



Association between neuroticism and amygdala responsivity emerges under stressful conditions

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ABSTRACT

Increased amygdala reactivity in response to salient stimuli is seen in patients with affective disorders, in healthy subjects at risk for these disorders, and in stressed individuals, making it a prime target for mechanistic studies into the pathophysiology of affective disorders. However, whereas individual differences in neuroticism are thought to modulate the effect of stress on mental health, the mechanistic link between stress, neuroticism and amygdala responsivity is unknown.

Thus, we studied the relationship between experimentally induced stress, individual differences in neuroticism, and amygdala responsivity. To this end, fearful and happy faces were presented to a large cohort of young, healthy males ($n = 120$) in two separate functional MRI sessions (stress versus control) in a randomized, controlled cross-over design.

We revealed that amygdala reactivity was modulated by an interaction between the factors of stress, neuroticism, and the emotional valence of the facial stimuli. Follow-up analysis showed that neuroticism selectively enhanced amygdala responses to fearful faces in the stress condition.

Thus, we show that stress unmasks an association between neuroticism and amygdala responsivity to potentially threatening stimuli. This effect constitutes a possible mechanistic link within the complex pathophysiology of affective disorders, and our novel approach appears suitable for further studies targeting the underlying mechanisms.

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Introduction

Major depressive disorder and anxiety disorders are the largest contributors to the worldwide rising burden of mental and behavioral disease, according to a recent report from the World Health Organization (Murray et al., 2012). To investigate the underlying neurobiology of these affective disorders and establish potential targets for treatment, functional neuroimaging studies have examined patients and compared them to healthy controls (Drevets et al., 2008; Etkin and Wager, 2007; Hamilton et al., 2012). One consistent finding is that depressed and anxious patients show stronger amygdala responsivity than controls (Drevets et al., 2008; Etkin and Wager, 2007; Hamilton et al., 2012). This enhanced amygdala responsivity is not a fixed trait, but dependent on the current state of the subject (Delaveau et al., 2011; van Wingen

et al., 2011b). For example, a critical precipitating factor for depression is stress, which could potentially be responsible for a shift from vulnerability to maladaptation (Caspi et al., 2003).

Stress can be induced in experimental settings by several different methods and is most often evaluated by changes in heart rate, stress hormone levels and mood (Dedovic et al., 2005; Kirschbaum et al., 1993; Schwabe et al., 2007; van Marle et al., 2009). A state like acute stress, even when mild, triggers a large-scale reallocation of neural processing shifting activity from an executive control network to a salience network including the amygdala, promoting fear and vigilance (Hermans et al., 2011; van Marle et al., 2009). This shift, however, appears to depend on individual trait factors of vulnerability, such as a specific genetic variance or previous exposure to severe stressors (Cousijn et al., 2010; van Wingen et al., 2011a). Thus, to understand the pathophysiology of affective disorders, it is essential to establish the role of these individual differences when examining the effects of acute stress on the brain.

In addition to genetic risk factors, behavioral endophenotypes also cause interindividual variance and represent another step in the

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pathophysiological pathway to psychiatric disease (Caspi et al., 2003; Franke et al., 2009). One of the most important psychological vulnerability factors for affective disorders is neuroticism (Kotov et al., 2010), a personality trait that by itself is characterized by persistent negative affect or dissatisfaction (Costa and McCrae, 1980; McCrae and Costa, 1999). For example, a longitudinal study has shown that neuroticism increases the risk for a first onset of depression with about 30%, and is therefore considered a strong risk factor (Kendler et al., 2006). Studies that have explored the neural correlates of neuroticism are inconclusive with respect to its neural underpinnings. Specifically amygdala responsivity is sometimes reported to be related to neuroticism, where other studies did not replicate this finding (Canli, 2004; Chan et al., 2009; Kennis et al., 2013; Servaas et al., 2013b; Stein et al., 2007). The majority of neuroimaging studies on neuroticism so far, however, did not consider that amygdala responsivity is state dependent. Thus, it is well conceivable that the inconsistency in the literature about neuroticism and amygdala responsivity might be caused by differences in the subject's state across studies. Indeed, neuroticism has been linked to increased stress responsiveness in physiological studies and heightened stress reactivity has even been suggested to constitute a core element of neuroticism (Depue, 2009; Ormel et al., 2013).

