Circumventing the deficit of context processing in schizophrenia:
An event-related brain potential study

J. Bruno Debruille a, b, c *, Namita Kumar a, c, Dominique Saheb a, c, Araba Chintoh a, b,
Daryoush Gharghi a, c, Claire Lionnet a, Suzanne King a, b

a Douglas Mental Health University Institute,
b Department of Psychiatry, McGill University
c Department of Neurology and Neurosurgery of McGill University
d Department of Psychology, Université de Montréal.

* Corresponding author: Human Neurocognitive Science Laboratory, F. B. C. Pavilion,
Douglas Mental Health University Institute, 6875 Blvd. LaSalle, Montréal, (Qc) H4H 1R3,
CANADA, e-mail: bruno.debruille@douglas.mcgill.ca
Phone: 1(514) 761 6131 #3405, Fax: 1(514) 888 4099
Abstract

The deficit in semantic processing observed in schizophrenia patients may be due 1) to a ‘genuine’ deficit in processing new semantic information and 2) to a deficit in the ability to process and maintain the context in which the new semantic information has to be integrated. In a previous study, we designed a paradigm to study only the processing of new information. The processing of context was eased in the hope that patients would perform it as do normals. The goal of the present work was to determine whether this was the case. To achieve this goal, the event-related brain potentials (ERPs) elicited by the two context words of the new protocol were examined in 35 schizophrenia patients and 30 normal controls. These two context words were ‘INACTION’ and ‘ANIMAL?’.

Each trial started by one or the other and continued with a target word. ‘INACTION’ announced that subjects had no decision to make for the target word. ‘ANIMAL?’ announced that subjects had to decide whether or not the target word could be integrated into the animal category. Two ERP differences were found between normals and patients. However, the first, for ‘inaction’, could be related to patients’ difficulties at inhibiting the planning of action and the second, for ‘animal’, to the preparation of their motor responses. No ERP difference was found that could have indexed a problem in encoding or in maintaining context. Thus, we conclude that this particular type of protocol could be helpful to focus on the study of the processing of the new semantic information conveyed by target words.

Key words: schizophrenia, context, semantic processing, event-related potentials
1. Introduction

1.1. Context processing in schizophrenia

The deficit in the processing of context information in schizophrenia patients has been the focus of multiple studies since it was proposed to account for various cognitive impairments of these patients (Cohen and Servan-Schreiber, 1992; Servan-Schreiber et al., 1996; Stratta et al., 1998; Cohen et al., 1999). This deficit would pertain to both the processing of context itself and the maintenance of its representation in working memory (Cohen et al., 1999). The context information at stake would include prior stimuli, results of prior processing, and/or task instructions (Hemsley, 2005; Phillips and Silverstein, 2003a, but see Titone and Debruille, 2003).

The context deficit is evidenced by lower performances of schizophrenia patients than healthy controls in a variety of cognitive tasks. In addition to behavioral measures of performance, such as mean reaction times (RTs) and accuracies, brain function assessed through electrophysiological changes also have been recorded. Among these event-related potential (ERP) measures, the N400 component has been used as an index of semantic processing (for a review see (Kutas and Federmeier, 2000). This electrical field of negative polarity, which is maximum around 400 milliseconds after the onset of a meaningful stimulus, varies according to preceding stimuli. Its amplitude is reduced when these stimuli are semantically related to the stimulus whose N400 is under study. In schizophrenia patients, this reduction is smaller than in normals, a result used to illustrate the deficit that patients have using a relevant context to prime the processing of upcoming information (Kostova et al., 2003; Hokama et al., 2003;
1.2. Attempting to circumvent the context processing deficit in schizophrenia

Nevertheless, the context deficit has an important consequence when analyzing the results of any experiment. Abnormal performance in patients can either be due to the context processing deficit, to a deficit in the processing of new information within that context, or both. This creates an important interpretation problem for many studies. In an attempt to focus on the latter type of processing and thus to circumvent the context deficit, we recently implemented a protocol (Debruille et al., 2007) in which context was made as easy to process as possible, so that patients would perform this process as well as normals. This context was the semantic category word ‘ANIMAL?’ . Its processing was eased by presenting this word before each target word. It thus occurred in a very repetitive manner. Moreover, it was displayed for an entire second and another second preceded the onset of target words, which were also presented for one second. The occurrence of the next trial was triggered only 3.5 to 6.5 seconds after target offset. This very slow pace was used to minimize the greater stress that is induced by tests in schizophrenia patients relative to normal controls. This was thought to help patients performing in a way that does not significantly differ from that of normals. An absence of ERP difference between schizophrenia patients and normal controls had already been found in an auditory oddball task the pace of which was slowed down in an extreme way (Mathalon and Ford, 2002).
Participants had to decide whether or not the target word belonged to the category. The behavioral and electrophysiological indices collected during this semantic categorization task were consistent with the idea that patients processed context as well as normals did. Namely, for both types of subjects, RTs were shorter when the target words matched the semantic category of the prior context stimulus, the prime, than when the targets did not match that category. Moreover, this effect, the RT priming effect, was of the same magnitude for the two population samples. As to the amplitudes of the N400s elicited by target words, they were reduced by semantic priming in patients to an extent similar to that found in healthy normals.

