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Short Communication

Amygdala volume and hypothalamic-pituitary-adrenal axis reactivity to social stress

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ABSTRACT

The amygdala plays a central role in emotional processing and has an activating influence on the hypothalamic-pituitary-adrenal (HPA) axis. Structural changes in the amygdala have been associated with early adversity and, in principle, may contribute to the later emergence of emotional pathologies by influencing the way that the brain responds to stress provocation. The present study examined the relationship between amygdala volumes and cortisol secretion in response to a social stressor among young adults who were or were not exposed to maternal postnatal depression (PND) early in development (referred to as PND offspring and controls, respectively). Hierarchical Linear Modelling (HLM) revealed that, on a sample-wide level, there was no evidence of a relationship between total amygdala volume, or the volume of the right or left hemisphere amygdala taken separately, and cortisol reactivity. Unexpectedly, for PND offspring, larger right hemisphere amygdala volume was associated with lower cortisol reactivity in response to stress, an effect that was not apparent in control offspring. We conclude that the relationship between amygdala volumes and stress reactivity may not be as clear as previous models suggested.

1. Introduction

Structural alterations in the amygdala have been associated with environmental adversities during early development. Enlarged amygdala volumes have been observed in samples of orphanage reared children, where environments are characterised by neglect (Tottenham et al., 2010); and in the context of chronic maternal depressive symptoms, an association hypothesised to be due to the withdrawn parenting typical of maternal depression (Lupien et al., 2011). In our own research we found that infant attachment insecurity, which may arise as a consequence of depression-related parenting difficulties, predicted greater total amygdala volume (Moutsiana et al., 2015), but we did not find direct effects of maternal depression.

The amygdala plays a central role in emotional processing and responding, and, correspondingly, studies have linked greater amygdala volumes with negative affectivity (Holmes et al., 2012), sensitivity to negative experiences (Barros-Loscertales et al., 2006; Gerritsen et al., 2012), and elevated anxiety (Baur et al., 2012; Tottenham et al., 2010). Such associations may partly arise due to limbic system influences on the HPA axis. The amygdala can have an activating influence on the HPA stress response system (Pruessner et al., 2010; Herman et al., 2005), particularly in relation to psychological stressors (Hand et al., 2002). This effect is predominantly mediated by central or medial amygdaloid nuclei, and is part of a larger system of limbic control (Herman et al., 2005).

Despite the evidence for amygdala modulation of HPA responding, there has been limited direct examination of whether volumetric alterations in amygdala, as identified in some at risk groups of humans, are related to HPA activity, and the available evidence is mixed. A study of 24 unipolar depressed inpatients and 14 healthy controls found no association between amygdala volume and basal cortisol secretion (Kronenberg et al., 2009). A second study of 76 unipolar depressed

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inpatients similarly found no overall evidence that amygdala volume was related to cortisol secretion in response to the combined dexamethasone-corticotrophic releasing hormone test (although there was tentative evidence that greater amygdala volume at baseline was positively associated with normalisation of HPA response to challenge following antidepressant treatment) (Schuhmacher et al., 2012). Further, research which identified larger amygdalae in trauma exposed versus non-exposed individuals also found no association between amygdala volumes and cortisol secretion in response to dexamethasone test (Cacciaglia et al., 2017). Importantly, none of these studies examined HPA activation in response to *psychological* stress, yet activation by the amygdala may be particularly relevant in this context. One study that did investigate amygdala volumes in relation to cortisol output during the Trier Social Stress Test (TSST) found the relationship to be complex: while there was a positive correlation between amygdala volume and cortisol reactivity for adolescents with major depressive disorder (MDD), control participants showed an inverse association (Klimes-Dougan et al., 2014).

Here, we sought to examine cortisol output in response to the TSST in relation to amygdala volumes in a longitudinally studied sample of 58 young adults (Moutsiana et al., 2015), where participants were originally recruited on the basis of the presence or absence of maternal PND. Previous analyses with this sample have found maternal PND to predict elevated offspring basal morning cortisol secretion at 13-years (Halligan et al., 2004), and greater TSST cortisol reactivity at 22-years (Barry et al., 2015). We therefore took account of PND group status and other key factors (gender, overall brain volume, history of depression) in our analyses. We hypothesised that greater amygdala volumes would be associated with heightened reactivity to the TSST. Given the moderation by MDD status reported by Klimes-Dougan et al. (2014) we also tested whether maternal PND related risk of depression similarly moderated effects.

2. Method

The study was approved by the ethics committees of the University of Reading (08/64) and the National Health Service (08H0606115). Participants provided informed consent.

