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Schizoaffective disorder – a possible MEG auditory evoked field biomarker

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Abstract

We recorded MEG auditory steady state responses (SSR) from 8 schizoaffective (SAD) subjects and compared resulting data to previously published findings in schizophrenics (SZ) and controls. SAD subjects exhibited SSR responses similar to controls in the left hemisphere and greater than controls in the right hemisphere, whereas SZ subjects exhibited deficits in both amplitude and phase control in both hemispheres. Our findings suggest preservation of GABAergic inhibitory interneuronal control of layer 3 pyramidal cell activity in primary auditory cortex in SAD.

Keywords

schizoaffective disorder; magnetoencephalography (MEG); steady state response (SSR)

1. Introduction

Schizoaffective disorder (SAD), initially described by Kasinin in 1933 (Kasinin, 1933), remains an enigma in terms of how the SAD diagnosis fits in to the schizophrenia (SZ)-bipolar spectrum, a situation not well clarified by several recent reviews (Abrams, et al., 2008; Cheniaux et al., 2008). In studies of SZ, subjects with SAD are often included in the SZ cohort, suggesting belief in a common pathophysiology. One of the more interesting electrophysiological abnormalities described in SZ is the EEG evoked potential (EP) response to auditory stimuli delivered at a repetition rate of 40Hz, often termed the steady state response (SSR). Auditory stimulation at 40Hz entrains the auditory neocortex at the stimulation rate, and the amplitude and phase locking of the resultant EP have both been found to be deficient in SZ (Kwon et al, 1999; Light et al., 2006; Spencer et al., 2008). Recent magnetoencephalography (MEG) studies have suggested the abnormal SSR in SZ is primarily due to impaired phase locking in the left hemisphere, which also results in an apparent amplitude decrement (Teale et al., 2008). We recently have had the opportunity to study a small cohort of SAD subjects recording MEG in the auditory SSR paradigm, and found results at variance with those in SZ. Those results are reported in this paper.

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2. Methods

All subjects received a full explanation of the experimental procedures in accordance with the guidelines of the Colorado Multiple Institutional Review Board, and signed informed consent.

2.1. Subjects

We studied eight right handed (mean Annett score = 0.78) (Annett, 1998) patients with SAD (three female, mean age 35.9 ± 11.5). We compared their data with that of fifteen subjects with SZ (2 female, mean age 37.9 ± 9.3), and fifteen comparison subjects (3 female, mean age 34.8 ± 8.0). The latter two groups' data has been previously reported in Teale et al, 2008. Diagnosis was determined using the Structured Clinical Interview for DSM-IV (SCID), and information from medical records. All patients were taking at least one atypical antipsychotic medication. SAD subjects were also taking antidepressant and/or mood stabilizing medications.

2.2. Stimuli and MEG recording

Steady state responses were produced using 500 ms duration 60 db HL 1 kHz sine waves amplitude modulated by 40 Hz sine waves. Stimuli were repeated every 3.5 seconds for 200 or more trials at each ear (monaural presentation) using foam insert earpieces. Magnetic evoked fields were recorded in the supine position using a whole head neuromagnetometer (Magnes 3600 WH) while subjects watched a silent video.

2.3. Data analysis

Detailed methods are provided in Teale et al. (Teale et al., 2008). Briefly, the MEG data were modeled with a single dipolar source in each hemisphere, which was then used with the method of source space projection to estimate the time course of the individual trial source strengths. These estimates of cortical current were then convolved with complex Morlet's wavelets to calculate inter-trial phase locking factor (PLF) and mean source strengths for frequencies between 20 and 70 Hz. Contralateral PLF and mean envelope of evoked source strength at 40 Hz (the modulus of the mean of the convolutions across trials) were analyzed statistically in two separate time windows: a transient gamma band region from 20 to 100 ms post stimulus onset, and the steady state region between 200 and 500 ms post stimulus. SPSS 16 was used to evaluate all statistical models. Each dependent variable was modeled using a 2×2 (group by hemisphere) ANOVA, with hemisphere treated as a repeated measure, and evaluated for significance at $\alpha = .05$. The group main effect was followed on with post-hoc Fisher's LSD tests to examine group differences in greater detail in main effects and/or interactions.

