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The Loudness Dependence of Auditory Evoked Potentials (LDAEP) in individuals at risk for developing bipolar disorders and schizophrenia

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HIGHLIGHTS

- We examined the Loudness Dependence of Auditory Evoked Potentials (LDAEP) in 187 individuals at risk for bipolar disorders and schizophrenia.
- We estimated the LDAEP by single electrode estimation and dipole source analysis.
- Bipolar at-risk subjects showed a weaker LDAEP than schizophrenia at-risk subjects.

ABSTRACT

Objectives: The Loudness Dependence of Auditory Evoked Potentials (LDAEP) is considered as an indicator of central serotonergic activity. Alteration of serotonergic neurotransmission was reported in bipolar disorders and schizophrenia. In line with previous reports on clinically manifest disorders, we expected a weaker LDAEP in subjects at risk for bipolar disorders and schizophrenia compared to healthy controls.
Methods: We analyzed LDAEP of individuals at risk for developing bipolar disorders ($n = 27$), with high-risk status ($n = 74$) and ultra-high-risk status for schizophrenia ($n = 86$) and healthy controls ($n = 47$).
Results: The LDAEP did not differ between subjects at risk for schizophrenia or bipolar disorders and controls. Among subjects without medication ($n = 122$), the at-risk-bipolar group showed a trend towards a weaker LDAEP than both the high-risk and the ultra-high-risk groups for schizophrenia.
Conclusions: The LDAEP did not appear as a vulnerability marker for schizophrenia or bipolar disorders. This suggests that an altered LDAEP may not be measurable until the onset of clinically manifest disorder. However, the hypothesis that pathogenic mechanisms leading to bipolar disorders may differ from those leading to schizophrenia is supported.
Significance: This is the first study investigating LDAEP in a population at risk for bipolar disorders.

1. Introduction

The Loudness Dependence of Auditory Evoked Potentials (LDAEP) has been described as an indicator of serotonergic activity in humans (Hegerl et al., 2001; Hegerl and Juckel, 1993, 2000; Juckel et al., 1999; Kenemans and Kähköhnen, 2011). It has been suggested that neuromodulators other than serotonin, such as dopamine (Juckel et al., 2008b) or nitric oxide (Kawohl et al., 2008a), may have also an effect on the LDAEP. The LDAEP is defined as the change in amplitude of auditory evoked potentials in response to different stimulus intensities. The LDAEP is thought to be inversely related to serotonergic activity – i.e. a weak LDAEP is considered to reflect a high serotonergic activity in the primary auditory cortex (Hegerl and Juckel, 1993; Juckel et al., 2003). The LDAEP was proposed as a putative biological marker in several psychiatric disorders involving a presumed serotonergic abnormality (O'Neill et al., 2008), such as obsessive compulsive disorders

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(Baumgarten and Grozdanovic, 1998; Stein, 2002), generalized anxiety disorders (Connor and Davidson, 1998; Hilbert et al., 2014), affective disorders (Brocke et al., 2000; Hensch et al., 2007; Park et al., 2014) and schizophrenia (Juckel et al., 2003, 2008a). Furthermore, the LDAEP was shown to predict treatment response in depression (Gallinat et al., 2000; Juckel et al., 2007; Lee et al., 2005; Linka et al., 2004; Paige et al., 1994; Park et al., 2011) and in generalized anxiety disorders (Park et al., 2011).

Bipolar disorders and schizophrenia share numerous clinical and epidemiological aspects and occur commonly within a comorbid presentation (schizo-affective disorders) while it is still discussed whether they arise from common or distinct pathophysiological mechanisms (Alaerts and Del-Favero, 2009; Kurnianingsih et al., 2011; Redpath et al., 2013; Whalley et al., 2012). Despite an increasing number of studies, knowledge about specific factors related to the underlying biology of bipolar disorders and schizophrenia is quite limited and often based on small and heterogeneous samples (Yung et al., 2005).

