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Information processing deficits in relatives of manic depressive patients

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ABSTRACT

Background. The importance of genetic factors in the aetiology of manic-depressive illness (MDI) has been repeatedly confirmed and indicators of vulnerability to the illness in families with affective disorders are needed. Abnormal event-related potentials (ERP) may be markers of genetic vulnerability to mental illness. Long latency and low amplitude of P300 have consistently been reported in schizophrenic patients and their relatives. A few studies have also shown P300 deficits in MDI patients, but no ERP study has been performed on their relatives.

Methods. ERPs were recorded during an auditory oddball task in 19 relatives belonging to families with two or more bipolar patients and in controls with no familial or personal history of affective disorders. The relatives were selected as having no affective disorders on a lifetime basis, but eight had an anxiety disorder.

Results. In all relatives, a lower P300 amplitude and a longer P300 latency was found, with much longer reaction time and post-N200 duration till button-press than controls. A lack of P300 amplitude dominance in the right hemisphere was also found in relatives in comparison with controls. There also appeared to be a frontal predominance of ERP abnormalities in relatives.

Conclusion. We report the first evidence of deficits in reaction time and in P300 amplitude and latency, and a lack of P300 right-sided dominance, in relatives of manic-depressive patients. This pattern may constitute an endophenotypic marker of manic-depressive disorder.

INTRODUCTION

In psychiatric genetics, the failure to replicate a number of well-published claims of linkage for manic-depressive illness (MDI) and schizophrenia may partly be attributed to the fact that progress in genetics has not been followed by an equivalent development in phenotypic description. Identifying subclinical traits among unaffected relatives, i.e. the 'endophenotype approach', is one strategy for identifying relevant phenotypes (Leboyer *et al.* 1998). Endophenotypes are traits associated with the expression of an illness and may express genetic vulnerability to the disorder in unaffected subjects. To meet criteria for an endophenotype, a marker must occur before the onset of the illness and must be found more frequently among relatives of patients than in the general population.

The importance of genetic factors in the aetiology of manic-depressive illness has been consistently confirmed. However, indicators of vulnerability to the illness need to be identified, thus reflecting brain dysfunction before symptoms occur. Large families including members with affective illness could be used to identify such indicators. Event-related potential (ERP) abnormalities are thought to be markers of genetic vulnerability to mental illness. Most studies of psychiatric patients have focused on the P300 wave. P300 is triggered if a response to an infrequent stimulus is required. It is related to the post-perceptual activity underlying cognitive

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processes. There are extensive and robust reports (since the seminal study by Roth & Cannon (1972), there have been at least 70 independent investigations) describing the low amplitude and the long latency of the P300 ERP in treated and drug-free schizophrenic patients (for reviews see Souza *et al*. 1995; Salisbury *et al*. 1999) and in their unaffected relatives (for review see Frangou *et al*. 1997). In comparison, there have been relatively few studies of ERP in patients with affective disorders (Bruder *et al*. 1991, 1992; Muir *et al*. 1991; Souza *et al*. 1995; Blackwood *et al*. 1996; Bange & Bathien, 1998; Strick *et al*. 1998; Salisbury *et al*. 1998, 1999). It has been reported in most studies that latency in the P300 component in MDI patients is long, but the presence of P300 amplitude reduction in affective disorder is somewhat equivocal and may reflect underlying psychosis (Salisbury *et al*. 1999). In one of the largest studies of auditory P300 in affective disorders, both P300 latency and P300 amplitude were found to be impaired in schizophrenics and in bipolar depressed patients compared to patients with unipolar affective disorders and normal controls (Muir *et al*. 1991). In a subsequent study by the same research team, this result was not replicated for P300 amplitude but the long latency was again found (Souza *et al*. 1995). Similarly, only P300 latency was found to be impaired in a recent study comparing bipolar and unipolar patients (Bange & Bathien, 1998). However, when examining topographical ERP indices, P300 amplitude abnormalities in the frontal region were found in bipolar patients (Strick *et al*. 1998; Salisbury *et al*. 1999), contrasting with low P300 amplitude at parietal sites in schizophrenic patients (Salisbury *et al*. 1999). Opposite left/right asymmetries were also found in depressed patients and schizophrenics. Schizophrenics generally show smaller P300 over the left side (Blackwood *et al*. 1994; Salisbury *et al*. 1994, 1998, 1999; Heidrich & Strick, 1997; Weisbrod *et al*. 1997; Weir *et al*. 1998) whereas several studies have indicated a right-sided dysfunction in depressed patients (Bruder *et al*. 1992, 1998; Weir *et al*. 1998; Salisbury *et al*. 1999).

To detect such information processing abnormalities among subjects who are potential carriers of genetic vulnerability to manic-depressive illness, we compared subjects who had no affective disorders and belonged to multiply-affected bipolar families with controls who had no familial or personal history of affective disorder.

