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The genetic and environmental influences of event-related gamma oscillations on bipolar disorder

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Abstract

Objectives—Gamma oscillations have been proposed to play an important role in neural information coding. There have been a limited number of electrophysiology studies in evoked gamma band responses (GBRs) in bipolar disorder (BPD). It is also unclear whether GBR deficits, if present, are potential endophenotypes for BPD as little is known about the heritability of GBRs. The present study aimed to examine whether GBRs derived from two auditory tasks, the oddball task and the dual-click paradigm, are potential BPD endophenotypes.

Methods—A total of 308 subjects were included in this study: 198 healthy controls, 59 BPD patients (22 monozygotic BPD twins and 37 BPD patients from 31 families), and 51 unaffected relatives. The evoked gamma responses were calculated using a Morlet wavelet transformation. Structural equation modelling was applied to obtain the genetic (heritability) and environment estimates in each GBR variable and their (genetic) overlap with BPD.

Results—The heritability estimates of GBR to standard stimuli were 0.51 and 0.35 to target stimuli in the oddball task. However, neither response type was impaired in BPD patients or their unaffected relatives. The heritability estimates of GBR to S1 stimuli were 0.54 and 0.50 to S2 stimuli in the dual-click paradigm. BPD patients had reduced gamma power and suppression to S1 stimuli but their unaffected relatives did not.

Conclusions—Evoked GBRs are heritable traits. However, GBR deficits are not observed in clinically unaffected relatives nor associated with BPD. Gamma responses do not appear to satisfy criteria for being BPD endophenotypes.

Keywords

bipolar disorder; endophenotype; gamma oscillation; heritability

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Bipolar disorder (BPD) is a common and serious mental illness and is highly heritable (1). However, the precise genetic architecture is complex and remains poorly understood (2). Beyond genetic complexity, BPD is phenotypically complex as well (3). The current Diagnostic and Statistical Manual of Mental Disorders, version 4 (DSM-IV) definition for BPD comprises descriptive syndromes and contains heterogeneous phenotypes (4). Although the advent of genome-wide association studies (GWAS) in recent years has begun to identify common modest-risk variants for BPD, very large samples of cases and controls (on the order of thousands or even tens of thousands) are typically required (5, 6), and the role that newly discovered genetic variants play in disease pathogenesis is relatively unknown (7).

To address uncertainties about phenotype definition and genetic complexity of BPD, the use of intermediate phenotypes, so-called *endophenotypes*, in genetic analyses has been proposed as an alternative strategy with aims to (i) more directly assay the effect of disease risk variants and reduce the phenotypic heterogeneity of BPD patients (8) and (ii) provide essential neurobiological insights into the mechanisms by which genetic variants act on the brain to produce BPD (9).

Over the past decade, many investigators have tried to define candidate endophenotypes for BPD (10). Results suggest that a number of neurocognitive processes and brain functions are robustly impaired in patients with BPD and in their unaffected relatives, including: alterations in gray and white matter (11); responses associated with inhibition and working memory measured by event-related potentials (ERPs) (12–14); circadian rhythm instability (15); neuropsychological measures of executive function, verbal learning, memory, and ventral prefrontal cortex related inhibitory processes (16, 17), facial-emotion processing (18); deficits in attention (19); and affective temperament (20).

Neural oscillations and synchronization in the gamma frequency band (30–80 Hz) have been proposed to play an important role in neural information coding (21). Gamma oscillations are associated with brain functions such as perceptual grouping or object representation (22), attention (23), sensory-motor integration (24), working memory (25), and associative learning (26). Many of these brain functions are altered in patients with BPD. The relatively few studies of gamma oscillations in BPD show that patients have a reduced gamma band response (GBR) to click trains (27, 28). This deficit has been hypothesized to reflect a manifestation of a neural circuit abnormality in BPD. Reduced GBRs to auditory steady-state stimuli are also found in early onset psychotic patients (29), first episode psychotic patients (30), and schizophrenia patients (31–33), suggesting a possible overlapping neural circuit dysfunction in psychosis in general. In contrast, studies using sensory gating dual-click paradigms reported reduced evoked GBR in patients with schizophrenia (34) but not in patients with BPD (35). To our knowledge, evoked GBR in BPD patients using more demanding cognitive tasks (e.g., oddball/discrimination task) has not been reported. In patients with schizophrenia, reduced evoked GBR to auditory oddball task has been documented in some (36, 37) but not all studies (38, 39). Improving our understanding of the patterns of brain responses in gamma frequency as a function of cognitive tasks that may independently characterize BPD and schizophrenia is clearly desirable.

