Dysfunction in early auditory processing in major depressive disorder revealed by combined MEG and EEG

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Background: Patients with major depressive disorder (MDD) show impairments in cognitive functions. However, neural mechanisms underlying these disturbances are poorly understood. We investigated whether MDD affects neural mechanisms of involuntary attention studied by auditory evoked potentials (AEPs) and auditory evoked magnetic fields (AEFs). **Methods:** AEPs and AEFs were studied in a passive odd-ball paradigm in 13 drug-free patients with unipolar MDD during an acute episode and 12 age- and sex-matched healthy subjects. Auditory responses to monaurally presented frequent "standard" tones, infrequent "deviant" tones (10% and 20% frequency change) and occasional "novel" sounds (complex sounds) were simultaneously recorded with whole-head magnetoencephalography (MEG) and electroencephalography (EEG). **Results:** P1 and P1*m* latencies were decreased in patients with MDD, compared with those in healthy subjects. Further, the mismatch negativity amplitude to the 10% frequency deviance in the EEG, but not in the MEG, was increased in MDD. We observed no differences in N1/N1*m* and P3a responses in the MEG and EEG. The magnitude of decrease in P1/P1*m* latency correlated negatively with the severity of depression in the patients. **Conclusions:** Early auditory processing is impaired in patients with MDD during an acute episode, probably reflecting dysfunctional frontotemporal neural circuits. These dysfunctions may contribute to the cognitive disturbances observed in people with MDD.

Contexte : Les patients atteints de trouble dépressif majeur (TDM) présentent des déficits au niveau des fonctions cognitives. On comprend toutefois mal les mécanismes nerveux qui sous-tendent ces déficits. Nous avons cherché à déterminer si le TDM a un effet sur les mécanismes nerveux de l'attention involontaire. Nous avons étudié à cette fin les potentiels évoqués auditifs (PEA) et les champs magnétiques évoqués auditifs (CMEA). **Méthodes :** On a étudié les PEA et les CMEA dans le cadre d'un paradigme irrégulier passif chez 13 patients qui ne prenaient pas de médicaments et avaient un TDM unipolaire au cours d'un épisode aigu et chez 12 sujets en santé jumelés selon l'âge et le sexe. On a enregistré simultanément par magnétoencéphalographie (MEG) de la tête au complet et électroencéphalographie (EEG) la réponse auditive à des tonalités «standards» fréquentes présentées de façon monaurale, à des tonalités «déviantes» peu fréquentes (changement de fréquence de 10 % et 20 %) et à des sons «nouveaux» occasionnels (sons complexes). **Résultats :** Les latences P1 et P1m ont diminué chez les patients qui avaient un TDM comparativement aux sujets en santé. De plus, l'amplitude de la négativité non jumelée face à la déviation de fréquence de 10 % dans l'EEG mais non dans la MEG a augmenté chez les sujets qui avaient un TDM. Nous n'avons observé aucune différence dans les réponses N1/N1m et P3a dans la MEG et l'EEG. Il y avait un lien négatif entre l'ordre de grandeur de la latence P1/P1m et la gravité de la dépressions chez les patients. **Conclusions :** Il y a déficit du début du traitement auditif chez les patents atteints de TDM au cours d'une crise aiguë, ce qui reflète probablement un dysfonctionnement des circuits nerveux frontotemporaux. Ces dysfonctionnements peuvent contribuer aux troubles de la cognition observés chez les personnes atteintes de TDM.

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Introduction

Patients with major depressive disorder (MDD) often complain of poor memory and inability to concentrate. Neuropsychological studies have revealed that patients with MDD exhibit disturbances in memory, attention and executive functions.[1–4] Dysfunctions in several brain areas, including the frontal and temporal cortices, have been shown to mediate these abnormalities.[5] However, neural mechanisms underlying these deficits and neural circuits responsible for these changes are poorly understood.

The neuronal bases of human sensory processing and cognition can be studied noninvasively with event-related potentials (ERPs) and event-related magnetic fields (ERFs), which are averaged electroencephalogram (EEG) or magnetoencephalogram (MEG) time-locked changes to external stimuli, respectively.[6,7] Both methods offer high-temporal resolution, but the localization of MEG brain sources is less complicated by the irregular distortions caused by the skull and tissue than is the EEG source localization. However, many brain responses relevant for studies on attention appear to be more evident in EEG than in MEG.[8–10] A combination of EEG and MEG can thus separate different sources contributing to the overall brain activity and provide complimentary information on the underlying neuronal processes.

The most common finding in MDD is the reduction of auditory P3 amplitude and the increase of P3 peak latency, which suggests that MDD affects neural mechanisms of active attention.[11–14] However, findings in these studies may be contaminated with motivational factors, because depressive patients often are not involved in the task required for P3 generation.

