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Sensory-gating deficit of the N100 mid-latency auditory evoked potential in medicated schizophrenia patients

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ABSTRACT

The clinical and neuro-cognitive correlates of the P50 and N100 auditory evoked responses gating deficits in schizophrenia have thus far eluded identification. Based on our prior results, we hypothesized that, in addition to the P50, gating of the N100 is significantly decreased in schizophrenia and that this deficit correlates with the negative symptoms dimension of schizophrenia. Amplitudes and gating measures of the P50 and N100 were compared between stable out-patients ($N=45$) (mainly on atypical antipsychotics) with chronic schizophrenia and age- and gender-matched healthy controls ($N=49$) and the clinical correlates examined. All subjects underwent the paired-stimulus paradigm in 3 or 4 different days. Data from day one and the mean of all days (MOAD) were examined. P50 and N100 amplitudes and gating measures were correlated with PANSS and Wisconsin Card Sorting Test data. Utilizing day one data, no amplitude or gating measures were significantly different between the groups. Utilizing MOAD data, both P50 and N100 gating were significantly decreased in schizophrenia patients. The N100 gating deficit correlated with the negative-symptoms cluster and measures of frontal lobe dysfunction. The data suggest a correlation between N100 gating deficit and the negative-cognitive deficits dimensions of schizophrenia. Data also suggest that improving the signal to noise ratio (MOAD data) increases the sensitivity for detecting gating abnormalities and assessing their clinical correlates.

1. Introduction

The ability to inhibit or suppress the response to incoming irrelevant or redundant sensory input is a well documented characteristic of the central nervous system that is believed to have a protective mechanism that prevents the flooding of higher cortical centers with irrelevant information (Venables, 1964). The P50 auditory evoked potential (AEP) component functions as a tool to examine habituation or sensory gating (SG) in schizophrenia (Bramon et al., 2004). Thus far only SG at the P50 stage of information processing has been extensively examined (Bramon et al., 2004; Heinrichs, 2004). Sensory-gating occurring at the N100 stage of information processing is yet to be fully explored (Boutros et al., 1999, 2004). Reliability of the N100 as a gating index has been demonstrated (Smith et al., 1994; Fuerst et al., 2007). The paradigm for examining SG is widely accepted (Smith et al., 1994; Rentzsch et al., 2008).

Demonstrating a clinical association of gating deficits utilizing the P50 AEP has been a difficult task with reports suggesting no correlations (Adler et al., 1990; Boutros et al., 2004), or correlating with attentional deficit (Erwin et al., 1991, 1998), anxiety, depression and anergia (Yee et al., 1998). More recent studies support the notion that P50 gating abnormalities

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may be more represented in the disorganized and negative symptoms subgroups of schizophrenia patients (Ringel et al., 2004; Louchart-de la Chapelle et al., 2005).

The N100 gating literature remains extremely limited. Hsieh et al. (2004) reported an association between N100 gating and verbal learning in healthy controls but not in schizophrenia patients. Most recently, the N100 gating was shown to be significantly impaired in a mixed sample of schizophrenia patients with and without neuroleptic treatment (Brockhaus-Dumke et al., 2008).

The current study had three goals. Our first goal was to further document SG abnormalities occurring at the N100 phase of information processing in schizophrenia patients. Our second goal was to specifically ascertain whether the N100 gating deficit correlates with the negative symptoms dimension of schizophrenia. Thirdly, examining the correlation between N100 SG and frontal lobe executive functions. This goal was motivated by the accumulating literature for a frontal lobe involvement in mediating SG (Weisser et al., 2001; Grunwald et al., 2003; Korzyukov et al., 2007).

2. Methods

2.1. Subjects

Data from forty five schizophrenia patients and forty nine healthy control subjects were included in this study. Patients were recruited from the outpatient clinics of Yale University (2002–2004; total recruited subjects, 74/37 patients) and Wayne State University (WSU) hospitals (2005–2006; total recruited subjects 31/19 patients). The majority of patients were on atypical antipsychotics. Patients with head injury with loss of consciousness as well as patients with uncontrolled medical conditions (e.g., diabetes or hypertension) were excluded). None of the patients had a psychiatric hospitalization or a change in their psychotropic medications in the four weeks prior to or during the study. Among smokers, the number of packs per day was recorded. Healthy subjects were recruited through news paper ads. Healthy controls were matched for age and sex (as a group). The study was explained and all questions were answered before signing the written consent. All procedures were identical between the two study locations. The study was approved by the Yale and WSU Human Investigations Committees.

