The stress connection: Neuroimaging studies of emotion circuits in social stress, personality, and stress-related psychopathology

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CHAPTER 7

Neuroticism and extraversion are associated with amygdala resting-state functional connectivity

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ABSTRACT

The personality traits neuroticism and extraversion are differentially related to socioemotional functioning, and susceptibility to affective disorders. However, the neurobiology underlying this differential relationship is still poorly understood. This discrepancy could perhaps best be studied by adopting a brain connectivity approach. Whereas the amygdala has repeatedly been linked to neuroticism and extraversion, no study has yet focused on the intrinsic functional architecture of amygdala-centered networks in relation to both traits. To this end, seed-based correlation analysis was employed to reveal amygdala resting-state functional connectivity (RSFC), and its associations with neuroticism and extraversion, in 50 healthy participants. Higher neuroticism scores were associated with increased amygdala RSFC with the precuneus, and decreased amygdala RSFC with the temporal poles, insula, and superior temporal gyrus ($p < .05$, cluster corrected). Conversely, higher extraversion scores were associated with increased amygdala RSFC with the putamen, temporal pole, insula, and several regions of the occipital cortex ($p < .05$, cluster corrected). The shifts in amygdala RSFC associated with neuroticism may relate to the less-adaptive perception and processing of self-relevant and socioemotional information that is frequently seen in neurotic individuals, whereas the amygdala RSFC pattern associated with extraversion may relate to the heightened reward sensitivity and enhanced socioemotional functioning in extraverts. We hypothesize that the variability in amygdala RSFC observed in the present study could potentially link neuroticism and extraversion to the neurobiology underlying increased susceptibility or resilience to affective disorders.

INTRODUCTION

Human personality describes the distinctive and persistent patterns of thoughts, emotions, and actions that occur across contexts and over time (Mischel, 2004). The influential Big Five model of personality suggests that individual variations in behavior can be described along five trait dimensions: neuroticism, extraversion, agreeableness, conscientiousness, and openness (McCrae & Costa, 1991). Of these traits, neuroticism and extraversion are the most widely studied dimensions (Kennis, Rademaker, & Geuze, 2013; McCrae & Costa, 1991), both describing individual differences in socioemotional functioning and susceptibility to affective disorders.

Neuroticism is linked to vulnerability to depression and anxiety (Bienvenu et al., 2001; Clark, Watson, & Mineka, 1994; Durrett & Trull, 2005), less favorable treatment outcomes in general (Geerts & Bouhuys, 1998), and a higher risk for comorbid psychiatric disorders (Khan, Jacobson, Gardner, Prescott, & Kendler, 2005). These negative consequences are hypothesized to originate from neuroticism's relationship with maladaptive cognitive and emotional functioning. This includes being extremely sensitive to negative social cues in the environment (McCrae & Costa, 1991), interpreting ambiguous social cues as threatening or negative (Bolger & Zuckerman, 1995), experiencing difficulties in affect regulation (Tamir, 2005), and demonstrating a more negative self-referential information processing style (Trapnell & Campbell, 1999). Extraversion, in contrast, is linked to a higher propensity for experiencing positive emotional states (Larsen & Ketelaar, 1991), and decreased susceptibility to affective disorders (Kotov, Gamez, Schmidt, & Watson, 2010). This is thought to stem from extraversion's relationship with sensitivity to positive and rewarding cues in the environment (McCrae & Costa, 1991). Extraverts show a strong tendency to engage in rewarding social interactions, are enthusiastic and optimistic in general, and tend to be assertive and talkative in social situations. To this end, it is not surprising that neuroticism and extraversion are commonly found to be inversely correlated (McCrae & Costa, 1991).

Structural and functional properties of the amygdala, a subcortical brain region, are deemed to be fundamental with regard to both neuroticism and extra-

version (Canli, Sivers, Whitfield, Gotlib, & Gabrieli, 2002b; Cremers et al., 2010; 2011; Haas, Omura, Constable, & Canli, 2007; Kennis et al., 2013; Montag, Reuter, Jurkiewicz, Markett, & Panksepp, 2013; Reuter et al., 2004; Stein, Simmons, Feinstein, & Paulus, 2007b; Vaidya et al., 2007). Functional magnetic resonance imaging (fMRI) studies have suggested that the amygdala is involved in emotional learning (Canli, Zhao, Brewer, & Gabrieli, 2000), emotional arousal (Phelps & LeDoux, 2005), and modulation of vigilance in the face of threat (Mobbs et al., 2007; Whalen, 1998). Existing evidence from primate studies has indicated highly interconnected anatomical connections between the amygdala and the prefrontal cortex (PFC), anterior cingulate cortex (ACC), and hippocampus (Amaral, 1986; Ghashghaei & Barbas, 2002). Additionally, functional imaging studies of the human brain have indicated functional coupling of the amygdala with the PFC, ACC, and hippocampus (Phillips, Drevets, Rauch, & Lane, 2003a; Roy et al., 2009; Stein et al., 2007a).

