Clinical Neurophysiology 128 (2017) 1923–1936

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Risk of depression enhances auditory Pitch discrimination in the brain as indexed by the mismatch negativity

L. Bonetti [a,*], N.T. Haumann [a], P. Vuust [a], M. Kliuchko [b,c], E. Brattico [a,b]

[a] Center for Music in the Brain, Department of Clinical Medicine, Aarhus University, & The Royal Academy of Music Aarhus/Aalborg, Denmark
[b] Cognitive Brain Research Unit, Institute of Behavioral Sciences, University of Helsinki, Finland
[c] BioMag Laboratory, HUS Medical Imaging Center, University of Helsinki and Helsinki University Hospital, Finland

ARTICLE INFO

Article history:
Accepted 1 July 2017
Available online 18 July 2017

Keywords:
Depression
Mismatch negativity
Pitch
Musical multi-feature paradigm
Magnetoenchephalography (MEG)

HIGHLIGHTS

- Mismatch negativity amplitudes (MMNs) to slide and pitch deviants are enhanced in individuals with risk of depression.
- MMN to pitch is larger for deviants in a musical major mode context than minor one.
- The relation between MMNs to pitch deviants and depression level is influenced by musicianship.

ABSTRACT

Objective: Depression is a state of aversion to activity and low mood that affects behaviour, thoughts, feelings and sense of well-being. Moreover, the individual depression trait is associated with altered auditory cortex activation and appraisal of the affective content of sounds.
Methods: Mismatch negativity responses (MMNs) to acoustic feature changes (pitch, timbre, location, intensity, slide and rhythm) inserted in a musical sequence played in major or minor mode were recorded using magnetoencephalography (MEG) in 88 subclinical participants with depression risk.
Results: We found correlations between MMNs to slide and pitch and the level of depression risk reported by participants, indicating that higher MMNs correspond to higher risk of depression. Furthermore we found significantly higher MMN amplitudes to mistuned pitches within a major context compared to MMNs to pitch changes in a minor context.
Conclusions: The brains of individuals with depression risk are more responsive to mistuned and fast pitch stimulus changes, even at a pre-attentive level.
Significance: Considering the altered appraisal of affective contents of sounds in depression and the relevance of spectral pitch features for those contents in music and speech, we propose that individuals with subclinical depression risk are more tuned to tracking sudden pitch changes.

1. Introduction

Depression is a state of aversion to activity and low mood that affects behaviour, thoughts, feelings and individual sense of well-being (Schnaas, 2003). A depressed mood is characterized by anxiety, sadness, anger and empty, hopeless, guilty, restless feelings (Rottenberg, 2005). If depressed mood occurs frequently, becoming a stable pathological state, it can lead to major depressive disorder (MDD). Moreover, differently from a non pathological sad state, depressed mood is characterized by the intensity and pervasiveness of the pain during patients activities, causing social and emotional limitations in their lives (Gotlib and Hammen, 2009).

Perception in several sensory domains is affected by a sad, depressed mood, according to the phenomenon that has been called 'congruency bias', a cognitive bias that arise when individuals accept the most immediate answer, frequently congruent to their states, without testing other hypotheses. (Byron, 1990). For instance, individuals affected by major depression tend to respond to visual and auditory unpleasant stimuli, such as faces, voices and musical excerpts, in a stronger way in comparison to the healthy ones (Gollan et al., 2008). Human speech and music are built on

* Corresponding author at: Center for Music in the Brain, Department of Clinical Medicine, Aarhus University, & The Royal Academy of Music Aarhus/Aalborg, Denmark.

E-mail address: leonardo.bonetti@clin.au.dk (L. Bonetti).

http://dx.doi.org/10.1016/j.clinph.2017.07.004
1388-2457/

some similar features such as pitch, time and silence (Juslin and Sloboda, 2013). These characteristics vary according to the individual mood and can represent significant cues to depression (France and Shiavi, 2000). For instance, depressed individuals show a speech characterised by monotony, constant speech with few changes of pitch (Darby and Hollien, 1977; Hollien, 1980) and silent pauses (Pope et al., 1970).

In the auditory domain, the impact of depression has been suggested by several studies. Michael et al. (2004), in an fMRI study, reported a significantly lower activation of the auditory cortex in people affected by major depressive disorder (MDD) in comparison to healthy ones. Also Tollkötter et al. (2006) argued that major depression disorder may imply an impaired auditory processing. Specifically they found out that depressed patients did not show a clear N1 m component in response to vowels and sine tones. Moreover, Christ et al. (2008) stated that major depression was associated with cortical dysfunctions such as impaired auditory processing of non-speech stimuli. They revealed that during stimulation by sine tones, patients affected by depression exhibited a multimodal recruitment of brain areas to sound processing and as such, the medial frontal cortex and areas of the secondary visual system (e.g. lingualis, cuneus) were involved. In addition to these findings it is remarkably acknowledged that serious major depressed patients exhibit deficits and difficulties in interpersonal communication, that is based also on both sounds production and perception (Chandrasekaran et al., 2014).

In an fMRI study Osuch et al. (2009) explored basic brain processes occurring when listening to enjoyable music in both depressed and healthy participants. Results showed that listening to the favorite music caused larger activation in control participants than in depressed patients in nucleus accumbens, ventral striatum and medial orbital frontal cortex, entailing an alteration in the brain of depressed patients when listening to their favorite and pleasant music. Depressed patients reported less interest in rewards from their favorite music in comparison to healthy controls.

Automatic discrimination of auditory stimuli of patients affected by depression disorders has also been investigated, reporting varied results. A reliable index of automatic auditory discrimination is the mismatch negativity (MMN) of an event-related potential (ERP), measured with electroencephalography (EEG) or magnetoencephalography (MEG) (Näätänen et al., 1978). The MMN is typically elicited with the oddball paradigm, as a response to an infrequent stimulus deviating from a sequence of coherent, repetitive stimuli in one or more physical features such as location, pitch, rhythm, intensity, timbre of sound source or in abstract features such as simple auditory rules (Näätänen, 1992; Näätänen et al., 2011). Furthermore MMN is affected in depression; Lepistö et al. (2004), for example, reported shorter MMNs latencies generated by deviant syllables in depressed children compared to the control group, without finding any amplitude differences. Higher MMNs amplitudes were observed in depressed patients in response to sound frequency deviants (Kahkonen et al., 2007).

Other research, in contrast, showed lower MMN responses in people affected by depression disorders. For example, Naismith et al. (2012) discovered reduced MMN amplitudes in depressed people compared to healthy ones when induced through an auditory two-tone passive oddball paradigm. In another ERP study related to the emotional prosody, Pang et al. (2014) assessed the emotional voice processing in major depressed patients presenting prosodies that involved meaningless syllables such as "dada" pronounced with angry, happy, sad, or neutral tones. They discovered that sad MMNs were not present in major depressed patients, whereas the angry and happy MMN components resulted similar when compared to the healthy group.

However, in all those studies the experimental sessions were very long potentially causing fatigue and also habituation, which by themselves might explain the discrepant findings.

Thus, a fast paradigm, called multi-feature (also known as "Optimal" paradigm), for obtaining MMN responses comparable to those obtained in the classical oddball paradigm, was introduced by Näätänen et al. (2004). It consists of various kinds of acoustic changes that are presented within the same sequence of sounds and that are alternating regularly with the repetitive and rarely occurred standard sound, while in the oddball paradigms deviants are presented more rarely (typically for a maximum of 20%). In order to obtain acoustic stimuli related to a more realistic musical context, Vuust et al. (2011) created the musical multi-feature paradigm, inserting six different feature changes in a four-tone pattern called the Alberti Bass, an a commonly used accompaniment in the Western music. This enables several MMN components related to various auditory attributes to be independently induced yielding the experimental duration to be less than 20 min (Vuust et al., 2012). Recently, Mu et al. (2016), using the musical multi-feature paradigm, found enhanced MMN amplitudes to the timbre deviant in patients affected by major depressive disorder as compared to a healthy control group. Even if the study utilized a relatively small subject sample, it suggests that MMNs can index music-related dysfunctions in depressed patients. It remains to be studied whether a risk of depression in individuals that are otherwise healthy can alone affect automatic discrimination of musical features, consequently altering neural mechanisms for perception of music and expressive sounds in general. Previous literature conceptualized the risk of depression as an enhanced probability to develop depressive disorders, presenting some correlated neural abnormalities (Carlson et al., 2015; Joormann et al., 2012; Troy et al., 2010).

In the present study, we wanted to investigate whether a subclinical risk of depression in individuals that are otherwise healthy affects the automatic discrimination of changes in the basic features of musical sounds within a musical context. In order to assess the participants' risk of depression we used the Montgomery–Åsberg Depression Rating Scale (MADRS) and the Depression subscale of the Hospital Anxiety and Depression Scale (HADS-D), two questionnaires developed to assess the severity of depressive episodes in patients as well as to discriminate depressed participants from individuals with absence of symptoms or risk of depression (Gabryelewicz et al., 2004; Leentjens et al., 2000; Montgomery and Asberg, 1979; Whelan-Goodinson et al., 2009). These scales are short and easy to administer. They are diagnostic tools, that are used by nurses and doctors in hospitals in order to reveal any signs of depression in adult individuals. Hence, MADRS and HADS-D allow for studying subclinical populations characterized by a high level of depression risk. To investigate discrimination of auditory stimuli relevant to emotional expression in individuals with subclinical risk of depression we used the musical multi-feature paradigm capitalizing from its inclusion of 4-tone patterns, half of which are in the major mode, the other half in the minor mode. Major and minor are well-known cues for emotional expression and the best predictor for valence assessment in melodies (Costa et al., 2004). Music in major is perceived as happy and bright, whereas musical excerpts within the minor scale are perceived as more sad, subdued, dark, wistful, and contemplative (Bonetti and Costa, 2017; Bonetti and Costa, 2016; Bowling et al., 2010; Cooke, 1959; Costa et al., 2000; Costa, 2012; Lahdelma and Eerola, 2016; Parncutt, 2014). We expected larger MMN amplitudes to deviants of musical multi-feature paradigm in participants with higher pronounced risk of depression. Furthermore, we predicted the emotional context provided by the major and minor stimuli to modulate the MMN amplitude differently.

2. Materials and methods

2.1. Participants

Eighty-eight Finnish participants were recruited, 40 males (45%) and 48 females (55%). Mean age was 28.40 ± 8.21 (29.36 ± 7.88 for males and 27.58 ± 8.46 for females). They were homogeneous for social and economic status, they all received an academic education and they did not report any previous or current abuse of drugs and alcohol.

