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MEG auditory evoked fields suggest altered structural/functional asymmetry in primary but not secondary auditory cortex in bipolar disorder

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Abstract

Objectives—Objective physiological indices independently characterizing affective and schizophreniform psychoses would contribute to our understanding of the nature of their relationships. Magnetoencephalography (MEG)-based metrics of altered structural/functional asymmetry in the superior temporal gyrus have previously been found to characterize schizophrenia at the level of both the primary auditory (AI) and the secondary auditory (AII) cortex. This study examines these markers in patients with bipolar disorder, with the goal of improved understanding of the patterns of brain asymmetry that may independently characterize affective and schizophreniform psychosis.

Methods—We studied 17 euthymic bipolar subjects and 17 matched controls. Auditory evoked fields were generated by both 40 Hz auditory stimuli eliciting steady state gamma band (SSR), activating the AI cortex, and discrete 1 kHz tone pips, activating the AII cortex. MEG was recorded from the hemisphere contralateral to the ear stimulated using a 37-channel MEG system. Source location estimates were calculated in both left and right hemispheres. Neuroanatomical location estimates for medial Heschl's gyri were determined from magnetic resonance images for correlation with MEG source locations.

Results—Bipolar subjects failed to demonstrate normal laterality of SSR AI responses, indicating altered patterns of asymmetry at the level of AI cortex, but demonstrated normal asymmetry of AII responses (right anterior to left). Medial Heschl's gyri centroids were similarly lateralized in both groups, however (right anterior to left), dissociating function from structure in the AI cortex in the bipolar group.

Conclusions—The findings are compatible with altered functional/structural relationships, including diminished left-right hemisphere asymmetry of the AI, but not the AII cortex in bipolar disorder. In schizophrenia, both the AI and AII cortices exhibit such derangements; thus, the findings support both shared and nonshared features of auditory cortical disruption between the two disorders. This functional disorganization may help explain previously reported decreases in amplitude and phase synchrony of SSR gamma band responses in bipolar subjects suggesting impaired neocortical synchrony in AI, possibly at a cortico-thalamic level, but perhaps not

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extending to heteromodal association cortex, and may relate to the cognitive impairments found in bipolar disorder.

Keywords

auditory cortex; auditory system; bipolar disorder; evoked fields; gamma band; M100; magnetoencephalography; schizophrenia; SSR

The relationship between schizophrenia and bipolar disorder has been a topic of considerable long-term interest, with viewpoints ranging from considering them the same basic disorder with variable phenotypic expression to entirely separate disorders. Kraepelin initially suggested a dichotomy between cognitive (e.g., schizophreniform) and affective (e.g., bipolar) disorders (1), but later authors have generally preferred a continuum model, with bipolar disorder and schizophrenia on opposite poles of a dimensional continuum. Proponents of this view have included Menninger (2) and more recently Crow (3), who have suggested that the psychoses are not a group of different disorders, but rather may reflect the variable expression of a single gene. Kendler and colleagues (4), however, examining the genetic data from the Roscommon Family Study, have stated, “These results suggest a relatively complex typology of psychotic syndromes consistent neither with a unitary model nor with a Kraepelinian dichotomy.”

Our understanding is compromised by the relative dearth of common pathophysiological measures characterizing these disorders. One physiological metric that has been noted by investigators in several laboratories to characterize patients with schizophrenia has been evidence of anomalous left-right asymmetry of auditory evoked field (EF) sources generated in both the primary auditory (AI) and the secondary auditory (AII) cortex, suggestive of cortical disorganization as well as anomalous left-right brain asymmetry at the level of the superior temporal gyrus (STG).

Initial reports of anomalous asymmetry of magnetic auditory EFs involved recordings of the major auditory EF component, occurring about 100 ms post stimulus receipt and termed the M100. This component is generated primarily in AII on the lateral aspect of Heschl’s gyrus and anterior bank of the temporal planum (5-9).

In 1989, the M100 was reported to demonstrate anomalous asymmetry in subjects with schizophrenia based on recordings with a single-channel gradiometer, with M100 source locations exhibiting less interhemispheric lateralization, and localized generally somewhat further anteriorly in the left hemisphere compared to nonschizophrenic control subjects (10). Subsequent reports from investigators in Finland (11) and Germany (12-15), as well as North America (10,16,17), also described anomalous, usually decreased lateralization of the M100, suggesting that it is a robust finding.

