

# Nonstereotyped Responding in Positive Schizotypy after a Single Dose of Levodopa

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Stereotyped behavior and left-sided orientation biases, associated with the dopamine (DA) system, were observed in populations of the schizophrenia spectrum disorders. We investigated whether heightened DA concentrations influence both side biases and stereotyped responding in a visuo-motor computer task, in which 90, 180, and 270° rotated objects had to be brought into a target position. To account for the role of the schizophrenia spectrum, task performance was also analyzed as a function of healthy participants' high or low magical ideation (MI), a positive schizotypal feature. The first 36 participants (20 women) remained substance free. In a second sample, 20 men received levodopa and 20 men a placebo in a double-blind procedure. Results showed that high MI scorers responded more stereotyped than low MI scorers, without being specifically biased towards the left side. Rotation preferences toward one or the other side made high MI scorers less flexible for objects efficiently to be rotated into the opposite direction. This inflexibility may reflect impaired left hemisphere functioning. Unexpectedly, in the levodopa group, high MI scorers performed superior to low MI scorers. Since DA actions appear to follow an inverted U-shape function, the 'low' performing high MI scorers profited from the enhanced DA availability. Our observation in the levodopa group points to a dissociation between schizotypy and schizophrenia: while cognitive improvement in schizophrenia can occur after treatment with atypical neuroleptic agents, in our positive schizotypal participants a DA agonist resulted in improved task performance. This dissociation may point to protective neurochemical mechanisms preventing healthy schizotypes from developing full-blown psychotic symptoms.

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## INTRODUCTION

Dopamine (DA) and the emergence of psychosis are incontestably tied. Patients with schizophrenia profit from DA antagonistic treatment (Laruelle and Abi-Dargham, 1999) and show worsening of psychotic symptoms after DA agonistic treatment (Abi-Dargham *et al*, 1998; Davidson *et al*, 1987). In healthy populations, DA agonists have the potential to trigger psychotic symptoms (Janowsky and Risch, 1979; Sekine *et al*, 2001). Consequently, acute psychotic symptoms were assumed to emerge from a hyperactive DA system (Davis *et al*, 1991; Laruelle and Abi-Dargham, 1999).

Among the behavioral markers for a hyperactive DA system are stereotyped movements. As known from the animal literature, the administration of DA agonists can trigger stereotyped behavior (Staton and Solomon, 1984; Kelley *et al*, 1988; Kuczenski and Segal, 1999), particularly after high doses (Randrup and Munkvad, 1974). It is thus not a surprise that stereotyped behavior is observed in patients with schizophrenia (Kraeplin, 1919; Bleuler, 1911/1950; Jones, 1965; Peralta and Cuesta, 2001) and in healthy persons after amphetamine abuse (Connell, 1958; Ridley *et al*, 1988). Rocking, walking backwards and forwards, biting and other repetitive movements of the jaw, part of limbs, or even whole limbs were described as stereotyped behavior in schizophrenia (Jones, 1965). Stereotyped behavior also occurs at the cognitive level (see also Garner *et al*, 2003) in various facets along the schizophrenia spectrum. For instance, perseverative errors in the Wisconsin Card Sorting Test (WCST) are elevated in patients with schizophrenia (Perry and Braff, 1998 for overview), schizotypal personality disorder (Raine *et al*, 1992; Cadenhead *et al*, 1999) and healthy schizotypal participants (Lenzenweger and Korfine, 1994; Gooding *et al*, 1999).

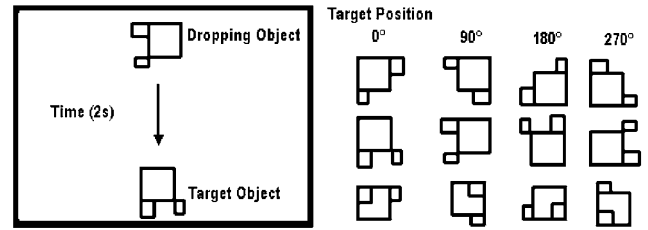
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During the generation of random sequences, patients with schizophrenia (Salamé *et al*, 1998; Brugger, 1997 for overview), healthy participants after amphetamine administration (Ridley *et al*, 1988), and healthy participants with elevated schizotypal features (Brugger *et al*, 1990; Avons *et al*, 2003) showed more pronounced response biases compared to their respective controls.

Another behavioral marker for a hyperactive DA system is turning behavior, which depicts a relatively hyperactive DA system in one over the other hemisphere. Well known from the animal literature (Pycock, 1983 for overview) and from one study with patients with asymmetrical Parkinson's disease (Bracha *et al*, 1987), the preferred side of whole-body turning occurs away from the hemisphere with the more active DA system. Supporting the notion of a relative hyperactivation of the right-hemispheric DA system, acutely psychotic patients (Bracha *et al*, 1993) and healthy participants with positive schizotypal features (Mohr *et al*, 2003a) displayed a significant preference for left- over right-sided turns.