Neural mechanisms of passive attention can be studied with mismatch negativity (MMN) and its magnetic counterpart MMN*m*. MMN is elicited by infrequent deviants among frequent standard tones and has been proposed to reflect the preattentive detection of stimulus changes in the human auditory cortex, which triggers involuntary attention shifting toward the novel stimuli.[7] Motivational factors do not contaminate the measurement because MMN can be elicited without attentional efforts being suitable for studies of neural bases of involuntary attention in patients with depression. MMN amplitude was increased in healthy subjects after acute tryptophan depletion (ATD), which produced depressed mood.[15] MDD has been shown to modulate the intensity dependence function of the auditory N1 and N2 components in EEG, which precede and partially overlap MMN generation[16,17]; this suggests that early auditory processing might be impaired in people with MDD.

Auditory information is transmitted from each ear to both auditory cortices via 2 ascending neural pathways. The whole-head magnetometer is ideal for measuring parallel processing because it offers the ability to simultaneously measure the activity over both hemispheres.[9] Imaging studies have revealed hemispheric differences in patients with MDD[18]; however, their functional role is poorly understood.

We investigated whether, during an acute episode of the illness, drug-free patients with MDD have disturbances in sensory processing and preattentive change detection that are thought to initiate involuntary attention switching in the human brain.[7] This was studied in a passive odd-ball paradigm measured with combined high-resolution MEG and EEG. Second, we investigated whether parallel auditory processing is impaired in people with MDD.

Material and methods

Subjects

Thirteen right-handed outpatients (mean age 44, standard deviation [SD] 14, yr; 5 women) participated in the study. All subjects underwent a *Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID)*,[19] and all patients met the *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition, (DSM-IV)[20] criteria for an MDD episode. All patients had a score of at least 18 (mean 23.9, SD 4.1) on the 17-item Hamilton Depression Rating Scale[21] at the time of the study procedure. We evaluated the severity of anxiety symptoms with the Beck Anxiety Inventory (BAI; mean 30, SD 11.8).[22] Two patients also had an anxiety disorder, and 1 had panic attacks. All patients were in good physical health, as determined by a physical examination and laboratory evaluation (including a complete blood count and glucose, hepatic enzyme and renal and thyroid analyses). We excluded patients with a history of bipolar disorder, schizophrenia or alcohol or drug dependence within 5 years, or if they had significant suicidal ideation. Patients had no history of electroconvulsive therapy. Before study enrolment, patients were required to have taken no psychotropic medication for at least 2 weeks. Electromagnetic findings were compared with those in 12 aged-matched right-handed healthy comparison subjects (mean age 42, SD 12, yr; 5 women). The comparison subjects had no DSM-IV axis I diagnosis in the SCID evaluation,[19] and none had significant medical illnesses. All were free from psychotropic medication, and none had a history of central nervous system disease. The study was approved by an ethics committee at the Helsinki University Central Hospital; all subjects gave written informed consent before enrolling in the study.

Stimulus design and data acquisition

During the MEG and EEG recordings, each subject sat in a comfortable chair in a magnetically and electrically shielded room (Euroshield, Finland). The auditory evoked magnetic fields (AEFs) and auditory evoked potentials (AEPs) were recorded with a 306-channel MEG, consisting of 204 planar gradiometers and 102 magnetometers (Vectorview, Neuro-Mag, Finland) and a 60-channel EEG. Only gradiometers were used for the subsequent analysis. The subjects watched a silent video and were instructed to ignore the tones presented through a plastic tube and an earpiece. Subjects were presented with pure tones monaurally in a randomized order to the left ear. These included the standard tone (700 Hz with 50-ms duration, $p = 0.8$), 2 types of deviants (665 Hz, $p = 0.066$ "smaller deviant") and 560 Hz ($p = 0.066$ "larger deviant")

and novel sounds (p = 0.066; 10 different complex sound bursts in random order) at 60 dB above the individually determined subjective threshold. The interstimulus interval was 599 ms. Each 2-channel sensor unit measured 2 independent magnetic field gradient components, $\partial B_z/\partial x$ and $\partial B_z/\partial y$, the z-axis being normal to the local helmet surface. The position of the subject's head relative to the recording instrument was determined by measuring the magnetic fields produced by marker coils in relation to cardinal points on the head (nasion and left and right preauricular points). The position was determined before the experiment with an Isotrak 3D-digitizer (Polhemus, Colchester, Vt.).

