

Lateralized semantic priming: modulation by levodopa, semantic distance, and participants' magical beliefs

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Abstract: We tested levodopa effects on lateralized direct and indirect semantic priming in 40 healthy right-handed men in a placebo-controlled, double-blind procedure. Crucially, priming was also analyzed as a function of participants' positive schizotypal features (magical ideation, MI), previously found to be associated with an enhanced semantic spreading activation (SSA) within the right hemisphere. Across both priming conditions, we observed increased semantic priming in the levodopa group 1) specifically after right visual field stimulations and 2) in high MI scorers. In both instances, increased semantic priming emerged from exceedingly long reaction times to unrelated targets reflecting 1) the left hemisphere's specialization for closely related concepts and 2) an opposite association between MI and SSA in the levodopa as compared with the placebo group. As a final finding, low MI scorers under levodopa performed like high MI scorers under placebo. Our findings speak against a general dopaminergic focusing of SSA, but one that respects each hemisphere's specialization. They also suggest that individuals' schizotypal features are important determinants of dopamine-induced changes in hemispheric functioning. We note that, in psychiatric patients, dopamine antagonists reportedly restore unusual lateralization. We discuss this dissociation between schizotypy and schizophrenia as supporting previous notions of protective brain mechanisms operating in the healthy "psychosis-prone" brain.

Keywords: schizophrenia, schizotypy, language, hemispheric asymmetries, dopamine, lexical decision paradigm

Introduction

Core features of schizophrenia are language and thought disturbances, of which loose associations have long been described (Bleuler 1911/50). Contemporary models propose that loose associations emerge from an enhanced semantic spreading activation (SSA) within cortical networks (Maher 1983; Spitzer 1997). This network model assumes that semantic concepts are neuronally represented as nodes. Semantic concepts with a close relatedness are represented by nodes located close to each other and are strongly interconnected. For concepts with a weak semantic relatedness, nodes are located more distant from each other and the interconnections are rather weak and indirect. Whenever a given node is activated, the surrounding nodes will be activated to a degree related to their closeness to the initially activated node (Collins and Loftus 1975). Consequently, in patients producing loose associations, the SSA might proceed along new lines, reaching several widespread, only loosely interconnected nodes.

SSA is commonly tested with semantic priming paradigms, in which a word stimulus primes lexical decisions about a subsequent target stimulus (Meyer and Schvaneveldt 1971). For instance, if participants have to decide whether ORANGE

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is a word or a non-word, they make faster decisions when this word was primed by the word LEMON (semantically related) than when it was primed by the word CHAIR (semantically unrelated). Supporting the idea of an increased SSA in schizophrenia, patients exhibited increased semantic priming as compared with controls (Manschreck et al 1988; Kwapil et al 1990). More recent studies suggest that “indirect” semantic priming (such as that from the word pair STRIPES–LION related by a third, mediating concept (TIGER) is a particularly sensitive measure of SSA (Spitzer, Braun, Hermle, et al 1993; Spitzer, Braun, Maier, et al 1993). This priming is enhanced overproportionally in patients with schizophrenia (see Spitzer 1997 for an overview). Indirect semantic priming effects in healthy participants are smaller than direct priming effects, corroborating the view that the amount of spreading activation is inversely related to the semantic distance (ie, number of related nodes) between the two semantic concepts. In thought-disordered patients, on the other hand, SSA appears to be increased to the degree that indirectly related targets are as easily detected as directly related targets.

Based on mathematical modeling of frontal cortical networks (Servan-Schreiber et al 1990), the Spitzer group suggested that dopamine (DA) increases signal-to-noise ratios and is thus a potent neuromodulator of SSA (Spitzer, Braun, Hermle, et al 1993; Spitzer 1997). Schizophrenia has been related to both a dysfunctional DA system (Davis et al 1991), and a hypofunctional frontal lobe system (Ingvar and Franzen 1974; Weinberger and Berman 1996). Taken together, according to Spitzer and colleagues (Spitzer, Braun, Hermle, et al 1993; Spitzer 1997), a frontal hypodopaminergia would attenuate signal-to-noise ratios leading to inappropriate processing (ie, unduly increased SSA in the present case). The idea of DA focusing the SSA has been supported by a recent study with healthy participants, in which a levodopa supplementation attenuated indirect semantic priming (Kischka et al 1996).

Although these considerations sound straightforward, a recent review on semantic priming in schizophrenia points to many inconsistencies between studies (Minzenberg et al 2002). These authors argue that the heterogeneous findings might result from individual differences in clinical variables such as illness acuteness and duration, medication type, and symptom heterogeneity (p 716). Studies with healthy schizotypes circumvent such confounding variables. Apart from the notion that schizotypes might have a certain risk for later psychosis (Chapman et al 1994; Kwapil et al 1997),

similarities between schizotypy and schizophrenia have been reported for numerous physiological and behavioral measures (eg, electrophysiology: Klein et al 1999; Pizzagalli et al 2000; cognition: Gooding et al 1999; Park 1999; attention: Brugger and Graves 1997; Sarkin et al 1998; Mohr, Bracha, et al 2003; and motor system parameters: Shaw et al 2001; Barnett and Corballis 2002; Mohr, Thut, et al 2003) including language functions described in more detail in the following paragraph.

Moritz et al (1999) showed that semantic priming was enhanced in healthy participants demonstrating language distortions qualitatively reminiscent of those reported from patients with schizophrenia. In their study, semantic priming was unrelated to participants’ schizotypy scores as measured by the SPQ scale (Raine 1991). In line with clinical observations, these authors concluded that enhanced SSA was specifically found in persons showing more or less severe signs of thought-disorder (but see Minzenberg et al 2002, p 712f). Independent observations would suggest that notably positive schizotypal thought relates to enhanced SSA. Individuals’ scoring high on magical ideation (MI; Eckblad and Chapman 1983) 1) produced an increased amount of “loose” associations” (Duchêne et al 1998; Gianotti et al 2001) and 2) showed an enhanced willingness to attribute relatedness to remotely associated words (Mohr et al 2001). Moreover, positive schizotypal individuals’ reaction times (RTs) to target words preceded by an indirectly related prime word were as brief as were those to targets preceded by directly related primes (Pizzagalli et al 2001). This increase in SSA was found, however, exclusively when targets were presented to the left visual field (LVF)/right hemisphere (RH) but not when presented to the right visual field (RVF)/left hemisphere (LH), mimicking observations from patients with thought-disorder (Weisbrod et al 1998). In both studies, such “loosening” of associations was suggested to emerge from overactive RH language functions preferring coarse as well as focused semantic analysis (see Rodel et al 1992; Beeman and Chiarello 1998; Faust and Lavidor 2003). In line with this suggestion, an “abnormally” high contribution of RH language processing was found in patients with schizophrenia (Sommer et al 2001, 2003) and healthy participants with positive schizotypal features (Brugger et al 1993; Leonhard and Brugger 1998).

