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Higher cortisol levels are associated with smaller left hippocampal volume in first-episode psychosis

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Abstract

This study investigated the relationship between cortisol secretion and hippocampal volume in first-episode psychosis and healthy controls. Hippocampal volume was measured by magnetic resonance imaging (MRI) in 24 first-episode psychosis patients and in 18 healthy controls, together with diurnal cortisol levels. Twelve patients received a second MRI scan at 3-month follow-up. Diurnal cortisol levels were inversely correlated with left hippocampal volume in patients, both at baseline and at follow-up, while no correlation was found in controls. Our findings suggest that smaller hippocampal volume in first-episode psychosis can partly be explained by stress-related processes in the brain, as measured by cortisol hyper-secretion.

Keywords

Cortisol; Hippocampus; Psychosis; HPA axis; Schizophrenia; Glucocorticoids

1. Introduction

Previous studies have shown a mainly left-sided smaller hippocampal volume in patients with first-episode psychosis (Steen et al., 2006; Velakoulis et al., 2006). The biological

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Contributors

Valeria Mondelli contributed to study design, recruitment of the subjects, data collection, analysis and interpretation, and writing of the manuscript. Carmine M. Pariante Marta Di Forti, Katherine J. Aitchison, Robin M. Murray and Paola Dazzan, contributed to study design, analysis and interpretation of the data, and writing of the manuscript. Serena Navari, Monica Aas, Alessandro D'Albenzio, Rowena Handley, Nilay Hepgul, Tiago Reis Marques and Heather Taylor contributed to the recruitment of the subjects, collection of the data and writing of the manuscript. Alessandro D'Albenzio contributed to measuring hippocampal volume in all the subjects. Andrew Papadopoulos contributed to the analysis of the cortisol samples, interpretation of the data and writing of the manuscript.

Conflict of interest

All the authors declare that they have no conflicts of interest.

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mechanisms leading to hippocampal volume reduction, however, remain unclear. Stress, the activation of the hypothalamic–pituitary–adrenal (HPA) axis, and raised cortisol levels have been suggested to play a role in the volumetric changes of the hippocampus. Indeed, animal studies have shown that psychosocial and restraint stress, or over-exposure to glucocorticoid hormones, induces reduction in hippocampal neuronal structures such as dendrite atrophy, neuronal death and reduced neurogenesis (Sapolsky et al., 1986; Sousa et al., 1998; Ekstrand et al., 2008). Studies in healthy individuals have shown negative correlations between cortisol levels and hippocampal volume in elderly samples (Ferrari et al., 2000; Lupien et al., 1998), but a lack of correlation in children and young adults (Wiedeayer et al., 2006; Tessner et al., 2007).

Previous studies have described elevated HPA axis activity, including increased cortisol levels, in the acute phases of chronic schizophrenia (Tandon et al., 1991), as well as at the time of the first psychotic episode (Ryan et al., 2004; Pariante et al., 2004; Pariante et al., 2005; Pariante and Lightman, 2008; Pariante, 2008; Mondelli et al., 2009). To our knowledge, there has been only one previous study investigating the relationship between diurnal cortisol levels and hippocampal volume in patients with first-episode schizophrenia: they did not find any significant association (Gunduz-Bruce et al., 2007). However, this study presented the correlations between cortisol and hippocampal volumes by analyzing patients and controls together, using sub-regional hippocampal volumes rather than total hippocampal volume, and without differentiating between right and left hippocampus (Gunduz-Bruce et al., 2007). Therefore, in the present study we aim to investigate the relationship between diurnal cortisol levels and left, right and total hippocampal volume, in a larger sample of patients with first-episode psychosis and in age-matched healthy controls.