METHOD

Subjects

Nineteen first-degree relatives (siblings and adult offspring) having no affective disorders on a lifetime basis (7 men, 12 women, mean age = 26·2 years, S.D. = 6·56), and belonging to multiply-affected bipolar families with at least two bipolar subjects in each pedigree, were included in the study. The families were recruited as part of ongoing linkage studies. Diagnoses of bipolar disorder among the affected probands were made by personal interview (M.L.) using the Interview for Genetic Studies (DIGS) (Nurnberger *et al*. 1994). Nineteen normal controls (mean age = 26·8 years, S.D. = 6·04) matched with the relatives for age, sex, tobacco intake and contraceptive methods, were recruited by advertising at Pitié-Salpêtrière teaching hospital. All subjects were under 40 years of age and none was undergoing treatment. The two experimental groups were selected after personal interviews using DIGS to assess the absence of lifetime affective disorders. The study was approved by the French institutional ethics committee and informed written consent was obtained from all subjects.

Experimental task

ERPs were recorded during an auditory oddball task. Subjects executed a motor task in which they had to respond as rapidly as possible with their right hand to high-pitched tones (targets = 1500 Hz) that were randomly and infrequently (20%) embedded in a series of low-pitched standard tones (non-targets = 1000 Hz, 80%). Stimuli were presented binaurally through headphones at 65 dB SPL for 100 ms. They were distributed into two sequences with 100 stimuli each, generating a total of 40 responses to infrequent stimuli. The rise/fall time of tones was 5 ms. The inter-trial interval varied randomly between 1100 and 1500 ms.

ERP recordings

Recordings were made in a sound-attenuated room with subjects seated in a reclining chair. EEG activity was recorded from the scalp through seven tin electrodes in preconfigured

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caps (ElectroCap International) complying with the international 10–20 electrode system (Jasper, 1958). These electrodes included three midline sites (frontal (Fz), central (Cz), parietal (Pz)). Recordings were also made on each hemisphere in the regions in which waves are largest, given the position of their generators, the sources fields of which are reflected on the scalp to a certain extent: N100 and P200 in the fronto-central region (F3, left; F4, right) and P300 in the parietal region (P3, left; P4, right). Linked-earlobes were used as the reference and a ground electrode was placed on the cheek. Bipolar recordings were made of vertical ocular movements using two electrodes located medially and supra- and infra-orbitally to the left eye so as to detect ocular artefacts. Trials contaminated by eye movements were eliminated on-line when EOG signals exceeded a ± 200 μV voltage threshold, and trials contaminated by all sorts of artefacts were rejected off-line when EEG data exceeded ± 100 μV following an EOG reduction by complex regression analyses (InstEP systems, Ottawa, Canada). Electrode impedances were controlled and maintained below 2 KΩ. Signals were low-pass filtered at 25 Hz and high-pass filtered at 0·16 Hz (-3 dB per octave) using analogue filters in the amplifiers. Data were digitized on-line at a sampling rate of 250 Hz using the InstEP system. The sampling period was 1024 ms (200 ms pre-stimulus to 824 ms post-stimulus). Prior to processing, all data were smoothed by a 10 Hz (-3 dB) low-pass digital frequency-based (zero phase shift) filter.

ERP measures

The motor response to target stimuli was measured as the reaction time (RT). Amplitude and latency of ERP triggered by target stimuli were measured for N100, which reflects sensory analysis and attentional processes (Näätänen & Picton, 1987), for N200, which evaluates stimulus categorization (Ritter *et al*. 1983), and for P300. Although P300 is the most studied ERP wave, its exact significance is still a matter for debate. It is thought to reflect either the post-perceptual updating of short-term working memory traces of expected environmental stimuli (Donchin, 1981), or the termination of stimulus evaluation (Desmedt, 1981). One important characteristic of P300 of relevance to our study is that it reflects a cognitive post-identification phenomenon associated with the activation of polysensory regions of the cortex and relatively independent of the response processes (McCarthy & Donchin, 1981). These interpretations of P300 concern the parietal P300 component (P3b), the reference component whenever the P300 component is not specified, and which is related to higher information processes. Another P300 component, recorded slightly earlier at frontal sites (P3a), reflects passive attention and may be related to automatic orientation (Squires *et al*. 1975). The P200 wave in response to targets was not measured as the peak was not always clearly identifiable. For non-targets, we measured the exogenous ERP components, N100 and P200 (reflecting stimulus encoding), the only waves obtained in such task conditions. The obligatory sensory components N100 and P200 are partly superimposed on the N200 component. Due to this temporal overlap, subtraction procedures must be used to extract the N200 wave. Responses to standard non-targets were subtracted from responses to deviant targets (N2d).[2] Stimuli are categorized as soon as N200 occurs, so the interval between this wave and the motor response (button-press) may be considered to be related to the duration of post-perceptual cognitive and motor processes. We therefore calculated the interval between the N200 peak and button-press (RT $-$ N200 latency) to estimate duration of post-perceptual stages. Latency is a measure of the speed of each information-processing operation (Renault *et al*. 1982; Ritter *et al*. 1982) and the amplitude indices reflect the energetical resources available to perform the operation in progress (Kok, 1990).

