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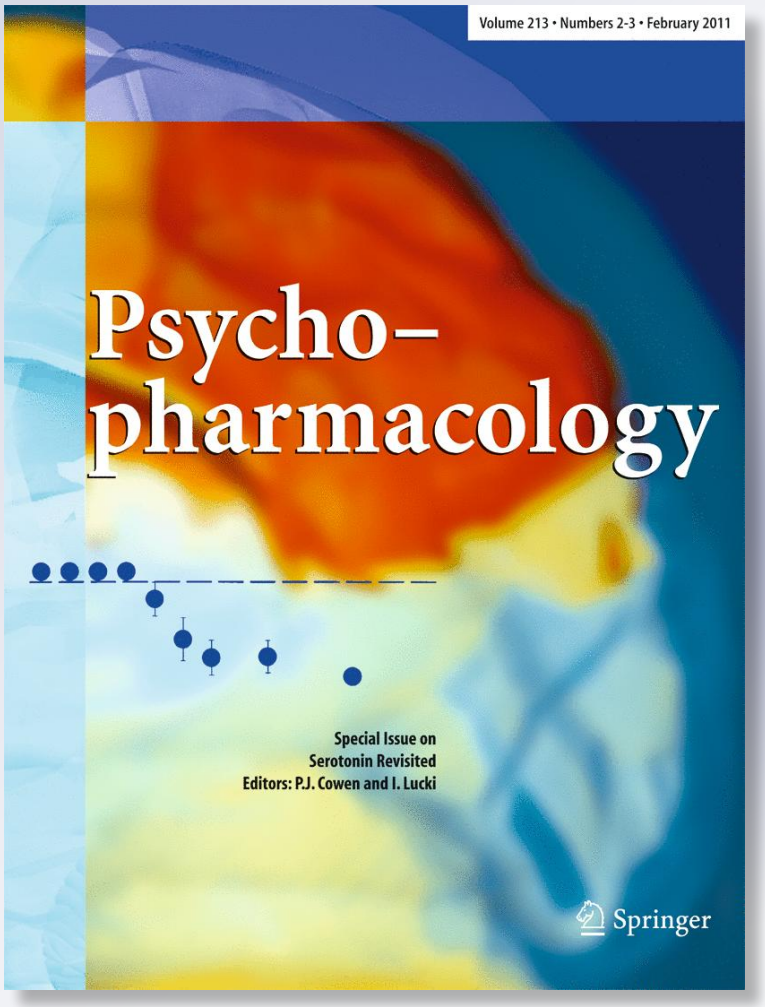

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ORIGINAL INVESTIGATION

The loudness dependence of the auditory evoked potential (LDAEP) as a predictor of the response to escitalopram in patients with generalized anxiety disorder

Young-Min Park · Do-Won Kim · Sangrae Kim · Chang-Hwan Im · Seung-Hwan Lee

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Abstract
Rationale The loudness dependence of the auditory evoked potential (LDAEP) has been proposed as a potential biological marker of central serotonergic activity. This study aimed to test the hypothesis that the LDAEP can be used to predict the response to escitalopram in patients with GAD.
Method Twenty-five patients with GAD were recruited. Scores on the Hamilton Anxiety Rating Scale (HAM-A), Clinical Global Impression-Severity Scale (CGI-S), and Beck Anxiety Inventory (BAI) were evaluated. To evaluate the LDAEP, the auditory event-related potential was measured before beginning medication. Peak-to-peak N1/P2 amplitudes and current source densities were calculated at five stimulus intensities, and the LDAEP was calculated as the linear-regression slope. The current source densities of the evoked potentials were analyzed by standardized low-resolution brain electromagnetic tomography (sLORETA). The loudness dependence of the current densities (sLORETA-LDAEP) was also calculated.
Results The pretreatment LDAEPs of all patients were positively correlated with the CGI-S response rates at 4 and 8 weeks, and with the HAM-A and BAI response rates at 8 weeks. The sLORETA-LDAEPs were positively correlated with the HAM-A response rates after 8 weeks of treatment. The HAM-A and CGI response rates at 8 weeks were higher in patients with a strong pretreatment LDAEP than in those with a weak LDAEP.
Conclusions The present study revealed that GAD patients with a favorable response to escitalopram treatment are characterized by a stronger pretreatment LDAEP. Measurement of the LDAEP appears to provide useful clinical information for predicting treatment responses in patients with GAD.