In addition, it is unclear whether GBR deficits are potential endophenotypes for BPD. To our knowledge, to date, no twin or family study of gamma oscillations in BPD has been reported. In addition, little is known about the genetic (i.e., heritability) and environmental influences of evoked gamma oscillations on BPD. Thus, the primary aims of the present study were to examine whether evoked GBRs to two auditory cognitive tasks, the oddball and the dual-click tasks, are potential endophenotypes of BPD. This study used the Maudsley Twin and Bipolar Family Study sample and advanced genetic model fitting

analyses to address the following questions: (i) Are evoked GBRs to standard and target stimuli in the oddball task reduced in BPD and their unaffected relatives compared with controls? (ii) Are evoked GBRs to S1 and S2 stimuli and the S1–S2 GBR difference in the dual-click paradigm reduced in BPD and their unaffected relatives compared with controls? (iii) Are GBRs to different types of stimuli in the oddball task and in the dual-click paradigm heritable traits? (iv) Are there genetic overlaps between BPD and evoked GBRs to different types of stimuli in the oddball task or in the dual-click paradigm?

Materials and methods

This study was approved by the UK Multi-centre Research Ethics Committee. The sample set was drawn from the Maudsley Twin Study of Bipolar Disorder and the Maudsley Family Study of Psychosis (14, 40). A total of 308 subjects were included in this study: 198 healthy controls [46 monozygotic (MZ) twin pairs, 32 dizygotic (DZ) twin pairs, and 42 singletons], 59 BPD patients (12 concordant MZ BPD twins, 10 discordant MZ BPD twins, and 37 BPD patients from 31 families), and 51 unaffected relatives.

Clinical status and diagnoses for all participants were confirmed by structured clinical interviews using the Schedule for Affective Disorders and Schizophrenia–Lifetime version (SADS-L) (41), the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) version 2.1 (42), or the Structured Clinical Interview for DSM-IV (SCID-IV) (43). Additional information regarding the timing and nature of symptoms was obtained for subjects who were interviewed using the SADS-L to enable DSM-IV diagnoses to be made. All BPD patients had experienced psychotic symptoms (delusions and/or hallucinations) during one or more manic episodes. All patients were outpatients at the time of assessment. The majority of patients were symptom free at the time of testing [Beck Depression Inventory (BDI) (44) score < 14] with the exception of eight patients who presented with mild to moderate depressive symptoms (BDI score: 14–24). BPD patients had a mean age of illness onset of 22 years (SD = 6.3 years) and a mean duration of illness of 21 years (SD = 10.9 years) (Table 1). Fourteen patients were nonmedicated for at least four weeks. Information regarding medication was unavailable in two patients. Of the remaining 43 patients: 9 were taking a single mood stabilizer (lithium $n = 4$, divalproex sodium $n = 1$, sodium valproate $n = 1$, carbamazepine $n = 2$, venlafaxine $n = 1$), and others were taking combinations of mood stabilizers, antipsychotics, and antidepressants. Of those patients who were taking mood stabilizers (excluding patients taking only a single medication), 18 of them were taking lithium, 12 were taking sodium valproate, 9 were taking carbamazepine, and 3 were taking divalproex sodium. Of those patients who were taking antipsychotics (excluding patients taking only a single medication), 8 were taking olanzapine, 2 were taking risperidone, 2 were taking flupentixol, 1 was taking clozapine, 1 was taking amisulpride, and 1 was taking trifluoperazine. Data on medication history were collected at the time of assessment. Controls were free of a personal or family history (to second-degree relatives) of psychotic disorder or BPD. Exclusion criteria that applied to all groups included a history of neurological disorder, hearing impairment, a history of head trauma resulting in loss of consciousness for more than 10 min, and current substance (excluding nicotine or caffeine) dependence within the last six months. Zygosity was determined using 12 highly polymorphic DNA markers.

There were age differences between groups such that control subjects were younger than patients ($p = 0.010$) and their relatives ($p = 0.004$). Also, there were significantly less females in the relative group than control or patient group, who did not differ from each other (Table 1). Controlling for age and sex, there were significant differences in parental socioeconomic status (SES), the proportion of current regular smokers, and the number of cigarettes per day between groups. Groups did not differ significantly in years of education. Parental SES was significantly higher in the well relatives than the other two groups who did

not differ from each other (Table 1). The proportion of current regular smokers was significantly higher in patients than in controls or well relatives [patients versus controls odds ratio (OR) = 2.94, 95% confidence interval (CI): 1.39–6.23] who did not differ from each other. Also, among smokers, patients smoked significantly more cigarettes per day than control subjects (estimated difference = 8.65, 95% CI: 2.44–14.86) (Table 1). Among relatives, 16 had a history of a nonpsychotic DSM-IV axis I disorders and 32 control subjects also had a lifetime diagnosis of nonpsychotic disorder (Table 1). All nonpatient subjects with a history of DSM diagnosis were symptom free and not receiving any psychotropic medication at the time of assessment.

Procedure and tasks

Event-related potential (ERP) results of the oddball task (i.e., P300) and the dual-click paradigm (i.e., P50) from this sample had been published elsewhere (14, 40). In the present study, we focused on the analyses of evoked gamma responses.