ERPs were averaged separately for target and non-target stimuli for each subject, then the averages of all subjects were pooled (grand average) for each group of subjects. Amplitudes were measured as the positive or negative maximum voltage observed in a time window determined from the grand average ERP waveforms. The voltage of all peaks was measured with respect to a baseline calculated on the 200 ms preceding the onset of the stimulus. Latencies were measured using the onset of the stimulus as the time reference. The recordings

[2] N100 and P200 amplitudes are not different for standard non-targets and deviant targets. After subtraction, the amplitudes of these waves are near zero and the N200 wave (or N2d) can emerge.

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were performed blind to the status of subjects (i.e. relatives or controls).

The time windows were (in milliseconds): 48–148 (targets) and 48–160 (non-targets) for N100; 160–280 for P200 (non-targets); 128–280 for N2d (targets minus non-targets); 250–500 for P300 (targets). The ERP variables were measured automatically by a computer algorithm, ensuring blindness to group characteristics as ERP traces might be noisier in relatives (as was frequently observed for patients) than in controls. In the case of multiple peaks, this algorithm calculates the mean of peaks differing by no more than 10% in amplitude in the given time window, so to measure P3a and P3b components different time windows are used at Fz and Pz. In these recordings, the same time window was used for Fz and Pz because a single peak was observed in all subjects (it is thought that in such a simple task, the processes reflected by P3a and P3b occur at about the same latency, and the two P300 components are indistinct). In some cases in which the computer did not discern a peak in the given time window, the peak was checked visually by the operator (5% of cases).

Statistical analyses

For each type of ERP measure, two separate mixed-model repeated-measures ANOVAs were executed: the first on the midline electrode sites ('midline ANOVA' with 'group' as the between-subjects factor, and 'site' (Fz, Cz, Pz) as the within-subjects factor), the second on the lateral sites ('hemisphere ANOVA' with 'group' as the between-subjects factor, region (frontal, parietal) and hemisphere (left, right) as the between-subjects factors). *Post hoc* comparisons were made using Student's *t*-tests on corrected LS-means with Tuckey–Kramer adjustment if necessary. The significance level was set at $P < 0{\cdot}05$. All analyses were carried out with the MIXED procedure of SAS Institute Inc. (Little *et al.* 1996).

RESULTS

Clinical results

The interview using the DIGS revealed no psychiatric disorders in controls, but the following psychiatric disorders were found on a lifetime basis among the relatives of MDI probands: generalized anxiety ($N = 4$); simple phobia or social phobia or agoraphobia ($N = 3$); and, panic disorder ($N = 1$). All these subjects were euthymic at the time of the recording as assessed with the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) (HRSD score, 3·4 (S.D. = 4·8) in relatives; and 1·2 (S.D. = 2·0) in controls). Two controls and one relative were excluded because of excessively noisy recordings. In view of the lifetime anxiety disorder in eight of the relatives, statistical analyses were performed, first comparing all 18 relatives (R) with the 17 controls (C), and then subdividing the relatives into two subgroups, those with a lifetime anxiety disorder (RAD, $N = 8$) and those unaffected, with no axis I psychiatric disorder (UR, $N = 10$).

ERP and behavioural results

Grand average ERP waveforms are shown in Fig 1. ERP amplitudes are given in Table 1 and ERP latencies in Table 2.

P300 wave

P300 amplitude was found to be lower in relatives than in controls as shown by the main effect of group, relatives (R) *v.* controls (C), found in midline analysis ($F(1, 33) = 6{\cdot}79$, $P = 0{\cdot}01$) and in hemisphere analysis ($F(1, 33) = 6{\cdot}64$, $P = 0{\cdot}01$). In relatives and controls, amplitude increased from frontal to parietal sites as indicated by a main effect of site in midline analysis ($F(2, 33) = 50{\cdot}32$, $P < 0{\cdot}0001$), and of region in hemisphere analysis ($F(1, 33) = 68{\cdot}04$, $P < 0{\cdot}0001$), and by the lack of group*site or group*region interactions. Therefore, the P300 wave was the largest in the parietal region as is usually observed, and this did not differ between relatives and controls.