AEPs were recorded with an electrode cap[23] and an amplifier[24] specifically designed and built for simultaneous EEG and MEG measurements. The nose electrode was used as a reference. Vertical and horizontal electrooculograms were recorded. The recording band-pass was 0.03–100 Hz for MEG, and the sampling rate was 397 Hz. Digital band-pass filtering was performed offline at 5–40 Hz for P1/P1*m*, 1–30 Hz for N1/N1*m* and 2–15 Hz for MMN/MMN*m* and P3a. The analysis period was 750 ms. First responses in the train, and all the epochs coinciding with EOG or MEG changes exceeding 150 μV or 3000 fT/cm, respectively, were omitted from averaging. At least 100 artifact-free standard and deviant responses were recorded and averaged. The distinct EPR/ERF peaks were obtained from latency ranges of 30–80 ms for P1/P1*m*, 50–150 ms for N1/N1*m*, 100–250 ms for MMN/MMN*m* and 250–500 ms for P3a. The responses were judged significant when they were 2 SDs larger than the prestimulus noise. MEG data from 1 patient were discarded for technical reasons. P1*m* and MMN*m* to smaller deviants from the ipsilateral hemisphere to the stimulated ear were not reliably detected from 2 patients and 1 control subject. The N1*m* of 1 patient from the ipsilateral hemisphere was not detected.

Data analysis

The sources of P1*m*, N1*m*, and MMN*m* were estimated with single equivalent current dipoles, found by a least squares fit of a fixed subset of 34 channels, separately, over each auditory cortex.[25] A spherical head model was used in the source modelling. Left monaural stimulation is known to elicit an MEG signal over both the right and left auditory cortices.[9] For EEG, the peak latencies of the different components were measured from the channel where a given deflection was largest. MMN and P3a (analyzed from responses to novel sounds) were determined from subtraction curves (deviant minus standard AEPs) at the electrode sites Fz or CFz. P1 and N1 was determined from standard responses at the Cz. The P1, N1, MMN and P3a amplitudes were determined from the averaged amplitude of 9 EEG channels (F1, Fz, F2, C1, Cz, C2, CP1, CPz, CP2).

Statistical analysis

Group differences in the MEG dipole strength were compared with a 2-way group (patients v. control subjects) by hemisphere (ipsilateral v. contralateral) repeated-measures analysis of variance (ANOVA). The group was the between–subjects and the hemisphere was the within–subjects repeated-measures variable. The EEG amplitudes were analyzed, using a group (patients v. control subjects) by electrode site (frontal v. central v. centroparietal) 2-way repeated-measures ANOVA. The group was the between–subjects and the electrode site was the within–subjects repeated-measures variable. We used the unpaired t test where appropriate and Bonferroni correction in multiple testing. We used Pearson's correlation to correlate the scores in the HDRS with MEG and EEG data. All tests were 2-sided. The results are expressed as mean and SD.

Results

Figure 1 shows the AEFs to standard tone in 1 healthy subject and 1 patient with depression. It also shows that the activity elicited by auditory stimuli was largest over the temporal pole. Table 1 summarizes the results of source modelling. ANOVA revealed a significant group main effect ($F_{1,19}$ = 14.6; p = 0.001) and a significant group-by-hemisphere interaction ($F_{1,19}$ = 11.3; p = 0.003) on P1*m* latencies. Patients with MDD showed shorter P1*m* latencies in the ipsilateral hemisphere to the stimulated ear, compared with healthy control subjects (t_{19} = –4.9, p = 0.005). No differences in dipole strengths of

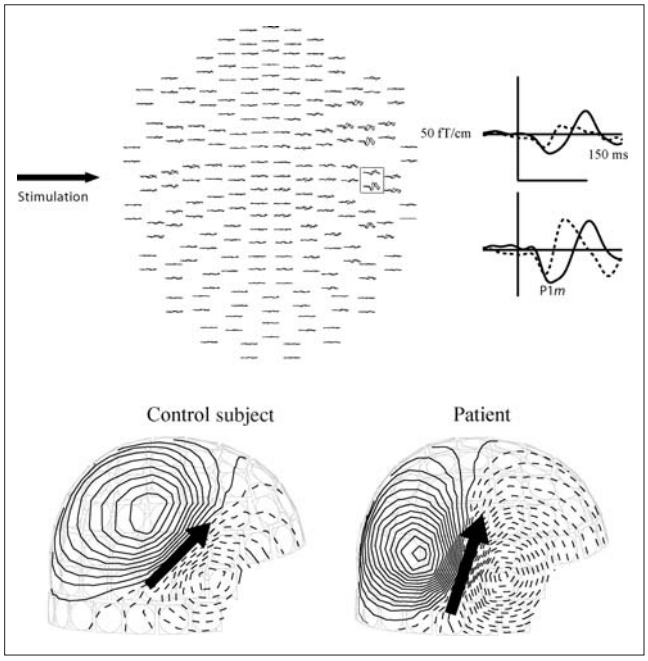

Fig. 1: (Top) auditory evoked magnetic field response to standard tone in healthy subjects (solid lines) and depressive patients (dotted lines) measured with a magnetometer. The stimuli were delivered to the left ear. The enlarged response presents the largest responses over the right temporal areas (contralateral to the ear stimulated). (Bottom) Contour maps at the peak of the P1*m*. Solid lines indicate where magnetic flux where it enters outside the head, and dotted lines indicate where magnetic flux exits within the head. Contour line separation is 10 ft. The arrows depict the strength and location of single equivalent current dipoles of P1*m* applied to data.

