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Letter to the Editor

N400 event-related brain potential evidence for semantic priming deficits in persons at clinical high risk for psychosis

Dear Editors,

The N400 electroencephalographic event-related potential (ERP) waveform normally occurs in response to any meaningful stimulus, such as a word or picture, and is smaller (less negative) for stimuli that are more related to preceding ones (Kutas and Federmeier, 2011). For example, after seeing the prime word *cat*, people exhibit smaller N400 s to the related word *mouse* than the unrelated word *arrow*. These "N400 semantic priming effects" are thought to occur because meaningful prime stimuli activate the neural representations of their concepts in semantic memory, our store of knowledge about the world, and this activation then extends to related concepts, making their corresponding stimuli easier to process, as reflected in smaller N400s (Kutas and Federmeier, 2011). Deficient semantic priming, in which related and unrelated stimuli are processed more similarly than normal, could plausibly underlie symptoms of schizophrenia including disorganized speech, with its sequences of unrelated or loosely related ideas; or delusions, which frequently involve beliefs that unrelated stimuli are connected or, conversely, that contextually congruent stimuli are unexpected or unusual. Numerous studies of patients with schizophrenia have in fact reported larger than normal N400 s to target stimuli related to preceding prime stimuli, and/or smaller than normal N400 semantic priming effects, at least when prime-target stimulus-onset asynchronies (SOAs) are longer than about 400 msec (e.g., Condray et al., 2010; Ditman and Kuperberg, 2007; Kiang et al., 2014; Kostova et al., 2005; Mathalon et al., 2010; Salisbury, 2008; reviewed in Mohammad and DeLisi, 2013).

It is unknown whether N400 semantic priming abnormalities precede frank psychosis in schizophrenia. To address this question, we aimed to test for the first time whether N400 abnormalities similar to those observed in schizophrenia are also present in individuals at clinical high risk (CHR) for developing schizophrenia or a related psychotic disorder. We hypothesized that, similar to schizophrenia patients, CHR patients would exhibit smaller than normal N400 semantic priming effects, due to larger than normal N400 amplitudes to related targets, at least at a relatively long SOA. This would provide evidence that these abnormalities are associated with prodromal stages of the psychotic process, consistent with a role for semantic priming deficits in the pathogenesis of psychosis.

Participants included 20 antipsychotic-naïve CHR patients and 20 healthy control participants (HCPs) (inclusion/exclusion criteria detailed in Supplementary Materials and Methods), whose demographic and clinical characteristics are shown in Supplementary Table 1. We recorded participants' continuous EEG while they viewed prime words each followed by a target that was either a related word (*METAL-STEEL*), an unrelated word (*DONKEY-PURSE*), or a pronounceable nonword (*DRESS-ZORES*), in a lexical-decision task. Equal numbers of related and unrelated word pairs were presented at a short and a long SOA (300 and 750 msec) for each participant. Details of stimuli and ERP analyses were similar to those in Kiang et al. (2014), and are described in Supplementary Materials and Methods. N400 amplitudes to target words were analyzed by repeated-measures ANOVA with Group (CHR vs. HCP) as between-subject variable; and SOA (300- vs. 750-msec), Target (related vs. unrelated), and Electrode (12 levels: T7/Cz/T8/CP5/CP1/CP2/CP6/P7/P3/Pz/P4/P8, corresponding to a contiguous array of centroparietal sites, where N400 effects are most prominent (Kutas and Federmeier, 2011)) as within-subject variables.

Across groups, as expected, N400 amplitude was larger (more negative) for unrelated than related targets (Target effect: $F_{1,38} = 31.75$, $\eta^2_P = 0.46$, $p < 0.0001$); and was larger medially (Target × Electrode interaction: $F_{11,418} = 13.51$, $\eta^2_P = 0.26$, $p < 0.0001$). There was no Group effect ($F_{1,38} = 0.38$, $\eta^2_P = 0.01$, $p = 0.54$); and no Group × Target ($F_{1,38} = 2.67$, $\eta^2_P = 0.07$, $p = 0.11$), Group × SOA ($F_{1,38} = 0.89$, $\eta^2_P = 0.02$, $p = 0.35$), or SOA × Target ($F_{1,38} = 0.31$, $\eta^2_P = 0.01$, $p = 0.58$) interactions. There was, however, a Group × Target × SOA interaction ($F_{1,38} = 4.14$, $\eta^2_P = 0.10$, $p = 0.049$); a Tukey HSD test ($p < 0.05$) indicated that at the 750-msec SOA, for controls, N400 amplitude was larger for unrelated than related targets, whereas for patients there was no N400 amplitude difference between these conditions. Grand average ERPs are shown for representative midline electrodes Cz (central) and Pz (parietal), for CHR and HCP groups, for the 300-msec SOA in Supplementary Fig. 1, and for the 750-msec prime-target SOA in Fig. 1. N400 amplitude values by group, target type and SOA are shown in Supplementary Table 2.

Consistent with our hypotheses, we found that CHR patients' N400 semantic priming effects were smaller than normal at the 750-msec prime-target SOA, but not at the 300-msec SOA. In other words, whereas controls, as expected, had smaller N400s to related than to unrelated items across SOAs, CHR patients exhibited no difference in N400 amplitude between related and unrelated items at the 750-msec SOA. These results suggest that, after encountering meaningful prime stimuli, CHR patients activate related over unrelated concepts in semantic memory normally over a shorter time interval, but are impaired in maintaining this selective activation over a longer interval. Thus N400 semantic priming deficits at longer SOAs, in particular, may be a reliable neurophysiological biomarker of psychosis risk, and may reflect a neurocognitive mechanism in the pathogenesis of psychosis.