Analyses performed on three groups, the controls (C) and the two subgroups of relatives (RAD and UR), revealed topographical differences. Although comparison of UR and RAD revealed no significant difference in P300 amplitude, topographical differences were found in separate comparisons of RAD with controls and UR with controls: the lower P300 amplitude in relatives than in controls was topographically widespread in RAD (significant at all sites except F3) whereas P300 amplitude was significantly

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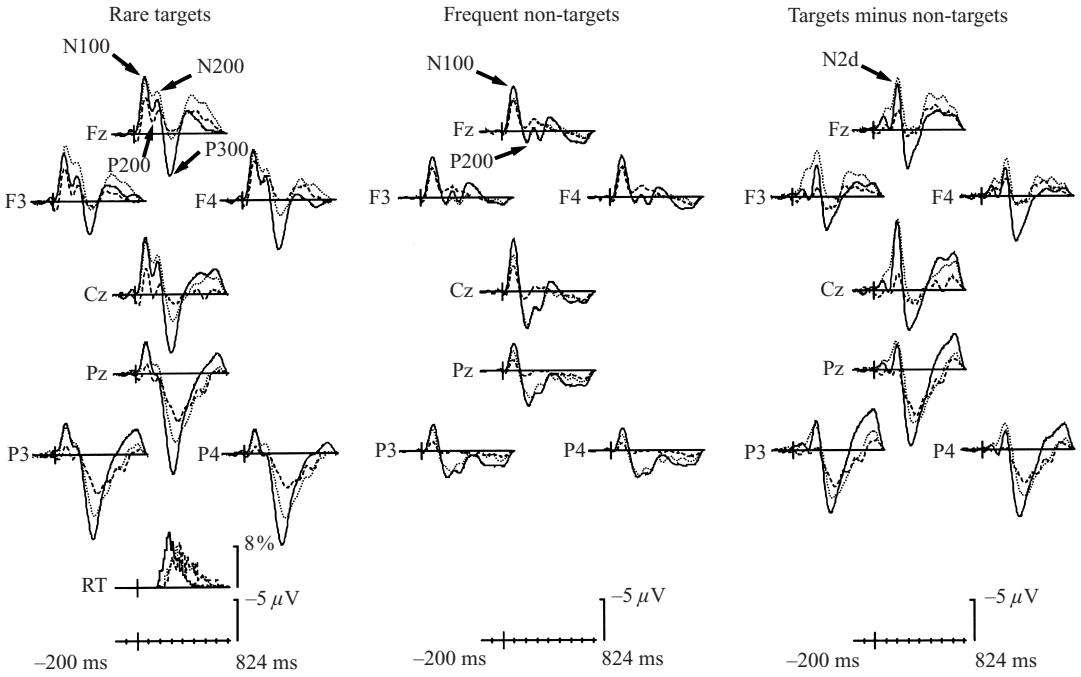


FIG. 1. Grand mean ERP waveforms observed for deviant targets, standard non-targets, and deviant targets minus standard non-targets at the various brain recording sites, and histogram of RT in response to targets (-----, relatives who had had an anxiety disorder; ·····, unaffected relatives; and ———, control subjects). The stimulus begins at zero on the *x*-axis. P300 for rare targets was significantly lower in amplitude and longer in latency in all relatives than in controls. Relatives did not show the higher right than left hemisphere P300 amplitude observed in controls.

lower in UR than in controls only at frontal sites: Fz ($t(32) = -2{\cdot}49$, $P < 0{\cdot}02$); F3 ($t(32) = -2{\cdot}15$, $P < 0{\cdot}05$); F4 ($t(32) = -2{\cdot}35$, $P = 0{\cdot}02$). However, differences between both subgroups of relatives and controls did not remain significant if the *t* test value was corrected (Fz, $P = 0{\cdot}27$; F3, $P = 0{\cdot}59$; F4, $P = 0{\cdot}46$ with Tuckey–Kramer adjustment).

Concerning differences between the left and the right hemispheres, a main effect was found ($F(1, 33) = 5{\cdot}57$, $P = 0{\cdot}02$), but a hemisphere ∗group interaction ($F(1, 33) = 5{\cdot}14$, $P < 0{\cdot}05$) indicated that relatives did not have the higher right than left hemisphere P300 amplitude observed in controls (controls, $t(33) = 3{\cdot}23$, $P < 0{\cdot}01$; relatives, $t(33) = 0{\cdot}07$, NS). The hemispheric P300 difference found in controls remained significant ($P = 0{\cdot}01$) following Tuckey–Kramer adjustment. The lack of P300 amplitude dominance in the right hemisphere in relatives was confirmed in analyses taking into account the RAD and UR subgroups: there was not a main effect of hemisphere, but a hemisphere ∗group interaction ($F(2, 32) = 3{\cdot}47$, $P < 0{\cdot}05$) indicated that the left/right difference was only significant in controls (controls, $t(32) = 3{\cdot}26$, $P < 0{\cdot}01$ ($P < 0{\cdot}05$ with the Tuckey–Kramer adjustment); UR, $t(32) = 0{\cdot}92$, NS; RAD $t(32) = 0{\cdot}92$, NS).