From the previous sections, it can be concluded that stereotyped movements and turning behavior seem to be promising behavioral markers to depict the activity of the DA system. Stereotyped behavior and left-sided turning biases along the schizophrenia spectrum suggest a (dysfunctional) hyperactive DA system relevant to all kinds of psychotic(-like) thought. However, it is not known how far nonspatial and spatial (turning) stereotyped behaviors in the schizophrenia spectrum are mediated by common dopaminergic actions. As noted above, both measures are enhanced under a presumably hyperdopaminergic state and attenuated with DA antagonistic treatment, in particular with second-generation antipsychotic medication (Levine *et al*, 1997; Kuczenski and Segal, 1999; Purdon *et al*, 2001; Harvey *et al*, 2003). Since the previous observations would suggest that the two measures are somehow interrelated, we determined the modification of both measures by a potentially hyperdopaminergic state in two experiments. In both experiments, the relative strength of hyperdopaminergia was inferred from individuals' positive schizotypal features, that is, magical ideation (MI, Eckblad and Chapman, 1983). In Experiment 2, participants' dopaminergic state was directly manipulated by levodopa administration.

In both experiments, we assessed nonspatial and spatial (turning) response stereotypies in a computer task (see Figure 1) resembling the popular TETRIS game. Objects 'dropped' down on the screen and had to be rotated (by 90, 180, or 270°) to match a target orientation indicated at the bottom of the computer screen (see Figure 1). In total, 2 s were allotted to accomplish one trial. By counting the number of key presses eliciting either a 90° left-sided or a 90° right-sided rotation, we could determine rotational preferences to either side. Critically, for target orientations rotated 180° relative to the dropping stimulus, left- or right-sided rotations would be equally efficient (two subsequent key presses in any case), but one side might be favored over the other. Moreover, in case of stereotyped responding towards one side, task performance would be most efficient for some stimuli, but inferior for other. For instance, stereotyped left-sided rotation preferences would facilitate task efficiency for 90° rotated objects (one left-sided key



**Figure 1** Sample trial of the computer task (left panel). Note that one left-sided key press or three right-sided key presses during 2 s would rotate the dropping object into the target position as indicated at the bottom of the screen. The right panel of the figure depicts the three different target positions used as well as the respective dropping objects in three different orientations each.

press), but would be disadvantageous for 270° rotated objects (three left-sided key presses instead of one right-sided key press). Under the assumption that rotations in a 2D plane are modulated by the DA system in a way comparable to those of one's body in 3D space, we predicted for our participants without levodopa supplementation an association between left-sided rotation preferences and elevated MI scores (Mohr *et al*, 2003a). In case of stereotyped responding, this left-sided rotation preference should result in an efficient rotation strategy for 90° objects, but an inefficient rotation strategy for 270° objects. DA agonists can trigger psychotic symptoms in healthy persons (Janowsky and Risch, 1979; Sekine *et al*, 2001) and worsen psychotic symptoms in patients (Davidson *et al*, 1987; Abi-Dargham *et al*, 1998). Thus, in case of a similar modulation of the two behavioral measures by the DA system, we would expect that participants, in particular those with high MI scores, would show an even stronger left-sided rotation preference and more stereotyped left-sided key presses (specifically evident for 270° objects) after levodopa as compared to placebo supplementation.

The use of the schizotypy approach in the present study is advantageous for several reasons. First, it would be unethical to provide DA agonistic substances to patients with schizophrenia, given their potential to worsen psychotic symptoms (Davidson *et al*, 1987; Abi-Dargham *et al*, 1998). Second, this line of research became well accepted to study brain functions related to schizophrenia free from confounding correlates of severe clinical symptoms such as medication and institutionalization (eg Gooding *et al*, 1999; Avons *et al*, 2003). In fact, preselected and unselected schizotypal individuals, thought to be 'psychosis-prone' (Chapman *et al*, 1994; Kwapil *et al*, 1997), perform similar to patients with schizophrenia for cognitive (Gooding *et al*, 1999; Park, 1999), attentional (Sarkin *et al*, 1998; Mohr *et al*, 2003a), behavioral (Barnett and Corballis, 2002; Mohr *et al*, 2003b) and physiological (Klein *et al*, 1999; Pizzagalli *et al*, 2000) measures. Finally, alterations of dopaminergic responsivity may accompany the schizophrenia spectrum disorders in a continuous manner; the DA metabolite homovanillin acid (HVA) correlated with severity of positive symptoms in schizophrenia (Pickar *et al*, 1984; Davidson and Davis, 1988) and the extent of schizotypal personality disorder (Siever *et al*, 1991, 1993).

## EXPERIMENT 1

### Participants

A total of 36 healthy participants (20 women) were recruited by flyers. Volunteers with any current medication or a history of drug abuse or neuropsychiatric illnesses had been excluded. The relevant screening followed the guidelines offered by Campbell (2000). All participants were right-handed according to a 13-item handedness questionnaire (Chapman and Chapman, 1987). The local ethics committee had approved the study, and after complete description of the study to the participants, written informed consent was obtained.

### Magical Ideation Scale

Each participant filled in a validated 30-item questionnaire that includes items such as 'I sometimes have a feeling of gaining or losing energy when people look at me or touch me,' (keyed true) or 'Some people can make me aware of them just by thinking about me' (keyed true). Scores on the MI scale range from 0 to 30, with higher scores indicating more pronounced magical thinking. The scale is published in full in Eckblad and Chapman (1983) and in Barnett and Corballis (2002), and normative data can be found in Garety and Wessely (1994).

### Visuo-Motor Rotation Task

**Stimuli.** Three different line drawings were composed from the same elements (one square, two rectangles; see Figure 1). The elements appeared on the computer screen in the following sizes: square: 10 mm × 10 mm, larger rectangle: 4 mm × 5 mm, and smaller rectangle: 4 mm × 3 mm.

