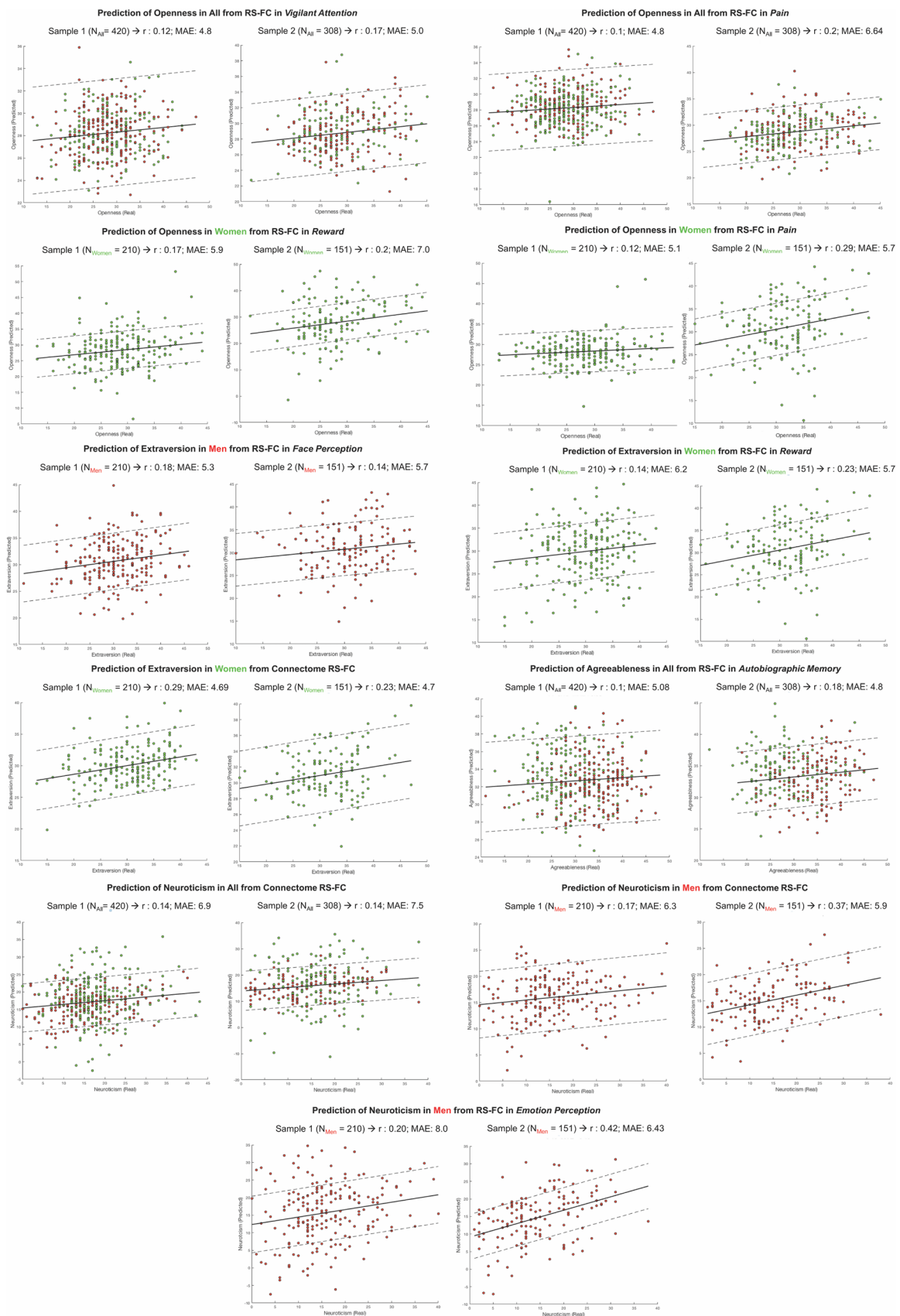


Fig. 3 Scatter plots of the predictions of personality scores significant at $p < 0.05$ in both samples. Continuous regression lines, dashed lines, representing the standard deviation, and mean absolute errors (MAE) are displayed

on the predictions that replicated in two different samples within the HCP data set.

These results capitalize on the as-yet largely untapped potential (though cf. Schilbach et al. 2016; Varikuti et al. 2016) of neuroimaging meta-analyses to provide robust, functionally specific ROIs to investigate individual task-free data (Lee et al. 2012). These can help to constrain the otherwise vast feature space for statistical learning on resting-state data in a functionally meaningful and anatomically specific manner (Wang et al. 2010). As we demonstrate here, combining meta-analytic network definitions with statistical learning approaches allows, at a moderate level, not only predicting complex individual characteristics such as personality traits, but also the characterization of functional brain networks by their capability to do so. Nonetheless, our results of prediction of personality based on whole-brain FC pattern highlight that, for some traits, it might be crucial to consider the global connectivity as well.

In the overall (gender-mixed) sample, RSFC within networks representing affective and executive brain systems predicted Openness, RSFC within mnemonic network predicted Agreeableness, while RSFC from the whole brain predicted Neuroticism. In the gender-split samples, however, the prediction of Openness from the executive network **VA** and that of Agreeableness from the mnemonic network **AM** were not replicated in any of the two sub-groups, an effect likely related to the moderate effect present in the overall sample not specifically driven by a particular sex. In contrast, the prediction from the affective network **Pain** was also predicted in the female-only subsample, indicating that more information on the respective phenotypes can be gained from RSFC data in one gender. The gender-specific analyses revealed further constellations in which personality traits could be predicted from particular networks (see Fig. 2). In fact, none of the network–trait combination was predictive in both female and male subsamples, but several functional networks were found to differentially predict personality traits in females vs. males. In addition, **Connectome** successfully predicted Extraversion (in Women) and Neuroticism (in the entire sample, but then also in Men only). This underlines the notion that gender is a fundamental factor with regard to brain–personality relationships.

Methodological considerations and limitations

In our analysis, we combined a priori selection of networks of interest, built upon the existing literature (cf. Kennis et al. 2013; Hu et al. 2011; DeYoung 2010), together with a

data-driven approach for learning of the predictive models. The benefits of this approach were twofolds: on one hand, with the a priori selection of networks, we could narrow down the networks of interest, which allowed us for a better functional interpretation of the results as the nodes represent brain regions robustly associated with the respective mental functions; on the other hand, the data-driven predictive models allowed for an explanatory analysis investigating which networks were informative in predicting a single trait, assuming, therefore, that many biological systems could contribute in explaining its inter-individual variance (Yarkoni 2015). Given that if only meta-analytically defined functional networks were employed, less consistently linked yet potentially critical regions might have been left out, we included also a purely explorative analysis employing the whole-brain FC.

In addition, as noted above, using a sparsity inducing method (RVM) which yielded compact regional modes has the advantage of providing regionally specific prediction models. As outlined above, our procedure provided a biologically informed feature reduction, as only the most relevant connections were taken in account in the prediction models. This has the advantage of reducing the complexity of the models avoiding overfitting (Hastie et al. 2009).

With respect to the prediction model, we here employed Relevance Vector Machine (RVM), which, in contrast to support vector regression or ridge regression, yields considerably sparser solutions (Tipping 2001). This allowed for identifying the most used connections and nodes (Fig. 4) that mainly drove the prediction and hence enabled a more specific interpretation of its neurobiological underpinnings. In this context, it is important to note that, for any given model, the entire set of connections with non-zero coefficients provides information about the personality trait (Orrù et al. 2012). For interpretation, however, we focused on the most consistently utilized connections (over 250 replications) as key components of the given prediction.

In accordance with recent recommendations, the current study used 10-fold cross-validation, which has been showed to be less susceptible to overly optimistic estimates as compared with a leave-one-out approach (LOO-CV) (Varoquaux et al. 2016). Moreover, we repeated the cross-validation procedure 250 times, averaging the prediction performance over all replications to obtain robust and generalizable estimates of the capability of different brain networks to predict personality scores in new individuals.

A last important methodological reflection is that, although it might be tempting to make use of the entire HCP sample (which, if requiring an equal number of males and females, and if considered the matching factors of age, education and twin status, would yield about 800 individuals), it systematically consists of related subjects (siblings and twins). In addition, there is considerable evidence for

Table 3 Gender differences in personality predictability

Predicted trait	Predicting network	Group	r (Sample 1)	$Z_{\text{Men}} - Z_{\text{Women}}$ (Cohen's q)	CI (lower limit/ upper limit)
O	VA	Men	0.06	0.013	– 0.176/0.205
		Women	0.07		
O	Pain	Men	0.08	0.039	– 0.153/0.231
		Women	0.12		
O	Rew	Men	– 0.06	0.236*	0.044/0.428
		Women	0.17		
O	Pain	Men	0.08	0.039	– 0.153/0.231
		Women	0.12		
E	Face	Men	0.18	0.054	– 0.138/0.246
		Women	0.12		
E	Rew	Men	0.08	0.055	– 0.137/0.247
		Women	0.14		
E	Connectome	Men	– 0.03	0.323 *	0.131/0.515
		Women	0.29		
A	AM	Men	0.10	0.190	– 0.002/0.382
		Women	– 0.09		
N	Connectome	Men	0.17	0.119	– 0.073/0.311
		Women	0.06		
N	Emo	Men	0.2	0.276*	0.084/0.468
		Women	– 0.07		

Comparison of the correlation coefficients between males and females and effect size of significant gender differences. Confidence intervals (CI) are computed on the Z-transformed difference between correlations in men and women for each prediction

*Significant gender difference at 95% of confidence

genetic influence on both personality (Jang et al. 1996; Bouchard and McGue 2003; Verweij et al. 2012; Power and Pluess 2015) and brain function (van den Heuvel et al. 2013; Colclough et al. 2017; Ge et al. 2017; Ktena et al. 2017). Consequently, the relationship structure in the HCP data is a critical aspect to this work, as the inclusion of related subjects would potentially hurt the model fitting but even more importantly would introduce an (optimistic) bias into the cross-validation. As a result, we thus performed our analyses primarily in the largest possible set of matched, unrelated subjects, replicate it in the then largest possible independent set of matched, unrelated subjects and only in a supplementary analysis pooled both of these sets for the analysis of around 750 subject.

Our approach, by building upon these methodological considerations, yielded insights into the relationships between brain, behaviour, and personality. However, there are some limitations which are worth consideration in the future studies. First, gender-stratified sub-analyses may reduce statistical power because of the smaller sample sizes. Further studies with a larger sample size, designed to separately analyze men and women, are required, especially monitoring their hormonal levels (Arélin et al. 2015; Weis et al. 2017). Second, even though meta-analytic networks are among the most reliable ways to infer a mental

function given a set of brain regions, we acknowledge that some regions of different functional networks can overlap. As a matter of fact, the employment of meta-analytically derived networks does not necessarily ensure a stringent and univocal relationship between the mental function supported by a particular network and a personality trait. Nonetheless, this approach can at least provide some confidence for the implication that a specific trait is related to a particular mental function in terms of the network that subserves them. A third consideration relates to the measurement of personality, i.e., the use of self-reported questionnaires. Self-reported questionnaire might have, indeed, contributed in increasing the noise in the data, as perception and report of own personality traits can be affected by many factors, e.g., men usually scoring low on Neuroticism as socialization effect (Viken et al. 1994).