For P300 latency, a main effect of group, relatives (R) *v.* controls (C), was found in midline analysis ($F(1, 33) = 4{\cdot}41$, $P < 0{\cdot}05$) and hemisphere analysis ($F(1, 33) = 5{\cdot}79$, $P = 0{\cdot}02$): P300 latency was 28 ms longer on average in relatives than in controls. In both analyses (midline and hemisphere), a site or region effect was found (midline analysis, $F(2, 33) = 4{\cdot}07$, $P < 0{\cdot}05$; hemisphere analysis, $F(1, 33) = 5{\cdot}16$, $P < 0{\cdot}05$) with no interaction with group, indicating that in all subjects, P300 latency was longer in the parietal than in the frontal region. No effect of hemisphere was observed. After division of the relatives into two subgroups, similar results were obtained.

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Table 1. *ERP amplitudes (in μV) in relatives of manic-depressive patients and controls*

ERP wave	Group of subjects	Fz Mean	Fz (S.D.)	Cz Mean	Cz (S.D.)	Pz Mean	Pz (S.D.)	F3 Mean	F3 (S.D.)	F4 Mean	F4 (S.D.)	P3 Mean	P3 (S.D.)	P4 Mean	P4 (S.D.)
N100	UR	−6·93	(2·44)	−6·93	(2·88)	−3·97	(2·26)	−7·00	(2·57)	−6·29	(2·51)	−4·13	(2·98)	−3·31	(2·73)
targets	RAD	−4·43	(2·16)	−3·38	(1·63)	−2·16	(2·52)	−4·21	(2·07)	−5·37	(2·73)	−1·74	(1·31)	−1·49	(1·08)
	C	−6·61	(2·80)	−6·55	(3·11)	−3·78	(2·34)	−5·47	(2·89)	−5·78	(2·15)	−3·96	(2·29)	−3·11	(1·89)
N200	UR	−6·72	(3·73)	−9·81	(5·19)	−4·55	(3·31)	−6·07	(3·83)	−5·06	(3·62)	−4·16	(2·67)	−4·08	(2·25)
(N2d)	RAD	−3·95	(3·47)	−3·16	(2·59)	−1·17	(2·20)	−2·98	(3·61)	−3·84	(3·15)	−1·43	(1·24)	−0·82	(1·77)
targets	C	−5·55	(3·98)	−8·72	(5·26)	−3·47	(3·68)	−3·88	(3·55)	−3·36	(3·38)	−3·73	(3·47)	−2·64	(3·51)
P300	UR	1·92	(4·08)	5·95	(6·37)	10·33	(7·25)	1·91	(3·18)	2·81	(3·85)	9·35	(6·11)	9·52	(6·75)
targets	RAD	0·62	(2·52)	1·27	(4·43)	5·78	(4·19)	1·93	(2·19)	1·48	(2·00)	5·42	(2·28)	4·67	(2·93)
	C	6·17	(4·96)	8·59	(6·59)	12·74	(6·44)	4·94	(4·14)	6·63	(4·81)	10·32	(5·46)	11·54	(5·16)
N100	UR	−4·66	(1·79)	−4·74	(2·21)	−2·43	(1·86)	−4·15	(1·42)	−4·58	(1·92)	−2·97	(1·94)	−2·34	(2·17)
non-targets	RAD	−3·63	(1·55)	−2·91	(1·18)	−1·48	(0·87)	−3·69	(1·54)	−3·49	(1·41)	−1·72	(1·20)	−1·20	(0·70)
	C	−5·54	(2·03)	−5·99	(2·48)	−4·10	(3·30)	−5·10	(1·95)	−5·04	(1·80)	−3·35	(1·98)	−2·77	(1·58)
P200	UR	1·45	(2·09)	4·69	(3·46)	3·93	(2·66)	1·04	(2·08)	1·05	(1·89)	3·19	(2·11)	3·71	(1·90)
non-targets	RAD	0·08	(1·91)	2·34	(2·04)	2·01	(1·47)	0·06	(1·85)	−0·09	(1·85)	1·05	(1·72)	1·14	(1·64)
	C	1·54	(2·89)	4·84	(3·51)	4·32	(2·67)	0·76	(2·62)	0·85	(2·55)	3·38	(2·37)	3·41	(1·92)

UR, unaffected relatives ($N = 10$); RAD, relatives having had an anxiety disorder ($N = 8$); C, control subjects ($N = 17$).

