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Clinical implications of loudness dependence of auditory evoked potentials in patients with atypical depression

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ABSTRACT

Objectives: The loudness dependence of auditory evoked potentials (LDAEP) has been proposed as a useful biomarker of serotonin activity, and the LDAEP value is low in patients with melancholic depression. In this study, we evaluated LDAEP levels in patients with atypical depression.
Methods: We recruited 53 patients with atypical depression and 68 patients with non-atypical depression. Subjects were evaluated by the Atypical Depression Diagnostic Scale (ADDS), Hamilton Rating Scale for Depression (HAMD), Hamilton Rating Scale for Anxiety (HAMA), Beck Scale for Suicidal Ideation (BSI), Behavioral Inhibition System and Behavioral Activation System (BIS/BAS) scales, and Hypomanic Personality Scale (HPS). To determine LDAEP, the peak-to-peak N1/P2 was measured at five stimulus intensities and the LDAEP was calculated as the linear-regression slope.
Results: Patients with atypical depression had stronger LDAEP values and higher BAS and HPS scores than those with non-atypical depression. LDAEP showed a pattern of gradual decrease according to ADDS score hierarchy in patients with major depressive disorder. In the atypical depression group, LDAEP showed significant negative correlation with the BSI score and significant positive correlation with BAS score. In the non-atypical depression group, LDAEP did not show any significant correlations with the scores of psychological scales.
Conclusions: Our results suggest that there is a relatively deficient serotonergic activity in patients with atypical depression and that LDAEP reflects mood reactivity. The transient drop of serotonergic activity induced by mood vulnerability might contribute to suicidal tendencies in patients with atypical depression.

1. Introduction

Major depressive disorder (MDD) with atypical features is a subtype of MDD, and is commonly called atypical depression. It is defined as a depressive disorder with mood reactivity as well as two or more of the following symptoms: increased appetite or weight gain, hypersomnia, leaden paralysis, and interpersonal rejection sensitivity (American Psychiatric Association, 2000). The prevalence of lifetime MDD with atypical features was reported as 10.23%–24.7% (Blanco et al., 2012; Gili et al., 2012), whereas that of MDD without atypical features was 6.31% (Blanco et al., 2012). Atypical symptoms appear to be more common in women and are associated with lower age of depressive onset, longer episode duration, increased axis I and II comorbidity, higher suicidal risk, and greater functional impairment (Agosti and Stewart, 2001; Blanco et al., 2012; Matza et al., 2003; Posternak and Zimmerman, 2002). Patients with bipolar I disorder more frequently show atypical features than those with MDD do (Blanco et al., 2012).

Early studies of atypical depression have focused on the response to treatment and/or symptomatic presentations to distinguish atypical depression from other related disorders (Quitkin et al., 1990). For example, Stewart et al. (1990) suggested a distinctive pathology between seasonal affective disorder and atypical depression based on differential treatment outcomes from light therapy in these two disorders (Quitkin et al., 1990). Notably, one of the core features of atypical depression, in contrast to typical depressive disorder, is that patients benefit from monoamine oxidase inhibitors rather than tricyclic antidepressants (Nierenberg et al., 1998). Joyce et al. (2004) suggested that an antidepressant (fluoxetine) that raises serotonin levels, as opposed to an antidepressant (nortriptyline) that boosts norepinephrine, is particularly helpful in treating atypical depression. However, atypical depression is not considered as atypical anymore and these symptoms are common in major depressive disorder according to modern diagnostic criteria.

Abbreviations: LDAEP, loudness dependence of auditory evoked potentials; ADDS, Atypical Depression Diagnostic Scale; HAMD, Hamilton Rating Scale for Depression; HAMA, Hamilton Rating Scale for Anxiety; BDI, Beck Depression Inventory; BSI, Beck Scale for Suicidal Ideation; BIS, Behavioral Inhibition System; BAS, Behavioral Activation System; HPS, Hypomanic Personality Scale.

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In imaging studies of atypical depression, Bruder et al. (2002) reported an increased right parietal temporal activation in atypical depression compared to melancholic depression when subjects observed chimeric facial stimuli. They suggested that this right hemispheric dominance of atypical depression could help to explain mood reactivity, rejection sensitivity, and other atypical features of this form of depression. Gold et al. (2002) suggested that there is hypothalamic–pituitary–adrenal (HPA) axis hypo-functioning, indicating hypothalamic corticotropin-releasing hormone (CRH) deficiency in patients with atypical depression as opposed to those with melancholic depression.

The loudness dependence of the auditory evoked potentials (LDAEP) has been proposed as a reliable indicator of the activity of the central serotonin system in humans (Hegerl and Juckel, 1993; Park and Lee, 2013). The LDAEP indicates changes in the auditory evoked N1/P2 component evoked by an increase in stimulus intensity and has been identified as being inversely associated with central nervous system serotonergic activity, whereby a weak LDAEP reflects high serotonergic neurotransmission and vice versa (Hegerl and Juckel, 1993). Based on these findings, the LDAEP has been proposed as a biological marker of central serotonergic activity in major depression with relevance to the clinical response to serotonergic antidepressants (Gallinat et al., 2000; Linka et al., 2004). LDAEP was demonstrated to be a useful biomarker in individuals who attempted suicide in several studies (Kim and Park, 2013; Uhl et al., 2012). Kim and Park (2013) reported that LDAEP values differed significantly between suicide attempters and non-suicide attempters. Suicide attempters were characterized by a strong LDAEP value, indicating low serotonergic activity. Uhl et al. (2012) also reported increased LDAEP levels about 1 week after suicide attempt. Recently, it has been shown that serotonin plays a role in behavioral inhibition, possibly through prefrontal–subcortical circuitry in human subjects (Drueke et al., 2013). Evidence from animal studies suggests the involvement of 5-HT depletion in the failure of response inhibition (Eagle et al., 2008; Yamada et al., 2013).