In sum, amygdala responsivity as a functional brain endophenotype can be closely linked to affective disorders, but not consistently to psychological vulnerability factors for these disorders, such as neuroticism. This inconsistency could be due to differences in stress levels between imaging studies probing the association between neuroticism and amygdala responsivity. Therefore, we induced a mild state of acute stress, and a normal control state in a fMRI study design that may allow us to uncover individual differences in amygdala responsivity associated with differences in neuroticism.

Material and methods

Participants

We included 120 healthy men (described in Table 1). Candidates for participation were recruited using a local participant database and advertisements. Screening was conducted by self-report questionnaires before participation. Participants were excluded if they reported a history of somatic disease potentially affecting the brain, current or past psychiatric or neurological disorder, medication or illicit drug use during the preceding 6 months, history of substance abuse, current or past alcohol dependence, or MRI contraindications. Women were also excluded because the menstrual cycle is known to influence correlates of the stress response (Fernández et al., 2003; Kirschbaum et al., 1999; Ossewaarde et al., 2011). One subject was excluded from all analyses because of extreme scores on NEO neuroticism, BDI and STAI-t (>3 SD above the average sample score). Due to fMRI data artifacts one other participant was excluded, leaving the total sample at 118 subjects. All participants received 60 Euros reimbursement for full participation.

Table 1
Characteristics of the study population (n = 118).

	Mean (SD)	SD	Range
Mean age during experiment	22.0	2.6	18.1–30.8
Mean NEO-FFI scores			
Neuroticism	28.3 ^a	6.5	14–46
Extraversion	42.6 ^a	6.0	23–54
Openness	40.5 ^a	6.3	28–57
Agreeableness	41.0 ^a	4.1	26–51
Conscientiousness	40.9 ^a	5.2	25–52
Mean STAI-t score	35.4 ^a	7.5	21–58
Mean BDI score	4.3 ^a	4.0	0–17
Mean interval between sessions (days)	12.7	13.0	5–100

^a These scores are within the normal range for a young, healthy male population (Creamer et al., 1995; Hoekstra et al., 1996; Knight, 1984). BDI: Beck Depression Inventory. STAI-T: State-Trait Anxiety Inventory (trait form). NEO-FFI: NEO-Five Factor Inventory.

After complete description of the study to the subjects, written informed consent was obtained. The study was approved by the local ethics committee (CMO Region Arnhem-Nijmegen, the Netherlands).

Procedure

All participants took part in a two session study with a randomized, counterbalanced order of the session type (stressful or control) (Fig. 1). The two sessions were separated by at least five days. The session order was counterbalanced across subjects and not associated with neuroticism scores ($T_{(116)} = 1.404$, $p = 0.163$). On both occasions, participants arrived one hour prior to the MRI session to avoid fluctuations in cortisol levels due to physical activity. During this first hour, participants received information about the study, practiced the tasks they would later have to perform in the scanner, and watched a relaxing nature documentary (Attenborough, 2010). This procedure was extensively standardized in order to create a highly similar experimental setting for all participants. After having watched the documentary, subjects were accompanied to the scanning facility, located in the same laboratory.

To induce a stressful state, highly aversive movie clips were shown in the MRI scanner during one of the sessions (Cousijn et al., 2010; Hermans et al., 2011; van Marle et al., 2009). These clips consisted of scenes of a movie (Noé, 2008) containing extremely aggressive behavior and violence against men and women. As a control condition, neutral, non-arousing scenes of another movie (Fontaine, 2005) were shown in the scanner during a separate session. The stressful and the neutral movie clips were similar in the amount of speech, human (face) presence, luminance, environment, and language. The participants were asked to watch the movie clips from an eye-witness perspective.

Immediately after the movie clip, subjects performed the dynamic facial expression task. This task consisted of passive viewing of photographs of emotionally neutral faces, morphing into two different emotion types: fearful or happy facial expressions (Ekman and Friesen, 1976). The morphing faces were presented in a block design (three blocks of each emotion, 25 s per block, 0.5 s per face, avoiding adjacent blocks of the same emotion), interleaved with blocks of fixation cross for baseline reference purposes (three blocks, 25 s per block). This task has been found to robustly elicit amygdala activation in previous studies (Cousijn et al., 2010; van Marle et al., 2009).

