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Event-Related Brain Potentials in Depression: Clinical, Cognitive and Neurophysiologic Implications

Gerard E. Bruder [*], Jürgen Kayser, and Craig E. Tenke

Division of Cognitive Neuroscience, New York State Psychiatric Institute
and
Department of Psychiatry, Columbia University College of Physicians & Surgeons

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Introduction

Individuals having a depressive disorder commonly experience difficulties in concentration, attention and other cognitive functions, such as memory and executive control (Austin et al., 2001; Porter et al., 2003). The recording of event-related brain potentials (ERPs) provides a noninvasive means for studying cognitive deficits in depressive disorders and their underlying neurophysiologic mechanisms. The precise temporal resolution of ERPs can reveal unique information about the specific stage of processing that may lead to disruption of performance on cognitive tasks, e.g., early sensory/attentional processing as reflected in the N1 potential or later cognitive evaluation as reflected in the P3 potential. Moreover, ERPs can provide noninvasive biological markers for assessing treatment effects and, most promisingly, for determining who will benefit from a particular course of treatment.

By far, the largest number of ERP studies of depression have focused on the cognitive P3 potential during target detection "oddball" tasks. We will review the findings of these studies and focus on recent studies that examined P3 subcomponents, which provide new evidence concerning specific cognitive operations that may be disturbed in depression. After reviewing these findings, we will examine ERP findings in depressed patients obtained during more challenging cognitive paradigms, including more demanding auditory or visual discrimination tasks. We will also review studies that have recorded ERPs in depressed patients during recognition memory tasks, which provide information on ERP correlates of episodic memory. Surprisingly few studies have measured ERPs of depressed patients during processing of emotional stimuli, and yet, such data may have particular relevance to mood disorders and will therefore be reviewed. A number of recent studies in depressed patients have found abnormalities of negative brain potentials associated with monitoring of cognitive performance, e.g., error-related negativity (ERN). These studies, as well as others measuring the intensity-dependency of auditory N1-P2 potentials, will be highlighted because they suggest the potential value of these ERP measures for predicting clinical response to antidepressants.

One aim of this review is therefore to bring together the findings of studies measuring ERPs in depressed patients during a variety of sensory, cognitive and emotional tasks, so as to contribute toward a better understanding of the specific processes and neurophysiologic mechanisms that are dysfunctional in depressive disorders. For instance, evidence of ERP abnormalities related to attentional or cognitive control processes are suggestive of deficits involving frontal or anterior cingulate cortex. Another aim is to highlight the clinical relevance of ERP findings in depressed patients by pointing to the relation of the patients' ERPs to their clinical features, most notably severity of depressive symptoms, diagnostic subtype, and therapeutic response to treatments. From a more methodological perspective, we will present new findings illustrating the power of combining current-source density (CSD) and principal components analysis (PCA) techniques, which take better advantage of both the temporal resolution of ERPs and the spatial resolution of dense electrode arrays than traditional analysis methods of reference-dependent surface potentials (Kayser & Tenke, 2006a,b).

P3 in Auditory and Visual Oddball Tasks

The P3 or P300 potential provides physiologic measures associated with attentional and working memory operations during cognitive task performance (see Polich, 2007; Chapter 7, this volume). It has typically been measured during oddball tasks, in which a subject responds to an infrequent target stimulus in a series of frequent nontarget standard stimuli. In the typical study, subjects hear a pseudorandom sequence of 90% low-pitched and 10% high-pitched tones, each presented for 50 ms at a rate of 1 per second, and the subject's task is to respond to the infrequent high-pitched tone (e.g., by pressing a button or silently counting). With

* Address reprint requests to: Gerard E. Bruder, New York State Psychiatric Institute, Division of Cognitive Neuroscience, Unit 50, 1051 Riverside Drive, New York, NY 10032, USA. Email: bruderj@pi.cpmc.columbia.edu

all common EEG recording reference schemes (nose, linked mastoids, average reference), the classical P3 potential (P3b) is maximal over midline parietal scalp sites and has a peak latency ranging from 300-500 ms. Figure 1 illustrates the average waveforms for healthy adults at midline frontal (Fz), central (Cz), parietal (Pz) and occipital (Oz) electrode sites (nose reference) to infrequent targets (solid line) and frequent nontargets (dashed line) in an oddball task. The waveforms are typical of those seen for auditory oddball tasks consisting of early N1 and P2 peaks to both targets and nontargets, followed by a negative peak and a late positive peak occurring about 200 ms (N2) and 350 ms (P3) relative to the onset of only the target stimuli. The P3b component has its maximum at Pz.

Most studies in depressed patients have used an auditory oddball task. Although specific procedures vary from study to study (e.g., frequency of target and nontarget tones, stimulus duration, interstimulus intervals, response mode), the use of the same basic task facilitates the comparison and summary of P3 findings across studies. However, despite the use of largely comparable oddball tasks, there have been conflicting findings as to whether depressed patients have reduced P3 amplitude. A review of early studies (Roth et al., 1986) using mostly oddball tasks found that only about half showed reduced P3 amplitude in depressed patients when compared to healthy controls. Table 1 summarizes the findings of more recent studies published over the last 20 years that compared P3 amplitudes for depressed patients and healthy controls in auditory oddball tasks. Sixty percent (12 of 20) of the comparisons listed in Table 1 found significantly smaller P3 amplitude in patients having a major depressive disorder (MDD) as compared to healthy controls (HC). These studies had moderate to large effect sizes, which ranged widely from 0.52 to 2.25 (Cohen's d). Among studies that failed to find significant differences, there were often trends for depressed patients to have smaller P3 than controls, but with small effect sizes ranging from 0.11 to 0.52. The mean effect size of studies reported in Table 1 is 0.85 (SD = 0.75; Median = 0.79), indicative of a moderate group difference. Thus, while there continue to be conflicting findings, the overall trend is for most studies using an auditory oddball paradigm to show at least some reduction of P3 amplitude in depressed patients.

The large difference in effect size across studies does, however, suggest that differences in the clinical characteristics of the patients in these studies may have played a role. Although differences in P3 amplitude among patients have generally not been found to be related to their overall severity of depression, there is evidence that some subtypes of depression show the greatest reductions of P3 amplitude. All three studies testing patients having a major depression with melancholic features found reduced P3 in patients, with large effect sizes of 0.85, 0.98 and 2.25 (Ancy et al., 1996; Gangadhar et al., 1993; Urretavizcaya et al., 2003). Melancholic features include profound loss of interest or pleasure, lack of reactivity to usual pleasurable stimuli, and associated symptoms, such as early morning awakening, worse in the morning, psychomotor retardation, weight loss and excessive guilt (American Psychiatric Association, 1994). Also, P3 has been found to be more reduced in patients having a psychotic than non-psychotic depression (Karaaslan et al., 2003; Kaustio et al., 2002) and patients who have attempted suicide compared to those without suicidal history (Hansenne et al., 1996). Smaller P3

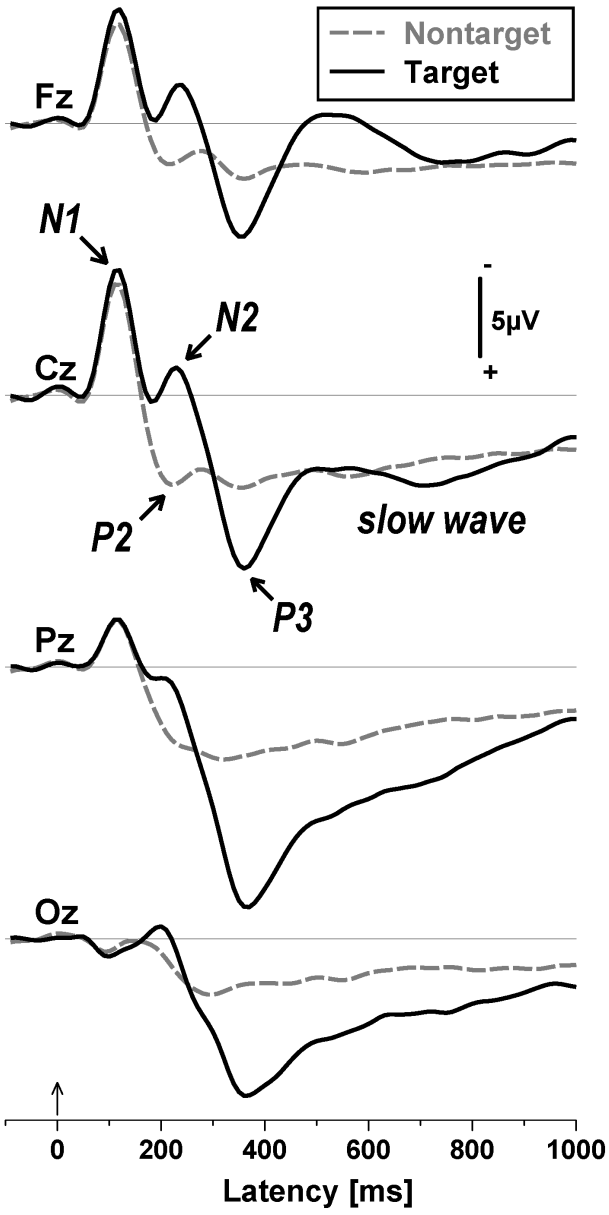

Figure 1. Grand mean, nose-referenced ERP waveforms for 26 healthy adults comparing targets (solid lines) and nontargets (dashed lines) in an auditory oddball task at frontal (Fz), central (Cz), parietal (Pz) and occipital (Oz) midline electrode sites (data from Kayser et al., 1998).

Table 1. Auditory Oddball Studies Comparing Depressed Patients and Healthy Controls.

Study	Sample [a]	EEG Montage	EEG Reference	P3 Amplitude	Effect Size [b]
Blackwood et al. (1987)	16 MDD (med-free), 59 HC	Cz	Left Ear	MDD < HC	.79
Muir et al. (1991)	46 MDD (35 med-free), 212 HC	Cz	Left Ear	MDD < HC	.52
Gangadhar et al. (1993)	17 MDD (med-free), 22 HC	Cz	Mastoids	MDD < HC	.98
Sara et al. (1994)	14 MDD (med-free), 27 HC	Fz, Cz, Pz	Linked Ears	MDD = HC	.18
	13 MDD (medicated)			MDD = HC	.31
Hansenne et al. (1996)	10 MDDwS (med-free), 20 HC	Cz	Left Ear	MDDwS<HC	1.72
	10 MDDwoS (med-free)			MDDwoS=HC	-.12
Ancy et al. (1996)	17 MDD (15 med-free), 15 HC	Cz	Mastoids	MDD < HC	.85
Yanai et al. (1997)	16 MDD (med-free), 17 HC	Pz	Linked Ears	MDD < HC	2.18
Wagner et al. (1997)	11 MDD (med-free), 10 HC	Fz, Cz	Right Mastoid	MDD < HC	-
Bruder et al. (1998)	40 MDD/DYS (med-free), 22 HC	12 sites	Nose	MDD/DYS = HC	-
Vandoolacghe et al. (1998)	35 MDD (med-free), 11 HC	Cz	Mastoids	MDD = HC	.52
Kaustio et al. (2002)	22 MDD/DYS (med-free), 22 HC	16 sites	Right Mastoid	MDD/DYS = HC	-
Anderer et al. (2002)	60 MDD (med-free), 29 HC	19 sites	Average Mastoids	MDD < HC	-
Röschke & Wagner (2003)	21 MDD (med-free), 21 HC	Cz, Pz	Right Mastoid	MDD < HC	-
Urretavizcaya et al. (2003)	50 MDD (med-free), 31 HC	C3, Cz, C4	Linked Ears	MDD < HC	2.25
Kaiser et al. (2003)	16 MDD (medicated), 16 HC	18 sites	Average	MDD = HC	.11
Karaaslan et al. (2003)	16 MDDwP (med-free), 20 HC	Cz	Linked Mastoids	MDDwP < HC	1.43
	20 MDDwoP (med-free)			MDDwoP = HC	.08
Kawasaki et al. (2004)	22 MDD (med-free), 22 HC	16 sites	Linked Ears	MDD < HC	.90

[a] MDD = major depressive disorder; HC = healthy controls; DYS = dysthymic disorder; MDDwS = MDD with suicide attempt; MDDwoS = MDD without suicide attempt; MDDwP = MDD with psychotic features; MDDwoP = MDD without psychotic features

[b] Cohen's *d* effect size

amplitude was associated with higher scores on scales for assessing suicidal risk (Hansenne et al., 1996) and psychotic symptoms (Santosh et al., 1994). Greater P3 reduction in psychotic depression is consistent with evidence that cognitive deficits on neuropsychological tests are more severe in psychotic than nonpsychotic depression (Castaneda et al., 2008) and with the robust P3 reduction seen in schizophrenia (Jeon & Polich, 2003; Chapter 18, this volume).

The patients in all but two of the studies in Table 1 were unmedicated at the time of testing. Although one of these studies found no difference in P3 between medicated and unmedicated patients (Sara et al., 1994), studies have generally found P3 amplitude to increase or normalize following treatment with antidepressants or ECT (Blackwood et al., 1987; Gangadhar et al., 1993; Nurminen et al., 2005; but see negative findings of Vandoolaeghe et al., 1998). Following vagus nerve stimulation, treatment responders but not nonresponders showed an increase in P3 amplitude, but no control group was tested and so it is not known whether this treatment normalized P3 (Neuhaus et al., 2007). These findings indicate that reduced P3 in depressed patients during an auditory oddball task is at least partially state-dependent and may normalize with improvement of depression during successful treatment. This is also supported by the finding that young women with a history of a major depressive episode, but no current depressive disorder, did not differ from normal controls in P3 amplitude during an auditory oddball task (Houston et al., 2004).

Fewer studies have measured P3 in depressed patients during visual oddball tasks, and as is case for auditory modality, there have been conflicting findings. Diner et al. (1985) conducted one of the first studies, in which 10 depressed patients and 10 controls were tested in a variant of a 3-stimulus visual oddball task with an infrequent target (letter string 'DTM'), a frequent standard ('RSC'), and infrequent nontarget three-letter words. P3 amplitude to targets was significantly smaller in depressed patients when compared to controls, and greater severity of depression was associated with smaller P3. In contrast, Bange and Bathien (1998) found no difference in P3 amplitude between patients having either unipolar major depressive disorder ($n = 12$) or bipolar depressive disorder ($n = 11$) and healthy controls ($n = 20$) in either single-stimulus or two-stimulus visual oddball tasks. They did, however, report that patients having a bipolar depressive disorder had significantly longer latency of the P3 peak compared to controls, and the depressed patients showed a reduction in P3 latency in remission. Although some studies have not found a difference in P3 latency between depressed patients and healthy controls in visual or auditory oddball tasks (Diner et al., 1985; Blackwood et al., 1987; Gangadhar et al., 1993), longer P3 latency in bipolar depressed patients, but *not* unipolar depressed patients, parallels the findings of Muir et al. (1991) for the auditory modality. This suggests

that patients who typically display psychomotor retardation, e.g., those having bipolar or melancholic depressions, may be most likely to show longer P3 latency suggestive of a slowing of cognitive processing. Schlegel et al. (1991) also found that longer P3 latency for depressed patients ($n = 36$) in an auditory task was correlated with their total score on the Bech-Rafaelsen Melancholia Scale and the four retardation items on this scale.

P3 in Cognitively Challenging Auditory and Visual Tasks

The conflicting findings for P3 amplitude in depressed patients may in part be due to the use of simple oddball tasks that are not cognitively challenging enough to elicit robust P3 reductions in patients having subtle cognitive deficits. We have argued that it would be more fruitful to measure P3 in depressed patients during cognitively demanding tasks (Bruder, 1992). Given evidence from neuropsychological and dichotic listening tests suggestive of right parietotemporal dysfunction in depression (Bruder et al., 1989; Heller et al., 1995), we reasoned that depressed patients might show greater P3 deficits in tasks that tap right hemispheric processing, e.g., those involving spatial or complex tonal processing. ERPs were measured in 25 unmedicated depressed patients and 27 healthy controls during spatial and temporal discrimination tasks in the auditory modality (Bruder et al., 1991). The spatial task used a dichotic paradigm to manipulate the apparent location of a click and the subject's task was to discriminate a difference in the location of standard and test stimuli. The temporal task required discriminating a difference in duration of a standard click train and a test click train. A titration procedure was used to determine the difference between standard and test stimuli in each task that would yield 75% correct responses for each subject, and these threshold values were used during the ERP measurements. To evaluate differences between subtypes of depression, patients were divided into those having either a typical, melancholic form of depression or an atypical depression. Patients meeting criteria for atypical depression showed symptoms that are in some respects opposite of those seen for melancholia, i.e., reactivity of mood with preserved pleasure capacity and one or more associated features – hypersomnia, overeating, rejection sensitivity or bodily inertia. There was no difference among the patient subgroups and healthy controls in behavioral thresholds for discriminating stimuli in the spatial or temporal tasks, and no difference in their P3 amplitudes. However, patients having a typical, melancholic depression had considerably longer P3 latency in the spatial task when compared to patients having atypical depression and healthy controls. In contrast, there was no difference among groups in P3 latency during the temporal discrimination task, which indicates that the cognitive task in which the P3 is measured is an important factor. The melancholic subgroup showed evidence of a slowing of cognitive processing only in the spatial task that involves predominantly right hemisphere processing. Moreover, it supports findings from oddball tasks suggesting that longer P3 latency is most evident in specific diagnostic subtypes, i.e., melancholic and bipolar depression.

