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# Increased Activation of Indirect Semantic Associations under Psilocybin

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## Introduction

The spread of activation in semantic networks can be measured using semantic and indirect semantic priming effects in lexical decision tasks (Spitzer et al 1993a and b). For example, in thought-disordered schizophrenic patients, activation spreads faster and farther than in non-thought-disordered patients and normal subjects, which results in an increased direct and indirect semantic priming effect (see below). This has been interpreted as the result of a decreased signal-to-noise ratio in cortical neural networks that process semantic information. Such a decreased signal-to-noise ratio has been related to a decreased dopaminergic modulation (Servan-Schreiber et al 1990; Cohen and Servan-Schreiber 1992, 1993), which we recently were able to confirm directly in a study on the effects of L-dopa on semantic and indirect semantic priming (Kischka et al 1995).

As *dopamine* was found to have a *focusing* effect on the activity in semantic networks, i.e., it increases the signal-to-noise ratio and reduces the spread of activation (measured as reduced indirect semantic priming), we set out to investigate the effect of

the hallucinogenic agent psilocybin on this task. Since *psilocybin* is known to act on the serotonin (5-HT) system and has effects of “broadening” conscious experiences, we hypothesized that it might exert a *defocusing* effect on semantic networks (i.e., decrease the signal-to-noise ratio), which should lead to an increased indirect semantic priming effect.

To test this hypothesis directly, we conducted a double-blind, placebo-controlled study on the effects of psilocybin on semantic and indirect semantic priming as part of a larger project that was designed to assess the behavioral effects and pharmacokinetic properties of this hallucinogenic agent (the results will be reported elsewhere; cf. Holzmann 1995).

## Methods

The same lexical decision paradigm as in previous studies was used (see Spitzer et al 1993a and b for details). The subject had to decide whether a given string of characters is a word or not. To investigate how far activation spreads, word pairs of different semantic distance—closely related words (“black–white”), indirectly related words (such as “lemon–sweet”), and nonrelated words (such as “cloud–cheese”)—are presented in quick (200 msec) succession, and the effect of the relation between the words on the reaction time of the lexical decision of the latter is measured. It is well established that a word (e.g., “black”) is recognized faster if it is preceded by a meaningfully related word (e.g., “white”). This effect is called semantic priming (cf. Spitzer et al 1994). If the relation between the words is indirect, there is no such gain in the speed of the response, i.e., “sweet” is not

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Table 1. Mean Reaction Times (RT, in Milliseconds) and (Direct) Semantic as Well as Indirect Semantic Priming Effects (SP and ISP, in Milliseconds and as Percentage Scores) per Semantic Condition and Intervention (Placebo vs. Psilocybin)

Semantic condition	Time after ingestion of agent (min)			
	0	50	150	220
RT placebo, related	598	595	611	600
RT placebo, indirectly related	608	608	620	621
RT placebo, nonrelated	670	742	704	644
RT psilocybin, related	646	735	674	634
RT psilocybin, indirectly related	671	743	704	645
RT psilocybin, nonrelated	693	852	748	673
Priming effects				
SP (msec) placebo	26	72	35	41
SP (msec) psilocybin	47	117	74	40
ISP (msec) placebo	15	59	26	21
ISP (msec) psilocybin	23	110	44	29
SP (%) placebo	4.5	10.5	5.2	6.2
SP (%) psilocybin	6.4	13.1	10.0	5.8
ISP (%) placebo	2.6	7.9	4.1	3.2
ISP (%) psilocybin	2.9	11.8	5.6	3.8

recognized faster when preceded by "lemon" in normal subjects (absent indirect semantic priming effect). As mentioned above, in thought-disordered schizophrenic patients, such an indirect semantic priming effect was found.

Permission to use psilocybin within an experimental setting was obtained from the local institutional review board as well as from the German equivalent of the Food and Drug Administration (Bundesgesundheitsamt, Bundesopiumstelle, Berlin). Eight normal male subjects (mean age: 39.4 years, 7 right-handed, 1 left-handed, all physicians who had given written informed consent before the beginning of the study) received either a capsule containing 0.2 mg/kg body weight of psilocybin or placebo, in random order, on 2 days at least 1 week apart at approximately the same time of day (11:00 AM). To avoid repetition effects, two versions of the lexical decision paradigm were used and alternatively performed by the subjects before drug intake and 50, 150, and 220 min after drug intake.

## Results

Mean reaction times, as well as (direct) semantic and indirect semantic priming effects per semantic condition and intervention (placebo vs. psilocybin) are presented in Table 1. The error rates were generally low (0–2%), and showed no relation to semantic condition or drug. In particular, there was no increase in the amount of errors under placebo in either semantic condition.

Hallucinogens are known to slow down reaction times, which we also observed in every semantic condition. To assess the specific effects of the hallucinogenic agent on semantic processes, priming effects were calculated not only as difference scores but also as percentage scores (i.e., as percent of speed gain due to the semantic relation of the words). This measure is more conservative since it takes into account general reaction time and compensates for the effect of general slowness, an issue we have

discussed in detail in our paper on indirect semantic priming in schizophrenia (cf. Spitzer et al 1993b).

A two-way analysis of variance (ANOVA) measuring the effect of intervention (placebo vs. psilocybin) and time (before drug intake vs. 50 min after drug intake) on the indirect priming effect (percentage score) produced a tendency only for time [ $F(1, 7) = 5.09$ ;  $p = .059$ ], but neither a main effect for intervention nor a significant interaction. With respect to indirect semantic priming, however, the more sensitive measure of spreading semantic activation, we specifically tested the priming effects for significance and found a nonsignificant increase of indirect semantic priming under placebo, whereas this increase was significant under psilocybin [ $t(7) = 2.82$ ;  $p = .026$ ]. Table 1 further indicates a nonsignificant increase in semantic priming (difference and percentage scores) after the intake of either placebo or psilocybin, with a numerically larger effect under psilocybin.