Addressing the issue of whether the anomalous lateralization reflected altered localization of Heschl’s gyri in schizophrenia, Rojas et al. (18) compared M100 functional lateralization to Heschl’s gyri structural lateralization in schizophrenia by computing the centroid of Heschl’s gyri in both hemispheres [obtained from magnetic resonance imaging (MRI) images]. This study found that both groups exhibited right anterior to left asymmetry, and demonstrated no statistically significant differences. The implication was that individuals with schizophrenia displayed cortical disorganization such that the functions subserving M100 generation were displaced compared to nonschizophrenic subjects.

Teale and colleagues provided data supporting the concept that the M100 was likely a composite component incorporating two subcomponents with latencies of approximately 75 (M100a) and 100 (M100b) ms (19), both of which were shown to exhibit abnormal

asymmetry in schizophrenia (20). This abnormal functional location and asymmetry of auditory EF sources with evidence of normal structural location of Heschl's gyri again supported the concept of cortical reorganization in the AII cortex in schizophrenia.

To date however, lateralization of the magnetoencephalography (MEG) M100 components generated in AII have not been described in patients with bipolar disorder, nor have estimates of lateralization of Heschl's gyri centroids been published in bipolar patients.

Subsequent studies utilized paradigms designed specifically to activate the AI cortex. Auditory stimulation at 40 Hz produces a steady state response (SSR) whose source generators are thought to be restricted to the AI cortex on the medial aspect of Heschl's gyri (5,21-23). There is some individual as well as interhemispheric variability of absolute location of auditory koniocortex with respect to Heschl's gyrus; while primarily restricted to Heschl's, there may be some koniocortex on the anterior temporal planum immediately adjacent to the postero-medial aspect of Heschl's (24). The SSR response represents the driving of the AI cortex at a resonant frequency in the gamma band range. This early AI component demonstrates abnormal (decreased) laterality in patients with schizophrenia compared to controls compatible with a developmental disturbance of cerebral asymmetry (25), but again, such measures have not been previously reported in bipolar subjects.

The present study was undertaken for the purpose of investigating, in patients with bipolar disorder, the source location of those auditory EF components previously found to demonstrate anomalous asymmetry in schizophrenia, including the SSR generated in the AI cortex, and the M100a and M100b components generated in the AII cortex. We also computed the centroids of the medial aspect of Heschl's gyri in these bipolar subjects to allow correlation of function (SSR source location) with the structural location of the purported source generators (medial Heschl's gyri). We believe such data will contribute to our improved understanding of the relationship between affective and schizophreniform illness on the basis of objective physiological measurements.

Since the SSR and M100 components are generated by fundamentally different experimental design and data-processing methods, the methods and results of the M100 and SSR experiments will be reported separately, as will the methods and results for anatomical determination of medial Heschl's gyri centroids.

Patients and methods

Study population

Subjects included 17 (8 male) currently euthymic (not meeting DSM-IV criteria for either mania or depression) patients with bipolar disorder (10 with a history of psychosis during mood episodes and seven with no history of psychosis), and 17 normal controls. Study participants were recruited from the Denver-Boulder (CO, USA) community, and bipolar patients were in outpatient treatment. After the procedures were fully explained, written informed consent was obtained from all subjects in accordance with the guidelines of the Colorado Multiple Institutional Review Board. Subjects and controls were aged matched since we have previously demonstrated that SSR responses may vary as a function of subject age (26).

Diagnosis was determined using the Structured Clinical Interview for the Diagnostic and Statistic Manual of Mental Disorders, 4th edition (SCID) (27) and a review of medical records. SCIDs were performed by a person trained in SCID administration under the supervision of the first author. Exclusionary criteria included any medical illness affecting central nervous system function, neurological disorder, history of head trauma, and current

substance abuse. Controls were community volunteers recruited to participate in our neuroimaging studies of psychosis. Controls met the same exclusionary criteria, had no Axis I disorder, and had no first-degree relative with an Axis I diagnosis. All but one of the subjects were right handed (28), and all subjects were tested for hearing acuity.

