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Neuroticism modulates amygdala–prefrontal connectivity in response to negative emotional facial expressions

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ABSTRACT

Neuroticism is associated with the experience of negative affect and the development of affective disorders. While evidence exists for a modulatory role of neuroticism on task induced brain *activity*, it is unknown how neuroticism affects brain *connectivity*, especially the crucial coupling between the amygdala and the prefrontal cortex. Here we investigate this relation between functional connectivity and personality in response to negative facial expressions. Sixty healthy control participants, from the Netherlands Study on Depression and Anxiety (NESDA), were scanned during an emotional faces gender decision task. Activity and functional amygdala connectivity (psycho–physiological interaction [PPI]) related to faces of negative emotional valence (angry, fearful and sad) was compared to neutral facial expressions, while neuroticism scores were entered as a regressor. Activity for fearful compared to neutral faces in the dorsomedial prefrontal (dmPFC) cortex was positively correlated with neuroticism scores. PPI analyses revealed that right amygdala–dmPFC connectivity for angry and fearful compared to neutral faces was positively correlated with neuroticism scores. In contrast, left amygdala–anterior cingulate cortex (ACC) connectivity for angry, fearful and sad compared to neutral faces was negatively related to neuroticism levels. DmPFC activity has frequently been associated with self-referential processing in social cognitive tasks. Our results therefore suggest that high neurotic participants display stronger self-referential processing in response to negative emotional faces. Second, in line with previous reports on ACC function, the negative correlation between amygdala–ACC connectivity and neuroticism scores might indicate that those high in neuroticism display diminished control function of the ACC over the amygdala. These connectivity patterns might be associated with vulnerability to developing affective disorders such as depression and anxiety.

Introduction

Neuroticism is a widely recognized trait in various theoretical approaches to human personality (Smits and Boeck, 2006; Zelenski and Larsen, 1999). Characteristics of this trait include a tendency to worry and to be anxious (Canli et al., 2001), and is related to the experience of negative affect (Larsen and Ketelaar, 1991; Robinson et al., 2007a; Zelenski and Larsen, 1999). Neuroticism is also associated with affective disorders such as social anxiety disorder (SAD) and depression (Bienvenu et al., 2001, 2004; Clark et al., 1994).

Functional magnetic resonance imaging (fMRI) studies have provided substantial evidence for the modulatory role of individual differences in neuroticism on neural activity related to emotion processing (Canli, 2004; Hamann and Canli, 2004). Regions where activity is associated with neuroticism (and related personality traits) include the amygdala (Haas et al., 2007; Reuter et al., 2004; Stein et al., 2007b), the anterior cingulate cortex (ACC) (Eisenberger et al., 2005; Reuter et al., 2004) and the medial prefrontal cortex (Britton et al., 2007; Haas et al., 2007; Rubino et al., 2007). However, these regions are functionally coupled, and such connectivity, especially between the amygdala and prefrontal regions, is crucial for the integration between emotion and cognition (Pessoa, 2008; Stein et al., 2007a). To gain a better understanding of the neural basis of individual differences in emotion processing related to neuroticism, a focus on functional connectivity between limbic and prefrontal regions is therefore required.

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Neuroticism is associated with alterations in cognitive–emotional functions such as affect regulation (Tamir, 2005), self-consciousness (Trapnell and Campbell, 1999) and self-regulation (Robinson et al., 2007b). Thus, dysfunctional interactions between the amygdala and regions related to these functions, such as ventrolateral PFC (vlPFC), dorsolateral PFC (dlPFC) and ACC (Ochsner & Gross, 2005; Pessoa, 2008) (cognitive control of emotion), and dorsomedial prefrontal cortex (dmPFC) (Amodio & Frith, 2006; Northoff & Bermpohl, 2004) (self-regulation and self-referential processing) are likely to be specifically associated with individual differences in neuroticism.

Only recently, fMRI studies have started to investigate personality-associated differences in functional connectivity during emotion processing. Whereas some of these studies focused on traits related to positive affect (Haas et al., 2006; Passamonti et al., 2008), one study reported *trait anxiety* differences in amygdala–ACC coupling (Kienast et al., 2008). A mood induction study during positron emission tomography (PET) showed that neuroticism is associated with changes in subgenual cingulate coupling with prefrontal regions during mood induction, possibly reflecting a susceptibility marker for depression (Keightley et al., 2003). Despite these initial findings, to the best of our knowledge, no study has systematically addressed the question on how individual differences in neuroticism are associated with amygdala–prefrontal cortex connectivity for various negative emotional facial expressions.