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Table 2. *ERP latencies (in ms) in relatives of manic-depressive patients and controls*

ERP wave	Group of subjects	Fz Mean	Fz (S.D.)	Cz Mean	Cz (S.D.)	Pz Mean	Pz (S.D.)	F3 Mean	F3 (S.D.)	F4 Mean	F4 (S.D.)	P3 Mean	P3 (S.D.)	P4 Mean	P4 (S.D.)
N100	UR	126·40	(30·00)	110·80	(19·23)	104·00	(27·71)	122·80	(19·33)	124·00	(21·50)	94·80	(21·34)	94·00	(23·04)
targets	RAD	113·87	(24·53)	109·63	(26·95)	108·12	(32·20)	113·13	(20·95)	113·75	(20·32)	108·00	(26·27)	106·00	(27·21)
	C	100·47	(19·07)	97·47	(16·10)	96·00	(21·17)	104·47	(17·71)	101·17	(21·94)	97·88	(14·77)	95·53	(16·61)
N200 (N2d)	UR	210·80	(28·54)	213·60	(21·84)	204·80	(26·98)	215·60	(26·02)	215·60	(31·91)	197·60	(25·80)	205·60	(21·18)
targets	RAD	223·50	(37·61)	211·00	(34·06)	202·50	(39·48)	219·00	(38·53)	226·50	(29·93)	216·00	(41·35)	215·00	(34·72)
	C	213·65	(16·31)	210·35	(15·88)	209·88	(21·03)	218·35	(20·45)	212·71	(23·46)	206·59	(17·55)	206·12	(20·98)
P300	UR	352·40	(44·40)	368·90	(75·53)	369·20	(71·21)	353·60	(42·51)	348·00	(45·45)	361·60	(68·72)	369·60	(54·23)
targets	RAD	329·50	(51·53)	380·50	(54·19)	358·50	(43·55)	343·00	(45·94)	349·00	(48·27)	364·50	(37·24)	363·00	(45·59)
	C	325·41	(31·46)	332·94	(54·71)	330·65	(43·45)	324·47	(33·13)	323·53	(31·84)	339·29	(33·71)	333·65	(37·60)
RT-N2d lat	UR	217·20	(69·45)	214·40	(70·13)	223·20	(75·43)	212·40	(68·81)	212·40	(71·18)	230·40	(81·54)	222·40	(71·70)
targets	RAD	222·00	(53·59)	234·50	(35·77)	243·00	(35·24)	226·50	(52·36)	219·00	(57·29)	229·50	(28·71)	230·50	(25·48)
	C	119·47	(46·06)	122·76	(43·89)	123·24	(46·37)	114·76	(48·23)	120·41	(47·24)	126·53	(42·30)	127·00	(45·02)
N100	UR	118·80	(32·28)	110·40	(29·22)	104·00	(34·10)	115·60	(26·36)	122·40	(31·00)	95·20	(20·55)	96·80	(25·07)
non-targets	RAD	117·50	(22·11)	101·50	(18·38)	103·50	(29·58)	116·50	(20·67)	118·00	(19·71)	113·00	(31·11)	102·50	(23·61)
	C	104·94	(14·25)	99·06	(11·62)	100·00	(14·28)	107·29	(13·95)	105·88	(14·29)	101·88	(15·24)	101·65	(13·27)
P200	UR	220·40	(24·55)	220·80	(24·06)	230·40	(26·81)	218·80	(24·15)	220·80	(25·00)	233·20	(37·53)	234·00	(37·06)
non-targets	RAD	217·00	(36·46)	221·50	(42·87)	217·00	(40·55)	219·00	(40·78)	215·50	(41·04)	222·20	(39·83)	220·00	(41·90)
	C	208·24	(24·84)	210·35	(21·31)	218·24	(22·00)	208·24	(22·25)	206·82	(23·14)	218·82	(25·76)	219·29	(25·74)

UR, unaffected relatives ($N = 10$); RAD, relatives having had an anxiety disorder ($N = 8$); C, control subjects ($N = 17$).

N100 wave

Relatives did not differ from controls in N100 amplitude when all relatives were examined together. A main effect of group was found only if the two subgroups of relatives were considered and only in midline analysis ($F(2, 32) = 3{\cdot}34$, $P < 0{\cdot}05$). Indeed, only RAD had an abnormally low N100 amplitude in comparison with both UR and C (RAD/UR, $t(32) = 2{\cdot}34$, $P = 0{\cdot}02$; RAD/C, $t(32) = 2{\cdot}30$, $P < 0{\cdot}05$); differences were close to the significant threshold when we used t tests with Tuckey–Kramer adjustment (0·06 for RAD *v*. UR; 0·07 for RAD *v*. C). The main effects of site or region and the lack of group∗site and group∗region interaction indicated that for all subjects N100 was largest in the fronto-central regions, as usually found.

In contrast to the results for N100 amplitude, a main effect of group in midline analysis indicated that N100 latency was longer in relatives than in controls ($F(1, 33) = 4{\cdot}18$, $P < 0{\cdot}05$). In hemisphere analysis, a group∗region interaction ($F(1, 33) = 4{\cdot}68$, $P < 0{\cdot}05$) indicated that the longer latency in relatives was only significant in the frontal region ($t(33) = 2{\cdot}49$, $P < 0{\cdot}02$; with Tuckey–Kramer correction $P = 0{\cdot}08$). If relatives were divided into RAD and UR, a longer N100 latency than that of the controls was again found for UR but only before Tuckey–Kramer adjustment ($t(32) = 2{\cdot}70$, $P = 0{\cdot}01$; with Tuckey–Kramer adjustment, $P = 0{\cdot}10$).

