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Brain Responses to Sound Intensity Changes Dissociate Depressed Participants and Healthy Controls

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Highlights

- ERPs to sound intensity changes dissociate depressed participants from controls
- N1 amplitude was enlarged which may reflect cortical over-excitability
- ERPs to intensity changes have potential as a future diagnostic tool for depression

ABSTRACT

Depression is associated with bias in emotional information processing, but less is known about the processing of neutral sensory stimuli. Of particular interest is processing of sound intensity which is suggested to indicate central serotonergic function. We tested weather event-related brain potentials (ERPs) to occasional changes in sound intensity can dissociate first-episode depressed, recurrent depressed and healthy control participants. The first-episode depressed showed larger N1 amplitude to deviant sounds compared to recurrent depression group and control participants. In addition, both depression groups, but not the control group, showed larger N1 amplitude to deviant than standard sounds. Whether these manifestations of sensory over-excitability in depression are directly related to the serotonergic neurotransmission requires further research. The method based on ERPs to sound intensity change is fast and low-cost way to objectively measure brain activation and holds promise as a future diagnostic tool.

Keywords: Depression, ERP, MMN, N1, pre-attentive processing, sound intensity

1. Introduction

Cognitive theories of depression have proposed that depression is associated with bias in information processing leading to selective attention to the negative aspects of experiences (Beck, 1967; Beck, 2008). This information processing bias is suggested to be automatic, rapid and involuntary (Beck, 2008). Many empirical studies give support for this theory by showing, for example, that depressed individuals have difficulty in disengaging from emotionally negative information and they show reduced inhibition of irrelevant emotional information (for a review, see Gotlib & Joormann, 2010). However, recent electrophysiological studies using event-related potentials (ERPs) suggest that depression-related bias in information processing is not restricted to emotional stimuli but can also be seen in the processing of basic sensory information (e.g. Chang et al., 2011; Kähkönen et al., 2007).

Auditory processing in depression has been under investigation because the primary auditory cortex is known to receive widespread projections from neurons using serotonin (Hegerl, Gallinat, & Juckel, 2001), a neurotransmitter that is closely associated with depression (Coppen, 1967; Leonard, 2000; Maes & Meltzer, 1995). A specific feature of auditory stimulus encoding, namely the intensity dependence of auditory evoked potentials (AEPs) may be relevant for depression, because it is suggested to reflect central serotonergic function (Hegerl et al., 2001; Hegerl & Juckel, 1993; Juckel, Hegerl, Molnár, Csépe, & Karmos, 1999; Juckel, Molnnár, Hegerl, Csépe, & Karmos, 1997; Strobel et al., 2003; Wutzler et al., 2008). Intensity dependence refers to a phenomenon where auditory responses increase when the intensity of an auditory stimulus increases (Hegerl et al., 2001). This reactivity can be seen when measuring early auditory evoked responses such as the N1. The

N1 is an automatic response elicited in the auditory cortex at approximately 100 ms after the stimulus onset, and reflects stimulus encoding (Näätänen, 1990). Intensity dependence is measured in experimental designs where sinusoidal sound stimuli of different intensities are presented in a random order. There are considerable individual differences in the strength of intensity dependence (Hegerl et al., 2001). Some individuals show a steeper increase in N1 responses to increases in stimulus intensity while others show only weak intensity dependence. Studies have linked strong intensity dependence to low serotonergic activity while weak intensity dependence (only a small increase in amplitude in response to an increase in stimulus intensity) reflects high serotonergic activity (Hegerl et al., 2001; Hegerl & Juckel, 1993; Juckel et al., 1997). However the link between intensity dependence and serotonergic system is mainly based on animal studies and also other neurotransmitters, such as dopamine, have been suggested to modulate the intensity dependence of AEPs (Bruneau, Barthelemy, Jouve, & Lelord, 1986; Juckel et al., 2008, 1997; I. Lee et al., 2011; O'Neill, Croft, & Nathan, 2008; Strobel et al., 2003). However studies with depressed participants have shown that individuals with strong intensity dependence have better treatment response with SSRI medications (selective serotonin reuptake inhibitors) compared to those with weaker intensity dependence (e.g. Gallinat et al., 2000; Jaworska et al, 2013; Juckel et al., 2007; B. Lee, Park, Lee, & Shim, 2015; T.-W. Lee, Yu, Chen, & Tsai, 2005).

Another auditory ERP-component that has been studied in depression is the mismatch negativity (MMN). MMN, an indicator of automatic change detection, is elicited by the temporofrontal network (Alain, Woods, & Knight, 1998) in response to a rarely presented deviant sound interspersed with frequently presented standard tones (Näätänen, Gaillard, & Mäntysalo, 1978). Alterations in MMN response are seen in many neuropsychiatric conditions, and they are thought to reflect cognitive decline or dysfunction

