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ORIGINAL PAPER

Loudness dependence of auditory evoked potentials (LDAEP) in clinical monitoring of suicidal patients with major depression: a pilot study

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Abstract Loudness dependence of auditory evoked potentials (LDAEP) is a validated in vivo marker of central serotonergic function. We aimed at measuring serotonergic activity in a follow-up study of suicidal patients. It should be investigated whether suicide attempts or suicidal states cause changes in the LDAEP. Thirteen patients (mean age, 40.9 ± 11.3 years; age range, 20–61, 6 male) with a major depressive episode who had attempted suicide or had suicidal plans (Hamilton Depression Rating Scale item 3 [suicidality] ≥3) were included in the study. LDAEP and psychometric measurements took place about 2, 5, 9 and 16 days after attempted suicide or suicidal action. On day 9, LDAEP was significantly higher compared to day 2 and day 16; there was a similar tendency compared to day 5. Instability of central serotonergic function is suggested resulting in reduced serotonergic activity about 1 week after suicide attempt. Further studies are necessary that include larger samples in order to distinguish between different psychiatric diseases and to consider confounding factors like gender, smoking, medication, impulsivity or lethality of suicidal action.

Keywords Suicidality · Serotonin · Depression · Auditory evoked potentials · Intensity dependence · LDAEP

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Introduction

According to most recent data of WHO statistics, the average suicide prevalence rate in Europe is 13.9 per 100,000 [16]. Mental disorders are one of the most significant risk factors for suicide or suicide attempts [35]. In psychiatric patients without regard to their diagnoses, low serotonergic function was found in relation to suicidal behaviour. Concentrations of the serotonin (5HT) metabolite 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF) were reduced [4, 24, 30]. They also correlated with Hamilton Depression Rating Scale (HAMD) item 3, measuring suicidality [1, 5, 9, 43]. Reduced 5-HIAA levels were used to predict suicide or suicide attempts [37, 47, 52]. Low 5-HIAA levels were found in subjects immediately or recently after suicide attempt [3, 12, 55] but not in patients with suicide attempts in their history [6, 34, 48].

However, the concept of a relation between the central serotonergic system and suicidality itself has to be critically discussed [32, 46]. Different aspects of suicidality, for example, impulsivity, autodestructive behaviour, suicidal intention or choice of suicide method, have to be taken into consideration.

The loudness dependence of auditory evoked potentials (LDAEP) is regarded as a method of measuring serotonergic activity, especially synaptically released serotonin. Low serotonergic activity is represented by a high LDAEP and vice versa [15, 17, 19–21, 44]. Regarding LDAEP and suicidality, it was shown that patients after attempted suicides, independent from their diagnoses, had a weaker LDAEP; however, people with acute suicidal ideas had a strong LDAEP [18]. These results correspond to an early study using somatosensory evoked potentials [2] but are in opposition to a study using visually evoked potentials [7].

Due to these earlier findings, we assumed that increased probability of suicidal behaviour might be associated with an instable serotonergic system. We hypothesized that acute suicidality is characterized by temporarily low serotonergic activity indicated by high LDAEP. Furthermore, we hypothesized that LDAEP would be lower during follow-up measurements. A follow-up study of depressed patients immediately after attempted suicide or with suicidal behaviour was designed in order to test these hypotheses.

Methods

Patients

Thirteen patients (mean age, 40.9 ± 11.3 years; age range, 20–61; 6 male) were included in the study after they had given written informed consent. All patients were diagnosed with a major depressive episode using structured clinical interview for DSM-IV disorders (SCID I and II). There were psychiatric co-morbidities in some patients (pathological gambling [$N = 1$], obsessive–compulsive disorder [$N = 1$], borderline personality disorder [$N = 1$], alcohol abuse [$N = 1$], social phobia [$N = 1$]). Patients were included in the study if HAMD item 3 was rated 3 or 4, that is, suicidal thoughts/behaviour or attempted suicide. Eight patients were included because of suicidal behaviour. Actual suicide attempts were made with medication overdose ($N = 2$), cutting ($N = 2$), combination of medication overdose and CO intoxication ($N = 1$). There was no relevant somatic co-morbidity in the patients. Patients were included in the study without consideration of their medication. Six patients were smokers.

