

Immediate effects of risperidone on cerebral activity in healthy subjects: a comparison with subjects with first-episode schizophrenia

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Objective: To test the hypothesis that administration of risperidone to healthy subjects produces reductions in metabolism in the frontal cortex similar to those produced by administration of risperidone to patients experiencing a first episode of schizophrenia. **Methods:** Positron emission tomography was used to measure the changes in regional metabolism produced by a single 2-mg dose of risperidone and by placebo, administered under randomized, double-blind conditions, in 9 healthy subjects. Conjunction analysis was used to identify those cerebral sites where changes in metabolism in the healthy subjects coincided with similar changes in metabolism observed in patients with schizophrenia. **Results:** Compared with placebo, risperidone produced reductions in metabolism in the left lateral frontal cortex and right medial frontal cortex in healthy subjects. Conjunction analysis revealed that these changes occurred at locations similar to the loci of change produced by risperidone in patients with schizophrenia. **Conclusion:** Because the reduction in metabolism in the medial frontal cortex produced by risperidone is associated with alleviation of positive symptoms in patients with schizophrenia, the observation of a reduction in metabolism at a similar site in healthy subjects supports the hypothesis that the antipsychotic effect of risperidone arises, at least in part, from a physiologic effect that occurs in both patients with schizophrenia and healthy subjects.

Objectif : Vérifier l'hypothèse selon laquelle l'administration de rispéridone à des sujets en bonne santé provoque, dans le cortex frontal, des baisses du métabolisme semblables à celles que produit l'administration de rispéridone à des patients victimes d'une première crise de schizophrénie. **Méthodes :** On a utilisé la tomographie par émission de positrons pour mesurer les changements du métabolisme régional produits par une seule dose de 2 mg de rispéridone et par un placebo, administrée à neuf sujets en bonne santé dans des conditions randomisées et à double insu. On a eu recours à l'analyse de corrélation pour identifier les sites du cerveau où des changements du métabolisme chez les sujets en bonne santé ont coïncidé avec des changements semblables du métabolisme observés chez des patients atteints de schizophrénie. **Résultats :** Comparativement au placebo, la rispéridone a produit des réductions du métabolisme dans le

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cortex frontal latéral gauche et le cortex frontal interne droit chez les sujets en bonne santé. L'analyse de corrélation a révélé que ces changements se produisaient à des endroits semblables à ceux des changements provoqués par la rispéridone administrée à des patients atteints de schizophrénie. **Conclusion :** Comme il y a un lien entre la réduction du métabolisme dans le cortex frontal interne que produit la rispéridone et l'atténuation des symptômes positifs chez les patients atteints de schizophrénie, l'observation d'une baisse du métabolisme à un endroit semblable chez des sujets en bonne santé appuie l'hypothèse selon laquelle l'effet antipsychotique de la rispéridone découle, du moins en partie, d'un effet physiologique qui se produit à la fois chez les patients atteints de schizophrénie et chez les sujets en bonne santé.

Introduction

The site of action of antipsychotic drugs remains a subject of debate. The fact that all established antipsychotic drugs block dopamine D₂ receptors, which are abundant in the basal ganglia, has directed attention toward the basal ganglia. However, functional imaging studies indicate that the symptoms of schizophrenia are associated with aberrant cerebral activity at a diverse array of cerebral sites, including the frontal and temporal cortex in addition to subcortical grey matter.¹⁻⁵ Therefore, an understanding of the way in which antipsychotic drugs produce changes in function in diverse cerebral areas is essential for a full understanding of antipsychotic action.

Most studies that have examined the effect of sustained treatment with antipsychotic drugs on regional cerebral metabolism in subjects with schizophrenia demonstrate that these drugs produce an increase in metabolism in the basal ganglia.⁶ About half of the studies reviewed by Liddle also reported a decrease in frontal lobe metabolism during antipsychotic treatment.⁶ In attempting to establish the relation of these observed changes to the therapeutic effects of antipsychotics, it is relevant to determine whether these changes are only seen in patients with psychosis or also in healthy individuals.

There have been no studies of the effects of sustained treatment with antipsychotic drugs on regional cerebral activity in healthy subjects, although several studies have examined the effects of a single dose. Bartlett et al⁷ found that 5 mg of haloperidol produced widespread reduction in cortical metabolism 12 hours later. However, in a subsequent study, they found no significant changes 2 hours after administration of haloperidol.⁸ Thus, there is partial congruence between the findings in patients and healthy subjects, in that some studies report that antipsychotic drugs produce reduced cortical metabolism in both groups. It is likely that factors such as differences in duration of treatment, dose and type of medication, and interval between medication and scanning account for at least some of the differences between the various findings

reported in patients and in healthy subjects.

