

Immediate effects of risperidone on cortico–striato–thalamic loops and the hippocampus

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Background Functional imaging studies indicate that delusions and hallucinations in schizophrenia are associated with overactivity of the left hippocampus and ventral striatum. Hippocampal neuronal firing modulates feedback to cortex via cortico–striato–thalamic loops.

Aims To test the hypothesis that recovery from psychosis is associated with decrease in activity in cortico–striato–thalamic circuits, and, furthermore, that reduction in hippocampal activity predicts the degree of alleviation of delusions and hallucinations.

Method Positron emission tomography (PET) was used to measure the effects of the atypical antipsychotic, risperidone, on glucose metabolism in eight first-episode schizophrenia patients.

Results A single dose of risperidone produced decreases in metabolism in ventral striatum, thalamus and frontal cortex. The magnitude of decreases in left hippocampus predicted subsequent reduction in delusions and hallucinations. After six weeks' treatment with risperidone, the decreases in frontal metabolism were more extensive.

Conclusions The mechanism of antipsychotic action of risperidone entails reduction of hippocampal activity together with reduced feedback via cortico–striato–thalamic loops.

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Several recent functional imaging studies have reported that overactivity of the ventral striatum and medial left temporal structures, especially the hippocampus and parahippocampal gyrus, is associated with the occurrence of delusions and/or hallucinations (Liddle *et al*, 1992; Silbersweig *et al*, 1995). On the basis of these observations, we propose a hypothesis regarding the mechanism by which delusions and hallucinations arise. This hypothesis predicts changes in cerebral activity in the frontal cortex, basal ganglia, thalamus and hippocampus during antipsychotic treatment.

Hypothesis

The ventral striatum is a cardinal component of the cortico–striato–thalamo–cortical feedback loops (Fig. 1) that play a part in regulating frontal cortical function (Alexander & Crutcher, 1990). Loops with

an even number of inhibitory neurons provide positive feedback that can enhance concurrent cortical activity, while those with an odd number provide negative feedback. Dopaminergic fibres from the ventral tegmental area modulate these feedback loops. The evidence indicates that increased dopaminergic activity promotes transmission in the positive feedback loops while diminishing transmission via the negative feedback loops (Alexander & Crutcher, 1990). The net effect of excess dopamine activity is likely to be enhanced positive feedback to the cortex, reinforcing concurrent cortical activity.

In addition, hippocampal activity regulates neural transmission through the ventral striatum. Single-cell recordings of electrical activity in the striatal neurons in animals demonstrate that input from the hippocampus can exert a gating action on neurotransmission in the cortico–striato–thalamo–cortical feedback loops (Grace *et al*, 1998). Firing of neurons in the prefrontal cortex results in transmission of action potentials via the striatum only when there is concurrent input to the striatum from the hippocampus.

Because the hippocampus receives input from many cerebral areas, its connections allow it to integrate information from diverse sources (Rolls, 1989). One function of the hippocampus is the recognition of context for an event (Chun & Phelps,