Participants' demographic data are shown in Table 1. Furthermore participants were recruited taking into consideration their musical expertise. Specifically they were 22 musicians, 30 amateurs and 36 non-musicians. This choice was driven by previous findings stating musical training is able to alter MMN responses (Brattico et al., 2009; Vuust et al., 2011, 2012). For that reason we decided to include the musical training variable as a factor in our study. Musicians were obtaining a professional musical education or graduated from Sibelius Academy and University of Helsinki. Amateur musicians studied music in an informal way or had only few years of musical training and had not been paid for music performance. Non-musicians had not received musical training outside of the school curriculum. Participants were volunteers, but they were compensated for their time in the lab with vouchers that they could use for culture and sports (e.g. concerts, museums or swimming pools). All participants were healthy, not under medication, did not report having had any neurological or psychiatric problems in their past, and declared to have normal hearing.

All participants compiled and signed an informed consent upon arrival to the laboratory and a researcher was present and available for assistance. All experimental procedures for this study, included in the larger research protocol called "Tunteet" were approved by the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (approval number: 315/13/03/00/11, obtained on March the 11th, 2012). All procedures were conducted in agreement with the ethical principles of Declaration of Helsinki.

2.2. MADRS and HADS-Depression questionnaires

In our study all subjects were screened for subclinical risk of depression by using the MADRS questionnaire and the Depression subscale of the Hospital Anxiety and Depression Scale (HADS-D).

The overall MADRS score ranges from 0 to 60, defining the following four main categories: (a) normal/absence of symptoms; (b) mild depression; (c) moderate depression; (d) severe depression. In the MADRS scale each item provide a score from 0 to 6. A global higher score expresses more severe depression. The questionnaire comprises questions about the following symptoms: (1) Apparent sadness; (2) Reported sadness; (3) Inner tension; (4) Reduced sleep; (5) Reduced appetite; (6) Concentration difficulties; (7) Lassitude; (8) Inability to feel; (9) Pessimistic thoughts; (10) Suicidal thoughts. Even if MADRS has been developed for clinical populations, several studies utilized it for assessing the depression level of non-clinical participants', as well as for dividing depressed from non-depressed participants (Gabryelewicz et al., 2004; Leentjens et al., 2000). The MADRS scores presented no significant differences ($p = 0.35$) among the three musical training groups, showing a mean score of 7.00 ± 4.12, with a maximum score of 17.

The Hospital Anxiety and Depression Scale (HADS) is a self-report measure developed to index the severity of anxiety and depression symptoms. It comprises 7 items for each subscales (Depression and Anxiety), scored from 0 to 3. Overall a person can score between 0 and 21 for both Depression and Anxiety. Participants' symptoms are divided into mild (8–10), moderate (11–14) or sever (>15). Although the HADS-D is usually administered in clinical environment, it has not been designed to be a clinical diagnostic tool (Whelan-Goodinson et al., 2009) and it has been found to perform well also with non-hospital groups (McDowell, 2006). The HADS-D scores were no significant ($p = 0.10$) among the three musical training groups, showing a mean score of 3.22 ± 2.19, with a maximum score of 11.

2.3. Stimuli and procedure

The stimuli were piano tones from the Wizoo Acoustic Piano sample sounds from the software sampler Halion in Cubase (Steinberg Media Technologies GmbH). The peak amplitude was normalized using Audition, Adobe Systems Incorporated©. We decided to use peak amplitude normalization, as it is useful for balancing sounds on the basis on their most salient portion, labeled as the sharp attack. The tones were organized in patterns of four, arranged in an arpeggiated chord (first–fifth–third–fifth). This musical figure is common in accompaniment in Western music and it is known as "Alberti bass". Each piano tone was of 200 ms in duration with 5 ms of raise and fall time. Interstimulus interval was 5 ms. The musical key of the presentation changed every six patterns in pseudorandom order. The keys were kept in the middle register. 24 keys were used (12 major and 12 minor). In each pattern, the third tone was replaced with a deviant of one of six types: pitch, timbre, location, intensity, slide and rhythm, as shown in Fig. 1. The deviant sounds were created by modifying one sound feature in Adobe Audition. The pitch deviant has been designed mistuning the third tone of the Alberti Bass by 24 cents, tuned downwards in the major mode and upwards in the minor one. To create timbre deviant, the "old-time radio" effect of Adobe Audition was applied to the sound. The location deviant was made by decreasing an intensity in one of the audio channels that resulted in perceptual shift of a sound source location from the center to a side. The intensity deviant was a reduction of a sound intensity by 6 dB. Slide deviant was made by gradual change of pitch from one note below up to the standard over the sound duration. The rhythm deviant was made by shortening a tone by 60 ms but keeping ISI of 5 ms, resulting in the consequent tone arriving earlier than expected. Each deviant was presented 144 times, half of which (72) was played in a major and another half in a minor mode. The presentation lasted about 12 min. The randomization was realized in Matlab and the stimuli were showed using Presentation software (Neurobehavioural Systems, Berkeley, CA).

Participants were instructed to passively listen to sound sequences using headphones, Sennheiser HD 210. Firstly, we performed a hearing threshold test utilizing the same sounds as in the experiment. We set the sound pressure level to 50 dB above the individual threshold. Then, participants were requested to

Table 1
Participants' demographic data, shown according to the different musical training groups.

Musical training group	Mean age of participants	Mean length of musical training	Sex (M/F)	Intelligence Quotient (IQ)	Handedness (L/R)
Musicians	29.26 ± 8.32	21.00 ± 7.44	13/9	119.71 ± 8.77	2/20
Amateurs	27.97 ± 7.89	6.56 ± 6.45	14/16	118.81 ± 6.78	1/29
Non musicians	28.26 ± 8.52	1.77 ± 2.78	15/21	117.21 ± 7.71	3/33

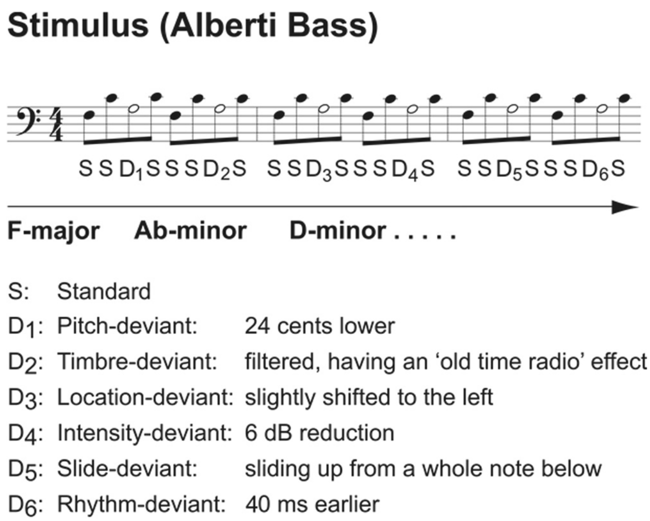

Fig. 1. Alberti bass stimulus. Each tone (except for the rhythm deviant) was 200 ms of duration. The tones were presented with ISI of 5 ms.

watch a silenced document movie while comfortably sitting on a chair in a shielded chamber.

Before the preparation for MEG/EEG recording, MADRS and subjects' background questionnaires were administered to participants. Measurements were equally arranged in the morning and in the afternoon.

2.4. MEG and EEG recording

We collected simultaneous MEG and EEG data at the Biomag Laboratory of the Helsinki University Central Hospital. The measurements were carried on in an electrically and magnetically shielded room (ETS-Lindgren Euroshield, Eura, Finland) with Vectorview™ 306-channel MEG scanner (Elekta Neuromag®, Elekta Oy, Helsinki, Finland) equipped with a compatible EEG system. The MEG scanner had 102 sensor elements comprised of 102 orthogonal pairs of two planar gradiometer SQUID sensors and 102 axial magnetometer SQUID sensors. A 64-channel EEG electrode cap was used. The ground electrode was placed on the right cheek, while the reference one was on the nose tip Blinks, as well as horizontal and vertical eye movements, were measured with four electrodes attached above and below the left eye and close to the external eye corners on both sides. We placed on top of the EEG cap four head position indicator coils. Their positions were located respectively to the nasion and the prearicular anatomical landmarks by Isotrack 3D digitizer (Polhemus, Colchester, VT, USA). MEG and EEG data were registered with a sample rate of 600 Hz.

2.5. Data analysis

2.5.1. Pre-processing of EEG and MEG signals

To minimize the influence of external and nearby noise sources and automatically detect and correct bad MEG channels we applied Elekta Neuromag™ MaxFilter 2.2 Temporal Signal Space Separation (tSSS) (Taulu and Hari, 2009) with the default inside expansion order of 8, outside expansion order of 3, automatic optimization of both inside and outside bases, subspace correlation limit of 0.980, and raw data buffer length of 10 s. The subsequent data processing was computed with FieldTrip version r9093, an open source toolbox for Matlab (Donders Institute for Brain, Cognition and Behaviour/Max Planck Institute, Nijmegen, the Netherlands) (Oostenveld et al., 2011) and Matlab R2013b (MathWorks, Natick, Massachusetts). On average 1.0 (0–10) bad EEG channels per subject for each condition were observed and replaced by interpolations of the waveforms measured in the neighboring channels, and the sampling rate was reduced from 600 to 300 Hz. To minimize the influence of baseline drifts and muscle artifacts we applied high- and low-pass filters before the Independent Component Analysis (ICA) analysis with half cut-off frequencies at 1 and 25 Hz. The influence of artifacts related to eye movements and cardiac activity was reduced by applying ICA with the logistic infomax algorithm implemented in the *runica* function for Matlab (Makeig et al., 1996). Artifact components were identified manually by inspecting the component topographies and waveforms. When a component representing a typical eye movement or cardiac artifact was identified the component was subtracted from the data. On average the total number of removed artifactual ICA components per subject for each condition was 1.9 (0–3) for the EEG, 2.6 (1–3) for the MEG magnetometers, and 2.6 (1–3) for the MEG gradiometers. The corrected data were segmented into responses to the six deviant types and standard trials, and a baseline from -100 to 0 ms pre-stimulus time window was applied. To further reduce influence of potentially remaining artifacts trials with amplitudes exceeding 100 μV, 2000 fT, or 400 fT/cm were rejected. On average 3% trials were rejected from the EEG data, 0% from the MEG magnetometer data, and 2% from the MEG gradiometer data, evenly distributed across deviant types and standard trials. After the artifact rejection the average number of trials per participant consisted of 142 ± 8 intensity deviants, 141 ± 8 localization deviants, 141 ± 8 pitch deviants, 141 ± 8 rhythm deviants, 141 ± 8 slide deviants, 141 ± 8 timbre deviants and 2545 ± 138 standard trials. To isolate the MMN waveforms for each participant the average response to each deviant type and to the standard stimuli was calculated across the trials. Peak MMN latencies after the grand average on all participants were: 170 ms (Intensity), 113 ms (Location), 203 ms (Pitch), 193 ms (Rhythm), 180 ms (Slide), 127 ms (Timbre). Then, the average standard response was subtracted from the average deviant responses for each subject and stimulus condition.

