
Asymmetric Rotational (Circling) Behavior, A Dopamine-Related Asymmetry: Preliminary Findings in Unmedicated and Never-Medicated Schizophrenic Patients

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Circling behavior is one of the best understood behaviors in animals. It is, for the most part, dopaminergically mediated and related to asymmetry in dopaminergic activity between the left and right basal ganglia or left and right frontal cortex. As a rule, animals rotate toward the hemisphere with lower striatal dopaminergic activity. A direct technique to find human analogs of circling behavior was not available. We have developed an automated rotometer with which we can apply the circling rodent model to humans. Left-prone circling behavior (neglect of right-sided turning) was found in 10 unmedicated schizophrenic patients, whereas 85 normal controls demonstrated almost equal right and left turning. These preliminary results may suggest the presence of a dopaminergic asymmetry in some unmedicated schizophrenic patients; that is, right anterior subcortical or cortical structures of the brain may manifest a relative dopaminergic overactivity compared to left anterior structures in at least some unmedicated patients with schizophrenia.

Introduction

Animal studies suggest that circling behavior (rotational preference, turning preference, asymmetric orienting response) may be related to asymmetry in dopaminergic activity between the left and right basal ganglia (Ungerstedt and Arbuthnott 1970; Christie and Crow 1971; Glick and Cox 1978; Glick and Ross 1981) or left and right frontal cortex (Crowne and Pathria 1982; Morency et al. 1985; Stewart et al. 1985). Posterior structures do not appear to be implicated in this motor activity (Pycock 1980). Manipulations of other neurotransmitter systems also produce circling. However, as Pycock and Marsden (1978) pointed out, "circling appears to depend ultimately on asymmetrical striatal DA receptor stimulation." For example, circling induced by anticholinergic drugs appears to

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Supported in part by a grant from the Veterans Administration.

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Received November 18, 1986; revised January 13, 1987.

depend on the integrity of dopaminergic function, as it can be abolished by blockade of either postsynaptic dopamine receptor sites with neuroleptic drugs or by inhibition of dopamine (DA) synthesis with α -methyl-*p*-tyrosine. In rats with unilateral locus coeruleus lesions, the rotation is transient and is accompanied by a similarly transient rise in DA in the ipsilateral striatum and a permanent fall in ipsilateral cerebral cortical norepinephrine (NE). Furthermore, pimozide, in the dosage used to block DA but not NE receptors, totally abolishes all circling in locus coeruleus lesioned animals, whereas propranolol plus phenoxybenzamine does not block the circling produced by DA agonists. Thus, as with the cholinergic system, the influences of NE on circling asymmetries appear to be mediated through a final common dopaminergic pathway (Costal and Naylor 1974; Donaldson et al. 1976; Pycock 1980).

As a rule, animals rotate toward the hemisphere with lower striatal dopaminergic activity, regardless of the immediate surroundings (Ungerstedt 1973; Jerussi and Glick 1976; Pycock 1980; Glick and Shapiro 1985). This is considered by some to be a manifestation of contralateral hemispatial neglect (hemisensory neglect, hemiattention) (Ungerstedt 1973; Watson et al. 1974). The dopaminergic asymmetry can be produced with nigrostriatal tract lesions or with amphetamine, which increases the endogenous interhemispheric asymmetry of dopamine in the striata of normal rats and causes the animals to rotate in tight circles toward the side with lower dopamine levels (Glick et al. 1981). Neuroleptics block amphetamine-induced rotation in rats (Pijnenberg et al. 1975; Jerussi and Glick 1976), and this rodent circling model has been used in screening new neuroleptic and antiparkinsonism drugs (Ungerstedt 1971; Crow and Gillbe 1973; Glick and Shapiro 1985). In monkeys, unilateral lesions of the ventral tegmentum involving the substantia nigra induce tremor and hypotonia on the contralateral side. Such results suggest that the basic efferent pathways from the basal ganglia of primates are similar to those of lower animals, such as the dog, cat, and rat (Pycock 1980). Animal studies also indicate that circling behavior requires activation of both striatal and limbic areas (Pijnenburg et al. 1975; Kelly and Moore 1976; Pycock and Marsden 1978).

