Brain Structure and Function

Predicting Personality from Network-based Resting-State Functional Connectivity

--Manuscript Draft--

Manuscript Number:	BSAF-D-17-00302R2
Full Title:	Predicting Personality from Network-based Resting-State Functional Connectivity
Article Type:	Original Article
Keywords:	functional networks; gender differences; hormonal influence; machine learning; NEO-FFI; resting state functional connectivity
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Funding Information:	Deutsche Forschungsgemeinschaft (DFG, EI 816/4-1, LA 3071/3-1) — Prof. Simon B Eickhoff
	National Institute of Mental Health (R01-MH074457) — Prof. Simon B Eickhoff
	Helmholtz-Gemeinschaft (Supercomputing and Modelling for the Human Brain) — Prof. Simon B Eickhoff
	Horizon 2020 (HBP SGA1) — Prof. Simon B Eickhoff
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 allow 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.

Authors' Response to the Review Comments

Journal: Brain Structure and Function

Title of Paper: Predicting Personality from Network-based Resting-State Functional Connectivity

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Dear Editor,

Please find enclosed the revised version of our manuscript entitled "Predicting Personality from Network-based Resting-State Functional Connectivity". We appreciate the time and efforts by the editor and referee in reviewing this manuscript.

We have carefully analyzed the requests of Reviewer 3, and concluded that they seem not to be applicable for our methods. The nature of the HCP, mainly composed of related individuals, together with the required independence assumptions on both input and target values, do not offer a proper setting for carrying out the analysis on the entire HCP sample. We, however, have tested in an extended HCP sample (N = 740) prediction performances of the previous significant results as further validation of their stability and now included them as supplementary material. With regards to the other "new" results discovered in this analysis, we would refrain from consider them as truly generalizable in a new population. This can be explained by the high chance for them to be driven especially by related individuals (most dramatic case of monozygotic twins sharing 100% of genetic makeup) and considering the vast literature showing heritability effects on both personality and brain imaging.

As for the second comment, the formulation of Relevance Vector Machine algorithm, simply does not allow the suggested approach of the Reviewer.

We are confident that our approach provides already a quite large sample, which at the same time is also very controlled on kinship and demographic factors. We, therefore, believe that these results represent a great improvement in understanding how personality is associated to brain function and hope to have reached the journal publication requirements.

Please note that the edited parts of the manuscript are now marked in yellow. If the entire section was modified, we marked its title.

Response to Comments from Reviewer 3

We would like to thank the Reviewer 3 for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions.

Comment 1:

Dividing the HCP data into two separate samples is not optimal. Although it seems appealing to show replication across two samples, this is rendered unnecessary by the authors' use of 10-fold validation, which already provides an index of the generalizability of the results to new data. Further, there is a serious loss of statistical power entailed by splitting the sample to run the analyses. In the current setup, neither subsample is sufficiently large to yield optimally stable correlations, especially when considering gender groups separately, which is something that the authors emphasize. The authors should redo their analyses in a single combined analysis of the whole HCP sample. (If this involves keeping subjects who are related, the authors should simply mention in a footnote whether excluding these subjects changes their conclusions. Further, it should be noted that the dependencies introduced by such subjects would affect estimates of confidence intervals but would not bias the parameter estimates themselves.) There is no good reason to analyze the sample in two pieces rather than whole, especially given the use of 10-fold validation.

Response:

We agree with the reviewer that this might be a potential limitation and acknowledge that the use of a bigger sample would provide much higher statistical power. However, there is major argument against this procedure, which is the specific nature of the sample. The HCP “s1200”

dataset is composed of 1125 of related individuals, with 581 twins and 534 not twins siblings, and only 76 of unrelated individuals. With regards to the effects of genetic mechanisms modulating personality traits, a vast number of studies agreed on accounting up to 40-60 % of the variance in the traits as heritable (Jang et al. 1996; Bouchard and McGue 2003; Verweij et al. 2012; Power and Pluess 2015). Also brain function was shown to be highly heritable (van den Heuvel et al. 2013; Colclough et al. 2017; Ge et al. 2017; Ktena et al. 2017). Of important note, two of these studies were carried out on the HCP sample itself, showing in one case (Colclough et al. 2017) that connectivity patterns of RS fMRI networks are progressively more similar as the strength of relationship is increased, from unrelated subjects, through siblings and dizygotic twins to monozygotic twins. In the other study (Ge et al. 2017), stable components of functional connectivity within and across large-scale brain networks were revealed as considerably heritable. Importantly, an increasing number of studies starts showing shared genetic influences in brain-personality relationships (Hulshoff Pol et al. 2006; Ge et al. 2018).

Given that both functional connectivity and personality traits have been shown to be heritable (see above) we thus selected only one member per family. That is, as pooling related subjects would have biased the assessment of generalizability and to avoid leakage between training and test samples from the same family, cross-validation was explicitly on unrelated individuals. Without controlling for kinship, siblings / dizygotic (Dz) / monozygotic (Mz) would be randomly assigned to the subsamples, thus predicting personality trait on, for example in case of Mz twins, an individual with nearly the same genetic makeup. To avoid overly optimistic predictions due to a relationship between subjects, we hence made use of the largest amount of unrelated participants by selecting one member per family and performed a replication analysis.

We would thus refrain from favoring the whole sample over the two “unrelated” samples.

Being aware of the issues that the related individuals might introduce, we still performed an analysis over the entire pooled sample and present in in the supplement. When performing the same modelling and cross-validation procedure on the pooled sample, i.e. 740 individuals, we noticed that our findings were well replicated (see Table S4). This evidently could be expected given the findings in the sub-samples making up the pooled cohort. We also found a number of significant predictions that were not found in the unrelated samples. Importantly, 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, i.e., an overestimation of generalizability.

In summary, we thank the Reviewer for raising this important issue and have changed the manuscript based on this comment in two ways. First, we introduce the issue of related subjects and the potentially ensuing bias in the cross-validation more clearly in the main manuscript. Second, we now present the pooled analysis, including related subjects, in the supplement.

In the main manuscript, paragraph ***2.1 Participants***, line 24 page 8:

"Additionally, Sample 1 and Sample 2 were combined to form the largest group of subjects available from the HCP data that is 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."

In the main manuscript, paragraph ***4.1 Methodological considerations and limitations***, line 17, page 19:

"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). And there is considerable evidence for 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."

