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N400 anomalies in schizophrenia are correlated with the severity of formal thought disorder

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Abstract

We explored the link between N400 anomalies and clinical profile in schizophrenia patients. N400 was recorded in 50 schizophrenia patients and 40 healthy controls during a lexical decision task with semantic priming. Comparison between controls and schizophrenia patients showed the classical anomalies reported for N400 in schizophrenia patients: greater amplitude for related words and lack of N400 effect. Analyses of the correlations between N400 effect and various symptoms of schizophrenia (formal thought disorder, positive symptoms, negative symptoms, overall symptoms, mean neuroleptic dose) or socioeducational data (age, vocabulary level, number of years of study) revealed that only the correlation with formal thought disorder was significant: the higher the scores for formal thought disorder, the lower the N400 effect observed.

Keywords: Schizophrenia; Thought disorder; N400; Language; Context processing

1. Introduction

Formal thought disorder, or disorganized speech, is one of the central signs of schizophrenia (Andreasen, 2003; Kircher et al., 2003; Kumar and Debruille, 2004). The importance of this disorder has led to intensive efforts to identify the cognitive dysfunctions involved. Although schizophrenia patients display impairment in all aspects of language (De Lisi, 2001), their deficit is generally thought to be due to an anomaly in semantic context processing (Hardy-Baylé et al., 2003; Kerns and Berenbaum, 2003).

Over the last fifteen years or so, a number of studies based on event-related potentials (ERP) have used the N400 paradigm to investigate language processing in schizophrenia. The N400 is a negative component of the ERP with a peak latency almost 400 ms after stimulus presentation that has been associated with language functions (Kutas and Hillyard, 1980). The N400 is elicited in sentence-pro-

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cessing studies and in lexical decision tasks in which context is reduced to the level of the word. The amplitude of the N400 component has been demonstrated to be larger for words preceded by semantically unrelated context than for words preceded by related context at centroparietal scalp sites, and at lateral sites over the right hemisphere than over the left hemisphere (Bentin et al., 1985; Chwilla et al., 1995; Holcomb, 1988). The modulation of N400 amplitude by semantic relatedness is referred to as the N400 effect. It is widely thought that the N400 effect reflects contextual integration processes (Kutas and Federmeier, 2000).

Various studies of N400 in schizophrenia patients have revealed anomalies in this ERP component: a) decreases in the N400 effect and/or increases in amplitude in response to words related to the context (Adams et al., 1993; Grillon et al., 1991; Hokama et al., 2003; Kostova et al., 2003a; Matsuoka et al., 1999; Mitchell et al., 1991; Nestor et al., 1997; Niznikiewicz et al., 1997; Ohta et al., 1999; Olichney et al., 1997; Strandburg et al., 1997), indicating an ineffective use of context and b) a delayed latency, which has been reported in most studies and indicates a generally slowing of information processing.

The N400 paradigm appears to be a useful means of identifying the cognitive anomaly underlying language disorders in schizophrenia patients (Kumar and Debruille, 2004). However, many questions remain unanswered, particularly as concerns the clinical characteristics of patients with N400 anomalies. Not all schizophrenia patients display N400 anomalies and even the earliest studies in this area reported that some schizophrenia patients had N400 amplitude anomalies, others had delayed latencies and still others had normal N400 responses (Grillon et al., 1991). The variability of N400 anomalies demonstrates the importance of defining the clinical characteristics of study groups very precisely. We need to know which patients have decreased N400 effects and which have normal N400 effects. Few studies have dealt with this issue. Some studies have reported decreases in N400 effects only in schizophrenia patients with an early age-at-onset and long duration of illness (Olichney et al., 1997); others have observed a correlation with formal thought disorder (Andrews et al., 1993) or with formal thought disorder and mean neuroleptic dose (Salisbury et al., 2000). The main purpose of our study was to explore the link between N400 anomalies and clinical profile in schizophrenia patients.

