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Clozapine but not Haloperidol Re-establishes Normal Task-Activated rCBF Patterns in Schizophrenia within the Anterior Cingulate Cortex

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Our previous work has identified that unmedicated volunteers with schizophrenia have regional cerebral blood flow (rCBF) activation patterns inappropriately related to the cognitive demand of a task in anterior cingulate cortex (ACC). Using positron emission tomography (PET) with ^{15}O water, we compared task-induced rCBF patterns induced by haloperidol or clozapine in individuals with schizophrenia. We hypothesized that clozapine, given its superior clinical action, would tend to normalize the abnormal task-activated response in ACC more than haloperidol. Schizophrenia volunteers (SVs) ($n = 6$) and normal volunteers (NVs) ($n = 12$) were trained to perform a tone discrimination task with 70–80% accuracy. They were then scanned during three task conditions: (1) Rest, (2) sensory motor control (SMC) task, and (3) decision task (DEC). SVs were initially scanned after withdrawal of all psychotropic medication and again after treatment with therapeutic doses of haloperidol ($n = 5$) and/or clozapine ($n = 5$). rCBF values, sampled in the grown maxima of the task-activated ACC cluster, were analyzed between groups and task conditions. Task performance was similar across the unmedicated, haloperidol- and clozapine-medicated SV groups. There was a reduction in accuracy in the haloperidol SV group compared to the NVs. Group and task conditions affected rCBF in the ACC. Clozapine, but not haloperidol, reversed the abnormal ACC rCBF pattern in unmedicated SV to normal. The clozapine-treated SV group showed a rCBF pattern similar to the NV group in that ACC activation was not observed during the control task but occurred during the decision condition. The pattern seen in the haloperidol-treated SV group was similar to the unmedicated SV group in that ACC activation was seen during the control task and no further activation was seen during the DEC. We report that clozapine, but not haloperidol, normalizes anterior cingulate rCBF patterns in schizophrenia during a cognitive task. Based on these preliminary data, we propose that this pattern may account for the superior therapeutic effect of clozapine and represents a surrogate marker of this action.
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Keywords: schizophrenia; PET imaging; clozapine; haloperidol; anterior cingulate cortex

INTRODUCTION

Clozapine demonstrates a superior antipsychotic action in schizophrenia compared to other first- or second-generation antipsychotics (Kane *et al*, 1988; Conley *et al*, 1998; Breier *et al*, 1999; Wirshing *et al*, 1999; Kane *et al*, 2001). Moreover, in addition, it is not associated with Parkinsonism, akathisia, or tardive dyskinesia, and may improve cognitive function in schizophrenia (Buchanan and McKenna, 2000). When detected, clozapine-induced cognitive gains are modest and limited to discrete measures, including verbal fluency, verbal memory, and attention (Goldberg *et al*, 1993; Hagger *et al*, 1993; Buchanan *et al*, 1994; Grace *et al*, 1996; Hoff *et al*, 1996; Galletly *et al*, 1997). Some aspects of clozapine's action on cognitive function, which form the basis for its long-term psychosocial benefits, may yet have to be quantified. These long-term psychosocial improvements occur in domains as diverse as quality of life (Galletly *et al*, 1997; Meltzer *et al*, 1990), compliance and treatment participation (Rosenheck *et al*, 1997; Luchins *et al*, 1998), violent behavior (Buchanan *et al*, 1998; Glazer and Dickson, 1998; Frankle *et al*, 2001), and substance abuse (Buckley *et al*, 1994). The mechanism of clozapine's unique antipsychotic efficacy is not known, but along with its benign motor effect profile, the clinical actions balance the significant agranulocytosis risk of the drug (Alvir *et al*, 1993).

Functional brain imaging techniques have advanced our understanding of the normal brain function and are now shaping our concepts of dysfunction in brain diseases.