Given evidence of right hemisphere dysfunction in depression, a subsequent study measured ERPs of 44 unmedicated depressed patients and 19 healthy controls during a complex tone test (Bruder et al., 1995). This is a cognitively demanding dichotic listening task that yields a left ear (right hemisphere) advantage in healthy adults for perceiving complex tones (Sidtis, 1981; Tenke et al., 1993). Depressed patients had significantly smaller P3 amplitude compared to controls and also failed to show either the behavioral left ear (right hemisphere) advantage or the hemispheric asymmetry of P3 seen for controls. The absence of any difference in early sensory potentials (e.g., N1) between depressed patients and controls supports the conclusion that the lack of a right hemisphere advantage for perceiving complex tones is related to a relatively late stage of cognitive processing reflected in the P3.

Arguing that binaural oddball tasks are too simple to consistently reveal cognitive dysfunction in depression, Tenke et al. (2008) developed a dichotic oddball task that increases the cognitive challenge. ERPs of 38 unmedicated depressed patients and 26 healthy controls were measured in tonal and phonetic tasks with dichotic presentation of stimuli. Tonal nontargets were pairs of complex tones (corresponding to musical notes G and B above middle C) presented simultaneously to each ear (L/R) in an alternating series (G/B or B/G). A different target tone (note A) replaced one of the pair on 20% of the trials. Phonetic nontargets were pairs of syllables (/ba/, /da/) presented simultaneously to each ear (L/R) in an alternating series and the target was a different syllable (/ta/). The subject's task was to respond to the target with a button press. Target detection was poorer in depressed patients than controls for both tones and syllables. Patients also showed reductions of current source density (CSD) for parietal and temporal lobe sources corresponding to P3. While reduction of the parietal source was related to the patients' poorer performance, temporal lobe source reductions were not. Given the involvement of primary and secondary auditory cortex in tonal and phonetic processing (Zatorre et al., 1992), these findings support evidence of temporoparietal dysfunctions in depression (e.g., Bruder et al., 1995; Deldin et al., 2000; Heller et al., 1995; Post et al., 1987). The P3 source reduction in depressed patients was not lateralized to one hemisphere, and the tonal and phonetic tasks did not yield consistent behavioral ear advantages in healthy adults. The above findings indicate that cognitively challenging dichotic listening tasks yield consistently smaller P3 amplitudes in

depressed patients when compared to healthy adults.

Two studies measuring ERPs during cognitively demanding visual tasks agreed in showing that individuals "at risk" for later development of depressive disorders had reduced P3 amplitude. Houston et al. (2003) used a visuospatial oddball task that challenged attention and a complex cognitive skill (i.e., mental rotation). Young women with a history of a major depression episode but no current depressive disorder ($n = 29$) had smaller P3 amplitude when compared to those with no history of depression ($n = 101$). Moreover, topographic maps of CSD measures corresponding to P3 indicated that the difference between the previously depressed and non-depressed groups was maximal over the right prefrontal region. Similarly, Zhang et al. (2007) measured ERPs of healthy adults with or without a family history of depression ($n = 14$ per group). The task was a visual go/no-go task, in which large or small letters H and O were presented on a monitor and subjects were required to respond with the right hand to a large H or with the left hand to a large O, and no response was required for smaller letters. Subjects with a family history of depression, who are at increased risk for developing a depressive disorder, showed smaller P3 amplitudes over temporoparietal regions when compared to low risk subjects. LORETA source localization methods pointed to decreased activation of the left middle temporal gyrus in the high risk subjects. The authors suggested that P3 decrement in visual tasks reflects a vulnerability marker for developing depression. This contrasts with the P3 findings for simple auditory oddball tasks, where subjects at high risk for depression did not differ from low risk subjects in P3 amplitude (Houston et al., 2004) and where P3 increase following remission of depression was suggestive of a more state-dependent effect. Thus, while P3 reductions in a simple auditory oddball task appear to reflect the patient's current clinical state, P3 reductions in more demanding visual tasks appear to reflect underlying vulnerability for a depressive disorder. It is interesting to note in this regard that we have found EEG evidence of reduced right posterior activity in offspring at risk for depressive disorders (Bruder et al., 2007), which implicates cortical regions known to mediate visual attention and perception as possible vulnerability indicators for depression.

P3 Subcomponents

P3 is not a unitary phenomenon but consists of two or more subcomponents associated with different cognitive operations and neural generators (see Chapter 7, this volume). Although the focus of most studies in depressed patients has been on the parietal maximum P3b, this component is often preceded by a component with a more frontocentral topography, i.e., P3a. This frontal aspect of P3 is prominent to novel distracter stimuli (e.g., environmental sounds) that are interspersed along with target and standard stimuli in a three-stimulus oddball task (Polich & Criado, 2006; Simons et al., 2001; Spencer et al., 1999). The importance of differentiating between P3 subcomponents is that the novelty P3 or P3a is thought to reflect frontal attention or orienting mechanisms, whereas P3b reflects temporoparietal mechanisms associated with context updating and memory processing (Polich, 2007). Studies examining P3 subcomponents in depressed patients could therefore provide new information concerning the nature of their cognitive deficit and underlying neurophysiologic mechanisms.

The first studies to examine P3a and P3b subcomponents in depressed patients used go/no-go reaction time tasks (Pierson et al., 1996) and divided patients into two subgroups to deal with the issue of clinical heterogeneity of depression. The authors referred to an initial study, in which they recorded ERPs during a simple forewarned reaction-time task and reported that a subgroup of anxious-agitated-impulsive patients had *greater* amplitude of the frontal P3a when compared to a subgroup of patients having retarded-blunted affect. In their subsequent study, they used a complex forewarned choice reaction-time task so as to measure P3 subcomponents in a more effortful and cognitively demanding task. Although they reported finding no difference in P3a amplitude among groups, peak-to-peak measures of N2b-P3a amplitudes were smaller in depressed patients than controls, and retarded-blunted affect patients had smaller N2b-P3a than the anxious-agitated-impulsive patients, with the same tendency when compared to controls. Also, the anxious-agitated-impulsive subgroup had larger P3b amplitudes when compared to either the retarded-blunted-affect subgroup or controls. These findings supported the importance of differentiating between P3 subcomponents and patients with different symptom features in studies of depressed patients.

In a study measuring ERPs during tonal or phonetic two-stimulus oddball tasks (Bruder et al., 2002), we used principal components analysis (PCA) to identify and measure overlapping P3 subcomponents in patients having a depressive disorder alone ($n = 58$), an anxiety disorder alone ($n = 22$), comorbidity of these disorders ($n = 18$), and healthy controls ($n = 49$). An early P3 subcomponent (peak latency 315 ms) was *larger* in patients having an anxiety disorder alone (primarily social phobia or panic disorder) when compared to depressed patients or healthy controls. Depressed patients having a comorbid anxiety disorder tended to have a smaller early P3 than healthy controls, but those having a depressive disorder alone did not. The timing and frontocentral topography of this early P3 subcomponent resembles that seen for P3a. It should be noted, however, that our study used a nose recording reference, as opposed to linked ears in Pierson et al. (1996), which has implications for P3 morphology and topography. Nevertheless,

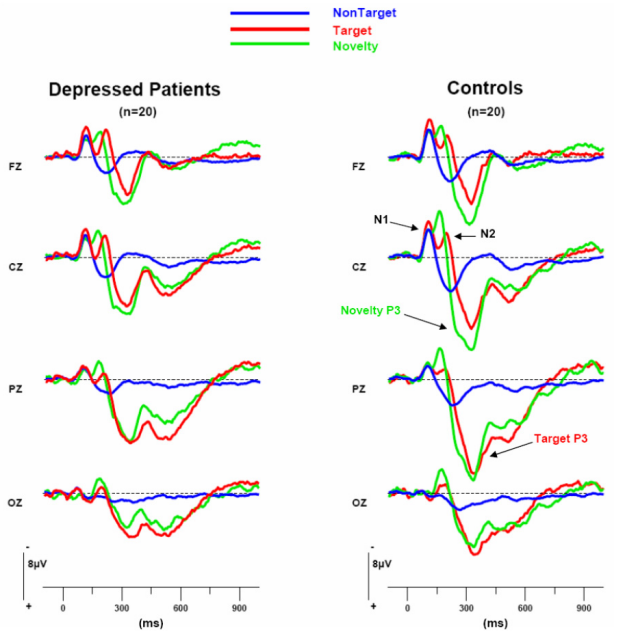

Figure 2. Grand average, nose-referenced ERP waveforms for 20 depressed patients and 20 healthy controls to nontarget, target and novel stimuli at midline sites (Fz, Cz, Pz, Oz).

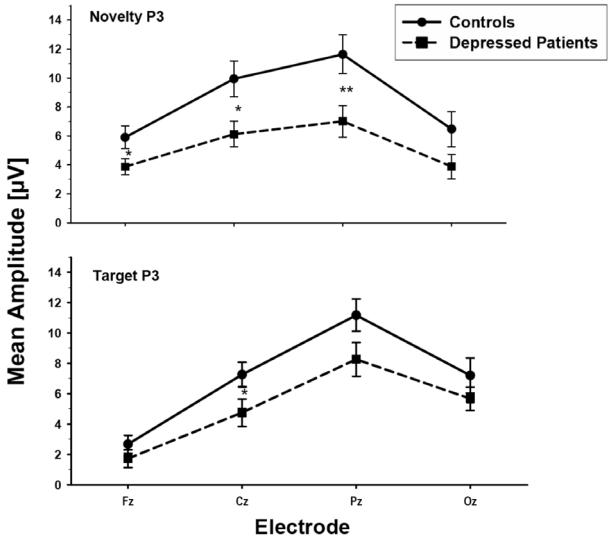

Figure 3. Mean integrated amplitude (± SEM) of novelty P3 and target P3b in 20 depressed patients and 20 healthy controls at frontal (Fz), central (Cz), parietal (Pz), and occipital (Oz) midline sites. Significant simple group effects at each site are indicated by: * <.05, ** <.01.

these findings appear to be in agreement with other evidence that P3a or novelty P3 is *heightened* in patients having an anxiety disorder. Thus, patients having a post traumatic stress disorder were reported to have a larger novelty P3 at frontal sites when compared to normal controls (Kimble et al., 2000). We also found that a later positive subcomponent (peak latency 400 ms) with a parietal maximum typical of P3b did not differ between patients having a depressive disorder alone and controls, but was larger in depressed patients having a comorbid anxiety disorder when compared to the other groups. The above findings suggest that patients having a depressive disorder, an anxiety disorder, or comorbidity of these disorders differ in the amplitude of P3 subcomponents.

A limitation of the above studies is that P3 subcomponents in depressed patients were measured in paradigms that are not ideal for measuring P3a or novelty P3. In a recent study (Bruder et al., in press), ERPs of 20 unmedicated depressed patients and 20 healthy controls were recorded from a 30-channel montage (nose reference) during a novelty oddball task (Friedman et al., 1993) with three stimuli: infrequent target tones ($p = .12$), frequent nontarget tones ($p = .76$), and infrequent novel stimuli (e.g., animal or environmental sounds; $p = .12$). Subjects responded as quickly as possible to target tones only. There was no difference between patients and controls in accuracy or reaction time. Figure 2 shows the grand average waveforms at midline electrode sites for patients and controls. The waveforms show the expected N1 and N2 potentials, which are most evident at vertex (Cz) and a novelty P3 that is also evident at this central site. The P3 to targets is largest at the mid-parietal site (Pz), which is typical of the P3b component. The greater P3 to novels than targets at Fz and Cz reflects the more frontocentral distribution of the novelty P3. As can be seen in Figure 2, both the novelty P3 and target P3 were reduced in depressed patients when compared to controls. Average ERP waveforms for each stimulus condition and for each subject were carefully inspected to select time windows that bracketed the peaks and optimized the measurement of mean integrated amplitude of the novelty P3 (220-375 ms) and target P3 (280-470 ms). Amplitude of the novelty P3 was significantly smaller in patients than controls at frontal ($p < .05$), central ($p < .05$) and parietal ($p < .01$) sites (see top portion of Figure 3). Patients also tended to have smaller P3 amplitude to targets at central ($p < .05$) and parietal ($p < .10$) sites (see lower portion of Figure 3). The difference between patients and controls at the parietal site had a large effect size for the novelty P3 (1.0) and a smaller effect size for the target P3 (0.61). There was no significant difference in the mean integrated amplitude between patients and controls in the N1 (70-145 ms) and N2 (150-240 ms) windows, which indicates that the reduced novelty P3 in patients was likely not due to an earlier deficit in detection of the deviant novel sounds.

The novelty P3 reduction in depressed patients is suggestive of a deficit in automatic shifting of attention (orienting) and evaluation of novel environmental sounds (Friedman et al., 2001; Polich, 2007). There are, however, two issues that needed further study. First, the novelty P3 component overlaps with the P3b component to targets, which leaves open the possible contribution of P3b to the

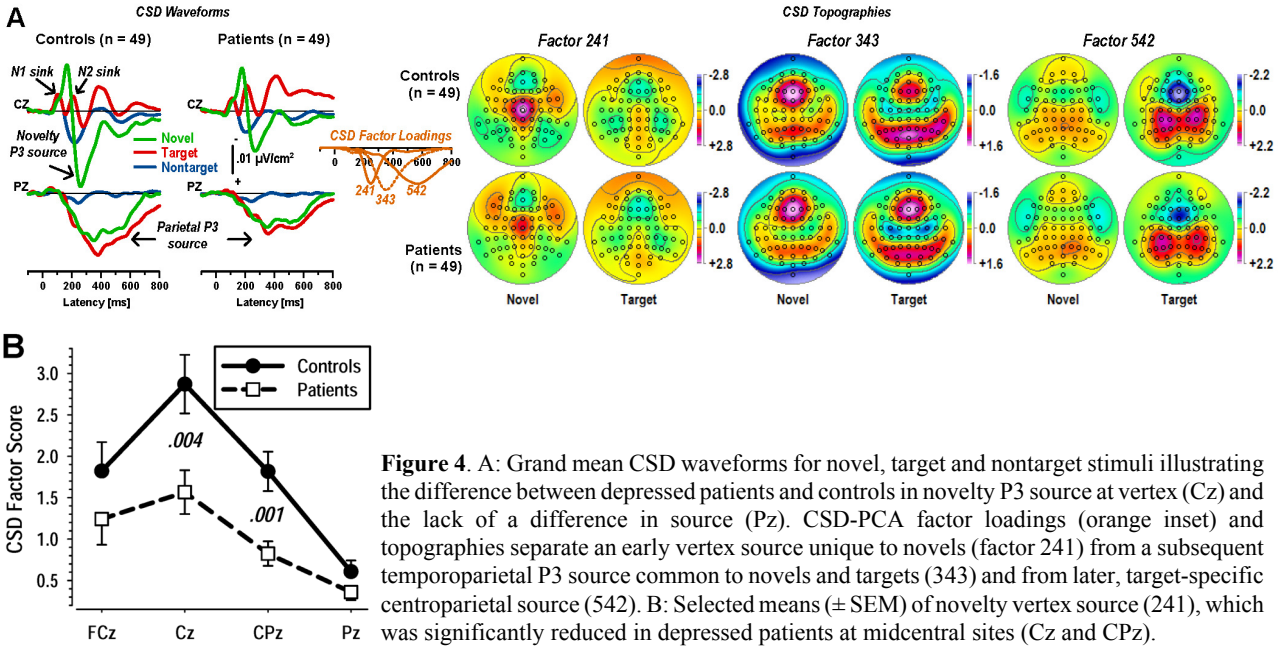

Figure 4. A: Grand mean CSD waveforms for novel, target and nontarget stimuli illustrating the difference between depressed patients and controls in novelty P3 source at vertex (Cz) and the lack of a difference in source (Pz). CSD-PCA factor loadings (orange inset) and topographies separate an early vertex source unique to novels (factor 241) from a subsequent temporoparietal P3 source common to novels and targets (343) and from later, target-specific centroparietal source (542). B: Selected means (± SEM) of novelty vertex source (241), which was significantly reduced in depressed patients at midcentral sites (Cz and CPz).

group differences in mean amplitude in the novelty P3 window. The use of multivariate statistics, such as principal components analysis (PCA), could aide in identifying and measuring these separate P3 subcomponents. Second, both neuroimaging and ERP studies have found evidence that prefrontal, anterior cingulate, and hippocampal regions are involved in novelty processing (Halgren et al., 1995; Knight et al., 1998; Polich, 2007), but the neural generators underlying the novelty P3 reductions in depressed patients remain unknown. An independent replication and extension of the above study was therefore performed, in which ERPs of a larger sample of depressed patients (n = 49) and healthy controls (n = 49) were recorded from 67 channels during the same novelty oddball task (Tenke et al., in press). Most importantly, we applied a combined CSD-PCA approach to help identify neural sources corresponding to P3 subcomponents (see Kayser & Tenke, 2006a,b for details).

