N400 and P300 modulation as functions of processing level in schizophrenia patients exhibiting formal thought disorder

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20 pages
3 Tables
2 Figures
Abstract

In a semantic priming paradigm, the effects of different levels of processing on N400 were assessed by changing task demands in 10 schizophrenics and 10 matched controls. In the lexical decision task subjects had to discriminate between words and nonwords, and in the physical task subjects had to discriminate between cyan and blue ink letters. A lexicality test of reaction times demonstrated that the physical task was performed non-lexically in both groups. Moreover, a semantic priming reaction time effect was obtained only in the lexical decision task for the control group. The level of processing clearly affected event-related potentials. An N400 priming effect was only observed for the control group in the lexical decision task. By contrast, in the physical task a P300 effect was observed for either related or unrelated targets in both groups. Taken together, these results indicate that FTD schizophrenics are impaired specifically when task performance induces the semantic aspects of words as indexed by reduction of the N400 priming effect.

Keywords: Schizophrenia, semantic memory, N400, P300, ERP, context monitoring.
Introduction

In the present study we examined the influence of task demands on the N400 semantic priming effect in a group of schizophrenia patients with Formal Thought Disorder (FTD) as compared to normal control subjects. In particular, we focused on the N400 effect of different levels of processing of stimuli. Semantic priming modulates the amplitude of the N400 component of the event-related potential. A target word elicits a smaller N400 when preceded by a semantically related prime word, which establishes context, than when preceded by a semantically unrelated word (Bentin et al. 1993; Chwilla et al. 1995). This difference in amplitude is referred to as the N400 priming effect. N400 amplitude varies as a function of the degree to which eliciting words relate to their preceding semantic context. Taken together, the results indicate that an N400 priming effect occurs only when semantic aspects of word stimuli are managed or monitored.

Schizophrenia is primarily a disorder of thinking and language. Investigators have suggested that a defect in language information processing may be the pathognomonic of the disorder (Minzenberg et al. 2002). The current widespread interest in neurocognitive aspects of the illness led schizophrenia researchers to explore priming effects in the semantic memory system (reviewed in (Spitzer et al. 1993; Pomarol-Clotet et al. 2008). At least two major theories have been proposed to explain the pathogenesis of this dysfunction. The first theory is that schizophrenia arises from impairment in the buildup and use of context (Kuperberg et al. 1998; Kostova et al. 2003; Kostova et al. 2005). The second is that it arises from abnormalities in the structure and function of semantic memory (Condray et al. 2003; Rossell and David 2006; Lecardeur et al. 2007). It is not yet fully understood whether this dysfunction is due to deficient encoding, storage, access, or response selection processes, or to some combination of those functions. Three mechanisms are considered to be semantic priming effects (Chwilla et al. 1995): (1) automatic spreading activation between nodes in semantic memory; (2) expectancy-induced priming, (a high proportion of related word pairs leads subjects to expect probe words that are related to the prime word); and (3) semantic matching (a post
lexical process where the detection of semantic similarity between probe word and prime word speeds up the lexical decision about the probe). Impairments in the former mechanism support the second theory, while impairments in the latter two mechanisms support the first theory. A number of studies indicate that schizophrenic patients exhibit variable semantic priming effects under automatic processing conditions, and consistent impairments under controlled/intentional conditions. Most studies support the view that N400 priming effects depend on conscious identification and lexical processing of stimuli (Kiefer and Spitzer 2000; Matsumoto et al. 2005). It is important to consider the level of processing of stimuli when addressing group differences in the N400. Mitchel et al. presented stimuli consisting of sentence frames completed with a pair of words, which served as the target pair. They required subjects either to decide whether or not at least one of the words in a terminal pair completed a sentence sensibly (semantic judgement task), or to indicate whether or not the two words in the final pair were identical (physical judgment task). Schizophrenic patients differed from controls in regard to the congruity effect on N400 amplitude in the semantic task, but not in the physical task, as the latter task putatively addressed passive attentional processes. Thus, the N400 of schizophrenic patients may only be disturbed when semantic processing is required by the task. The purpose of the present study was to test the hypothesis that FTD schizophrenic patients would demonstrate impairment in reaction time and N400 modulation compared to a normal control group only in the semantic priming paradigm. Moreover, we aimed to provide experimental data indicating that processing level is a key point contributing to impairment among FTP schizophrenia patients.

