Immediate and delayed effects of risperidone on cerebral metabolism in neuroleptic naïve schizophrenic patients: correlations with symptom change

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Objective: Different symptom patterns have been shown to be associated with specific patterns of cerebral metabolic activity in schizophrenia. Treatment with various antipsychotic drugs results in decreased metabolism in frontal cortical regions. The temporal and regional relation between changes in metabolism and symptom improvement after treatment with risperidone was studied in eight previously unmedicated schizophrenic patients.

Method: Cerebral metabolic activity was measured using PET before neuroleptic exposure, after the first dose of risperidone, and after 6 weeks of treatment. Pearson correlations were calculated for regions of significant change in metabolism and symptom change.

Results: After 6 weeks of treatment significant deactivations were seen in the left lateral cortical frontal region and medial frontal cortex. Significant changes were detectable in the medial frontal region 90 minutes after the first dose of risperidone. Patients with higher baseline activity in the identified medial frontal cluster had higher baseline positive symptom scores and reduction in medial frontal metabolism was correlated with reduction in positive symptom score.

Conclusion: The evidence suggests that the reduction in medial-frontal activity after treatment with risperidone is a direct effect of risperidone and not a consequence of symptom improvement. Reduction of medial frontal metabolism may be one of the physiological mechanisms by which risperidone alleviates symptoms of psychosis in schizophrenia.

Most studies that have examined the pattern of cerebral activity associated with psychotic symptoms suggest that positive psychotic symptoms, such as delusions, hallucinations, and disorganisation phenomena are associated with overactivity of the frontal and temporal cortex, thalamus, and basal ganglia. For example, disorganisation is associated with overactivity of the medial frontal cortex and thalamus. Delusions and/or hallucinations have been reported to be associated with overactivity in the temporal lobe, frontal cortex, and ventral striatum. However, there are some discrepancies in the data, Ebmeier et al found that delusions and hallucinations were associated with temporal lobe underactivity. Andreasen et al found that acute schizophrenia was associated with frontal underactivity. Overall, most of the evidence supports the hypothesis that delusions, hallucinations, and disorganisation phenomena are associated with cortical overactivity, and also overactivity in at least some subcortical regions, particularly the ventral striatum.

The anatomical location and the time course of the changes in cerebral function associated with the therapeutic effects of antipsychotic drugs remain a subject of debate. Previous studies indicate that antipsychotic treatment causes a decrease in cortical metabolism, especially frontal metabolism and an increase in subcortical metabolism. Several studies have reported that sensitivity to change in regional metabolism after administration of antipsychotic drugs is correlated with treatment responsiveness.

Taken together, the findings of the effect of antipsychotic drugs on cerebral metabolism and the patterns of cerebral activity associated with psychotic symptoms suggest that the mechanism of antipsychotic action should produce a reduction in cortical metabolism, especially in the frontal and temporal cortex.

Although placebo controlled trials indicate that the antipsychotic effect of neuroleptic medications become statistically significant over a period of several weeks the reduction in psychotic symptoms is usually non-significantly greater in patients receiving the active drug from the first assessment time point. Furthermore, clinical observation indicates that the effects on mental state can be discerned within hours of the first dose. The immediate effects include not only a reduction in agitation (which might be attributed to any of several pharmacological mechanisms) but also extrapyramidal effects such as acute dystonia, which are likely to arise from blockade of dopamine receptors. Studies with PET demonstrate that D2 receptor occupancy can reach 80% within 2 hours of administration of a single dose of risperidone (4 mg). This suggests the possibility that the therapeutic effect may evolve gradually from the beginning of treatment. The failure to detect significant improvement in the early phase of treatment may be due to lack of statistical power to detect relatively small effects. The question of whether the immediate effects of antipsychotic medication on cerebral function evolve and are related to subsequent therapeutic effects might in principle be addressed by a longitudinal study employing PET to measure regional cerebral glucose metabolism. Furthermore, a longitudinal study offers the possibility of determining whether or not a specific cerebral change precedes symptom change, or vice versa. Such information would help determine whether the relevant cerebral metabolic change is related to the cause of symptom reduction, or merely the consequence of it.

