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Hydrocortisone induced regional cerebral activity changes in schizophrenia: a PET scan study

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Abstract

Background. There is evidence that, even during remission, schizophrenia (SZ) patients are especially vulnerable to decompensate under stress, and that they tend to have a high baseline serum cortisol levels. This study was undertaken to determine whether raising serum cortisol by the infusion of hydrocortisone, in the absence of additional psychological stress, would result in different cerebral activity changes in schizophrenic patients compared to normal controls (CON). We were especially interested in cerebral activity in regions such as the medial temporal lobe and hippocampus, since structural abnormalities in these brain regions were frequent in association with schizophrenia.

Methods. Serum cortisol levels were raised, by infusing hydrocortisone, in 8 pairwise-matched SZ patients and 8 CONs. The associated regional cerebral activity changes were analyzed using statistical parametric mapping (SPM).

Results. There was increased regional cerebral activity in response to elevated cortisol in the left hippocampal region in the SZ group, while the controls showed evidence of decreased regional cerebral activity in the same anatomical location. For the rest of the brain regions, cerebral activity increases and decreases, in response to raised serum cortisol, in the SZ followed the same regional pattern as in the control group, but with a smaller overall magnitude of change. The blunted response in SZ was most marked in the regions that showed greatest regional cerebral activity changes in normal subjects.

Conclusion. Patients with schizophrenia showed an abnormal increased regional cerebral activity response to cortisol infusion in the left hippocampal region, and similar but attenuated regional cerebral activity response in other regions, when compared to matched controls.

Keywords: Schizophrenia; Hydrocortisone; Statistical parametric mapping; Stress; Hippocampus; PET

1. Introduction

There is substantial evidence that SZ patients are more vulnerable to stress, even when in remission (see Walker and Diforio, 1997 for a review). The physiologic underpinning of this stress vulnerability remains obscure. There have also been numerous studies showing impairment in the slow (tonic) feedback inhibition of hypothalamic pituitary axis (HPA) activation with chronic elevation of cortisol that comes about with chronic stress (Sapolsky et al., 1985; Sapolsky and Plotsky, 1990; Stein-Behrens et al., 1994). Numerous morphometric studies have shown an inverse relationship between hippocampal region size and raised cortisol levels (Bremner et al., 1995; Sapolsky et al., 1985; Starkman, 1982). It has been reported that on the neuronal level, (3*H*)corticosterone shows the most extensive nuclear binding in certain sectors of the hippocampus (Stumpf et al., 1989), suggesting that circulating levels of glucocorticoid

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Table 1
Demographics of the sample

Group	African–American		Caucasian		Mean age ± SD[a]
	Male	Female	Male	Female	
Schizophrenics	3	1	2	2	39.6 ± 14.2
Controls	3	1	2	2	36.9 ± 11.4

[a] Age was matched within 5 years for each patient-control pair.

hormone could potentially exert a more potent effect on neurons in this brain region. It has been speculated that raised cortisol levels cause neurotoxicity by binding to both the glucocorticoid and the GABA receptors (Stein-Behrens et al., 1994). Previous studies have additionally implicated the hippocampal region in the fast (phasic) feedback central regulation of cortisol physiology (Young et al., 1991). Thus converging lines of evidence point to the hippocampal region as a component of the organism's response to psychological stress as well as subject to physical alterations as a consequence of stress.

In studies of brain structure in schizophrenia, considerable evidence has accumulated for associated abnormalities (generally atrophic) in the hippocampus, parahippocampal region, and associated medial temporal cortical structures (Harrison, 1999).

In view of all the preceding published studies showing evidence of multiple abnormalities in the hippocampal region in SZ, abnormalities in cortisol regulation as outlined above, and also evidence of raised cortisol in SZ (Altamura et al., 1989), we undertook this study with the hypothesis that the hippocampal physiological response to cortisol, in the absence of additional psychological stress, would also be different in schizophrenia patients, when compared to matched normal controls.

