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**Semantic hyperpriming in schizophrenic patients:
Increased facilitation or impaired inhibition in semantic association processing?**

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Abstract

Previous studies analyzing semantic priming in schizophrenic patients have reported conflicting results. In the present study, we explored semantic priming in a sample of schizophrenic patients with mild thought disorders. We wondered if distinct cognitive processes, such as facilitation and/or inhibition, underlie semantic hyperpriming and are variously impaired in schizophrenic patients. Using a lexical decision task, we evaluated semantic priming in 15 schizophrenic patients (DSM-IV) with mild thought disorders and 15 healthy controls matched for sex, age, and education level. The task was designed to divide semantic priming into two additive components, namely facilitation effect and inhibition effect. One-sample *t*-tests were performed to investigate differences in semantic priming, facilitation, and inhibition within each group. ANOVAs were performed to compare the effects of semantic priming, facilitation, and inhibition between groups. Patients displayed greater semantic priming than controls (i.e., hyperpriming), but this was not due to increased facilitation in processing semantically related pairs. On the contrary, hyperpriming was the result of prolonged response time to process semantically unrelated pairs, corresponding to a requirement to inhibit unrelated information. We demonstrated semantic hyperpriming in stabilized schizophrenic patients with mild severity of symptoms. Thus, semantic hyperpriming may be an intrinsic feature of schizophrenia that is not related to the clinical state of patients. Semantic hyperpriming was due to an inhibition effect involved in processing semantically unrelated information not to increased facilitatory effect for related pairs.

Keywords: Schizophrenia; Semantic memory; Semantic priming; Inhibition; Automatic processes; Controlled processes

1. Introduction

Impairments of semantic associations have been described in schizophrenic patients as far back as the seminal work of Bleuler (1911). The spoken language of some schizophrenic patients is characterized by inappropriate associations, completely unrelated or only obliquely related to the subject, that disrupt the intelligibility of what is being said (Manschreck et al., 1988; Spitzer et al., 1993). Manschreck (1988) suggested that language disorders which contribute to thought disorders could be linked with impairment of cognitive processes that mediate association activation and/or inhibition in the semantic network.

These cognitive processes can be investigated using the semantic priming (SP) paradigm. SP corresponds to the decrease in time required to process a target after exposure to a semantically related prime as compared to the time required after exposure to a semantically unrelated prime (Neely, 1991). SP relies on two types of processes, i.e., automatic spreading of activation (ASA) and controlled processes. The latter encompasses inhibitory process which allows to inhibit semantically unrelated information (Posner and Snyder, 1975; Schneider and Shiffrin, 1977).

Previous studies analyzing SP in schizophrenic patients have reported conflicting results (Lecardeur et al., 2006; Minzenberg et al., 2002). Some reported similar SP in schizophrenic patients and controls (Chapin et al., 1989) and concluded that automatic and controlled processes are unimpaired in patients; others found that schizophrenic patients exhibit “hyperpriming,” that is, greater SP than controls. Hyperpriming was usually interpreted as reflecting abnormally high ASA (Manschreck et al., 1988; Moritz et al., 2001). Interestingly, enhanced ASA and priming was not hypothesized for all subtypes of schizophrenia. According to Spitzer (1997), semantic activation should spread farther and further in the semantic network of thought disordered patients and result in increased activation of semantically related information. Several studies (Aloïa et al., 1998; Barch et al., 1996; Manschreck et al., 1988) compared semantic priming (SP) effects in patients with thought disorders and controls, but the results were controversial. Still other studies

observed “hypopriming,” that is, lower SP in patients than in controls (Ober et al., 1995). This has often been interpreted as reflecting an impairment of controlled processes (Henik et al., 1992), with patients having ASA either equal to (Passerieux et al., 1997) or lower than (Aloia et al., 1998) that of controls.

Given these contradictory results (Maher et al., 2005), we wondered if distinct cognitive processes might underlie semantic hyperpriming and be variously impaired in schizophrenic patients. This explains why SP was decomposed into a facilitation effect and an inhibition effect: the former reflects the decreased time to process a target when the prime is semantically related, while the latter reflects the increased time required to inhibit a semantically unrelated prime. A facilitation effect manifests ASA and an inhibition effect manifests the setting up of controlled processes. Theoretically, in healthy subjects, tasks that require only automatic processes (i.e., ASA) would induce only a facilitation effect, whereas tasks requiring both automatic and controlled processes would induce facilitation effect and, in addition, an inhibition effect (Neely, 1991).