To investigate the modulatory role of neuroticism on amygdala–prefrontal cortex connectivity during emotion processing, we applied a standardized face paradigm with different negative emotional facial expressions (angry, fearful and sad) in a large subject sample. This sample represented the healthy control subjects as part of the Netherlands Study on Depression and Anxiety (NESDA) (Penninx et al., 2008). We hypothesize that *activity* in the medial PFC, ACC and the amygdala is associated with neuroticism scores when processing negative as compared to neutral facial expressions. We also hypothesize that *connectivity*, between the amygdala on one hand and the lateral and medial prefrontal regions and the ACC on the other, should vary with individual differences in neuroticism.

Methods

Participants

Sixty healthy participants were selected from the general population (mean age = 39.9, range: 21–56, 37 females). Participants were recruited as healthy control participants in a large multi-center cohort study, the Netherlands Study of Depression and Anxiety (NESDA). Participants were tested at the Amsterdam Medical Center (AMC), Leiden University Medical Center (LUMC) and University Medical Center Groningen (UMCG). The exclusion criteria for these healthy participants were (1) a lifetime diagnosis of DSM axis I and/or axis II disorders, psychotic disorder or dementia, (2) current alcohol or substance abuse, (3) a history of seizure or head injury, (4) current use of beta-blockers medication, (5) hypertension (high blood pressure) 180/130 mm Hg, (6) more than 5 cigarettes smoked per day, (7) older than 57 years and (8) MRI incompatible implants or tattoos. During the preliminary analysis, 4 participants were excluded because of head movement artifacts. Written informed consent from each participant was obtained prior to the scanning session. The study was approved by the ethical review boards of each participating center.

Personality scores

To asses personality traits, all participants completed the NEO Five Factor Inventory (Costa and McGrae, 1992). This questionnaire consists of 60 items and measures five different personality traits: neuroticism, extraversion, openness, agreeableness and conscientiousness. Of these traits, neuroticism and extraversion are most closely related to emotion processing and alterations in neural activity (Canli, 2004). Examples of the neuroticism questions include, 'I often feel nervous and tense', and 'Sometimes I feel completely worthless'.

Experimental design

Color photographs of faces depicting angry, fearful, sad, happy, and neutral facial expressions were presented together with scrambled faces in an event-related design. Photographs were selected from the Karolinska Directed Emotional Faces System (Lundqvist et al., 1998) representing standardized facial expressions of emotions presented by amateur actors. Twenty-four faces were selected for each of the five facial expressions, comprising of 12 female and 12 male faces, and 80 scrambled faces. A total number of 200 photographs were presented pseudorandomly, such that there were maximally two faces presented before the presentation of a scrambled face, and there were no repetitions of the same emotional expressions. Each photograph was presented on the screen for 2.5 s, with an inter-stimulus interval (black screen) varied between 0.5 and 1.5 s (jitter). The total duration of the task was 747 s. The experimental paradigm was presented using E-prime software (Psychological Software Tools, Pittsburgh, PA, USA). Images were projected onto a translucent screen at the end of the scanner bed, visible via a mirror above the participant's head. Participants were instructed to indicate the gender by pressing one of two buttons of two magnet-compatible button boxes with the index finger of the left or right hand. During the presentation of scrambled faces, participants had to press left or right buttons in conformity with the instructions present on the screen, indicating either left or right by an arrow. Responses and reaction times were recorded. Participants were not aware that the implicit emotional variable was under study in the experiment.

Image acquisition

Images were acquired on a Philips Intera 3T MR-scanner. A sense-8 (UMCG and LUMC) and a sense-6 (AMC) channel head coil was used for radio frequency transmission and reception. For each subject a series of echo planar imaging (EPI)—sensitive to the blood oxygenation level dependent effect—volumes were obtained, entailing a T2*-weighted gradient echo sequence (repetition time [TR] = 2300 ms, echo time [TE] = 28.0 ms at UMCG and TE = 30.0 ms at AMC and LUMC, flip angle 90 using axial whole-brain acquisition, with an interleaved slice acquisition order). The interslice gap was 0 mm and the plane thickness was 3 mm. The matrix sizes were: 64 × 64 voxels at UMCG and 96 × 96 voxels at AMC and LUMC. The EPIs were acquired at 39 slices at UMCG and 35 slices at AMC and LUMC. The in-plane resolution was 3 × 3 mm at UMCG and 2.29 × 2.29 mm at AMC and LUMC. The axial images were acquired parallel to the anterior–posterior commissure plane. Functional data comprising 310 volumes were obtained per subject. A T1-weighted anatomical MRI was also acquired for each subject (TR = 9 ms, TE = 3.5 ms, matrix size 256 × 256).

