

Evidence of Disrupted Prepulse Inhibition in Unaffected Siblings of Bipolar Disorder Patients

Stella G. Giakoumaki, Panos Roussos, Maria Rogdaki, Costandina Karli, Panos Bitsios, and Sophia Frangou

Background: Prepulse inhibition (PPI) of the startle response refers to a reduction in the response to a strong stimulus (pulse) if preceded shortly by a weak stimulus (prepulse). Disrupted PPI is thought to reflect abnormalities in the inhibitory control of information processing. Reduced PPI has been reported in mania, although it is not clear whether it represents a trait feature of bipolar disorder (BD). To address this issue, the present study examined whether disrupted PPI is present in individuals at high risk for BD.

Methods: Twenty-one remitted BD patients and 19 of their unaffected siblings were compared with 17 age- and gender-matched healthy volunteers on tests of acoustic startle reactivity and PPI of the startle response.

Results: There were no group differences in startle reactivity. Compared with healthy individuals, BD patients and their unaffected siblings showed lower PPI. In the patient group, no significant correlations were found between PPI and measures of symptom and disease severity or medication.

Conclusions: This is the first study to report reduced PPI in remitted BD patients and their unaffected first-degree relatives. This finding, although in need of replication, suggests that PPI disruption may represent a trait deficit in BD associated with genetic predisposition.

Key Words: Bipolar disorder, familial high risk, prepulse inhibition, trait marker

Prepulse inhibition (PPI) of the acoustic startle response refers to a reliable reduction in the magnitude of the blink reflex component of the startle response to a strong auditory stimulus (the pulse) if it is preceded for 50 to 300 msec by a weak stimulus (the prepulse) (Graham 1975). Prepulse inhibition is considered a measure of "sensorimotor gating," whereby prepulses reduce the effect of subsequent sensory stimuli to protect the brain from sensory overload (Graham 1975). Prepulse inhibition is a stable neurobiological marker with high reliability across repeated test sessions (Cadenhead *et al.* 1999).

Prepulse inhibition deficits have been described in a number of brain disorders where abnormalities in inhibitory mechanisms controlling sensory, motor, or cognitive function are considered a shared core feature. These include neurological disorders such as Tourette syndrome (Castellanos *et al.* 1996) and Huntington disease (Swerdlow *et al.* 1995), as well as several psychiatric syndromes. Lower PPI has been observed in attention-deficit/hyperactivity disorder (Ornitz *et al.* 1992), panic disorder (Larsen *et al.* 2002; Ludewig *et al.* 2002), obsessive-compulsive disorder (Schall *et al.* 1996; Swerdlow *et al.* 1993), and schizophrenia (Braff *et al.* 2001). Prepulse inhibition deficits have also been described in unaffected relatives of patients with schizophrenia and subjects with schizotypal personality disorder (Cadenhead *et*

al. 2000), suggesting a genetically transmitted deficit in sensorimotor gating in psychotic disorders.

Abnormalities in inhibitory control are characteristic of mania (Christodoulou *et al.* 2006; Murphy *et al.* 1999), the diagnostic hallmark of bipolar disorder (BD), and PPI deficits have been observed in acutely manic patients (Perry *et al.* 2001). Deficits in tests of response inhibition have been consistently reported in remitted BD patients (Frangou *et al.* 2005; Martinez-Aran *et al.* 2004; Quraishi and Frangou 2002; Robinson *et al.* 2006), as well as in their unaffected first-degree relatives (Frangou *et al.* 2005; Zalla *et al.* 2004), suggesting that dysfunction in inhibitory control may be a trait feature of BD associated with genetic predisposition to the disorder. However, PPI in remitted adult (Barrett *et al.* 2005) and pediatric (Rich *et al.* 2005) BD patients has been reported to be comparable with that of control subjects. Both studies included patients on treatment with mood-stabilizing and antipsychotic medications. Both types of medication can affect PPI; lithium (O'Neill *et al.* 2003) and, in schizophrenic patients, antipsychotics (Leumann *et al.* 2002; Weike *et al.* 2000) appear to have a normalizing effect, while valproate may have the opposite effect. Therefore, the contribution of medication to existing findings regarding PPI in BD remains unclear. Alternatively, mechanisms other than abnormal sensorimotor gating may be involved in the observed deficits in inhibitory control in remitted BD patients and their first-degree relatives.