It appears difficult to reduce the two ideas of 1) a hypodopaminergic frontal lobe and 2) a hyperactive RH language system to a common denominator. In fact, if a hypodopaminergic frontal lobe attenuated signal-to-noise ratios, one would not assume in the first line that a

hyperactive RH language system caused “loosening” of associations. Of specific interest to the role of DA as different for the two hemispheres of the brain is the finding that acutely psychotic patients and healthy positive schizotypal populations appear to have a relatively hyperactive RH DA system. This was inferred from convergent evidence in various behavioral paradigms for left-sided attentional biases (Harvey et al 1993; Brugger and Graves 1997) and systematic left-turning biases (Bracha et al 1993; Mohr, Bracha, et al 2003) in both acute psychotic patients and healthy schizotypes. A hyperactive RH DA system might thus cause loose associations by enhancing the salience of remotely associated concepts (see also Kapur 2003). As already suggested by Weisbrod et al (1998), a failure to establish LH language dominance in schizophrenia (Crow 2000) might lead to an overproportional reliance on the RH language functions specialized for the analysis of both semantically strongly and weakly related concepts (Faust and Lavidor 2003). Analysis of weak associates would enter current lines of thought as “intrusions”. Weisbrod et al (1998) not only reported pronounced indirect semantic priming after LVF target presentations, but also after RVF presentations. Healthy controls and non-thought-disordered psychiatric patients did not show a comparable aberrant enhancement of SSA after RVF presentation. A more symmetrical language system in schizophrenia might cause a patient’s LH to reveal RH language processing, blurring division of labor between hemispheres, and consequently suppress primarily LH-mediated thought (see Weisbrod et al 1998, p 145).

Before accepting or rejecting one of two apparently contradictory ideas on dopaminergic modulation of SSA by the two hemispheres, direct dopaminergic influences have first to be tested. We here assessed lateralized direct and indirect semantic priming in healthy participants, of whom half received levodopa and half a placebo. Furthermore, to test whether schizotypy would modulate potential effects of levodopa on lateralized semantic processing, each participant filled in the MI scale introduced by Eckblad and Chapman (1983) as an “indicator of schizotypy”. We predicted enhanced SSA, particularly after LVF presentations, and more so for participants with elevated MI scores. These predictions are based on 1) the previous literature reviewed above (especially Bracha et al 1993; Harvey et al 1993; Brugger and Graves 1997; Weisbrod et al 1998; Pizzagalli et al 2001; Mohr, Bracha, et al 2003), 2) the potential of dopaminergic drugs to trigger psychotic symptoms in normals (Sekine et al 2001) and worsen them in

patients (Abi-Dargham et al 1998), and 3) the amelioration of thought-disorder and loose associations with neuroleptic treatment (Shimkunas et al 1967; Spohn et al 1986).

Methods

Subjects

A total of 40 healthy men were recruited on and around the campus of the University of Zurich by flyers and personal contact. All participants were right-handed according to a 13-item handedness questionnaire (Chapman and Chapman 1987). Their mean age was 25.1 ± 3.8 years and their mean education was 16.9 ± 3.2 years. All contacted individuals also filled in a self-report questionnaire asking about current or previous medical, neurological, or psychiatric histories (guidelines see Campbell 2000). Those indicating any current medication, history of previous or current drug abuse, or neuropsychiatric illnesses, were not further tested. Because of the potential of DA agonists to trigger psychotic symptoms (Abi-Dargham et al 1998; Sekine et al 2001), especially in individuals with high MI scores, those scoring in the upper quartile of this scale (MI scores > 22 ; see next paragraph) were also excluded. The local Ethics Committee of the University Hospital Zurich had approved the study given this precaution 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 (eg, Leonhard and Brugger 1998; Mohr et al 2001; Barnett and Corballis 2002; Mohr, Bracha, et al 2003; Mohr, Thut, et al 2003). After a complete study description, all participants gave written informed consent before participation. They were also paid 100 Swiss Francs after study completion (see Mohr et al 2004; Mohr, Krummenacher, et al 2005; Mohr, Landis, et al 2005 for additional data on the same individuals).

Questionnaires

MI scale

We assessed subjects’ MI with a validated 30-item questionnaire that included items such as “I sometimes have a feeling of gaining or losing energy when people look at me or touch me,” (keyed true) or “I have never had the feeling that certain thoughts of mine really belonged to someone else” (keyed false). Scores on the MI scale range from 0 to 30, 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).

Double-blind procedure

The study was a randomized, double-blind, between-subjects (levodopa/placebo) design. A dual-release formulation of 200 mg levodopa/50 mg benserazide (Madopar® DR, Roche Pharma AG, Reinach, Switzerland) with 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 about possible side-effects of levodopa administration. Each subject fasted overnight and arrived at 0900 h on the day of the experiment. Subjects were also instructed not to consume alcohol or any other drugs for at least 24 hours prior to testing. After having provided informed consent, subjects received either Madopar DR or a placebo. They consumed 200 ml of water directly after substance administration, and a standardized breakfast was provided 15 minutes later. In order to ensure that subjects were under significant levodopa concentration throughout the experiment, 2 blood samples of about 5–7 ml each were drawn. The first blood sample was collected 30 minutes after substance intake, just before the experiment started. The second blood sample was collected as soon as experiments were finished (about 120–150 minutes after levodopa intake). For details on blood sample collection and analysis see Mohr et al (2004). The semantic priming study was conducted about 15 minutes after the first blood sample.

Semantic priming task

All stimuli were letter strings between 3 and 7 characters. The 120 prime-target pairs had already been used in our previous study (Pizzagalli et al 2001), and were divided into 4 categories of prime-target relations. While all primes were nouns ($n = 120$), the target was a directly related noun ($n = 20$), an indirectly related noun ($n = 20$), an unrelated noun ($n = 20$), or a pronounceable non-word ($n = 60$). Thirty-nine participants not included in the subsequent study had rated the semantic relatedness between prime and target words on a 7-point scale (1 = unrelated, 7 = strongly related). The prime-target pairs of the three categories were highly significantly different according to their semantic relatedness ($F(2,57) = 1999.97$; $p < 0.0001$), with mean values of 6.66 ± 0.10 for directly related, 3.20 ± 0.42 for indirectly related, and 1.39 ± 0.17 for unrelated word pairs,

respectively (all p values < 0.0001). Emotionality as rated on a 7-point scale (1 = unemotional, 7 = highly emotional) by another 11 independent subjects did not differ between words of the different categories ($F(2, 78) = 2.24$, $p = 0.11$), with mean emotionality scores of 4.52 ± 0.99 for directly related, 4.41 ± 0.87 for indirectly related, and 4.08 ± 1.02 for unrelated words. Words of the different categories did not differ with respect to word length and frequency of occurrence in German texts (Ruoff 1990).

Stimulus presentation.