Analysis

Preprocessing

Functional data were preprocessed and analyzed using the statistical parametric mapping software package (SPM5, http://www.fil.ion.ucl.ac.uk) implemented in Matlab 7.2 (The MathWorks Inc., http://www.mathworks.com).

The EPI volumes were reoriented in respect to the anterior commissure selected on the first volume. Time series were corrected for differences in slice acquisition times. The reference slice was 39 at UMCG and 2 at AMC and LUMC. After spatial realignment to the first image, a mean EPI was created. The movement parameters for each

participant were inspected. If a participant moved more than 3 mm in any direction (anterior–posterior, right–left, inferior–superior) the data were excluded from further analysis. The anatomy scan was coregistered to the mean EPI image. Subsequently, T1, and with it EPI images, were spatially normalized to a standard stereotaxic space (Montreal Neurological Institute). During normalization, data were resampled into a 3 × 3 × 3 mm grid with 7th degree B-spline interpolation. The functional data were smoothed with a 3D isotropic Gaussian kernel of 8 mm full-width at half-maximum.

Imaging analysis

Low-frequency noise was removed by applying a high-pass filter (cut-off of 128 s) to the fMRI time series at each voxel. Significant hemodynamic changes for each condition were calculated using the general linear model (Friston et al., 1995), with respect to the event-related response convolved with canonical hemodynamic response function. To identify activity in regions related to face processing, we computed a *t*-contrast of all faces combined to the baseline, and tested this contrast at $p<0.05$ family wise error (FWE) corrected for multiple comparisons. To the test the hypotheses between the relation of neuroticism and negative affect, the analysis was subsequently restricted to the negative emotional facial expressions. *T*-contrasts for "angry > neutral", "fearful > neutral", "sad > neutral" were calculated for each subject. Results of these weighted contrast (contrast images) were then entered in a second level random effect model. For each negative emotional facial expression (compared to neutral), neuroticism, extraversion, age and gender were entered as regressors. A one-sample *t*-test was applied to test the positive and negative effect of the neuroticism scores regressor. Effectively, this analysis corresponds to detecting partial correlations between brain activity and neuroticism, when correcting for extraversion, age and gender. Since the amygdala, the ACC and the dmPFC all shown to have neuroticism dependent variation in activity when processing emotional stimuli they were defined as regions of interest (ROI). The amygdala and ACC volumes were based on the WFU pickatlas (Maldjian et al., 2003). The dmPFC was defined as a 10 mm sphere around the peak voxel coordinates reported in a study on phobic pronenesss in relation to the processing of negative emotional faces (Rubino et al., 2007). We applied an initial significance threshold of $p<0.005$ (uncorrected) and a spatial extent of five voxels ($k\geq5$), restricted to our a priori regions of interested (ROI): the amygdala, the ACC and the dmPFC. Furthermore we report activation outside our ROIs at $p<0.001$, $k\geq10$ voxels uncorrected for multiple comparisons. Activations are reported in standard Montreal Neurological Institute (MNI) space.

Functional connectivity analysis: psycho–physiological interaction (PPI)

Psycho–physiological interaction (PPI) analyses were used to assess how activity in a brain region of interest covaries with a source region in response to the experimental condition (Friston et al., 1997). Within each condition (different negative emotional faces compared to neutral faces), we seperately examined functional connectivity from the left and right amygdala as a source region. To identify the amygdala activation for each participant we examined the contrast of all faces compared to the baseline at $p<0.05$ uncorrected. The deconvolved time series from a 5 mm radius sphere around the individually defined peak activated voxel within the amygdala (defined by the WFU pickatlas mask) (Maldjian et al., 2003) was extracted (44 participants). The PPI was calculated as the element by element product of the left and the right amygdala time series (the first eigenvariate from all voxels' time series) and a vector coding for the effect of task ("anger > neutral", "fear > neutral", and "sad > neutral"). This product was subsequently re-convolved with the hemodynamic response function (HRF). This interaction term was then entered as a regressor in a first level model together with the time series of the amygdala and the vector coding for the task effect. The models were estimated and contrasts generated to test the effects of positive and negative PPIs. This analysis identified regions that display stronger functional connectivity with the amygdala for an emotional compared to a neutral facial expression, and for neutral compared to emotional facial expressions respectively.