The groups were matched for gender composition (nine women and eight men each). The ages of the subjects with bipolar disorder (39.41 ± 8.95 years) did not differ significantly from the controls (36.59 ± 8.96 years), $t(32) = 0.92$, $p > 0.10$. The subjects with bipolar disorder and control subjects also did not differ significantly in terms of handedness (bipolar: 0.84 ± 0.15 ; control: 0.75 ± 0.56), $t(32) = 0.68$, $p > 0.10$. However, the control subjects had significantly higher mean education levels (16.59 ± 1.84 years) compared to the subjects with bipolar disorder (14.00 ± 2.35 years), $t(32) = 3.58$, $p < 0.002$.

A total of 14 of the 17 bipolar subjects were medicated, with 6 taking mood stabilizers, 9 antipsychotics (3 subjects were taking two separate antipsychotic medications), and 9 antidepressants (one subject was taking two separate antidepressant medications). Nine of the 17 patients with bipolar disorder were taking 12 medications for which chlorpromazine equivalency has been reported (29). Their mean dose at the time of study was 315.56 mg/day (SD = 356.56). Subject demographic information is shown in Table 1.

General MEG recording/analysis procedures

Magnetic field data from the hemisphere contralateral to the ear being stimulated were obtained with a Magnes I 37-channel superconducting biomagnetometer (4-D, San Diego, CA, USA), located inside a magnetically shielded room. Data were collected using a 16-bit A/D converter with a sampling rate of 1041.7 Hz. Gain was set to produce a resolution of approximately 1.5 fT. Raw data were notch filtered at 60, 120, and 180 Hz using a custom-built tracking, fourth order, elliptic filter with 40 dB of attenuation (National Semiconductor, Data Acquisition Databook, 1995, LMF90 4th order LMCMOS programmable elliptic notch filter). Additional bandpass filtering was achieved using a 1-Hz single pole analog highpass filter and a 200-Hz lowpass.

Fiducial points (left and right pre-auricular points and nasion) were used to establish a coordinate system defined as: y-axis being the line between the pre-auricular points (left-right), positive left; x-axis being perpendicular to the y-axis at the midpoint and contained in the plane formed by the nasion and pre-auricular points thus being anterior-posterior in direction; and z-axis being perpendicular to the x-y plane (up-down), positive up. Each source estimate thus had an x, y, and z coordinate with reference to this coordinate system.

Magnes (MSI) data files were converted, using our own software, to SCAN (NeuroSoft, Inc., Herndon, VA, USA) 4.0 data format and custom coil location files to facilitate both automatic and interactive artifact rejection. All subsequent signal processing, with the exception of source modeling, was done using the SCAN software. Source modeling employed our own custom software (30), fitting a single equivalent current dipole (ECD) in a homogeneous conductive sphere (31) at individual time points. Coil coordinates were translated to a generic best-fit sphere system prior to source analysis as described in Teale et al. (32).

Statistical methods

Statistica 6.1 (Statsoft, Tulsa, OK, USA) was used for statistical analyses. All significance tests were two-tailed and evaluated for significance at 0.05 alpha. For demographic variables (e.g., age, education, etc.) independent Student *t*-tests were conducted to assess group differences. To evaluate the primary hypothesis concerning reduced anterior-posterior

asymmetry, a $2 \times 2 \times 2$ ANOVA (group $\times$ hemisphere $\times$ component) was performed on the x-coordinates derived from the MEG source analyses described below.

M100 Methods (All cortex)

