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Event-related brain potential study of semantic priming in unaffected first-degree relatives of schizophrenia patients

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ABSTRACT

Schizophrenia is associated with abnormalities in using meaningful stimuli to activate or prime related concepts in semantic long-term memory. A neurophysiological index of this activation is the N400, an event-related brain potential (ERP) waveform elicited by meaningful stimuli, which is normally reduced (made less negative) by relatedness between the eliciting stimulus and preceding ones (*N400 semantic priming*). Schizophrenia patients exhibit N400 semantic priming deficits, suggesting impairment in using meaningful context to activate related concepts. To address whether this abnormality is a trait-like marker of liability to schizophrenia or, alternatively, a biomarker of the illness itself, we tested for its presence in schizophrenia patients' unaffected biological relatives. We recorded ERPs from 12 unaffected first-degree relatives of schizophrenia patients, 12 schizophrenia patients, and 12 normal control participants (NCPs) who viewed prime words each followed at 300- or 750-ms stimulus-onset asynchrony (SOA) by an unrelated or related target word, or a nonword, in a lexical-decision task. As expected, across SOAs, NCPs exhibited smaller (less negative) N400 amplitudes for related versus unrelated targets. The same pattern held in relatives, whose N400 amplitudes for related and unrelated targets did not differ from NCPs'. In contrast, consistent with previous results, schizophrenia patients exhibited larger N400 amplitudes than NCPs (and relatives) for related targets, such that patients' N400 amplitudes for related and unrelated targets did not differ. N400 amplitudes for unrelated targets did not differ between the three groups. Thus, N400 semantic priming deficits in a visual word-pair paradigm may be an illness biomarker for schizophrenia.

1. Introduction

Researchers have proposed that positive symptoms of schizophrenia, such as disorganized speech and delusions, arise from abnormalities in how contextual stimuli activate related concepts in semantic long-term memory, our store of knowledge about concepts and their relationships. Semantic memory has been modeled as a neural network in which concepts are nodes, and relationships between concepts are connections between nodes (Collins and Loftus, 1975). Normally, after a concept node is activated – e.g., by its corresponding object or word stimulus – this activation spreads to related concepts, falling off with decreasing relatedness. Greater activation of a concept is reflected in greater priming, or facilitation, of its processing (e.g., faster recognition of the corresponding word).

Conceptual activation in semantic memory can be probed at the neural level using electroencephalographic event-related brain potentials (ERPs), which measure voltage changes at the scalp during cognitive processing, reflecting synchronous activity of cortical pyramidal neurons. The N400 is a negative-going ERP waveform occurring around 400 ms after any meaningful stimulus, such as a word or a picture. Normally, its amplitude is made smaller (less negative) by factors that activate or prime the corresponding concept, including relatedness to preceding context (Kutas and Hillyard, 1980; Holcomb and Neville, 1990; Holcomb and McPherson, 1994). Thus, following the prime word *CAT*, the related target word *MOUSE* elicits a smaller N400 than the unrelated word *ARROW*. These *N400 semantic priming effects* are thought to reflect use of context to predict upcoming items by pre-activating their neural representations (Kutas and Federmeier, 2000; DeLong et al., 2005).

N400 studies have found evidence of abnormal priming of related concepts in schizophrenia (reviewed by Mohammad and DeLisi, 2013). Several studies have found increased priming of contextually related targets, as reflected in smaller (less negative) than normal N400s to these stimuli (Mathalon et al., 2002; Salisbury, 2008), or larger than normal N400 semantic priming effects (Kreher et al., 2008). These observations, however, appear specific to the combination of weakly related targets, short prime-target time intervals (i.e., stimulus-onset asynchronies or SOAs) of <300 ms, and patients with disorganized speech. Thus, hyperpriming of weakly related concepts may be a neurophysiological mechanism of disorganized speech in particular (Ditman and Kuperberg, 2007; Salisbury, 2008).

In contrast, numerous studies have reported larger than normal N400s to targets both strongly and weakly related to preceding primes,

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Table 1
Demographic and clinical characteristics of the study sample (means ± SD given where applicable).

	Relatives of schizophrenia patients ($n = 12$)	Schizophrenia patients ($n = 12$)	NCPs ($n = 12$)
Age, years	45.0 ± 13.3	42.1 ± 11.7	34.9 ± 6.3
Sex	9 female, 3 male	4 female, 8 male	6 female, 6 male
Handedness (Oldfield, 1971)	10 right, 1 left, 1 ambidextrous	11 right, 1 left	10 right, 2 left
Parental socioeconomic status (Blishen et al., 1987)	43.3 ± 12.7	46.3 ± 8.9	44.0 ± 12.5
Years of education	14.4 ± 2.8	14.3 ± 1.7	16.2 ± 4.3
National Adult Reading Test (O'Carroll et al., 1992) estimated IQ	107.1 ± 10.0	104.5 ± 9.9	110.2 ± 12.5
SANS total score	–	7.9 ± 4.4	–
SAPS total score	–	4.3 ± 3.7	–
SANS/SAPS factor scores			
Negative	–	5.3 ± 2.8	–
Psychotic	–	2.8 ± 2.6	–
Disorganized	–	1.4 ± 1.7	–