The amygdala's anatomical and functional connections with the PFC, ACC, and hippocampus are thought to constitute an integrated neural circuit dedicated to various aspects of emotional processing and regulation. The amygdala, subgenual ACC, ventrolateral PFC, and orbitofrontal cortex (OFC) form a ventral system involved in the identification of the emotional significance of a stimulus and the production of an affective state in response to that stimulus (Phillips, Drevets, Rauch, & Lane, 2003a; Stein et al., 2007a). The supragenual ACC, dorsomedial PFC, dorsolateral PFC, and hippocampus, on the other hand, are implicated in a dorsal system that exerts cognitive control, regulates affective states, and provides contextual information (Pessoa, 2008; Phillips, Drevets, Rauch, & Lane, 2003a; Stein et al., 2007a). There is ample evidence for increased sensitivity of the ventral system and decreased regulatory ability of the dorsal system in affective disorders (Phillips, Ladouceur, & Drevets, 2008; Phillips, Drevets, Rauch, & Lane, 2003b; Price & Drevets, 2010), which is hypothesized to underlie the affective symptomatology. Given that neuroticism is a strong vulnerability factor for affective psychopathology, increased sensitivity of the ventral system and decreased regulatory control of the dorsal system could be expected in neurotic individuals. Such an imbalance between the dorsal and ventral systems seems to be less likely, or even reversed, in extraverts, since extraver-

sion typically serves as a protective factor against affective psychopathology. In addition, extraversion is likely to involve enhanced functional integrity of brain networks subserving reward and motivation. Compatible with this notion, extraverts typically show higher activity within the reward circuitry in response to rewarding stimuli (Canli et al., 2002; Cohen, Young, Baek, Kessler, & Ranganath, 2005; Deckersbach et al., 2006; Kumari, ffytche, Williams, & Gray, 2004).

The human brain is believed to comprise functionally integrated networks that serve complex behavioral phenotypes (Raichle, 2011). The activity within these functional networks can best be viewed as dimensional, ranging from underactive to normal to overactive (Sylvester et al., 2012), and thus providing a framework for describing both normal and abnormal behavior. For example, high trait anxiety and anxiety disorders involve overactivity in the cingulo-opercular and ventral attention networks, as well as underactivity in the frontoparietal and default mode networks (Sylvester et al., 2012). Relatedly, self-reported anxiety has been linked to stronger functional connectivity (FC) within the salience network (Markett et al., 2013; Seeley, Menon, et al., 2007b), which includes the insular, frontal, and cingulate cortices, as well as subcortical regions such as the amygdala. Of interest to the present study, FC analysis of amygdala-centered networks previously has revealed network disorganization in anxiety patients (Etkin, Prater, Schatzberg, Menon, & Greicius, 2009). Specifically, decreased amygdala FC with the insular and cingulate regions, and increased amygdala FC with a compensatory frontoparietal executive control network were demonstrated. Equally relevant, a recent study has shown that amygdala FC with the anterior insula relates to state anxiety, whereas structural connectivity between these regions is related to trait anxiety (Baur, Hänggi, Langer, & Jäncke, 2013). Adopting a brain connectivity approach may thus prove useful for investigating the association between individual differences in neuroticism and extraversion and the functional architecture of amygdala-centered networks.

A recent fMRI study demonstrated decreased FC between the amygdala and the dorsal ACC in response to emotional stimuli in individuals with higher neuroticism scores (Cremers et al., 2010), which could reflect reduced inhibitory control over the amygdala. In addition, a resting-state functional connectivity (RSFC)

study suggested that neuroticism relates to the RSFC of brain regions implicated in self-evaluation and emotion regulation (e.g., PFC and precuneus), whereas extraversion relates to the RSFC of brain regions implicated in reward and motivation (e.g., striatum) (Adelstein et al., 2011). Although they are informative on the neurobiology underlying human personality, these studies are either limited by the complexity of their experimental designs and task performance (Cremers et al., 2010) or lack specific information on amygdala-centered networks (Adelstein et al., 2011). Therefore, the purpose of the present study was to examine in a healthy population whether neuroticism and extraversion are associated with amygdala RSFC.

On the basis of the established anatomical and functional connections of the amygdala, and of the studies reviewed above, we expected participants with higher neuroticism scores to demonstrate increased amygdala RSFC with regions of the ventral affective system, including the subgenual ACC, ventrolateral PFC, and OFC. Such a relationship could be indicative of a higher propensity to experience (negative) emotional arousal. In contrast, we expected participants with higher neuroticism scores to demonstrate decreased negative amygdala RSFC with regions of the dorsal control system, including the supragenual ACC, dorsomedial PFC, dorsolateral PFC, and hippocampus, potentially indicating less adaptive emotion regulation. In addition, we expected higher extraversion scores to be associated with increased amygdala RSFC with brain regions implicated in reward processing, such as the medial PFC and striatum, which could reflect the tight relationship between extraversion and reward sensitivity. Finally, considering the inverse correlation between neuroticism and extraversion, these traits could demonstrate opposing relationships within regions functionally connected to the amygdala.

METHODS

PARTICIPANTS

A group of 54 right-handed healthy participants were selected from the MRI study of the large-scale multicenter Netherlands Study of Depression and Anxiety (NESDA;

Penninx et al., 2008). Participants were scanned at one of the three participating centers: Academic Medical Center (AMC; n = 17) Amsterdam, Leiden University Medical Center (LUMC; n = 26), and University Medical Center Groningen (UMCG; n = 11). The exclusion criteria for the participants were: 1) a history of neurological disorders or head injury, 2) a lifetime diagnosis of DSM Axis I and/or Axis II disorders, 3) use of any medication affecting the cardiovascular and/or central nervous system, 4) current alcohol and/or substance abuse, 5) hypertension, 6) pregnancy, and 7) general MRI contra-indications. Four of the participants (one from AMC and three from LUMC) were excluded from the study due to large susceptibility artifacts in their resting-state (RS) data. Consequently, 50 healthy participants (32 female, 18 male, age: M = 40.51, SD = 9.45) were included in the imaging study. The study was approved by the medical ethics committees of the participating centers, and written informed consent was obtained from all participants prior to scanning.

