Fronto-Temporal Alterations Within the First 200 ms During an Attentional Task Distinguish Major Depression, Non-Clinical Participants With Depressed Mood and Healthy Controls: A Potential Biomarker?

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Abstract: Attentional impairment in depression is a cardinal feature of depression and has been proposed as a candidate endophenotype for major depressive disorder. Event-related potentials (ERPs) elicited by oddball signal detection tasks provide objective markers of selective stimulus processing, and are pertinent endophenotypic markers for depression. While previous studies have sought to determine objective markers for attentional impairment in depression, evidence is inconsistent and may involve heterogeneity in relatively small samples. Here, we brought together oddball ERP recording with source localization of neural correlates of selective attention in outpatients with major depressive disorder (MDD; $n = 78$) and participants with depressed mood (PDM; $n = 127$) relative to healthy controls (CTL; $n = 116$). The key finding was a dimensional exaggeration of the P200 (140–270 ms) to both target (signal) and non-target (noise) stimuli, most pronounced in MDD, followed by PDM, relative to CTL. This exaggeration was coupled with slower and more variable response times, suggesting that neural systems are attempting to compensate for a difficulty in discriminating signal from noise. P200 alterations were localised to limbic (hippocampal), temporal and ventral prefrontal regions, key components of the signal detection network. A subsequent reduction and delay in the P300 was also revealed for MDD indicating that the pronounced lack of discrimination in clinical depression may also lead to impaired stimulus evaluation. This P200 increase in depression could provide a potential mechanism for the attentional impairment frequently observed in depression and consequent alterations in the P300 may differentiate clinically significant depression. *Hum Brain Mapp* 30:602–614, 2009. © 2008 Wiley-Liss, Inc.

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INTRODUCTION

The ability to distinguish and selectively attend to significant changes in the environment is key to effective information processing, learning and adaptive decision-making. Attentional impairment including a diminished ability to attend and concentrate and a specific impairment in selective attention, is a cardinal feature of depression and has been proposed as a candidate endophenotype for major depressive disorder [APA 2000; Austin et al., 1999; Hasler et al., 2004; Mayberg et al., 1999; Miallet et al., 1996]. This impairment may be associated with a decrease in cognitive resources allocated to the external environment and a concomitant increase in self-focused attention [Ingram et al., 1987; Landro et al., 2001; Miallet et al., 1996; Mor and Winquist, 2002; Purcell et al., 1997; Ravnkilde et al., 2002]. Delayed reaction times and increased variability of this data have been reported in patients with depression [Austin et al., 1999; Bange and Bathien, 1998; Beats et al., 1996; el Massioui et al., 1996; Purcell et al., 1997]. However, the usefulness of reaction-time tasks is limited in that they measure the delay between stimulus presentation and the behavioural response of the participant, which comprises motor and cognitive components [Miallet et al., 1996]. Assessment of brain function using event-related potentials (ERPs) during attentional tasks may help to understand which components of the temporal processing stream elicited during attentional tasks are impaired in depression. Although a number of previous brain function studies have addressed attention-related impairment in depression, the sometimes contradictory nature of the findings may reflect comparatively small samples (discussed below). In this study, we included comparatively larger groups of both major depressive and non-clinically depressed individuals, relative to controls, to determine neural correlates of impairment in the ability to distinguish and attend to significant, task-relevant stimuli and the regional localisation of this impairment.

ERPs provide an index of the brain's transient electrical response to sensory stimuli and associated cognitive processing, and are pertinent endophenotypic markers for depression [e.g. Katsanis et al., 1997]. Robust ERPs are elicited by the standard auditory oddball task, which assesses the fundamental aspects of selective attention. According to William's model of significance processing, significance of the stimulus is the property that gives the stimulus its relevance and allows it to rise as the signal above the noise [Williams, 2006]. In the oddball task, significant task-relevant 'target' signals are defined as unex-