The aim of the present study was to explore SP in schizophrenic patients with mild thought disorders. Specifically, we wanted to determine if facilitatory and/or inhibitory processes were impaired in schizophrenic patients.

2. Method

2.1. Pre-experimental material

Our aim was to characterize dysfunctional semantic associations in schizophrenic patients. Previously, two sets of French stimuli (Besche et al., 1996; Besche et al., 1997; Passerieux et al., 1995; Passerieux et al., 1997; Quelen et al., 2005) were used to assess SP effects in schizophrenics, but those stimuli did not allow us to vary the semantic relationship between primes and targets. Therefore, we selected our own stimuli. Our word set, drawn from Giffard et

al. (2001), was composed of word pairs of the same semantic level (e.g., coordinate relation, tiger-lion) and pairs of words in which the target was an attribute of the prime (e.g., attribute relation, zebra-stripe). Two hundred and twenty-six words were selected from French verbal-association bases (Rozenzweig, 1957; Ferrand and Alario, 1998) according to word length (3-10 letters), lexical frequency (Content et al., 1990), imageability (Desrochers and Bergeron, 2000), concreteness, age of acquisition, and living/nonliving distribution. We controlled for the affective valence of words by removing affective words such as fear, death, and happiness from the word set. These words were used as inductors in a restricted verbal association task. In this task, 233 students had to produce, as quickly as possible, the first word that came to mind in response to each inductor word. To control for list effects and tiredness, half the list was presented according to the alphabetic order of the inductor words and the other half in a reverse order. From this task, we obtained a first set of 2082 words.

We then constructed a computerized lexical decision task (LDT) to check that the words selected as targets were understandable, unambiguous and recognized as French words with a low proportion of errors and in a homogeneous temporal interval. This task utilized 640 target words selected from our first set of words (see below) and 640 pseudo-words constructed by changing one letter per syllable but keeping the lexical structure of French. The 16 students who performed the LDT had to decide as quickly as possible whether a string of letters constituted a French word or not. If the letter string was recognized as a French word, the subject was to press the “yes” key as quickly as possible with their right index finger. If the letter string had no meaning, the subject was to press the “no” key as quickly as possible with the right middle finger.

We then excluded from the target-word list all words and pseudo-words eliciting from any subject a reaction time (RT) differing by more than 3 standard deviations from the mean or leading to more than one classification error. Subsequently, it remained no extreme value and our data (RT) were normally distributed.

Finally, the experimental list of prime/target pairs was definitively created (800 pairs). It contained four types of prime/target pairs: related, unrelated, those having the word “neutral” as prime, and those with a pseudo-word as target (Fig. 1).

2.2. Subjects

Thirty subjects were recruited. Fifteen were schizophrenic outpatients from the university hospital of Caen, France, and 15 control subjects from the Caen community. All gave informed written consent, and the local ethics committee (CCPPRB de Basse-Normandie, France) approved the study. Patients and controls were matched subject by subject for gender, age, and level of education (Table 1). All subjects reported French as their first language.

The diagnosis of schizophrenia was established using DSM-IV criteria (American Psychiatric Association, 1994) and the patients’ clinical state was evaluated with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Thought Language Communication scale (TLC) (Andreasen, 1979). Ten patients were residual, three were paranoid and two were disorganized (DSM-IV). Low thought and language disorders were reported with TLC (Mean: 3.0; Standard Deviation: 4.58; Range: 16.0) and PANSS disorganization score (Mean: 1.67; Standard Deviation: 1.59; Range: 5.0). We collected clinical information such as age of onset and duration of illness. Each patient was treated with atypical antipsychotics (clozapine, amisulpride, olanzapine and risperidone) and daily dose was converted into chlorpromazine-equivalents (Ban, 1971; Forster, 1989). Schizophrenic outpatients were stabilized, with no change in treatment over the 4 months prior to the start of the study. Controls did not meet criteria for psychotic disorders or substance (including alcohol) dependence, as assessed by the Structural Clinical Interview for DSM-IV (First et al., 1997).

