Genetic overlap between bipolar illness and event-related potentials

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ABSTRACT

Background. Electrophysiological endophenotypes are far less explored in bipolar disorder as compared to schizophrenia. No previous twin study of event-related potentials (ERPs) in bipolar illness has been reported. This study uses a twin design and advanced genetic model fitting analyses aiming to (1) assess and quantify the relationship of a range of ERP components with bipolar disorder with psychotic features, and (2) examine the source of the relationship (due to genetic or environmental factors).

Method. P300, P50 suppression and mismatch negativity (MMN) were recorded in 10 discordant monozygotic (MZ) bipolar twin pairs, six concordant MZ bipolar twin pairs and 78 control twin pairs. Statistical analyses were based on structural equation modelling.

Results. Bipolar disorder was significantly associated with smaller P300 amplitude and decreased P50 suppression. Genetic correlations were the main source of the associations, estimated to be -0.33 for P300 amplitude and 0.46 for P50 ratio. Individual-specific environmental influences were not significant. MMN and P300 latency were not associated with the illness.

Conclusions. The results provide supporting evidence that P300 amplitude and P50 suppression ratio are ERP endophenotypes for bipolar disorder.

INTRODUCTION

Bipolar disorder is a highly heritable, chronic and disabling illness and has a complex aetiology (Shastry, 2005). No genes for bipolar disorder have been identified definitively, although there are many promising candidates (Levinson *et al.* 2003; DePaulo, 2004; Craddock *et al.* 2005; Green *et al.* 2005; McQueen *et al.* 2005; Raybould *et al.* 2005). Attempts have been made to find endophenotypes that can reduce the phenotypic complexity of bipolar disorder,

improve the power in identification of possible gene carriers, and help to clarify the biological and genetic basis of the disorder (Lenox *et al.* 2002; Hasler *et al.* 2006).

The event-related potential (ERP) components, P50 suppression, P300 amplitude and latency, and mismatch negativity (MMN) have been proposed as potential endophenotypes for schizophrenia on the basis of family studies (Jeon & Polich, 2001, 2003; Bramon *et al.* 2004; Umbricht & Krljes, 2005). Few studies, however, have investigated these ERPs in patients with bipolar disorder. In addition, the potential of using the ERP measures as endophenotypes for bipolar disorder is far less explored than for schizophrenia. Of the ERP studies reported,

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bipolar patients show some similar impairments with schizophrenic patients, but results are far from conclusive.

One study observed both reduced P300 amplitude and prolonged latency in bipolar patients (Muir et al. 1991), one reported amplitude reductions (Salisbury et al. 1999), and one latency delays (Souza et al. 1995). There are two family reports, one demonstrating both reduced P300 amplitude and prolonged latency in relatives (Pierson et al. 2000) and the other finding prolonged latency in relatives (Schulze et al. 2005).

As for P50 suppression, earlier studies suggested that abnormal P50 suppression in patients may be state dependent (Franks et al. 1983; Adler et al. 1990; Baker et al. 1990). However, these studies included both psychotic and non-psychotic bipolar patients. A recent study found that psychotic bipolar patients showed impairment of P50 suppression, similar to patients with diagnosis of schizo-affective disorder, bipolar type, and schizophrenia, while non-psychotic bipolar patients have normal P50 suppression (Olincy & Martin, 2005). Our group has investigated P50 suppression in relatives of bipolar patients and found impairment in both patients and relatives, suggesting that P50 suppression may be associated with genetic liability to psychotic bipolar illness (Schulze et al. 2006).

Deficits in MMN have not been observed in bipolar patients (Catts et al. 1995; Umbricht et al. 2003). Both Catts et al. (1995) and Umbricht et al. (2003) have found that, while MMN amplitude is clearly reduced in schizophrenic patients, it is normal in bipolar patients. A preliminary family study of bipolar disorder reported no evidence of MMN deficits in unaffected relatives (Schulze, personal communication). These results suggest that MMN deficits may be fairly specific to schizophrenia.

The classical twin design compares the difference in phenotypic similarity between monozygotic (MZ) twins and dizygotic (DZ) twins to untangle the effects of genes from the effects of family environment on any trait (Neale & Cardon, 1992; Kendler, 2001; Rijsdijk & Sham, 2002). In addition, the twin design, when augmented by sophisticated structural equation modelling techniques, is able to examine the extent of genetic overlap between two traits, such as a disease and its putative endophenotype (Neale & Kendler, 1995; Boomsma et al. 2002; Rijsdijk & Sham, 2002; Cannon, 2005; Koenen et al. 2005). Understanding the extent of genetic overlap may be crucial, because a significant genetic association validates the proposed phenotypic measure as an endophenotype for the disorder and may be used in linkage and association analyses (Allison et al. 1998; Lenox et al. 2002; Gottesman & Gould, 2003).

There is, to our knowledge, no twin study of ERP in bipolar illness. The present study is the first to use a twin design and advanced genetic model fitting analyses aiming to (1) assess and quantify the relationship of each ERP component with bipolar disorder with psychotic features, and (2) examine the source of the relationship (due to genetic or environmental factors). Based on the literature findings reviewed above, we predicted that (a) bipolar affected individuals would show deficits on the P300 and P50 measures, but normal MMN, and (b) bipolar disorder would be associated with P300 and P50 suppression but not MMN.