P1*m*, N1*m*, and MMN*m* or in latencies of N1*m* and MMN*m* were observed in patients with MDD when compared with healthy control subjects. Dipole locations were not different in patients, compared with healthy control subjects. P1*m* latencies at the contralateral hemisphere to the stimulated ear negatively correlated with the HDRS scores (Fig. 2; $r_{10} = -0.60$, $p = 0.04$) but not with the BAI scores.

Table 2 shows the results of AEPs. Figure 3 shows that the

Table 1: P1*m*, N1*m* MMN*m* source activities and latencies in subjects with major depressive disorder and in and healthy control subjects

	Group; mean (and SD)							
	With MDD				Control subjects			
	Source activity (nAm)		Latency, ms		Source activity (nAm)		Latency, ms	
Component	Contralateral hemisphere	Ipsilateral hemisphere	Contralateral hemisphere	Ipsilateral hemisphere	Contralateral hemisphere	Ipsilateral hemisphere	Contralateral hemisphere	Ipsilateral hemisphere
P1*m*	13 (7)	8 (4)	46 (10)	52 (7)*	11 (6)	7 (4)	49(8)	66 (6)
N1*m*	18 (10)	13 (7)	88 (14)	101 (12)	15 (10)	11 (8)	97 (14)	107 (20)
MMN*m* (smaller deviant)	22 (17)	20 (12)	157 (24)	167 (27)	17 (8)	15(8)	143 (27)	154 (31)
MMN*m* (larger deviant)	23 (17)	20 (12)	186 (30)	188 (32)	16 (8)	15 (18)	171 (32)	178 (29)

MMNm = the negative counterpart of mismatch negativity; SD = standard deviation; MDD = major depressive disorder; nAm = nano ampere meter.
*Unpaired *t* test between subjects with MDD and control subjects, $p < 0.01$.

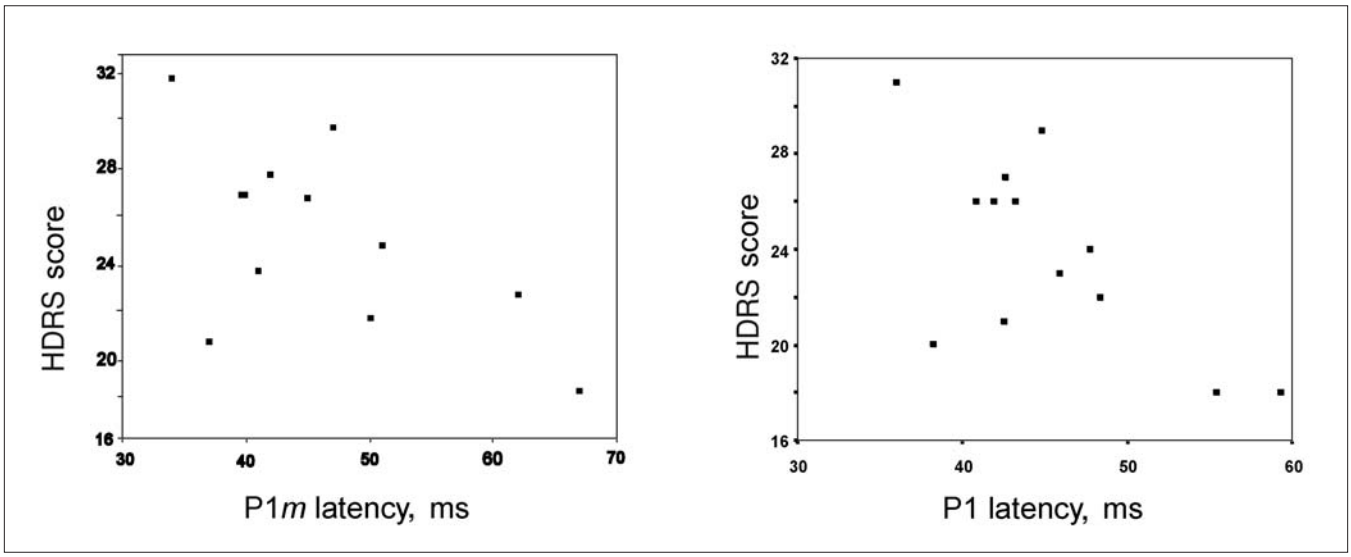

Fig. 2: Relation between P1*m* (left) and P1 latencies (right) and severity of depression, as measured by the Hamilton Depression Rating Scale (HDRS).

