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ORIGINAL PAPER

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Levodopa reverses gait asymmetries related to anhedonia and magical ideation

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Abstract Animals and men turn preferentially away from the hemisphere with the more active dopamine (DA) system. Consistent with the idea of a right-hemispheric hyperdopaminergia in schizophrenia, a left-sided turning bias was described for unmedicated psychotic patients. We investigated the modulating role of DA and schizophrenia-like thought on whole-body turns in a controlled double-blind study. The number of veers to either side when walking blindfolded straight ahead (20 meter) was assessed in 40 healthy right-handed men (20 men received levodopa, the remaining participants placebo). Side preferences were analyzed in terms of individuals' positive (Magical Ideation, MI) and negative (Physical Anhedonia, PhysAn) schizotypal features. In the placebo group, increasing MI scores were related to increasing left-sided veering and increasing PhysAn scores were related to increasing right-sided veering. In the levodopa group, this relationship between preferred veering side and type of schizotypy was reversed. The finding in the placebo group suggests an association between MI and a relative right-hemispheric hyperdopaminergia. Unexpectedly, levodopa did not enhance this veering bias, but reversed it, suggesting that psychosis-protective mechanisms exist in the healthy positive "schizotypic" brain. Also unexpectedly, levodopa made "anhedonics" veer like "magics" after placebo, suggesting that DA agonists suppress negative schizotypal symptoms.

Key words dopamine · asymmetry · hemispheres · schizotypy · turning · neuropharmacology

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Introduction

Schizotypy is associated with a mild and non-clinical "schizophrenia-like" thinking style in healthy populations and is commonly assessed by self-report questionnaires. The "schizotypy" concept, originally introduced as a genetic diathesis-stress model for schizophrenia (Meehl 1962), has frequently been applied in research on psychosis-proneness (Chapman et al. 1994; Kwapil et al. 1997). The idea of a relationship between schizotypy and overt clinical psychosis is supported by studies that found that highly schizotypal subjects reveal cognitive (Gooding et al. 1999; Park et al. 1995), attentional (Gooding et al. 2000; Sarkin et al. 1998), behavioral (Barnett and Corballis 2002; Shaw et al. 2001) and physiological (Klein et al. 1999; Pizzagalli et al. 2000) peculiarities comparable to those described for patients with schizophrenia. However, neuropsychological similarities between schizotypy and schizophrenia are not limited to highly schizotypal subjects, but can also be observed in random samples of participants (Kalaycioglu et al. 2000; Brugger and Graves 1997; Mohr et al. 2003a; Taylor et al. 2002), for whom schizotypal features are quantitatively less prominent yet qualitatively equivalent.

The advantage of the schizotypy approach to investigate brain functioning in "psychosis-prone" populations without illness-related epiphenomena such as prior psy-

chosis, antipsychotic medication, and hospitalization has well been recognized (e. g., Gooding et al. 1999; Claridge et al. 1992; Taylor et al. 2002). This approach would also offer a possibility to test for drug actions in unmedicated healthy but "psychosis-prone" subjects. It has, however, received surprisingly little direct (Kumari et al. 1999; Williams et al. 1997) and indirect (Gray et al. 2002; Kopp et al. 2002) attention. In particular, the neurotransmitter dopamine (DA) is an excellent candidate for such an approach. Ever since the discovery that DA antagonists ameliorate acute psychotic symptoms (e. g., Klein and Davis 1969; Matthysse 1973), it has been accepted that this neurotransmitter plays a major role in the pathophysiology of schizophrenia (Laruelle and Abi-Dargham 1999). Since DA agonists can not only worsen positive psychotic symptoms in patients but also trigger psychosis in healthy people (Abi-Dargham et al. 1998; Angrist et al. 1985; Davidson et al. 1987; Janowsky and Risch 1979; Sekine et al. 2001), a hyperactive DA system might be involved along the whole schizophrenia spectrum. The DA metabolite homovanillin acid (HVA) has been shown to positively correlate with positive dimension of symptoms in schizophrenia (Davidson and Davis 1988; Pickar et al. 1984) and schizotypal personality disorder (Siever et al. 1991, 1993). Although the role of DA for even mild forms of schizotypy was emphasized (Mohr et al. 2003a; Brugger and Graves 1997; Gray et al. 2002; Kopp et al. 2002), direct relationships between schizotypy and the DA system have rarely been investigated (Kumari et al. 1999; Williams et al. 1997).