To address these issues, we examined PPI in remitted BD patients and their unaffected siblings. Our hypothesis was that if disrupted PPI is indeed a trait deficit in BD, then it should be present in individuals at high risk for the disorder by virtue of their positive family history.

Methods and Materials

Subjects

The study was approved by the Ethics Committee of the University of Crete. Patients with bipolar disorder I (BDI), as defined in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (American Psychiatric Association 1994) were recruited through outpatient facilities at the University Hospital of Heraklion, Crete, if they met the following inclusion

From the Department of Psychiatry and Behavioral Sciences (SGG, PR, MR, CK, PB), Medical School, University of Crete, Crete, Greece; and Section of Neurobiology of Psychosis (SF), Institute of Psychiatry, London, United Kingdom.

Address reprint requests to Panos Bitsios, M.D., Ph.D., Department of Psychiatry and Behavioral Sciences, Faculty of Medicine, PO Box 2208, University of Crete, Heraklion 71003, Crete, Greece; E-mail: pbitsios@med.uoc.gr.

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criteria: 1) age: 18 to 50 years; 2) met DSM-IV criteria for remission and scored less than 7 on both the Hamilton Depression Rating Scale and Young Mania Rating Scale on the day of testing; 3) were on the same type and dose of medication for the preceding 3 months; and 4) had an unaffected sibling of the same sex and within 4 years of age of the patient. Exclusion criteria were: 1) additional Axis I diagnoses; 2) family history of schizophrenia (up to second-degree relatives); 3) the presence of a neurological disorder; 4) substance abuse in the preceding 6 months; 5) a positive result on urine toxicology screen at the time of study entry; 6) history of head injury with loss of consciousness; 7) the presence of an unstable medical condition or contraindications to individual study investigations (e.g., current treatment with steroids, antihypertensives, and similar medications); and 8) electroconvulsive treatment in the past 12 months. In addition, relatives (high-risk group [HR]) were excluded if they had a personal history of mood disorder or psychosis. Healthy comparison subjects matched to the HR individuals for gender, age, and years of education were also recruited from the local community via advertisement. Additional exclusion criteria for comparison subjects were the presence of personal or family history of mood or schizophrenia spectrum disorders.

Based on the above criteria, 21 BD patients (11 men, 10 women), 21 of their unaffected siblings (11 men, 10 women), and 19 healthy comparison subjects (10 men, 9 women) were recruited. All participants underwent the same diagnostic evaluation. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) were used for Axis I and II diagnoses, respectively (First *et al.* 1994, 1997). Psychopathology was rated using the Hamilton Depression Rating Scale (HAM-D) (Hamilton 1960), the Young Mania Rating Scale (YMRS) (Young *et al.* 1978), and the Global Assessment of Functioning (GAF). Family history of psychiatric disorders was assessed using the Family Interview for Genetic Studies (FIGS) (Maxwell 1992), supplemented by medical notes as necessary.

After complete description of the study to the subjects, written informed consent was obtained.

Procedure

Patients underwent PPI assessment only if they had been remitted and on the same type and dose of medication for the preceding 3 months and had a total score of 7 or less on the HAM-D and YMRS on the day of their assessments. All participants underwent PPI assessment only if they had a hearing threshold of 1 kHz > 20 dB. None of the participants were excluded for not meeting this criterion. All participants had been instructed to maintain their normal patterns of caffeine and nicotine consumption until the morning of the experimental testing to avoid possible effects of caffeine (Swerdlow *et al.* 2000) and nicotine withdrawal (Kumari and Gray 1999) on PPI, but they were required to refrain from smoking cigarettes for one-half hour before testing because of reported modulatory effects of nicotine on PPI (Swerdlow *et al.* 1999).