(for a review, see Näätänen et al., 2011). Studies on depression have shown mixed results; some studies have reported decreased MMN response to duration and frequency changes in sound in the depressed group compared to the controls (Chen et al., 2015; Naismith et al., 2012; Qiao et al., 2013; Takei et al., 2009 for a negative result see Umbricht et al., 2003) while others have demonstrated increased MMN responses to frequency changes in individuals with depression (He et al., 2010; Kähkönen et al., 2007; Restuccia, Vollono, Scaloni, Buccelletti, & Camardese, 2015). The conflict in these findings could be explained by differences in depressed populations or in experimental designs employing changes in frequency or duration. However, to our knowledge intensity-MMN has not been previously studied, which is surprising since intensity dependency is associated with the serotonergic system affected in depression (Hegerl et al., 2001; Hegerl & Juckel, 1993; Juckel et al., 1997). However, Restuccia et al. (2015) compared the frequency-MMN between depressed and healthy controls in high- and low-intensity conditions. The MMN was increased in depressed patients compared to controls only when high-intensity stimuli were applied. This phenomenon is in line with the previously referenced intensity dependence studies that show larger responses to increasing stimulus intensities in a subgroup of individuals with depression (Gallinat et al., 2000; Hegerl et al., 2001; Jaworska et al., 2013; Juckel et al., 2007; B. Lee et al., 2015; T.-W. Lee et al., 2005). Also in those MMN studies that used relatively high-intensity stimuli (60 dB above hearing threshold, or 80 dB), the MMN response increased in depressed participants compared to the controls (He et al., 2010; Kähkönen et al., 2007). Together these results hint that depressed individuals have sensory system that is particularly sensitive to high-intensity sounds. However, it is not clear whether brain responses to sound intensity as such or the change detection process is affected in depressed.

To this end, the present study capitalizes on previous findings on the intensity dependency of auditory evoked potentials (Gallinat et al., 2000; Hegerl et al., 2001; Jaworska et al., 2013; Juckel et al., 2007; B. Lee et al., 2015; T.-W. Lee et al., 2005) and those on auditory change detection (He et al., 2010; Kähkönen et al., 2007; Restuccia et al., 2015). Namely, we will measure automatic ERP responses, N1 and MMN, to rare changes in intensity in depressed and control participants

We will compare the processing of intensity change between controls and participants with different depression diagnosis, namely first-episode depression and recurrent depression. Earlier studies have shown that compared to first-episode depression recurrent depression is associated with more severe cognitive dysfunction (see for example Chen et al., 2013; Fossati et al., 2004; Talarowska, Zajaczkowska, & Galecki, 2015) as well as more pronounced alterations in the structural (review McKinnon, Yucel, Nazarov, & MacQueen, 2009) and metabolic function (de Diego-Adeliño et al., 2013) within the hippocampus. However, there is only one ERP study comparing auditory change detection in first-episode and recurrent depression patients (Chen et al., 2015). In this study no differences between depression groups were found in MMN response to duration deviant sounds. Here we assumed that intensity deviant sounds presented in oddball condition would be particularly sensitive to depression-related dysfunction in sensory encoding and automatic change detection. Based on earlier intensity dependence studies on N1 (Gallinat et al., 2000; Hegerl et al., 2001; Jaworska et al., 2013; Juckel et al., 2007; B. Lee et al., 2015; T.-W. Lee et al., 2005) and MMN-studies that used frequency deviant sounds but with high sound intensities (He et al., 2010; Kähkönen et al., 2007; Restuccia et al., 2015) we hypothesize that there will be increased N1 and MMN response amplitude in depressives compared to controls. However, we cannot predict whether the ERP effects will differentiate both the first-

episode depression and recurrent depression groups from the control group or just one of the depression groups from the control group.

2. Methods and materials

2.1 Participants

The participants were a group of volunteers recruited with announcements in a local newspaper and via e-mail lists at the University of Jyväskylä. A written informed consent was obtained from the participants before their participation. The experiment was undertaken in accordance with the Declaration of Helsinki. The ethical committee of the University of Jyväskylä approved the research protocol.

The inclusion criteria for all participants were: aged 18-64 years, self-reported normal or corrected-to-normal vision, normal hearing, and right-handedness. The exclusion criteria for both depressive and healthy participants were an anamnesis of any neurological condition such as brain injury, epilepsy, migraine, or sleep apnea. The exclusion criteria for depressed participants also included depression with psychotic features and diagnoses of a psychiatric disorder other than depression, such as substance abuse or addiction within the past year, schizophrenia or other psychotic disorders or bipolar disorders. The information related to inclusion and exclusion criteria was collected with a questionnaire and was also confirmed in a psychiatric interview (see below). In the questionnaire the participants were asked about previous psychiatric diagnoses related to depression or other psychiatric disorders (what was the diagnosis, when diagnosed and in which health care institute). Three participants with self-reported previous psychiatric diagnoses other than depression were included to the sample: one with undefined anxiety disorder, one with anorexia nervosa and one with unclear diagnosis. The exclusion criterion for the control participants also included anamnesis of any psychiatric diagnosis and a mean score of more than 10 in the Beck Depression Inventory-II (BDI-II, Beck, Steer, & Brown, 1996).