METHOD

Sample

The study was approved by the UK Multi-centre Research Ethics Committee. Probands were referred from across the UK by their treating psychiatrist or recruited from national media advertisements for the Maudsley Twin Study of bipolar disorder. Another source was by advertisement in the Manic Depressive Fellowship. Control twins were recruited from the Institute of Psychiatry Volunteer Twin Register and through advertisements. Written informed consent was obtained from all participants after a detailed description of the study aims and design.

The sample consisted of 10 MZ twin pairs discordant for bipolar disorder [mean age (S.D.) 41·8 (13·7) years], six MZ twin pairs concordant for bipolar disorder [mean age (S.D.) 40·3 (14·5) years] and 78 control twin pairs: 46 MZ [mean age (S.D.) 33·3 (10·3) years] and 32 DZ twin pairs [mean age (S.D.) 40·2 (12·6) years]. Of those control twin pairs, 19 MZ pairs (eight male, 11 female, mean age 36·76 years) were tested on two occasions with an average inter-test interval of 17·8 days (range 7–56 days), so that the

measurement error of each ERP component could be estimated.

Clinical assessment

All subjects underwent the same extensive clinical assessment. Diagnoses were based on all available clinical information concerning each twin, including structured clinical interviews using the Schedule for Clinical Assessment in Neuropsychiatry (version 2.1) or the Structured Clinical Interview for DSM-IV (SCID; First *et al*. 1997). Exclusion criteria applied to all groups included a history of neurological disorder, hearing impairment, a history of head trauma resulting in loss of consciousness of more than 10 min, and current substance dependence. Data on medication history were collected at the time of assessment. The probability that any of the discordant twins would become concordant in the future was low, as an average of 21·2 years (s.D. = 11·28) had elapsed since the onset of the probands' illness (Belmaker *et al*. 1974). All patients met DSM-IV diagnosis for bipolar I disorder, except one who was diagnosed with schizo-affective, bipolar type, disorder. All patients except one (95%) had a history of psychotic symptoms some time in their life. Control subjects had no personal or family history of any psychotic or bipolar disorder.

Eleven of the patients were taking antipsychotic in combination with mood stabilizer and/or antidepressants, three were taking antidepressant medications in combination with mood stabilizers, two were taking mood stabilizers only and one was taking antidepressants only. The remaining five patients were not currently receiving any psychiatric medication. Six had a history of alcohol dependence and one member of a concordant twin pair met criteria for current alcohol abuse. Three had a history of drug abuse and one with dependence. All patients were clinically stable at the time of assessment with no recent changes to their medication.

Four non-bipolar co-twins from the discordant groups and 19 controls had a history of DSM-IV diagnosis of major depression. One non-bipolar co-twin and six controls had a history of anxiety disorder. None were taking psychotropic medications at the time of study, with exception of one co-twin who was taking a low dosage of amitriptyline 20–30 mg daily.

Zygosity was determined using 12 highly polymorphic DNA markers and a standardized twin likeness questionnaire.

Study design

The study design was based on power analyses that used simulated data to estimate the number of twin pairs required to detect different levels of heritability of the ERPs and their genetic correlation with bipolar disorder under a range of assumptions. The power of this design was sufficient to detect a heritability of 60% for an ERP component and, at this heritability, a genetic correlation of 0·40 between the ERP and bipolar disorder (data available upon request).

Procedure and tasks

Three separate recordings, P50, MMN and P300, were carried out in a fixed order using a methodology described in detail elsewhere (Hall *et al*. 2006). In brief, data were collected using Neuroscan software. Electroencephalogram (EEG) data were recorded according to the 10/20 International System (Jasper, 1958), referenced to the left ear. Eye movements were recorded from the outer canthus of each eye, above and below the left eye. Electrode impedances were below 6 kΩ. EEG activity was amplified 1000 times with 0·03 high-pass and 120 low-pass filters, and digitized at a 500 Hz rate. Subjects had last smoked a minimum of 40 min before data collection (Adler *et al*. 1993).

P300

P300 was assessed using an auditory oddball paradigm [400 binaural 80 dB, 20 ms stimuli, 20% target (1500 Hz) and 80% standard (1000 Hz) tones]. Participants pressed a button in response to a target tone. EEG data were epoched (-100 to 800 ms), digitally filtered (0·15–40 Hz), low-pass filtered (8·5 Hz) and baseline corrected. Eye-blink artefacts were corrected using regression based weighting coefficients (Semlitsch *et al*. 1986). Epochs were rejected if amplitudes exceeded 50 μV in F7, F8, Fp1 or Fp2 and if residual horizontal eye movements were present in the -100 to 800 ms period. Separate average waves for target and standard tones were calculated and measured at PZ between 280 and 600 ms.