pected sensory changes (high pitch tones), presented among more frequent task-irrelevant 'noise' (non-target, low pitch) stimuli (see Hillyard and Picton, 1987 for review). This task requires differentiation and selective responses to the target signals, drawing on the processes of initial sensory sensitivity, selective attention and context updating. The N100 and P200 components of the ERP respond primarily to physical characteristics of the stimulus while the N200 and P300 are determined more by task requirements and associated cognitive processing of the stimulus [see Barry et al., 2003; also Polich and Kok, 1995]. Biophysical modeling, based on real physiological parameters, shows that the initial exogenous component complex (N100/P200) reflects the first volley of sensory information to the cortex, while the latter complex (N200/P300) relies on corticothalamo-limbic feedback associated with selective attention to target stimuli in particular [Rennie et al., 2002]. The N100 component is thought to reflect initial extraction of information from sensory analysis of the stimulus [Barry et al., 2003; Naatanen and Picton, 1987], and an increase in the N100 during attentional tasks such as the oddball is interpreted as greater sensory sensitivity [Barry et al., 2003; Burkhart and Thomas, 1993]. In terms of physiology, these increases reflect heightened initial cortical innervation [Rennie et al., 2002]. The P200 is thought to represent the initial differentiation of task-relevant from irrelevant stimuli, allowing for the focus on the former [Barry et al., 2003; Hegerl and Juckel, 1993; Lindholm and Koriath, 1985], which also reflects the initial engagement of cortical networks [Rennie et al., 2002]. Subsequent N200/P300 components are elicited by selective target processing in particular. The N200 reflecting further evaluation of targets, and feasibly response selection [Crottaz-Herbette and Menon, 2006; Kopp et al., 2006; Naatanen and Gaillard, 1983; van Veen and Carter, 2002] Most research has focused on the P300 (also known as 'P3b') which, when elicited by a standard two-tone oddball task, is interpreted as reflecting voluntary detection of targets, and the updating of activity in corticolimbic circuits during attention and working memory [Donchin and Coles, 1988; Hillyard and Picton, 1987; Polich and Herbst, 2000; Polich and Kok, 1995; Soltani and Knight, 2000; Verleger, 1988].

The dominant intra-cerebral sources associated with generation of these ERP components have also been described, comprising the superior temporal gyrus (including auditory cortex, Brodmann areas (BA) BA41, BA42, BA22) for all four components as well as additional activations in the precuneus (BA7,BA5) for the P200 component, a medial

frontal source (BA9, BA10, BA32) for the N200 component, and the prefrontal cortex (BA9, BA10, BA46, BA47), the inferior parietal cortex (supramarginal gyrus, BA40, BA39) and the posterior cingulate (BA31) for the P300 component [e.g. Anderer et al., 2004]. Other work has highlighted that multiple cerebral generators may be involved in the generation of these ERP components suggesting that the scalp-recorded peaks may not be simply related to 1 or 2 sources in the brain [Giard et al., 1994; Naatanen and Picton, 1987; Picton et al., 1999]. For example, the sources relating to the N100 component appear to include supratemporal primary auditory cortex, temporoparietal junction, frontal motor and premotor cortices which reflect the physical and temporal aspects of the stimulus and general state of the subject as well as endogenous temporal and frontal components that may be dependent on for example, attention, expectancy and conscious effort [Giard et al., 1994; Naatanen and Picton, 1987; Picton et al., 1999]. Using functional magnetic resonance imaging (fMRI), we have reported complementary evidence which suggests that activation of amygdala and ventral medial and lateral frontal cortical regions in response to target stimuli is associated with the appraisal of salience and novelty, while activation of dorsal lateral frontal cortex and supramarginal gyrus in response to the same stimuli is associated with sensory and context evaluation [Williams et al., 2007].

The most commonly reported ERP finding in depression is a reduction of P300 amplitude during this task [Gangadhar et al., 1993; Hansenne et al., 1996; Kawasaki et al., 2004; Roschke et al., 1996; Urretavizcaya et al., 2003] [but see Giedke et al., 1981; Sara et al., 1994; Vandoolaeghe et al., 1998] and less frequently, a longer P300 peak latency [Bruder et al., 1998]. Consistent with these findings, lower P300 cortical current source densities measured using LORETA have also been reported in depressed patients over bilateral temporal lobes, left frontal region and right temporal-parietal area [Kawasaki et al., 2004]. Although a number of studies have examined the impact of clinical depression on selective attention, studies have tended to focus on specific ERP components to targets (often only the P300) and to ignore responses elicited to background stimuli, making it unclear whether attentional impairment in depression commences prior to voluntary response to stimuli and associated P300 response. Other findings have been reported for clinically depressed participants comprising a reduction in N100 amplitude in response to both target and non-target stimuli [Burkhart and Thomas, 1993; el Massioui and Lesevre 1988; Hansenne et al., 1996; Roth et al., 1981], and increases in the P200 component [Sara et al., 1994; Vandoolaeghe et al., 1998], consistent with our findings in non-clinical depression, which focused on participants classified as non-depressed, mild-moderately or severely depressed [Kemp et al., 2006]. In our study, while no differences in behavioural performance was observed, we found that the mild-moderately depressed group was distinguished by increased P200 amplitude to targets relative to the other groups, along with decreased N100 ampli-

tude compared to the non-depressed group. These findings in combination with those reported for clinical participants, point to the possibility that depression may impact on initial cortical responsivity associated with earlier differentiation of task-relevant stimuli. The absence of P300 differences accords with findings from other non-clinical samples [Sumich et al., 2006; Yee et al., 1992] indicating that impairment of voluntary processes is not apparent until the depressed mood meets clinical criteria. However, a direct comparison of clinically depressed with non-clinically depressed individuals remains to be undertaken. Additional conflicting N200 amplitude findings have been reported in clinically depressed subjects [Bruder et al., 1998; el Massioui et al., 1996; Sara et al., 1994; Sumich et al., 2006] and may depend on gender, task parameters and sub-components.