In the supplementary material, paragraph **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 well 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 (Table S5). 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

			Replication-analysis results				***Pooled-analysis results***	
Predicted Trait	Predicting Network	Group	r Sample 1	*p-value Sample 1*	r Sample 2	*p-value Sample 2*	r Sample 3	*p-value Sample 3*
O	***VA***	All	0.12	*0.006*	0.17	*0.001*	0.1	*0.004*
O	***Pain***	All	0.1	*0.018*	0.2	*0.0*	0.16	*0.0*
O	***Rew***	Women	0.17	*0.006*	0.2	*0.006*	0.11	*0.017*
O	***Pain***	Women	0.12	*0.048*	0.29	*0.0*	0.15	*0.018*
E	***Face***	Men	0.18	*0.005*	0.14	*0.04*	0.01	*0.4*
E	***Rew***	Women	0.14	*0.02*	0.23	*0.002*	0.1	*0.03*
E	***Conn***	Women	0.29	*0.0*	0.23	*0.002*	0.13	*0.01*
A	***AM***	All	0.1	*0.018*	0.18	*0.001*	0.12	*0.0*
N	***Conn***	All	0.14	*0.018*	0.14	*0.04*	0.07	*0.06*
N	***Conn***	Men	0.17	*0.0*	0.38	*0.0*	0.12	*0.02*
N	***Emo***	Men	0.2	*0.002*	0.42	*0.0*	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

Predicting Network	Predicted Trait	Group	r Sample 3	*p-value Sample 3*
AM	O	All	0.09	*0.01*
AM	O	Men	0.17	*0.00*

AM	O	Women	0.15	*0.00*
Emo	O	Women	0.11	*0.02*
Emp	O	All	0.07	*0.04*
Emp	O	Women	0.13	*0.01*
Face	O	Women	0.21	*0.00*
Pain	O	All	0.16	*0.00*
Pain	O	Men	0.06	*0.04*
Pain	O	Women	0.15	*0.00*
Rew	O	All	0.10	*0.00*
Rew	O	Men	0.07	*0.03*
Rew	O	Women	0.11	*0.02*
SM	O	All	0.07	*0.03*
SM	O	Men	0.13	*0.00*
VA	O	All	0.10	*0.00*
VA	O	Women	0.18	*0.00*
WM	O	Women	0.11	*0.02*
Face	C	Women	0.13	*0.01*
Conn	C	All	0.10	*0.00*
Conn	C	Men	0.10	*0.03*
WM	C	Women	0.12	*0.01*
AM	E	Women	0.13	*0.01*
Pain	E	Women	0.09	*0.04*
Conn	E	All	0.16	*0.00*
Conn	E	Women	0.13	*0.01*
Rew	E	All	0.11	*0.00*
Rew	E	Women	0.10	*0.03*
AM	A	All	0.12	*0.00*
AM	A	Men	0.12	*0.00*
AM	A	Women	0.13	*0.01*
Emp	A	Men	0.15	*0.00*
Face	A	All	0.06	*0.05*
Rew	A	All	0.14	*0.00*
SM	A	All	0.12	*0.00*

SM	A	Men	0.11	*0.00*
VA	A	Men	0.14	*0.00*
WM	A	All	0.09	*0.01*
Emp	N	Women	0.18	*0.00*
Face	N	All	0.08	*0.02*
Conn	N	All	0.07	*0.03*
Conn	N	Men	0.12	*0.01*
Rew	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.

Comment 2:

The authors emphasize gender differences in the abstract and in the analyses, but they do not use the optimal procedure to test for these differences. They split the sample(s) into male and female and run separate analyses, then test for differences in the strength of effects between groups. This is backwards from the way the analyses should be run. First, they should compute interaction terms, using personality scores multiplied by a dummy variable for gender; then gender, personality, and their interactions should be used simultaneously to predict connectivity values in the whole sample. Only when the interaction terms are significant predictors should they then characterize the interaction by running the analyses separately in each gender group. This will prevent the situation that they describe in the following sentence: "Notably, not all associations that were only found predictive in one subgroup showed significant differences in predictability between males and females." There is no reason to even report any associations that do not show significant differences in predictability between males and females, and this can be avoided by testing for these differences in the whole sample first, using interaction terms. The approach I recommend here also has greater statistical power than their approach.

Response:

We are sorry for the apparent confusion and if we were not clear enough that connectivity measures are predicting personality scores, not the other way around, as suggested by this comment. Unfortunately, this very interesting idea will not be feasible in the current setting for the following reasons.

1. Using interactions terms between gender dummies and personality traits does not apply given the fact that personality in our models represents, as said above, the dependent variable which is predicted by RSFC features.
2. Using interaction terms between gender dummies and RSFC features could have been a viable approach to assess group differences, but this would have required that personality traits were modelled with a linear model. However, this is not the case as Relevance Vector Machine does not estimate a coefficient for each feature as in a linear model, but the coefficients are associated to the subjects (because of the dual formulation of the model). Therefore, the significance of the interaction terms' coefficients is not defined and cannot be statistically tested.
3. A last but more fundamental consideration is that the group differences that we aim to outline using out-of-sample predictions, do not to reflect differences in the strength of the associations between two variables (for example correlations between RSFC and personality traits). With this approach, we compare across groups the strength of prediction performances of the same network – trait combination resulted significant in at least one group. As a result, correlations are used to statistically testing the capability of the algorithm to predict and generalize across genders, not gender differences in the associations between RSFC and personality.

We thank the reviewer for the in-depth analysis and useful comments. We are sorry if the responses could not fully satisfy the requests, but believe that an open and honest discussion about these points have certainly benefit the authors and hopefully the reviewer. We would be glad to respond to any further questions and comments that you may have.

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Predicting Personality from Network-based Resting-State Functional Connectivity

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Short title: Prediction of personality from RSFC

Keywords: functional networks, gender differences, hormonal influence, machine learning, NEO-FFI, 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 allow 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.

1. Introduction

Interindividual 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 & 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 behavior 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 behavior 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 to 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 behavior. Similarly, Openness has also been associated to 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 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). 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-centred 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, Lancaster, Laird, & Eickhoff, 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. Oktar & Oktar, 2015; Gael Varoquaux & Thirion, 2014), provide 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 web sites (Marcus et al. 2006) or social networks (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 literature between psychological functions (and deputed networks) with personality. Accordingly, we chose functional networks associated to 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 in order to test if personality can be better predicted by specific functional networks or a rather unspecific whole-brain network. Additionally, in light of 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; Hjelmervik 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.