MMN

MMN was elicited by a duration auditory odd-ball task using four blocks of 400 binaural 80 dB stimuli (ISI: 0·3 s) with 85% standards (25 ms, 1000 Hz, 5 ms rise/fall time) and 15% deviants (50 ms). EEG data were epoched (-100 to 300 ms), filtered (0·1–30 Hz) and baseline corrected. Epochs were rejected if amplitudes exceeded 100 μV in any channel. Eyeblink artefacts were corrected as above. MMN was extracted by subtracting standard from deviant averaged waveforms. MMN amplitude was measured at FZ between 50 and 200 ms.

P50 suppression

P50 waves were recorded with a conditioning-testing paradigm separated by 500-ms and 10-s inter-trial intervals. Participants were presented with four or five blocks of 30 conditioning (C)–test (T) click pairs. Blocks were separated by 1-min breaks. Stimulus intensity was adjusted individually to 43 dB above hearing threshold. EEG signals were epoched (-100 to 400 ms), filtered (1 Hz high pass) and baseline corrected. Epochs with activity exceeding 20 μV in the CZ or EOG channel between 0 and 75 ms post-stimulus were automatically rejected. Epochs were averaged separately for the condition and test waveforms, digitally filtered (10 Hz high pass) and smoothed (7-point twice). P50 ERPs were reported at CZ. For the conditioning response, the most prominent peak 40–75 ms post-stimulus was selected as the P50 peak. The preceding negative trough was used to calculate the amplitude. For the test response, the positive peak with latency closest to that of the conditioning P50 peak was selected as the test response and its amplitude determined as for the conditioning wave. P50 suppression ratio was calculated as $(T/C) \times 100$.

Statistical analyses

Comparison of means

For each ERP measure, we compared the means of the following groups: MZ concordant for bipolar disorder, MZ discordant affected, MZ discordant unaffected, and healthy control twins. An observed ERP impairment in the unaffected MZ discordant twins similar to that of their affected co-twins would suggest a genetic effect, whereas values intermediate between patients and healthy controls would indicate that deficits are caused by illness progression as well as the genetic predisposition.

Mean comparisons were analysed using the regression command in STATA (Stata Corporation, College Station, TX, USA), which allows for non-independent observations (i.e. twin pairs) by using a robust sandwich estimator to estimate standard errors. Gender and age were included as covariates. Linear or logistic (for categorical variables) regression analyses were applied to assess overall group differences in demographic variables. A simple t test was used for assessing differences in age at onset between groups.

Structural equation modelling

A more sophisticated approach to the analysis of twin data is by using structural equation models, which aim to explain the pattern of correlations between variables within individuals and across twins by a linear model of relationships between latent and observed variables (Boomsma et al. 2002; Rijsdijk & Sham, 2002; Posthuma et al. 2003; Cannon, 2005; Koenen et al. 2005). Twin modelling was performed using the Mx statistical program (Neale et al. 1999). Twin correlations and genetic analysis were based on sex- and age-regressed residuals.

For the present study, however, model fitting was complicated by a number of factors: (a) the multivariate nature of the data, involving bipolar disorder and multiple ERP measures, (b) repeated measurements for the MZ control twin group, (c) the dichotomous nature of bipolar disorder, and (d) the uncertain ascertainment process for MZ twins concordant and discordant for bipolar disorder. We used four analytical strategies to overcome each of these difficulties:

(a) We used multivariate models that consider the patterns of covariances between multiple variables both within individuals and across twins (Baare et al. 2001). We also considered each of the ERP paradigms separately in the model fitting analyses as we found no evidence of a genetic overlap between these paradigms (Hall et al. 2006).

(b) We included additional observed variables in the covariance model for the MZ control pairs that were retested. For example, for

the P300 paradigm, each MZ twin member had five variables in the data, while each DZ twin member had three variables.

(c) We used liability-threshold models for both bipolar disorder and ERP variables (Falconer & Mackay, 1996). The liability-threshold models for the dichotomized bipolar phenotype (affected *versus* non-affected) assume that risk is normally distributed on a continuum and that the disorder occurs only when a certain threshold is exceeded (Neale & Kendler, 1995). As the Mx software used did not allow simultaneous analyses of dichotomized and continuous data, we modelled both bipolar disorder and ERP as threshold traits. Data from each ERP variable were recoded into seven equal ordinal classes that should capture most of the information in the continuous data.

(d) We fixed the genetic model parameters for bipolar disorder to values supported by studies in the literature (Rijsdijk *et al.* 2005). We based values on the report of McGuffin *et al.* (2003), which includes the largest affected twin pair sample ascertained so far, as no published meta-analysis is available to date. We use three different sets of values for the bipolar parameters: the point estimates (model 2: $h^2 = 0.85$, $c^2 = 0$, $e^2 = 0.15$), the lower (model 3: $h^2 = 0.73$, $c^2 = 0$, $e^2 = 0.27$) and upper 95% confidence interval (CI) (model 1: $h^2 = 0.93$, $c^2 = 0$, $e^2 = 0.07$). In addition, we fixed the bipolar prevalence rate to a lifetime risk of 1%.

Twin correlations

Twin correlations between the ERP measures and bipolar disorder were estimated by fitting a correlation matrix to the corresponding observed MZ/DZ raw data. The correlation matrix for each ERP variable was constrained to produce (i) the same cross-trait within-twin correlation regardless of zygosity, twin order and occasion; (ii) the same MZ cross-twin within-trait correlation regardless of occasion; (iii) the same MZ cross-twin cross-trait correlation regardless of twin order and occasion; and (iv) the same DZ cross-twin cross-trait correlation regardless of twin order.

