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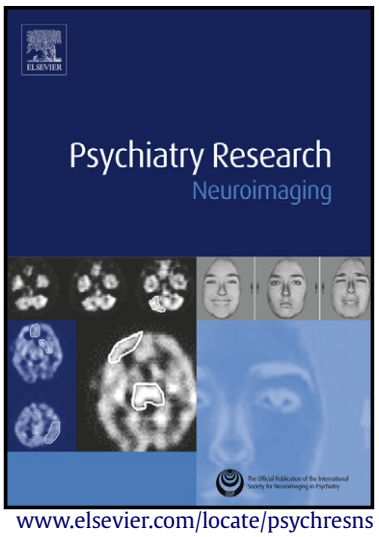

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The relationship between stress, HPA axis functioning and brain structure in first episode psychosis over the first 12 weeks of treatment

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Abstract

Stress and abnormal hypothalamic-pituitary-adrenal axis functioning have been implicated in the early phase of psychosis and may partly explain reported changes in brain structure. This study used magnetic resonance imaging to investigate whether biological measures of stress were related to brain structure at baseline and to structural changes over the first 12 weeks of treatment in first episode patients (*n*=22) compared with matched healthy controls (*n*=22). At baseline, no significant group differences in biological measures of stress, cortical thickness or hippocampal volume were observed, but a significantly stronger relationship between baseline levels of cortisol and smaller white matter volumes of the cuneus and anterior cingulate was found in patients compared with controls. Over the first 12 weeks of treatment, patients showed a significant reduction in thickness of the posterior cingulate compared with controls. Patients also showed a significant positive relationship between baseline cortisol and increases in hippocampal volume over time, suggestive of brain swelling in association with psychotic exacerbation, while no such relationship was observed in controls. The current findings provide some support for the involvement of stress mechanisms in the pathophysiology of early psychosis, but the changes are subtle and warrant further investigation.

Keywords: First episode psychosis; Stress; HPA axis; Cortical thickness; Hippocampal volume; White matter volume

1. Introduction

Although knowledge about the aetiology of structural brain changes in psychotic disorders is still limited (Jacobson et al., 2010; Cullen et al., 2013; Sprooten et al., 2013; Cooper et al., 2014), there is increasing evidence that such changes arise during the onset phase. Over the period of transition, reductions have been observed in grey matter volume of superior and inferior frontal, cingulate, insular, temporal and parietal areas (Pantelis et al., 2003; Sun et al., 2009a; Takahashi et al., 2009b; Takahashi et al., 2009c; Fusar-Poli et al., 2011a; Fusar-Poli et al., 2011b), with similar findings for cortical thickness (Jung et al., 2011; Benetti et al., 2013) and white matter volume (Walterfange et al., 2008; Witthaus et al., 2008; Carletti et al., 2012; Colombo et al., 2012; Ziermans et al., 2012). These changes in brain structure become more extensive throughout the first episode and the later phase of chronic illness (Sun et al., 2009b; Takahashi et al., 2009a; Hulshoff Pol and Kahn, 2008; Bora et al., 2011; Olabi et al., 2011; Asami et al., 2012; Vita et al., 2012). One possible mechanism that may mediate some of these progressive brain changes is elevated stress, associated with the onset and course of illness, marked by hypothalamic-pituitary-adrenal (HPA) axis dysfunction and increased cortisol release (Phillips et al., 2006; Thompson et al., 2007b). Increased levels of cortisol may affect both brain structure and function, leading to increased vulnerability to stress-related psychiatric disorders (Phillips et al., 2006; Frodl and O'Keane, 2013). Indeed, higher cortisol levels in both humans and animals have been associated with hippocampal volume reductions over time, although not consistently (Hibberd et al., 2000; Coe et al., 2003; Brown et al., 2004; Frodl and O'Keane, 2013), and there are possible relations with post-traumatic stress disorder (Bremner, 2006) and early life maltreatment , both being associated with changes in the volume of the hippocampus and prefrontal cortex (Frodl and O'Keane, 2013).

Increased cortisol levels and evidence of reduced negative feedback of the HPA axis, as indexed by the combined dexamethasone corticotrophin releasing hormone (DEX/CRH) test, have been reported in subjects experiencing attenuated psychotic symptoms and those developing frank psychosis (Thompson et al., 2007a), together with increased pituitary and reduced hippocampal volumes (Garner et al., 2005; Aiello et al., 2012), which are not explained by the effects of medication (Pariante et al., 2005). Similar findings have been reported for first degree relatives of individuals with psychosis (Mondelli et al., 2008; Yildirim et al., 2011). The early phase of psychosis can be a very distressing time and may therefore be most vulnerable to the effects of stress. Stress is consequently thought to play an important role in both the development and pathophysiology of psychotic illnesses (Wolkowitz et al., 2001; Phillips et al., 2006; Gunduz-Bruce et al., 2007; Walker et al., 2008; Aiello et al., 2012; Holtzman et al., 2013).