2. Materials and methods

2.1 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, year 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 22-37 years, mean: 28.3 ± 3.5; years of education: 14.9 ± 1.8) and 205 females (117 non-twins, 93 twin subjects; aged 22-36 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 twins subjects; aged 22-36 years, mean: 28.2 ± 3.4; years of education: 14.8 ± 1.8) and 151 females (76 non-twins, 75 twin subjects; aged 22-35 years, mean: 28.9 ± 3.5; years of education: 15.0 ± 1.8). For an overview on the samples selection, see **Fig 1**.

Additionally, **Sample 1** and **Sample 2** were combined to form the largest group of subjects available from the HCP data that is 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.

Figure 1 about here please

2.2 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 analysed 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 by 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.

2.3 Meta-analytically derived networks

2.3.1 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, Beaton, & Eickhoff, 2012); three networks related to affective processing: reward (***Rew;*** Liu, Hairston, Schrier, & Fan, 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 & Eickhoff, 2013); two networks related to long-term memory: autobiographic memory (***AM;*** Spreng, Mar, & Kim, 2008) and semantic processing (***SM;*** Binder, Desai, Graves, & Conant, 2009).

2.3.2 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, 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**.

Table 1 about here please

2.4 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.

2.5 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 x 2 x 2 mm^3, FoV= 208 x 180 mm^2, matrix = 104 x 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 (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) by using the "unified segmentation" approach in order 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.

In order 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 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 grey 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.

2.6 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) in order 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 in order 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-folds 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 dataset. 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 group ($Women_{Sample1}$: n = 210; $Women_{Sample2}$: n = 151) in order 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).

3. Results

3.1 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 ($t_{407} = -0.41$; $p = 0.15$).

3.2 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**).

3.2.1 Predictions in the entire sample (balanced males & 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).

Figure 2 & 3 about here please

Table 2 about here please

3.2.2 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 subgroup. However, in the gender-specific groups additional significant predictions were observed: in males, Extraversion was predicted by the RSFC patterns of ***Face*** and Neuroticism by ***Emo*** networks (**Table 2**, **Fig 2-3)**. In females, Openness was predicted by ***Rew*** network. Furthermore, in females, Extraversion was predicted by ***Rew*** network and the ***Connectome*** (**Table 2**, **Fig 2-3**).

3.3 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 subgroups.

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 subgroup 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**).

Table 3 about here please

4. 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 on the predictions that replicated in two different samples within the HCP dataset.

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 of Agreeableness from the mnemonic network ***AM*** were not replicated in any of the two subgroups, 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 versus males. Additionally, ***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.

4.1 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 two-folds: on the 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-folds 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). And there is considerable evidence for 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).

4.2 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 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 are 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 sub-group 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**).

Figure 4 about here please

4.4 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 paragraph **4.3**, 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 are 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 to 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 patter 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 **4.6**) 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 has 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; Ziomkiewicz 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 interindividual 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.

4.5 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.

4.6 Predicting Neuroticism

In Men, self-reported Neuroticism was predicted by RSFC within the emotional processing network (***Emo***). Additionally, 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-Freeing 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).

4.7 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 to 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.

Also, 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. Lastly, 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 in order 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.

4.8 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. Additionally, 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.

Conflict of Interest Statement

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.

Acknowledgments

This study was supported by the Deutsche Forschungsgemeinschaft (DFG, EI 816/4-1, LA 3071/3-1), the National Institute of Mental Health (R01-MH074457), the Helmholtz Portfolio Theme "Supercomputing and Modelling for the Human Brain" and the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement No. 7202070 (HBP SGA1).

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Captions to figures

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 remaing 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.

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, 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 (triangules) of the five personality circles, the connectome is represented as well as a circle. Triangules 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**.

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.

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.