Genetic model fitting

Genetic model fitting was applied to estimate (1) the heritability of each ERP variable, (2) genetic and environmental correlations of bipolar disorder with each ERP index, and (3) the measurement errors of each ERP index. The applied full ACEM bivariate liability-threshold model (for both P50 and MMN paradigms) is illustrated in Fig. 1. The liability-threshold model for bipolar and the P300 paradigm was analysed in a similar way, except that the model included both the amplitude and latency. The source of the phenotypic correlations is derived from comparing the correlation between one twin's bipolar liability and the co-twin's ERP score. Significantly greater MZ cross-trait cross-twin correlations compared to the DZ correlations suggest that genetic effects contribute to the bipolar–ERP association. The genetic correlation (r_g) indicates the extent to which genetic factors on bipolar disorder are the same as those on the ERP component.

Models were fitted directly to raw data. 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 correlational model. Submodels of the full ACEM model 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.

RESULTS
Subject

The demographic characteristics of the participants are given in Table 1. Groups did not differ in age, sex or years of education. However, controlling for age and sex, there were significant differences in parental socio-economic status (SES), the proportion of current regular smokers and the number of cigarettes smoked per day between groups. Parental SES was significantly lower for the concordant twin pairs than other twin groups, who did not differ from each other. The proportions of current regular smokers were significantly higher in patients of the concordant twins *versus* control [odds ratio (OR) 6·5, 95% CI 1·80–23·65] and in patients of discordant twins *versus* control (OR 7·9, 95% CI 1·96–31·50). In addition, among smokers, patients in the concordant twin group smoked significantly more cigarettes per day (estimated difference 10·4, 95% CI 2·81–18·05) than the

Table 1. *Demographic characteristics of each twin group*

Characteristic	BP CC ill (n=12)	BP DC ill (n=10)	BP DC well (n=10)	Controls (n=154)	Statistics	p value
Age, mean (S.D.), years	40·3 (14·5)	41·8 (13·7)	41·8 (13·7)	36·03 (11·75)	F=1·07	0·35
Age at onset, mean (S.D.), years	20 (4·2)	20·6 (5·4)	N.A.	N.A.	t=−0·29	0·77
Female sex, n (%)	6 (50)	8 (80)	8 (80)	120 (75)	χ²=4·09	0·25
Education, mean (S.D.), years	13·4 (3·8)	15·7 (2·4)	15 (2·9)	14·7 (2·23)	F=1·76	0·16
Parental SES, mean (S.D.)	3·7 (0·5)	2·6 (0·8)	2·6 (0·8)	2·9 (0·9)	F=3·77	0·01
Current smoker, n (%)	6 (50)	5 (50)	1 (10)	25 (16)	χ²=15·27	0·002
No. cigarettes per day, if smoker	19·8 (12·5)	11·4 (12·0)	15	9·5 (5·8)	F=2·68	0·06

BP, Bipolar disorder; CC ill, concordant affected; DC ill, discordant affected; DC well, discordant unaffected; S.D., standard deviation; N.A., not applicable; SES, socio-economic status, based on details of parental occupation at birth of the participant, derived from Office of Population Censuses and Surveys Standard Occupational Classification (1 indicates highest, 5 lowest).
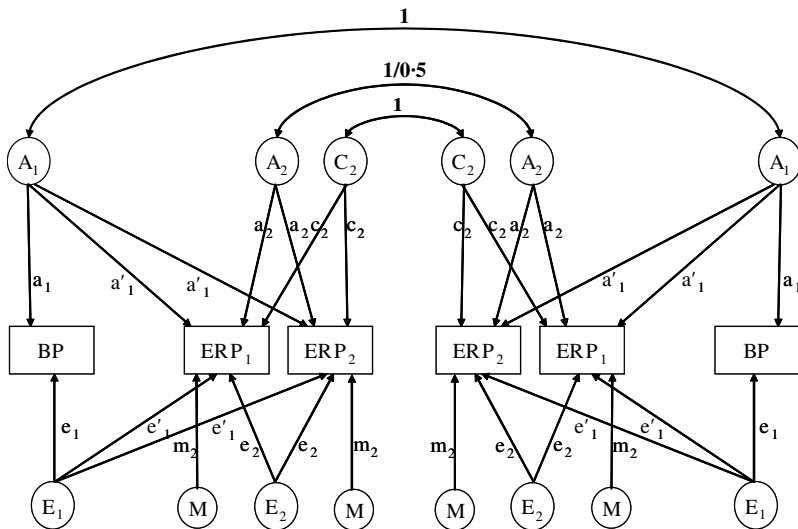

FIG. 1. Example of a path diagram of the ACEM genetic model for bipolar disorder and an event-related potential (ERP) measure [e.g. P50 ratio or mismatch negativity (MMN) amplitude] for monozygotic (MZ) pairs. ERP_1 and ERP_2, ERP measurements on occasions 1 and 2 respectively; A, additive genetic effects; C, common environment; E, specific environment; M, measurement error. In the model, two common factors (genetic A_1 and specific environmental E_1 effects) influence both bipolar (path coefficients a_1 and e_1) and ERP variables (path coefficients a'_1 and e'_1). A_2, C_2, E_2 and M_2 are factors that influence only ERP (path coefficients a_2, c_2, e_2, m_2). Parameters for the bipolar disorder (heritability, shared and specific environmental estimates) are fixed values according to McGuffin *et al.* (2003). Parameters of bipolar familial environmental effect and its correlation with ERP measure were constrained to be 0.

other three groups, who did not differ from each other.