Table 2: P1, N1, MMN, and P3a amplitudes and latencies in MDD and healthy control subjects

	Group; mean (and SD)							
	Depression				Control			
	Amplitude, μV				Amplitude, μV			
Component	Frontal	Central	Centroparietal	Latency, ms	Frontal	Central	Centroparietal	Latency, ms
P1	1.3 (0.6)	1.5 (0.7)	0.6 (0.4)	45 (7)*	0.7 (0.9)	1.3 (0.5)	1.0 (0.5)	53 (7)
N1	–1.2 (1.3)	–2.0 (1.1)	–0.9 (0.89)	93 (10)	–1.2 (1.0)	–1.8 (1.2)	–0.7 (0.5)	101 (11)
MMN to smaller deviant	–2.5 (2.0)	–2.4 (1.8)	–1.0 (0.9)	181 (39)	–1.2 (1.0)	–1.6 (1.1)	–0.9 (0.6)	154 (37)
MMN to larger deviant	–2.6 (3.2)	–3.2 (1.5)	–1.3 (1.4)	167 (30)	–2.3 (1.1)	–3.8 (3.5)	–1.6 (2.9)	166 (35)
P3a	3.0 (1.9)	5.8 (2.0)	3.5 (1.7)	274 (26)	2.0 (3.7)	5.0 (2.9)	2.7 (2.6)	292 (46)

MMN = mismatch negativity; MDD = major depression disorder; SD = standard deviation.
*Unpaired *t* test between subjects with depression and control subjects, $p < 0.01$.

regions of high-amplitude MMN responses after smaller deviant tones (but not after larger deviant and novel tones) are much larger in patients with depression, compared with healthy subjects. P1 latencies at the Cz electrode were significantly shorter in patients with MDD compared with control subjects (t_{23} = –2.9, p = 0.008). ANOVA showed significant electrode–group interaction on MMN amplitude after presenting a smaller deviant ($F_{2,46}$ = 4.01; p = 0.025), but not after presenting a larger deviant. No differences in P3a amplitudes or latencies were observed. P1 latencies (but not MMN amplitudes) negatively correlated with the scores of the HDRS (Fig. 2; r_{11} = –0.67, p = 0.01). P1 latencies and MMN amplitudes did not correlate with the BAI scores.