The HPA axis governs the release of glucocorticoids, such as cortisol, in response to stress. With acute stress, dehydroepiandrosterone (DHEA) is co-released and protects against the damaging effects of excessive cortisol (Maninger et al., 2009). Under conditions of chronic stress, however, DHEA concentrations decline while cortisol levels are maintained or even rise (Wolkowitz et al., 2001), resulting in an imbalance of these hormones. Such a hormonal imbalance over longer periods of time could have damaging effects on the body (McEwen, 2000) and may underlie reported changes in brain structure (as reviewed in Holtzman et al., 2013). The hippocampus plays a prominent role in the regulation of the HPA axis and the stress response (Herman et al., 2005), and it has been consistently implicated in the pathophysiology of psychosis (Velakoulis et al., 2001; Velakoulis et al., 2006; Wood et al., 2010), and therefore this study focussed on the effects of biological measures of stress on the whole brain and the hippocampal region in particular.

Reduced hippocampal volume is the most common subcortical finding across the psychosis spectrum. Reduced volumes have been found in some (Witthaus et al., 2009; Witthaus et al., 2010; Wood et al., 2010; Mechelli et al., 2011; Walter et al., 2012) but not all (Phillips et al., 2002; Velakoulis et al., 2006; Buehlmann et al., 2010) studies of individuals at ultra-high risk for psychosis and in first episodes of psychosis (Velakoulis et al., 2006; Witthaus et al., 2009; Buehlmann et al., 2010; Adriano et al., 2012), and in chronic psychotic illness (Velakoulis et al., 2006; Adriano et al., 2012). The effects of stress and cortisol on hippocampal volume in psychosis have revealed conflicting findings. Mondelli et al. (2011, 2010b) reported reduced left hippocampal volumes with increased cortisol levels in first episode psychosis while others (Gunduz-Bruce et al., 2007; Thompson et al., 2007b) failed to find such an association in first episode psychosis and in those at ultra-high risk for psychosis.

The current study investigated the relationship between biological measures of stress and brain structure in first episode patients in comparison to matched healthy controls. Despite indications that complex brain processes depend on networks including white matter interconnections (Kumar and Cook, 2002), and suggestions that changes in both grey and white matter volume are associated with increased levels of perceived stress (Li et al., 2014), existing research has focussed on grey matter structure. Given that the first episode of psychosis is associated with progressive brain changes in frontal, temporal as well as parietal areas, the relationship between biological measures of stress and whole brain measures of cortical thickness and white matter volume was examined. We obtained levels of serum cortisol as part of the dexamethasone suppression test (for more information, see Phassouliotis et al., 2013) and plasma DHEA in its sulphated form (DHEAS), and calculated the ratio between cortisol and DHEAS (for more information, see Garner et al., 2011) . Patients were expected to have reduced cortical thickness, a smaller hippocampus and

reduced white matter volume in frontal, temporal and parietal areas compared with controls. We hypothesised that these reductions would be associated with increased levels of cortisol and a higher cortisol/DHEAS ratio at baseline. We investigated the relationship between baseline neuroendocrine measures and changes in brain structure over the first 12 weeks of treatment: we predicted that progressive brain changes would be associated with higher levels of baseline cortisol in patients compared with controls.

2. Methods

2.1. Participants

Participants comprised 25 antipsychotic -naive or minimally treated (10 days or less treatment with any psychotropic medication) first episode psychosis patients and 26 healthy controls. First episode patients were recruited through the Early Psychosis Prevention and Intervention Centre (EPPIC) at Orygen Youth Health in Melbourne, Australia. Inclusion criteria were based upon the following entry criteria for EPPIC: age 15-25 years, experiencing a first episode of psychosis, and resident in the North/North-Western suburbs or metropolitan Melbourne. Exclusion criteria were IQ<70, organic brain disorder, any significant medical illness, use of steroid medication and shift work. Healthy controls were recruited from similar socio-demographic areas as the patients through advertisements and opportunity sampling. In addition to the exclusion criteria for patients, healthy controls were excluded from the study if they had a current or past history of psychiatric illness or any psychotic illness in the immediate family.

