Schizophrenia Bulletin vol. 37 no. 4 pp. 778–787, 2011
doi:10.1093/schbul/sbp134
Advance Access publication on November 27, 2009

The Early Auditory Gamma-Band Response Is Heritable and a Putative Endophenotype of Schizophrenia

Mei-Hua Hall[1,2], Grantley Taylor[2], Pak Sham[5], Katja Schulze[3], Fruhling Rijsdijk[4], Marco Picchioni[3], Timothea Toulopoulou[3], Ulrich Ettinger[6], Elvira Bramon[3], Robin M. Murray[3], and Dean F. Salisbury[2]

[2]Cognitive Neuroscience Laboratory, Harvard Medical School, McLean Hospital, 115 Mill Street, Belmont, MA 02478; [3]Division of Psychological Medicine; [4]Social Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry, London, UK; [5]Department of Psychiatry, University of Hong Kong, Hong Kong; [6]Department of Psychiatry, University of Munich, Germany

Background: **Reduced power and phase locking of the early auditory gamma-band response (EAGBR) have been reported in schizophrenia, but findings are equivocal. Further, little is known about genetic (heritability) and environmental influences on the EAGBR or its potential as an endophenotype of schizophrenia. The present study used a twin design to examine whether EAGBR power and phase locking are heritable and reduced in schizophrenic patients and their unaffected co-twins and thus putative endophenotypes of schizophrenia.** ***Methods:*** **The study sample included a total of 194 individuals, consisting of 15 monozygotic [MZ] twin pairs concordant for schizophrenia, 9 MZ twin pairs discordant for schizophrenia, and 42 MZ and 31 dizygotic (DZ) control pairs. Evoked power and phase-locking factor of the EAGBR were computed on Morlet wavelet–transformed electroencephalogram responses to standard tones during an auditory oddball target detection task. Structural equation modeling was applied to estimate heritability and genetic and environmental correlations with schizophrenia for the EAGBR measures.** ***Results:*** **Both evoked power and phase-locking phenotypes were heritable traits (power: $h^2 = 0.65$; phase locking: $h^2 = 0.63$). Impaired EAGBR measures were significantly associated with schizophrenia. Patients with schizophrenia and their unaffected identical co-twins exhibited significantly reduced EAGBR power compared with control subjects. In each phenotype, shared genetic factors were likely the source of the observed associations with schizophrenia.** ***Conclusions:*** **Our results support EAGBR measures as putative endophenotypes of schizophrenia, likely reflecting an ubiquitous local cortical circuit deficit.**

Key words: gamma oscillation/endophenotype/schizophrenia/twin/heritability

Introduction

There is growing interest in measuring brain electrical oscillations to study abnormal brain dynamics, synchronization, and connectivity in schizophrenia, particularly the gamma frequency band (30- to 80-Hz range, centered around 40 Hz).[1,2] Stimulus-evoked gamma-band responses (GBRs) have been associated with widespread sensory and cognitive processes including perceptual and associative learning,[3] object representation,[4] and selective attention.[5] The early phase-locked (evoked, exogenous) GBR occurring within 100 milliseconds after stimulus onset has been hypothesized to reflect the synchronization of neural assemblies involved in perceptual processing of sensory input within a local area and across different regions of the brain in order for coherent sensory registration and integration of stimulus events.[6–8]

There is supporting evidence from electroencephalogram (EEG) studies suggesting that the core pathophysiology of schizophrenia is related to disturbed neural synchrony in the gamma frequency band within and across different specialized brain areas leading to impaired perceptual experiences and cognitive dysfunction.[2,9–13] Early GBR can be (1) automatically generated in response to direct, repetitive stimulation (ie, the gamma driving response) or (2) ''cognitively evoked'' when performing higher order cognitive or perceptual tasks (ie., the GBR to tones or visual stimuli). Reduced auditory gamma-driving responses during auditory steady-state evoked potential paradigms have been reported in schizophrenia,[14–17] unaffected family members of schizophrenia patients,[16] and first hospitalized psychosis patients,[18,19] suggesting that neural synchrony or functional connectivity abnormalities might be a biological marker of this disorder at early stage of perceptual processing. Reductions in evoked GBRs have been reported for tasks involving higher order cognitive tasks

[1]To whom correspondence should be addressed; tel: 617-855-3632, fax: 617-855-2778, e-mail: mhall@mclean.harvard.edu.

using visual or auditory oddball paradigms. These tasks typically involve complex cognitive functions such as attention and working memory. However, studies of using higher order cognitive tasks in patients with schizophrenia are fewer, and results are inconsistent. For example, in the visual modality, Spencer et al[20,21] found that schizophrenic patients had abnormal early evoked phase-locking GBRs compared with healthy individuals in a Gestalt perception task. In the auditory modality, Roach and Mathalon[22] found reduced early auditory gamma-band response (EAGBR) phase locking to standard tones in patients with schizophrenia using an oddball task. Three other studies using similar but not identical paradigms, however, failed to find such EAGBR impairments.[21,23,24]

In addition to the equivocal findings on EAGBR reductions in schizophrenia, little is known about the genetic (heritability) and environmental influences on the EAGBR or its potential as a biological marker (endophenotype) of schizophrenia. Endophenotypes are heritable, disease-associated neurophysiologic, cognitive, or neurobiological traits that are believed to be in the etiological pathway (ie, intermediate) between risk genotype and the clinical syndrome more proximally related to the genetic substrate than is the higher order construct of a "disorder."[25–28] The use of endophenotypes has been proposed as a strategy to accelerate gene identification[25–28] and characterization[29] for psychiatric disorders.

In this study, we sought to examine whether EAGBR measures (both phase-locking factor [PLF] and power) to standard stimuli during an auditory oddball task were in fact reduced in schizophrenia and might serve as putative endophenotypes of schizophrenia. Specifically, we wanted to determine whether EAGBR measures were (1) impaired in patients with schizophrenia and their unaffected monozygotic (MZ) co-twin members, (2) heritable traits, and (3) genetically associated with schizophrenia. The current study used twin design and employed sophisticated structural equation modeling analyses to optimally examine and quantify the heritability of the EAGBR measures and the genetic and environmental overlap between EAGBR measures and schizophrenia.[30–32] Comparing the resemblance (covariance) of MZ twin pairs for a trait with that of DZ twin pairs provides an indication of the extent to which genetic and environmental variation contributes to phenotypic variation of that trait.[33] When multiple traits (such as schizophrenia diagnosis and GBRs) are collected in the same MZ and DZ twin pairs, it is possible not only to estimate the heritability of GBRs but also to examine whether an overlapping set of genes accounts for variation in both phenotypes (eg, schizophrenia and impaired GBRs), and if so, to what extent these shared genes explain the covariation between the phenotypes.[32,34] This is, to our knowledge, the first twin study in schizophrenia of EAGBR.