Subjects were seated comfortably in a reclining chair and they were instructed to keep their eyes open. A commercially available electromyographic (EMG) startle system (EMG SR-LAB, San Diego Instruments, San Diego, California) was used to examine the eyeblink component of the acoustic startle response. This was used to deliver acoustic startle stimuli and record the electromyographic activity for 150 msec (sample interval = 1 msec) starting from the onset of the startle stimulus, and the raw data were stored for later application of rejection criteria and

averaging. Acoustic stimuli were administered binaurally through headphones (model TDH-39-P, Maico Minneapolis, Minnesota). The eyeblink component of the startle reflex was indexed by recording EMG activity of the orbicularis oculi muscle directly beneath the right eye, by positioning two miniature silver/silver chloride electrodes filled with Signa Gel electrolyte paste (Parker Laboratories, Inc, Fairfield, New Jersey) with a ground electrode behind the right ear on the mastoid ($R < 10 \text{ k}\Omega$). Electromyographic activity was band-passed (100–1000 Hz) filtered and a 50-Hz filter was used to eliminate the 50-Hz interference.

The startle session began with a 3-minute acclimation period of 70 dB white noise, which continued throughout the session, followed by one block of 24 trials, which consisted of 6 trials for each of the two prepulse conditions (see below), 6 prepulse-alone trials, and 6 pulse-alone trials, presented in pseudorandom order with the constraint that no two identical trials occurred in succession. The startle stimuli consisted of 115 dB [A] 40-msec bursts of broadband white noise with near instantaneous rise-fall time. The prepulse stimuli consisted of 20-msec 85-dB white noise, which preceded the startle stimulus by 60 msec and 120 msec. The intertrial interval averaged 15 sec with a range of 8 to 22 sec. The entire test session lasted approximately 10 minutes. Prior to scoring and data analysis, all recordings were screened for spontaneous eyeblink activity. Trials were excluded if excessive EMG activity (>20 digital units = 48.8 μV) was observed during the first 20 msec of recording or when onset latencies (defined by a shift of 20 digital units = 48.8 from the baseline value, occurring within 20 to 85 msec after the onset of the pulse stimulus) and peak latencies (the point of maximal amplitude) differed by more than 95 msec (Braff *et al.* 1992). The percentage of rejected trials based on these criteria was 7% for the patient group, 8% for the siblings, and 4% for the control group. Subjects were excluded from further analysis if they had negligible startle responses (mean amplitude < 10 mV) and/or if they had more than three trials per trial type discarded. Two HR individuals (one male, one female) and two healthy comparison subjects (two females) were excluded based on these criteria. Data were therefore analyzed from 21 patients (M:F = 11:10), 19 HR subjects (M:F = 11:8), and 17 control subjects (M:F = 10:7). The maximum absolute amplitudes of the raw EMG data occurring in the 20 to 150 msec time window of the nonrejected trials were scored offline, averaged across all trials of the same type, and stored for data analysis.

The following EMG startle measures were examined:

1. EMG activity was defined as the mean EMG activity to all the prepulse-alone trials.
2. Baseline startle response was defined as the mean magnitude of the startle response to all the pulse-alone trials.
3. Habituation of the startle response was measured by assessing the decrement in the magnitude of the startle response to pulse-alone trials across all of the pulse-alone trials over the entire session.
4. Prepulse startle modification was calculated as the percent decrement (%PPI) in startle magnitude in the presence of the prepulse compared with the magnitude without the prepulse according to the formula $[(\text{Amplitude}_{\text{Pulse-alone}} - \text{Amplitude}_{\text{prepulse-pulse}}) / \text{Amplitude}_{\text{Pulse-alone}}] \times 100$. Prepulse inhibition data were inspected for normality and homogeneity using the Kolmogorov-Smirnov test.