2. Materials and methods

2.1. Subjects

Fifty subjects (36 men, 14 women) meeting DSM-IV schizophrenia diagnosis criteria (American Psychiatric Association, 1994) participated in this study. Diagnosis was made by an experienced independent clinician. Patients were recruited during hospitalization (Psychiatric Department, Versailles Hospital) or during outpatient follow-up. All patients had stable symptoms and were on neuroleptic treatment. Psychotic symptoms were evaluated using the Positive and Negative Syndrome Scale, PANSS (Kay et al., 1987). Formal thought disorder was evaluated using the Thought, Language and Communication disorders scale, TLC (Andreasen, 1979). The control group consisted of 40 healthy subjects (19 men, 21 women) matched with the schizophrenia patients for age, socioeducational level (number of years of study) and vocabulary level (Binois and Pichot, 1959). 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

Table 1
Socioeducational and clinical characteristics of the participants

	Controls $n=40$	Schizophrenia patients $n=50$	F	p
Age	28.92 ± 8.71	31.59 ± 8.91	1.99	0.16
Years of study	12.95 ± 2.58	12.31 ± 3.18	1.04	0.31
Vocabulary[a]	26.44 ± 4.42	24.67 ± 6.67	2.02	0.16
TLC[b]		13.16 ± 6.60		
PANSS[c] total score		82.75 ± 18.77		
PANSS positive scale		21.08 ± 6.50		
PANSS negative scale		22.28 ± 5.46		
Neuroleptics[d]		656.63 ± 283.48		

Note: means ± standard deviations.
[a] Vocabulary: Binois–Pichot test.
[b] TLC: Thought, Language and Communication Disorders.
[c] PANSS: Positive and Negative Syndrome Scale.
[d] Neuroleptic dose (chlorpromazine equivalent).

50 years; history of neurological illness; regular or recent use of illicit substances; electroconvulsive treatment in the last 6 months; sectioning; first language other than French; vision (including corrected vision) less than 8/10. All participants were informed of the general objectives of the study and gave written consent.

2.2. Task and stimuli

We used the lexical decision task with semantic priming (Meyer and Schvaneveld, 1971). The experimental material consisted of two lists, each containing 300 pairs of items: 150 word–nonword pairs and 150 word–word pairs. For the word–word pairs, there were 100 pairs of unrelated words (including 50 filler pairs[1]) and 50 pairs of related words (16.7 % related words). Items from each of the lists were presented in random order. All the subjects saw the same target words and the same nonwords. The lists were constructed so as to counterbalance the presentation of the material, with target words appearing as related words in one list and as unrelated words in the other. Two lists of 90 items each were constructed using the same rules, for training purposes.

2.3. Procedure

The subjects 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 and that 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. They responded by pressing a button on the mouse with their writing hand. The left button of the mouse corresponded to a "yes" and the right button, to a "no". The first stimulus was 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 participants performed a training session before the task. The entire recording period lasted approximately 30 min.

2.4. Data collection and analysis

We recorded EEG, using 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 in the left (T3) and one in the right (T4) temporal region 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 k Ω. The EEG was continuously recorded, using the InstEP system, with a frequency of 512 points per second, and eye movements were then corrected off-line by an automatic program. Finally, 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. The data were analyzed by calculating, separately for each subject, the mean ERP amplitude for each stimulus type for the midline electrodes (Fz, Cz and Pz) for a time window of 250 to 400 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 amplitude, comparing groups (controls, schizophrenic patients), using "Relatedness" (related words, unrelated words) and "Electrode" (Fz, Cz, Pz) as intragroup factors. Significant interactions were analyzed, using post-hoc Scheffé tests. We carried out a similar analysis on the amplitude of the N400 effect (difference waveform obtained by subtracting N400 amplitude for related words from that for unrelated words).

We then calculated Pearson correlation coefficients for the relationships between N400 effect at Pz and TLC scores, PANSS scores (positive and negative scales and total scores), mean neuroleptic dose (chlorpromazine equivalent), age, socioeducational level (number of years of study) and vocabulary level.

[1] The *fillers* had the same characteristics as the rest of the material but were excluded from the analysis.