All of the published studies that have examined the effects of antipsychotic agents on regional cerebral activity in patients, or in healthy subjects, have used doses associated with a risk of akinesia⁹ or other extrapyramidal side effects. Therefore, it is possible that the reported cerebral changes are related to akinesia or other extrapyramidal side effects rather than the therapeutic effect.

We report a study in which we examined the effects of an antipsychotic drug on regional cerebral metabolism in healthy subjects using the same drug at the same dose and the same interval between drug administration and scanning as used in a companion study of patients who were experiencing a first episode of schizophrenia.¹⁰ We employed risperidone at a dose of 2 mg, because at this dose the risk of extrapyramidal side effects is low. Positron emission tomography (PET) studies indicate that dopamine receptor occupancy following a 2-mg dose is about 70%–80%,¹¹ which is in the range associated with antipsychotic effect, yet below the level associated with overt extrapyramidal effects.¹²

In our earlier study,¹⁰ not only were the effects of a single dose of risperidone examined, but also the effects of 6 weeks of sustained treatment. After 6 weeks' treatment, there were statistically significant reductions in cerebral metabolism in the medial frontal cortex and the left lateral frontal cortex. The magnitude of the reduction in the medial frontal cortex was correlated with the change in positive symptoms during treatment, supporting the hypothesis that this change was related to the therapeutic effect. Furthermore, at exactly the same site in the medial frontal cortex, there was a statistically significant reduction immediately after the first dose (2 mg) of risperidone, suggesting that changes associated with the therapeutic effect were discernible immediately after the first dose.

Placebo-controlled trials indicate that the antipsychotic effect of neuroleptic medications becomes statistically significant over a period of several weeks.¹³ Whereas a nonsignificant reduction in psychotic symptoms is usually discernible in patients receiving the

active drug at the first assessment within the first week of treatment,¹⁴ the observed decrease in metabolism in the medial frontal cortex within the first 2 hours of the initial dose in our companion study¹⁰ occurred at a time when the degree of symptom resolution would be expected to be minimal. These results suggest that the decrease in metabolism observed following the initial dose of risperidone is unlikely to be a mere epiphenomenon of symptom alleviation.

The reduction in metabolism in the left lateral frontal cortex after 6 weeks' treatment was unrelated to the change in symptom severity, and there was no significant reduction in metabolism after the first dose at the site of most significant change after 6 weeks' treatment. Nonetheless, changes elsewhere in the left lateral frontal cortex were discernible after the first dose.

In the companion study,¹⁰ we also observed that risperidone produced a reduction in metabolism in the ventral striatum, although this change was not statistically significant after a modified Bonferroni correction allowing for an examination of the entire brain. A separate analysis, which was confined to restricted brain regions to test the specific hypothesis that acute psychosis entails overactivity of corticostriato-thalamic circuits, revealed significant reductions in metabolism in the ventral striatum that were discernible after the first dose of risperidone and after 6 weeks' treatment.¹⁵ However, no significant metabolic changes in the dorsal striatum were observed. In light of the fact that risperidone produces minimal extrapyramidal side effects at low doses, these observations raise the possibility that the increases in metabolism in the basal ganglia reported in studies of the effects of typical antipsychotic drugs⁶ might reflect extrapyramidal side effects, whereas, in contrast, antipsychotic action might entail a reduction in metabolism in the ventral striatum.

On the basis of the observation in our companion study¹⁰ that changes in the left lateral frontal cortex were not related to symptom change in subjects with schizophrenia, we hypothesized that similar changes would be seen in this region in healthy subjects. The expectation for changes in the medial frontal lobe and in the ventral striatum in healthy subjects is less clear. It is possible that the therapeutic effects in patients might arise from a pharmacologic process that also occurs in healthy subjects. Alternatively, the therapeutic effects might arise from an effect that involves the pathophysiology of psychosis. To clarify this issue, we performed a conjunction analysis to identify sites at which reductions of metabolism in healthy subjects coincided with similar reductions in patients with schizophrenia after a single dose of risperidone.

