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Scalp- and sLORETA-derived loudness dependence of auditory evoked potentials (LDAEPs) in unmedicated depressed males and females and healthy controls

Natalia Jaworska [a,b,c,*], Pierre Blier [a,d], Wendy Fusee [a], Verner Knott [a,c,d,e]

[a] University of Ottawa Institute of Mental Health Research, Ottawa, ON, Canada
[b] Department of Psychiatry, University of Calgary, Calgary, AB, Canada
[c] Department of Psychology, University of Ottawa, Ottawa, ON, Canada
[d] Department of Psychiatry & Cellular and Molecular Medicine, University of Ottawa, Ottawa, ON, Canada
[e] Department of Psychology/Behavioral Neuroscience, Carleton University, Ottawa, ON, Canada

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HIGHLIGHTS

- The loudness dependence of auditory evoked potentials (LDAEP) was unaltered in depression, though the LDAEP derived from primary auditory cortex activity correlated negatively with depression ratings.
- Smaller auditory evoked potentials (AEPs) existed in depressed versus control males.
- Females had enhanced cortical responses to auditory stimuli.

ABSTRACT

Objective: As major depressive disorder (MDD) is associated with altered 5-HT activity, we probed intensity-dependent auditory evoked potentials (AEPs) and loudness dependence of the AEP (LDAEP) slopes, shown pre-clinically to be inversely related to 5-HT activity, in MDD.
Methods: AEPs and LDAEP slopes were measured in MDD ($N = 50$; 27 females) and controls ($N = 43$; 23 females). Correlations between scalp AEPs/LDAEPs and low-resolution electromagnetic tomography (sLORETA)-derived indices were assessed.
Results: Smaller scalp intensity-dependent N1 and N1/P2 amplitudes in MDD versus control males and longer P2 latencies in MDD versus control females were found; no LDAEP group differences existed. Females had greater scalp AEPs, steeper N1 and N1/P2 scalp LDAEPs as well as greater intensity-dependent primary auditory cortex activation during the N1 than males. Scalp LDAEPs correlated weak-moderately with sLORETA counterparts. P2 LDAEP-sLORETA correlated negatively with MADRS scores. Female P2 and N1/P2 LDAEP-sLORETA correlated negatively with HAMD-17 and MADRS scores.
Conclusions: MDD was not associated with altered LDAEPs. Impaired processing or potentiated inhibition of auditory stimuli was found in MDD males; longer processing existed in MDD females. Inverse relationships between LDAEPs and clinical scores may be related to treatment history, personality and/or MDD features.
Significance: MDD was not associated with an altered LDAEP, though subtle AEPs alterations were noted in MDD.

1. Introduction

Event-related potentials (ERP) are averaged from electroencephalographic (EEG) activity resulting from summed postsynaptic potentials triggered by neurotransmitter release (Mitzdorf, 1994). Thus, ERPs are, to a certain degree, direct manifestations of neurotransmitter activity. High 5-hydroxytryptamine (5-HT) concentrations have been found in primary sensory cortices, such the primary auditory cortex (Berger et al., 1988); comparatively less 5-HT innervation and activity exists in the secondary cortex (Azmitia and Gannon, 1986; Hegerl et al., 2001). Thus, 5-HT neurotransmission is likely implicated in modulating sensory-level processing of auditory input into the primary auditory cortex.

Two auditory evoked potentials (AEPs), the N1 and P2, are generated in the primary auditory and association cortices. Their peak-to-peak amplitude difference (N1/P2) correlates positively with

* Corresponding author. Address: Clinical Neuroelectrophysiology & Cognitive Research Laboratory, Royal Ottawa Mental Health Center, 1145 Carling Avenue, Room 3128, Ottawa, ON, Canada K1Z 7K4. Tel.: +1 613 722 6521x6297; fax: +1 613 722 5048.
E-mail address: Natalia.Jaworska@rohcg.on.ca (N. Jaworska).