Hormonal contraceptives reduce cortisol release in response to stress (Simunkova et al., 2008; Roche et al., 2013) and lower DHEA(S) excretion (Greco et al., 2007; Bayle et al., 2009), and therefore two patients and four controls were excluded from the analysis. One patient who showed an extreme outlier value for the cortisol/DHEAS ratio (34.5, a level

comparable to that observed in females using contraceptives) was also excluded from the analysis. This resulted in a final sample of 22 patients and 22 controls. DSM-IV diagnosis of psychotic disorder was determined using the Structured Clinical Interview for DSM-IV Axis 1 Disorders (SCID-I) (First et al., 2012), and 13 patients had a diagnosis on the schizophrenia spectrum (9 schizophreniform disorder, 3 schizoaffective disorder, 1 schizophrenia); the remainder had a mixture of diagnoses (2 substance-induced psychotic disorder, 2 psychotic disorder not otherwise specified, 1 delusional disorder, 2 major depressive disorder with psychotic features, 1 bipolar unspecified, 1 bipolar disorder with psychotic features). The median duration of untreated psychosis was 3 weeks (range 0-12 months). Eight (36%) patients were antipsychotic-naive at the time of assessment. The remaining patients had received a median of 5 days (range 2-10) of antipsychotic medication. Their doses of antipsychotic medication were converted to chlorpromazine (CPZ) equivalents using recommended guidelines (Woods, 2003) and, before their assessment, these patients received the equivalent of a median daily dose of 200 mg CPZ (range 50-200mg).

2.2. Procedures

Clinical assessments included the Brief Psychiatric Rating Scale extended version 4 (BPRS) (Faustman, 1994), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989), and the Perceived Stress Scale (PSS) (Cohen et al., 1983) (which was also administered to controls). Blood samples were taken from all participants, and all participants underwent magnetic resonance imaging (MRI). All participants provided written informed consent and the study was approved by the local Research and Ethics Committee.

A subset of participants (12 patients and 15 controls) was followed up after 12 weeks and underwent the same procedure as at baseline. Diagnosis was reassessed with all 12 patients being found to have a schizophrenia spectrum diagnosis (8 schizophreniform

disorder, 2 schizoaffective disorder, 2 schizophrenia). Information regarding antipsychotic medication over the period between the baseline and follow-up assessments was complete for only five patients. One of these patients received placebo while the remaining four patients were on a median CPZ-equivalent daily dose of 200 mg (range 33.50-500 mg) with a cumulative dose of 24,558 mg. Two patients received lithium treatment during the follow-up period: one patient for 6 days (median 500 mg, range 250-1,000 mg) and one patient for 1 day (250 mg).

2.3. Blood sampling

Blood samples (20 ml) were obtained between 09.00 and 10.00 am, before administration of dexamethasone (for more information, see Phassouliotis et al., 2013). Serum cortisol and plasma DHEAS levels were analysed by Gribbles Pathology, Melbourne, Australia, and Melbourne Pathology, Melbourne, Australia, respectively. The cortisol/DHEAS ratio was calculated as cortisol/DHEAS × 100.

2.4. MRI acquisition

T1-weighted volumes were acquired using a 3T Siemens Trio scanner at the Royal Children's Hospital, Melbourne: 124 slices with a voxel size of 1.0×0.5×0.5 mm, repetition time=3.6 s, echo time=9 ms, flip angle=35°, matrix= 56×256, field of view=24 cm.

2.5. Data analysis

Behavioural data were analysed using IBM SPSS Statistics 20 for Windows (IBM Corp., Armonk, NY). MRI scans were automatically processed using FreeSurfer software version 5.0.0 (http://surfer.nmr.mgh.harvard.edu/) and the optimised voxel-based morphometry (VBM8) toolbox (http://dbm.neuro.uni-jena.de/vbm/) in statistical parametric

mapping software (SPM8, Friston, Welcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Mean signal intensity values in the observed clusters were extracted using MARSBAR software (http://marsbar.sourceforge.net). Change in cortical thickness over time was calculated using the automated longitudinal stream in FreeSurfer version 5.1.0 as this option was not functional in the previous version. Coordinates are reported in Talairach space (Talairach and Tournoux, 1988).

Cortical reconstruction and volumetric segmentation of the images were performed using the automated processing pipeline in FreeSurfer (Sled et al., 1998; Fischl and Dale, 2000; Fischl et al., 2002; Fischl et al., 2004; Segonne et al., 2004; Segonne et al., 2007). Cortical areas were parcellated relative to the manually delineated brain atlas (Desikan et al., 2006) using the standard brain segmentation procedure in FreeSurfer (Fischl et al., 2002). Image outputs from each processing stage were carefully inspected and manually corrected as recommended by the software guidelines. Cortical thickness was calculated as the closest distance from the grey matter/white matter boundary to the grey matter/cerebrospinal fluid boundary at each vertex on the tessellated surface (Fischl and Dale, 2000). Hippocampal volumes were extracted and normalised using intracranial volume (Buckner et al., 2004) to control for variation in head size. Total hippocampal volume was calculated by summing the left and right volumes.