1.3. Testing whether the context processing deficit in schizophrenia has actually been circumvented

The results obtained were thus encouraging and suggested that the protocol used could actually allow researchers to focus on the study of semantic processing of new information in patients. Nevertheless, a much stronger case, that the context word is actually processed by patients as well as it is processed by normals, could be made if one could demonstrate that the physiological responses to the context prime word itself ERPs to the context prime word in patients to those of the normal controls. In psycholinguistic studies using event-related brain potentials, the ERPs elicited by the items that precede target words can be seen in four studies (Salisbury et al., 2000; Mathalon et al., 2002; Strandburg et al., 1997a; Koyama et al., 1994). In each of these studies, these visual comparisons demonstrate large ERP differences between patients and normal controls. In all psycholinguistic protocols, prime words changed from one trial to the
next. This led us to think that the use of the same words should be tried in order to ease the task for patients and prevent information processing differences with normals. Note that, in order to prevent the habituation to the context prime word ‘animal’, this word was replaced by the context prime word ‘inaction’ in one third of the trials. In these trials, subjects do not have any decision to make for target words. We thus looked at both the ERPs elicited by the prime word ‘animal’ (the task instruction) and those elicited by the prime word ‘inaction’ (the no-task instruction).

In the protocol used, there was a 2 second time interval between the onset of the context prime word and the onset of the target word. The first ERP components elicited during this delay were related to visual processing and are maximal at occipital and occipito-temporal scalp sites, namely, the P1 and the N1. Together with the P2, the amplitudes of these early deflections, especially the N1, are modulated by the attention paid to visual stimuli (Hillyard et al., 1998; Mangun and Hillyard, 1995; Davenport et al., 2006a). If patients paid as much attention to the task instructions as normal controls did, these amplitudes should be similar. Although this similarity was not observed in some studies it was found in others. The ability to allocate attention to a region of the visual space different from that of the fixation point may be at stake. Indeed, Bruder et al., (1998) found very large early ERP differences between patients and controls when visual stimuli were presented on each side of the fixation point whereas Niznikiewicz et al. (1997) found no such differences when word stimuli occurred centrally. In our protocol, our word stimuli were presented centrally. Thus, early ERPs of patients could be similar to that of normal controls.
Later deflections were to be expected, such as the late positive complex (LPC), that is, a complex including a P3-like component and a slow positive wave (SPW or PSW according to authors) (Ruchkin et al., 1990; Garcia-Larrea and Cezanne-Bert, 1998). Indeed, the LPC is obtained for any stimulus that conveys information that could not be predicted (Donchin and Coles, 1988; Donchin and Coles, 1988). This was the case for the context prime words since subjects could not know whether the next trial was to begin with the task or the no-task instruction. The P3, probably the best known of the ERPs, peaks between 280 and 800 ms after the onset of the stimulus (Kutas et al., 1977). It indexes the end of the stimulus evaluation and the up-dating of the representation of context in working memory (Donchin and Coles, 1988). It was thus absolutely essential to find an absence of difference between patients and normal controls for this deflection. Note that this prediction was contrary to the fact that P3s have consistently been found to be smaller in schizophrenia patients than in normal controls (for reviews see Ford, 1999; Friedman, 1991). In fact, this is one of the strongest differences ever found between patients and normals. However, an absence of difference was possible. This has already been the case with visual, rather than auditory stimuli (Shelley et al., 1996), possibly because auditory stimuli can be heard regardless of the degree of attention paid to them, while the visual modality forces subjects to pay attention in order to converge and focus on stimuli.

The second component of the LPC, the positive slow wave (PSW), is known to emerge after the P3 whenever target detection leads to a complex subsidiary task (for a review see Garcia-Larrea and Cezanne-Bert (1998). In some cases, such PSWs appear as secondary peaks or ‘bumps’ (Squires et al., 1975; Johnson and Donchin, 1985;
Meanwhile, in many instances, the overall effect of late 'slow waves' is to produce a delay in the return to baseline of the late positive complex, by decreasing the slope of its negative-going branch. Although there is converging evidence that PSWs reflect processes related to the response demands, rather than to stimulus evaluation, widely divergent opinions have arisen as to which particular aspect of the response is responsible for their appearance. A few of these opinions could be relevant for the study of the task instruction 'animal' versus the no-task instruction 'inaction'. The PSWs have been related to the amount of processing required for a decision (Ruchkin et al., 1982) or to the decision itself (Johnson and Donchin, 1985) and to sustained attention to task performance (Gevins et al., 1996). Given that 'animal?' and 'inaction' provide critical information for the decision to act and the preparation for the target word, different PSWs could be expected for these two stimuli. Meanwhile, no clear prediction can be made as to the PSW differences that might exist between patients and normal controls according to the literature. Indeed, no PSW studies were found comparing these two populations. While smaller PSWs in patients than in normals could be observed because of the general cognitive deficit of patients (Chapman, 1978; Miller et al., 1995) similar PSWs, at least for ‘ANIMAL?’, would confirm that the critical context is processed in the same way in the protocol.