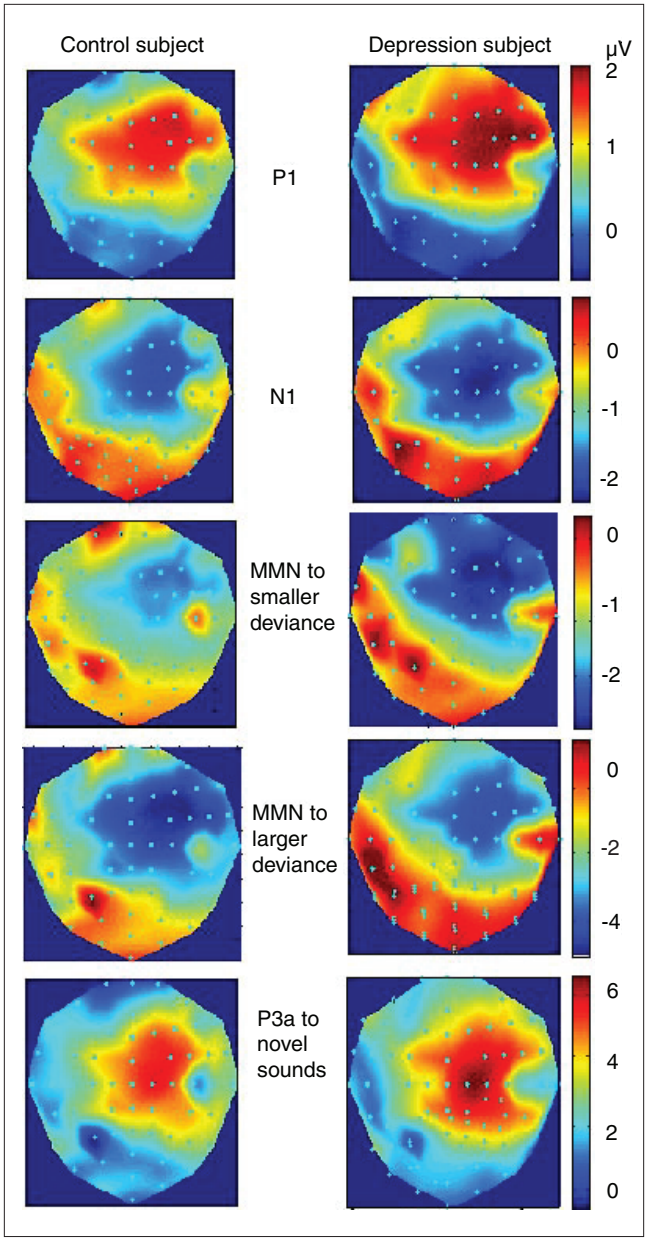

Fig. 3: Grand-averaged potential maps at the peak latency of the P1, N1, mismatch negativity (MMN) and P3a. Uppermost positions = frontal electrodes; lowermost positions = occipital electrodes. Blue dots indicate the locations of electrodes.

Discussion

The main findings in this study were that drug-free acutely ill patients with MDD showed shorter P1*m* latencies at the ipsilateral auditory cortex to the ear stimulated and shorter P1 latencies, which were accompanied by increased MMN to a smaller deviant in EEG. We observed a linear relation between P1 latency in the MEG and EEG in the HDRS scores. Thus, the more severe the patient's depression, the less the P1/P1*m* latency. The MMN increase was present in EEG but not in MEG. Because MMN*m* is thought to reflect a source identical to the auditory-cortex component of the MMN, it is possible that the increased amplitude reflects changes predominantly in the frontal MMN subcomponent. Finally, N1/N1*m* presumed to be a brain correlate of sound detection,[26] and P3a, probably reflecting the attention shifting,[27] were not significantly affected in this study. Our findings of unaltered N1/N1*m* contradict those of Urretavizcaya and colleagues,[14] who found increased N1 latencies in patients with severe MDD. However, our results agree with those of Sara and others.[28] Differences in stimulation paradigms and patient populations (a larger sample size could more reliably detect small differences in AEPs and AEFs in our study) may partly explain these discrepancies.

The detection of a sound change is proposed first to elicit the temporal MMN subcomponent; the subsequent involuntary attention shift to this sound change is probably reflected by the later frontal MMN subcomponent.[7,29,30] The frontal subcomponent might be radially oriented, judging from the fact that it is not detected by MEG.[30] This prefrontal mechanism might be part of top-down modulation of the deviance detection system in the brain. In our study, MMN amplitudes were increased in the EEG of patients with MDD but not in the MEG, which suggests that frontal MMN components were primarily affected. There is increasing evidence from different neuroimaging studies that the frontal MMN generator is located in the right prefrontal cortex independent of the stimulated ear (Paavilainen et al,[31] Opitz et al,[32] Doeller et al,[33] Molholm et al[34]). Interestingly, several studies have shown that the right prefrontal cortex is involved in mood regulation in healthy subjects and in patients with MDD.[35] Consistent with the limbic-cortical model, imaging studies in patients with unipolar depression have consistently found decreased frontal volumes and functioning.[29] This includes decreased glucose metabolism and cerebral blood flow in the dorsolateral prefrontal cortex. These changes are linked to the impairments of cognition that are observed in depression.[36]

The functional role of the frontal MMN is not yet fully understood. It has been suggested that this subcomponent reflects initiation of involuntary attention shifting.[27,37] Alternatively, the frontal MMN subcomponent could reflect an enhancing mechanism for stimulus changes that are small and difficult to detect.[32,33] Our data suggest that this frontal system could be impaired in acutely ill MDD patients. Because the MMN did not change in remitted patients with MDD,[38] the

observed neurophysiological abnormalities could be specifically associated with the acute MDD episode.

The present results indicated that preattentive parallel auditory processing in the auditory cortex, as reflected by changes in P50*m* latencies, was accelerated in the ipsilateral hemisphere. In humans, auditory information is transmitted from each ear to both auditory cortices via 2 ascending neural pathways. The major proportion of fibres crosses the midline in the brainstem and reaches the contralateral auditory cortex, while a smaller proportion of fibres ascends to the ipsilateral auditory cortex.[39] It cannot be excluded that these fibres are more vulnerable in patients with MDD. Another explanation may be that the left hemisphere is functionally affected due to alterations in other brain areas.[29]

