
N400 Abnormalities in Late Life Schizophrenia and Related Psychoses

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The N400, an event-related brain potential (ERP) sensitive to semantic congruity, has been reported to have increased latency and/or reduced amplitude in young adults with schizophrenia. Little is known, however, regarding the N400 in older schizophrenia patients, especially those with late onset. We studied 18 middle-aged and elderly patients with schizophrenia and related psychoses (nine with early-onset psychosis (EOP) and nine with late-onset psychosis (LOP)), and nine normal comparison (NC) subjects. Subjects read words which were semantically incongruent (50%) or congruent (50%) with a preceding spoken phrase which defined either an antonymic or categorical relationship. The LOP group had a significantly later peak latency of the N400 congruity effect compared to the NC group. Seven of 18 psychosis patients, but none (0/9) of the normal subjects, had an abnormal latency or amplitude ($p = 0.04$), measured at T6 (right temporal). Smaller amplitudes were associated with more severe negative symptoms ($r_p = 0.58$; $p = 0.01$). N400 abnormalities in older schizophrenia patients likely reflect abnormal processing of semantic information. © 1997 Society of Biological Psychiatry

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Introduction

Schizophrenia is associated with multiple cognitive deficits, which include attentional and information-processing impairments and a number of mild language abnormalities. Abnormalities of schizophrenic speech include loos-

ening of associations, poverty of content, and neologisms (Andreasen and Grove 1986). In addition, mild disturbances of comprehension (Green and Walker 1985), syntactic processing (Levin et al 1989), and coherence of discourse (Hoffman 1986) have been described. Overinclusive thinking (Payne 1973) has been suggested to be central to the thought disorder in schizophrenia and an "outward shift" of semantic category boundaries has been implied by reaction times in category decision tasks (Chen et al 1994). Abnormal semantic priming has been indicated by several measures such as reaction time or perceptual threshold to target words as a function of their semantic relatedness to preceding priming words. Some tasks have revealed increased priming (Spitzer et al 1994;

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Kwapil et al 1990) while others have yielded decreased (Bullen and Hemsley 1987; Ober et al 1995) priming effects (e.g., smaller changes in reaction time) in schizophrenia. While it is difficult to compare across experiments with different individuals, verbal stimulus types, tasks (e.g., lexical decision, perceptual threshold), and presentation rates, many of the abnormal priming effects in schizophrenia can be explained by either an increase in activation (to loosely related words) or a decrease in inhibition (to unrelated words) (Manschreck et al 1988; Spitzer et al 1994; Chen et al 1994).

The N400 is a language-sensitive brain potential which has a scalp negative peak at approximately 400 msec poststimulus onset in young adults; its amplitude is maximal at temporoparietal sites and shows a slight right hemisphere amplitude and duration bias (Kutas and Hillyard 1982, 1984). Words which are semantically incongruent with their context elicit much larger N400s than words which are congruent; however, even congruent words elicit some N400 activity whose amplitude is an inverse function of the word's predictability in the context. Moreover, numerous investigators have demonstrated that the amplitude of the N400 is modulated by semantic relations and factors that influence semantic priming in a variety of tasks (e.g., Bentin et al 1985; Holcomb 1988; Kutas and Hillyard 1989; Chwilla et al 1995). In general, semantically primed words elicit smaller N400s than unprimed words.

Given the known language abnormalities in schizophrenia, we would expect those patients with semantic processing deficits to show abnormal N400 effects. In fact, results of the published N400 studies performed in younger schizophrenia patients suggest delayed latencies and variable amplitudes. For example, Koyama et al (1991), using Japanese Kanji characters, found longer latencies but normal N400 amplitudes in a study of 13 patients. Grillon et al (1991), in a study of 14 patients with schizophrenia, found that some patients had longer than normal latencies, while others had reduced amplitudes, but were unable to explain the observed variability. Andrews et al (1993), in a study of 19 patients, found a marginal increase in the N400 latency and a correlation between N400 amplitude and severity of positive thought disorder. All these studies involved predominantly young adults with schizophrenia. To our knowledge, there have been no reports of the N400 in older cohorts with schizophrenia or related psychoses.

While the generators of the scalp N400 are unknown, several different lines of evidence suggest some involvement of temporal lobe structures and surrounding areas (e.g., Smith et al 1986; Nobre et al 1994; Nobre and McCarthy 1995a; Nobre and McCarthy 1995b). Temporal lobe and hippocampal abnormalities have frequently been

observed in schizophrenia (Conrad et al 1991; Kovelman and Scheibel 1984; Jeste and Lohr 1989; Shenton et al 1992) and may be related to the reduced P300 amplitude (another late cognitive ERP elicited by task-relevant stimuli) common among schizophrenia patients (for review, see Ford et al 1992). For these reasons, the N400 seems to be an appropriate brain measure to detect subtle disorders of language comprehension, semantic expectancy, and dysfunction of the temporal lobe, all of which are reported characteristics of schizophrenia.