There were 4 stimulus blocks, each consisting of 60 trials (prime-target pairs) belonging to 4 categories: 10 directly related, 10 indirectly related, 10 unrelated prime-target pairs, and 30 word/non-word pairs (making up a total of 240 trials). All prime words within each category were presented centrally on the computer screen. Half of the targets were presented to the LVF/RH and the other half to the RVF/LH. Across the 4 blocks each target appeared twice, once in each visual hemifield. Stimuli were presented white on a gray background. Target eccentricity was between 4° and 8° of visual angle.

Each trial consisted of 3 displays following each other without time gaps: first, a central fixation cross appeared for 1000 ms, replaced by a prime for 200 ms, also presented in the center of the screen. Subsequently, a lateralized target was presented for 150 ms while the central prime remained visible (as in Pizzagalli et al 2001). Thus, prime-target stimulus onset asynchrony (SOA) was 200 ms, ensuring automatic rather than controlled processing (Neely 1991). The screen remained blank until the subject's manual response initiated the next trial. Manual responses consisted of pressing 2 lateral keys simultaneously with both index fingers (on detecting a real word) or of pressing the space bar simultaneously with both thumbs (on detecting a non-word). Speed and accuracy were equally emphasized in the instructions, and number of correct responses and the corresponding RTs were automatically recorded.

After 20 practice trials, each subject received the same pseudorandom sequence of trials, with the constraint that 1) no more than 3 trials of the same category were presented consecutively, and 2) no more than 3 targets in the same visual field were presented consecutively. A PC with ERTS software (BeriSoft Cooperation, Frankfurt, Germany) was used for stimulus presentation and RT recording. A chin and headrest kept the distance between subject's eyes and the PC screen constant (55 cm). The subject performed the 4 blocks twice in succession with a rest of 10 minutes in between.

Data analysis

As in previous studies (Blum and Freides 1995; Passerieux et al 1997; Moritz et al 1999) priming effects were determined in the following way: the median RT of the experimental condition (direct or indirect semantic priming condition, respectively) was subtracted from the median RT of the unrelated condition. Consequently, a positive difference indicates a direct or indirect semantic priming effect, respectively. We also determined priming effects for accuracy data: mean number of correct responses in the direct or indirect semantic condition minus mean number of correct responses in the unrelated condition. Thus, a positive difference indicates a performance advantage for the direct or indirect semantic priming condition, respectively.

Semantic priming effects for subtle differences in prime-target relationships (direct, indirect) are not necessarily detected when comparing medians/means of several groups with multivariate analysis of variance (ANOVAs). Thus, following previous studies (Kwapil et al 1990; Spitzer, Braun, Hermle, et al 1993; Spitzer, Braun, Maier, et al 1993; Kischka et al 1996; Weisbrod et al 1998; Pizzagalli et al 2001), we performed the following statistical comparisons on the semantic priming data: (a) to test whether a semantic priming effect was present at all, we planned one-group t-tests against zero separately for each condition, substance group, MI group, and visual fields. Given the small sample sizes, we applied conservative, non-parametric Wilcoxon matched pairs tests; (b) the difference scores on RT and accuracy, respectively, were each subjected to separate 4-way ANOVAs with substance groups (levodopa vs placebo) and MI groups (low vs high) as between-subject factors, and visual field (RVF and LVF) and experimental condition (direct and indirect semantic priming) as repeated measures; (c) difference scores do not indicate whether significant differences emerge from a superior performance for directly or indirectly related prime-target pairs or from enhanced RTs for unrelated prime-target pairs. Thus, we performed analogous ANOVAs as described in (b), but with the three prime-target pairs as

repeated measures. Post-hoc single comparisons were conducted using Newman-Keuls Tests correcting for multiple comparison. All p values are, if not otherwise stated, two-tailed.

Due to an error in the randomization of placebo and levodopa, 21 participants were in the placebo group and 19 subjects in the levodopa group. Furthermore, we excluded 2 participants. Subsequent to testing, 1 participant was identified as a native French speaker (see also Mohr, Krummenacher, et al 2005). The other participant produced extreme outliers for the directly related (LVF: 744.5 ms; RVF: 862.3 ms) and indirectly related (LVF: 863 ms, RVF: 662 ms) conditions (difference scores of the remaining individuals were, for the directly related condition, $148.4 \text{ ms} \pm 130.5 \text{ ms}$ (LVF) and $172.3 \text{ ms} \pm 137.5 \text{ ms}$ (RVF) and, for the indirectly related condition, $66.4 \text{ ms} \pm 102.7 \text{ ms}$ (LVF) and $96.0 \text{ ms} \pm 116.7 \text{ ms}$ (RVF). Thus, analyses were performed on 18 participants in the levodopa group and 20 participants in the placebo group. To perform parametric testing, we ascertained that all dependent variables were normally distributed (Kolmogorov-Smirnov Tests: all d values < 0.14 , all p values > 0.20).

Results

Subjects

The mean (\pm SD) MI score of the whole population was 7.3 ± 5.2 (range: 1–21). A split at the median scale score (6) produced a high ($n = 20$, placebo: $n = 1$; levodopa: $n = 9$) and low ($n = 18$, placebo: $n = 9$, levodopa: $n = 9$) MI group. Three separate 3-way ANOVAs with substance groups and MI groups as between-group factors on 1) MI groups, 2) age, and 3) years of education showed no significant main effect for age and years of education, and no interactions (all F values < 0.30 , all p values > 0.60 , see Table 1). The levodopa blood serum concentrations in the placebo group were zero. A 2-way ANOVA for the levodopa group with MI groups as between-subject measure on levodopa blood serum concentrations for the first and second blood sampling

Table 1 Descriptive data of the study sample

	Levodopa group		Placebo group	
	Low MI group	High MI group	Low MI group	High MI group
MI scores	3.3 ± 1.0	9.6 ± 5.0	3.4 ± 1.5	11.9 ± 4.6
Age (yr)	24.9 ± 4.4	24.4 ± 4.9	25.6 ± 3.1	25.7 ± 3.6
Education (yr)	15.4 ± 3.4	16.7 ± 3.4	18.2 ± 2.9	17.1 ± 3.3
Levodopa T1 (ng/ml)	203.3 ± 171.9	239.7 ± 284.9	–	–
Levodopa T2 (ng/ml)	128.2 ± 123.0	159.7 ± 192.0	–	–

Abbreviations: MI, magical ideation; T1/T2, levodopa blood serum concentration of the first (T1) and second (T2) blood sample.