After this task, the subjects completed several other cognitive tasks in the scanner. These will be reported elsewhere. A structural scan was obtained at the end of the stressful session. The total duration of scanning was approximately 105 min per session.

MR data acquisition

MR data of were acquired on a 1.5 T Avanto MR scanner (Siemens, Erlangen, Germany) at the Donders Institute in Nijmegen, the Netherlands. A series of 129 T2*-weighted functional images were acquired using gradient echo-planar imaging (EPI) with the following parameters: 32 oblique transverse slices, voxel size = $3.5 \times 3.3 \times 3.3$ mm, repetition time (TR) = 2.34 s, flip angle $\alpha = 90^\circ$, echo time (TE) = 35 ms. A 3D magnetization-prepared rapid gradient echo (MPRAGE) anatomical T1-weighted image was acquired for normalization purposes (176 slices, 1.0 mm isotropic, TR = 2730 ms, TE = 2.95 ms).

Salivary hormone sampling

During each session, three saliva samples were obtained using saliva collection tubes (Sarstedt, Rommelsdorf, Germany). One sample was taken just before the start of the scanning procedure ($t = -15$ s), while the second sample was taken just after the face morphing experiment ($t = 18$ s) (Fig. 1). Given that diurnal variation in cortisol levels can bias stress-induced cortisol reactions, all testing took place between noon and 6 pm. For reference purposes, participants were asked to

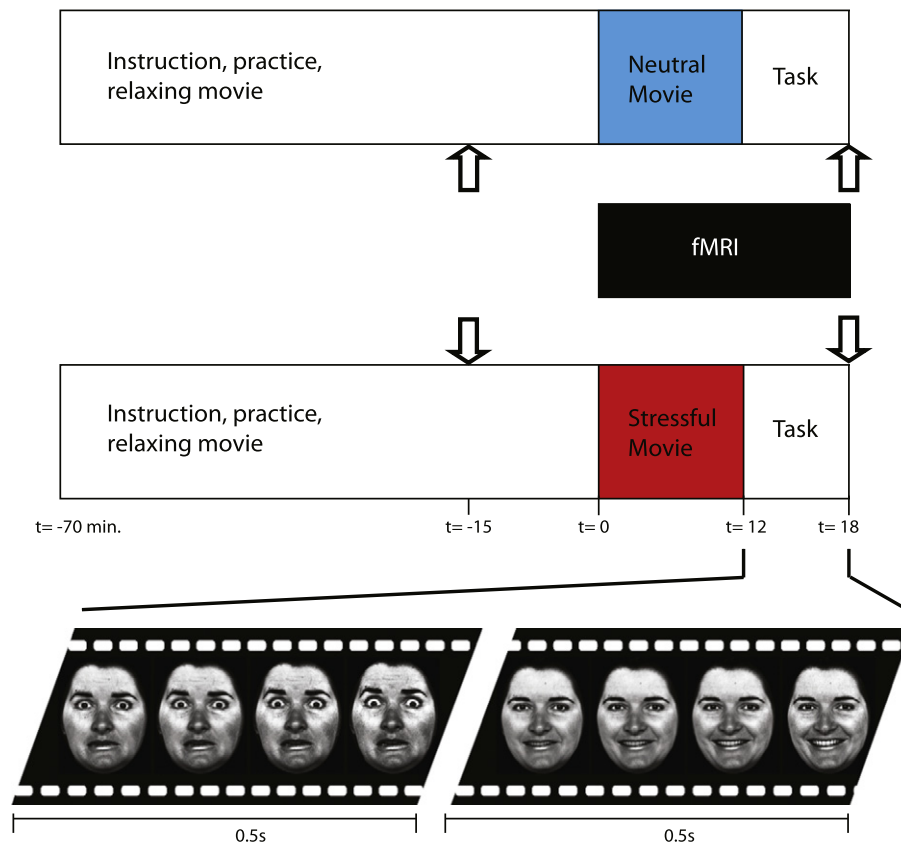


Fig. 1. Overview of the experimental design. Time is indicated in minutes relative to the start of the movie. Subjects entered the scanner after a period of relaxation, after which either the stressful movie or the neutral movie followed. The emotional face processing task was the same between the two conditions. Cortisol and alpha-amylase levels, blood pressure and the PANAS questionnaire were measured just before entering the scanner ($t = -15$) and after the task ($t = 18$), indicated by the arrows. Heart rate was measured continuously during scanning.