The current study builds on previous oddball ERP studies by including a comparatively large sample of participants, including both unmedicated outpatients and non-clinically depressed participants. Given evidence that sex differences may contribute to oddball ERPs in depression, we also took gender into account. This study also brings together analysis of each of the oddball ERP components, with source localization of neural correlates to examine the intra-cerebral sources that generate altered ERPs in depression. It was hypothesised that patients with clinical depression would display slowed and more variable reaction times, reduced P300 amplitude, and similar early perceptual processing differences (decreased N100 and increased P200 amplitudes) as previously observed in non-clinical participants but at a much greater level of severity (i.e. that depression would impact dimensionally on these components) consistent with the proposal that clinical depression is a manifestation of a syndrome discernable in healthy participants [Judd et al., 2002; Lovibond and Lovibond 1995; but see Parker, 2000].

METHODS

Participants

Seventy-eight, out-patient participants with a primary diagnosis of major depressive disorder (MDD), 127 participants with depressed mood (PDM) and 116 healthy controls (CTL) participated in this study (see Table I for detailed group characteristics). All participants were medication free for at least five half-lives, had no history of brain injury, loss of consciousness, stroke, neurological disorder or other serious medical conditions and provided written informed consent to participate in accordance with the National Health and Medical Research Council guidelines.

MDD participants were recruited by collaborating clinicians and community advertising. Diagnoses were made by trained research officers using the Mini-International Neuropsychiatric Interview [MINI, Sheehan et al., 1998],

TABLE I. Participant characteristics: mean $\pm$ SD

	Patients with major depressive disorder (MDD)	Participants with depressed mood (PDM)	Healthy controls (CTL)	Summary Statistics
N	78	127	116	
Age (years)	36.52 $\pm$ 11.75	36.47 $\pm$ 11.28	34.77 $\pm$ 11.10	No significant differences
Gender	F: 45, M: 33	F: 61, M: 66	F: 64, M: 52	No significant differences
Depression ^a	DASS: 27.44 $\pm$ 9.34 HAM-D: 21.58 $\pm$ 4.99:	16.79 $\pm$ 7.43	2.12 $\pm$ 2.32	All groups differ, Tukey HSD: $P < 0.001$
Anxiety ^a	12.07 $\pm$ 10.38	6.66 $\pm$ 6.48	1.34 $\pm$ 2.00	All groups differ, Tukey HSD: $P < 0.001$
Stress ^a	21.44 $\pm$ 9.06	14.35 $\pm$ 8.75	4.70 $\pm$ 4.59	All groups differ, Tukey HSD: $P < 0.001$

^aDASS-21 scores were converted to full-scale scores by multiplying the DASS-21 scores by 2, as recommended by the DASS manual (Lovibond and Lovibond 1995).

which is compatible with both the International Classification of Diseases (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). MDD participants with a secondary anxiety disorder were included in the study to maximise generalisability of the findings and the ecological-validity of the sample. Secondary diagnoses included generalised anxiety disorder ($n = 33$), agoraphobia ($n = 27$), panic disorder ($n = 13$), and post-traumatic stress disorder ($n = 10$). As well as MINI diagnostic assessment, patients were assessed with the Structured Interview Guide for the Hamilton Depression Rating Scale [SIGH-D, Hamilton, 1960; Williams, 1988]. Non-patient participants were recruited by community advertising and were excluded if they self-reported a history or presence of psychiatric illness. These participants were further screened for an Axis I disorder using the Somatic and Psychological Health Report questionnaire (SPHERE-12) [Hickie et al., 2001]. All participants completed the Depression Anxiety and Stress Scales [DASS-21, Lovibond and Lovibond, 1995], a self-report measure of depression, anxiety and stress severity. Non-clinical participants were categorised with and without depressed mood using the DASS-21 depression scale.

Procedure

The study was reviewed and approved by the Sydney West Area Health Service and the University of Sydney Human Research Ethics Committees. Participants were seated in a sound and light controlled room at 24°C while the auditory oddball task was completed and electroencephalogram data was collected. This task requires participants to press buttons with the index finger of each hand in response to 'target' tones (1,000 Hz) but not to respond to 'non-target' tones (500 Hz). Participants were given a practice session to distinguish between target and non-target tones, both speed and accuracy of the response were emphasised. A total of 280 non-target and 60 target tones were presented in a random order and target probability was 12%, with two targets never appearing consecutively.