Methods

Subjects

Eleven healthy subjects were recruited via advertisement and screened for a current or past history of psychiatric illness using the structured clinical interview for diagnosis (SCID).¹⁶ The exclusion criteria for healthy subjects were as follows:

- a lifetime history of psychotic illness, or current Axis 1 diagnosis, according to DSM-IV criteria¹⁷
- a history of schizophrenia, delusional disorder or bipolar disorder in a first-degree relative
- use of any psychotropic medication or drugs for the preceding 6 weeks (by history)
- a current general medical illness (by history)

The University of British Columbia Clinical Research Ethics Board and the Vancouver Hospital and Health Sciences Centre Ethics Committee approved the experimental procedure, and all subjects gave written informed consent.

One subject withdrew from the study following the first scan and another was excluded due to poor positioning in the PET camera. A total of 9 subjects (5 men, 4 women) were entered into the analysis. Eight of the 9 subjects were right-handed. The age range (18–42 [mean 28] yr) was similar to that of the patients with schizophrenia examined in the companion study (18–36 [mean 26.5] yr).

Experimental design and imaging procedure

Healthy subjects were administered either a placebo or 2 mg of risperidone orally under double-blind randomized conditions on 2 occasions, separated by 1 week. On each occasion, ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) was injected 90 minutes after the administration of the placebo or risperidone, and scanning began 40 minutes later. To ensure a standard mental state during the period of uptake of ¹⁸F-FDG, the subjects were engaged in a repeated-stimulus continuous performance task. Digits were presented 1 at a time on a visual display unit, and the subject was instructed to press a bar whenever 2 identical digits were presented consecutively.

Images of regional glucose metabolism were obtained with a CTI 953B PET camera (CTI, Knoxville, TN) using ¹⁸F-FDG, according to a modified version of the procedure described by Hamacher et al.¹⁸ Between-plane collimating septa were retracted to permit oblique photon paths to allow reconstruction of images in 3 dimensions.¹⁹ Data were reconstructed into 31 contiguous axial slices covering an axial field of view of 10.8 cm. For each scan, 2 mCi of tracer was adminis-

tered by slow injection over 1 minute through a forearm cannula. To permit estimation of the input of tracer to the brain, the concentration of ^{18}F -FDG in the plasma of arterialized venous blood was measured in 15 samples collected over a period of 120 minutes after injection. Three-dimensional image data were collected in three 5-minute frames starting 40 minutes after tracer injection. Correction for absorption of radiation was made using data from a transmission scan obtained using a germanium 68 rod source.

In our companion study of patients with schizophrenia,¹⁰ the experimental procedure was similar, except that placebo and risperidone were administered under single-blind conditions in a fixed order about 3 hours apart, with placebo being administered first. It would have been both impractical and unethical to have randomly allocated the order of administration of placebo and risperidone, because this would have entailed withholding treatment from acutely ill patients during a period long enough to allow return to baseline after the administration of the first dose of risperidone or placebo. The difference in randomization procedure between the studies potentially reduces the power to detect similarities between the effects in patients and healthy subjects, but it is unlikely to introduce spurious similarity.

Image analysis

Image analysis was performed using Statistical Parametric Mapping software (SPM96, Wellcome Department of Cognitive Neurology, University College London, London). For each scan, the three 5-minute frames were aligned and averaged. The post-risperidone image was then aligned to the post-placebo image, and a mean image was computed. The mean image was spatially normalized to match the PET image template in SPM96, and the normalization parameters were applied to the post-placebo and post-risperidone images. Images were smoothed using a 10-mm isotropic Gauss-

ian filter to improve the ratio of signal to noise. After testing to ensure that there was no significant difference in global image intensity between the post-placebo and post-risperidone images, variation between scans in mean global image intensity was removed by proportional scaling, using SPM96. For each voxel, the general linear model was used to estimate the mean change in scaled image intensity between the post-placebo image and the post-risperidone image. Correction for multiple comparisons was performed using a procedure based on the theory of random Gaussian fields.²⁰

To identify those sites where there was a conjunction between the effects of a single dose of risperidone in healthy subjects with that in patients with schizophrenia, conjunction analysis was performed using SPM96. This procedure identifies voxels in which there are supra-threshold changes in metabolism in both groups and computes the combined probability of the occurrence of these changes. The selected threshold was $p < 0.05$, not corrected for multiple comparisons. The significance of the conjunctions was estimated after correction for multiple comparisons based on the theory of random Gaussian fields.