Ideally, patients were included in the study on the day of their admittance to LWL University Hospital Bochum, Clinic of Psychiatry, Psychotherapy and Preventive Medicine. The first testings were performed approximately 2 days (T1) after attempted suicide or suicidal behaviour. Consecutive testings were performed five (T2), nine (T3), and 16 days (T4), one (T5), three (T6) and six (T7) months later. However, 1, 3 and 6 months later, an increasing number of patients had dropped out of the study deliberately or could not be contacted anymore; so these testing days were not included in the final analysis. On each testing day, LDAEP measurement was taken. Moreover, a full psychiatric status was collected, and BDI, HAMD21 and BPRS questionnaires had to be answered. For further details about testing days and psychopathological data, see Table 1.

At T1, six patients received psychopharmacologic medication, that is, duloxetine, mirtazapine, escitalopram, fluoxetine, bupropion, olanzapine and quetiapine. Some patients were treated with promethazine, chlorprothixene, pipamperone or lorazepam additionally. At T2, 12 patients received psychotropic medication, among them several antidepressants (escitalopram, bupropion, venlafaxine, duloxetine, mirtazapine and fluoxetine), but patients were also treated with lorazepam, temazepam, flunitrazepam, quetiapine, olanzapine, promethazine, chlorprothixene or pipamperone. While most antidepressive treatments remained quite unchanged in the course of the study, accompanying medication was generally reduced and discontinued after some time.

Loudness dependence of auditory evoked potentials (LDAEP)

Testing of auditory evoked potentials took place in an electrically shielded and sound-attenuated room adjacent to the recording apparatus (BrainVision BrainAmp®, MR, Brain Products GmbH, Munich, Germany). A clinical EEG measurement was taken before AEP testing in order to exclude patients with pathological EEG. The subjects were seated in a slightly reclined chair with a head rest. They were asked to keep their eyes open during the entire testing. AEP were recorded with 32 non-polarizable Ag–AgCl electrodes referred to FCz, placed according to the international 10/20-system. We controlled for eye movements with an electrode located 1 cm below the left outer canthus. Impedances remained below 5 kOhm during the entire testing. Auditory stimuli were presented binaurally

Table 1 Means and SD of psychopathological and LDAEP data on four testing days (T1–T4)

	T1	T2	T3	T4	Statistical analysis (p)
Days post-attempted suicide	1.77 ± 1.24	4.58 ± 1.38	8.75 ± 1.36	15.77 ± 1.3	
HAMD	25 ± 7.9	19 ± 5.6	16 ± 5.8	16 ± 6.7	0.001
HAMD, item 3	3.39 ± 0.5	1.8 ± 1.1	1.1 ± 1.1	1.1 ± 1.0	0.000
BPRS	44 ± 7.5	42 ± 5.7	38 ± 5.1	34 ± 4.2	0.001
BPRS-ANDP	16 ± 3.5	15 ± 2.3	14 ± 2.1	12 ± 2.9	0.003
BDI	37 ± 13	35 ± 14	25 ± 15	22 ± 13	0.184, n.s.
LDAEP	0.1715 ± 0.1826	0.1766 ± 0.1608	0.3052 ± 0.2328	0.1827 ± 0.1836	0.078, n.s.

Statistical analyses were performed using Friedman test. Level of significance was set at $p < 0.05$

via headphones. Pure sinus tones (1,000 Hz, 40-ms duration, 10-ms rise/fall time and ISI 1,800–2,200 ms) of five different intensities (60, 70, 80, 90, and 100 dB SPL; 70 stimuli per intensity) were presented in a pseudorandomized way using Presentation 11.3® (Neurobehavioral Systems Inc., Albany, CA, USA). Data were collected with a sampling rate of 500 Hz and an analogous band-pass filter (0.16–70 Hz). Subjects were included in further analysis if at least 40 artefact-free sweeps per intensity (maximum amplitude range ±100 μV during a 350 ms prestimulus and an 800 ms post-stimulus period) were available. Using BrainVision Analyzer® (Brain Products GmbH, Munich, Germany), artefact-free stimuli were averaged and auditory evoked potentials were calculated further at Cz, which is the point of the maximum amplitude of N1 and P2. The N1 amplitude was regarded as the lowest point between 50 and 150 ms after the stimulus, P2 as the highest point between 100 and 250 ms post-stimulus. These amplitudes were collected semi-automatically. The N1/P2 amplitude was then calculated as the amplitude difference between N1 and P2. The loudness dependence of the scalp data was calculated as an exponential slope of the amplitudes of the single loudness levels.