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stimulus intensity. By plotting N1/P2 amplitude against intensity, a loudness dependence of the AEP [LDAEP; or intensity dependence of AEP (IDAEP)] slope is constructed, which has been proposed to index 5-HT activity. Cortical 5-HT efferents from the dorsal raphe nucleus (DRN) are characterized by a pacemaker discharge (Jacobs and Azmitia, 1992). As such, 5-HT neurotransmission is well suited for tonic modulation of cortical activity in the primary auditory cortex (Hegerl et al., 2001). As cortical hyper-activation (with increased intensity) could be damaging, enhanced 5-HT activity may inhibit excessive neural activity (Juckel et al., 1999). Hegerl and Juckel (1993) proposed that 5-HT DRN neurons provide tonic pre-activation to the primary auditory cortex. They further suggested that low 5-HT pre-activation, indexing 5-HT system hypoactivity, would be associated with steeper LDAEPs than when 5-HT pre-activation is higher, and reflected by shallow LDAEPs (Mulert et al., 2005).

Preclinical work has indicated an inverse relationship between the LDAEP slope and ascending DRN 5-HT discharge (Waterhouse et al., 1990; Juckel et al., 1997, 1999; Wutzler et al., 2008). However, while pre-clinical research suggests that the LDAEP is sensitive to central 5-HT neurotransmission, evidence in humans is less consistent. With acute tryptophan depletion (ATD), which transiently lowers CNS 5-HT, several studies found no effect on the LDAEP (Debener et al., 2002; Massey et al., 2004), while one found only weak evidence for its increase (Norra et al., 2008). Yet others have noted that ATD decreased intensity-dependent N1/P2 amplitudes (Dierks et al., 1999; Kähkönen et al., 2002). Studies probing the effects of SSRIs in healthy individuals have also yielded mixed results on LDAEP/AEPs sensitivity to acute 5-HT changes. Several groups have documented no LDAEP effects with acute SSRI administration in healthy individuals (Uhl et al., 2006; Guille et al., 2008), while others have shown the predicted LDAEP slope decreases (Nathan et al., 2006; Segrave et al., 2006). Chronic SSRI administration in healthy individuals also induced shallower LDAEPs (Simmons et al., 2011). Further evidence for a link between the 5-HT system and AEP intensity modulations comes from associations between altered LDAEP slopes and polymorphisms in 5-HT_{1B} terminal autoreceptor (Juckel et al., 2008) and 5-HT transporters (5-HTT; Lee et al., 2011; Gallinat et al., 2003; Strobel et al., 2003; Hensch et al., 2006). Combined, these studies indicate a link between auditory processing and genetic variants in the 5-HT system. Nevertheless, clinical evidence for a direct association between the LDAEP (and associated AEPs) and CNS 5-HT activity is tenuous.

It is feasible that individuals with aberrant 5-HT system function, as is thought to occur in major depressive disorder (MDD), may be more likely to exhibit altered LDAEPs. However, relatively few studies have directly compared intensity-dependent AEPs in such groups. Two studies (Linka et al., 2007; Park et al., 2010) found no LDAEP changes in MDD, though others noted greater N1/P2 amplitudes with increasing intensity in the disorder (Gopal et al., 2004). Similarly, a steeper LDAEP existed in diabetic depressed patients (no differences existed in non-diabetic patients versus controls; Manjarrez-Gutierrez et al., 2009). Depressed individuals with a history of suicide were also found to exhibit steeper LDAEP slopes than those without such a history (Chen et al., 2005). However, melancholic MDD patients had a shallower LDAEP than non-melancholic patients (Fitzgerald et al., 2009). Finally, a positive correlation between the N1 LDAEP slope and specific somatic symptoms in MDD has been noted (Linka et al., 2009). Given the scarcity and inconsistency of research probing the LDAEP in MDD few conclusions can currently be drawn regarding its profile in the disorder. Interestingly, the LDAEP appears to predict antidepressant drug response, with steep pre-treatment slopes indicating a positive outcome to 5-HT-targeting drugs (Gallinat et al., 2000; Mulert et al., 2002; Lee et al., 2005), while shallow slopes seem to index positive outcome to other antidepressants (Linka et al., 2005; Juckel et al., 2007; Mulert et al., 2007).