In the present study, we tested a DA-mediated behavior, i. e., lateralized whole-body movements, in a levodopa placebo controlled double-blind design. We assessed veering behavior as a function of healthy participants' positive (magical ideation, MI; Eckblad and Chapman 1983) *and* negative (physical anhedonia, PhysAn, Chapman et al. 1976) schizotypal features. An extensive literature in animals (Pycock 1983 for overview), but also in patients with asymmetrical Parkinson's disease (Bracha et al. 1987) showed that whole-body turns are directed towards the cerebral hemisphere with the less active DA system. Thus, the left-sided turning preference reported from unmedicated patients with positive psychotic symptoms was taken as support for the notion of their relative hyperactive right-hemispheric DA system (Bracha 1989; Bracha et al. 1993). The magnitude of this left-sided turning bias was not only correlated to symptom severity (Bracha et al. 1993) but was also absent in patients treated with DA antagonists (Levine et al. 1997). However, this long-term spontaneous turning measure is not suited to measure short-lasting drug effects in a controlled experimental setting. Bracha and collegues used a belt-mounted, direction-sensitive device monitoring changes in the orientation of the dorsal-ventral axis (Bracha et al. 1987). Unaware of the kind of measurement, the individuals wore the device for several hours during every-day activities. In more recent studies, we showed dopaminergic mediation of veering behavior, i. e., side deviations during blindfolded straight ahead walking (Mohr et al. 2003b, 2004). Thus, veering can be regarded as an experimentally controlled analogue to the long-term spontaneous turning measure suited to test for short-term drug effects. Interestingly, it was only veering behavior and not stepping (walking blindfolded on a given spot) behavior, which was under dopaminergic control (Mohr et al. 2004). Moreover, we assessed veering behavior as used in the present study as well as spontaneous turning behavior in the same subjects (Mohr et al. 2003a). Both measures were similarly modulated by enhanced MI scores; specifically, overall right-sided spatial deviations were attenuated. In analogy to the findings from patients with schizophrenia (Bracha 1989; Bracha et al. 1993), we suggest that schizotypy of the positive type may be associated with a relatively hyperactive right-hemispheric DA system.

Since DA agonists led to psychotic relapses in patients with schizophrenia (Abi-Dargham et al. 1998; Angrist et al. 1985; Davidson et al. 1987), and since the degree of positive symptoms in these patients is correlated with a left-sided spatial bias (Bracha et al. 1993), we hypothesize that DA supplementation in high MI subjects would enhance their left-sided veering tendency. To our knowledge, no previous work has ever assessed the relationships between spatially directed whole-body movements and negative symptoms, either in schizophrenic patients or in schizotypal subjects. Hence, we do not formulate any a priori hypothesis.

Methods

Subjects

A total of 40 healthy men were recruited by flyers and personal contact. All of them were right-handed according to a 13-item handedness questionnaire (Chapman and Chapman 1987). Their mean (± SD) age was 25.1 ± 3.8 yrs. and their mean education was 16.9 ± 3.2 yrs. Subjects with any current medication, history of drug abuse or neuropsychiatric illness, as assessed with an extended clinical interview (Campbell 2000), had been excluded. Because of the potential of DA agonists to trigger a psychotic breakdown (Janowsky and Risch 1979; Sekine et al. 2001), especially in subjects with high MI scores, subjects scoring in the upper quartile of this scale (MI scores > 22; see next paragraph) were also excluded, as required by the local ethics committee. After complete description of the study to the subjects, written informed consent was obtained.

Questionnaires

Magical ideation scale

We assessed subjects' MI with a validated 30-item questionnaire which 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 0–30, with higher scores indicating more pronounced magical thinking. The scale is published in full in Eckblad and Chapman (1983); Barnett and Corballis (2002), and normative data can be found in Garety and Wessely (1994).

Physical anhedonia scale

This originally 61-item questionnaire (revised German version: 50-items, Meyer and Hautzinger 1999; Scherbarth-Roschmann and Hautzinger 1991) includes items about sensory, tactile and movement experiences (Chapman et al. 1976). Illustrative items for this questionnaire are "On seeing a soft, thick carpet, I have sometimes had the impulse to take off my shoes and walk barefoot on it" (keyed false) and "Sex is OK but not as much fun as most people claim it is" (keyed true). Scores on the PhysAn scale range from 0–50, with higher scores indicating more pronounced PhysAn. The scale is published in full in Chapman et al. (1976). Normative values of an American sample are found in Chapman et al. (1980) and of a German sample in Meyer and Hautzinger (1999).