2.5.2. Statistical analysis

Statistical analyses were conducted only for MEG gradiometers because of their better signal-to-noise-ratio compared to EEG and MEG magnetometers (quantitative measure of signal to noise ratio for this same dataset can be found in Haumann et al., 2016). However we decided to report waveforms and isopotential maps also for EEG and MEG magnetometers to show whether effects could potentially be replicated using these measurement modalities. First, to study the hypothesized effect of the affectively relevant major/minor context on the MMN responses in relation to MADRS, a repeated-measures ANCOVA, using peak MMN amplitude channels for each deviant, was performed inserting Musical Modes, Deviants as within-subjects factors, the three musical training groups (musicians, amateurs, non-musicians) as between-subjects factor and the MADRS scores as an independent variable. The between-subjects factor musical training groups was included because it has been demonstrated that professional musicians showed higher MMN amplitudes to the musical multi-feature paradigm deviants than amateurs and non-musicians (Vuust et al., 2012). As we did not find any interactive effect on the MMN between major and minor modes and MADRS scores, in the successive analyses we did not include the musical mode.

In order to determine which deviants were related to the depression tendency, a multivariate ANCOVA was conducted inserting the peak MMN amplitude channels for each deviant (Pitch, Timbre, Intensity, Slide, Localization, Rhythm) as dependent variables, the three musical training groups as between-subjects factor and the MADRS scores as an independent variable. Subsequently, because MADRS only showed significant effects on Pitch and Slide deviants, a repeated-measures ANCOVA was performed inserting Pitch and Slide deviants (recorded at the highest MMN amplitude channels), Hemispheres, Channels as within-subjects factors, the three musical training groups as between-subjects factor and MADRS scores as independent variable. Peak MMN amplitude channels used in the last two ANCOVAs are showed in Fig. 2.

In order to increase the reliability of the results, we performed a further ANCOVA involving a higher number of channels. Thus, we defined four regions of interest (ROIs) above both frontal and parietal lobes per hemisphere (anterior-medial, posterior-medial, anterior-lateral and posterior-lateral; Fig. 3). Each ROI was composed of four neighbouring channels. Thus, we performed a further repeated-measures ANCOVA, inserting Pitch and Slide deviants, Regions, Laterality, Hemispheres, Channels as within-subjects factors, the three musical training groups as between-subjects factor and MADRS scores as an independent variable.

Two linear regressions were conducted to assess the direction of the relations between MADRS and MMN amplitudes to Pitch and Slide. In accordance with the results of the previous ANCOVA, we inserted the average amplitude recorded at channels within the anterior-medial area of the right hemisphere for both Pitch and Slide.

Then, in order to improve the reliability of the relation between MMN and MADRS score, we performed a further analysis using the Depression scale of the Hospital Anxiety and Depression Scale (HADS-D). Specifically, we computed a repeated-measures ANCOVA using the same channels layout used in the previous ANCOVA (see Fig. 3). We inserted Pitch and Slide deviants, Regions, Laterality, Hemispheres, Channels as within-subjects factors, the

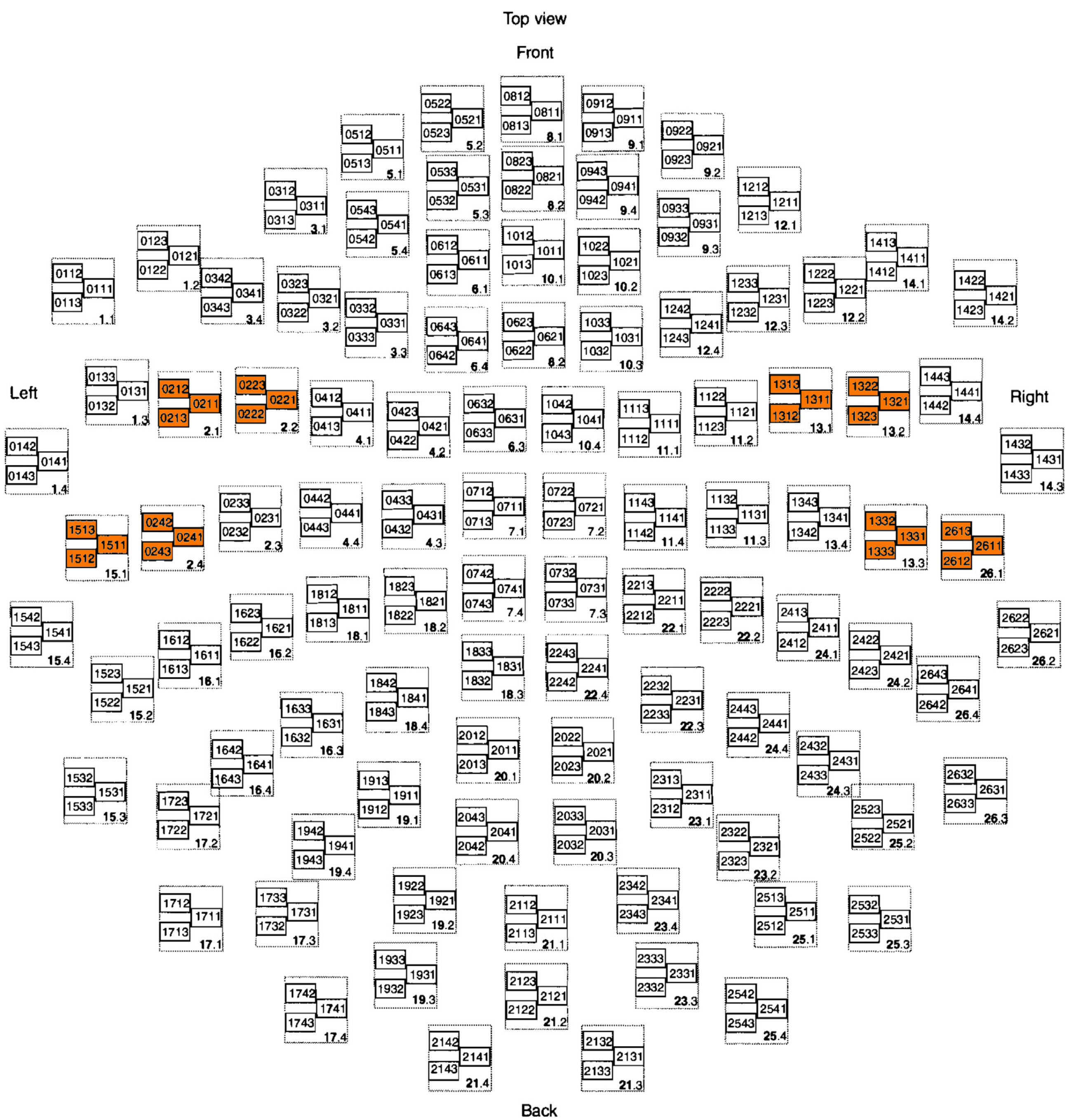

Fig. 2. Peak MMN amplitude channels used in the first two ANCOVAs in left and right hemispheres.

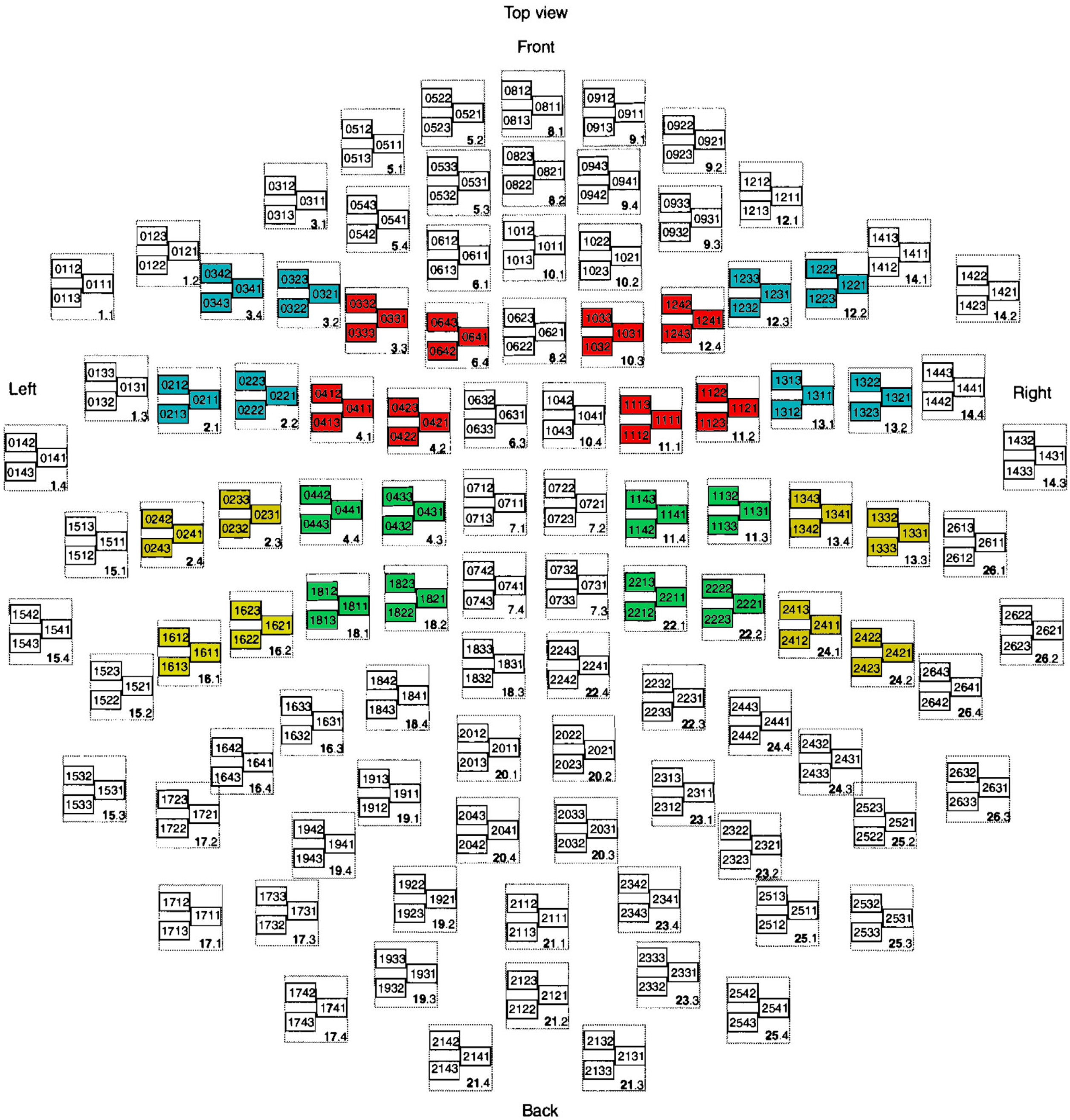

Fig. 3. Selected channels used in the last ANCOVA assembled in different brain areas in both hemispheres: anterior-medial (red), anterior-lateral (blue), posterior-medial (green), posterior-lateral (yellow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

three musical training groups as between-subjects factor and the HADS-D score as independent variable. The, two linear regressions were performed to assess the direction of the relations between HADS-D and MMN amplitudes to Pitch and Slide. We inserted the HADS-D score as independent variable and, as previously done, the average amplitude recorded at channels within the anterior-medial area of the right hemisphere for both Pitch and Slide as dependent variable.