Keywords LDAEP · Serotonin · Generalized anxiety disorder · Current source density · sLORETA

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Introduction

The loudness dependence of the auditory evoked potential (LDAEP) has been proposed as a reliable indicator of the central serotonin (5-HT) system in humans (Hegerl and Juckel 1993). The LDAEP indicates the change 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 (Strobel et al. 2003), with a weak LDAEP reflecting high serotonergic neurotransmission and vice versa (Juckel et al. 2003).

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 SSRIs. Namely, there is a significant correlation between a

strong LDAEP—indicating low serotonergic function—and a favorable response to SSRIs in depressed patients (Gallinat et al. 2000; Linka et al. 2004).

Some studies have found a relationship between 5-HT dysfunction and generalized anxiety disorder (GAD). Reduced platelet paroxetine binding was found in patients with GAD (Iny et al. 1994). It was reported that *m*-chlorophenylpiperazine, which is a 5-HT1 and 5-HT2 receptor agonist, increased anxiety and hostility in patients with GAD (Germine et al. 1992). It was also reported that several antidepressants, such as venlafaxine, duloxetine, paroxetine, and escitalopram, have proven therapeutic efficacy against GAD (Davidson 2009). However, few studies have investigated the LDAEP and GAD. Senkowski et al. (2003) found that the LDAEP was weaker in patients with GAD than in healthy control subjects. We previously compared the LDAEP strength between healthy controls and patients with several major psychiatric disorders including major depressive disorder (MDD), bipolar disorder, schizophrenia, panic disorder, GAD, and posttraumatic stress disorder (Park et al. 2010) and found that the LDAEP did not differ significantly between healthy control subjects and patients with either GAD or MDD. Thus, whether or not the LDAEP is a trait marker remains controversial.

Source activity analysis of auditory N1/P2 components has recently been introduced and found to be of comparable power to scalp-measured LDAEPs (Mulert et al. 2002; Guille et al. 2008). Thus, it was considered interesting to explore the usefulness of the loudness dependence of the source activity to assess the responses of GAD patients to treatment.

We hypothesized that, like MDD, the LDAEP can be used to predict the response to escitalopram in patients with GAD. In this study, we assessed the predictive value of the pretreatment LDAEP and the loudness dependence of the source activity in a sample of patients with GAD exclusively treated with escitalopram, which is a highly selective 5-HT reuptake inhibitor. To our knowledge, this is first study to have investigated treatment responses using the LDAEP in patients with GAD.

Materials and methods

Patients

A total of 25 patients participated in this study. They were from 18 to 75 years old and met GAD criteria according to diagnoses on axis I of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (American Psychiatric Association, 1994). At the screening visit, patients were included if they had a total score of >18 on the Hamilton Anxiety Rating Scale (HAM-A). Patients were excluded if they had another axis I disorder that was considered the predominant diagnosis within the previous 6 months. To rule out comorbid depressive disorder, patients were excluded if they had a total score of >18 on the Hamilton Depression Rating Scale (HAM-D) at the screening visit. Patients with any severe medical illness, high suicidal risk, a history of neurological disorder, substance abuse, mental retardation, or brain trauma, and pregnant women were also excluded. Patients who took any psychotropic drugs within 2 weeks prior to screening were also excluded. Only one of the patients smoked. Written informed consent was obtained from all patients, and the study protocol was approved by the Ethics Committee of Inje University Ilsan-paik Hospital.