**Methods**

**Patients**

Ten male patients, all schizophrenic according to DSM-IV criteria for schizophrenia (Kay et al. 1987; A.P.A. American Psychiatric Association 1994), participated in this study. Diagnosis was
made by an experienced independent clinician using the Structured Clinical Interview for DSMIV (SCID) (First et al. 1977). Patients were recruited during hospitalization (Psychiatric Department, Versailles Hospital or Clinique de Chailles, Loire et Cher). All patients had stable symptoms and were on neuroleptic treatment, taking stable doses of neuroleptic medications equivalent to 545 mg/day chlorpromazine. Five patients were receiving atypical antipsychotic medications. Two patients were also taking 5 mg of benzodiazepine. No patient received antidepressant or anticholinergic medication. Psychotic symptoms were evaluated using the Positive and Negative Syndrome Scale, PANSS (Kay et al. 1987) and formal thought disorders were evaluated using the Thought, Language and Communication disorders scale (TLC; (Andreasen and Grove 1986; Bazin et al. 2002)). A TLC score equal to or higher than 10 was used as the cut-off (Simpson and Davis 1985; Harvey et al. 1992). The control group consisted of 10 healthy participants (6 men, 4 women) matched with the schizophrenia patients for age, socioeducational level (number of years of study), and vocabulary level (Binois and Pichot 1959). Healthy participants were recruited from the hospital staff and were evaluated with semi-structured interview M.I.N.I. (Lecrubier et al. 1997) to assure that they had no past or present psychiatric disorders. Table 1 summarizes the clinical and socioeducational characteristics of all the participants. The exclusion criteria for participation as a patient or control were: age less than 20 years or over 45 years; history of neurological illness; regular or recent use of illicit substances; electroconvulsive treatment in the last 6 months; first language other than French; and vision (including corrected vision) less than 8/10. All participants were informed of the general objectives of the study and gave written consent. This research was approved by the local Ethical Committee in accordance with the World Medical Association (Declaration of Helsinki) Code of Ethics.

Tasks and stimuli

Lexical decision task
We used a lexical decision task to elicit semantic priming. In this task, the experimental material consisted of three lists, each containing 300 pairs of items: 150 word-nonword pairs and 150 word-word pairs. For the word-word pairs, there were 50 pairs of unrelated words, 50 pairs of related words (16.7% related words) and 50 neutral condition pairs with the word "context" as prime. The lists were constructed so as to counterbalance the presentation of the material, with target words appearing as related words in one list, as unrelated words in the other and preceded by the word "context" in the third. All participants were tested with one of three lists and viewed target words and nonwords once. Each subject viewed each target word only once. Primes and targets were presented with black ink.

Physical Task

We constructed another list including 300 pairs of items as described above (150 word-nonword pairs, 50 related word pairs, 50 unrelated pairs and 50 neutral pairs). There were no significant statistical differences between semantic and physical stimulus lists regarding linguistic characteristics of the target words (in terms of number of letters, frequency, and cloze probability). In this task, half of targets were displayed in blue ink and the other half were displayed in cyan. A pilot study was conducted to verify that patients and controls perceived the physical stimuli at the same levels of accuracy. Two sets of 90 items each were constructed using the same rules, for training purposes.

Procedure

Participants were seated comfortably about 80 cm in front of a computer screen. They were told that they were going to see two sequences of letters. In the lexical decision task, they had to decide as quickly and accurately as possible whether or not the second sequence of letters was a word in the French language. In the physical task they had to decide whether the color of the target word was
displayed in blue or cyan color. They responded by pressing a button on the mouse with their writing hand. The left button of the mouse corresponded to a "yes" or "blue" and the right button, to a "no" or "cyan" response. The first stimulus was always displayed in black lower case letters on the white computer screen for 200 ms. The screen then became totally white again for 250 ms before the second stimulus was displayed (stimulus onset asynchrony, or SOA, of 450 ms). The second stimulus was displayed for 1200 ms. The interval between two pairs of items was 2000 ms. The order of presentation of the two tasks was randomized among subjects. The participants performed a training session before the task. The entire recording period lasted approximately 30 min.