Furthermore, we tested whether even the MMN latencies were modulated by the deviants that resulted significant in the previous ANCOVAs. To this purpose, we performed a repeated-measures ANCOVA using the temporal channel highlighted in Fig. 3 and inserting latencies of Pitch and Slide, Regions, Laterality, Hemispheres, Channels as within-subjects factors, the three musical training groups as between-subjects factor and the MADRS score as independent variable. In all of the repeated-measures ANCOVAs the factor Hemispheres, as conceivable, included both left and right brain hemispheres. Results are provided with Greenhouse–Geisser corrected test values. To test the direction of the effects obtained in the repeated-measures ANCOVAs, we computed post hoc tests using the Bonferroni correction. We also indicated the effect sizes as indexed by partial eta-squared (η_p^2).

3. Results

3.1. Deviants, musical mode and MADRS score

The repeated-measures ANCOVA showed a statistical significance in the interaction Musical Mode x Deviants x MADRS

($F(5, 420) = 3{,}23$, $p = 0.007$, $\eta_p^2 = 0.04$), even though we did not observe a main effect of mode ($p = 0.57$). Post hoc analysis using Bonferroni correction revealed higher MMN amplitudes in the major mode compared to the minor one only in Pitch deviant, as shown in Figs. 4 and 5 ($p < 0.001$, mean MMN amplitudes: "major" 29.66 ± 21.94 fT/cm, "minor" 25.34 ± 20.64 fT/cm).

3.2. Deviants and MADRS

The multivariate ANCOVA showed significant differences between the deviants in relation to the MADRS scores, specifically the significant results were found for Pitch and Slide (see Table 2). For this reason only Pitch and Slide deviants were considered in the successive ANCOVAs.

In the repeated-measures ANCOVA, MMN amplitudes differed according to the MADRS scores and in relation to the three Musical training groups (see Table 3). Post hoc analysis applying Bonferroni correction revealed a higher MMN amplitudes in musicians compared to non-musicians in Pitch ($p = 0.02$) and Slide ($p < 0.001$).

Furthermore, we observed significant interactions (see Table 4) as Channels × Musical training groups × MADRS, Deviants × Channels × MADRS and Hemispheres × Channels × MADRS. Post hoc analyses using Bonferroni correction revealed higher MMN amplitudes in musicians compared to non-musicians for Slide deviant compared to the Pitch one across all the analyzed channels ($p < 0.001$) and higher MMN amplitudes in the right hemisphere

Table 2
Relations between MMN amplitudes to six deviants and MADRS score, across the peak amplitude channels, calculated through a multivariate ANCOVA (in bold the deviants resulted significant).

Deviant	$F(1, 87)$	p	η_p^2
Intensity	3.630	0.06	0.04
Localization	3.815	0.06	0.04
Pitch	**5.040**	**0.02**	**0.06**
Rhythm	1.119	0.29	0.01
Slide	**14.029**	**<0.001**	**0.14**
Timbre	1.537	0.22	0.02

Table 3
Main effects emerged from the repeated-measures ANCOVA performed inserting the peak amplitude channels.

Main effect	$F(1, 84)$	p	η_p^2
MADRS	5.09	0.02	0.06
Musical training groups	8.42	<0.001	0.17

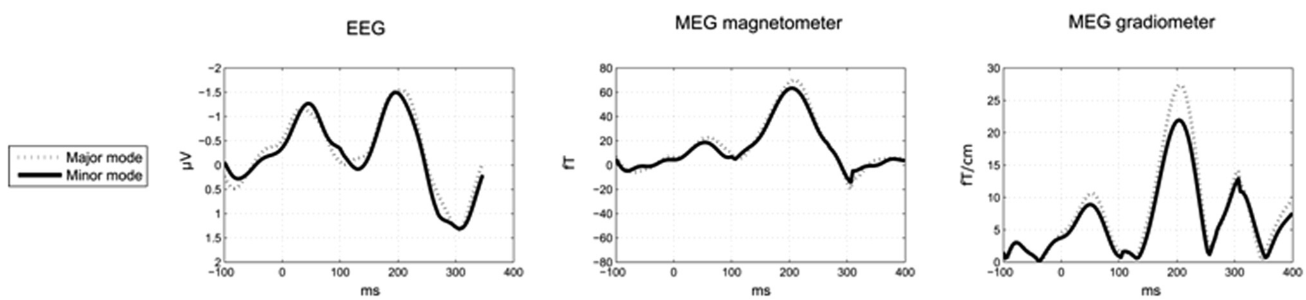

Fig. 4. Grand average MMNs for each subject and stimulus condition to the Pitch deviant in relation to major and minor mode. Showing waveforms in the peak amplitude channels in the right hemisphere: EEG 12, magnetometer 1411, and gradiometers 1322 + 1323.

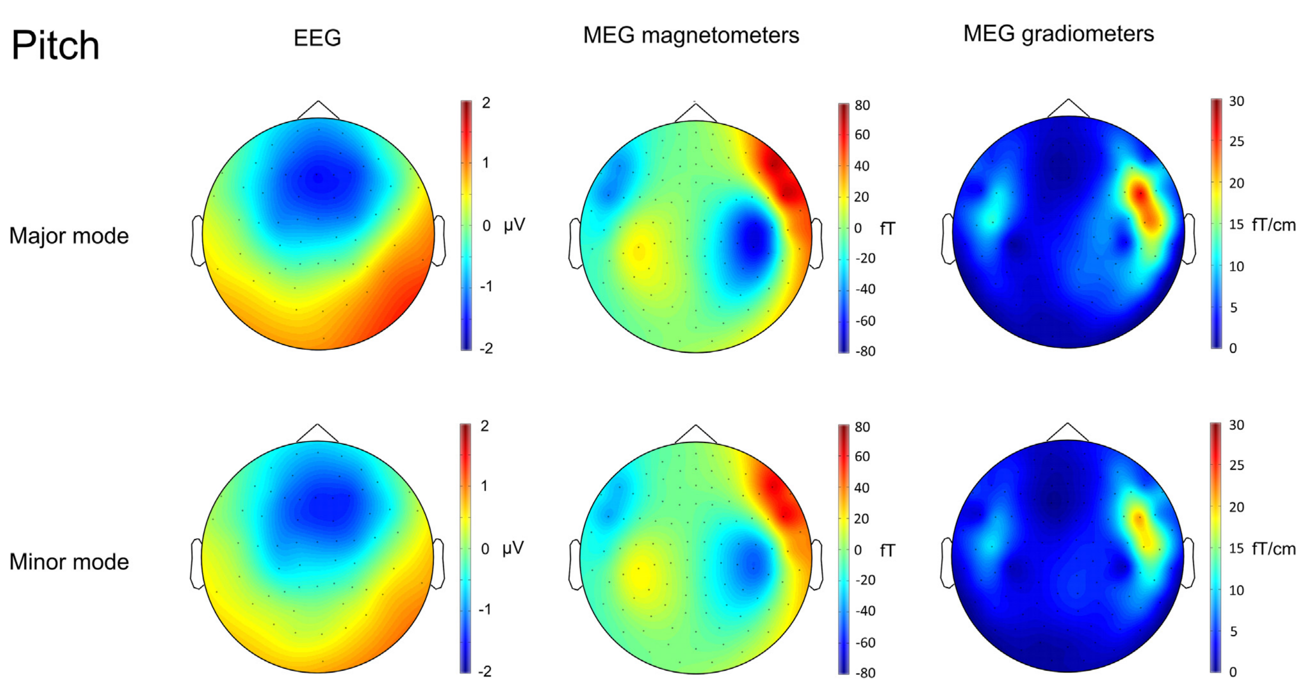

Fig. 5. Voltage isopotential maps of the differences between the responses to the Pitch deviant in relation to major and minor mode averaged for each subject and stimulus condition in an interval of ± 15 ms around maximal peak amplitudes.

Table 4
Interactions emerged from the repeated-measures ANCOVA performed inserting the peak amplitude channels.

Interactions	F	p	η_p^2
Channels × Musical training groups × MADRS	F(6, 252) = 5.29	0.04	0.05
Deviants × Channels × MADRS	F(3, 252) = 5.29	0.001	0.06
Hemispheres × Channels × MADRS	F(6, 252) = 6.67	<0.001	0.07

compared to the left one across all the analyzed channels ($p < 0.001$). These results took into account also the MADRS score reported by participants.

3.3. Distribution of the relation between MMNs and MADRS along the MEG sensors

The repeated-measures ANCOVA confirmed a significant difference only for Pitch and Slide deviants in relation to the MADRS scores (Figs. 6, 7, 8, 9, 10) as well as a significant main effect for Musical training groups (see Table 5). Post hoc tests applying Bonferroni correction confirmed higher MMNs in musicians compared to non-musicians ($p = 0.001$).

Furthermore we reported the following significant interaction Deviant x Regions x MADRS x Musical training groups ($F(2, 249) = 4.00$, $p = 0.02$, $\eta_p^2 = 0.09$. Post hoc tests applying Bonferroni correction revealed higher MMNs in musicians compared to non-musicians and in relation to the MADRS score for Slide deviant within the medial part of the anterior compared to posterior ROIs of the right hemisphere ($p < 0.05$).

3.4. Regression analysis of MMN amplitudes to Pitch and Slide deviants and MADRS

A linear regression model showed a small but significant linear trend between MADRS and Pitch deviant amplitude ($F(1, 86) = 10.00$, $p = 0.002$, adjusted $R^2 = 0.10$, $\beta = 0.32$), meaning that larger MMN amplitudes to Pitch corresponded to higher MADRS scores (Figs. 11 and 13).

Similarly, a linear relation between MADRS and Slide deviant amplitude was assessed in a second regression model ($F(1, 86) = 24.39$, $p < 0.001$, adjusted $R^2 = 0.21$, $\beta = 0.47$), showing that larger MMN amplitudes to Slide corresponded to higher MADRS scores (Figs. 12 and 14).

3.5. MMN and HADS-D score

The main effect of the Depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) resulted significant: $F(1, 87) = 4.69$, $p = 0.03$, $\eta_p^2 = 0.05$.

The regression calculated for Slide confirmed the significance: $F(1, 89) = 6.98$, $p = 0.01$, adjusted $R^2 = 0.06$, $\beta = 0.27$, while the one related to Pitch approached the significance, showing the same tendency: $F(1, 89) = 3.21$, $p = 0.07$, adjusted $R^2 = 0.03$, $\beta = 0.20$.

3.6. MMN latencies and MADRS score

The main effect of the independent variable MADRS score was not significant ($p = 0.40$) indicating that MMN latencies to Pitch and Slide were not affected by the depression risk of participants.