collect two extra samples at the same time-of-day on the day before the visits. The average of both samples taken at home was used as baseline for statistical analyses. All samples were stored at -20°C until assaying. Laboratory analyses were performed at the Department of Biopsychology, Technical University of Dresden (Dresden, Germany). Biochemical analysis of free cortisol in saliva was performed using a commercially available chemiluminescence immunoassay (IBL Inc.). Concentration of α -amylase in saliva was measured by an enzyme kinetic method (Rohleder et al., 2004).

Psychophysiological measurements

Before scanning ($t = -15$ min.), resting blood pressure measures of participants were obtained using a standard automatic blood pressure device. Blood pressure was also measured immediately after the task ($t = 18$ min.), using a semi automatic MR-compatible blood pressure device. Heart rate was continuously assessed during scanning by the use of an MR-compatible pulse oximeter.

Questionnaires

Changes in affect during the scanning procedure were assessed using the Positive and Negative Affect Scales (Watson et al., 1988). This was also done at two time points during each test day: at baseline before scanning ($t = -15$ min.), and immediately after the face processing task ($t = 18$ min). In addition, participants completed several self-report questionnaires. The following personality/trait scales were used: the Dutch versions of the trait/state anxiety inventory

(Spielberger et al., 1970), the Beck Depression Inventory (Beck et al., 1961) and the NEO-FFI (McCrae and Costa, 1999).

Data analysis

MR data quality checks were performed by visual inspection of the structural and functional scans, spike checks, signal-to-noise (SNR) ratio plots and assessment of movement. One subject was excluded based on clear signal drop-out due to scanner malfunctioning. One other subject exceeded our initial critical movement threshold of 3.5 mm (1 voxel) by 0.09 mm. We verified the results of this study by performing all analyses without this subject and found no significant differences. Therefore we decided to keep the data of this subject in our analyses.

Functional MRI data were analyzed using SPM8 (UCL, London). For preprocessing, voxel time series were interpolated to correct for non-simultaneous slice acquisition within each volume and were corrected for three-dimensional motion. After realignment and spatial co-registration of both the structural and the functional images, all functional images were normalized into standard stereotactic space (Montreal Neurological Institute [MNI]152 T1-template). Smoothing was performed with a Gaussian kernel of 8 mm full-width at half-maximum. Tissue probability maps were estimated to classify gray matter, white matter and cerebrospinal fluid for each subject and these images were used to create a study specific mean total brain mask (gray + white matter). Subsequently, a General Linear Model was used to characterize voxel-wise signal covariation with task parameters for voxels encompassing the brain mask. The two emotion types (fearful and happy) were modeled separately as boxcar regressors and

convolved with the canonical hemodynamic response function implemented in SPM8. Six realignment parameters were included to model potential movement artifacts. Contrast parameter images were then generated at the single subject level (emotion type compared to fixation). These individual parameter estimate maps were statistically scrutinized at a second level. We used a factorial ANOVA with stress condition and emotion type as within-subject factors, and the individual scores on the NEO-FFI Neuroticism subset of the questionnaire as covariate of interest. This model resulted in statistical parametric maps, which were superimposed upon the mean anatomical image across all subjects for localization purposes. Our statistical threshold for these voxel-wise analyses was set at $p = 0.05$ Family-Wise Error (FWE) corrected for multiple comparisons with Gaussian random field theory as implemented in SPM8.