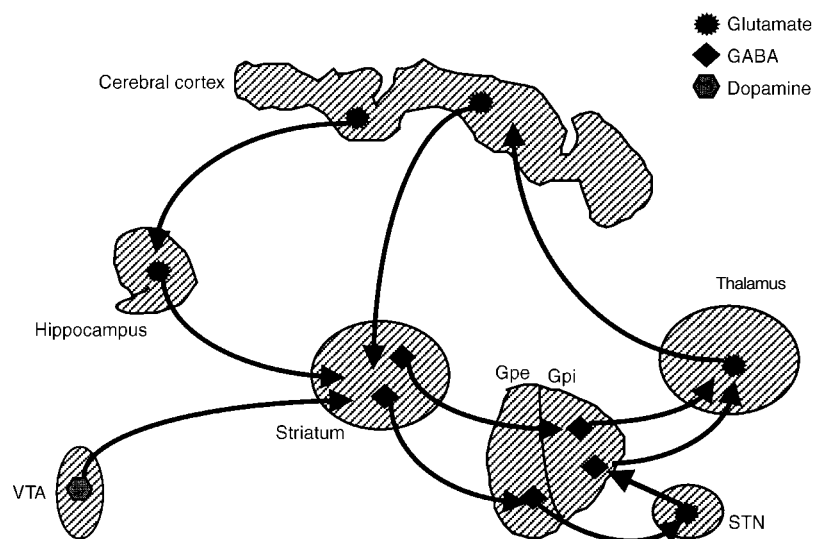


Fig. 1 Cortico–striato–thalamo–cortical circuits. GABA, γ -aminobutyric acid; VTA, ventral tegmental area; Gpe, globus pallidum externa; Gpi, globus pallidum interna; STN, sub-thalamic nucleus.

1999). Together with the evidence that the hippocampus can gate the cortico–striato–thalamo–cortical feedback loops, this observation suggests that firing of hippocampal neurons during a mental event that occurs in context would reinforce the pattern of cerebral activity, representing that mental event more strongly than if the event had occurred in isolation. Such a process might account for the cardinal role of the hippocampus in new memories (Rolls, 1989). When an idea is novel, it is evaluated by reference to past and present contextual information. Eventually, once its neural pattern has been sufficiently reinforced, it can be invoked without the need for contextual support, and it becomes an item of semantic memory, accepted without reference to the context in which it first occurred.

If hippocampal neurons were to fire inappropriately because of a pathological condition, the consequence might be reinforcement of a pattern of cerebral activity representing a contextually uncorroborated mental event. In this case, the idea might be treated as if it were an accepted fact, resulting in a delusion. Alternatively, internally generated mental events might be interpreted as if they had arisen via sensory perception, resulting in a hallucination. This suggests that the cardinal event in the generation of delusions and hallucinations might be aberrant hippocampal firing that reinforces mental events out of context.

We propose that, during acute psychosis, two processes are required for the generation of delusions and hallucinations. Dopaminergic overactivity, possibly arising from stress, would enhance the predisposition to psychotic symptoms by virtue of increasing positive feedback to the cortex. The cardinal event that might generate a specific delusion or hallucination is hippocampal firing that reinforces a mental event inappropriately. We report a study of the effects of antipsychotic treatment on the pattern of cerebral activity using positron emission tomography (PET) in patients with acute psychosis, designed to test two specific hypotheses that arise from the proposed mechanism of delusions and hallucinations.

- (a) During treatment of acute psychosis, cerebral activity in the ventral striatum, thalamus and prefrontal cortex will decrease.
- (b) The magnitude of decrease in hippocampal activity produced by treatment

will be correlated with the degree of subsequent alleviation of delusions and hallucinations.

We studied first-episode schizophrenia patients treated with the novel antipsychotic, risperidone, because such patients are likely to respond to a dose low enough to avoid extrapyramidal side-effects, which might be associated with potentially confounding changes in striatal activity.

METHOD

Patients

Eight patients satisfying DSM–IV criteria for schizophrenia or schizophreniform psychosis (American Psychiatric Association, 1994) were recruited and scanned during their first episode of psychotic illness. Apart from one individual who had previously received two doses of risperidone (1 mg), subjects had not taken antipsychotic medication at any time prior to the first PET scan.

Experimental design

On the first scanning day, a placebo capsule was administered under single-blind conditions 90 minutes prior to the injection of tracer for a baseline PET scan. At the completion of the baseline PET scan, 2 mg risperidone was administered (single blind). Eighty minutes later, a 10-minute duration pre-injection emission scan was performed to measure residual radioactivity remaining from the first injection of tracer. Ninety minutes after administration of risperidone, tracer was injected and a second ('first-dose') PET scan was performed. The next day, patients received 2 mg risperidone in divided doses. On the third day, the dosage was increased to 4 mg (in divided doses) and subsequently to a maximum of 6 mg daily if clinically indicated. Dosages were decreased as necessary to minimise side-effects. The mean dosage after 6 weeks of treatment was 3.75 mg/day (range 2–6). After 6 weeks, a third ('post-treatment') PET scan was performed after the morning dose of risperidone.