Study design

This study commenced with a 1-week screening period followed by an 8-week open-label period with flexible doses of escitalopram (10–20 mg/day). The washout period lasted at least 2 weeks if patients were taking any psychotropic drugs before escitalopram treatment. During the open-label period, patients received escitalopram at 10 mg/day, which could be increased to 20 mg/day at weeks 2, 4, or 8, if clinically indicated. The LDAEP was evaluated by measuring the auditory event-related potential (ERP) before beginning escitalopram. Concomitant drugs including other antidepressants, antipsychotics, and mood stabilizers were not allowed except low-dosage alprazolam (up to 0.5 mg) or lorazepam (up to 1 mg). In addition to HAM-A, scores on the Clinical Global Impression-Severity Scale (CGI-S) and Beck Anxiety Inventory (BAI) were obtained at baseline and at 2, 4, and 8 weeks after beginning medication. Response was defined as a decrease of at least 50% in the HAM-A, CGI-S, or BAI score after 4 and 8 weeks.

Electrophysiological assessment and amplitude analysis

All of the patients were seated in a comfortable chair in a sound-attenuated room. Auditory stimulation comprised 1,000 stimuli with an interstimulus interval that was randomized between 500 and 900 ms. Tones of 1,000 Hz and 80-ms duration (10-ms rise and 10-ms fall) were presented at five intensities (55, 65, 75, 85, and 95 dB SPL) via headphones (MDR-D777, Sony, Tokyo, Japan). These stimuli were generated by E-Prime software (Psychology Software Tools, Pittsburgh, USA). EEG data were recorded from 64 scalp sites (FP1, FPZ, FP2, AF3, AF4, F7, F5, F3, F1, FZ, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FCZ, FC2, FC4, FC6, FT8, T7, C5, C3, C1, CZ, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPZ, CP2, CP4, CP6, TP8, P7, P5, P3, P1, PZ, P2, P4, P6, P8, PO7, PO5, PO3, POZ, PO4, PO6, PO8, CB1, O1, OZ, O2, CB2, M1, and M2) using silver/silver-chloride electrodes according to the international 10–20

system (impedance <10 kΩ) and using an Auditory Neuroscan SynAmp amplifier (Compumedics USA, El Paso, TX, USA). Data were collected at a sampling rate of 1,000 Hz using a bandpass filter of 1–100 Hz.

Data were reanalyzed with a 1- to 30-Hz bandpass filter using Scan 4.3 software, and ocular contamination was removed using established mathematical procedures (Semlitsch et al. 1986). ERP sweeps with artifacts exceeding 70 μV were rejected at all electrode sites. For each intensity and for each subject, the N1 peak (most-negative amplitude between 80 and 130 ms after the stimulus) and P2 peak (most-positive peak between 130 and 230 ms after the stimulus) were then determined at the Fz, Cz, Pz, C5, and C6 electrodes.

The peak-to-peak N1/P2 amplitudes were calculated for the five stimulus intensities, and the LDAEP was calculated as the linear-regression slope.

Analysis of current source densities using standardized low-resolution brain electromagnetic tomography

Based on the averaged scalp-recorded electric potential, standardized low-resolution brain electromagnetic tomography (sLORETA) was used to estimate current density (http://www.uzh.ch/keyinst/NewLoreta/LORETA01.htm; Pascual-Marqui 2002). sLORETA estimates the standardized source current density using the realistic three-shell head model based on the Montreal Neurological Institute (MNI) 152 template provided by the Brain Imaging Center of the MNI (Fuchs et al. 2002) under the assumption that the activity at any single neuron should be highly synchronized to the activity of its closest neighbors. The solution space is restricted to the cortical gray matter and hippocampus of the head model and partitioned into 6,239 voxels at a spatial resolution of 5 mm. Anatomical labels such as Brodmann areas (BAs) are provided by using an appropriate transformation from MNI to Talairach space (Brett et al. 2002).

The loudness dependence of the source activity (LDAEP-sLORETA) was determined by calculating sLORETA images for each subject and each sound pressure level. Four electrodes (CB1, CB2, VEO, and HEO) were not used in the sLORETA analysis since these electrode locations are not supported by the sLORETA software. The calculated standardized current density was averaged between 60 and 240 ms poststimulus from the primary auditory cortex (BA41) in accordance with a previous study (Mulert et al. 2002). We calculated the three values of current density for the left, right, and averaged data, one from both hemispheres over the voxels that fall under the primary auditory cortex (Table 1).