Table 2 Mean median RTs (ms, \pm SD) and priming effects of the high and low MI groups in the levodopa and placebo group, respectively

		Levodopa group		Placebo group	
		High MI	Low MI	High MI	Low MI
LVF/RH	DIR	655.3 \pm 101.6	627.9 \pm 108.9	600.7 \pm 85.0	727.3 \pm 173.7
	IND	736.5 \pm 156.0	738.6 \pm 179.6^c	660.7 \pm 130.8	808.2 \pm 283.6
	UNR	829.5 \pm 158.1	742.3 \pm 127.7	708.1 \pm 144.1	934.0 \pm 362.1
	Diff DIR	174.2 \pm 77.6 ^b	114.4 \pm 94.2 ^b	107.5 \pm 118.9 ^b	206.7 \pm 195.0 ^b
	Diff IND	93.0 \pm 85.3 ^a	3.7 \pm 117.3	47.5 \pm 81.9	125.8 \pm 98.4 ^b
RVF/LH	DIR	595.7 \pm 112.3	592.8 \pm 78.0	590.6 \pm 84.1	690.5 \pm 119.3
	IND	687.9 \pm 116.5	684.4 \pm 94.3	632.5 \pm 135.7	777.6 \pm 166.2
	UNR	890.5 \pm 116.4	782.9 \pm 158.8	689.6 \pm 156.5	812.0 \pm 173.5
	Diff DIR	294.8 \pm 84.2 ^b	190.2 \pm 130.9 ^b	99.0 \pm 132.0 ^a	121.5 \pm 118.2 ^a
	Diff IND	202.6 \pm 110.1 ^b	98.6 \pm 129.9 ^a	57.1 \pm 79.5 ^a	34.4 \pm 83.8

^a $p < 0.05$, ^b $p < 0.01$, significant unprotected 2-tailed t-tests of semantic priming effects against zero (see also Spitzer, Braun, Hemle, et al 1993; Spitzer, Braun, Maier, et al 1993; Weisbrod et al 1998).

^cBold numbers indicate those response latencies which are discussed in more detail in the text.

Abbreviations: Diff, difference values (ms); DIR, directly related targets; IND, indirectly related targets; LVF, (left visual field)/RH (right hemisphere); MI, magical ideation; RT, reaction time; RVF, (right visual field)/LH (left hemisphere); UNR, unrelated targets.

as repeated measure was not significant (F values < 0.002 , p values > 0.95 , see Table 1). None of the subjects reported any remarkable substance-induced side-effects.

Semantic priming task

Presence of semantic priming effects (see data analysis, part a)

Semantic priming effects (Table 2) in the placebo group occurred for directly related prime-target pairs in both MI groups and visual fields. For indirectly related prime-target pairs, however, the difference score against zero was not significant for the low MI group after RVF presentation and for the high MI group after LVF presentation (Table 2, bold print). Thus, unrelated and indirectly related prime-target pairs yielded comparably long RTs by *low* MI participants when projected to the RVF (LH) and comparably fast RTs by *high* MI participants when projected to the LVF (RH). As opposed to the placebo group, 1) high MI scorers in the levodopa group showed significant semantic priming effects for each visual field and 2) low MI scorers in the levodopa group did not show indirect semantic priming after LVF presentation (Table 2, bold print).

Accuracy

The ANOVA on the difference score (see data analysis, part b) showed a significant main effect for substance groups ($F(1, 34) = 4.36$, $p = 0.04$); the difference score was higher in the levodopa (10.6 ± 5.4) than placebo (7.3 ± 0.0) group. Visual inspection of the mean accuracy for each prime-target pair condition indicated that this enhanced semantic priming

effect resulted from a low detection accuracy for specifically the unrelated prime-target pairs (21.1 ± 8.1 ; placebo: 25.9 ± 7.2) rather than from a high detection accuracy for the directly related pairs (35.1 ± 4.8 ; placebo: 36.3 ± 4.8) or the indirectly related pairs (30.2 ± 6.5 ; placebo: 28.3 ± 6.5). There was also a significant main effect for experimental condition ($F(2,34) = 106.35$, $p < 0.0001$) showing that the difference score was higher for directly related (12.1 ± 6.3) than indirectly related (5.7 ± 4.2) prime-target pairs.

The ANOVA on mean accuracy for the three prime-target conditions separately (see data analysis, part c) showed significant main effects for target conditions ($F(2,68) = 125.38$, $p < 0.0001$: directly related (35.7 ± 4.8) $>$ indirectly related (29.3 ± 6.5) $>$ unrelated prime-target pairs (23.6 ± 7.9)) and visual field ($F(1,34) = 6.59$, $p = 0.01$: RVF (30.6 ± 5.5) $>$ LVF (28.5 ± 7.2)). The interaction between substance and MI groups ($F(1,34) = 4.89$, $p = 0.03$) indicated that the high MI individuals tended to make less correct lexical decisions in the levodopa (25.7 ± 6.1) than placebo (32.2 ± 4.3) group ($p = 0.07$). Lexical decision performance by the low MI individuals did not differ between the levodopa (30.6 ± 4.7) and placebo (29.1 ± 7.1) group ($p = 0.55$).

Reaction times

The ANOVA on the difference score (see data analysis, part B) revealed a significant main effect for target condition ($F(1,34) = 45.67$, $p < 0.0001$, directly related ($160.4 \text{ ms} \pm 106.3 \text{ ms}$) $>$ indirectly related prime-target condition ($81.2 \text{ ms} \pm 86.8 \text{ ms}$)). In line with the accuracy data, the levodopa group tended to have stronger semantic