Predicting Openness to experience

Our results indicated that self-reported Openness to experience can be linked to RSFC patterns in the networks subserving reward (**Rew**) and pain (**Pain**) processing in Women, while, in the overall sample, Openness was significantly predicted by RSFC in the vigilant attention (**VA**) network and, again, from **Pain**. Openness to experience has been linked

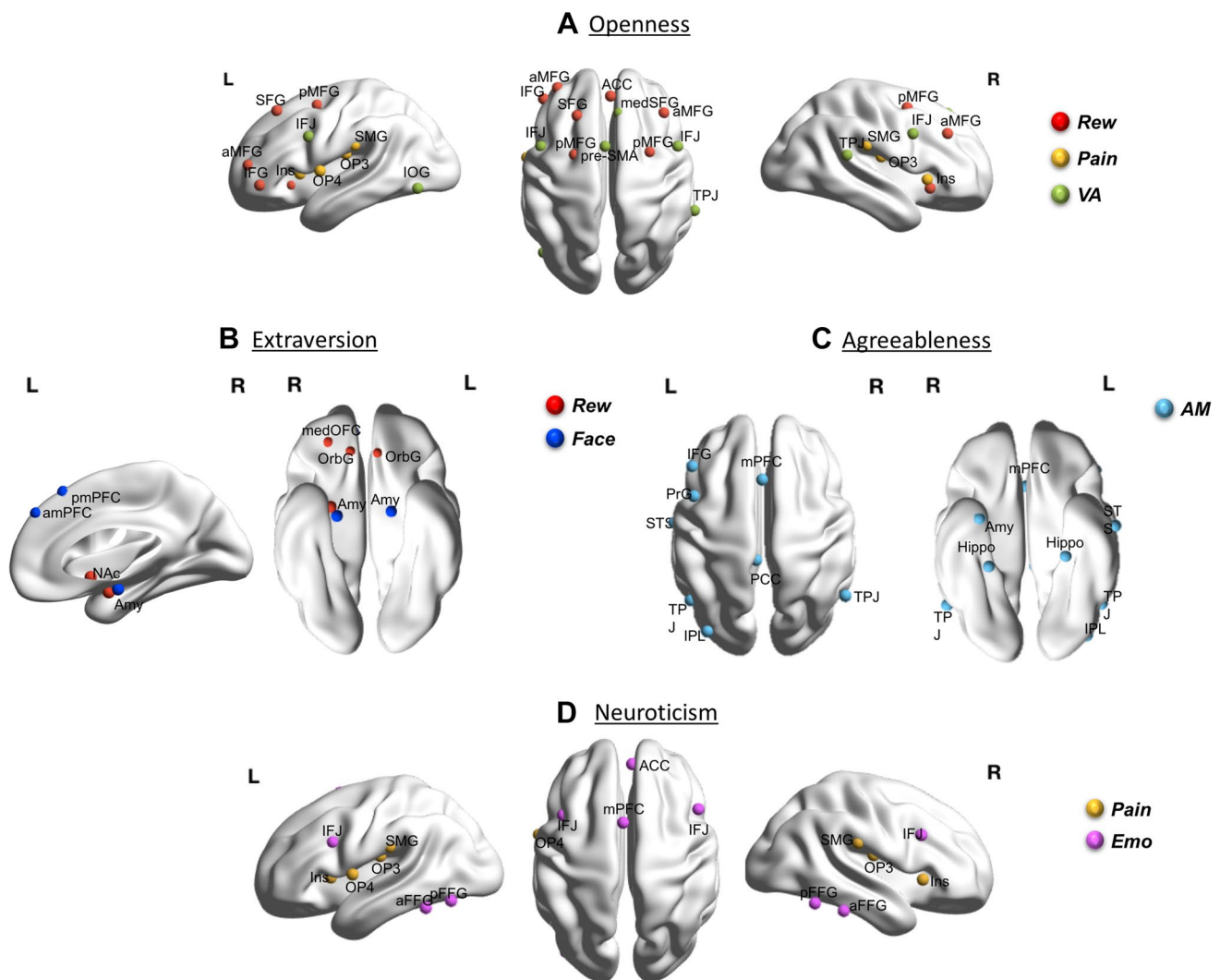


Fig. 4 Summary of the most used nodes (i.e., above 80% of the models) between regions from **a** the reward (**Rew**), vigilant attention (**VA**), and pain processing (**Pain**) networks in the prediction of Openness; **b** the Rew and face processing (**Face**) networks in the prediction

of Extraversion. Summary of the most used connections between regions from **c** the autobiographic memory (**AM**) network in the prediction of Agreeableness, **d** the Pain and emotional processing (**Emo**) networks in the prediction of Neuroticism

to “need for cognition,” that is, an individual’s tendency to engage in effortful cognitive processing (Fleischhauer et al. 2010): high levels of Openness were found to positively affect work outcomes for highly complex jobs while increasing dissatisfaction when jobs become mechanical and unchallenging (Mohan and Mulla 2013). Such monotonous and intellectually unchallenging tasks were exactly the tasks investigated in the **VA** meta-analysis of Langner and Eickhoff (2013), which revealed the brain network involved in dealing with sustained attentional demands in boring situations. Thus, the predictability of Openness from FC in the **VA** network may reflect a neural substrate of the challenge experienced by individuals scoring high on Openness when faced with repetitive tasks and standardized routines. High-Openness participants might, therefore, need to recruit this

network differently than low-Openness individuals to keep focused on a tedious, repetitive task over time. Indeed, connections used throughout all prediction models from the **VA** network of Openness in both samples is between pre-supplementary motor cortex and medial prefrontal cortex (both involved in task-set re-energizing and outcome monitoring), between left inferior occipital gyrus (IOG) and right temporo-parietal junction (crucial for re-orienting the signalling), and left IOG and inferior frontal junction (known for its contribution in the input/output transformation) (see Fig. 4 for the most informative connections and Langner and Eickhoff 2013 for more details on the regions’ functions).

Behaviours associated with the trait of Openness, such as cognitive exploration, have been attributed to high dopamine (DA) functioning (DeYoung et al. 2005). This, indeed, led to

the inclusion of Openness in the meta-trait “ β ” (or plasticity, c.f. DeYoung 2010), a higher order factor representing the shared variance between Openness and Extraversion, which are suggested to be both modulated by the dopaminergic system. DA is the main neurotransmitter modulating the reward network (cf. Berridge and Robinson 1998), and, in line with this, RSFC within the **Rew** network could predict both Openness and Extraversion (in Women and in Men, respectively), possibly via affecting the reactivity of the dopaminergic system. Interestingly, in predicting Openness, the weights of the nodes (i.e., number of incident edges) most used across the predictive models showed a stronger involvement of the dlPFC, corroborating previous findings that showed an association between Openness and the dopaminergic mesocortical branch, which projects directly onto the dlPFC (DeYoung 2013; Passamonti et al. 2015). On the other hand, regions like amygdala, nucleus accumbens (NAc), and orbitofrontal cortex (OFC), which constitute the other main dopaminergic branch, the mesolimbic pathway, were significantly less recruited. We would thus suggest that DA neurons populating the mesocortical branch, by encoding specifically the saliency of the stimulus (i.e., reward value of information, cf. Bromberg-Martin et al. 2010), can be potentially more informative for high-Open individuals, characterized by the automatic tendency to perceive salient information in everyday experience (DeYoung 2013). Interestingly, we found that Openness could be predicted by FC of the **Rew** network significantly better in Women, compared to Men ($r=0.17$ in Women and $r=-0.06$ in Men of **Sample 1**). This might be explained by the fact that **Rew** functioning is highly influenced by the ovarian hormones estrogen and progesterone during the menstrual cycle (Dreher et al. 2007). In addition, estrogens have been related to dlPFC functioning, going along with cognitive decline which follows the drop of estrogens in menopause (Shanmugan and Epperson 2014). Despite the lack of studies exploring a direct relationship between females’ hormonal cycling and the trait of Openness, there is evidence for its indirect modulation by estrogen. That is, the catechol-*O*-methyltransferase gene, which is associated with the trait of Openness (Konishi et al. 2014), is influenced by estrogen (Harrison and Tunbridge 2008). We thus suggest that the influence of ovarian hormones on RSFC in the **Rew** network as well as on perceived Openness induces joint intra-individual variation (i.e., shared variance), which in turn increases the strength of the neural and phenotypical association across women. This should then result in the observed higher predictability of Openness in female participants.

Across the entire sample, but then also in the female subgroup only, Openness could additionally be predicted in both samples based on FC within the pain network (**Pain**). Relationships between pain and Openness have been demonstrated in terms of a higher threshold for pain tolerance

(Yadollahi et al. 2014) and as protective factor in migraine occurrence (Magyar et al. 2017) in individuals reporting higher levels of Openness. However, very little is known about the association between this trait and the neural correlates of pain. Indirect evidence, however, comes from research in avoidance learning, which suggests that the successful avoiding of an aversive stimulus is experienced as an “intrinsic” reward (Kim et al. 2006). Endogenous opioid peptides, which are highly dense in the pain network (Baumgartner et al. 2006), were, indeed, found to modulate the dopaminergic system in response to aversive stimuli, resulting in the enhancement of a pleasure feeling boosted by DA (Sprouse-Blum et al. 2010). We thus suggest that high- and low-Open individuals differ in their ability to detect possible aversive stimuli (via diverse reactivity of the **Pain** network) and, by avoiding them, differently experience “intrinsic” reward.

In summary, the predictions from the **Rew**, **VA**, and **Pain** networks of Openness might, therefore, jointly point to the importance of saliency processing of stimuli, which can be rewarding (**Rew**), monotonous (**VA**), or aversive (**Pain**), turning high Open individuals as highly receptive and permeable to relevant information. Ultimately, connections between regions specially targeted by ovarian hormones (e.g., dlPFC) might underlie the significant gender difference in the predictability of Openness from FC in **Rew** network (Fig. 4).

Predicting Extraversion

Extraversion was predicted by the RSFC patterns within the networks of reward (**Rew**) in Women and face perception (**Face**) in Men. Moreover, in Women, this trait was also significantly predicted by the whole-brain (**Connectome**) RSFC. Extraversion is generally described as behavioural exploration and sensitivity to specific rewards. Importantly, a distinction has been also made between “Agentic Extraversion”, reflected in assertiveness, dominance, and ambition aspects, and a “Affiliative Extraversion” which is more related to sociability and affiliative social bonding (DeYoung et al. 2007; c.f. Allen and DeYoung 2016).

As discussed previously in the paragraph “**Predicting Openness to experience**”, the traits of Extraversion and Openness exhibit a shared variance, known as “ β ” factor, and are genetically influenced by the dopaminergic system (c.f. Allen and DeYoung 2016). Notably, while for Openness, **Rew**’s most used nodes encompassed the mesocortical pathway (see above), for Extraversion, it was regions along the mesolimbic branch that were mostly used (amygdala, NAc and OFC). Thus, we suggest that even though FC of **Rew** predicts both Openness and Extraversion, the functional connectivity of two different subsystems of the **Rew** network is informative for the two different traits, namely the mesocortical and mesolimbic pathway, respectively. In favour of

this distinction, extraverts were shown to be more sensitive toward the motivational content of the reward stimulus, encoded by DA neurons along the mesolimbic pathway (Bromberg-Martin et al. 2010; DeYoung 2013). We thus believe that the prediction of Extraversion from the FC within **Rew** might well-capture the “Agentic” dimension of Extraversion, given the motivational value of the rewarding stimuli and drive toward a goal prompted by the dopaminergic mesolimbic system.

While extraversion in Women was found to be associated with FC of **Rew**, relationships of this trait, in Men, were found with FC in **Face** network. Faces are arguably the most important social stimuli for humans and it has been shown that extraverts compared to introvert, by spending more time on people, are significantly better at recognizing faces (Li and Liu 2010). Extraversion’s hedonic experience of goal achievement is enclosed in the “Affiliative” component (DeYoung et al. 2007; c.f.; Allen and DeYoung 2016) and its genetic variation has been also pointed to the opiate system, due to its involvement in the hedonic response to the stimulus (Peciña et al. 2006). It is, therefore, possible that the endogenous opioid system via modulation of amygdala and medial prefrontal cortex (Tejeda et al. 2015; Selleck and Baldo 2017), most used regions in the connections of **Face**, mediate both the perception of faces (Martin et al. 2006) and the social bonding (Pasternak and Pan 2013). We thus suggest that functional connectivity within the **Face** network in Men is mostly related to the “Affiliative” aspect of Extraversion.

The last prediction of Extraversion is based on whole-brain FC in Women (**Sample 1**: $r=0.29$; **Sample 2**: $r=0.23$, both $p<0.05$; for gender comparison in **Sample 1**, Cohen’s $q=0.323$, $p<0.05$). However, a major issue using whole-brain connectivity pattern might be the lack of anatomical localization for the most informative features, as none of them resulted to be used more than 40% of the predictive models, indicating a heterogeneous mosaic of connections which contribute to the prediction of Extraversion. The only theory in personality neuroscience which relates the functioning of entire cortex to Extraversion (and Neuroticism, see below “Predicting Neuroticism”) is Eysenck’s biological theory of personality (Eysenck 1967). Here, Extraversion is thought to depend on the variability in cortical arousal, with introverted individuals having lower response thresholds consequently more cortical arousal compared to extraverts. In favour of this hypothesis, the topological properties of whole-brain RSFC have shown that brains of more extraverted individuals behave more similarly to a “small-world” compared to a “random” network, with higher clustering coefficient compared to introverts (Gao et al. 2013). A “small-world” clustered configuration, which supports a more modularized information processing and fault tolerance, can, therefore, be associated with higher arousal

threshold in extraverts’ cortex. We also observed that this prediction performance was significantly stronger in Women compared to Men ($r=0.29$ in Women and $r=-0.03$ in Men of **Sample 1**). Again, a possible cause might be the involvement of ovarian hormones, targeting specifically the most densely interconnected hub structures of the connectome (Alawieh et al. 2015) as well as influencing level of Extraversion (Jokela et al. 2009; Ziolkiewicz et al. 2012). However, more studies are needed to prove this interaction between Extraversion, estrogen, and the topographical properties of whole-brain functional connectivity.