The Clinical Research Center (CRC) on Late-Life Psychosis at the University of California, San Diego has been following a cohort of older schizophrenia patients, some of whom had onset of illness after 45 years of age, i.e., late-onset schizophrenia. Neuropsychological evaluations show that the patients with late-onset schizophrenia have qualitatively similar but slightly milder deficits than those with early-onset schizophrenia (Jeste et al 1995). The present study was conducted to extend the finding of N400 abnormalities to a cohort of patients with late-life psychoses, predominantly schizophrenia. We hypothesized that abnormal N400s would be more frequent in patients with psychosis than in normal comparison (NC) subjects, and more common in early-onset psychosis (EOP) than in late-onset psychosis (LOP) patients, mirroring the neuropsychological data. We also postulated that severity of psychopathology and of cognitive impairment would correlate positively with severity of N400 abnormalities.

Methods

Subjects

We studied 18 patients with late-life psychotic disorders (nine with EOP and nine with LOP) and nine NC subjects. All the EOP and LOP subjects met criteria for a diagnosis of schizophrenia, with the exception of two EOP subjects (one with delusional disorder, and one with schizoaffective disorder) and one LOP subject (with psychosis not otherwise specified). The EOP, LOP and NC groups were matched by gender and handedness, and were of comparable age, ethnicity (predominantly Caucasian), and educational level. An onset of illness after age 45 was used to define the LOP group, and an onset of symptoms prior to age 45 defined the EOP group. All the subjects were participants in the CRC on Late-Life Psychosis at the University of California, San Diego. All of them had undergone an extensive clinical assessment generally within 30 days of the ERP recordings, including the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984; Andreasen and Olsen 1982), the

Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1982; Andreasen and Olsen 1982), and the Mini-Mental State Examination (MMSE) (Folstein et al 1975). All clinical diagnoses were based on the Structured Clinical Interview for DSM-III-R or SCID (Spitzer et al 1988) given by a Geriatric Psychiatry Fellow, and were confirmed by at least two board-certified psychiatrists at the research staffing. The subjects were instructed not to take any CNS-active medications on the day of the ERP testing, until after the recordings. Twelve patients were on stable neuroleptic dosages for 30 days or longer prior to the ERP testing, while six patients (two EOP and four LOP) were not receiving any neuroleptic treatment at the time of the testing. Subjects with a history of a major neurological disorder (e.g., stroke, brain tumor, epilepsy), or current serious medical illnesses were excluded. Only native English speakers were tested. No subjects fulfilled DSM-III-R (American Psychiatric Association 1987) criteria for current alcohol abuse or dependence or other substance abuse or dependence.

N400 Paradigm

Subjects were fitted with an electrode cap and then seated in a comfortable chair 125 cm from a microcomputer video terminal. The N400 paradigm consisted of two conditions: opposites and semantic categories. The experimenter read auditory statements each of which was followed approximately 1000 ms later by a target word flashed on a video monitor for a duration of 300 ms (subtending a visual angle of 0.7 degrees). For the opposites condition, 100 statements, each of which stated an antonymic relationship (e.g., "The opposite of white"), were read. Half of these statements were followed by a visual presentation of the expected or "congruent" target word (e.g., "black" for the above example). The other 50% of trials were completed by an "incongruent" target word (e.g., "cat" for the above statement). For the category condition, 100 statements, each of which defined a categorical relationship (e.g., "a type of wood"), were read aloud. One-half of the trials were followed by a member of the category (e.g., cedar) and the rest by a nonmember word (e.g., dog). Subjects were instructed not to blink or speak for three seconds following target presentation and then to say aloud the word seen followed by a "yes" or "no" indicating whether or not it was semantically congruent with the preceding statement. ERPs were synchronized to the onset of the appearance of the target words.

Electrophysiologic recording techniques

The electroencephalogram (EEG) was recorded from 21 sites using an elastic electrode cap (Electro-Cap Interna-

tional) with embedded tin disk electrodes, referenced to the average of left and right mastoid recordings off line. The electrode sites were from the following locations using the International 10–20 System (Jasper 1958): midline frontal (Fz), midline central (Cz), midline parietal (Pz), lateral pairs at frontal (F7, F8), temporal (T5, T6) and occipital sites (O1, O2). Additionally, electrodes approximating Broca's area and its contralateral homologue placed half the distance between F7 and T3 (BL), or F8 and T4 (BR), Brodmann area 41 placed 33% of the interaural distance lateral to the vertex (41L, 41R), and Wernicke's area and its contralateral homologue placed 30% of the interaural distance lateral to Cz and 12.5% of the nasion-inion distance posterior to Cz (WL, WR) were used. Vertical and horizontal eye movements were monitored by electrooculography (EOG), using electrodes directly beneath and lateral to each eye. The EEG and EOG were amplified by Nicolet Biotop 6R12 amplifiers with a bandpass of 0.016 to 100 Hz. The amplified signals were digitized on line at a sampling rate of 250 Hz for a sampling epoch of 1024 ms duration (100 ms prestimulus and 924 ms poststimulus). Trials contaminated with eye blinks or movements, excessive muscle activity, or amplifier blocking were rejected by a computer algorithm prior to averaging (Iragui et al 1993). Overall, 19.9 percent of the trials were rejected due to artifacts (means \pm standard deviations: NC = $15.4 \pm 8.3\%$, EOP = $20.9 \pm 13.1\%$, LOP = $23.4 \pm 13.3\%$; $p = 0.35$).