2. Methods and materials

2.1. Patient selection

The subjects were 8 schizophrenic patients, who were receiving outpatient treatment at the Schizophrenia Treatment and Research Center at Western Psychiatric Institute and Clinic, and 8 non-psychiatrically ill individuals, living in the same communities as the patients. Each patient was pair-wise matched for gender, race, and age (within 5 years) to a control. The demographic characteristics of the subjects are in Table 1. All subjects were right-handed, had no history of head trauma, and did not meet DSM-III-R criteria for substance abuse (except for smoking) (American Psychiatric Association, 1987) within one month of being studied. A schedule for affective disorders and schizophrenia (SADS) interview was administered to all subjects, by trained interviewers. The data from this interview, and all other sources of information, including medical records, were presented at an ongoing weekly research diagnostic conference, attended by at least two psychiatrists and the interviewer, and consensus DSM-III-R diagnoses were arrived at. This center has had extensive experience using this method. We had used the same technique for a previous paper (Ganguli et al., 1996).

All patients were physically healthy at the time of the study, met criteria for DSM-III-R chronic schizophrenia, and were clinically stable, which was operationally defined as follows:

1. Currently on antipsychotic medication and considered to be good responders to treatment.
2. Judged by their treating clinicians to be in stable remission and exhibiting minimal or no psychotic symptoms.
3. No change had been required in the dosage of antipsychotic medication for at least 3 months prior to enrollment in our study.

Controls were also administered the SADS interview and did not meet the criteria for the lifetime diagnosis of any DSM-III-R Axis 1 disorder, and were physically healthy at the time of the study.

3. PET procedures

Subjects were studied in the supine position using a Seimens ECAT951r/31 PET camera. An intravenous catheter was placed in an antecubital vein for radiopharmaceutical injection. Subjects' heads were immobilized in the head holder using an individually molded thermoplastic facemask and were instructed to remain still and to visually fixate on a target in front of them. The PET gantry was rotated and tilted so that

the lowest imaging plane was parallel to, and approximately 1 cm above the canthomeatal line. Using a system of 3 lasers, the face was marked with washable ink in 5 places to allow checks for movement during the study. A ten minute transmission scan using 3 rotating 'pin' sources of $^{68}Ge/^{68}Ga$ for the purpose of calculating attenuation factors preceded the blood flow studies.

Cerebral blood flow (CBF) was measured following an injection of 50 mCi of $[^{15}O]$–H_2O in approximately 5–7 ml of saline. Twenty seconds after injection emission scanning was initiated with a 60 s image and reconstructed to approximately 8 mm full-width half-maximum to create the qualitative map of cerebral blood flow.

Hydrocortisone infusion was closely modeled on the approach previously taken by Young et al. (1991), and was designed to raise the serum cortisol into the upper end of the physiological range. The infusion rate of hydrocortisone in saline was adjusted for each subject to provide a steady 5 $\mu g\ kg^{-1}\ min^{-1}$, and lasted for 1 h. The intravenous line was placed half an hour prior to the first block of 2 PET scans during which normal saline, without cortisol, was infused at the same rate which would be employed for the cortisol infusion. After the first block of 2 PET scans, the infusion of the cortisol was timed to start at 8:00 AM and acquisition of the second block of 2 PET scans was started 30 min later.