Abbreviations: FDG, fluorodeoxy glucose; CGI, clinical global impression severity scale; SAPS, scale for assessment of negative symptoms; SANS, scale for assessment of positive symptoms; EPS, extrapyramidal side effects
In this study we investigated the effects of risperidone on cerebral metabolism 90 minutes after first exposure to risperi-
done and after 6 weeks of treatment in a group of first episode schizophrenia patients. We studied first episode patients to
avoid possible confounding effects of prior antipsychotic
treatment, and also because a substantial reduction in symp-
tom severity might be expected after 6 weeks of treatment
with moderate doses of antipsychotic medication in a
substantial proportion of such patients. We employed risperi-
done because low to moderate doses of this antipsychotic drug
produce relatively few extrapyramidal side effects, which
might be associated with changes in metabolism that would
confound the interpretation of the results. The timing of the
second scan was selected so as to detect change that occurred
very soon after the administered drug entered the brain, and
before any adaptive changes mediated by gene expression
would be anticipated. Ideally, measurement at additional time
points would be more informative; three scans a patient is the
maximum that is feasible using PET with the ligand fluorode-
oxoy glucose (FDG), on account of radiation exposure.
We tested the hypothesis that 6 weeks of treatment with
risperidone would lead to a decrease in activity in frontal and
temporal cortical regions. We explored the relation between
changes found and clinical improvement. For areas where
there is a significant relation between metabolic changes after
6 weeks of treatment and symptom improvement we
performed a directed search for significant changes after the
first dose of risperidone.

METHOD
Eight patients meeting DSM IV criteria for schizophrenia or
schizophreniform psychosis with no history of exposure to
neuroleptic drugs were recruited into this study. They each
gave written informed consent for their participation. Illness
severity was rated on the clinical global impression severity
scale (CGI): a seven point scale on which 1 = normal, 2 =borderline ill, 3 = mildly ill, 4 = moderately ill, 5 =markedly
ill, 6 = severely ill, and 7 = among the most extremely ill
patients). Clinical improvement at 6 weeks was rated on the
clinical global impression improvement scale (CGI-I): a seven
point scale on which 1 = very much improved, 2 = much
improved, 3 = minimally improved, 4 = no change, 5 =mini-
mally worse, 6 = much worse, and 7 = very much worse).
Symptom severity was assessed using the scale for assessment
of negative symptoms (SANS) and scale for assessment of
positive symptoms (SAPS) at baseline and after 6 weeks of
treatment. Benzodiazepine treatment was allowed for the
management of anxiety and agitation before the first scan.
Extrapyramidal side effects (EPS) were monitored using the
Simpson Angus scale for parkinsonian symptoms.

On the first scanning day, the patients underwent two PET
scans, one after administration of a placebo tablet and the
other after administration of risperidone, under single blind
conditions. For each scan, 2 mg FDG were given by bolus
injection delivered over 1 minute. A placebo tablet was
administered 90 minutes before the injection of FDG for the
first scan. Immediately after completion of the first scan, 2 mg
risperidone was administered orally, 90 minutes before the
injection of FDG for the second scan. The patients were blind
to the order of administration of risperidone and placebo.

For each scan, arterialised venous blood samples were taken
over 120 minutes after the bolus injection to provide an
estimate of blood activity curves for the residual correction
method described below. To maintain a similar mental state
during uptake of \(^{18}\)F-fluorodeoxyglucose patients engaged in a
continuous performance task in which they were instructed to
press a response button whenever two consecutive letters pre-
sented sequentially on a computer monitor were identical.
Scans were obtained commencing 40 minutes after each
injection of FDG with an ECAT 953B PET Camera (Knoxville
TN, USA) with between plan septa retracted for three dimen-
sional image acquisition. Data were collected in 31 contigu-
sous slices covering a 10.8 cm field of view. Images were
acquired in four consecutive 5 minute frames to allow for rea-
lignment due to intrascanner movement over the acquisition
period. Correction for radiation absorption was made using
data from a transmission scan employing a germanium ring
source. Ten minutes before administration of the second injec-
tion of FDG, a "preinjection" scan of 10 minutes in duration
was performed to measure residual activity from the first
tracer injection.

Patients received 2 mg risperidone on the second day and 4
mg (in divided dosages) on the third day. Dosages were
adjusted to a maximum of 6 mg/day as clinically indicated.
Dosages were decreased as necessary to minimise side effects.
After 6 weeks of treatment a third (post-treatment) scan was
performed 90 minutes after the morning dose of risperidone.