Electroencephalogram (EEG) data were recorded (0.03–120 Hz, 500-Hz digitization) using a Neuroscan system 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 k Ω . Subjects were not allowed to smoke a minimum of 40 min before data collection. In the oddball task subjects responded to infrequent (probability = 0.2, total trials = 80) 1,500 Hz target tones randomly interspersed amid a series of 1,000 Hz standard tones (probability = 0.8, total trials = 320) using a button press device. In the dual-click paradigm, stimuli were 160 pairs of identical clicks (S1 and S2) separated by 500 msec and a 10 sec inter-trial interval.

Signal processing was performed offline using BrainVision Analyzer software (Brain Products, Gilching, Germany). EEG signals of the oddball task were first filtered between 10 and 80 Hz, segmented from –100 to 500 msec relative to stimulus onset and baseline corrected using the 100-msec prestimulus interval. Next, epochs containing artifacts > 50 μ V were removed. The number of artifact-free trials in frequency responses to standard and target stimulus did not differ significantly between the groups (all p-values > 0.10). Artifact-free epochs were averaged separately for target and standard tones. A Morlet wavelet transformation function was applied to the averaged standard and target ERP waveforms with $c = 7$ in 1 Hz steps from a range of 10–80 Hz and from –100 to 500 msec. EEG signals of the dual-click paradigm were processed in the same way with one difference: individual EEGs were segmented from –100 to 400 msec instead. The number of artifact-free trials in frequency responses to S1 and S2 stimulus did not differ significantly between the groups (all p-values > 0.10). Evoked power (μ V²) was then computed in Microsoft Excel on the wavelet-transformed waveforms for each stimulus condition at each time point and wavelet frequency to yield time-frequency maps (22). Average baseline values were subtracted from each time-frequency map (–100 to 0 msec).

In the oddball task, inspection of the data indicated that the maximal evoked GBRs were similar in time and frequency windows in each group. Thus, the average evoked power for target and standard stimuli was computed in the time window (10–80 msec) and frequency band (30–50 Hz) at electrode Cz in each individual regardless of group memberships. In the dual-click paradigm, the maximal evoked power in time and wavelet frequency windows differed between groups: controls 25–45 Hz, 16–66 msec; patients 24–44 Hz, 12–62 msec; relatives 28–48 Hz, 10–60 msec. Therefore, evoked power to S1 and S2 stimuli in each subject was computed using the above group specific windows at electrode Cz.

Statistical analyses

Comparison of means—Linear regression analyses using standard errors that are robust against nonindependence of observations from individuals within twin pairs (clusters) and against departures from normal assumptions were carried out in STATA (version 10; Stata Corp, College Station, TX, USA). The patient group and the unaffected relative group were compared to the control group (including MZ/DZ healthy twins and singletons) for each gamma variable separately. In the oddball task, dependent variables were GBRs to the standard and target tones. In the dual-click paradigm, they were GBRs to S1 and S2 stimuli and the difference between S1 and S2 responses, a measure of gamma suppression. Age and sex were included in the regression model as covariates. Effects of clinical parameters (age of onset, duration of illness, number of hospitalization) and other possible confounding variables (year of education, smoking status, and number of cigarettes) on each of the dependent variable were assessed using partial correlations. Significant clinical variables, if found, were included in the regression model as covariates. A *t*-test was used for comparing GBR differences between medicated and nonmedicated individuals. Extreme outliers, defined as values > 3 standard deviations of the group mean, were excluded from analyses. In the dual-click paradigm there were four outliers (three controls and one patient), and in the oddball task there were three outliers (two controls and one patient). A 0.05 level of significance was used.

Genetic model fitting—Twin correlations were estimated by fitting two separate correlation models, one for each task, to the corresponding observed raw data for MZ twins and non-MZ members using the Structural Equation Modeling (SEM) program Mx (45). SEM was applied to estimate (i) the heritability of each gamma response variable, and (ii) genetic and environmental correlations of BPD with each gamma variable. The SEM-based analysis, also known as genetic model fitting, has been described in detail by Rijdsdijk et al. (46) and by Hall et al. (14, 47). Briefly, BPD prevalence rate of lifetime risk was fixed to 1% and parameters for BPD were fixed to three sets of values based on the report of McGuffin et al. (1) (which includes the largest BPD twin sample ascertained in the literature to date) to adjust for sample ascertainment: the point estimates (Model 2: $h^2 = 0.85$, $c^2 = 0.00$, $e^2 = 0.15$), and the lower (Model 1: $h^2 = 0.73$, $c^2 = 0.00$, $e^2 = 0.27$) and upper 95% CI estimates (Model 3: $h^2 = 0.93$, $c^2 = 0.00$, $e^2 = 0.07$).

Genetic and environmental influences on each GBR variable were estimated by comparing correlations between MZ twins and non-MZ family members. Significantly greater MZ correlations than the correlations of non-MZ family members suggest genetic effect (heritability) on a trait. The phenotypic relationship between BPD and a GBR variable is derived from the covariance between the two traits and the overall correlation between one family member's bipolar status and his/her relative's gamma response informs us the source of the phenotypic correlations (genetic or environmental association with BPD). The genetic (r_g) and environmental (r_e) correlation estimates indicate the extent to which genetic (or environmental) factors on BPD overlap with those on a GBR variable. A genetic correlation equal to 1 would indicate that genetic influences on BPD and the GBR variable completely overlap, whereas a genetic correlation < 1 indicates that at least some genes are specific to only evoked gamma responses.