4. PET image analyses

PET images were analyzed using the statistical parametric mapping (Friston et al., 1991; Poline et al., 1995) method. Images were registered using an algorithm to correct for head movements (Woods et al., 1992). Images for each subject were then transformed into standard stereotactic co-ordinates, by identifying the inter-commissural line and then rotating the image to match this axis, and stretching the image into the atlas co-ordinates (Talairach and Tournaux, 1988). All data were then normalized to an average value of 50 ml/100 ml/min using ANCOVA to control for global differences in blood flow within and between subjects. A gaussian filter (12 mm full-width half-maximum) was then applied to the image data to reduce high frequency noise and reduce the effect of individual differences in gyral anatomy. Finally, to contrast regional cerebral activity pre- and post-cortisol, a *t*-statistic was computed on a pixel-by-pixel basis, using the mean regional cerebral activity value for scans pre-and post-cortisol for a given group of subjects, together with the associated error variance. The resulting pixel-by-pixel distribution of *t*-statistics was then transformed to *Z*-scores to allow the associated display to be independent of the degrees of freedom. The critical value for alpha for these comparisons was set at $p < 0.001$ ($Z = 3.29$). This value was chosen as it is a standard conservative threshold for functional activation studies that has provided reliable protection against type 1 error in studies at our center.

5. Group comparisons

The distribution of significant pixels for each group (patients and controls) was displayed as both surface and look through projection images to provide a qualitative comparison of regional cerebral activity changes (increases and decreases) associated with intravenous cortisol in the two groups. Referring the pixel locations exceeding threshold to the Tailarach atlas co-ordinates (Talairach and Tournaux, 1988) mapped by SPM identified anatomical regions in which significant activation was found. Regions were not considered activated unless pixels exceeded threshold in more than one contiguous slice. Anatomical regions thus identified were then compared between patients and controls. To test our hypothesis that there is an abnormal response to cortisol challenge in schizophrenia, a comparison of the magnitude of regional cerebral activity changes in each of the two groups was done comparing voxel-by-voxel, and a fixed effects analysis was used as is standard in SPM 95. The critical value for alpha for these comparisons was set at $p < .001$ for a two-tailed test ($Z = 3.29$).

6. Results

Both normal controls and patients showed regions of significant increase and regions of significant decrease in regional cerebral activity associated with cortisol challenge. These regions are shown as

orthogonal projection views in Fig. 1. Regions showing significant regional cerebral activity decreases are given in Table 2, while regions showing significant regional cerebral activity increases are given in Table 3.

6.1. Controls

When the areas of regional cerebral flow changes in the controls is divided into cortical and sub-cortical regions, the following patterns emerge.

Cortical region: On cortisol infusion, controls showed decreased regional cerebral activity in the bilateral inferior temporal, left mid-temporal, right inferior parietal and bilateral inferior frontal and bilateral orbital regions. They showed increased regional cerebral activity in the right hippocampus, left parietal fusiform cortex, right anterior cingulate gyrus and extra-striate visual cortex (lingual gyrus and right fusiform gyrus).

Sub-cortical region: Controls showed increased regional cerebral activity on cortisol infusion in the thalamus, right putamen, and fusiform gyrus regions. No region in the sub-cortical region showed a decrease on cortisol challenge in the control group.

6.2. Patients

Patients generally showed changes in the same direction as in the controls but of a smaller magnitude. Statistically, the only significant differences were a lesser magnitude of decrease in regional cerebral activity in response to cortisol in patients as compared to controls in the left inferior temporal region and a lesser magnitude of increase, (i.e. an attenuated response) in regional cerebral activity in right thalamus, putamen and fusiform gyrus bilaterally.

The one region in which cortisol had the opposite effect in patients as compared to the controls was in the left hippocampus, in which regional cerebral activity increased in patients but decreased in controls.

7. Discussion

The results of this study provide preliminary evidence for a differential response of the hippocampus in the SZ group to cortisol when administered in the physiological range. Overall, the pattern of blood flow changes to cortisol was the same in schizophrenia patients and the controls, with the regional cerebral activity changes being attenuated in the patient group. This blunted response in the schizophrenia patient group was most marked in regions that showed increased regional cerebral flow in normal subjects in response to cortisol, and included the dorsal thalamus and the caudate-putamen. However, one region, the left hippocampus, showed preliminary evidence for increased activity after cortisol challenge in the schizophrenia group, but not the controls. This difference however was not of statistical significance.