Data collection and analysis

EEGs were recorded from 12 electrodes arranged on the scalp according to standard international convention: three electrodes in the frontal region (F3, Fz, F4), three in the central region (C3, Cz, C4), three in the parietal region (P3, Pz, P4), one each in the left (T3) and right (T4) temporal regions, and one in the occipital area (Oz). Four electrodes were used to record the electrooculogram (EOG): two at the level of the external canthi, and one above and one below the eye. All impedances were kept below 1.8 kV. The EEG was recorded (using the InstEP system) with a frequency of 256 points per second. Eye movement and blink artefacts were corrected using an algorithm operating in the time and frequency domains (Woestenburg et al. 1983). Data were digitally filtered using a bandpass of 0.80 to 12 Hz. Average waveforms were calculated separately for each subject and stimulus type with reference to the 200 ms prestimulus baseline. At least twenty trials minimum (range 20-25) contributed to each waveform for each experimental condition and diagnostic group. The data were analyzed by calculating separately for each subject the mean ERP amplitude for each stimulus type for electrodes Fz, C3, Cz, C4, and Pz for a time window of 290 to 440 ms after prime presentation to assess any differences in the prime and for two time windows (early: 300 to 450 ms, and late: 450 to 600 ms) after target presentation. The window was
determined based on visual inspection of the plots. STATISTICA software was used for statistical
analysis. We first carried out multivariate analyses of variance (MANOVAs) on N400 or P300
amplitude, comparing groups (controls vs. schizophrenic patients), using Task (semantic, physic),
"Relatedness" (related words, unrelated words, nonword), Window (early, late), and "Electrode" (Fz,
C3, Cz, C4, Pz) as intragroup factors. Significant interactions were analyzed, using post-hoc
Scheffe’ tests. Reaction time (RT) data were used to evaluate the lexicality effect, and to assess
whether the physical task was indeed performed non-lexically. For each subject, the mean RT was
calculated for correct responses to all word targets (related and unrelated combined) and to all
nonword targets. To analyze RT priming effects, separate ANOVAs were conducted for both Tasks
(semantic, physical) with Relatedness (related, unrelated) as within factors and Group (control,
schizophrenic) as a between factor.

Results

Behavioral Results

The results of the RT analyses revealed a Group main effect indicating that mean RTs were longer in
the Schizophrenic group (664ms) than in the Control group (514 ms) (F(1,17) = 12.94 p < .002).
The lexicality test demonstrated that the physical task was performed non-lexically in both groups,
and on the basis of non-lexical forms of information only. In the physical task (PT), no difference in
mean RT was found between the 150 word targets (514 ms) and the 150 nonword targets (511 ms).
In the lexical decision task (LDT), the lexical effect was significant in both word targets (645 ms)
and nonword targets (685 ms) (F (1,17)= 13.02, p < .002).
A priming effect was observed in the LDT but not in the PT (F1,17) = 5.90, p < .026. We did not
find a significant Group x Task x Relatedness interaction. RT results for the priming effect are
summarized in Table 2.
Electrophysiological Results

Grand averages elicited by the targets in the lexical and the physical tasks for the control and schizophrenic groups are presented in Figure 1 (Lexicality effect) and Figure 2 (Priming effect).

We did not find any significant effects on the prime stimulus for any factors.

The main results of the statistical analyses are summarized in Table 3. According to word/ nonword ERP amplitude comparison, a significant effect with respect to Task x Lexicality x Electrode x Window indicated that the N400 lexical modulation was significant only for the LDT (Rao R Form_2 (4.14) = 3.64; p = .04), for the 300-450 ms epoch on Cz (0.13 vs. -0.49 μV), C4 (0.24 vs. -0.36 μV), and Pz (0.24 vs. -0.36 μV) sites. In addition, a Group x Task x Window interaction (F(1,17) = 6.65; p = .02) showed that the P300 amplitude was larger in the PT (3.64 μV) compared to the LDT (-0.37 μV) for the 300-450 ms window (see figure 1 Left panel in comparison LTD (up) and PT (bottom) in the Control group only.

According to related/ unrelated word ERP amplitude comparison, a Group x Task x Window interaction F(1,17) = 6.00; p = .03) emphasized a larger P300 amplitude for the earlier window (4.04 μV) than the later (-0.01 μV) for the PT in the Control group. Taken together, these results strongly suggested a P300 component effect in the control group for the PT for the 300 – 450 ms range and a 150 ms latency shift in the LDT (see Figure 2 left panel in comparison P300 peak at Pz in LDT (top) and in PT (bottom). Finally, a Group x Task x Prime x Windows significant effect (F(1,17) = 4.46; p = .05) demonstrated a priming effect occurring only in the Control group, for LDT, for the earlier window (see Figure 2 upper panel, comparing control (right) and schizophrenic (left) groups).