Symptoms were assessed using the Scale for Assessment of Negative Symptoms and the Scale for Assessment of Positive Symptoms (Andreasen, 1987) on the day of the first PET scan, and subsequently at 2, 4 and 6 weeks. A score for reality distortion was derived by adding the global delusions and global hallucinations scores (Liddle,

1987). Overall severity of illness was assessed using the Global Assessment Scale (Endicott *et al.*, 1976). Handedness was assessed using the Annett (1970) handedness questionnaire. Social status of patients was assessed on the basis of parental occupation, according to the criteria specified by Andreasen (1987). The experimental procedure was approved by the University of British Columbia and Vancouver Hospital's ethical review boards, and all subjects gave written, informed consent.

Imaging procedure

Images of regional glucose metabolism were obtained with a CTI 953B PET camera (CTI, Knoxville, TN) using ^{18}F -fluoro-deoxyglucose (^{18}F -FDG), prepared by the procedure of Hamacher *et al.* (1986). Between-plane collimating septa were retracted to allow reconstruction of images in three dimensions. Data were collected in 31 contiguous axial slices covering an axial field of view of 10.8 cm. For each scan, 2 mCi (74 MBq) tracer was administered by slow injection over 1 minute, via a forearm cannula. To permit estimation of the input of tracer to the brain, the concentration of ^{18}F -FDG in the plasma of arterialised venous blood was measured in 15 samples collected over a period of 120 minutes following injection. To ensure a standard mental state, the subjects were engaged in a continuous performance task during the period of uptake of ^{18}F -FDG. Digits were presented one at a time on a visual display unit at a rate of one per second, and the subject was instructed to press a bar whenever two identical digits were presented consecutively. Three-dimensional image data were collected in four 5-minute frames commencing 60 minutes after tracer injection. Correction for absorption of radiation was made, using data from a transmission scan obtained employing a ^{68}Ge -germanium rod source.

Data analysis

Image analysis was performed using statistical parametric mapping software (SPM 96; Wellcome Department of Cognitive Neurology, London). The four 5-minute frames in each scan were aligned and averaged. The 'first-dose' and 'post-treatment' images were then aligned to the baseline image. The residual activity from the baseline scan injection remaining during the first-dose scan was computed using the expression for tissue radioactivity as a

function of time, derived by Phelps *et al* (1979). Using this expression, the rate coefficient for the loss of tracer from the metabolic pool due to dephosphorylation (k_4) was estimated from the observed radioactivity during the baseline scan and that measured 10 minutes prior to the second injection. Then, the residual radioactivity during the first-dose scan was calculated from the radioactivity measured prior to the second injection using Phelps' expression with the estimated value of k_4 . Residual activity was subtracted from the observed image intensity during the first-dose scan to provide an estimate of tracer concentration attributable to the second injection of ^{18}F -FDG. We will refer to this image as the 'corrected first-dose scan'.

For each subject, a mean image was derived by averaging the baseline, corrected first-dose and post-treatment images, and this mean image was spatially normalised to match the PET image template in SPM 96. This template is located in the Talairach coordinate frame which has its origin at the mid-point of the anterior commissure, y -axis passing from back to front through the posterior and anterior commissures, and x -axis directed from left to right (Talairach & Tournoux, 1988). The parameters for the transformation were then applied to each of the three images for each subject. After spatial normalisation, images were smoothed with a 10-mm full-width at half-maximum Gaussian filter.