The diagnosis of bipolar disorders is defined by two or more episodes in which the patient's mood and activity levels are significantly disturbed (ICD-10, DSM 5), first symptoms emerging in youth or young adulthood (Lish et al., 1994; Perlis et al., 2004). Along with a substantial body of neuroanatomic changes in bipolar disorders (Kempton et al., 2008), there is also evidence for serotonin playing a pivotal role in the pathophysiology of bipolar disorders (Kawohl et al., 2008b; Mahmood and Silverstone, 2001; Park et al., 2011). A weak LDAEP has been reported in patients with bipolar disorders (Park et al., 2010). Moreover, research on serotonergic activity has provided differentiated results according to the patients' mood status. Higher LDAEP suggesting decreased serotonergic neurotransmission has been shown in patients with bipolar mania (Lee et al., 2012; Shiah and Yatham, 2000), while an increased activity of the serotonergic system was indicated by weak LDAEP in patients with bipolar disorder in euthymic state at time of the experiment, as compared to healthy controls (Lee et al., 2012). Furthermore, low serotonergic activity has been related to the suicidality of depressed subjects (Chen et al., 2005; Kim and Park, 2013) and to higher degree of somatic symptoms of depression (Linka et al., 2009). However LDAEP strength of patients with major depression has been shown not to differ from healthy controls (Linka et al., 2007; Park et al., 2010).

Schizophrenia is thought to be a heterogeneous group of illnesses, clinically diagnosed by a set of 'positive' (e.g., hallucinations, delusions, thought disorder) and 'negative' (e.g., emotional flattening, social withdrawal and apathy) symptoms. Quantitative and qualitative abnormalities in brain structure have been shown in association with the pathophysiology of schizophrenia, including, e.g., enlarged ventricles and decreased cortical volume (Harrison, 1999; Kasai et al., 2002). Although changes in neurotransmitter activity are more difficult to measure in humans than structural changes, research on serotonin – besides numerous studies on dopamine – gained growing attention because of the newer "atypical" antipsychotic medication often acting via different neurotransmitter systems and receptors including the serotonergic system (Meltzer and Fatemi, 1996; Meltzer and Massey, 2011). Several fields of research such as postmortem studies, genetic studies and neuroimaging findings have shown evidence for increased serotonergic neurotransmission in schizophrenia (e.g. Dean, 2003; Eastwood et al., 2001; Harrison, 1999; Ngan et al., 2000; van Veelen and Kahn, 1999). A large body of neurophysiologic studies reports a weaker LDAEP in patients with schizophrenia as compared to healthy controls (Gudlowski et al., 2009; Juckel et al., 2003, 2008a; Park et al., 2010). However, considering the heterogeneity of the disorder and the dimensional – and broad – phenotype, Wyss et al. (2013) found that a higher LDAEP in the right hemisphere in patients with schizophrenia as compared to controls was associated with more negative symptoms, while Ostermann et al. (2012) reported no difference between healthy controls and schizophrenia patients.

Usually, both bipolar disorders and schizophrenia do no abruptly break out but rather develop subtly during a so called prodromal phase. Early recognition programs assume a large overlap between schizophrenic and bipolar disorders, e.g. regarding genetic risk and psychotic symptoms (Bechdolf et al., 2014; Brietzke et al., 2012). In this paper, 'psychotic symptoms' were considered to occur in different severity on a continuum from the subclinical level to manifest schizophrenia (van Os, 2014; Zavos et al., 2014). The term 'psychosis risk syndrome' indicates a possible risk to develop psychosis based on the presence of subclinical disturbances (Correll et al., 2010; Schultze-Lutter et al., 2008) and can be divided into those thought to be more distant and those to be near to the onset of psychosis (Schultze-Lutter, 2009; Yung et al., 1996). It defines only a probability of disease progression, but global function level and quality of life can already be seriously disturbed at this stage (Bechdolf et al., 2005; Ruhrmann et al., 2008).