Comparison of means

Apart from one possible outlier (a P300 latency score of a discordant co-twin member), no extreme scores were observed in any of the ERP variables. When we repeated the analyses of P300 latency excluding this possible outlier, results of both mean and genetic analyses remained essentially unchanged (details available from authors

on request). We therefore reported results from the original analyses.

As predicted, there was no mean difference in MMN between the bipolar groups and the controls (Table 2). Bipolar patients from concordant twin pairs had reduced P300 amplitude, delayed P300 latency, and abnormal P50 suppression ratio, all significant compared to controls. Bipolar patients and their co-twins from discordant twin pairs also had lower P300 amplitude and prolonged latency compared to

Table 2. *Summary statistics of ERP indices and results of mean group comparisons (standard deviations)*

	BP CC ill (n=12)	BP DC ill (n=10)	BP DC well (n=10)	Control twins (n=154)	BP CC ill versus control		BP DC ill versus control		BP DC well versus control	
					t	p	t	p	t	p
MMN amplitude (μV)	−2·98 (2·00)	−3·30 (1·01)	−2·73 (1·16)	−3·38 (1·46)	0·64	0·52	−0·45	0·66	0·98	0·33
P50 ratio (%)	69·12 (40·39)	35·60 (24·67)	48·06 (27·55)	33·67 (24·64)*	2·44	0·02	0·27	0·79	1·65	0·10
P300 amplitude (μV)	8·80 (2·69)	13·61 (6·44)	15·30 (7·07)	16·82 (5·45)*	−5·87	<0·0001	−1·46	0·15	−0·54	0·59
P300 latency (ms)	378·17 (39·72)	353·80 (26·20)	361·00 (57·72)	347·49 (31·55)*	2·86	0·005	0·46	0·65	0·63	0·53

ERP, Event-related potential; BP, bipolar disorder; CC ill, concordant affected; DC ill, discordant affected; DC well, discordant unaffected; MMN, mismatch negativity.

* *n*=151.

Table 3. *Maximum likelihood estimates of correlations between bipolar and ERP variables and MZ/DZ twin correlations (and 95% CI)*

ERP variables	Correlation of ERPs across twins		Correlation with bipolar disorder across twins		Bipolar–ERP phenotypic correlation
	MZ	DZ	MZ	DZ	
MMN amplitude	0·56 (0·35–0·71)	0·29 (−0·09 to 0·60)	0·22 (0·02–0·40)	0·30 (−0·46 to 0·76)	0·11 (−0·08 to 0·30)
P50 T/C ratio	0·63 (0·47–0·77)	−0·17 (−0·52 to 0·14)	0·31 (0·11–0·49)	0·11 (−0·48 to 0·79)	0·24 (0·05–0·42)
P300 amplitude	0·79 (0·67–0·87)	0·34 (0·01–0·58)	−0·27 (−0·46 to −0·08)	−0·19 (−0·82 to 0·32)	−0·33 (−0·51 to −0·12)
P300 latency	0·45 (0·26–0·62)	0·40 (0·02–0·63)	0·15 (−0·01 to 0·31)	−0·15 (−0·36 to 0·69)	0·21 (−0·03 to 0·40)

ERP, event-related potential; MZ, monozygotic; DZ, dizygotic; CI, confidence interval; MMN, mismatch negativity; T/C ratio, test/conditioning ratio.

The bipolar correlation is constrained to be 0·85 in MZ twins and 0·425 in DZ twins based on the point estimates, and 1% prevalence. Intervals including 0 indicate non-significance.

controls, but these differences did not reach significance. Contrary to our prediction, patients of discordant twin pairs had mean P50 suppression similar to that of controls. Significant mean differences between patients of concordant twin pairs and those of discordant twins were found for the P300 amplitude ($p=0·03$), latency ($p=0·04$) and P50 ratio ($p=0·04$). Patients of discordant twins did not differ significantly from their well co-twins for any of the measures.

Relationship between bipolar and MMN amplitude

The full genetic ACEM model for each ERP paradigm fitted the data well (MMN $p=0·73$; P50 $p=0·18$; P300 $p=0·06$). Table 3 shows maximum likelihood estimates of twin correlations. Genetic model fitting results are presented in Tables 4 and 5.

MZ within-trait cross-twin correlation was greater than the DZ, suggesting a genetic contribution to MMN (Table 3). Significant

heritability ($h^2=0·55$, 95% CI 0·01–0·71) was found in model 1 with no shared environmental influences ($c^2=0·01$). Significant individual specific-environmental effects were also found ($e^2=0·27$, 95% CI 0·09–0·49) across all three models (Table 4).