Results

In the healthy subjects, there were extensive decreases in metabolism in the left lateral frontal cortex and the right medial frontal cortex after risperidone compared with placebo. Only the reduction in the left lateral frontal cortex remained statistically significant after correcting for multiple comparisons (Table 1). There was no evidence of changes in the basal ganglia or in the left temporal lobe even when a lenient criterion of significance ($p < 0.05$) (1-tailed, uncorrected) was applied. There were no statistically significant differences in global metabolism between the risperidone and placebo scans. There were no areas of significant

Table 1: Decreases in metabolism after risperidone, 2 mg, in healthy subjects

Location of decrease in metabolism	Talairach coordinates of the most significant change	Peak z^*	Uncorrected p value for peak z	Corrected p value for peak z^\dagger	Cluster size (voxels) ‡	p value for cluster size §
Left lateral frontal cortex	-48, 38, 28	3.88	< 0.001	0.039	338	0.038
Right medial frontal cortex	14, 42, 32	3.57	< 0.001	0.11	125	0.22

*The peak z is the z score corresponding to the t statistic for the difference in the specified voxel.

† The corrected p value represents the probability of observing a change as large as that observed under the null hypothesis, after correcting for multiple comparisons.

‡ The cluster size is the number of contiguous voxels in which the uncorrected p value for the observed z value is less than 0.05.

§ The p value for cluster size represents the probability of observing a cluster as large as the observed cluster under the null hypothesis.

increase in metabolism following risperidone administration in the healthy subjects.

Conjunction analysis revealed 2 clusters of voxels in which there were significant reductions in metabolism after risperidone in both healthy subjects and patients with schizophrenia. One cluster was located in the left lateral frontal cortex; the other was in the medial frontal cortex (Fig. 1). These conjunctions were statistically significant after correcting for multiple comparisons (Table 2).

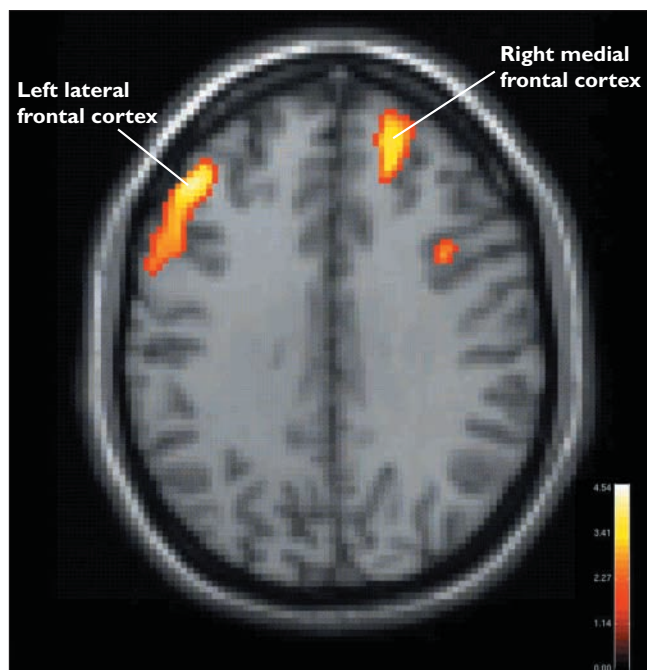


Fig. 1: Areas of conjunction between decreased metabolism observed in both healthy subjects and patients with schizophrenia after risperidone, 2 mg, in an axial slice 30 mm above the intercommissural plane. For coloured voxels, the joint probability is less than 0.05 under the null hypothesis. The colour scale in the lower right corner depicts the range of z values, extending from 0 to 4.54.

Discussion

The finding of decreased frontal cortical metabolism in healthy subjects after a single dose of risperidone is broadly consistent with the extensive reduction in cortical metabolism 12 hours after a 5-mg dose of haloperidol reported by Bartlett et al.⁷ The difference in the extent of the changes reported in the 2 studies might reflect the differences in the type of antipsychotic drug administered, the dose and the time interval between drug administration and scanning.

The healthy subjects in this study were not matched for gender with the patients with schizophrenia in the companion study. Because of the small sample, we cannot confidently exclude the possibility of gender differences in the effects of risperidone on regional cerebral metabolism, especially because the correction for multiple comparisons required in voxel-based image analysis to protect against type 1 error reduces the power to exclude type 2 errors (i.e., failure to detect real differences). However, any gender differences would have tended to increase differences between the healthy group and the patient group. The similarity between the patients and healthy subjects in the effects of risperidone in the medial and lateral frontal cortex, on which we base our conclusions, cannot be accounted for by gender differences at these sites.