The contrast images for the PPI effects were then entered in a second level analysis. In a similar manner to the conventional analysis, neuroticism, extraversion, age and gender were entered as regressors. Subsequently, the effects of neuroticism were tested, which identified brain regions that showed connectivity with the amygdala correlating positively or negatively with neuroticism scores, respectively. We applied an initial uncorrected threshold of $p<0.005$, $k\geq5$, restricted to our a priori regions of interest, the ACC, the dmPFC, dlPFC and vlPFC. The ACC mask was based on the WFU pickatlas, while the dmPFC, dlPFC and vlPFC (lateral orbitofrontal cortex) masks were defined as a 15 mm sphere around the peak coordinates reported in a study on amygdala connectivity based on a large fMRI data set on processing angry and fearful faces (Stein et al., 2007a). Furthermore we report activation outside our ROIs at $p<0.001$, $k\geq10$ voxels uncorrected for multiple comparisons.

Results[1]

Behavioral results

For the entire group, mean reaction times (RT) for the different emotional faces were: angry RT = 825 ms, SD = 158, fear RT = 879 ms, SD = 166, sad RT = 874 ms, SD = 163 and neutral RT = 888 ms SD = 155. There was a main effect of emotion on reaction time, driven by a faster RT for angry compared to neutral faces $t(55)=-7.6$, $p<0.05$. Accuracy overall was high: for angry 98.3%, fear 98.5%, sad 96.1% and neutral 95.4% correct. There were no significant correlations between neuroticism (or extraversion) and the differences scores of each negative compared to neutral facial expression or for accuracy, (for each correlation $p>0.05$).

Personality scores

The sample scores for neuroticism were mean 24.3 (range: 13–36), SD = 5.3. For extraversion these scores were mean 44.4 (range: 27–56), SD = 6.6. There was a significant negative correlation between neuroticism and extraversion, $r=-0.49$, $p<0.05$. Since individual differences in extraversion also influence emotion processing, we aimed to exclude any possible effect by adding extraversion as a regressor in our model (see Passamonti et al., 2008 for a comparable approach).

fMRI results

Main effects of emotional faces versus baseline

We compared all emotional faces together against the scrambled faces baseline to assess activity related to face processing. Main effects of the face processing were found in the bilateral fusiform gyrus (left, −42/−54/−24, $z=6.1$ $k=25$; right, 39/−45/−24, $z=7.26$, $k=110$), bilateral amygdala (left, −18/−6/−15, $z=6.95$, $k=126$; right, 21/−6/−15, $z=7.13$, $k=82$), and the right inferior frontal gyrus (51/27/21, $z=6.37$, $k=174$). All activations were $p<0.05$, whole brain FWE corrected.

[1] Because data were acquired at different sites, we conducted additional stepwise regression analyses to test whether this factor "site" would affect significance levels. When the model was extended with the factor site, no significant additional variance was explained compared to the model without the factor site (for each regression analysis $p > 0.05$ for change in explained variance of the extended model, while neuroticism remained significant, $p < 0.005$ for each extended model).

Table 1
Brain areas displaying a correlation between neuroticism scores and activity for angry, fearful and sad facial expressions.

Contrast	Region	Side	Voxels	*Z* values	*P* values	MNI coordinates		
						x	*y*	*z*
Angry > Neutral								
Fear > Neutral								
Positive	**dmPFC**	**R**	**10**	**2.95**	**0.002**	**6**	**57**	**33**
	Calcarine gyrus	L	17	3.71	<0.001	−3	−93	6
Sad > Neutral								
Positive	Posterior cingulate gyrus	R	10	3.65	<0.001	6	−48	30

A priori regions of interest are shown in bold. dmPFC: dorsomedial prefrontal cortex. Other activations at a threshold of $p<0.001$, and minimal 10 contiguous voxels are also reported. No negative correlations were found.

Brain activity for emotional versus neutral faces and relation with neuroticism

In order to identify activity in brain regions that varied as a function of neuroticism scores, we tested the effect of neuroticism in a regression model. This resulted in the identification of activity in brain regions that was positively or negatively correlated with neuroticism in response to emotional facial expressions compared to neutral facial expressions. Table 1 shows activation clusters and peak coordinates. As one can see, of our a priori regions of interest, only the right dmPFC showed an effect of neuroticism. We found a positive relation between activity in this region for fearful compared to neutral emotional faces and neuroticism scores. The main effects of each contrast (regardless of individual differences) are provided as online supplementary material.

Functional connectivity: PPI analysis

In order to investigate how neuroticism is associated with functional connectivity of the amygdala and the prefrontal cortex, we tested the effect of neuroticism as a regressor in a model of connectivity with the left and right amygdala (separately) as source regions. This analysis resulted in the identification of brain regions showing connectivity with the amygdala that was either positively or negatively correlated with neuroticism scores when viewing emotional compared to neutral facial expressions.