Statistical Analysis

The distribution of all variables using the Kolmogorov-Smirnov test was found to be normal. To assess group differences in

habituation, mean startle magnitude for the pulse-alone trials was assessed using repeated measures analysis of variance (ANOVA) with trial (six levels) as the within-subject and group (three levels) and gender (two levels) as the between-subject factors. Prepulse inhibition data were analyzed with repeated measures ANOVA (group [3 levels] and gender [2 levels] as the between-subject and lead interval [2 levels] as the within-subject factors).

Demographic data (age, years of education, number of smokers) were compared between the groups using either analysis of variance or Pearson's chi-square.

The effect of medication and clinical features (age of onset, illness duration, and episode frequency) on PPI for each of the interval conditions was explored using Pearson's correlation coefficient. For patients on antipsychotic medication, the correlations with dose were examined twice using conversion to chlorpromazine (CPZ) equivalents and clinically equivalent doses, as there is no agreed method for converting the dose of atypical antipsychotics (Bezchlibnyk-Butler and Jeffires 2000).

Results

Demographic, Clinical, and EMG Data

The mean age of patients was 32.86 ± 7.29 years, siblings was 31.63 ± 7.50 years, and control subjects was 31.64 ± 6.90 years. Patients had, on average, 11.17 ± 4.19 years of education, their siblings 12.10 ± 3.93 years, and control subjects 13.06 ± 4.08 years. The mean EMG activity for the patients, their siblings, and the control subjects was 13.6 ± 9.9 , 23.7 ± 33.9 , and 15.1 ± 6.5 , respectively. Mean baseline startle was 77.72 ± 53.15 for patients, 88.77 ± 55.89 for their siblings, and 115.98 ± 94.11 for control subjects. The groups did not differ in age [$F(2,56) = .19$; $p = .83$], years of education [$F(2,56) = 1.02$; $p = .37$], gender ratio (Pearson $\chi^2 = .19$, $df = 2$, $p = .91$), EMG activity [$F(2,56) = 1.33$; $p = .27$], or baseline startle [$F(2,56) = 1.51$; $p = .23$], but there were more smokers in the BD patient group (Pearson $\chi^2 = 6.78$, $df = 2$, $p < .034$). Table 1 shows the clinical description of the patient group. All BD patients were medicated with either lithium

Table 1. Clinical Characteristics of the BD Group

	Bipolar Patients (n = 21)
Mean Duration of Untreated Illness (SD) in Months	27.81 (41.22)
Mean Duration of Illness (SD) in Months	119.52 (97.62)
Mean Age at Onset (SD) in Years	23.57 (5.80)
Mean Number of Total Episodes	5.38 (4.34)
Mean HAMD Total Score (SD)/Range	3.43 (2.48)/(0–7)
Mean YMRS Total Score (SD)/Range	3.29 (2.28)/(0–7)
Mean BPRS Total Score (SD)	27.00 (5.18)
Mean GAF Score (SD)	72.71 (9.83)
% (number) on Antipsychotic Medication	71.42 (15)
% (number) on Typical; Atypical; Combined	23.8 (5); 33.33 (7); 14.28 (3)
Mean Antipsychotic Dose (SD) CPZ Equivalents (mg)	450.07 (363.08)
Mean Antipsychotic Dose (SD) Clinical Equivalents (mg)	367.63 (313.56)
% (number) on Lithium/Mean Dose (SD) (mg)	28.57 (6)/1265 (324.45)
% (number) on Valproate/Mean Dose (SD) (mg)	23.8 (5)/1060 (631.86)
% (number) on Carbamazepine/Mean Dose (SD) (mg)	52.38 (11)/654.55 (350.32)

HAMD, Hamilton Depression Scale; YMRS, Young Mania Rating Scale; BPRS, Brief Psychiatric Rating Scale; GAF, Global Assessment of Functioning; CPZ, chlorpromazine; SD, standard deviation.