ERP Measures

For each subject, separate ERP averages were obtained for congruous and incongruous target words (collapsed across opposites and category task conditions for this analysis). All ERPs were subjected to low-pass filtering using a 15 Hz cutoff, to reduce high-frequency perturbations. Latencies and amplitudes were quantified by computer in both the ERPs to congruent and incongruent words, separately, and in the difference waves derived from a point-by-point subtraction of the congruous from the incongruous word ERPs. This difference wave was referred to as the N400 congruity effect. The N400 peak amplitude was identified as the maximal negativity occurring between 350 and 650 ms post-stimulus, relative to the baseline voltage over the 100 ms pre-stimulus period; N400 peak latency was the time point at which this peak occurred. Mean amplitudes were measured over the 350–650 ms epoch to define the N400 mean amplitude, and over three consecutive 100 ms windows within this period to quantify the early (350–450 ms), middle (450–550 ms), and late (550–650 ms) portions of the N400 congruity effect. For individual subject analyses, the N400 was primarily defined at T6 (right temporal) because this is one of the posterior sites at which

normal subjects show the most reliable N400 congruity effects to visually presented words (e.g., Kutas and Hilliard 1989). Analogous measures of the N400 were made at the homologous site over the left hemisphere (T5) to investigate possible interhemispheric differences.

The visual N1 and P2 potentials were most reliably present at occipital sites (O1 and O2); thus, analyses were restricted to these sites. The N1 peak amplitude and latency were measured at the peak negativity between 100–200 ms, except in two cases (one EOP, one LOP) where visual inspection showed large preceding positivities with onset near 100 ms (P1 potentials) which obscured relatively smaller negative peaks between 168–180 ms, considered to be the actual N1. The P2 peak amplitude and latency were measured at the peak positivity between 200–295 ms.

Statistical Analyses

Two-way split-plot analyses of variance (ANOVAs) were conducted for the peak latencies, peak amplitudes, and mean amplitudes of the N400 congruity effect with subject group and electrode site (all 15 nonreference sites, 12 lateral and 3 midline) as factors. Preliminary topographical analyses were performed on the mean amplitudes of the N400 congruity effect, for each consecutive 100 ms epoch between 350–650 ms, using split-plot ANOVAs with subject group as a between-subject factor and two within-subject factors—electrode site (all lateral sites) and hemisphere. To adjust for violations of the assumption of sphericity, the Greenhouse-Geisser (1959) correction procedure was used where appropriate. Subsequent one-way ANOVAs and posthoc *t* tests were done at individual electrode sites when significant main effects of subject group or electrode site or interactions were found.

To analyze the N1 and P2 potentials, split-plot ANOVAs were used with one between-subject factor (group) and two within-subject factors—congruity (incongruent/congruent) and electrode site (O1/O2). Greenhouse-Geisser corrections were applied where appropriate. One-way ANOVAs (or *t* tests when only two subject groups were applicable) were used for between group comparisons on demographic and clinical variables. Kruskal-Wallis one-way ANOVAs were used when nonparametric analyses were appropriate.

For individual subject analyses, an abnormality of the N400 latency was defined as any individual subject value greater than two standard deviations above the mean of the NC group, at T6. An abnormal N400 amplitude was defined as any value which was reduced by more than two standard deviations relative to the mean of the NC group. We compared the proportion of subjects with abnormal latency or amplitude in the combined psychosis group

Table 1. Demographic and Clinical Characteristics of the Three Subject Groups

	NC (n = 9)	EOP (n = 9)	LOP (n = 9)
Age (years)	61.0 (8.1)	59.0 (8.5)	62.4 (7.7)
Education (years)	13.3 (2.0)	12.7 (2.2)	11.3 (3.1)
Gender (M:F)	7:2	7:2	7:2
# Right-handed	8	8	8
Age of Onset of Illness (years)	—	25.6 (7.0)	56.9 (7.1)†
Duration of Illness	—	33.4 (9.5)	5.6 (4.0)†
Neuroleptic Dose (mg CPZE daily)	0	536 (1043)	215 (265)
BPRS total	19.6 (1.2)***	32.0 (9.2)	32.7 (5.5)
SAPS score	0.7 (1.3)*	6.1 (4.3)	6.8 (4.3)
SANS score	0.8 (0.8)**	8.3 (4.7)	7.6 (3.8)
MMSE total	28.9 (1.1)	26.6 (3.0)	27.4 (3.6)

Values for continuous variables represent means (with S.D.).

* $p < 0.005$ (Kruskal-Wallis).

** $p < 0.001$ (Kruskal-Wallis).

*** $p < 0.0005$ (Kruskal-Wallis).

† $p < 0.0001$ (*t* test).

NC = normal comparison group.

EOP = early-onset psychosis.

LOP = late-onset psychosis.

BPRS = brief psychiatric rating scale.

SAPS = the scale for the assessment of positive symptoms.

SANS = the scale for the assessment of negative symptoms.

MMSE = mini-mental state examination.

($n = 18$) with that in the NC group ($n = 9$) using Fisher's Exact Probability test.