Given our a priori hypothesis, we then specifically aimed our analysis at the amygdala by applying a small volume correction. For this purpose, we used a predefined anatomical mask of the bilateral amygdala, provided in the Automated Anatomical Labeling (AAL) toolbox in SPM (Tzourio-Mazoyer et al., 2002). Visualizations of correlations were created by superimposing T-contrasts thresholded at $p < 0.001$ uncorrected onto the mean anatomical image across all subjects. The MarsBar SPM toolbox (<http://marsbar.sourceforge.net>) was used to extract the mean responses from individual subjects in post-hoc defined regions of interest (ROIs) for visualization purposes.

All other data (baseline variables, questionnaire scores, heart rate, heart rate variability, blood pressure, cortisol and alpha amylase levels, and PANAS scores) were analyzed in SPSS 19 (IBM) using either dependent or independent T-tests. The stress response was calculated as the difference level between sessions at $t = 18$ s (immediately following the dynamic facial expression task). The heart rate was calculated as 60/mean interbeat interval and heart rate variability as the root mean squares of successive differences between successive interbeat intervals. Offline artifact correction and analysis of the heart rate frequency and variability were done with in-house software.

For correlational analyses non-parametric tests were used (Spearman correlations), since extracted amygdala beta values, stress responses, BDI and STAI questionnaires were not normally distributed. All reported analyses were performed with outliers (>3 standard deviations) removed.

Results

Study population

NEO, STAI and BDI scores for our population were in a normal range (Table 1) (Creamer et al., 1995; Hoekstra et al., 1996; Knight, 1984).

Neuroticism scores did not deviate from normality. In line with previous research, neuroticism scores correlated significantly with both STAI-t ($\rho_{(116)} = 0.548$, $p < 0.001$) and BDI ($\rho_{(116)} = 0.729$, $p < 0.001$) scores and inversely with NEO extraversion scores ($\rho_{(116)} = -0.304$, $p = 0.001$).

Stress induction

Stress induction was successful and replicated the results of previous studies using a similar stress induction procedure (Cousijn et al., 2010; Hermans et al., 2011; van Marle et al., 2009).

Salivary cortisol levels were significantly higher following stress induction as compared to the neutral control induction (stress mean: 101.4% of baseline, control mean: 90.9% of baseline, $SD = 45.7\%$, $T_{(112)} = 1.46$, $p = 0.016$). In this study, no significant effect of stress induction was found on alpha amylase levels ($p = 0.865$).

Systolic blood pressure and diastolic blood pressure both showed a modest but robust effect of stress induction (respectively stress mean: 108.5 mm Hg, control mean: 106.5 mm Hg, $SD = 6.7$, $T_{(116)} = 3.24$, $p = 0.002$; stress mean: 69.9 mm Hg, control mean: 68.4 mm Hg,

$SD = 4.7$, $T_{(117)} = 3.23$, $p = 0.002$). Heart rate increased during the stressful movie (stress mean: 67.1 BPM, control mean: 63.9 BPM, $SD = 7.6$, $T_{(110)} = 4.36$, $p < 0.001$), but not significantly during the following dynamic facial expression task ($p = 0.374$), compared to the movie and task in the control condition. Heart rate variability was decreased during the stressful movie (stress mean: 62.2 ms, control mean: 68.6 ms, $SD = 26.2$, $T_{(109)} = 4.36$, $p = 0.012$), but this difference was not significant during the following task ($p = 0.157$), compared to the movie and task in the control condition. Negative affect increased substantially after stress induction (stress mean: 17.1, control mean: 13.7, $SD = 5.9$, $T_{(116)} = 6.28$, $p < 0.001$) whereas positive affect showed no effect of stress ($p = 0.943$).

In sum, as expected, our measures show that the stressful movie led to significant, but short-lived changes in heart rate, heart rate variability and led to longer lasting increases in blood pressure, cortisol levels and negative affect ratings.

