Fine Structure of the Auditory M100 in Schizophrenia and Schizoaffective Disorder

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Background: Several studies have demonstrated anomalous asymmetry of the 100-msec latency auditory-evoked field (M100) in schizophrenia. Recent evidence suggests this may be a compound component, however. Our study examines the localization of two M100 subcomponents in patients with schizophrenia and schizoaffective disorder.

Methods: Magnetoencephalographic recordings of auditory-evoked fields were obtained for 14 subjects with schizophrenia, 12 with schizoaffective disorder, and 23 control subjects. Two M100 subcomponents were identified and localized in each hemisphere.

Results: Both patient groups exhibited different lateralization compared with control subjects, with the second subcomponent tending to be less lateralized.

Conclusions: The second subcomponent may be the major contributor to previously reported laterality differences. Future studies might benefit by separating M100 subcomponents so that specific functions could be addressed.

Key Words: Schizophrenia, schizoaffective disorder, magnetoencephalography, M100, auditory-evoked fields, laterality

Introduction

Psychosis has been associated with anomalous brain asymmetry (Crow 1990). Several studies have described abnormal asymmetry of the 100-msec latency auditory-evoked field component (M100) in schizophrenia (less asymmetric or more variable in schizophrenia) as a manifestation of this anomaly (Hajek et al 1997; Reite et al 1989, 1997; Tiitinen et al 1998). Some evidence suggests such anomalies in M100 lateralization may be a manifestation of a different auditory cortical organization in schizophrenia (Rojas et al 1997). All previous magnetoencephalography (MEG) studies in schizophrenia, however, have considered the M100 a unitary component. The associated evoked potential, designated N100, is generally considered to be a superposition of responses produced by as many as six separate sources ( Näätänen and Picton 1987) having different spatial and temporal characteristics. Several of these generators are thought to be radial in orientation and therefore will not produce measurable magnetic fields. Recent MEG work suggests the M100 is a compound component (Lu et al 1992; Sams et al 1993; Teale et al 1998; Zouridakis et al 1998). In normal subjects, the M100 component may actually be generated by two active regions separated in time (by 25 msec) and in space (later source about 0.1 cm anterior in the L hemisphere, and 0.8 cm anterior in the right hemisphere; Teale et al 1998).

Independent localization of these two components has not been reported in subjects with psychosis. In light of the laterality differences reported in the literature for the combined component in subjects with psychosis, we wished to determine if one of the two putative subcomponents might be selectively contributing to the variance reported for M100 lateralization.

Methods and Materials

Our subject population consisted of 14 individuals with schizophrenia (mean age 36.7 ± 6 years), 12 with schizoaffective disorder (mean age 36.8 ± 10 year), and 23 control subjects (mean age 34 ± 10 year) recruited from the Denver metropolitan area. All patients were in outpatient treatment, and most were medicated. All were men. Diagnosis was determined using the Structured Clinical Interview for DSM-IV and review of medical records. Mean age of onset for the subjects with schizophrenia was 21.62 ± 5.35 years and 22.00 ± 8.24 years for the schizoaffective group. All were right handed based on the Annett criteria (Annett 1985). All had normal hearing thresholds at 1 kHz as determined by audiometry. Informed consent was obtained from all subjects in accordance with the Colorado Multiple Institutional Review Board.

Recordings were obtained inside a magnetically shielded room, with subjects semi-reclining in a nonmagnetic chair, using a BTI Model 607 seven-channel second order biomagnetometer with 18-mm coil diameter and 4-cm baseline. A custom bite plate was fabricated for each subject. Sufficient measurements cen-
tered over the temporal lobe were made using five instrument positions (5 × 7 = 35 B-field measurements) on each hemisphere to assure adequate modeling of both generators with a single equivalent current dipole (ECD) at their respective latencies. Subjects viewed a silent video throughout the duration of the recording to maintain a reasonably constant attentional state.

Stimuli were computer-generated, 30-msec duration (5-msec rise and fall), 85-dB sound pressure level (measured at the ear), 1-kHz tone pips delivered via polyurethane tubing to the ear opposite the hemisphere being recorded. The interstimulus interval was fixed at 6 sec.

A sonic digitizer was used to establish a head frame coordinate system and coregister the position of instrument. The X axis was determined by the line connecting the preauricular points (positive X is outward through the right ear). The Y axis was the line orthogonal to the midpoint of the X axis (the origin) and contained in the plane established by the X axis and the nasion (positive Y anterior). The Z axis was normal to X and Y at the midpoint and exits the top of the head (positive Z is above the origin).

Magnetencephalographic recordings were wide band (0.1–1 kHz) and digitized at a rate of 2.275 kHz. Recordings included a 200-msec prestimulus baseline and 250 msec following stimulus delivery. Artifact-free responses to 50 stimuli were averaged and then filtered with a phase invariant digital filter (24 dB/octave slope) with a pass band of 0 to 55 Hz.