Table 2 shows the modulatory effect of neuroticism on the connectivity of the left amygdala. For angry and fearful faces, connectivity of the left amygdala and right ACC was negatively associated with neuroticism scores. For sad compared to neutral faces, a similar relation between neuroticism and amygdala connectivity (with a more the dorsal part of the ACC) was observed. Both these findings indicate that the higher the neuroticism scores, the lower the functional coupling for negative emotional compared to neutral facial expressions between the left amygdala and the ACC. These effects are shown in Fig. 1. For display purposes the partial correlation scores for neuroticism (the residuals after correcting neuroticism for extraversion, age and gender) were linear transformed (mean added and a scaled standard deviation) to approximate the original neuroticism scores.

Table 3 displays the positive and negative correlations between neuroticism and regions functionally coupled with the right amygdala for each of the negative emotional compared to neutral emotional facial expressions. A positive correlation was found between the amygdala connectivity with the right dorsomedial prefrontal (dmPFC) cortex for both angry and fearful compared to neutral facial expressions. This indicates that the higher the neuroticism scores, the stronger the coupling for fearful and angry compared to neutral faces between the right amygdala and the right dmPFC (see Fig. 2).

It is important to note that within each of the neuroticism related connectivity effects in the ACC and dmPFC there were no significant main effects (irrespective of individual differences) of each contrast, even at a threshold of $p<0.05$ uncorrected. Within our other regions of interest we only found significant effects of a positive PPI (with the left amygdala) for the fear > neutral contrast in the ventral lateral prefrontal cortex (−36/33/−8, $z=3.58$, $p<0.05$ FWE, small volume corrected). No other contrasts showed a positive or negative PPI effect in our ROIs.

Discussion

Neuroticism modulates brain activity in the dmPFC during the processing of fearful faces

In this study, we investigated the modulatory role of neuroticism on brain activity and functional connectivity while processing negative compared to neutral facial expressions. Our results showed that activation in the dmPFC varied as a function of neuroticism scores in response to fearful facial expressions. This finding is broadly in line with studies in which dmPFC activity was found to be related to neuroticism (Haas et al., 2008) and phobic proneness (Rubino et al., 2007) during the processing of sad, respectively fearful and angry facial expressions. Both studies discuss these findings within a framework of self-referential processing, a construct strongly associated with this brain region (Amodio and Frith, 2006; Northoff et al., 2006). In accordance with these notions, neuroticism has been associated with an individual's self-schema, i.e. a '[…] constellation of self-referent information of one's own unique traits […]' which '[…] serves to guide the processing of personally relevant information' (Winter and Kuiper, 1997). Trapnell and Campbell (1999) found that

Table 2
Association between neuroticism and functional connectivity with the left amygdala for angry, fearful and sad facial expressions.

Contrast	Region	Side	Voxels	*Z* values	*P* values	MNI coordinates		
						x	*y*	*z*
Angry > Neutral								
Positive	Parahippocampal gyrus	R	12	4.39	<0.001	30	−39	−6
Negative	**ACC**	**R**	**7**	**2.96**	**0.002**	**12**	**36**	**12**
Fear > Neutral								
Negative	**ACC**	**R**	**15**	**3.26**	**0.001**	**9**	**30**	**15**
Sad > Neutral								
Negative	**Dorsal ACC***	**R**	**41**	**4.08**	**<0.001**	**12**	**12**	**30**

A priori regions of interest are shown in bold.
* Small volume corrected, FWE $p<0.05$. ACC, anterior cingulate cortex. Other activations at a threshold of $p<0.001$, and minimal 10 contiguous voxels are also reported.