Finally, a contingent negative variation (CNV) should develop during the two seconds existing between the onset of context prime words and the onset of target words, especially in the case the context prime word is the task instruction ‘animal?’. The CNV was initially recorded in a forewarned simple reaction time task as a sustained negative potential shift obtained in the interval of 1 s between a warning stimulus (S1)
and an “imperative” stimulus (S2) (Walter et al., 1964). Originally interpreted as an electrical expression of expectation, a more detailed explanation soon developed. Using longer S1-S2 intervals, it became clear that the CNV was composed of an early and a late component (Connor and Lang, 1969). The early component is observed predominantly frontally and is related to the attention to S1. To this extent, it was hoped, as for the PSWs, that the early CNVs of patients would be similar to those of normals in the chosen protocol. This would mean that a similar amount of attentional resources has been allocated to the processing of the context prime words. However, against this prediction, it has to be noted that early CNVs generally appear to be smaller in schizophrenia patients than in normals (e.g., Verleger et al., 1999; Heimberg et al., 1999). Nevertheless, in the first study S1 was presented for a relatively brief duration (200 ms), whereas, in the second study, it consisted of previously unknown and complex figures, which were thus difficult to process. In the present study, S1 was a well-known word presented for a long time (i.e., 1000 ms). The early CNV of patients could thus be similar to that of normal controls.

The late component of the CNV is more centrally distributed and has been associated with motor readiness, and, therefore, to the so-called readiness potential (RP) (Rohrbaugh et al., 1986). Although there are different views on the relationship between late CNV and the RP, data suggest that the late CNV includes a stimulus preceding negativity, or SPN, in addition to the RP (Brunia, 1999). This SPN would index exclusively anticipatory attention and preparedness processes to the up-coming stimulus (Brunia and van Boxtel, 2001); (Brunia and van Boxtel, 2004). Therefore, neither the RP nor the SPN index the processing of the context prime word. Thus, no predictions were
made as to these components for the chosen protocol. However, it should be noted that the late CNV appears to be of smaller amplitude in patients than in normals (e.g., (Verleger et al., 1999; Heimberg et al., 1999).

In summary, it was thus planned to compare the ERPs elicited by the context prime word ‘animal?’ and by the context prime word ‘inaction’ in schizophrenia patients to those elicited by these two words in normal controls. Any difference in the time windows of the P1, N1, P2, LPC and early CNV would lead to conclude that patients do not process context in the way normals do. An absence of difference in these time windows would be taken as a further confirmation that, in the particular protocol chosen, patients process context like normals do.

2. Material and methods

2.1. Participants

Aged between 18 and 45 years, participants had normal or corrected-to-normal vision and either French or English as their mother tongue. Potential subjects with a history of head injury with loss of consciousness longer than 10 minutes were excluded, as well as subjects with a neurological or medical condition compromising brain functioning. It was possible to exclude all potential participants who were using illegal drugs except a few cannabis users (see Table 1), but all participants agreed not to take cannabis or alcohol the day before or the day of the recording. All gave written informed consent prior to participation after procedures were fully explained according to the Douglas Hospital Research Ethics Board’s criteria, which follows the latest version of the Declaration of
Thirty-seven stable patients were recruited from outpatient services of the Douglas Institute in Montreal. Four were left-handed. All patients had been taking stable doses of antipsychotic medication for the preceding three months or more, except for one patient who was not taking any medication. All patients had a history of two or more hospitalizations. The diagnosis of schizophrenia was the first diagnosis mentioned for each of their hospitalizations and for their follow-up at out-patient clinics, despite the fact that, quite often, different psychiatrists were responsible for their care along their trajectory. The first 18 patients had the Structured Clinical Interview for DSM (SCID-IV) (First et al., 1995) conducted by a psychiatrist (J.B.D.) to verify that they met DSM-IV criteria for schizophrenia. This was the case for the 18 patients. We thus concluded that our selection method was appropriate and that the SCID was not necessary for the rest of the patients.

The expanded version of the Brief Psychiatric Rating Scale (BPRS-E, (Ventura J et al., 1993) was used to assess the severity of the symptoms of patients during the preceding two weeks. This was done by two raters trained on the BPRS-E. The first rater (DS), a PhD student in clinical psychology, was trained by a qualified BPRS trainer (SK) to a high level of inter-rater reliability (better than 80%) on both videotaped and live interviews before the start of data collection. The second interviewer (NK), an MSc student in clinical neuroscience, was trained by another qualified BPRS trainer through video tapes as well as through live interviews with a psychiatrist (JBD) and finally with DS, the first interviewer, until she reached an inter-rater reliability better than 80%.
Interviews were conducted in these patients’ mother tongue (either French or English) by one of the two students within two weeks before the ERP recording (see Table 1). In addition to the scores for delusions (i.e., unusual thought content) and hallucinations, a score for disorganization was computed by summing the scores for item 15 (conceptual disorganization), item 14 (disorientation) and item 12 (bizarre behavior). As well, we computed a negative symptom factor by summing the ratings for self-neglect (item 13), blunted affect (item 16), emotional withdrawal (item 17) and motor retardation (item 18).

Two patients were excluded due to an excess of artifactual trials (see Data processing and measure section). Among the 35 remaining patients, 16 were of the paranoid, 3 of the disorganized and 16 of the undifferentiated subtype. 8 patients were taking risperidone, 13 had olanzapine, 6 quietapine, 1 trifluoperazine, 3 fluphenazine decanoate, 1 loxapine, 2 clozapine and 1 was not taking any medication. Three of the five patients taking classical antipsychotics were having anticholinergic medications. Among these patients 4 were left-handed, 10 had English as their mother tongue, 17 had French, and 8 were bilingual. Table 1 further specifies the characteristics of each subgroup.