Images processed using VBM8 were written out to 1.5×1.5×1.5 mm isotropic voxels in standard anatomical space (Montreal Neurological Institute, http://www.bic.mni.mcgill.ca/brainweb) and segmented into grey matter, white matter and cerebrospinal fluid. Data quality and homogeneity of the sample were checked, and the modulated normalised images were convolved with an 8-mm full-width at half-maximum Gaussian kernel. Employing the General Linear Model, statistical analysis was performed on a voxel-by-voxel basis. Regionally specific between-group differences in the relation of

baseline levels of biological measures of stress with white matter volume were assessed using multiple regressions with gender and age as covariates of no interest. Spatial extent threshold was determined by 10,000 Monte Carlo simulations conducted using 3dClustSim (AFNI, http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html) (Cox, 1996), which yielded a cluster extent of 309 voxels at a voxel-wise threshold of $p<0.002$. Non-stationarity correction was applied to correct for non-uniform smoothness of the data (Worsley et al., 1999; Hayasaka et al., 2004).

Data of participants from whom a baseline and follow-up scan were obtained were automatically processed using the longitudinal stream in FreeSurfer (Reuter et al., 2012). This involved creation of an unbiased within-subject template space and image (Reuter et al., 2010), followed by initialisation of several processing steps, spherical surface maps and parcellations with common information from the within-subject template to increase reliability and statistical power (Reuter et al., 2012).

3. Results

3.1. Baseline characteristics

Characteristics of the baseline sample are presented in Table 1. Patients were significantly younger than the controls, and they perceived situations in their lives as significantly more stressful. As we found previously (Garner et al., 2011), these self-reported levels of stress did not correlate with baseline levels of cortisol but showed a significant negative relationship with DHEAS levels ($r=0.45$, $p<0.05$) and a trend significant relationship with the cortisol/DHEAS ratio in the controls ($r=-0.39$, $p=0.07$) but not the patients. There were no significant differences ($p>0.05$) between patients and controls on measures of cortisol, DHEAS or the cortisol/DHEAS ratio (see Table 1). There were no significant differences in cortical thickness, hippocampal volume or white matter volume

between the groups. No interaction effect between the biological measures of stress and cortical thickness or hippocampal volume was observed. This did not change when the analysis was limited to those patients with a schizophrenia spectrum diagnosis (n=13).

Significant associations were identified between biological measures of stress and white matter volumes. Higher levels of cortisol were associated with smaller white matter volumes in the cuneus ([9 -84 8], k=389) and anterior cingulate ([12 37 -1], k=350) (see Fig. 1a+b). This relationship was significantly stronger in patients than controls, with 42% (cuneus) and 27% (anterior cingulate) of the variance being explained in patients and 21% and 19%, respectively, in controls (see Fig. 1, Supplementary material). Only the cluster in the cuneus survived non-stationarity correction. No significant relationship was found between the cortisol/DHEAS ratio and white matter volume. The addition of self-reported levels of perceived stress as a covariate of no interest did not significantly alter these findings. Duration of untreated psychosis in the patients was not related to the observed signal intensities in the cuneus and anterior cingulate.

3.2. Change over time

Characteristics of the follow-up sample are presented in Table 2. At follow-up, levels of perceived stress did not differ significantly between patients and controls. The percentage change in perceived levels of stress for the patients showed a positive relationship with their percentage change in negative symptoms (r=0.65, p<0.05) but was not related to the percentage change in positive symptoms, the percentage change in levels of cortisol, or the percentage change in the cortisol/DHEAS ratio in this group. Time between scans did not significantly differ between the groups (t(10.12)=1.49, p>0.05) (first episode psychosis mean=105.33, SD=20.43 days; control mean=93.53, SD=8.37 days).

Patients showed a significant (p<0.05 Monte Carlo corrected) reduction in thickness of the left posterior cingulate over time compared with controls (see Fig. 2). Higher cortisol levels at baseline were associated with an increased rate of cortical thinning of left superior frontal and entorhinal cortex, and left posterior cingulate, and thickening of right fusiform and inferior parietal regions in patients compared with controls (see Fig. 2, Supplementary material). However, unlike the overall posterior cingulate reduction, these subtle changes did not survive Monte Carlo correction for multiple comparisons. No relationships were observed between the cortisol/DHEAS ratio and changes in cortical thickness over time.

In patients, higher baseline cortisol levels were associated with a significant increase in hippocampal volume (r=0.66, p<0.05) over time (see Fig. 3). This effect was most prominent in the left hemisphere. No such relationship was observed for controls, and this lack of relationship showed a non-significant trend difference from the relationship observed in the patients (z=1.79, p=0.07, two-tailed).