MMN amplitude was not associated with bipolar disorder. The phenotypic correlation (r_{ph}) was not significant ($p=0·13$) and could be dropped from the model, suggesting no overlap between the two traits (Table 5).

Relationship between bipolar and P50 suppression

Substantial heritability ($h^2=0·56$–$0·57$, 95% CI 0·26–0·72) and significant individual specific-environmental influences ($e^2=0·24$, 95% CI 0·05–0·46) were found (Table 4). Measurement error was estimated at around 0·20.

A significant phenotypic correlation of bipolar disorder with P50 suppression ratio was found across all three models ($r_{ph}=0·23$–$0·26$, 95% CI 0·04–0·43, Table 5), such that bipolar disorder

Table 4. *Additive genetic, common and specific environmental estimates (with 95% CI) of full ACEM genetic models for each ERP index*

	h^2	c^2	e^2	m^2	$\Delta\chi^2$ (df)	p value
MMN amplitude						
Model 1	0·55 (0·01–0·71)	0·01 (0–0·56)	0·27 (0·09–0·49)	0·17 (0·08–0·34)	15·80 (20)	0·73
Model 2	0·55 (0–0·71)	0·01 (0–0·56)	0·27 (0·09–0·49)	0·17 (0·08–0·35)		
Model 3	0·54 (0–0·71)	0·01 (0–0·56)	0·27 (0·09–0·49)	0·17 (0·08–0·35)		
P50 ratio						
Model 1	0·57 (0·26–0·72)	0 (0–0·24)	0·24 (0·05–0·46)	0·19 (0·09–0·41)	25·49 (20)	0·18
Model 2	0·56 (0·26–0·72)	0 (0–0·24)	0·24 (0·05–0·46)	0·20 (0·09–0·41)		
Model 3	0·56 (0·26–0·72)	0 (0–0·24)	0·24 (0·05–0·46)	0·20 (0·09–0·41)		
P300 amplitude						
Model 1	0·75 (0·36–0·85)	0·02 (0–0·37)	0·12 (0·01–0·25)	0·11 (0·05–0·23)	51·70 (37)	0·06
Model 2	0·77 (0·34–0·86)	0 (0–0·01)	0·12 (0·01–0·25)	0·11 (0·05–0·24)		
Model 3	0·75 (0·35–0·86)	0·02 (0–0·38)	0·12 (0·01–0·25)	0·11 (0·05–0·23)		
P300 latency						
Model 1	0·21 (0·01–0·60)	0·26 (0–0·52)	0·27 (0·07–0·48)	0·26 (0·15–0·46)	51·70 (37)	0·06
Model 2	0·16 (0–0·61)	0·31 (0–0·52)	0·27 (0·07–0·49)	0·26 (0·15–0·46)		
Model 3	0·17 (0–0·61)	0·31 (0–0·52)	0·27 (0·07–0·49)	0·26 (0·15–0·46)		

ERP, Event-related potential; CI, confidence interval; MMN, mismatch negativity; df, degrees of freedom; h^2, c^2, e^2 and m^2 are heritability, shared environmental, non-shared environmental and measurement error estimates respectively.

CIs including zero indicate non-significance.

Fixed genetic models for bipolar disorder used: (1) $h^2 = 0.93$, $c^2 = 0$, $e^2 = 0.07$ (2) $h^2 = 0.85$, $c^2 = 0$, $e^2 = 0.15$ and (3) $h^2 = 0.73$, $c^2 = 0$, $e^2 = 0.27$.

was associated with decreased P50 gating responses. Genetic correlation ($r_g = 0.43$–0.51), significant across all three models, was the main source for the phenotypic correlation; the environmental correlation (r_e) was non-significant.

Relationship between bipolar and P300 amplitude and latency

Across all three bipolar models, P300 amplitude showed substantial heritability ($h^2 = 0.75$–0.77, 95% CI 0·34–0·86) and significant individual specific-environmental influence ($e^2 = 0.12$, 95% CI 0·01–0·25) with no shared environmental effect ($c^2 = 0.02$) and low measurement error ($m^2 = 0.11$) (Table 4). P300 latency, on the contrary, showed relatively low heritability ($h^2 = 0.21$, 95% CI 0·02–0·62), significant only in model 1. A significant familial effect was found in models 2 and 3 but there was insufficient power to distinguish genetic (A) and shared environmental (C) effects, such that both A and C components could be dropped independently but not simultaneously [$\Delta\chi^2$ (df = 2) = 27·64, $p < 0.0001$].

A significant phenotypic correlation was found between bipolar and P300 amplitude ($r_{ph} = -0.33$ to -0.34, 95% CI -0.50 to -0.12, Table 5) but not between bipolar and latency ($p > 0.09$), indicating that bipolar disorder was associated with significantly smaller P300 amplitudes, not prolonged latencies.

Across all three bipolar models, shared genetic factors are the main source of the phenotypic correlations between bipolar disorder and amplitude, and the genetic correlation (r_g) was estimated to be between -0.33 and -0.35 (Table 5). Environmental correlations (r_e) were non-significant.