Normal controls were recruited by newspaper advertisements to match the mean demographic characteristics of the patients (see Table 1). Three were left-handed. They were screened by telephone and excluded for any significant history of Axis I psychiatric illness. To assess the extent to which they differed from the patients, they were asked to
complete the Schizotypal Personality Questionnaire (the SPQ, (Raine, 1991; Dumas et al., 2000). Subjects having a total SPQ score greater than 25 were excluded. Among the 30 subjects selected, 9 had English as their mother tongue, 16 had French and 5 were bilingual.

2.2. Task

Subjects were seated comfortably in a sound-attenuated, dimly lighted room in front of a computer screen placed 1 m from their eyes. Black stimuli were presented on a white background at the center of this screen. Trials were made of three serially presented stimuli (Fig 1). The first, the context prime category stimulus, was the question word ‘ANIMAL?’ in two thirds of the trials, that is, in 120 trials. In the other third, and thus in 60 trials, it was the word ‘INACTIO’. Both words have the same spelling in English and French. According to the Lexique database (New et al., 2004), the frequency of ‘animal’ is 82, and that of ‘inaction’ is 2. These context prime category stimuli occurred for a 1s duration and were followed, one second after their offset, by a second item, which was also presented for 1s (Fig 1). This second item, the target word, either matched the animal category (e.g., lion) or mismatched it (e.g., hammer). Target words were in English when the mother tongue of the subject was English. They were in French when the mother tongue of the subject was French. For bilingual subjects, the English or the
French version of the experiment was chosen according to which written language the subject used most frequently in the past five years. The characteristics of the target words used can be found in Debruille et al. (2007). When the first stimulus was the question word ‘ANIMAL?’, subjects had to respond Yes for matching targets and No for mismatching targets as rapidly and as accurately as possible by pressing one of two keys with their right index finger. When the first stimulus was the word ‘INACTION’, no response had to be given: Subjects were just asked to pay attention. These inaction trials were there to force subjects to process the first word of each trial since they could not predict whether the trial would be an action or an inaction trial. The third (and last) stimulus of each trial was a ‘Blink’ instruction, which appeared 1.5 to 2.5 s after the offset of each target stimulus. Subjects were thus instructed to blink for that stimulus and to restrain from blinking afterwards as much as possible. The occurrence of the subsequent trial was triggered by the experimenter 2 to 4 s later, once the EEG signals appeared to be free from eye artifacts, excessive myogram, amplifier saturations or analog-to-digital clipping.

2.3. Data acquisition

Accuracy and reaction time were recorded for each trial. The electro-encephalogram was recorded with tin electrodes from an ECI (Electro-Cap International) cap, which were placed according to the modified expanded 10-20 system (Electrode nomenclature committee, 1991) with a right ear lobe reference. There were three montages of electrodes: the sagittal montage included Fz, FCz, Cz, and Pz; the parasagittal montage, FP1/2, F3/4, FC3/4, C3/4, CP3/4, P3/4, and O1/O2; and the lateral montage,
F7/8, FT7/8, T3/4, TP7/8, and T5/6. Eye movements and blinks were monitored by inspecting channels closest to the eyes, that is, F7 and F8, for horizontal movements, and FP2 and an additional electrode placed on the right cheek for vertical movements. Impedance was kept below 5KΩ. The half amplitude cut-offs of high and low pass frequency filters were set at 0.01 and 100 Hz, respectively. In addition, a 60 Hz electronic notch filter was used. EEG signals were digitized at a 256 Hz sampling frequency and stored along with the stimulus and response codes.

2.4. Data processing and measures

Error rates were computed as the percentage of motor responses occurring in the ‘Inaction’ no-task instruction and as the percentage of absences of such responses in the ‘Animal?’ task instruction condition. As the purpose of the experiment was to assess the processing of primes, and how well they were taken into account by subjects, EEG epochs of error trials were also used to compute ERPs.

EEG epochs including eye movements, blinks, and excessive myogram were rejected when amplitudes exceeded +/- 75 microvolts. Trials with amplifier saturations or analog to digital clipping longer than 100 ms were also excluded. Our criterion for keeping a participant in the study was that at least 30 out of the 60 inaction trials and at least 60 out of the 120 trials animal trials could be kept to compute the average. This led to the exclusion of 2 patients for whom no ERPs were computed. Event-related potentials for the task and the no-task instruction conditions were computed relative to a -200 to 0 ms baseline by averaging the 2.2 s EEG epochs of non-rejected trials. ERP measures of the P1, the N1, the P2, the P3, the PSW, the early and the late CNV were
made by computing the mean voltage amplitude in the 80-120, 120-220, 220-320, 320-
500, 500-700, 700-1000 and 1800-2000 ms time windows, respectively. These
measures were computed using signed deviations from the -200 – 0ms baseline. For the
P1 time window, measures were made only at occipital and occipito-temporal electrode
sites (O1/2 and T5/6). In contrast, measures were made for all electrodes of the three
montages for all the other time windows. The first three time-windows were centered on
the latencies of the peaks of the P1, N1 and P2 deflections observed on the grand
average at T6 (see Figure 2). The fourth time window, that of the P3, was centered on
the peak of the first large positive deflection observed at Pz (Fig. 3 & 4). The next two
time-windows (500-700 and 700-1000 ms) were chosen accordingly, to follow that of the
P3, whereas the last one (1800-2000 ms) was chosen to immediately precede the onset
of targets.