As a preliminary step, the effect of risperidone treatment on global metabolism was examined. The Phelps-Sokoloff model (Phelps *et al*, 1979) was employed to calculate metabolism in each voxel, using Metab Tool software (CTI, Knoxville, TN). Mean global metabolism (MGM) was taken to be the mean value for all intra-cerebral voxels in the middle ten slices of the image. Mean global metabolism at baseline, after the first dose and after 6 weeks' treatment, was computed for each subject. This procedure demonstrated that risperidone produced no significant change in MGM. Consequently, when changes in regional metabolism were analysed, variation between scans in MGM was removed by proportional scaling, thereby removing noise due to errors in measurement of blood radioactivity.

For each voxel, the general linear model was used to estimate the mean change in scaled image intensity between the baseline scan and corrected first-dose image, and also between the baseline scan and the

post-treatment image. For the purpose of testing the specified hypotheses regarding ventral striatum and thalamus, only those voxels within the pre-specified volumes of interest in the ventral striatum and thalamus were examined. The ventral striatum was defined as that part of the corpus striatum lying below the inter-commissural plane. The significance of the change for each voxel was determined using the method developed by Worsley *et al* (1996), based on the theory of Gaussian fields, as applied to finite search volumes. In effect, Worsley's method determines the number of independent measurements within the brain volume examined, taking account of the fact that the image intensity in adjacent voxels is correlated, and applies the appropriate Bonferroni-type correction.

In order to test the hypothesis that there would be a reduction in prefrontal cortex metabolism (defined as all areas of the cortex anterior to $y=20$ mm in the Talairach coordinate frame) after the first dose, and also after 6 weeks' treatment, we employed the test for distributed non-focal activations proposed by Worsley *et al* (1995). This procedure evaluates the significance of the observed sum of squares of z values for all voxels in the specified volume, taking account of the fact that the number of degrees of freedom is less than the number of voxels, owing to correlations between adjacent voxels. It is an appropriate procedure for identifying changes that are expected to be extensive but relatively small in magnitude.

A separate analysis was performed to test the hypothesis that the change in reality distortion symptoms after 6 weeks' treatment would be significantly related to the immediate change in metabolism in the left hippocampus produced by the first dose. The first step was to create difference images representing the change in globally normalised image intensity between the baseline image and the corrected first-dose image. The general linear model was employed to determine the regression of difference in image intensity on change in symptom score at 6 weeks for each voxel lying within a left hippocampal volume of interest. The volume of interest comprised 3375 voxels, each $2 \times 2 \times 2$ mm. Significance was determined employing the Worsley correction appropriate for small search volumes (Worsley *et al*, 1996). A similar analysis was also performed to identify left hippocampal voxels in which there was a significant relationship between

change in image intensity between baseline and post-treatment scans and change in severity of reality distortion after 6 weeks' treatment.

RESULTS

The characteristics of the patients are given in Table 1. The mean score for reality distortion at baseline was 5.1, and the mean reduction after 6 weeks' treatment was 4.0 (s.d.=2.2). At 6 months after onset of illness, all patients satisfied DSM-IV criteria for schizophrenia.

In accordance with prediction, there were statistically significant decreases in regional metabolism between the baseline scan and the scan performed after the first dose in the right ventral striatum and right thalamus, but not in the left ventral striatum and left thalamus (see Table 2 and Fig. 2). The decrease in the right ventral striatum remained significant after 6 weeks' treatment (Table 2).

The test for non-focal change in the prefrontal cortex revealed a significant reduction in metabolism after the first dose ($\chi^2=205.8$; d.f.=112; $P<0.005$). The proportion of all cerebral voxels anterior to $y=20$ mm that exhibited a decrease satisfying the criterion $P<0.05$ (uncorrected) was 20.3%. The frontal lobe voxels exhibiting a decrease in metabolism after the first dose of risperidone formed clusters in the dorso-medial frontal cortex bilaterally, ventro-medial frontal cortex bilaterally and left lateral frontal cortex. After 6 weeks' treatment, the test for non-focal change again revealed a significant decrease in frontal metabolism ($\chi^2=251.5$; d.f.=93; $P<0.001$). The clusters of suprathreshold voxels in which there was a decrease in metabolism had increased in size, and the proportion of all cerebral voxels anterior to $y=20$ mm that satisfied the criterion $P<0.05$ (uncorrected) was 40%.