4. Discussion

The current study observed no significant differences in biological measures of stress, cortical thickness or hippocampal volume between first episode psychosis patients and controls at baseline. No significant difference in the relationship between biological measures of stress and cortical thickness or hippocampal volume was found, but a stronger relationship between baseline levels of cortisol and smaller white matter volumes of the cuneus and anterior cingulate was observed in patients compared with controls. Over the first 12 weeks of treatment, reduced thickness of posterior cingulate and subtle relationships between baseline cortisol and change in cortical thickness over time were observed in patients compared with controls. Patients showed a significant positive relationship between baseline

cortisol and change in hippocampal volume over time, while no such relationship was observed in controls.

Increased cortisol levels have been reported in individuals at risk for psychosis and in those experiencing a first episode (Ryan et al., 2004; Gunduz-Bruce et al., 2007; Aiello et al., 2012). However, we did not detect increased cortisol in our patients, and we were also unable to demonstrate a difference in DHEAS or the cortisol/DHEAS ratio, in line with previous findings (Garner et al., 2011). A subgroup of these patients have previously been shown to exhibit enhanced (as opposed to reduced) HPA regulation and decreased cortisol in a low-dose dexamethasone suppression test (Phassouliotis et al., 2013), suggesting that there may be distinct profiles of HPA axis dysfunction in psychosis that may be differentially responsive to the effects of stress. While in the current study no significant differences were observed in biological measures of stress, patients did report higher levels of perceived stress at baseline, a finding consistent with the stress-vulnerability model for psychosis and the observation of enlarged pituitary immediately preceding psychosis onset and during the early stages of illness (Pariante et al., 2004; Pariante et al., 2005). Interestingly, patients' levels of perceived stress were lower at follow-up and fell within the range of the controls. As this reduction in perceived levels of stress was related to negative symptoms at follow-up but not to biological measures of stress, a response to their first 12 weeks of antipsychotic treatment seems likely, but the finding could also suggest patients' adaptation to the situation or amelioration of psychosis.

The current study showed no significant difference in cortical thickness, hippocampal volume or white matter volume between the patients and controls at baseline, possibly due to the patients in our study showing a wide range of diagnoses, with 13 out of 22 (59%) having a diagnosis on the schizophrenia spectrum. While this wide range of diagnoses is

characteristic of a first episode sample (Rosen et al., 2012), Velakoulis et al. (2006) showed that hippocampal reductions in the first episode were only present in patients with schizophrenia, but not schizophreniform psychosis. Likewise, a meta-analysis by De Peri et al. (2012) showed that at the onset of illness, whole grey matter volume reductions and lateral ventricular enlargement are more prominent in first episode schizophrenia, while white matter volume reductions are more prominent in bipolar disorder. This suggests that the pattern of structural change observed in first episode patients may be different according to psychotic diagnosis. We investigated this by rerunning the analyses including only patients with a schizophrenia spectrum diagnosis. This did not change the findings. While the analysis was likely underpowered (n=13), we recently reported significant grey matter differences by diagnosis in a similar first episode cohort (Ansell et al., 2014), though further study is needed to assess white matter differences.

Higher baseline levels of cortisol were associated with smaller white matter volumes in the cuneus and anterior cingulate. This relationship was significantly stronger for patients than controls. Although baseline levels of cortisol did not significantly differ between patients and controls, the relationship between cortisol and white matter volume differed between groups, suggesting that this difference may be associated with pathology. The group difference was evident at baseline, in contrast to measures of cortical thickness and hippocampal volume. This implies that white matter may be most vulnerable to stress during the early phase of illness. Indeed, white matter volume reductions have been observed in individuals at ultra-high risk for psychosis (Witthaus et al., 2008; Walterfang et al., 2009; Ziermans et al., 2012), with more severe deficits being associated with illness chronicity (Bora et al., 2011). The observed association between white matter volume reduction and increased levels of cortisol is novel; as such, the finding requires replication and further research into its underlying mechanisms. This should be done in combination with measures

of fractional anisotropy and diffusion, which may potentially provide evidence of less efficient transfer and integration of information in relation to structural integrity and stress (Li et al., 2014), particularly in already vulnerable patients.