Materials and Methods

The study was approved by the UK Multi-centre Research Ethics Committee. Probands were ascertained from UK national psychiatric services and the Maudsley Twin Study of Schizophrenia. Control twins were recruited from the Institute of Psychiatry Volunteer Twin Register and through advertisements. Written informed consent was obtained from all participants.

Sample

A total of 194 individuals participated, consisting of 97 twin pairs (15 MZ twin pairs concordant for schizophrenia [mean age = 41.2, range = 23–64], 9 MZ twin pairs discordant for schizophrenia [mean age = 31.6, range = 23–52], and 42 MZ [mean age = 32.6, range = 19–56] and 31 dizygotic [DZ, mean age = 40.6, range = 20–58] control pairs). The concordant twin pairs had a higher male-to-female ratio ($P < .001$), had lower parental socioeconomic status ($P = .01$), and smoked more cigarettes per day ($P < .001$) than discordant and control twins who did not differ from each other. Patients (concordant and discordant twins) received significantly less education than control subjects (both P's $<.05$). We had previously reported the analyses of event-related potential (ERP) measures (ie, P300) from this sample[35]; however, the analyses of EAGBR have not been published before. For all participants, exclusion criteria were a history of neurological illness or of systemic illness with known neurological complication, a history of head injury with loss of consciousness of more than 1 minute, and substance abuse (excluding smoking) or dependence within the last 6 months.

Clinical Assessment

Clinical status and diagnoses for all participants were confirmed by structured clinical interviews using the Schedule for Affective Disorders and Schizophrenia—Lifetime Version or the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*). Zygosity was determined using multiple polymorphic DNA markers. The probability that any of the discordant twins would become concordant in the future was low as an average of 11.02 years (SD = 6.49) had elapsed since the onset of the probands' illness.[36] The comparison subjects were free of a personal or family history of psychotic spectrum disorder to second-degree relatives. At the time of assessment, all but 2 of the patients were taking antipsychotic medication; 11 were also treated with antidepressant medication. All subjects had been free of any substance abuse for at least 2 years at the time of testing. Three patients (2 from the concordant group) and 1 nonschizophrenic co-twin had lifetime diagnoses of substance abuse (mainly for cannabis), while 1 nonschizophrenic co-twin had cannabis abuse and alcohol dependence in

the past. One patient from a discordant pair had a history of substance abuse and alcohol dependence. One patient from a concordant pair had a history of substance and alcohol abuse, while 2 patients from the concordant group had alcohol abuse histories. All patients were clinically stable at the time of assessment, with no recent changes to their medication. Over one-half (56%) of the unaffected co-twins had a history of major depression, and 15 of the comparison twins satisfied the *DSM-IV* criteria for a lifetime Axis I disorder (mainly major depression). None was unwell at the time of assessment or was taking psychotropic medication.

EEG data were recorded (0.03–120 Hz, 500-Hz digitization) using Neuroscan software at 16 scalp sites and referenced to the left earlobe. Eye movements were recorded from the outer canthus of each eye and above and below the left eye. Electrode impedances were below 6 kΩ. Subjects were not allowed to smoke a minimum of 40 minutes before data collection. Subjects performed an oddball task (400 binaural 80 dB, 20-msec stimuli, and 20% target [1500 Hz] and 80% standard [1000 Hz] tones) in which they were instructed to press a button every time they heard a target tone. Interstimulus interval was variable between 1.8 and 2.2 seconds.[35] Signal processing was performed off-line using Brain Vision Analyzer software. EEG signals were first filtered between 20 and 80 Hz before wavelet analyses to restrict activity to within the gamma range of interest, 30–60 Hz, with our a priori hypothesis that EAGBR would be in the 35- to 46-Hz range. The low cutoff was also used to remove eye movement EEG signals that occurred at lower frequency ranges. EEG signals were segmented from −100 to 500 milliseconds relative to standard stimulus onset and baseline corrected using the 100-millisecond prestimulus interval. Then, epochs containing artifacts >50 μV were removed. Individual trials were exported for time frequency analysis in Matlab. The number of artifact-free trials did not differ significantly (all *P*'s >.05) between the groups (mean ± SD trials surviving artifact rejection: healthy control subjects = 317.9 ± 3.6 trials, schizophrenia concordant = 314.0 ± 17.0 trials, schizophrenia discordant ill = 317.3 ± 5.2 trials, schizophrenia discordant well = 319.0 ± 1.7 trials).

We examined both evoked power and intertrial PLF (defined as event-related phase consistency across trials within a single electrode) of the EAGBR to standard stimuli. Wavelet analysis in Matlab utilizing software provided by C. Torrence and G. Compo (available at URL: http://atoc.colorado.edu/research/wavelets) of both individual trials and the average of individual trials, ie, the averaged ERP waveform, provided the basis for PLF and evoked power, respectively. A complex Morlet wavelet with Morlet's constant $\sigma_f/f = 6$ and fixed cycle length 6 was used over the 20- to 80-Hz range with 11 frequency bins, centered at 20.2, 23.1, 26.6, 30.6, 35.1, 40.3, 46.3, 53.2, 61.0, 70.4, and 80.6 Hz. Evoked power was derived from the squared amplitude coefficient of the wavelet transform of the average ERP waveform. Phase information was extracted from the arc tangent of the ratio of the imaginary and real coefficients of the transform for each individual trial. PLF was calculated as 1 − the variance of phase across trials, ie, circular variance, for each time-frequency point.[21,37] At each frequency, the mean of the 100-millisecond prestimulus interval was used for baseline correction. Time frequency maps for the grand average of control subjects and patients at Cz provided the basis for determining a region of interest. The mean value in the 35- to 46-Hz, 20- to 80-millisecond window for evoked power and PLF was calculated for each subject.