In the initial step for this approach, all averaged ERP waveforms are transformed into reference-free current source density (CSD) estimates using spherical spline surface Laplacian algorithm suggestged by Perrin et al. (1989). CSD is a mathematical transformation (2nd spatial derivative), which provides a representation of the direction, location, and intensity of current generators that underlie an ERP topography. CSD maps represent the magnitude of radial (transcranial) current flow entering (sinks) and leaving (sources) the scalp (Nunez, 1981; Nunez, & Srini vasan, 2006). CSD is a reference-free technique that provides topographies with more sharply localized peaks than those of scalp potentials and eliminate volume-conducted activity from distant regions (Tenke & Kayser, 2005). In the next step, the averaged CSD waveforms are submitted to an unrestricted temporal principal components analysis (PCA), followed by Varimax rotation of covariance loadings (Kayser & Tenke, 2006a). This approach yields distinctive PCA components (factor loadings) and corresponding weighting coefficients (factor scores), which provide a concise, effient simplification of the temporal and spatial distribution of neuronal generators (Kayser & Tenke, 2003, 2006c). Temporal PCA not only aids in determining the relevant statistically independent components within a data set, it also generates efficient measurements of these overlapping components. The combined CSD-PCA method overcomes two critical limitations of ERP research: (1) the dependence of ERP surface potentials on a reference location (e.g., linked mastoids or nose)[1] and (2) the definition and measurement of ERP components (e.g., peak or integrated amplitudes in specified time windows). The use of reference-free CSD measures sharpens topographies related to underlying neuronal generators, and PCA allows identification and quantification of statistically independent factors (sources and sinks) corresponding to ERP/CSD components. The CSD-PCA technique provides a conservative source localization method that avoids any biophysical assumptions, unlike other popular tools (e.g., BESA or LORETA).

[1] No recording reference anywhere on the human body can be considered neutral or inactive (e.g., sternum, neck, mastoid, nose, ear lobe) and any site will be differentially affected by a given combination of neuronal generators through volume-conducted activity (see Kayser & Tenke, 2006a). The choice of the reference is, therefore, essential for identifying both spatial and temporal information in ERP recordings, as the reference will invariably affect the spatio-temporal activation of ERP generator patterns. Although some reference choices may enhance or reduce a particular generator topography, all reference schemes, including a montage-dependent average reference, are subject to the same reference problem. Using multiple reference schemes may help for recognition of distinct ERP components, but will not solve the reference problem.

Figure 4A shows the grand mean CSD waveforms for novel, target and nontarget stimuli for depressed patients and controls. In addition to the expected N1 and N2 sinks to target stimuli at vertex (Cz), there was an early source to novel stimuli, but *not* targets. There was also a prominent source over mid-parietal sites (Pz), which corresponds to the late-positive, parietal-maximum P3b component. The extracted CSD-PCA factor loadings (orange inset in Figure 4A) and topographies separate the early vertex source unique to novels (241 ms peak latency of factor loadings) from parietotemporal P3 source activity common to targets and novels (343 ms loadings peak) and from later target-specific centroparietal source activity (542 ms loadings peak). The novelty vertex source (factor *241*) was markedly reduced in depressed patients when compared to controls ($p = .01$), with the largest group difference at the midline central site (Group by Electrode interaction, $p < .001$; see Figure 4B). Group differences were less evident for the later P3 sources to targets (factors 343 and 542). Thus, a vertex source that was *only* present to novel distracter stimuli, and had a shorter latency (241 ms) than the source corresponding to the parietal P3b, was markedly reduced in depressed patients when compared to healthy controls.

Our studies indicate that the novelty P3 is reduced in depressed patients. The findings using the CSD-PCA technique are remarkable for two reasons. First, the novelty vertex source that discriminated between patients and controls had a shorter peak latency, i.e., 241 ms from onset of novel stimuli, than the sources corresponding to the parietal P3b component. This suggests that the novelty P3 reduction in depressed patients is indicative of a deficit in early shifting of attention (i.e., orienting) to novel distracter stimuli and not to later cognitive evaluation of these stimuli. Second, the novelty vertex source was localizable to the frontocentral region within and along the longitudinal fissure. Studies using other source localization techniques have localized generators of novelty P3 to the region of the anterior cingulate cortex (ACC), whereas P3b to target stimuli has prominent sources in the region of the temporal-parietal junction (Dien et al., 2003; Mecklinger & Ullsperger, 1995). Contributions of other cortical areas (including frontal gyrus, insula, posterior cingulate) to these components are, however, also known (Kiehl et al., 2001). Despite convergent evidence for involvement of ACC in the novelty P3, anatomical and biophysical considerations demand caution when interpreting putative generators of midline ERPs. The radial orientation of an equivalent dipole within the longitudinal fissure that is typical of inverse solutions is not normal to the surface of the cingulate gyrus, but rather is tangential to the local alignment of cortical neurons. This paradoxical alignment requires additional assumptions before the generator can be considered to be physiologically plausible (Tenke & Kayser, 2005; Kayser & Tenke, 2006a; Kayser et al., 2007; Tenke & Kayser, 2008). Frontal cortex, including the anterior cingulate, is known to be of key importance for attention, and has been found to be dysfunctional in depressed patients (Bremmer et al., 2004; Drevets et al., 1997; Siegle et al., 2004). Although this may point to the frontal cortex – and in particular the ACC – as being responsible for novelty P3 reductions in depression, studies indicate that the hippocampus and other cortical structures are also involved in the generation of the novelty P3 (Halgren et al., 1995; Knight, 1996; Kiehl et al., 2001), and therefore further research is needed to pinpoint the origins of this deficit in depressed patients.

ERPs During Processing of Emotional Words or Pictures

Studies in healthy adults have consistently found that emotionally arousing words or pictures elicit a late positive potential (i.e., beyond 300 ms) extending into a slow wave, and the amplitude of this potential is greater for negative or positive emotional stimuli when compared to neutral stimuli (Johnston et al., 1986; Kayser et al., 1997; Naumann et al., 1992; Palomba et al., 1997). Several studies in depressed patients have reported abnormalities of P3 to visually-presented emotional stimuli. In one of the first studies, Blackburn et al. (1990) recorded ERPs from 3 midline sites referenced to the left ear and found that depressed patients ($n = 15$) had *smaller* P3 amplitude to negative than neutral or positive words, whereas healthy controls ($n = 15$) showed larger P3 amplitude to negative words than neutral or positive words. Inspection of their data also suggests that depressed patients had smaller P3 amplitude than controls to negative words, but not to neutral or positive words, but no statistics were presented to support the significance of group differences in P3 amplitude. All the patients in the Blackburn et al. study were taking antidepressant medications and its impact on their findings is unknown. Using a 30-channel montage, Kayser et al. (2000) measured nose-referenced ERPs of 30 unmedicated depressed patients and 16 healthy controls during passive viewing of negative pictures of patients with dermatological diseases or neutral control pictures of these patients after surgical treatment. As shown in Figure 5A, depressed patients had significantly smaller amplitude of a late P3 potential (460 ms peak latency of a surface potential factor derived from unrestricted temporal PCA followed by Varimax rotation) when compared to controls. As in prior studies (Cacioppo et al., 1993, 1996; Kayser et al., 1997), healthy controls showed enhanced late P3 (P460) amplitude to negative compared to neutral stimuli and this enhancement was greatest over the right parietal region (see Figure 5B). In contrast, depressed patients did not show this increase in late P3 to negative as compared to neutral stimuli over either hemisphere. Interestingly, the PCA-based ERP decomposition also revealed an early P3 subcomponent (330 ms peak latency of

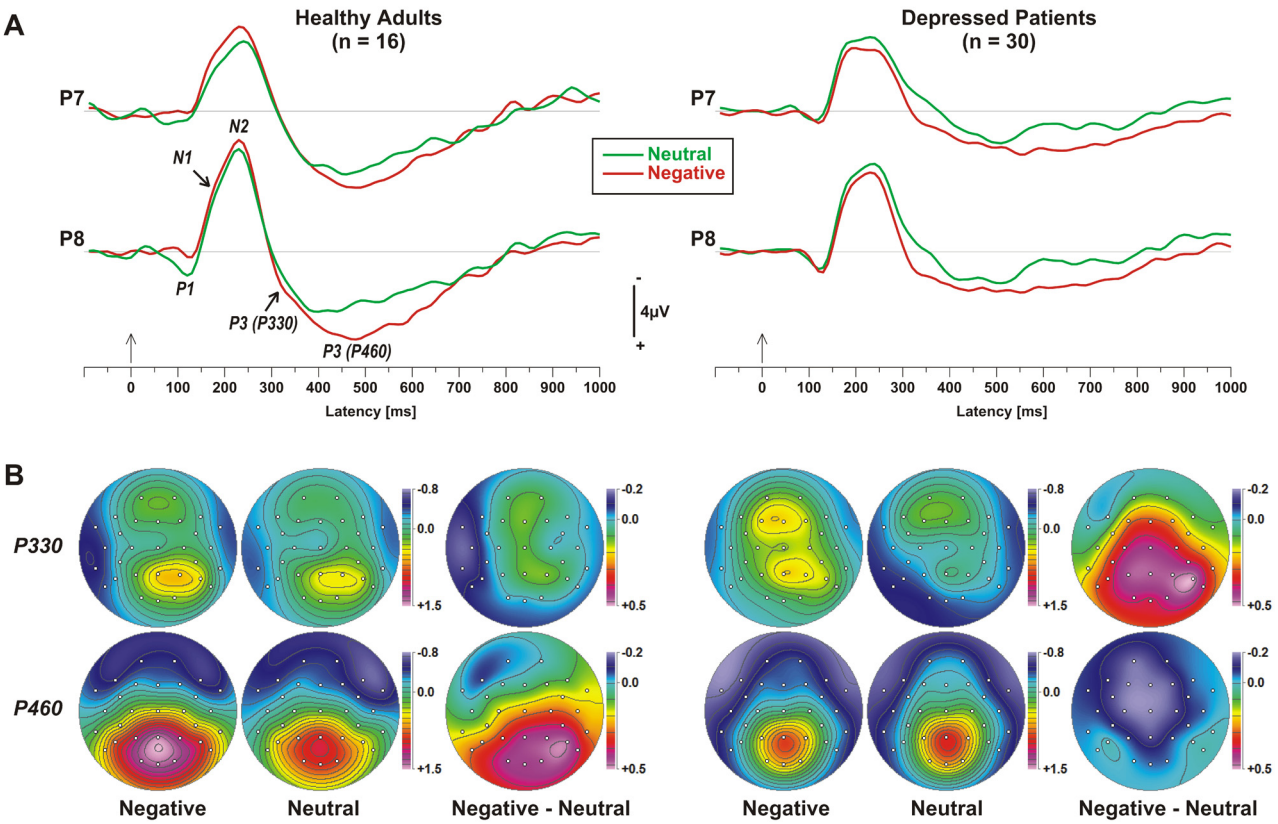

Figure 5. A: Grand mean, nose-referenced ERP waveforms at lateral-parietal (P7/8) sites comparing neutral and negative stimuli for healthy and depressed participants. Distinct ERP components (P1, N1, N2, early and late P3) are labeled for healthy adults at site P8. Data-driven ERP measures of P3 subcomponents were determined by means of PCA (factors *P330* and *P460*; cf. Kayser et al., 2000). B: Topographies of PCA factor scores for factor *P330* (early P3 rising phase) and factor *P460* (classic parietal P3) comparing negative and neutral stimuli and their differences (pooled across visual fields of lateralized presentations) for healthy and depressed participants. Unlike healthy adults, depressed patients showed no effect of emotional content for factor *P460*, but showed instead an emotional content effect for factor *P330* with comparable right-posterior lateralization.

factor loadings) consisting of a right parietal and frontal positivity, which showed a right-lateralized, negative-larger-than-neutral emotion effect in patients, suggesting intact early classification but impaired late evaluation of affective significance in depression. There was also no difference between depressed patients and healthy controls in valence and arousal self-report measures to these stimuli, which further suggest preserved (cognitive) classification of emotional stimuli in depression.

While subjects in the Kayser et al. (2000) study passively viewed the emotional pictures to reduce the impact of cognitive processing resulting from specific task demands (e.g., target detection, matching paradigm), Deldin et al. (2000) recorded ERPs (linked mastoids) from 9 sites to positive, neutral and negative face and word stimuli during a recognition memory task. They found a lateralized abnormality of the N2 potential in depressed patients (n = 19) when compared to healthy controls (n = 15). N2 amplitude over right parietal region was reduced in the depressed patients and this reduction was most evident during the processing of pleasant faces. If one assumes that the recording location of referenced surface potentials reflects differential activation of the underlying cortical regions, the findings of both Kayser et al. (2000) and Deldin et al. (2000), involving different ERP components and methods, appear to be consistent with the hypothesis that depressed patients have impaired activation of right parietal regions during the processing of emotional stimuli (Heller, 1990, 1993). Of course, further study of the neural generators of these effects is needed before this conclusion can be drawn with confidence. Additional evidence of reduced P3 amplitude to emotional stimuli in depressed subjects was obtained by Cavanagh and Geisler (2006), but it was present only for midline electrode sites. They recorded ERPs (linked ears) from 7 sites during a visual oddball task in which neutral faces served as standards and happy or fearful faces were targets. Depressed subjects (n = 36) had reduced P3 amplitude to happy faces when compared to non-depressed controls (n = 18). In summary, the most consistent finding across studies was reduced late P3 (P3b) amplitude to emotional stimuli in depressed subjects, but the valence of stimuli to which this occurs and the laterality of

this P3 deficit are less clear. However, only Kayser et al. (2000) used a sufficiently dense EEG montage to evaluate lateralized P3 activity over inferior temporal and parietal regions.

Given evidence that depressed patients have a negative bias for processing information during memory tasks, several studies have measured ERPs of depressed patients in memory tasks with stimuli of different valence to assess processing bias. Studies recording ERPs during recognition memory tasks have found that the influence of emotional valence of stimuli on late positive or P3 potentials in healthy adults was less evident for depressed subjects (Deldin et al., 2001b; Dietrich et al., 2000a). Although the specific findings differ across studies using word or face stimuli, evidence of mood congruent biases in depressed patients have been reported in studies measuring slow wave amplitudes during sustained processing of positive, neutral or negative stimuli in working memory tasks (Deldin et al., 2001a; Deveney & Deldin, 2004; Shestyuk et al., 2005).

ERPs to Olfactory Stimuli

Given the overlapping cortical and limbic systems involved in olfaction, emotional processing, and depression (most notably, the amygdala and orbitofrontal cortex), the study of ERPs to olfactory stimuli may hold particular promise for elucidating neurophysiologic dysfunctions responsible for abnormalities of emotional reactivity in depressed patients. Odors appear to be powerful emotional stimuli with distinctive hedonic valence (Pause et al., 2003). Importantly, the emotional content of odors can be perceived with little cognitive mediation (Ehrlichman & Bastone, 1992), allowing a more direct assessment of emotional processing in depression. Although there is evidence of differences in emotional evaluation of odors between depressed patients and controls (Pause et al., 2000; Steiner et al., 1993), we know of only one study that used ERPs to study olfactory processing in depressed patients. Pause et al. (2003) measured olfactory ERPs at 30 scalp locations (linked ears reference) in 22 patients having a MDD and 22 healthy controls in a task requiring discrimination of pleasant (phenyl-ethyl alcohol = rose) and unpleasant (isobutyraldehyde = rotten butter) odors presented using a constant-flow olfactometer. Control tasks measured visual ERPs to colors or emotional pictures (Lang et al., 1999). Although patients performed as well as controls, they showed reduced amplitude of P2 and early P3 potentials at frontal sites. In contrast, only visual ERPs reflecting later cognitive processing (P3b and slow wave) were reduced in depressed patients to colors or emotional slides. The authors attributed the reduction of the olfactory P2 potential in depressed patients to a deficit in the ability to preattentively encode the pleasantness of odors. Reduced early P3 at frontal sites in depressed patients was thought to reflect a reduction in early cognitive evaluative processes. They further proposed that reduced olfactory P2 and P3 in depressed patients may be related to specific alterations in the amygdala and orbitofrontal cortex, respectively. When 14 of the 22 patients were retested after successful antidepressant treatment, these patients no longer showed smaller olfactory ERPs. However, reduced sample power and possibility of selective patient dropout or repeated testing may have contributed to these null findings. In addition to significant problems regarding olfactory ERP component definition and measurement, this study did not control for medication and no information was given about the relation of the olfactory ERP deficits to severity of depressive symptoms. Further studies recording ERPs to odors of positive and negative valence are needed to replicate and expand on the encouraging findings of Pause et al. (2003).

During Recognition Memory Tasks

A meta analysis indicated that depression is associated with memory impairments for tests of both recall and recognition (Burt et al., 1995). This memory loss is not universal but appears to depend on patient characteristics, such as diagnostic subtype, severity of depression and age (Purcell et al., 1997). Unmedicated outpatients having a major depressive disorder demonstrated a deficit in verbal episodic memory on the California Verbal Learning Test (Otto et al., 1994). Impaired verbal episodic memory in depressed patients may stem from left prefrontal and medial temporal deficits, in particular involving the hippocampus. Thus, Sapolsky (2000) reviewed evidence from volumetric MRI studies in patients having severe, repeated depressive episodes and found evidence of hippocampal atrophy, which was greater on the left side. These hippocampal deficits in depressed patients have been linked to explicit memory impairments (Sapolsky, 2000; Shah et al., 1998). However, studies have rarely measured neurophysiologic functioning of depressed patients while they were engaged in a memory task.