Table 1 The Montreal Neurological Institute coordinates of the standardized low-resolution brain electromagnetic tomography region of interest (primary auditory cortex: Brodmann area 41)

Left hemisphere			Right hemisphere		
x	y	z	x	y	z
−55	−25	5	35	−35	15
−55	−20	5	40	−35	5
−55	−30	10	40	−30	5
−55	−25	10	40	−40	10
−55	−20	10	40	−35	10
−50	−25	5	40	−30	10
−50	−30	10	40	−25	10
−50	−25	10	40	−35	15
−50	−20	10	45	−30	5
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−45	−35	15	50	−25	5
−45	−30	15	50	−30	10
−45	−25	15	50	−25	10
−40	−35	5	50	−20	10
−40	−30	5	50	−35	15
−40	−40	10	50	−30	15
−40	−35	10	55	−25	5
−40	−30	10	55	−20	5
−40	−25	10	55	−30	10
−35	−35	10	55	−25	10
−35	−35	15	55	−20	10
			55	−15	10

Statistical analysis

Spearman's correlation was used to assess the association between the LDAEP and LDAEP-sLORETA, and the clinical response rate using the method of last observation carried forward for missing values. Patients were divided into two subgroups based on their LDAEP values (dichotomized at the median), and the Mann–Whitney *U* test was used to compare the response rate between the two groups. All of the analyses were performed using standard software (SPSS for Windows), and *p* values smaller than 0.05 were considered statistically significant.

Results

In total, 35 GAD patients were recruited. However, ten subjects dropped out during the study due to withdrawal of informed consent (n=3), or protocol violation (n=7), and hence data

Table 2 Demographics and clinical characteristics of the patients with generalized anxiety disorder

Number	25
Age (years)	52.4±12.7
Sex (males/females)	10/15
Education (years)	10.3±2.8
Duration of illness (months)	13.7±10.3
Escitalopram dosage (mg)	13.4±5.7
HAM-A score (baseline/8 weeks)	26.7±7.0/8.3±7.9
BAI score (baseline/8 weeks)	25.2±11.5/8.6±8.0
CGI-S score (baseline/8 weeks)	5.7±0.7/2.4±1.1

Data are mean and SD values

HAM-A Hamilton Anxiety Rating Scale, *BAI* Beck Anxiety Inventory, *CGI-S* Clinical Global Impression-Severity Scale

from 25 GAD patients were analyzed using the method of last observation carried forward. Table 2 presents the demographic and clinical characteristics of the patients with GAD.

Amplitude analysis of LDAEP

In the Cz area, the LDAEP of all patients was positively and significantly correlated with the CGI-S response rate (r=0.41; p=0.040) at week 4, and with the HAM-A response rate (r=0.46; p=0.020), BAI response rate (r=0.43; p=0.033), and CGI-S response rate (r=0.68; p=0.00019) at week 8 (Fig. 1). In the Fz and Pz areas, the LDAEP of all patients was also positively correlated with the HAM-A response rate (at Fz, r=0.40; p=0.044) and the CGI-S response rate (at Fz, r=0.59; p=0.002; at Pz, r=0.55; p=0.004) at week 8 of treatment. In the C5 and C6 areas, no significant correlations were found between the response rates and the LDAEP.

Current source density analysis of LDAEP

Figure 2 depicts the current density of the primary auditory cortex (BA41) in both hemispheric regions (Fig. 2a) and the current densities of an averaged voxel according to increasing sound pressure (Fig. 2b). The sLORETA-LDAEPs were positively and significantly correlated with the HAM-A response rate in the left hemisphere (r=0.41; p=0.040), the right hemisphere (r=0.48; p=0.013), and the averaged data (r=0.54; p=0.005; Fig. 3) at week 8. However, there were no significant correlations with the BAI and CGI-S response rates.

Comparison between groups with strong and weak LDAEP

The patients were divided into the following two subgroups based on the median LDAEP (=0.67) at the Cz electrode (Gallinat et al. 2000): a strong-LDAEP group (n=12) and a weak-LDAEP group (n=13) (Table 3). The HAM-A response rate (p=0.040) and CGI-S response rate (p=0.005) at week 8 were significantly higher in patients with a stronger baseline LDAEP.