Our findings of a lack of relationship between biological measures of stress and baseline hippocampal volume are supported by previous research (Gunduz-Bruce et al., 2007; Thompson et al., 2007b). However, the finding of a relationship between higher levels of baseline cortisol and greater increases in hippocampal volume over time is certainly not (Mondelli et al., 2011; Mondelli et al., 2010b). Contrary to the current study, Mondelli et al. (2010b) reported greater reductions in left hippocampal volumes at baseline and 3-month follow-up in relation to increased baseline cortisol levels. Although the sample sizes of both studies are similar, Mondelli and colleagues used salivary cortisol, derived from several measurements during the day, while our study used a single morning blood sample. This is important because the association between higher cortisol levels and smaller hippocampal volumes is most consistently found in studies deploying a diurnal measure of cortisol, rather than a single measure (Frodl and O'Keane, 2013). Moreover, participants in the study of Mondelli and colleagues were significantly older (29.6 ± 1.4 years vs. 21 ± 2.3 years) and had at baseline been exposed to antipsychotic treatment for a longer period of time (50.5 ± 6.5 days vs. 4.9 ± 2.1 days) than the patients in our study. In addition, we corrected for variation in head size, which was not conducted by Mondelli and colleagues. Antipsychotic medication has been shown to normalise HPA axis functioning (Tandon et al., 1991; Walker et al., 2008; Mondelli et al., 2010a) but also to cause brain changes such as increased basal ganglia and ventricular volumes (Navari and Dazzan, 2009; Moncrieff and Leo, 2010), while differences in type of antipsychotic may also be important (Ansell et al., 2014). At baseline, our sample was antipsychotic-naive or minimally treated, and this factor may have contributed to an effect of medication on the change in brain structure over time in the current sample. Two

patients in our study were additionally treated with lithium. Lithium treatment has neuroprotective effects and has been associated with increases in hippocampal volume (Diniz et al., 2013), although not consistently (Velakoulis et al., 2006). As both patients were on lithium for a short period of time and showed a decrease in hippocampal volume over time, the effects of lithium may only be minimal. Nonetheless, there is potential support for increased hippocampal volume over time associated with baseline cortisol. Garver and colleagues (2000) showed that psychotic exacerbation was associated with increases in brain volume which may reflect a 'swelling' caused by processes such as neural inflammation that take place during a period of acute psychosis (Cropley et al., 2013). The hippocampus inhibits stress-induced HPA activation and is densely populated with glucocorticoid receptors (Herman et al., 2005), making it a target region for immunological processes associated with increased levels of cortisol (Cropley et al., 2013).

Reductions in the thickness of the posterior cingulate were observed in the group comparison of change over time and in the relationship between baseline cortisol levels and change in cortical thickness over time in patients relative to controls. The posterior cingulate has previously been shown to be reduced bilaterally before illness onset (Pantelis et al., 2003), in the right hemisphere in first episode patients compared with individuals at ultra-high risk for psychosis (Benetti et al., 2013) and in the right hemisphere of patients with chronic schizophrenia compared with individuals at ultra-high risk for psychosis and controls (Jung et al., 2011). Likewise, grey matter volume reductions in this area have been observed in first episode patients relative to individuals at ultra-high risk for psychosis and controls (Witthaus et al., 2009) and in individuals at ultra-high risk for psychosis who subsequently made a transition to psychosis compared with those who did not Fornito et al., 2008a; Fornito et al., 2008b; Koo et al., 2008; Fornito et al., 2009; Rothlisberger et al., 2012). Other areas that showed a negative relationship between cortisol levels and change in cortical

thickness over time are the left superior frontal and entorhinal cortex, while a positive relationship was observed for the right fusiform and inferior parietal regions. The changes observed in these areas in relationship to baseline cortisol did not survive Monte Carlo correction for multiple comparisons, and therefore suggestions of vulnerability of these areas to the impact of stress are only tentative. Further research on the impact of biological measures of stress on these areas is warranted, particularly in the setting of large longitudinal studies that involve multimodal imaging assessments combining anatomical, functional and molecular data.

There are several limitations to the current study including the small sample size, the heterogeneity of the diagnoses in the patient group, cortisol sampling at one time point as opposed to measurement of the diurnal profile, and the possible effects of treatment on HPA axis functioning and brain structure. In addition, the follow-up period was very short (only 12 weeks) and structural changes detected over this period of time can only be expected to be subtle. In addition, the blood samples were not always obtained on the same day as the brain scan and, while significantly steeper increases in cortisol have been observed after awakening (Wilhelm et al., 2007), information on waking times of the participants was not available.

The findings of the current study suggest a role for cortisol in relation to alterations in brain structure over the first 12 weeks of treatment in patients with first episode psychosis. These effects are subtle, however, and warrant further investigation in conjunction with research into the impact of stress mechanisms on the progression of illness.

Contributors

P.M., L.P., B.G. and S.W. designed the study and wrote the protocol (NHMRC project grant ID: 628884). C.P. and C.M. contributed to the recruitment of participants and data collection, and C.P. conducted blood processing. R.R. and S.W. managed the literature searches and analyses. R.R. undertook the statistical analysis and wrote the first draft of the manuscript. All authors contributed to the interpretation of the findings and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Table 1. Baseline sample