Source localization analysis was performed across the entire poststimulus window from 0 to 245 msec using a single moving ECD in a conductive sphere model (Sarvas 1987) and a sliding 10-msec width time window at 1 msec increments for each hemisphere. The mean B-field amplitude for each coil for the 10-msec window (starting 5 msec before and ending 5 msec after, each time point) was computed by averaging the samples (23) in this interval. To identify the two candidate sources, a goodness of fit measure (F) was computed at each time point by dividing the root mean square (RMS) value of the error (i.e., the difference between the measured field amplitudes and the final iteration of the forward solution) by the RMS value of the data. This measure was then evaluated in the window from 60- to 145-msec poststimulus by searching for local minima in 5-msec blocks and then discarding all but the two lowest values (i.e., these are the latencies when the ECD best modeled the data). Mean latencies were 77 ± 11 msec poststimulus for the early source and 100 ± 11 msec for the late source. We have previously reported that the two sources, so determined, were significantly different from one another. Additional details are provided in Teale et al (1998).

**Statistical Procedures**

All statistical analyses were performed using Statistica 5.5 (StatSoft, Tulsa OK). Analyses were conducted using α = .05. Sums of squares for all analyses of variance designs were type III. We employed a 3 × 2 × 2 analysis of variance (ANOVA; group by hemisphere by source latency), with hemisphere and source latency treated as repeated measures and y location of the sources as the dependent variable, to test differences in source location. To examine our hypothesis concerning schizophrenia and schizoaffective disorder, two orthogonal interaction contrasts were coded within this ANOVA to test 1) whether the schizoaffective and schizophrenia groups, when combined together, differed from the control group and 2) whether the schizophrenia group and schizoaffective group differed from each other.

**Results**

The first contrast was significant \[F(1,46) = 4.03, p < .05\], indicating that schizophrenic and schizoaffective subjects differed from control subjects. The second contrast was nonsignificant \[F(1,46) = 0.03, p > .05\], indicating that schizoaffective and schizophrenic patients did not differ significantly from each other in overall source location. In control subjects, the second source was more lateralized than the first \[F(1,46) = 3.76, p < .06\]. The early and late sources were not lateralized in either patient group \[F(1,46) = 0.03, p > .05\]. Figure 1 illustrates the mean anteroposterior dipole locations for each group for the early and late source.

**Discussion**

Our findings suggest the second subcomponent could be a major contributing factor to the laterality differences previously reported for the combined M100 in schizophrenia. Thus, experimental demands, or signal processing differences that inadvertently emphasize one of the two subcomponents, could influence the laterality differences reported in the literature. Low-pass filtering, for example, would likely preferentially emphasize the subcomponent with the highest amplitude (assuming the subcomponents are similar in waveform) and so shift source parameter estimates. A recent report by Rockstroh and colleagues (Rockstroh et al 1998) demonstrated a failure in the development of contralateral dominance in patients with schizophrenia as indexed by M100 ECD strength. Source estimates, however, did not differentiate between control subjects and patients with respect to left–right, anterior–posterior location. In this case, data were low-pass filtered at 20 Hz. Consideration of a two source model might produce a larger difference in these parameters.

Anomalalous lateralization of the M100 component previously described in patients with schizophrenia has been suggested to reflect evidence of a different cortical organization in schizophrenia (Rojas et al 1997). The present findings do not directly address the issue of cortical organization but suggest that such work might profitably include independent consideration of the several subcomponents contributing to the M100. Schizophrenic subjects did not differ from subjects with schizoaffective disorder on this metric, implicating a commonality of the temporal lobe pathology in the schizophreniform psychoses. Sub-
jects with affective psychoses have yet to be studied in this regard.

The M100 complex has previously been associated with auditory sensory memory or echoic memory (Imada et al. 1993; Lu et al. 1992; Sams et al. 1993). Lu et al. (1992) suggested that two components of the M100 complex, what they termed L100m (an earlier, posterior component) and N100m (a later, more anterior component) had different trace lifetimes and suggested different functional roles for each source. In a later paper, Sams et al. (1993) also observed two sources underlying the M100 complex, which they termed N100mp and N100ma (early posterior and later anterior, respectively). Sams et al. (1993) also observed differing trace decays for the two sources, with the N100mp exhibiting shorter time constant of decay than the N100ma, in agreement with the findings of Lu et al. (1992). Loveless et al. (1996) suggested that these two sources might reflect the short and long term auditory stores first proposed by Strous and colleagues (Strous et al. 1995) on the basis of behavioral data. Our data indicate that the differences between the control group and two psychotic groups are largely confined to the later source (N100ma), suggesting an impairment in the longer term auditory store. By implication, experimental paradigms with different memory demands may preferentially activate one subcomponent. If, for example, the amplitude of one was increased, the apparent localization of the combined source might appear to move forward or backward. It might be important to determine the extent to which attentional mechanisms may be involved in the activation of the second course. Such mechanisms, thought to be disturbed in schizophrenia, might preferentially alter strength of location of this source. Clearly, there are concerns relating to the variable nomenclature of these auditory evoked field components, which to date, in the absence of agreed upon terminology, tend to be laboratory specific. We hope our discussion will help relate the somewhat varying nomenclatures.

One caveat in considering these findings is that they are based on a sequential source model. Improvements in the accuracy of localization might be obtained with the application of a true two-source model in the time window during which both sources are active. This might involve a two-pass modeling strategy wherein the first pass would be as reported here and the second pass would involve a pair of simultaneously active spatiotemporal ECDs covering the latency window between the two sources identified in pass one.

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References