The mechanism of action by which typical and atypical neuroleptic drugs cause a reduction in frontal cortical metabolism remains unknown. The induction of immediate early genes (IEGs) by both typical and atypical neuroleptic agents has been widely investigated, and it has been suggested that the induction of these genes is related to the therapeutic effects.²¹⁻²³ More recently, Cochran et al²⁴ have demonstrated that therapeutic dosages of a single intraperitoneal injection of both typical (haloperidol) and atypical (clozapine) neuroleptics cause both increases in IEG expression and re-

Table 2: Sites identified by conjunction analysis at which both healthy subjects and patients with schizophrenia exhibited a decrease in metabolism after risperidone, 2 mg

Location of decrease in metabolism	Talairach coordinates of the most significant change	Peak z	Uncorrected p value for peak z*	Corrected p value for peak z†	Cluster size (voxels)‡	p value for cluster size§
Left lateral frontal cortex	-46, 44, 2	4.54	< 0.001	0.002	2599	0.031
Right medial frontal cortex	18, 44, 32	3.75	< 0.001	0.039	415	0.43

*The uncorrected p value represents the joint probability of a change as large as the observed change in the specified voxel under the null hypothesis.

†The corrected p value represents the probability after correcting for multiple comparisons.

‡Cluster size refers to the number of contiguous voxels in which the joint p value is less than 0.05.

§The p value for cluster size represents the probability of observing a cluster as large as the observed cluster under the null hypothesis.

duction in local glucose metabolism in many limbic circuit regions, including the anterior cingulate. The changes in IEG expression were identified 45 minutes after drug exposure, whereas changes in local glucose metabolism were observed after 90 minutes. These findings are consistent with the time course of our current study and suggest that induction of IEG might contribute to the mechanism by which risperidone alters brain function and induces the observed localized decreases in glucose metabolism.

Effects in the medial frontal cortex

In both patients with schizophrenia and healthy subjects, metabolism was decreased after risperidone in the right medial frontal cortex. In patients with schizophrenia, sustained treatment with risperidone produced a decrease in activity in the medial frontal cortex that is correlated with a decrease in the severity of positive symptoms.¹⁰ This is consistent with the observation that medial frontal overactivity is associated with both disorganization symptoms^{2,3,5} and with hallucinations.⁴ Furthermore, the observation that a single dose of risperidone produces an immediate decrease in metabolism in the medial frontal cortex in patients with schizophrenia, whereas symptom resolution occurs on a time scale of several weeks, suggests that the decrease in metabolism precedes the change in symptoms. This is consistent with the hypothesis that the decrease in metabolism might play a causal role in the therapeutic effect. However, the fact that risperidone also produces a decrease in metabolism in the medial frontal cortex in healthy subjects indicates that this therapeutic effect is a consequence of a physiologic effect of risperidone that occurs in healthy subjects as well as in individuals with schizophrenia.

The behavioural data for the continuous performance task were only retrievable for 9 of the 22 subject sessions (5 placebo, 4 risperidone) because of a computer hard drive failure after completion of the study. There were no significant effects of risperidone between groups on reaction time, on errors where participants incorrectly identified a stimulus as being identical to the preceding stimulus or on errors where participants failed to recognize that a stimulus was identical to the preceding stimulus. These results suggest that the observed reduction in cortical metabolism after a single dose of risperidone is unlikely to be the result of decreased performance or decreased engagement in the task; however, this conclusion should be interpreted with caution because of the reduced power associated with the smaller remaining sample.

Effects in the lateral frontal cortex

Conjunction analysis revealed that risperidone produced reductions in metabolism at the same location in the left lateral frontal cortex in healthy subjects and in patients with schizophrenia. In the patients, the reduction in left lateral frontal metabolism was unrelated to change in symptom severity.¹⁰ Therefore, that study provided no evidence that the reduction in metabolism in the lateral frontal cortex produced by risperidone is related to its antipsychotic effect.

What might be the expected effects of diminished lateral frontal activity? The lateral frontal cortex is engaged during a variety of cognitive tasks, especially working memory and executive processes.²⁵ Blumer and Benson²⁶ reported that lesions of the dorsolateral prefrontal cortex can produce a pseudodepression syndrome characterized by apathy and impoverished speech. Furthermore, underactivity of the left lateral frontal cortex has been reported to be associated with negative symptoms of schizophrenia.^{2,3,5} Thus, it might be predicted that a reduction in lateral frontal cortex activity would lead to impairment in working memory and executive tasks, and perhaps to apathy and impoverished speech.