A goodness-of-fit index (χ^2) was obtained by computing the difference in likelihoods (and degrees of freedom) between the genetic models and the polychoric correlation model. Submodels of the full model (ACE) were evaluated by comparing the difference in χ^2 relative to the difference in degrees of freedom, according to principals of parsimony, operationalized by the significance of the difference in χ^2 . CIs of parameter estimates were obtained by the maximum likelihood method (48).

Results

The distributions of GBRs to S1 and S2 stimuli as well as to standard and target stimuli were skewed, therefore, data were log transformed prior to the analyses. Table 2 shows log transformed group means and standard deviation of GBR to each stimulus type at Cz.

Oddball task

Although BPD patients showed smaller GBRs to both standard and target stimuli compared to control subjects, these differences were not statistically significant (Table 2 and Fig. 1). Clinical variables were not significantly associated with either standard or target stimuli (Supplementary Table 1). There was a trend association between the number of hospitalization and GBR to standard stimulus ($r = 0.30$, $p = 0.05$). Nonmedicated BPD individuals had smaller GBRs than medicated ones [*Standard*: nonmedicated = 0.63 (SD = 1.60), medicated GBR = 0.90 (SD = 1.40), $p = 0.80$; *Target*: nonmedicated = 1.00 (SD = 1.40), medicated GBR = 1.10 (SD = 1.30), $p = 0.80$] but differences were not significant. Control subjects and relatives of BPD did not differ significantly in either standard or target stimuli (Table 2 and Fig. 1).

Dual-click paradigm

Compared with control subjects, BPD patients showed significantly reduced gamma power to S1 stimuli ($p = 0.02$). Age of onset was significantly associated with S1 gamma power ($r = 0.33$, $p = 0.02$) (Supplementary Table 1); the younger the age of onset, the smaller the S1 gamma response. Gamma power to S2 stimuli was not significantly different between BPD patients and controls ($p > 0.05$), nor was there a significant association between S2 stimuli and age of onset (Table 2 and Fig. 2). For S1–S2 difference (gamma suppression), patients showed significantly less gamma suppression ($p = 0.05$) compared with controls. Age of onset was not significantly associated with gamma suppression ($r = 0.28$, $p > 0.05$). Control subjects and relatives of BPD did not differ significantly to any of the gamma response variables (Table 2 and Fig. 2).

Medication treatment was found to be associated with the GBRs. Although the majority of patients were on psychotropic medication at the time of testing ($n = 43$), a small number of patients were nonmedicated ($n = 14$). Comparing patients on and off medication, there was a significant group difference in gamma S1 responses, such that nonmedicated patients had smaller GBR activity than the medicated patients [nonmedicated = 0.42 (SD = 1.90), medicated = 1.22 (SD = 1.30), $p = 0.04$]. Similar trends were found in the GBR suppression measure [nonmedicated = 0.72 (SD = 1.40), medicated = 1.03 (SD = 0.99)] and the S2 gamma responses [nonmedicated = -0.17 (SD = 1.60), medicated = 0.26 (SD = 1.10)] but these differences were not statistically significant (all p -values > 0.05).

Structural equation modeling

Heritability of oddball task—Table 3 shows maximum likelihood estimates of twin/relatives correlations. Results of genetic model fitting do not differ substantially between the three models, therefore only Model 2 (point estimate) results are reported in Table 4. Results of Model 1 and Model 3 are presented in the supplementary material (see Supplementary Tables 2 and 3, respectively). MZ cross-member correlations of GBR to standard and target stimuli were greater than the corresponding sibling/parent–offspring correlations suggesting genetic contributions [*Standard*: MZ = 0.53 (95% CI: 0.52–0.59), non-MZ relatives = 0.28 (95% CI: 0.01–0.48); *Target*: MZ = 0.49 (95% CI: 0.48–0.59), non-MZ relatives = 0.27 (95% CI: -0.04 –0.32)] (Table 3). Significant heritabilities of GBRs were found to standard stimuli ($h^2 = 0.51$, 95% CI: 0.11–0.68) (Table 4) and to target stimuli ($h^2 = 0.35$, 95% CI: 0.08–0.54) with little or no shared environmental influences. Individual environmental

contributions of GBR to standard and target stimuli were estimated to be 0.49 and 0.65, respectively. The phenotypic correlations of evoked GBRs to standard and target stimuli with BPD were not significant (Table 3).