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Functional imaging methodologies are used to understand how effective medications alter brain function to produce their therapeutic actions. Here, we present data contrasting a first-generation with a second-generation antipsychotic effects on task-activated regional cerebral blood flow (rCBF) in schizophrenia to determine the extent to which these medications can improve or 'normalize' the rCBF response in persons with the illness. Previous imaging studies have examined the effects of antipsychotics upon measures of attention. These reported increased metabolic rates in the striatum with haloperidol (Buchsbaum *et al*, 1992) and in the limbic cortex with clozapine and fluphenazine (Cohen *et al*, 1997). In this study, we postulated that clozapine, given its superior clinical action, would tend to normalize the abnormal task-activated rCBF response in persons with schizophrenia in anterior cingulate cortex (ACC) more than haloperidol (Holcomb *et al*, 2000).

MATERIALS AND METHODS

Volunteers

Six medically healthy persons with schizophrenia, treated with a variety of first- and second-generation antipsychotic medications, and 12 healthy normal volunteers (NVs) were recruited to participate in this study.

Persons with schizophrenia were recruited from the Residential Research Unit of the Maryland Psychiatric Research Center in Baltimore, MD, USA. Each underwent a structured clinical interview (SCID) for DSM-III-R at hospital admission. Two research psychiatrists reached a consensus diagnosis of schizophrenia based on the clinical interview plus all other sources of data utilizing DSM-III-R criteria.

The schizophrenia volunteer (SV) group, all right handed, included five male and one female persons with a mean age of 31.5 $\pm$ 6.9 years and a mean illness duration of 10.7 $\pm$ 8.1 years (see Table 1). All six were partially treatment-responsive patients, who later, were discharged to community-based programs.

Experimental Design

At the start of the study, the SVs treatment was switched to a fixed dose (0.3 mg/kg) of haloperidol and no other neurally active medications for at least 4 weeks before medication withdrawal. After the four initial haloperidol week, all volunteers were withdrawn from haloperidol for 19.2 $\pm$ 4.8 days (range = 10–23 days). All other aspects of inpatient treatment, such as groups or activity therapy, were continued. Single dose of lorazepam (1–2 mg) was occasionally given, but not within 48 h of scanning. The initial off-medication scan was completed in all six patient participants (see Table 1); then, five of the six patients were scanned again after receiving optimal therapeutic doses of haloperidol (average dose: 12 $\pm$ 4.5 mg/day) for 12 $\pm$ 10 weeks. Later, five of the six patient's medication was switched to clozapine; the switch was carried out by gradually increasing clozapine's dosage while tapering their antipsychotic treatment. They were scanned after receiving optimal therapeutic doses of clozapine (average dose: 280 $\pm$ 135 mg/day) for 23 $\pm$ 12 weeks. This was an open study where patients were not blind to medication status. In the haloperidol condition, the BPRS Total and the BPRS Psychosis mean scores off-drug were 33.0 $\pm$ 8.4 and 7.6 $\pm$ 2.5, respectively; on haloperidol, these scores were 38.2 $\pm$ 14.0 and 7.2 $\pm$ 2.6, respectively. In the clozapine condition, the BPRS Total and Psychosis mean scores off-drug were 37.5 $\pm$ 6.0 and 9.3 $\pm$ 2.5, respectively; on clozapine, they were 36.0 $\pm$ 7.3 and 7.8 $\pm$ 1.7, respectively. No comparisons of symptom scale scores between the medicated or unmedicated status showed differences.

The 12 NVs were recruited from the community through newspaper advertising and screened by telephone for lack of major medical or psychiatric illness. If suitable, they were further screened in face-to-face interviews using the SCID-nonpatient (SCID-NP) and structured interview for DSM III-R personality disorders (SIDP-R) to rule out current or past history of Axis I or Axis II disorders. A family history of schizophrenia in any first-degree relative of the prospective healthy volunteer was ruled out. Six controls were male and six were female, all were right handed, and their mean age was 28.4 $\pm$ 4.6 years.