MATERIALS

Personality assessment

The personality profile of the participants was assessed using the NEO Five-Factor Inventory (NEO-FFI; Costa & McCrae, 1992). This inventory consists of 60 items that measure five different personality dimensions (12 questions each): neuroticism, extraversion, openness, agreeableness, and conscientiousness. The items of this questionnaire are descriptive statements that can be rated on a 5-point Likert scale (0 = *strongly disagree* to 4 = *strongly agree*). Our sample's neuroticism (M = 12.02, SD = 4.46, range = 1–23) and extraversion (M = 32.4, SD = 6.69, range = 15–44) scores were within the lower and upper ranges, respectively, of a normal nonclinical reference population (Costa & McCrae, 1992). In line with previous reports (Costa & McCrae, 1992; Cremers et al., 2011; 2010), neuroticism and extraversion were negatively correlated (r = –.44, p < .01). Importantly, neuroticism and extraversion scores did not differ between the three scan sites, $F(2, 47) = 1.21$, p = .31, and $F(2, 47) = 0.76$, p = .47, for neuroticism and extraversion respectively.

Image acquisition

Participants were scanned at one of the three participating centers. RS-fMRI images were acquired while the participants were instructed to lie still with their eyes closed but not to fall asleep. RS-fMRI data were acquired at the end of a fixed imaging protocol, after completion of three task-related functional MRI runs and the acquisition of an anatomical scan (scan sequence: Tower of London, word encoding, T_1-weighted scan, word recognition, and perception of facial expression).

Philips 3T MRI scanners (Philips Healthcare, Best, The Netherlands) were used to acquire the imaging data, using a six-channel (AMC) or an eight-channel (LUMC and UMCG) SENSE (Sensitivity Encoding) head coil. For anatomical reference, a T_1-weighted anatomical scan was acquired for each participant with the following scan parameters: repetition time (TR) = 9 ms, echo time (TE) = 3.5 ms, 170 sagittal slices with an isotropic voxel resolution of 1.0 mm^3, no slice gap, and FOV = 256 × 256 mm. For the RS functional brain images, 200 T_2^*-weighted gradient-echo echo-planar imaging (EPI) volumes were acquired, using the following scan parameters at AMC and LUMC: TR = 2300 ms, TE = 30 ms, flip angle = 80° , 35 axial slices with an in-plane voxel resolution of 2.3 mm^2, 3.0 mm slice thickness, no slice gap, FOV = 220 × 220 mm, and interleaved slice acquisition. At UMCG the parameters were the same, except for the following: TE = 28 ms, 39 axial slices with an in-plane voxel resolution of 3.45 mm^2. The total RS acquisition time was 7 min 40 s.

Image preprocessing

The RS-fMRI data of all participants were preprocessed and analyzed using FEAT (FMRI Expert Analysis Tool) version 5.9, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The preprocessing consisted of: 1) non-brain tissue removal, 2) motion correction, 3) grand-mean intensity normalization of the entire 4D data set by a single scaling factor, 4) spatial smoothing with a 6-mm full width at half maximum Gaussian kernel, 5) high-pass temporal filtering using Gaussian-weighted least-squares straight line fitting with a 0.01-Hz cutoff to remove low-frequency artifacts, and 6) registration of the RS data to the T_1-weighted anatomical image (rigid body transformation), as well as normalization of the T_1 image to the 2-mm

Montreal Neurological Institute (MNI) standard space image (linear affine transformation). Both registration matrices were combined into a single matrix describing the transformation from the RS data to MNI standard space, and its inverse matrix was calculated. The maximum allowable displacement due to excessive head motion was set at 3 mm translation or 3° rotation in any direction.

Functional connectivity analysis

The functional connectivity analysis was conducted employing a seed-based correlation approach (e.g., Fox & Raichle, 2007). Using the probabilistic Harvard–Oxford subcortical atlas (MNI standard space) included in FSL, we defined regions of interest (ROIs) in the left and right amygdala: In the center of a group of voxels having a probability of at least 80 % to represent the amygdala, a spherical mask with a radius of 4 mm was created for both the left and right amygdala (Veer et al., 2011; Veer, Oei, van Buchem, Elzinga, & Rombouts, 2012). For each participant, both amygdala masks were registered to the RS data set. Mean time series of each individual participant's ROIs were then extracted and used as predictors in a general linear model (GLM). Signal from the deep white matter and cerebrospinal fluid, as well as six motion parameters, and the global signal were added to this model as covariates of no interest. Contrasts were created for the left and right amygdala separately, and both amygdala combined, to identify voxels that demonstrated either positive or negative temporal correlations with these ROIs. This resulted in individual RSFC maps of the left and right amygdala, both separately and combined, which were then fed into a higher-level mixed effects multiple linear regression analysis, again using the GLM. In order to examine the association between neuroticism, extraversion, and amygdala RSFC, NEO-FFI neuroticism and extraversion scores were included in the model as predictors, together with sex, age, and scan site as covariates of no interest. Both traits were entered in the same higher-level model to take into account possible shared variance, given the theoretical and statistical (i.e., the anticorrelations commonly found) relations between the two traits. Separate contrasts were defined for neuroticism and extraversion, which, in the context of the GLM, should reveal amygdala RSFC uniquely associated with each of the two traits. A cluster-corrected threshold of $p <$