It is, therefore, paradoxical that risperidone has been reported to be effective in treating working memory deficits²⁷ and negative symptoms²⁸ in schizophrenia. However, it should be noted that the studies that have demonstrated these effects have compared risperidone with haloperidol. For example, in the study by Marder and Meibach,²⁸ various doses of risperidone were compared with haloperidol at a dose of 20 mg per day. At that dose, haloperidol can produce marked akinesia.⁹ Thus, it is possible that despite being beneficial compared with haloperidol, risperidone can nonetheless produce subclinical hypokinesia even at small doses. This possibility is consistent with the observation that the most common psychologic adverse effect of risperidone in long-term treatment is asthenia/lassitude/increased fatigability.²⁹

Alternatively, it may be that the reduction in lateral frontal cortex metabolism produced by risperidone might serve a beneficial purpose in schizophrenia. For example, it is possible that a reduction in baseline activity might actually facilitate task-related engagement of the frontal cortex. This speculation is supported by the evidence that treatment with risperidone enhances activation in the lateral frontal cortex in schizophrenia during the performance of a working-memory task relative to a control condition.³⁰

More recently, Mendrek et al³¹ reported that treatment of patients with first-episode schizophrenia using

atypical antipsychotic agents (either risperidone or olanzapine) resulted in an increase in lateral frontal lobe activity during a 2-back working-memory task (where stimuli are presented sequentially, and the participant is required to respond when the current stimulus matches that presented 2 items previously), in comparison with the level of activity during a comparison 0-back condition, which placed a minimal demand on working memory. However, inspection of the changes relative to a resting baseline condition revealed that the relative increase during the 2-back condition was in fact the result of a reduction in activity during the 0-back condition. Working-memory performance also improved during treatment. That finding suggests that a pharmacologic effect leading to reduced task-irrelevant activity in the lateral frontal lobe is associated with improved performance in tasks that normally engage the lateral frontal cortex. It is plausible that the reduction in lateral frontal metabolism, which we observed in both patients with schizophrenia and in healthy subjects during the performance of an undemanding continuous performance test after a single dose of risperidone, might in fact reflect a reduction in task-irrelevant frontal activity. Furthermore, such a reduction might enhance performance in executive tasks in patients.

Further investigation of the effects of atypical antipsychotic drugs on lateral frontal activity during a variety of different cognitive conditions is required to clarify this issue. In contrast to the situation in the medial frontal cortex, where the observed reduction in metabolism appears to be associated with the antipsychotic effect of risperidone, it remains uncertain whether or not the reduction in left lateral frontal metabolism, which we have observed in both healthy subjects and in patients with schizophrenia, reflects a harmful or a beneficial effect of the administration of risperidone.

Basal ganglia

In view of the risk of type 2 errors when the sample is small, the absence of significant effects in a specific brain region should be interpreted with caution. Nonetheless, the absence of any significant change in metabolism in the basal ganglia in healthy subjects, even when setting a lenient criterion for significance, suggests that the reduction in ventral striatal metabolism observed in the patients after a single dose of risperidone¹⁵ is an effect that is confined to patients with schizophrenia. This is consistent with the hypothesis that the reduction in ventral striatal metabolism in patients reflects alleviation of pathologic overactivity,

which is a manifestation of acute illness.¹⁵ On the other hand, the absence of significant changes in metabolism in the dorsal striatum, in either the healthy subjects examined in this study or in patients with schizophrenia,^{10,15} is consistent with the low propensity of risperidone to cause extrapyramidal side effects when administered at low doses.

Conclusion

In summary, decreases in medial and lateral frontal activity were observed in healthy subjects 90 minutes after a single oral dose of risperidone. This finding complements our previous report of decreased activity in these same areas in a group of neuroleptic-naïve patients with schizophrenia 90 minutes after their first oral dose of risperidone.¹⁰ Taken together, these 2 studies suggest that the observed reductions in medial frontal and lateral frontal activity are the direct effects of risperidone and not an epiphenomenon of symptom reduction. This ability to induce reduction in cerebral metabolism may be the mechanism by which risperidone alleviates symptoms of psychosis.

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