The tones were presented binaurally via headphones with the task lasting ~6 min. The reliability of this task has been reported on previously [Williams et al., 2005].

The standard procedures for the recording of brain electrical activity during this task have been previously described [Gordon et al., 2005; Williams et al., 2005]. An electrode cap (QuikCap) was used to record the electroencephalogram (EEG) data from 26 standard electrode sites positioned according to the 10/10 international system. Electrode sites included Fp1, Fp2, Fz, F3, F4, F7, F8, FC3, FCz, FC4, Cz, C3, C4, T3, T4, CPz, CP3, CP4, T5, T6, Pz, P3, P4, O1, O2, and Oz (Compumedics Neuroscan Nuamps). Data was recorded relative to averaged mastoids and an electrode on the forehead acting as a ground. A low pass filter was set at 100 Hz prior to digitization, at a sampling rate of 500 Hz. Electrode impedance was generally maintained below 5 k Ω . Horizontal and vertical eye movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye, and electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eye-lid. Electrooculogram (EOG) correction was conducted offline according to published techniques [Gratton et al., 1983].

ERP Data Analysis

ERP data were extracted from EEG recordings associated with target stimuli, using a window from -300 ms to 700 ms, relative to the stimulus onset. Each single trial waveform was then filtered at 25 Hz with a Tukey or cosine taper to 35 Hz, after which conventional ERP averages for each recording site were formed in relation to each target stimulus. ERPs were scored using an automated algorithm, which were then validated by experienced scorers. ERP components are scored base to peak and averages to target stimuli are associated with correct responses only. Auditory oddball ERP components and latency windows had been previously determined [Bahramali et al., 1999; Williams et al., 2000]. These included N100 (80-140 ms, targets and non-targets), P200 (140-270 ms, targets and

non-targets), N200 (180–320 ms, targets only), and P300 (270–550 ms, targets only). Variables were screened for outliers and cases with data >3.5 standard deviations from the mean of all cases (regardless of group) were removed from the dataset (<1% of data was removed following this procedure).

Statistical Analysis Using SPSS

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS, version 15). Behavioural data was analysed using one-way analysis of variance (ANOVA), N100 and P200 amplitude and latency components were analysed using a repeated measures ANOVA with a 3 (group: non-depressed, depressed mood, MDD) $\times$ 2 (gender) $\times$ 2 (stimulus: targets, non-targets) $\times$ 3 (midline sites: Fz, Cz, Pz) design for early components, and N200 and P300 components were analysed using a 3 (group) $\times$ 2 (gender) $\times$ 3 (midline sites) design as these later components are only elicited to target stimuli. Main effects of group were analysed using post-hoc, pair-wise, between group comparisons with the Tukey correction for multiple comparisons, while interaction effects were analysed using simple main effects analysis. Significant simple main effects of Group were further analyzed by pair-wise comparisons using the Sidak adjustment for multiple comparisons (LSD probability is reported if Sidak not significant). Significant effects were set at $P < 0.05$, while findings were labelled as trends if $P < 0.1$, and $P > 0.05$. Only effects involving group are reported and interactions with gender were explored only when findings reached the statistical threshold ($P < 0.05$) given the secondary interest of gender in this study.

Source Localisation Using LORETA

Low resolution brain electromagnetic tomography (LORETA) was employed in addition to the analysis of ERP components to provide convergent evidence for attentional impairment in depression. LORETA reveals parts of the brain's structural network that make the major contributions to the generation of the ERP component [Anderer et al., 2002; Pascual-Marqui et al., 2002]. The LORETA procedure computes the three dimensional distribution of the electrically active neuronal generators in the brain as a current density value ($\mu\text{A}/\text{mm}^3$) at each voxel. The linear LORETA solution relies on a criterion of contiguity, that the activity at any given voxel in cortical gray matter must be as similar as possible to the average activity of neighboring voxels. This criterion draws on electrophysiological evidence for the highly synchronized activity of neighbouring neurons, necessary for generating the EEG [Pascual-Marqui et al., 2002]. LORETA was used with a three-shell spherical head model registered to the neuroanatomical atlas of Talairach and Tournoux [1988]. Non-parametric statistical analyses were conducted using exact

critical t -values for $P < 0.05$ calculated via randomisation [Nichols and Holmes, 2002]. Independent sample t -tests were conducted for each component using previously determined latency windows [Bahramali et al., 1999; Williams et al., 2000] to determine significant differences between groups.