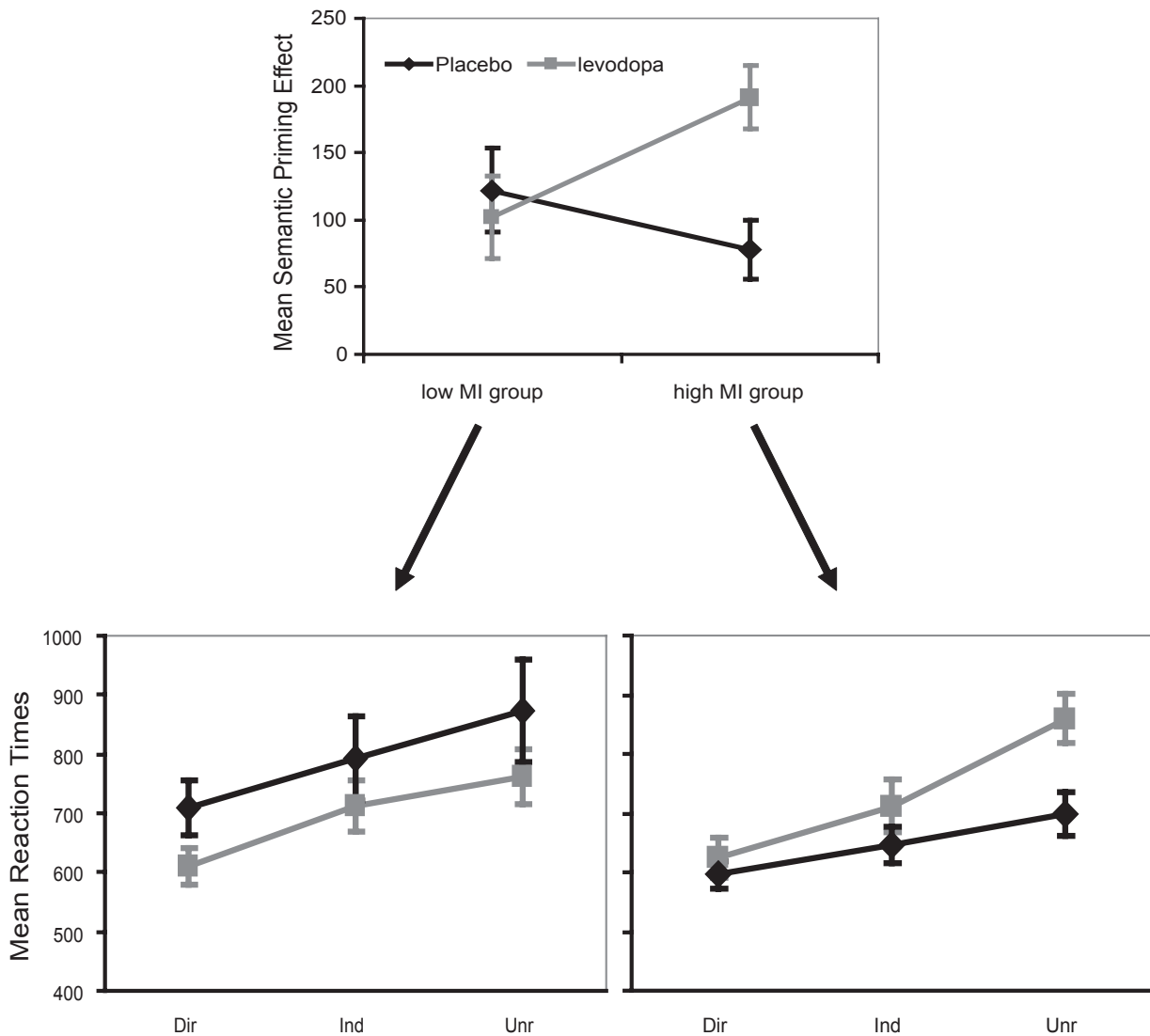


Figure 1 In the upper part of the figure, mean semantic priming effects (ms) collapsed over directly and indirectly related prime-target pairs are displayed for the levodopa and placebo group separately for the two MI groups. In the lower part of the figure, the contribution of the different prime-target conditions to the overall semantic priming effect shown in the upper part is displayed, again separately for the two MI groups. These lower graphs demonstrate the crucial contribution of unrelated prime-target pairs in the high MI group to the increased semantic priming effect in the levodopa group (note that priming is expressed as the difference between RTs to unrelated and those to related prime-target pairs). Vertical bars denote SE.

Abbreviations: DIR, directly related targets; IND, indirectly related targets; MI, magical ideation; RT, reaction time; UNR, unrelated targets.

priming effects ($146.4 \text{ ms} \pm 92.0 \text{ ms}$) than the placebo group ($97.7 \text{ ms} \pm 83.6 \text{ ms}$; $F(1,34) = 3.00$, $p = 0.09$). Again, visual inspection of mean RT data for each prime-target condition showed that this enhanced priming effect in the levodopa group resulted mainly from longest RTs for unrelated prime-target pairs ($811.3 \text{ ms} \pm 137.1 \text{ ms}$; placebo: $777.2 \text{ ms} \pm 209.2 \text{ ms}$), and shortest RTs for directly related prime-target pairs ($617.9 \text{ ms} \pm 93.9 \text{ ms}$; placebo: $646.6 \text{ ms} \pm 121.6 \text{ ms}$). RTs for indirectly related prime-target pairs were intermediate in both substance groups (levodopa: $711.8 \text{ ms} \pm 126.0 \text{ ms}$; placebo: $712.8 \text{ ms} \pm 175.7 \text{ ms}$). The significant interaction between substance and MI groups

($F(1,34) = 6.21$, $p = 0.02$) reflected the fact that high MI scorers in the levodopa group had a stronger semantic priming effect than 1) high MI scorers in the placebo group ($p = 0.03$), and 2) low MI scorers in the levodopa group ($p = 0.06$, Figure 1, top panel). The interaction between substance group and visual field ($F(1,34) = 14.52$, $p = 0.0006$) showed that semantic priming effects in the levodopa group were especially pronounced after RVF target stimulation (in fact significantly larger than in any other condition; all p values < 0.02 , see Figure 2, top panel).

The ANOVA on RTs for the three prime-target conditions separately (see data analysis, part c) showed a significant