As already mentioned in the introduction, hippocampus seems to be affected in most conditions involving chronic stress. Besides numerous studies showing an inverse relationship to stressful conditions and the hippocampal size, there is additional evidence that the hippocampal size seems to be decreased even in those situations where high cortisol levels are present in the absence of any evident stressor, for example, patients with Cushings syndrome (Starkman et al., 1992). While our study did not find a statistically significant difference in regional cerebral activity on cortisol challenge, there was never the less preliminary evidence of increased activity in this region.

The strengths of this study include the care taken in matching the patients and controls and standardization of the cortisol infusion. The weakness include the small number of subjects studied, the medication status of the patient group (they were all on antipsychotics, the details of which were not available) and the fact that the scans took place in a fixed order, in which the two cortisol scans always followed the two baseline scans and were not counter balanced. Additional possible limitations may be the lack of matching for socio-economic status, lack of inclusion of tobacco in the exclusion criteria for substance abuse. Also, differences in the striatal regional cerebral activity response after cortisol challenge observed in the current study may reflect direct effects of antipsychotic drugs on the physiology of this region. This is however less likely in the case of the thalamus or the hippocampus.

It should be pointed out that the experience of undergoing the PET scan was probably stressful in and of itself. The physiological effects of this stress may also have been different in patients versus