Statistical Analyses

Comparison of Means. Linear regression analyses using SEs that are robust against nonindependence of observations from individuals within twin pairs (clusters) and against departures from normal assumptions were carried out with the regress command and combined "robust" and "cluster" options in STATA (version 10; Stata Corp, College Station, TX). An advantage of this approach is to maintain correct type 1 error rates given cluster-correlated data (ie, situations where data are observed in clusters [in this case, twin pairs], such that observations within a cluster may be correlated while observations between clusters are uncorrelated).

Concordant MZ schizophrenic twins, discordant MZ schizophrenic twins, and discordant MZ well co-twins were compared with healthy control twins in a single analysis, separately for the evoked power and phase-locking response as the dependent variable. Gender and age were included as covariates. Correlations of the EAGBR measures with clinical parameters (medication, age of onset, duration of illness, the Scale for the Assessment of Positive and Negative symptoms [SAPS and SANS]) were assessed using Pearson correlations.

Statistical Modeling of the Data. Twin correlations between schizophrenia and the evoked power or the phase-locking value were estimated by fitting 2 separate correlation models to the corresponding observed raw data for MZ and DZ twins using Mx software. Genetic model fitting was applied to estimate (1) heritability and (2) genetic and environmental correlations with schizophrenia for EAGBR-evoked power and phase locking.[38] The genetic model fitting analysis has been described in detail by Rijsdijk et al[39] and Hall et al.[35,40] Briefly, in the genetic models, schizophrenia prevalence rate of lifetime risk was fixed to 1%, and parameters for schizophrenia were fixed to 3 sets of values to adjust for sample ascertainment: the point estimates (model 2: $h^2 = 0.81$, $c^2 = 0.11$, $e^2 = 0.08$) and the lower (model 3: $h^2 = 0.73$, $c^2 = 0.19$, $e^2 = 0.08$) and upper 95% confidence interval

(CI) (model 1: $h^2 = 0.90$, $c^2 = 0.03$, $e^2 = 0.07$) based on a meta-analysis report.[41] Models were fitted directly to the raw data. A goodness-of-fit index (χ^2 value) was obtained by computing the difference in likelihoods (and *df*) between the genetic models and the correlational model. Submodels of the full model were evaluated by comparing the difference in χ^2 values relative to the difference in *df* and by Akaike information criterion (AIC), according to the principles of parsimony, operationalized by the significance of the difference in χ^2. A small χ^2 with nonsignificant *P* value and smaller AIC value (more negative) indicate a good fit. Parameters that included 0 in the CI were considered nonsignificant.

Results

Comparison of Means

Regression analyses showed that, compared with the control subjects, the patients with schizophrenia had significantly reduced EAGBR power (concordant vs control subjects: $t = -3.46$, $df = 96$, $P = .001$; discordant vs control subjects: $t = -2.45$, $df = 96$, $P = .02$) and reduced EAGBR PLF (concordant vs control subjects: $t = -4.01$, $df = 96$, $P < .001$; discordant vs control subjects: $t = -3.12$, $df = 96$, $P = .002$) to standard stimuli (table 1, figure 1). The well co-twins from the discordant twin pairs also had significantly reduced EAGBR power, similar to their affected twin members ($t = -2.74$, $df = 96$, $P = .01$), suggesting that this phenotype is likely influenced by genetic liability to schizophrenia. For PLF, the difference between the well co-twins and the control subjects was at the trend level ($t = -1.80$, $df = 96$, $P = .076$). Post hoc analyses showed that there was no significant difference between patients from concordant pairs, patients from discordant pairs, or well co-twins from discordant pairs. We observed no significant correlations between any of the clinical parameters and the evoked GBR measures. Smoking status or number of cigarette smoked per day was not associated with reduced EAGBR power ($r = -0.11$, $P = .53$) or PLF ($r = -0.07$, $P = .69$) measures.

Structural Equation Modeling

The distribution of EAGBR-evoked power was skewed and thus inverse log transformed prior to model fitting. Table 2 shows maximum likelihood estimates of twin correlations. For both evoked power and PLF, MZ within-trait cross-twin correlations were greater than the DZ correlations, suggesting genetic contributions (table 2). Significant phenotypic correlations were found between schizophrenia and reduced EAGBR-evoked power ($R_{ph} = -0.32$, 95% CI = −0.47 to −0.14) and between schizophrenia and decreased EAGBR PLF ($R_{ph} = -0.34$, 95% CI = −0.49 to −0.16). MZ cross-trait cross-twin correlations (ie, correlation with schizophrenia across members) were significantly greater than those of DZ pairs, suggesting that the source of the phenotypic correlations is likely due to genetic factors (table 2).

Genetic models of EAGBR-evoked power and PLF fitted the data well (both *P*'s >.80). Heritability estimates were reported in table 3. Significant heritability ($h^2 = 0.65$, 95% CI = 0.01–0.78) was found for evoked power in model 1. The shared environmental factor was not significant. Individual-specific environmental effects including measurement error accounted for the remaining variance ($e^2 = 0.35$, 95% CI = 0.22–0.53). In models 2 and 3, we observed significant familial effects (genetic and shared environment factors combined) but with insufficient power to distinguish between these 2 components, ie, either component could be dropped independently but not simultaneously. This was most likely due to small sample size and hence reduced statistical power in discriminating genetic and shared environmental factors. Comparing the full ACE model with submodels revealed that the submodel containing genetic (h^2) and individual-specific environmental (e^2) factors (ie, AE model, table 3) fitted the data the best as the χ^2 difference between the submodel and the full model was nonsignificant ($P = .91$), and AIC value was the smallest (AIC = −6). For PLF, significant heritability was found across all 3 models ($h^2 = 0.63$, 95% CI = 0.01–0.76) with no shared environmental influence. The individual-specific environmental factor accounted the rest of the variance ($e^2 = 0.37$, 95% CI = 0.24–0.56, table 3). The AE submodel was again the best fitting model.