4. Discussion

We found a significant relation between depression risk and MMN amplitudes to Slide and Pitch deviants inserted in a complex musical context. Specifically, we recorded higher MMN amplitudes to both Slide and Pitch deviants in healthy participants with higher tendency to depression. We observed these relations principally in the frontal ROI of the right hemisphere that we outlined. These effects were more pronounced in participants with a musical background. Furthermore, MMN latencies to Pitch and Slide resulted not to be modulated by the depression risk of participants.

Consistently with previous literature, our results highlight that brain responses to acoustic stimuli are affected by individual tendency to depression. Previous studies showed how more acoustic features responsible for the expression and experience of auditory emotions (Escoffier et al., 2013; Juslin and Laukka, 2003; Scherer, 1995) were related to a state of depression. Kahkonen et al. (2007), for example, observed higher MMN amplitudes in depressed patients in response to tone deviants. In an ERP study on emotional prosody, Pang et al. (2014) assessed the emotional voice processing in major depressed patients presenting prosodies including sad, angry, happy or neutral tones. They discovered that MMN sad tones were absent in case of patients with MDD, whereas the angry and happy MMNs resulted similar when compared to the healthy group. In a previous study that used the musical multi-feature paradigm in relation to major depression disorder, Mu et al. (2016) found higher MMNs amplitudes to the timbre deviant in patients affected by MDD compared to the healthy control group. However, that result has been obtained in a relatively small

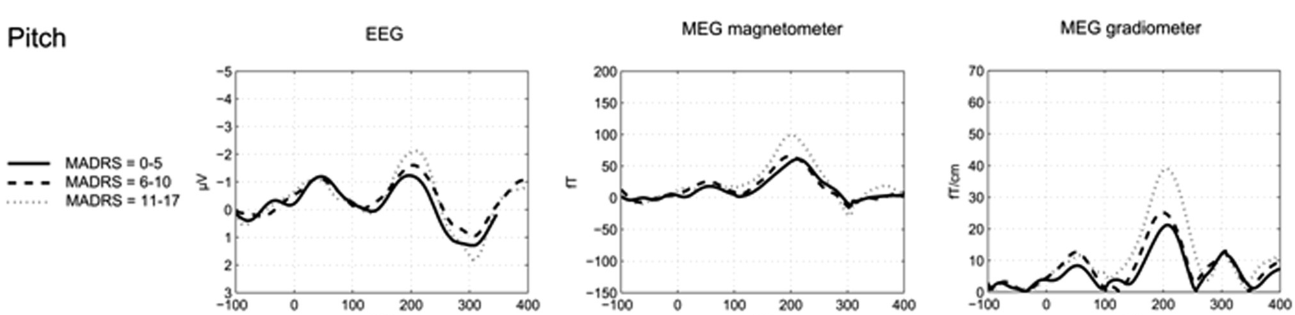

Fig. 6. Grand average MMNs for each subject and stimulus condition to the Pitch deviant in relation to three different MADRS score groups. Showing waveforms in the peak amplitude channels in the right hemisphere: EEG 12, magnetometer 1411, and gradiometers 1322 + 1323.

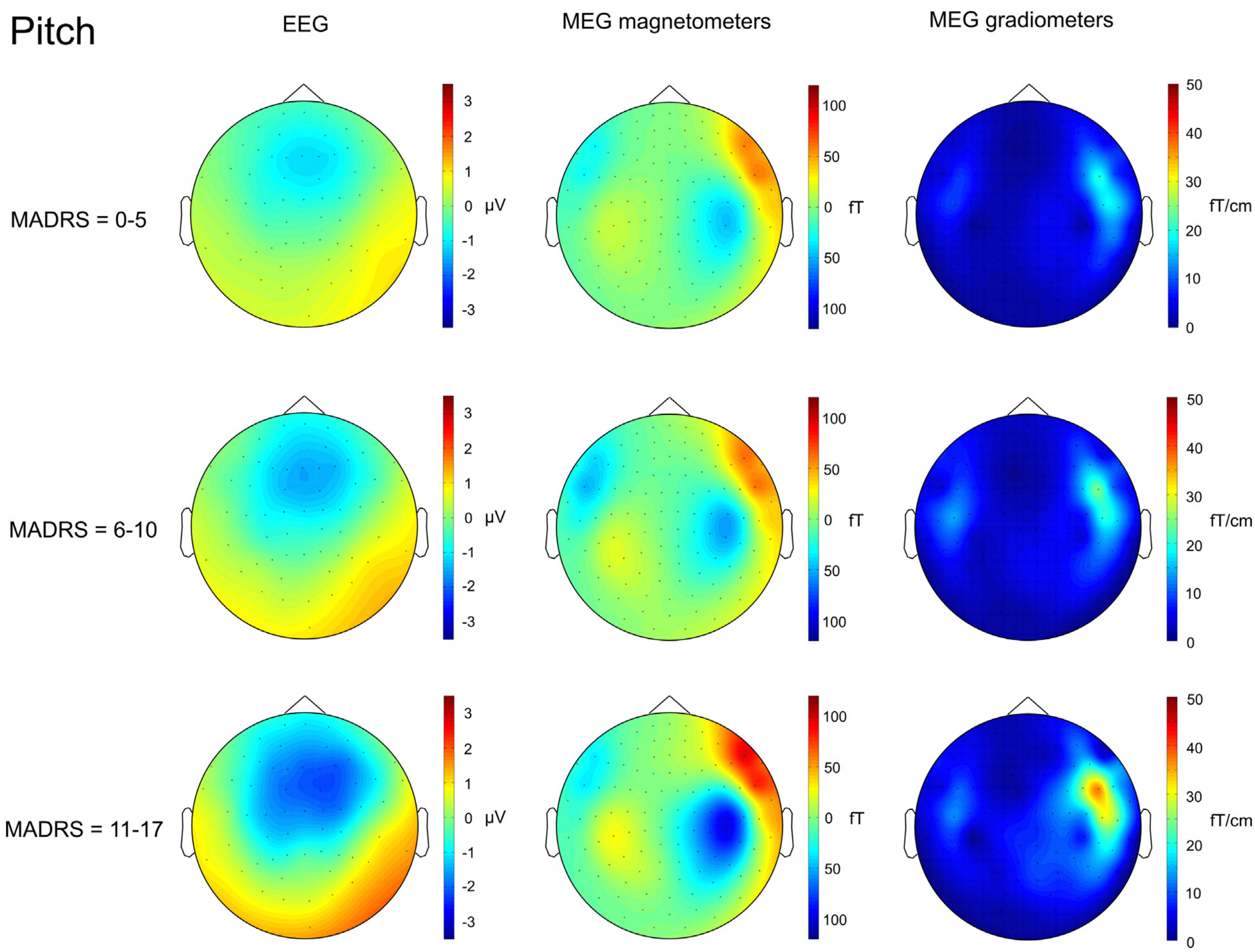

Fig. 7. Voltage isopotential maps of the differences between the responses to the Pitch deviant in relation to three different MADRS score groups averaged for each subject and stimulus condition in an interval of ± 15 ms around maximal peak amplitudes.

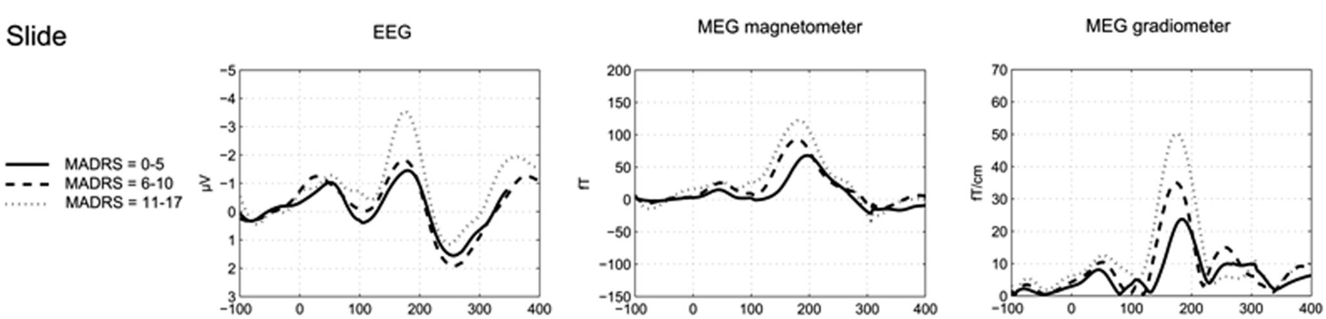

Fig. 8. Grand average MMNs for each subject and stimulus condition to the Slide deviant in relation to three different MADRS score groups. Showing waveforms in the peak amplitude channels in the right hemisphere: EEG 12, magnetometer 1411, and gradiometers 1322 + 1323.

sample of non-musicians only, with MMN responses recorded by using EEG instead of MEG as here. Interestingly both Mu et al. (2016) and our study reported higher MMN amplitudes in participants clinically depressed or with higher level of depression risk, even if Mu et al. (2016) found a difference in relation to the Timbre deviant, while we observed significant differences for pitch and slide deviants.

In the present study we found a bond between alteration of the neural mechanisms for general perception of expressive sounds and risk of depression, even in healthy individuals. Specifically we found higher responses to sound deviants obtained mistuning and altering pitch of the stimuli. A possible explanation of this phenomenon may be ascribed to the theory of ‘congruency bias’, a cognitive bias that arise when individuals accept the most immediate answer, frequently congruent to their states, without testing other hypotheses (Byron, 1990). For example, individuals affected by major depression tend to respond to visual and auditory unpleasant stimuli in a stronger way in comparison to the healthy ones (Gollan et al., 2008). In an fMRI study Osuch et al. (2009) explored the basic brain processes arisen when listening to enjoyable music involving depressed patient and healthy controls. Results showed that favorite music produced larger activation of the pleasure circuits in controls than depressed patients when listening to their favorite and pleasant music. This evidence showed