**Procedure.** The line drawings appeared one after the other at the top of a computer screen (18 cm height; 25 cm width). Each of them appeared for 2 s. During this time period, the drawings 'fell down' continuously in a straight line toward a target object presented at the bottom of the screen (Figure 1, left). The target object was identical to the dropping object, but the dropping object appeared either in the same orientation (0°), or 90°, 180°, or 270° rotated from the target object (Figure 1, right). Each line drawing was presented nine times. Thus, there were 27 stimulations per object orientation. The participant was instructed to turn the object as fast and accurately as possible into the target position by pressing either a key for 90° counterclockwise (button: ←) or another key for 90° clockwise (button: →)

rotations. For instance, to match a 180° object with the target position, participants could rotate the object by two presses of the same key (either in the clockwise or counterclockwise direction). Participants could also complete a trial by pressing another key (button: ↓). On pressing this key, the object dropped down immediately. The whole experiment of 108 trials was conducted twice, once with the right hand and once with the left hand. Half of the participants started with the left, the other half with the right hand. The number of key presses to the left and right, respectively, were summed for each object orientation and across the two performing hands.

### Data Analysis

Despite the fact that participants were explicitly instructed to rotate the objects in the fastest and most accurate way, two participants did not obey to these instructions and were excluded from the analyses. One participant made use of the left-sided key only nine times (MI score = 4), while the remaining participants made on average  $149.9 \pm 68.8$  left-sided key presses. The other participant made only 27 correct trials across blocks (MI score = 12), while the remaining participants made at least 139 correct responses ( $182.3 \pm 21.4$ ). The remaining group of 34 participants was split at the median MI scale score (9) into a high ( $n = 18$ ) and low ( $n = 16$ ) MI group.

To obtain a measure indicating rotational preferences to the left or right side, we calculated a conventional laterality index score (number of left-sided key presses minus number of right-sided key presses divided by the sum of all key presses; Marshall *et al*, 1975) for 90°, 180° and 270° objects separately. Consequently, positive values indicate a left-sided rotation preference and negative values a right-sided rotation preference. A three-way ANOVA with MI groups (high vs low) and gender (men vs women) as between-subject measure was performed on the laterality index scores for 90°, 180°, and 270° objects as repeated measure. To test whether rotational biases were associated with task efficiency (accuracy), we calculated the same index scores as described above, but only for correct responses. We performed an analogous ANOVA as described above, but on the laterality index scores for correct trials. *Post hoc* single comparisons were assessed with Duncan's multiple range tests correcting for multiple comparisons. All tests were two-tailed and the alpha-level was set at 0.05.

**Table 1** Descriptive Data of the Study Sample of Experiment 1, for the Two Magical Ideation (MI) Groups and Women and Men Separately

	Low MI group		High MI group	
	Women	Men	Women	Men
Age (years)	31.4 ± 7.3	28.8 ± 5.4	27.3 ± 4.3	30.0 ± 7.2
Education (years)	21.0 ± 4.2	18.5 ± 3.4	18.8 ± 3.3	18.3 ± 3.3
MI scores	4.6 ± 2.6	5.1 ± 3.0	14.5 ± 5.8	12.3 ± 2.4

**Table 2** Mean ( $\pm$ SD) Laterality Index Score for 90°, 180°, and 270° Rotated Objects for the Whole Sample as well as for the Gender Groups Separately

		All trials		Correct trials	
		Low MI group	High MI group	Low MI group	High MI group
90°	All	0.18 $\pm$ 0.45	0.25 $\pm$ 0.45	0.51 $\pm$ 0.58	0.54 $\pm$ 0.53
	Men	0.11 $\pm$ 0.55	0.22 $\pm$ 0.44	0.48 $\pm$ 0.52	0.52 $\pm$ 0.52
	Women	0.25 $\pm$ 0.34	0.27 $\pm$ 0.47	0.53 $\pm$ 0.67	0.54 $\pm$ 0.57
180°	All	-0.007 $\pm$ 0.49	0.20 $\pm$ 0.41	0.05 $\pm$ 0.55	0.18 $\pm$ 0.52
	Men	-0.03 $\pm$ 0.51	0.24 $\pm$ 0.45	0.08 $\pm$ 0.54	0.29 $\pm$ 0.52
	Women	0.02 $\pm$ 0.50	0.18 $\pm$ 0.40	0.01 $\pm$ 0.59	0.11 $\pm$ 0.53
270°	All	-0.27 $\pm$ 0.33	-0.006 $\pm$ 0.46	-0.64 $\pm$ 0.26	-0.15 $\pm$ 0.66
	Men	-0.43 $\pm$ 0.30	-0.04 $\pm$ 0.50	-0.71 $\pm$ 0.24	-0.07 $\pm$ 0.63
	Women	-0.10 $\pm$ 0.27	0.01 $\pm$ 0.46	-0.57 $\pm$ 0.28	-0.20 $\pm$ 0.70

Values are presented for the two magical ideation (MI) groups for all trials (correct+incorrect) and correct trials, only.

## RESULTS AND BRIEF DISCUSSION

### Participants

Separate three-way ANOVAs with MI groups (high vs low) and gender (women vs men) on (1) age, and (2) years of education were not significant (all  $F$ -values  $<$  1.7,  $df = 1,30$ ; all  $p$ -values  $>$  0.20; Table 1). A comparable ANOVA on MI scores ruled out any gender difference with respect to the MI scores in the two MI groups, since there was neither a main effect for gender ( $F(1,30) = 0.36$ ,  $p = 0.55$ ) nor an interaction between gender and MI group ( $F(1,30) = 0.91$ ,  $p = 0.35$ ; Table 1).