2. Methods

Twenty-four patients (18 males and 6 females) presenting with a first-episode of a functional psychosis were recruited from the South London and Maudsley (SLAM) NHS Foundation Trust, as part of the Genetic and Psychosis (GAP) study (Mondelli et al., 2009). Patients with organic psychosis, learning disabilities or requiring a translator because of lack of English fluency were excluded from the study. All subjects underwent a brain MRI scan (see below) as well as saliva samples collection for cortisol measurement (see below). Twelve of the 24 patients also underwent a follow-up head MRI scan 3 months after the first assessment (mean±Standard Error Mean days between baseline and follow-up MRI scan: 122±10). The mean age of the patients was 29.6±1.4 years. Eighteen healthy subjects (age: 27.4±1.0 years; 13 males and 5 females) were also recruited and assessed (brain MRI scan and salivary cortisol). Only eight patients and ten controls in the whole sample were white (British or Caucasian; chi square: 2.1, p=0.2), and this reflects the ethnic distribution of this geographical area of London (Mondelli et al., 2009). 37.5% of patients reported 11 years or less of education, while all the controls reported more than 11 years of education (chi square=8.2, p=0.005). The study was approved by the local Ethical Committee and written informed consent was obtained from all participants.

Validation of clinical diagnosis according to DSM-IV criteria (American Psychiatric Association, 2000)was obtained using the Operational Criteria (OPCRIT) (McGuffin et al., 1991). Seven patients had a diagnosis of schizophrenia, 5 of schizophreniform disorder, 1 of schizoaffective bipolar disorder, and 11 of other psychotic disorders. The mean duration of antipsychotic treatment was 50.5±6.5 days (ranging between 0 and 131 days). All patients were taking atypical antipsychotics, except for 1 on haloperidol and 2 drug naïve.

Saliva samples were collected to measure salivary cortisol using Salivettes (Sarstedt, Leicester, UK) at 0 min after awakening and at 12 pm and 8 pm. Saliva cortisol

concentrations were determined using the “Immulite”— DPC's Immunoassay analyser (www.diagnostics.siemens.com), as previously described (Mondelli et al., 2009). The method had analytical sensitivity of 0.2 nmol/l and inter/intra assay precision (% CV) of less than 10% (cortisol concentration range 5 to 25 nmol/l).

Magnetic resonance imaging scans were acquired with a GE Signa 1.5-T system (GE Medical Systems, Milwaukee), at the Maudsley Hospital, London. The whole brain was scanned with an axial inversion recovery prepared SPGR volume. TR was 11.2 ms, TI was 300 ms, TE was 4.8 ms, and the flip angle was 18°, slice thickness was 1.1 mm. The images were obtained with in plane resolution 1.1mmx1.1 mm, in 280×280 mm field view. Hippocampal volume was measured blind to group status or cortisol levels, by one single rater (AD) using the software program MEASURE (version 0.8, Johns Hopkins University, Baltimore, MD). This image analysis program uses stereologically unbiased estimation of volume. The program and the measurement procedure have been previously described in detail (Schulze et al., 2003).

Data were analyzed using the Statistical Package for Social Sciences, Version 15.0 (SPSS Inc.). Cortisol levels during the day are presented as Area Under the Curve (AUC) of cortisol levels at 0 min after awakening, noon and 8 pm. ANCOVA was used to test differences in hippocampal volume between the groups using cortisol levels as covariate, and to test the interaction between group and cortisol levels (factor by covariate interaction) for left, right and total hippocampal volume. Because the ANCOVA revealed significant group by cortisol levels interactions (see Results), Pearson's correlation was used to test the correlation between cortisol measures and hippocampal volumes separately in patients and controls.