Forty-three participants with depressive symptoms (15 males) and 22 healthy controls (eight males) volunteered to participate in the experiment. After this, the data of two depressed and one control participant were omitted due to excessive artefacts in the ERP recording. The mean age of the depressed participants was 42.8 (*SD* 11.2) years, ranging between 18-64 years. The mean age for the controls was 39.0 (*SD* 11.9) years, ranging between 21-64 years. There was no significant difference in age, $t(60) = 1.25$, $p = .217$, or gender, $x^2(1) = 0.95$, $p = .758$, between the depressed and non-depressed group. In the depression group, the mean score of the BDI-II self-report questionnaire was 23 (*SD* 8.48) and the range was 3-43. Two participants had low BDI-II scores (under 5 points), but they were included in the study because they were diagnosed as depressed in a psychiatric interview (see below). In the control group, the mean score in the BDI-II was 2.8 (*SD* 3.21, range 0-10).

A psychiatric interview, administered by a physician independent of the study, was used to establish the eligibility of participants of the depressed group and to examine the diagnostic status and other background information of them. The diagnosis of depression was based on the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10, World Health Organization, 2005) criteria and the information available from the interviewee. The diagnostic interview applied was the same that is commonly used in primary health care in Finland for diagnosing depression (structured interview based on ICD-10 criteria). The depression symptoms included in ICD-10 definition of depression, were carefully gone through with a structured interview. The comorbidity was assessed by asking the participant about other psychiatric symptoms and previous diagnoses. However, the interview did not contain detailed questions on symptoms related to other psychiatric disorders than depression and therefore it was not possible to conduct a comprehensive

differential diagnosis. It is thus possible that some participants could have had comorbid psychiatric disorders along with depression.

Eleven participants met the criteria for mild depression (*F*32.0), and two participants were diagnosed with a mild dysthymic disorder (*F*34.1). Fifteen participants were diagnosed with a recurrent depressive disorder with a mild current episode (*F*.33.0). Five participants met the criteria for moderate depression (*F*32.1), and eight participants were diagnosed with a recurrent depressive disorder with a moderate current episode (*F*33.1). Seventeen of 41 depressed participants used antidepressant medication during the study. If in the psychiatric interview or the other phases of the study concern about the participant's risk for suicide was raised, the participant was asked to contact the professionals in the local health care center, and they were provided with the contact information.

For the data analysis, the participants were further divided into healthy control group (CTRL-group; $n = 21$), first-episode depression (FE-dep; $n = 16$) and recurrent-episode depression group (REC-dep; $n = 25$). The two participants with a mild dysthymic disorder were included in the REC-dep group because they had experienced continuous long-term depression. In FE-dep group there was one depressed participant with previous diagnosis of anorexia nervosa. In REC-dep group there were two depressed participants with previous psychiatric diagnoses: one with undefined anxiety disorder and the other with unclear diagnosis. There were no significant differences in one-way ANOVA, $F(2,59) = 0.97$, in age between the FE-dep and CTRL-group, $p = 1.000$, or between the FE-dep and REC-dep group, $p = 1.000$, or between the REC-dep and CTRL-group, $p = .510$. The three groups did not differ in number of male and female participants, $x^2(1) = 1.08$, $p = .562$.

Further, the two depression groups did not differ significantly in medication status, $x^2(1) = 1.13$, $p = .288$ or depression severity (mild or moderate), $x^2(1) = 0.003$, $p = .960$. The

difference between BDI-II scores, $t(38) = 2.02$, $p = .050$ was marginally significant. To assess anxiety symptoms in the depressed group the participants were asked to fill the DASS questionnaire (Depression, anxiety, stress scales; Lovibond & Lovibond, 1995) and the anxiety subscale was calculated from it. There was no difference between FE-dep and REC-dep group in DASS-anxiety scores $t(38) = -0.46$, $p = .648$. See further details in Table 1.

2.2 Procedure

During the ERP experiment, the participants sat in a comfortable chair in a dimly-lit room. They were instructed to watch a movie and ignore the sounds that were presented from a loud speaker situated above them. Each participant was monitored during the ERP recordings via a video camera positioned on top of the screen.

2.3 Stimuli

During the brain activity measurement, sinusoidal sounds of 1000 Hz in frequency, and 50 ms (5-ms onset and offset ramps) in duration were presented. The experiment consisted of two different stimulus blocks whose order was counterbalanced across the participants. In the high-intensity condition, the standard sound was 60 dB (sound pressure level, SPL) and the deviant sound was 80 dB (SPL). In the low-intensity condition, the intensities between the standards and deviants were reversed. Standard and deviant sounds were presented pseudo-randomly with the restriction that no less than two standard sounds would occur between consecutive deviants. The stimulus-onset asynchrony (SOA) in the stimulus presentation was randomly set at 400, 450, or 500 ms. In each of the stimulus

blocks, there were 50 deviant sounds among 450 standard sounds (the probability for the deviant sound was 10%).

The stimulus presentation was controlled with E-Prime 2.0 software (Psychology Software Tools, Inc., Sharpsburg, MD, USA). The sound pressure level was measured with a sound level meter (type 2235, Bruel & Kjaer, Nærum Denmark) with C-weighting (optimized for 40–100 dB measurement).

2.4 Electroencephalography recording and data analysis

The EEG data was recorded using a 128-channel EEG system. The amplifier used to amplify the electric activity of the brain was a Net Amps 200 (Electrical Geodesics Inc.), and the software for data recording was the Net Station version 4.2.1. The sampling rate for the EEG recording was 1000 Hz and the data were filtered online from 0.1 to 400 Hz. The HydroCel Geodesic Sensor Net was used. The EEG was online referred to the vertex electrode (Cz).