Data analysis
Image analysis was performed using Statistical Parametric
Mapping software (SPM96; Wellcome Department of Cogni-
tional Neurology, London, UK). The four 5 minute frames from
each scan session were realigned to the first frame and
averaged. The residual activity from the first tracer injection at
the time of the second scan acquisition was calculated using
individual estimates of the rate coefficient for the loss of tracer
from the metabolic pool due to dephosphorylation (k4) for
each patient. The method uses the residual activity measured
before the second injection and the measured plasma activity

"corrected" image was derived using data from the residual
active pool measured following the second injection. The rate
parameter for the remaining free pool was determined from
the first time after the injection of FDG with the

Dosages were decreased as necessary to minimise side effects.
After 6 weeks of treatment a third (post-treatment) scan was
performed 90 minutes after the morning dose of risperidone.

The residual activity from the baseline scan was subtracted
from the scan the after the second dose to produce a "corrected
second scan". This "corrected image" was used for all
subsequent analysis. The averaged images for each of the three
scan sessions were aligned to the image from the baseline ses-
tion. A mean image produced from which normalisation
parameters for spatial normalisation to the PET image
template in SPM96 were determined. After normalisation
images were smoothed with a 10 mm gaussian filter resulting
in final images with smoothness of 13.3, 15.1, and 12.1 mm
(full width half maximum) in the x, y, and z directions respec-
tively.

To control for variation in global image intensity between
patients normalised metabolic images were created by
proportional scaling after ensuring that there were no signifi-
cant differences in group mean global metabolism across the
three conditions. Differences in normalised metabolism were
calculated voxel by voxel with correction for multiple
comparisons based on the theory of random gaussian fields
employed in SPM 96 for both the first dose-baseline contrast
and the post-treatment baseline contrast. When examining
changes in individual voxels after 6 weeks of treatment,
the primary criterion for statistical significance was p<0.05 after
correcting for multiple comparisons assuming examination of
the entire brain. In addition, we identified significant clusters
of contiguous suprathreshold voxels, satisfying the criterion
p<0.05 after correcting for multiple comparisons, determined
by the test for cluster significance proposed by Friston et al.
and implemented in SPM. The threshold for inclusion of a
voxel in a cluster was z=2.33 (corresponding to p=0.01). In
the case of the changes after the first dose, the risk of type 2
error when applying a stringent test for multiple comparisons
is especially high because the anticipated changes in metabo-
lism are small. Therefore, when examining the changes after
the first dose, we initially examined only selected voxels. Our main objective in studying the effects of a single dose was to determine whether or not change could be discerned after the first dose at the sites where significant change developed after 6 weeks. Therefore, we selected the voxel at which the change after 6 weeks was most significant, within each of the clusters that were significant after 6 weeks of treatment. We then examined the significance of change after the first dose at these selected voxels, applying a criterion of p<0.01, uncorrected.

We examined the relation between symptoms and normalised metabolism in the identified significant clusters. Pearson correlations between baseline metabolism, change in metabolism, baseline symptom severity, and change in symptom severity were calculated. Clinical variables used in the bivariate analysis included a positive symptom score (sum of global items in SAPS), negative symptom score (sum of global avolition, anhedonia, alogia, and affective flattening), a disorganisation score (positive formal thought disorder, inappropriate affect, and poverty of content) and a score for reality distortion (sum of hallucination global and delusions global scores). It should be noted that the items contributing to a global score for positive symptoms overlap with those contributing to scores for reality distortion and disorganisation. We examined

the positive/negative dichotomy because many treatment trials examine therapeutic effects on these two groups of symptoms. We also examined the reality distortion/disorganisation/psychomotor poverty trichotomy because of evidence that these three clusters of symptoms might be associated with different patterns of brain activity.¹

RESULTS
Clinical effects

Patient demographics are shown in table 1. One patient was considered severely ill, one markedly ill, four moderately ill, and 2 mildly ill (CGI) at baseline. Four patients were very much improved, three patients much improved, and one patient minimally improved (CGI) after 6 weeks of treatment. The mean improvement at 6 weeks in positive symptoms was 78.1% (range 50%−100%), negative symptoms 53.0% (range 20%−100%), disorganisation 68.7% (range 40%−100%) and reality distortion 75.7% (range 0%−100%). The reduction in positive symptom severity was significantly correlated with baseline positive symptom severity (r=0.92, p=0.001, df=7).

Two patients had their dosage of risperidone reduced during the course of treatment due to emergent extrapyramidal symptoms (EPS). These two patients had discernable EPS at 6 weeks. The remaining six patients showed no detectable EPS.