Heritability of dual-task stimuli—MZ cross-member correlations of GBRs to S1 and S2 stimuli were greater than the corresponding sibling/parent–offspring correlations [*S1*: MZ = 0.64 (95% CI: 0.41–0.77), non-MZ relatives = 0.29 (95% CI: –0.01–0.42); *S2*: MZ = 0.57 (95% CI: 0.32–0.72), non-MZ relatives = 0.27 (95% CI: –0.06–0.48)], suggesting genetic contributions (Table 3). Significant heritabilities of GBRs were found to S1 stimuli ($h^2 = 0.54$, 95% CI: 0.05–0.75) and to S2 stimuli ($h^2 = 0.50$, 95% CI: 0.05–0.69) (Table 4). In contrast, correlations in gamma power to S1–S2 difference were similar between MZ twins ($= 0.18$) and non-MZ family members ($= 0.11$), suggesting environmental effect on this phenotype (Table 3). Results of genetic analysis showed that the variance of gamma suppression was explained mainly by individual specific environmental factor (e^2), estimated to be 0.79 (95% CI: 0.56–0.97) (Table 4). Shared environmental effect (c^2) was nonsignificant 0.20 (95% CI: 0–0.36) and could be dropped from the model. Heritability estimate of gamma suppression was close to nil (Table 4).

A significant phenotypic correlation between reduced S1 GBR and BPD was found and estimated to be –0.08 (95% CI: –0.19 to –0.04). The source of this phenotypic correlation, due to genetic (R_g) or environmental (R_e) overlap with BPD, could not be determined as either parameter could be dropped from the model independently but not simultaneously. Evoked GBRs to S2 stimuli and to S1–S2 difference were not significantly associated with BPD (Table 3).

Discussion

This study is the first to examine evoked gamma oscillations in psychotic BPD patients and their clinically unaffected relatives using two different cognitive tasks and the first to investigate the genetic and environmental contributions of the GBRs in each condition by applying sophisticated structure equation modeling techniques.

Auditory oddball task

Genetic model fitting analyses revealed that evoked GBRs to both standard and target stimuli in the oddball task were heritable traits with little or no evidence of shared environmental effects. The heritability estimates were 0.51 to standard and 0.35 to target stimuli, respectively. Despite the evidence of being heritable traits, we found no evidence of significant impairment of GBR to either stimulus type in either patients with BPD or their unaffected relatives. This result was further supported by genetic analyses showing nonsignificant phenotypic associations of gamma responses with BPD. Evoked GBRs to stimuli in the oddball task, both standard and target, did not therefore emerge as an endophenotype for psychotic BPD.

The electrophysiological responses measured in the auditory oddball task have been hypothesized to reflect attention, working memory, and information processing speed (49). Early evoked gamma oscillations, occurring within 100 msec of stimulus onset, are believed to reflect localized neuronal activity within small areas of the brain and functionally important for early sensory registration such as perception of a sound stimulus. Although attention may modulate early evoked oscillatory responses (50) differences in GBRs to target stimuli were not significantly different than those of standard stimuli ($p > 0.05$) (Table 2). In addition, the magnitudes of GBRs to S1 stimuli in the dual-click paradigm were similar to GBRs to either stimulus type in the active oddball paradigm suggesting a primarily bottom-up early sensory registration process. The primary auditory cortex is likely

to be one of the brain regions where evoked GBRs are generated (51). In the present sample, no group differences were found between BPD patients, their relatives, and controls suggesting preserved neuronal activation in gamma frequency in processing of both standard and target tones. In contrast, in patients with schizophrenia reduced evoked GBR to standard tones have been reported by Roach and Mathalon (37) and by Hall et al. (36) but inconsistent results are also documented (38, 39). Family studies including unaffected relatives of schizophrenia patients are rare. A study from our group found that comparing to control subjects, unaffected MZ co-twin members of schizophrenic patients exhibit reduced evoked GBR to standard stimuli, similar to their affected MZ twins and this deficit is associated with schizophrenia diagnosis (36). Thus, evoked GBR deficits perhaps reflect an additional neural-connectivity dysfunction not seen in patients with psychotic BPD and could be considered as an endophenotype with potential specificity for schizophrenia. Future studies in first episode psychosis patients and in patients with affective illnesses (with or without psychosis) will be able to clarify whether evoked GBR deficits to higher cognitive task occur selectively in schizophrenia.

Dual-click paradigm

Compared to control subjects, BPD patients showed significant reductions in gamma power to S1 stimuli and to gamma suppression but patients were not significantly different from controls in their gamma power to S2 stimuli. Unaffected relatives did not differ from control subjects in any of the measures, suggesting deficits were specific to patients with psychotic BPD. One study by Carroll and colleagues (35) reported that patients with BPD, irrespective of psychosis history, did not differ from healthy controls on the evoked GBRs to either S1 or S2 stimuli. However, sample size of this study was moderate (psychosis positive $n = 13$, psychosis negative $n = 16$) and effects of age of onset on GBR were not assessed.

