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Brief report

# Loudness dependence of the auditory evoked N1/P2 component as an indicator of serotonergic dysfunction in patients with schizophrenia — A replication study

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**Abstract**

Serotonergic dysfunction appears to be involved in the pathogenesis of schizophrenia. The loudness dependence of auditory evoked potentials (LDAEP) has been suggested to be a valid indicator of the brain serotonin system's activity in humans. Patients with schizophrenia showed weaker LDAEP, indicating high serotonergic activity, in comparison to healthy controls. Thus, we were able again to demonstrate electrophysiological evidence for an upregulated serotonergic system in schizophrenia.


*Keywords:* Serotonin; Schizophrenia; Auditory evoked potentials; Loudness dependence

## 1. Introduction

The most dominant neurochemical hypothesis of schizophrenia is the dopamine hypothesis, which originated from the relationship between the efficacy of the classical neuroleptics and their affinity for dopamine receptors (Seeman et al., 1976). Besides that, other neurotransmitter systems appear to contribute to the pathophysiology of schizophrenia as well. Serotonergic neurotransmission is of growing scientific interest in schizophrenia research particularly due to the role of serotonergic mechanisms in the therapeutic effects of atypical neuroleptics (Meltzer, 1999). Furthemore, postmortem studies, cerebrospinal fluid studies of 5-hydroxyindoleacetic acid, genetic studies and neuroimaging findings show an increased serotonergic neurotransmission in schizophrenia (Sawa and Snyder, 2002).

Until recently, there has been a lack of valid indicators of central serotonergic activity. Peripheral serotonergic measurements only indirectly reflect serotonergic brain function, without reflecting short-term changes in this system (Hegerl and Juckel, 1993). The loudness dependence of auditory evoked potentials (LDAEP) has been proposed as a valid indicator for the serotonergic system.

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The LDAEP is a measure of auditory cortex activity that reflects the increase or decrease of the auditory evoked N1/P2 component with increasing tone loudness. Previous studies on animals as well as on psychiatric patients found an inverse association between this parameter and serotonergic activity (Hegerl and Juckel, 1993; Juckel et al., 1999; Nathan et al., 2006), although there are also conflicting results (Hensch et al., 2006; Uhl et al., 2006). A weak LDAEP indicates high serotonergic activity and vice versa. In line with the hypothesis of an increased serotonergic tone in schizophrenia, a previous study reported a decreased LDAEP in unmedicated patients with schizophrenia compared with healthy volunteers (Juckel et al., 2003). In the present study, the LDAEP was investigated again to replicate the previously reported abnormalities in schizophrenic patients compared with healthy subjects as well as to explore whether or not a decreased LDAEP can also be found in medicated patients, indicating that enhanced serotonergic neurotransmission could be a trait characteristic and the weak LDAEP a marker for serotonergic activity.

## 2. Methods

Subjects comprised 36 male patients with schizophrenia (all medicated: 11 with only typical neuroleptics, 19 with only atypical neuroleptics, and 6 with both) and 36 age-matched healthy volunteers. Table 1 presents the demographic and clinical data. The patients were inpatients and outpatients from the Psychiatric Hospital of the Ludwig-Maximilians—University in Munich. Healthy controls were selected from the general population of Munich. The study was carried out in accordance with the Declaration of Helsinki and was approved by the ethical committee of the university. All subjects gave their written informed consent after the study was fully explained to them.

The functional level of the schizophrenic patients was assessed with the Global Assessment of Functioning (GAF; DSM-IV). The psychopathological state of the patients was rated on the Positive and Negative Syndrome Scale (PANSS) and on the Brief Psychiatric Rating Scale (BPRS).

Table 1
Demographic and clinical data

| | Patients with schizophrenia | Healthy controls |
|---|---|---|
| Number | 36 | 36 |
| Age (years) | 30.89±8.53 | 30.72±8.60 |
| Duration of illness (months) | 87.44±90.24 | |
| Duration of illness (years) | 7.32±7.54 | |
| GAF | 56.56±19.64 | |
| BPRS | 41.00 | |
| PANSS (positive) | 12.75±4.95 | |
| PANSS (negative) | 25.22±7.27 | |

Subjects were seated with eyes opened in a sound-attenuated and electrically shielded room adjacent to the recording apparatus (Synamps-Neuroscan) in a slightly reclined chair and were asked to look at the wall 3 m in front of them. Evoked responses were recorded with 33 electrodes referred to Cz (32 channels). Sinus tones (1000 Hz, 40-ms duration with 10-ms rise and 10-ms fall times, interstimulus intervals (ISI) randomized between 1800 and 2200 ms) of five intensities (60, 70, 80 90 und 100 dB sound pressure level) were presented binaurally by earphones in random order. Data were collected with a sampling rate of 256 Hz and an analogous bandpass filter (0.16–70 Hz). Prestimulus (200 ms) and poststimulus (600 ms) periods were evaluated for 100 sweeps of each intensity (all together 500 sweeps). Before averaging, the first five responses to each intensity were excluded in order to reduce short-term habituation effects. For artifact suppression, all trials were automatically excluded from averaging when the voltage exceeded ±50 μV. For each patient, the remaining sweeps were averaged separately for the five intensity levels. The investigator analyzing the AEP data was blind with regard to the clinical state and course of the subjects.

Dipole source analysis was performed with the Brain Electrical Source Analysis (BESA, Scherg and Picton, 1991). BESA decomposes the scalp-measured AEP N1/P2 component into two dipole source activities per hemisphere. One of the dipoles, located in the superior temporal region, has a tangential orientation and mainly reflects the activity of the primary auditory cortex. The other dipole, located in the temporal lobe, has a radial orientation and mainly reflects activity of the secondary auditory cortex. For each patient, an individual dipole model was calculated to obtain the best fitting location and orientation of the dipoles, using a standard dipole model based on the data of healthy volunteers (for details, see Hegerl et al., 1994). In every patient, the magnitude of the tangential and radial dipole activity was separately measured for the five intensities as N1/P2-epoch amplitude. The median slope was calculated from the slopes of all possible straight lines ($n=10$) connecting the five amplitude values. The LDAEP of the tangential and radial dipole activities per hemisphere was used for statistical analyses.

All variables that were analyzed showed a normal distribution, as revealed by the Kolmogorov–Smirnov test. Values were expressed by mean±standard