Other ERP waves

No result of interest was found for other ERP waves. N200 for targets as well as N100 and P200 for non-targets were the largest at Cz in all subjects, as generally shown. For the target N200 and for the non-target P200, no differences between groups were found, either for amplitude or for latency. For the non-target N100 amplitude, a main effect of group was found only in midline analysis: N100 amplitude was lower in R than in C subjects ($F(1, 33) = 10{\cdot}22$, $P < 0{\cdot}01$), but after subdivision of relatives, this result was not significant for UR. For the non-target N100 latency, a main effect of site and a group∗region∗hemisphere interaction indicated that differences between R and C subjects were restricted to the right frontal region ($t(33) = 2{\cdot}04$, $P < 0{\cdot}05$); this result was insignificant after Tuckey–Kramer adjustment ($P = 0{\cdot}47$). After subdivision of relatives, the same result was obtained in UR, but statistical probabilities became 0·06 (without adjustment) and 0·73 (after adjustment).

Reaction time (RT) and interval between N200 and button-press (RT − N200 latency)

Reaction time (RT in ms) was much longer in relatives (mean = 435, S.E. = 12·62) than in controls (mean = 333, S.E. = 12·98) ($F(1, 33) = 32{\cdot}16$, $P < 0{\cdot}0001$). This lengthening of RT was also found in both subgroups of relatives separately, RAD (mean = 445, S.E. = 19·07) and UR (mean = 428, S.E. = 17·07) (UR/C, $t(32) = 4{\cdot}41$, $P < 0{\cdot}0001$; RAD/C, $t(32) = 4{\cdot}86$, $P < 0{\cdot}0001$). All relatives also had an abnormally long interval after the N200 wave, as indicated by values of (RT − N200 latency) (See Table 2). For the midline sites, $F(1, 33) = 34{\cdot}24$, $P < 0{\cdot}0001$ for all relatives together; $F(2, 32) = 16{\cdot}96$, $P < 0{\cdot}0001$ if relatives were divided into RAD and UR. For the hemispheres, $F(1, 33) = 33{\cdot}71$, $P < 0{\cdot}0001$ for all relatives together; $F(2, 32) = 16{\cdot}43$, $P < 0{\cdot}0001$ if relatives were divided into RAD and UR. This effect was observed not only for the fronto-central electrodes, for which N200 was the largest, but for all electrodes (there was no statistical effect of site or region, no group∗site or group∗region interactions). There was no difference between UR and RAD for either variable, RT and (RT − N200 latency), and both subgroups differed from controls in exactly the same way.

There was also a positive correlation between the post-N200 duration (RT − N200 latency) and RT, both in relatives ($r = 0{\cdot}88$) and controls ($r = 0{\cdot}90$), whereas N200 latency was significantly correlated with (RT − N200 latency) only in controls. This correlation was negative (means for all fronto-central site; $r = -0{\cdot}50$ in controls; $r = -0{\cdot}19$ in relatives).

DISCUSSION

In non-affected relatives belonging to multiply-affected bipolar families, we explored sensory-motor information processing using an auditory oddball task. We found a lower P300 amplitude and a longer P300 latency in relatives than in controls and a delay in motor response (102 ms).

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Relatives also showed a lack of P300 amplitude dominance in the right hemisphere in contrast to controls. This pattern may be an endophenotypic marker of manic-depressive disorder. A frontal predominance of ERP abnormalities in relatives may also be suggested.

In early studies, P300 deficits appeared to be very similar in patients with different disorders such as schizophrenia, unipolar/bipolar depression, alcoholism, dementia, borderline personality disorder and mental handicap. Abnormalities in P300 latency and/or amplitude have also been reported in non-affected relatives of schizophrenic patients (Friedman *et al.* 1982; Blackwood *et al.* 1991; Kidogami *et al.* 1992; Roxborough *et al.* 1993; Squires-Wheeler *et al.* 1993; Frangou *et al.* 1997) and in relatives of alcoholic patients (Hill *et al.* 1995; Ramachandran *et al.* 1996; Cohen *et al.* 1997). This raises questions about the specificity of P300 abnormalities, as previously discussed (Blackwood *et al.* 1994; Souza *et al.* 1995). However, the non-specificity of P300 deficits in early studies may partly be due to these studies having not addressed the topography of P300 abnormalities in patients with mental illness. In several studies, electrode sites were restricted to those situated on the midline, with sometimes only a single electrode. In the last 5 years, the combination of ERP recordings and other techniques of brain imaging, and the extension of the number of recording sites has allowed ERP topography to be studied. As pointed out by Salisbury *et al.* (1999), although unequivocal knowledge of neural generators cannot be derived from topography alone, differences in topography imply different generator configurations. Dipole source models have also started to be used in psychiatric research and are very promising, particularly for yielding information about specific brain mechanisms (Shajahan *et al.* 1997) and for separating trait and state markers (Turetsky *et al.* 1998; Frodl-Bauch *et al.* 1999).