Genetic analyses revealed that evoked GBRs to both S1 and S2 stimuli were heritable traits. The heritability estimates were 0.54 to S1 and 0.50 to S2 stimuli, respectively. Shared environmental contribution to either condition was nonsignificant. A significant relationship between reduced S1 gamma activity and BPD was found and quantified to be -0.08 (CI: -0.19 to -0.04). However, the source of this association, due to genetic or environmental overlap with BPD, could not be determined due to a relative weak association. In subsequent analyses by comparing the full genetic model with its submodels to derive the best fitted model, we found that submodel containing shared genetic parameter (R_g) fitted the data better ($\chi^2 = 0.08$, $df = 1$) than the submodel containing shared environmental parameter (R_e) ($\chi^2 = 1.85$, $df = 1$), suggesting that shared genes were likely to account for the observed phenotypic correlation. Despite a possible genetic overlap, the relative weak association of evoked S1 GBR activity with BPD greatly limits its usefulness as endophenotype in molecular genetic studies.

In comparison to S1 and S2 responses, the majority of variance of the gamma S1–S2 score was attributed to the individual specific environmental effect (0.79) that includes measurement error (Table 4). The usefulness of S1 and S2 difference score as a measure of suppression depends, in part, on its reliability. The high individual specific environmental estimate might be the effect of background activity embedded in this secondary derived measure rather than true signals that are relevant to the suppressed neuronal activity. In the visual domain, the reliability of evoked GBR depends on the use of stimulation in the experiment paradigms and stimulus factors such as size (52, 53) and that reliable measurement of evoked GBRs is only possible if the stimulation is appropriate (54). In the present study, the MZ twin correlation could, to some extent, be perceived as a ‘reliability’ index, the negative lower confidence interval for the MZ correlation indicates that the distributional and statistical properties of this score are not optimal.

Alternatively, there might be real individual specific environmental effects influencing the strength of the gamma suppression measure but in the present study the precise environmental factors are unclear. We found that age of onset was significantly correlated with GBR to S1 stimuli (partial $r = 0.33$, $p = 0.02$) but not to gamma suppression (partial $r = 0.28$, $p = 0.11$) or to S2 stimuli (partial $r = 0.17$, $p = 0.26$). Other clinical variables including number of hospitalization, age of first hospitalization were not significantly associated with gamma suppression deficit (Supplementary Table 1). The effects of smoking tobacco on evoked GBRs have been documented in the literature showing that, in healthy individuals, smokers exhibit larger GBRs and gamma suppression than nonsmokers (55). In the current sample, we found a similar trend in healthy controls and in relatives such that smokers had larger gamma responses to both S1 (healthy control mean: smoker = 1.61 versus nonsmoker = 1.39; relatives mean: smoker = 1.65 versus nonsmoker = 1.13) and S2 stimuli (healthy control mean: smoker = 0.57 versus nonsmoker = 0.30; relatives mean: smoker = 0.45 versus nonsmoker = 0.40) and greater gamma suppression (healthy control mean: smoker = 1.31 versus nonsmoker = 0.97; relatives mean: smoker = 1.08 versus nonsmoker = 0.93). However, these differences were not statistically significant (all p -values > 0.05). In BPD patients, smokers had larger GBR to S2 stimulus than nonsmokers (smoker = 0.21 versus nonsmoker = 0.12, $p > 0.05$) but smaller GBRs to S1 stimulus and to gamma suppression than nonsmokers (S1 mean: smoker = 0.79 versus nonsmoker = 1.13, $p > 0.05$; gamma suppression mean: smoker = 0.43 versus nonsmoker = 0.73, $p > 0.05$).

Another possible environmental factor, medication treatment, was found to be associated with the GBRs. Nonmedicated patients had significantly smaller GBR activity to S1 stimuli than the medicated individuals. Similar trends were found in the GBR suppression measure and the S2 gamma responses as well as in the GBR responses to stimuli in the oddball task. Medication treatments thus appear to enhance gamma responses in BPD patients. The fast synaptic inhibitory GABA neurons appear to be critically involved in generating gamma-band oscillations (56). The observed medication effect on GBRs is likely induced by altering GABAergic neurotransmission resulting in enhanced inhibitory inputs from GABAergic interneurons and improved synchronized neuronal activity.

Comparing patients who are taking a single medication with those who are taking multiple medications, GBR activities were not statistically different (S1 stimulus: single = 1.53, poly = 1.14; S2 stimulus: single = 0.14, poly = 0.29; S1–S2: single = 1.35, poly = 0.95; all p -values > 0.05). To our knowledge, the effects of mood stabilizers and polypharmacy on evoked gamma oscillations in BPD have not been systematically evaluated. Future studies will need to confirm the enhancement impact of psychotropic medicines and the effect of a specific medication on GRBs in BPD.