To sum up, connectivity of regions encoding the motivational value and the drive toward a goal (**Rew**) and the hedonic processing of the goal itself (**Face**) were informative to predict inter-individual variability in the trait of Extraversion possibly capturing the “Agentic” and “Affiliative” aspects of the trait, respectively (Fig. 4). Importantly, given the modulation of ovarian hormones on both the trait of Extraversion and on the topological properties of the **Connectome**, we would suggest that sex hormones might be a possible mediator of this trait–network relationship, resulting in better prediction performance in Women.

Predicting Agreeableness

RSFC patterns in the **AM** network could predict the individual level of perceived Agreeableness while grouping men and women in both samples. This trait reflects a high desire to avoid interpersonal conflicts (Jensen-Campbell and Graziano 2001) and strong affect regulation (Ryan et al. 2011). In line with this, positive correlations have been demonstrated between Agreeableness and regions supporting social functioning (Hooker et al. 2008; DeYoung et al. 2010; Hassabis et al. 2014) and midline regions of the default mode network (DMN), as deputed to self-referential process (Adelstein et al. 2011; Sampaio et al. 2014). Our prediction of Agreeableness from the **AM** network supports a crucial role of self-reference, strongly linked to autobiographical memory (Molnar-Szakacs and Arzy 2009), in how high agreeable individuals deal with social demands. Self-related cognition has been often discussed at the neural level as the product of interaction between the DMN and the mirror neuron system (MNS), the first responsible for high-level mentalizing function and the second for embodied simulation-based representation (Keysers and Gazzola 2007; Qin and Northoff 2011; c.f.; Molnar-Szakacs and Uddin 2013). As a result, the privileged access to the own physical and mental states would allow a better insight into others’ physical and mental states, and consequent appropriate social responses.

Interestingly, within the **AM** network, most used connections that informed about the trait in both samples reflected the interaction between the DMN and MNS systems: nodes with highest weights belonged, indeed, to DMN subsystem,

such as medial PFC, posterior cingulate cortex, medial temporal lobe (amygdala and hippocampus) and lateral parietal cortex (temporo-parietal junction). The remaining nodes with the highest weights belonged to the MNS, such as inferior frontal gyrus, precentral gyrus, inferior parietal cortex, and superior temporal sulcus. Our result, hence, supports the interplay of these two subsystems in the context of self-processing (here expressed via memory recollection about past experiences, **AM**) and that this knowledge about the self can significantly predict Agreeableness, the trait most reflecting enhanced social skills.

Predicting Neuroticism

In Men, self-reported Neuroticism was predicted by RSFC within the emotional processing network (**Emo**). In addition, the RSFC from the whole brain (**Connectome**) significantly predicted this trait across the entire sample and then specifically in Men only. Neuroticism represents a broad dimension of individual differences in the tendency to experience negative, distressing emotions. High-Neuroticism scores entail the experience of fear, anger, sadness, embarrassment, the incapacity to control cravings and urges, and to cope with stress (Costa and McCrae 1987). Within this trait, it is possible to delineate two major divisions: one related to the experience of anxiety, fear and passive avoidance, and referred in literature as the aspect *Withdrawal*, and the other related to irritability, anger and active defensive responses, or *Volatility* (DeYoung et al. 2007). Neuroticism is arguably the most studied personality trait and is an important predictor of many different mental and physical disorders (Lahey 2009). Furthermore, the two aspects of Neuroticism (*Withdrawal* and *Volatility*) highly reflect the dimension of Behavioural Inhibition System (BIS) and Fight-Flight-Freezing System (FFFS) from the Gray's Reinforcement Theory (Gray and McNaughton 2000), conceptualized in term of their neurobiology. Interestingly, this distinction between the *Volatility*/FFFS and *Withdrawal*/BIS seems to be captured by the two networks showing predictability power for Neuroticism, **Emo** and **Pain**. Even though this last prediction (**Pain**) was found significant in **Sample 1** (with $r=0.15$, $p<0.05$ in Men) but not fully replicated in the **Sample 2** (with $r=0.2$, $p=0.05$ in Men) (Fig. 4), we would still suggest that recruitment of this network in association to Neuroticism might indicate that perception of the aversive stimulus via the **Pain** network (Iannetti and Mouraux 2010; Hayes and Northoff 2012) could lead high-Neuroticism men to inhibit their behaviours such to avoid potential threats and punishments (*Withdrawal*). Conversely, **Emo** network would trigger emotional responses for either escaping or eliminating the threat, but in both cases showing a strong emotional lability (*Volatility*). Beyond associations with specific networks, Neuroticism could also be predicted from

the whole-brain RSFC (**Connectome**) in Men and across genders. This is nicely in line with graph analysis studies (Gao et al. 2013; Servaas et al. 2015), showing that the neurotic brain displays topological properties of a “random network” and overall weaker FC. Here, cortisol might play a specific role, the hormone that is most closely associated with a biological reaction to stress and found to correlate with Neuroticism. However, the directionality of correlation seems to depend on gender: many studies converged in discovering that Neuroticism was positively correlated with baseline cortisol in men, but the opposite was true in women (Zobel et al. 2004; Oswald et al. 2006; DeSoto and Salinas 2015). Thus, especially in men, the overabundance of cortisol by potentiating neuronal degeneration (Sapolsky 1994) might be responsible for the overall smaller brain volume (Liu et al. 2013), white-matter (Bjørnebekk et al. 2013), and gray-matter (Servaas et al. 2015) functional disconnectivity found in high-Neuroticism individuals compared to the more emotional stable. Given that all the three networks (**Emo**, **Pain**, **Connectome**) showed a stronger predictability in Men compared to Women (statistically significant for the first two, and a strong trend for the third, see Table 3), we suggest that gender may moderate Neuroticism's relationship to cortisol. However, more (direct) studies are needed to better understand this intricate relationship between RSFC, cortisol, Neuroticism, and gender, and to shed light on the neural mechanisms that make women's brain more susceptible to Neuroticism-related mental disorders (Jorm 1987).

Implications for the neurobiology of FFM

Contrary to other important theories of personality, such as Cloninger's Tridimensional Personality Questionnaire (TPQ) or Gray's Reinforcement Sensitivity Theory (RST), the FFM is not based on biological grounds. However, variability in its personality factors had been associated with the brain, given that personality traits are the product of our actions, emotions and, more generally, cognitive processes. In this way, the cognitive mechanisms work as intermediate bridge between the psychometric constructs of personality and plausible biological substrates. However, the relationships among these factors (brain, behaviour, and personality) can be misleading in the context of personality predictions, which, in fact, were significant only to a moderate level, compared to other findings: contrary to predictions of sustain attention (Rosenberg et al. 2016) or reading comprehension (Cui et al. 2017) which tap predictability of cognitive process itself, personality traits are mostly modulators of these cognitive processes. This may make it more difficult to find brain correlates of personality in specific networks associated with those functions.

In addition, the hierarchy of the FFM model might have contributed in enlarging the gap: in our findings, we

highlighted the possibility that the predictions of one trait from different networks could reflect different components within this trait, also known as aspects and facet (cf. DeYoung et al. 2007; Koelsch et al. 2013; Haas et al. 2015). For example, we discussed the prediction of Extraversion from **Rew** and **Face** as potentially capturing the “Agentic” and “Affiliative” aspects, respectively, or the prediction of Neuroticism from **Pain** and **Emo** as linked to *Withdrawal* and *Volatility*. Conversely, when the same network was predicting two different traits (e.g., **Rew** predicting Openness and Extraversion, discussed in light of the saliency and motivational contribution for the two traits), the prediction might have, indeed, boosted if investigating the meta-trait “ β ”, which reflects their shared variance within the dopaminergic system and thus more prone to be predicted by the network of reward processing (DeYoung 2013). Therefore, the level of abstraction of the five traits might not mapped well to particular brain systems, and more studies are encouraged for testing both more specific and homogeneous sub-dimensions as well as more heterogeneous higher order factor structure. Finally, many biological mechanisms participate in evoking the same cognitive process, e.g., changes in brain structure, function, or genetic, which are then intrinsically connected with personality. We here used RSFC as “marker” for the individual expression of personality traits, enduring across time and situations. However, a downside of FC in resting conditions might be that it has not so much to do with how personality factors come together to “produce” stable modulations of a whole range of cognitive processes. Therefore, other brain measurements (as structural connectivity, task-based functional activation, or molecular genetics) might be also useful in gaining more knowledge on the biology of personality and its relationship with specific mental functions. Keeping in mind that we cannot expect biological mechanisms to show clear-cut as the respective psychometric dimensions (Yarkoni 2015), but, conversely, many biological mechanisms (function, structure, neurotransmitters) as well as many mental functions can be informative for a given personality trait, we, therefore, support the need for a multi-level approach in future studies as proposed by Yarkoni to achieve a unified description of the biological bases of personality traits.

However, even though all these aspects might affect the relationship between brain function (and structure) and personality, we here do provide insights on the relation between brain and personality: when analysing the entire sample while adjusting for gender effects, only two predictions (**VA** predicting Openness and **AM** predicting Agreeableness) can be found not specifically driven by one gender-group. However, when looking at men and women separately, we observed much more and larger effects, evidence which highly remarks the importance of gender while investigating the neural correlates of personality. Specifically, the current findings propose a link

between Openness and executive and affective domain. Agreeableness with memory domain. Extraversion with social and affective networks and lastly Neuroticism with the affective system. Interestingly, these last two traits could be predicted as well from the entire **Connectome**. An interesting consideration is that Openness could be significantly predicted by three different, barely overlapping networks (**Pain**, **Rew**, **VA**), but could not be predicted from the whole-brain, which was covering the nodes of all the three at the same time. We thus argue for a better predictability of Openness from specific and separate functional networks. Contrarily, Extraversion and Neuroticism could be significantly predicted by both meta-analytic networks and the whole brain, pointing to the importance of also global effects, besides specific functions. This is particularly true for Extraversion, which showed significantly higher prediction performance from global RSFC (**Connectome**) with a very vast nodes contribution, rather than from the specific networks of **Rew** and **Face**, thus favouring the global effects over the specific functions for this trait.

Conclusions

Using multivariate machine learning, we showed that personality traits can be predicted from RSFC patterns in affective, social, executive, and memory networks of the brain, as well as from the whole-brain. Our observation that for most of these networks predictive power was gender-specific complements previous morphometric findings (Nostro et al. 2016) in highlighting the crucial role of gender when trying to understand the neurobiology of personality. In addition, the many-to-many associations between mental functions and personality traits indicate the complexity of the biological substrates of personality, as many functional systems may contribute to the observable differences in each trait (for a critical review see Yarkoni 2015). Maybe, even more fundamental are the implications for the concept of personality, given that even a trait as complex and broad as, for instance, Openness, seems to have a neurobiological underpinning in pre-defined functional networks that enables estimation of the individual level of that trait in a new subject.

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Compliance with ethical standards

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Table S1: Influence of zygosity on the traits distribution

We performed a Kolmogorov-Smirnov (KS) test in order to verify that the distribution for each trait in monozygotic and dizygotic twins was not significantly different (null hypothesis). Therefore, from the S1200 release we selected only twin participants (N= 563) and later extracted a subsample of unrelated subjects (N = 262, 131 males and 131 females). All the statistics result not significant, i.e. the distribution of each trait in Mz and Dz does not differ.

Trait	K-S statistic (Mz vs Dz)	P value
Openness	0.10	0.47
Conscientiousness	0.06	0.96
Extraversion	0.07	0.87
Agreeableness	0.13	0.23
Neuroticism	0.07	0.93

Table S2: Correlations between factors

Supplementary Table 1: Intercorrelations (Pearson's r) among the 5 personality factors for Sample 1 and Sample 2, across the overall samples, in males, and females.