The strong-LDAEP group consisted of 11 responders—defined as a decrease in the HAM-A score of at least 50%—and one non-responder at week 8, while the weak-LDAEP subgroup consisted of nine responders and four non-responders. The number of responders did not differ significantly between the two subgroups on HAM-A (P=0.322). Similarly, the strong-LDAEP subgroup consisted of 11

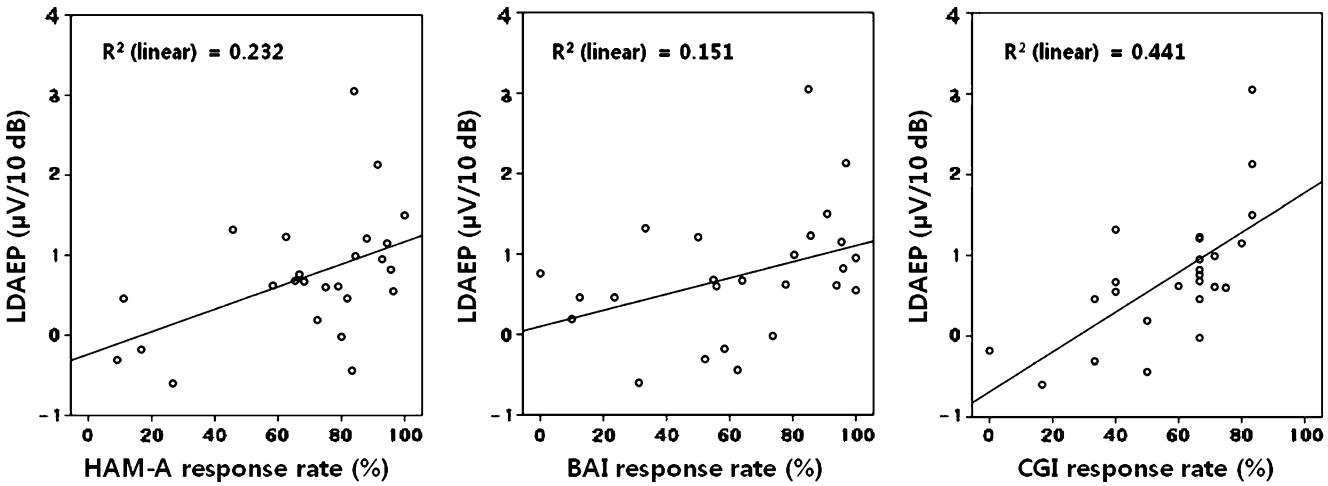

Fig. 1 Scattergrams between the loudness dependence of the auditory evoked potential (*LDAEP*) and symptom response rates in 25 patients with generalized anxiety disorder treated with escitalopram. The response rate was calculated as (week8 − −baseline) × 100/baseline. Spearman's rho values for correlations of the Hamilton Anxiety Rating Scale (*HAM-A*), Beck Anxiety Inventory (*BAI*), and Clinical Global Impression (*CGI*) response rates with LDAEP were 0.46 (p=0.020), 0.43 (p=0.033), and 0.68 (p=0.00019), respectively