The EEG signal was analyzed with Brain Vision Analyzer 2.1. software (Brain Products GmbH, Munich, Germany). Offline, an average from all the channels was calculated and applied as a new reference. The electrode signals were filtered with 0.1 Hz low cut-off and 30 Hz high cut-off, both with 24 dB/octave roll-off. Also, a 50-Hz notch filter was applied. Six-hundred-ms time segments were extracted relative to the stimulus onset: from 100 ms before stimulus onset to 500 ms after the stimulus onset. The mean of a 100-ms pre-stimulus period served as a baseline for each segment. Eye movements were corrected with

(independent component analysis (ICA) individually for each participant as implemented in the Brain Vision Analyzer. A detection algorithm was used to find ICA components for the blinks, and after this, the best representation for vertical or horizontal blinks was determined from the ICA components by visual inspection. After the ICA correction, bad channels were interpolated. Next, the remaining segments with signal amplitudes beyond the range between −150 μV and 150 μV in any recording channel within a 200-ms period were omitted. Also, segments with more than a 50 μV difference between two consecutive time points were deleted from further analysis.

For the averaging, only responses to standard sounds immediately preceding the deviant sounds were calculated. This procedure allows the same number of segments, and thus a similar signal-to-noise ratio, for both standard and deviant responses. Whenever there were less than 30 segments left for the averaging, the participant's data for the condition was not applied. On average, the number of analyzed trials for the deviants in high-intensity and low-intensity conditions was 47.0 and 46.6 in CTRL-group, 48.3 and 46.2 in FE-dep group, and 48.4 and 48.1 in REC-dep group, respectively. There were no group differences in One-way ANOVA in the number of analyzed trials in high-intensity, $F(2,59) = 1.93$, $p = .154$, or in low-intensity condition, $F(2,59) = 1.71$, $p = .191$.

Visual observation of the grand-averaged waveforms indicated that N1 and MMN responses were elicited, but P3a response was not evident. Accordingly, N1 and MMN amplitudes were analyzed. Based on the grand-averaged waveforms and previous literature (Näätänen, 1990), mean standard and deviant response amplitude values for the N1 and MMN were calculated for the latency of 90 - 140 ms and 150 - 200 ms after the stimulus onset, respectively. Both standard and deviant responses were extracted from the MMN time window, in order to investigate whether possible group difference is associated either to

memory trace formation for the standard stimulus or to deviance detection. It has been recently acknowledged that taking stimulus type to statistical model can reveal the underlying mechanism of group differences in change detection (Kremláček et al., 2016). Since the MMN is traditionally analyzed as a differential response, also an analysis based on it was applied. The amplitude values were extracted from the fronto-central electrodes (channels 3, 10, 11, 15, 16, 18, 23, 24, 27, 123, and 124 in the EGI 128-channel system, Supplemental Figure 1).

2.5 Statistical analysis

A three-way repeated measures of Multivariate Analysis of Variance (MANOVA) with within-subjects variables stimulus type (deviant, standard) and condition (high-intensity, low-intensity), and a between-subjects variable group (CTRL vs. FE-dep vs. REC-dep) was conducted separately for N1 and MMN. An additional two-way repeated measures of MANOVA was conducted for MMN by applying differential response (deviant minus standard) with condition (high-intensity, low-intensity) as a within-subjects variable and group (CTRL vs. FE-dep vs. REC-dep) as a between-subjects variable. Partial eta-squared η_p^2 presents effect size estimates for MANOVA and Cohen's d for t-tests. Cohen's d was computed using pooled standard deviations (Cohen, 1988). One-way Analysis of Variance (ANOVA) with Bonferroni correction was used as a post hoc test for between-group comparisons, and paired t-tests with Bootstrap statistics based on 1000 samples when within-group comparisons were applied.

Whenever an effect of a group or any of its interaction effect was found a further test with a variable 'medication status' as a covariate was conducted. 'Medication status' is a dichotomous variable indicating whether the depressed participant was currently taking medication for depression or not. In addition, an analysis with the participants without current medication was conducted (FE-dep, $n = 11$, REC-dep, $n = 13$). In MANOVA between-subjects variable was group (CTRL vs. FE-dep vs. REC-dep) and within-subjects variables were stimulus type (deviant, standard) and condition (high-intensity, low-intensity). Finally, Pearson's correlation coefficients were computed to examine the relationship between the ERPs and BDI-II and between ERPs and DASS-anxiety scores whenever the interaction effect with the group was indicated by MANOVA.

Bonferroni corrected or Bootstrap-based *P*-value smaller than .05 was considered significant, but marginally significant interaction effects ($p \leq .075$) were also further studied.

3. Results

Here we report significant group effects and interactions with it. The results describing other main effects and interactions are presented in supplementary materials (Table S1, Table S2, Table S3). In Figure 1, grand-average waveforms are depicted separately for the two experimental conditions: the high-intensity condition (deviant sound 80 dB and standard sound 60 dB) and the low-intensity condition (deviant sound 60 dB and standard sound 80 dB). Differential waveforms (deviant minus standard response) are presented in Figure 2. Topographical maps of response amplitudes to deviant sounds in N1 and MMN time windows are shown in Figure 3. Mean amplitude values and significant group differences in these are shown in Figure 4.