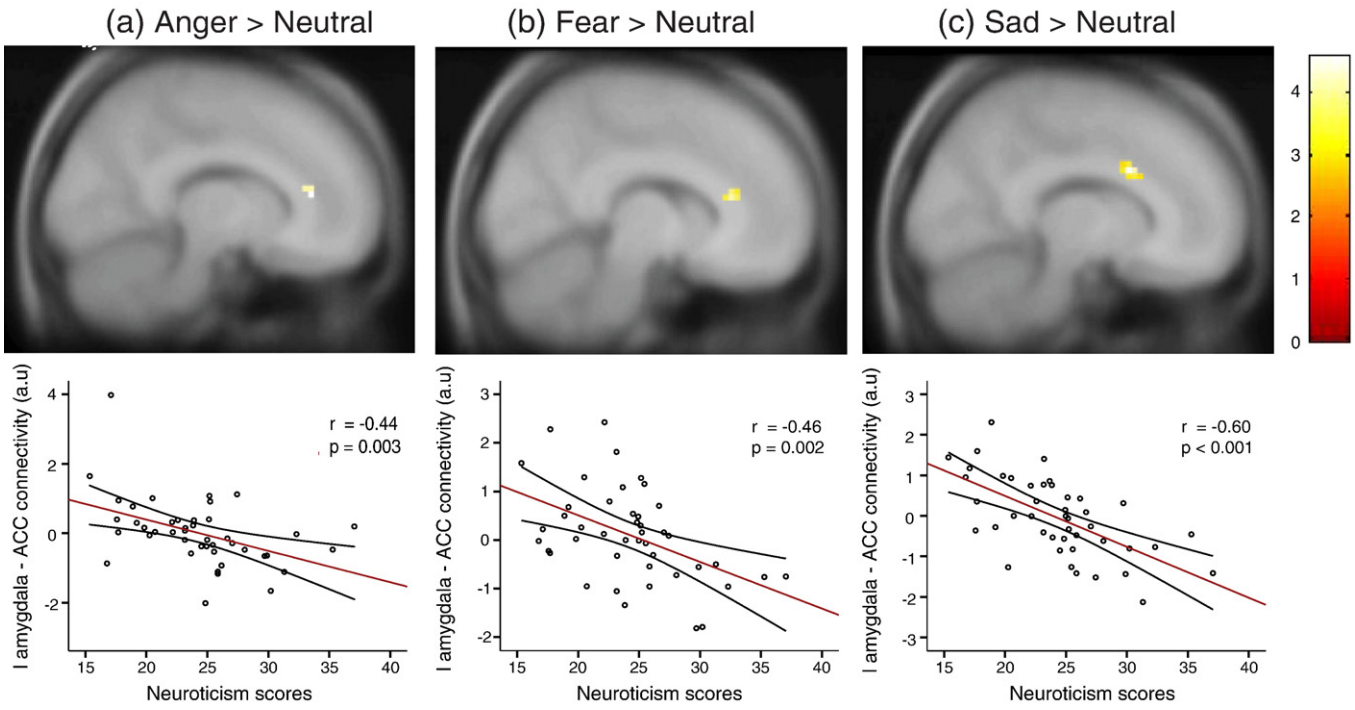

Fig. 1. Brain regions displaying association between neuroticism and functional connectivity with the left amygdala for emotional compared to neutral faces. (a) Right anterior cingulate cortex for angry compared to neutral facial expressions. (b) Right anterior cingulate cortex for fearful compared to neutral facial expressions. (c) Right dorsal anterior cingulate cortex for sad compared to neutral facial expressions. The regression line and 95% confidence intervals are shown. The color bar represents the t-values.

neuroticism related positively to *ruminative* self-consciousness (but not to *reflective* self-consciousness), which is associated with psychological distress (Trapnell and Campbell, 1999). Hence, our results may imply that higher levels of neuroticism are associated with a higher degree of self-referential negative appraisal during the processing of fearful expressions.

Neuroticism modulates amygdala–ACC and amygdala–dmPFC connectivity

We did not observe an effect of neuroticism on activity in the amygdala during processing of negative emotional expressions. However, and crucial to our hypothesis, connectivity analysis showed that neuroticism distinctively modulated connectivity between the 'left amygdala–right ACC' and 'right amygdala–right dmPFC'. We found no significant main effect for these regions, which is broadly in line with previous research, applying the same functional connectivity measure, that showed relatively small effects of functional coupling between the amygdala and these prefrontal regions when processing fearful compared to neutral faces (Williams et al., 2006). Our results suggest that it is worthwhile to account for individual differences in neuroticism when studying functional connectivity related to the processing of negative emotional facial expressions.

We found that connectivity of the left amygdala with the ACC for angry and fearful, and dorsal ACC for sad facial expressions, correlated negatively with neuroticism scores. This indicates that subjects high in neuroticism, while processing negative compared to neutral emotional expression, displayed relatively less amygdala and ACC functional coupling. Numerous studies have shown the importance of amygdala–ACC functional connectivity in the context of emotion processing. For example, Etkin et al. (2006) found that during high conflict trials in an emotional Stroop paradigm the amygdala and the rostral part of the ACC were negatively functionally coupled, suggesting an inhibitory role of the ACC over the amygdala. In line with our findings, a study on trait anxiety (Kienast et al., 2008) showed a negative correlation of this trait with amygdala–ACC connectivity when viewing negative compared to neutral scenes. Moreover, Pezawas et al. (2005), found that carriers of the short allele of the serotonin transporter gene (a polymorphism related to anxiety) showed relatively less functional coupling between the amygdala and ACC when processing angry and fearful faces. These findings suggest that persons high in neuroticism (or other individual differences

Table 3
Association between neuroticism and functional connectivity with the right amygdala for angry, fearful and sad facial expressions.