2.5. Analyses

A repeated-measures mixed-model ANOVA was run to test the significance of mean
group differences for error rates. It had diagnosis (controls vs. patients) as the between
subject factor and instruction (‘ANIMAL?’ vs. ‘INACTION’) as the within subject factor.
For the ERP measures of all the time-windows, except the first one, three similar
repeated-measures mixed-model ANOVAs were made. The first, run for the sagittal
montage, had the electrode site (Fz vs. FCz vs. Cz vs. Pz) as a second within subjects
factor, the second and the third ANOVAs had hemiscalep (right vs. left) as a third within
subjects factors. For the first time window (i.e., that of the P1), the electrode site factor
had occipital versus occipito-temporal sites as levels. Geisser and Greenhouse’s (1959)
procedure was used to compensate for the heterogeneity of variance for the factor that had more than two levels, that is, the electrode factor. The results of the analyses are reported with the original degrees of freedom and the corrected probability level. Note that no procedure was used to normalize ERP topography data based on Urbach and Kutas (2002) who have argued that these procedures should no longer be used.

3. Results

3.1 Behavioral

The rate of errors were the percentages of motor responses for targets when the context prime word was the ‘Inaction’ instruction and the percentages of absence of motor response for targets when the context prime word was the instruction ‘Animal?’. For the inaction instruction, these percentages were 5.37% (SD: 5.5) for patients and 2.58% (SD: 3.5) for normal controls. For the animal instruction, they were 2.18% (SD: 3.3) and 1.17% (SD: 1.7), respectively. Error rates were significantly greater for patients than for normals ($F(1-63) = 6.98, p = .01$), with a very slight tendency to be larger after the inaction than after the action instruction ($F(1-63) = 2.11, p = .15$).
3.2 Electrophysiological

The visual inspection of Figure 2 revealed no major ERP differences between groups in the P1 and N1 time windows (80-120 and 120-220 ms) for either the action or the inaction conditions. The ANOVA conducted in the first time-window did not show any significant diagnosis effect ($F(1-63) = .43, p = .51$) nor any significant interaction of this factor with the instruction, the electrode site or the hemiscalp factors. The ANOVAs run in the N1 time-window showed no significant effect associated with diagnosis in the sagittal montage. ($F(1-63) = 1.81, p = .18$). In the parasagittal montage, diagnosis had no main effect ($F(1-63) = 1.85, p = .179$) but it marginally interacted with electrode site and hemiscalp ($F(6-378) = 2.72, p = .046$). The post-hoc ANOVAs run with Fp1/2 and then with O1/2 measures to find the source of the interaction revealed no effect of diagnosis ($F(1-63) = 1.37, p = .25$), ($F(1-63) = .72, p = .34$), respectively. In the lateral montage, the ANOVA did not reveal any main effect of diagnostic group ($F(1-63) = 1.15, p = .29$) nor any interaction of diagnosis with the other factors.

In the P2 time window, the visual inspection of anterior electrodes (F7/8, Fp1/2 Figures 3 and 4) suggest smaller P2 in patients than in controls. The ANOVA performed with the measures of the sagittal montage revealed an absence of effect of diagnosis ($F(1-63) = .337, p = .564$), as did the ANOVA run for the parasagittal montage ($F(1-63) = .337, p = .564$).
.703, $p = .405$). For these two montages, there was no significant interaction of diagnosis with the other factors. In the lateral montage, there also was no significant effect of diagnosis ($F(1-63) = .722, p = .399$) but this factor interacted with electrode site ($F(4-252) = 4.33, p = .034$). The posthoc ANOVA performed with the measures made at F7/8 to look for the source of this interaction revealed a marginally significant effect of diagnosis ($F(1-63) = 4.08, p = .048$), with smaller P2s for patients than for normals.

In the P3 time window (320-500 ms), inspection of Figures 3 and 4 suggest that the ERPs appeared less positive for patients than for normals. Nevertheless, the analyses made did not find any significant effect of diagnosis at the sagittal ($F(1-63) = 2.17, p = .643$), the parasagittal ($F(1-63) = .700, p = .406$) and the lateral montage ($F(1-63) = 1.01, p = .319$) or any interaction of diagnosis with other variables.

In the positive slow wave time-window (500-700 ms) the analyses conducted in order to test the significance of the differences visible on Figures 3 and 4 revealed no main effect of diagnosis at the sagittal montage but indicated an interaction of this factor with task ($F(1-63) = 7.15, p = .01$). The post-hoc analysis made in the inaction condition to find the source of the interaction revealed a significant effect of diagnosis ($F(1-63) = 4.45, p = .039$), showing that, in this condition, PSWs were of smaller amplitudes in patients than in controls at the sagittal montage. For the parasagittal and the lateral montages, no effect of diagnosis and no interaction between diagnosis and other factors were found. In contrast, the post-hoc analysis made in the action condition did not reveal any effect of diagnosis, or any interaction of diagnosis with the other variables. The effect of task was examined for that particular time window since this effect interacted with the diagnosis factor. The inaction instruction led to more positive ERPs than the
action instruction in the PSW time window in the sagittal ($F(1\text{-}63) = 26.33, p < .001$), the parasagittal ($F(1\text{-}63) = 24.73, p < .001$) and the lateral montages ($F(1\text{-}63) = 7.09, p = .010$), without any significant interaction with the other variables.