Table 1 Characteristics of Study Population

SV	Sex	Race	Age (years)	Length of illness (years)	Schizophrenia subtype	PAS[a]	PRO[b]	DF[c] (days)	DF scan[d]	Haloperidol scan	Haloperidol dose (mg/day)	Clozapine scan	Clozapine dose (mg/day)
1	M	C	35	16	Undiff.	0.31	3	21	Yes	Yes	5	Yes	200
2	M	C	32	15	Undiff.	0.24	3	18	Yes			Yes	350
3	M	C	23	3	Paranoid	0.45	2	10	Yes	Yes	15	Yes	300
4	M	C	23	2	Undiff.	0.35	8	23	Yes	Yes	15		
5	F	C	38	6	Paranoid	0.15	5	21	Yes	Yes	15	Yes	100
6	M	A	38	22	Paranoid	0.25	6	22	Yes	Yes	10	Yes	450

SV, schizophrenic volunteers; C, Caucasian individuals; A, Asian individuals; Undiff., Undifferentiated.
[a]Premorbid Adjustment Scale: Age scales total score (lower score is better).
[b]Prognostic Scale: General items total score (higher score is better).
[c]Drug-free (DF) period.
[d]Drug-free (DF) scan.

Informed Consent

The University of Maryland School of Medicine's Institutional Review Board approved this protocol. Normal and schizophrenic volunteers were fully informed about the nature of the protocol and afterwards each of them gave informed consent. Only patients who were competent and judged clinically to be capable of understanding and appreciating the risks involved in this study were selected to participate. Separate clinicians including both the principal investigator and noninvestigator clinicians presented the nature of the protocol on several occasions and assessed their willingness to be involved. Prior to giving consent, schizophrenic volunteers completed an 'evaluation to sign consent' form, a questionnaire probing their understanding of various aspects of the study. Family members or caregivers were involved in the information process when available. Volunteers were reconsented prior to each new scanning session.

Task Description and Training During rCBF

The task condition (DEC) was a graded error rate, forced-choice auditory discrimination task, described previously (Holcomb *et al*, 2000). Subjects were instructed to press a button held in their right hand immediately when they recognized a high-frequency reference tone (1500 Hz) and the button in their left hand with a lower-frequency tone (800–1492 Hz). An equal number of high and low tones lasting 100 ms each was randomly presented in each stimulus condition; 100 trials comprised each training set and 60 trials, each imaging set. An intertrial interval of 2 s (onset of first tone to onset of the subsequent tone) was fixed. Failure to respond was scored as an error. Response time was calculated from the onset of the stimulus to the button press.

During the active control task (sensory motor control, SMC), subjects heard the same sets of tones presented during the DEC task condition and merely alternated right- and left-hand button presses in synchrony with tone presentation. During the Rest condition, subjects were instructed to lie quietly: eyes were open and earphones were in place.

All subjects began training on the auditory discrimination task 2–5 weeks prior to the scan sessions. The purposes of the training were to eliminate stimulus or task novelty, determine what frequency difference would reliably provide 80% performance accuracy for each subject, and to reduce performance variability within and between volunteer groups. Volunteers were trained until they consistently achieved the required performance accuracy. Volunteers with schizophrenia were retrained prior to scan performed on haloperidol and clozapine.

Positron Emission Tomography (PET) Imaging

PET scans were obtained using the general electric 4096+ system, which produces 15 brain image slices at an intrinsic resolution of 6.1 mm in each dimension. The bolus $H_2^{15}O$ method (Raichle *et al*, 1983) was used without arterial blood sampling. Approximately, 62 mCi $H_2^{15}O$ were administered on each occasion. Between scans 10–12 min elapsed. The rCBF distribution was measured in each of the three condition: (1) Rest, (2) SMC, and (3) DEC utilizing four scans per condition (12 scans per subject). The order of the scans was fixed for all subjects: Rest, SMC, and DEC, consecutively repeated four times. Within a given scan, the frequencies of the two tones were held constant. The frequencies were chosen based on the training accuracy for that individual. In all, 60 trials were delivered during each scan; tones began 15 s prior to tracer delivery, and scan acquisition began 20 s after dose delivery. PET data were acquired for 60 s.