2.1. Participants

Participants were part of a longitudinal study examining the development of 100 children of postnatally depressed and well mothers from infancy. At age 22 years, 38 offspring of PND mothers and 38 controls were available to attend the university for a day of testing, including a structural MRI scan at 11:00 h and the TSST at 15:00 h (for details see Barry et al. (2015)). Of these, 14 participants met exclusion criteria due to medical conditions which made scanning unsafe (diabetes, epilepsy or metal implants). Loss of scanning data also occurred due to significant structural abnormalities (n = 2), poor image resolution (n = 1) and incomplete scanning (n = 1), resulting in a final sample of 58 participants, 27 PND offspring and 31 controls (age M = 22.4 yrs, SD = 0.6; females n = 28). As previously reported, there was evidence of selective attrition, with fewer PND (50.9%) versus control group (75.6%) offspring participating (χ^2 = 5.95, p = 0.015) (Barry et al., 2015).

2.2. TSST

The TSST is a social stress test that reliably stimulates cortisol secretion. It was administered according to standard protocols, combining a 5-min mental arithmetic task and a personally relevant speech delivered to a panel of two unresponsive observers (Kudielka et al., 2007). Saliva smples were collected via passive drooling prior to TSST instructions, immediately post-test and then 10-, 20-, 30- and 45-min post-test. Samples were storeat −20C and later thawed and centrifuged at 3000 rpm for 5 min to produce clear supernatant fractions of low viscosity. Free cortisol was assayed by luminescence immunoassay (Immuno-Biological Laboratories, Hamburg, Germany). Inter- and intra-assay coefficients of variation were <7%.

2.3. MRI data acquisition and processing

High-resolution three-dimensional (3D) T1-weighted images were acquired on a 3-T whole-body scanner (Siemens MAGNETOM Trio) with a 12-channel Head Matrix coil. The MRI parameters of the 3D magnetization-prepared rapid gradient-echo sequence were the following: FOV = 250 × 250 mm^2, TR/TE/TI/FA = 2020 ms/2.52 ms/1.1/9°. Images were acquired with an in-plane spatial resolution of 0.9765 mm and 176 contiguous sagittal 1 mm thick slices, generating nearly isotropic three-dimensional MR data sets for accurate volumetric MR measurements. Data processing was conducted using FMRIB's Software Library (FSL) version 4.1.8 (www.fmrib.ox.ac.uk/fsl). Non-brain tissue was removed from the high resolution anatomical images using BET (Smith, 2002), and remaining voxels summed to give an estimate of the total intracranial volume per participant, which we used as a covariate in analyses. Volume of interest analysis was carried out using individual amygdala masks using the automated FSL tool, FMRIB's Integrated Registration and Segmentation Tool version 1.2. Manual checks identified no segmentation errors. Non-zero voxels/volumes within the masks were calculated in mm^3 using Fslstats (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Fslutils).

2.4. Statistical analysis

Missing cortisol data (6% of samples due to insufficient saliva) were estimated using the SPSS Expectation-Maximization algorithm based on available cortisol samples. Four outliers (±3 *SD* from the mean) were excluded from analyses. Cortisol values were log transformed to reduce skew. The relationships between total amygdala volume, as well as right and left hemisphere amygdala volumes, and cortisol reactivity over the TSST were analysed using separate two-level HLMs conducted in MLwiN 2.28 (http://www.bristol.ac.uk/cmm/software/mlwin/). A level-1 model estimated the intercept and linear and quadratic slopes of change of log transformed cortisol reactivity over the TSST, with times coded as decimals of the actual time in minutes. Level-2 models estimated the variance in the intercept and slopes that were predicted by person-level differences in total and right and left hemisphere amygdala volume separately. The effects of gender and whole brain volume were controlled for due to established relationships with cortisol reactivity and amygdala volume. We also examined whether maternal PND moderated any of the effects of amygdala volume on cortisol reactivity, by including PND group status (present/absent) in level 2 models as a main effect and in interaction with amygdala volumes.

3. Results

Sample characteristics are presented in Table 1. The level-1 model evidenced sufficient variation in cortisol parameters between participants to support modelling as a function of other variables (see Barry et al., 2015).

3.1. Cortisol reactivity and amygdala volumes

Cortisol reactivity over time was modelled as a function of amygdala volume, controlling for the effects of gender and whole brain volume (see Table 2). Neither total amygdala volume, nor right or left hemisphere amygdala volumes predicted significant variance in the intercept or the linear or quadratic slopes for cortisol reactivity over time. As previously reported for these data (Barry et al., 2015), gender predicted a significant amount of the variance in the linear and quadratic slopes of cortisol reactivity over time, such that males showed greater cortisol reactivity than females.