### Visuo-Motor Rotation Task

Laterality index scores for all trials, irrespective of correctness (see Table 2): The ANOVA showed a significant main effect for object orientation ( $F(2,60) = 8.68$ ,  $p = 0.0005$ ). Participants showed left-sided rotation preferences for 90° objects ( $0.22 \pm 0.44$ ) and right-sided rotation preferences for 270° objects ( $-0.13 \pm 0.42$ ) ( $p = 0.0002$ ). Critically, a left-sided rotation preference was also observed for 180° objects ( $0.10 \pm 0.46$ ); the mean laterality index score did not differ from that for 90° objects ( $p = 0.20$ ) but from that for 270° objects ( $p = 0.006$ ).

Laterality index scores for *correct* trials (see Table 2): Also, this ANOVA showed a significant main effect for object orientation ( $F(2,60) = 44.81$ ,  $p < 0.0001$ ) with all *post hoc* comparisons being significant (all  $p$ -values  $<$  0.0003). The left-sided rotation preference for 90° objects ( $0.52 \pm 0.54$ ) and the right-sided rotation preference for 270° objects ( $-0.38 \pm 0.56$ ) were more pronounced than that for all trials, but the left-sided preference for 180° objects was small ( $0.12 \pm 0.53$ ). The significant interaction between MI groups and object orientation ( $F(2,60) = 3.29$ ,  $p = 0.04$ ) emerged from differences between the MI groups for 270° objects; the low MI group revealed a more pronounced rightward rotation bias than the high MI group ( $p = 0.0005$ ),

no group differences were found for 90° ( $p = 0.84$ ) and 180° ( $p = 0.26$ ) objects.

The findings from Experiment 1 confirmed that objects were preferentially rotated along the shortest trajectory. In addition, participants showed a leftward rotation preference for 180° objects, which was statistically comparable to the one for 90° objects. This, together with the observation that rightward rotation preferences for 270° objects were lesser pronounced than leftward rotation preferences for 90° objects, points to an overall leftward rotation preference. The different laterality index scores in the high and low MI group for 270° objects supports our original prediction that stereotyped leftward rotations of high MI scorers would attenuate task performance for objects efficiently to be rotated into the nonpreferred direction. The low MI group adapted efficiently to a rightward rotation preference for 270° objects and a leftward rotation preference for 90° objects. Conversely, the high MI group showed a leftward rotation preference for 90° objects, but only a negligible side preference for 270° objects. This latter observation indicates that participants rotated 270° objects more often along the time consuming, inefficient counterclockwise trajectory, not overcoming the stereotyped responding towards the preferred counterclockwise direction. This relative leftward rotation bias in high MI scorers would add further evidence for a relative right-hemispheric hyperdopaminergia in this population (see also Brugger and Graves, 1997; Mohr *et al*, 2003a). Note that this evidence derives from a task investigating object rotation in the 2D plane, while the previous studies focused on rotational biases in 3D space.

## EXPERIMENT 2

### Participants

A total of 40 healthy men were recruited by flyers and personal contact. None of them had participated in Experiment 1. All of them were right-handed according to a 13-item handedness questionnaire (Chapman and

Chapman, 1987). Again, participants with any current medication, history of drug abuse, or neuropsychiatric illness had been excluded during an extended clinical interview (Campbell, 2000). After a full description of the study, written informed consent was obtained from all participants.

### Magical Ideation Scale

In a procedure identical to Experiment 1, each participant filled in the MI scale prior to experimental testing (Eckblad and Chapman, 1983). In the present experiment, we did not test participants, who scored in the upper quartile of this scale (MI scores >22), since DA agonists might trigger a psychotic breakdown (Janowsky and Risch, 1979; Sekine *et al*, 2001), with a presumably elevated risk for participants with high MI scores. The local Ethics Committee had approved the study provided such precautions would be taken. This exclusion was considered unlikely to drastically influence results, since neuropsychological performance patterns described in schizophrenia or healthy schizotypal individuals have even been observed in random samples of completely healthy participants as a function of MI scores (Brugger and Graves, 1997; Mohr *et al*, 2001, 2003a, b).

### Visuo-Motor Rotation Task

Task and procedure were identical to Experiment 1.

### Double-Blind Procedure

The study was a randomized, double-blind levodopa/placebo design. A dual-release formulation of levodopa/benserazide (brand name: Madopar<sup>®</sup> DR, Roche Pharma (Schweiz) AG, Reinach, Switzerland) with a fast absorption within the first hour and sustained concentration levels thereafter (Gasser *et al*, 1999) was administered. Prior to the study, participants were informed about the experimental procedure and the possible side effects of levodopa. Each participant fasted overnight and arrived at 9 a.m. on the experimental day. Participants were also instructed not to consume any alcohol or other drugs for at least 24 h before testing. After having provided informed consent, participants received either Madopar<sup>®</sup> DR or a placebo. Participants consumed 200 ml water directly after substance administration, and a standardized breakfast was provided 15 min later. In order to insure that participants were under significant levodopa concentration throughout the experiment, two blood samples of about 5–7 ml each were drawn. The first blood sample was collected 30 min after drug administration. The experiments started afterwards. The first trial of the computer task was conducted about 1 h after the first blood sample and the second trial about 45 min after the first trial. As soon as the experiments were finished (about 120 min after the first blood sample), a second blood sample was drawn.