RESULTS

Behavioral Results

For auditory oddball behavioural data, groups differed significantly on reaction time ($F(2,305) = 12.08$, $P < 0.001$), and reaction time variability (standard deviation) ($F(2,305) = 10.35$, $P = 0.001$). No differences in false negatives (errors of omission) or false positives (errors of commission) were observed. Post-hoc comparisons revealed that MDD had a slower reaction time (MDD M: 383.19, SD: 79.38; PDM M: 347.61, SD: 66.25; CTL M: 337.51, SD: 43.82; Tukey HSD pair-wise probability: $P < 0.001$), and increased reaction time variability (MDD M: 74.21, SD: 36.13; PDM M: 62.66, SD: 23.75; CTL M: 56.51, SD: 19.11; Tukey HSD pair-wise probability: MDD vs. CTL, $P < 0.001$; MDD vs. PDM, $P = 0.008$) than both groups of controls. PDM did not differ from CTL on any of the behavioral variables.

Early Non-target and Target ERPs: N100 and P200

This section reports on between-group findings for N100 and P200 ERPs. (See also Figs. 1, 2 and Table II).

N100 amplitude and latency

A trend towards a significant main effect of Group ($2,284) = 2.883$, $P = 0.058$, partial $\eta^2 = 0.020$) but no Group by Stimulus interaction was observed for N100 amplitude. Post-hoc tests revealed an increased amplitude regardless of stimulus type i.e., presentation of targets and non-targets in MDD, relative to PDM (Tukey HSD pair-wise probability: $P = 0.07$), but not relative to CTL. PDM did not significantly differ from CTL. No effects were observed for N100 latency.

P200 amplitude and latency

A trend towards a significant main effect of Group ($2,258) = 2.741$, $P = 0.066$, partial $\eta^2 = 0.021$) was observed for P200 amplitude. Post-hoc tests revealed an increased amplitude regardless of stimulus in MDD relative to CTL (Tukey HSD pair-wise probability: $P = 0.052$), but not relative to PDM. While these effects are significant at trend levels (at two-tailed significance levels), the direction of these effects were hypothesised and therefore met criteria for 1-tailed statistical significance

($P = 0.026$).^{1,2} Additional analysis conducted at fronto-central sites (P200 amplitude is maximal at these locations) provided confirmatory evidence for such an effect (Group(2,279) = 3.546, $P = 0.03$, partial $\eta^2 = 0.025$). PDM did not significantly differ from CTL. These results and visual inspection of Figure 1 at frontocentral sites suggests a dimensional exaggeration of the P200 to both target (signal) and non-target (noise) stimuli, most pronounced in MDD, followed by PDM, relative to CTL. A significant Group by Stimulus interaction ($F(2,255) = 4.828$, $P = 0.009$, partial $\eta^2 = 0.036$) was observed for P200 latency and simple effects analyses revealed a main effect of Group for targets ($F(2,255) = 4.11$, $P = 0.018$, partial $\eta^2 = 0.031$) and a trend towards a main effect of Group for non-target stimuli ($F(2,255) = 2.549$, $P = 0.08$, partial $\eta^2 = 0.02$). Pair-wise comparisons revealed delayed latency in MDD relative to PDM (Tukey HSD pair-wise probability: $P = 0.014$) but not CTL during presentation of targets, but enhanced latency in MDD relative to CTL during presentation of non-targets (Tukey HSD pair-wise probability: $P = 0.087$). However PDM did not significantly differ from CTL during presentation of non-target or target stimuli.

Target ERPs at Midline Sites

This section reports on between-group findings for N200 and P300 ERPs in response to target stimuli. (See also Figs. 1, 2 and Table II).

N200 amplitude and latency

No significant effects were observed.

¹Results were further confirmed in two sub-analyses, each of which focused on a random selection of ~50% of cases in each sub-group ($F(2,129) = 3.911$, $P = 0.022$; $F(2,132) = 2.802$, $P = 0.064$). Each analysis supported the finding that P200 amplitude was greatest in MDD and smallest in CTL.

²Depression is frequently comorbid with the anxiety disorders. Indeed, depression is more common with, than without anxiety (Kaufman and Charney, 2000, *Depress Anxiety* 12:69–76). For this reason it was decided that participants would be included regardless of such comorbidity. However, additional analysis was conducted to investigate whether a main group effect would be observed between a random selection of healthy controls ($n = 44$), and two MDD sub-groups comprising of 1 group with and 1 group without comorbid anxiety ($n = 41$ and $n = 24$, respectively). There was a trend towards a significant main effect of group ($F[2,105] = 2.732$, $P = 0.07$), and post-hoc tests revealed a trend towards a significantly increased P200 amplitude in patients without comorbidity relative to controls ($P = 0.086$) and a significant increase in P200 amplitude in patients with comorbidity relative to controls. Importantly, there was no significant difference between MDD sub-groups ($P = 0.930$), suggesting that P200 amplitude findings are observed in MDD patients with and without comorbidity. However, as it is not the purpose of this article to examine the impact of comorbidity, this issue will not be discussed further.