The analysis of relationships between metabolism after the first dose and change in reality distortion after 6 weeks revealed a statistically significant correlation between reduced left hippocampal metabolism and reduced severity of reality distortion (Fig. 3). The coordinates of the most significant voxel were -24 , -14 , -18 in millimetres relative to the mid-point of the anterior commissure, and the peak z value was 3.23 ($P=0.04$ after correction for multiple comparisons). The corresponding Pearson correlation between

Table 1 Characteristics of subjects with schizophrenia

Variable	Mean	(s.d.)
Age (years)	26.5	(5.6)
Gender (female:male)	6:2	
Handedness (right:left)	7:1	
Social class	3.75	(1.3)
Years of education	11.8	(2.9)
Mean years of parents' education	13.5	(2.2)
Clinical features on scan day 1		
Duration of current hospitalisation (days)	5.1	(3.2)
Global Assessment Scale	31.9	(6.5)
Clinical Global Impression	4.1	(0.99)
SANS sum of item scores ¹	21.4	(15.1)
SAPS sum of item scores ²	20.3	(14.1)
Clinical features after 6 weeks' treatment		
Clinical Global Impression	2.0	(0.93)
SANS sum of item scores ¹	10.6	(10.1)
SAPS sum of item scores ²	3.6	(3.8)

1. Sum of items from avolition, affective flattening, avolition and anhedonia sub-scales.

2. Sum of items from hallucination, delusion, bizarre behaviour and positive formal thought disorder sub-scales. SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

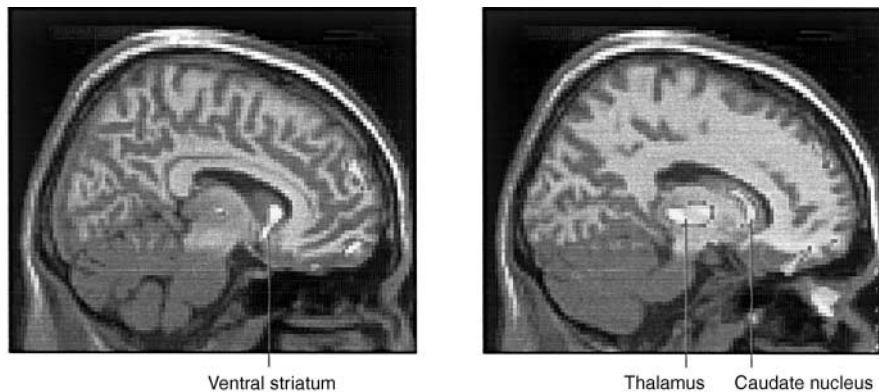


Fig. 2 Right para-sagittal slices at $x=8$ and 14 mm, showing decreases in metabolism in ventral striatum, thalamus and medial prefrontal cortex produced by 2 mg risperidone.

change in metabolism in this voxel after the first dose and reduction in severity of reality distortion after 6 weeks was 0.92 . Furthermore, change in metabolism in the left hippocampus after 6 weeks' treatment was also significantly correlated with reduction in severity of reality distortion after 6 weeks. The most significant voxel was located at $-32, -6, -32$ ($z=3.25, P=0.04$ corrected). There were no statistically significant relationships between change in reality distortion and changes in metabolism in the ventral striatum or thalamus, either after the first dose of risperidone or after 6 weeks' treatment.

A subsidiary analysis of changes in metabolism in the entire basal ganglia region after the first dose, and also after 6 weeks' treatment, revealed several clusters of voxels in the dorsal striatum and globus pallidum in which there was an increase in metabolism at the level $P<0.05$ (uncorrected) and several clusters in which there were decreases of similar magnitude. However, none of these changes was significant after correction for multiple comparisons.