Subsequently, we evaluated possible interactions with trait neuroticism scores. Out of all of the stress measures we assessed, only the relative systolic blood pressure increase correlated with neuroticism ($\rho_{(115)} = 0.248$, $p = 0.007$). None of the other measures significantly interacted with neuroticism, suggesting that there was limited influence of neuroticism on physiological or subjectively reported stress in this healthy population.

fMRI results: main effects of task

The presentation of emotional faces produced activation in a distributed network of brain regions (Table A.1 and Fig. A.1). These brain regions included the bilateral amygdala, the visual processing network, and prefrontal regions. Across the entire sample, there were no regions that showed stronger activation in the stress as compared to the neutral condition. The response to fearful faces compared to happy faces was greater in the bilateral inferior occipital gyrus and fusiform gyrus (face-processing regions), whereas no regions responded more to happy faces (Table A.1). The interaction stress \times emotion type revealed no significant clusters. In sum, viewing emotional faces produced highly significant activation in regions important for emotional perception which was slightly stronger for fearful than happy faces. However, there was no significant effect of stress across all our participants. We therefore focused on identifying individual differences in the effects of stress on the emotional processing network.

fMRI results: correlations with neuroticism

Next we examined correlations between neuroticism and brain responses to happy and fearful faces in the stress and control conditions. Whole brain analysis revealed one significant cluster, located in the precentral gyrus (FWE-corrected $p < 0.01$). Given our a priori hypothesis regarding the relationship between emotional face processing and amygdala activation, we then specifically aimed our analysis at the amygdala. As presented in Table 2, we found an interaction between condition and facial expression in the right amygdala (Fig. 2a). In the left amygdala a similar pattern was found (peak voxel $-22 -4 -26$), but only when lowering the statistical threshold to $p < 0.05$ uncorrected.

When exploring this interaction, we found that amygdala responsivity was enhanced only for fearful faces in the stressful as compared to the neutral condition for the more neurotic individuals (Fig. 2b). To avoid inflated correlations (Vul et al., 2009), no statistics were performed on these extracted data from the region specified in Fig. 2a. Importantly, this correlation was also significant for the extracted beta values of the anatomically defined right amygdala (NEO-FFI Neuroticism score versus stress-related signal change for fearful faces: $\rho_{(116)} = 0.186$, $p = 0.043$).

To test whether amygdala responsivity was really only enhanced for the more neurotic individuals, we divided our sample into a low-neuroticism ($n = 60$) and high-neuroticism group ($n = 58$) using

Table 2
Amygdala responsivity in interaction with neuroticism.

Effect	Region	Hemi-sphere	Cluster size	Peak MNI coordinates			Peak F/T value
				x	y	z	
F-test interaction stress \times emotion \times neuroticism	Precentral gyrus	Right	257	32	−8	32	28.02**
	Amygdala	Right	48	30	2	−22	16.99##
Positive interaction stress \times emotion \times neuroticism (stress(fear > happy) > neutral(fear > happy))	Precentral gyrus	Right	340	32	−8	32	5.29**
	Amygdala	Right	74	30	2	−22	4.12##
Negative interaction stress \times emotion \times neuroticism (stress(fear > happy) < neutral(fear > happy))	None	–	–	–	–	–	–
Interaction stress \times neuroticism for fearful faces (stress(fear) > neutral(fear))	Amygdala	Right	11	30	2	−22	3.47#
Interaction stress \times neuroticism for happy faces (stress(happy) < neutral(happy))	None	–	–	–	–	–	–

MNI, Montreal Neurological Institute. Initial analyses are FWE-corrected: ** $p < 0.01$. All other analyses are small volume corrected with an initial whole brain voxel-wise threshold of $p < .001$ uncorrected for multiple comparisons: # $p < 0.05$, ## $p < 0.01$.

a cut-off neuroticism score of 28 (median split). We then made a new factorial ANOVA with stress and emotional facial expression as within-subject factors, and neuroticism (low versus high) as between-subject factor. Testing the interaction stress \times emotion (stress(fear > happy) > neutral(fear > happy)) in the high neuroticism group lead to a significant cluster in the right amygdala (small volume corrected, $p = 0.012$, peak voxel 32 −4 −20). Testing the opposite interaction (stress(fear > happy) < neutral(fear > happy)) in the low neuroticism group did not lead to any significant effect at the significance level of $p < 0.001$ uncorrected.

This pattern of results was confirmed when comparing the extracted beta values of the anatomically defined right amygdala. One-sample t-tests revealed that only for the highly neurotic individuals there was a trend effect for the stress-related signal change for fearful faces ($T(57) = 1.730$, $p = 0.089$ in the high-neuroticism group versus $T(59) = -1.298$, $p = 0.199$ in the low-neuroticism group).