Image Analysis

The qualitative PET blood flow images were analyzed with modified statistical parametric mapping (SPM) routines (Friston *et al*, 1996). The scans from each subject were realigned using the first as a reference. The alignment procedure was modified to use 10 iterations to optimize the spatial correlation between data sets; the default procedure uses three iterations. Following realignment, all images were transformed into a standard anatomical space (Talairach and Tournoux, 1988). Prior to generating the $SPM_{(Z)}$ map, the data were smoothed using a 12-mm Gaussian kernel. Only clusters of connected voxels (face or edge) above a threshold ($Z = 2.33$ $P = 0.01$, one-tailed, uncorrected for multiple comparisons) were tested for significance by means of spatial extent statistics, which set at an alpha level of < 0.05 after correcting for multiple comparisons (Friston *et al*, 1996). The full-width at half-maximum of the average noise subtraction image was used to determine the number of resels (Worsley *et al*, 1992) available for analysis.

STATISTICAL ANALYSIS

Behavioral Measures

Behavioral outcome measures were extracted from all trials generated in DEC PET scans sessions. Outcome measures for two scanning sessions (one on haloperidol, one on clozapine) were unavailable because of computer recording problems. These measures include mean accuracy, mean response time, and mean frequency differences between high and low tones for accurate trials. Differences on those measures among each of the three SV groups (unmedicated, haloperidol, and clozapine medicated) and the NV group were tested using a Wilcoxon rank-sum test on all pairs. Differences among the three SV groups were tested using Kruskal–Wallis test. For behavioral measures generated in SMC PET scans sessions, differences among the three SV groups were tested using Kruskal–Wallis test.

IMAGING

Region of Interest Analysis

We evaluated the *a priori* hypothesis that clozapine would 'improve' the abnormal ACC rCBF pattern in schizophrenia to a greater degree than haloperidol. The maxima of the anterior cingulate/medial frontal cortex cluster activated with the normal performance of this task was identified (Talairach coordinates—02, 12, and 48) (Holcomb *et al*,

2000). rCBF values were sampled in that maxima, grown to a $3 \times 3 \times 3$ pixel ROI, in each group during Rest, SMC, and DEC. A two-way ANOVA was performed to test for effects of task (Rest, SMC, and DEC) and group, for each of the SZ groups compared to the NV group. When an interaction was observed, a one-way ANOVA testing each of the tasks separately was obtained. Repeated measure ANOVA was performed to test the unmedicated SZ *vs* the haloperidol SV and the unmedicated SZ *vs* the clozapine SZ groups.

RESULTS

Task Performance With and Without Medication

Performance characteristics of the SV on the auditory discrimination task during rCBF imaging were similar in the unmedicated, haloperidol-, and clozapine-medicated SV groups with respect to accuracy of task performance, response time, and frequency differences to achieve that accuracy (Table 2). There was no difference in response time between any of the SV groups compared to the NVs. However, there was a reduction in accuracy in the haloperidol SV group compared to the NVs (Kruskal–Wallis, $\chi^2 = 4.02$, df = 1, $P < 0.045$). Moreover, a greater frequency difference to achieve target accuracy was required in all of the SV groups compared to the NVs (for clozapine, $\chi^2 = 5.89$, df = 1, $P < 0.015$; for haloperidol, $\chi^2 = 7.13$, df = 1, $P < 0.008$; and without medication, $\chi^2 = 10.1$, df = 1, $P < 0.002$). Thus, all the SVs required a greater frequency difference between tones to perform the task at approximately 80% accuracy, which provided task performance at nearly the accuracy and response time level as the NVs. There were no significant differences in omission rate during the task between the unmedicated and haloperidol-medicated SV groups and between the unmedicated and clozapine-medicated SV groups. There were no significant differences in the performance characteristics during the control task between the unmedicated, haloperidol- and clozapine-medicated SV groups.