Veering task

Subjects were positioned at the end of a corridor (width: 1.60 m; length: 20 m). Before being blindfolded, each subject could visually explore the corridor as well as the line along its middle. Subjects had to go blind-folded, the ears plugged, and without shoes to the end of the corridor. The experimenter walked in front of the subject. When walking deviation from the line was larger than 0.2 m for both feet, the subject was stopped and a veer to the respective side was counted. After a veer, a metal strip was placed onto the line between subject's feet. This allowed reorientation to the line-course by touching the strip with the feet. Start side in the corridor was counterbalanced between subjects. The number of deviations (*veers*) to the left and right, respectively, was summed.

Double-blind procedure

The study was a randomized, double-blind levodopa/placebo design. A dual-release formulation of levodopa/benserazide (brand name: Madopar® 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, subjects were informed about the experimental procedure and the possible side effects of levodopa administration. Each subject fasted overnight and arrived at 9 a. m. on the experimental day. Subjects were also instructed not to consume any alcohol or other drugs for at least 24 hours before testing. After having provided informed consent, subjects received either Madopar® DR or a placebo. Subjects consumed 200 ml water directly after substance administration, and standardized breakfast was provided 15 min later. In order to ensure that subjects 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 before experiments started. The veering task was conducted about one hour after the first blood sample. 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 ultra-pure 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 done by internal standard method. Analytical reproducibility was 10 % and the quantification limit was 3 ng/ml.

Data analyses

To investigate whether MI scores or PhysAn scores were related to side-biases in the veering task, four Pearson Product-Moment correlation analyses were calculated for each schizotypy scale and substance group, separately. Side-biases were determined by calculating a difference score (number of left veers minus number of right veers). Thus, positive values indicate a left-sided preference and negative values a right-sided preference. The values were correlated with the schizotypy scores in the two substance groups, respectively. Normal distribution to justify application of parametric statistics was confirmed by Kolmogorov-Smirnov tests ($0.23 > d\text{-values} > 0.16$, all p-values > 0.20 for MI raw scores; PhysAn raw scores, and the difference score for the two substance groups separately). If not otherwise stated, all p-values are two-tailed.

Results

Due to an error in the randomization of placebo and levodopa, 21 subjects were in the placebo group and 19 subjects in the levodopa group. Neither age ($t38 = 0.74$, $p = 0.45$) nor education ($t38 = 0.55$, $p = 0.59$) differed between the placebo (age: 25.5 ± 3.5 yrs., education: 17.1 ± 2.9 yrs.) and levodopa group (age: 24.6 ± 4.2 yrs.; education: 16.6 ± 3.6 yrs.). The ranges of observed MI scores for the placebo group (1–20) and levodopa group (2–21) overlapped[1]. The same was true, although to a lesser extent, for the ranges of the PhysAn scores (placebo: 1–27, levodopa: 3–22). Neither age (MI: $r = 0.11$, $p = 0.49$; PhysAn: $r = 0.05$, $p = 0.74$) nor education (MI: $r = -0.06$, $p = 0.73$; PhysAn: $r = -0.02$, $p = 0.90$) were significantly correlated with MI and PhysAn scores, respectively.

Levodopa concentrations

In the levodopa group, the mean levodopa serum concentration was 212.4 ng/ml (range: 5–953 ng/ml) for the first blood sample and 137.2 ng/ml (range: 0–597 ng/ml) for the second blood sample ($t18 = 1.36$, $p = 0.19$). A similar number of subjects had higher levodopa concentrations for the first ($n = 11$) and second sample ($n = 8$) (Chi-square = 0.47, $df = 1$, $p = 0.49$). None of the subjects reported any remarkable substance effect. Levodopa serum concentrations in the placebo group were zero throughout.

Schizotypy and veering behavior

The mean difference score was -0.1 ± 1.3 veers for the whole population (possible range: –3.0 to 3.0). It did not differ between the levodopa (0.2 ± 1.2) and placebo

[1] As pointed out by an anonymous referee, future studies would benefit from determining subjects' schizotypy scores *before* pharmacological treatment. This would control 1) for the range of schizotypy scores, which in the present experiment simply happened to be highly similar in the levodopa and placebo groups, but also 2) for the distribution of schizotypy scores within substance groups

(–0.3 ± 1.3) group ($t_{38} = 1.37$, $p = 0.18$). The two correlation analyses for the placebo group revealed a significant relationship between MI scores and the difference score ($r = -0.52$, $p = 0.02$). With increasing MI scores, subjects displayed an increasing relative shift to the left side (see Fig. 1A). The inverse relationship for increasing PhysAn scores fell short of significance ($r = 0.42$, $p = 0.06$). The two correlation analyses for the levodopa group were both significant. Subjects with increasing MI scores showed an increasing relative shift to the right side ($r = 0.49$, $p = 0.04$, see Fig. 1). Increasing PhysAn scores were associated with opposite lateral preferences ($r = -0.56$, $p = 0.01$, see Fig. 1).