ERP correlates of memory processes have been examined during a continuous word recognition memory task (Friedman, 1990). Subjects viewed a series of words, some of which were repeated after a number of intervening words, and their task was to decide whether each word was new (not previously presented) or old (previously presented). A robust, replicable finding in healthy adults has been a more positive-going potential for correctly recognized old than new words about 250 to 800 ms after word onset, referred to as the "old-new effect" (see Chapter 14, this volume). Intracranial recordings in and around medial temporal structures of epilepsy patients have shown similar old-new effects, suggesting generators in the hippocampus, parahippocampal gyrus or amygdala (Elger et al., 1997; Smith et al., 1986). Moreover, patients with left anterior

temporal lobectomy showed a dramatic reduction of the old-new effect for word recognition when compared to patients with right temporal lobectomy or controls (Johnson, 1995; Smith & Halgren, 1989; Rugg et al., 1991).

Given evidence of memory impairments and hippocampal deficits in depressed patients, one would predict that they will show a reduced old-new effect during a word recognition task. One published study reported findings consistent with this prediction (Dietrich et al., 2000a). They measured ERPs of 11 unmedicated depressed patients and 11 healthy controls during a continuous word recognition memory task. The depressed patients were significantly poorer in recognizing the repeated (old) items and showed smaller old-new effect when compared to controls. Moreover, the reduction of the old-new effect for words persisted following clinical improvement of depression (Dietrich et al., 2000b). This study, however, had several methodological weaknesses, such as the use of a right mastoid reference (which is problematic for examining laterality effects), a small sample size, and a younger control group showing unusually large P3 amplitudes (group mean > 20 μV), which limit the impact of the findings.

In a recent study (Kayser et al., in preparation), we measured 31-channel ERPs from 37 right-handed, unmedicated depressed patients (21 men) and 40 right-handed, healthy controls (19 men) during continuous recognition memory tasks, in which a series of words were presented in either the visual or auditory modality. Subjects indicated for each word whether it was "new" or "old" by pressing one of two buttons (for procedural details see Kayser et al., 2007). Although all subjects had adequate, above-chance performance (86.4% overall correct recognition of repeated words; *SD* = 12.7), depressed women showed poorer recognition memory than healthy women, but there was no group difference in men (group by gender interaction, $p < .05$). There was, however, no significant group difference in

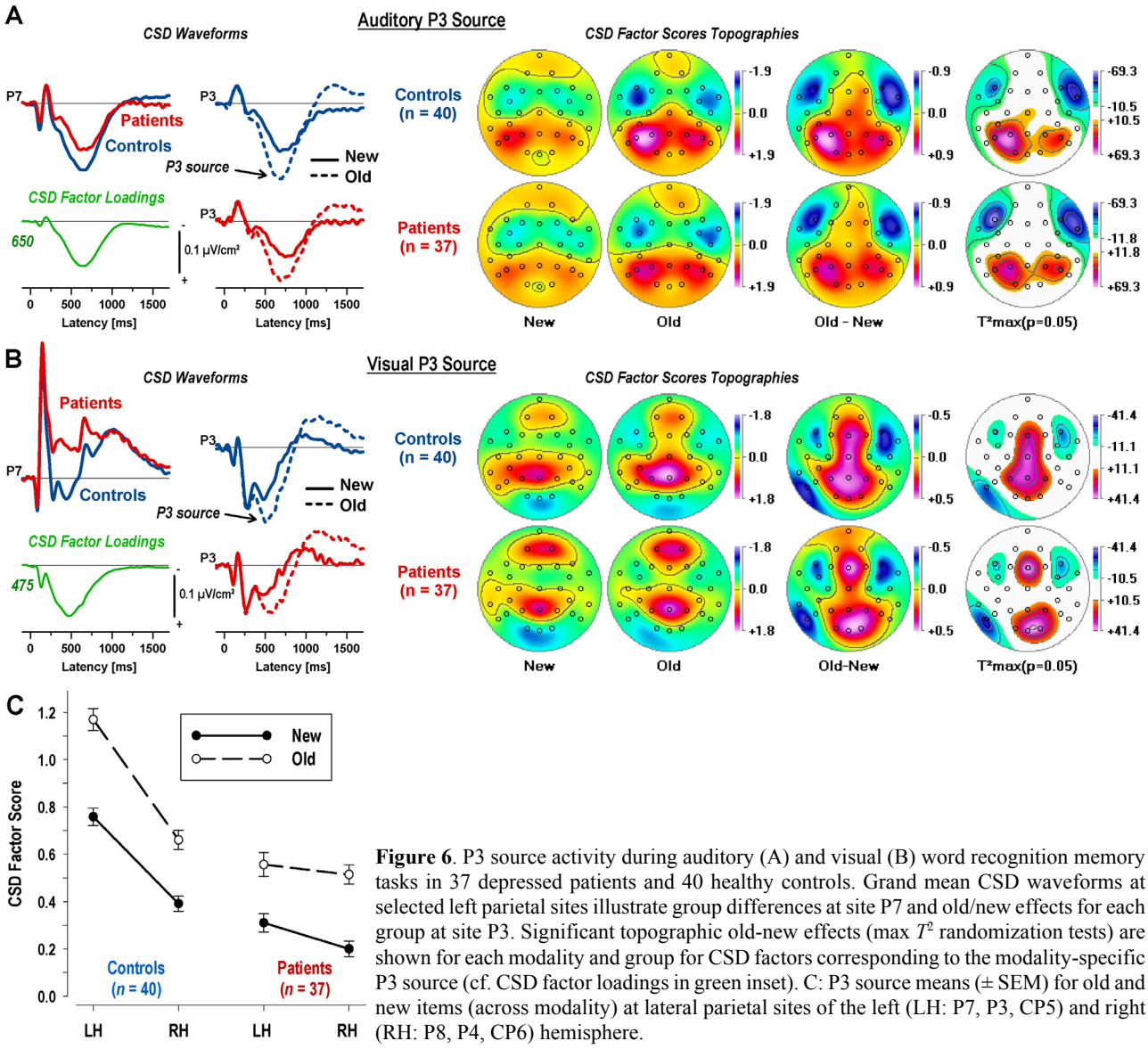

Figure 6. P3 source activity during auditory (A) and visual (B) word recognition memory tasks in 37 depressed patients and 40 healthy controls. Grand mean CSD waveforms at selected left parietal sites illustrate group differences at site P7 and old/new effects for each group at site P3. Significant topographic old-new effects (max T^2 randomization tests) are shown for each modality and group for CSD factors corresponding to the modality-specific P3 source (cf. CSD factor loadings in green inset). C: P3 source means (± SEM) for old and new items (across modality) at lateral parietal sites of the left (LH: P7, P3, CP5) and right (RH: P8, P4, CP6) hemisphere.

response latency for visual or auditory word presentations. For improved spatial and temporal characterization of the ERP old-new effects, the data were analyzed using our newly developed CSD-PCA technique (Kayser & Tenke, 2006a,b; Kayser et al., 2007).

Both patients and controls showed the expected old-new effects, with greater late source activity (positivity) at posterior sites to correctly recognized old words for both auditory (Figure 6A) and visual (Figure 6B) modalities. This source activity, corresponding to the late P3b potential, was identified in separate PCAs for each modality by the auditory CSD factor *650* (peak latency of factor loadings in ms) and the visual CSD factor *475* (peak latency in ms; see green factor loading waveforms in Figure 6A,B). Based on response-locked averages, these P3 source factors peaked about 170 ms and 140 ms, respectively, prior to response onset in either modality (cf. Kayser et al., 2007). As evident for both groups in the CSD factor topographies, increased lateral-parietal P3 sources (warm colors) for old as compared to new auditory stimuli were accompanied by increased lateral-frontal sinks (right portion of Figure 6A), and similar old-new effects with mid-parietal and mid-frontal P3 sources were found for visual stimuli (right portion of Figure 6B). These old-new effects were present for both groups, as indicated by the significant pairwise max (T^2) randomization tests (Maris, 2004) for each group and modality (last column in Figure 6A,B). However, there were notable topographic group differences in the visual P3 old-new effect, which was shifted towards occipital sites in depressed patients. A repeated measures ANOVA of P3 source factor scores from both modalities was computed at homologous left and right lateral-parietal sites (P3/4, P7/8, CP5/6), where the P3 source was prominent. This analysis revealed a significant Group main effect ($p < .001$) and interactions of Group by Hemisphere ($p = .001$) and Group by Hemisphere by Condition (new, old) ($p < .01$). Healthy adults had overall greater P3 source activity at lateral-parietal sites when compared to depressed patients, particularly over the left hemisphere (Figure 6C). Although the condition main effects, indicative of the old-new effects, were highly significant for both groups ($p < .0001$), the old-new effect was larger over the left than right hemisphere in controls ($p = .01$), but not in patients, and there was a significant simple Group by Condition interaction at the left ($p < .05$) but not right hemisphere. An analogous ANOVA for the accompanying sink activity at lateral-frontal sites (FC5/6, F7/8, FT9/10) revealed only a marginally significant Group main effect ($p = .07$), but a significant Group by Gender interaction ($p < .05$), stemming from reduced sinks in depressed compared to healthy women, but no group difference in men.

In summary, although the findings show only small behavioral impairment of recognition memory for words in depressed women and none in depressed men, they indicate that the ERP correlate of conscious episodic memory retrieval is reduced in depressed patients over the left parietal region and this reduction is largely independent of processing modality, which suggests a deficit in accessing semantic (i.e., lexicon) information during continuous word recognition. Event-related fMRI studies in healthy adults have found that recognition of "old" words involves a left-lateralized network including frontal, lateral parietal, posterior cingulate and the precuneous (Henson et al., 2000). Also, given evidence of left medial temporal lobe involvement in the old-new effect for words (Johnson, 1995; Smith & Halgren, 1989; Rugg et al., 1991), a distributed network including the hippocampus or other medial temporal lobe structures may also contribute to the reduced old-new effect for depressed patients. Further studies using ERP measures in conjunction with neuroimaging techniques are needed to further resolve the neural basis of the episodic memory deficit in depression.

N1 and Intensity Dependence of Auditory ERPs

Up to this point we have focused on late cognitive potentials, but studies have also examined earlier negative brain potentials (N1 or N2) in depressed subjects. The N1 potential is known to reflect early sensory processing of stimuli and is also modulated by attention and arousal level (see Chapters 4 and 11, this volume). However, unlike the omnipresent mid-parietal P3b potential, the amplitude and topography of N1 and N2 change considerably with the recording reference, dependent on processing modality. For example, for a visual N1 peaking at approximately 140 ms, the nose-referenced ERP morphology will reveal a distinct inferior parietal negativity, which will reverse into a distinct positive deflection at mid-parietal sites when re-referencing these ERPs to linked mastoids, leaving only a substantially reduced negative deflection over lateral parietal regions (e.g., Kayser et al., 2003, 2007). In contrast, the auditory N1 peaking at about 100 ms will maintain a central maximum with most common reference schemes, because the direction and location of the known underlying generator within the primary auditory cortex will always result in a mid-central negativity, unless a vertex reference is used. The reason is that the reference location, like all other electrodes included in the EEG montage, is an active site, and the differential activity (i.e., the potential difference or ERP) between any two recording sites will tend to be smaller with closer proximity, or larger with increasing distance (e.g., cf. chapter 3 in Luck, 2005).

There have been reports of reduced N1 amplitude in depressed subjects when compared to non-depressed controls (Burkhart & Thomas, 1993; Knott & Lapierre, 1987; El Massioui & Lesevre, 1988; Sandman et al., 1987). These four studies recorded ERPs primarily at central sites

(linked-ears reference) in dichotic listening or tone counting tasks, but one study used a visual RT task (Knott & Lapierre, 1987). Twice as many studies did not, however, find evidence of N1 reduction in depressed patients in auditory tasks (Blackwood et al., 1987; Bruder et al., 1995; Bruder et al., 1998; El Massioui et al., 1996; Knott et al., 1991; Ogura et al., 1993; Sara et al., 1994; Tenke et al., 2008). All four studies that recorded ERPs mainly at midline sites (2 linked ears, 1 left ear, and 1 nose reference) during binaural oddball tasks found no difference in N1 amplitude between depressed patients and controls (Blackwood et al., 1987; Bruder et al., 1998; Ogura et al., 1993; Sara et al., 1994). The remaining four studies that found no N1 reduction in depressed patients recorded ERPs during different dichotic listening tasks (2 linked ears and 2 nose reference). The lack of a N1 reduction in depressed patients was also evident in our findings for a novelty oddball task (see Figures 2 and 4) and for auditory and visual word recognition memory tasks (Figure 6). Although medication differences across studies is not an issue (all patients were off medication), the extent to which differences in clinical characteristics of patients could account for the conflicting findings is unclear.

Although our CSD-PCA study using the novelty oddball task did not focus on N1 sink activity (Tenke et al., in press), a subsequent analysis of a subgroup of depressed patients who responded favorably to antidepressants showed reduced amplitude of an N1 sink (120 ms loadings peak) to novel sounds. The depressed patients were tested during a pretreatment session and subsequently treated as part of ongoing clinical trials in which they received 8-12 weeks of monotherapy with escitalopram or other selective serotonin reuptake inhibitor (SSRI), the noradrenaline/dopamine reuptake inhibitor (NDRI) bupropion, or dual therapy with both SSRI and NDRI antidepressants. Following treatment, the Clinical Global Impression: Improvement (CGI-I) scale was used by an independent clinician to rate the treatment response of the patients. Responders (rated as being much or very much improved) showed reduced N1 sink activity (maximum anterior to Sylvian fissure) compared to either nonresponders ($p < .05$) or healthy controls ($p = .01$), whereas no difference was found between nonresponders and controls (see blue regions in Figure 7A). Although samples were small, it is interesting to note that responders to monotherapy had the smallest N1 and nonresponders to dual therapy had the largest N1 (see Figure 7B). The CSD-PCA topographies (Figure 7A) indicate that N1 sinks were coupled with sources posterior to the Sylvian fissure, and are thereby consistent with tangentially-oriented generators in or adjacent to primary auditory cortex. Given the high serotonergic innervation of primary auditory cortex (Lewis et al., 1986; Campbell et al., 1987), it is possible that reduced pretreatment N1 to novel, distracter sounds may

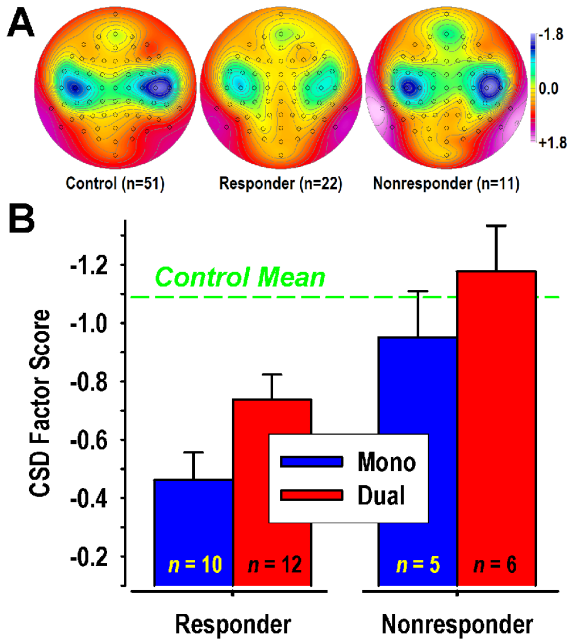

Figure 7. A: N1 sink (factor 120) topography for 51 healthy controls, 22 treatment responders or 11 treatment nonresponders. B: N1 sink means (± SEM) for subgroups of treatment responders and nonresponders to mono or dual therapy.

reflect lower level of serotonin neuronal activity in responders. Interestingly, a study of the effects of tryptophan depletion on mismatch negativity (MMN) in healthy adults suggested that decreased serotonin may decrease involuntary attention shifting to task-irrelevant sounds (Ahveninen et al., 2002). Further study should therefore examine whether the reduced N1 sink activity in depressed patients who respond favorably to antidepressants may be associated with decreased automatic directing of attention to the task-irrelevant novel sounds.

