



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

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### 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.

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### 1. 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., 2003a,b; 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

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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.

## 2. Methods

### 2.1. 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 DSM-IV (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.

### 2.2. Tasks and stimuli

#### 2.2.1. 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.

#### 2.2.2. 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 the 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.

### 2.3. 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.

### 2.4. 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.,

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

	Schizophrenics <i>n</i> = 10	Controls <i>n</i> = 10
Age	31.6 ± 6.42	27.20 ± 4.98
Years in education	12.70 ± 2.11	12.50 ± 2.12
Vocabulary	28.40 ± 6.38	29.30 ± 4.27
PANSS total score	82.53 ± 13.98	
Thought language and communications	17.80 ± 7.51	
Neuroleptics <sup>a</sup>	921.40 ± 781.05	

Note: Mean values ± standard deviation.

<sup>a</sup> Chlorpromazine equivalent (Hardy-Baylé, Hardy and Dantchev, 1993).

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