M100 auditory stimulation and data analysis

M100 source locations over left and right hemispheres were obtained using a paradigm in which stimuli were 30 ms 80 dB SPL 1-kHz tone bursts ($n = 200$, ISI = 4 sec) delivered to the contralateral ear. Data were acquired in 450 ms epochs with a 200 ms prestimulus interval. Averaged data were low pass (forward/backward Butterworth, 24 db/octave) filtered at 50 Hz and DC offset corrected relative to the prestimulus mean. Source generator locations were estimated using a single moving dipole model. The M100 was conceived as a complex component, having been produced by two temporally consecutive generators in each hemisphere providing estimates for an early and late source as previously described in this laboratory (19). The auditory EFs were evaluated over the time window from 50 to 120 ms following stimulus onset. ECDs were fit at 1-ms intervals using a sliding 10-ms width window wherein the mean B-field amplitude for each coil for the 10-ms window (starting 5 ms before and ending 5 ms after each time point) was computed by averaging the samples (10) in this interval. A search through this time period (50 to 120 ms) was then conducted to determine the maximum root mean square (RMS) field amplitude subject to the constraint that the ECD at that latency had to have a negative vertical strength component (Q_z), i.e., the dipole had to be downward pointing. Next, the full-width-half-maximum (FWHM) RMS latencies were determined using this latency as the center. Two subwindows were then defined from the first FWHM latency to the center and from the center to the second FWHM. Within these subwindows, the ECD parameters were then averaged if the individual ECDs met the following criteria: the absolute value of the y (medial-lateral) location coordinate was greater than 2.5 cm; the value of the z (superior-inferior) location coordinate was less than 7 cm; the magnitude of the source strength $\|Q\|$ was less than 200 nA-m, and the goodness of fit, F (defined as the RMS error divided by the RMS data), was < 0.4 (this corresponds to a threshold of > 0.84 using the more typical MEG F of 1—the squared error/squared data). A typical M100 waveform is illustrated in Figure 1.

M100 Results

We were able to obtain dipole fits for both early and late components on 13 subjects with bipolar disorder and 13 matched control subjects. To evaluate the early and late M100 subcomponents, a $2 \times 2 \times 2$ mixed model ANOVA (group by hemisphere by component) was evaluated separately for the x, y, z, Q, theta, and latency variables. The main effect of diagnosis on x-coordinate values was not significant [$F(1,24) = 1.11$, $p > 0.05$, partial $\eta^2 = 0.08$]. Similarly, the diagnosis-by-component interaction [$F(1,24) = 0.13$, $p > 0.05$, partial $\eta^2 = 0.005$], the diagnosis-by-hemisphere interaction [$F(1,24) = 1.05$, $p > 0.05$, partial $\eta^2 = 0.04$], and the diagnosis-by-component-by-hemisphere interaction [$F(1,24) = 1.39$, $p > 0.05$, partial $\eta^2 = 0.05$] were all nonsignificant, indicating no diagnosis interaction effects for the x-coordinate. There was a significant hemisphere main effect [$F(1,24) = 21.68$, $p < 0.0001$, partial $\eta^2 = 0.48$], indicating that for both groups and both M100 subcomponents, the right hemisphere source location was significantly anterior to the left. There was also a significant component main effect [$F(1,24) = 41.69$, $p < 0.0001$, partial $\eta^2 = 0.08$, partial $\eta^2 = 0.64$], indicating that for both groups and both hemispheres, the later M100 subcomponent was located anteriorly to the earlier subcomponent. For the y-coordinate, the only significant effect was for hemisphere [$F(1,24) = 14.10$, $p < 0.001$, partial $\eta^2 = 0.37$], indicating that the sources in the right hemisphere were slightly more lateral than those in the left. No significant effects were observed for the z-coordinate, Q, or theta. For source latency, a significant main effect of component was observed [$F(1,24) = 1189.8$, $p < 0.0001$, partial η^2

= 0.98]. Sources in the left hemisphere were also noted to be significantly longer in latency than those in the right [$F(1,24) = 23.42$, $p < 0.0001$, partial $\eta^2 = 0.49$]. No other significant latency effects were apparent. Tables 2 and 3 present the means and standard deviations for the early and late M100 subcomponents, respectively.

There were no significant group differences or group interaction terms for the y- and z-coordinate values (y being left-right, z being up-down), source strengths, source latencies, and orientations, which were separately evaluated in ANOVA models identical to the model used for the x-coordinate.

Overall, we found no significant difference between bipolar subjects and controls in these MEG-based metrics of AII function/structure relationships previously shown to separate schizophrenics from controls.

SSR Methods (AI cortex)

SSR auditory stimulation and data analysis

SSR stimuli consisted of 2 ms, 65 dB SPL, biphasic (as measured at the earpiece) pulses delivered every 25 ms for a total of 500 ms. These pulse trains were repeated to each ear (i.e., monaural presentation) 150 times every 1.5 seconds. Data were acquired in 1-sec epochs with a 200-ms prestimulus baseline. An illustration of a typical SSR waveform is displayed in Figure 2.