### Blood Sample Collection and Analysis

The blood was collected in plastic tubes containing lithium heparinate as an anticoagulant and plasma was separated by centrifugation. The samples were stored immediately at

–80°C pending analysis. In a first analytical step, to eliminate interfering substances, an internal standard was added to the blood serum samples. Then, the blood serum was fixed on activated alumina, in basic media, and thoroughly vortexed. The liquid phase was discarded and the alumina was finally washed with ultrapure water. Then, levodopa and the internal standard were eluted in acidic media and determined by high-pressure liquid chromatography (HPLC) with electrochemical detection (ECD). The substances were separated on a reversed-phase column and detected by ECD in amperometric mode. Quantification was carried out by internal standard method. Analytical reproducibility was 10% and quantification limit was 3 ng/ml.

### Data Analysis

Due to an error in the randomization of placebo and levodopa, 21 participants were in the placebo group and 19 participants in the levodopa group. Two participants (one placebo participant and one levodopa participant) rarely made any leftward key presses ( $n < 10$ ), thus disobeying instructions. One placebo participant made use of the left-sided key only seven times (MI score = 3) and one levodopa participant (MI score = 5) never made use of the left-sided key, while the remaining participants made on average  $128.1 \pm 58.2$  left-sided key presses. They were excluded from further analyses. Moreover, one additional placebo participant (MI score = 4) was excluded because he performed an overproportionally large number of rightward key presses for 90° objects ( $n = 127$ ), while the remaining participants made on average only  $28.0 \pm 27.5$  rightward key presses for 90° objects. Since participants scoring in the upper quartile of the MI scales have not been included in this study, the median (6) of the whole group was lower than in Experiment 1. The median split created a high ( $n = 20$ ; nine levodopa participants and 11 placebo participants) and low ( $n = 17$ ; nine levodopa participants and eight placebo participants) MI group.

We performed analogous ANOVAs as described for Experiment 1, except that gender was excluded (only men were tested) and substance group (levodopa versus placebo) was added as a between-subject factor. *Post hoc* single comparisons, if not otherwise stated, were assessed with Duncan's multiple range tests correcting for multiple comparisons. All tests were two-tailed and the  $\alpha$ -level was set at 0.05.

## RESULTS AND BRIEF DISCUSSION

### Participants

The three-way ANOVAs with substance groups (placebo *vs* levodopa) and MI groups (high *vs* low) as between-subject factors on (1) age and (2) years of education were not significant (all  $F$ -values < 1.70,  $p$ -values > 0.20, Table 3). A comparable ANOVA on MI scores ruled out any difference in the substance groups with respect to the MI scores in the two MI groups, since neither the main effect for substance group ( $F(1,33) = 1.40$ ,  $p = 0.25$ ) nor the interaction between gender and MI group ( $F(1,33) = 0.60$ ,  $p = 0.45$ ) were significant.

**Table 3** Descriptive Data of the Study Sample in Experiment 2 for the Two Magical Ideation (MI) and Substance Groups Separately

	Low MI group		High MI group	
	Levodopa group	Placebo group	Levodopa group	Placebo group
MI scores	3.0 ± 0.9	3.6 ± 1.6	9.6 ± 5.0	11.9 ± 4.6
Education (years)	16.6 ± 3.0	17.6 ± 3.1	15.8 ± 3.5	17.3 ± 2.9
Age (years)	23.9 ± 3.5	25.9 ± 3.2	24.4 ± 4.9	25.7 ± 3.6

**Table 4** Mean (±SD) Laterality Index Score for All Trials (correct+incorrect) for 90°, 180°, and 270° Rotated Objects and the Two Magical Ideation (MI) and Substance Groups, Separately

	Low MI group		High MI group	
	Levodopa group	Placebo group	Levodopa group	Placebo group
90°*	0.23 ± 0.59	0.65 ± 0.38	0.68 ± 0.44	0.0 ± 0.38
180°**	-0.02 ± 0.59	-0.04 ± 0.68	0.41 ± 0.45	-0.24 ± 0.33
270°	-0.32 ± 0.56	-0.24 ± 0.65	-0.41 ± 0.39	-0.41 ± 0.33

Interaction significant \* $p < 0.001$ , \*\* $p = 0.07$

**Table 5** Mean (±SD) Laterality Index Score (Correct Responses) for 90°, 180°, and 270° Rotated Objects and the Two Magical Ideation (MI) and Substance Groups, Separately

	Low MI group		High MI group	
	Levodopa group	Placebo group	Levodopa group	Placebo group
90°*	0.55 ± 0.50	0.86 ± 0.17	0.86 ± 0.26	0.53 ± 0.29
180°**	-0.03 ± 0.62	-0.02 ± 0.67	0.41 ± 0.45	-0.23 ± 0.34
270°	-0.59 ± 0.45	-0.64 ± 0.51	-0.76 ± 0.20	-0.72 ± 0.23

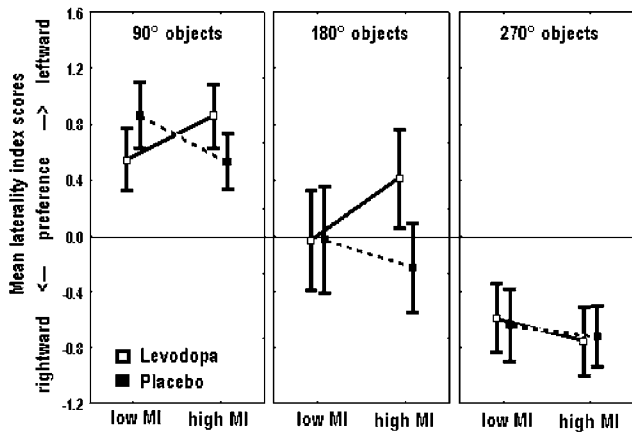
Interaction significant \* $p = 0.006$ , \*\* $p = 0.07$ .