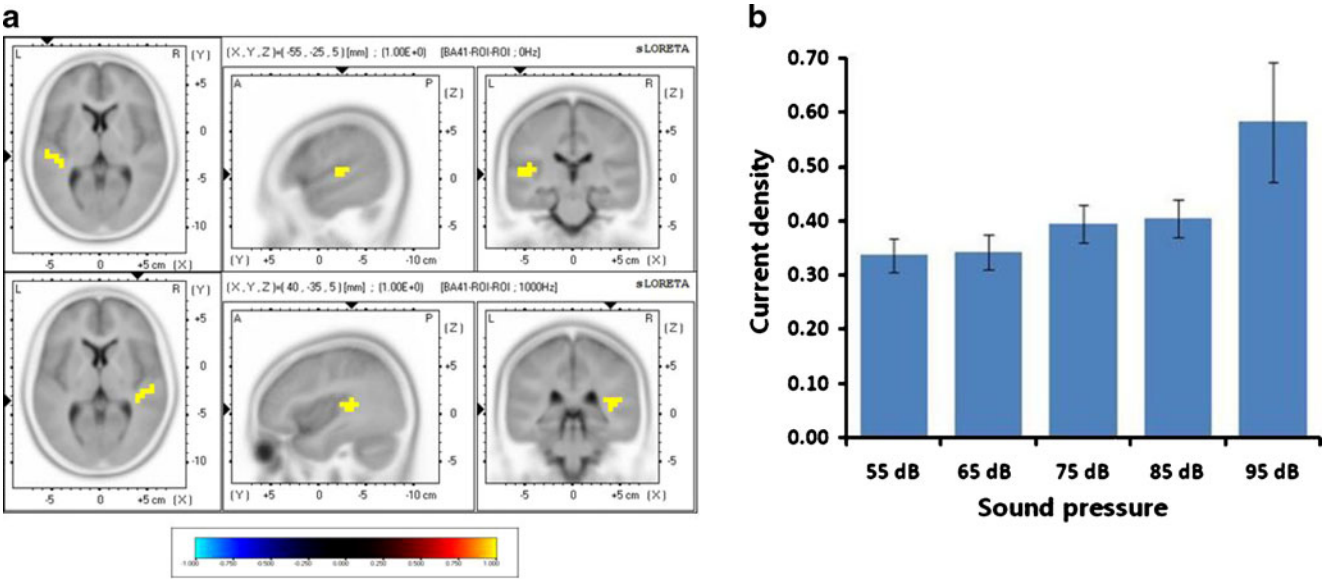

Fig. 2 **a** Current activity of the primary auditory cortex (Brodmann area 41 (*BA41*)) in both hemispheres, as calculated by standardized low-resolution brain electromagnetic tomography (*sLORETA*). **b** The change in current densities for an averaged voxel at five sound pressures.

responders—defined as a decrease in the CGI-S score of at least 50%—and one non-responder at week 8, while in the weak-LDAEP subgroup consisted of seven responders and six non-responders. Although there was no significant difference in the number of CGI-S responders between the two groups (p=0.073), the strong-LDAEP group tended to have more responders.

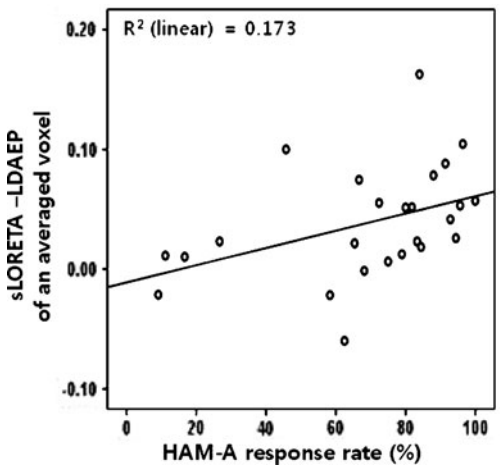

Fig. 3 Scattergram showing the relationship between sLORETA-loudness dependence of auditory evoked potential (*LDAEP*) data and Hamilton Anxiety Rating Scale (*HAM-A*) symptom response rate in 25 patients with generalized anxiety disorder treated with escitalopram. sLORETA-LDAEP in this figure was calculated as the slope of the linear regression from an averaged current density of all voxels of the primary auditory cortex of both hemispheres. The response rate was calculated using the following formula: (week8 − −baseline) × 100/baseline. HAM-A response rates were correlated (Spearman's rho) with sLORETA-LDAEP (r=0.54; p=0.005)