	First episode patients (*n*=22) Mean (SD)	Controls (*n*=22) Mean (SD)	Group comparison
Gender (M:F)	18:4	18:4	*
Age	20.64 (2.38)	22.48 (1.95)	$t(42)=-2.80$, $p=0.008$
BPRS positive symptoms	15.23 (4.19)		
BPRS hostility and suspiciousness	9.36 (1.92)		
SANS total	19.18 (11.98)		
Perceived stress**	32.48 (8.66)	21.82 (6.58)	$t(41)=4.56$, $p<0.001$
Cortisol (nmol/l)	465.82 (136.66)	475.64 (134.02)	$t(42)=-0.24$, $p=0.811$
DHEAS (nmol/l)	9336.36 (2794.31)	9100.00 (3656.44)	$t(42)=0.24$, $p=0.811$
Cortisol/DHEAS ratio	5.38 (2.27)	5.89 (2.40)	$t(42)=-0.73$, $p=0.470$
Corrected left hippocampal volume (mm^3)	4411.71 (551.27)	4449.94 (511.54)	$t(42)=-0.24$, $p=0.813$
Corrected right hippocampal volume (mm^3)	4497.53 (507.81)	4475.90 (521.52)	$t(42)=0.14$, $p=0.890$
Corrected total hippocampal volume (mm^3)	8861.57 (659.64)	9133.26 (631.11)	$t(42)=-1.40$, $p=0.170$

BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms.

* $\chi 2$ test not conducted as expected frequencies <5.

** *n*=21 for patients at baseline as data of one participant were missing

Table 2. Longitudinal sample

	First episode patients (*n*=12) Mean (SD)		Controls (*n*=15) Mean (SD)		Group comparison
	Baseline	Follow up	Baseline	Follow up	
Gender (M:F)	11:1		12:3		*
Age	20.88 (2.31)		22.74 (1.39)		*t*(25)=-2.60, *p*=0.015
BPRS positive symptoms**	15.09 (4.55)	7.0 (3.95)			*t*(10)=5.79, *p*<0.001
BPRS hostility and suspiciousness**	9.09 (2.39)	4.64 (1.69)			*t*(10)=5.27, *p*<0.001
SANS total**	17.36 (10.85)	12.45 (9.05)			*t*(10)=1.23, *p*=0.246
Perceived stress	31.50 (9.44)	25.00 (6.77)	21.87 (5.66)	24.20 (9.58)	Baseline: *t*(25)=3.29, *p*=0.003 Follow-up: *t*(23)=0.23, *p*=0.822

BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms.

* $\chi 2$ test not conducted as expected frequencies <5.

** n=11 as data of one participant at follow-up were missing

Highlights

- Cortisol concentration is associated with brain structure in early psychosis
- Over time, patients showed a reduction in thickness of posterior cingulate compared to controls
- In patients, greater baseline cortisol predicted greater hippocampal volume increase over time

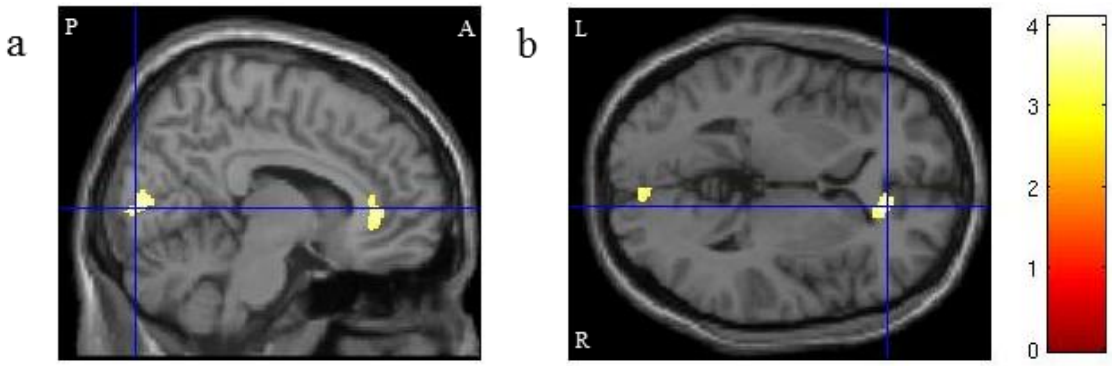

Figure 1

Patients showed a stronger negative relationship between baseline cortisol levels and white matter volume in the cuneus and anterior cingulate than controls. a) Crosshairs at cuneus with peak voxel [9 -84 8]. b) Crosshairs at anterior cingulate with peak voxel [12 37 -1]. Colour bar shows statistical *t* score.