We also followed up on the cluster that was located in the precentral gyrus by exploring the interaction neuroticism \times condition per facial expression, but this revealed no significant clusters (FWE-corrected $p > 0.2$).

Importantly, we ruled out that the observed association was a side effect of blood pressure differences between high and low neurotic subjects. In a repeated measures analysis on the extracted amygdala responses, adding blood pressure as a covariate did not significantly change the three-way interaction between stress, neuroticism scores and amygdala responses to the fearful faces (interaction condition \times face expression \times neuroticism corrected for systolic blood pressure change: $F_{(115, 1)} = 14.74$, $p < 0.001$).

Discussion

In the present study we demonstrate for the first time in a large, homogeneous sample of healthy males that higher trait neuroticism levels predict a greater response of the amygdala to fearful faces, but that this effect depends on the current stressful state of the individual. These findings indicate enhanced amygdala responsivity in individuals that are at risk for developing stress-related disorders, yet strongly dependent on the stress level of the individual and the valence of the present stimulus.

Our results confirm that trait neuroticism is associated with enhanced amygdala responsivity, as has been shown previously by several studies (Chan et al., 2009; Cunningham et al., 2010; Haas et al., 2007; Harenski et al., 2009), whereas a recent meta-analysis did not find an association between neuroticism and enhanced amygdala response (Servaas et al., 2013b). The authors speculate that it is either the speed of amygdala recovery (and not the initial response of the amygdala) that is responsible for the negativity bias associated with neuroticism or that reduced connectivity between frontal regions and the amygdala is the basis for heightened emotional responses to negative events. On the basis of our findings, we suggest that some studies did not find any differences in amygdala responsivity because stress levels were uncontrolled. Although prefrontal regions such as the anterior cingulate cortex and ventromedial prefrontal cortex are critical regions for the regulation of amygdala responsivity, the precise impact of neuroticism on top-down control of these regions over the amygdala is not yet established (Motzkin et al., 2014; Murray et al., 2012; Ochsner and Gross, 2005). Thus far, some studies found decreased connectivity between these regions in relation with neuroticism, whereas others found no effect or an opposite effect (Adelstein et al., 2011; Cremers

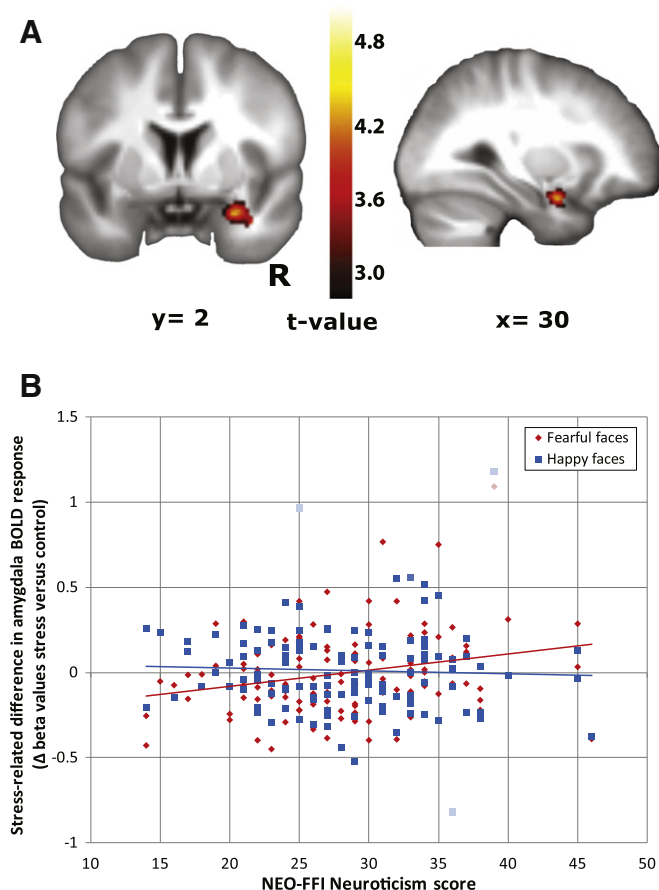


Fig. 2. Positive interaction stress \times emotion type \times neuroticism in the amygdala. (A) T-contrasts are projected on an average normalized T1 over all subjects and masked with an anatomical mask for the bilateral amygdala. (B) Interaction graph with linear trend lines representing the interaction neuroticism \times stress for fearful and happy faces separately. The signal change represents the mean activity in the ROI presented in (A).