Figure 1_ Samples description

Click here to download Figure Fig1.tiff

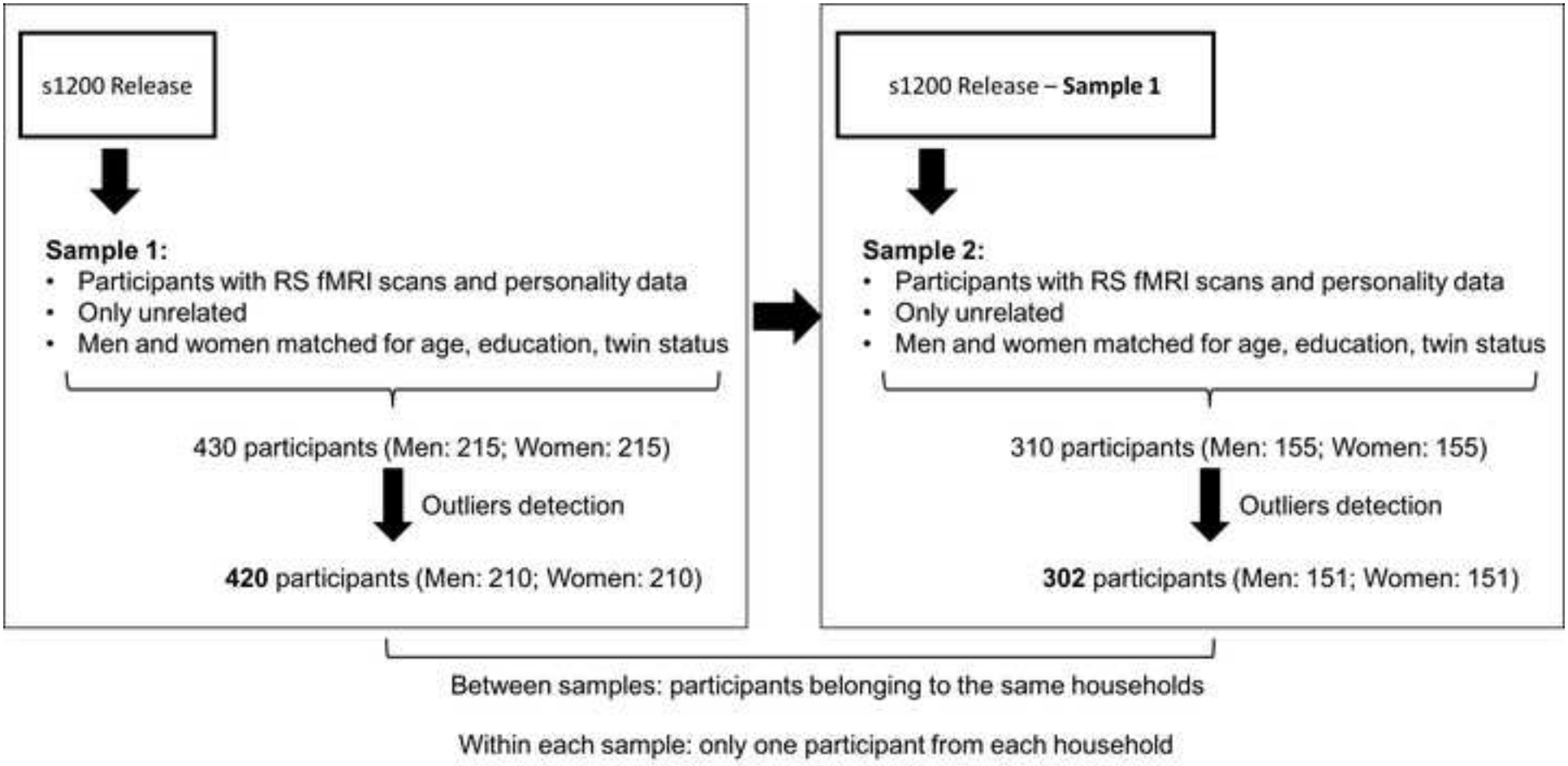


Figure 2_ Summary of the significant predictions

Click here to download Figure Fig2.tiff

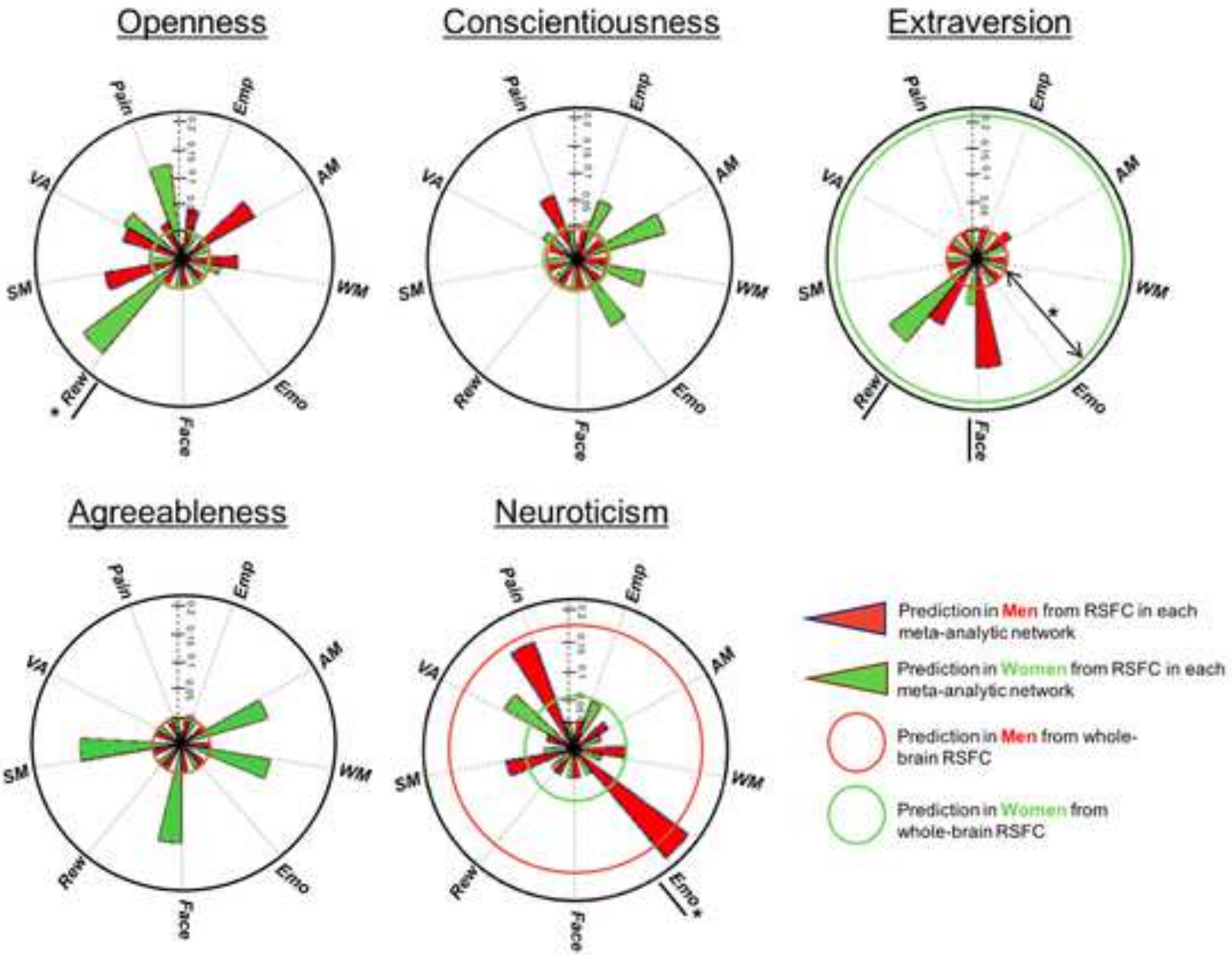


Figure 3_Correlation Plots of significant predictions

Click here to download Figure Fig3.tiff

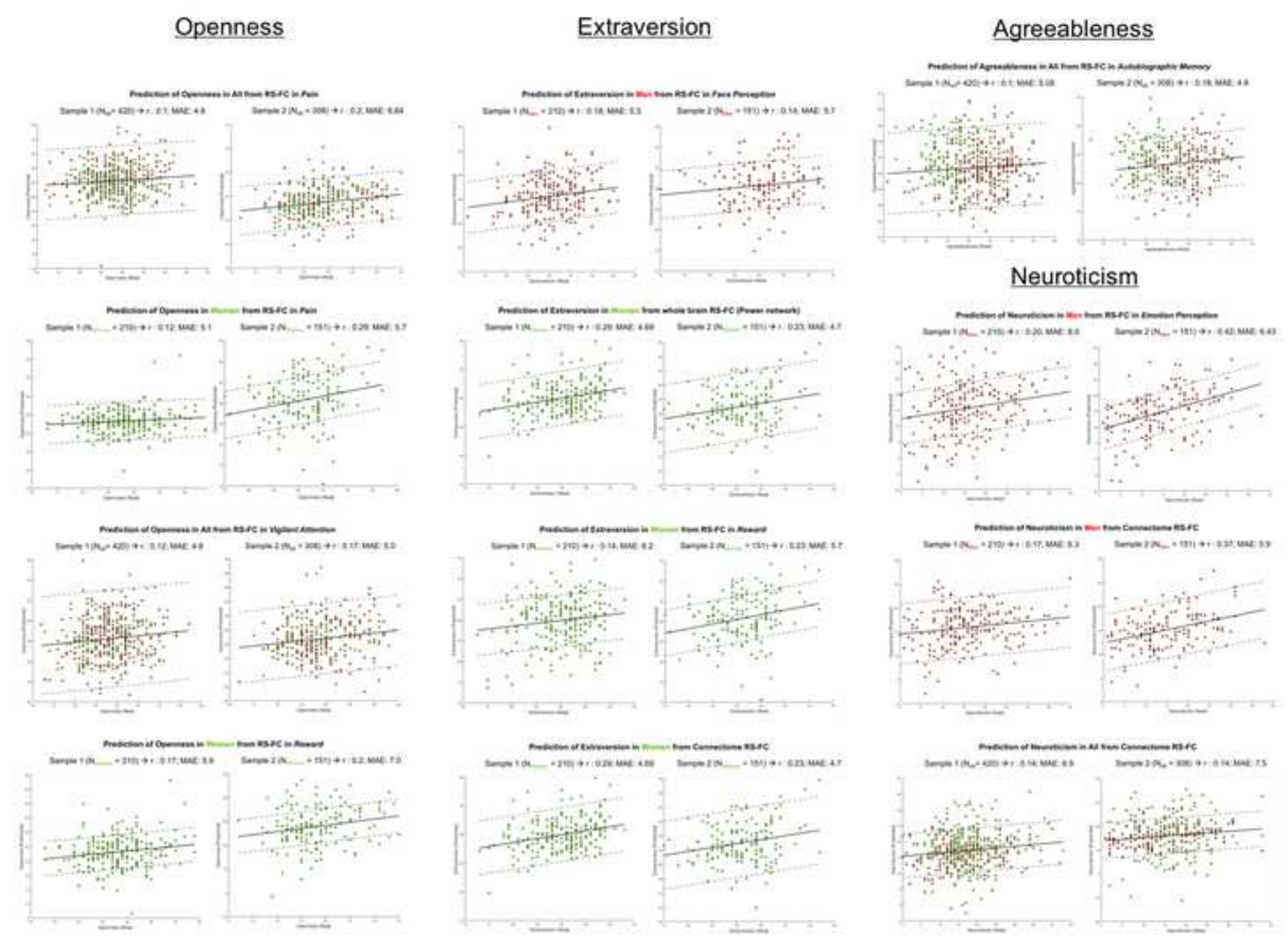


Figure 4_ Most used nodes

Click here to download Figure Fig4.tiff

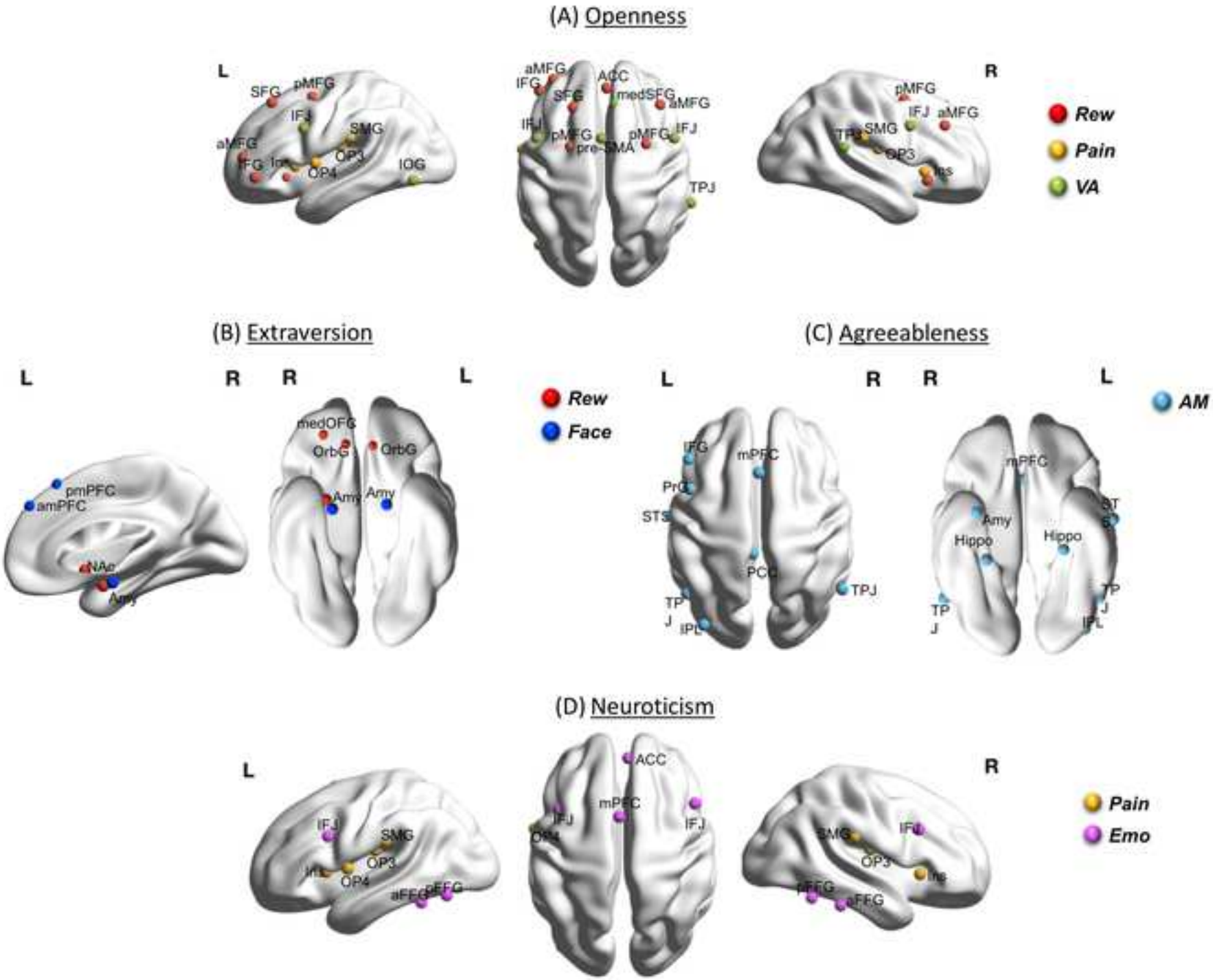


Table 1: Description of the meta-analytic derived networks

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	***Emo***	Sabatinelli, 2012	Table n.2 (emotional	24	Regions consistently activated during

	scenes and faces			face>neutral face) & Table n.3 (emotional scenes>neutral scenes)		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 10s
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

Table 2: Results of the Relevance Vector Machine

Predicted Trait	Predicting Network	Group	r (Sample1)	*p-value (Sample1)*	r (Sample2)	*p-value (Sample2)*
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*	0.38	*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).