Averaged data were digitally (forward/backward Butterworth) bandpass filtered from 35 to 45 Hz. Signal-to-noise ratio (SNR) tests were performed on each channel by dividing the RMS amplitude of the poststimulus response from 50 to 550 ms by the RMS value of the 200 ms prestimulus response. Channels with SNRs lower than 1.2 were excluded from the following evaluations. Source localization was performed across the window from 10 to 600 ms using a sliding 5-ms width window at 1-ms increments. The mean amplitude for each channel (starting 2.5 ms before and ending 2.5 ms after each time point) was computed by averaging the samples in this interval.

These procedures resulted in 590 ECD estimates per hemisphere. For each estimate, a goodness-of-fit parameter F was computed. A search for minimum F values in this dataset from 50 to 550 ms typically yielded 40 time points—two for each stimulus pulse, separated by about 12.5 ms. It has been reported that these ECD estimates are consistent over the response window (21,33). Hence, dipole coordinates were averaged across these time points, subject to the constraint that the fit be better than 0.45 (> 0.80 using the common MEG F).

Results: SSR

To evaluate the SSR dipole fits, separate 2×2 model (group by hemisphere) ANOVA designs were computed for the x, y, and z coordinates, with hemisphere treated as a repeated measure. We found a significant main effect of hemisphere which suggests that sources were more anterior in the right hemisphere than in the left [$F(1,32) = 6.15$, $p < 0.02$, partial $\eta^2 = 0.16$]. The group main effect was not significant [$F(1,32) = 0.14$, $p > 0.10$, partial $\eta^2 = 0.004$]; however, the interaction term was significant [$F(1,32) = 5.79$, $p < 0.03$, partial $\eta^2 = 0.15$], indicating that the asymmetry was only present for control subjects. No significant main effects or interactions were observed for the y- or z-coordinate data. However, a strong trend was noted for the z-coordinate interaction term [$F(1,32) = 4.12$, $p = 0.051$, partial $\eta^2 = 0.11$], suggesting that while for control subjects the right source was superior to the left, no such hemispheric asymmetry was observed in the subjects with bipolar disorder. SSR results are presented in Table 4.

Methods: Medial Heschl's gyri centroid estimations

T1 weighted MRI images of the brain (124 contiguous 1.7mm coronal slices encompassing the entire head) were obtained from all subjects using a 1.5T GE MRI instrument at the University of Colorado Hospital. DICOM image sets were transmitted to the MEG laboratory, and IDL software was used for image processing. Rules for identification and cutting of Heschl's gyri were as described by Rojas et al. (18). Briefly, Heschl's gyri were manually segmented from the coronal series by ER, who was blind to subject classification. For each hemisphere, the medial one half of the total segmented volume was isolated and its centroid calculated. These centroid locations were identified by x, y, and z locations in the MEG headframe system to permit comparison with MEG-determined SSR locations in the same headframe.

For medial Heschl's gyrus centroid data, separate 2×2 mixed model ANOVAs were evaluated for the x, y, and z coordinates, and transformed into the same coordinate system as the MEG data to facilitate comparison. The volumes of Heschl's gyri were also evaluated in a separate, identical design.

An illustration of a typical SSR source location in left and right hemispheres superimposed upon STG anatomy from the same subject is illustrated in Figure 3. This figure, obtained from a typical control subject, shows both medial Heschl's centroids (red circles) and SSR source locations (white circles) to be asymmetric, being relatively more anterior in the right hemisphere. The SSR source in the left hemisphere lies over the junction of Heschl's gyrus and the temporal planum adjacent to posterior-medial Heschl's, consonant with the extent of auditory koniocortex as described by Galaburda and Sanides (24).