Sample 1

		Openness	Conscientiousness	Extraversion	Agreeableness	Neuroticism
Openness	Overall	-	-0.14*/	0.07/	0.17*/	0.0/
	Males		-0.15/	0.06/	0.17*/	0.07/
	Females		-0.11	0.09	0.18*	-0.08
Conscientiousness	Overall	-	-	0.27*/	0.19*/	-0.35*/
	Males			0.32*/	0.24*/	-0.37*/
	Females			0.24*	0.12	-0.36*
Extraversion	Overall	-	-	-	0.26*/	-0.32*/
	Males				0.23*/	-0.32*/
	Females				0.34*	-0.3*
Agreeableness	Overall	-	-	-	-	-0.26*/
	Males					-0.29*/
	Females					-0.31*
Neuroticism		-	-	-	-	-

Sample 2

		Openness	Conscientiousness	Extraversion	Agreeableness	Neuroticism
Openness	Overall	-	-0.17*/	0.13/	0.13/	0.07/
	Males		-0.11/	0.09/	0.13/	0.09/
	Females		-0.2	0.18	0.18	0.08
Conscientiousness	Overall	-	-	0.25*/	0.21*/	-0.47*/
	Males			0.32*/	0.26*/	-0.54*/
	Females			0.17	0.13	-0.43*
Extraversion	Overall	-	-	-	0.43*/	-0.41*/
	Males				0.40*/	-0.42*/
	Females				0.46*	-0.41*
Agreeableness	Overall	-	-	-	-	-0.39*/
	Males					-0.39*/
	Females					-0.45*
Neuroticism		-	-	-	-	-

* Marks significance at $p < 0.05$ (Bonferroni corrected)

Table S3: Coordinates of each network included in the RS functional connectivity network analysis

Empathy					
Bzdok et al., 2012					
x	y	z	Macroanatomical location	Original labeling in the Meta-analysis	Cytoarchitectonic Assignment
2.0	56.0	18.0	rdmPFC	dmPFC	Area p32
-8.0	54.0	34.0	ldmPFC	dmPFC	-
36.0	22.0	-8.0	raIns/IFG	raIns	-
54.0	16.0	20.0	rIFG	rIFG	Area45
50.0	30.0	4.0	rIFG (p.Tr)	rIFG	-
-30.0	20.0	4.0	laIns	laIns	-
50.0	12.0	-8.0	rSTG	rIFG	-
-44.0	24.0	-6.0	lIFG(p.Orb)	lIFG	-
-4.0	18.0	50.0	SMA	SMA	

-2.0	28.0	20.0	aMCC	aMCC	Area 33
-4.0	42.0	18.0	pACC	rostral ACC	Areap32
-2.0	-32.0	28.0	PCC	PCC	Retrosplenial Area a30
52.0	-58.0	22.0	rTPJ	rTPJ	Area PGp
-56.0	-58.0	22.0	lTPJ	lTPJ	Area PGa
22.0	-2.0	-16.0	rAm	rAm	Amygdala: SF, CM
54.0	-8.0	-16.0	rMTG	rMTG	-
52.0	-36.0	2.0	rpSTS	rpSTS	-
-12.0	-4.0	12.0	laTh	laTh	Th:Prefrontal,
6.0	-32.0	2.0	rpTh	rpTh	
26.0	-26.0	-12.0	r Hippo	rHippo	Subiculum
2.0	-20.0	-12.0	Midbrain	Midbrain	-
14.0	4.0	0.0	rGP	rGP	Th:Prefrontal
Face processing Grosbras et al., 2012					
x	y	z	Macroanatomical Location	Original labeling in the Meta-analysis	Cytoarchitectonic Assignment
42.0	-78.0	-8.0	r lOeC	r lOeC	hOe4la
-40.0	-82.0	-8.0	lOeC	l lOeC	hOe4la
26.0	-100.0	2.0	rOePole	rOePole	hOe2
-14.0	-98.0	-4.0	lOePole	lOePole	hOe1
52.0	-44.0	8.0	rMTG	rMTG/pSTS	-
-56.0	-58.0	36.0	lTPJ	lMTG/pSTS	Area PFm
28.0	-52.0	42.0	rIPS	rSPL	Area hIP1
4.0	-58.0	28.0	rPre	rPCC	-
52.0	24.0	26.0	rIFS	rIFG	Area45
-46.0	20.0	22.0	lIFG	lIFG	IFS1/IFS2
0.0	20.0	54.0	l pre-SMA	pre-SMA	-
42.0	12.0	30.0	rIFS	rMFG	IFS4
12.0	52.0	16.0	pACC	rMFG	Area p32
8.0	46.0	36.0	r amSFG	rmPFC	-
14.0	28.0	50.0	r pmSFG	rSFG	-
-24.0	24.0	42.0	lMFG	lSFG	-
36.0	2.0	42.0	rMFG	rPrG	-
20.0	-8.0	-14.0	rAm	rAm	Am: SF
-16.0	-6.0	-12.0	lAm	lAm	-
Reward Liu et al., 2011					
x	y	z	Macroanatomical Location	Original labeling in the Meta-analysis	Cytoarchitectonic Assignment
12.0	10.0	-6.0	rNAc	rNAc	NAc_fundus
-10.0	8.0	-4.0	lPal	lPal	Striatum_scgp

36.0	20.0	-6.0	raIns	rIns	-
-32.0	20.0	-4.0	laIns	lIns	-
0.0	24.0	40.0	aMCC	dmPFC	Area 32'
0.0	54.0	-8.0	mOFC	mOFC	Fp2
24.0	-2.0	-16.0	rAm	rAm	Am: LB
4.0	-14.0	8.0	rTh	rTh	Th: Temp
0.0	8.0	48.0	l pre-SMA	SMA	-
8.0	-18.0	-10.0	rBrainstem	rBrainstem	-
2.0	44.0	20.0	rpACC	rACC	Area p32
-24.0	2.0	52.0	lpMFG	lMFG	-
-38.0	-4.0	6.0	lpIns	lIns	Area Id3
24.0	40.0	-14.0	r SOrbG	r midOFC	Area Fo3
-16.0	42.0	-14.0	lSOrbG	l midOFC	-
40.0	32.0	32.0	rpMFG	rMFG	-
-28.0	-56.0	48.0	lIPS	lIPL	hIP3
28.0	-58.0	50.0	rIPS	rAG	hIP3
0.0	-32.0	32.0	PCC	PCC	
-36.0	50.0	10.0	laMFG	lFP	-
-46.0	42.0	-4.0	lIFG	l IOFC	-
30.0	4.0	50.0	raMFG	rMFG	-
-22.0	30.0	48.0	lSFG	lSFG	-
Pain Kogler et al., 2015					
x	y	z	Macroanatomical Location	Original labeling in the Meta- analysis	Cytoarchitectonic Assignment
38.0	18.0	0.0	rIns	rIns	-
52.0	12.0	-4.0	rSTG	rSTG	Area 44
60.0	6.0	2.0	rIFG	rTP	Area 44
22.0	0.0	-4.0	rPal	rPal	-
-38.0	14.0	4.0	laIns	lIns	OP7
-58.0	0.0	6.0	lIOP	lOP4	OP6
-20.0	6.0	2.0	lPut	lPut	Striatum_PM
4.0	6.0	46.0	rSMA	rSMA	Area 24dv
0.0	14.0	36.0	laMCC	lMCC	Areas 24c'v,24c'd
-42.0	-18.0	18.0	lpOP	lOP3	OP3
-54.0	-24.0	24.0	lSMG	lSMG	Area PFop
-36.0	-20.0	2.0	lpIns	lIns	OP7, OP6
-14.0	-12.0	10.0	lTh	lTh	Th: Pref
10.0	-18.0	4.0	rTh	rTh	Th: Pref
56.0	-24.0	24.0	rSMG	rSMG	Area PFop
44.0	-14.0	16.0	r pOP	rOP3	OP3
38.0	50.0	12.0	rMFG	rMFG	-
-24.0	-66.0	-26.0	lCb	lCb	LobuleVI

Emotion perception Sabatinelli et al., 2012					
x	y	z	Macroanatomical location	Original labeling in the Meta-analysis	Cytoarchitectonic Assignment
4.0	47.0	7.0	pACC	medPFC	pv24c; pd24cv; pd24cd
42.0	25.0	3.0	rIFG	rIFG	
-42.0	25.0	3.0	lIFG(p.Tr)	lIFG	-
48.0	17.0	29.0	rIFJ	rMFG	IFJ1
-42.0	13.0	27.0	lIFJ	lMFG	IFJ1
-2.0	8.0	59.0	l pmSFG	lSFG	
20.0	-4.0	-15.0	rAm	rAm	Amygdala: SF
-20.0	-6.0	-15.0	lAm	lAm	Amygdala:SF
-20.0	-33.0	-4.0	lHippo	lPHG	.
14.0	-33.0	-7.0	rHippo	rPHG	Subiculum
53.0	-50.0	4.0	rMTG	rMTG	-
38.0	-55.0	-20.0	r aFFG	rFFG	FG3
-40.0	-55.0	-22.0	l aFFG	lFFG	Lobule VI
38.0	-76.0	-16.0	r pFFG	rpFFG	hOc4v
-40.0	-78.0	-21.0	lpFFG	lpFFG	hOc4v
-4.0	52.0	31.0	lamSFG	medPFC	-
36.0	25.0	-3.0	rIns	rOFC	-
-38.0	25.0	-8.0	lIFG(p.Orb)	lOFC	-
2.0	19.0	25.0	aMCC	rACC	Area a24a', a23b'
0.0	-15.0	10.0	lTh	Th	Th: Temporal
-2.0	-31.0	-7.0	Superior Colliculus	Pulvinar	-
-28.0	-70.0	-14.0	lFFG	lFFG	FG1
46.0	-68.0	-4.0	r lOcC	r lOcC	hOc4lp
-48.0	-72.0	-4.0	l lOcC	l lOcC	hOc4lp
Working Memory Rottschy et al., 2012					
x	y	z	Macroanatomical location	Original labeling in the Meta-analysis	Cytoarchitectonic Assignment
-32.0	22.0	-2.0	l aIns	laIns	-
-48.0	10.0	26.0	lIFG	lIFG (p.Orb)	Area 44
-46.0	26.0	24.0	lIFS	l plPFC	IFS1/IFS2
-38.0	50.0	10.0	lMFG	l alPFC	-
36.0	22.0	-6.0	r aIns	raIns	-
50.0	14.0	24.0	rIFG	rIFG (p.Tr)	Area44
44.0	34.0	32.0	rpMFG	r plPFC	-
38.0	54.0	6.0	raMFG	r alPFC	-
2.0	18.0	48.0	r dmPFC	pmedFC	-
-28.0	0.0	56.0	lSFG	l pSFG	-

30.0	2.0	56.0	rSFG	r pSFG	-
-42.0	-42.0	46.0	lIPS	lIPS	hIP2
-34.0	-52.0	48.0	lSPL	lSPL/IPS	hIP3
-24.0	-66.0	54.0	lSPL	lpSPL	Area7A
42.0	-44.0	44.0	rIPS	rIPS	hIP2
32.0	-58.0	48.0	rIPS	rIPS	hIP3
16.0	-66.0	56.0	rSPL	rpSPL	Area7A
-12.0	-12.0	12.0	lTh	lTh	Th: Pref
-18.0	4.0	6.0	lPutament	lPutamen	Striatum:PoStP
12.0	-10.0	10.0	rTh	rTh	Th: Pref
-34.0	-66.0	-20.0	lFFG/Cb	lCb/FFG	FG2
32.0	-64.0	-18.0	rFFG/Cb	rCb/FFG	FG1
Vigilant Attention Langner et al., 2012					
x	y	z	Macroanatomical location	Original labeling in the Meta-analysis	Cytoarchitectonic Assignment
-2.0	8.0	50.0	l pre-SMA	a paracentral lobule	-
8.0	32.0	46.0	r mSFG	r pmed SFG	-
0.0	26.0	34.0	l MCC	l/r dorsal MCC	Area 32'
50.0	8.0	32.0	r IFJ	r IFJ	
40.0	22.0	-4.0	r aIns	r aIns	-
46.0	36.0	20.0	r MFG	r IFS	-
-40.0	-12.0	60.0	l PrG	l PrG	-
-46.0	-68.0	-6.0	l IOG	l IOG	hOc4lp; hOc4d; hOc3d
-48.0	8.0	30.0	l IFJ	l IFJ	area 44
62.0	-38.0	17.0	r IPL	r TPJ	area PF
8.0	-12.0	6.0	r Th	r a/mTh	Th: temporal
32.0	-90.0	4.0	r MOG	r MOG	hOc4la
-42.0	12.0	-2.0	l aIns	l aIns	-
-10.0	-14.0	6.0	l Th	l a/m Th	Th: prefrontal
6.0	-58.0	-18.0	r Cb	l/r Cb	lobule V
44.0	-44.0	46.0	r IPS	r IPL	hIP2
Autobiographical memory Spreng et al., 2008					
x	y	z	Macroanatomical location	Original labeling in the Meta-analysis	Cytoarchitectonic Assignment
-1.0	-53.0	21.0	lPrc	l/rPrc	-
-26.0	-28.0	-17.0	lHippo	lHippo	Subiculum
-49.0	-61.0	31.0	lTPJ	lTPJ	Area PGa
-2.0	51.0	-11.0	lFP	l medPFC	Fp2
-60.0	-9.0	-18.0	lSTS	lSTS/MTG	-
-50.0	27.0	-12.0	lSOrbG	l vlPFC	Fo5