Table 3: Gender differences in personality predictability

Predicted Trait	Predicting Network	Group	r (Sample1)	Z_{Men} - Z_{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. Note * marks significant gender difference at 95% of confidence.

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 lOcC	r lOcC	hOc4la
-40.0	-82.0	-8.0	lOcC	l lOcC	hOc4la
26.0	-100.0	2.0	rOcPole	rOcPole	hOc2
-14.0	-98.0	-4.0	lOcPole	lOcPole	hOc1
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	rPrc	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 lOFC	-
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	lfOP	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	lFP	l lFP	-
26.0	-14.0	-23.0	rHippo	raHippo	DG
52.0	-5.0	-18.0	rMTG	rTP/MTG	-
-39.0	13.0	-41.0	lTP	lTP	-
-38.0	-82.0	38.0	lIPL	lOC	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	lFP	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	lPCC	lPCC	-
-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	lFFG	-
-55	-3	-24	laMTG	lMTG	-
-7	-57	17	lPrc	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; Prc= 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; lOcC= 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

			Replication-analysis results				***Pooled-analysis results***	
Predicted Trait	***Predicting Network***	Group	r Sample 1	*p-value Sample 1*	r Sample 2	*p-value Sample 2*	r Sample 3	*p-value 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

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

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

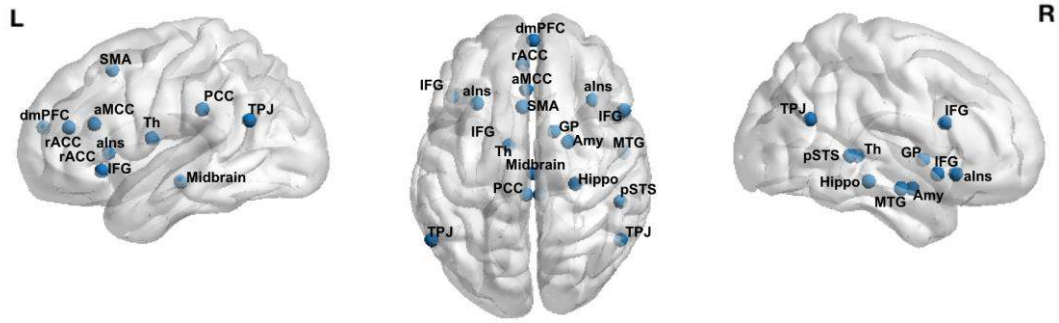
Predicted Trait: O: Openness; C: Conscientiousness; E: Extraversion; A: Agreeableness; N: Neuroticism.

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.

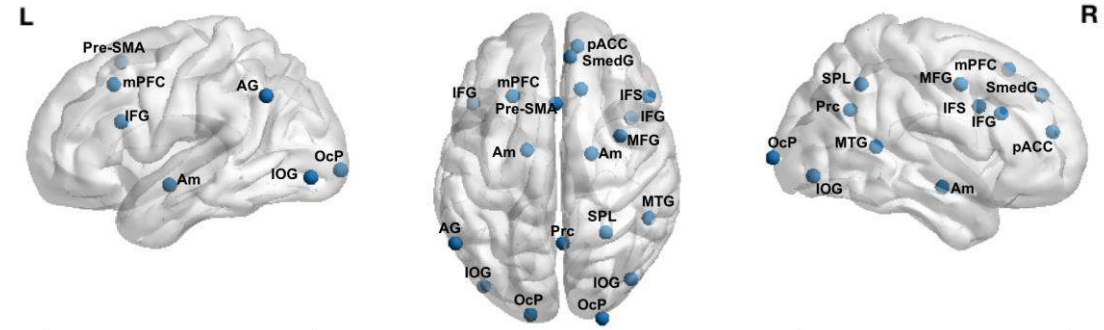
Correlation coefficients between real and predicted values which resulted significant at $p < 0.05$ Sample 3.