Relationship Between Schizophrenia and EAGBR

Results of the decomposed source of the phenotypic correlations between schizophrenia and EAGBR measures are presented in table 4. Of the 3 sets of schizophrenia models examined, a significant genetic correlation between schizophrenia and evoked power was found in model 1 ($\boldsymbol{R}_g = -0.37$, 95% CI = −1 to −.06, table 4). Environmental correlations with schizophrenia were not significant. In models 2 and 3, although similar correlation estimates were obtained, there was insufficient power to formally separate genetic and environmental correlations as either could be dropped independently but not simultaneously. Comparing the full model with submodels revealed that the submodel containing shared genetic ($\boldsymbol{R}_g$) and specific environmental ($\boldsymbol{R}_e$) factors with schizophrenia was preferred as the best fitted model given that it has the smallest AIC value (AIC = −6) and is more parsimonious (table 4). For EAGBR PLF, shared individual-specific environmental factors ($\boldsymbol{R}_e$) contributed significantly to the correlation with schizophrenia across all 3 models ($\boldsymbol{R}_e = -0.66$, 95% CI = −0.96 to −0.12, table 4). Either shared genetic or shared environmental correlations could be dropped from the model separately but not simultaneously,

Table 1. Comparison of Group Mean (SD) Differences for the Early Auditory Gamma-Band Response Power and Phase-Locking Factor to Standard Stimuli[a]

	Measurement, Mean (SD)	CC Schizophrenia Patients Vs Control Subjects; *t* (*df* = 96), *P* Value	DC Schizophrenia Patients Vs Control Subjects; *t* (*df* = 96), *P* Value	DC Well Co-twins Vs Control Subjects; *t* (*df* = 96), *P* Value
Evoked power				
CC ill twins (*N* = 30)	1.36 (1.35)	−3.46, *P* = .001	−2.45, *P* = .02	−2.74, *P* = .01
DC ill twins (*N* = 9)	1.25 (1.98)			
DC well twins (*N* = 9)	1.51 (1.23)			
Comparison twins (*N* = 147)	3.44 (3.80)			
Phase locking				
CC ill twins (*N* = 30)	0.11 (0.08)	−4.01, *P* < .001	−3.12, *P* = .002	−1.80, *P* = .076
DC ill twins (*N* = 9)	0.09 (0.08)			
DC well twins (*N* = 9)	0.13 (0.08)			
Comparison twins (*N* = 147)	0.18 (0.11)			

Note: Linear regression analyses were carried out with evoked power or phase-locking value as dependent variable and including age and gender as covariates. Monozygotic concordant (CC) patients, monozygotic discordant (DC) patients, or monozygotic DC well co-twins were compared with the control twin group.
[a]Data from Fz revealed equivalent results (details are available upon request).

suggesting that, in addition to the individual specific-environmental factor, shared familiar factor also contributed significantly to the observed association with schizophrenia. This was confirmed in the subsequent model fitting analysis showing that the submodel containing shared genetic ($\boldsymbol{R}_g$) and specific environmental ($\boldsymbol{R}_e$) factors with schizophrenia was preferred as the best fitted model (table 4).

Discussion

To our knowledge, this is the first study to assess EAGBR-evoked power and PLF in twins with schizophrenia. We found that EAGBR measures of power and trial-to-trial phase synchrony to standard stimuli in an auditory oddball task were in fact reduced in schizophrenia. We further demonstrated, using twin design and model fitting analyses, that both power and

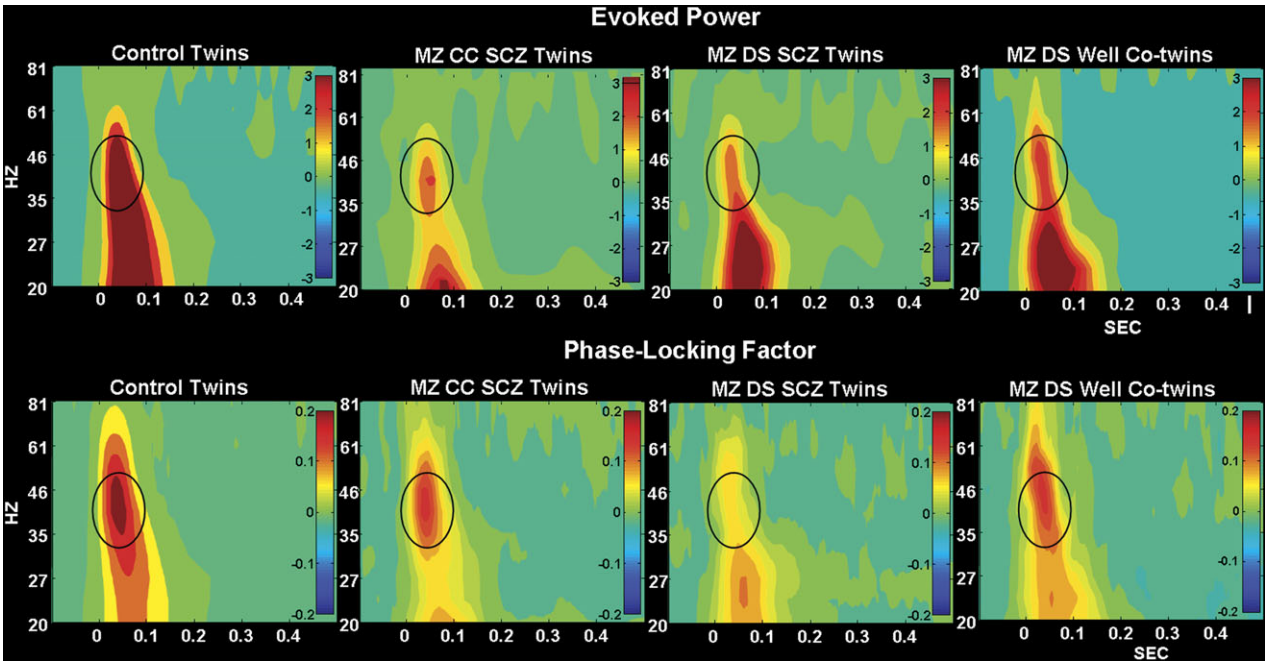

Fig. 1. Time/Frequency Analyses of Evoked Power (Top) and Phase-Locking Factor (Bottom) Gamma-Band Response to the Standard Stimuli at Cz in Control Twins, Monozygotic (MZ) Twins Concordant With Schizophrenia (SCZ), MZ Twins Discordant With Schizophrenia, and Unaffected Co-twin Members.