To investigate the relationship between our main ERP measures and clinical status, Pearson correlation coefficients were calculated for the N400 congruity effect peak latencies and peak amplitudes with selected demographic and clinical variables (age, education, age of onset of illness), psychopathology rating scale (BPRS, SAPS, SANS) scores, global cognitive functioning (MMSE score), and daily neuroleptic dosage (in mg chlorpromazine equivalent or CPZE; (Jeste and Wyatt 1982)). For age, education, and BPRS, and MMSE scores, these correlations were computed across all subjects ($n = 27$). For age of onset, and duration of illness, SAPS and SANS scores, and neuroleptic dose, these correlations were computed across the two patient groups only (EOP and LOP, $n = 18$). All the statistical tests were two-tailed.

Results

Demographic and Clinical Variables

The demographic characteristics of the subject groups are shown in Table 1. Reflecting our selection criteria, there were no significant intergroup differences in age, education, gender, or handedness. There was no significant difference between the EOP and LOP groups in daily neuroleptic dose or psychopathology rating scale scores.

As expected, there was a large difference in age of onset and duration of illness between the EOP and LOP groups.

N1 and P2 potentials

There was no significant effect of group for N1 peak amplitude (NC = $-6.7 \pm 4.7 \mu\text{V}$, EOP = $-3.5 \pm 4.0 \mu\text{V}$, LOP = $-5.1 \pm 4.1 \mu\text{V}$; $F(2,24) = 1.32$, $p = 0.29$) or latency (NC = 145 ± 20 ms, EOP = 159 ± 25 ms, LOP = 158 ± 24 ms; $F(2,24) = 1.10$, $p = 0.35$). There also were no significant main effects or interactions of electrode site and congruity.

For the P2, there were no significant intergroup differences in peak amplitude (NC = $3.1 \pm 3.1 \mu\text{V}$, EOP = $6.1 \pm 4.1 \mu\text{V}$, LOP = $5.4 \pm 4.4 \mu\text{V}$; $F(2,24) = 1.48$, $p = 0.25$) or peak latency (NC = 247 ± 24 ms, EOP = 264 ± 23 ms, LOP = 266 ± 26 ms; $F(2,24) = 1.93$, $p = 0.17$). There was a significant effect of electrode site on the P2 amplitude, with larger amplitudes at the right than left occipital site (O2 = $5.3 \pm 3.8 \mu\text{V}$, O1 = $4.2 \pm 4.0 \mu\text{V}$; $F(1,54) = 11.49$, $p = 0.002$), but no significant effect of congruity nor any significant interactions. None of the within-subject factors had a significant effect (all p 's > 0.11) on P2 peak latency.

N400 Topography

The grand average ERP data for congruent and incongruent target words are shown in Figure 1 for all three groups. The N400 congruity effect in the grand average waveforms for all lateral electrode sites is shown in Figure 2. Visual inspection shows that over the posterior right hemisphere the congruity effect has the longest onset-latency (near 350 ms) in the LOP group. Also, the congruity effect appears widespread in distribution across the scalp and somewhat larger over the left hemisphere in the LOP compared to the EOP group. Compared to the NC group, the congruity effect appears somewhat more frontally distributed in the LOP group, however this effect was not statistically significant (p values for electrode \times group interaction all ≥ 0.061 after Greenhouse-Geisser corrections). For each 100 ms epoch between 350–650 ms, the N400 congruity effect was significantly larger over the right hemisphere (all p 's < 0.0002) and posterior electrode sites (p 's < 0.002), with a significant electrode site \times hemisphere interaction (p 's < 0.0001) reflecting greater asymmetry for frontal than occipital sites.

N400 Peak Latency

A two-way ANOVA with all three groups and all electrodes as factors showed that the N400 peak latency was significantly later in the LOP patients [$F(2,24) = 3.55$; $p = 0.04$]. There was also a significant main effect of

electrode ($p = 0.02$ after Greenhouse-Geisser correction). Posthoc corrected t tests at individual channels showed significant latency delays (all p 's < 0.05) in the LOP group compared to the NC group at three right hemisphere sites (T6, R41, and F8) and at all three midline sites (Pz, Cz, Fz). Table 2 shows the peak latencies and amplitudes over right and left posterior temporal electrodes (T6 and T5, respectively). Specifically, the N400 peak latency was significantly delayed in the LOP group (compared to the NC group) at T6, while the trend for both the EOP and LOP groups to have later latencies at T5 did not reach significance.

N400 Peak Amplitude

An ANOVA of N400 peak amplitudes showed a main effect of electrode site [$F(14,28) = 24.01$; $p < 0.0001$] indicating that the congruity effect was large posteriorly, especially at midline and right hemisphere sites. There was a trend for a difference among groups [$F(2,24) = 2.58$; $p < 0.10$] and posthoc t test showed that the EOP group had a marginally significant amplitude reduction relative to the LOP group ($p = 0.05$). There was a highly significant main effect of electrode ($p < 0.00005$). t tests at individual channels showed that the EOP group had smaller peak amplitudes than the LOP group ($p < 0.05$) at three anterior right hemisphere sites (F8, BR, and R41) and at BL and WL on the left. Similar trends, although nonsignificant ($0.10 > p > 0.05$; t tests), were present at T5 and L41. All of these potential differences seemed to reflect the broader distribution of the N400 congruity effect in the LOP group, relative to NC and EOP (larger over anterior and left hemisphere sites) (Figure 2). Table 2 illustrates that the NC group had the largest mean peak amplitude over the right temporal area, but the LOP group had the largest peak amplitudes over the left temporal area.