3. Results

The study did not aim to directly compare cortisol levels or hippocampal volumes between patients and controls. Nevertheless, it was reassuring that results were consistent with published studies, with hippocampal volume being smaller in patients than controls (effect size: d=−0.2 for left hippocampus, d=−0.6 for right hippocampus, d=−0.5 for total hippocampus) and cortisol AUCs being larger in patients than controls (effect size d=0.5). The effect sizes did not significantly change after using cortisol levels as covariate (effect size: d=−0.3 for left hippocampus, d=−0.7 for right hippocampus, d=−0.6 for total hippocampus). The ANCOVA analyses showed a significant interaction between group and cortisol levels for the left (F=5.0, df=1,41, p=0.03) and for total hippocampus (F=4.8, df=1,41, p=0.03), and a trend for the right hippocampus (F=3.2, df=1,41, p=0.08). Subsequent analyses of the correlations between hippocampal volumes and cortisol levels were therefore conducted separately in patients and controls.

The results of the correlation analyses are presented in Table 1 and Fig. 1.In first-episode psychosis patients, cortisol levels during the day correlated negatively with baseline left hippocampal volume (r=−0.45), and even more strongly with left hippocampal volume at the 3-month follow-up MRI scan (r=−0.74; see Table 1). We repeated the analyses after excluding one subject who had particularly high cortisol levels, and we still found a significant negative correlation between cortisol levels during the day and the left hippocampal volume (n=23; r=−0.42, p=0.039; see Fig. 1). In contrast, cortisol levels during the day did not correlate with right hippocampal volume, at baseline or follow-up (see Table 1). No significant correlation was found between diurnal cortisol levels and hippocampal volume in healthy controls (see Table 1).

4. Discussion

Our findings show that higher cortisol levels during the day are significantly associated with smaller left hippocampal volume, at baseline and at 3-month follow-up, in first-episode psychosis patients.

The negative correlations between cortisol levels and left hippocampal volume support the hypothesis that the smaller left hippocampal volume described by previous studies in first-episode psychosis (Steen et al., 2006; Velakoulis et al., 2006) is, at least in part, the result of stress-related processes in the brain. Indeed, we and other authors have previously described HPA axis hyperactivity in first-episode psychosis, as indicated by evidence of high cortisol levels and larger pituitary volume (Ryan et al., 2004; Pariante et al., 2004, 2005; Mondelli et al., 2009). Interestingly, smaller left hippocampal volume has been previously reported in relation to childhood trauma both in patients with major depression and patients with post-traumatic stress disorder (Vythilingam et al., 2002; Bremner et al., 1997), also supporting an effect of stress on the left hippocampus.

The lack of significant findings in the only previous study investigating cortisol levels and hippocampal volumes in first-episode schizophrenia may be related to the different methodological approach in that study: using sub-regions rather than whole hippocampal volume, and without distinction, in their correlation analyses, between patients and controls and between left and right hippocampus (Gunduz-Bruce et al., 2007). The study of regional abnormalities of the hippocampal formation in schizophrenia has given conflicting results; some authors have found reduction in anterior hippocampal volume (Szeszko et al., 2003; Pegues et al., 2003) and others in the posterior hippocampal volume (Narr et al., 2002) probably due to differences in anatomic boundaries used in different studies.

Our findings also suggest that stress-related processes might reduce hippocampal volume in patients with psychosis but have not the same effect on the hippocampal volume of healthy controls. Interestingly, a negative correlation between cortisol levels and overall hippocampal volume has been previously reported in elderly, but not in young, healthy subjects (Lupien et al., 1998; Vythilingam et al., 2002; Wiedeayer et al., 2006; Tessner et al., 2007). This difference across age-groups led previous authors to hypothesize a developmental change in the nature of the relation between cortisol levels and hippocampal volume (Tessner et al., 2007). Indeed, the lack of a negative association between diurnal cortisol levels and the volume of the hippocampus in our young healthy control sample is consistent with previous studies (Wiedeayer et al., 2006; Tessner et al., 2007). Theoretically, the negative correlation between cortisol levels and hippocampal volume in our young, age-matched first-episode psychosis patients may suggest an early “aging process” in these patients. Alternatively, exposure to chronic stress and continuous HPA axis hyperactivity due to the psychosis may lead to the hippocampal volume reduction in patients only: studies by us and others have shown HPA axis hyperactivity and increased levels of stress for months before the onset of psychosis (Garner et al., 2005; Walker et al., 2008), perhaps linked to an adverse social environment (Kirkbride et al., 2007; Morgan et al., 2006). A third alternative explanation is that both the cortisol hyper-secretion and the smaller hippocampus are genetically-driven (Mondelli et al., 2008; Goldman et al., 2008). Theoretically, the association between higher cortisol levels and smaller hippocampus could also be one of the mechanisms leading to cognitive deficits in first-episode psychosis, especially for function localised in this brain region (Reichenberg and Harvey, 2007; Reichenberg et al., 2009).