Region of Interest Analysis: rCBF in ACC

A significant interaction between tasks and groups was found between the NV and the unmedicated SZ groups (F[2, 15] = 7.72; $P = 0.005$) and a trend between the NV and haloperidol SZ groups (F[2, 14] = 2.28; $P = 0.089$). There was no interaction between the NV and clozapine SZ groups. rCBF differences in ACC were identified between the NV and unmedicated SZ groups during the control (F[1, 16] = 11.5; $P = 0.004$) and during the decision (F[1, 15] = 12.36; $P = 0.003$) tasks, but not during Rest. Between the NV and haloperidol SZ groups, rCBF differences were identified during the control task (F[1, 15] = 6.19; $P = 0.025$), but not during Rest or the decision task (DEC). (Figure 1). An inspection of the data suggests that the pattern of rCBF change across tasks was similar to the NV group when SV were treated with clozapine, but more similar to the unmedicated SV group when they were treated with haloperidol. Mean changes in rCBF values in ACC during the control and the DECs are presented in Table 3.

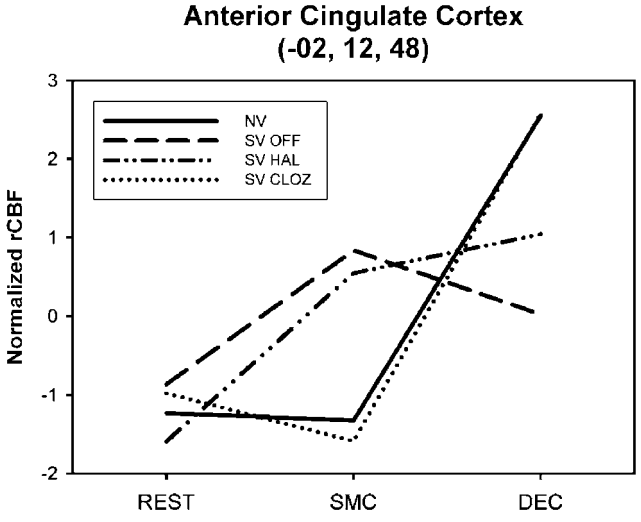

Figure 1 Normalized rCBF values sampled in the maxima of the anterior cingulate/medial frontal cortex cluster activated with the normal performance of the auditory DEC. Values were sampled at Rest, during the control task (SMC) and during the DEC. The clozapine group (SV OFF) ($n = 5$) showed a rCBF pattern similar to the NV group (NV) ($n = 12$) and the haloperidol group (SV HAL) ($n = 5$) showed a pattern similar to the unmedicated schizophrenia group (SV OFF) ($n = 6$).

Table 2 Auditory Recognition Task: Group Performance Characteristics

	% Accuracy mean, SD	% Omission mean, SD	Reaction time mean, SD	Mean frequency difference (Hz) mean, SD
Drug-free SV volunteers ($n = 6$)	76.8 (± 14.9)	1.0 (± 1.0)	766.8 (± 203.2)	346.6* (± 355.1)
Haloperidol SV volunteers ($n = 4$)	73.7* (± 10.4)	1.4 (± 2.4)	632.5 (± 236.7)	346.1* (± 354.5)
Clozapine SV volunteers ($n = 4$)	76.3 (± 8.0)	1.0 (± 1.8)	678.2 (± 152.8)	314.4* (± 340.6)
Healthy volunteers ($n = 12$)	80.6 (± 4.7)	0.7 (± 0.9)	735.0 (± 102.0)	17.2 (± 8.3)

*Significantly different between this SV group and NVs.
There was no difference among the three SV groups on those measures.