There is also evidence that intensity-dependence of early auditory ERPs (N1-P2) may be of value for identifying a subgroup of depressed patients with a serotonin deficit responsive to treatment with antidepressants that act on the serotonergic neural system. Increases in tone intensity from 60 to 100 dB are known to result in a linear increase in N1-P2 amplitude in healthy adults. Hegerl and Juckel (1993) reviewed findings from basic and clinical studies suggesting that the slope of the function relating tone intensity and N1-P2 amplitude provides a noninvasive indicator of central serotonergic activity. Juckel et al. (1999) found direct evidence of an inverse relationship between serotonergic neural activity in the dorsal raphé and intensity dependence of auditory ERPs recorded from primary auditory cortex in cats. Hegerl and Juckel (2001) suggest that seotonergic neurons modulate activity in primary auditory cortex by providing a stable, tonic firing rate. A high firing rate of serotonergic neurons is associated with a weak intensity

dependence, i.e., only a small increase in N1/P2 amplitude with increasing tone intensity, whereas a low tonic firing rate is related to a strong intensity dependence, i.e., a large increase in N1/P2 amplitude. Depressed patients having low serotonergic activity, as evidenced by pronounced intensity dependence of N1-P2 potentials before treatment, responded better to an SSRI antidepressant compared to patients having evidence of high serotonergic activity (Gallinat et al., 2000; Hegerl and Juckel, 2001; Paige et al., 1994). Paige et al. (1995) also found that small samples of responders (n = 4) and nonresponders (n = 4) to the NDRI bupropion showed similar differences in intensity dependence, which could raise questions about the specificity of this finding to SSRI antidepressants. Three studies do, however, suggest that the relation of intensity dependence of auditory ERPs and clinical improvement differs for serotonergic and noradrenergic antidepressants. Linka et al. (2004) tested 16 inpatients having a MDD episode before receiving 3-4 weeks of treatment with the SSRI citalopram. Stronger intensity dependence of N1 was associated with greater decrease in depression following treatment, which is in accord with earlier findings for SSRIs (Gallinat et al., 2000; Hegerl and Juckel, 2001; Paige et al., 1994). In their next study (Linka et al., 2005), 14 inpatients having a major depressive episode were tested before receiving the selective noradrenaline reuptake inhibitor (NARI) reboxetine. In contrast to findings for SSRIs, *smaller* intensity dependence of N1 was associated with greater improvement in depression following 3-4 weeks of treatment with an NARI antidepressant. Patients were not, however, randomly assigned to treatment, which weakens the comparison of findings for the SSRI and NARI antidepressants. More recently, Mulert et al. (2007) measured the intensity dependence in depressed patients who were randomly assigned to treatment with either the SSRI citalopram or the noradrenergic antidepressant reboxetine. Indices of intensity dependence were obtained using LORETA analyses to measure the tomographic current source distribution in primary auditory cortex for the latency window 60-240 ms following stimulus onset. They found a significant difference between citalopram responders (n = 7) and nonresponders (n = 4), with responders showing the expected stronger intensity dependence. In contrast, reboxetine responders (n = 3) and nonresponders (n = 6) did not show a significant difference in intensity dependence. These are encouraging findings, but given the small samples in these studies, further research is needed to investigate the specificity of intensity dependency as a predictor of SSRI treatment response.

If intensity dependence of auditory ERPs provides a marker of central serotonergic activity, the slope of this function would be expected to decrease following treatment with an SSRI. Gallinat et al. (2000) retested 19 depressed patients following 4 weeks of treatment with an SSRI and found no change in the intensity dependence function, which agrees with prior findings for two studies using SSRI or other antidepressants (Paige et al., 1994, 1995). In contrast, a double-blind placebo controlled study in healthy adults did find a decrease in the slope of the N1-P2 function during acute administration with a single dose of the SSRI citalopram (Nathan et al., 2006). However, acute depletion of serotonin in healthy adults after trytophan administration did not affect intensity dependence (Debener et al., 2002; Dierks et al., 1999).

Studies of intensity dependence of auditory ERPs as predictors of response to antidepressants are of particular interest because of the potential for clinical application, but they have suffered from a number of limitations. Sample sizes have generally been small, most studies used open treatment with only a single antidepressant, and retest intervals when patients were on an SSRI have been too short to expect significant enhancement of serotonin. Also, a variety of different methods have been used to measure intensity dependence, including measures of scalp potentials, LORETA, and dipole source analysis of N1, P2 or N1-P2 difference waveforms. Interestingly, reliabilities (temporal stability, internal consistency) of intensity-dependent ERP amplitude slope estimates can be substantially improved by using PCA-based as opposed to peak-based amplitude measures (Beauducel et al., 2000), which suggests possible avenues of improvement for predicting treatment response.

Nd, N2 and MMN

Studies have also used auditory ERPs to study selective attention in depressed subjects. Negativity in the region of the N1is known to be greater to attended than unattended stimuli, which has allowed the measurement of "attention-related" N1, and more specifically, the negative difference (Nd) potential, i.e., the difference in ERP to attended and ignored stimuli (see Chapter 11, this volume). Three studies have agreed in finding no difference in attention-related N1 or Nd in depressed subjects and healthy controls (Burkhart & Thomas, 1993; Massioui & Lesevre, 1988; Knott et al., 1991). Thus, depression does *not* appear to involve a deficit in voluntarily directing attention to specific stimuli.

There is, however, less agreement concerning the N2 potential in depression, with some studies finding increased N2 amplitude in depressed or dysthymic subjects when compared to non-depressed controls (Bruder et al., 1998; Giese-Davis et al., 1993; Sandman et al., 1992), and others finding no difference (Blackwood et al., 1987; Kaiser et al., 2003) or reduced N2 in depressed subjects (Deldin et al., 2000; Massioui et al., 1996; Massioui & Lesevre, 1988; Sandman et al., 1987). While this difference in N2 findings could in part stem from differences in clinical characteris-

tics of patients, Sara et al. (1994) found no evidence of a relation between N2 amplitude and severity of depression. They did find that drug-free patients having a major depression showed greater N2 amplitude when compared to medicated depressed patients and healthy controls, which differs from the lack of medication effects on P3 in their study. However, the subjects in most studies were off medication and this is therefore not likely to be a factor. Differences in tasks used in the above studies may well have contributed to different findings. Specifically, the three studies finding increased N2 amplitude in depressed subjects used auditory oddball (Bruder et al., 1998), tone discrimination (Giese-Davis et al., 1993) or tone counting tasks (Sandman et al., 1992). In contrast, two studies finding decreased N2 amplitude used auditory selective attention tasks (Massioui et al., 1996; Massioui & Lesevre, 1988) and one used a visual recognition memory task (Deldin et al., 2000). Moreover, the studies differed widely in the methods used to compute N2 amplitude. Some studies computed N2 amplitude based on difference waveforms (e.g., target minus nontargets) to reduce the influence of exogenous components (N1, P2), while others used baseline-to-peak or peak-to-peak measures that may have been more affected by these overlapping components. Moreover, N2 identification, and accordingly the experimenter's decision of how and where to measure it, is considerably affected by the choice of ERP recording reference.

As seen for P3, N2 is composed of two or more overlapping subcomponents (Näätänen & Gaillard, 1983). Mismatch negativity (MMN) or N2a is associated with automatic detection of a mismatch between stimuli (see chapter 6, this volume). This precedes and overlaps N2b, which is associated with categorization and controlled processing of target stimuli. Both are typically computed by obtaining difference waveforms, subtracting the waveforms for frequent from rare stimuli. The problem is that little attention has been directed to obtaining separate measures of MMN and N2b in depressed patients. In an auditory oddball task, Ogura et al. (1993) measured mean integrated amplitude of N2 from difference waveforms (rare minus frequent stimuli; linked ears) in 36 unmedicated depressed patients and 36 healthy controls. To obtain estimates of N2 subcomponents, they measured the mean amplitude of N2a in the latency range of 120-165ms and N2b in the latency range of 170-235ms. The mean amplitudes were smaller in depressed patients in both the early and late windows. While the N2a estimate for rare stimuli was reduced in depressed patients compared to controls, negativity in the N2b latency range was *greater* to frequent stimuli in depressed patients. They concluded that the automatic processing of mismatch was reduced in depressed patients, whereas the later controlled processing of nontargets was more activated in these patients. Another possibility not considered by the authors is that N2 and P2 typically overlap in auditory oddball tasks, such that P2 is present for frequent nontarget tones but replaced (or overlapped) by N2 for infrequent target tones (cf. Kayser et al., 1998). In this case, their findings for frequent stimuli could be interpreted as a reduced nontarget P2 in depressed patients. A critical limitation of this study, however, is that N2a was not obtained in a standard MMN paradigm, where subjects do not attend to tones and parameters are optimized for measuring MMN. Giese-Davis et al. (1993) used the paradigm of Sams et al. (1983) to provide separate measures of N2a (150-250 ms) and N2b (150-350 ms) using difference waveforms (linked mastoids). They found no difference between dysthymic subjects and controls in N2a in an "ignore" condition, but dysthymics had markedly greater N2b than controls. Umbricht et al. (2003) also found no difference in MMN (nose reference) between 22 depressed patients and 25 healthy controls in a standard paradigm.

Sumich et al. (2006) compared the amplitude of N2 (linked mastoids) to target tones in 70 subclinically-depressed subjects (i.e., those scoring 2 or more on the Depression Anxiety and Stress Scale) and 70 subjects with no signs of depression. While these groups did not differ in overall level of N2, the nondepressed subjects showed greater N2 amplitude over the right than left central sites, but subclinically depressed subjects did not show a hemispheric asymmetry of N2. Although in a different modality, this parallels the finding of reduced N2 amplitude over right parietal sites in depressed patients during the processing of pleasant faces (Deldin et al., 2000). These findings are also of interest given reports that depressed patients show reduced P3 amplitude over right temporoparietal sites (Kawasaki et al., 2004) or fail to show the right-greater-than-left P3 asymmetry seen in healthy adults for tonal stimuli (Bruder et al., 1998) or emotional pictures (Kayser et al., 2000). The above findings support the hypothesis that depression is associated with reduced activation of right temporoparietal regions during the processing of tonal or emotional stimuli.

N2 has also been measured in tasks designed to study conflict processing or response inhibition in depressed patients. In the visual modality, a negative potential, i.e., N270, was measured in 25 unmedicated depressed patients and 25 matched controls at frontal (F3/4) and parietal (P3/4) electrodes (linked ears reference) during an S1-S2 paradigm (Mao et al., 2005). Subjects indicated whether the S2 stimulus (colored dot) matched the S1 stimulus or was a mismatch. The N270 potential was elicited to S2 stimuli that differed from the S1 stimulus and was measured from its peak amplitude in the difference waveform (mismatch minus match conditions). Depressed patients had smaller N270 amplitude in the difference waveforms compared to

controls at frontal and parietal electrode sites. Mao et al. interpreted the reduced N270 as evidence of impairment of a "conflict processing system", involving anterior cingulate and dorsal lateral prefrontal cortex. This system, which is active under mismatch or stimulus discrepancy conditions, is thought to involve the same brain processes as response conflict or error detection. In the auditory modality, Kaiser et al. (2003) measured 61-channel ERPs (average reference) of 16 medicated depressed patients and 16 healthy controls during a go/no-go task. The Go task was a modification of an auditory oddball task, but the No-Go task required inhibition of responses to rare tones. Depressed patients did not differ from controls in performance or ERPs during the Go task, but performed more poorly than controls in the No-Go task. Also, the patients showed a reduction of inferior frontotemporal positivity in the N2 latency range (i.e., polarity-inverted N2) during the No-Go task. They interpreted this as suggesting a deficit in response inhibition in depression, which is thought to involve a prefrontal executive control system.

Error-Related Negativity and Post-Error Processing

Following errors in two-choice reaction-time tasks, such as go/no-go or Eriksen flanker tasks, there is an increase in response-locked frontocentral negativity referred to as error-related negativity (ERN) or error negativity (N_e; see Chapter 10, this volume). This component peaks 50-150 following an incorrect response and is maximum over midline frontocentral sites. The ERN has been considered an electrophysiologic index of a response-monitoring or conflict detection with likely generators in the region of the anterior cingulate (Dehaene et al., 1994; Ruchsow et al., 2002; van Veen & Carter, 2002; see Falkenstein et al., 2000, for a review). Given the substantial evidence for the role of the ACC in depression (Drevets, 2000), it is not surprising that studies have found abnormalities of ERN in depressed subjects. Chiu and Deldin (2007) measured ERN (linked mastoids) in 18 individuals having a current major depressive episode and 17 nondepressed controls during an arrow flanker task, in which a target arrow was flanked by congruent, incongruent or neutral distracters and subjects responded in the direction of the target arrow. Subjects were also given accuracy feedback under reward, punishment or neutral conditions. The amplitude of ERN was greatest at frontal and frontocentral sites, and the depressed group showed greater ERN amplitude than the controls, particularly in the punishment condition. More recently, Holmes and Pizzagalli (2008) measured the ERN (129-channel montage, average reference) of 20 unmedicated patients with MDD and 20 matched healthy controls during a Stroop task. The depressed patients had significantly larger ERN than controls. Using LORETA analyses they found that depressed patients, relative to controls, showed greater current density in rostral ACC and medial prefrontal cortex at the time of maximal ERN (80 ms following errors). Moreover, functional connectivity analyses revealed that activity in these regions was correlated with subsequent activity in left dorsolateral prefrontal cortex in healthy controls but not in depressed patients. This supported their hypothesis that exaggerated error processing (i.e., increased ERN) in depressed patients is not followed by recruitment of prefrontal-based cognitive control.

There is evidence that enhanced ERN depends on the severity of depression or negative affect. First, in the study by Chiu and Deldin (2007), the magnitude of ERN in their neutral condition was larger in subjects with greater severity of self-ratings of depression. Second, Tucker et al. (2003) found evidence of larger feedback-related negativity in subjects having a major depression when compared to non-depressed controls, and this difference was greatest in subjects with moderate depression, but less in those with more severe depression. Third, two studies measured ERN during an Eriksen flanker task or a Go/NoGo Task in patients having a major depressive disorder "in remission" and found no difference between the patients and controls (Ruchsow et al., 2004, 2006). Moreover, remitted depressed patients in both studies showed *less* ERN than controls for error trials following another error.

Enhanced ERN is not specific to depression but is seen in children and adults having an obsessive-compulsive disorder (Gehring et al., 2000; Hajcak et al., 2008). Moreover, college students with high scores on scales measuring general "negative affect" had greater ERN amplitude than those with lower negative affect (Hajcak et al., 2004; Luu et al., 2000). Given that negative affect is evident in both depression and anxiety, these findings are consistent with the conclusion that enhanced ERN is present in both depressive and anxiety disorders. This raises the question as to whether increased ERN is associated with depression per se or anxiety states that often accompany depressive disorders. No study has directly compared ERN in patients having a depressive disorder alone, an anxiety disorder alone, or comorbidity of these disorders. Importantly, two studies in elderly depressed patients suggest that elevated ERN is associated with poor outcome of treatment with an SSRI antidepressant. In their initial study, Kalayam and Alexopoulos (2003) measured ERN (linked mastoids) in 22 elderly depressed patients (over 60 years old) during a Stroop interference task. They compared the ERN of 13 patients whose depression remitted during 6 weeks of treatment with the citalopram and 9 unremitted patients. The unremitted patients had greater ERN than the remitted patients, with the greatest difference between groups at the left frontal site (F3). Greater ERN amplitude at this site was correlated with less change in depressive symptoms during treatment and abnormal initiation/

perseveration scores on the Mattis Dementia Rating Scale. They hypothesized that anterior cingulate dysfunction contributes to limited improvement in depression during treatment. In their next study, Alexopoulos et al. (2007) recorded ERPs (128-channel montage, average reference) of 12 elderly depressed patients in an emotional Go/No-Go task, citing neuroimaging evidence that this task activates the rostral anterior cingulate. The 6 patients who remained symptomatic after 8 weeks of treatment had larger ERN at midline frontal and frontocentral sites when compared to the 6 patients who were remitters. The nonremitters also had smaller amplitude of error-related positivity 150-350 ms after an incorrect response. These findings are intriguing given evidence from neuroimaging and electrophysiologic studies linking increased rostral anterior cingulate activity and clinical response to antidepressants (Mayberg et al., 1997; Pizzagalli et al., 2001). The studies do, however, have several limitations. The samples were extremely small, there was no placebo control group, and the lack of a normal control group makes it difficult to know whether the nonremitters had abnormally large ERN or remitters abnormally small ERN. Also, findings for geriatric depression may not generalize to younger depressed patients.

There is also a question as to why *both* increased ERN and dysfunction of rostral ACC should be related to poorer response to antidepressants. A possible explanation is provided by the EEG findings of Pizzagalli and his associates. Pizzagalli et al. (2006) measured resting EEG prior to subjects performing an Eriksen flanker task. Subjects having high scores on the Beck Depression Inventory, unlike subjects with low scores, showed lower accuracy after incorrect than correct trials. Also, topographic analyses of resting EEG using LORETA indicated that depressed subjects had reduced pre-task gamma band activity localized to the region of the rostral ACC. Also, higher pretask gamma was predictive of post-error adjustment in behavioral performance. They interpreted these findings as suggesting that depressed subjects have deficits in pre-task tonic activity in rostral ACC and in making behavioral adjustments after errors. Although increased affective reactions to errors in depressed patients might be expected to be associated with greater ERN during task performance, no ERP data were reported in this study.

Pizzagalli et al. (2001) previously reported that greater resting EEG theta activity, localized by LORETA to the rostral region of the ACC, was predictive of more favorable response to treatment with the antidepressant nortriptyline. They suggested that in treatment responders, rostral ACC hyperactivity prior to treatment may reflect increased sensitivity to affective conflict or the ability to monitor the outcome of actions and adjust behavior, e.g., by making post-error behavioral adjustments. In treatment nonresponders, this adaptive action monitoring may be dysfunctional leading to reduced post-error behavioral adjustments. Following suggestions that resting and task related theta at anterior midline sites may reflect a common process (Tenke & Kayser, 2005; Tzur & Berger, 2007; Wang et al., 2005), it may be predicted that treatment nonresponders, as compared to responders, will have smaller resting EEG theta activity and greater ERN associated with failure to adjust their behavior during task performance. Future studies measuring both resting EEG and ERN in depressed adults prior to treatment are needed to evaluate this hypothesis.