Table 2
Results of MANOVAs on N400 amplitudes along midline electrodes (Fz, Cz and Pz) in the controls and schizophrenia patients

Effect	*df*[a]	*F*	p
Group (G)	1, 88	10.32	0.002
Relatedness (R)	1, 88	46.52	0.0001
Electrode (E)	2, 176	1.97	0.14
G × R	1, 88	11.39	0.001
G × E	2, 176	1.27	0.28
R × E	2, 176	1.17	0.31
G × R × E	2, 176	0.24	0.79

[a] degrees of freedom.

We did not analyze behavioral data, but all the subjects included in the analyses obtained more than 50 % correct responses.

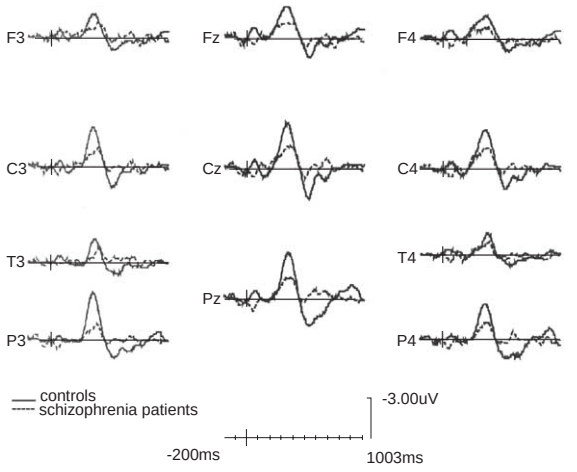

Fig. 2. Difference waveforms in controls and schizophrenia patients.

3. Results

3.1. Multivariate analyses of variance

The results of the statistical analyses are shown in Table 2. There was a main effect of "Group" as shown by the higher N400 amplitudes for schizophrenia patients than for controls (0.2 and 1.6 mV, respectively). We also observed a main effect of "Relatedness" with more positive amplitudes for related than for unrelated words: N400 effect (1.6 and 0.2 mV, respectively). Finally, there was a significant "Group" × "Relatedness" interaction, with the difference in amplitude between related and unrelated words significant in the control group but not significant in the schizophrenic group (controls: related words 2.6 mV, unrelated words 0.5 mV, $p < 0.0001$; schizophrenics: related words 0.5 mV, unrelated words −0.2 mV, $p > 0.05$). The lack of modulation of N400 amplitude by semantic relatedness in schizophrenia patients was due to the higher N400 amplitude for related words in schizophrenia patients than in controls ($p < 0.0001$). These results are illustrated in Fig. 1.

Analysis of the difference waveform (N400 amplitude for unrelated–related words) confirmed the smaller N400 effect in schizophrenia patients (controls: 2.1 mV; schizophrenics: 0.7 mV; $F(1, 88) = 10.64$; $p < 0.002$). These results are illustrated in Fig. 2.