Discussion

In animals, threatening events are thought to increase synaptic 5-HT levels (Handley 1995). 5-HT_{1A}-knockout mice exhibit a decreased immobility in the forced swim test, an effect that is commonly associated with antidepressant treatment (Ramboz et al. 1998). 5-HT_{1A} receptor agonists, such as buspirone, have been shown to be effective in treating GAD in animal models (Taylor et al. 1985). Clinical trials have found a relationship between 5-HT levels and the severity of GAD. One study found that reduced platelet paroxetine binding was observed in patients with GAD (Iny et al. 1994), while another study showed that administration of *m*-chlorophenylpiperazine, a nonspecific 5-HT1 and 5-HT2 agonist, led to increased anxiety and hostility in patients with GAD (Germine et al. 1992). Yet another study found that elevated urinary levels of the 5-HT metabolite 5-hydroxyindoleacetic acid predicted higher anxiety levels in patients with GAD (Garvey et al. 1995). In addition, several 5-HT-related antidepressants, such as venlafaxine, duloxetine, paroxetine, sertraline, and escitalopram, were shown to be particularly effective in the treatment of GAD (Bandelow et al. 2008). Thus, there is evidence both from animal models and clinical trials that 5-HT functioning is abnormal in GAD (Connor and Davidson 1998).

Hettema (2008) reported that GAD and MDD are linked in some way, probably biologically, but certainly phenomenologically. Up to 80% of subjects with lifetime GAD also have a comorbid mood disorder during their lifetime (Gorwood 2004). Furthermore, GAD and MDD have a

Table 3 Comparison of patients with strong and weak pretreatment LDAEP (dichotomized at the median)

	Strong LDAEP (n=12)	Weak LDAEP (n=13)	Mann–Whitney U
Sex (males/females)	7/5	3/10	0.111 (Fisher's test)
Age (years)	51.2±13.0	53.5±12.9	0.567
Escitalopram dose (mg, 8 weeks)	14.6±6.2	12.3±5.3	0.285
HAM-A score (baseline)	26.9±7.9	26.5±6.5	0.956
BAI score (baseline)	24.5±9.9	25.8±13.1	0.892
CGI-S score (baseline)	5.9±0.5	5.5±0.9	0.252
HAM-A score (8 weeks)	5.3±5.3	11.1±9.0	0.053
BAI score (8 weeks)	6.9±9.3	10.2±6.5	0.107
CGI-S score (8 weeks)	1.8±0.6	2.9±1.1	0.006*
HAM-A response rate (%, 8 weeks)	80.9±16.8	58.3±30.9	0.039*
BAI response rate (%, 8 weeks)	72.4±31.3	55.0±28.8	0.135
CGI-S response rate (%, 8 weeks)	70.1±12.1	46.4±22.2	0.005*

Data are mean and SD values

HAM-A Hamilton Anxiety Rating Scale, *BAI* Beck Anxiety Inventory, *CGI-S* Clinical Global Impression-Severity Scale

*p<0.05

common connection to the neuroticism personality trait (Kendler et al. 2007). It was found that the presence of the 5-HT transporter (5-HTT) SS genotype may increase the risk of GAD (You et al. 2005). Thus, like MDD, GAD is also related to 5-HT dysfunction. No data related to the treatment response and the LDAEP of patients with GAD have been reported previously, and hence this is first report of treatment responses based on the LDAEP in GAD.

According to several preclinical and clinical studies, the LDAEP is one of the best validated indicators of serotonergic function (Hegerl et al. 2001). Juckel et al. (1997, 1999) found an increased intensity dependence of the cat's auditory evoked potential component, with the N1/P2-component exhibiting the highest functional similarity to this in humans following stimulation of the presynaptic 5-HT1A receptor and antagonism of the 5-HT2 receptor. In contrast, they also found that stimulation of the postsynaptic 5-HT1A receptor and antagonism of the presynaptic 5-HT1A receptor decreased the loudness dependence of the cat's auditory evoked potential component. Manjarrez et al. (2005) obtained the same results in rats. Nathan et al. (2006) were the first to report a reduced LDAEP after an acute increase in 5-HT levels following the administration of citalopram, which supported the inverse relationship between 5-HT and the LDAEP in humans. Juckel et al. (2008) reported that 5-HT1B alleles were related to an increased LDAEP in healthy volunteers.