Suppression of the P50 ERP in the dual-click paradigm has been used in human and animals as a putative measure of the strength of inhibitory mechanisms in the central nervous system (57). However, the validity of gamma suppression for probing the same inhibitory mechanism as the P50 ERP has not been supported in the literature. Although P50 ERP has been suggested to be a subcomponent of the GBRs and that P50 sensory gating ERP may be a proxy for GBR suppression (58), a report by Carroll et al. (35) found while patients with BPD as a group show P50 ERP sensory gating deficit comparing to control group, gamma suppression was not significantly different between groups, suggesting separate neuronal response processes. Brenner and colleagues (59) also found no group differences in gamma S1–S2 difference score between patients with schizophrenia and control subjects. Furthermore, a study by Clementz and Blumenfeld (60) reported a significant P50 ERP sensory gating deficit but normal gamma suppression in schizophrenic patients. In the current sample, gamma suppression was not significantly correlated with P50 sensory gating ERP (controls $r = -0.05$, BPD patients $r = -0.12$, well relatives $r = 0.03$; all $p > 0.05$). This

finding is consistent with Hong et al. (61) and Hall et al. (34) who reported nonsignificant correlations between P50 sensory gating and gamma suppression. The populations in these two studies included patients with schizophrenia and their unaffected relatives. Taken together, it seems that across different populations the components of information processing assessed by gamma frequency-specific gating measure appear to be, for the most part, functionally distinct from those mediated by P50 ERP sensory gating.

On the other hand, we found that the GBR responses to the S1 and S2 stimuli were significantly correlated with the conventional ERP amplitude measures (e.g., P50). Correlations between the GBR S1 response and the ERP S1 amplitude were 0.42 ($p < 0.01$) for controls, 0.59 ($p < 0.01$) for patients, and 0.40 ($p = 0.08$) for relatives. Correlations between the GBR S2 response and the ERP S2 amplitude were 0.38 ($p < 0.01$) for controls, 0.41 ($p = 0.03$) for patients, and 0.47 ($p = 0.01$) for relatives. These results are in agreement with those of Kisley and Cornwell (62) who reported significant positive correlations between P50 ERP amplitudes and gamma power to S1 and S2 stimuli. The positive relationships between GBRs and P50 amplitude responses to both S1 and S2 stimuli suggest a contribution of gamma frequency to P50 ERP activity.

Reduced auditory evoked gamma responses to 40 Hz click trains during auditory steady-state driving paradigm have been reported in BPD patients (27, 29–31). Although such data are not available in the current sample and a direct comparison is not possible, both the steady-state driving paradigm and dual-click paradigm are simple auditory tasks that require little engagement of top-down cognitive processes. In contrast, the oddball task involves higher level of cognitive modulation. Deficit of gamma S1 responses in the dual-click task but not in the oddball task thus may be associated with differences in auditory paradigm used in the experiment. The role of attentional engagement to task-relevant features of stimulus processing has been reported by examining ERPs with time-frequency methods (35). A subgroup of BPD patients without a history of psychosis exhibit significant reduced low-frequency activity compared to those with a history of psychosis or nonpsychiatric controls. In the current sample, all patients have a history of psychosis. An additional group of BPD patients without a history of psychosis is needed to clarify the potential influence of controlled selective attention on the early, stimulus-evoked low-frequency activity in BPD patients.

In summary, the present study indicates that gamma responses to standard and target stimuli in the oddball task and to S1 and S2 stimuli in the dual-click tasks are heritable traits. However, deficits are not observed in clinically unaffected relatives. S1 gamma activity in the dual-click paradigm was associated with BPD, although the weak association limits its use as endophenotype. Evoked GBRs to other stimulus types do not appear to satisfy criteria for being BPD endophenotypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Evoked gamma activity to standard and target stimuli in oddball task in healthy controls, bipolar disorder (BPD) patients, and unaffected relatives of BPD patients.

Fig. 2.
Evoked gamma activity to S1 and S2 stimuli in dual-click paradigm in healthy controls, bipolar disorder (BPD) patients, and unaffected relatives of BPD patients.

Table 1

Demographic characteristics of the sample

	BPD patients (n = 59)	Well BPD relatives (n = 51)	Controls (n = 198)	Statistic (df)	p-value
Age, years	42.34 (11.7) ^a	42.79 (11.9) ^b	37.22 (12.1)	$F(2,165) = 5.42$	0.01
Age range, years	22–61	21–61	18–60		
Female sex, n (%)	39 (66.1)	23 (47.9) ^b	136 (69.4)	$F(2,165) = 3.61$	0.03
Education, years	14.27 (3.2)	15.13 (3.0)	14.82 (2.4)	$F(4,164) = 1.06$	0.35
Parental SES	2.64 (1.2) ^c	2.28 (0.9) ^b	2.79 (0.9)	$F(4,155) = 6.45$	0.04
Age of onset, years	21.96 (6.3)	n/a	n/a	–	–
Duration of illness, years	20.98 (10.9)	n/a	n/a	–	–
No. of hospitalizations	4.81 (4.8)	n/a	n/a		
Lifetime DSM diagnosis of substance abuse or dependence	(A) dependence = 4 (A)/(S) abuse = 4 (S) abuse = 1	(A) dependence = 2 (A)/(S) dependence = 1 (A)/(S) abuse = 1 (S) abuse = 3	(A) abuse = 4 (A)/(S) dependence = 1 (A)/(S) abuse = 1 (S) abuse = 3	–	–
Current smoker, n (%)	20 (34.5) ^a	9 (19.1)	36 (18.4)	$F(4,164) = 4.28$	< 0.01
No. cigarettes/day	19.6 (12.2) ^a	8.89 (4.8)	9.75 (5.2)	$F(4,49) = 3.90$	< 0.01

Data are presented as mean (SD) unless otherwise indicated. BPD = bipolar disorder; SES = socioeconomic status (A) = alcohol; (S) = substance.