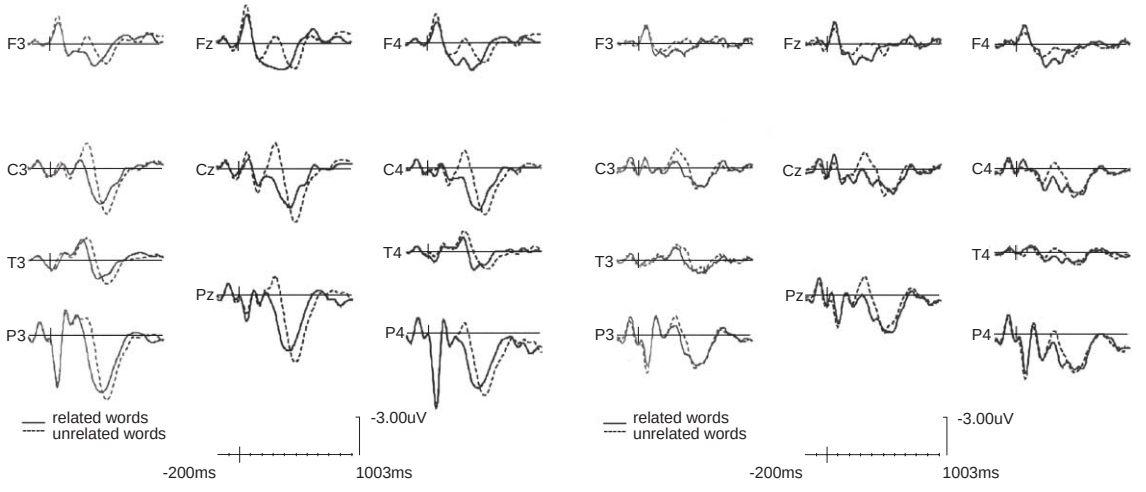

Fig. 1. N400 for related and unrelated words in controls and schizophrenia patients.

Table 3
Correlations between amplitude of the N400 effect at Pz (mV) and clinical and socioeducational variables

	r	t	p
TLC[a]	0.53	4.05	0.0002
PANSS negative scale[b]	0.30	1.78	0.08
PANSS positive scale	0.14	0.80	0.43
PANSS total score	0.13	0.87	0.39
Neuroleptics[c]	−0.21	−1.36	0.18
Age	−0.05	−0.37	0.72
Years of study	−0.15	−1.07	0.29
Vocabulary[d]	−0.09	−0.61	0.55

[a] TLC: Thought, Language and Communication Disorders.
[b] PANSS: Positive and Negative Syndrome Scale.
[c] Neuroleptic dose (chlorpromazine equivalent).
[d] Vocabulary: Binois–Pichot test.

3.2. Correlation analysis

TLC scores were significantly correlated with N400 effect at Pz: the higher the TLC scores for formal thought disorder, the lower the N400 effect observed (Table 3). With the exception of this correlation, only negative symptom scores on the PANSS scale displayed a consistent relationship to N400 effect, although this correlation was not significant. No other clinical or socioeducational variable was correlated with N400 effect.

4. Discussion

We recorded N400 in a lexical decision task with semantic priming. Comparison between controls and schizophrenia patients showed the classical anomalies reported for N400 in schizophrenia patients (see Section 1): greater amplitude for related words and lack of N400 effect. Analyses of the correlations between N400 effect and various symptoms of schizophrenia (formal thought disorder, positive symptoms, negative symptoms, overall symptoms, mean neuroleptic dose) or socioeducational data (age, vocabulary level, number of years of study) revealed that only the correlation with formal thought disorder was significant.

Our results are consistent with those reported by Andrews et al., 1993 and Salisbury et al., 2000.

For example, Andrews et al., 1993 analyzed the correlations between N400 amplitude and the BPRS general psychopathology scale (Overall and Gorham, 1962), scales for the evaluation of negative symptoms, SANS (Andreasen, 1983), and positive symptoms, SAPS (Andreasen, 1984), neuroleptic dose and age. They observed a correlation only with the pattern of thought disorder, as assessed by BPRS score, with N400 amplitude increasing with score for this item. However, at the cognitive level, this result is difficult to interpret given that the electrophysiological index used for the analysis was general N400 amplitude, all conditions confounded, rather than N400 effect, which reflects the quality of context processing much more directly. Indeed, some studies have reported a general increase in N400 amplitude with a normal N400 effect (Nestor et al., 1997; Niznikiewicz et al., 1997). This was indeed the case for Andrews et al., who found no difference in N400 effect between schizophrenia patients and controls performing a passive sentence reading task.

Salisbury et al., 2000 studied N400 amplitude in subjects performing a task in which homographic words were inserted in a sentence context. They reported a correlation between N400 amplitude for words associated with the non-dominant meaning of the homograph and BPRS thought disorder score. The correlation was again positive, with greater N400 amplitude being associated with a higher thought disorder score, reflecting greater difficulty in the use of context to find infrequently used meanings of words. No correlation was found between thought disorder and N400 amplitude for words related to the dominant meaning of the homograph. However, in this case, N400 amplitude was positively correlated with mean neuroleptic dose.