Results: Medial Heschl's gyrus

The absolute values for medial Heschl's centroid localizations are provided in Table 5. The group main effect for the x-coordinate was nonsignificant [$F(1,32) = 0.01$, $p > 0.05$, partial $\eta^2 < 0.00$], while the hemisphere main effect was significant [$F(1,32) = 7.26$, $p < 0.02$, partial $\eta^2 = 0.19$], indicating that the right medial Heschl's centroid was further anterior than the left hemisphere centroid. The interaction term was nonsignificant [$F(1,32) = 0.94$, $p > 0.05$, partial $\eta^2 = 0.03$]. For the y-coordinate, no significant main effects or interactions were observed. However, a possible trend was noted for the main effect of diagnosis [$F(1,32) = 3.10$, $p = 0.09$, partial $\eta^2 = 0.09$], suggesting that medial Heschl's centroids for control subjects tended to be more laterally located than those of subjects with bipolar disorder. For the z-coordinate, the diagnosis main effect was significant [$F(1,32) = 4.21$, $p < 0.05$, partial $\eta^2 = 0.12$], indicating that control subjects had more superiorly located medial Heschl's gyri centroids than subjects with bipolar disorder. The hemisphere main effect and group-by-hemisphere interaction term were not significant for the z-coordinate. For medial Heschl's volumes, there was no significant diagnosis or diagnosis-by-hemisphere effect. However, the volumes of the left medial Heschl's gyrus were significantly larger than the right hemisphere across both groups [$F(1,32) = 9.06$, $p < 0.005$, partial $\eta^2 = 0.22$].

Discussion

The finding in the AI cortex in our bipolar subjects is quite similar to that previously described in patients with schizophrenia in terms of significantly diminished lateralization of SSR sources in left and right hemispheres. The auditory SSR generators fail to exhibit the same degree of left-right interhemispheric asymmetry as found in control subjects (as is also the case in schizophrenia). Medial Heschl's gyri centroid asymmetry, however, a putative marker reflecting AI location, is similar in bipolar subjects and controls, indicating that the

relationship of the estimated source generators to the anatomical metric of medial Heschl's gyri centroids is at variance in bipolar subjects, again as is the case in schizophrenia. On these measures, then, bipolar and schizophrenic subjects demonstrated quite similar abnormalities. A composite illustration of the locations of the SSR gamma band generators in the bipolar and control subjects described in this paper as well as in previously published localizations of SSR generators in schizophrenic subjects is provided in Figure 4.

Of interest in Figure 4, in addition to the diminished laterality of sources in both bipolar and schizophrenic subjects, is the possible evidence of a more general anterior placement of sources in both hemispheres of the schizophrenic subjects, possibly related to a greater degree of developmental cortical disorganization in schizophrenia.

This difference in source laterality is not seen in the later M100 components, however, which, while demonstrating abnormal (decreased) asymmetry in schizophrenia appear to demonstrate similar asymmetry in bipolar disorder as in controls. Overall, then, this assembly of findings supports the concept of a continuum, as has been suggested by Crow and others. An illustration of the source localization values for both M100 components for the bipolar subjects in this paper compared to previously published values for schizophrenic subjects is illustrated in Figure 5.

Lack of significant differences in location and lateralization of the M100 components in the bipolar patients in this study, previously shown to be abnormal in patients with schizophrenia, could be related to the fact that these later components are generated primarily in the AII cortex, most likely more closely related to the heteromodal association cortex that Schlaepfer and colleagues (34) found selectively reduced in schizophrenia compared to bipolar disorder.

While disturbances in brain asymmetry may reflect a disturbed neurodevelopmental trajectory, specific mechanisms or genetic or epigenetic contributions remain obscure. Twin studies of brain and planum temporale asymmetry support both genetic and epigenetic influences (35,36). Crow (37) has suggested that brain asymmetry is uniquely developed in the hominid line, relating to the development of language, and has suggested the protocadherin XY gene in the Xq21.3/yp region as a candidate to determine brain asymmetry. Such measurements have yet to be incorporated in MEG studies of brain asymmetry. Our findings include several other structural differences in the bipolar cohort, including a slightly lower placement of medial Heschl's centroids in the bipolar subjects compared to controls ($p < 0.05$), as well as a strong trend toward a slight relative lateral displacement ($p = 0.066$). While supporting an alteration in neuronal development, we do not consider these findings sufficiently robust nor our subject N sufficiently large to say anything other than that they might be considered as interesting variables in future studies.