However, only a few studies of event-related potentials (ERPs) have been conducted in atypical depression. Bruder et al. (1991) reported that patients with atypical depression have preserved P3 latency and hemispheric asymmetry, while patients with melancholic depression show long P3 latency and abnormal lateral asymmetry. Fitzgerald et al. (2009) reported that MDD patients with melancholic features had a significantly weaker LDAEP slope than did non-melancholic patients, independent of depression severity or age. However, there have been no studies investigating LDAEP change in MDD patients with atypical features.

In this study, the primary aim was to examine whether differences existed between the LDAEP values of MDD patients with atypical features and those of MDD patients without atypical features. Furthermore, the symptom characteristics and their relationship with LDAEP were explored in patients with atypical depression. We hypothesized that a stronger LDAEP would be observed in patients with atypical depression than in patients with non-atypical depression.

2. Methods

2.1. Participants

We recruited 121 patients with MDD (mean age 42.10; 23 men) from the Psychiatry Department of Inje University Ilsan Paik Hospital. All the patients were diagnosed using the Statistical Manual of Mental Disorders, 4th Edition (American Psychiatric Association, 2000) by two board certified psychiatrists. All patients with MDD were drug-naive for at least 2 weeks. Exclusion criteria included the presence of any identifiable neurological disorder, hearing impairment, head injury, mental retardation, alcohol or substance abuse, psychiatric disorders other than MDD, and any physical illness that can affect cognitive function or cause hearing loss. All participants were right-handed, as determined by asking which hand they tended to use for writing and for other precise motor skills. After being informed of the details of the study, all subjects provided their written informed consent prior to participation.

The study protocol was approved by the Institutional Review Board of Inje University Ilsan Paik Hospital. The demographics of the two groups are provided in Table 1; there were no significant differences between the groups with regard to gender distribution, age, education, or symptom severity of depression and anxiety.

2.2. Psychological measures

To assess the atypical feature of patients with MDD, the Atypical Depression Diagnostic Scale (ADDS) was used, which was developed by Stewart et al. (1993). To meet the diagnostic criteria for atypical depression it is necessary to have mood reactivity, as well as two or more of the following symptoms: hypersomnia, leaden paralysis, hyperphagia, and rejection sensitivity (Stewart et al., 1993). Patients with MDD were grouped into 4 categories: 1) non-mood reactivity depression, 2) simple mood reactivity depression, 3) probably atypical depression, and 4) definitely atypical depression. Atypical depression was confirmed when the patients satisfied the 4th category.

All participants were evaluated for their severity of depressive and anxiety symptoms with Hamilton Rating Scale for Depression (HAMD) (Hamilton, 1960) and Hamilton Rating Scale for Anxiety (HAMA) (Hamilton, 1959). We used the Beck Scale for Suicidal Ideation (BSI) developed by Beck et al. (1979), because it is widely used to assess suicidal intention. It has good internal consistency (0.74) and moderately high correlations with other suicidal and hopelessness scales in Korean sample groups (Lee and Kwon, 2009). The Behavioral Inhibition System and Behavioral Activation System (BIS/BAS) scales of Carver and White (1994) were used to measure two general motivational systems: a behavioral inhibition system and a behavioral activation system. It has good internal consistency (0.78) and test–retest reliability (0.79) in Korean samples (Kim and Kim, 2001). The Hypomanic Personality Scale (HPS) developed by Eckblad and Chapman (1986) was used to assess hypomanic personality traits such as overactive, gregarious style associated with episodes of hypomanic euphoria. It contains 48 items of hypomania and has good internal consistency (Cronbach's alpha = 0.87).

2.3. Electrophysiological assessment

2.3.1. EEG recording

All of the subjects were seated in a comfortable chair in a sound-attenuated room. Auditory stimulation comprised 1000 stimuli with an inter stimulus interval that was randomized between 500 and 900 ms. Tones of 1000 Hz and 80-ms duration (10-ms rise and 10-ms fall) were presented at 5 intensities: 55, 65, 75, 85, and 95 dB SPL through MDR-D777 headphones (Sony, Tokyo, Japan). These stimuli were generated by E-Prime software (Psychology Software Tools, Pittsburgh, USA). Electroencephalogram (EEG) data were recorded and amplified using a Neuroscan SynAmp amplifier (Compumedics USA, El Paso, TX, USA) with 64 Ag–AgCl electrodes mounted in a Quick Cap using a modified 10–20 placement scheme (impedance < 10 kΩ). The vertical electrooculogram (EOG) was recorded using two electrodes, one located above and one below the right eye. The horizontal EOG was recorded at the outer canthi of each eye. The ground electrode was placed on the forehead and the reference was located at bilateral mastoids. EEG data were recorded with a 0.1–100-Hz band-pass filter and a 1000-Hz sampling rate. EEG data were processed using Scan 4.3. Eye blinks were removed from the data using standard blink correction algorithms (Semlitsch et al., 1986). Trials were rejected if they included significant physiological artifacts (e.g., amplitude exceeding ±70 V) at all 62 electrode sites, except for M1 and M2. After artifact removal, baseline correction was conducted by subtracting the mean of 100 ms of prestimulus data from the post-stimulus data for each trial.