The functional correlation with formal thought disorder observed here is consistent with previous reports of correlations at the neuroanatomical level. McCarley et al., 1999 reported a strong correlation ($r=-0.81$) between formal thought disorder and decreases in the volume of gray matter in the left superior temporal gyrus. This region, which is considered to be the neurobiological substrate for language, includes the primary auditory cortex, a large portion of the temporal planum and Wernicke's area. In schizophrenia patients, decreases in the volume of gray matter in the left superior temporal gyrus are also correlated with decreases in the volume of the amygdalo–hippocampus complex and the parahippocampic gyrus in the left hemisphere. These regions are known to play a critical role in verbal memory.

We have demonstrated a correlation between N400 anomalies and formal thought disorder. The relationship between N400 anomalies and clinical profiles is interesting for a number of reasons. Firstly, if N400 reflects an influence of semantic context on on-line language processing, the clinical description of patients with N400 anomalies is a vital stage in studies of the experimental factors that may reveal the deficit or compensate for it. For example, a study published by our team has shown that schizophrenia patients are able to use *certain* semantic context processing strategies (Kostova et al., 2003b). We believe that functional analysis of the context processing deficit in schizophrenia patients depends on prior definition of the clinical subgroup affected by the anomaly in question. Secondly, if N400 anomalies account for certain symptoms (Hardy-Baylé et al., 2003), then the development of new neuroleptic drugs targeting the cognitive anomalies indicated by N400 could open up a new field of psychopharmacological investigation.

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References

Adams, J., Faux, S.F., Nestor, P.G., Shenton, M.E., Marcy, B., Smith, S., 1993. ERP abnormalities during semantic processing in schizophrenia. Schizophr. Res. 10, 247–257.

American Psychiatric Association, A.P.A., 1994. Diagnostic and Statistical Manual of Mental Disorders, Fourth ed. (DSM-IV).

Andreasen, N.C., 1979. Thought, language and communication disorders: I. Clinical assessment, definition of terms and evaluation of their reliability. Arch. Gen. Psychiatry 36, 1315–1321.

Andreasen, N.C., 1983. The Scale for the Assessment of Negative Symptoms (SANS). The University of Iowa, Iowa City.

Andreasen, N.C., 1984. The Scale for the Assessment of Positive Symptoms (SAPS). The University of Iowa, Iowa City.

Andreasen, N.C., 2003. A unitary model of schizophrenia: Bleuler's "fragmented phrene" as schizencephaly. Arch. Gen. Psychiatry 56, 781–787.

Andrews, S., Shelley, A.M., Ward, P.B., Al, E., 1993. Event-related potentials indices of semantic processing in schizophrenia. Biol. Psychiatry 34, 443–458.

Bentin, S., Mc Carthy, G., Wood, C.C., 1985. Event-related potentials, lexical decision and semantic priming. Electroencephalogr. Clin. Neurophysiol. 60, 343–355.

Binois, R., Pichot, P., 1959. Test de Vocabulaire. Editions du Centre de Psychologie Appliquée (ECPA), Paris.

Chwilla, D.J., Brown, C.M., Hagoort, P., 1995. The N400 as a function of the level of processing. Psychophysiology 32, 274–285.

De Lisi, L.E., 2001. Speech disorder in schizophrenia: review of the literature and exploration of its relation to the uniquely human capacity for language. Schizophr. Bull. 27, 481–496.

Grillon, C., Ameli, R., Glazer, M., 1991. N400 and semantic categorisation in schizophrenia. Biol. Psychiatry 29, 467–480.

Hardy-Baylé, M.C., Sarfati, Y., Passerieux, C., 2003. The cognitive basis of disorganization symptomatology in schizophrenia and its clinical correlates: toward a pathogenetic approach to disorganization. Schizophr. Bull. 29, 459–471.

Hokama, H., Hiramatsu, K., Wang, J., Donnell, B.O., Ogura, C., 2003. N400 abnormalities in unmedicated patients with schizophrenia during a lexical decision task. Int. J. Psychophysiol. 48, 1–10.

Holcomb, P.J., 1988. Automatic and attentional processing: an event-related brain potential analysis of semantic priming. Brain Lang. 35, 66–85.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–274.