A strength of our study was that patients were antipsychotic-naïve; hence their ERPs were not subject to possible confounding effects of these medications. A limitation of the study was its relatively small sample size. Larger studies are necessary to further validate N400 semantic priming deficits as an early neurophysiological biomarker of psychotic illness. Larger studies with greater statistical power are also required to distinguish whether patients' N400 semantic priming deficits at the long SOA occurred because N400 amplitudes were larger than normal for related targets, smaller than normal for unrelated targets, or both.

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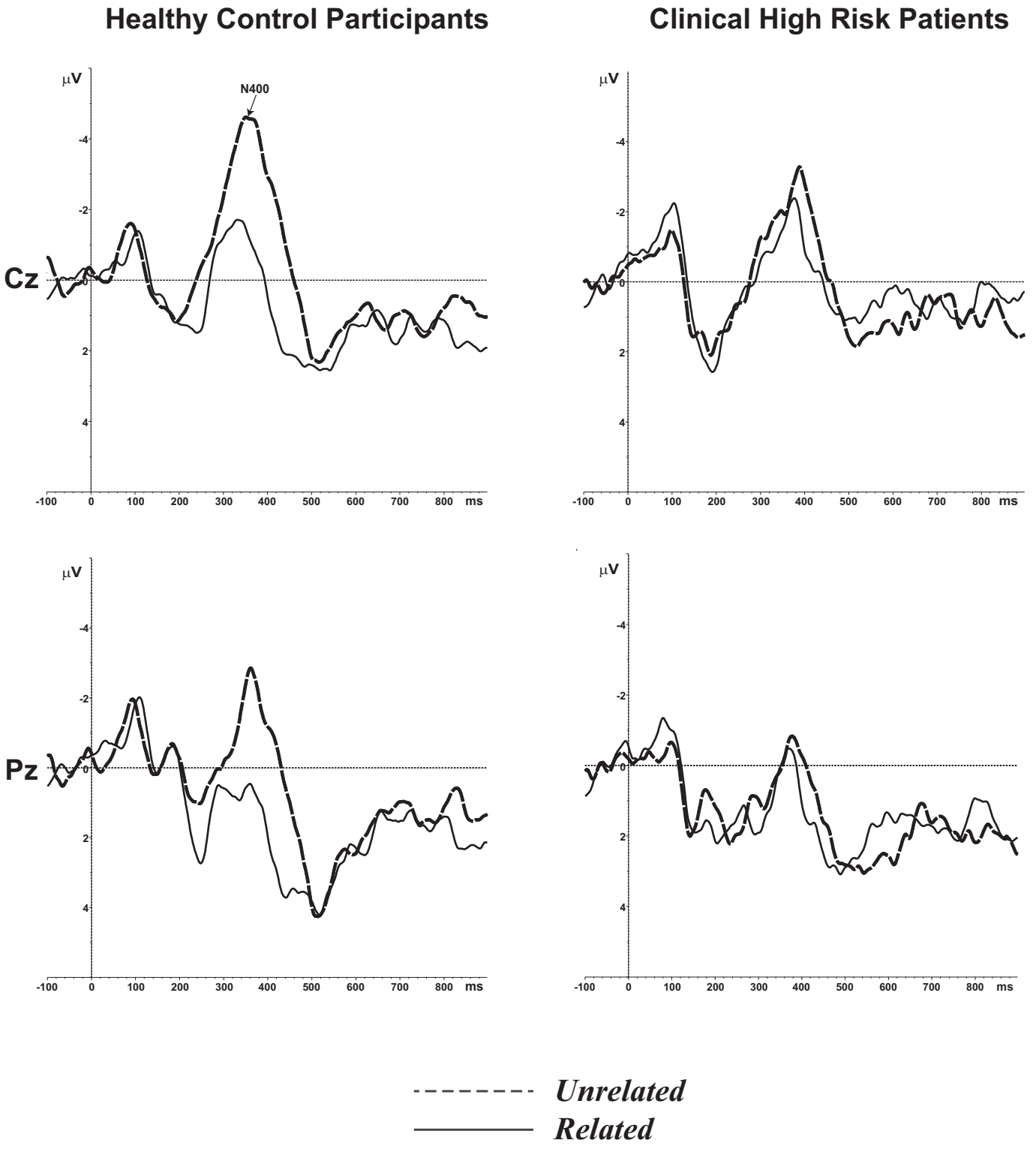

Fig. 1. Grand average event-related potentials to related (solid line) and unrelated (dashed line) word targets, at the 750-msec prime-target stimulus-onset asynchrony, at the electrode sites Cz (midline central) and Pz (midline parietal), for healthy control participants and clinical high risk patients.

Another limitation of the study was its cross-sectional nature. Longitudinal studies could help ascertain whether severity of N400 semantic priming deficits further predicts risk of developing psychosis within the CHR population. If so, this N400 abnormality could complement other ERP biomarkers of the CHR state that hold promise for contributing to algorithms that refine our ability to predict outcome in this population (Mohammad and DeLisi, 2013; Nieman et al., 2014; Schmidt et al., 2017), in order to provide patients with more personalized prognostic information, and target interventions to those most at risk.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.08.033.

Conflict of interest

The authors declare no conflicts of interest in relation to the subject of this study.

Contributors

Michael Kiang and Romina Mizrahi designed the study and supervised all aspects of data collection and analyses. Michele Korostil and R. Michael Bagby contributed to study design.

Jennifer Lepock, Margaret Maheandiran, Cory Gerritsen, Lauren Drvaric and Sarah Ahmed collected and analyzed data. Lepock and Kiang wrote the first draft of the manuscript. All authors contributed to and approved the final manuscript.

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