Results

As calculated using Kolmogorov–Smirnov test, data were not normally distributed. Therefore, further statistical analyses were performed with the help of Friedman and Wilcoxon tests. Level of significance was set at $p < 0.05$. If all examination days were calculated, LDAEP data only differed by tendency when calculated using Friedman test ($p = 0.078$). However, LDAEP seemed to be elevated on the third testing day (Fig. 1). Thus, we calculated Wilcoxon signed rank tests to compare T3 with the other testing days. There were significant differences if T3 was compared to T1 ($p = 0.015$) and to T4 ($p = 0.019$). A tendency was seen if T2 and T3 were compared ($p = 0.075$).

Regarding psychometrical scales, there were highly significant decrease in HAMD score ($p = 0.001$), HAMD item 3 ($p = 0.000$), BPRS score ($p = 0.001$) and BPRS subscore for anxiety and depression (BPRS-ANDP; $p = 0.003$) when T1, T2, T3 and T4 were taken into consideration. Interestingly, BDI was the only self-rating scale applied and did not change significantly in the course of the time ($p = 0.184$).

Discussion

To the best of our knowledge, this is the first follow-up study on serotonergic activity, which included acutely suicidal patients and considered exact times post-suicide attempt in order to investigate the course of serotonergic activity in such an exceptional state. We found higher LDAEP, that is, lower serotonergic activity, on the 9th day after attempted suicide. Directly after the suicide attempt (days 2 and 5) and at the later date (day 16), LDAEP was on similarly lower levels. This effect was significant if T3 was compared to T1 and T4 individually with Wilcoxon signed rank tests; there was a tendency if T3 and T2 were compared. The comparison of all four testing days using Friedman test only revealed a tendency which may be explained by the small sample size.

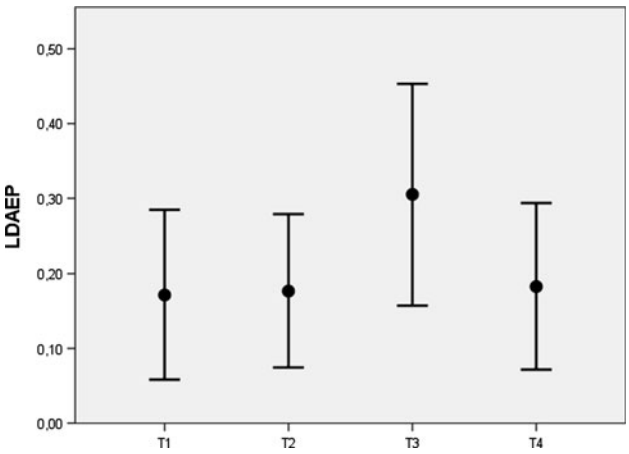

Fig. 1 LDAEP of the subjects on four testing days. *T1,* 2 days post-suicide attempt or suicidal behaviour; *T2,* 5 days post-suicide attempt or suicidal behaviour, *T3,* 9 days post-suicide attempt or suicidal behaviour; *T4,* 16 days post-suicide attempt or suicidal behaviour

In an early study, increased LDAEP was found in acutely suicidal depressed patients [18]. The same article reported on independent patient samples whose subjects suffered from major depression, affective disorders or alcohol dependence and had a previous history of suicide attempts; LDAEP was decreased in these patients. As far as we know, Chen et al. [8] are the only other group who investigated LDAEP in suicidal patients. They found LDAEP to be increased in depressed patients with a previous suicide attempt compared to non-suicide attempters. However, although acutely suicidal patients were examined, exact information about suicidality or suicide attempt is not provided in that study so comparison with the present study is difficult. Other studies on evoked potentials in suicidal patients are rather old and used visually [7] or somatosensory evoked potentials [2].

After all, considering the current data, the present results are difficult to explain. We hypothesized that LDAEP would be strong in acutely suicidal patients, indicating reduced serotonergic activity but would decrease in the course of the study. Thus, a general instability of the serotonergic system might be shown. In healthy subjects,

LDAEP has been proven to be quite stable throughout the lifetime and to be independent from acute serotonergic challenges [39–41, 54], although there are also opposing results concerning acute and chronic administration of serotonergic medication [33, 50]. As suicidal patients examined in this study were diagnosed with depression, it should be considered that the serotonergic system in psychiatric diseases might be more sensitive to changes in serotonin-dependent states like mood or impulsivity. This was shown in borderline personality disorder; LDAEP was stronger in more impulsive patients suffering from this disease [38]. In the present study, it might be postulated that higher LDAEP on the third testing day may represent a fluctuation due to serotonergic dysregulation following the exceptional state of suicide attempt. It could be speculated that serotonergic activity tends to be in a more balanced state again on the fourth testing day. Thus, a serotonergic dysfunction being involved in suicidal behaviour as hypothesized by Nordström and Asberg [36] is underlined by the present results.