Further study should also examine the possible relation of ERN abnormalities in depression and anxiety disorders to neurotransmitter systems. In this regard, there is evidence that the serotonin transporter gene (5-HTTLRP) is associated with ERN amplitude in healthy subjects (Fallgatter et al., 2004). Those with one or two copies of the low-activity 5-HTTLRP short genotype showed greater ERN compared to those homozygous for the long allele. Individuals with the short allele are at increased risk for developing depression in response to stress, which raises the possibility that heightened ERN may be a risk marker for a form of depression that responds poorly to treatment with antidepressants.

Conclusions

Cognitive P3 Potential

The classical P3 potential with parietal maximum has been extensively studied in depressed patients. Although there have been conflicting findings, the general trend is for depressed patients to show some reduction of P3 to target stimuli in an auditory oddball task (mean effect size = 0.85). Differences in P3 findings across studies could well stem from differences in the clinical features of the patients, with patients having melancholic or psychotic depressions having the largest P3 reductions. Reduced P3 amplitude in depressed patients is at least partially state-dependent, in that clinical improvement during treatment is accompanied by an increase in P3. Although there are fewer reports of abnormal P3 latency in depression, there is evidence that P3 latency is longer in patients having a bipolar or melancholic depression who typically show psychomotor retardation or cognitive slowing.

The moderate size of the P3 reduction in depression may also stem from the use of simple oddball tasks with relatively little cognitive demand. Studies measuring P3 in cognitively challenging auditory or visual tasks have more consistently found a P3 reduction in depressed patients. Also, depressed patients show an overall reduced P3 to visually-presented affective stimuli and they fail to show greater late P3 amplitude to negative as compared to neutral stimuli, which is seen in healthy adults. Overall, the P3 decrement in depressed patients suggests a deficit in

temporoparietal regions involved in context updating, memory, and emotional processing, although frontal regions may also play a role. P3 reduction is not, however, specific to depression, but is seen in other neuropsychiatric disorders that display cognitive deficits, such as schizophrenia, alcoholism, Alzheimer's disease or Parkinson's disease (Jeon & Polich, 2003; Polich & Herbst, 2000; see also Chapters 17, 18, and 20, this volume).

One of the problems is that most studies in depressed subjects have not differentiated P3 subcomponents. The P3a or novelty P3 has a more frontocentral distribution than the classical P3b potential and may contribute to the P3 reduction in depressed patients. P3a or novelty P3 is reduced in depressed patients, but is *increased* in patients having an anxiety disorder. This also underscores the importance of taking the patients specific clinical features, and particularly comorbidity of depression and anxiety, into account. The reduced novelty P3 in depression suggests an orienting deficit or dysfunction of automatic switching of attention to task-irrelevant stimuli, which is thought to involve prefrontal, anterior cingulate and hippocampal regions.

Old-New Effect During Recognition Memory Tasks

The increased late positive potential to correctly recognized words, i.e., the old-new effect, is thought to be a neurophysiologic correlate of conscious episodic memory retrieval. Studies of continuous word recognition indicate that this old-new effect is reduced in depressed patients. Given evidence of left medial temporal involvement in the old-new effect for words, the reduced old-new effect is consistent with neuroimaging findings of reduced hippocampal volumes in depressed patients. Although the old-new deficit appears to be greatest over the left parietal region, further study is needed to determine whether this is specific to recognition memory for words or occurs for nonverbal stimuli as well.

N1 and Nd Potentials

Most studies have not found a reduction of N1 amplitude in depressed patients. Also, studies have agreed in finding no difference between depressed subjects and controls in attention-related N1 or the Nd potential. These findings argue against any deficit in early sensory processing or voluntarily directing attention in depressed patients. A subgroup of depressed patients who respond favorably to antidepressants were found to have reduced auditory N1 to novel distracters, which may be related to the extensive serotonergic innervation of primary auditory cortex. There is evidence that the intensity dependence of early auditory potentials (N1-P2) provides an index of central serotonergic activity. Depressed patients with pronounced intensity dependence of N1-P2 prior to treatment have better response to treatment with SSRI antidepressants when compared to patients with less intensity dependence. Small sample sizes and methodological weaknesses in studies of intensity dependence do, however, limit the strength of the conclusions from these studies. Also, further study is needed to examine the extent to which findings are specific to SSRI antidepressants or generalize to other classes of antidepressants with different mechanisms of action.

N2 and MMN Potentials

N2 amplitude in depressed or dysthymic subjects has been reported to be increased, decreased or no different when compared to healthy controls. Differences in the tasks, clinical characteristics of patients, or medication status may have contributed to these different findings. Methodological difficulties in identifying and measuring N2, particularly when using an EEG montage with a limited number of recording channels, has also contributed to inconsistent findings. Tasks involving simple discrimination or counting of tones have shown increased N2 in depressed patients, whereas those involving more complex decisions or response inhibition (e.g., selective attention or recognition memory tasks) were more likely to show decreased N2. Studies have reported that depressed patients have reduced amplitude of potentials in the N2 latency range during visual S1-S2 or auditory go/no-go tasks under stimulus mismatch or response conflict conditions. It was suggested that executive control systems, involving prefrontal and anterior cingulate cortex, may be responsible for these deficits. As is the case for P3 studies in depressed subjects, little attention has been directed to separating N2 subcomponents (i.e., MMN and N2b). Two studies that measured MMN under standard "ignore" conditions found no difference between dysthymic or depressed patients and controls, while two studies found evidence of enhanced N2b in dysthymic or depressed subjects. Further study of MMN and N2b in depressed patients using conditions known to maximize these potentials, as well as techniques for separately measuring them, are needed to draw more definitive conclusions.

Performance-monitoring Potentials

Healthy adults show an increase in frontocentral negativity following errors in two-choice reaction time tasks or following negative feedback. Studies have found that error-related negativity (ERN) is *heightened* not only in depressed subjects, but also children or adults having anxiety disorders, and college students with general "negative affect." This is therefore not specific to depressive disorders and is likely to be particularly high in subjects having comorbidity of depression and anxiety, but this has yet to be studied. The clinical relevance stems from findings that ERN is greater in elderly patients whose depression failed to remit following treatment with an SSRI

antidepressant when compared to remitters. Given evidence that ERN is generated in medial frontal areas in or near the anterior cingulate, these findings are consistent with EEG and neuroimaging evidence that the rostral ACC is associated with clinical response to antidepressants. However, the sample sizes in these studies have been very small and the studies lacked healthy adult or placebo control groups. Heightened ERN has also been found in healthy adults with the low-activity serotonin transporter allele (5-HTTLRP short), suggesting that heightened ERN may be a risk marker for developing a form of depression that responds poorly to treatment.

Future Directions

Given the conflicting P3 findings for depressed patients during a standard two-stimulus, auditory oddball task, continued use of this task in depressed patients would appear to be of limited value. On the other hand, ERPs continue to be a useful tool for studying the nature of cognitive deficits in depression and for providing information about their neurophysiologic underpinnings. It is of value to measure ERPs during more challenging cognitive tasks that allow evaluation of hypotheses concerning the specific cognitive or neurophysiologic deficits in depression. For instance, the measurement of N2 and P3 during go/no-go tasks can be used to test hypotheses about response inhibition or conflict monitoring in depression (Donkers & van Boxtel, 2004; Kaiser et al., 2003). ERN can also be measured during go/no-go or flanker tasks to test hypotheses concerning performance monitoring and ACC dysfunction in depression (Chiu & Deldin, 2007; Ruchsow et al., 2006). Similarly, measuring the "old-new" effect during recognition memory tasks provides a means for evaluating hypotheses concerning conscious memory retrieval deficits in depression and their neurophysiolologic correlates (Kayser et al., 2007).

Future studies of the N2 and P3 potentials in depression should also differentiate subcomponents that involve different cognitive operations and neuronal generators. The novelty oddball task can be of particular value for measuring P3a or novelty P3 in depression (Bruder et al., in press; Tenke et al., in press). It is also important to use techniques that are capable of providing separate measures of neuronal sources underlying these subcomponents, e.g., the use of combined CSD-PCA measures (Kayser & Tenke, 2006a,b). In general, the use of denser EEG montages and appropriate methods to capture the temporal and spatial dynamics of ERPs and define ERP components would be advantageous (Kayser & Tenke, 2005).

Surprisingly few studies have used ERPs to study the processing of emotional information in depressed patients. ERPs can be used to measure neurophysiologic responses to emotional stimuli without a cognitive task, so as to yield a purer measure of affective processing in depressed patients (Kayser et al., 1997, 2000). In this regard, one area that is ripe for exploration is the measurement of ERPs to olfactory stimuli (Pause et al., 2003). Measurement of ERPs to olfactory stimuli provides a window for studying neurophysiologic correlates of emotional processing because of the direct projections to cortical and limbic structures that are known to be involved in emotional processing and depression, in particular the amygdala, orbitofrontal cortex, and medial temporal cortex. On the other hand, there is also growing interest in the interaction of cognitive control and emotional processing regions (Ochsner & Gross, 2005), which can be readily studied with ERPs, e.g., using cognitive control or interference tasks with emotional distracters (Fales et al., 2008).

In future ERP studies of cognitive and affective processing, it would also be important to examine subtypes of depression, but this requires sufficiently large samples because small subgroups ($n < 10$) are of limited value. Comparison of ERPs in depressed versus control groups is a useful first step, but fails to adequately account for the clinical and biological heterogeneity of depressive disorders. Studies comparing ERPs in subtypes with different symptom features are particularly important when studying P3 subcomponents (Bruder et al., 2002; Pierson et al., 1996). The influence of comorbidity with anxiety also needs further attention in these studies, as well as those of performance monitoring (i.e., ERN) in depression. Another useful approach is to subtype patients on the basis of their clinical response to antidepressants with a specific mechanism of action, which would require even larger samples. Some of the most promising findings concern the relation between ERN and intensity dependence of auditory ERPs (N1-P2) to outcome of treatment with antidepressants. Studies with larger samples comparing the value of these measures for predicting response to different classes of antidepressants (e.g., SSRI or NDRI antidepressants) are needed to confirm the specificity of their relation to SSRI antidepressants. Further study should also be directed toward determining the neurotransmitter systems that may be related to ERP abnormalities in depressed patients. In addition to the relation of the serotonin system to intensity dependence of N1-P2 and ERN, there is evidence that P3 subcomponents are dependent on dopamine or norepinephrine systems (Polich, 2007; Turetsky & Fein, 2002). Pharmacological studies measuring ERPs before and during acute treatment with drugs that selectively act on specific neurotransmitter systems would be of value here.

Findings linking the serotonin transporter gene (5-HTTLPR) with both intensity dependence of N1-P2 (Strobel et al., 2003) and ERN (Fallgatter et al., 2004) also indicate the importance of additional study of the genetic correlates of ERP abnormalities in depressed patients. Lastly, both intensity dependence of N1-P2 (Hegerl & Juckel, 1993) and

ERN amplitude in depressed subjects (Pizzagalli et al., 2006) have been hypothesized to be related to pre-test, tonic EEG activity in specific frequency bands. Studies should therefore examine how findings for antidepressant responders and nonresponders on these ERP measures depend on differences in resting EEG oscillations.

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References

American Psychiatric Association (1994). Diagnostic and Statistical Manual of Mental Disorders., 4th ed. APA, Washington, DC.

Ahveninen, J., Kahkonen, S., Pennanen, S., Liesivuori, J., Ilmoniemi, R. J., & Jaaskelainen, I. P. (2002). Tryptophan depletion effects on EEG and MEG responses suggest serotonergic modulation of auditory involuntary attention in humans. *NeuroImage*, *16*, 1052-1061.

Alexopoulos, G. S., Murphy, C. F., Gunning-Dixon, F. M., Kalayam, B., Katz, R., Kanellopoulos, D., Etwaroo, G. R., Klimstra, S., & Foxe, J. J. (2007). Event-related potentials in an emotional go/no-go task and remission of geriatric depression. *NeuroReport,* 18, 217-221.

Ancy, J., Gangadhar, B. N., & Janakiramaiah, N. (1996). "Normal" P300 amplitude predicts rapid response to ECT in melancholia. *Journal of Affective Disorders*, 41, 211-215.

Anderer, P., Saletu, B., Semlitsch, H. V., & Pascual-Marqui, R. D. (2002). Structural and energetic processes related to P300: LORETA findings in depression and effects of antidepressant drugs. *Methods and Findings in Experimental and Clinical Pharmacology*, 24, 85-91.

Austin, M. P., Mitchell, P., & Goodwin, G. M. (2001). Cognitive deficits in depression. *British Journal of Psychiatry*, 178, 200-206.

Bange, F., & Bathien, N. (1998). Visual cognitive dysfunction in depression: An event- related potential study. *Electroencephalography and Clinical Neurophysiology*, 108, 472-481.

Beauducel, A., Debener, S., Brocke, B., & Kayser, J. (2000). On the reliability of augmenting/reducing: peak amplitudes and principal components analysis of auditory evoked potentials. *Journal of Psychophysiology*, *14*, 226-240.

Blackburn, I. M., Roxborough, H. M., Muir, W. J., Glabus, M., & Blackwood, D. H. R. (1990). Perceptual and physiological dysfunction in depression. *Psychological Medicine*, 20, 95-103.

Blackwood, D. H. R., Whalley, L. J., Christie, J. E., Blackburn, I. M., St. Clair D. M., & McInnes, A. (1987). Changes in auditory P3 event-related potential in schizophrenia and depression. *British Journal of Psychiatry*, 150, 154-160.

Bremner, J. D., Vythilingam, M., Vermetten, E., Vaccarino, V., & Charney, D. S. (2004). Deficits in hippocampal and anterior cingulate functioning during verbal declarative memory encoding in midlife major depression. *American Journal of Psychiatry*, 161, 637-645.

Bruder, G.E. (1992). P300 findings for deprssive and anxiety disorders. *Annuals of the New York Academy of Sciences,* 658, 205-222.

Bruder, G. E., Kayser, J., Tenke, C. E., Leite, P., Schneier, F. R., Stewart, J. W., & Quitkin, F. M. (2002). Cognitive ERPs in depressive and anxiety disorders during tonal and phonetic oddball tasks. *Clinical Electroencephalography*, 33, 119-124.

Bruder, G. E., Kroppmann, C. J., Kayser, J., Stewart, J. W., McGrath, P. J., & Tenke, C. E. (in press). Reduced brain responses to novel sounds in depression: An electrophysiological study. *Psychiatry Research.*

Bruder, G. E., Quitkin, F. M., Stewart, J. W., Martin, C., Voglmaier, M. M., & Harrison, W. M. (1989). Cerebral laterality and depression: differences in perceptual asymmetry among diagnostic subtypes. *Journal of Abnormal Psychology*, *98*, 177-186.

Bruder, G. E., Tenke, C. E., Stewart, J. W., Towey, J. P., Leite, P., Voglmaier, M., & Quitkin, F. M. (1995). Brain event-related potentials to complex tones in depressed patients: Relations to perceptual asymmetry and clinical features. *Psychophysiology*, 32, 373-381.

Bruder, G. E., Tenke, C. E., Towey, J. P., Leite, P., Fong, R., Stewart, J. E., McGrath, P. J., & Quitkin, F. M. (1998). Brain ERPs of depressed patients to complex tones in an oddball task: Relation of reduced P3 asymmetry to physical anhedonia. *Psychophysiology*, 35, 54-63.

Bruder, G.E., Tenke, C.E., Warner, V., Weissman, M.M. (2007). Grandchildren at high and low risk for depression differ in EEG measures of regional brain asymmetry. Biological Psychiatry, 62, 1317-1323.

Bruder, G. E., Towey, J. P., Stewart, J. W., Friedman, D., Tenke, C., & Quitkin, F. M. (1991). Event-related potentials in depression: Influence of task, stimulus hemifield and clinical feautres on P3 latency. *Biological Psychiatry*, 30, 233-246.

Burkhart, M. A., & Thomas, D. G. (1993). Event-related potential measures of attention in moderately depressed subjects. *Electroencephalography and Clinical Neurophysiology,* 88, 42-50.

Burt, D. B., Zembar, M. J., & Niederehe, G. (1995). Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychological Bulletin*, 117, 285-305.

Cacioppo, J. T., Crites, S. L., Bernston, G. G., & Coles, M. G. (1993). If attitudes affect how stimuli are processed, should they not affect the event-related potential. *Psychological Science*, 4, 108-112.

Cacioppo, J. T., Crites, S. L., & Gardner, W. L. (1996). Attitudes to the right: evaluative processing is associated with lateralized late positive event-related potentials. *Personality and Social Psychology Bulletin*, 22, 1205-1219.

Campbell, M. J., Lewis, D. A., Foote, S. L., & Morrison, J. H. (1987). Distribution of choline acetyltransferase-, serotonin-, dopamine-beta-hydroxylase-, tyrosine hydroxylase-immunoreactive fibers in monkey primary auditory cortex. *Journal of Comparative Neurology*, *261*, 209-220.