In the early CNV time window (700-1000 ms), no significant effect of diagnosis was found at the sagittal ($F(1\text{-}63) = 0.375, p = .543$), the parasagittal ($F(1\text{-}63) = 0.031, p = .861$) or the lateral montage ($F(1\text{-}63) = 0.025, p = .875$) nor was any interaction of diagnosis with other variables found. In the late CNV time window (1800-2000 ms), visual inspection of Figures 3 and 4 suggested smaller late CNVs in patients than in normals especially in the action condition. This was confirmed by the analysis made for the sagittal montage ($F(1\text{-}63) = 4.15, p = .046$), which also revealed an interaction of diagnosis with task ($F(1\text{-}63) = 4.34, p = .041$). The post-hoc analysis made in the action condition to find the source of the interaction revealed a significant effect of diagnosis in that condition ($F(1\text{-}63) = 6.28, p = .015$). Meanwhile, in the inaction condition, no effect of diagnosis was found. At the parasagittal and lateral montages, there were neither significant effects of diagnosis nor any interaction of this factor with other factors. The effect of task was examined because of the interaction with the diagnosis. Late CNVs were significantly greater after the action than after the inaction instruction at the sagittal montage ($F(1\text{-}63) = 35, p < .001$). This effect interacted with site ($F(3\text{-}189) = 5.28, p = .008$), due to a greater amplitude at Cz. A significant effect of task was also found at the parasagittal montage ($F(1\text{-}63) = 30.14, p < .001$), which interacted with hemiscalp ($F(1\text{-}63) = 5.58, p = .021$) due to a greater amplitude of the effect on the left than on the right side. There was also a hemiscalp x site x task interaction ($F(6\text{-}378) = 2.58, p = .036$), due to a greater effect at left central sites. Finally, there was also a significant effect of
task at the lateral montage \((F(1-63) = 13.6, p < .001)\), with no interaction with other variables.

All the above analyses were recomputed three times: once after the exclusion of the five patients who were taking typical rather than atypical neuroleptics, a second time after excluding the three patients who were taking anticholinergics, and at third time after excluding the eight participants who were using one ‘cigarette’ of cannabis daily (but who did not have any during the 24 hours that preceded the testing). Each time, similar results were obtained leading to the same significant and insignificant effects.

4. Discussion

ERPs elicited by instruction prime context words were studied in a protocol that had been built to ease as much as possible the processing of context in order to compensate for the deficit of schizophrenia patients at this processing. It was hypothesized that no difference between patients and normal controls would exist in the way these context words were processed. Consistent with this hypothesis, no differences were found in the P1, N1, and P3 time windows. In contrast, patients had marginally smaller P2s at lateral frontal sites, smaller positive slow waves for the inaction instruction prime word and smaller late CNVs for the action instruction prime word than for normal controls.

The absence of P1, N1, and P3 differences between patients and normal controls is striking. P1s have been found to be reduced in schizophrenia patients in several studies (Schechter et al., 2005; Foxe et al., 2005; Doniger et al., 2002a). Nevertheless, an absence of P1 difference has previously been reported in a protocol using faces as
stimuli (Johnston et al., 2005) and the results of one study suggested that P1 differences may depend on the severity of symptoms (Connolly et al., 1983; Debruille et al., 2007). While further studies are thus necessary to understand the circumstances under which P1 differences can be found, the absence of a difference observed here is consonant with the notion that the early visual processing of the context words was normal in patients under the conditions of the present experiment. In contrast, visual N1s have been found intact in schizophrenia (Niznikiewicz et al., 1997; Doniger et al., 2002b; Foxe et al., 2001; Debruille et al., 2006) with only few exceptions (Bruder et al., 1998). Like the absence of P1 differences, the present N1 results suggest that the early visual processing of patients was similar to that of normals. With regard to the P2 amplitude, one study using visual words as stimuli has reported an absence of difference (Niznikiewicz et al., 1997) while P2s were recently found to be less increased by attention in patients than in normals in another study (Davenport et al., 2006b). Here, we obtained marginally smaller P2s in patients than in normals only at lateral frontal sites (F7/8). This could be due to a real difference in the way patients processed instruction words. Given its anterior location, this difference would then be unlikely to pertain to the processing of the physical features of the visual stimuli. Its functional significance would remain to be elucidated. Alternatively, it could be due to some noise remaining on these electrodes which are close to the eyes. In any case, taken together, the absence of P1, N1 and posterior P2 differences obtained here not only suggest that the early processing of context words by patients was similar to that of normals but also that patients allocated approximately the same amount of attentional resources to this processing in the chosen protocol. Indeed, the amplitudes of the P1, N1 and posterior P2 deflections
are well known to vary with the amount of attentional resources allocated to the processing of the stimulus (Hillyard et al., 1998; Mangun and Hillyard, 1995; Davenport et al., 2006a).