There is furthermore evidence suggesting an association of substance use and increased risk of developing psychotic symptoms (Addington et al., 2013). As the success of therapy is related to the time of intervention respectively the duration of untreated psychosis (DUP), the identification of neurobiological markers appears crucial for the early recognition and treatment of individuals when first impairments emerge. It was suggested that structural brain and connectivity abnormalities are already apparent in the premorbid stage of psychosis (Pantelis et al., 2003; Wotruba et al., 2014). For example, the density of a cerebral serotonin receptor (5-HT_{2A}R) was suggested as a biological measure of increased risk for schizophrenia with positron emission tomography (Hurlemann et al., 2009). In this line, neurophysiologic abnormalities, e.g. an alteration of the LDAEP as a – noninvasive – marker for alterations of serotonergic neurotransmission, can be hypothesized in subjects before the onset of the disorder. In accordance to this, Gudlowski et al. (2009) found a lower LDAEP in patients at risk for developing schizophrenia, which remained decreased throughout the disease progression.

The aim of the present study was to investigate the LDAEP as an indicator of serotonergic neurotransmission in subjects at risk for developing psychosis. In line with previous reports on patients with clinically manifest schizophrenia and bipolar disorders, we expected to find a weaker LDAEP in subjects at risk for schizophrenia and bipolar disorder compared to healthy controls. Additionally, we examined the LDAEP in relation to symptom severity, medication and substance use (alcohol, cannabis). We separated our AEP analysis into dipole source localization vs. single electrode estimation at Cz, in order to facilitate across-study comparison, as these methods are still used in literature as they were equivalent but are supposed to lead to different results (Hagenmuller et al., 2011).

2. Methods

2.1. Subjects

Subjects at risk for psychosis ($n = 200$) were recruited in the context of a prospective longitudinal multi-level-approach on early recognition of psychosis within the framework of the "Zurich Program for Sustainable Development of Mental Health Services" (Zürcher Impulsprogramm zur nachhaltigen Entwicklung der Psychiatrie, i.e. ZInEP, http://www.zinep.ch). Details of the study are given in Theodoridou et al. (2014). The study was approved by the regional ethics committee of the canton of Zurich and was

in accordance with the Declaration of Helsinki. For assessment of psychopathological symptoms all participants of the study were examined carefully by clinical psychiatrists and psychologists. Inclusion criteria for our study were at least one of the following:

(1) High-risk status for schizophrenia (HR-SZ, $n = 78$), with at least one cognitive–perceptive (COPER) basic symptom or at least two cognitive disturbances (COGDIS) basic symptoms, assessed by the adult (Schultze-Lutter et al., 2007a) or children-youth (Schultze-Lutter and Koch, 2010) version of the Schizophrenia Proneness Interview (SPI-A/SPI-CY).
(2) Ultra-high-risk status for schizophrenia (UHR-SZ, $n = 91$) as rated by the Structured Interview for Prodromal Syndromes (SIPS, McGlashan et al., 2001), with at least one attenuated psychotic symptom, or at least one brief limited intermittent psychotic symptom, or a positive state-trait criterion (reduction in global assessment of functioning of >30% in the past year, plus either schizotypal personality disorder or first degree relative with psychosis).
(3) At-risk state for bipolar disorder (HR-BIP, $n = 31$), defined with a score of >14 on Hypomania Checklist (HCl, Angst et al., 2005) and/or a score of >12 on the Hamilton Depression Scale (HAMD, Williams, 1988) or a positive state criterion (first degree relative with a bipolar disorder and a reduction in global assessment of functioning of >30% in the past year).

Exclusion criteria for study participation were clinically manifest schizophrenic, substance-induced or organic psychoses or bipolar disorders, current substance or alcohol dependence; age below 13 or above 35 years; or low intellectual abilities with IQ < 80.

Among the 200 participants at risk who completed the LDAEP-trial, 11 participants had to be excluded from the analysis because of bad data quality and 2 because of hearing impairment.

Fifty healthy controls (HC) matched regarding age and gender proportionally to the whole at-risk group were enrolled in the study. The presence of any mental illness was excluded using the Mini-International Neuropsychiatric Interview, (MINI resp. MINI-Kid for participants younger than 18 years) (Sheehan et al., 1998). Three control participants had to be removed from analysis due to bad data quality.