Table 2. Maximum Likelihood Estimates of Correlations Between Schizophrenia and the Early Auditory Gamma-Band Response (Power and Phase-Locking Factor) to Standard Tones and MZ/DZ Correlations (and 95% Confidence Interval)[a]

	Correlation of GBR Across Members		Correlation With Schizophrenia Across Members		
	MZ	DZ	MZ	DZ	Correlation With Schizophrenia
Evoked power	**0.66 (0.47 to 0.79)**	0.27 (−0.14 to 0.55)	**−0.28 (−0.44 to −0.10)**	0.10 (−0.98 to 0.27)	**−0.32 (−0.47 to −0.14)**
Phase locking	**0.63 (0.45 to 0.73)**	**0.25 (0.01 to 0.50)**	**−0.22 (−0.38 to −0.05)**	0.11 (−0.94 to 0.28)	**−0.34 (−0.49 to −0.16)**

Note: Confidence intervals including 0 indicate nonsignificance. Significance of values are highlighted in bold. MZ, monozygotic; DZ, dizygotic.
[a]Data from Fz revealed equivalent results (details are available upon request).

phase synchrony measures were heritable traits and that impairments in each of these phenotypes were significantly associated with schizophrenia. (Data from Fz revealed equivalent results; details are available upon request).

For a trait to be an appropriate endophenotype, it should be heritable, associated with disease, and observed in genetically at-risk but behaviorally unaffected relatives of patients.[25,31,42,43] In this study, significant higher MZ than DZ correlations were observed in both power and PLF measures suggesting genetic contributions. Significant heritability estimates (0.65 for the power and 0.63 for the PLF) of each measure suggested that they satisfy the first endophenotype criteria.

Because an endophenotype is conceptualized as an expression of the genetic liability for a disorder, it should occur in patients with the illness and appear more prevalent in individuals who are at risk for the disorder (ie, unaffected relatives of patients). Analyses of means between groups revealed that patients with a diagnosis of schizophrenia and their unaffected identical co-twins had reduced EAGBR measures as compared with control subjects. However, the fact that a trait "runs in families" is not sufficient evidence to assume that the observed association is genetic because families may share predisposing environments as well as genes. In order to partition the association between an endophenotype and a disorder into genetic and environmental components, we employed a twin study design.[32] Modeling fitting analyses of twin data revealed significant associations (ie, phenotypic correlations) between schizophrenia and reduced power and smaller PLF responses. The analyses were able to further decompose and quantify the source of these observed associations into genetic, shared, and unique environmental components. Results suggested that in each phenotype, shared genes rather than shared environment were likely the main contributors to the observed associations with schizophrenia. In addition to genetic overlapping, individual-specific environment factors also contributed significantly to the observed association between schizophrenia and PLF. These results suggested that reduced EAGBR power and PLF measures had fulfilled the second and third endophenotypes criteria as well and therefore could

Table 3. Heritability (h^2), Shared Environmental (c^2), and Nonshared Environmental (e^2) Estimates of Full Model and Best Fitting Model for the Early Auditory Gamma-Band Response Power and Phase-Locking Factor[a]

	% Variance Accounted for		
Model	h^2	c^2	e^2
Evoked power			
Model 1	**0.65 (0.01–0.78)**	0.0 (0.0–0.58)	**0.35 (0.22–0.53)**
Model 2	0.65 (0.0–0.78)	0.0 (0.0–0.59)	**0.35 (0.22–0.53)**
Model 3	0.65 (0.0–0.78)	0.0 (0.0–0.59)	**0.35 (0.22–0.53)**
Best fitting model	**0.65 (0.47–0.78)**		**0.35 (0.22–0.53)**
Phase locking			
Model 1	**0.63 (0.01–0.76)**	0.00 (0.0–0.54)	**0.37 (0.24–0.56)**
Model 2	**0.63 (0.01–0.76)**	0.00 (0.0–0.54)	**0.37 (0.24–0.56)**
Model 3	**0.63 (0.01–0.76)**	0.00 (0.0–0.54)	**0.37 (0.24–0.56)**
Best fitting model	**0.63 (0.44–0.76)**		**0.37 (0.24–0.56)**

Note: Significant values are indicated in bold. Three sets of genetic models for schizophrenia were used: (1) $h^2 = 0.90$, $c^2 = 0.03$, $e^2 = 0.07$; (2) $h^2 = 0.81$, $c^2 = 0.11$, $e^2 = 0.08$; and (3) $h^2 = 0.73$, $c^2 = 0.19$, $e^2 = 0.08$. Results of the best fitting model using point estimates (ie, fixed schizophrenia parameters as in model 2) are reported.
[a]Data from Fz revealed equivalent results (details are available upon request).

Table 4. Full and Best Fitted Model Estimates of the Decomposed Source of the Phenotypic Correlations ($R_{ph\text{-}a}$, $R_{ph\text{-}c}$, $R_{ph\text{-}e}$) of the Early Auditory Gamma-Band Response Power and Phase-Locking Factor With Schizophrenia and the Genetic (R_g), Shared Environmental (R_c), and Nonshared Environmental (R_e) Correlations (and 95% Confidence Intervals)

	$R_{ph\text{-}a}$	$R_{ph\text{-}c}$	$R_{ph\text{-}e}$	R_g	R_c	R_e
Evoked power						
Model 1	−0.28 (−0.51 to −0.04)	0.00 (−0.13 to 0.13)	−0.04 (−0.11 to 0.05)	−0.37 (−1.0 to −0.06)	−0.80 (−1.0 to 1.0)	−0.24 (−0.67 to 0.29)
Model 2	−0.28 (−0.58 to 0.06)	0.00 (−0.26 to 0.22)	−0.04 (−0.12 to 0.05)	−0.38 (−1.0 to 1.0)	−0.94 (−1.0 to 1.0)	−0.24 (−0.67 to 0.29)
Model 3	−0.27 (−0.61 to 0.13)	−0.01 (−0.34 to 0.28)	−0.04 (−0.12 to 0.05)	−0.39 (−1.0 to 1.0)	−1.0 (−1.0 to 1.0)	−0.24 (−0.67 to 0.29)
Best fitting model	−0.28 (−0.44 to −0.10)		−0.04 (−0.12 to 0.05)	0.38 (−0.61 to −0.14)		−0.24 (−0.67 to 0.29)
Phase locking						
Model 1	−0.23 (−0.45 to 0.01)	0.00 (−0.13 to 0.12)	−0.11 (−0.17 to −0.02)	−0.30 (−1.0 to 1.0)	−0.35 (−1.0 to 1.0)	−0.66 (−0.96 to −0.12)
Model 2	−0.22 (−0.53 to 0.10)	0.00 (−0.24 to 0.22)	−0.11 (−0.18 to −0.02)	−0.31 (−1.0 to 1.0)	−0.30 (−1.0 to 1.0)	−0.66 (−0.95 to −0.11)
Model 3	−0.22 (−0.56 to 0.17)	−0.01 (−0.32 to 0.28)	−0.11 (−0.18 to −0.02)	−0.32 (−1.0 to 1.0)	−0.93 (−1.0 to 1.0)	−0.66 (−0.95 to −0.11)
Best fitting model	−0.22 (−0.38 to −0.05)		−0.11 (−0.18 to −0.02)	−0.31 (−0.54 to −0.07)		−0.66 (−0.95 to −0.11)