Supplement Fig S1: Meta-analytically derived networks

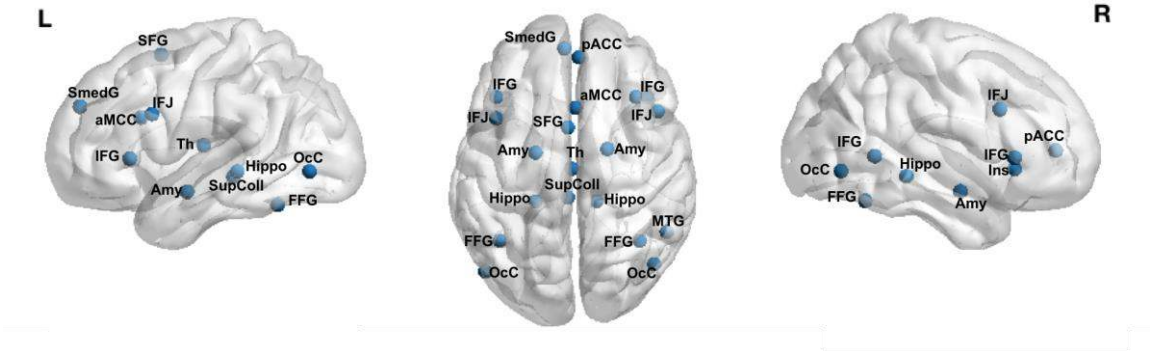
Empathy



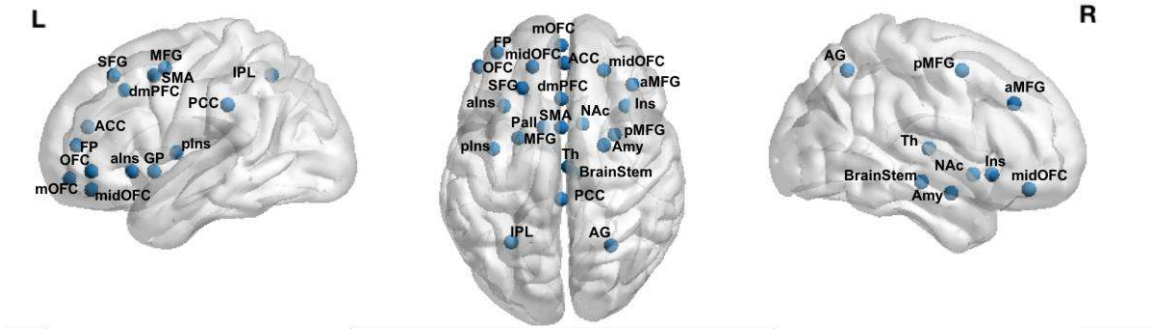
Static Face Perception



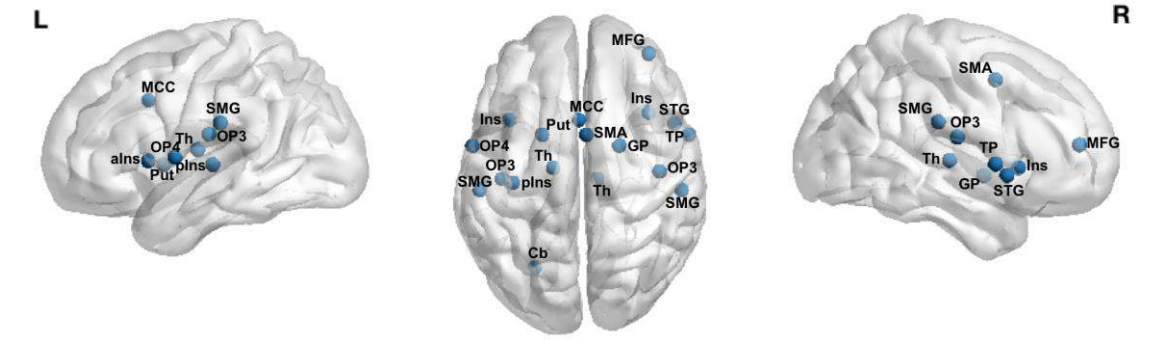
Perception of emotional scenes and faces