Descriptive characteristics of the sample are given in Table 1. The participants of the UHR-SZ group were significantly younger than the participants of the other groups ($p < .01$). Clinical treatment of ZInEP participants was independent of the study. In cases of attenuated psychotic symptoms associated with distress or depressive symptoms, some doctors decided to treat with antipsychotic or antidepressive medication. Antipsychotic medication status is given in number of subjects treated and mean chlorpromazine-equivalent (CPZe) dosage (Andreasen et al., 2010). Substance use (alcohol and cannabis) was assessed with the MINI (Sheehan et al., 1998) and the frequency of substance consumption additionally with an open-ended question. Subjects reporting several times a week, weekly and monthly substance use were grouped together to obtain the group "substance users". The opposed group of "substance-non-users" comprised individuals reporting no or rare use (less frequently than monthly). We could not obtain information about cannabis use of 43 subjects in the risk groups and 8 subjects in the HC group, as well as about alcohol use of 34 subjects in the risk groups. No information was available about alcohol use in the HC group. Clinical characteristics of the risk groups as rated by the adult and children/youth version of the Schizophrenia Proneness Instrument (SPI-A/-CY) and the Structured Interview for Prodromal Syndromes (SIPS) are given in Table 2.

Table 1
Descriptive characteristics of the participants in the healthy control (HC), at-risk-bipolar (HR-BIP), high-risk (HR-SZ) and ultra-high-risk (UHR-SZ) groups.

	HC	HR-BIP	HR-SZ	UHR-SZ
N	47	27	74	86
Sex: w/m	21/26	9/18	28/46	33/53
Age (yrs): mean ± sd	21 (6)	25 (7)	23 (6)	19 (5)
IQ	109	106	104	102
Medication: NL (CPZe)[a]/AD[b]	–	2 (97)/8	11 (109)/19	21 (225)/15
Alcohol yes/no	n.i.	13/10	43/25	27/35
Cannabis yes/no	2/37	4/18	15/48	15/44

[a] Neuroleptics: number of subjects treated (mean chlorpromazine-equivalent dosage).
[b] Antidepressants: number of subjects treated; n.i.: no information.

2.2. Electrophysiological assessment

Subjects were seated in a chair with their eyes open in front of a computer screen. During recording the subjects were asked to be silent and to avoid facial muscle movements to minimize muscle artifacts. A "Mr. Bean" movie without sound was presented during the recording in order to distract their attention away from the auditory stimuli. Tones in five intensities (60, 70, 80, 90, 100 dB) with a frequency of 1000 Hz (sinustones) were presented during 12 min in a pseudo-randomized order (ISI randomized between 1800 and 2400 ms). The tones were presented binaurally via earphones using PRESENTATION software (Neurobehavioral System, Inc. San Pablo, CA). EEG data was recorded using 32 electrodes placed via the EASYCAP System (Herrsching-Breitbrunn, Germany) according to the international 10–20 system (Jasper, 1958). FCz was chosen as reference electrode. Electrode impedances were kept below 10 kΩ. Data was collected using a 32 channels BrainAmp amplifier and the software BRAIN VISION RECORDER (Brain Products GmbH, München, Germany) with a sampling rate of 1000 Hz and a band pass filter of 0.5–80 Hz.

2.3. Data pre-processing

The data were processed using the BRAIN ELECTRICAL SOURCE ANALYSIS (BESA) Software (Version 5.1.8; MEGIS Munich, Deutschland). Before individual averaging the data were divided into epochs of 400 ms including a 100-ms prestimulus baseline. Eye artifact correction was performed with ICA in BESA. To further reduce muscle artifact, trials with a change in amplitude greater than 100 μV were excluded from further evoked potential analysis. The remaining segments (at least 60% for each intensity, i.e. $n = 42$ segments) were averaged for each subject separately and further filtered with a low pass filter of 40 Hz (12 dB/octave roll-off) before peak determination (at Cz and with dipole source analysis).

2.4. Auditory evoked potential analysis

The N1 and P2 peaks were defined for each intensity as the most negative and the most positive value during the latency range of 80–180 ms and 150–250 ms, respectively. To evaluate the peak-to-peak N1/P2 amplitude, we used single electrode estimation and dipole source analysis. Using single electrode estimation, the peaks were determined at Cz electrode from individual data, with an average reference (Fig. 1).

