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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.

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 × 3.3 × 3.3 mm, repetition time (TR) = 2.34 s, flip angle $\alpha = 90°$, 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