26.0	-33.0	-15.0	rHippo	rpHippo	Subiculum
-1.0	20.0	57.0	lmSFG	MFG	-
55.0	-58.0	30.0	rTPJ	rTPJ	Area PGa
-47.0	9.0	46.0	lPrG	l plPFC	-
-42.0	53.0	7.0	IFP	l IFP	-
26.0	-14.0	-23.0	rHippo	raHippo	DG
52.0	-5.0	-18.0	rMTG	rTP/MTG	-
-39.0	13.0	-41.0	ITP	ITP	-
-38.0	-82.0	38.0	lIPL	IOC	Area PGp
-48.0	29.0	17.0	lIFG	l dlPFC	Area 45
52.0	31.0	-11.0	rSOrbG	r vlPFC	Fo5
-11.0	62.0	9.0	IFP	lmedFP	Fp1
4.0	-8.0	2.0	rTh	rTh	Th: Temporal
-4.0	39.0	16.0	lACC	lrACC	Area pv24c, pd24cv, pd24cd
-5.0	-34.0	36.0	IPCC	IPCC	-
-29.0	16.0	51.0	lSFG	lSFS	-
31.0	1.0	-26.0	rAm	rAm	Amygdala: LB
Semantic Memory Binder et al., 2009					
x	y	z	Macroanatomical Location	Original labeling in the Meta- analysis	Cytoarchitectonic Assignment
-46	-70	21	lIPL	lSTG	Area PGp
-50	-56	31	lAG	lSTG	Area PGa
-64	-44	-4	lMTG	lMTG	-
-47	-24	-17	lMTG	lIFG	-
-55	-3	-24	laMTG	lMTG	-
-7	-57	17	lPrec	lPCC	-
-20	36	44	lSFG	lSFG	-
-31	29	45	lMFG	lMFG	-
-53	26	-1	lIFG	lMFG	Area 45
-39	17	44	lMFG	lIFG	-
53	-59	29	rAG	rSTG	Area PGa
43	-72	31	rpIPL	rMTG	Area PGp
-1	51	-7	medFP	lACC	Area Fp2
-5	56	24	lmSFG	lSFG	Area p32
-31	-34	-16	lFFG	lParaHippo	-
-8	29	-10	sACC	lACC	Area s32
-46	25	23	lIFS	lMFG	IFS1/IFS2
64	-41	-2	rMTG	rMTG	-
-43	-53	55	rIPL	lIPL	Area PFm
-1	-18	40	rMCC	lCC	-
51	20	26	rIFJ	rMFG	IFJ1

64	-38	32	raIPL	rSMG	Area PF
-23	26	-16	rFP	lIFG	Area Fo3

x, y and z coordinates denote the center of gravity in MNI space.

Reference for probabilistic cytoarchitectonic mapping of amygdala and hippocampus (Amunts et al. 2005); superior parietal cortex (Scheperjans et al. 2008); intraparietal sulcus (Choi et al. 2006); parietal operculum (Eickhoff et al. 2006); ventral extrastriate cortex (Rottschy et al. 2007); dorsal extrastriate cortex (Kujovic et al. 2013); gyrus fusiformis (Caspers et al. 2013); lateral occipital cortex (Malikovic et al. 2016); Broca's regions (Amunts et al. 1999); Cingulate cortex (Palomero-Gallagher et al. 2015). Cerebellar atlas (Diedrichsen et al. 2009). Thalamic connectivity atlas (Behrens et al. 2003).

Abbreviations: r= right; l= left; a= anterior; p= posterior; s= sub-genual; m/med=medial; Tr.= pars; triangularis; Orb. = pars orbitalis; dmPFC= dorso-medial prefrontal cortex; SMA= supplementary motor area; MCC= middle cingulate cortex; ACC= anterior cingulate cortex; PCC= posterior cingulate cortex; Am= amygdala; Th= thalamus; Hippo= hippocampus; GP/Pal= globus pallidus; Prec= precuneus; mSFG= superior medial gyrus; Nac= nucleus accumbens; Put= putamen; PrG= pre-central gyrus; Ins= insula; IFS= inferior frontal sulcus; IFJ= inferior frontal junction; IFG= inferior frontal gyrus; MFG= middle frontal gyrus; SFG= superior frontal gyrus; OFC= orbito-frontal cortex; SOrbG= superior orbital gyrus; FP= frontal pole; STS= superior temporal gyrus; STG= superior temporal gyrus; MTG= middle temporal gyrus; ITG= inferior temporal gyrus; FFG= fusiform gyrus; SPL= superior parietal lobe; IPL= inferior parietal lobe; IPS= intra-parietal sulcus; fOP= frontal operculum; pOP= parietal operculum; TPJ= temporo-parietal junction; SMG= supramarginal gyrus; AG= angular gyrus; IOcC= lateral occipital cortex; OcPole= occipital pole; MOG= middle occipital gyrus; IOG= inferior occipital gyrus; Cb= cerebellum

Predictions based on the pooled sample

Subjects Selection

From the “s1200” release, Sample 1 and Sample 2 were generated by selecting only one member per family and then matching the male and female subgroups by age, years of education and twin-status. To perform the analysis on the largest (balanced and matched) possible set of HCP subjects (henceforth Sample 3), we combined the two unrelated samples, noting that now virtually all subjects will have a close relative in the sample. This procedure was preferred over the use of the entire HCP sample (n = 1096 participants with FIX-denoised RS-fMRI data and personality measurements) in order to keep the gender-ratio balanced and maintain control over age, education and twin status, which is still matched between male and female. Thus, Sample 3 resulted in a total of 740 subjects: 370 males (196 non-twin, 174 twin subjects; aged 22-37 years, mean: 28.3 ± 3.5 ; years of education: 14.8 ± 1.8) and 370 females (196 non-twin, 174 twin subjects; aged 22-36 years, mean: 28.7 ± 3.5 ; years of education: 14.9 ± 1.8).

Results of the Relevance Vector Machine in Sample 3

The analysis on the pooled Sample 3 revealed that the majority of the predictions discovered in the two unrelated samples could be replicated (see Table S4). This can be easily explained by the fact that whenever a prediction truly reflected an association between trait and brain network, the presence of related individuals in the training and in the test groups would not harm the prediction, but rather lead to an overestimation of the performance of the model due to the genetic shared variance between twins (100% between Mz twins, 50% between Dz). On the other hand, introducing related subjects in the analysis (Sample 3) yielded a consistent number of predictions not found in the unrelated Samples 1 and 2. However, it is impossible to disentangle, whether these additional results were driven by the higher power due to the larger number of subjects or the optimism-bias introduced by including related subjects.

Table S4: Comparison of the significant predictions across the three samples

Predicted Trait	Predicting Network	Group	Replication-analysis results				Pooled-analysis results	
			r	p-value	r	p-value	r	p-value
			Sample 1	Sample 1	Sample 2	Sample 2	Sample 3	Sample 3
O	VA	All	0.12	0.006	0.17	0.12	0.1	0.004
O	Pain	All	0.1	0.018	0.2	0.1	0.16	0.0
O	Rew	Women	0.17	0.006	0.2	0.17	0.11	0.017
O	Pain	Women	0.12	0.048	0.29	0.12	0.15	0.018
E	Face	Men	0.18	0.005	0.14	0.18	0.01	0.4
E	Rew	Women	0.14	0.02	0.23	0.14	0.1	0.03
E	Conn	Women	0.29	0.0	0.23	0.29	0.13	0.01
A	AM	All	0.1	0.018	0.18	0.1	0.12	0.0
N	Conn	All	0.14	0.018	0.14	0.14	0.07	0.06
N	Conn	Men	0.17	0.0	0.37	0.17	0.12	0.02
N	Emo	Men	0.2	0.002	0.42	0.2	0.05	0.1

Predicted Trait: O: Openness; E: Extraversion; A: Agreeableness; N: Neuroticism.

Predicting Network: **VA**: vigilant attention; **Pain**: pain processing; **Rew**: reward; **AM**: autobiographic memory; **Face**: face perception; **Conn**: whole-brain network; **Emo**: emotional processing. Correlation coefficients between real and predicted values which resulted significant at $p < 0.05$ in **both** samples 1 and 2 (**Replication-analysis results**), compared with the performance of the same network-trait association in Sample 3 (**Combination-analysis results**). In red, predictions that resulted significant at $p < 0.05$ also in Sample 3.

Table S5: Results of the Relevance Vector Machine in Sample 3

<i>Predicting Network</i>	Predicted Trait	Group	r Sample 3	<i>p-value</i> Sample 3
<i>AM</i>	O	All	0.09	<i>0.01</i>
<i>AM</i>	O	Men	0.17	<i>0.00</i>
<i>AM</i>	O	Women	0.15	<i>0.00</i>
<i>Emo</i>	O	Women	0.11	<i>0.02</i>
<i>Emp</i>	O	All	0.07	<i>0.04</i>
<i>Emp</i>	O	Women	0.13	<i>0.01</i>
<i>Face</i>	O	Women	0.21	<i>0.00</i>
<i>Pain</i>	O	All	0.16	<i>0.00</i>
<i>Pain</i>	O	Men	0.06	<i>0.04</i>
<i>Pain</i>	O	Women	0.15	<i>0.00</i>
<i>Rew</i>	O	All	0.10	<i>0.00</i>
<i>Rew</i>	O	Men	0.07	<i>0.03</i>
<i>Rew</i>	O	Women	0.11	<i>0.02</i>
<i>SM</i>	O	All	0.07	<i>0.03</i>
<i>SM</i>	O	Men	0.13	<i>0.00</i>
<i>VA</i>	O	All	0.10	<i>0.00</i>
<i>VA</i>	O	Women	0.18	<i>0.00</i>
<i>WM</i>	O	Women	0.11	<i>0.02</i>
<i>Face</i>	C	Women	0.13	<i>0.01</i>
<i>Conn</i>	C	All	0.10	<i>0.00</i>
<i>Conn</i>	C	Men	0.10	<i>0.03</i>
<i>WM</i>	C	Women	0.12	<i>0.01</i>
<i>AM</i>	E	Women	0.13	<i>0.01</i>
<i>Pain</i>	E	Women	0.09	<i>0.04</i>
<i>Conn</i>	E	All	0.16	<i>0.00</i>
<i>Conn</i>	E	Women	0.13	<i>0.01</i>
<i>Rew</i>	E	All	0.11	<i>0.00</i>
<i>Rew</i>	E	Women	0.10	<i>0.03</i>
<i>AM</i>	A	All	0.12	<i>0.00</i>
<i>AM</i>	A	Men	0.12	<i>0.00</i>
<i>AM</i>	A	Women	0.13	<i>0.01</i>
<i>Emp</i>	A	Men	0.15	<i>0.00</i>
<i>Face</i>	A	All	0.06	<i>0.05</i>

<i>Rew</i>	A	All	0.14	0.00
<i>SM</i>	A	All	0.12	0.00
<i>SM</i>	A	Men	0.11	0.00
<i>VA</i>	A	Men	0.14	0.00
<i>WM</i>	A	All	0.09	0.01
<i>Emp</i>	N	Women	0.18	0.00
<i>Face</i>	N	All	0.08	0.02
<i>Conn</i>	N	All	0.07	0.03
<i>Conn</i>	N	Men	0.12	0.01
<i>Rew</i>	N	Men	0.09	0.01

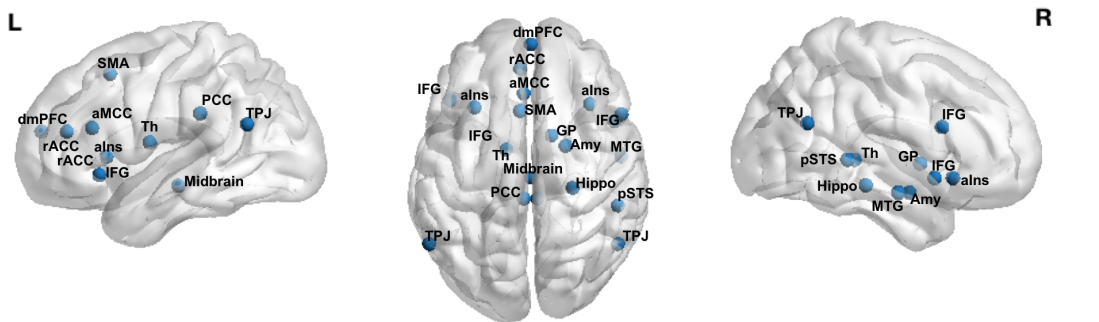
Predicted Trait: O: Openness; C: Conscientiousness; E: Extraversion; A: Agreeableness; N: Neuroticism.

Predicting Network: *AM*: Autobiographic Memory; *Emp*: Empathy; *Emo*: Emotional processing; *Face*: Face perception; *Pain*: Pain processing; *Rew*: Reward; *SM*: Semantic Memory; *VA*: Vigilant Attention; *WM*: Working Memory; *Conn*: Connectome.