Table 3 Changes in Adjusted rCBF Values in ACC During Tasks

	Control task (SMC–Rest)	Decision task (DEC–SMC)
NV ($n=12$)	-0.1 ± 1.9	3.8 ± 2.3
Unmedicated SV ($n=6$)	1.7 ± 2.9	-0.8 ± 1.5
Haloperidol SV ($n=5$)	2.1 ± 2.6	0.5 ± 3.3
Clozapine SV ($n=5$)	-0.6 ± 1.6	4.2 ± 3.8

Descriptively, the NV group did not show ACC rCBF activation during the control task, but did show activation during the DEC. The clozapine SV group showed a similar pattern to the NV group. The unmedicated SV group showed ACC activation during the control and no further increase during the DEC. Similarly, the haloperidol SV group activated during the control task with no further increase during the DEC.

DISCUSSION

These results show that clozapine reverses the rCBF abnormalities in ACC found in schizophrenia whereas haloperidol does not. We, and others, have previously described the abnormal functioning of the ACC in schizophrenia using rCBF, with the activation patterns inappropriately related to the cognitive demand of the task (Holcomb *et al*, 2000; Carter *et al*, 1997, 2001). This experiment confirms the previously identified pattern of ACC dysfunction in unmedicated SVs, and shows a clozapine-induced normalization of that dysfunction, strikingly different from the haloperidol-induced action. As task-activated rCBF is thought to represent changes in neuronal activity, these results suggest a physiologic basis for the superior action of clozapine in schizophrenia. There are two possible framework interpretations for our study: one is clozapine's superior therapeutic efficacy, the other is clozapine's effect on cognition.

In a landmark study, Kane *et al* (1988) demonstrated that clozapine was more effective than chlorpromazine for the treatment of positive symptoms in severe treatment-refractory inpatients. Subsequent studies have confirmed these results (Rosenheck *et al*, 1997; Buchanan *et al*, 1998; Pickar *et al*, 1992; Breier *et al*, 1994; Essock *et al*, 1996; Conley *et al*, 1999). The advantage of clozapine over a first-generation antipsychotic medication was also found in partially responsive, community-based, schizophrenic patients (Kane *et al*, 2001; Buchanan *et al*, 1998; Breier *et al*, 1994). There is now convincing evidence that the ACC is involved in a distributed neural network that mediates psychosis (Cleghorn *et al*, 1992; Silbersweig *et al*, 1995; Szechtman *et al*, 1998; Shergill *et al*, 2000). rCBF in ACC significantly correlates with psychosis levels in unmedicated SV (Tamminga *et al*, 2001; Lee *et al*, 2003). Psychosis exacerbation with the NMDA antagonist, ketamine, is accompanied by increases in ACC rCBF and the induced behavioral changes correlate with the ACC rCBF (Lahti *et al*, 1995; Holcomb *et al*, 2001). Thus, the suggestion that the normalization of rCBF in the schizophrenic ACC by clozapine mediates that drug's clinical advantage in psychosis is not without basis.

However, the rCBF changes with clozapine were seen during the performance of a task and clozapine treatment is associated with improved cognition. Several open-label and double-blind studies comparing clozapine to traditional antipsychotic with neurocognitive batteries have reported, almost unanimously, an improvement in verbal memory, visual attention, and verbal fluency with clozapine (Goldberg *et al*, 1993; Hagger *et al*, 1993; Buchanan *et al*, 1994; Grace *et al*, 1996; Hoff *et al*, 1996; Galletly *et al*, 1997). The gains, however, were modest and some negative effect, in visual memory for example, was noted as well (Goldberg and Weinberger, 1994).