Using a structured neurological examination, we previously observed similar asymmetric rotation in research subjects with schizophrenia (Bracha et al. 1985b). Although asymmetric circling is only one of several lateralizing neurological signs in schizophrenic disorders, the large quantity of animal studies in the literature on this particular sign and its connection to dopamine, and our new ability to quantify it, may make rotational behavior one of the more useful asymmetries described in schizophrenia. To characterize this neurological phenomenon more carefully, we developed an automated noninvasive hip-mounted electronic rotometer, which we will describe in the following. Using the rotometer, we established that in humans, the rotational preference has a significant test-retest reliability and a well-defined normal range. We also found that while rotational preference is only minimally affected by handedness, it is affected by gender (Bracha et al. 1987a), supporting the hypothesis that the female brain may be more lateralized as far as motor functions are concerned. Using the same instrument, we recently demonstrated an abnormally asymmetric spontaneous rotational behavior in five neurological patients with a well-documented striatal dopamine asymmetry, i.e., hemiparkinsonism (Bracha et al. 1987b). As neuroleptic-induced hemiparkinsonism cannot be ruled out as the explanation for this asymmetry in patients currently or recently on neuroleptic medication, we have now examined never-medicated or chronically unmedicated symptomatic schizophrenic patients.

Table 1. Inclusion Criteria

Male, age between 20 and 40 years
Normal neurological examination
Meet DSM-III (APA 1980) criteria for subchronic or chronic schizophrenia (per consensus of a team of three psychiatrists)
Acutely psychotic and requiring psychiatric hospitalization ^a
Neuroleptic blood levels: zero
Never-before medicated with neuroleptics, or
Neuroleptic-free for at least 180 days (6 months)
No clinical signs of parkinsonism or tardive dyskinesia
Has given written informed consent

^aAll but one.

Methods

Subjects

To avoid neuroleptic effects, such as residual parkinsonism, we studied either first-break, never-medicated patients with schizophrenia or acutely relapsed schizophrenic patients who had been off neuroleptics for at least 6 months. All but one of the patients were identified from among emergency admissions to the San Diego Veterans' Administration Medical Center over a 15-month period, using strict inclusion criteria (Table 1).

Of the 10 schizophrenic patients studied (Table 2), 3 were first-break patients who had never been medicated at the time of our study; 7 others were acutely symptomatic and had been off neuroleptic medication for at least 6 months (26 weeks). Most of the patients were noncompliant with their prescribed neuroleptics and had been psychotic for several months before admission, but were living in isolation or with exceptionally good family support systems. Two patients relapsed during an unsuccessful attempt to maintain their remission with non-neuroleptic agents (lorazepam, lithium). Seven patients who

Table 2. Patient Characteristics

Patient	Age (years)	DSM-III diagnosis ^a	Years with illness	Neuroleptic free (months)	Hand/eye/foot	Drug screen	Total full turns/8 hr
W.M.	24	PS	0.5	Never treated with neuroleptics	RRR	Negative	28
J.R.	31	US	1	Never treated with neuroleptics	LLL	Negative	33
E.D.	24	PS	1	Never treated with neuroleptics	RRR	Lorazepam	30
L.W.	35	CPS	16	12	RLR	Negative	292
L.S.	28	CUS	4	6	RRR	Negative	47
M.G.	34	CPS	10	24	RRR	Negative	61
O.T.	24	CUS	2.5	24	RRR	Negative	106
S.B.	27	CUS	7	6	LLR	Negative	110
D.C.	32	CUS	2	6	RRR	Lorazepam	82
B.M.	35	CPS	3.5	36	RRR	Lithium Amphetamine	53

^aPS, paranoid schizophrenia; US, undifferentiated schizophrenia; CPS, chronic paranoid schizophrenia; CUS, chronic undifferentiated schizophrenia.

remained unmedicated 1–20 days after the initial study were studied a second time to assess test–retest reliability.