Other monoamine systems are known to influence the LDAEP. For instance, the LDAEP has been shown to be influenced by dopamine (DA) transporter availability (Lee et al., 2011), DA levels (Beucke et al., 2010) and DA receptor stimulation (Juckel et al., 1997). Additionally, MDD individuals who responded favorably to chronic bupropion treatment, which modulates 5-HT, NA and DA systems, exhibited a steeper pre-treatment P2 intensity-dependence slope (P2 LDAEP; Paige et al., 1995). Though others examining the effects of altered DA levels and/or activation/antagonism of DA or noradrenaline (NA) receptors have found no associated LDAEP changes (O'Neill et al., 2006, 2008; Oliva et al., 2010). Such evidence challenges the proposed exclusive 5-HT system influence on the LDAEP.

Some of the mixed clinical findings regarding the LDAEP and 5-HT modulations may be sex-dependent. Though several groups have indicated no sex effects on the LDAEP (Linka et al., 2009; Park et al., 2010; Simmons et al., 2011), others have (Buchsbaum and Pfefferbaum, 1971; Hensch et al., 2008). A recent study specifically probing the influence of sex on the LDAEP also found higher slopes in females than males (Oliva et al., 2011). In support of the putative influence of sex on the LDAEP, estrogen pre-treatment in females enhanced the LDAEP (Guille et al., 2010). This is consistent with PET research indicating that females have lower baseline 5-HT neurotransmission levels than males (Nishizawa et al., 1997; Sakai et al., 2006). As such, steeper LDAEP slopes may exist in MDD females versus males, possibly due to the effects of female sex hormones on 5-HT neurotransmission.

Single-electrode estimation (at Cz) and dipole source analysis (DSA) are typically used in generating the LDAEP. Few studies have assessed LDAEP slopes derived via standardized low-resolution brain electromagnetic tomography (sLORETA or LORETA; Pascual-Marqui, 2002). The handful of studies that have assessed s/LORETA-derived LDAEP (s/LORETA-LDAEP) yield comparable results to scalp-derived indices (Mulert et al., 2002; Park et al., 2011).

This study examined whether differences between males and females with MDD and controls exist on the LDAEP. As two previous studies found no group differences, we expected comparable results. Given that 5-HT disturbances are associated with MDD, we predicted that clinical ratings may be positively related with LDAEP slope, though precedent literature probing this issue has found limited associations between depression symptom/severity and LDAEPs (Chen et al., 2005; Fitzgerald et al., 2009; Beucke et al., 2010). In addition to the N1/P2 LDAEP slope, we also examined N1 and P2 LDAEP slopes, as previous work has sometimes documented only modulations of N1 or P2 LDAEP slopes and/or intensity-dependent AEP amplitudes when probing monoamine system alterations. A third aim was to correlate scalp-derived (Cz) LDAEP indices with intensity-dependent activation in the primarily cortex using sLORETA (LDAEP-sLORETA). Given some evidence for a correlation between the two, we expected comparable results. Finally, we probed the effect of sex on AEPs and LDAEPs; we predicted steeper LDAEP slopes in females.

2. Methods

2.1. Participants

Fifty-three ($N = 53$) adults with a primary diagnosis of MDD (Table 1) were recruited from the Mood Disorders Research Unit at the University of Ottawa Institute of Mental Health Research Center. Patients were diagnosed by trained psychiatrists using the Structured Clinical Interview for DSM (Diagnostic and Statistical Manual of Mental Disorders) IV-TR Diagnoses, Axis I, Patient Version (SCID-IV-I/P; First et al., 1997). The 17 and 29 item versions of the Hamilton