The visual inspection of the ERP Figures revealed a small, negative going deflection that followed the P2, peaked around 290 ms post onset and appeared to be maximal at the midline central site (Cz). This N290 is reminiscent of an N400 that would have been dramatically decreased by the intense repetition of the prime words across trials (see Delong and Kutas, 2005 for such early N400s, and see Kutas and Federmeier, 2000 for a review of the N400). Indeed, the N400 is known to be smaller at the second than at the first presentation of a word in an experiment, with further decreases induced by further repetitions (Rugg, 1990b; Jiang et al., 2000; Van Strien et al., 2005). Another variable that has an important impact on the N400 amplitude is the frequency with which the word is used in the language. Words of low frequency elicit larger N400s than words of high frequency (e.g., (Rugg, 1990; Young and Rugg, 1992). Accordingly, the prime word 'inaction', given its lower frequency, should have induced a smaller N400 than the prime word ‘animal’. Nevertheless, the decrease of the N400 with repetition is larger for words of low than for words of high frequency. The result is that, at their second presentation, high and low frequency words elicit small N400s which are similar in amplitude (Rugg, 1990). Accordingly, with the very high rate of repetition used in the present study, no effect of frequency should distinguish ‘ANIMAL?l’ from ‘INACTION’ and the N400s they elicit should be of minimal amplitude. This seems to be the case. When looking (Fig 4) at the negative peak that follows the P2 at electrode sites at which the N400 is usually maximum, that is, at centro-parietal sites, one can see that
the small negative deflection is of similar amplitude for ‘animal’ and ‘inaction’ at midline parietal site (Pz). At the midline central site Cz, there is a little difference. The small negative deflections for the low frequency word ‘inaction’ seem to be smaller than that for the high frequency word ‘animal’. This difference is thus in a direction opposite to that of the frequency effect on N400. It is thus most unlikely to be a frequency effect on N400. Rather, it appears as a difference due to the larger late positive complex (LPC) that immediately follows and partially overlap the small negative deflection.

This LPC is also modulated by frequency and repetition. It is of greater amplitude for repeated words than for words that are presented for the first time in the experiment. This effect is also larger for words of low than for words of high frequency of occurrence (Rugg, 1990; Young and Rugg, 1992). Given that ‘inaction’ had a low frequency relative to ‘animal’, it could be argued that the larger LPCs elicited by ‘inaction’ than by ‘animal?’ were due to the effect of the repetition of a word of lower frequency. However, ‘inaction’ occurred 60 times in the experiment whereas the repetition effect seems to reach a floor after only a few repetitions (Besson et al., 1992; Young and Rugg, 1992; Kazmerski and Friedman, 1997; Van Strien et al., 2005). Most likely, 60 presentations is an extreme repetition rate at which the amplitude of the LPC does not increase any more, as supported by the usual amplitude of the LPC deflections observed here (4 to 8 microvolts). Accordingly, the LPC difference observed between ‘INACTION’ and ‘ANIMAL’ is unlikely to be due to frequency or repetition.

A third variable is known to affect the amplitude of the P3b, an ERP component included in the LPC. It is the probability of occurrence of a stimulus in an experiment. Rare stimuli, that is, stimuli with a low probability of occurrence in an experiment, are
known to elicit P3b of much larger amplitude than stimuli of high frequency of occurrence. This effect, called the oddball effect, can be seen for any type of stimuli, including words (Kutas et al., 1977). In the present experiment, it thus seems that this effect could account for the larger LPCs that were found for the word ‘inaction’, the frequency of occurrence of which was only 34%, than for ‘Animal’, whose frequency of occurrence was 66%. However, it has been shown that the frequency effect on the P3b disappears when inter trial intervals are longer than 4 seconds (Gonsalvez et al., 2007; Gonsalvez and Polich, 2002; Polich and Bondurant, 1997). In the present study, these times intervals varied between 5.5 and 8.5 s. Thus, probability was unlikely to provide a significant contribution to the LPC. Therefore, the larger LPCs obtained for the ‘INACTION’ than for the ‘ANIMAL?’ prime word may not be due to its lower probability of occurrence. This idea is reinforced by the location on the scalp of the maximum of this difference (Fig 4), which clearly appears to be at the midline central site (Cz), rather than at the midline parietal site (Pz) where probability effects on P3b are maximal.

The absence of a group difference in the P3 time-window is certainly the most crucial finding. Indeed, in addition to its sensitivity to attention, the P3 has been recognized as an index of the end of the cognitive evaluation of the stimulus and the updating of working memory. To show that patients evaluated context prime words and put them in working memory as well as normals did it was thus critical to observe similar P3s. These similar P3s could appear surprising given that so many studies reveal large amplitude differences between patients and normals (Ford, 1999). Nevertheless, when the time interval between two adjacent trials (ITI) in the experiment is long (several seconds), patients have P3 amplitudes that do not differ from those of normals (Roth et
al., 1991; Mathalon and Ford, 2002). By providing enough time to patients to store new information in working memory, the long ITIs used here (from 5.5 to 8.5 s between the target stimuli of two adjacent trials) may prevent the deficit in working memory among patients from exhibiting a detrimental effect. As mentioned in the introduction, the use of visual, rather than auditory stimuli, may also have helped to prevent P3 differences (Shelley et al., 1996). Finally, the fact that context primes were instruction stimuli, rather than targets, may also be a factor. In the overwhelming majority of protocols where smaller P3s in patients than in normals were found, P3-evoking stimuli were targets.