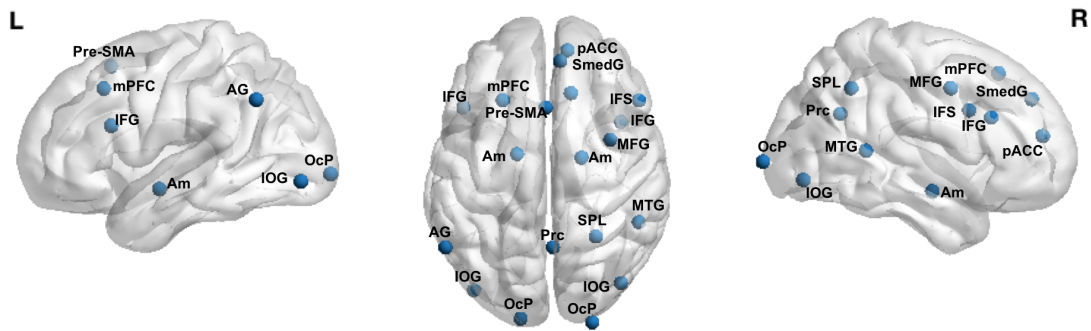
Correlation coefficients between real and predicted values which resulted significant at $p < 0.05$ Sample 3.

Supplement Fig S1: Meta-analytically derived networks

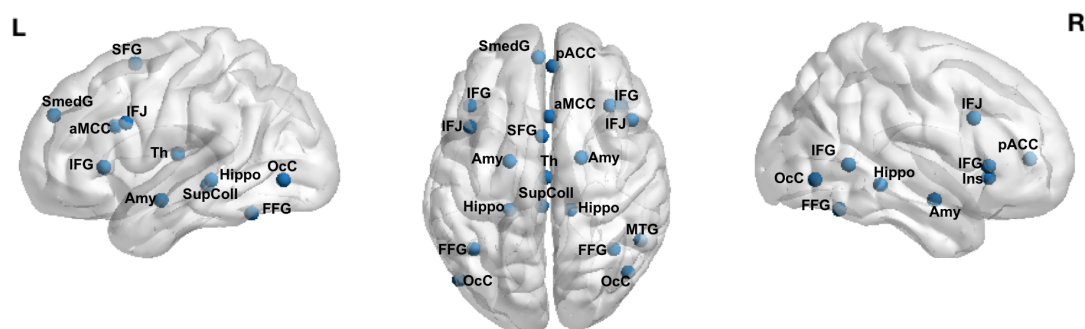
Empathy



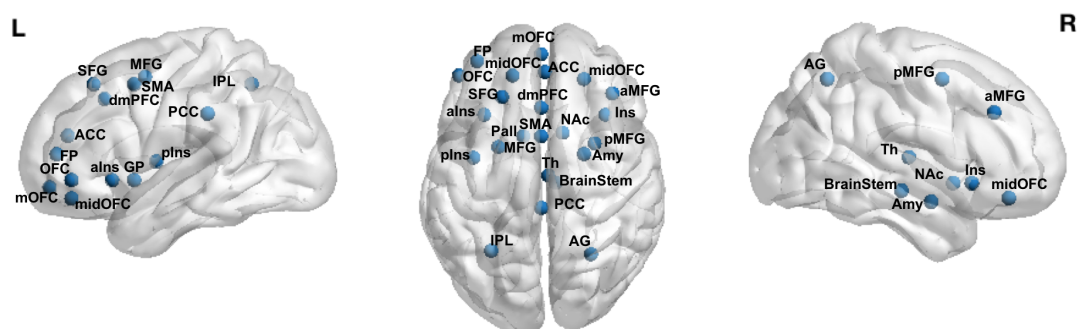
Static Face Perception



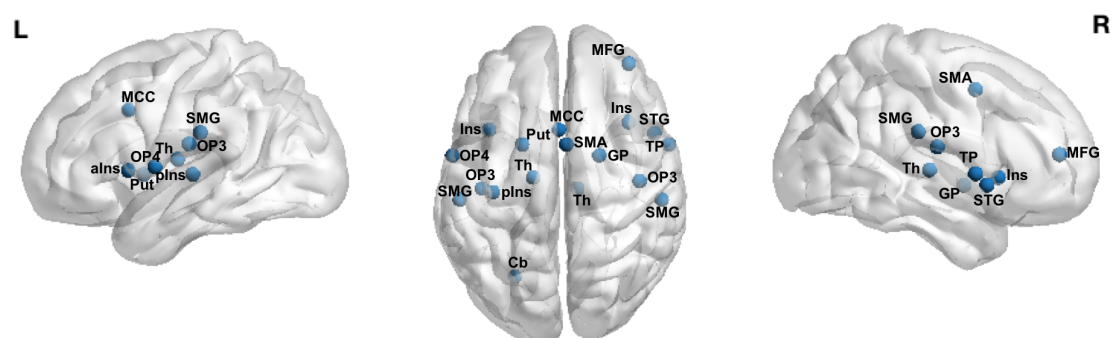
Perception of emotional scenes and faces



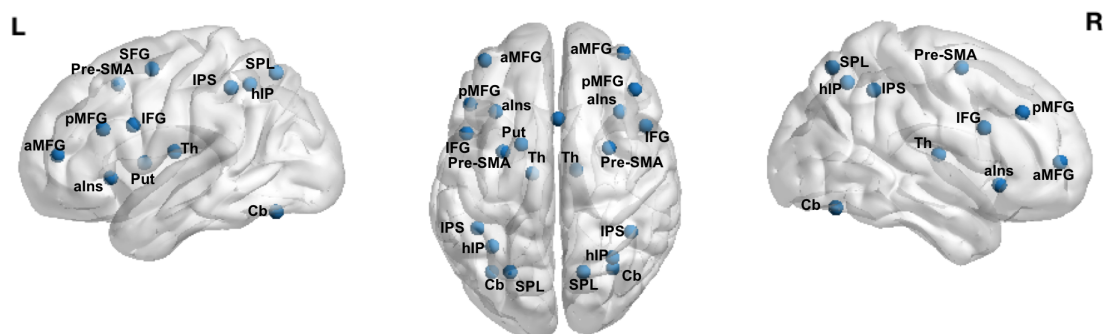
Reward



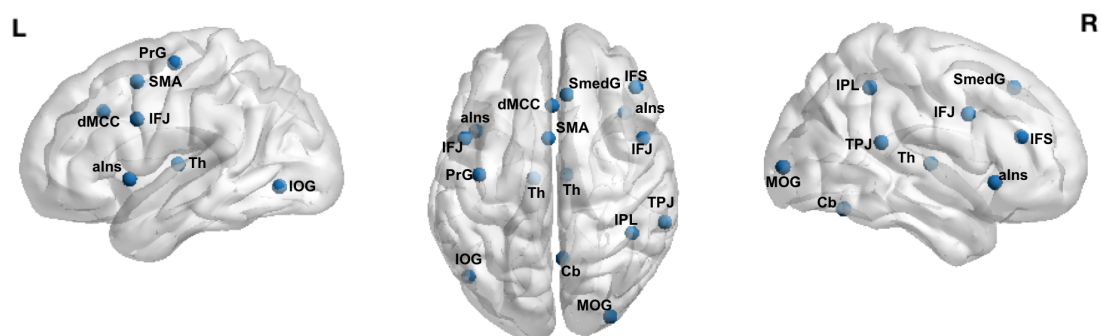
Pain



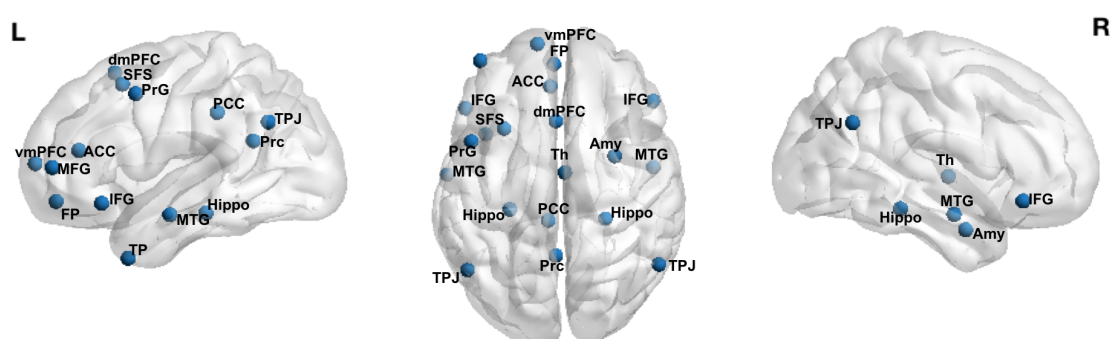
Working Memory



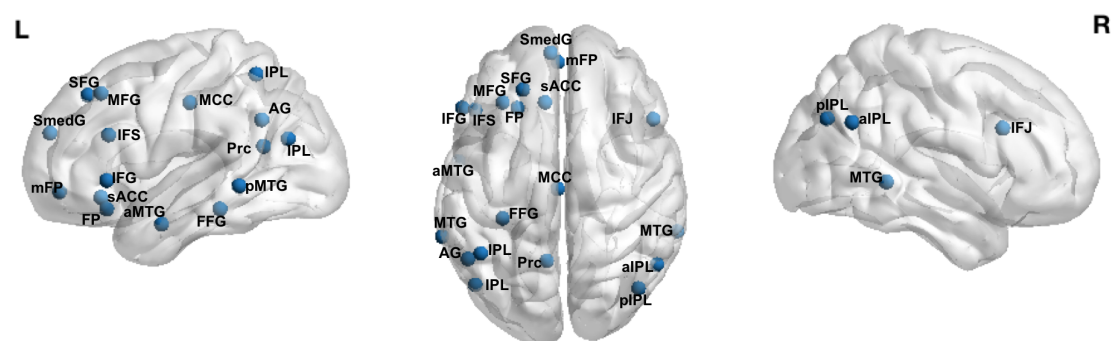
Vigilant Attention



Autobiographic Memory



Semantic Memory

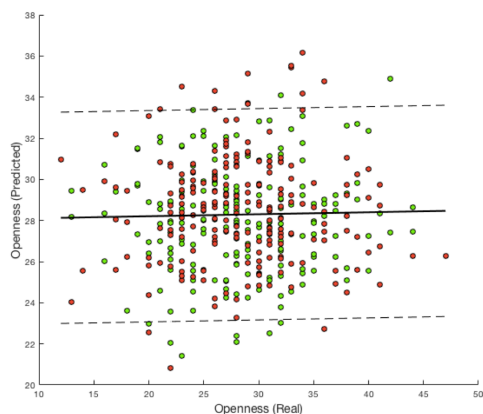


Regions constituting the meta-analytically defined network defined according to the SPM anatomy toolbox 2.1 (Eickhoff et al. 2005, 2007). Red labels indicated regions already defined in previous sections.

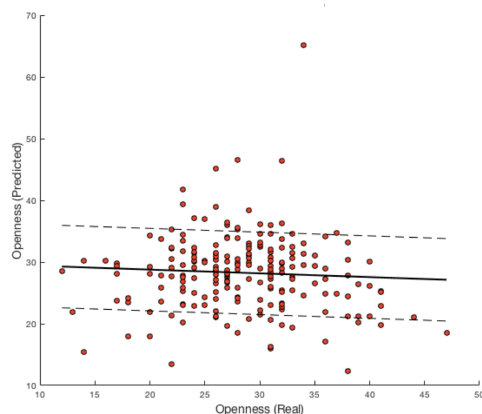
Supplement Fig 2: Comparison of the predictions across groups. Scatter plots of real and predicted personality score in the entire samples (all) as well as for males and females separately. Predictions are reported if they are significant in at least one out of the three groups. Only for the significant predictions, continuous regression lines and dashed lines, representing the standard deviation, are displayed.