Changes in metabolism after 6 weeks of treatment

There were two extensive clusters of voxels in which there were decreases in metabolism after 6 weeks (fig 1). The largest cluster, located predominantly in the left lateral frontal cortex, embracing both middle and inferior frontal gyri, comprised 5400 (2x2x2mm) suprathreshold voxels. The significance of the cluster as a whole was p<0.001, corrected for multiple comparisons. The mean change in activity in this cluster after 6 weeks of treatment was −7.8%. The most significant reduction in an individual voxel was located at x,y,z=−10,34,−18 mm (z=4.96; p=0.008 corrected for multiple comparisons).

Table 1  Patient demographics

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>26.5</td>
<td>5.6</td>
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<tr>
<td>GAS at admission</td>
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<td>Lifetime stays in hospital (months)</td>
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<td>0.2</td>
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<td>Clinical global impression severity</td>
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<tr>
<td>Sex (female:male)</td>
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<tr>
<td>Handedness (right:left)</td>
<td>7:1</td>
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</table>

Figure 1  Surface rendering of areas of significant reduction in normalised metabolism after 6 weeks of treatment with risperidone.
The second largest cluster was located in medial frontal cortex. This cluster embraced 2456 suprathreshold voxels. The significance of this cluster as a whole was p=0.004, corrected for multiple comparisons. The mean change in activity in this cluster after 6 weeks of treatment was −7.6%. The most significant reduction in an individual voxel was located at x, y, z=−4, 24, 32 mm (z=4.56; p=0.04 corrected for multiple comparisons).

There was a small extension of the left lateral cluster into the left temporal lobe. The most significant reduction in metabolism in an individual voxel in the left temporal lobe cluster was located at x, y, z=−34, −6, −40 mm (z=4.22; p=0.0001 uncorrected; p=0.146 corrected for multiple comparisons).

There were no changes in metabolism in the basal ganglia that remained significant after correcting for multiple comparisons. In the ventral striatum, there was a small cluster of voxels in which metabolism decreased after treatment (peak significance at x, y, z = 6, −8, −8 mm; z=3.22, p=0.0006, uncorrected).

Changes in metabolism after the first dose

For the most significant voxel after 6 weeks of treatment, the largest suprathreshold cluster extending from the lateral frontal cortex to the orbital frontal cortex, there was no evidence of a significant change after the first dose. In the cluster in the medial frontal cortex, for the voxel exhibiting the most significant reduction in metabolism after 6 weeks treatment (located at x, y, z=−4, 24, 32 mm), there was a significant reduction after the first dose (z=2.54; p=0.006, uncorrected). This voxel was part of a cluster of 117 suprathreshold voxels. The most significant voxel in this cluster was located at x, y, z=−6, 30, 40 (z=3.64, p=0.0001, uncorrected). The mean change in activity in this cluster after a single dose of risperidone was −5.8%.

In an indirect search of the entire brain, there were no changes in metabolism after the first dose that were significant after a stringent correction for multiple comparisons. In view of the risk of type 2 errors when applying a stringent criterion for significance, we note that there were changes in the lateral frontal cortex and temporal lobe that satisfied less stringent criteria. In view of the prior evidence implicating the lateral frontal cortex and temporal lobes in the expression of schizophrenic symptoms\(^1\--^3\) less stringent criteria might be justified. None the less, these findings should be interpreted with caution. In the lateral frontal cortex, the most significant change was located at x, y, z=−36, 56, 8 (z=3.25, p=0.0006, uncorrected) within a contiguous cluster of 310 suprathreshold voxels. In the temporal cortex, the most significant change was at x, y, z=−50, −16, −8, (z=3.32, p=0.0004, uncorrected) within a contiguous cluster of 71 suprathreshold voxels.

Correlations between symptoms and metabolism

The baseline metabolism in the significant cluster of 2456 voxels in medial frontal cortex in which metabolism subsequently decreased during 6 weeks of treatment was positively correlated with baseline positive symptoms (r=0.80, p=0.016) and subsequent change in positive symptoms (r=0.85, p=0.008) and change in disorganisation (r=0.84, p=0.009, table 2).