2.2. Clinical evaluation

Subjects were administered the Structured Clinical Interview for DSM-IV (SCID-I). Subjects meeting criteria for schizophrenia and who had no drug or alcohol use for the last 3 months (as verified by toxicology and confirmed by treating clinician) were administered the Positive and Negative Symptoms Scale (PANSS) and the Wisconsin Card Sorting Test (WCST).

2.3. Evoked potential paradigm

Each subject underwent one recording block using a paired-stimulus condition per each recording day. Subjects were invited to return for additional identical recordings three more times (four recording sessions total). This design was adopted in order to examine the test–retest reliability of the P50 and N100 gating measures. These data have been reported elsewhere (Fuerst et al., 2007). Briefly, all N100-derived measures showed good test–retest reliabilities while among the P50 gating measures the S2–S1 difference measure stood out as most reliable. This design also allowed the examination of possible beneficial effects of increasing the signal to noise ratio (SNR) by including more single trials in computing the AEPs. Recording sessions were maximally one week apart. If a patient's clinical condition changed (medication change or hospitalization) they were dropped of the study.

The recording procedure is described in detail elsewhere (Nagamoto et al., 1989; Boutros et al., 2004). Relevant to the current report is that sixty pairs of stimuli were presented and a minimum of 40 artifact-free trials were necessary to accept the resulting averages. Recording was made from the Fz, Cz, Pz, Oz, F7, F8, T3, T4, P5, and P6 locations and referred to linked ears. P50 and N100 measurements were made from the Cz electrode. Band-pass filters were set at .05 and 300 Hz and digitized at 1000 Hz for off-line averaging. Epochs were 300 ms starting 50 ms before stimulus. In order to improve the SNR, we further refiltered the EEG data between 1–50 Hz (Clementz et al., 1997).

Amplitudes of the P50 and N100 were measured both from peak to the preceding peak (PP) or from peak to baseline (PB). All components were identified independently by two fully trained research associates (SB and ME) who were blind to all rating scale scores and to theoretical predictions. Fig. 1 shows how these measures are calculated. In order to identify a component as the P50 (S1) the component had to have an amplitude of 0.5 μV or higher and be larger than the level of noise in the 50 ms pre-stimulus period. This procedure was adopted by this group to increase the confidence in the components identified as P50. Smaller components cannot be confidently distinguished from noise. For PB measurements, a portion of the P50 must be on the positive side of the baseline. If the entire component was on the negative side, the component was not selected for this measurement. If the S2 response could not be found within a 15 ms (for the P50) or 30 ms (for N100) of the latency of S1 response in the same trial, the response was

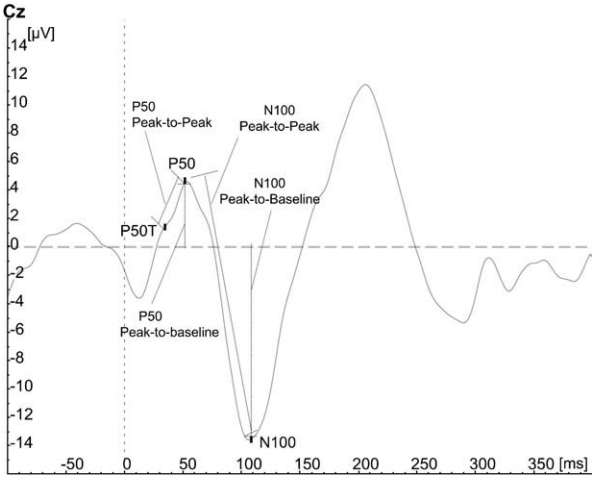

Fig. 1. Example of the P50, N100, P200 MLAER complex showing the points from which the P50 and N100 components are measured.