N400 Mean Amplitude

There were no significant intergroup differences in the overall mean amplitude (350–650 ms) of the N400 congruity effect [$F(2,24) = 2.0$; $p = 0.15$], although it tended to be smallest in the EOP group, especially at T5 (Figure 2). Fractionating the mean amplitude of the N400 congruity effect into 100 ms time-windows showed a trend for a reduction in both the EOP and LOP groups relative to the NC group for the earliest (350–450 ms) of these time windows at T6 (Table 3).

Individual Subject N400 Abnormalities

The individual subject variability for the congruity effect is shown in Figure 3. Abnormal latencies of the N400 congruity effect (as defined in Methods above) were

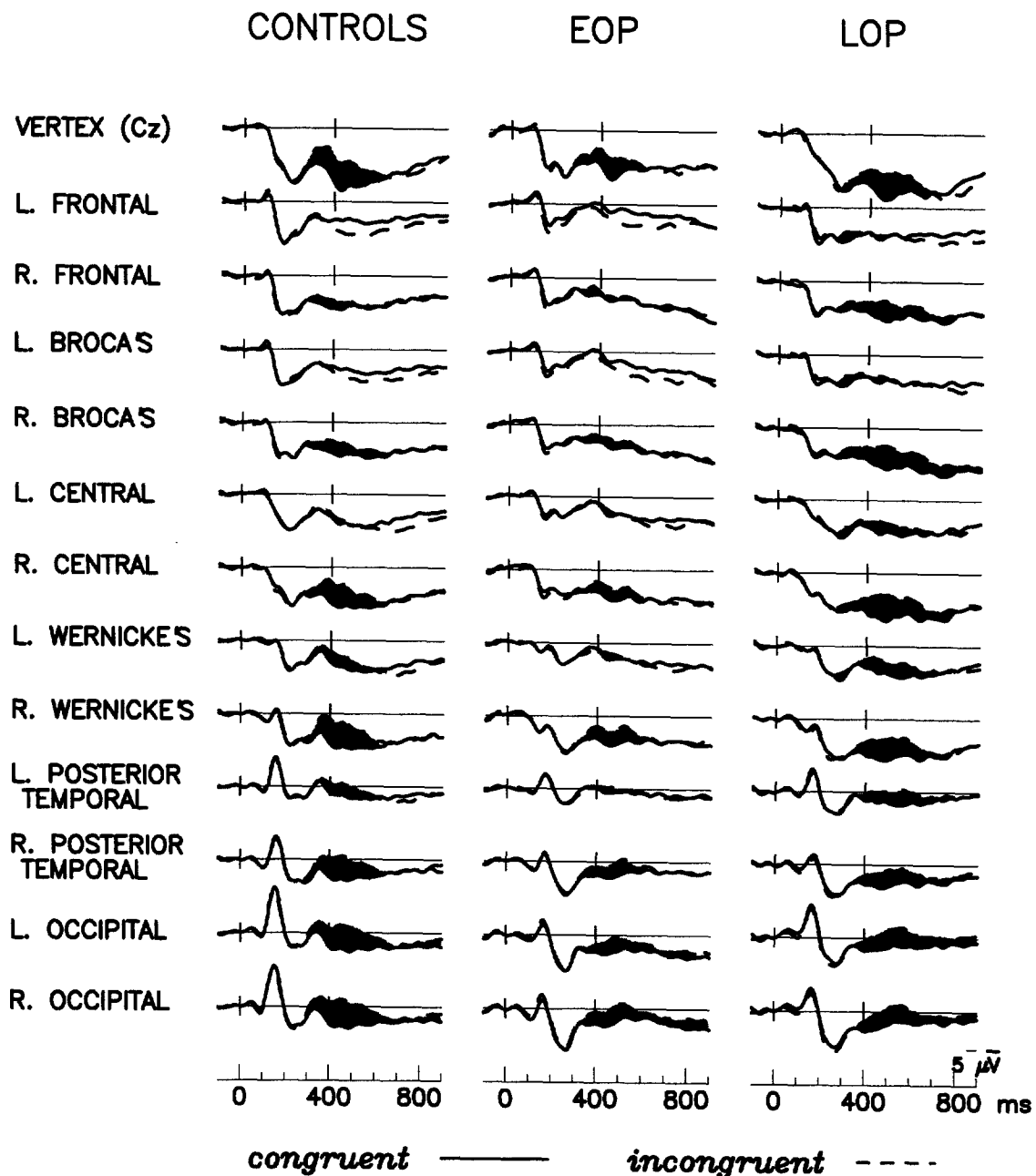


Figure 1. Grand average ($N = 9/\text{group}$) ERPs for congruent (solid line) and incongruent (dashed line) target words at all electrode sites. These data are collapsed across the opposites and category conditions. Shaded area represents the congruity effect. Active sites were referenced to an off-line average of activity at left and right mastoids. ERPs are plotted negative up in this and all subsequent figures. NC = normal comparison group; EOP = early-onset psychosis; LOP = late-onset psychosis.

observed in two of the nine EOP subjects and four of the nine LOP subjects. Amplitude was abnormal in only one case (an EOP subject with a normal peak latency). Thus, the N400 congruity effect had an abnormal latency or amplitude in 3/9 EOP and 4/9 LOP subjects, i.e., a total of 7/18 patients with psychosis, compared to none of the NC subjects ($p = 0.04$, Fisher's Exact Probability test).