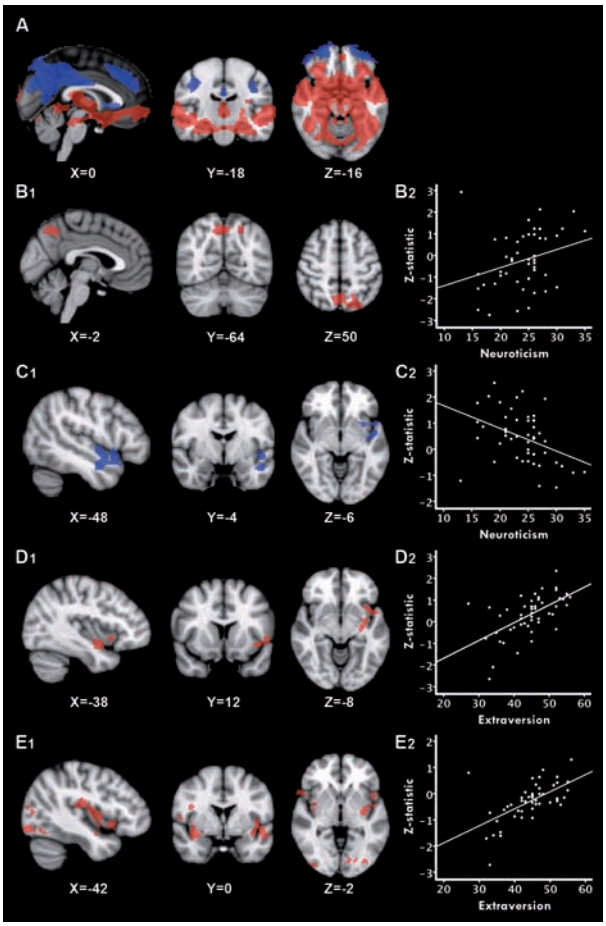


Figure 7.1 (**A**) Resting-state functional connectivity (RSFC) of the bilateral amygdala. Red indicates positive, blue indicates negative amygdala RSFC. (**B1**) Association between neuroticism and left amygdala RSFC with the precuneus. (**C1**) Negative association between neuroticism and left amygdala RSFC with the temporal pole, insula, and superior temporal gyrus (STG). (**D1**) Positive association between extraversion and right amygdala RSFC with the insula and putamen. (**E1**) Positive association between extraversion and left amygdala RSFC with the temporal pole, insula, and occipital cortex. Associations for each effect are plotted in (**B2-E2**). *Z*-statistical maps are corrected for multiple comparisons at the cluster level ($z > 2.3$, $p < .05$), and superimposed on the 2 mm MNI-152 T_1 standard brain. The right side of the images corresponds to the left side of the brain, and vice versa.

.05 with an initial cluster-forming threshold of $z > 2.3$ was used for multiple-comparisons correction. This yielded group-level RSFC maps for the left and the right amygdala separately, as well as for both amygdala combined, and their associations with the neuroticism and extraversion scores. Given our a priori expected associations between neuroticism and/or extraversion, and amygdala FC with regions in the medial and lateral PFC, hippocampus, and striatum, a combined pre-threshold mask of these regions (number of voxels [2 mm MNI] = 95,746) was created to reduce the number of multiple comparisons. Again, a cluster-corrected significance threshold of $p < .05$, with an initial cluster-forming threshold of $z > 2.3$, was used within this mask.

RESULTS

Whole-brain analysis of amygdala RSFC revealed connectivity patterns largely consistent with those from previous RS-fMRI studies (Roy et al., 2009; Stein et al., 2007a; Veer et al., 2011) (see **Figure 7.1a**). The amygdala showed positive RSFC with brain regions implicated in the identification of the emotional significance of a stimulus and in the production of an affective state in response to that stimulus (e.g., subgenual ACC, ventrolateral PFC). On the other hand, negative amygdala RSFC was found with brain regions that are assumed to exert cognitive control and regulate affective states (e.g., dorsomedial PFC, supragenual ACC). **Supplemental Table 7.1** provides clusters and peak coordinates of the amygdala RSFC.

Neuroticism was positively associated with RSFC of the left amygdala with the precuneus (see **Figure 7.1b** and **Table 7.1**). That is, the negative RSFC between the left amygdala and the precuneus observed in our sample, and reported by previous RS-fMRI studies (Roy et al., 2009; Stein et al., 2007a; Veer et al., 2011), was preserved in participants with lower neuroticism scores, yet this connectivity increased to positive in participants with higher neuroticism scores. In contrast, neuroticism was negatively associated with RSFC of the left amygdala with the left temporal pole, insula, and superior temporal gyrus (STG; see **Figure 7.1c** and **Table 7.1**). Specifically, the positive left amygdala RSFC with the temporal pole, insula, and STG ob-

Table 7.1 Clusters and coordinates of the association between amygdala RSFC and neuroticism.

Region	Hemisphere	Voxels	*z*-value	Peak voxel MNI coordinates		
				x	y	z
left amygdala RSFC						
postive						
precuneus		890	5.17	4	-66	50
lateral occipital cortex	L		3.33	-22	-68	50
negative						
middle temporal gyrus	L	858	4.28	-48	-4	-22
planum polare	L		3.72	-50	-2	-6
temporal pole	L		3.76	-50	12	-12
insula	L		3.51	-40	-12	12
insula	L		2.89	-36	4	-14

Note: all *z*-values are corrected for multiple comparisons at the cluster-level ($z > 2.3$; $p < .05$).

served in our sample was preserved in participants with lower neuroticism scores, but this connectivity diminished, and even became negative, in participants with higher neuroticism scores. No relation between neuroticism and right amygdala RSFC was observed at the set threshold.

Extraversion was positively associated with right amygdala RSFC with the insula and putamen (see **Figure 7.1d** and **Table 7.2**) and with left amygdala RSFC with the temporal pole, insula, putamen, and several regions in the occipital cortex (see **Figure 7.1e** and **Table 7.2**). That is, increased amygdala RSFC with these regions was observed in participants with higher extraversion scores, whereas this connectivity decreased to negative in participants with lower extraversion scores.

Because a contrast defined on only one of the regressors, as was done here for neuroticism and extraversion separately, explains variance uniquely associated with that regressor, orthogonalizing the one trait with respect to the other should not change the results. Nevertheless, to check this assumption we repeated the analysis while orthogonalizing neuroticism with respect to extraversion, and vice versa. As we expected, the results remained as described above.

The analysis restricted to the voxels of the pre-threshold mask did not reveal connectivity associated with either neuroticism or extraversion within our a-pri-

Table 7.2 Clusters and coordinates of the association between amygdala RSFC and extraversion.