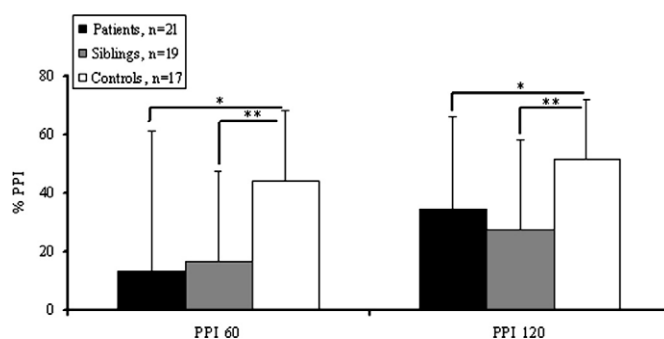


Figure 1. Percentage prepulse inhibition (%PPI) of the three groups across the trial types. Columns represent group means and bars represent standard deviations (SDs). * $p = .01$, ** $p = .009$. PPI, prepulse inhibition.

or an anticonvulsant (one patient was on a combination). Fifteen patients were also prescribed antipsychotics. Of these, 10 had a history of psychotic symptoms during mood episodes. In most cases, the antipsychotic drug prescribed was not used to treat past or current psychotic symptoms but rather as a mood stabilizer. Details of the medication are also shown in Table 1.

Startle Reactivity and Habituation

Startle reactivity and habituation were examined across the test session by using data from pulse-alone startle trials. Comparison of the three groups using a $3 \times 2 \times 6$ (group \times gender \times trial) repeated measures ANOVA showed no significant group or gender differences in startle reactivity [$F(2,51) = 1.33$; $p = .28$ and $F(1,51) = .08$; $p = .78$, respectively]. There was a significant trial effect [$F(5,255) = 7.51$; $p = .000$] that reflected startle habituation, but the group \times trial [$F(10,255) = 1.16$; $p = .32$], gender \times trial [$F(5,255) = 1.29$; $p = .27$], group \times gender [$F(2,51) = .15$; $p = .86$], and the group \times gender \times trial [$F(10,255) = .69$; $p = .74$] interactions were not significant.

Prepulse Inhibition

Comparison of the three groups using a $3 \times 2 \times 2$ (group \times gender \times lead interval) repeated measures ANOVA showed a significant main effect of group [$F(2,51) = 3.96$; $p = .025$]. Follow-up with Dunnett's test showed that the patient and the sibling group had significantly lower PPI compared with the control group ($p = .01$ and $p = .009$, respectively; Figure 1). There was a significant main effect of lead interval [$F(1,51) = 9.31$; $p = .004$] but not gender [$F(1,51) = 1.18$; $p = .28$]. No interactions were significant.

A comparison of patients with and without a history of psychotic features during mood episodes ($n = 10$ and $n = 11$, respectively) did not reveal group differences or a significant group by lead interval interaction (all F values < 1). Patients receiving antipsychotic treatment had smaller baseline startle compared with patients who were not [$F(1,19) = 7.54$; $p < .013$], but they did not differ in PPI. There were no significant correlations between PPI at 60 msec and 120 msec and the dose of antipsychotics in CPZ or clinical equivalent doses (all p 's $> .247$), lithium (all p 's $> .885$), valproate (all p 's $> .629$), and carbamazepine (all p 's $> .195$). Similarly, the levels of psychopathology, age of onset, duration of illness, and episode frequency did not show any significant correlation with PPI at 60 msec or 120 msec (all p 's $> .197$).

Seven patients, five siblings, and one control subject showed prepulse facilitation (PPF) at 60 msec interval. There is no consensus regarding the mechanisms underpinning PPF. Aasen

et al. (2005) suggested that PPI and PPF (with discrete prepulses) both reflect sensorimotor gating and perhaps genetic predisposition to BD may be associated with a general downward shift in the inhibition curve and upward shift (greater negative values means greater PPF and thus an upward shift) in the facilitation curve.