Discussion

The present study was carried out to explore the electrophysiological correlates of two different levels of processing in schizophrenic and control groups. There were two main ERP findings. First, the N400 effect (the difference in amplitude of the N400 to nonwords relative to words) occurred
only at the semantic processing level in both groups, indicating that schizophrenic and control
groups displayed a lexicality effect only for the lexical decision task. Second, only the control group
displayed an N400 priming effect (the difference in amplitude of the N400 to unrelated relative to
related words) at the semantic processing level and a large P300 component at the physical
processing level. The P300 physiological interpretation suggested by Polich (Polich 2007), as “a
neural inhibitory activity organized to delimit task-extraneous events to sculpt attentional focus and
promote memory operations for target stimuli”, is in line with our results. These results are
consistent with those published by Mitchell et al. (Mitchell et al. 1991), although they used a task
different from ours (sentence vs. word priming task).

In terms of reaction time, the lexicality test showed that performing the two tasks induced different
levels of processing. There was no difference between the reaction times for word and nonword
targets in the physical task, indicating that these tasks were performed non-lexically. In contrast, a
significant lexicality effect was observed in the lexical decision task.

In the control group, an N400 priming effect clearly developed in the LTD and was absent in the
physical task (Figure 2 left panel). The N400 was modulated by the relatedness of prime and target,
and yielded much larger amplitudes for unrelated than for related word pairs. In contrast, no
indication for an N400 priming effect was observed in the physical task. This result suggests that the
modulation of N400 amplitude requires that subjects explicitly attend to the meaning of stimuli, and
that the meaning of the word becomes part of episodic trace in working memory. Under shallow
processing conditions (physical task), we interpreted the lack of lexicality and priming N400 effects
in the two groups as reflecting that word meaning was prevented from becoming part of episodic
trace in working memory despite access to semantic memory.

In the schizophrenic group, the physical task produced results in keeping with our previous
publication (Baribeau and Laurent 1986; Laurent and Baribeau 1992). Our studies have shown a
consistent reduction of the auditory P300 in schizophrenia. This is one of the most consistent
findings in schizophrenia patients during auditory tasks, while the visual attention findings have been mixed (Kawasaki et al. 2007). The interpretation of these results is a subject of controversy. On one hand, it has been proposed that auditory, and possibly visual, P300 amplitudes track fluctuations in clinical state (Mathalon et al. 2000; Wood et al. 2006; Mucci et al. 2007). However, we demonstrated in a previous paper (Laurent et al. 1992) that auditory P300 amplitude reduction is a trait marker in FTD but a state marker in non-FTD schizophrenics, and we have recently confirmed this finding in a new population of FTD patients (Passerieux et al. submit). In the present study we have recorded a visual P300. The decrease of P300 amplitude modulation by the task in schizophrenic compared to control groups (see figures 1 and 2 left panel) was significant, and may be interpreted as a statistical confound linked to P300 amplitude reduction in schizophrenics. Moreover, the data argue in favor of the state nature of semantic priming impairments, and of the trait nature of attentional deficits, in FTD patients. Gouzoulis-Mayfrank et al. (Gouzoulis-Mayfrank et al. 2003) have also recorded behavioral data arguing in favor of semantic impairments as episodic markers, and as clearly state-dependent, in FTD schizophrenics. Kiang’s N400 data (Kiang et al. 2007), showing a trend toward reduced differences in amplitude between non-exemplars and low-typicality exemplars correlated with psychotic symptoms, may be interpreted as state marker of psychotic symptoms.

In the LTD, the decreased N400 modulation in FTD group suggests two hypotheses. One hypothesis regarding how abnormal activation in semantic memory may lead to disorganized speech postulates a broader spread of activation to weakly or remotely related items (Moritz et al. 2003). Some semantic priming data support this hypothesis. Consistent with the increased spread of activation to weak associates, an abnormally large priming effect for indirectly related words has been found in thought-disordered schizophrenia patients (Barch et al. 1996). The other hypothesis attributes disorganized speech in schizophrenia to an impaired ability to use context to activate related items, or to inhibit unrelated items (Cohen and Servan-Schreiber 1992; Sitnikova et al. 2002; Hardy-Baylé
et al. 2003). Importantly, this abnormality and increased spreading activation are not necessarily mutually exclusive, as they could occur sequentially. For instance, schizophrenia patients displayed less priming than normal controls for closely related words at a long SOA (an insufficient connectivity seems to hold), but not at shorter SOAs where an excessive connectivity appears to operate (Kuperberg et al. 1998; Condray 2005). In a sentence-context study (Strandburg et al. 1997; Kostova et al. 2003; Kostova et al. 2005) both schizophrenia patients and controls were slower to recognize a sentence-final word when it was semantically incongruent with the context than when it was congruent, but patients with high thought-disorder ratings were delayed less than were either controls or patients with low thought-disorder ratings. This is consistent with an impaired use of context.