Gender difference in prediction of Openness from RS-FC in *Reward*

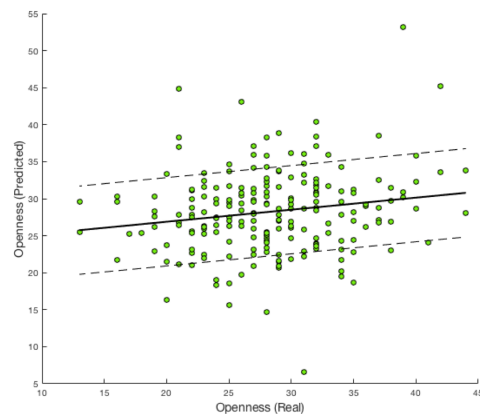
Sample 1 ($N_{\text{men \& Women}} = 420$) $\rightarrow r: 0.02$; MAE: 5.1



Sample 1 ($N_{\text{Men}} = 210$) $\rightarrow r: -0.06$; MAE: 6.7

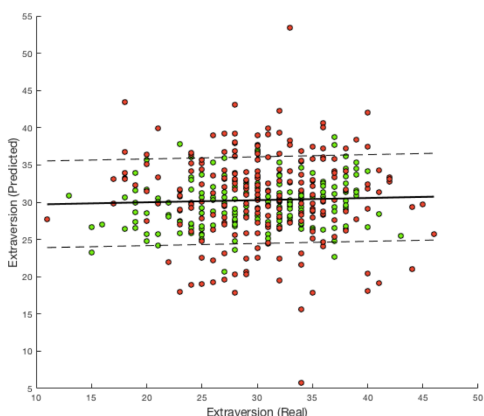


Sample 1 ($N_{\text{Women}} = 210$) $\rightarrow r: 0.17$; MAE: 5.9

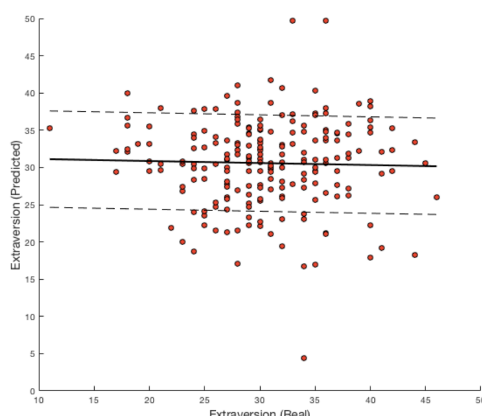


Gender difference in prediction of Extraversion from whole-brain FC (Power network)

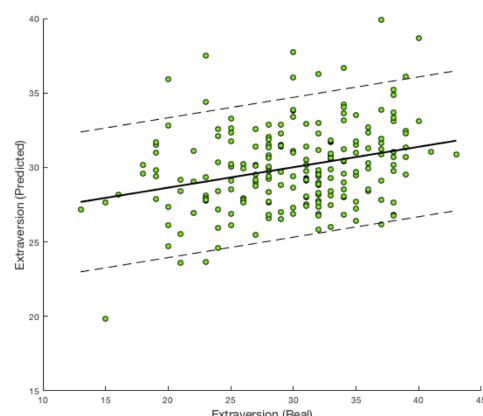
Sample 1 ($N_{\text{men \& Women}} = 420$) $\rightarrow r: 0.04$; MAE: 5.8



Sample 1 ($N_{\text{Men}} = 210$) $\rightarrow r: -0.03$; MAE: 6.5

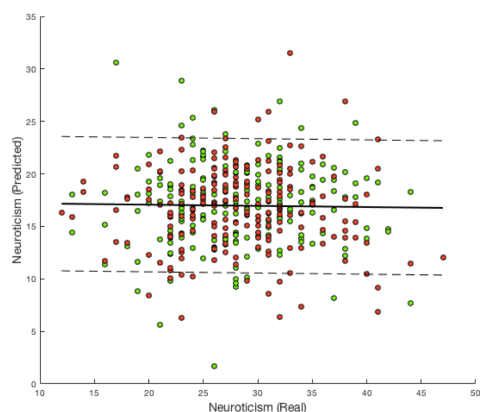


Sample 1 ($N_{\text{Women}} = 210$) $\rightarrow r: 0.29$; MAE: 4.7

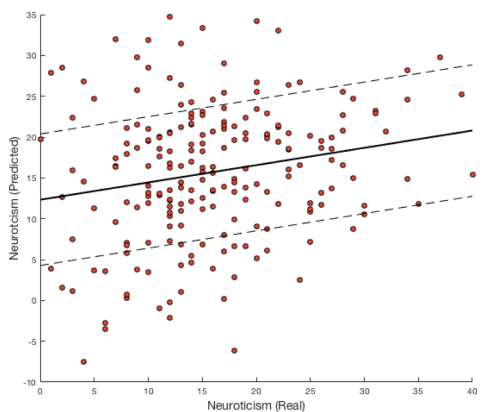


Gender difference in prediction of Neuroticism from RS-FC in *Emo*

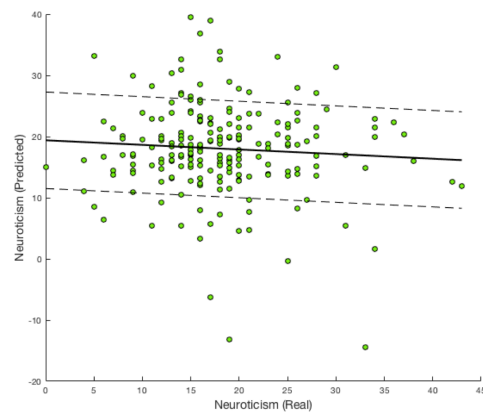
Sample 1 ($N_{\text{men \& Women}} = 420$) $\rightarrow r: 0.08$; MAE: 6.4



Sample 1 ($N_{\text{Men}} = 210$) $\rightarrow r: 0.2$; MAE: 8.0



Sample 1 ($N_{\text{Women}} = 210$) $\rightarrow r: -0.07$; MAE: 8.0



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VI SUMMARY AND GENERAL DISCUSSION

These two studies investigated the structural and functional correlates of personality traits (assessed by the NEO FFI), with a critical attention on the gender-commonalities and differences in the brain-trait relationships.

Specifically, in Study 1, whole brain voxel-based morphometry was used to investigate the influence of gender on the associations between personality traits and GMV in a large sample of 182 males and 182 age-matched females. Personality-GMV relationships were assessed across the entire sample as well as separately for males and females. Core findings were no significant correlations between any personality scale and GMV in the overall sample, and, conversely, the significant associations with GMV detected for Neuroticism, Extraversion, and Conscientiousness only in males. Interestingly, GMV in left precuneus/parieto-occipital sulcus correlated with all three traits, such that the more emotionally stable, extrovert and conscientious men display higher GMV in Prc/POS.

In Study 2, we aimed to predict scores of personality traits from resting-state functional connectivity in meta-analytically defined brain networks, and tested if prediction performance was influenced by gender. We assessed 9 meta-analytic networks representing regions consistently activated by different social (empathy, face perception), affective (reward, pain, emotion perception), executive (working memory, vigilant attention) and mnemonic (autobiographic and semantic memory) functions, all previously associated with personality in literature. For a more exploratory analysis, also the entire connectome was tested in its predictive power. RSFC of all networks was computed in a sample of 210 males and 210 well-matched females and in a replication sample of 155 males and 155 females. Using the relevance vector machine-learning algorithm, we attempted to predict the five scores based on FC between all nodes of each network, in the overall sample and then separately for males and females. Here, only two predictions resulted to be independent on gender (i.e. only detected in gender-combined sample). The rest of the predictions was significant either for one or the other gender group. It therefore indicated that more information can be found about personality trait – functional brain networks relationships while investigating men and women separately.

6.1 *Personality is reflected in the neurobiology: Extraversion and Neuroticism*

Study 1 and 2 demonstrated that changes in brain structure and systematic co-activation patterns can be found in association with the Big Five, even though they were developed with a descriptive, lexical approach (Digman 1990; Costa and McCrae 1992b), and not based on a biological theory.

It needs to be said that a major challenge in neuroimaging is still to clarify the relationships between brain structure and function: a region with higher GMV might be more functionally active, given the higher amount of somatodendritic space and neuropil. At the same time, a region with lower GMV can also result as highly functioning, due to the more efficient compensatory mechanisms (Barulli and Stern 2013; Marques et al. 2016). However, we can still reach some conclusions by integrating the two studies together with the existing literature, especially for the traits Extraversion and Neuroticism which are by far the most studied in the field.

Extraversion and Neuroticism, in Study 1, correlated with GMV in the occipito-parital cortex, which functional decoding pointed among others to social cognition (for E) and emotion (for N) domains, and in the left FFG/Cb, also linked to the emotion domain. Importantly, these results were exclusively in men. In Study 2, the same traits were predicted respectively by the Face and the Emo networks, again in men only. As a side note, even though not overlapping with the region resulting from Study 1 (POS/Cun), in Study 2, nodes encompassing occipital cortex and precuneus were present in both Emo and Face network, while left FFG/Cb (Study 1) was present only in Face network (Study 2).

These results from different neuroimaging modalities (RSFC and VBM) jointly point to a crucial relationship of socio-emotional regions to N and E. With regards to E, a previous study showed increased amygdala-visual cortex FC, implicated in face recognition in highly extraverts (Pang et al. 2015), thus suggesting that the prediction of E from Face network might be reached by connectivity strength along with the score of E. Combination of (potentially) increased FC in the network deputed to perceiving and processing faces (Study 2) and increased GMV in occipito-parietal cortex and FFG, regions functionally characterized by the social and emotional domains (Study 1), hints to a relation between emotional face recognition and social communication skills with Extraversion.

Similarly, N negatively correlated with GMV in the regions of occipito-parietal cortex and FFG,

functionally characterized by their link with the emotional domain (Study 1). It was then also predicted in Study 2 by the RSFC in the network deputed to the processing of emotions (Emo). Noteworthy, highly neurotics individuals have been found to display overall weaker functional connections (Servaas et al. 2015), as well as more specific impaired connection between fusiform gyrus and amygdala (Walter and Jensen 2014). Furthermore, on a behavioral level, neurotics performed worst in facial emotion recognition tasks than the more emotionally stable individuals (Andric et al. 2015). Building on these findings, the decreased GMV in regions deputed to facial emotional perception (as the Cun/POS and FFG) in Study 1, as well as RSFC pattern in Emo which allowed the prediction of N in Study 2, corroborate the hypothesis that neurotic individuals (especially men) might display an altered processing of facial emotions.

In study 1, the functional decoding of left FFG revealed by the two-way conjunction (E and N) further showed that task-based activations within the emotion domain were more specifically paradigms of facial emotion discriminations (see above) and anticipation of monetary reward. Study 2 then also showed that E can be predicted based on FC within the Rew network. Noteworthy, the left FFG is not comprised in the employed meta-analytic Rew network, but yet, both studies pointed to an involvement of reward-related regions with the trait, via either local changes of GMV (exclusively in men) or more distributed pattern of FC (exclusively in women). Despite the “gender” incongruence, it is still important to highlight the association between E and reward, as this trait has been conceptually developed as behavioral exploration toward specific rewards (Costa and McCrae 1992; cf. Allen and DeYoung 2016). Therefore, either higher GMV in or RSFC between reward-sensitive regions in extravert men and women respectively seems to subserve the approach behavior toward rewarding and positive stimuli, manifested at high level of Extraversion (Lei et al. 2015).

6.2 Personality is reflected in the neurobiology: Conscientiousness

The remaining VBM finding was a small cluster in the Prc/POS, whose GMV positively correlated with Conscientiousness in men. In Study 2, no significant predictions of this trait were found (across the two samples) from any functional networks. Since C reflects the degree to which individuals perform tasks and organize their lives, exhibiting a tendency to self-discipline, act dutifully, and aim for achievement (Ozer and Benet-Martínez 2006), the functional network supporting vigilant attention (and thus rigid cognitive control) would have been expected, among

the ones employed, to predict C according to the previous literature (DeYoung et al. 2010; Kunisato et al. 2011; Farr et al. 2012). Additionally, given the behavioral correlation with subjective memory (Pearman 2009) and the structural correlation with Prc/POS, functionally associated to explicit memory (Study 1), also mnemonic networks were good candidates to predict C. Yet, neither of them was able to predict the trait in any of the gender-split or in gender-mix groups.

The lack of predictions for C might be explained by two considerations. The first comes from the existing evidences on C, which seem to be better characterized in terms of structural (DeYoung et al. 2010; Jackson et al. 2011; Bjørnebekk et al. 2013; Kapogiannis et al. 2013; Forbes et al. 2014) rather than functional (Adelstein et al. 2011; Kunisato et al. 2011) associations, thus suggesting a more structurally-based biology of C. Importantly, among the above structural studies, Bjørnebekk and colleagues reported, by using the NEO-PI-R (Costa, & McCrae 1992), positive correlations between cortical surface area around Prc/POS with the facets of Competence, Order, Dutifulness and Self-Discipline. This finding thus complements the structural association found in Study 1 between C and Prc/POS by specifically revealing the facets driving this association. From here, the second possible reason for the lack of predictions: the FFM hierarchy. As already discussed in the section 4.7 of Study 2, the FFM pyramid (superfactors/ factors/ aspects/ facets, respectively from the top to the bottom (cf. DeYoung et al. 2007)) might have contributed in enlarging the gap between brain and personality traits. While this might not affect much GMV, a robust measure able to detect a coarse-grained signal at the trait level, FC in specific networks appear to be more affected, paving the possibility that they might be instead better at uncovering more fine-grained facets. Coinciding with this, VA network was shown to be specifically associated to Self-Discipline (Rueda et al. 2011), or Rew network to Achievement Striving (Cerasoli et al. 2014). The use of the NEO-PI-R allowing the investigation of the different facets of C might have therefore unveiled more detailed predictions.