Discussion

It is not yet known whether DA plays a role in schizotypy, a mild non-pathological analogue to schizophrenia. We, therefore, assessed axial whole-body movements, well established for its dopaminergic mediation, to investigate the relationship between short-term levodopa effects and schizotypal features. From the animal literature (Pycock 1983) it is known that spontaneous turning behavior occurs towards the hemisphere with the less active DA system. In men with asymmetric DA deficiencies, analogous turning preferences were described (Bracha et al. 1987). These studies were mainly based on a long-term spontaneous turning behavior not suitable for the study of short-term drug effects. Consequently, we tested the veering behavior during walking blindfolded straight ahead. This behavior is reportedly modulated by 1) dopamine (Mohr et al. 2003b, 2004), and 2) a subject's MI scores in similar ways as is spontaneous turning behavior (Mohr et al. 2003a).

In the present double-blind study, we found that veering tendencies after placebo or levodopa were inversely related to individuals' MI or PhysAn scores. As predicted for the placebo group, increasing MI scores were significantly related to a shift towards the left hemispace. Increasing PhysAn scores were related to opposite side preferences, although this relationship fell short of statistical significance. For the levodopa group, our predictions failed. We did not find an enhancement of the veering bias found in the placebo group. On the contrary, high PhysAn scores were associated with left-sided and high MI scores with right-sided veering preferences. It appears as if subjects with enhanced MI scores in the levodopa group depict "normalized" or even reversed (right-sided) veering preferences when compared to the left-sided veering bias in individuals with enhanced MI scores in the placebo group. Subjects with elevated PhysAn scores in the levodopa group, on the other hand, veered like subjects with elevated MI scores in the placebo group.

The opposite side preferences with respect to MI and PhysAn in the placebo group might simply be an expression of an overall high or low DA level, respectively, leading to opposite hemispheric DA asymmetries. Glick et al. (1982) measured DA concentrations in post-mortem brain tissue from healthy subjects. They found right greater than left hemisphere DA concentrations in subjects with an overall high DA level, but a left greater than right hemisphere DA concentration in those with overall low DA level. High MI can be understood as a non-clinical analogue to positive psychotic symptoms (Eckblad and Chapman 1983) typically linked to a hyperdopaminergic state (Davis et al. 1991). Therefore, in line with previous studies on schizophrenia (Bracha 1989; Bracha et al. 1993; Harvey et al. 1993; Posner et al. 1988) and schizotypy (Mohr et al. 2003a; Brugger and Graves 1997; Taylor et al. 2002), we interpret the left-sided veering displayed by subjects with increasing MI scores as a consequence of a relative right-hemispheric hyperdopaminergia. Importantly, it is the severity of exclusively positive schizophrenic symptoms or positive