N400/Clinical Correlations

Correlational analyses showed that the peak latency of the N400 congruity effect was significantly correlated with education ($r = -0.41$, $p = 0.03$), wherein longer latencies were associated with fewer years of education. Peak amplitude was most strongly correlated with severity of

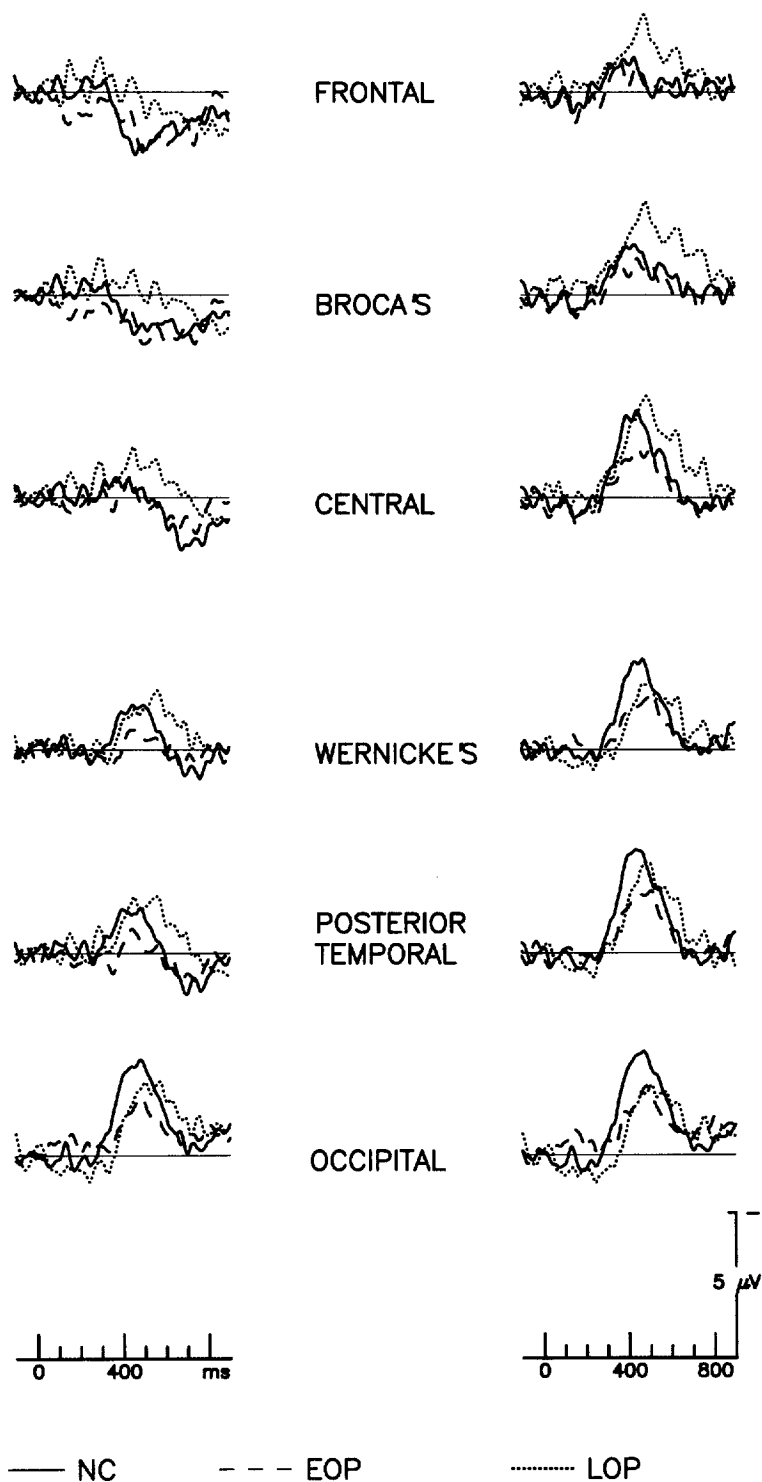


Figure 2. Grand average difference ERPs (incongruous minus congruous) at all left hemisphere (shown on left) and all right hemisphere (shown on right) sites shown superimposed for the 3 groups. CENTRAL denotes the electrode sites near left and right Brodmann's area 41. NC = normal comparison group; EOP = early-onset psychosis; LOP = late-onset psychosis.