3.1 N1 (90–140 ms)

In MANOVA a significant stimulus type x group interaction, $F(2,59) = 3.56$, $p = .035$, $\eta_p^2 = 0.11$, was observed[1]. For post hoc tests, a one-way ANOVA was performed to compare the responses to different stimulus types among the three groups. The ANOVA showed group difference in responses to deviant stimuli, $F(2,59) = 4.96$, $p = .010$, but no significant difference between groups in responses to standard stimuli, $F(2,59) = 0.59$, $p = .559$, was observed (Figure 4).

Follow-up pairwise comparisons showed that the FE-dep group had larger negative responses to deviant stimuli ($M = -1.05$, $SD = 1.06$) compared to the REC-dep group ($M = -0.40$, $SD = 0.49$), $p = .020$, d = 0.866, and to CTRL-group ($M = -0.38$, $SD = 0.62$), $p = .020$, d = 0.821 (Figure 4). No difference in deviant responses between REC-dep and CTRL-group was found, $p = 1.000$, d = 0.046. Mean difference in deviant response between FE-dep and REC-dep group was -0.65 µV, 95% CI [-1.27, -0.14], and between FE-dep and CTRL-group -0.67 µV, 95% CI [-1.32, -0.14].

Paired t-tests comparing deviant and standard stimulus responses (averaged over the conditions) were also performed separately in each group. Responses to standard and deviant stimulus differed in FE-dep, $t(15) = 4.11$, $p = .004$, d = 0.896, and in REC-dep group, $t(24) = 2.73$, $p = .012$, d = 0.697 but not in CTRL-group, $t(20) = 1.16$, $p = .266$, d = 0.296 (Figure 4). Mean amplitude difference in FE-dep group was -0.81 µV, SD = 0.79 and 95% CI [-1.23, -

[1] Also the data without the two participants with low BDI-scores were analyzed. The stimulus type x group interaction was still marginally significant, $F(2,57) = 2.862$, $p = .065$, $\eta_p^2 = .091$

0.48], in REC-dep group -0.36 μV, SD = 0.67 and 95% CI [-0.61, -0.12], and in CTRL-group -0.18 μV, SD = 0.73, 95% CI [-0.52, 0.13].

The stimulus x group interaction remained marginally significant when controlling for medication status $F(2,58) = 4.16$, $p = .050$, $\eta_p^2 = .098$. In a MANOVA between non-medicated depression groups and CTRL-group (FE-dep vs. REC-dep vs. CTRL) the stimulus type x group interaction was marginally significant, $F(2,42) = 2.95$, $p = .063$, $\eta_p^2 = .123$. For post hoc tests, a one-way ANOVA was performed. One-way ANOVA showed group difference in responses to deviant stimuli, $F(2,42) = 4.08$, $p = .024$, but no significant difference between groups were found in responses to standard stimuli, $F(2,42) = 0.28$, $p = .761$. Follow-up pairwise comparisons showed that FE-dep group had larger negative responses to deviant stimuli compared to CTRL-group, $p = .033$. Difference between FE-dep and REC-dep was marginally significant, $p = .059$. REC-dep and CTRL-group did not differ, $p = 1.000$.

No correlations were found between BDI-II scores and N1 responses or between DASS-anxiety scores and N1 responses (to the deviants or standards, or deviant minus standard differential response) within the depressed participants (all $p > .156$). In addition, no such correlations were found either in FE-dep group (all $p > .164$), or in the REC-dep group, (all $p > .321$) when the groups were studied separately.

3.2 MMN (150–200ms):

In the MMN time window, both analyses, based on standard and deviant responses and on differential response, showed no group differences or interaction effects with the group (all $p > .200$)[2].

4. Discussion

Here we used an intensity change detection paradigm that allowed us not only to study the intensity dependency of ERPs (Hegerl et al., 2001; Hegerl & Juckel, 1993; Juckel et al., 1997), but also the function of the change detection mechanism that is known to be affected in many neuropsychiatric disorders, including depression (for the MMN, see Näätänen et al., 2011). We found that the first-episode depression group had larger ERP amplitudes to rare changes in sound intensity in the obligatory N1 response compared to control participants. The recurrent depression group did not differ in N1 responses to deviant sounds from the control group. However, both depression groups showed larger N1 amplitude to deviant than to standard stimuli while in the control group no such difference was found. MMN was elicited to both high- and low-intensity deviant sounds as expected but it did not reflect any group differences.