Region	Hemisphere	Voxels	*z*-value	Peak voxel MNI coordinates		
				x	y	z
right amygdala RSFC						
postive						
insula	L	451	3.95	-38	14	-8
putamen	L		3.23	-32	-12	-8
left amygdala RSFC						
postive						
precuneus	R	1761	3.94	18	-60	18
lateral occipital cortex	R		3.94	42	-62	18
intracalcarine cortex	R		3.09	12	-68	4
brain stem			3.38	4	-36	-14
putamen	L	1314	4.06	-32	-10	-4
temporal pole	L		3.17	-64	14	-10
insula	L		2.87	-44	10	-4
insula	R	1129	4.29	38	0	-12
inferior frontal gyrus	R		3.85	48	34	14
lateral occipital cortex	L	778	3.51	-36	-78	6
lateral occipital cortex	R	500	3.94	42	-62	18

Note: all *z*-values are corrected for multiple comparisons at the cluster-level ($z > 2.3$; $p < .05$).

ori-defined ROIs. To aid ROI selection in future studies, rather than for inference in the present study, we additionally report the connectivity maps at an uncorrected threshold of $z > 2.3$ in the **Supplemental Material**.

DISCUSSION

In the present study, we examined whether individual differences in neuroticism and extraversion are associated with alterations in RSFC of the amygdala. Although we did not find an association between neuroticism and amygdala RSFC with our a priori hypothesized regions, we did demonstrate that individual differences in neuroticism are associated with altered RSFC of the amygdala with the precuneus, temporal poles, insula, and STG. Extraversion scores were associated with RSFC of the

amygdala with the putamen, as was hypothesized, the temporal poles, bilateral insula, and several regions within the occipital cortex. Lastly, neuroticism and extraversion showed contrasting amygdala RSFC with the temporal pole and insula. This is the first study to demonstrate such associations between individual differences in both neuroticism and extraversion and functional connectivity of the amygdala at rest.

Amygdala RSFC and neuroticism

Our analysis showed that neuroticism was associated with increased left amygdala RSFC with the precuneus. The precuneus plays a pivotal role in self-referential information processing (Buckner & Carroll, 2007; Cavanna & Trimble, 2006). For example, perception and processing of personality trait adjectives that are self-descriptive, and thus that closely reflect our own personality, are related to increased activity in this region (Kircher et al., 2002), whereas activity appears to decrease as processed information becomes less self-relevant (Lou et al., 2004). Furthermore, the precuneus is thought to mediate the retrieval of remote, but context-rich, autobiographical memories (Buckner & Carroll, 2007; Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004). Bearing in mind the role of the amygdala in (negative) emotional arousal (Phelps & LeDoux, 2005), our finding may thus relate to disproportionate emotional coloring of self-referential or autobiographical information processing. This adds to the notion of increased self-conscious rumination and aberrant self-referential information processing frequently seen in neurotic individuals (Lam, Smith, Checkley, Rijsdijk, & Sham, 2003; Stöber, 2003; Trapnell & Campbell, 1999). Moreover, our finding may also provide some clues as to neuroticism's relationship with affective disorders. Aberrant self-referential information processing, perhaps partly driven by increased amygdala-precuneus RSFC, may increase the propensity for psychosocial stress and negative emotions, and thus promote affective psychopathology. Consistent with this notion, psychosocial stress has been shown to induce increased amygdala–precuneus FC (Veer et al., 2011), whereas augmented functional interactions between these regions have been implicated in social anxiety and panic disorder (Liao et al., 2010; Pannekoek et al., 2013).

Our analysis also revealed decreased left amygdala RSFC with the left tem-

poral pole, insula, and STG in participants with higher neuroticism scores. The temporal pole and insula have strong reciprocal connections with the amygdala, and both play crucial roles in socioemotional behavior such as recognizing and understanding others' intentions, desires, and emotions (Olson, Plotzker, & Ezzyat, 2007; Singer, 2006; Singer, Critchley, & Preuschoff, 2009). The STG is deemed a key component of a neural circuit dedicated to the perception and processing of facial information (Adolphs, 2002), and STG–amygdala FC in particular is considered vital to facial emotion recognition (Adolphs, 2002; Hennenlotter & Schroeder, 2006). Decreased RSFC between the amygdala and these regions may thus hinder the process of recognizing social cues and recruiting emotional mechanisms to interpret these cues, a process crucial to adaptive socioemotional functioning (Hughes & Dunn, 1998; Singer, 2006). Consistent with this notion, socioemotional impairments are frequently seen in neurotic individuals. These impairments include being extremely sensitive to negative social cues (McCrae & Costa, 1991) and misinterpreting ambiguous social cues as being threatening or negative (Bolger & Zuckerman, 1995; Schmidt & Riniolo, 1999). Our finding of decreased left amygdala RSFC with the temporal poles, insula, and STG may also hint at a complex neural circuitry that links neuroticism to vulnerability to affective disorders by impairing adaptive socioemotional functioning. In line with this hypothesis, impairments in socioemotional functioning are frequently reported in depressed patients (Kerr, Dunbar, & Bentall, 2003; Zobel et al., 2010), which tend to persist during remission (Inoue, Tonooka, Yamada, & Kanba, 2004).

Within this framework, aberrant amygdala–insula FC may be of particular importance in negative emotionality and the susceptibility to affective disorders, because recent data have suggested a central role for a salience network (Seeley, Menon, et al., 2007b) that has the insula as one of its key nodes. While decreased amygdala–insula FC may impede emotional awareness and identification of emotional cues (Craig, 2009; 2010), abnormally increased anterior insular FC with the dorsal ACC and dorsolateral PFC is thought to interfere with salience processing (Seeley, Menon, et al., 2007b). As such, diminished amygdala-insula coupling is reported in anxiety and depression (Etkin et al., 2009; Perlman et al., 2012; Veer et al., 2010; Zeng et al., 2012), whereas increased insula coupling with the dorsal ACC and dorsolateral PFC

strongly relates to state and trait anxiety in healthy participants (Markett et al., 2013; Seeley, Menon, et al., 2007b). The present report, therefore, further supports the idea that abnormal FC with regions of the salience network relates to negative affect and susceptibility to affective psychopathology.