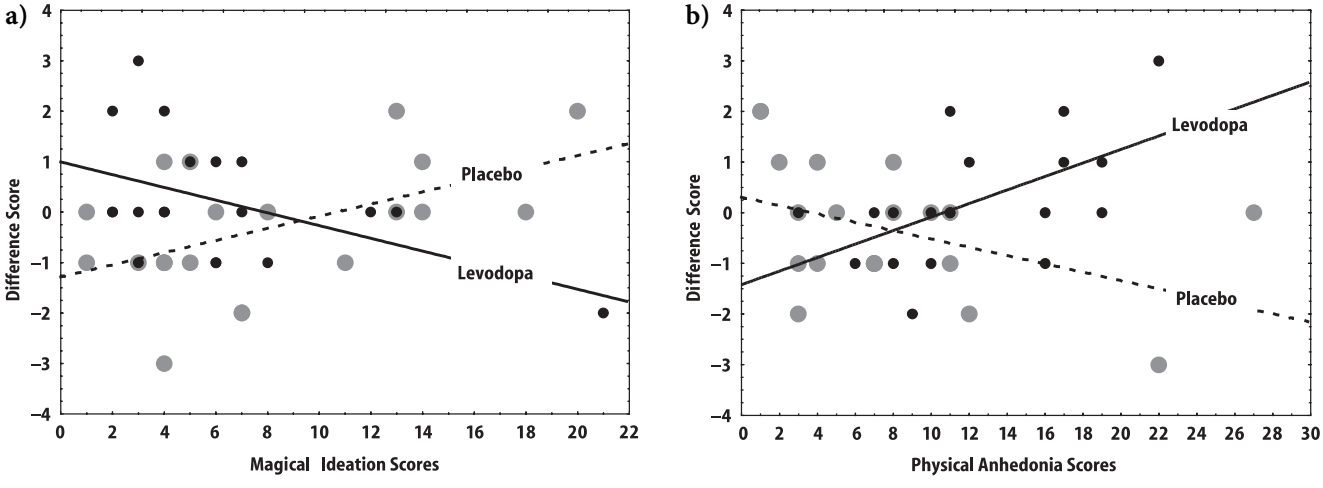

Fig. 1 Relationship between schizotypy scale scores (**a** Magical Ideation, **b** Physical Anhedonia) and lateral deviations in veering (difference score: positive values indicate left-sided deviations and negative values right-sided deviations). Data are presented for the two substance groups separately (levodopa group (n = 19): small black circles, straight regression line; placebo group (n = 21): large gray circles, dotted regression line)

features of schizotypy, respectively, that correlated to the size of these asymmetries in spatial orientation. In contrast, PhysAn is a non-clinical analogue to negative psychotic symptoms (Chapman et al. 1976, 1980), linked to a hypodopaminergic state (Davis et al. 1991). Therefore, PhysAn would be related to a left-hemispheric hyperdopaminergia and, consequently a right-sided veering bias. This is exactly the trend we found in our placebo group.

Since DA agonists induce (Janowsky and Risch 1979; Sekine et al. 2001) or worsen psychotic symptoms (Abi-Dargham et al. 1998; Angrist et al. 1985; Davidson et al. 1987), we expected that a levodopa supplementation would increase the right-hemispheric hyperdopaminergia in subjects with high MI scores and in parallel increase the left-sided veering bias. However, we rather found a reversal of the interhemispheric DA balance as inferred by the opposite veering preferences as a function of type of schizotypy (i. e., positive vs. negative) and pharmacological treatment. We can only speculate about this reversal in the levodopa group.

In patient populations, behavioral and attentional asymmetries, and by inference, neurochemical asymmetries, were found to be attenuated or even reversed when treated with DA antagonists (Levine et al. 1997; Maruff et al. 1995; Tomer and Flor-Henry 1989). While functional interhemispheric balance might have been restored by DA decrease in patients, a similar balancing may occur by DA agonists in healthy subjects with high MI scores. This dissociation between schizotypy and schizophrenia suggests the existence of neurochemical differences between these populations, at least with regard to positive symptoms. Levodopa seemed to have restored interhemispheric DA symmetry, rather than exaggerating asymmetry. Thus, as speculated for subjects with a schizotypal personality disorder (Kirrane and Siever 2000; Shihabuddin et al. 2001; Siever and Davis, 2004), protective brain mechanisms might also be active in schizotypal subjects (see also Mohr et al., in press, for similar conclusions drawn from findings obtained from the same population using a completely different experimental paradigm, i.e, a visuo-motor computer task). This may explain why even large longitudinal studies on subjects 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).

The second unexpected finding concerns the veering behavior with respect to PhysAn scores in the levodopa treated group. Elevated PhysAn scores were related to a "pathological" left-sided veering bias similar to that observed for elevated MI scores in the *placebo* group. Previous studies already claimed that along the schizophrenia spectrum from normality to schizophrenia, depressive or negative schizotypal states precede schizophrenia (Meehl 1962; Tsuang et al. 2002; van Os et al. 1999). Anhedonia has not only been understood as a negative symptom of schizophrenia or schizotypy, but also as a core feature of depression (Loas et al. 1999) and, in pharmacological terms, was associated with a deficiency of dopaminergic function (Davis et al. 1991; Brown and Gershon 1993). Moreover, apart from an enhanced rate of psychosis, high schizotypal subjects also revealed a high rate of mood disorders in a longitudinal study (Chapman et al. 1994; Kwapil et al. 1997). Our result that the veering behavior after levodopa treatment was identically related to PhysAn scores as it was related to MI scores after placebo treatment raises the question whether anhedonic subjects would benefit from levodopa treatment. This proposition appears particularly warranted in view of the fact that *DA antagonists* have little effects on negative symptoms in schizophrenia (Andreasen 1995) and DA agonists might improve a hypofunctional frontal system in chronic schizophrenia (Daniel et al. 1991; Szeszko et al. 1999).

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