Previous studies have found increased intensity dependence in a subgroup of depressed patients responsive to antidepressants (see for example Gallinat et al., 2000; Jaworska et al., 2013; Juckel et al., 2007; B. Lee et al., 2015; T.-W. Lee et al., 2005). This increased intensity dependence is thought to reflect, at least partly, low serotonergic neurotransmission (Hegerl et al. 2001; Hegerl & Juckel, 1993; Juckel et al., 1997, 1999; Wutzler et al., 2008). Therefore, our finding of increased N1 responses to intensity deviant

[2] Also the data without the two participants with low BDI-scores were analyzed. The results remained non-significant (all p > .200).

sounds in first-episode depression may potentially indicate weaker serotonergic neurotransmission in that group comparing to the recurrent depression group and control group. However, the finding of statistically significant differential response (deviant vs. standard stimulus) in both depression groups, but not in the control group, may indicate a decreased threshold for a trigger to allocate attention towards changes in depression (Näätänen, 1990). Moreover, it indicates that it is, indeed, the change detection mechanism, not sound encoding in general, which is affected in depression. Considering this, it was surprising that the MMN response reflected no group differences. To our knowledge MMN responses to rare changes in intensity have not been previously measured in depression, but instead earlier studies have investigated alterations in the processing of duration or frequency changes. Our results are in contrast with the earlier MMN studies that found depression-related alteration of the MMN in response to duration and frequency changes in tones (Chen et al., 2015; He et al., 2010; Kähkönen et al., 2007; Naismith et al., 2012; Qiao et al., 2013; Restuccia et al., 2015; Takei et al., 2009).This discrepancy might be explained by the different neural sources the different sound features activate in the brain (Alho, 1995; Rosburg, 2003).

It is not clear why the first-episode depression group showed more pronounced auditory over-excitability to intensity changes than the recurrent depression group. Even if both depression groups had significant difference between the N1 response amplitudes to standard and deviant sound, the effect size for this difference was clearly larger for the first-episode depression group than for the recurrent depression group ($d = 0.896$ and $d = 0.697$, respectively). The previous studies investigating automatic change detection between first-episode and recurrent depression have not been able to dissociate first-episode and recurrent depression groups (Chen et al., 2015; Umbricht et al., 2003). To our knowledge no study

related to change detection in sound intensity has previously compared first-episode and recurrent depression groups. The cortical over-excitability found in our experiment may thus be specifically related to automatic sensory processing of sound intensity.

One difference between the depression groups is the medication history. Because participants in the recurrent depression group had previous depression episodes, they also had more participants who had previously used antidepressants. Most of the participants in recurrent depression group had used antidepressants previously (19 out of 25 participants), while only a few participants in the first-episode depression group had previous medication history (4 out of 16 participants). It is not known, if the previous medication that was more often used in the recurrent depression group, could explain the differences between the ERP responses in first-episode and recurrent depression groups. One potentially relevant aspect related to previous medication is treatment resistance. It can be assumed that the recurrent depression group included participants who are treatment-resistant, e.g. unresponsive to at least two antidepressants (for a review, see Berlim & Turecki, 2007). In treatment-resistant depression also other neurotransmitter systems than serotonergic system have been suggested to be dysfunctional (e.g. glutamatergic, Berman et al., 2000; Zarate et al., 2013). This also supports the above mentioned interpretation that our ERP results may reflect more profound dysfunction of serotonergic system in first-episode depression compared to recurrent depression.

The participants in the recurrent depression group reported slightly more depression symptoms than the participants in the first-episode depression group. Therefore the larger N1 amplitudes in first-episode group compared to recurrent group and control group could not be explained by the amount of depression symptoms as such. Furthermore, we found no

association between depression scores and the brain responses, suggesting that the alterations in brain responses are not related to the severity of depression. This is in line with previous MMN studies that found no correlations between the number of symptoms and brain responses to auditory changes (Kähkönen et al., 2007; Naismith et al., 2012; Pang et al., 2014; Takei et al., 2009).

This study is not without limitations. In our sample both depression groups had participants with medication, but the groups did not differ significantly in the amount of medicated vs. non-medicated participants. Furthermore, the medication status did not explain the observed group differences as the results remained mostly the same even after controlling for current medication status. An additional analysis with the subgroup of participants with no current medication for depression further suggested that the medication status did not explain the results.

One limitation is that the diagnostic interview was not a validated clinical interview, e.g. Structured Clinical Interview for DSM-IV, SCID (First et al., 2002), and it was not conducted by a psychiatrist. Instead, a structured interview based on ICD-10 criteria for depression was conducted by a physician. This procedure is, however, a common practice for diagnosing depression in primary health care context in Finland. Since the interview did not contain detailed questions about symptoms related to other psychiatric disorders than depression, it did not allow a comprehensive differential diagnosis. It is thus possible that some participants could have had comorbid psychiatric disorders along with depression.

Participants' hearing ability was not objectively measured and we did not evaluate their intelligence. Another limitation is related to the ERP analysis. We did not separate the N1 and MMN responses for example with blind source separation methods or using source localization, but through visual inspection of the grand-averaged waveforms. It is thus

possible that the analyzed responses do not purely reflect N1 and MMN but they may partly overlap.

In sum, the method based on ERPs to rare changes in sound intensity was efficient to dissociate the depression groups from the control group, indicating potential deficits in the automatic auditory change detection in depression. Future studies should investigate to what extent the deficit in auditory change detection is directly associated to the function of serotonergic or other neurotransmission system in depression. In this study, we employed an intensity change detection paradigm to combine the benefits from previous intensity dependency and change detection studies, which both have shown promise in exploring cortical over-excitability in depression. This paradigm can quickly and cost-efficiently measure obligatory brain responses in depression which encourages to study further its possibility to be used as a diagnostic tool in future.