Amygdala RSFC and extraversion

Extraversion was associated with increased RSFC of the right amygdala with the insula and putamen, and of the left amygdala with the putamen, temporal pole, insula, and several regions within the occipital cortex. The putamen, together with the amygdala, is part of an integrated neural circuitry dedicated to various aspects of reward processing (Haber & Knutson, 2010). Striatal regions, including the putamen, respond to the anticipated magnitude, probability, and immediacy of rewards (Ballard & Knutson, 2009; Knutson, Taylor, Kaufman, Peterson, & Glover, 2005; Yacubian et al., 2006), whereas the amygdala is mainly involved in stimulus–reward association learning (Murray, 2007). The increased amygdala RSFC with the putamen in participants with higher extraversion scores may thus suggest an enhanced functional integration of the reward circuitry in extraverts. In keeping with this notion, it was found that high levels of extraversion predict RSFC of brain regions that have been implicated in reward and motivation in a previous study (Adelstein et al., 2011). Our results may thus suggest a mechanism for the protective effects of extraversion against affective psychopathology: Heightened reward sensitivity, as reflected by enhanced functional integration of the reward circuitry, could increase the propensity to experience positive emotions, and promote psychological well-being. Conversely, diminished reward sensitivity on both the behavioral and neuronal level is frequently reported in affective disorders (DeVido et al., 2009; Henriques & Davidson, 2000), which is thought to relate to some of the affective symptoms.

Our group recently showed positive associations between extraversion and right amygdala volume (Cremers et al., 2011). In the present analyses, we therefore controlled for volumetric variation in a post-hoc analysis, but the results remained the same. This suggests that morphological differences of the amygdala are unlikely to underlie the connectivity effects found in the present study.

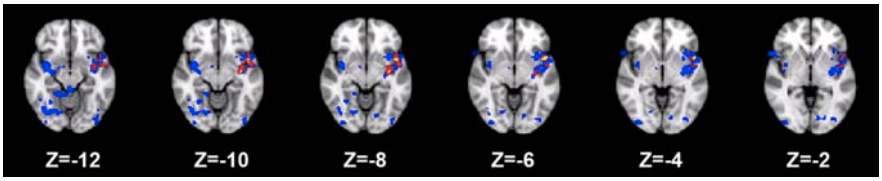


Figure 7.2 Overlap of the associations between neuroticism/extraversion and amygdala RSFC with the temporal cortex and insula. Blue denotes regions where an association was found between extraversion and left amygdala RSFC (see **Figure 7.1e**). Red denotes either an overlap of the association between extraversion and right amygdala RSFC and the association between neuroticism and right amygdala RSFC (see **Figure 7.1c and 7.1d**), an overlap of the association between extraversion and left amygdala RSFC and the association between neuroticism and right amygdala RSFC (see **Figure 7.1c and 7.1e**), or an overlap of the association between extraversion and left and right amygdala RSFC (see **Figure 7.1d and 7.1e**). Yellow denotes the voxels where all three effects overlap. The results are overlaid on the 2 mm MNI-152 T_1 standard brain. The right side of the images corresponds to the left side of the brain, and vice versa.

Our results further revealed increased amygdala RSFC with the temporal pole and insula in extraverts. This clearly contrasts our finding of decreased, and even negative, amygdala RSFC with the temporal pole and insula in the more neurotic individuals, which is in agreement with the inverse correlation between the two traits found in the present study, as well as in previous studies. As we stated earlier, amygdala FC with the temporal pole and insula may be particularly important in recognizing social cues and recruiting emotional mechanisms to interpret these cues. Thus, whereas decreased FC between the amygdala and these regions may hinder adaptive socioemotional functioning, and consequently promote psychopathology, preserved amygdala FC with these regions may curb this susceptibility.

Functional specificity within the insula

In this study, we found associations between neuroticism/extraversion and amygdala functional connectivity in both the anterior and posterior parts of the insula. As a recent meta-analysis has illustrated, the insula can be roughly subdivided into four regions that are each associated with a general functional domain: sensorimotor (dorsal mid and dorsal posterior), cognitive (dorsal anterior), chemical sensory (ventral mid),

and socioemotional (ventral anterior) (Kurth, Zilles, Fox, Laird, & Eickhoff, 2010). However, specific functions, such as empathy, interoception, and pain, were found to be associated with both the anterior and posterior insula. Unfortunately, it is always problematic to assign functional significance to RS results, as is the case in our study, so we cannot state exactly what function our findings may relate to. However, the overarching function of the insula seems the monitoring of saliency in both the internal and external environment, which naturally complements the role of the amygdala as general salience detector. Hence, we argue that reduced amygdala-insula RSFC in more neurotic individuals could be reminiscent of less well-integrated salience monitoring and detection, which may in turn be associated with vulnerability to psychopathology, whereas the opposite could be the case for high extraverts.

When exploring the overlap in amygdala-insula RSFC between neuroticism and extraversion, this seems to be most evident in the dorsal anterior insula, though this can also be observed in the more posterior portion (see **Figure 7.2**). It has been suggested that the dorsal anterior insula is a site for functional integration of the different functional domains represented in the insula (Kurth et al., 2010). As such, we hypothesize that this area could be a suitable candidate to mediate the differential effects of neuroticism and extraversion on affective networks.

