Acute Social Stress Increases Amygdala Functional Connectivity with Posterior Cingulate Cortex and Medial Orbitofrontal Cortex

I. M. Veer[1,2], N. Y. Oei[1,3], M. A. van Buchem[1,2], B. M. Elzinga[1,3], and S. A. Rombouts[1,2]
[1]Leiden Institute for Brain and Cognition (LIBC), Leiden, Netherlands, [2]Department of Radiology, Leiden University Medical Center (LUMC), Leiden, Netherlands, [3]Leiden University - Institute of Psychology, Leiden, Netherlands

Introduction

When confronted with a stressful situation, an adaptive stress response is highly beneficial to prepare for appropriate action. One brain area that is affected by stress, is the amygdala (Roozendaal et al., 2009). Alterations in amygdala function after severe stress are thought to play a pivotal role in the pathogenesis of stress-related psychiatric disorders such as posttraumatic stress disorder (Shin et al., 2006). The amygdalae are known to be crucial in mediating stress effects on learning and memory, as they enhance the processing of emotionally salient stimuli and color memories with affective experience (McGaugh et al., 1996). In regulating stress effects, the amygdalae have extensive interplay with other regions, as reflected by the abundant afferent and efferent connections with other brain areas, such as the medial prefrontal cortex, cingulate cortex, hippocampus, brainstem and hypothalamus. Stress is known to affect several of these areas, possibly by influencing the synaptic crosstalk between them (Roozendaal et al., 2009). Acute stress effects on functional connectivity between amygdala and these brain regions have not yet been studied. Therefore, the goal of the current study was to investigate whether amygdala functional connectivity is altered after acute social stress in brain circuits known to be involved in the processing and regulation of emotional experiences.

Methods

Subjects were healthy males (age 23.94 ± 2.78, range 20-30). In a randomized experimental between-subjects design, the stress group (n=18) was exposed to an acute social stress task (Trier Social Stress Test) before going into the MRI scanner, while the control group (n=20) underwent a control procedure. As part of a larger scan procedure, resting-state (RS)-fMRI data were acquired from all 38 subjects 45 minutes after the end of the stress-induction. During RS assessment, subjects had to lie still with their eyes closed in the darkened scanner room and were instructed not to fall asleep. The following scan parameters were used: 160 T_2^*-weighted gradient echo EPI volumes, 38 slices, TR=2.2s, TE=30ms, flip angle=80°, 2.75mm isotropic voxels, 0.25mm slice gap, FOV=220×220mm. A high resolution EPI volume and a T_1-weighted image were acquired for registration and normalization of the RS data. To confirm efficacy of the stress manipulation, cortisol levels in saliva and blood pressure were sampled at multiple time points during the experiment. Data were analyzed using FSL (www.fmrib.ox.ac.uk/fsl). Preprocessing steps included: motion correction, removal of non-brain tissue, spatial filtering with a 6mm FWHM Gaussian kernel, temporal filtering with a band pass of 0.01-0.35Hz, and normalization to the 2mm T_1 MNI standard space template. Amygdala time series were extracted for each subject using a bilateral spherical region of interest in standard space with a 3.5mm radius placed in the middle of the structure. Next, the amygdala signal was regressed against all other voxels using the GLM, with additional regressors included consisting of the global signal, CSF, WM, and six motion parameters. Functional connectivity maps of the amygdala were calculated per subject and subsequently fed into a higher level random effects analysis, testing for between groups differences using a two sample *t*-test. The resulting group difference map was thresholded at $p \leq 0.001$, uncorrected, since analyses were restricted to functional connectivity differences between a priori defined regions of interest, based on known anatomical and functional connections of the amygdala (Stein et al., 2007).

Results

Both cortisol- and blood pressure levels were increased in the stress group, while in the control group these levels showed a steady decrease or remained stable (all $p<.005$), confirming the effectiveness of the stress manipulation. Compared to the control group, the stress group showed increased functional connectivity of the amygdalae with the posterior cingulate cortex (PCC) and medial orbitofrontal cortex (mOFC) (see Figure 1). There were no changes in connectivity between the two groups in any of the other regions of interest. Exploratory, it was investigated whether a higher stress cortisol response was associated with higher connectivity between amygdala and the PCC and mOFC. However, there were no correlations between mean area under the curve cortisol (AUC-increase) values and individual *z*-scores extracted from these regions.

Discussion

After acute social stress, increased amygdala connectivity with the PCC and mOFC, brain regions that are both anatomically connected to the amygdala (Barbas, 2007). The PCC is hypothesized to play a role in the top-down control of amygdala responses (Stein et al., 2007). Increases in connectivity between the amygdala and this region may indicate a higher propensity to downregulate the amygdala after a stressful event. Increased connectivity with the mOFC, on the other hand, might be indicative for augmented emotional stimulus-association learning after stress, consistent with behavioral findings of increased recall of emotional material after a stressful experience (Roozendaal et al., 2008). No association was found with cortisol response, however. In conclusion, the current results show that acute psychosocial stress has prolonged effects on functional connectivity between the amygdala with areas known to be involved in emotion processing and regulation. These findings might relate to the pathophysiology of stress-related psychiatric disorders.

References:

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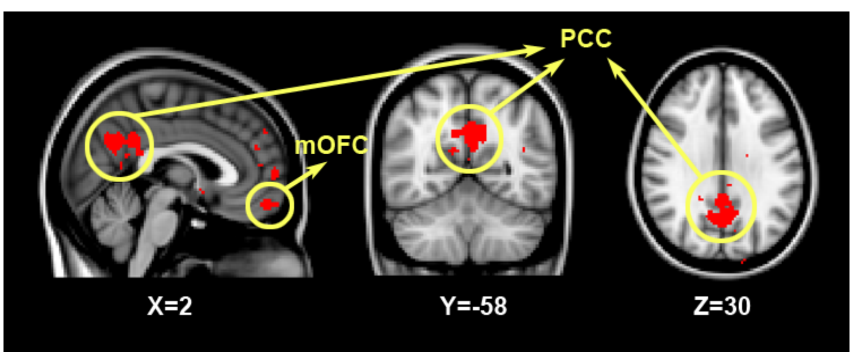

Figure 1 Group differences, stress>controls ($p \leq 0.001$, uncorrected). Shown here is increased connectivity of the amygdala with the PCC and mOFC of the stress group compared to the controls.