Contrast	Region	Side	Voxels	*Z* values	*P* values	MNI coordinates		
						x	*y*	*z*
Angry > Neutral								
Positive	**dmPFC**	**R**	**16**	**3.37**	**0.001**	**21**	**42**	**36**
Fear > Neutral								
Positive	**dmPFC***	**R**	**49**	**3.22**	**0.001**	**21**	**42**	**36**
	dmPFC*	**L**	**15**	**3.26**	**0.001**	**−6**	**48**	**36**
Sad > Neutral								
Positive	IFG	L	23	3.69	<0.001	−27	42	3

A priori regions of interest are shown in bold.
* Small volume corrected, FWE $p<0.05$. dmPFC, dorsomedial prefrontal cortex; IFG, inferior frontal gyrus. Other activation at a threshold of $p<0.001$, and minimal 10 contiguous voxels are also shown.

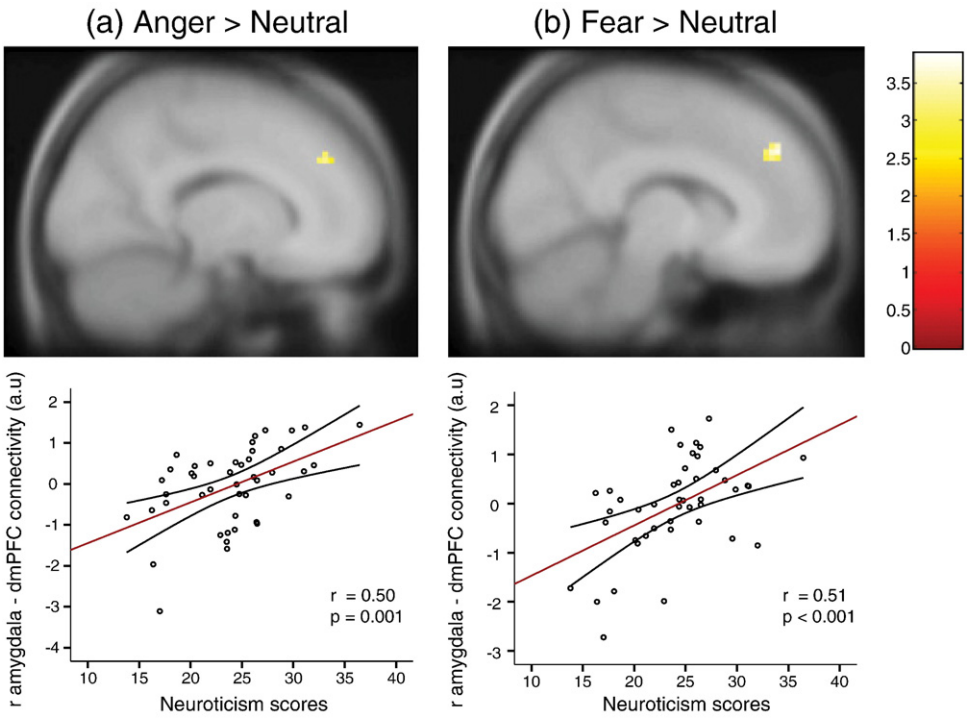

Fig. 2. Brain regions displaying association between neuroticism and functional connectivity with the right amygdala for emotional compared to neutral faces. (a) Right dorsomedial prefrontal cortex for angry compared to neutral facial expressions. (b) Right dorsomedial prefrontal cortex for fearful compared to neutral facial expressions. The regression line and 95% confidence intervals are shown. The color bar represents the t-values.

related to anxiety) display less ACC related inhibitory control over the amygdala. It is of interest that the opposite pattern was found for a personality trait associated with positive affect and approach motivation; the behavioral activation system (BAS) (Passamonti et al., 2008). These authors found that BAS positively predicted amygdala–ACC connectivity for angry compared to neutral faces. The studies mentioned demonstrate the relevance of amygdala–ACC connectivity in emotion processing and emotion regulation. These reports also suggest that individual differences in personality traits modulate amygdala–ACC functional connectivity, and that the direction of this correlation is different for traits related either to negative or positive affect.