The smaller amplitudes of the positive slow waves in patients than in controls cannot be used to argue that the critical instruction, that is, the question word ‘Animal?’, was not processed as well in patients as it was in normals. Indeed, smaller PSWs were observed only for the inaction instruction. A functional significance of these results can be suggested on the basis of the larger PSWs for the inaction than for the action instruction, which are reminiscent of the larger PSWs obtained by Golob et al. (2002) for rare invalid- than for valid-target stimuli. Given that PSWs have been related to the amount of processing required for a decision (Ruchkin et al., 1982) or to the decision itself (Johnson and Donchin, 1985) the larger PSWs for ‘Inaction’ could be related to the fact that making the decision not to act was more difficult than to make the decision to act in this protocol. Indeed, the inaction instruction was less frequent (33.3% of the trials) than the action instruction (66.6% of the trials). It could also be linked to the inhibition of the plan to act that may be performed once subjects realize no decision should be made. The difference between patients and normals could then be understood as an expression of the inhibition difficulties of schizophrenia patients (Kiehl et al., 2000). It is
to be noted that one of the most frequently used tasks to study context processing in schizophrenia, the AX task, resembles the task of the present study. Indeed, in these AX tasks, the cue letter A means that the subject will have to provide responses for following probe stimuli, X. Meanwhile, subjects have to refrain responding to these probes when they appear after other cue letters, which are named B cues. Therefore, in these protocols, the A cue can be compared to our task instruction and the B cue, to our inaction instruction. In AX protocols, the event-related fMRI technique is often used to measure the activity of the dorsolateral prefrontal cortex that is triggered by the cues. Lower activities are found for patients than for controls in the right middle frontal gyrus (Broadman area 9) following the B cue (Holmes et al., 2005; MacDonald et al., 2005). Our differences correspond to these findings given that they appear to be largest at an electrode site located precisely over the right dorsolateral prefrontal cortex (F4, Fig. 4).

The absence of significant differences between patients and normals in the time window of the early CNV observed here contrasts with the significant differences found by others in smaller groups (e.g., Verleger et al. 1999). Our finding suggests that the processing of instruction and its consequences was similar in patients and normals. Meanwhile, the smaller late CNVs found in patients suggests smaller stimulus-preceding negativities (SPNs), less motor preparation with smaller readiness potentials (RPs), or both. While the first anomalies could have an impact on the processing of target stimuli, they are, however, a little less likely than the second type of anomalies given the absence of late CNV differences in the inaction condition (Figure 3). This absence suggests that SPNs are roughly intact and that it is mainly the RPs that are smaller in patients, as suggested by the (non-significant) left lateralization aspect of the difference
(see Figure 2 at C3 vs. C4), and by the literature (Verleger et al., 1999; Singh et al., 1992). In any case, the late CNV differences observed between patients and normals pertain to the processing of the upcoming stimulus, not to the processing of context prime words as such. Nevertheless, it could be argued that smaller RPs in patients were due to a poor processing or to a poor maintenance of the meaning of the instruction ‘animal?’, which would have been insufficient to trigger strong motor preparations. However, this is unlikely since much smaller late CNVs are also observed in patients with non semantic stimuli (Verleger et al., 1999; Singh et al., 1992).

Therefore, the results obtained support the hypothesis that, in the particular protocol chosen, schizophrenia patients process the critical context prime word, that is, the instruction question ‘Animal?’, in a way that is very similar to the way this word is processed by normal controls. The results thus strengthen the idea that this type of protocol, in which the context remains practically constant and is presented at each trial, compensates for the difficulties that schizophrenia patients often have in processing context. This ERP protocol may allow studies focused on the semantic processing of meaningful target stimuli that are free from the impact of context deficits.


Polich, J. and Bondurant, T., 1997. P300 sequence effects, probability, and interstimulus interval. Physiol Behav. 61, 843-849.


Figure legends

Figure 1
Fragment of the stimulus sequence showing the stimulus durations, the stimulus onset asynchronies (SOAs) and including the four possible types of trials of the experiment, that is, in the order of presentation, from left to right, an action-mismatch, an inaction-match, an action-match and an inaction-mismatch trial.

Figure 2
Grand average of the early event-related brain potential evoked by the ‘animal?’ and the ‘inaction’ context prime words at occipital (O1/2) and occipito-temporal (T5/6) electrode sites.

Figure 3
Grand averages of event-related brain potentials evoked by the ‘animal?’ context prime word in the two population samples at all electrode sites.

Figure 4
Grand averages of event-related brain potentials evoked by the ‘Inaction’ context prime word in the two population samples.
Table legends

Table 1

Characteristics of the schizophrenia patients and of the normal controls who participated in the experiment. SES indicates parental socio-economic status computed according to (Hollingshead and Redlich, 1958), small numbers indicated higher status. BPRS stands for Brief Psychiatric Rating Scale, expanded version (Ventura J et al., 1993).
###NORMAL CONTROLS

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<tr>
<td><strong>Sex</strong></td>
<td>24 males/6 females</td>
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<td><strong>Age</strong></td>
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<td>6.1</td>
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<td><strong>Education (years)</strong></td>
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<td><strong>Cannabis (number of cigarettes)</strong></td>
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###SCHIZOPHRENIA PATIENTS

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<tr>
<td><strong>Sex</strong></td>
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<td><strong>Age</strong></td>
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<td>4.9</td>
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<td>12.1</td>
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<td>4.5</td>
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<td><strong>Chlorpromazine equivalents (mg)</strong></td>
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<td><strong>Delusion: unusual thought content</strong></td>
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<tr>
<td><strong>Hallucination</strong></td>
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<td>1.30</td>
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<tr>
<td><strong>Conceptual disorganization</strong></td>
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<td>1.50</td>
<td>3</td>
<td>9</td>
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<tr>
<td><strong>Negative symptoms</strong></td>
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<td>1.87</td>
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<tr>
<td><strong>Total BPRS</strong></td>
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<td>66</td>
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<td><strong>BPRS-ERP intersession lag</strong></td>
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<tr>
<td><strong>Alcohol (number of drinks)</strong></td>
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<tr>
<td><strong>Cannabis (number of cigarettes)</strong></td>
<td>0: n=23 1/wk: n=6 1/day: n=6</td>
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**TABLE 1**
Fig. 1