In the levodopa group, the mean levodopa serum concentration was  $213.5 \pm 232.6$  ng/ml for the first blood sample and  $142.2 \pm 158.5$  ng/ml for the second blood sample ( $t_{17} = 1.23$ ,  $p = 0.24$ ). None of the participants reported any remarkable substance effect. Levodopa serum concentrations in the placebo group were zero, throughout.

### Visuo-Motor Rotation Task

Laterality index scores for all trials, irrespective of response correctness (see Table 4): The ANOVA revealed a significant main effect for object orientation ( $F(2,66) = 39.01$ ,  $p < 0.0001$ ). *Post hoc* comparisons showed significant differences between objects (all  $p$ -values  $< 0.0002$ ) with a pronounced leftward rotation preference for 90° objects ( $0.36 \pm 0.53$ ) and rightward preference for 270° objects ( $-0.38 \pm 0.47$ ) as well as almost no side preference for 180° objects ( $0.02 \pm 0.55$ ). The interaction between MI groups and substance groups was significant ( $F(1,33) = 4.99$ ,  $p = 0.03$ ) indicating that high MI participants showed a rightward rotation preference in the placebo group

( $-0.22 \pm 0.29$ ), but a leftward rotation preference in the levodopa group ( $0.22 \pm 0.27$ ,  $p = 0.03$ ). Single comparisons with respect to the low MI groups were not significant (placebo group:  $0.08 \pm 0.45$ ; levodopa group:  $-0.04 \pm 0.48$ ; all  $p$ -values  $> 0.11$ ). The three-way interaction was also significant ( $F(2,66) = 5.52$ ,  $p = 0.006$ ). We performed three ANOVAs on each laterality index score separately. The interaction between MI groups and substance groups in the ANOVA on 90° objects was significant ( $F(1,33) = 13.32$ ,  $p = 0.0009$ ). The high MI group had a stronger leftward rotation bias in the levodopa than (1) placebo group ( $p = 0.005$ ) and (2) low MI participants in the levodopa group ( $p = 0.05$ ). In the placebo group, the low MI group had a stronger leftward rotation preference than the high MI group ( $p = 0.006$ ). A somewhat similar picture was observed for the ANOVA on 180° objects. Although the interaction was only a statistical trend ( $F(1,33) = 3.45$ ,  $p = 0.07$ ), the high MI group's leftward rotation bias was stronger in the levodopa group than its rightward rotation bias in the placebo group ( $p = 0.02$ ). The ANOVA on 270° objects was not significant (all  $F$ -values  $< 0.20$ ).



**Figure 2** Mean laterality index scores for correct trials in the two substance groups (dashed line placebo group, black line levodopa group). Performance is depicted for the high and low MI groups and the three object types separately. Vertical bars denote 0.95 confidence intervals.

Laterality index scores on *correct* trials (see Table 5): The ANOVA again showed a significant main effect for stimulus orientation ( $F(2,66) = 168.02$ ,  $p < 0.0001$ ) with all *post hoc* comparisons being significant ( $p$ -values  $< 0.0002$ ). The three-way interaction was again significant ( $F(2,66) = 3.91$ ,  $p = 0.02$ ). As for the ANOVA on all trials, we conducted three separate ANOVAs on the laterality index scores separately. The interaction for 90° objects was significant ( $F(1,33) = 8.67$ ,  $p = 0.006$ , Figure 2). The leftward rotation bias was (1) stronger in high MI participants in the levodopa group relative to that of high MI participants in the placebo group ( $p = 0.05$ ); and (2) in the high MI levodopa participants than in the low MI levodopa participants ( $p = 0.05$ ). In the placebo group, the leftward rotation bias was stronger in the low than high MI group ( $p = 0.05$ ). A somewhat similar picture was observed for the ANOVA on 180° objects (Figure 2). Although the interaction was only a statistical trend ( $F(1,33) = 3.49$ ,  $p = 0.07$ ); the high MI group's leftward rotation preference was stronger in the levodopa group than its rightward bias in the placebo group ( $p = 0.02$ ). The ANOVA on 270° objects did not produce any significant main effects nor interactions (all  $F$ -values  $< 1.10$ , Figure 2).

As in the participants of Experiment 1, rotational preferences occurred preferentially along the shortest trajectory. However, the patterns of rotational biases as a function of participants' MI scores were quite different in the present sample (placebo group) from the population tested in Experiment 1. We neither replicated a general leftward rotation preference in the placebo group nor did we find a more pronounced leftward rotation bias in the high compared to the low MI group. On the contrary, high MI scorers revealed a rightward rotation bias in the placebo group, but a leftward rotation bias in the levodopa group. Moreover, in the placebo group, low MI scorers had a stronger leftward rotation bias than high MI scorers. The opposite rotational biases in the high MI groups clearly speak against our original idea that high MI scores would generally relate to leftward orientation bias for object rotations in the 2D plane. Thus, we have to reconsider our initial assumption that a relative right-hemispheric hyperdopaminergia in high MI scorers might lead to stereotyped

leftward rotation preferences, at least when rotational preferences are assessed for object rotations in the 2D plane. The absence of a consistent rotational bias towards one side in the present visuo-motor task would also highlight the need to determine more precisely those 'turning' tasks and related experimental parameters, which reportedly are under dopaminergic mediation (Mohr *et al*, 2004). As a further consequence, we are reluctant to interpret the observed leftward rotation preference in high MI scorers in the levodopa group as a result of a substance-induced right-hemispheric hyperdopaminergia.