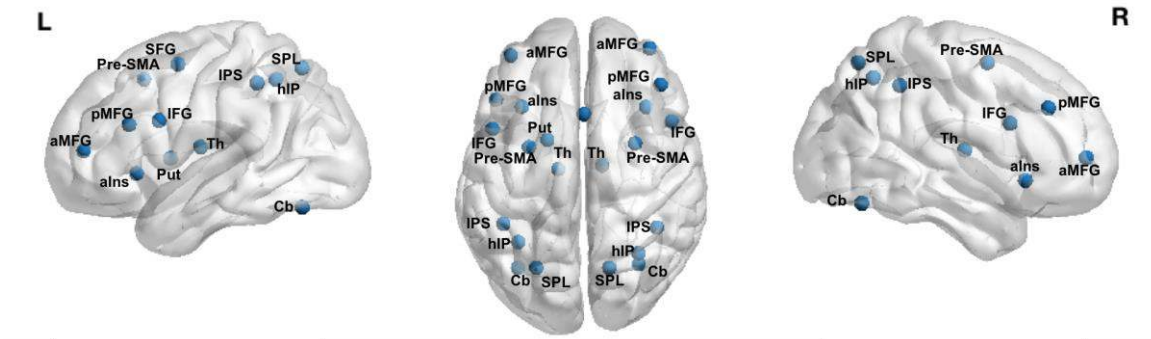
Reward



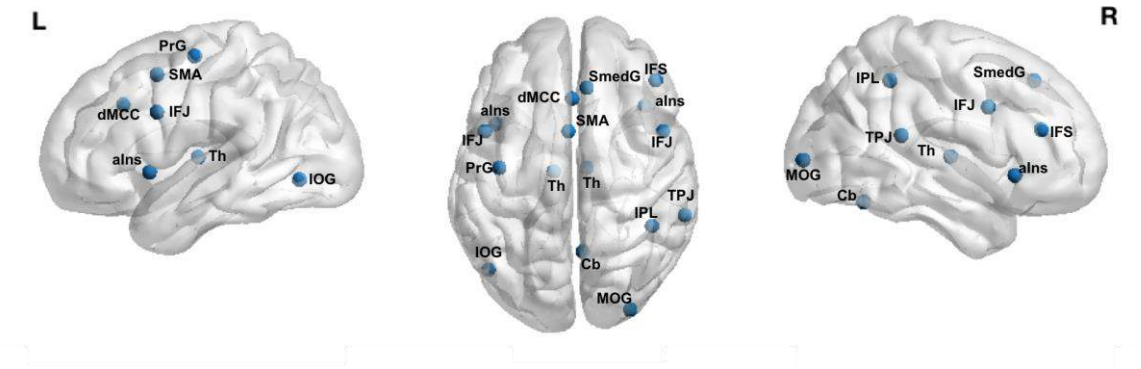
Pain



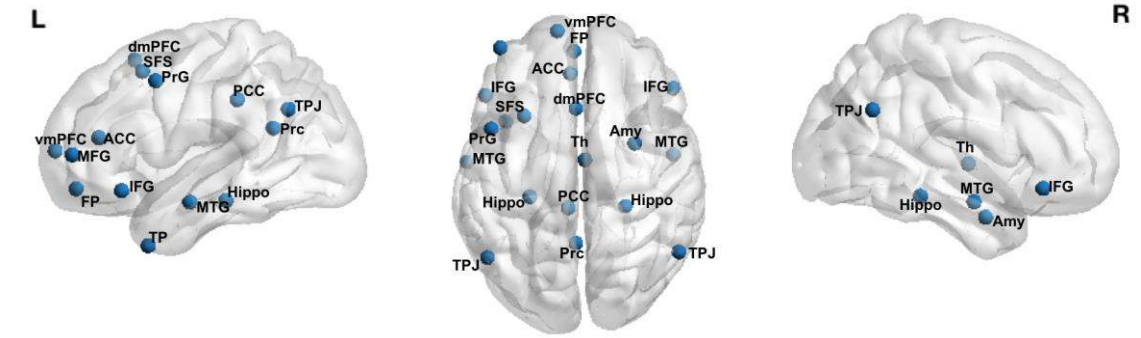
Working Memory



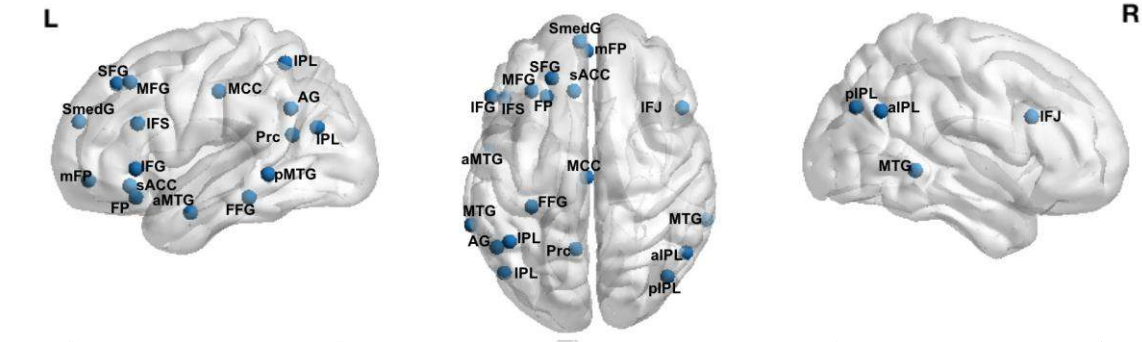
Vigilant Attention



Autobiographic Memory

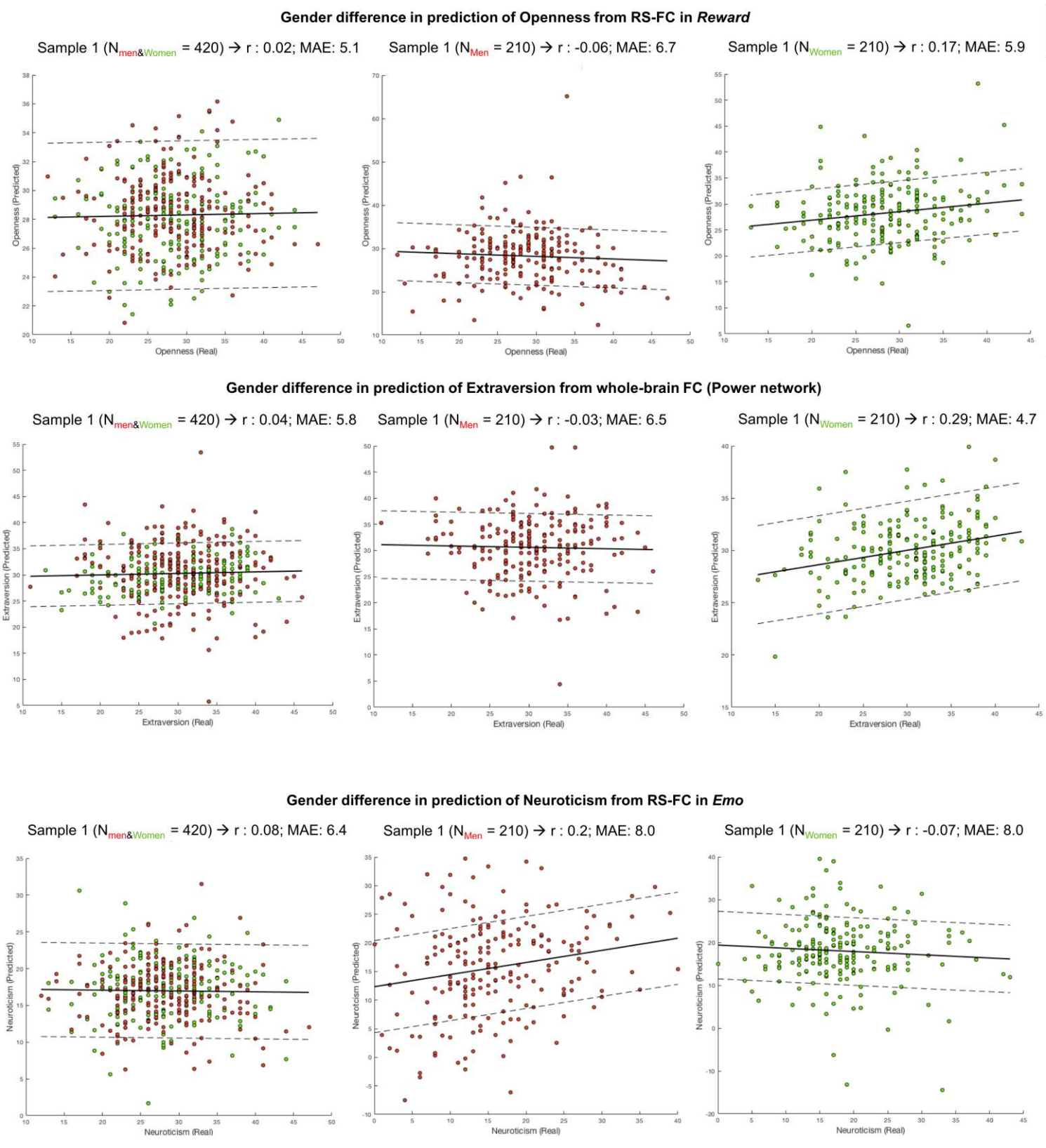


Semantic Memory



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.



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New Acknowledgement Section:
THIS STUDY WAS SUPPORTED BY THE DEUTSCHE FORSCHUNGSGEMEUNSCHAFT (DFG, EI 816/4-1, LA 3071/3-1), THE NATIONAL INSTITUE OF MENTAL HEALTH (R01-MH074457), THE HELMHOLTZ PORTFOLIO THEME "SUPERCOMPUTING AND MODELLING FOR THE HUMAN BRAIN" AND THE EUROPEAN UNION'S HORIZON 2020 RESEARCH AND INNOVATION PROGRAMME UNDER THE GRANT AGREEAMENT NO.7202070 (HBP SGA1).

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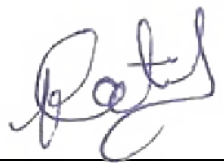
7th author	KAUSTUBH R.	PATIL	I agree to the proposed new authorship shown in section 4 /**and the addition of my**		1.Institute of Systems Neuroscience, Medical Faculty Heinrich-Heine University Düsseldorf. 3.Institute of Neuroscience and Medicine (INM-	05/01/2018

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