Altered neuronal migration patterns, either genetic or epigenetic or both, could be reflected in the apparent altered location of auditory functional mechanisms with respect to more coarse structural anatomy (e.g., medial Heschl's gyri centroids). Recent findings in molecular cytogenetics concerning the role of altered DISC-1 proteins as they may impact neuronal migration might be considered in this regard. DISC-1 proteins are involved in neuronal migration, neurite formation, synaptogenesis, and glutamatergic and GABAergic transmission (38,39). Evidence that they appear to cosegregate with psychotic disorders as well as disturbed cognitive function, also seen in psychosis, supports a common pathophysiology contributing to a possible schizophrenia–schizoaffective disorder–bipolar continuum (40). Again, however, MEG studies have not yet incorporated such metrics, although they could perhaps guide future experimental design.

Most of our subjects were medicated, and the role of specific medications in influencing MEG-based metrics of this type remains largely unknown. Current thinking generally supports the notion that mood-stabilizing and antipsychotic medications may serve to normalize otherwise disturbed function, but data specifically related to these metrics are not yet available.

The relationship of structural/functional abnormalities such as these to physiological functions of the AI cortex or possible auditory perceptual alterations in bipolar disorder is not yet understood. For the most part, few studies of auditory processing exist as compared, for example, to schizophrenia. Several studies have been conducted by Bruder's group which have found evidence of difficulties in detecting transient auditory signals in patients with affective psychosis (41), differences in auditory processing of dichotic stimuli in patients with affective disorders possibly related to lateralization variables or measures of processing asymmetry (42), and evidence of impaired sensory processing of complex tones in the right hemisphere of manic patients (43). Whether these were state versus trait findings is uncertain, although the 1994 study (43) suggested that the finding may be state related, as performance improved in the euthymic state. At this point, additional research is required to relate either the functional/structural abnormalities described here or the gamma phase control abnormalities described by Maharajh et al. (44) to specific measures of auditory processing.

The SSR generated by auditory stimuli produces both evoked and induced gamma band responses centered around 40 Hz that are thought to reflect the function of GABAergic inhibitory mechanisms. Scalp electroencephalography studies have reported abnormalities in both amplitude and phase control of these gamma band responses in both schizophrenic (45,46) and bipolar (47) subjects. More recently, MEG studies have suggested that these abnormalities in SSR gamma amplitude and phase control in both bipolar and schizophrenic subjects reflect dysfunction at the level of medial Heschl's gyri, most likely resulting from dysfunction of GABAergic inhibitory interneuron function mediating layer 3 pyramidal cell firing in the AI cortex (44,48); dysfunction of GABAergic inhibitory systems in bipolar disorder has been suggested by a number of clinical and preclinical studies (49).

It is of interest that both DRD4 alleles and DAT1 polymorphisms have been shown to modulate the AI cortex-generated gamma band response to auditory stimulation (50), and there is evidence of both DRD4 on the short arm of chromosome 11 (51) and DAT1 (52) involvement in bipolar disorder, where similar gamma band abnormalities have been described (44). It is not unreasonable to suggest that such genetic factors might also be involved in the development of the abnormalities described in this paper, but such data do not yet exist.

Summary

This study suggests that bipolar subjects exhibit evidence of AI functional structural dissociation of a type similar to that found in schizophrenia, but no evidence of similar AII abnormalities. The findings may support a continuum hypothesis, and suggest that the neurodevelopmental abnormalities that may underlie these abnormalities are primarily restricted to the AI cortex in euthymic bipolar subjects, with wider auditory cortical disruption present in schizophrenia. Possible physiological correlations may relate to disturbance in GABAergic inhibitory interneurons as they modulate layer 3 pyramidal cell-firing patterns in the AI cortex. The relationship of such disturbances to either phenomenology or cognitive disturbances found in bipolar subjects remains to be determined, as do specifics of the relationship to possible underlying genetic mechanisms.

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Fig. 1.
Illustration of a typical M100 waveform from a control subject. y-axis = amplitude in Tesla (T); x-axis = time in msec. Stimulus occurs at time 0.

Fig. 2. Illustration of a typical steady state response (SSR) waveform from a control subject. y-axis = amplitude in Tesla (T); x-axis = time in msec. Note that SSR amplitudes are an order of magnitude less than M100 amplitudes. Stimulus occurs at time 0.