The normal control subjects [some of whom are described in detail by Bracha et al. (1987a)] were 85 physicians, students, or hospital employees at the University of California, San Diego. As we had shown (Bracha et al. 1987a) that gender affects rotational preference in normal controls, all patients and controls were men. All subjects were unaware of the type of counts being registered. Ages, as well as hand, foot, and eye preference (Reitan 1979), and number of hours wearing the rotometer were comparable for patients and controls (Table 3).

In animals, both cocaine and amphetamine increase the asymmetry of spontaneous rotational behavior (Glick et al. 1981; Glick and Shapiro 1985). Therefore, we screened for drugs of abuse in the urine and sera of patients in this study (Table 2). Cocaine and amphetamine abuse among hospital employees may be high (McAuliffe et al. 1986). However, drug screening on the 85 normal controls would not have been practical, so it is conceivable that a verifiably drug-free control group would show an even narrower normal range of circling behavior than the present control group shows.

Procedure

As designed for humans, the rotometer is a lightweight, rechargeable, belt-mounted device consisting of a position sensor and an electronic processing circuit. The position sensor monitors changes in the orientation of the dorsal–ventral axis of the subject. Magnetic north is used as an external reference and is tracked by a compass. A compass transducer system moves with the subject relative to the needle. A microchip is programmed with algorithms for registering left and right full (360°) turns, as well as left and right quarter (90°) turns (Bracha et al. 1987a). The output is determined by precisely the same logic employed with an analogous apparatus commonly used for rodents (Greenstein and Glick 1975; Glick and Cox 1978). If a subject enters four quadrants sequentially in the same direction (i.e., turns 360°), a full turn is counted for that direction. However, if a subject enters three quadrants sequentially in the same direction, then enters a quadrant in the opposite direction, a new count begins. Using the rotometer we were able to study unobtrusively the spontaneous movements of these severely symptomatic inpatients during the 12–72-hr initial observation periods in which they were without pharmacological treatment. Each patient and each control wore the rotometer for about 8 hr, starting

Table 3. Subject Variables, Group Means, and Standard Deviations

n	Controls (n = 85)	Schizophrenic patients (n = 10)	<i>p</i> ^a
Age	30.5 ± 10.9	30.4 ± 4.6	NS
Hours monitored	7.8 ± 0.9	7.9 ± 2.4	NS
Percent left hemisphere "dominant"	63%	70%	NS
XQT	738 ± 776	695 ± 619	NS
Total full turns	66.8 ± 33.8	84.2 ± 78.8	NS
Percent right preference	49.9 ± 11.3	30.7 ± 14.0	0.0004

^aWilcoxon two-sample test.