P300 amplitude and latency

A significant main effect of group ($F(2,290) = 5.279$, $P = 0.006$, partial $\eta^2 = 0.035$) for P300 amplitude. Post hoc contrasts found that MDD had decreased amplitude relative to PDM (Tukey HSD pair-wise probability: $P = 0.004$) and CTL (LSD pair-wise probability: $P = 0.063$). PDM did not significantly differ from CTL. Visual inspection of Figure 1 provides convergent evidence of these findings further suggesting that P300 amplitude is smallest in MDD and greatest in PDM.). A significant group $\times$ site interaction ($F(3,783, 548.507) = 4.158$, $P = 0.003$, partial $\eta^2 = 0.028$, Greenhouse-Geisser corrected) was also observed for P300 latency. Simple main effects analysis, revealed a main effect of Group at Fz ($F(2,292) = 3.756$, $P = 0.025$, partial $\eta^2 = 0.025$) and Cz ($F(2,292) = 2.770$, $P = 0.064$, partial $\eta^2 = 0.019$), but not Pz. Pair-wise comparisons revealed a delayed P300 latency in MDD than CTL (Sidak probability for Fz: $P = 0.02$; Sidak probability for Cz: $P = 0.06$). PDM did not significantly differ from CTL.

Target ERPs: Source Localisation Using LORETA

Patients were observed to display significantly greater current source densities (CSDs) for the P200 component relative to both groups of controls (MDD versus CTL: $t_{\text{thresh}}=2.973$; MDD versus PDM: $t_{\text{thresh}}=2.928$) (see Fig. 3). These differences were observed in right superior temporal (BA22, with significant activation extending into BA41 and BA42) ($X = 67$, $Y = -18$, $Z = 1$, $t_{\text{max}} = 3.336$), bilateral parahippocampal (BA35) ($X = -24$, $Y = -25$, $Z = -13$, $t_{\text{max}} = 3.417$ and $X = 18$, $Y = -32$, $Z = -13$, $t_{\text{max}} = 3.109$) and right orbitofrontal (orbital surface of the superior frontal gyrus) (BA11) ($X = 18$, $Y = 59$, $Z = -20$, $t_{\text{max}} = 3.001$) gyri relative to healthy controls and the left precuneus of the parietal lobe (BA7) ($X = -10$, $Y = -74$, $Z = 50$, $t_{\text{max}} = 3.121$) relative to participants with depressed mood. No significant between-group differences were observed in CSDs for any other component, nor were any differences observed between PDM and CTL groups.

DISCUSSION

This study examined the impact of depression on the ability to selectively attend to significant stimuli. Although previous studies have investigated this issue, the literature is inconsistent and may involve heterogeneity in relatively small samples. Previous studies have also not included participants with depressed mood in addition to patients with clinical depression so that the impact of clinical status on observed electrophysiological markers may be examined. The key finding in this study was a dimensional exaggeration of the P200 amplitude regardless of stimulus type (i.e. target and non-target stimuli) in depressed participants and a concomitant increase in P200 current source densities in clinically depressed patients. This finding suggests that relevant as well as irrelevant stimuli are over-

Figure 1.

Group ERP waveform data for non-target and target stimuli at midline sites (Fz, Cz, Pz) displaying key between-group findings in P200 (red arrows) and P300 (grey arrows) components. The key finding was a dimensional exaggeration of the P200 to both

target (signal) and non-target (noise) stimuli, most pronounced in MDD, followed by PDM, relative to CTL, while additional impairments in P300 may differentiate clinically significant depression. (See also Fig. 2).

processed, which may then impact on later stimulus evaluation processes (reduced P300). This overprocessing may reflect atypical inhibition of sensory input from further processing [Johnstone et al., 2001] by an automatic mechanism that is crucial for early stimulus discrimination, allowing for voluntary selective attention [Hegerl and Juckel 1993; Lindholm and Koriath, 1985] [see Barry et al., 2003 for review]. It is possible that increased inhibition is related to increased self-focused attention (and a subsequent decrease in cognitive resources allocated to the

external environment) associated with emotional and psychological distress observed in depressed individuals [Mor and Winquist, 2002]. It is proposed that this atypical inhibition results in a difficulty to differentiate relevant information from irrelevant, and that this difficulty occurs early in the temporal processing stream and prior to the explicit cognitive processing of the stimulus.