2.3. Experiment

SP was evaluated using an LDT, the most accurate type of task for assessing automatic and controlled processing (Neely 1991). To discern whether schizophrenic patients are characterized by a dysfunction of automatic processes, controlled processes, or both, we constructed two types of LDTs, following experimental criteria described in the literature (Posner and Snyder, 1975). To preferentially elicit automatic processes, the first LDT (automatic task, Fig. 1-a) used short stimulus onset asynchrony (SOA, 250 ms) and a low proportion of pairs of related words (10%) and instructed subjects to respond to the target only. The second LDT (automatic/controlled task, Fig. 1-b) elicited both automatic and controlled processes by using a long SOA (500 ms) and a high proportion of related pairs (30%) and explicitly instructing subjects to process the prime. Facilitation effect corresponds to the shorter time required to process a target when the prime is semantically related to the target (as compared to the time required when the prime is neutral); inhibition effect corresponds to the longer time required to process a target when the prime is semantically unrelated to the target.

2.4. Procedure

Stimuli were presented using Superlab 1.68 software (Cedrus Corporation, Phoenix, Arizona, USA), which allows RT to be measured to within 1 ms. All stimuli were presented as black, lower-case letters 2 cm high centered on a blank screen.

During each trial (Fig. 2), the subject saw on the screen a fixation point lasting 500 ms followed by a prime word lasting either 200 ms (automatic task) or 450 ms (automatic/controlled task). The screen then remained blank for 50 ms before the target appeared, giving an SOA of either 250 ms (automatic task) or 500 ms (automatic/controlled task). We chose to have the target remain on the screen until a response was made to avoid patients responding by chance. Indeed, if the target quickly disappeared from the screen, we could not be sure that patients had enough time to process it. Once a response was made, the screen was blank for 1500 ms before another trial

appeared.

If the letter string was recognized as a French word, the subject was to press the “yes” key as quickly as possible with their right index finger. If the letter string had no meaning, the subject was to press the “no” key as quickly as possible with the right middle finger.

SP tasks were divided into 7 subtests (5 for the automatic task and 2 for the automatic/controlled task), each lasting 7–8 minutes in order to minimize loss of attention and tiredness. The automatic task was always performed before the automatic/controlled task so as to prevent voluntary, conscious processing of the primes during the automatic task. In order to familiarize the subject with the tasks, 6 sample trials and 30 practice trials using different word pairs were performed before each type of task. Total duration of tasks was about 1 hour.

2.5 Statistical analysis

SP, facilitation, and inhibition effects were calculated from RTs obtained for correct responses (Fig. 1).

2.5.1 Intra-group comparisons

One-sample *t*-tests were used to determine whether SP, facilitation, and inhibition effects occurred during each task in each group.

2.5.2. Inter-group comparisons

Separate two-way analyses of covariance (ANCOVAs) were used with SP, facilitation, or inhibition effects as dependant measures, group (patients and controls) and task (automatic and automatic/controlled) as main factors, and simple reaction time as covariate.

3. Results

3.1 Demographic data

Verbal Intellectual Quotient (WAIS-III) did not differ significantly between patients and controls, $t(14) = -0.906$, $p = 0.37$, but simple reaction time (Attention Assessment Test) was longer in patients than in controls, $t(14) = -2.499$, $p = 0.019$.

3.2. Intra-group comparisons

3.2.1. Semantic priming

SP was significant during the automatic task in both patients ($t(14)=2.81$, $p = 0.014$) and controls ($t(14) = 3.956$, $p = 0.0014$). During the automatic/controlled task, SP was significant in both patients ($t(14)= 4.985$, $p < 0.001$) and in controls ($t(14) = 6.614$, $p < 0.001$).

3.2.2 Facilitation effect (Fig. 3)

A facilitation effect was observed in controls during the automatic task ($t(14) = 4.12$, $p = 0.001$). No significant facilitation effect was observed in schizophrenic patients ($t(14) = 0.377$, $p = 0.712$).

During the automatic/controlled task, the facilitation effect was significant in both controls ($t(14) = 2.72$, $p = 0.017$), and schizophrenic patients ($t(14) = 3.06$, $p = 0.008$).

3.2.3. Inhibition effect (Fig. 3)

During the automatic task, no significant inhibition effect was observed in controls ($t(14)=0.845$, $p = 0.412$). In contrast, this effect was significant in schizophrenic patients ($t(14) = 2.302$, $p = 0.037$).

During the automatic/controlled task, the inhibition effect was significant in both controls ($t(14) = 2.944$, $p = 0.011$) and in schizophrenic patients ($t(14) = 3.078$, $p = 0.008$).