et al., 2010; Drevets et al., 2008; Etkin and Wager, 2007; Hamilton et al., 2012; Servaas et al., 2013a). To our knowledge, no other neuroimaging study has been performed in which specific effects of acute stress on emotion processing have been studied in relation to neuroticism.

Remarkably, on a molecular level it has already been suggested that studies investigating the etiology of neuroticism have focused too much on the simple gene effects and thereby overlooked the importance of gene–environment interactions, leading to contradictory results (Canli, 2008; Ebstein, 2006). One possible explanation for these inconsistent genetic findings is that risk allele carriers only develop higher neuroticism levels when confronted with stressors (Canli, 2008) and hence gene by environment interactions are relevant for this vulnerability path. Indeed, longitudinal research has shown that both positive and negative life stressors are important determinants of the individual's neuroticism levels at a given time, emphasizing the essential role of environmental factors when modeling the pathophysiology of neuroticism (Jeronimus et al., 2013). Notably negative stressful events seem to be responsible for the close link between neuroticism and depression, supporting our finding of enhanced amygdala responsivity under stress in healthy subjects with high scores in neuroticism (Jeronimus et al., 2013). In conclusion, findings from the genetic field confirm the importance of environmental stress in the pathophysiology of neurotic traits in the healthy individual.

Importantly, in our study we found no influence of neuroticism on stress-dependent differences in the neural processing of positive faces. It has been hypothesized that in neurotic individuals a heightened emotional reactivity to positive events would co-occur with a heightened reactivity to negative events, addressing a potential positive side of trait neuroticism (Ormel et al., 2013). Our findings, however, suggest that the heightened emotional reactivity in neuroticism is specific for negative stimuli, in line with the findings of most previous studies (Servaas et al., 2013b).

Previous experience with the dynamic facial expression task indicated that stress causes a shift of amygdala function to higher levels of sensitivity and lower levels of specificity in healthy subjects (van Marle et al., 2009). In the current study, however, we did not observe this augmentation and generalization of emotion processing under stressful conditions. A possible explanation for this difference is that the prior study included only female subjects, whereas we included only males. Women are known to have higher neuroticism levels than men (Costa et al., 2001). Moreover, sex differences are known to influence emotion processing and amygdala function, as well as the acute stress response, possibly causing diverging results in males and females (Cahill, 2006; Kudielka and Kirschbaum, 2005).

Several limitations have to be addressed. Firstly, we only included male subjects. Men and women have even been found to show opposite amygdala responses under noradrenergic arousal, underlining that generalization of our results to females is an important subject for future studies (Schwabe et al., 2013).

We argue that our study population reflects a representative variety in neuroticism levels for the healthy population since they were not pre-selected on their (extremes in) neuroticism levels. Nevertheless, there is a possibility that we underestimate the effects of neuroticism by studying a relatively resilient group and that we may have found larger effects when comparing two groups with very high and very low neuroticism levels. In addition, we exposed them to only mild stress, reflected by the fact that neuroticism scores did not substantially influence physiological and behavioral stress measures. Although the nature of the stressor is mild, we do believe that the modest, but robust physiological and behavioral stress responses we see in our large sample enable us to make conclusions based on stress-related changes in this population. However, we acknowledge that we cannot make inferences with certainty to neural consequences of more severe stress.

In summary, we show using a well-controlled fMRI study design that the association between neuroticism and amygdala responsivity is dependent on the stressful state of the individual and selective for fearful

facial stimuli. This effect constitutes one possible neural mechanism for the increase in stress sensitivity and disease risk associated with high neuroticism levels. In addition, it suggests that coping with negative stressful events should constitute an essential part of treatment for people with high neuroticism levels, when preventing progression to disease. Future studies are recommended to consider this important interaction with environmental stressors when further investigating the neurobiology of neuroticism.

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