Note: $R_{ph\text{-}a}$, $R_{ph\text{-}c}$, $R_{ph\text{-}e}$—decomposed phenotypic correlation due to additive genetic, shared environment, and specific environmental source; R_g, R_c, and R_e—genetic, shared, and specific environmental correlations. Confidence intervals including zero indicate nonsignificance. Three sets of genetic models for schizophrenia were used: (1) $h^2 = 0.90$, $c^2 = 0.03$, $e^2 = 0.07$; (2) $h^2 = 0.81$, $c^2 = 0.11$, $e^2 = 0.08$; and (3) $h^2 = 0.73$, $c^2 = 0.19$, $e^2 = 0.08$. Results of the best fitting model using point estimate are reported. Significance of values are highlighted in bold.

be considered as putative endophenotypes for schizophrenia.

The 2 metrics of the gamma oscillation, evoked power and PLF, are different measures that are independent but highly correlated. Evoked power is derived from the individual's averaged response and captures the magnitude of the oscillations time locked to task events across trials. Oscillations that are not strongly time locked (out of phase) with respect to stimulus onset across trials are canceled out during averaging. Evoked power reflects a true event-related oscillation (ERO) whose morphology is dependent on the overall amplitude of the response trial to trial and the temporal jitter of the response from trial to trial. In contrast to evoked power, PLF is based on activity on each trial. It measures the variance of EEG phase across single trials independently of amplitude. Rather than measuring differences in phase angle between sites, it measures differences in phase angle between single trials at a specific site. In this regard, it is a measure of temporal stability of a specific evoked response and is sensitive to oscillatory behavior that is averaged out in power measures. The PLF provides a measure of temporal consistency in neural synchrony. It is possible that a large trial-to-trial signal with a low PLF may result in a smaller ERO than a small trial-to-trial signal with a high PLF. Both measures have given complementary information on the functional component of cognitive processing, although the precise cognitive and neurophysiological concomitants of each measure are unknown at present.

Attention has been shown to modulate early GBRs.[44,45] A study in healthy individuals has shown that increased task difficulty and mental effort was associated with greater evoked GBR amplitude.[46] It is not clear the degree to which attentional modulation of the EAGBR on this active target detection task contributes to group differences. The present data are unable to distinguish between a purely sensory deficit vs a top-down attentional modulation deficit. We are currently examining this issue using a different experimental paradigm.

The reduced EAGBR power and PLF in patients with schizophrenia found in the present study was in accord with Roach and Mathalon[22] but not Galliant et al[23] and Spencer et al.[21] It is not entirely clear why 2 other studies failed to find such impairments. We hypothesize that methodological difference may account for these discrepant results. Specifically, our paradigm used a total of 400 stimuli (320 standards) as compared with a total of 180 stimuli with 150 standards in Spencer et al[21] and 230 stimuli with 175 standards in Gallinat et al[23] who also used click pairs as standard stimuli rather than single tones. Because of the number of standards used, our paradigm is likely to produce greater signal-to-noise ratios, which leads to better

power to distinguish individuals with deficits and those without.

In our sample, we observed no significant correlations between any of the clinical parameters (including medication, age of onset, duration of illness, and SAPS and SANS) and the EAGBR measures. Moreover, medications effects are unlikely to account for the observed EAGBR deficits in twins with schizophrenia as the well co-twins from the discordant twin pairs who were free from psychotropic medications had reduced EAGBR as well.

In addition to genetic associations between EAGBR deficits and schizophrenia, we observed a significant individual-specific environmental overlapping effect between schizophrenia and PLF, raising the possibility that individual specific environment factors such as illness progression also play important roles in EAGBR deficit. Correlations of PLF with clinical parameters (medication, age of onset, duration of illness, SAPS, and SANS) were nonsignificant, however. It remains to be determined which aspects of individual-specific environments are contributory. One possibility is obstetric complications at birth. Studies have found that some obstetric complications seem to be more common in the affected co-twins from MZ pairs discordant for schizophrenia.[47] Unfortunately, such data are unavailable in the present study. A future twin study is needed to resolve this issue.

The cellular mechanisms of EAGBR are believed to involve networks of γ-aminobutyric acid (GABA)ergic, glutamate, and acetylcholine neurotransmitter systems. The fast synaptic inhibitory GABA neurons appear to be critically involved in generating gamma-band oscillations.[48] In patients with schizophrenia, evidence of reduced numbers of GABA neurons and reduced synaptic connectivity between GABA neurons and postsynaptic cells have been observed. These cellular deficits, coupled with deficits in glutamate receptor–mediated excitation of interneurons,[49] may contribute to the observed gamma oscillation dysfunction in patients with schizophrenia and their relatives and are consistent with current theory suggesting that the mechanism underlying abnormal gamma activity is due to lack of inhibitory neuronal pathways.[2,50,51] That is, dysfunction of gamma oscillation may reflect a state of neuron hyperarousal (hyperexcitability) because of reduced inhibitory input from GABAergic interneurons to efficiently suppress spontaneous neuronal activity that is triggered by inputs unrelated to the stimulus being studied or to block unrestrained local circuit processing spread of activation. As a result, synchronized neuronal activity is reduced and this is reflected in reduced scalp gamma oscillations. Future study combining molecular genetics and basic neuroscience may provide important insight into the neurobiological mechanism of the glutamate receptor–mediated excitation and the GABA neuron–mediated inhibition feedback loop underlying the EAGBR deficits in schizophrenia and facilitate the development of therapeutic intervention.[49,50]

Using click trains stimuli, deficits in evoked gamma oscillatory activity have been found in patients with schizophrenia,[14,15,19] bipolar disorder,[51] early-onset psychosis,[18,19] and autism,[53] as well as in the unaffected family members of schizophrenia probands.[16] Similar deficits are documented in parents of children with autism[54] using a transient stimulus, suggesting that abnormal gamma driving responses that are automatically generated in response to direct, repetitive stimulation may also be a putative endophenotype for bipolar disorder and autism. However, family studies of gamma oscillations employing an auditory oddball task in patients with bipolar disorder or autism are few. Whether EAGBR deficits are also putative endophenotypes for these disorders will need to be clarified in the future.