Increased MMN amplitudes and decreased P1/P1*m* latencies detected in patients with MDD could reflect reduced inhibition and increased excitability of cortical neurons responsible for the regulation of involuntary attention. Our findings are in line with those of Tollkötter and colleagues,[40] who showed altered auditory perception and missing habituation with MEG in patients with depression. Observed patterns of MMN change were similar to those obtained in healthy volunteers after ATD, a procedure known to decrease serotonin synthesis in the brain.[15,41] Further, another study during a dichotic listening task showed that ATD abolished the P50 increase induced by a dichotic listening task.[10] These findings are in line with the results of Yamashita and others,[42] which showed that negatively (but not positively) charged visual stimuli affected early auditory processing at the same time range indexed by P50*m* suppression. Taken together, these studies suggest that deficiency in the serotonin metabolism observed in MDD[43] may disrupt brain inhibitory mechanisms during the acute phase of the illness, regulating early sensory and attentional processing. However, there is also evidence that other neurotransmitters (e.g., NMDA [*N*-methyl-D-aspartate]-receptor mediated glutamate and dopamine, play an important role in the generation of MMN).[44,45] Understanding the mechanisms responsible for augmentation of MMN and shortened P1/P1*m* latencies requires careful studies of transmitter systems and the neural structures involved in neural bases of involuntary attention in MDD.

In conclusion, this study showed that patients with MDD have deficits in early auditory processing that are indexed by accelerated P1/P1*m* and increased MMN amplitudes. The magnitude of increase in P1/P1*m* latency predicted the severity of depression in the patients. These impairments may be mediated by serotonin, which reduces inhibition and increases excitability of cortical neurons responsible for regulating involuntary attention. Dysfunctional early auditory processing in MDD may be mediated through the frontotemporal neural circuit.

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References

1. Austin M-P, Mitchell P, Goodwin GM. Cognitive deficits in depression: possible implications for functional neuropathology. *Br J Psychiatry* 2001;178:200-6.
2. Burt DB, Zembar MJ, Niederehe G. Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychol Bull* 1995;117:285-305.
3. Shenal BV, Harrison DW, Demaree HA. The neuropsychology of depression: a literature review and preliminary model. *Neuropsychol Rev* 2003;13:33-42.
4. Veiel HOF. A preliminary profile of neuropsychological deficits associated with major depression. *J Clin Exp Neuropsychol* 1997;19:587-603.
5. Ottowitz WE, Dougherty DD, Savage CR. The neural network basis for abnormalities of attention and executive function in major depressive disorder: implications for application of the medical disease model to psychiatric disorders. *Harv Rev Psychiatry* 2002;10:86-99.
6. Hari R, Lounasmaa OV. Recording and interpretation of cerebral magnetic fields. *Science* 1989;244:432-6.
7. Näätänen R. *Attention and brain function.* Hillsdale (NJ): Erlbaum; 1992. p. 495.
8. Näätänen R, Ilmoniemi R, Alho K. Magnetoencephalography in studies of human cognitive brain function. *Trends Neurosci* 1994; 17:389-95.
9. Kähkönen S, Ahveninen J, Jääskeläinen IP, et al. Effects of haloperidol on selective attention, a combined whole-head MEG and high-resolution EEG study. *Neuropsychopharmacology* 2001;25: 498-504.
10. Ahveninen J, Jääskeläinen IP, Pennanen S, et al. Auditory selective attention modulated by tryptophan depletion in humans. *Neurosci Lett* 2003;340:181-4.
11. Vandoolaeghe E, van Hunsel F, Nuyten D, et al. Auditory event related potentials in major depression: prolonged P300 latency and increased P200 amplitude. *J Affect Disord* 1998;48:105-13.
12. Houston RJ, Bauer LO, Hesselbrock VM. Depression and familial risk for substance dependence: a P300 study of young women. *Psychiatry Res* 2003;124:49-62.
13. Roschke J, Wagner P. A confirmatory study on the mechanisms behind reduced P300 waves in depression. *Neuropsychopharmacology* 2003;28(Suppl 1):S9-12.
14. Urretavizcaya M, Moreno I, Benlloch L, et al. Auditory event-related potentials in 50 melancholic patients: increased N100, N200 and P300 latencies and diminished P300 amplitude. *J Affect Disord* 2003;74:293-7.
15. Kähkönen S, Mäkinen V, Jääskeläinen IP, et al. Serotonergic modulation of mismatch negativity. *Psychiatry Res* 2005;138:61-74.
16. el Massioui F, Everett J, Martin MT, et al. Attention deficits in depression, an electrophysiological marker. *Neuroreport* 1996;7:2483-6.
17. Hegerl U, Gallinat J, Juckel G. Event-related potentials. Do they reflect central serotonergic neurotransmission and do they predict clinical response to serotonin agonists? *J Affect Disord* 2001;62:93-100.
18. Drevets WC. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Curr Opin Neurobiol* 2001;11:240-9.
19. First MB, Spitzer RL, Williams JBW, et al. *Structured clinical interview for DSM-IV-patient edition (SCID-P).* Washington: American Psychiatric Press; 1994.
20. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders.* 4th ed. Washington: The Association; 1994.
21. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62.
22. Beck AT, Epstein N, Brown G, et al. An inventory for measuring

clinical anxiety: Psychometric properties. *J Consult Clin Psychol* 1988;56:893-7.