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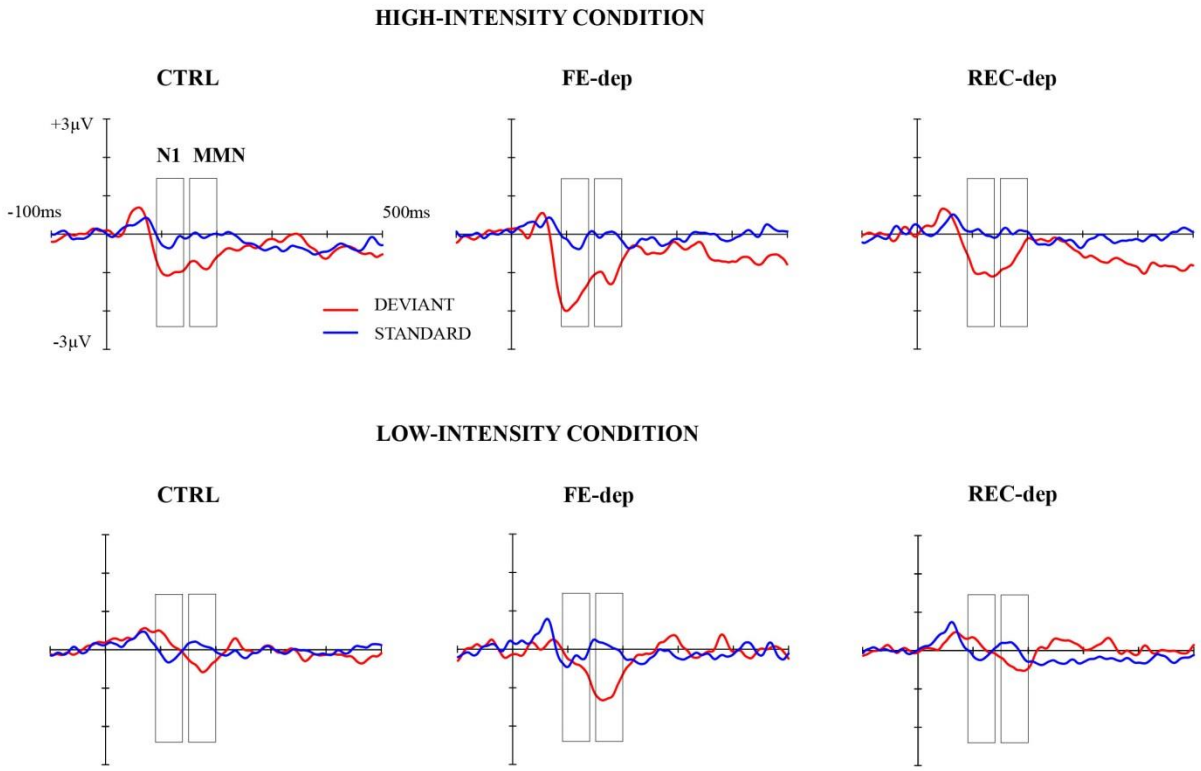

Figure 1. Grand-averaged waveforms of responses to deviant and standard stimulus separately in each group and condition (averaged for analyzed electrodes). The rectangles represent the analysis windows for N1 (90-140 ms) and MMN (150-200 ms). The Y-axis shows the stimulus onset. CTRL = control group, FE-dep = first-episode depression group, REC-dep = recurrent depression group.

(Suggested width of the picture 2 columns)

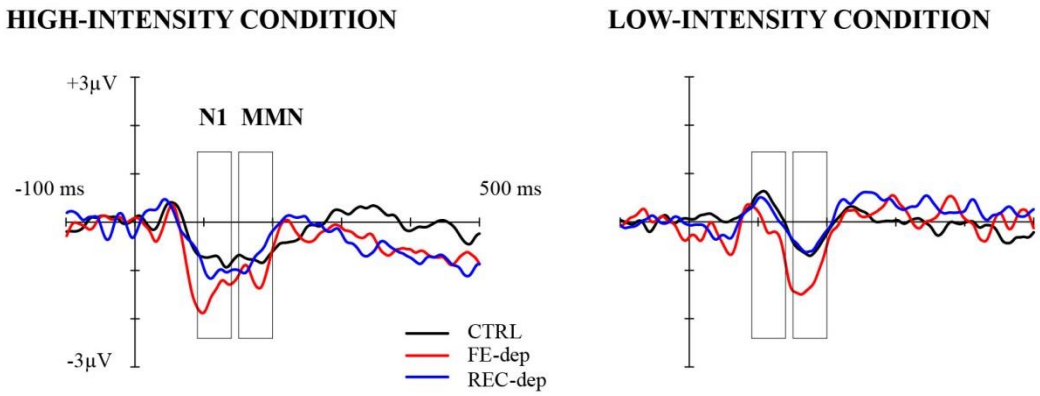

Figure 2. Grand-averaged differential responses (deviant minus standard) for each group and condition (averaged for analyzed electrodes). The rectangles represent the analysis windows for N1 (90-140 ms) and

MMN (150-200 ms). The Y-axis shows the stimulus onset. CTRL = control group, FE-dep = first-episode depression group, REC-dep = recurrent depression group. (Suggested width of the picture 1.5 columns)