The P200 amplitude increases observed in clinically depressed patients were localised to limbic (hippocampal), temporal and ventral prefrontal regions, providing further

Figure 2.

(A) P200 non-target and target, amplitude and latency at midline sites (mean $\pm$ SE). **(B)** P300 amplitude and latency at midline sites (mean $\pm$ SE).

insights into the nature of attentional impairment in depression. While a potential limitation of the present study is reliance upon a limited number of electrodes for source analysis (possibly impacting on the accuracy of localisation), it should be noted that the uncertainty of the localized source in both groups is the same, thus in the case of the present study, the problem is transformed from an absolute source problem into a relative source (difference between groups) problem. The increased sample sizes of groups as compared to previous studies, also compensates, in part, for the increased uncertainty associated with a reduced number of electrodes. Importantly, the identified regions are key components of the oddball signal detection network [Downar et al., 2001; Williams et al., 2007], providing support for the validity of the procedure. The superior temporal gyri is a key region involved in the generation of the ERP waveform elicited by auditory stimuli [Anderer et al., 2004; Jancke et al., 1999; Mitchell et al.,

2005; Naatanen and Picton 1987]. The hippocampal/parahippocampal gyri are involved in sensory and context evaluation and in the context of the oddball task, are involved in the evaluation of salient sensory information, along with interactions with frontal and parietal cortices [Crottaz-Herbette et al., 2005] [see also Williams et al., 2007]. The orbital prefrontal cortex (including BA11) is involved in sensory integration, and in combination with the anterior cingulate cortex, appears to be gateway for subjective conscious experience [Kringelbach, 2005]. We also identified increased current source densities in the precuneus in patients relative to participants with depressed mood. The precuneus is part of a network (including posterior cingulate and medial and orbital prefrontal cortices) that is responsible for integration of information continuously collected from the general senses and for determining the significance of this information [Gusnard et al., 2001] [see also Cavanna and Trimble, 2006 for

TABLE II. Summary of between-group non-target and target ERP findings at midline sites for healthy controls (CTL), participants with depressed mood (PDM) and patients with depression (MDD)

ERP	Statistic: Midline	Finding
N100 amp	Targets and Non-targets: Group: $P = 0.058$, partial $\eta^2 = 0.020$	Targets and Non-targets: MDD displayed increased amp regardless of stimulus relative to PDM
N100 lat	Null	N/A
P200 amp	Targets and Non-targets: Group: $P = 0.066$, partial $\eta^2 = 0.021$	Targets and Non-targets: MDD displayed increased amp relative to CTL
P200 lat	Targets and Non-targets: Group by Stimulus: $P = 0.009$, partial $\eta^2 = 0.036$	Targets and Non-targets: MDD displayed enhanced latency during presentation of non-target stimuli but delayed latency during targets
N200 amp	Null	N/A
N200 lat	Null	N/A
P300 amp	Targets: Group: $P = 0.006$, partial $\eta^2 = 0.035$;	Targets: Group: MDD had decreased amp relative to both groups of controls.
P300 lat	Targets: Group by Site: $P = 0.003$, partial $\eta^2 = 0.028$	Targets: Group by Site: MDD displayed delayed lat relative to CTL at Fz and Cz.

review of the precuneus]. In summary, it is proposed that increased current source densities in the network of regions revealed here, reflects ongoing, continuous over-sampling of data, which may contribute to suboptimal selective attention (reduced P300). Heightened P200 activity therefore suggests a potential explanation for the attentional impairments observed in depression.

Previous studies have seldom examined the P200 component in depressed samples and rarely report on responses to frequent non-target as well as target stimuli. Vandoolaeghe et al. [1998] reported increased P200 amplitude and heightened responses in patients that did not respond to antidepressant treatment relative to treatment responders and normal volunteers. Another study found the mean P200 amplitude to target stimuli was most pronounced for a drug-free depressed group, followed by a medicated depressed group and then controls, although no significant differences between groups were displayed (possibly due to small sample size) [Sara et al., 1994]. The current study extends on these findings indicating that depressed participants display a dimensional exaggeration of P200 amplitude responses regardless of stimulus type as well as concomitant increases in current source densities in patient participants, highlighting the importance of examining this component in future studies. While reductions in the P200 have been reported previously [Anderer et al.,

Figure 3.

LORETA findings. (A) Patients relative to Healthy Controls: increased current source densities (CSDs) in superior temporal, parahippocampal and orbitofrontal cortices. (B) Patients versus Participants with depressed Mood: increased current source densities displayed in left precuneus.