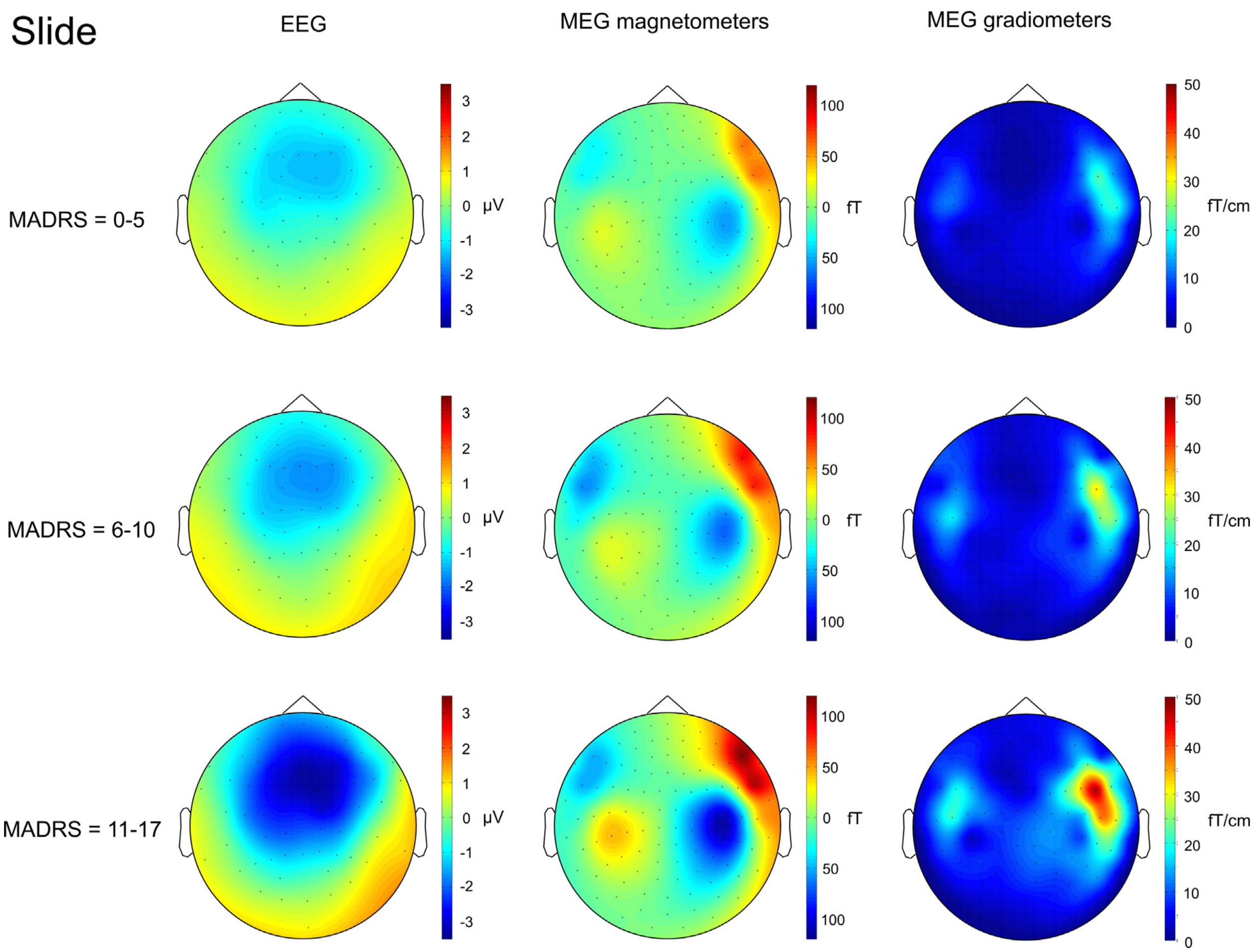

Fig. 9. Voltage isopotential maps of the differences between the responses to the Slide deviant in relation to three different MADRS score groups averaged for each subject and stimulus condition in an interval of ± 15 ms around maximal peak amplitudes.

that depressed patients reported less reward from their favorite music in comparison to healthy individuals.

From a point of view related to music perception it can be argued that in the musical multi-feature paradigm, applied in the present study, the pitch deviant is obtained by lowering the third note of the Alberti Bass about one quarter of a tone (by 24 cents). Despite this interval is recognizable by people belonging to Western culture, the quarter of a tone tends to elicit an experience of unfamiliarity, mistuning and unpleasantness (Ayers et al., 1980; Burns, 1974; Deutsch, 1999; Pratt, 1928). In the Western music culture it is often taught even to avoid the quarter of a tone interval during the intonation of sounds in voices or non-determined sound instruments such as violins (Poltronieri, 2002). Moreover, previous studies highlighted how a slight mistuning of a tone is able to produce a sense of unpleasantness (Garza Villarreal et al., 2011; Marmel et al., 2008). Therefore, it is possible to argue that mistuning an Alberti Bass of a quarter of tone tends to produce an experience of unpleasantness and unfamiliarity, at least in individuals belonging to the Western musical culture. Previous literature, referring to the trait congruency hypothesis, reported that depressed patients tend to be more sensitive to negative and unpleasant stimuli (Segal et al., 1992; Takahira, 2000), suggesting a possible higher sensitivity for mistuned tones in individuals with higher risk of depression, which is consistent with the increased MMN amplitude for the pitch deviants observed in the present study.

Even though the fundamental difference between major and minor musical modes and their strong emotional connotation, in our study only pitch deviant elicited different MMN amplitudes when separately analyzed for major and minor modes in relation to MADRS score. The pitch deviant showed larger MMN amplitude to major stimuli compared to minor ones. Possibly, the salient deviant stimulus was able to mask the difference between major and minor modes along the other feature deviants, explaining that no interactive effect on MMN amplitudes was found between major and minor modes and MADRS scores. An explanation of the difference between major and minor modes only in pitch deviant could be obtained considering its nature: the difference between major and minor modes consists in a pitch difference of a third note of the scales (Parncutt, 2014). Since in the paradigm used in our study the deviant sounds were modifications of a note that is the third of a scale, it is quite reasonable that the only deviant in which it was possible finding a difference caused by mode was the deviant related to a change of pitch. Moreover, the higher MMN amplitudes to the pitch deviant found in the major mode compared to the minor mode is consistent with the evidence reported by Pang et al. (2014), who discovered that depressed patients were impaired in their capacity of processing automatically sad prosody, without reporting any difference when compared to the controls in the elaboration of angry and happy prosodies. Furthermore, as minor mode is already able to express sadness while major mode is related to happiness, it is reasonable expecting to find higher amplitude of the MMN component in participants with higher risk of depression in response to a contrasting negatively valued lowered pitch in a major mode context associated with happiness in comparison to an already negatively valued minor mode context.

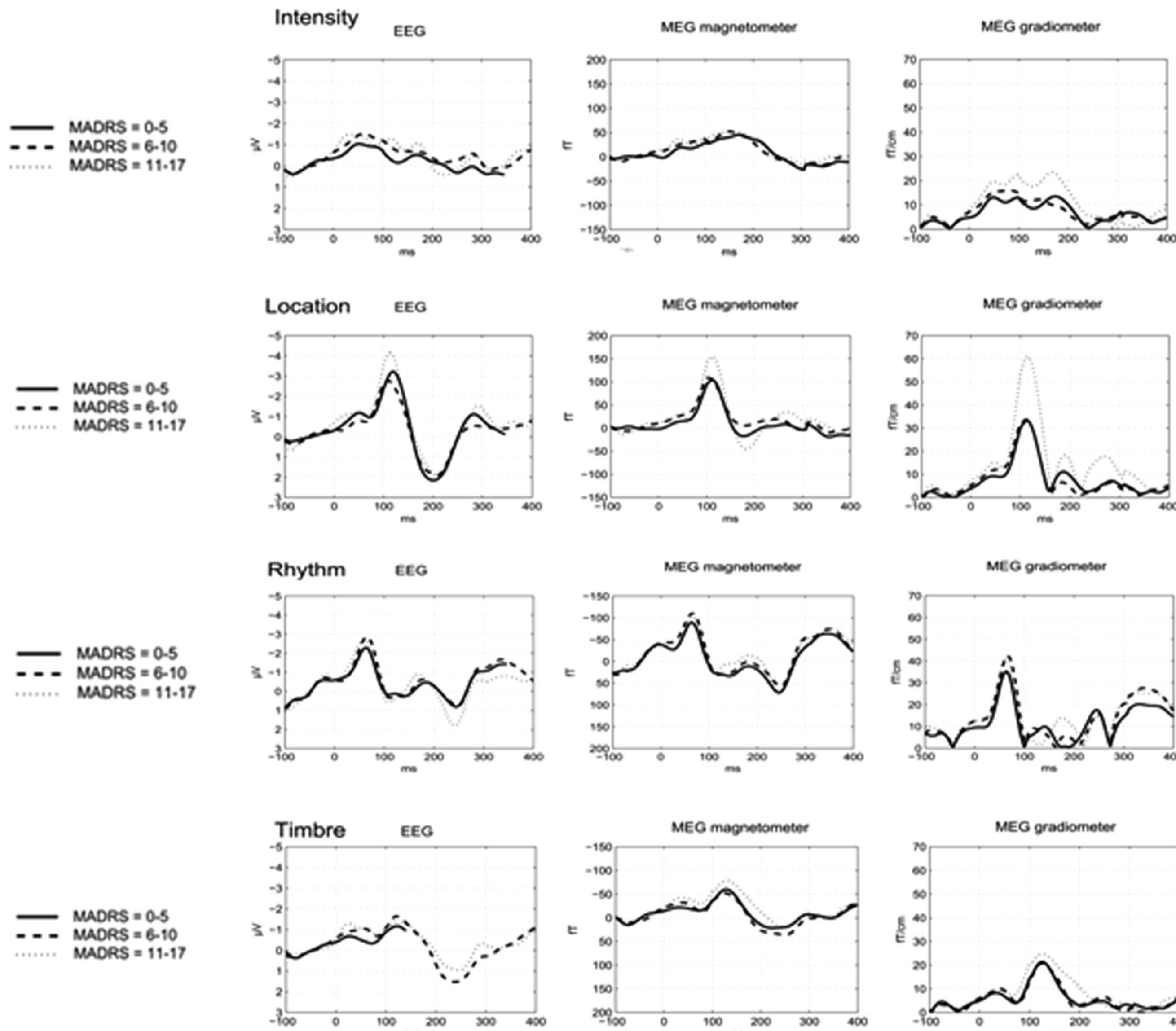

Fig. 10. Grand average MMNs for each subject and stimulus condition to Intensity, Location, Rhythm and Timbre deviants in relation to three different MADRS score groups. Showing waveforms in the peak amplitude channels in the right hemisphere: EEG 12, magnetometer 1411, and gradiometers 1322 + 1323.

Table 5
Main effects emerged from the repeated-measures ANCOVA performed inserting the four ROIs per hemisphere.

Main effect	$F(1, 84)$	P	η^2_p
MADRS	11.68	<0.001	0.12
Musical training groups	6.78	0.002	0.14

Our results show an interaction between MMNs recorded across the different musical training groups and the level of depression risk reported by participants. Specifically the relation between depression risk and MMN amplitudes resulted higher in musicians compared to non-musicians. This tendency may be explained by the higher responsivity of musician brain to sound-feature deviants (Brattico et al., 2009; Van Zuijen et al., 2005). Being musicians more sensitive to those deviants, it is possible that the relation between MMNs to sound-feature deviants and the risk of depression emerges more explicitly and clearly in participants with musical background than in those without it.