^aSignificant difference between patients and controls ($p < 0.05$).

^bSignificant difference between relatives and controls ($p < 0.05$).

^cSignificant difference between relatives and patients ($p < 0.05$).

Table 2
Summary statistics and mean (SD) group comparisons of evoked gamma power response (μV^2) indices

	Controls	BPD patients	Well BPD relatives	BPD versus controls	Relatives versus controls
Oddball paradigm					
Standard	1.18 (1.2)	0.85 (1.4)	1.14 (1.2)	$t = -1.03, p = 0.30$	$t = 0.06, p = 0.95$
Target	1.29 (1.3)	1.09 (1.5)	1.27 (1.3)	$t = -0.31, p = 0.75$	$t = 0.74, p = 0.46$
Dual-click paradigm					
S1 click	1.44 (1.1)	1.00 (1.5)	1.21 (1.4)	$t = -2.38, p = 0.02$	$t = -0.32, p = 0.40$
S2 click	0.33 (1.2)	0.14 (1.3)	0.42 (1.2)	$t = -0.88, p = 0.38$	$t = 0.24, p = 0.81$
S1-S2 difference	1.04 (1.1)	0.61 (1.3)	0.77 (1.4)	$t = -1.94, p = 0.05$	$t = -0.20, p = 0.84$

Age, sex, and age of onset were included in regression model as covariates. Values have been normalized using a log transformation. BPD = bipolar disorder.

Table 3

Maximum likelihood estimates (95% CI) of correlations between bipolar disorder (BPD), gamma band responses (GBR), and monozygotic (MZ)/relatives correlations

GBR variable	Correlation of GBR across members		Correlation with BPD across members		Correlation with BPD
	MZ	Sib/Parent-offspring	MZ	Sib/Parent-offspring	
Oddball task					
Standard	0.53 (0.52–0.59)	0.28 (0.01–0.48)	–0.05 (–0.06–0.13)	–0.04 (–0.06–0.04)	–0.09 (–0.21–0.03)
Target	0.49 (0.48–0.59)	0.27 (–0.04–0.32)	0.02 (0.00–0.05)	–0.02 (–0.10–0.06)	–0.08 (–0.18–0.04)
Dual-click paradigm					
S1 click	0.64 (0.41–0.77)	0.29 (–0.01–0.42)	–0.14 (–0.29–0.01)	0.04 (–0.11–0.19)	–0.08 (–0.19 to –0.04)
S2 click	0.56 (0.35–0.68)	0.30 (0.02–0.48)	–0.13 (–0.28–0.03)	0.00 (–0.15–0.16)	–0.11 (–0.22–0.01)
S1–S2 difference	0.18 (–0.13–0.45)	0.11 (–0.12–0.37)	–0.13 (–0.30–0.04)	–0.03 (–0.18–0.12)	–0.10 (–0.22–0.02)

Confidence intervals (CI) including zero indicate nonsignificance.

Heritability, shared- and individual-specific environmental estimates (95% CI) of full genetic models for each gamma band response index

Table 4

	h^2	c^2	e^2	R_g	R_e
Oddball: Standard					
Model 2	0.51 (0.11–0.68)	0.00 (0.00–0.00)	0.49 (0.32–0.71)	–0.05 (–0.30–0.18)	–0.21 (–0.63–0.24)
Oddball: Target					
Model 2	0.35 (0.08–0.54)	0.00 (0.00–0.15)	0.65 (0.46–0.85)	–0.05 (–0.30–0.18)	–0.21 (–0.63–0.24)
Dual-click paradigm: S1 click					
Model 2	0.54 (0.05–0.75)	0.07 (0.00–0.43)	0.39 (0.24–0.61)	–0.15 (–0.55–0.07)	0.08 (–0.37–0.53)
Dual-click paradigm: S2 click					
Model 2	0.50 (0.05–0.69)	0.03 (0.00–0.37)	0.47 (0.30–0.69)	–0.17 (–0.26–0.12)	0.02 (–0.41–0.45)
Dual-click paradigm: S1–S2 difference					
Model 2	0.01 (0.00–0.01)	0.20 (0.00–0.36)	0.79 (0.56–0.97)	–1.00 (–1.00–1.00)	–0.01 (–0.39–0.39)

Confidence intervals including zero indicate nonsignificance. Parameters for bipolar disorder in Model 2 were fixed to: $h^2 = 0.85$, $c^2 = 0.00$, $e^2 = 0.15$. Results of Models 1 and 3 are reported in the *Supplementary Material*. h^2 = heritability estimates; c^2 = shared environmental estimates; e^2 = nonshared environmental estimates; R_g = genetic; R_e = environmental.