Neuroticism, extraversion, and amygdala RSFC with the PFC

In the present study, we did not find the expected association between neuroticism or extraversion, and amygdala RSFC with regions of the ventral (subgenual ACC, ventrolateral PFC, and OFC), and dorsal (supragenual ACC, dorsomedial PFC, and dorsolateral PFC) systems. We offer two possible explanations for these null findings. First, given that studies on the relationship between amygdala RSFC and both traits are lacking, our hypotheses were primarily based on previous task-dependent fMRI findings. Although FC patterns during rest and task performance show similarities (Smith et al., 2009), it is conceivable that specific functional networks might be more context-dependent and could only be mapped by using specific tasks (e.g., threat-related stimuli). This might to some extent account for the inconsistencies between our and the previous task-dependent findings. Second, our sample did not include partic-

ipants with neuroticism scores in the clinical range, and neither did our participants have very low extraversion scores. A relation to the aberrant amygdala FC with regions of the ventral and dorsal PFC, which has been demonstrated in affective disorders (Pezawas et al., 2005; Phillips, Drevets, Rauch, & Lane, 2003b), might have been found if we were to include a group of highly neurotic individuals more susceptible to affective disorders, or of their low-extravert counterparts. Nonetheless, inspection of the uncorrected connectivity maps does reveal preliminary evidence that both traits might be associated with these target regions in the PFC. These findings could guide ROI selection in future studies, and thereby facilitate the mapping of amygdala-PFC circuits in relation to personality traits associated with either sensitivity or resilience to psychiatric disorders.

Limitations and future directions

The present study has several limitations that should be noted. First, the mean neuroticism and extraversion scores obtained from our sample were below and above average, respectively, as compared to the norm scores of the healthy population. This was to be expected, given that the participants included were originally recruited to serve as controls for anxiety and depression patients. As such, the exclusion criteria for controls in the NESDA study might have biased our sample toward lower than average neuroticism, but higher extraversion scores. Nonetheless, we do report a shift in amygdala functional connectivity with higher neuroticism and extraversion scores, which closely follows the altered amygdala connectivity that has been found in previous studies of stress and depression from our lab (Veer et al., 2010; 2011).

Second, physiological fluctuations (of heart rate and respiration) were not recorded during the RS data acquisition, although this may have been a source of noise influencing our data. However, we chose to include the global signal in our model as a nuisance regressor in order to minimize the effect of physiological fluctuations on our fMRI data (Fox & Raichle, 2007). Although global signal regression is believed to remove global sources of noise and minimize the influence of physiological fluctuations, some studies have suggested that it may also introduce artifactual anticorrelations (e.g., Murphy, Birn, Handwerker, Jones, & Bandettini, 2009). Recent data,

however, have shown that global signal regression suppresses false correlations and improves connection specificity, and more importantly, evidence for anticorrelations can be seen even without global signal regression (Fox, Zhang, Snyder, & Raichle, 2009; Weissenbacher et al., 2009). Further analysis of our data without global signal regression confirmed our findings. Although the results remained largely the same, some effects did not pass statistical significance, which was probably caused by higher residual noise in the data.

Third, by defining the most certain amygdala voxels as our seed region, alterations in FC of specific amygdalar nuclei may have gone unobserved. Whereas the amygdala is composed of functionally distinct nuclei (Balleine & Killcross, 2006), we still lack a well-established method for parcellating these subnuclei, due to their small size and homogeneous appearance. Although manually defining amygdalar nuclei in native space is susceptible to human error, using probability-based masks of amygdalar nuclei in standard space is susceptible to registration errors and disregards individual variations in neuroanatomy (Bach, Behrens, Garrido, Weiskopf, & Dolan, 2011; Saygin, Osher, Augustinack, Fischl, & Gabrieli, 2011). In light of the limitations pertaining to amygdala parcellation, we opted to examine connectivity of the most certain amygdala voxels rather than connectivity of the amygdalar nuclei separately.

Fourth, the potential influence of an emotional-task paradigm that preceded the RS data acquisition should be noted. Although this may have had negligible confounding effects on the data, it might also reveal the prolonged effects of emotional processing on amygdala RSFC. In that case, the increased amygdala-precuneus RSFC reported here is in line with findings from a recent study that examined the prolonged effects of social stress on amygdala RSFC (Veer et al., 2011).

Fifth, data acquisition was conducted at three different sites. Although the same scanner type was used, differences in scan quality might still have existed. Additionally, one of the sites scanned using slightly different imaging parameters. To reduce the possible effect of scan site in our analysis, we included this as a confound variable in our higher-level model. Moreover, it seems unlikely that differences between scan sites drove our results, since neuroticism and extraversion scores were distributed equally within each of the three scan sites.

Sixth, adding two correlated traits to the same linear regression model has the advantage that when a contrast is specified for one of the traits only, any variance that is shared with the other trait will be removed from this contrast. Consequently, only variance (in this context, RSFC) will be shown that is uniquely explained by the corresponding trait, which means variance over and above what can be explained by the other trait. This implies that the other trait could still account for variance in the same regions to some extent, though this would not show up in the results. Therefore, our results are limited to connectivity patterns uniquely associated to either one of the traits, and they do not necessarily describe the full range of amygdala RSFC associated with each trait.