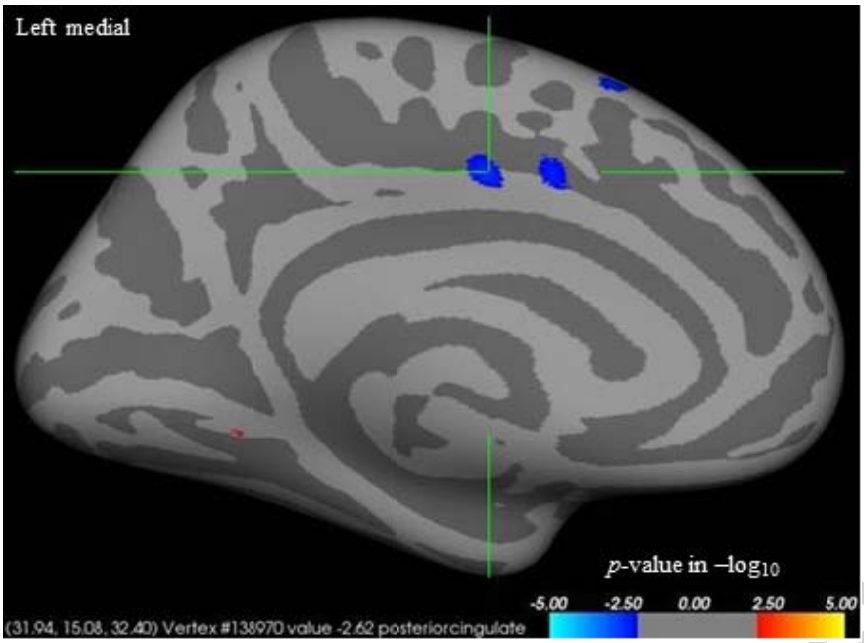

Figure 2

Patients showed a significant (p<0.05 Monte Carlo corrected) reduction in thickness of left posterior cingulate over time compared to controls.

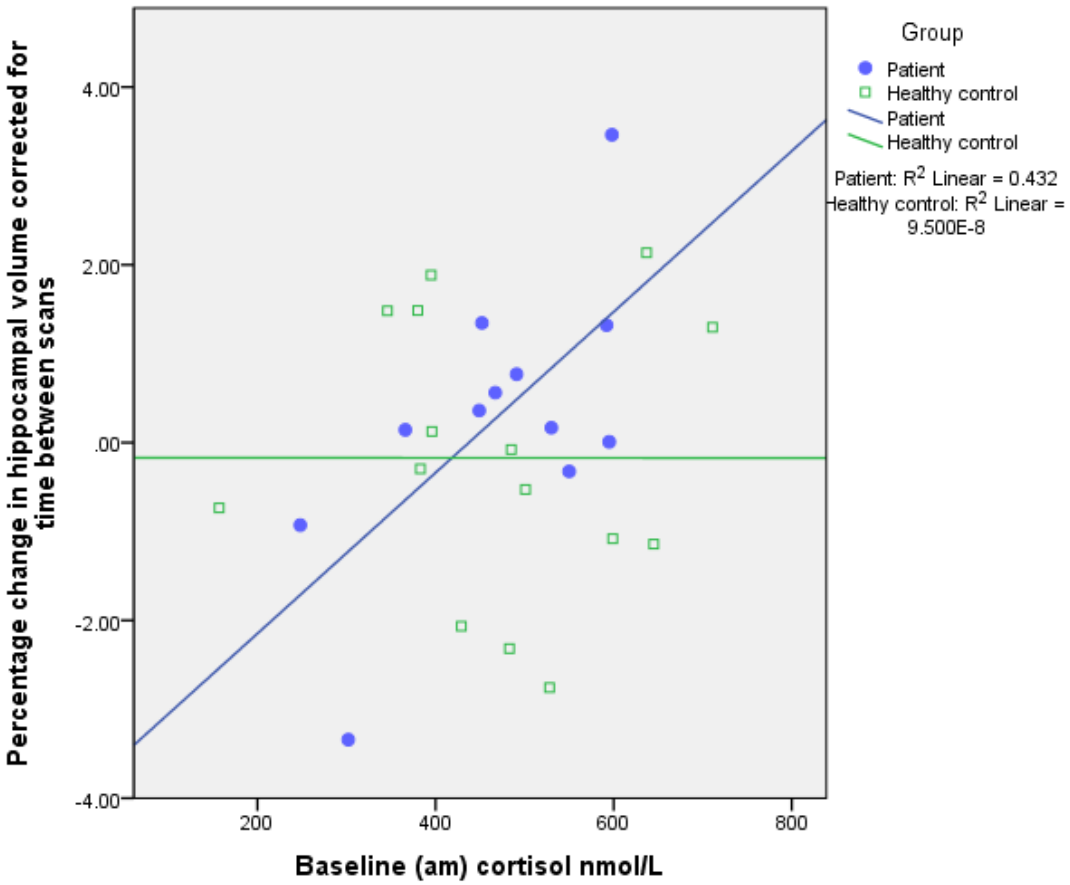

Figure 3

In patients, higher cortisol levels at baseline were associated with a significant increase in hippocampal volume (r=0.66, p<0.05) over time. R^2 = R squared.