Consequently, it seems plausible to conclude that, in the case of C, different modalities are entailed in studying different layers of the pyramid, from the more coarse grained components (VBM) to the finest grained characterizations (RSFC) (see below “6.5 Future Work”).

6.3 *Personality is reflected in the neurobiology: Agreeableness and Openness*

While C was only related to GMV, Agreeableness and Openness did not have any structural relationships but could rather be predicted based on FC. Specifically, A was significantly predicted from RSFC within the AM network and O by RSFC within VA, Pain and Rew networks.

There are evidences which support the hypothesis that these traits might be better studied by investigating RSFC rather than morphometric measurements. For example, the two largest VBM studies (Bjørnebekk et al. 2013; Liu et al. 2013) after Study 1, also failed in detecting GMV correlations with A, while studies with smaller sample sizes only found inconsistent results (DeYoung et al. 2010; Kapogiannis et al. 2013). Similarly for O, VBM findings have not revealed any consistent brain regions whose structure correlate with this trait (DeYoung et al. 2010; Hu et al. 2011; Bjørnebekk et al. 2013; Liu et al. 2013). More evidences are instead available at the functional level for both A and O (Adelstein et al. 2011; Sampaio et al. 2014). These two studies by investigating FC among the major hubs of the default mode network (DMN), showed that A positively correlated with FC among its midline hubs (ACC, mPFC, Prc/PCC), deputed to self-referential processes. They also found results for O, in one case associated to FC in the midline hubs of mPFC and PCC (Adelstein et al. 2011), while in the another, with more the parietal components of the DMN (Sampaio et al. 2014). Additionally, FC studies investigating only O, revealed further associations with the entire efficiency of the DMN (Beaty et al. 2016) as well as with the dopaminergic mesocortical pathway subserving the reward system (Passamonti et al. 2014).

As a matter of fact, the functional literature on these two traits (especially O) is much more abundant than their morphological characterization and our findings are well in line with this separation, given the lack of correlations in Study 1, while the predictions of those traits were significant in Study 2. More specifically, A was predicted by RSFC in the AM network, first “source of the self” (Fivush and Haden 2003) and composed by nodes belonging to the DMN and mirror neuron system (MNS). These systems are well known for their involvement in high-level mentalizing function (DMN) and for embodied simulation-based representation (MNS) (Keysers and Gazzola 2007; Qin and Northoff 2011), whose integration might support the social skills characterizing high agreeable individuals. It should be noticed that the network of Emp did

not predict A, probably because this trait might be explained by a more complex self-cognition (better represented by the AM network), rather than the specific empathic skill.

Openness, on the other hand, was predicted by RSFC among regions supporting executive (VA) and affective (Rew and Pain) functions. In Study 2, discussion of these associations pointed to the importance for open individuals to detect the saliency of different kind of stimuli, either monotonous (VA), rewarding (Rew) or aversive (Pain). Thus, contrary to previous findings (Adelstein et al. 2011; Sampaio et al. 2014; Beaty et al. 2016) which, related O to internal mental activity detached from the external world (stimulus-independent thought) supported by the DMN (Mason et al. 2007), our results mainly suggest that O is more related to the attention toward an external stimulus (stimulus-dependent thought) and supported by the VA, Rew and Pain networks.

6.4 Brain-personality relationships and the role of gender

Study 1 revealed personality-brain structure relationships only apparent in males but not in females or in the entire sample. In line with Study 1, Study 2 also revealed that gender plays a crucial role in brain-behavior relationships. Specifically, i) none of the significant network-trait combinations was present in both female and male subsamples, but several functional networks showed different predictive power in males and females; ii) from the four predictions detected in the gender-mix group, only two of them were not replicated in any of the gender-split groups, while for the other two, the prediction performance increased while looking at men and women separately (e.g. Neuroticism being predicted by Connectome in All: $r = 0.14$; Neuroticism being predicted by Connectome in men only: $r = 0.38$), meaning that more information can be gained considering gender.

Study 1 and 2 together thus point to the importance of gender influences on the morphometric as well as the functional neural correlates of personality. A first hypothesis advanced in Study 1 and 2 on how gender could influence the neural correlates of personality, involved the role of sex hormones. They were indeed shown to be quite relevant in changes of perceived personality traits, for example in women over the menstrual cycle (Seeman 1997; Berlin et al. 2001; Sassoon et al. 2011; Daendee et al. 2013), as well to have prominent effects on a neural level. With regards to changes in GMV, consisting findings driven by sex hormones were reported

during puberty (Neufang et al. 2009; De Bondt et al. 2013) and aging (Boccardi et al. 2006; Ha et al. 2007), while less consistently during adulthood (Protopopescu et al. 2008; De Bondt et al. 2013 but see Hagemann et al. 2011). It is in fact possible that in longer time window (as puberty and aging) structural connections (and possibly also GMV), are modified by a more gradual increase (in puberty) or decrease (in aging) of endogenous steroid levels (cf. Schulz et al. 2009). On the other hand, especially in women's adulthood, variations of sex hormones happen in a much shorter time window (i.e. monthly fluctuations over the menstrual cycle) and it is still debated how much those changes are able to modify GMV in the brain over some days. There are indeed conflicting results showing either hormone-dependent changes (Protopopescu et al. 2008) or a lack of them (Hagemann et al. 2011; Peper et al. 2011) over the menstrual cycle. What it does seem more established in women's adulthood is the influence of sex hormones on functional connectivity: high levels of estradiol and progesterone were consistently shown to facilitate female RS interhemispheric connectivity, such decreasing brain lateralization (cf. Weis and Hausmann 2010), a mechanism that was proposed to ultimately underlie gender differences in functional cerebral asymmetries (FCA) (Hausmann 2002; Weis and Hausmann 2010). Functional connections, additionally, were shown to be activated by single administrations of sex steroids (Ottowitz et al. 2008; van Wingen et al. 2010), so to be more susceptible to changes over short time window. Also according to the review from Peper et al (2011), structural changes seem to happen over longer window of time, by a more gradual changing levels of sex steroids, such as during puberty or aging. Functional connections, conversely, seems to be modulated during rapidly changing hormonal fluctuation such as over the menstrual cycle or after a single administration of sex steroids (cf. Peper et al. 2011). In line with this explanation, we can thus speculate that it is this difference in the synchronization between changes happening at behavioral level (or at least with self-report of personality) and at neural level that allowed, in women, the characterization of personality functionally, but not structurally (Figure 2 for a schematic representation).

Figure 2

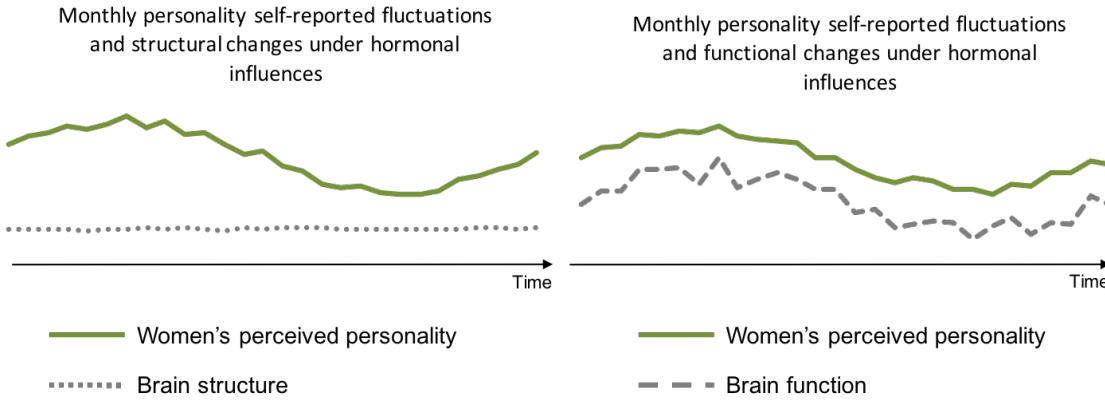


Figure 2. Schematic representation of the monthly influence of sex hormones on brain structure and function, as well as the reported personality traits in women: GMV changes are not synchronous with personality fluctuation, while RSFC-personality fluctuations appear more synchronous

In Study 2 we were also able to detect significant brain-personality relationships in women, that were not revealed in Study 1. A possible explanation might be found in the different brain organization between males and females. In fact, the short-time influence of ovarian hormones on RSFC seems to promote even more the decentralization and hemispheric connectivity of the female brain, such explaining the difference in functional brain organization between male and female brain (Weis and Hausmann 2010; Zaidi 2010; Ingallhalikar et al. 2014). As a result, the investigation of RSFC in brain networks, rather than local morphological effects, and the employment of MVPA rather than more traditional general linear model (i.e. exploiting the entire pattern of FC in a distributed network vs. voxel-wise effects), might be better suitable to characterize the functional correlates of personality in women.

6.5 Future work

As previously discussed (see paragraph 4.1), the relationship between morphometric and activation measurements is not fully understood, while relationship between structural and functional connectivity seems to be by now better comprehended, given many studies showing that functional connectivity, even though not entirely, is driven and shaped by structural connectivity between brain systems (Honey et al. 2009; Van Den Heuvel et al. 2009; Messé et al. 2014). Therefore the use of structural connectivity measurements, such as structural covariance

(Mechelli 2005) as well as diffusion-tensor imaging (Johansen-Berg et al. 2004), can further elucidate whether regions found in Study 1 or in the networks employed in Study 2 are also less or more structurally connected. It is indeed important to pursue a characterization of the neural bases of personality in a multimodal manner, firstly, within the neuroimaging field to further reach an intersection with other fields such as molecular genetics, also highly involved in the neural investigation of personality.

A multi-level approach is also recommended, for each modality, at different layers of the personality pyramid: instead of using the NEO-FFI questionnaire, the NEO-PI-R could allow researchers to specifically investigate personality from the top (Super-factors) to the bottom (Facets) of its hierarchy, revealing effects which cannot be detected by looking only at the traits. Lastly, a fundamental factor, by far underestimated, is the consideration of gender in such relationships. Much more studies are needed where gender is not treated as a covariate of NO interest, but where effects of gender are investigated. Importantly, given the very speculative arguments on the sex hormones role on the self-reported perceived personality as well as on the brain structure and function, an important step forward the understanding of such mechanisms would be to monitor the hormones level of the participants and investigate their effects on brain-behavior relationships.

6.6 *Conclusions*

In the present thesis, the neural bases of personality traits were investigating via multimodal MRI approaches, namely sMRI by carrying out a VBM analysis and fMRI by employing MVPA on network-based RSFC. Additionally, the gender differences in brain structure and function as well as the reported gender differences in personality scores, prompted the focus on the role of gender in brain-personality relationships.

As a matter of fact, sexual dimorphisms emerged in both structural and functional correlates of the Big Five, as the findings revealed in the gender-mix analyses were either null (Study 1) or scarce (Study 2). On the contrary, for the gender-split groups, structural correlates of three traits (C, E, N) were specifically detected in male brains, and functional correlated of four traits (O, A, E, N) were differentially detected in male and female brains. These results remarkably showed the importance of a multimodal approach, i.e. different MRI modalities yielded to different

characterizations of brain-personality relationships, either according to the “gender of the brain” (with women’s personality preferentially being characterized by connectivity instead GMV), but also with regards to the personality trait under investigation: Openness and Agreeableness’ neural correlates resulted only depicted by RSFC, Conscientiousness’ by only GMV changes and lastly Extraversion and Neuroticism’ neural correlates by both modalities. In fact, RSFC in Face and Emo networks similarly to changes of GMV in regions subserving facial emotion discrimination, jointly pointed to the importance that perception of faces and emotions has with regard to Neuroticism and Extraversion, cues of threats for the first and of rewarding approach for the latter.

The employment of different MRI techniques further elucidated that men and women might display different brain mechanisms supporting the same process. One instance of this was the reward characterization of Extraversion, in men supported by changes in GMV in regions associated to reward, while in women by the RSFC within the reward network itself.

To conclude, the two studies together indicate that personality traits are related to the brain, structurally and functionally, thus providing new insights into the biology of personality. An even more profound reflection is the fact that personality traits were not only shown to correlated with brain structure, but that they could also be predicted in novel subjects only based on RSFC in specific networks. Furthermore, the lack of correlations with GMV in Study 1, together with several RSFC predictions in Study 2 indicated that female brains can be better characterized by measures of connectivity, thus promoting the need for a multimodal approach in the brain study of personality.

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**“I duri hanno due cuori... Col cuore buono amano un po' di più'
I duri hanno due cuori... Col cuore guasto odiano sempre un po' di più”**

Luciano Ligabue