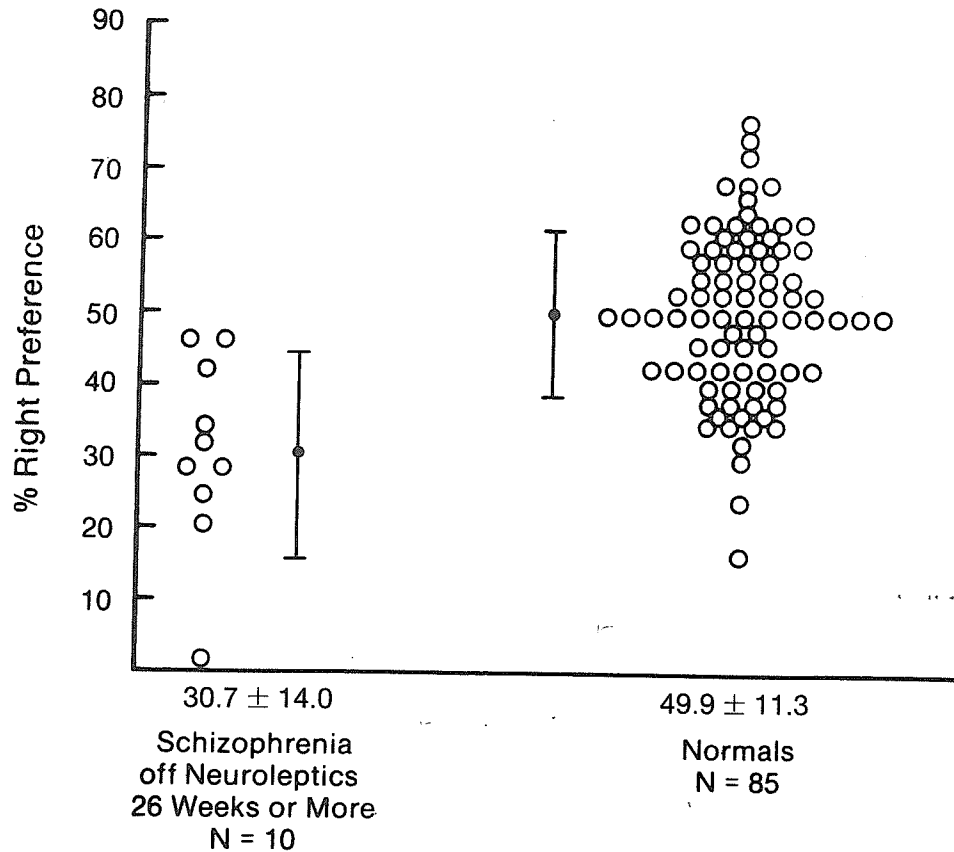


Figure 1. Percent of spontaneous full (360°) turns to the right (% right preference) during 8 hr of automated monitoring. Male subjects, $p < 0.0004$, Wilcoxon two-sample test.

between 8:00 and 9:00 AM. Subjects were not given any specific instructions and were unaware of the type of counts obtained by the device.

Percent right preference is used as the index of rotational asymmetry. This is defined as the percentage of full turns to the right (clockwise). It is important to recognize that this measure is independent of activity level; it reflects a behavioral asymmetry and is independent of the absolute amount of circling in either direction. Unless otherwise stated, all references to circling phenomena refer to an asymmetry or preference, not to a difference in the number of total turns.

On the other hand, extra quarter turns (XQT) is a standard measure of nonlateralized activity (Greenstein and Glick 1975), referring to the remainder when four times the number of full turns is subtracted from the total of quarter turns.

Results

Results (presented in Figure 1) show that:

1. All 10 schizophrenic patients turned more to the left (counterclockwise) than to the right, as compared with normals (Figure 1). Patients and controls differed

significantly in percent right preference. For the normal male subjects, percent right preference was $49.9\% \pm 11.3\%$ (mean \pm SD); the patients' mean percent right preference was $30.7\% \pm 14.0\%$.

2. All 10 schizophrenic patients registered percent right preference below the mean of the normal group. For 3 of the 10 patients, percent right preference was more than 2 SD below the mean for normal controls (Figure 1).
3. Patients did not differ from controls in XQT, a measure of general nonlateralized activity (Table 3).
4. Patients did not differ from controls in total (left and right) 360° turns (Table 3).
5. As was previously shown to be the case in normals (Bracha et al. 1987a), rotational preference had good test-retest reliability among the schizophrenic patients, with a significant intraclass correlation coefficient (Bartko 1966) of 0.65 ($F = 4.77$, $p < 0.03$) (SAS Inc. 1985).

Discussion

This preliminary report suggests the presence of an abnormal asymmetry in a dopamine-related neurological phenomenon in symptomatic chronically unmedicated schizophrenic patients. Although showing no clinical signs of parkinsonism and while off neuroleptics for at least 6 months, all 10 schizophrenic subjects demonstrated what may be a subtle hemispatial neglect that is similar to that reported by us in right-sided hemiparkinsonian patients (Bracha et al. 1987b).

As to the mechanisms that may underlie abnormal rotational preference in schizophrenia, current understanding of the pathophysiology of schizophrenia suggests several possibilities that are not mutually exclusive.