2002], these findings were observed in an older cohort of depressed postmenopausal patients diagnosed according to DSM-III criteria, and is therefore quite a different sample of patients to those used in the current study. In addition to P200 findings and consistent with hypotheses, we found depressed patients to display slower and more variable reaction times as well as reduced P300 amplitude and delayed latency. Reaction time findings suggest that clinical (but not non-clinical depression) may be characterised by impaired selection and execution of motor responses (psychomotor retardation) as reported previously [e.g. el Massioui et al., 1996]. P300 findings suggest that clinical depression may also be associated with impairment in cognitive evaluation and categorisation processes. Although two previous studies have reported P300 component current source density differences in depression [Anderer et al., 2002; Kawasaki et al., 2004], Anderer et al. reported on an older cohort of postmenopausal participants [Anderer et al., 2002], while the sample size in the study conducted by Kawasaki et al. (2004) was smaller than the present one ($n = 22$ versus $n = 78$) suggesting inter-individual variability in the source strength of the P300 component. Unlike Kawasaki et al., the current study also included participants with a secondary diagnosis of anxiety to maximise the ecological-validity of the study.

Our study included non-clinical as well as patients diagnosed with clinical depression, allowing for the impact of clinical status to be determined. There has been much debate and discussion as to whether clinical depression should be considered as a manifestation of a syndrome discernable in healthy participants, but at a much greater level of severity or a disorder categorically different from that observed in non-clinical depression [Judd et al., 2002; Lovibond and Lovibond 1995; Parker 2000]. For instance, Judd et al. have noted that prospective follow-up of neurotic depression may show progression to major, endogenous and even bipolar depression. These authors argued that depressive illness should be viewed along a spectrum of severity ranging from 'subsyndromal to syndromal levels, in which subthreshold symptoms acquire clinical relevance'. [Judd et al., 2002]. However, others have argued that clinical manifestations such as psychotic features or psychomotor retardation should be used to distinguish psychotic, melancholic and nonmelancholic classes of depression [Parker, 2000]. The classification of depression according to a dichotomous (categorical) diagnosis (present, absent) versus a continuous measure of psychopathology (dimensional) is also important for the (re-)conceptualisation of the mood disorders for the next edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), such that a dimensional approach would yield a greater amount of clinically relevant information while a categorical approach may be more conducive to clinical decision making [Bruder et al., 1998]. Findings from the current study (partly) support the proposal that depression is a dimensional construct that differs along a spectrum of severity, particularly in terms of the P200 ERP component

which displayed the most robust changes relative to control groups with respect to amplitude, latency and concomitant source strength. The P200 amplitude was observed to be smallest in healthy controls, increased in participants with depressed mood and largest in patients with clinical depression. Moreover, P200 source strength differed in more regions when patients were compared with healthy controls than when patients were compared with participants with depressed mood. By contrast, a reduction in P300 amplitude, the most commonly reported ERP finding in depression, was only displayed in clinically significant depression (P300 amplitude was greatest in PDM). Previous work indicates that ERP components including P200, are under partial genetic control [Katsanis et al., 1997], suggesting that this electrophysiological marker is a pertinent endophenotypic marker for depression. Future studies should consider longitudinal designs that include re-assessment of the same individuals following treatment and family-study designs that include clinically unaffected first-degree relatives of patients to help clarify the endophenotypic status of the P200 component [Cannon and Keller, 2006]. In this regard, it will be important to determine whether an increase in the P200 (or a decrease in the P300) component is an enduring characteristics that can also be detected following treatment or in first-degree relatives.

This study has several advantages including use of participants with depressed mood to examine the impact of clinical status on identified markers, the testing of a large sample of participants, recruitment of unmedicated patients and examination of responses to target and non-target stimuli. Moreover, this is one of the first studies to simultaneously utilise ERPs and LORETA techniques, so that attentional impairment in depression may be better (and more comprehensively) characterised. In summary, the key finding was a dimensional exaggeration of the P200 component regardless of whether the stimulus was a target (signal) and non-target (noise), and this exaggeration was most pronounced in MDD, followed by PDM, relative to CTL. This exaggeration was coupled with slower and more variable response times, suggesting that neural systems are attempting to compensate for a difficulty in discriminating signal from noise. This effect was localised to limbic (hippocampal), temporal and ventral prefrontal regions, key components of the signal detection network. A subsequent reduction and delay in the P300 was also revealed for MDD indicating that the pronounced lack of discrimination in clinical depression may lead to impaired stimulus evaluation. These findings indicate that P200 has promise as a marker of risk for depression, while additional impairments in P300 may differentiate clinically significant depression. Although future studies will need to determine the specificity of these findings by comparison of depressed patients with other patient populations including attention deficit hyperactivity disorder and schizophrenia, we conclude that the P200 component may reflect a biomarker of attentional impairment in depression

and that impairments in the P300 may differentiate clinically significant depression.

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