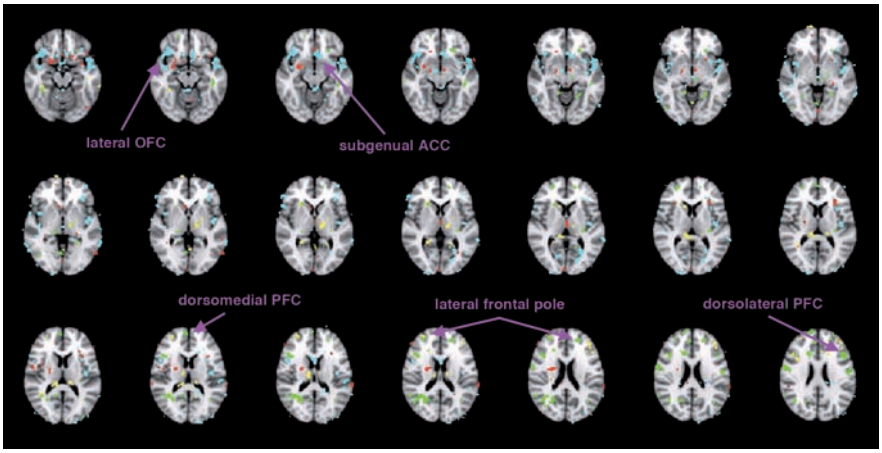
Finally, the scope of our findings is limited to the Big Five model of personality used in this study, since it is just one of many classifications for describing human personality. Nevertheless, the Big Five model has proven extremely useful in studying both normal and abnormal behavior and is currently the most widely used taxonomy of personality (Deyoung et al., 2010). Moreover, the Big Five traits are strongly heritable (Riemann, Angleitner, & Strelau, 1997), with a genetic factor structure that is invariant across cultures (Yamagata et al., 2006), rendering the traits particularly suitable for studying the neural substrates of personality. Yet, for a deeper understanding of personality, it would be both important and interesting to examine whether the present findings could be replicated using different but closely related classification schemes.

Future studies are warranted to investigate whether the altered amygdala FC reported here actually affects self-relevant, socioemotional, and reward-related processing. To this end, both RS and task-dependent fMRI could be employed in conjunction, given that these techniques provide complementary information on brain functioning. Moreover, to improve our comprehension of the mechanisms that link neuroticism to psychopathology, our findings need to be extended to healthy participants whose neuroticism scores would be extending toward those of a clinical population.

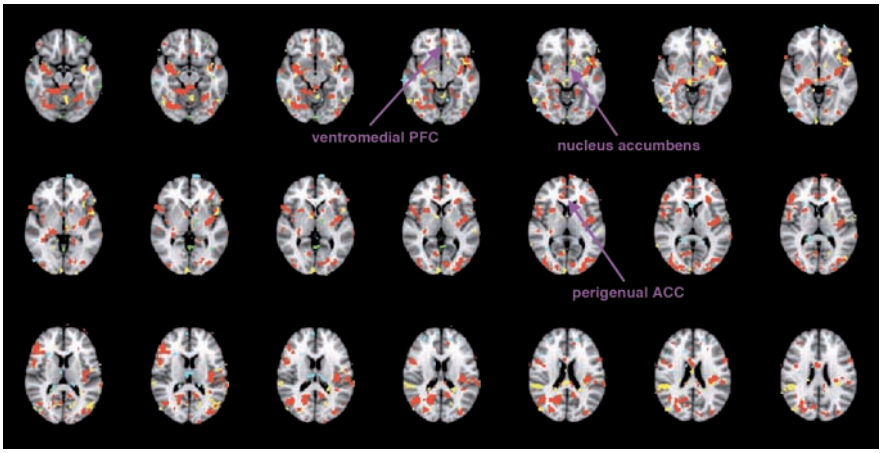
Conclusion

In sum, the results of the present study have revealed trait-specific amygdala RSFC patterns that may partly underlie functional differences between neuroticism and extraversion. Neuroticism was associated with increased amygdala RSFC with the precuneus and decreased amygdala RSFC with the temporal pole, insula, and STG. This may relate to less adaptive perception and processing of self-relevant and socioemotional information in neurotic individuals. Conversely, extraversion was associated with increased amygdala RSFC with the putamen, temporal pole, and insula, which could relate to the heightened reward sensitivity and enhanced socioemotional functioning in extraverts. We hypothesize that these trait-specific RSFC patterns could potentially link neuroticism and extraversion to the neurobiology underlying increased susceptibility or resilience to affective disorders.

SUPPLEMENTAL MATERIAL



Supplemental Figures Amygdala resting-state functional connectivity associated with neuroticism (above) and extraversion (below) at an uncorrected threshold of $z > 2.3$. Red and yellow denote a positive association with functional connectivity of the left and right amygdala, respectively. Blue and green denote a negative association with functional connectivity of the left and right amygdala, respectively. The results are superimposed on the 2 mm MNI-152 standard brain. The right side of the images corresponds to the left side of the brain and vice-versa.



Supplemental Table 7.1 Joint amygdala resting-state functional connectivity results.

Region	Hemisphere	Voxels	*z*-value	Peak voxel MNI coordinates		
				x	y	z
postive						
temporal pole	R	34848	6.47	-52	12	-24
	L		6.40	-54	12	-12
middle temporal gyrus	R		6.43	60	-4	-18
	L		5.55	-60	-6	-18
hippocampus	R		6.20	22	-18	-18
	L		6.28	-24	-26	-16
orbitofrontal cortex	R		6.12	20	12	-20
	L		6.82	-16	12	-22
hypothalamus	R		5.12	6	-4	-12
	L		5.30	-6	-4	-16
subcallosal cortex	R		5.10	2	22	-12
	L		5.01	-2	-24	-12
superior temporal gyrus	R		5.04	56	0	-12
	L		4.51	-56	0	-10
putamen	R		4.84	28	4	-4
	L		4.43	-28	0	-4
brainstem			4.82	8	-36	-22
insula	R		4.58	40	-2	-8
	L		4.74	-38	4	-10
dorsal anterior cingulate	R		4.73	2	34	-8
cortex	L		3.55	-2	44	-8
negative						
paracingulate gyrus	R	45148	5.35	4	34	36
	L		5.23	-2	32	36
posterior cingulate cortex	R		5.16	2	-42	32
	L		5.70	-2	-34	32
precuneus	R		4.73	2	-64	38
	L		4.80	-2	-66	38
lateral frontal pole	R		4.70	40	56	2
	L		3.87	-40	54	0
middle frontal gyrus	R		4.44	44	30	36
	L		4.45	-46	26	36

Note: all *z*-values are corrected for multiple comparisons at the cluster-level ($z > 2.3$; $p < .05$).