23. Virtanen J, Rinne T, Ilmoniemi RJ, et al. MEG-compatible multichannel EEG electrode array. *Electroencephalogr Clin Neurophysiol* 1996;99:568-70.
24. Virtanen J, Parkkonen L, Ilmoniemi RJ, et al. Biopotential amplifier for simultaneous operation with biomagnetic instruments. *Med Biol Eng Comput* 1997;35:402-8.
25. Hämäläinen M, Hari R, Ilmoniemi RJ, et al. Magnetoencephalography–theory, instrumentation, and applications to noninvasive studies of working brain. *Rev Mod Phys* 1993;65:413-98.
26. Parasuraman R, Beatty J. Brain events underlying detection and recognition of weak sensory signals. *Science* 1980;210:80-3.
27. Escera C, Alho K, Winkler I, et al. Neural mechanisms of involuntary attention to acoustic novelty and change. *J Cogn Neurosci* 1998;10:590-604.
28. Sara G, Gordon E, Kraiuhin C, et al. The P300 ERP component: an index of cognitive dysfunction in depression? *J Affect Disord* 1994;31:29-38.
29. Alho K. Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNm) elicited by sound changes. *Ear Hear* 1995;16:38-51.
30. Rinne T, Alho K, Ilmoniemi RJ, et al. Separate time behaviors of the temporal and frontal MNN sources. *Neuroimage* 2000;12:14-9.
31. Paavilainen P, Alho K, Reinikainen K, et al. Right hemisphere dominance of different mismatch negativities. *Electroencephalogr Clin Neurophysiol* 1991;78:466-79.
32. Opitz B, Rinne T, Mecklinger A, et al. Differential contribution of frontal and temporal cortices to auditory change detection: fMRI and ERP results. *Neuroimage* 2002;15:167-74.
33. Doeller CF, Opitz B, Mecklinger A, et al. Prefrontal cortex involvement in preattentive auditory deviance detection: neuroimaging and electrophysiological evidence. *Neuroimage* 2003;20:1270-82.
34. Molholm S, Martinez A, Ritter W, et al. The neural circuitry of preattentive auditory change-detection: an fMRI study of pitch and duration mismatch negativity generators. *Cereb Cortex* 2005;15:545-51.
35. Liotti M, Mayberg HS. The role of functional neuroimaging in the neuropsychology of depression. *J Clin Exp Neuropsychol* 2001;23:121-36.
36. Mayberg HS, Liotti M, Brannan SK, et al. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am J Psychiatry* 1999;156:675-82.
37. Schröger E, Wolff C. Attentional orienting and reorienting is indicated by human event-related brain potentials. *Neuroreport* 1998;9:3355-8.
38. Umbricht D, Koller R, Schmid L, et al. How specific are deficits in mismatch negativity generation to schizophrenia? *Biol Psychiatry* 2003;53:1120-31.
39. Kelly JP. Hearing. In: Kandel ER, Schwartz JH, Jessell TM, editors. *Principles of neural science*. New York: Elsevier; 1991. p. 481-99.
40. Tollkötter M, Pfleiderer B, Soros P, et al. Effects of antidepressive therapy on auditory processing in severely depressed patients: a combined MRS and MEG study. *J Psychiatr Res* 2006;40:293-306.
41. Nishizawa S, Benkelfat C, Young SN, et al. Differences between males and females in rates of serotonin synthesis in human brain. *Proc Natl Acad Sci U S A* 1997;94:5308-13.
42. Yamashita H, Okamoto Y, Morinobu S, et al. Visual emotional stimuli modulate auditory sensory gating studied by magnetic P50 suppression. *Eur Arch Psychiatry Clin Neurosci* 2005;255:99-103.
43. Maes M, Melzer HY. The serotonin hypothesis of major depression. In: Bloom FE, Kupfer D, editors. *Psychopharmacology: the fourth generation of progress*. New York: Raven Press; 1995. p. 933-44.
44. Umbricht D, Schmid L, Koller R, et al. Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: implications for models of cognitive deficits in schizophrenia. *Arch Gen Psychiatry* 2000;57:1139-47.
45. Kähkönen S, Ahveninen J. Combination of magneto- and electroenceplalography in studies of monoamine modulation on attention. *Methods Find Exp Clin Pharmacol* 2002;24:27-34.