Castaneda, A. E., Tuulio-Henriksson, A., Marttunen, M., Suvisaari, J., & Lönnqvist, J. (2008). A review on cognitivie impairments in depressive and anxiety disorders with a focus on young adults. *Journal of Affective Disorders*, 106, 1-27.

Cavanagh, J., & Geisler, M. W. (2006). Mood effects on the ERP processing of emotional intensity in faces: A P3 investigation with depressed students. *International Journal of Psychophysiology*, 60, 27-33.

Chiu, P. H., & Deldin, P. J. (2007). Neural evidence for enhanced error detection in major depressive disorder. *American Journal of Psychiatry*, 164, 608-616.

Debener, S., Strobel, A., Kurschner, K., Kranczioch, C., Hebenstreit, J., Maercker, A., Beauducel, A., & Brocke, B. (2002). Is auditory evoked potential augmenting/reducing affected by acute tryptophan depletion? *Biological Psychology*, *59*, 121-133.

Dehaene S., Posner, M., & Tucker, D. (1994). Commentary: localization of a neural system for error detection and compensation. *Psychological Medicine*, 5, 303-305.

Deldin, P. J., Deveney, C. M., Kim, A. S., Casas, B. R., & Best, J. L. (2001a). A slow wave investigation of working memory biases in mood disorders. *Journal of Abnormal Psychology,* 110, 267-281.

Deldin, P. J., Keller, J., Gergen, J. A., & Miller, G. A. (2001b). Cognitive bias and emotion in neuropsychological models of

depression. *Cognition and Emotion*, 15, 787-802.

Deldin, P. J., Keller, J., Gergen, J. A., & Miller, G. A. (2000). Right-posterior face procesing anomaly in depression. *Journal of Abnormal Psychology*, 109, 116-121.

Deveney, C. M., & Deldin, P. J. (2004). Memory of faces: A slow wave ERP study of major depression. *Emotion,* 4, 295-304.

Dien, J., Spencer, K. M., & Donchin., E. (2003). Localization of the event-related potential novelty response as defined by principal components analysis. *Cognitive Brain Research*, 17, 637-650.

Dierks, T., Barta, S., Demisch, L., Schmeck, K., Englert, E., Kewitz, A., Maurer, K., & Poustka, F. (1999). Intensity dependence of auditory evoked potentials (AEPs) as biological marker for cerebral serotonin levels: Effects of tryptophan depletion in healthy subjects. *Psychopharmacology*, *146*, 101-107.

Dietrich, D. E., Emrich, H. M., Waller, C., Wieringa, B. M., Johannes, S., & Munte, T. F. (2000a). Emotion/cognition-coupling in word recognition memory of depressive patients: an event-related potential study. *Psychiatry Research*, *96*, 15-29.

Dietrich, D. E., Kleinschmidt, A., Hauser, U., Schneider, U., Spannhuth, C. W., Kipp, K., Huber, T. J., Wieringa, B. M., Emrich, H. M., & Johannes, S. (2000b). Word recognition memory before and after successful treatment of depression. *Pharmacopsychiatry*, *33*, 221-228.

Diner, B. C., Holcomb, P. J., & Dykman, R. A. (1985). P300 in major depressive disorder. *Psychiatry Research*, 15, 175-184.

Donkers, F. C. L., & van Boxtel, G. J. M. (2004). The N2 in go/no-go tasks reflects conflict monitoring not response inhibition. *Brain and Cognition*, 56, 165-176.

Drevets, W. (2000). Neuroimaging studies of mood disorders. *Biological Psychiatry*, 48, 813-829.

Drevets, W. C., Price, J. L., Simpson, J. R. Jr., Todd, R. D., Reich, T., Vannier, M., & Raichle, M. E. (1997). Subgenual prefrontal cortex abnormalties in mood disorders. *Nature*, 386, 824-827.

Ehrlichman, H., & Bastone, L. (1992). Olfaction and emotion. In J. Serby & K.L. Chobor (Eds.), *Science of olfaction* (pp.410-438). New York: Springer.

El Massioui, F., Everett, J., Martin, M. T., Jouvent, R., & Widlocher, D. (1996). Attention deficits in depression: an electrophysiological marker. *Neuroreport*, *7*, 2483-2486.

El Massioui, F., & Lesevre, N. (1988). Attention impairment and psychomotor retardation in depressed patients: an event-related potential study. *Electroencephalography and Clinical Neurophysiology*, *70*, 46-55.

Elger, C. E., Grunwald, T., Lehnertz, K., Kutas, M., Helmstaedter, C., Brockhaus A, Van Roost, D., & Heinze, H. J. (1997). Human temporal lobe potentials in verbal learning and memory processes. *Neuropsychologia*, 35, 657-667.

Fales, C. L., Barch, D. M., Rundle, M. M., Mintun, M. A., Snyder, A. Z., Cohen, J. D., Mathews, J., & Sheline, Y. I. (2008). Altered emotional interference processing in affective and cognitive-control brain circuitry in major depression. *Biological Psychiatry*, 63, 377-384.

Falkenstein, M., Hoormann, J., Christ, S., & Hohnsbein, J. (2000). ERP components on reaction errors and their functional significance: a tutorial. *Biological Psychology*, *51*, 87-107.

Fallgatter, A. J., Herrmann, M. J., Roemmler, J., Ehlis, A., Wagener, A., Heidrich, A., Ortega, G., Zeng, Y., & Lesch, K. (2004). Allelic variation of serotonin transporter function modulates the brain electrical response for error processing. *Neuropsychopharmacology*, 29, 1506-1511.

Friedman, D. (1990). ERPs during continuous recognition memory for words. *Biological Psychology*, 30, 61-87.

Friedman, D., Cycowicz, Y. M., & Gaeta, H. (2001). The novelty P3: an event-related brain potential (ERP) sign of the brain's evaluation of novelty. *Neuroscience and Biobehavioral Reviews*, 25, 355-373.

Friedman, D., Simpson, G., & Hamberger, M. (1993). Age-related changes in scalp topography to novel and target stimuli. *Psychophysiology*, 30, 383-396.

Gallinat, J., Bottlender, R., Juckel, G., Munke Puchner, A., Stotz, G., Kuss, H. J., Mavrogiorgou, P., & Hegerl, U. (2000). The loudness dependency of the auditory evoked N1/P2-component as a predictor of the acute SSRI response in depression. *Psychopharmacology*, *148*, 404-411.

Gangadhar, B. N., Ancy, J., Janakiramaiah, N., & Umapathy, C. (1993). P300 amplitude in non-bipolar, melancholic depression. *Journal of Affective Disordors*, 28, 57-60.

Gehring, W. J., Himle, J., Nisenson, L. G. (2000). Action-monitoring dysfunction in obsessive-compulsive disorder. *Psychological Science*, 11, 1-6.

Giese-Davis, J. E., Miller, G. A., & Knight, R. A. (1993). Memory template comparison processes in anhedonia and dysthymia. *Psychophysiology*, 30, 646-656.

Hajcak, G., Franklin, M. E., Foa, E. B., & Simons, R. F. (2008). Increased error-related brain activity in pediatric obsessive-compulsive disorder before and after treatment. *American Journal of Psychiatry*, 165, 116-123.

Hajcak, G., McDonald, N., & Simons, R. F. (2004). Error-related psychophysiology and negative affect. *Brain and Cognition*, 56, 189-197.

Halgren, E., Baudena, P., Clarke, J. M., Heit, G., Marinkovic, K., Devaux, B., Vignal, J. P., & Biraben, A. (1995). Intracerebral potentials to rare target and distractor auditory and visual stimuli. II. Medial, lateral and posterior temporal lobe. *Electroencephalography and Clinical Neurophysiology*, 94, 229-250.

Hansenne, M., Pitchot, W., Moreno, A. G., Zaldua, I. U., & Ansseau, M. (1996). Suicidal behavior in depressive disorder: an event-related potential study. *Biological Psychiatry*, 40, 116-122.

Hegerl, U., & Juckel, G. (1993). Intensity dependence of auditory evoked potentials as an indicator of central serotonergic neurotransmission: A new hypothesis. *Biological Psychiatry*, *33*, 173-187.

Hegerl, U., Gallinat, J. & Juckel, G. (2001). Event-related potentials: Do they reflect central serotonergic neurotransmission and do they predict clinical response to serotonin agonists? *Journal of Affective Disorders*, 62, 93-100.

Heller, W. (1990). The neuropsychology of emotion: developmental patterns and implications for psychopathology. In N.L. Stein, B. Leventhal & T. Trabasso (Eds.), *Psychological and Biological Approaches to Emotion,* (pp. 167-211). Hillside, NJ: Lawrence Earlbaum Associates.

Heller, W. (1993). Neuropsychological mechanisms of individual differences in emotion, personality and arousal. *Neuropsychology*, 7, 476-489.

Heller, W., Etienne, M. A., & Miller, G. A. (1995). Patterns of perceptual asymmetry in depression and anxiety: implications for neuropsychological models of emotion and psychopathology. *Journal of Abnormal Psychology*, *104*, 327-333.

Henson, R. N., Rugg, M. D., Shallice, T., & Dolan, R. J. (2000). Confidence in recognition memory for words: dissociating right prefrontal roles in episodic retrieval. *Journal of Cognitive Neuroscience*, 12, 913-923.

Holmes, A. J., & Pizzagalli, D. A. (2008). Spatiotemporal dynamics of error processing dysfunctions in major depressive disorder. *Archives of General Psychiatry*, 65, 179-188.

Houston, R. J., Bauer, L. O. & Hesselbrock, V. M. (2003). Depression and familial risk for substance dependence: a P300 study of young women. *Psychiatry Research: Neuroimaging,* 124, 49-62.

Houston, R. J., Bauer, L. O., & Hesselbrock, V. M. (2004). P300 evidence of cognitive inflexibility in female adolescents at risk for recurrent depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 28, 529-536.

Jeon, Y.W., & Polich, J. (2003). Meta-analysis of P300 and

schizophrenia: Patients, paradigms, and practical implications. *Psychophysiology*, 40, 684-701.

Johnson, R., Jr. (1995). Event-related potential insights into the neurobiology of memory systems. In F. Boller & J. Grafman (Eds.), *Handbook of Neuropsychology* (Vol. 10, pp. 135-164). Amsterdam: Elsevier.

Johnston, V. S., Miller, D. R., & Burleson, M. H. (1986). Multiple P3s to eomtional stimuli and their theoretical significance. *Psychophysiology*, 23, 684-694.

Juckel, G., Hegerl, U., Molnar, M., Csepe, V., & Karmos, G. (1999). Auditory evoked potentials reflect serotonergic neuronal activity--a study in behaving cats administered drugs acting on 5-HT1A autoreceptors in the dorsal raphe nucleus. *Neuropsychopharmacology*, *21*, 710-716.

Kaiser, S., Unger, J., Kiefer, M., Markela, J., Mundt, C., & Weisbrod, M. (2003). Executive control deficit in depression: Event-related potentials in a Go/Nogo task. *Psychiatry Research*, 122, 169-184.

Kalayam, B., & Alexopoulos, G. S. (2003). A preliminary study of left frontal region error negativity and symptom improvement in geriatric depression. *American Journal of Psychiatry*, 160 2054-2056.

Karaaslan, F., Gonul, A. S., Oguz, A., Erdinc, E., & Esel, E. (2003). P300 changes in major depressive disorders with and without psychotic features. *Journal of Affective Disorders*, 73, 283-287.

Kaustio, O., Partanen, J., Valkonen-Korhonen, M., Viinamäki, H., Lehtonen, J. (2002). Affective and psychotic symptoms relate to different types of P300 alteration in depressive disorder. *Journal of Affective Disorders*, 71, 43-50.

Kawasaki, T., Tanaka, S., Wang, J., Hokama, H., & Hiramatsu, K. (2004). Abnormalities of P300 cortical current density in unmedicated depressed patients revealed by LORETA analysis of event-related potentials. *Psychiatry and Clinical Neurosciences*, 58, 68-75.

Kayser, J., Bruder, G. E., Tenke, C. E., Stewart, J. W., & Quitkin, F. M. (2000). Event-related potentials (ERPs) to hemifield presentations of emotional stimuli: Differences between depressed patients and healthy adults in P3 amplitude and asymmetry. *International Journal of Psychophysiology*, 36, 211-236.

Kayser, J., Fong, R., Tenke, C. E., & Bruder, G. E. (2003). Event-related brain potentials during auditory and visual word recognition memory tasks. *Brain Research. Cognitive Brain Research*, *16*, 11-25.

Kayser, J., & Tenke, C.E. (2003). Optimizing PCA methodology for ERP component identification and measurement: Theoretical rationale and empirical evaluation. *Clinical Neurophysiology*, *114*, 2307-2325.

Kayser, J., Tenke, C. (2005). Trusting in or breaking with convention: towards a renaissance of principal components analysis in electrophysiology. *Clinical Neurophysiology*, *116(8)*, 1747-1753.

Kayser, J., & Tenke, C. E. (2006a). Principal components analysis of Laplacian waveforms as a generic method for identifying ERP generator patterns: I. Evaluation with auditory oddball tasks. *Clinical Neurophysiology*, *117*, 348-368.

Kayser, J., & Tenke, C. E. (2006b). Principal components analysis of Laplacian waveforms as a generic method for identifying ERP generator patterns: II. Adequacy of low-density estimates. *Clinical Neurophysiology*, *117*, 369-380.

Kayser, J., & Tenke, C. E. (2006c). Consensus on PCA for ERP data, and sensibility of unrestricted solutions. *Clinical Neurophysiology*, *117*, 703-707.

Kayser, J., Tenke, C. E., & Bruder, G. E. (1998). Dissociation of brain ERP topographies for tonal and phonetic oddball tasks. *Psychophysiology*, *35*, 576-590.

Kayser, J., Tenke, C. E., Gates, N. A., & Bruder, G. E. (2007). Reference-independent ERP old/new effects of auditory and visual word recognition memory: joint extraction of stimulus- and response-locked neuronal generator patterns. *Psychophysiology*, *44*, 949-967.

Kayser, J., Tenke, C.E., Gates, N.A., Stewart, J.W., McGrath, P.J., Bruder, G.E. (in preparation). Event-related brain potentials (ERPs) during auditory and visual word recognition memory tasks in affective disorders.

Kayser, J., Tenke, C., Nordby, H., Hammerborg, D., Hugdahl, K., & Erdmann, G. (1997). Event-related potential (ERP) asymmetries to emotional stimuli in a visual half-field paradigm. *Psychophysiology*, *34*, 414-426.

Kiehl, K. A., Laurens, K. R., Duty, T. L., Forster, B. B., & Liddle, P. F. (2001). Neural sources involved in auditory target detection and novelty processing: an event-related fMRI study. *Psychophysiology*, *38*, 133-142.

Kimble, M., Kaloupek, D., Kaufman, M., & Deldin, P. (2000). Stimulus novelty differentially affects attentional allocation in PTSD. *Biological Psychiatry*, *47*, 880-890.

Knight, R. (1996). Contribution of human hippocampal region to novelty detection. *Nature*, 383, 256-259.

Knight, R. T., & Scabiani, D. (1998). Anatomic bases of event-related potentials and their relationship to novelty detection in humans. *Journal of Clinical Neurophysiology*, 15, 3-13.

Knott, V., Lapierre, Y., Griffiths, L., de Lugt, D., & Bakish, D. (1991). Event-related potentials and selective attention in major depressive illness. *Journal of Affective Disorders*, 23, 43-48.

Knott, V. J., & Lapierre, Y. D. (1987). Electrophysiological and behavioral correlates of pychomotor responsivity in depression. *Biological Psychiatry*, 22, 313-324.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1999). *International Affective Picture System (IAPS): Technical manual and affective ratings.* Gainesville, FL: The Center for Research in Psychophysiology, University of Florida.

Lewis, D. A., Campbell, M. J., Foote, S. L., & Morrison, J. H. (1986). The monoaminergic innervation of primate neocortex. *Human Neurobiology*, *5,* 181-188.

Linka, T., Müller, B. W., Bender, S., & Sartory, G. (2004). The STET intensity dependence of the auditory evoked N1 component as a predictor of response to Citalopram treatment in patients with major depression. *Neuroscience Letters*, 367, 375-378.

Linka, T., Müller, B. W., Bender, S., & Sartory, G., & Gastpar, M. (2005). The intensity dependence of auditory evoked ERP components predicts responsiveness to Reboxetine treatment in major depression. *Pharmacopsychiatry*, 38, 139-143.

Luck, S.J. (2005). An introduction to the event-related potential technique. Cambridge: The MIT Press.

Luu, P., Collins, P., & Tucker, D. M. (2000). Mood, personality, and self-monitoring: Negative affect and emotionality in relation to frontal lobe mechanisms of error monitoring. *Journal of Experimental Psychology: General*, 129, 43-60.

Mao, W., Wang, Y., & Wang, D. (2005). Cognitive impairment in major depressive disorder revealed by event-related potential N270. *Clinical EEG and Neuroscience*, 36, 9-14.

Maris, E. (2004). Randomization tests for ERP topographies and whole spatiotemporal data matrices. *Psychophysiology*, *41*, 142-151.

Massioui, F., Everett, J., Martin, M. T., Jouvent, R., & Widlöcher, D. (1996). Attention deficits in depression: an electrophysiological marker. *NeuroReport* 7, 2483-2486.