In contrast to our results regarding left amygdala–ACC connectivity, we found a positive relation between neuroticism scores and right amygdala–right dmPFC connectivity. Participants with higher scores on neuroticism displayed relatively enhanced connectivity between the right amygdala and right dmPFC during the processing of angry and fearful compared to neutral faces. This finding relates to a study on functional connectivity in generalized social phobia (GSP) while processing self-referential praise and criticism (Blair et al., 2008). Their results showed that patients (compared to healthy control participants) displayed stronger functional connectivity between amygdala and dmPFC for self-referential criticism. The authors argue that this finding may '[…] reflect a negative attitude toward the self, particularly in response to social stimuli […]', and that the mPFC may modulate amygdala engagement to initiate and maintain aspects of GSP (Blair et al., 2008). In keeping with our finding of neuroticism related differences in dmPFC *activity*, our amygdala–dmPFC *connectivity* results also suggest that persons high in neuroticism might demonstrate stronger self-referential processing in response to negative emotional faces.

There is substantial evidence for the role of neuroticism in the development of, for example, anxiety disorders (Bienvenu et al., 2001, 2004). The pattern we found in the relation between functional connectivity and neuroticism might provide insight in the neural basis of neuroticism-linked susceptibility to negative affect, and its associated vulnerability for the development of affective disorders. Taken together, our amygdala-ACC connectivity results indicate that high levels of neuroticism are associated with relatively less inhibitory control over negative facial expressions. Based on dmPFC activity and amygdala–dmPFC connectivity, we suggest that those high in neuroticism demonstrate stronger self-reference to negative facial expressions. Furthermore, it is of interest to note the apparent dissociation between neuroticism and connectivity from the left and the right amygdala. A recent meta-analysis on amygdala function showed evidence for a dissociation between the left and right amygdala regarding temporal dynamics (Sergerie et al., 2008), but did not find evidence for specific interactions between amygdala lateralization and valence or gender (Sergerie et al., 2008) in line with a previous meta-analysis (Baas et al., 2004). Despite this knowledge on amygdala activity much less is known regarding lateralization of amygdala connectivity, and future research should therefore further explore possible lateralization in functional pathways from the amygdala.

Limitations

The interpretation of our connectivity analysis is restricted by the inherent limitations of functional connectivity measures. In our application of psycho–physiological interaction analysis, it is a measure of *functional*, but not *effective* connectivity (Friston et al., 1997). The main difference between these concepts is that the former is a correlation method and its results do not imply a causal relation between regions involved. PPI analysis in and of itself, is therefore insufficient to assess the direction of effects (i.e., reciprocal or unidirectional) between the amygdala and the dmPFC and ACC. This is an important limitation considering, for example, the argued regulatory role of the ACC over the amygdala. Nonetheless, other studies, applying different methodologies, have provided more direct evidence for a top–down regulatory role of the ACC over the amygdala. One tracing study, for example, showed that the ACC has more projections to the amygdala than vice versa (Ghashghaei et al.,

2007). Furthermore, deep brain stimulation experiments in depressed patients suggest that stimulating the ACC—through its connectivity pathways—affects several subcortical regions, including the amygdala (Johansen-Berg et al., 2008; Mayberg et al., 2005).

In this experiment, we found differences in amygdala–prefrontal connectivity associated with neuroticism during an emotion processing task, with only very mild demands on cognitive control over emotional functions. It is therefore very well possible that when engaged in more cognitively demanding tasks, additional amygdala–PFC connectivity pathways strongly involved in inhibitory control, would show associations related to individual differences in personality. For example, some studies have shown subcortical–prefrontal connectivity in relation to functions such as re-appraisal (Banks et al., 2007; Wager et al., 2008), extinction learning (Quirk and Beer, 2006) and response conflict (Etkin et al., 2006). Future research on negative affect should therefore incorporate individual differences in neuroticism in functional connectivity on more challenging emotion regulation tasks. We would argue that in such paradigms individual differences are likely to be associated with, for example, amygdala–ventromedial or ventral lateral prefrontal connectivity.

Conclusion

Our present study indicates that individual differences in neuroticism are of importance in modulating functional connectivity of amygdala and prefrontal regions when processing negative emotional material. Neuroticism was negatively associated with amygdala–ACC, and positively related to amygdala–dmPFC connectivity when processing negative emotional facial expressions. These findings may provide insight into the neural mechanisms associated with susceptibility to negative emotional material, and may be relevant to the development of affective disorders.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2009.08.023.

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