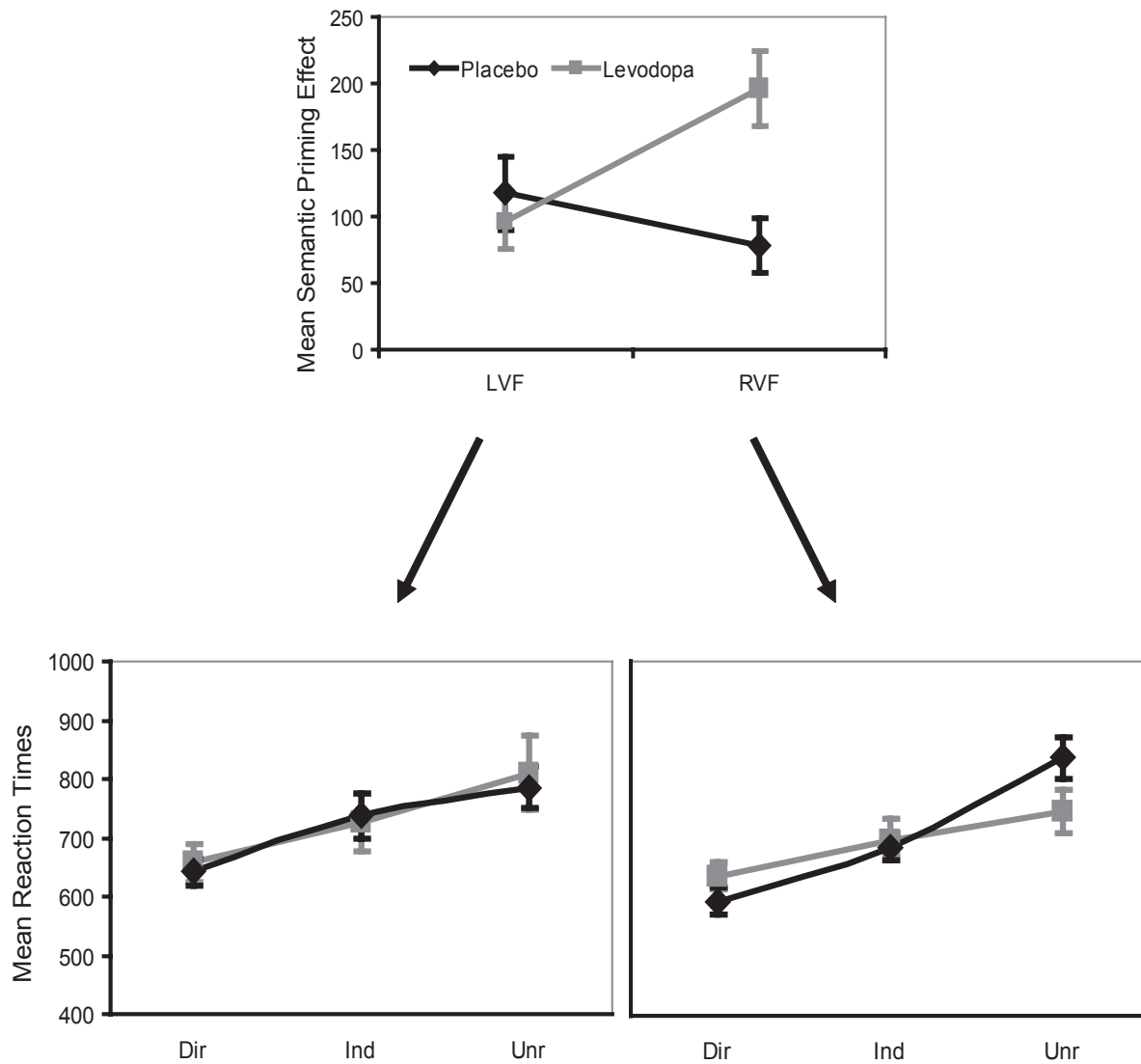


Figure 2 In the upper part of the figure, mean semantic priming effects (ms) collapsed over directly and indirectly related prime-target pairs are displayed for the levodopa and placebo group separately for the two visual fields. In the lower part of the figure, the contribution of the different prime-target conditions to the overall semantic priming effect shown in the top part is displayed, again separately for the two visual fields. These lower graphs demonstrate the crucial contribution of unrelated prime-target pairs to the increased semantic priming effect in the levodopa group (note that priming is expressed as the difference between RTs to unrelated and those to related prime-target pairs). Vertical bars denote SE.

Abbreviations: DIR, directly related targets; IND, indirectly related targets; LVF, left visual field; RH, right hemisphere; RT, reaction time; RVF, right visual field; LH, left hemisphere; UNR, unrelated targets.

main effect for prime-target condition ($F(2,68) = 69.88, p < 0.0001$) confirming that fastest RTs were obtained from directly related prime-target pairs (633.0 ± 108.9), followed by indirectly related prime-target pairs (712.1 ± 152.2), and finally unrelated prime-target pairs (793.4 ± 177.2). There was a significant interaction between prime-target condition, MI group and substance group ($F(2,68) = 3.96, p = 0.02$). To uncover the nature of this triple interaction, we calculated two ANOVAs, one for each substance group, with MI group as between-group factor and prime-target condition as the

repeated measure. The ANOVA for the placebo group showed differences in semantic priming effects between all prime-target conditions ($F(2,36) = 24.83, p < 0.0001$; all p values < 0.002 , see Figure 1 bottom) and a significant main effect for MI group ($F(1,18) = 4.46, p < 0.05$; high MI group shorter RTs than low MI group). The ANOVA for the levodopa group again showed a significant main effect for prime-target condition ($F(2,32) = 46.00, p < 0.0001$, all p values < 0.002 , see Figure 1, bottom), but also a significant interaction with MI group ($F(2,32) = 3.34, p < 0.05$).

In the high MI group, all differences between prime-target conditions were significant (all p values < 0.02). In the low MI group, however, indirectly related and unrelated prime-target pairs were responded to with comparable speed ($p = 0.19$). Figure 1 (bottom) shows that RTs to unrelated prime-target pairs were particularly elevated in high MI, but not in the low MI subjects.

Finally, there was a significant interaction between visual field, prime-target condition, and substance groups ($F(2,68) = 7.48$, $p = 0.001$). To uncover the nature of this triple interaction, we again calculated two ANOVAs, one for each substance group, with visual fields and prime-target condition as the repeated measures. The ANOVA for the placebo group showed only the significant main effect for prime-target condition ($F(2,38) = 23.59$, $p < 0.0001$, all post-hoc p -values < 0.002). The ANOVA for the levodopa group again showed the significant main effect for prime-target condition ($F(2,34) = 40.43$, $p < 0.0001$, all p values < 0.0003), but also a significant interaction with visual field ($F(2,34) = 10.88$, $p = 0.0002$). All post-hoc comparisons were significant, indicating that RTs to directly and indirectly related prime-target pairs were shorter when presented to the RVF than LVF, but RTs to unrelated prime-target pairs were shorter when presented to the LVF than RVF. These particularly long RVF RTs explain the increased semantic priming effect for the levodopa group: the magnitude of the difference score is clearly due to the particularly long RTs to unrelated prime-target pairs and not to particularly short RTs to related prime-target pairs (whether directly or indirectly related; Figure 2 bottom).

Discussion

We investigated, in a double-blind, between-subject (levodopa/placebo) design with healthy right-handed men the influence of DA on lateralized semantic priming for directly related, indirectly related, and unrelated prime-target pairs. We also analyzed task performance as a function of individuals' positive schizotypal features. Three major findings emerged that we will address now in turn:

First, semantic priming effects were stronger in the levodopa than in the placebo group. This result is opposite to what would be predicted by the model by Spitzer and colleagues (Spitzer, Braun, Hermle, et al 1993; Spitzer 1997), which proposes increased semantic priming under a hypo- rather than a hyper-dopaminergic state (see Spitzer, Braun, Hermle, et al 1993, Figures 7 and 8). The present experiment did not produce evidence for an improved task performance in the levodopa group, neither for directly

nor indirectly related prime-target pairs. Rather, the major finding concerned unrelated prime-target pairs, which were responded to less accurately and with the longest RTs.

Second, the stronger semantic priming effects in the levodopa compared with the placebo group were prominently found after RVF presentations and in the participants with elevated positive schizotypy scores (high MI scorers). Thus, dopaminergic modulation of SSA depended on the hemisphere of target presentation and on individuals' schizotypal features (see discussion below).

Finally, the performance pattern of low and high MI scorers in the levodopa group was the mirror image of that displayed by the high and low MI scorers, respectively, in the placebo group. After placebo supplementation, high MI scorers treated indirectly related and unrelated prime-target pairs equally fast after LVF presentations (see also Pizzagalli et al 2001), a behavior observed in low MI scorers in the levodopa group. In contrast, high MI scorers in the levodopa group responded slowly to unrelated prime-target pairs (both visual fields) resulting in significant direct and indirect semantic priming effects, again similar to the behavior of low MI scorers in the placebo group.

Before discussing these major findings in more detail, we emphasize that participants' performance was comparable to that of healthy participants reported in previous studies using comparable designs: 1) superior lexical decision performance was obtained for RVF/LH than LVF/RH stimulus presentation (Pizzagalli et al 2001; Coney 2002; Faust and Lavidor 2003), 2) RTs were fastest and accuracy was highest for directly related prime-target pairs, followed by indirectly related prime-target pairs, and finally unrelated prime-target pairs (Moritz et al 1999; Pizzagalli et al 2001; Coney 2002; Faust and Lavidor 2003), and 3) semantic priming (RTs, accuracy) was stronger for directly related than indirectly related prime-target pairs (Moritz et al 1999; Pizzagalli et al 2001; Faust and Lavidor 2003).