In our study we assessed the relation between MMN and depression risk considering several MEG sensors along the skull. Although we recorded, consistently with previous literature (May and Tiitinen, 2010; Näätänen and Picton, 1987), the highest MMN amplitudes in the auditory cortex, we decided to define ROIs within both frontal and auditory cortices. This choice was driven by previous literature that showed a remarkable affection of the frontal cortex in depressive disorders (Davidson et al., 2002). We revealed stronger relations between depression risk and MMNs in the more frontal areas that we considered. Although the relatively poor spatial resolution of the MEG sensors, this evidence might suggest that a tendency to depression may be reflected in a higher sensitivity to deviants of the frontal compared to the auditory cortex, even if the deviants are sound-related.

It is important to underline that we assessed a healthy population with participants who presented only a risk to depression. Moreover a limitation of the study is represented by the use of MADRS and HADS-D scales that, despite their advantages, are mainly a diagnostic tool that may not be the most sensitive one for assessing depression risk.

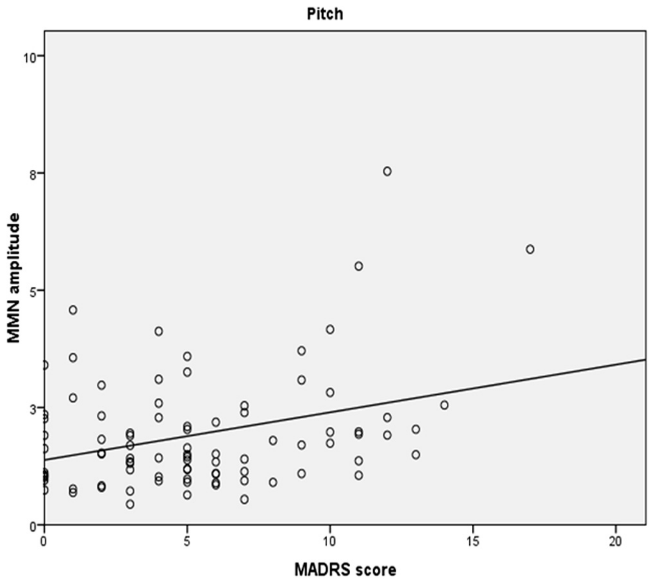

Fig. 11. Regression between the independent variable MADRS score and the dependent variable MMN amplitude to Pitch in fT/cm, obtained averaging the amplitude of the four channels belonging to the anterior-medial area of the right hemisphere.

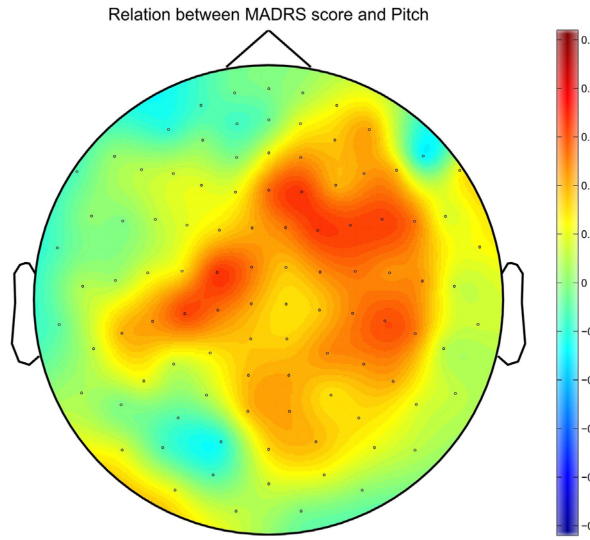

Fig. 13. Pearson's correlation maps between MMN responses to Pitch deviant averaged for each subject and stimulus condition in an interval of ± 15 ms around maximal peak amplitudes and MADRS scores along all of the MEG sensors.

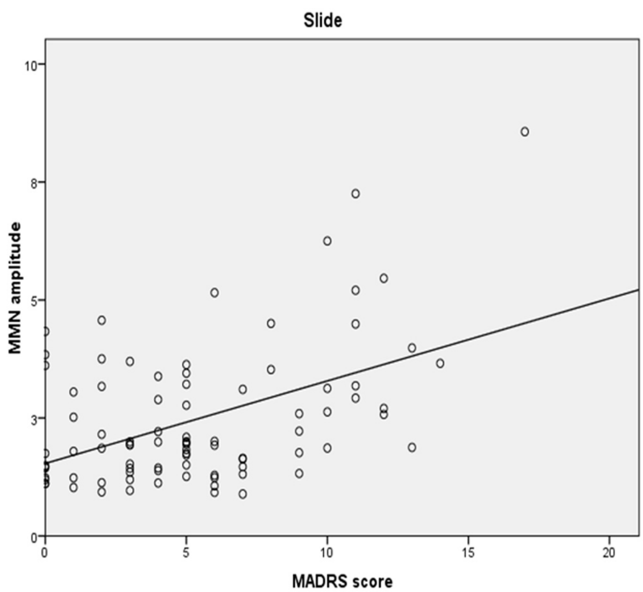

Fig. 12. Regression between the independent variable MADRS score and the dependent variable MMN amplitude to Slide in fT/cm, obtained averaging the amplitude of the four channels belonging to the anterior-medial area of the right hemisphere.

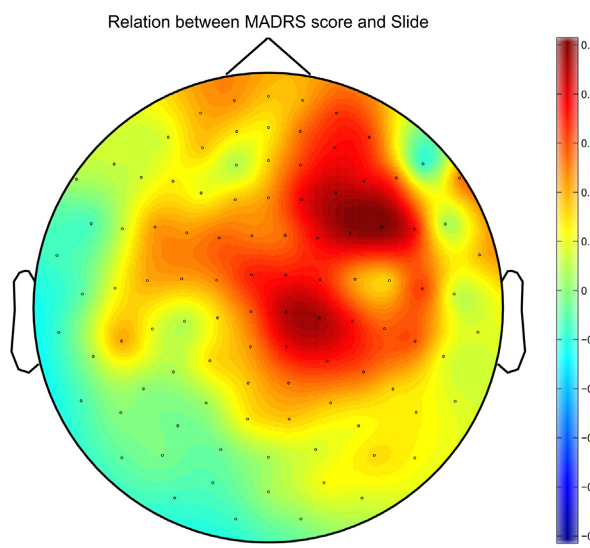

Fig. 14. Pearson's correlation maps between MMN responses to Slide deviant averaged for each subject and stimulus condition in an interval of ± 15 ms around maximal peak amplitudes and MADRS scores along all of the MEG sensors.

In this study we highlighted different MMNs to pitch and slide deviants according to depression risk of healthy individuals, using the musical multi-feature paradigm. These results suggest a higher responsivity to sound frequency changes in the brains of individuals with tendency to depression, even if they only belonged to a sub-clinical population. Thus, the current relation between MMN amplitudes and the risk of depression assessed through MADRS and HADS-D scores calls for a follow-up study on a clinically depressed population. Moreover, considering similarities and discrepancies between our and Mu et al. (2016) findings, future experiments might better explain the nature of the MMNs to the different deviants of the musical multi-feature paradigm in major depressed patients, taking into consideration also the influence of individual musical background.

In this study we focused on the MMN, namely broad band analysis of evoked responses whose calculation generally does not require specific narrow band analysis. However, a possible development of our study might relate the depression risk to specific frequency bands (e.g. alpha, gamma) of participants' brain responses to acoustic deviants. Furthermore future studies, using a different paradigm without other sound deviants, could explore the relation between depression level of participants and their MMN responses to major and minor modes. Considering the clear emotional connotation of musical modes, future experimental paradigms might show a relation between MMN amplitudes to tones in major and minor modes and the level of depression, in both clinical and subclinical populations.

Conflict of interest

The authors declared no potential conflicts of interest.

Acknowledgements

The authors would like to thank Dr. Jyrki Mäkelä, Dr. Mari Tervaniemi, Dr. Minna Huotilainen, Dr. Simo Monto, Suvi Lehto, Benjamin Gold, Brigitte Bogert, Alessio Falco, and Anja Thiede for their help with different aspects of the data acquisition.

This study has been conducted with the financial support of the The Danish National Research Foundations's Center for Music in the Brain (Aarhus University, Denmark) and of the Cognitive Brain Research Unit, Institute of Behavioral Sciences (University of Helsinki, Finland).