We found that the LDAEP at Cz of all subjects was positively correlated with the HAM-A, BAI, and CGI response rates at week 8. These findings suggest that a strong LDAEP is related to a favorable outcome to escitalopram therapy in patients with GAD. Some investigators have reported that a strong LDAEP is related to a favorable response to acute SSRI treatment in MDD (Paige et al. 1994; Gallinat et al. 2000). Furthermore, the same authors also found no reduction of the LDAEP after SSRI treatment, although a treatment period of 4 weeks was shown to be too short to induce significant changes in the LDAEP (Gallinat et al. 2000). In contrast, responders to reboxetine, a noradrenergic antidepressant, were reportedly characterized by a weak LDAEP at baseline (Juckel et al. 2007). Meanwhile, Paige et al. (1995) reported that a strong LDAEP also predicts a favorable response to bupropion. In addition, Strobel et al. (2003) reported that the association between a functional polymorphism in the promoter region of the 5-HTT gene (5-HTTLPR) and the LDAEP is stronger when a functional polymorphism in the dopamine D4 receptor gene (DRD4 exon III) is considered in analyses in healthy controls. These results indicate that the use of the LDAEP to predict the response to antidepressants is not confined to serotonergic antidepressants (Hegerl et al. 2001).

Linka et al. (2004) showed that all LDAEPs at each of Fz, Fcz, and Cz were negatively correlated with the pretreatment HAM-D score. However, we found that the LDAEPs at Fz and Pz of all patients were positively correlated only with the CGI response rate, with most of the positive correlations found at Cz. As in our study, Gallinat et al. (2000) and Gudlowski et al. (2009) found positive correlations between the LDAEP in MDD and schizophrenia patients at Cz, respectively. We previously also found several positive correlations between the LDAEP and various psychiatric diseases at Cz (Park et al. 2010). Thus, it is possible that Cz is the most appropriate site for measuring N1/P2 of the LDAEP.

Linka et al. (2007) reported no general abnormality of the LDAEP in patients with MDD in comparison to healthy

control subjects. These findings suggest that specific alterations of the LDAEP are generally not to be expected in MDD. Likewise, the mean LDAEP did not differ significantly between patients with GAD and healthy control subjects in our previous study (Park et al. 2010). It is assumed that GAD, like MDD, comprises heterogeneous subgroups, and such heterogeneity could produce mixed responses to serotonergic antidepressants in patients with GAD.

sLORETA-LDAEP revealed a significant positive correlation between the current source density and the HAM-A response rate in the left and right hemispheres, and the averaged data. Although no significant correlation was found with BAI and CGI-S response rates, the correlation between the HAM-A response rate and sLORETA-LDAEP was stronger than between the HAM-A response rate and LDAEP. We conclude that the power of sLORETA-LDAEP as an analytical tool is comparable to that of scalp-measured LDAEP.

This study had several limitations. Firstly, the relatively small sample limits the generalizability of our findings. Secondly, we did not control for the menstruation cycle in female patients, which can influence serotonergic function. *Given the mean age of the patients, the majority may have been postmenopause.* Thirdly, we did not retest the LDAEP after 8 weeks of treatment, like Gallinat et al. (2000), who did not find a significant difference between the pre- and posttreatment LDAEP after 4 weeks in patients with MDD. Fourthly, although we did not exclude subjects with comorbid depression, subjects were excluded if they had a total score of >18 on the HAM-D at the screening visit. However, our subjects had GAD as a principal diagnosis; other GAD studies have used this as an inclusion criterion (Sramek et al. 1996; Coric et al. 2009). Fifthly, the number of responders and non-responders did not differ significantly in each group (i.e., strong LDAEP and weak LDAEP). It is currently difficult to apply LDAEP analysis to the individual patient. Studies with larger samples are needed to allow more definite conclusions to be drawn.

In summary, the present study revealed that GAD patients with a strong pretreatment LDAEP responded more favorably to escitalopram treatment than patients with a weak pretreatment LDAEP. Measurement of the LDAEP appears to provide useful clinical information for predicting the treatment response in patients with GAD. Future studies should include larger samples whilst controlling for interfering variables, such as the menstruation cycle.

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