3.3. Inter-group comparisons

3.3.1. Semantic priming (Table 2)

A group main effect was found ($F(1,52) = 3.92, p = 0.053$). Globally, patients obtained larger SP (214.77 ms) than controls (100.6 ms). A task main effect was found ($F(1,52) = 15.97, p < 0.001$). SP was larger with the automatic/controlled task (248.36 ms) than with the automatic task (67.01 ms). Group \times Task Interaction was not significant ($F(1,52) = 0.03, p = 0.864$).

3.3.2. Facilitation effect

There was neither a main group effect ($F(1,52) = 0.174, p = 0.68$) nor a main task effect ($F(1,52) = 3.23, p = 0.078$). Group \times Task Interaction did not attain statistical significance ($F(1,52) = 0.085, p = 0.77$).

3.3.3. Inhibition effect

A main group effect was found ($F(1,52) = 2.53, p < 0.01$). Globally, patients showed greater RT difference (148.36 ms) than controls (40.03 ms). A task main effect was found ($F(1,52) = 6.05, p = 0.004$). Inhibition effect was greater with the automatic/controlled task (155 ms) than with the automatic task (33.38 ms). Group \times Task interaction did not attain statistical significance ($F(1,52) = 0.16, p = 0.694$).

4. Discussion

We observed greater semantic priming in patients compared to matched healthy controls in automatic and automatic/controlled tasks. Moreover, the partition of SP into facilitatory and inhibitory effects allowed us to better understand the cognitive processes underlying hyperpriming in schizophrenic patients.

One of our objectives was to determine whether hyperpriming occurred in a sample of schizophrenic patients with mild thought disorders. Our results indicated that it did, and they were particularly interesting since hyperpriming has generally been reported in patients with thought disorders. Thus, enhanced semantic priming might be an intrinsic feature of schizophrenia that is unrelated to the clinical state of a patient. Consequently, hyperpriming could be viewed as relevant clue of semantic association disturbances in schizophrenic patients beyond thought disorders.

The present study is the first to document enhanced SP in schizophrenic patients with two distinct procedures. Because of widely varying experimental designs (Lecardeur et al., 2006), previous studies inconsistently reported hyper-, hypo-, or normal SP in schizophrenia (Minzenberg et al., 2002). In this way, hyperpriming was reported in schizophrenic patients following short stimulus onset asynchrony (100- 250 milliseconds), but the proportion of related pairs was too great (50- 67%) to ensure that controlled processes did not occur (Henik et al., 1995; Manschreck et al., 1988, Spitzer et al., 1993; Weisbrod et al., 1998). Our experimental conditions (stimulus onset asynchrony, the proportion of related pairs, instructions) prevented controlled processing during automatic tasks. Moreover, we included a neutral condition in our experimental paradigm in order to distinguish facilitation and inhibition in SP. In contrast to controls, patients did not display a facilitatory effect during the automatic task. Consequently, hyperpriming in patients could not be explained by enhanced facilitation in processing semantically related information. The lack of facilitation is not consistent with greater spreading activation through semantic associations in schizophrenic patients, as suggested by Manschreck (1988). In fact, semantic hyperpriming in patients was due to greater effect of inhibition. Indeed, the inhibitory effect was significant in patients during both tasks. Theoretically, there is no inhibitory effect, only automatic spreading of activation, in healthy subjects during an automatic task (Schneider and Shiffrin, 1977), as we observed in controls. On the contrary, patients ever displayed inhibition effect, even in the automatic task. Thus, our results suggest that an inhibition process is required during the

automatic task in patients. This inhibitory process might allow control of inefficiently orientated ASA induced by unrelated information in the semantic network. Such a process may also occur during the automatic/controlled task.

Semantic priming was defined by subtracting the RT of related words from the RT of unrelated words. Thus, processing semantically related information requires less time than processing semantically unrelated information. Consequently, SP is generally viewed as facilitation of processing related information compared to unrelated information. In this way, hyperpriming in schizophrenic patients was interpreted as an enhanced facilitation in processing semantically related information (Manschreck et al., 1988; Moritz et al., 2001). However, studies that included a neutral condition showed that, in healthy subjects, semantic priming does not reflect only facilitation of related word processing but also inhibition of unrelated information. Current study demonstrated that including a neutral condition in a semantic priming paradigm is crucial for determining hyperpriming effects in schizophrenic patients. Indeed, hyperpriming was unexpectedly due to the greater time required to inhibit unrelated information, not greater facilitation in processing related information, as postulated previously.