Kerns, J.G., Berenbaum, H., 2003. The relationship between formal thought disorder and executive functioning component processes. J. Abnorm. Psychology 112, 339–352.

Kircher, T., Liddle, P., Brammer, M., R, M., P, M., 2003. Neural correlates of "negative" formal thought disorder. Nervenarzt 74, 748–754.

Kostova, M., Passerieux, C., Laurent, J., Hardy-Baylé, M., 2003a. An electrophysiologic study: can semantic context processes be mobilized in patients with thought-disordered schizophrenia? Can. J. Psychiatry 48, 615–623.

Kostova, M., Passerieux, C., Laurent, J.P., Saint-Georges, C., Hardy-Bayle, M.C., 2003b. Functional analysis of the deficit in semantic context processes in schizophrenic patients: an event-related potentials study. Neurophysiol. Clin. 33, 11–22.

Kumar, N., Debruille, J., 2004. Semantics and N400: insights for schizophrenia. J. Psychiatry Neurosci. 29, 89–98.

Kutas, M., Federmeier, K.D., 2000. Electrophysiology reveals semantic memory use in language comprehension. Trends Cogn. Sci. 4, 463–470.

Kutas, M., Hillyard, S.A., 1980. Event-related brain potentials to semantically inappropriate and surprisingly large words. Biol. Psychol. 11, 99–116.

Matsuoka, H., Matsumoto, K., Yamazaki, H., Sakai, H., Miwa, S., Yoshida, S., 1999. Lack of repetition priming effect on visual event-related potentials in schizophrenia. Biol. Psychiatry 46, 137–140.

McCarley, R.W., Niznikiewicz, M.A., Salisbury, D.F., Nestor, P.G., O Donnell, B.F., Hirayasu, Y., Grunze, H., Greene, R.W., Shenton, M.E., 1999. Cognitive dysfunction in schizophrenia: uni-

fying basic research and clinical aspects. Eur. Arch. Psychiatry Clin. Neurosci. 249 (Suppl 4), 69–82.

Meyer, D.E., Schvaneveld, T.R.W., 1971. Facilitation in recognizing pairs of words: evidence of a dependence between retrieval operations. J. Exp. Psychol. 90, 227–234.

Mitchell, P.F., Andrews, S., Fox, A.M., Catts, S.V., Ward, P.B., Mcconaghy, N., 1991. Active and passive attention in schizophrenia: an ERP study in information processing in a linguistic task. Biol. Psychol. 32, 101–124.

Nestor, P.G., Matthew, O.K., O'donnell, B.F., Smith, L., Niznikiewicz, M.A., Shenton, M.E., 1997. Aberrant semantic activation in schizophrenia: a neurophysiological study. Am. J. Psychiatry 154, 640–646.

Niznikiewicz, M.A., O'donnell, B.F., P.G, N., Smith, L., Law, S., Karapelou, M., 1997. ERP assessment of visual and auditory language processing in schizophrenia. J. Abnorm. Psychology 106, 85–94.

Ohta, K., Uchiyama, M., Matsushima, E., Toru, M., 1999. An event-related potential study in schizophrenia using Japanese sentences. Schizophr. Res. 40, 159–170.

Olichney, J.M., Iragui, V.J., Kutas, M., Nowacki, R., Jeste, D.W., 1997. N400 abnormalities in late life schizophrenia and related psychoses. Biol. Psychiatry 42, 13–23.

Overall, J.E., Gorham, D.R., 1962. The brief psychiatric rating scale. Psychol. Rep. 10, 799–812.

Salisbury, D.F., O'Donnell, B.F., Mccarley, R.W., Al, E., 2000. Event-related potentials elicited during a context-free homograph task in normal versus schizophrenic subjects. Psychophysiology 37, 456–463.

Strandburg, R.J., Marsh, J.T., Brown, W.S., Asarnow, R.F., Guthrie, D., Harper, R., 1997. Event-related potential correlates of linguistic information processing in schizophrenics. Biol. Psychiatry 42, 596–608.