However, this assumption does not explain all aspects of the LDAEP changes. An influence of medication might be discussed. On day 2, seven patients were treated with antidepressants. On days 5 and 9, nine and ten patients, respectively, received antidepressive medication, which was not changed considerably during the follow-up period. Thus, a medication effect seems unlikely, but cannot be ruled out. Moreover, it is still controversial if selective serotonin reuptake inhibitors (SSRI) increase suicidality [31] so deductions from medication effects are not only difficult with respect to LDAEP but also regarding psychopathological conditions.

Further studies investigating serotonergic function and suicidality have focused on different methods like measuring CSF levels of serotonin or its metabolites or on neuroimaging. Findings of reduced CSF levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in patients immediately after suicide attempt [14, 23, 25, 34, 48, 53, 55] led to the serotonin deficiency hypothesis of suicidal behaviour [28]. It was postulated that low serotonergic activity increases the probability of suicidal behaviour. However, in patients with a history of earlier suicide attempts, reduced 5-HIAA has not been found [6, 34, 48], which may also suggest dynamic changes of serotonergic activity in suicidality.

Other groups emphasized that the suicide method should be taken into account. In impulsive compared to non-impulsive suicide attempters, plasma 5-HIAA was low while platelet serotonin levels were increased; moreover, plasma 5-HIAA correlated with impulsivity [51]. Using ^{18}F-FDG PET, Oquendo et al. [42] showed hypometabolism in the prefrontal cortex in high-lethality attempters compared to low-lethality attempters. In ^{123}I-beta-CIT studies, impulsiveness in suicide attempters negatively correlated with serotonin transporter–binding potential [26, 49]. Mann et al. [29] found a relationship between CSF 5-HIAA and history of planned suicide attempts and suicide attempts with greater medical damage.

There have been further attempts to predict suicide risk using other methods like relating serotonergic function to HPA axis abnormalities [10, 45], serum cholesterol levels [11], fenfluramine challenge or prolactin response [22]. As these methods provide contradictory results and measure serotonergic activity in an indirect way, it seems more appropriate to use a direct indicator of serotonergic function such as LDAEP.

As an earlier study showed that LDAEP of smokers is decreased compared to non-smokers, smoking might have influenced the results [13]. A study by Malone et al. [27] showed an inverse relation between cigarette smoking and serotonin function as measured with fenfluramine challenge test and CSF 5-HIAA levels. As smokers in that study were more likely to attempt suicide, effects of smoking in the present study cannot be ruled out.

However, despite the extensive research about suicide prediction, comparing this study to others on serotonergic function in suicidality is difficult. On the one hand, this is due to the technique of LDAEP measurement, which has only been used in very few studies on suicidality. On the other hand, it might be useful to follow the patients even further in order to screen for future suicide attempts or try to assess completed suicides.

The most important limitation of the study is the small sample size, which is due to the rigorous inclusion conditions. Moreover, because of the small sample size, it seems inappropriate to define subsamples of patients according to age, gender or suicide method. Furthermore, non-suicidal controls were not examined. Thus, this study must be regarded as a pilot study. It definitively has the character of a throughout naturalistic study in standard clinical situation. Although the participation in the study was restricted to patients with major depression who were screened very carefully, different psychiatric diseases should be taken into consideration in the future.

Psychopharmacologic medication of the patients could have influenced the results; because of ethical reasons, all kinds of medication were accepted in this sample of severely ill patients.

Despite these limitations, the study points to the importance of establishing neurobiological parameters in the assessment of suicidality. Serotonergic function as measured with LDAEP may be an important marker of suicidal states, and these preliminary results should encourage future research on this topic.

In conclusion, this is one of the first studies to measure LDAEP in a sample of psychiatric patients in a consecutive

way. In patients after suicide attempt, an increased LDAEP was found about 9 days later, while on the days 2, 5 and 16, LDAEP was on lower levels. We hypothesized that these results might be due to an instable serotonergic system and to counter the regulations of serotonergic activity. However, large replication studies including a wide variety of neuropsychiatric diagnoses and longer follow-up periods as well as non-suicidal controls are necessary.

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Conflict of interest None.

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