The specificities of P300 abnormalities may be related to topographical differences. In particular, we suggest that the lack in relatives of the P300 amplitude dominance in the right hemisphere observed in controls might indicate vulnerability to manic-depressive disorder. Our results should be discussed in the light of ERP studies in affective disorders. Salisbury *et al.* (1999) observed a left greater than right asymmetry in bipolar patients with psychotic features and controls, whereas schizophrenics showed the opposite asymmetry. In contrast, no pathological P300 asymmetries were found by Strick *et al.* (1998) in bipolar patients without psychotic features. In bipolar patients with a history of hypomania, Bruder *et al.* (1992) reported a smaller N100 (but not P300) amplitude for left than right hemifield stimuli, in both audiospatial and temporal discrimination task, by comparison with unipolar patients and normal controls. This suggested a right-sided dysfunction at relatively early stages of information processing in bipolar patients. In depressed patients with high anhedonia, the lack of P300 asymmetry observed by Bruder *et al.* (1998), in comparison with the greater radial current flow over right than over left central regions in controls, was considered to be abnormal and to suggest a dysfunction of right hemisphere mechanisms. A deficit in the right auditory P300 distribution was also observed by Weir *et al.* (1998) in major depressive illness without any psychotic features. Although there is no consensus about the processing stages impaired, these reported right deficits in depressives, in contrast to the left deficits often reported in schizophrenics (Blackwood *et al.* 1994; Salisbury *et al.* 1994, 1998, 1999; Heidrich & Strick, 1997; Weisbrod *et al.* 1997; Weir *et al.* 1998) and in patients with schizotypal personality disorder (Salisbury *et al.* 1996), may provide some support for our finding showing a lack of P300 amplitude dominance in the right hemisphere in relatives of bipolar patients without psychotic features, in contrast to controls.

Few studies have focused on ERP anterior–posterior differences. A low P300 amplitude at frontal sites was found in bipolar patients (Strick *et al.* 1998; Salisbury *et al.* 1999) contrasting with a low P300 amplitude at parietal sites in schizophrenics (Salisbury *et al.* 1999). In both studies, the authors concluded that a reduced frontal lobe activity was probably the basic functional mechanism of manic disorders. The predominance of P300 amplitude abnormalities in frontal regions found here in relatives of manic-depressive patients became non-significant after statistical correction. This is disappointing given the frontal predominance observed by Strick *et al.* (1998) and by Salisbury *et al.* (1999) in manic-depressive patients, but we

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would remind that this correction is based on the total number of *post hoc* comparisons, a great proportion of which are non-relevant as regards topography.

Along with P300 deficits, a slow RT has long been the most consistent finding in schizophrenia (Friedman *et al*. 1982). In depression, results are more inconsistent and depend on the type of depression and the symptomatology: typical *v*. atypical (Bruder *et al*. 1991), retarded *v*. non-retarded (Schlegel *et al*. 1991), blunted-affect *v*. impulsiveness with anxious agitation (Pierson *et al*. 1991, 1994, 1996; Partiot *et al*. 1993). Findings also depend on the type of task and on the sensory modality (Bruder *et al*. 1992). Few RT results have been published for bipolar patients although a long RT was found in a recent study (Bange & Bathien, 1998). Indeed, RT measures are not of great interest if indices relevant to processes that may have caused the RT abnormalities are not obtained. In our study, given that N200 latencies did not differ between relatives and controls, it seems that most of the between-group differences observed in our study may be attributed to post-N200 stages i.e. post-perceptual processes (for N100, results are not clear: the longer N100 latency was found only in the subgroup with unaffected relatives). The positive correlation found in all subjects between RT and (RT − N200 latency) confirms that the retardation of motor response in relatives was due mainly to a lengthening of post-N200 stages in information processing. The negative correlation between post-N200 duration and N200 latency found in controls was not observed in relatives. This suggests that, unlike controls, relatives cannot compensate for a retardation in perceptual stages by an acceleration of later stages. We have previously observed abnormally long post-perceptual cognitive stages and motor preparation in depressed patients with psychomotor retardation and blunted-affect (Pierson *et al*. 1996) but no findings from ERP studies have been published concerning motor processes in bipolar patients.

In conclusion, our study suggests that a pattern associating P300 amplitude and latency deficits with long RT may be endophenotypic marker in families of bipolar patients. Although not specific to this population, such abnormalities in P300 are reported for the first time in relatives of manic depressive patients. Specificities should be looked for in topographical indices. In comparison with controls, a lack of P300 amplitude dominance in the right hemisphere has been observed, but a predominance of ERP abnormalities in frontal regions has to be confirmed by further research. Advanced techniques such as topographical mapping, with the calculation of current densities and dipole source models, will be very helpful for this purpose.

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