Having listed the critical points that emerged from the apparently divergent findings between the two experiments, we now point to one interesting pattern, common to Experiments 1 and 2 (placebo group). High MI scorers responded more stereotyped than did low MI scores. In the placebo group of Experiment 2, the high MI group showed a stereotyped rightward rotation bias resulting in an efficient rightward preference for 270° objects, a rightward rotation preference for 180° objects, and an inefficient laterality index score around zero for 90° objects (all trials). The laterality index score for 90° objects on *correct* trials was positive, indicating that high MI participants performed many inefficient rightward rotations for 90° objects leading to many incorrect trials. Thus, high MI scorers' response stereotypy consisted of a rotation bias in a rightward direction. This conclusion is also supported by the findings that these high MI scorers showed (1) a pronounced rightward bias for 180° objects (which was around zero for low MI scorers) and (2) a stronger rightward bias than low MI scorers for 270° objects. Taking these results and those from Experiment 1 together, we conjecture that, whatever the direction of the rotational bias may be in a given sample, high MI scorers perform more stereotyped than low MI scorers. This makes them less efficient in swiftly adopting different rotation strategies in response to current task demands.

However, high MI scorers did not respond even more stereotyped in the levodopa than in the placebo group. Rather, they showed a more sophisticated rotation strategy than did the low MI scorers. Despite a general leftward rotation bias in the levodopa group, high MI scorers showed a pronounced rightward bias for 270° objects (Tables 4 and 5). Low MI scorers, on the other hand, showed less of a leftward rotation bias in the levodopa compared to the placebo group. This was particularly evident for 90° objects, for which a leftward bias is the optimal rotation strategy. These results suggest that elevated DA concentrations do not increase stereotyped responding in high MI scorers, but result in most efficient task performance. In contrast, low MI scorers' performance, if influenced at all by levodopa treatment, appeared to deteriorate (Figure 2).

## General Discussion

As reviewed in the introduction, stereotyped spatial and nonspatial responding has been described for patients with schizophrenia, schizotypal personality disorder, healthy participants showing schizotypal features, and healthy participants after the administration of DA agonists. We tested healthy participants' stereotyped responding in clockwise and counterclockwise directions in a computer

task resembling the popular TETRIS computer game. Within 2 s, 'dropping' line drawings had to be rotated into a target orientation, indicated by a second object depicted at the bottom of the computer screen. We predicted more stereotyped responding for high compared to low scorers on the MI scale (Eckblad and Chapman, 1983). This prediction was born out in Experiment 1 and in the placebo group of Experiment 2. Opposite to our expectancies, in the levodopa group of Experiment 2, high MI scorers did not yield even more stereotyped responding, but performed the task in a most efficient and adaptive way.

Successful performance in our visuo-motor rotation task depends on complex attentional and executive functions (see also Haier et al, 1992). Results from previous studies would suggest that functions of the left hemisphere play a more important role for these functions than those of the right hemisphere (Haier et al, 1992; Koeppe et al, 1998). Haier et al (1992), for instance, showed that novices' performance in the TETRIS game was related to increased cerebral blood flow in the supramarginal gyrus and lateral occipital areas of the left hemisphere. Another PET study reported enhanced endogenous striatal DA release, in particular in the left hemisphere, during a goal-directed visuo-motor computer game (Koeppe et al, 1998). Selectively impaired left hemisphere functioning has been reported for healthy participants with elevated positive schizotypal features (Mohr et al, 2001; Park, 1999) and unmedicated patients with schizophrenia (Purdon and Flor-Henry, 2000). Thus, the inferior rotation strategy in high MI scorers might be yet another example for a relative impairment of primarily left-hemisphere mediated functions.

However, such impairment does not explain the efficient rotation strategy observed in high MI scorers in the levodopa group. Originally, we expected that performance would deteriorate under a DA agonist given that (1) DA agonists can worsen psychotic symptoms in patients with schizophrenia (Davidson et al, 1987; Abi-Dargham et al, 1998) and trigger psychotic symptoms in healthy participants (Janowsky and Risch, 1979; Sekine et al, 2001); (2) schizotypy and schizophrenia share cognitive (Gooding et al, 1999; Park, 1999), attentional (Sarkin et al, 1998; Mohr et al, 2003a), behavioral (Barnett and Corballis, 2002; Mohr et al, 2003b), and physiological (Klein et al, 1999; Pizzagalli et al, 2000) similarities; and (3) DA agonists increase stereotyped responding in animals (Randrup and Munkvad, 1974; Staton and Solomon, 1984; Kelley et al, 1988) and healthy populations (Connell, 1958; Ridley et al, 1988). Findings from animal (Arnsten, 1997; Williams and Goldman-Rakic, 1995) and human (Mehta et al, 2000) studies propose that dopaminergic actions follow an inverted U-shape function, with an improvement of cognitive performance from low to medium, but deterioration from medium to high doses. This characteristic inverted U-shape function is thought to explain DA actions on cognition as a function of individuals' overall baseline performance. Animals (Granon et al, 2000) and humans (Kimberg et al, 1997; Mattay et al, 2000; Mehta et al, 2000) performing low at baseline profited from the substance and those performing high at baseline deteriorated after substance intake. Thus, applied to the present study, individuals performing low in the substance-free state (high MI scorers in Experiment 1 and the placebo group of Experiment (2)

performed best in the levodopa group. On the other hand, individuals performing high in a substance-free state (low MI scores in Experiment 1 and the placebo group of Experiment 2) performed similar or even worse in the levodopa group.<sup>1</sup>