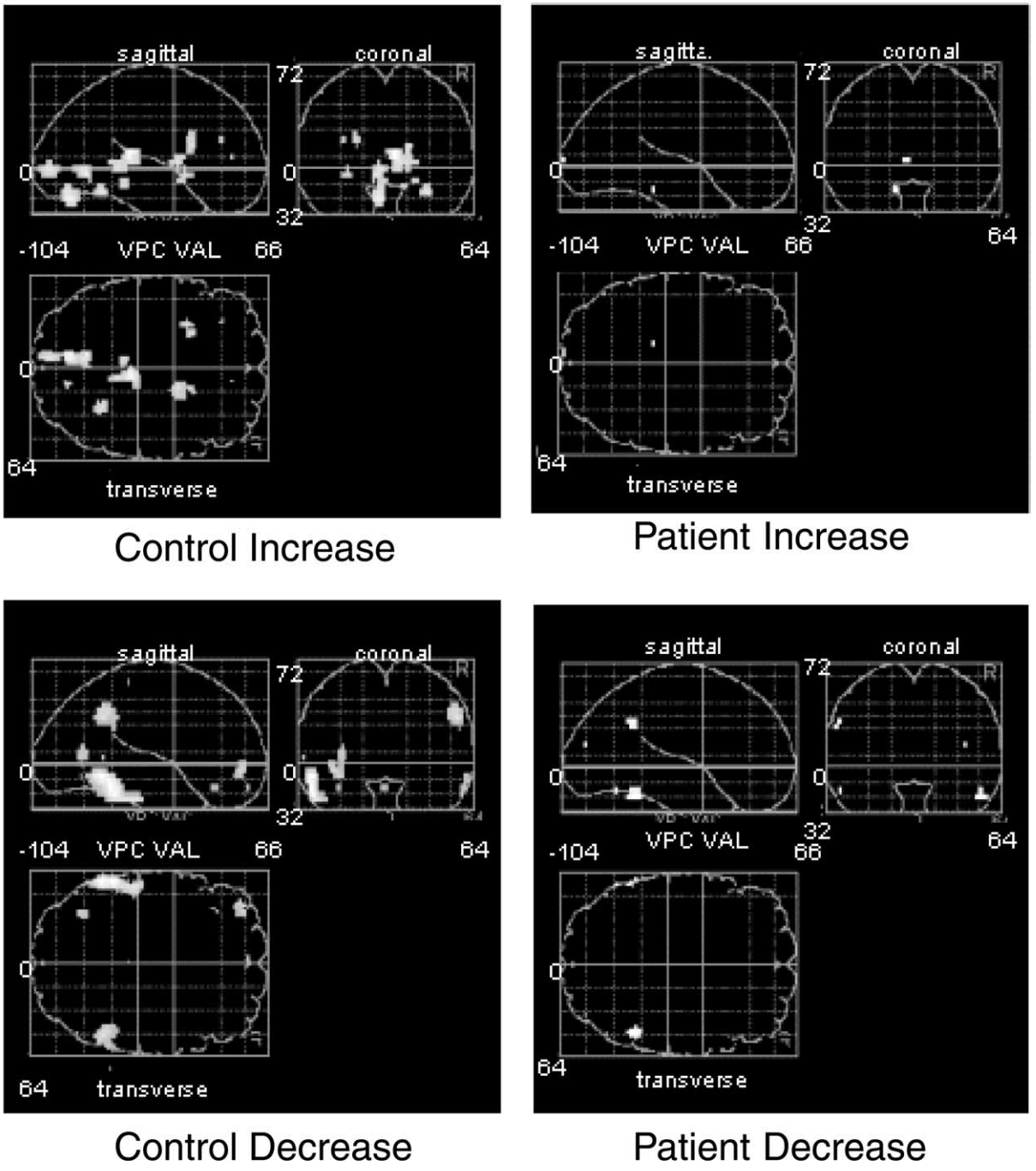

Fig. 1. Orthogonal projections (SPM 95) showing pixels in which changes in regional cerebral activity exceeded the threshold (two tailed alpha $p < .001$, $Z = 3.29$) in at least two contiguous pixels.

Table 2
Areas of *decreased* regional cerebral activity after i.v. Hydrocortisone (Talairach co-ordinates in parentheses)

Region	Bilateral inferior temporal gyrus	Right inferior parietal gyrus	Left inferior and orbital frontal gyri	Left middle temporal gyrus	Left inferior parietal cortex	Right middle temporal gyrus
Patients	(L) $Z = 3.34$ (−54, −64, −16) (R) $Z = 3.34$ (58, −50, −20)	–	–	–	$Z = 3.57$ (−56, −52, 32)	$Z = 3.34$ (36, −86, 16)
Controls	(L) $Z = 4.96$ (54, −54, −8) (R) $Z = 3.67$ (54, −50, −20)	$Z = 4.15$ (50, −52, 32)	$Z = 4.10$ (−38, 48, −4)	$Z = 3.79$ (−32, −66, 4)	–	$Z = 3.58$ (58, −50, −8)

Table 3
Areas of *increased* regional cerebral activity after i.v. Hydrocortisone (Talairach co-ordinates in parentheses)

Region	Right thalamus	Right striatum	Left striatum	Right hippocampus	Left hippocampus	Right fusiform gyrus	Left cuneus
Patients	–	–	–	–	$Z = 3.46$ (−14, −36, −16)	–	$Z = 3.31$ (−4, −100, 4)
Controls	$Z = 4.53$ (6, −32, 12)	$Z = 3.85$ (6, 12, 16)	$Z = 3.70$ (−30, 8, −4)	$Z = 3.80$ (8, −40, 4)	–	$Z = 3.54$ (−12, −78, 12)	$Z = 4.03$ (−6, −92, 0)

controls. However, the aim of our study was to compare the effects on cerebral activity of a further increase in the cortisol associated with its infusion. Since the stress of the PET scanning, insertion of the IV line 30 min prior to the first scan etc. would have presumably exerted its effect prior to the first 2 (baseline scans), we believe that our results are indeed a reflection of the effects associated with the change in serum cortisol resulting from the infusion.

To the best of our knowledge, this would be the first time that the effect of cortisol on schizophrenia patients, in the absence of additional psychological stress, has been studied. How the differences in hippocampal response in remitted schizophrenia patients relate to the susceptibility to stress remains to be examined, but our preliminary findings of an abnormal response in the hippocampal region, in schizophrenia patients is very intriguing. Larger studies, with better controls are needed to answer questions raised by this preliminary study.

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