SSR Generators with Heschl's Gyri and STGs

Fig. 3.

Illustration of medial Heschl's centroid co-located on a reconstruction of left and right superior temporal gyri (STG) from a control subject. View is looking from above. Heschl's gyri indicated in green. Centroid of medial Heschl's outlined in red. SSR source indicated by white circle whose size represent 95% confidence interval.

40 Hz SSR Generator Locations By Group

Fig. 4.

Steady state response (SSR) generator locations in the left and right hemispheres by group. The squares are the means for the control subjects ($n = 17$), the circles for the schizophrenic subjects ($n = 17$), and the triangles for the bipolar subjects ($n = 17$). All units are in centimeters. The data for the schizophrenic subjects were previously published in Teale et al. 2003 (25).

Fig. 5.

Comparison of M100a (early source–left panel) and M100b (late source–right panel) location in left and right hemispheres for the bipolar ($n = 13$) and control ($n = 13$) subjects in this paper compared to previously published values from schizophrenic subjects ($n=14$) from Teale et al. 2000 (20).

Demographic characteristics of 17 patients with bipolar disorder and 17 normal comparison subjects

Table 1

Characteristic	Patients with bipolar disorder		Comparison subjects		t-statistic (df = 34)
	Mean	SD	Mean	SD	
Age (years)	39.41	8.9	36.59	9.0	-0.92
Education (years)	14.00	2.3	16.59	1.8	3.58 ^c
Parental socioeconomic status ^a	38.32	14.0	44.63	13.0	1.28
Full Scale IQ	105.94	11.90	125.94	13.41	4.60 ^d
Handedness ^b	0.84	0.15	0.75	0.56	-0.67

^a Hollingshead four-factor index score (53).

^b Annett Handedness Scale score (28). All but one of the subjects was right-handed.

^c p < 0.05.

^d p < 0.001.

Table 2

Means and standard deviations for early source M100 localizations

Study sample	Left hemisphere (cm)			Right hemisphere (cm)		
	x	y	z	x	y	z
Control (n = 13)	-0.73 ± 0.65	4.89 ± 0.34	4.44 ± 0.67	0.037 ± 0.43	-5.20 ± 0.53	4.52 ± 0.64
Bipolar (n = 13)	-0.46 ± 0.62	5.04 ± 0.29	4.47 ± 0.51	0.088 ± 0.63	-5.42 ± 0.55	4.20 ± 0.76

Table 3

Means and standard deviations for late source M100 localizations

Study sample	Left hemisphere (cm)			Right hemisphere (cm)		
	x	y	z	x	y	z
Control (n = 13)	-0.56 ± 0.61	4.97 ± 0.63	4.39 ± 0.70	0.43 ± 0.50	-5.29 ± 0.69	4.42 ± 0.73
Bipolar (n = 13)	-0.16 ± 0.65	5.00 ± 0.42	4.33 ± 0.69	0.41 ± 0.70	-5.48 ± 0.53	4.18 ± 0.68

Table 4

Means and standard deviations for 40hz steady state response (SSR) localizations

Study sample	Left hemisphere			Right hemisphere		
	x	y	z	x	y	z
Control (n = 17)	-0.80 ± 0.97	4.41 ± 0.76	4.28 ± 0.70	0.34 ± 1.07	-4.50 ± 0.80	4.68 ± 0.74
Bipolar (n = 17)	-0.39 ± 0.73	4.57 ± 0.59	4.47 ± 0.63	-0.19 ± 0.86	-4.55 ± 0.65	4.16 ± 0.70

Table 5

Means and standard deviations for medial Heschl's gyri centroids

Study sample	Left hemisphere (cm)			Right hemisphere (cm)		
	x	y	z	x	y	z
Control (n = 17)	-0.64 ± 0.87	3.78 ± 0.30	5.12 ± 0.45	-0.33 ± 0.71	-3.87 ± 0.20	5.10 ± 0.47
Bipolar (n = 17)	-0.55 ± 0.57	3.71 ± 0.34	4.86 ± 0.42	-0.34 ± 0.52	-3.78 ± 0.21	4.80 ± 0.34