Levodopa effects on semantic priming

performance

Accuracy

In accordance with our own observation, Kischka et al (1996) had reported a higher error rate in their levodopa (2.7%) compared with their placebo (1.4%) group. Unfortunately, error rate in their study was low, preventing the authors to report error rates for the different prime-target conditions separately. In the present study, error rates were much higher (23.0% in the placebo group and 29.6% in the levodopa group)

than those repeatedly obtained from the prime-target pairs used by Spitzer and coworkers (Spitzer, Braun, Hermle, et al 1993; Spitzer, Braun, Maier, et al 1993; Kischka et al 1996; Kiefer et al 1998; Weisbrod et al 1998). Error rates in the present study increased linearly (see Result section) from least errors for directly related prime-target pairs in the placebo group to most errors for unrelated prime-target pairs in the levodopa group. In the studies performed by the Spitzer group, all stimuli were presented centrally (Spitzer, Braun, Hermle, et al 1993; Spitzer, Braun, Maier, et al 1993; Kischka et al 1996; Kiefer et al 1998). Since targets in our study were presented lateralized, task demands were more challenging and automatically resulted in a higher error rate. However, we note that lateralized target presentation in the Weisbrod et al (1998) also yielded relatively low error rates. Thus, the higher error rate in our study may additionally be a consequence of the stimulus pairs, exposure duration of the targets (150 ms in the present study, 200 ms in Weisbrod et al 1998), or target eccentricity (visual angle was between 4° and 6° in the present study, but around 2° in Weisbrod et al 1998).

In summary, whether accuracy was almost at ceiling (Kischka et al 1996) or lower as in the present study, a levodopa supplementation had a detrimental effect on word recognition performance in healthy populations. Such a decrease in word detection accuracy under an enhanced DA availability, unless specific to unrelated prime-target pairs, speaks very clearly against the idea that DA generally focuses SSA in cortical networks for lexical-semantic analysis (Spitzer, Braun, Hermle, et al 1993). To further account for this argument, further studies should report accuracy data for all prime-target pairs separately.

Reaction times

In previous studies (Kischka et al 1996; see also Copland et al 2003), diminished semantic priming effects after levodopa intake were silently assumed to reflect a decrease in SSA, without considering the necessity to inspect reaction times for the different prime-target pairs separately. Little if any attention was thus paid to the fact that a decrease in priming may have emerged from faster responding to unrelated prime-target pairs and not from slowed responding to indirectly related prime-target pairs (Kischka et al 1996) or to prime-target pairs with subordinate meanings (Copland et al 2003). It has been argued that only difference scores that are weighted for RTs to unrelated prime-target pairs are relevant for inferences about SSA (eg, Kwapil et al 1990, p 220). However, the

Spitzer, Braun, Hermle, et al model (1993, figures 7 and 8), within which much work has been framed, does not predict that DA shortens distances between concepts in semantic space. Since diminished semantic priming in the levodopa groups (see Kischka et al 1996; Copland et al 2003) emerged from fast responding to unrelated prime-target pairs, we have to assume that unrelated targets became easily accessible under a “higher-than-normal” DA availability. This assumption would imply that either SSA increased under a heightened DA availability or the distances between semantic concepts may have shrunk (ie, facilitating efficient access to specifically remotely separated nodes).

In the present study, however, we did not observe especially fast RTs to unrelated prime-target pairs in the levodopa group. We rather found the opposite: unrelated prime-target pairs yielded longest RTs in the levodopa group, specifically after RVF presentation. Different processing styles may be at work when targets are presented either centrally or lateralized, probably explaining the inconsistencies between the previous studies (Kischka et al 1996; Copland et al 2003) and the present one as well as between theoretical assumptions and empirical observations as just discussed above. When targets are presented centrally, both hemispheres interact in processing the incoming information. On the other hand, when targets are presented lateralized to only one visual hemi-field, the contralateral hemisphere receives the information first. It is here where functional hemispheric asymmetry in semantic processing enters the picture. Each hemisphere would engage in the processing of those associative relationships it is specialized for: the RH would dominate the course analysis of both close and remote associations and the LH that of close associations (see Rodel et al 1992; Beeman and Chiarello 1998; Faust and Lavidor 2003). Thus, slowed responding to unrelated targets after RVF presentation may have occurred because the LH is specialized for close associations, rendering access to remote associations more difficult under a “higher-than-normal” DA availability (see Figure 2). DA may increase the signal-to-noise ratio in semantic networks, but it does so in different ways for the two hemispheres, probably in response to qualitative differences between the hemispheres in receptive language functions (Taylor and Regard 2003).

Weisbrod et al (1998) found strong indirect semantic priming effects after LVF target presentations, but an indirect semantic priming effect after RVF presentation only in thought-disordered patients. Visual inspection of RT data indicate that it took thought-disordered patients a long time

to respond to indirectly and unrelated targets after RVF presentations, but RTs to directly related and indirectly related targets after LVF presentation were relatively fast. Patients with schizophrenia are assumed to suffer from a frontal “hypodopaminergia” (Davis et al 1991) and the patients in the Weisbrod et al (1998) study were all under DA antagonistic treatment. Consequently, longer RTs for remotely associated concepts after RVF presentation were found in patients during an even “lower-than-normal” DA availability. Conversely, in our healthy populations, prolonged RTs for remotely associated concepts after RVF presentation were observed under a “higher-than-normal” DA availability.

Facing this pharmacological dissociation between healthy and psychiatric populations, we point to previous reports from schizophrenia research, which suggest a neuroleptic modulation of semantic priming (Barch et al 1996; Goldberg et al 2000) and note that most semantic priming studies tested patients under neuroleptic treatment (eg, Spitzer, Braun, Hermle, et al 1993; Spitzer, Braun, Maier, et al 1993; Weisbrod et al 1998; medication not reported). Concerning accuracy, Kwapil et al (1990), for instance, presented targets centrally and kept accuracy levels around 50% (which would be close to the error rate obtained in our study, in particular in the levodopa group). These authors’ patients with schizophrenia performed worse to unrelated prime-target pairs and superior to related prime-target pairs when compared with patients with bipolar disorders or healthy controls. Fifteen out of the 21 patients with schizophrenia were under neuroleptic medication. Thus, increased semantic priming was observed under a “lower-than-normal” DA availability with improved task performance for closely related prime-target pairs and, critically, inferior task performance for unrelated prime-target pairs. These patients showed lowered task accuracy to unrelated prime-target pairs, as did our healthy population after a DA agonist. With respect to RTs, Barch et al (1996) investigated the influence of neuroleptic treatment on semantic priming. They found increased semantic priming with increased concentrations of neuroleptic treatment (at stimulus onset asynchronies below 950 ms). The higher DA antagonistic treatment doses, the higher was the difference between RTs to directly related and unrelated prime-target pairs, which was interpreted as a facilitated access to concepts in semantic networks. Unfortunately, a differential influence of DA on the processing of directly related vs unrelated prime-target pairs cannot be ascertained in retrospect,

since conclusions in the Barch et al (1996) study were drawn from regression analyses. Finally, Goldberg et al (2000) tested priming effects for highly related, moderately related, and low related intracategorical prime-target pairs as a function of medication status in patients with schizophrenia. The authors observed increased priming for highly related and low related word pairs when patients were on medication, while no priming was evident when patients were withdrawn from medication.