Malfunctions of specific cognitive processes such as working memory (Goldman-Rakic, 1999), planning (Morris *et al*, 1995), context evaluation (Cohen *et al*, 1999), response selection and error monitoring (Carter *et al*, 2001), and learning and cognitive flexibility (Goldberg *et al*, 1990), have been implicated in the generation of the broad neuropsychologic deficits in schizophrenia (Saykin *et al*, 1991, 1994). The ACC is key to the performance of several of these basic mental operations, including attention, response selection, and error monitoring (Ghering *et al*, 1993; Carter *et al*, 1999, Peterson *et al*, 1999; Bush *et al*, 2000). Consistent with its demand on response selection, error monitoring and attention, the auditory task used in this study activates the caudal region of the ACC (Holcomb *et al*, 2000). One possible interpretation of our findings is that patients with schizophrenia already engage these processes during the control task (R/L button press) and that, with clozapine, they allocate these resources only during the DEC. Improved function in ACC could affect various aspects of cognition. For example, a normally functioning ACC could provide conflict-signal information and engage other part of the brain in adaptive cognitive processes (Carter *et al*, 1999). Subtle changes in cognition and daily functioning could be expected. This study suggests that even more comprehensive neurocognitive battery should be evaluated in connection with clozapine treatment.

Thus, there is adequate background support to interpret this study both as an effect on therapeutic efficacy and on cognition. In this study, our patient's clinical status did not significantly worsen during medication withdrawal. This and the small number of patients in this study do not provide enough power to perform correlations between ACC rCBF and behavioral changes. Thus, one can only speculate whether these changes are linked more to clozapine's therapeutic superiority on psychosis or its effects on cognition.

Several neurochemical mechanisms could be involved in the improved anterior cingulate function with clozapine. Clozapine has a relatively lower D2 receptor occupancy and a much broader receptor affinity profile than haloperidol, including high affinity for some of the serotonin,

adrenergic, and cholinergic receptors (Arnt and Skarsfeldt, 1998). Several laboratories have shown that clozapine releases dopamine in frontal cortex in animal preparations, an action possibly related to its serotonin and/or noradrenergic receptor affinity (Pehek *et al*, 1994; Pehek, 1996; Rollema *et al*, 1997; Moghaddam and Bunney, 1999; Hertel *et al*, 1999; Youngren *et al*, 1999). In electrophysiologic and immediate-early gene studies, clozapine and other second-generation antipsychotics demonstrate limbic selectivity in that they preferentially affect dopamine neurons projecting to limbic areas (Chiodo and Bunney, 1983; White and Wang, 1983; Robertson and Fibiger, 1992). Also, unlike traditional antipsychotics, clozapine selectively antagonizes PCP or MK-801 actions on the CNS in animal behavioral models (Bakshi *et al*, 1994; Corbett, 1995; Arvanov and Wang, 1999). Whether clozapine's effect on rCBF patterns is linked to one or several of these properties needs to be established.

The flow differences reported here occur in the face of matched behavioral performance across the unmedicated and medicated SV groups. The lower performance associated with the haloperidol compared to the NV group does not appear to be related to a disrupting learning effect of haloperidol or the result of insufficient practice as all patients were trained to perform at a required level prior to the scanning session. These data are based on scans completed off all medication and on each drug alone (four of six volunteers were scanned in all three conditions; two of six in unmedicated and one drug conditions). In spite of these advantages, there are several limitations to this study. The number of patients studied is small. The study utilizes a fixed crossover design that cannot address possible order effects. These data, thus, should be considered as preliminary and replication will have to be established with larger samples.

We have identified that clozapine, but not haloperidol, normalizes cingulate rCBF patterns during a cognitive task. We propose that this pattern is associated with and represents a surrogate marker of the superior action of clozapine. As clozapine is the only second-generation antipsychotic with demonstrated superior efficacy (Conley *et al*, 1998; Breier *et al*, 1999; Wirshing *et al*, 1999), the mechanism of its therapeutic profile is particularly important to understand. The rCBF patterns identified here could lend guidance for preclinical antipsychotic models, strengthening or weakening current hypothesis. More importantly, they can provide rCBF pattern targets for the evaluation of potential new molecules for the treatment of schizophrenia. The availability of tissue-response targets could hasten the early and quick identification of promising drug candidates.

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