References

Ayers T, Aeschbach S, Walker EL. Psychoacoustic and experiential determinants of tonal consonance. J Aud Res 1980;20(1):31–42.
Bonetti L, Costa M. Intelligence and musical mode preference. Emp Stud Arts 2016;34(2):160–76. http://dx.doi.org/10.1177/0276237416628907.
Bonetti L, Costa M. Musical mode and visual-spatial cross-modal associations in infants and adults. Mus Scien 2017. http://dx.doi.org/10.1177/1029864917705001.
Bowling DL, Gill K, Choi JD, Prinz J, Purves D. Major and minor music compared to excited and subdued speech. J Acou Soc Ame 2010;127(1):491–503. http://dx.doi.org/10.1121/1.3268504.
Brattico E, Pallesen KJ, Varyagina O, Bailey C, Anourova I, Järvenpää M, et al. Neural discrimination of nonprototypical chords in music experts and laymen: an MEG study. J Cogn Neur 2009;21(11):2230–44. http://dx.doi.org/10.1162/jocn.2008.21144.
Burns EM. Octave adjustment by non-Western musicians. J Acoust Soc Am 1974;56(S1):25–6.
Byron J. Thinking and deciding, vol. 35. Cambridge University Press; 1990. doi: http://dx.doi.org/10.1037/029149.
Carlson E, Saarikallio S, Toiviainen P, Bogert B, Kliuchko M, Brattico E. Maladaptive and adaptive emotion regulation through music: a behavioral and neuroimaging study of males and females. Front Hum Neurosci 2015;9:1–13. http://dx.doi.org/10.3389/fnhum.2015.00466.
Chandrasekaran B, Van Engen K, Xie Z, Beevers CG, Maddox WT. Influence of depressive symptoms on speech perception in adverse listening conditions. Cogn Emot; 2014 (December), 1–10. doi: http://dx.doi.org/10.1080/02699931.2014.944106.
Christ M, Michael N, Hihn H, Schüttke A, Konrad C, Baune BT, et al. Auditory processing of sine tones before, during and after ECT in depressed patients by fMRI. J NeuTran 2008;115(8):1199–211. http://dx.doi.org/10.1007/s00702-008-0036-5.
Cooke D. The language of music. Oxford: Oxford University Press; 1959.
Costa M. Effects of mode, consonance, and register in visual and word-evaluation affective priming experiments. Psych Mus 2012;41(6):713–28. http://dx.doi.org/10.1177/0305735612446536.
Costa M, Fine P, Ricci Bitti PE. Interval distributions, mode, and tonal strength of melodies as predictors of perceived emotion. Mus Perc 2004;22(1):1–14. http://dx.doi.org/10.1525/mp.2004.22.1.1.
Costa M, Ricci Bitti PE, Bonfiglioli L. Psychological connotations of harmonic musical intervals. Psych Mus 2000;28(1). http://dx.doi.org/10.1177/0305735600281002.
Darby JK, Hollien H. Vocal and speech patterns of depressive patients. Fol Phon (Bas) 1977;29:279–91.
Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K. Depression: perspectives from affective neuroscience. Annl RevPsych 2002;53:545–74. http://dx.doi.org/10.1146/annurev.psych.53.100901.135148.
Deutsch D. The psychology of music, 2nd ed. (Academic P). San Diego; 1999.
Escoffier N, Zhong J, Schirmer A, Qiu A. Emotional expressions in voice and music: same code, same effect? Hum Bra Map 2013;34(8):1796–810. http://dx.doi.org/10.1002/hbm.22029.
France DJ, Shiavi RG. Acoustical properties of speech as indicators of depression and suicidal risk. IEEE Trans Biom Eng 2000;47(7):829–37. http://dx.doi.org/10.1109/10.846676.
Gabryelewicz T, Styczynska M, Pfeffer a, Wasiak B, Barczak A, Luczywek E, et al. Prevalence of major and minor depression in elderly persons with mild cognitive impairment–MADRS factor analysis. Int J Ger Psych 2004;19(12):1168–72. http://dx.doi.org/10.1002/gps.1235.
Garza Villarreal EA, Brattico E, Leino S, Østergaard L, Vuust P. Distinct neural responses to chord violations: a multiple source analysis study. Brain Res 2011;1389:103–14. http://dx.doi.org/10.1016/j.brainres.2011.02.089.
Gollan JK, Pane HT, McCloskey MS, Coccaro EF. Identifying differences in biased affective information processing in major depression. Psych Res 2008;159(1–2):18–24. http://dx.doi.org/10.1016/j.psychres.2007.06.011.
Gotlib IH, Hammen CL. Handbook of depression. In: Handbook of depression, 2nd ed.; 2009. p. xi, 708.<http://ovidsp.ovid.com/ovidweb.cgi?T = JS&CSC = Y&NEWS = N&PAGE = fulltext&D = psyc6&AN = 2008-18597-000>.
Haumann NT, Parkkonen L, Kliuchko M, Vuust P, Brattico E. Comparing the performance of popular MEG/EEG artifact correction methods in an evoked-response study. Comp Int Neur 2016. http://dx.doi.org/10.1155/2016/7489108.
Hollien H. Vocal indicators of psychological stress. Ann New York Aca Scie 1980;347:47–72.
Joormann J, Cooney RE, Henry ML, Gotlib IH. Neural correlates of automatic mood regulation in girls at high risk for depression. J Abn Psych 2012;121(1):61–72. http://dx.doi.org/10.1037/a0025294.
Juslin PN, Laukka P. Communication of emotions in vocal expression and music performance: different channels, same code? Psych Bull 2003;129(5):770–814. http://dx.doi.org/10.1037/0033-2909.129.5.770.
Juslin PN, Sloboda JA.. Music and emotion. In: The psychology of music; 2013. p. 583–645. doi:http://dx.doi.org/10.1016/B978-0-12-381460-9.00015-8.
Kahkonen S, Yamashita H, Rytsala H, Suominen K, Ahveninen J, Isometsa E. Dysfunction in early auditory processing in major depressive disorder revealed by combined MEG and EEG. JPsychNeur 2007;32(5):316–22.
Lahdelma I, Eerola T. Single chords convey distinct emotional qualities to both naive and expert listeners. Psych Mus 2016;44:37–54. http://dx.doi.org/10.1177/0305735614552006.
Leentjens AFG, Verhey FRJ, Lousberg R, Spitsbergen H, Wilmink FW. The validity of the Hamilton and Montgomery-Åsberg depression rating scales as screening and diagnostic tools for depression in Parkinson's disease. Int J Ger Psych 2000;15(7):644–9.
Lepistö T, Soininen M, Čeponiene R, Almqvist F, Näätänen R, Aronen ET. Auditory event-related potential indices of increased distractibility in children with major depression. Clin Neur 2004;115(3):620–7. http://dx.doi.org/10.1016/j.clinph.2003.10.020.
Makeig SJ, Bell A, Jung TP, Sejnowski TJ. Independent component analysis of electroencephalographic data. Adv NeuInfoProc Syst 1996;8(3):145–51. http://dx.doi.org/10.1109/ICOSP.2002.1180091.
Marmel F, Tillmann B, Dowling WJ. Tonal expectations influence pitch perception. Percept Psychophys 2008;70(5):841–52. http://dx.doi.org/10.3758/PP.
May PJC, Tiitinen H. Mismatch negativity (MMN), the deviance-elicited auditory deflection, explained. Psych 2010. http://dx.doi.org/10.1111/j.1469-8986.2009.00856.x.
McDowell, I., 2006. Measuring health: a guide to rating scales and questionnaires. doi: http://dx.doi.org/10.1002/sim.4780081017.
Michael N, Ostermann J, Soros P, Schwindt W, Pfleiderer B. Altered habituation in the auditory cortex in a subgroup of depressed patients by functional magnetic resonance imaging. Neur 2004;49(1):5–9. http://dx.doi.org/10.1159/000075331.
Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Brit J Psych 1979;134(4):382–9. http://dx.doi.org/10.1192/bjp.134.4.382.
Mu Z, Chang Y, Xu J, Pang X, Zhang H, Liu X, et al. Pre-attentive dysfunction of musical processing in major depressive disorder: A mismatch negativity study. J Affect Disord 2016;194:50–6. http://dx.doi.org/10.1016/j.jad.2016.01.028.
Näätänen R. Attention and brain function. London: Psychology Press; 1992.
Näätänen R, Gaillard AWK, Mäntysalo S. Early selective-attention effect on evoked potential reinterpreted. Acta Psych 1978;42(4):313–29. http://dx.doi.org/10.1016/0001-6918(78)90006-9.
Näätänen R, Kujala T, Kreegipuu K, Carlson S, Escera C, Baldeweg T, et al. The mismatch negativity: an index of cognitive decline in neuropsychiatric and neurological diseases and in ageing. In: Brain, vol. 134; 2011. p. 3432–50). doi: http://dx.doi.org/10.1093/brain/awr064.
Näätänen R, Pakarinen S, Rinne T, Takegata R. The mismatch negativity (MMN): Towards the optimal paradigm. Clin Neur 2004;115(1):140–4. http://dx.doi.org/10.1016/j.clinph.2003.04.001.
Näätänen R, Picton TW. The N1 wave of the human electric and magnetic response to sound: A review and an analysis of the component structure. Psych 1987;24:375–425.
Naismith SL, Mowszowski L, Ward PB, Diamond K, Paradise M, Kaur M, et al. Reduced temporal mismatch negativity in late-life depression: An event-related potential index of cognitive deficit and functional disability? J Aff Dis 2012;138(1–2):71–8. http://dx.doi.org/10.1016/j.jad.2011.12.028.
Oostenveld R, Fries P, Maris E, Schoffelen J. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comp Int Neur: CIN 2011;2011:1–9. http://dx.doi.org/10.1155/2011/156869.
Osuch Ea, Bluhm RL, Williamson PC, Théberge J, Densmore M, Neufeld RWJ. Brain activation to favorite music in healthy controls and depressed patients. Neur 2009;20(13):1204–8. http://dx.doi.org/10.1097/WNR.0b013e32832f4da3.
Pang X, Xu J, Chang Y, Tang D, Zheng Y, Liu Y, Sun Y. Mismatch negativity of sad syllables is absent in patients with major depressive disorder. PLoS One 2014;9(3). http://dx.doi.org/10.1371/journal.pone.0091995.
Parncutt R. The emotional connotations of major versus minor tonality: One or more origins? Music Sci 2014;18(3):324–53. http://dx.doi.org/10.1177/1029864914542842.
Poltronieri N. Lezioni di teoria musicale. Roma: Edizioni SEDAM; 2002.
Pope B, Blass T, Siegman AW, Raher J. Anxiety and depression in speech. J Cons Clin Psych 1970;35(1):128–33.
Pratt C. Quarter-tone music. Ped Sem J Gen Psych 1928;35:286–93.
Rottenberg J. Mood and emotion in major depression. Curt DirPsychl Scie 2005. http://dx.doi.org/10.1111/j.0963-7214.2005.00354.x.

Scherer KR. Expression of emotion in voice and music. J Voice 1995;9(3):235–48. http://dx.doi.org/10.1016/S0892-1997(05)80231-0.
Schnaas FJ. Handbook of depression. J Clin Psych 2003; 64. doi: http://dx.doi.org/10.4088/JCP.v64n1218c.
Segal ZV, Shaw BF, Vella DD, Katz R. Cognitive and life stress predictors of relapse in remitted unipolar depressed patients: test of the congruency hypothesis. J Abn Psych 1992;101(1):26–36. http://dx.doi.org/10.1037/0021-843X.101.1.26.
Takahira M. An examination of the congruency hypothesis in hopelessness theory of depression. Jap J Psych 2000;71(3):197–204.
Taulu S, Hari R. Removal of magnetoencephalographic artifacts with temporal signal-space separation: demonstration with single-trial auditory-evoked responses. Hum Brain Map 2009;30(5):1524–34. http://dx.doi.org/10.1002/hbm.20627.
Tollkötter M, Pfleiderer B, Sörös P, Michael N. Effects of antidepressive therapy on auditory processing in severely depressed patients: a combined MRS and MEG study. J Psych Res 2006;40(4):293–306.
Troy AS, Wilhelm FH, Shallcross AJ, Mauss IB. Seeing the silver lining: cognitive reappraisal ability moderates the relationship between stress and depressive symptoms. Emot 2010;10(6):783–95. http://dx.doi.org/10.1037/a0020262.
Van Zuijen TL, Sussman E, Winkler I, Näätänen R, Tervaniemi M. Auditory organization of sound sequences by a temporal or numerical regularity - a mismatch negativity study comparing musicians and non-musicians. Cogn Brain Res 2005;23(2–3):270–6. http://dx.doi.org/10.1016/j.cogbrainres.2004.10.007.
Vuust P, Brattico E, Glerean E, Seppänen M, Pakarinen S, Tervaniemi M, et al. New fast mismatch negativity paradigm for determining the neural prerequisites for musical ability. Cortex 2011;47:1091–8. http://dx.doi.org/10.1016/j.cortex.2011.04.026.
Vuust P, Brattico E, Seppänen M, Näätänen R, Tervaniemi M. The sound of music: Differentiating musicians using a fast, musical multi-feature mismatch negativity paradigm. Neur 2012;50(7):1432–43. http://dx.doi.org/10.1016/j.neuropsychologia.2012.02.028.
Whelan-Goodinson R, Ponsford J, Schonberger M. Validity of the hospital anxiety and depression scale to assess depression and anxiety following traumatic brain injury as compared with the structured clinical interview for DSM-IV. J Affect Disord 2009;114(1–3):94–102. http://dx.doi.org/10.1016/j.jad.2008.06.007.