Biological Psychology 127 (2017) 74–81

Contents lists available at ScienceDirect

Biological Psychology

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

Brain responses to sound intensity changes dissociate depressed participants and healthy controls

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ARTICLE INFO

Keywords:
Depression
ERP
MMN
N1
Pre-attentive processing
Sound intensity

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.

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; 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

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http://dx.doi.org/10.1016/j.biopsycho.2017.05.008
Received 20 June 2016; Received in revised form 4 May 2017; Accepted 7 May 2017
Available online 10 May 2017
0301-0511/

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; Lee, Park, Lee, & Shim, 2015; 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; Lee et al., 2015; 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; Lee et al., 2015; 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; Lee et al., 2015; 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 and 64 years. The mean age for the controls was 39.0 (*SD* 11.9) years, ranging between 21 and 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, 2010) 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