Massioui, F., & Lesèvre, N. (1988). Attention impairment and psychomotor retardiation in depressed patients: an event-related potential study. *Electroencephalography and Clinical Neurophysiology*, 70, 46-55.

Mayberg, H. S., Brannan, S. K., Mahurin, R. K., Jerabek, P. A., Brickman, J. S., Tekell, J. L., Silva, J. A., McGinnis, S., Glass, T. G., Martin, C. C., & Fox, P. T. (1997). Cingulate function in depression: A potential predictor of treatment resonse. *NeuroReport*, 8, 1057-1061.

Mecklinger, A., & Ullsperger, P. (1995). The P300 to novel and target events: A spatiotemporal dipole model analysis. *Neuroreport*, 7, 241-245.

Mulert, C., Juckel, G., Brunnmeier, M., Karch, S., Leicht, G., Mergl, R., Moller, H. J., Hegerl, U., & Pogarell, O. (2007). Prediction of treatment response in major depression: integration of concepts. *Journal of Affective Disorders*, *98*, 215-225.

Muir, W. J., St. Clair, D. M. & Blackwood, D. H. R. (1991). Long-latency auditory event-related potentials in schziophrenia and in bipolar and unipolar affective disorder. *Psychological Medicine*, 21, 867-879.

Nathan, P. J., Segrave, R., Phan, K. L., O'Neill, B., & Croft, R. J. (2006). Direct evidence that acutely enhancing serotonin with the selective serotonin reuptake inhibitor citalopram modulates the loudness dependence of the auditory evoked potential (LDAEP) marker of central serotonin function. *Human Psychopharmacology*, *21*, 47-52.

Näätänen, R., & Gaillard, A. W. K. (1983). The orienting reflex and the N2 deflection of the event-related potential (ERP). In A.W. K. Gaillard & W. Ritter (Eds.), *Tutorials in ERP research: Endogenous components.* Amsterdam: North-Holland.

Naumann, E., Bartussek, D., Diedrich, O., & Laufer, M. (1992). Assessing cognitive and affective information processing functions of the brain by the means of the late positive complex of the event-related potential. *Journal of Psychophysiology*, 6, 285-298.

Neuhaus, A. H., Luborzewski, A., Rentzsch, J., Brakemeier, E. L., Opgen-Rhein, C., Gallinat, J., & Bajbouj, M. (2007). P300 is enhanced in responders to vagus nerve stimulation for treatment of major depressive disorder. *Journal of Affective Disorders,* 100, 123-128.

Nunez, P. (1981). *Electric fields of the brain.* New York: Oxford University Press.

Nunez, P.L., & Srinivasan, R. (2006). *Electric fields of the brain: The neurophysics of EEG.* New York: Oxford University Press.

Nurminen, M., Valkonen-Korhonen, M., Mervaala, E., Paakkonen, A., Partanen, J., Viinamaki, H., & Lehtonen, J. (2005). Enhanced attention-dependent auditory processing by electroconvulsive therapy in psychotic depression. *The Journal of ECT*, 21, 19-24.

Ochsner, K., & Gross, J. J. (2005). The cognitive control of emotion. *Trends in Cognitive Science,* 9, 242-249.

Ogura, C., Nageishi,Y., Omura, F., Fukao, K., Ohta, H., Kishimoto, A., & Matsubayashi, M. (1993). *Biological Psychiatry*, 33, 720-726.

Otto, M. W., Bruder, G. E., Fava, M., Delis, D. C., Quitkin, F. M., & Rosenbaum, J. F. (1994). Norms for depressed patients for the California Verbal Learning Test: associations with depression severity and self-report of cognitive difficulties. *Archives of Clinical Neuropsychology*, 9, 81-88.

Paige, S. R., Fitzpatrick, D. F., Kline, J. P., Balogh, S. E., & Hendricks, S. E. (1994). Event-related potential amplitude/intensity slopes predict response to antidepressants. *Neuropsychobiology*, *30*, 197-201.

Paige, S. R., Hendricks, S. E., Fitzpatrick, D. F., Balogh, S., & Burke, W. J. (1995). Amplitude/intensity functions of auditory event-related potentials predict responsiveness to bupropion in major depressive disorder. *Psychopharmacology Bulletin*, *31*, 243-248.

Palomba, D., Angrilli, A., & Mini, A. (1997). Visual evoked potentials, heart rate responses and memory to emotional pictorial stimuli. *International Journal of Psychophysiology*, 27, 55-67.

Pause, B. M., Miranda, A., Nysterud, M., & Ferstl, R. (2000). Olfactory and emotional stimulus evaluation in patients with major depression. *Zeitschrift für Klinische Psycholologie und Psycho-therapie*, 29, 16-23.

Pause, B. M., Raack, N., Sojka, B., Goder, R., Aldenhoff, J. B., & Ferstl, R. (2003). Convergent and divergent effects of odors and emotions in depression. *Psychophysiology,* 40, 209-225.

Perrin, F., Pernier, J., Bertrand, O., & Echallier, J.F. (1989). Spherical splines for scalp potential and current density mapping [Corrigenda EEG 02274, EEG Neurophysiol, 1990, 76, 565]. *Electroencephalography and Clinical Neurophysiology,* 72, 184-187.

Pierson, A., Ragot, R., Van Hooff, J., Partiot, A., Renault, B., & Jouvent, R. (1996). Heterogeneity of information-processing alterations according to dimensions of depression: An event-related potentials study. *Biological Psychiatry*, 40, 98-115.

Pizzagalli, D., Pascual-Marqui, R. D., Nitschke, J. B., Oakes, T. R., Larson, C. L., Abercrombie, H. C., Schaefer, S. M., Koger, J. V., Benca, R. M., & Davidson, R. J. (2001). Anterior cingulate activity as a predictor of degree of treatment response in major depression: Evidence from brain electrical tomography analysis. *American Journal of Psychiatry*, 158, 405-415.

Pizzagalli, D. A., Peccoralo, L. A., Davidson, R. J., & Cohen, J. D. (2006). Resting anterior cingulate activity and abnormal responses to errors in subjects with elevated depressive symptoms: A 128-channel EEG study. *Human Brain Mapping*, 27, 185-201.

Polich, J. (2007). Updating P300: An integrative theory of P3a and P3b. *Clinical Neurophysiology*, 118, 2128-2148.

Polich, J., & Criado, J. R. (2006). Neuropsychology and neuropharmacology of P3a and P3b. *International Journal of Psychophysiology*, 60, 172-185.

Polich, J., & Herbst, K.L. (2000). P300 as a clinical assay: rationale, evaluation, and findings. *International Journal of Psychophysiology*, 38, 3-19.

Porter, R. J., Gallagher, P., Thompson, J. M., & Young, A. H. (2003). Neurocognitive impairment in drug-free patients with major depressive disorder. *British Journal of Psychiatry*, 1 82, 214-220.

Post, R. M., DeLisi, L. E., Holcomb, H. H., Uhde, T. W., Cohen, R., & Buchsbaum, M. S. (1987). Glucose utilization in the temporal cortex of affectively ill patients: Positron emission tomography. *Biological Psychiatry*, 22, 545-553.

Purcell, R., Maruff, P., Kyrios, M., & Pantelis, C. (1997). Neuropsychological function in young patients with unipolar major depression. *Psychological Medicine*, 27, 1277-1285.

Röschke, J., & Wagner, P. (2003). A confirmatory study on the mechanisms behind reduced P300 waves in depression. *Neuropsychopharmacology*, 28, S9-S12.

Roth, W. T., Duncan, C. C., Pfefferbaum, A., & Timsit-Berthier, M. (1986). Applications of cognitive ERPs in psychiatric patients. In W.C. McCallum, R. Zappoli & F. Denoth (Eds.), *Cerebral Psychophysiology: Studies in Event-Related Potentials*, (Suppl. 38, pp. 419-438). Amsterdam: Elsevier.

Ruchsow, M., Grothe, J., Spitzer, M., & Keifer, M. (2002). Human anterior cingulate cortex is activated by negative feedback: evidence from event-related potentials in a guessing task. *Neuroscience Letters,* 325, 203-206.

Ruchsow, M., Herrnberger, B., Beschoner, P., Grön, G., Spitzer, M., & Kiefer, M. (2006). Error processing in major depressive disorder: evidence from event-related potentials. *Journal of Psychiatric Research*, 40, 37-46.

Ruchsow, M., Herrnberger, B., Beschoner, P., Gron, G., Spitzer, M., & Kiefer, M.Drevets, W. (2000). Neuroimaging studies of mood disorders. *Biological Psychiatry*, 48, 813-829.

Ruchsow, M., Herrnberger, B., Wiesend, C., Gron, G., Spitzer, M., & Kiefer, M. (2004). The effect of erroneous responses on response monitoring in patients with major depressive disorder: A study with event-related potentials. *Psychophysiology*, 41, 833-840.

Rugg, M. D., Roberts, R. C., Potter, D. D., Pickles, C. D., & Nagy, M. E. (1991). Event-related potentials related to recognition memory. Effects of unilateral temporal lobectomy and temporal lobe epilepsy. *Brain*, 114, (5), 2313-2332.

Sams, M., Alho, K., & Näätänen, R. (1983). Sequential effects on the ERP in discriminating two stimuli. *Biological Psychology*, 17, 41-58.

Sandman, C., Gerner, R., O'Halloran, J., & Isenhart, R. (1987). Event-related potentials and item recognition in depressed, schizophrenic and alcoholic patients. *International Journal of Pyschophysiology*, 5, 215-225.

Sandman, C. A., Vigor-Zierk, C. S., Isenhart, R., Wu, J., & Zetin, M. (1992). Cardiovascular phase relationships to the cortical event-related potential of schizophrenic, depresed and normal subjects. *Biological Psychiatry*, 32-778-789.

Santosh, P. J., Malhotra, S., Raghunathan, M., & Mehra, Y. N. (1994). A study of P300 in melancholic depression--correlation with psychotic features. *Biological Psychiatry*, *35*, 474-479.

Sapolsky, R. M. (2000). Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders.- *Archives of General Psychiatry*, 57, 925-935.

Sara, G., Gordon, E., Kraiuhin, C., Coyle, S., Howson, A., & Meares, R. (1994). The P300 ERP component: an index of cognitive dysfunction in depression? *Journal of Affective Disorders*, 31, 29-38.

Schlegel, S., Nieber, D., Herrmann, C., & Bakauski, E. (1991). Latencies of the P300 component of the auditory event-related potential in depression are related to the Bech-Rafaelsen Melancholia Scale but not to the Hamilton Rating Scale for Depression. *Acta Psychiatrica Scandinavica*, 83, 438-440.

Shah, P. J., Ebmeier, K. P., Glabus, M. F., & Goodwin, G. M. (1998). Cortical grey matter reductions associated with treatment-resistant chronic unipolar depression. Controlled magnetic resonance imaging study. *British Journal of Psychiatry*, 172, 527-532.

Shestyuk, A. Y., Deldin, P. J., Brand, J. E., & Deveney, C. M. (2005). Reduced sustained brain activity during processing of positive emotional stimuli in major depression. *Biological Psychiatry*, 57, 1089-1096.

Sidtis, J. J. (1981). The complex tone test: Implication for the assesment of auditory laterality effects. *Neuropsychologia*, 19, 103-112.

Siegle, G. J., Steinhauer, S. R., & Thase, M. E., (2004). Pupillary assessment and computational modeling of the Stroop task in depression. *International Journal of Psychophysiology*, 52, 63-76.

Simons, R., Graham, F., Miles, M., & Chen, X. (2001). On the relationship of P3a and the novelty-P3. *Biological Psychology*, 56, 207-218.

Smith, M. E., & Halgren, E. (1989). Dissociation of recognition memory components following temporal lobe lesions. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 15, 50-60.

Smith, M. E., Stapleton, J. M., & Halgren, E. (1986). Human medial temporal lobe potentials evoked in memory and language tasks. *Electroencephalography and Clinical Neurophysiology*, 63, 145-159.

Spencer, K., Dien, J., & Donchin, E. (1999). A componential analysis of the ERP elicited by novel events using a dense electrode array. *Psychophysiology*, 36, 409-414.

Steiner, J.E., Lidar-Lifschitz, D., & Perl, E. (1993). Taste and odor: Reactivity in depressive disorders, a multidisciplinary approach. *Perceptual and Motor Skills*, 77, 1331-1346.

Strobel, A., Debener, S., Schmidt, D., Hünnerkopf, R., Lesch, K. P., & Brocke, B. (2003). Allelic variation in serotonin transporter function associated with the intensity dependence of the auditory evoked potential. *American Journal of Medical Genetics,* 118B, 41-47.

Sumich, A. L., Kumari, V., Heasman, B. C., Gordon, E., & Brammer, M. (2006). Abnormal asymmetry of N200 and P300 event-related potentials in subclinical depression. *Journal of Affective Disorders*, 92, 171-183.

Tenke, C. E., Bruder, G. E., Towey, J. P., Leite, P., & Sidtis, J. J. (1993). Correspondence between brain ERP and behavioral asymmetries in a dichotic complex tone test. *Psychophysiology*, 30, 62-70.

Tenke, C. E., & Kayser, J. (2005). Reference-free quantification of EEG spectra: combining current source density (CSD) and frequency principal components analysis (fPCA). *Clinical Neurophysiology*, *116*, 2826-2846.

Tenke, C.E., & Kayser, J. (2008). ERP generators within the longitudinal fissure: Are putative inverses flawed? Program No. 872.28. 2008 Neuroscience Meeting Planner. Washington, DC: Society for Neuroscience, 2008. [Available at: http://psychophysiology.cpmc.columbia.edu/mmedia/sfn2008/sfn2008.pdf]

Tenke, C. E., Kayser, J., Fong, R., Leite, P., Towey, J. P., & Bruder, G. E. (1998). Response- and stimulus-related ERP asymmetries in a tonal oddball task: A Laplacian analysis. *Brain Topography*, *10*, 201-210.

Tenke, C. E., Kayser, J., Shankman, S. A., Griggs, C. B., Leite, P., Stewart, J. W., & Bruder, G. E. (2008). Hemispatial PCA dissociates temporal from parietal ERP generator patterns: CSD components in healthy adults and depressed patients during a dichotic oddball task. *International Journal of Psychophysiology,* 67*,* 1-16.

Tenke, C.E., Kayser, J., Stewart, J.W., Bruder, G.E. (in press). Novelty P3 reductions in depression: characterization using principal components analysis (PCA) of current source density (CSD) waveforms. *Psychophysiology.*

Tucker, D., Luu, P., Frishkoff, F., Quiring, J., & Poulsen, C. (2003). Frontolimbic response to negative feedback in clinical depression. *Journal of Abnormal Psychology*, 112, 667-678.

Turetsky, B. I., & Fein, G. (2002). Alpha2-noradrenergic effects on ERP and behavioral indices of auditory information processing. *Psychophysiology*, *39*, 147-157.

Tzur, G., & Berger, A. (2007). When things look wrong: theta activity in rule violation. *Neuropsychologia,* 45, 3122-3126.

Umbricht, D., Koller, R., Schmid, L., Skrabo, A., Grübel, C., Huber, T., & Stassen, H. (2003). How specific are deficits in mismatch negativity generation to schizophrenia? *BiologicalPsychiatry*, 53, 1120-1131.

Urretavizcaya, M., Moreno, I., Benlloch, L., Cardoner, N., Serrallonga, J., Menchon, J. M., & Vallejo, J. (2003). Auditory event-related potentials in 50 melancholic patients: Increased N100, N200 and P300 latencies and diminished P300 amplitude. *Journal of Affective Disorders*, 74, 293-297.

Wagner, P., Röschke, J., Fell, J., & Frank, C. (1997). Differential pathophysiological mechanisms of reduced P300 amplitude in schizophrenia and depression: a single trial analysis. *Schizophrenia Research*, 25(3), 221-229.

Van Veen, V., & Carter, C. (2002). The timing of action-monitoring processes in the anterior cingulate cortex. *Journal of Cognitive Neuroscience,* 14, 593-602.

Vandoolaeghe, E. van, Hunsel, F., Nuyten, D., & Maes, M. (1998). Auditory event related potentials in major depression: prolonged P300 latency and increased P200 amplitude. *Journal of Affective Disorders*, 48, 105-113.

Wang, C., Ulbert, I., Schomer, D.L., Marinkovic, K., & Halgren, E. (2005). Responses of human anterior cingulate cortex micro-domains to error detection, conflict monitoring, stimulus-response mapping, familiarity, and orienting. *Journal of Neuroscience*, 25, 604-613.

Yanai, I., Fujikawa, T., Osada, M., Yamawaki, S., & Touhouda, Y. (1997). Changes in auditory P300 in patients with major depression and silent cerebral infarction. *Journal of Affective Disorders,* 46, 263-271.

Zatorre, R. J., Evans, A. C., Meyer, E., & Gjedde, A. (1992). Lateralization of phonetic and pitch discrimination in speech processing. *Science*, 256, 846-849.

Zhang, Y., Hauser, U., Conty, C., Emrich, H. M., & Dietrich, D. E. (2007). Familial risk for depression and P3b component as a possible neurocognitive vulnerability marker. *Neuropschobiology*, 55, 14-20.