The sample size of the present study was relatively small. In particular, we had limited statistical power in separating genetic from environmental correlations across all 3 sets of models. For example, shared genetic factors only emerged as statistically significant when schizophrenia heritability was assumed to be as high as 90% (model 1) for evoked power. Nonetheless, the greater MZ-to-DZ cross-trait cross-twin correlations and the best fitted submodels of each phenotype suggested that shared genes rather than shared environment are more likely the main contributors to the observed phenotypic associations. Abnormal lateralization of gamma power[23] has been reported in patients with schizophrenia compared with control subjects. Unfortunately, the low-resolution electrode array use in this study and small oscillation signals observed at temporal-parietal regions have limited the power of our study for examining hemisphere differences between groups and for performing modeling analyses.

In summary, evidence of reduced EAGBR power and PLF measures in twins with schizophrenia and their unaffected co-twin members, significant heritability of each phenotype, and substantial genetic overlapping between schizophrenia and these measures support EAGBR power and PLF measures as putative endophenotypes for schizophrenia.

Funding

Harvard Medical School (Kaplen Fellowship to M.-H.H.); National Alliance for Research on Schizophrenia and Depression (Sidney R. Baer, Jr. Foundation Young Investigator Award to M.-H.H.); Adam Corneel Young Investigator Award (to M.-H.H.); National Institutes of Mental Health (T32 MH016259-29A1 Fellowship to M.-H.H., MH RO1-58704 to D.F.S.); Wellcome Trust (Research Training Fellowship 064971 to M.P.).

Acknowledgments

All authors reported no potential conflicts of interest.

References

1. Herrmann CS, Demiralp T. Human EEG gamma oscillations in neuropsychiatric disorders. *Clin Neurophysiol*. 2005;116:2719–2733.
2. Uhlhaas PJ, Haenschel C, Nikolic D, Singer W. The role of oscillations and synchrony in cortical networks and their putative relevance for the pathophysiology of schizophrenia. *Schizophr Bull*. 2008;34:927–943.
3. Miltner WH, Braun C, Arnold M, Witte H, Taub E. Coherence of gamma-band EEG activity as a basis for associative learning. *Nature*. 1999;397:434–436.
4. Tallon-Baudry C, Bertrand O. Oscillatory gamma activity in humans and its role in object representation. *Trends Cogn Sci*. 1999;3:151–162.
5. Tiitinen H, May P, Reinikainen K, Naatanen R. Attentive novelty detection in humans is governed by pre-attentive sensory memory. *Nature*. 1994;372:90–92.
6. Singer W. Neuronal synchrony: a versatile code for the definition of relations? *Neuron*. 1999;24:49–65,111–125.
7. Basar-Eroglu C, Struber D, Schurmann M, Stadler M, Basar E. Gamma-band responses in the brain: a short review of psychophysiological correlates and functional significance. *Int J Psychophysiol*. 1996;24:101–112.
8. Joliot M, Ribary U, Llinas R. Human oscillatory brain activity near 40 Hz coexists with cognitive temporal binding. *Proc Natl Acad Sci U S A*. 1994;91:11748–11751.
9. Lee KH, Williams LM, Breakspear M, Gordon E. Synchronous gamma activity: a review and contribution to an integrative neuroscience model of schizophrenia. *Brain Res Brain Res Rev*. 2003;41:57–78.
10. Symond MP, Harris AW, Gordon E, Williams LM. "Gamma synchrony" in first-episode schizophrenia: a disorder of temporal connectivity? *Am J Psychiatry*. 2005;162:459–465.
11. Williams LM, Whitford TJ, Gordon E, Gomes L, Brown KJ, Harris AW. Neural synchrony in patients with a first episode of schizophrenia: tracking relations with grey matter and symptom profile. *J Psychiatry Neurosci*. 2009;34:21–29.
12. Williams LM, Whitford TJ, Nagy M, et al. Emotion-elicited gamma synchrony in patients with first-episode schizophrenia: a neural correlate of social cognition outcomes. *J Psychiatry Neurosci*. 2009;34:303–313.
13. Wynn JK, Light GA, Breitmeyer B, Nuechterlein KH, Green MF. Event-related gamma activity in schizophrenia patients during a visual backward-masking task. *Am J Psychiatry*. 2005;162:2330–2336.
14. Light GA, Hsu JL, Hsieh MH, et al. Gamma band oscillations reveal neural network cortical coherence dysfunction in schizophrenia patients. *Biol Psychiatry*. 2006;60:1231–1240.
15. Kwon JS, O'Donnell BF, Wallenstein GV, et al. Gamma frequency-range abnormalities to auditory stimulation in schizophrenia. *Arch Gen Psychiatry*. 1999;56:1001–1005.
16. Hong LE, Summerfelt A, McMahon R, et al. Evoked gamma band synchronization and the liability for schizophrenia. *Schizophr Res*. 2004;70:293–302.
17. Brenner CA, Sporns O, Lysaker PH, O'Donnell BF. EEG synchronization to modulated auditory tones in schizophrenia, schizoaffective disorder, and schizotypal personality disorder. *Am J Psychiatry*. 2003;160:2238–2240.
18. Wilson TW, Hernandez OO, Asherin RM, Teale PD, Reite ML, Rojas DC. Cortical gamma generators suggest abnormal auditory circuitry in early-onset psychosis. *Cereb Cortex*. 2008;18:371–378.
19. Spencer KM, Salisbury DF, Shenton ME, McCarley RW. Gamma-band auditory steady-state responses are impaired in first episode psychosis. *Biol Psychiatry*. 2008;64:369–375.
20. Spencer KM, Nestor PG, Niznikiewicz MA, Salisbury DF, Shenton ME, McCarley RW. Abnormal neural synchrony in schizophrenia. *J Neurosci*. 2003;23:7407–7411.
21. Spencer KM, Niznikiewicz MA, Shenton ME, McCarley RW. Sensory-evoked gamma oscillations in chronic schizophrenia. *Biol Psychiatry*. 2008;63:744–747.
22. Roach BJ, Mathalon DH. Event-related EEG time-frequency analysis: an overview of measures and an analysis of early gamma band phase locking in schizophrenia. *Schizophr Bull*. 2008;34:907–926.
23. Gallinat J, Winterer G, Herrmann CS, Senkowski D. Reduced oscillatory gamma-band responses in unmedicated schizophrenic patients indicate impaired frontal network processing. *Clin Neurophysiol*. 2004;115:1863–1874.
24. Haig AR, Gordon E, De Pascalis V, Meares RA, Bahramali H, Harris A. Gamma activity in schizophrenia: evidence of impaired network binding? *Clin Neurophysiol*. 2000;111:1461–1468.
25. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003;160:636–645.
26. Braff DL, Freedman R, Schork NJ, Gottesman II. Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. *Schizophr Bull*. 2007;33:21–32.
27. Meyer-Lindenberg A, Weinberger DR. Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nat Rev Neurosci*. 2006;7:818–827.
28. Thaker GK. Neurophysiological endophenotypes across bipolar and schizophrenia psychosis. *Schizophr Bull*. 2008;34:760–773.
29. Hall M-H, Smoller JW. A new role for endophenotypes in the GWAS era: functional characterization of risk variants. *Harv Rev Psychiatry*. 2010;18:67–74.
30. Martin N, Boomsma D, Machin G. A twin-pronged attack on complex traits. *Nat Genet*. 1997;17:387–392.
31. Hall MH, Rijsdijk F. Validating endophenotypes for schizophrenia using statistical modeling of twin data. *Clin EEG Neurosci*. Apr 2008;39:78–81.
32. Boomsma D, Busjahn A, Peltonen L. Classical twin studies and beyond. *Nat Rev Genet*. 2002;3:872–882.
33. Falconer DS, Mackay TFC. *Introduction to Quantitative Genetics.* 4th ed. Harlow, UK: Longman; 1996.
34. Rijsdijk FV, Sham PC. Analytic approaches to twin data using structural equation models. *Brief Bioinform*. 2002;3:119–133.
35. Hall M-H, Rijsdijk FV, Picchioni M, Schulze K, Ettinger U, Toulopoulou T, et al. Substantial shared genetic influences on schizophrenia and event-related potentials. *Am J Psychiatry*. 2007;164:804–812.
36. Belmaker R, Pollin W, Wyatt RJ, Cohen S. A follow-up of monozygotic twins discordant for schizophrenia. *Arch Gen Psychiatry*. 1974;30:219–222.
37. Tallon-Baudry C, Bertrand O, Delpuech C, Pernier J. Stimulus specificity of phase-locked and non-phase-locked