Prime-target word pairs (Niznikiewicz et al. 1999; Condray et al. 2003; Kostova et al. 2003) were associated with larger N400 amplitudes to related targets in schizophrenia patients or schizotypal personalities than in normal controls, while amplitudes to unrelated targets did not differ between patients and controls. These results suggest decreased activation of related targets in schizophrenia, consistent with the impaired context use hypothesis. Overall, the results of these N400 studies, like those of RT priming studies, suggest that schizophrenia patients generally show abnormal semantic priming, although hypothetically for different reasons at different prime-target intervals. Specifically, at relatively short SOAs (approximately \(\leq 300 \text{ ms}\)), there may be increased or more broadly spreading activation of related concepts (Lecardeur et al. 2007), as reflected in smaller N400 amplitudes for related targets. However, at longer SOAs, including within a sentence context, schizophrenia patients’ ability to use context to activate related or expected items may be impaired, as reflected in larger N400s to these items.

In conclusion, our results support the idea that cognitive impairments presented by FTD schizophrenics in language processing are related either to semantic memory deficit (functional or structural deficit) or to context and attentional monitoring. Our present study did not address these
questions specifically. Further studies must be conducted to delineate the impact of attentional and context factors on schizophrenic patients’ semantic damage. In this study, our goal was merely to demonstrate that FTD schizophrenics are specifically impaired in the lexical integration process of words, and not in all features of communication.
Legends

Figure 1. Patterns of evoked potentials recorded during the presentation of target non-words (dark) and target words (light) in the control group (left) and the schizophrenic group (right) in LDT (top) and PT (bottom), with 5 electrodes between -200 ms and 1000 ms.

Figure 2. Patterns of evoked potentials recorded during the presentation of target unrelated words (dark) and target related words (light) in the control group (left) and the schizophrenic group (right) in LDT (top) and PT (bottom), with 5 electrodes between -200 ms and 1000 ms.
References


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Rossell S. L. and David A. S., 2006. Are semantic deficits in schizophrenia due to problems with access or storage? Schizophrenia Research 82(2-3): 121-134.


Table 1. Demographic, cognitive, and clinical data for patients and control participants

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenics n = 10</th>
<th>Controls n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31.6 ± 6.42</td>
<td>27.20 ± 4.98</td>
</tr>
<tr>
<td>Years in education</td>
<td>12.70 ± 2.11</td>
<td>12.50 ± 2.12</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>28.40 ± 6.38</td>
<td>29.30 ± 4.27</td>
</tr>
<tr>
<td>PANSS total score</td>
<td>82.53 ± 13.98</td>
<td></td>
</tr>
<tr>
<td>Thought Language and Communications</td>
<td>17.80± 7.51</td>
<td></td>
</tr>
<tr>
<td>Neuroleptics&lt;sup&gt;a&lt;/sup&gt;</td>
<td>921.40 ± 781.05</td>
<td></td>
</tr>
</tbody>
</table>

Note: Mean values ± standard deviation

<sup>a</sup> Chlorpromazine equivalent (Hardy-Baylé, Hardy and Dantchev, 1993).
### Table 2. Reaction Time (ms) for the priming effect in schizophrenic and control groups

<table>
<thead>
<tr>
<th>Task</th>
<th>Related</th>
<th>Unrelated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lexical Task</td>
<td>626 ± 50.66</td>
<td>654 ± 55.12</td>
</tr>
<tr>
<td>Physical Task</td>
<td>510 ± 60.12</td>
<td>520 ± 61.66</td>
</tr>
</tbody>
</table>

Note: Mean values ± standard deviation
**Table 3.** Main statistical results on ERPs

<table>
<thead>
<tr>
<th>Effects</th>
<th>df</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lexicality comparison</td>
<td>1.17</td>
<td>6.65</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Task x Lexicality x Electrodes x Windows(^1)</td>
<td>4.14</td>
<td>3.64</td>
<td>&lt;.04</td>
</tr>
<tr>
<td>Priming comparison</td>
<td>1.17</td>
<td>6.00</td>
<td>&lt;.03</td>
</tr>
<tr>
<td>Group x Task x Relatedness x windows</td>
<td>1.17</td>
<td>4.40</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

\(^1\) For this effect the Rao R Form was computed because the electrode factor presented 5 levels
Figure 2