Semantic hyperpriming was not related to IQ, slowing, or severity of symptoms. Indeed, there was no difference in verbal IQ between patients and controls. Since RT was taken into account as a covariable, hyperpriming was not due to slowing in patients. We cannot exclude an effect of antipsychotic medication on SP since all the patients were treated with antipsychotics. However, numerous studies did not find a relationship between dose of neuroleptics and SP (Moritz et al., 2001; Quelen et al., 2005; however see Barch et al.; 1996).

5. Conclusion

We demonstrated that semantic hyperpriming could be reported in stabilized schizophrenic patients with mild thought and language disorders. The strength of our study lies in revealing that

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semantic hyperpriming was due to an inhibition effect in processing semantically unrelated information, not to increased facilitation effect.

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Table 1. Characteristics of the population

| | Patients | | Controls | | <i>P</i> * |
|--|-----------------|----------|-----------------|---------|------------|
| | <i>(n = 15)</i> | | <i>(n = 15)</i> | | |
| | Mean | (SD) | Mean | (SD) | |
| Gender (F/M) | 3/12 | | 3/12 | | |
| Education (secondary school/university) | 7/8 | | 7/8 | | |
| Age (years) | 36.3 | (7.5) | 38.1 | (8.9) | 0.57 |
| Verbal IQ (WAIS-III) | 93.4 | (14.55) | 97.8 | (11.91) | 0.372 |
| Simple reaction time (milliseconds) | 357.55 | (72.254) | 303.421 | (42.63) | 0.019 |
| Age of onset of illness (years) | 23.3 | (4.29) | | | |
| Length of illness (years) | 12.2 | (4.75) | | | |
| Doses of antipsychotics (CPZ equivalent) | 387.23 | (191.36) | | | |
| Severity of illness (Total score of PANSS) | 43.4 | (9.77) | | | |

* *P values*: Non-paired *t*-tests

SD: Standard Deviation; F/M: Female/male; WAIS-III: Wechsler Adult Intelligence Scale–III; CPZ: Clorpromazine; PANSS: Positive And Negative Syndrome Scale

Table 2. Mean difference of response times in milliseconds.

| | Schizophrenic patients | | | | Healthy controls | | | |
|----------------------------------|------------------------|--------|-----------------------------|--------|------------------|--------|-----------------------------|--------|
| | Automatic task | | Automatic / controlled task | | Automatic task | | Automatic / controlled task | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| RT related | 1010.69 | 367.24 | 955.08 | 385.99 | 642.2 | 106.22 | 543.03 | 110.05 |
| RT unrelated | 1088.71 | 346.62 | 1306.61 | 591.12 | 698.2 | 145.92 | 688.23 | 173.55 |
| RT neutral | 1025.26 | 278.53 | 1073.33 | 423.96 | 694.87 | 143.25 | 611.49 | 182.37 |
| SP ^a | 78.01 | 107.64 | 351.53 | 273.13 | 56 | 54.83 | 145.2 | 85.03 |
| Facilitation effect ^b | 14.57 | 149.72 | 118.25 | 149.49 | 52.68 | 49.52 | 68.46 | 97.57 |
| Inhibition effect ^c | 63.45 | 106.73 | 233.28 | 293.49 | 3.33 | 15.25 | 76.74 | 100.95 |

^a SP effect: [(mean RT unrelated) - (mean RT related)]; ^b Facilitation effect: [(mean RT neutral) – (mean RT related)]; ^c Inhibition effect: [(mean RT unrelated) – (mean RT neutral)]

Response Time (RT); Standard Deviation (SD); Semantic Priming (SP)

Figure 1: Lexical Decision Tasks with Semantic Priming.

Figure 1-a: Automatic task was elaborated thanks to a short SOA (250ms), a low proportion of related pairs of words (10%) and instructions to bring low level of attention to the prime.

Figure 1-b: Automatic/controlled task was elaborated thanks to a long SOA (500ms), a high proportion of related pairs (30%) and explicit instructions to process the prime.

Semantic Priming: RT (unrelated) – RT (related); Facilitation: RT (neutral) – RT (related);

Inhibition: RT (unrelated) – RT (neutral)

RT: Response Time; SP: Semantic Priming; SOA: Stimulus Onset Asynchrony

Figure 2: Typical sequence of events in a single trial

Figure 3: Facilitation and inhibition effects for both patients and controls in both automatic and automatic/controlled tasks

RT: Response Time