DISCUSSION

Changes in the cortico-striato-thalamic circuits

In accordance with the predictions of the proposed mechanism of reality distortion, a single dose of risperidone produced significant reduction of metabolism (relative to mean global metabolism) in the ventral striatum, thalamus and prefrontal cortex. The changes in striatal and thalamic metabolism were significant only in the right hemisphere. This lateralisation had not been predicted, although it is of interest to

Table 2 Decreases in regional metabolism in the right ventral striatum and right thalamus after the first dose of risperidone and after 6 weeks' treatment

Region	Talairach coordinate			Z at peak voxel	Uncorrected P	Corrected P^1	Search volume
	x	y	z				
After first dose							
Right ventral striatum	10	10	-6	2.78	0.003	0.05	512 mm ³
Right thalamus	16	-24	0	3.55	0.0002	0.04	3375 mm ³
After 6 weeks' treatment							
Right ventral striatum	6	8	-8	3.22	0.0006	0.02	512 mm ³
Right thalamus	22	-34	4	2.21	0.014	NS	3375 mm ³

1. Corrected for multiple comparisons using the Worsley *et al* (1996) finite volume correction.

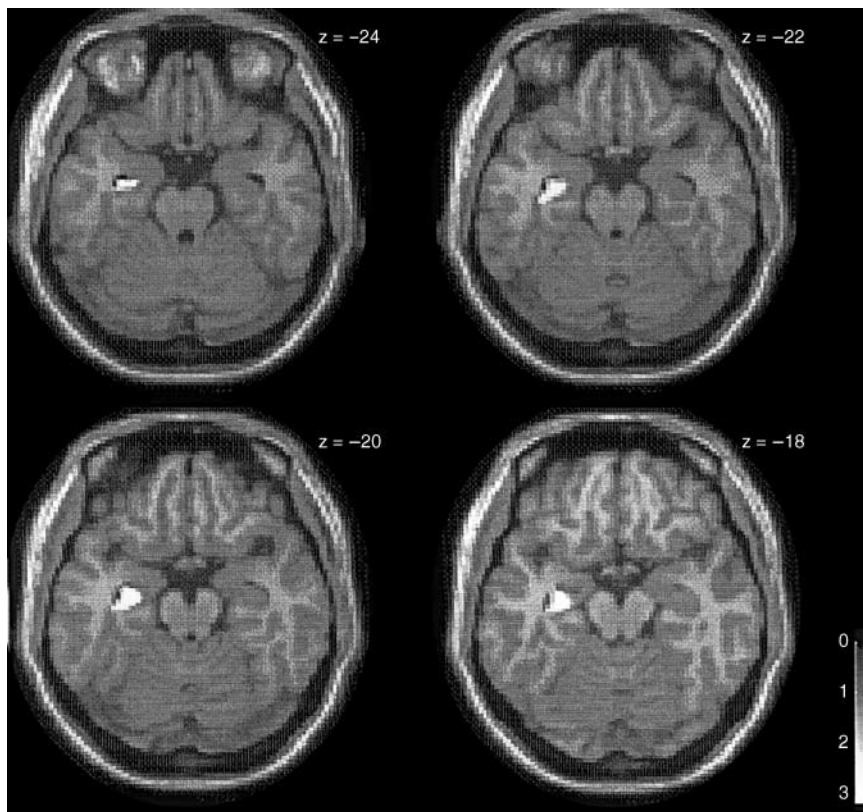


Fig. 3 Axial slices showing voxels in the left hippocampus, in which there was a significant relationship between reduction in metabolism after the first dose of risperidone and the subsequent reduction in reality distortion after 6 weeks' treatment.

note that in their study of cerebral activity associated with hallucinations, Silbersweig *et al* (1995) reported overactivity in the right striatum and thalamus, together with overactivity in the left hippocampus, a pattern consistent with the reductions in metabolism we observed after administration of risperidone.