1. Abnormal rotational preference may reflect asymmetric striatal involvement in schizophrenia. Glucose utilization has been found to be asymmetrically decreased in the striatum in schizophrenic patients (Buchsbaum et al. 1982). Postmortem (Stevens 1982) and neuropsychological studies (Schneider 1984) suggest that basal ganglia dysfunction may be associated with schizophrenia. Mannerisms and catatonia were reported in schizophrenia, even in the preneuroleptic era, and may be striatal signs. Furthermore, psychotic symptoms in Huntington's chorea suggest striatal involvement in psychosis. Therefore, even if it is only a striatal dopaminergic marker, rotational preference may be of interest in schizophrenia.
2. Asymmetric overactivity (right > left) of the mesoprefrontal dopaminergic system may be manifested as a "frontal hemispatial neglect" syndrome in schizophrenia. In animals, mesolimbic DA asymmetry alone does not produce circling behavior (Pijnenburg et al. 1973; Kelly and Miller 1975; Kelly and Moore 1976). On the other hand, the dorsolateral prefrontal cortex (area 46) and the adjacent frontal eye fields (area 8) have been implicated both in circling (Crowne and Pathria 1982; Morency et al. 1985; Stewart et al. 1985) and in human hemispatial neglect syndrome (Heilman and Valenstein 1972; Ungerstedt 1973; Marshall and Teitelbaum 1974; Heilman and Watson 1977) as well as in schizophrenia (Levin 1984, Weinberger et al. 1986). We have reported that schizophrenic patients who have visual hallucinations report experiencing these internal stimuli more frequently in the right visual hemifield (Bracha et al. 1985a). Schizophrenic patients also have longer response latencies to external stimuli presented to the right visual hemifield (Con-

nolly et al. 1979). Our present results suggest that a good explanation for these asymmetries may be a subtle right-hemispatial neglect (right hemi-inattention) syndrome.

Conclusions drawn from the data presented here must be considered to be tentative. The most obvious limitation is the small number of schizophrenic subjects, a result of our stringent inclusion criteria (Table 1). A second limitation is the setting in an acute admission ward, which did not allow for administration of psychosis rating scales. However, this setting was chosen because it allowed us to reexamine our earlier observations (Bracha et al. 1985b) in a group that was 6 months or more drug free and included some never-medicated subjects. Such patients rarely volunteer to enter schizophrenia research units, and we felt that reaching them was important, as neuroleptics abolish rotational behavior in animals (Jerussi and Glick 1976) and are still present in human brain tissue more than 2 months after drug withdrawal (Korpi et al. 1984). A third limitation of this report is that the controls used here may be less than ideal. However, it is relevant that a group of 16 medicated patients meeting DSM-III criteria for chronic schizophrenia, who were housed on the same unit as the unmedicated schizophrenic patients, did not significantly differ from the controls in their rotational symmetry, nor did a group of 11 drug-free research subjects with major depression (Dupont, Bracha, Gillin, et al.: manuscript in preparation). Rotational preference in female schizophrenic patients remains to be studied.

Handedness has been shown to be significantly, albeit weakly, correlated with schizophrenia (Gur 1977), specifically paranoid schizophrenia (Lishman and McMeekan 1976; Nasrallah et al. 1981). Rotational preference is not significantly correlated with handedness or footedness scores in normal controls (Bracha et al. 1987a). Also, all seven strictly right-handed schizophrenic patients in this study turned preferentially to the left. Limb preference is probably much less sensitive than rotational preference as a probe of the symmetry of ascending DA systems and frontotemporal structures in mammals. It may primarily reflect asymmetry in parietal lobe function.

Our findings suggest that the postulated overactivity of the ascending dopaminergic system (Wong et al. 1986) may be asymmetric (more marked in the right hemisphere) in a subgroup of unmedicated schizophrenic patients. Unlike hemiparkinson's disease, any asymmetry of the DA system in schizophrenia is more likely to be postsynaptic in origin. In an effort to assess the role of pre- and postsynaptic elements of the dopaminergic synapse in this asymmetry, we are currently studying the effect of direct dopamine receptor agonists on rotational preference of unmedicated schizophrenic patients and controls.

In conclusion, left-prone circling behavior (neglect of right-sided turning) was found in 10 unmedicated schizophrenic patients, whereas 85 normal controls demonstrated almost equal right and left rotational behavior.

I thank Drs. Dilip Jeste, Marc Schuckit, J. Christian Gillin, and Clifford Shults and two anonymous reviewers for their comments on earlier versions of the paper, as well as S. Khansarinia and the staff and patients of ward 2-south at the San Diego VA Medical Center.

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