negative symptoms ($r = 0.58, p = 0.01$), with smaller (less negative voltage) N400 amplitudes being associated with higher SANS scores. Smaller peak amplitudes were also found in association with younger age ($r = -0.40, p = 0.04$), higher BPRS scores ($r = 0.43, p = 0.03$), and

lower MMSE scores ($r = -0.40, p = 0.04$). None of the other clinical measures in this analysis was significantly correlated with either the peak latency or the peak amplitude of the N400 congruity effect. Specifically, daily neuroleptic dose showed no significant correlation with

Table 2. Peak Latencies and Amplitudes of the N400 Congruity Effect at Right (T6) and Left (T5) Temporal Electrodes

	T6		T5	
	Peak latency	Peak amplitude	Peak latency	Peak amplitude
NC	458 (34)	-3.8 (1.4)	489 (51)	-2.5 (1.3)
EOP	489 (90)	-2.6 (1.9)	547 (82)†	-1.8 (0.6)#
LOP	530 (87)*	-3.3 (1.4)	539 (64)†	-3.0 (1.9)

Values are means (with SD) of latencies expressed in milliseconds, and amplitudes expressed in microvolts.

* $p = 0.03$ vs NC (t test).

† $p \leq 0.10$ vs NC (t test).

$p \leq 0.10$ vs LOP (t test).

NC = normal comparison group; EOP = early-onset psychosis; LOP = late-onset psychosis.

either latency ($r = 0.27$, n.s.) or amplitude ($r = 0.08$, n.s.). Also, age was not significantly correlated with peak latency ($r = 0.08$, n.s.).

Discussion

To our knowledge, the present study is the first to report on the N400 in older patients with schizophrenia and related psychoses. Overall, our data appear at least partially consistent with the existing literature on the N400 in younger patients with schizophrenia. Similar to Koyama and colleagues (Koyama et al 1991) who used a lexical decision task, we found abnormalities predominantly in N400 latency, rather than in amplitude; however, we also found a tendency for the early portion of the N400 congruity effect to be reduced in amplitude in the LOP group (this appears due to longer latency of onset), and for this reduction to be somewhat more sustained in the EOP group. This is similar to the reduced congruity effect amplitudes observed in some patients by Grillon et al (1991) using unrelated and related word pairs. Andrews and colleagues (Andrews et al 1993) found a longer latency for the N400 congruity effect which was more pronounced than the delay in the N400 per se. These authors noted that the congruity effect in young adults with schizophrenia extended into later time-windows in

Table 3. Mean Amplitudes of the N400 Congruity Effect Divided into 100ms Time Windows at T6

	Mean amplitude 350-450ms	Mean amplitude 450-550ms	Mean amplitude 550-650ms
NC	-2.5 (1.3)	-2.5 (1.0)	-1.1 (1.3)
EOP	-1.2 (1.4)†	-1.7 (2.1)	-0.7 (1.6)
LOP	-1.0 (1.9)†	-2.1 (1.6)	-1.7 (1.9)

Values are mean (with S.D.) amplitudes in microvolts.

† $p = .07$ vs NC (t test).

NC = normal comparison group; EOP = early-onset psychosis; LOP = late-onset psychosis.

which the late-positive component (LPC) became prominent, at least as indicated by their normative data. Therefore, they could not rule out the possibility that the later congruity effect was due to a decreased LPC, rather than an increased N400, for incongruous words.

Our data show that abnormalities of the N400 potential, particularly the N400 congruity effect, are present in a significantly greater proportion of older patients with psychosis, than in normal subjects. With our current sample size, the only significant intergroup difference present across electrode sites was an increased latency in the LOP patients compared to the NC subjects. In our older cohort, the EOP group had a much longer duration of illness than LOP, making this increased latency in LOP all the more remarkable. The LOP group did not show significantly delayed N1 or P2 components, indicating that the delayed congruity effect in these patients was not simply due to generalized slowing of sensory-perceptual processing.

The mean amplitude of the early (350-450 ms) portion of the N400 congruity effect showed a trend toward reductions in both the EOP and LOP groups. For the EOP group there was a tendency for this mean amplitude to remain lower than that of the NC group throughout the ERP congruity effect (350-650 ms). This trend is interesting in light of a neuropsychological study recently completed at our Center (Paulsen et al 1996) in which the extent to which schizophrenia patients generated normal semantic associations during a verbal fluency test (animal naming) was measured. The inferred semantic network organization of the early-onset schizophrenia patients, but not that of the late-onset schizophrenia patients, differed from that of the normal comparison subjects. One speculative interpretation of these findings could be that smaller amplitudes, rather than later latencies, of the N400 congruity effect relate more directly to abnormal semantic network organization. This would be consistent with prior studies of cognitively normal adults (Kutas and Hillyard 1984), showing a very robust inverse correlation ($r = -0.88$ to -0.97 at posterior electrode sites) between N400 amplitude and the predictability of the eliciting word given the sentence context (the "cloze probability") as determined by normative questionnaires.