DISCUSSION

Genetic analyses showed that all ERP measures, with the exception of P300 latency, demonstrated substantial heritability (h^2) with no evidence of shared environmental (c^2) effects. For P300 latency there was insufficient power to distinguish genetic (A) and shared environmental (C) effects.

The results of the present study revealed a significant phenotypic relationship between P300 amplitude and bipolar disorder (-0.33), and between P50 suppression and bipolar disorder (0·24). Genetic factors (r_g) were the main source of these associations and were robust across three sets of bipolar heritability values. Environmental factors (r_e) were not significant. P300 latency and MMN amplitude, however, were not associated with bipolar disorder.

Table 5. *Phenotypic correlations (r_{ph}), the decomposed source of the correlations (r_{ph-a} and r_{ph-e}) predicted by the full ACEM models and correlation estimates (with 95% CI)*

	r_{ph-a}	r_{ph-e}	r_{ph}	R_g	R_e
MMN amplitude					
Model 1	0·18 (−0·02 to 0·36)	−0·05 (−0·13 to 0·03)	0·13 (−0·07 to 0·31)	0·25 (−0·03 to 1)	−0·39 (−0·97 to 0·20)
Model 2	0·18 (−0·01 to 0·37)	−0·07 (−0·18 to 0·04)	0·11 (−0·08 to 0·30)	0·27 (−0·01 to 1)	−0·37 (−0·94 to 0·20)
Model 3	0·19 (0–0·38)	−0·09 (−0·23 to 0·05)	0·10 (−0·09 to 0·28)	0·31 (0–1)	−0·36 (−0·89 to 0·19)
P50 ratio					
Model 1	0·31 (0·12–0·48)	−0·05 (−0·13 to 0·03)	0·26 (0·07–0·43)	0·43 (0·17–0·72)	−0·41 (−1 to 0·22)
Model 2	0·32 (0·13–0·49)	−0·08 (−0·18 to 0·04)	0·24 (0·05–0·42)	0·46 (0·19–0·77)	−0·40 (−1 to 0·21)
Model 3	0·33 (0·14–0·50)	−0·10 (−0·24 to 0·05)	0·23 (0·04–0·40)	0·51 (0·21–0·85)	−0·39 (−1 to 0·19)
P300 amplitude					
Model 1	−0·29 (−0·46 to −0·08)	−0·04 (−1 to 0·02)	−0·33 (−0·50 to −0·12)	−0·34 (−0·61 to −0·18)	−0·47 (−1 to 0·27)
Model 2	−0·27 (−0·46 to −0·06)	−0·06 (−0·15 to 0·04)	−0·33 (−0·51 to −0·12)	−0·33 (−0·62 to −0·08)	−0·47 (−1 to 0·28)
Model 3	−0·26 (−0·44 to −0·05)	−0·08 (−0·19 to 0·05)	−0·34 (−0·51 to −0·13)	−0·35 (−0·64 to −0·07)	−0·46 (−1 to 0·25)
P300 latency					
Model 1	0·17 (−0·02 to 0·35)	0·04 (−0·05 to 0·12)	0·21 (−0·03 to 0·39)	0·39 (−0·05 to 1)	0·29 (−0·39 to 0·98)
Model 2	0·16 (−0·04 to 0·34)	0·05 (−0·08 to 0·17)	0·21 (−0·03 to 0·40)	0·45 (−0·09 to 1)	0·26 (−0·39 to 0·96)
Model 3	0·15 (−0·04 to 0·34)	0·06 (−0·08 to 0·21)	0·21 (−0·03 to 0·40)	0·44 (−0·11 to 1)	0·24 (−0·36 to 0·88)

CI, Confidence interval; MMN, mismatch negativity; r_{ph}, total phenotypic correlation; r_{ph-a} and r_{ph-e}, phenotypic correlation due to additive genetic and specific environmental influence; R_g and R_e, genetic and specific environmental correlations.
Confidence intervals including zero indicate non-significance.
Fixed genetic models for bipolar disorder used: (1) $h^2 = 0.93$, $c^2 = 0$, $e^2 = 0.07$ (2) $h^2 = 0.85$, $c^2 = 0$, $e^2 = 0.15$ and (3) $h^2 = 0.73$, $c^2 = 0$, $e^2 = 0.27$.

For P50 suppression and P300 amplitude, the mean analyses and model fitting analyses showed contrasting results. There are two possible explanations. One may be that model fitting produced artificial genetic correlations between bipolar disorder and P300 amplitude and P50 ratio, perhaps because of model misspecification: (i) the heritability of bipolar disorder may have been fixed at too high a value and (ii) the shared environmental component was omitted in the model. First, significant genetic correlations were found even for the lowest heritability models for bipolar disorder (75%), which is realistic given estimates reported by other small population-based twin studies (Kendler *et al.* 1993; Cardno *et al.* 1999). Second, as no relevant meta-analysis is available, fixed parameters of heritability and family environment in bipolar disorder were based on the results of the largest published bipolar twin study. This report found no significant shared environment contribution to liability to the disorder. By constraining the familial environmental effect for bipolar disorder to be zero, it is not possible to estimate a shared environmental correlation. It could be argued that our results may have optimized the genetic correlation. However, the MZ cross-trait cross-twin correlations for P300 amplitude are about twice as large as those of the DZ twins and more than twice as large for the P50 ratio, suggesting that shared environmental effects are unlikely to contribute to the phenotypic correlations.