Groups did not differ significantly on any of the demographic characteristics ($p > 0.05$).

and/or smaller than normal N400 semantic priming effects, in schizophrenia (Bobes et al., 1996; Strandburg et al., 1997; Ohta et al., 1999; Condray et al., 2003; Kostova et al., 2003; Iakimova et al., 2005; Kostova et al., 2005; Ditman and Kuperberg, 2007; Kiang et al., 2008; Salisbury, 2008; Guerra et al., 2009; Condray et al., 2010; Mathalon et al., 2010; Kiang et al., 2011; Kiang et al., 2012). These studies provide evidence of a general reduction in semantic priming, at least over intervals of approximately ≥300 ms (including during sentence reading). Several studies found such abnormalities to correlate with psychotic symptoms — raising the possibility that subnormal activation of contextually related concepts may underlie development and maintenance of delusions (Salisbury et al., 2000; Kiang et al., 2007, 2008).

These N400 semantic priming abnormalities may be useful either as a neurophysiological endophenotype of schizophrenia (Guerra et al., 2009; Mohammad and DeLisi, 2013), or as a disease state biomarker disease state (Kiang et al., 2013). Endophenotypes are measurable trait markers of genetic liability for a disorder (Gottesman and Gould, 2003; Turetsky et al., 2007), which are useful for identifying genetic determinants of the disorder in population studies, and elucidating biological mechanisms whereby such genes contribute to clinical symptoms. One criterion for establishing a candidate endophenotype's validity is its presence in unaffected biological relatives of patients with the disorder. In contrast, a non-endophenotypic biomarker of schizophrenia would be found only in patients who have developed symptoms of

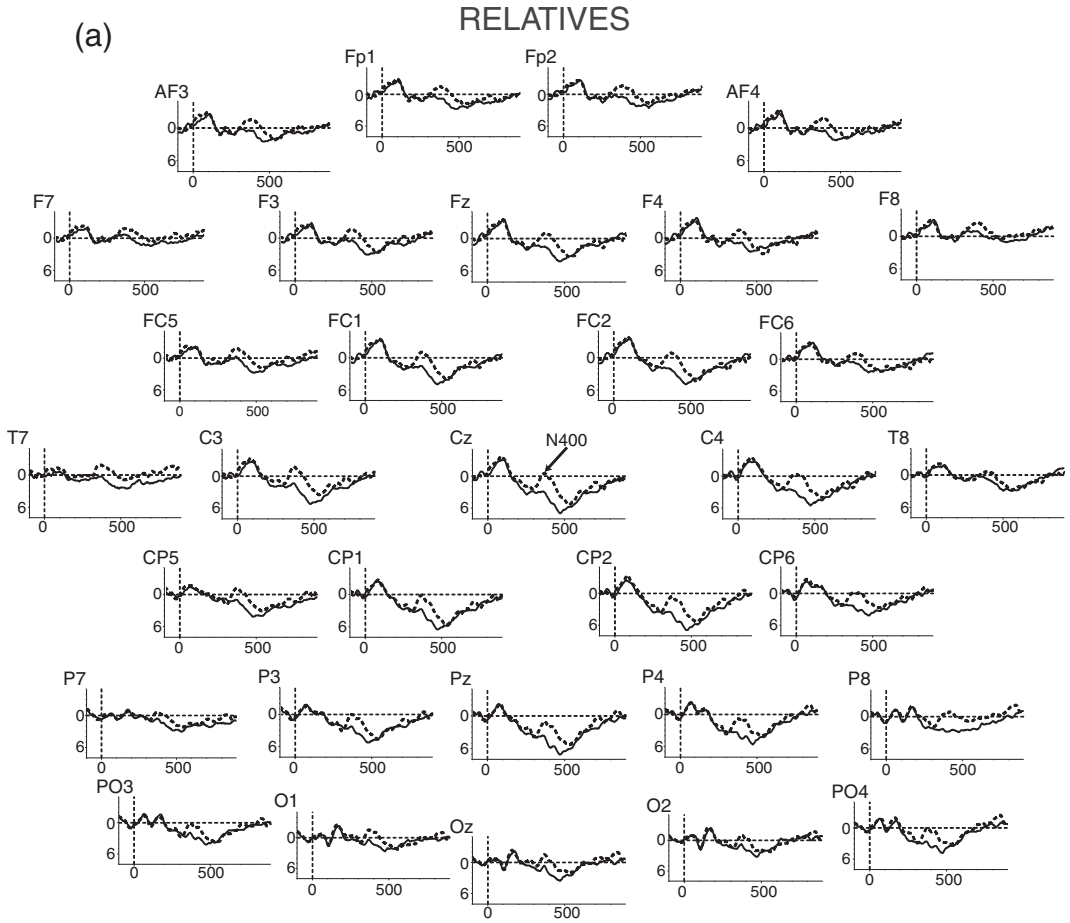

Fig. 1. Grand average ERPs to target words related (solid lines) and unrelated (dashed lines) to prime words, at the 300-ms prime-target SOA, at all electrode sites, for: (a) first-degree relatives of schizophrenia patients, (b) schizophrenia patients, and (c) NCPs. Voltage is plotted in μV on the *x*-axis with negative plotted upward, and time is plotted in ms on the *y*-axis.