Whether targeting behavior or pharmacology, most research so far focused on similarities rather than on dissimilarities between schizophrenia and schizotypy. If similarities between schizotypy and schizophrenia existed on the neurochemical level, one would expect task performance to improve in schizotypal individuals with (second-generation) DA antagonists. Specifically, atypical neuroleptic agents were found to improve neuropsychological functioning including immediate recall, visuo-spatial construction, executive functions, verbal fluency, attention, and working memory (see eg Cuesta et al, 2001; Meltzer and McGurk, 1999; Purdon et al, 2001; Sumiyoshi et al, 2003 for overviews). However, our schizotypal participants performed in a most adaptive way after a DA agonist. This dissociation would point to neurochemical differences between schizotypy and schizophrenia. It could be argued that such differences emerge from a pathological 'hypo-frontality' in patients with schizophrenia (Andreasen et al, 1992). In fact, stereotyped and/or perseverative behavior in schizophrenia is not necessarily related to a generally hyperactive DA system but to a selective hypofunctioning within the frontal lobes (Perry and Braff, 1998). It was thus challenging to propose that a hypofunctional frontal system in schizophrenia might improve with DA agonist treatment, which, in fact, was the case, but only (1) when patients were prior stabilized with DA antagonists (Daniel et al, 1991; Szeszko et al, 1999), and (2) DA activity was kept on an intermediate level (Szeszko et al, 1999).

In conclusion, we showed that high positive schizotypy is associated with stereotyped behavior in a visuo-motor computer task. After levodopa administration, however, stereotyped behavior was absent in the high MI scorers, and task strategy was even superior to that of low MI participants. We conjecture that healthy participants with high MI scores are able to compensate a single DA challenge rather than to further deteriorate. For populations with a

<sup>1</sup> Two anonymous reviewers pointed to the relevance of gender or deficit-like or negative symptoms to the dopamine-mediated findings of the present two experiments (see also Siever and Davis, 2004 for overview). Female participants were tested in Experiment 1, but only men were tested in Experiment 2. Moreover, deficit-like symptoms might be more prevailing in female participants or in participants with high MI scores in one but not the other substance group. Thus, our results might be rather a result of different distributions of negative schizotypal features in the two MI groups in (1) women and men (Experiment 1 or 2) in the levodopa and placebo group (Experiment 2). We assessed participants' scores on the physical anhedonia scale (Chapman et al 1976, revised German version Meyer and Hautzinger, 1999). An ANOVA with MI groups and gender as between-subject measures (Experiment 1) on physical anhedonia scores did not show a significant interaction ( $F(1,30) = 1.14; 0.29$ ). Likewise, an ANOVA with MI groups and substance groups as between-subject measures (Experiment 2) on physical anhedonia did not show a significant interaction ( $F(1,33) = 0.12, p = 0.73$ ). Thus, we assume that deficit-like symptoms, among which physical anhedonia is a key feature, were not the major determinant for the findings observed in the present study. However, future studies would profit from a more careful assessment of different symptom dimensions.



diagnosis of schizotypal personality disorder, accumulated evidence for intact compensatory and/or protective brain mechanisms against full-blown psychosis has recently been discussed (Siever and Davis, 2004). Moreover, Siegel *et al* (1996) showed that DA agonistic treatment in schizotypal personality disorder reduced perseverative errors in the Wisconsin Card Sorting Test. Wuebben and Winterer (2001) found frontally pronounced resting EEG activity in patients with schizophrenia but not healthy schizotypal participants. Thus, our present findings would extend the observations of potential protective brain mechanisms along the schizophrenia spectrum including healthy schizotypal populations. In addition to these considerations, such protective mechanisms may explain why even large longitudinal studies on participants with high MI scores, as undertaken by the Chapman group (Chapman *et al*, 1994; Kwapil *et al*, 1997), failed to convincingly predict a later psychotic breakdown from elevated positive schizotypal features alone (see also Verdoux and van Os, 2002). Indeed, high MI might also predict a later mood disorder (Chapman *et al*, 1994) and is a common feature not only of the schizophrenia spectrum disorders but also a symptom of some personality disorders (eg Lyons *et al*, 1995; Kwapil *et al*, 1997). Thus, positive schizotypy may be accompanied by a relative hyperdopaminergia, but yet reflects just one of the many DA-mediated variations of the human mind and personality (Horrobin, 1998; Previc, 1999) accompanied by distinct cognitive capacities (Gianotti *et al*, 2001; Weinstein and Graves, 2002) and, ultimately, an unusual way of perceiving the world (Wolfradt *et al*, 1999; Stöckenius and Brugger, 2000; McCreery and Claridge, 2002; Van de Ven and Merckelbach, 2003).

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