Discussion

We found lower PPI in remitted, medicated BD patients and in their unaffected siblings. To our knowledge, this is the first study to examine PPI differences between healthy control subjects and subjects at high familial risk for BD.

Previous literature suggested that disrupted PPI was a state-dependent abnormality, present in mania (Perry *et al.* 2001), and not a trait feature of BD, as two studies had reported PPI to be comparable with that of control subjects in remitted BD patients (Barrett *et al.* 2005; Rich *et al.* 2005). However, in this study, PPI was found to be disrupted in remitted BD patients. Differences in methodology and sampling frame may account for this discrepancy. Rich *et al.* (2005) examined BD patients aged 9 to 17 years, with a mean age of about 12 years, and compared their levels of PPI with those of age- and gender-matched control subjects. Although sensorimotor gating mechanisms are reported to reach maturation by the age of 8 years (Ornitz *et al.* 1986), the authors noticed that the PPI levels in their young healthy subjects were lower than those commonly observed in adults. This may have reduced the power of the study to detect group differences. A further consideration is whether disrupted PPI is associated with the presence of psychosis. Participants in the Barrett *et al.* (2005) study were not screened for psychosis, and only 4 of the 16 patients in the study by Rich *et al.* (2005) had a history of psychosis. It is difficult to argue in favor of psychosis being a key determinant here, as disrupted PPI has been noted in nonpsychotic conditions (such as obsessive-compulsive disorder). In this study, having a history of psychosis did not seem to impact on PPI measures in BD patients, while PPI was disrupted in their unaffected first-degree relatives who did not have a personal history of mental illness. Finally, all studies that have examined PPI in BD patients have included medicated samples. Existing evidence suggests that antipsychotics (Leumann *et al.* 2002; Weike *et al.* 2000) and lithium (O'Neill *et al.* 2003) tend to normalize PPI, although it is not clear whether this effect is mediated by symptomatic improvement (Kumari *et al.* 2000). On the other hand, there is tentative evidence that valproate may disrupt PPI (Barrett *et al.* 2005). Given that most patients in all studies, including our own, were prescribed more than one type of medication and were assessed only cross-sectionally, the net impact of pharmacological treatment on PPI levels cannot be determined.

The finding of reduced PPI in the unaffected siblings of the BD patients suggests that abnormalities in sensorimotor gating mechanisms may represent a trait deficit in BD associated with genetic predisposition to the disorder. The main advantage of including this high-risk sample is that the possible confounding effects of medication, psychopathology, or other illness-related features could be avoided. Lower PPI in unaffected relatives of BD patients is consistent with enhanced susceptibility to interference and reduced response inhibition that has already been reported in neurocognitive studies of relatives of patients with BD (Christensen *et al.* 2006; Frangou *et al.* 2005; Zalla *et al.* 2004). Abnormalities in tests of interference and response inhibition have also been noted in remitted BD patients, most commonly when performing different versions of the Stroop

Color Word Task (SCWT) (Frangou *et al.* 2005; Robinson *et al.* 2006). Furthermore, functional magnetic resonance imaging (fMRI) studies of remitted BD patients performing the SCWT have consistently shown dysfunction in the ventral prefrontal cortex (Blumberg *et al.* 2003; Kronhaus *et al.* 2006). In healthy participants undergoing fMRI, performance of a passive PPI paradigm was associated with increased cortical activation in the ventral prefrontal cortex (inferior frontal gyrus), among other regions (Kumari *et al.* 2003). Although highly speculative, it is tempting to suggest that perhaps ventral prefrontal dysfunction may be the neural mechanism underlying observed abnormalities in PPI and in interference and response inhibition observed in BD patients and their relatives.

In summary, we found lower PPI in remitted BD patients and their unaffected siblings, thus providing the first evidence for disrupted PPI being a genetically mediated trait abnormality in BD.

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