Our correlational analyses also suggested that the peak amplitude of the N400 congruity effect related more closely to the clinical status than did its peak latency. Smaller amplitudes were seen in the patients with greater degrees of psychopathology (particularly negative symptoms) and worse global cognitive function. Prior work has linked negative symptoms (e.g., poverty of thought, alogia) of schizophrenia to poor linguistic abilities (Thomas et al 1990), poor cognitive function and poor prognosis (McGlashan and Fenton 1994). Prior ERP studies have

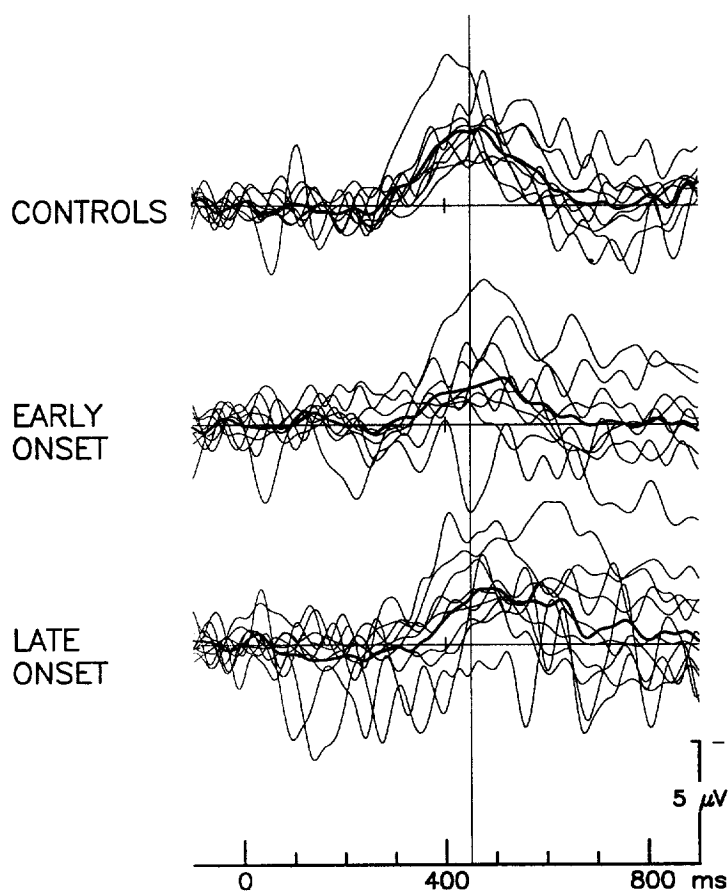


Figure 3. Shown overlapped are the individual subject difference ERPs (incongruous minus congruous) for the right posterior temporal site (T6) for each of the three groups, separately. The thicker line in each case represents the grand average ERP of the individual subject data (thinner lines). NC = normal comparison group; EOP = early-onset psychosis; LOP = late-onset psychosis.

shown that P300 amplitude is also sensitive to severity of psychopathology—some linking smaller P300s with negative symptoms (Strik et al 1994) and others with positive symptoms (McCarley et al 1993). Large P300s are usually elicited by infrequent task-relevant stimuli and the P300 is quite sensitive to attentional allocation (Donchin et al 1986). To minimize the likelihood of eliciting P300 potentials, the present experiment was designed such that the incongruent and congruent target trials occurred with equal probability and engaged similar attentional resources.

The present study had small sizes, and included a few patients with related psychoses along with schizophrenia patients. Thus, there are possibilities of both type I and type II errors. On the other hand, the patient groups were carefully diagnosed and clinically well-characterized. The EOP, LOP, and NC groups were matched on critical demographic variables, and the N400 assessment was done in a highly standardized manner.

In conclusion, our N400 findings in older patients with schizophrenia and related psychoses partially replicate those reported in younger patients. The longer latency in the LOP group is consistent with the suggestion that

late-onset schizophrenia shares a number of clinical and neurobiological similarities with “typical” schizophrenia beginning in adolescence or early adulthood (Jeste et al 1995). The older EOP patients studied to date did not, as a group, show significant N400 latency abnormalities, although some tendency for both latency and amplitude abnormalities was noted. Reduced N400 amplitudes were related to severity of negative symptoms, global psychopathology and cognitive impairment. The clinical correlates of a delay in peak latency are less clear. It is conceivable that N400 latency abnormalities are due to largely subclinical nondominant hemisphere dysfunction, or to white-matter disease. Supporting the hypothesis that LOP patients may have less dominant hemisphere (and perhaps relatively more nondominant hemisphere) dysfunction than EOP patients with similar psychopathology severity, is the relatively normal semantic network organization described in LOP (Paulsen et al 1996). In contrast, there is a substantial literature which shows a predilection for more dominant hemisphere abnormalities in typical schizophrenia cohorts of early-onset (for review, see Flor-Henry 1983b). The relevance of white-matter disease to LOP is controversial: some neuroimaging stud-

ies have reported striking increases in deep white matter abnormalities (Breitner et al 1990; Miller et al 1991) while others have not (Krull et al 1991; Howard et al 1995). Whether any ERP differences between EOP and LOP (e.g., the later peak latency in LOP or the trend for lower peak amplitude at left temporal and frontal sites in the EOP group) relate directly to differences in the age of

onset of schizophrenia remains to be seen. Further studies with larger sample sizes are necessary to replicate and extend these findings.

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