A second explanation may be that model fitting is more powerful than analysis of means. Mean comparisons do not use all available information and thus were unable to capture an overall profile of the data, whereas the model fitting analysis was able to detect a model that can best describe the overall correlation patterns in the dataset. We performed a mean scores based simulation (F. Rijsdijk, unpublished data) to explore the overall profiles of mean differences between groups (controls, concordant, discordant affected and discordant unaffected twins). These simulation results suggest that the mean scores of both twins from concordant pairs and unaffected co-twins of the discordant twins are crucial in determining the overall profiles of mean differences between groups, while the mean scores of affected discordant twins remain unchanged regardless of the nature

of the correlation with the disorder. The present study observed an impairment in the scores of concordant twin pairs, an elevated score in the well co-twin group (although non-significant) and normal P50 scores in the discordant ill twins. These results were most consistent with the simulation results when genetic, but not environmental, correlation was present.

Several studies have found prolonged P300 latency in bipolar patients (Muir *et al.* 1991; Souza *et al.* 1995; Strik *et al.* 1998; O'Donnell *et al.* 2004). In the present study a significant familial effect was found, but it was not possible to distinguish between heritable and shared environment effects. The genetic contribution to the observed correlation between latency and bipolar disorder is a function of the two sets of heritabilities that influence the traits, and of the correlation between these two sets. The low heritability of P300 latency means that the genetic contribution to the observed correlation will also be low. It is clear that, for the latency variable, we do not have sufficient power to detect small effects suggested by the results. Therefore, it is possible that a relationship between P300 latency and bipolar disorder exists, that would be detectable in a larger sample.

Consistent with reports of the case–control and family studies, MMN was not associated with the bipolar disorder: subjects with bipolar disorder had normal MMN functioning. This may reflect a relatively preserved neuronal function and perhaps a normal genetic architecture related to MMN (Umbricht *et al.* 2003).

Patients from the concordant twin group consistently showed severer deficits than patients of the discordant twin group in both P300 and P50 paradigms, suggesting that there may be differences in genetic liability between the two groups; that is, concordant twin pairs may have a greater genetic liability to the bipolar disorder than discordant twin pairs (Markow & Gottesman, 1989) and the extent of epigenetic differences in MZ discordant may be greater than in MZ concordant twin pairs (Petronis, 2003; Wong *et al.* 2005). Disease heterogeneity, however, may be an alternative explanation.

The proportion of smokers was significantly higher in the patient group than in unaffected individuals. The number of cigarettes smoked per day was significantly higher in patients from concordant twin pairs who had the most impaired suppression ratio. P50 suppression has been associated with lower alpha-7 nicotinic receptor level in schizophrenics and their relatives (Freedman *et al.* 1997). It is possible that these concordant bipolar patients may have lower levels of nicotine receptors, similar to schizophrenic patients, and therefore smoke more cigarettes to compensate for the deficit level of nicotine receptors.

This study is subject to a number of limitations. First, the sample size was small, particularly for the concordant bipolar twin pairs. Second, disease parameters could not be based on meta-analysis results. Third, we cannot entirely rule out effects of medications in the patients group. Patients received various psychotropic medications at the time of the ERP recording. However, there were no differences in ERP responses between patients and their unaffected, unmedicated co-twins, suggesting that medication was unlikely to have contributed significantly to the ERP differences observed in our data. Fourth, the incidence of life-time diagnosis of major depression was significantly higher in the unaffected co-twin of the discordant twin group ($p = 0.03$) compared to controls, suggesting an overlap in aetiology. The current study was unable to assess the relationship between major depression and mania. However, McGuffin *et al.* (2003) reported that 'although mania and depression are correlated genetically, most of the genetic influence on liability to mania is distinct from the genetic liability to depression'.

In conclusion, we report the first ERP study in twins with a diagnosis of bipolar disorder and found significant genetic associations between bipolar disorder and P300 amplitude and P50 suppression, suggesting that these two ERP components are endophenotypes for bipolar disorder. The identification of susceptibility genes for complex disorders such as bipolar disorder will require convergence in biological evidence of the risk variant's impacts on the pathogenesis of the disease (Kendler, 2005). The use of endophenotypes can help in two ways. First, individual differences in liability of an endophenotypic trait can be quantified on a continuous scale, thus providing a significant improvement in power to identification of possible gene carriers. Second, endophenotypes allow a disorder to be studied on a more

elementary level and therefore may also help to elucidate the pathophysiology of the disorders. Hypotheses about biological deficits in bipolar disorder could be studied further in animal models, where invasive studies of specific neurobiological mechanisms such as receptors, neurotransmitters and growth factors can be performed (Freedman *et al.* 1999; de Geus, 2002; Gottesman & Gould, 2003; Gould & Gottesman, 2006). In this way, the gap in our knowledge between statistically significant gene findings and the biological basis linking these genes to the disorder can be remedied by increased understanding of the biology, and the results of the new biological investigations can be supported by the findings from genetic analysis.

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DECLARATION OF INTEREST

None.

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