To demonstrate the effect of psilocybin on indirect semantic priming, the difference of the priming effects between the psilocybin and the placebo runs was plotted, using the more conservative percentage scores (Figure 1).

## Discussion

The finding that psilocybin increases indirect semantic priming in normal subjects adds to our general understanding of the effects of hallucinogenic agents on cognitive functions. From anecdotal records and very few controlled studies these agents are believed to have subjective effects that sometimes are referred to as "broadening consciousness" and "enhancing creativity" (references in Pletscher and Ladewig 1994). Although most objective measures have failed to support these claims, our data suggest that the agent in fact leads to an increased availability of remote associations and thereby may bring cognitive

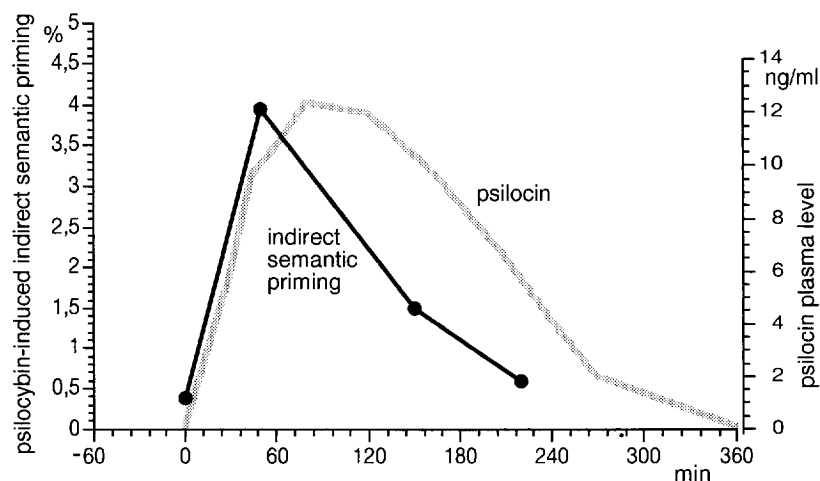


Figure 1. Mean plasma levels of psilocin, the main metabolite of psilocybin, which is formed rapidly after drug intake (data from Holzmann 1995), and hallucinogen-induced increase in indirect semantic priming.

contents to mind that under normal circumstances remain non-activated; however, the generally decreased psychological performance under hallucinogenic agents suggests that the increased indirect priming effect is due to a decreased capacity to use contextual information for the focusing of semantic processing. Hence, subjectively experienced increases in creativity as well as the broadening of consciousness have been found to parallel decreases in objective performance measures.

From a methodological perspective, our data indicate that indirect semantic priming is a highly sensitive measure that appears to respond not only to pharmacologic intervention, but also to the psychological effects of the setting of the study. The following post hoc suggestion may account for the finding of consistent (though nonsignificant) increases of priming effects under placebo. It is noteworthy that before testing, subjects appeared anxious, tight, and tense, a state known to produce stereotyped verbal associations and decreased priming effects (cf. Spitzer 1995). When about 30–40 min after drug intake the

subject became aware of either being on placebo or being on psilocybin, they tended to become more relaxed and unwinding, which is a state known to facilitate access to a wider scope of associative material. This is a testable hypothesis and we currently plan to use indirect semantic priming to investigate several nonpharmacologically induced states of anxiety and general arousal.

In conclusion, we have demonstrated the effect of a hallucinogenic agent, known to affect the 5-HT system, on the spread of activation during lexical access. This may serve as an example of how subjective psychopathology, objective psychological measurements, and underlying brain physiology (viz., neuromodulation) can be linked within a single conceptual framework.

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## References

- Cohen JD, Servan-Schreiber D (1992): Context, cortex and dopamine: A connectionist approach to behavior and biology in schizophrenia. *Psychol Rev* 12:45–77.
- Cohen JD, Servan-Schreiber D (1993): A theory of dopamine function and its role in cognitive deficits in schizophrenia. *Schizophr Bull* 19:85–104.
- Holzmann PP (1995): Bestimmung von Psilocybin-Metaboliten im Humanplasma und -urin (Analysis of psilocybin metabolites in human plasma and urine). PhD thesis, Tübingen, Germany.
- Kischka U, Kammer T, Weisbrod M, Maier S, Thimm M, Spitzer M (1995): Dopaminergic modulation of semantic network activation (in submission).
- Pletscher A, Ladewig D (eds) (1994): *50 Years of LSD. Current Status and Perspectives of Hallucinogens*. New York, London: Parthenon.
- Servan-Schreiber D, Printz H, Cohen JD (1990): A network model of catecholamine effects: Gain, signal-to-noise ratio, and behavior. *Science* 249:892–895.
- Spitzer M (1995): A neurocomputational approach to delusions. *Comp Psychiatry* 36:83–105.
- Spitzer M, Braun U, Maier S, Hermle L, Maher BA (1993a): Indirect semantic priming in schizophrenic patients. *Schizophr Res* 11:71–80.
- Spitzer M, Braun U, Hermle L, Maier S (1993b): Associative semantic network dysfunction in thought-disordered schizophrenic patients: Direct evidence from indirect semantic priming. *Biol Psychiatry* 34:864–877.
- Spitzer M, Weisker I, Maier S, Hermle L, Maher BA (1994): Semantic and phonological priming in schizophrenia. *J Abnorm Psychology* 103:485–494.