It is important to emphasize that the association between higher cortisol levels and smaller hippocampi does not imply that cortisol is itself the cause of such volumetric changes, but simply that the underlying mechanisms are linked to activation of the stress response, such

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as altered glutamatergic transmission or activation of inflammatory pathways (Stone et al., 2009; Marsland et al., 2008).

In conclusion, our study suggests that stress-related processes, as indicated by high cortisol levels, have a role in determining small hippocampal volume observed in psychosis, already at the first-episode of illness.

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The funding sources had no role in study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

Abbreviations

HPA	hypothalamic–pituitary–adrenal
AUC	area under the curve

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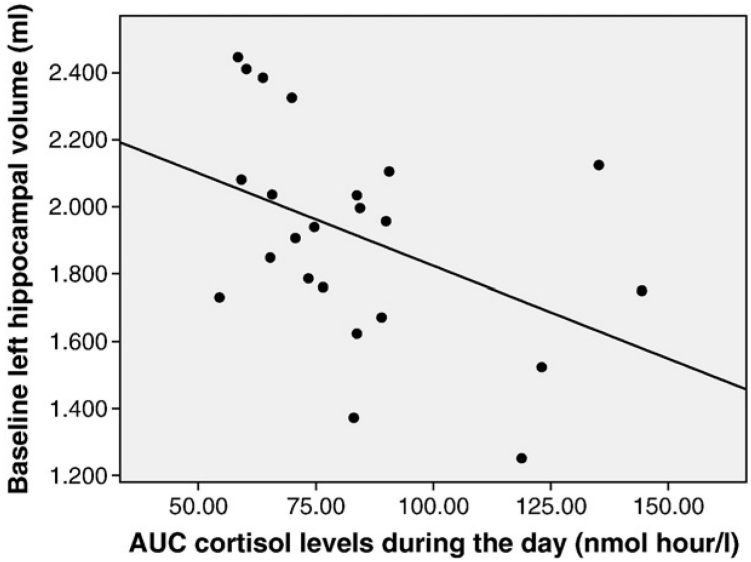

Fig. 1.
Correlation analyses between AUC of diurnal cortisol levels (baseline) and left hippocampal volume (baseline) in first-episode psychosis patients (n=23).

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Table 1

Correlation analyses between AUC of diurnal cortisol levels (baseline) and hippocampal volume (baseline and follow-up) in first-episode psychosis patients and between AUC of diurnal cortisol levels (baseline) and hippocampal volume (baseline) in healthy controls.

	Patients (baseline *n* = 24; follow-up *n* = 12)	**Controls (*n* = 18)**
	Diurnal cortisol	**Diurnal cortisol**
Baseline	$r = -0.36$	$r = 0.40$
Total hippocampal volume	$p = 0.087$	$p = 0.099$
Baseline	$r = -0.45$	$r = 0.38$
Left hippocampal volume	$p = 0.027$	$p = 0.1$
Baseline	$r = -0.19$	$r = 0.38$
Right hippocampal volume	$p = 0.4$	$p = 0.1$
Follow-up	$r = -0.56$	–
Total hippocampal volume	$p = 0.058$	
Follow-up	$r = -0.74$	–
Left hippocampal volume	$p = 0.006$	
Follow-up	$r = -0.32$	–
Right hippocampal volume	$p = 0.3$	