3. Results

The **transient** gamma band PLF demonstrated a significant main effect for both hemisphere and diagnosis. The right hemisphere exhibited significantly higher phase locking than the left ($p < .05$). Controls had significantly higher PLF values than the SZ group ($p = .01$), but were not significantly different from the SAD subjects ($p = .49$).

For the **steady state** region the right hemisphere had greater amplitudes than the left, $F(1,35) = 33.26$, $p < .001$. The group by hemisphere interaction was also significant, $F(2,35) = 8.04$, $p < .01$. Posthoc comparisons indicated that in the right hemisphere, the schizoaffective group had significantly higher evoked amplitudes than either the controls ($p = .02$) or the schizophrenia group ($p = .002$). The **steady state** PLF revealed both a significant group main effect $F(2,35) = 7.36$, $p < .01$ and a hemisphere main effect ($F(1,35)$

= 43.24, $p < .001$) with a higher phase-locking factor in the right hemisphere. The group by hemisphere interaction term was significant, $F(2,35) = 4.60$, $p < .02$. In the left hemisphere controls had significantly higher phase-locking than the SZ subjects ($p = .01$), but were not significantly different from the SAD subjects ($p = .15$). Additionally, the SAD subjects had significantly higher PLF values than the SZ subjects ($p = .001$). In the right hemisphere, while SZ subjects also had lower PLF values than controls ($p = .05$), SAD subjects had higher PLF than both controls ($p = .01$) and SZ subjects ($p = .001$).

Figure 1 illustrates the gamma band phase locking factor for the three groups.

4. Discussion

These findings support preservation of MEG auditory evoked SSR amplitude and phase locking factor in SAD, compared to impaired phase control previously described in MEG studies of SZ subjects which were consistent with Andreasen's notion of "cognitive dysmetria" as a fundamental processing deficit in schizophrenia (Andreasen et al., 1998). Such SSR amplitude and phase control metrics likely reflect efficiency of GABAergic inhibitory interneuronal activity controlling the timing of layer 3 AI pyramidal cells (Teale et al., 2008), which would also be expected to impact improved performance of secondary auditory cortex (AII) in its multiple functions, possibly including auditory prosody which is thought to depend extensively on the proper functioning of right hemisphere, perhaps especially right hemisphere middle and superior temporal gyri (Mitchell et al., 2003) wherein both primary and secondary auditory cortex as well as the generators of the SSR activity we report reside. Auditory emotional prosody is significantly impaired in SZ (Hoekert et al., 2007), where it may be an independent predictor of outcome (Kee et al., 2003), but has not been independently reported in SAD. In the right hemisphere SAD subjects exhibited amplitudes and PLF's greater than controls. This observation, if replicated, may suggest increased inhibitory control, the implications of which are not clear at this point.

All of our subjects were medicated, and the role of medication in influencing MEG metrics of this type is unknown. In SZ subjects, the 40Hz SSR has been shown to be possibly increased by atypical antipsychotics (Hong et al., 2004), and the benzodiazepine-like agent MK-0777 with selective activity at GABA_A receptors has been shown to increase induced frontal gamma band activity in SZ (Lewis et al., 2008). Effects of such agents on gamma activity in SAD have not been reported, but presumably would be similar, and there is no reason to suspect their influences on MEG activity would be substantially different than on EEG, essentially in the direction of normalizing differences.

Martin et al suggest there may be subdivisions within the schizoaffective classification based upon variation in genetic and physiological measures relating to possible endophenotypes (Martin et al., 2007), and Gruber and colleagues have suggested that preservation of articulatory rehearsal in verbal working memory may constitute a neurocognitive endophenotype separating SAD from SZ (Gruber et al., 2006). Certainly such observations along with our findings would support further evaluations of schizoaffective disorder as a possible independent entity.

In summary, our findings while preliminary and in need of replication in a larger patient cohort, suggest a difference in SAD patients, compared to SZ, with relative preservation of left and right auditory cortex GABAergic interneuronal inhibitory control of pyramidal cell timing, which would support SAD as a phenotype independent of SZ at least in this domain.

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Figure 1. Auditory SSR phaselocking factor (PLF) by time in left and right hemispheres for our 3 subject groups. Upper panels controls, center panels SAD, lower panels SZ. PLF values range from 0 (no evidence of phase locking) to 1.0 (perfect phase locking).