40 Hz visual responses in human. *J Neurosci*. 1996; 16:4240–4249.

38. Neale MC, Maes HH. *Methodology for Genetic Studies of Twins and Families*. BV Dordrecht, The Netherlands: Kluwer Academic Publishers; 2004.
39. Rijsdijk FV, van Haren NE, Picchioni MM, et al. Brain MRI abnormalities in schizophrenia: same genes or same environment? *Psychol Med*. 2005;35:1399–1409.
40. Hall MH, Schulze K, Sham P, et al. Further evidence for shared genetic effects between psychotic bipolar disorder and P50 suppression: a combined twin and family study. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147B: 619–627.
41. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry*. 2003;60:1187–1192.
42. Freedman R, Adler LE, Leonard S. Alternative phenotypes for the complex genetics of schizophrenia. *Biol Psychiatry*. 1999;45:551–558.
43. Cannon TD, Keller MC. Endophenotypes in the genetic analyses of mental disorders. *Annu Rev Clin Psychol*. 2006;2:267–290.
44. Tiitinen H, Sinkkonen J, Reinikainen K, Alho K, Lavikainen J, Naatanen R. Selective attention enhances the auditory 40-Hz transient response in humans. *Nature*. 1993;364:59–60.
45. Steinmetz PN, Roy A, Fitzgerald PJ, Hsiao SS, Johnson KO, Niebur E. Attention modulates synchronized neuronal firing in primate somatosensory cortex. *Nature*. 2000;404:187–190.
46. Mulert C, Leicht G, Pogarell O, et al. Auditory cortex and anterior cingulate cortex sources of the early evoked gamma-band response: relationship to task difficulty and mental effort. *Neuropsychologia*. 2007;45:2294–2306.
47. McNeil TF, Cantor-Graae E, Torrey EF, et al. Obstetric complications in histories of monozygotic twins discordant and concordant for schizophrenia. *Acta Psychiatr Scand*. 1994;89:196–204.
48. Bartos M, Vida I, Jonas P. Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nat Rev Neurosci*. 2007;8:45–56.
49. Demiralp T, Herrmann CS, Erdal ME, et al. DRD4 and DAT1 polymorphisms modulate human gamma band responses. *Cereb Cortex*. 2007;17:1007–1019.
50. Gonzalez-Burgos G, Lewis DA. GABA neurons and the mechanisms of network oscillations: implications for understanding cortical dysfunction in schizophrenia. *Schizophr Bull*. 2008;34:944–961.
51. Benes FM. Emerging principles of altered neural circuitry in schizophrenia. *Brain Research Reviews*. 2000;31:251–269.
52. O'Donnell BF, Hetrick WP, Vohs JL, Krishnan GP, Carroll CA, Shekhar A. Neural synchronization deficits to auditory stimulation in bipolar disorder. *Neuroreport*. 2004;15:1369–1372.
53. Wilson TW, Rojas DC, Reite ML, Teale PD, Rogers SJ. Children and adolescents with autism exhibit reduced MEG steady-state gamma responses. *Biol Psychiatry*. 2007;62:192–197.
54. Rojas DC, Maharajh K, Teale P, Rogers SJ. Reduced neural synchronization of gamma-band MEG oscillations in first-degree relatives of children with autism. *BMC Psychiatry*. 2008;8:66.