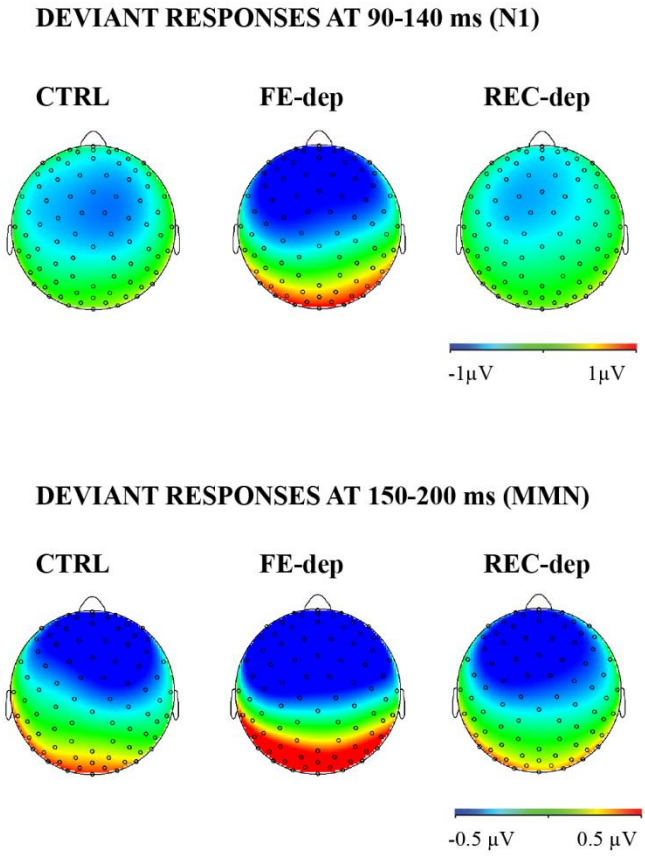

Figure 3. Grand-averaged topographical maps of the N1 and MMN responses for the deviant sounds in each group (high-intensity and low-intensity conditions are averaged). CTRL = control group, FE-dep = first-episode depression group, REC-dep = recurrent depression group. *(suggested width of the picture 1 column)*

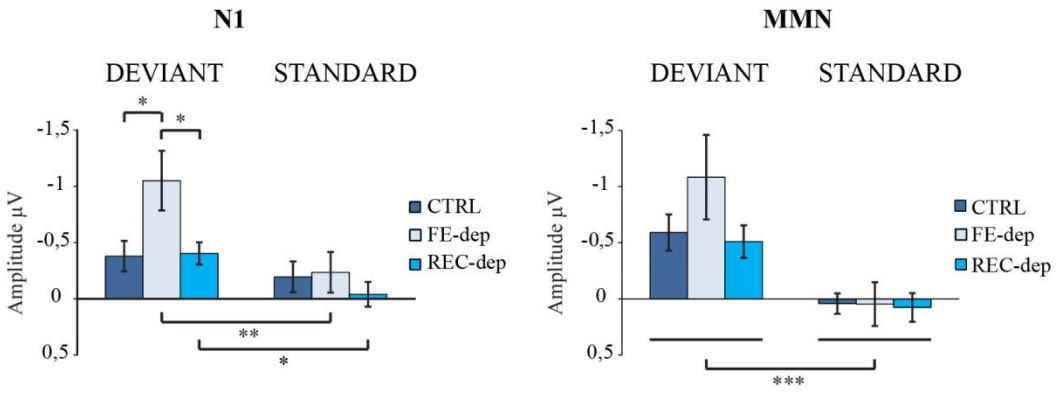

Figure 4. Mean amplitudes for N1 and MMN to deviant and standard stimuli in each group (averaged for high-intensity and low-intensity conditions and analyzed electrodes). For the MMN only the main effect of stimulus type was significant. Error bars represent standard error. CTRL = control group, FE-dep = first-episode depression group, REC-dep = recurrent depression group, *$p < .05$, **$p < .01$, ***p $< .001$ *(suggested width 1.5 columns)*

Table 1. Demographics and Clinical Measures for the Participant Groups. CTRL = control group, FE-dep = first-episode depression group, REC-dep = recurrent depression group, SD = standard deviation

	CTRL (*n* = 21)	FE-dep (*n* = 16)	REC-dep (*n* = 25)
Male/Female	8 / 13	7 / 9	7 / 18
Age: Mean (SD) [range]	40.0 (11.9) [21-64]	41.4 (13.4) [18-64]	43.7 (9.7) [25-64]
Medicated/non-medicated	Na	5 / 11	12 / 13
Previously medicated/previously non-medicated*	Na	4/11†	19/6
Medication type**	Na	3 SSRI 2 SNRI	5 SSRI 5 SNRI 2 other
Mild/Moderate depression	Na	11 / 5	17 / 8
BDI-II Mean (SD) [range]	2.8 (3.2) [0-10]	19.8 (8.5) [3-36]†	25.2 (8.11) [12-43]
DASS-anxiety (SD) [range]	Na	8.69 (6.8) [0-22]	9.92 (9.1) [0-31]

* number of participants who reported having used/not having used antidepressants previously
**SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin and norepinephrine reuptake inhibitors, other = other depression medication
† One participant's value missing