The change in activity in this cluster after 6 weeks of treatment was positively correlated with baseline positive symptoms (r=0.75, p=0.031) and with change in positive symptoms (r=0.74, p=0.037). There were no significant correlations between baseline or change in activity in the left lateral frontal cluster and any baseline or symptom change measures used in this analysis. There were no significant correlations between baseline negative symptom severity, improvement in negative symptoms, and measures in metabolism.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Correlations of baseline symptom severity and change in symptom severity after 6 weeks treatment, with baseline metabolism and change in metabolism after 6 weeks treatment in the significant cluster of 2456 voxels in the medial frontal cortex, in which metabolism subsequently decreased during 6 weeks treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline metabolism</td>
<td>Change in metabolism</td>
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<tr>
<td>Baseline symptom severity</td>
<td>Disorganisation</td>
</tr>
<tr>
<td>Disorganisation</td>
<td>0.35</td>
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<tr>
<td>Reality distortion</td>
<td>0.27</td>
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<tr>
<td>Total positive symptoms</td>
<td>0.80*</td>
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<tr>
<td>Change in symptom severity</td>
<td>Disorganisation</td>
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<tr>
<td>Reality distortion</td>
<td>0.42</td>
</tr>
<tr>
<td>Total positive symptoms</td>
<td>0.85**</td>
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</table>

*p<0.05, **p<0.01.

DISCUSSION

Risperidone produces decreases in metabolism in the frontal cortex, consistent with previous findings.\(^4\) This reduction was found in both the medial and the lateral frontal cortex. In accord with the prediction based on prior findings that medial prefrontal overactivity is associated with severity of disorganisation\(^5\) and with hallucinations,\(^6\) we found that the decrease in medial frontal cortex metabolism is related to alleviation of positive symptoms. This association can be accounted for largely by the finding that in this region, baseline metabolism is correlated with baseline severity of symptoms.

There was evidence for discernible changes in both medial and left lateral frontal cortex within 2 hours of the first dose, although these reductions were less extensive than those found after 6 weeks of treatment. The fact that a decrease in metabolism in the medial frontal cortex is discernible within 2 hours of the first dose, at a time when the degree of symptom resolution would be expected to be minimal, suggests that the decrease in metabolism is not merely a consequence of alleviation of symptoms.

Studies of cognitive activation with PET have fairly consistently reported diminished activation of the frontal lobe during a demanding relative to a less demanding baseline condition in schizophrenic patients. In particular, Spence et al\(^7\) found that schizophrenic patients exhibited recovery of the normal increase in activation in dorsolateral prefrontal cortex during a demanding motor task relative to a resting baseline, as symptoms resolved during treatment. Such a recovery could arise from increase in activity during the demanding task; a decrease during the non-demanding baseline condition; or both. In an fMRI study of first episode schizophrenic patients, Mendrek et al\(^8\) found a partial recovery of normal frontal activation during a demanding 2-back working memory task relative to that during a non-demanding 0-back condition, during treatment.\(^9\) Furthermore, Mendrek et al demonstrated that this recovery was largely due to a decrease in an abnormally high level of activity during the non-demanding 0-back condition, during treatment.\(^10\) In our study, patients performed a non-demanding continuous performance task that could also be described as a 1-back working memory task, during uptake of the tracer. Our findings indicate that frontal activation during this relatively non-demanding condition decreases during treatment. They do not rule out the possibility that activity during a demanding task might increase relative to that during a non-demanding baseline condition.

In the absence of a healthy control group, it is not possible to ascertain whether or not the changes in metabolism are...
unique to patients. Furthermore, randomisation of the order of the first and second scans was not feasible in a study of patients, because such randomisation would have necessitated a substantial time interval between the scans, leading to a delay in initiation of treatment. Therefore it is not possible to exclude the possibility that the changes reflect scan-order effects, such as changes associated with a reduction in anxiety, which are unrelated to the pharmacological effect of risperidone treatment. However, in a separate study of 12 healthy subjects, in which a similar PET procedure was employed to measure metabolism 90 minutes after placebo and 90 minutes after 2 mg risperidone, administered in random order 2 weeks apart, we found reductions in metabolism after risperidone at similar sites in the medial and lateral frontal cortex (Lane et al., unpublished data). These findings indicate that the reductions in metabolism at these sites are not entirely due to scan-order effects unrelated to treatment. Furthermore, the finding of a change in the medial frontal cortex in healthy subjects similar to that found to be associated with the subsequent reduction in severity of hallucinations: a study of regional cerebral blood flow with 99mTc-HM-PAO-SPECT in patients with auditory hallucinations, tactile hallucinations, and normal controls. Comp Psychiatry 1989;30:99–108.


15 Buchsbaum MS, Patkin SG, Siegel BV. Striatal metabolic rate and clinical response to neuroleptics in schizophrenia. Arch Gen Psychiatry 1992;49:966–74.