In summary, findings from these clinical studies indicate an increase in semantic priming in patients under DA antagonistic treatment. This observation is in obvious opposition to our observation of increased semantic priming in the levodopa group compared with the placebo group, in particular after RVF presentations. However, the pharmacological dissociation discussed herein needs replication from future studies testing the modulating role of medication in patients with schizophrenia and DA challenges in schizotypal individuals on lateralized semantic priming performance.

Magical ideation

Healthy participants’ MI scores in the two substance groups markedly modulated lateralized semantic priming performance. In the levodopa group, high MI scorers were least accurate and showed increased semantic priming due to excessively long RTs to unrelated prime-target pairs. Most interestingly, comparably slow responding was not observed in any of the remaining conditions: First, in the placebo group, high MI scorers responded generally faster than low MI scorers. Second, high MI scorers in the levodopa group responded to directly and indirectly related prime-target pairs faster than did the low MI scorers in the levodopa group and the high MI scorers in the placebo group (see Figure 1). Thus, the experimentally induced hyperdopaminergia in high MI scorers appeared to have impaired access to most remotely related (ie, unrelated) prime-target pairs. This observation is important, given that participants with elevated positive schizotypal scale scores have repeatedly been shown to access remote semantic associations more efficiently than low MI scorers (Gianotti et al 2001; Mohr et al 2001; Pizzagalli et al 2001). On the basis of these observations we had originally expected high MI scorers to show even more pronounced SSA when treated with a DA agonist. However, access to remote associations was rather attenuated in high MI scorers after a DA agonist. In the placebo group, high MI scorers showed high SSA after LVF presentations; they responded fast to both indirectly and unrelated prime-target

pairs, which resulted in a non-significant indirect semantic priming effect. This absence of priming is unlikely the result of long RTs to indirectly related prime-target pairs, since these participants showed fastest responding to unrelated prime-target pairs, suggesting facilitated access to the most extreme form of “remote associations”, ie, the absence of relatedness. We have interpreted this exaggerated availability to extreme remoteness/unrelatedness as a consequence of an increased SSA within RH-mediated semantic network functioning (Gianotti et al 2001; Mohr et al 2001; Pizzagalli et al 2001). Low MI scorers, on the other hand, showed both direct and indirect semantic priming after LVF presentation (see Table 2); they responded particularly slowly to unrelated prime-target pairs, arguably to a focusing of SSA that rendered access to unrelated targets more difficult. Low MI scorers revealed a generally more focused SSA; after RVF presentation, they did not show indirect semantic priming due to relative long RTs to both indirectly related and unrelated prime-target pairs (see Table 2). Thus, in the substance-free state, high MI scorers may have profited from enhanced SSA within the RH, while low MI scorers showed focused SSA within both hemispheres, but more prominently within the LH.

In the levodopa group, high MI scorers did not show this advantage for remotely associated targets, neither after LVF nor RVF presentations (Table 2). This finding suggests that DA focuses SSA in participants for whom an increased SSA in the substance-free state has been proposed (Gianotti et al 2001; Mohr et al 2001; Pizzagalli et al 2001). Unexpected was the observation in the levodopa group that SSA was enhanced for low MI scorers after LVF presentation; they performed like high MI scorers in the placebo group (Table 2; see also Mohr et al 2004; Mohr, Landis, et al 2005). Thus, the performance pattern of low and high MI scorers in the levodopa group was the mirror image of that observed in high and low MI scorers, respectively, in the placebo group. Consequently, levodopa did not focus SSA in a general way, but decreased it for high MI scorers and increased it for low MI scorers. Given that this reversal was originally unexpected (but see Mohr, Krummenacher, et al 2005; Mohr, Landis, et al 2005 for similar findings obtained from the same participants using different paradigms), we can presently only speculate about its nature.

In patient populations, behavioral and attentional asymmetries, and by inference, neurochemical asymmetries were found to be attenuated or even reversed after treatment with DA antagonists (Tomer and Flor-Henry 1989; Maruff et al 1995; Levine et al 1997; Purdon and

Flor-Henry 2000). 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 for high MI scorers, instead of exaggerating asymmetries (see Mohr et al 2004; Mohr, Krummenacher, et al 2005; Mohr, Landis, et al 2005 for a discussion of inverted U-shape functions of dopaminergic actions also relevant to the present observation). Thus, as speculated for subjects with a schizotypal personality disorder (Siever and Davis 2004), protective brain mechanisms might play a role in more moderate forms of schizotypy, ie, high scorers on the MI scale (see Mohr et al 2004; Mohr, Landis, et al 2005 for a more detailed account on this argument). 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). In fact, it appears to need more than just being schizotypal (ie, negative environmental life events) to possibly turn a potential genetic predisposition for psychosis into severe mental illness (eg, Meehl 1989; Jang et al 2005).

Conclusion

We summarize the main findings from our admittedly complex study design by suggesting that

- 1) levodopa focuses SSA in neuronal networks according to the semantic specialization of the two hemispheres. For RVF (left hemisphere) presentation, access to more directly related semantic concepts is facilitated, while access to unrelated semantic concepts is rendered more difficult. On the other hand, SSA is unconstrained by levodopa in the RH.
- 2) Lateralized semantic priming is modulated by individuals' positive schizotypal features (Pizzagalli et al 2001). High MI scorers in the placebo group evidenced facilitated access to remotely associated concepts when targets were presented to the LVF (right hemisphere). However, a similar performance was observed in low MI scorers in the levodopa group. On the other hand, high MI scorers in the levodopa group evidenced direct and indirect semantic priming after either visual

field presentation, a performance pattern observed in low MI scorers in the placebo group. The slope of lexical decision latencies in high MI scorers in the levodopa group was a result of particularly long RTs to unrelated prime-target pairs. Thus, variations in cognitive performance as well as their modulation by pharmacological agents depend in important ways on individual differences (Fleming et al 1995; Kosslyn et al 2000), ie, belief in magical causations, in the present case.

- 3) We observed an inverse task performance in high and low MI scorers in the levodopa as compared with the placebo group. Discrepancies between previous findings from semantic priming studies with patients with schizophrenia and the present results concerning healthy participants' schizotypal features were also emphasized. We think that both these inconsistencies are meaningful in that they add further evidence to previous notions of protective brain mechanisms along the schizophrenia spectrum (Mohr et al 2004; Siever and Davis 2004; Mohr, Landis, 2005).

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