Changes in the hippocampus

In addition, the magnitude of reduction in metabolism in the left hippocampus was strongly predictive of reduction in severity of reality distortion after 6 weeks' treatment. This is consistent with the hypothesis that reduction in aberrant hippocampal firing is a prerequisite for subsequent resolution of reality distortion.

It should be noted that in the principal analysis, we tested for significant changes only at the cerebral sites specified in the hypothesis, because statistical power is markedly reduced when the entire cerebral volume is examined, owing to the much more severe Bonferroni correction required. This reduction in power would impair the

detection of changes in small structures such as the hippocampus and ventral striatum, where the signal is reduced by partial volume effects. An analysis of changes in other brain regions will be presented elsewhere (further details available from the first author upon request).

Relationships to previous findings

Our findings are consistent with recent animal studies in rats, which show decreases in local cerebral glucose utilisation of the hippocampus and dorsomedial nucleus of the thalamus following acute administration of risperidone (Huang *et al*, 1999). Furthermore, our observation that risperidone produces a decrease in frontal metabolism is consistent with previous findings that typical antipsychotics (De Lisi *et al*, 1985; Wolkin *et al*, 1985; Buchsbaum *et al*, 1987) and also risperidone (Berman *et al*, 1996) produce a decrease in frontal metabolism in patients with schizophrenia. However, in contrast to our finding of a decrease in metabolism in the ventral striatum, several previous studies have reported

that typical antipsychotics produce an increase in metabolism in the basal ganglia (De Lisi *et al*, 1985; Wolkin *et al*, 1985; Buchsbaum *et al*, 1987). It is possible that this difference reflects the lower propensity of risperidone to cause extrapyramidal side-effects (Peuskens & Risperidone Study Group, 1995). It is also possible that the difference arises from the fact that in our principal analysis we examined the significance of changes in a specified region of the basal ganglia that included only the ventral striatum. In a subsidiary analysis that included the entire basal ganglia, we did observe increases in metabolism in parts of the dorsal striatum (significant at $P < 0.05$, uncorrected), but these increases were not statistically significant after correcting for multiple comparisons.

Our finding of a correlation between reduction in hippocampal metabolism and subsequent symptom resolution is consistent with previous evidence indicating that reality distortion syndrome is associated with overactivity in the left medial temporal lobe (Liddle *et al*, 1992; Silbersweig *et al*, 1995), but is, at first sight, inconsistent with the evidence that removal of the hippocampus can evoke psychotic symptoms (Falconer & Taylor, 1968). However, it is possible that, following resection of the hippocampus, denervation supersensitivity might lead to spurious firing of the post-synaptic neurons downstream of the hippocampus, producing the same effect as aberrant hippocampal firing.

We did not find a correlation between decrease in severity of reality distortion and change in metabolism in either the striatum or thalamus following the first dose of risperidone. It is likely that the reduction of activity in the cortico-striato-thalamo-cortical circuits reduces the propensity to all of the symptoms characteristic of an acute schizophrenic episode, including not only reality distortion but also disorganisation and psychomotor excitation.

Our findings support both the hypothesis that aberrant hippocampal activity is involved in the generation of delusions and hallucinations, and the hypothesis that overactivity in the ventral striatum is associated with acute psychosis, irrespective of symptom profile.

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CLINICAL IMPLICATIONS

- The therapeutic effects of risperidone are associated with reduced activity in the ventral part of the corpus striatum.
- Alleviation of delusions and hallucinations requires not only reduction in activity in the ventral striatum but also a reduction of hippocampal firing.
- The cerebral changes associated with alleviation of symptoms are discernible after the first dose of risperidone.

LIMITATIONS

- The findings should be interpreted with caution because of the small number of subjects.
- The observation of unilateral change in metabolism in the ventral striatum and thalamus was not predicted.
- Because it was not possible to randomise the ordering of the baseline and post-treatment scans, we cannot yet exclude the possibility that the observed decreases in metabolism in the frontal cortex, striatum and thalamus were unrelated to treatment.

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