By using dipole source analysis (DSA), activities from the primary auditory cortex can be assessed separately from the secondary auditory cortex. This is of interest, as it was hypothesized that the central serotonergic system modulates the intensity dependence of the evoked N1/P2-response of primary auditory

Table 2
Magnitude of symptoms as rated by the adult and children/youth version of the Schizophrenia Proneness Instrument (SPI-A/-CY), the Structured Interview for Prodromal Syndromes (SIPS), the Hamilton rating scale for depression (HAMD) and the hypomania-checklist (HCL) in the at-risk-bipolar (HR-BIP), high-risk (HR-SZ) and ultra-high-risk (UHR-SZ) groups (given in mean and standard deviation).

		HR-BIP	HR-SZ	UHR-SZ	p^a
N		27	74	86	
SPI-A/-CY[b]	Affective-dynamic disturbances	1.36 (1.10)	2.18 (1.32)	2.32 (1.68)	**
	Cognitive-attentional impediments	.88 (.82)	1.75 (1.36)	2.13 (1.47)	***
	Cognitive disturbances	.66 (.63)	1.25 (.95)	1.58 (1.31)	***
	Disturbances in experiencing the self and surroundings	.65 (.49)	1.03 (.87)	1.68 (1.12)	***
	Body perception disturbances	.25 (.50)	.32 (.51)	.57 (.64)	**
	Perception disturbances	.30 (.48)	.67 (.65)	.81 (.88)	**
	Optional basis symptoms	1.05 (.48)	1.31 (.52)	1.49 (.95)	*
SIPS[c]	Positive symptoms	.66 (.60)	.93 (.67)	2.16 (.66)	***
	Negative symptoms	1.27 (1.02)	1.71 (.98)	2.20 (.99)	***
	Disorganized symptoms	.51 (.43)	.79 (.53)	1.45 (.80)	***
	General symptoms	1.21 (.86)	1.81 (.89)	2.09 (.90)	***
HAMD[d]	Total score	11.0 (5.9)	13.6 (5.8)	16.4 (7.6)	**
HCL[e]	Total score	15.6 (6.0)	17.9 (5.4)	17.1 (5.9)	n.s.

[a]MANOVA, $p < .05^{*}$, $p < .005^{**}$, $p < .001^{***}$, using Pillai's trace, there was a significant effect of group, [b]on SPIA-scores: $V = .22$, $F(14,358) = 3.18^{***}$, [c]on SIPS-scores, $V = .56$, $F(8,364) = 17.58^{***}$, [d]ANOVA, effect of group $F(2,187) = 6.73$, HR-BIP < UHR-SZ**, [e]ANOVA, no effect of group $F(2,170) = 1.62$.

cortex (Hegerl et al., 1994; Scherg, 1990). This analysis was performed according to the BESA tutorial by M. Scherg and K. Hoechstetter (http://www.besa.de). On the basis of the grand average from all control subjects, two dipole models were calculated. A low-intensity dipole model for 60, 70 and 80 dB was computed with one regional source for each hemisphere in order to localize the auditory cortex. A high-intensity model was computed for 90 and 100 dB. Within this high-intensity model, a third source was added in the frontal area, as a frontal inhibitory mechanism is expected to be activated during tones of high intensities, as illustrated by Fig. 2 (Bruneau et al., 1985; Knight et al., 1989; Yamaguchi and Knight, 1990). These two models were then applied to the individual averaged data in order to determine the spatio-temporal information of the activation in the auditory cortex for each intensity.

2.5. LDAEP estimation

The LDAEP was calculated as the median slope of all possible connections between the five different N1/P2 amplitudes (in nAm for DSA and in μV for single electrode estimation) corresponding to the five different intensities (Hegerl et al., 1994).

2.6. Statistical analysis

Statistical tests were performed using the SPSS version 20 for Windows. The Kolmogorov–Smirnov test revealed that the data were normally distributed, therefore parametrical tests were used. Demographic and clinical characteristics were compared between groups using student's *t*-tests or analysis of variance (ANOVA or MANOVA) with a Bonferroni *post hoc* test. LDAEP differences

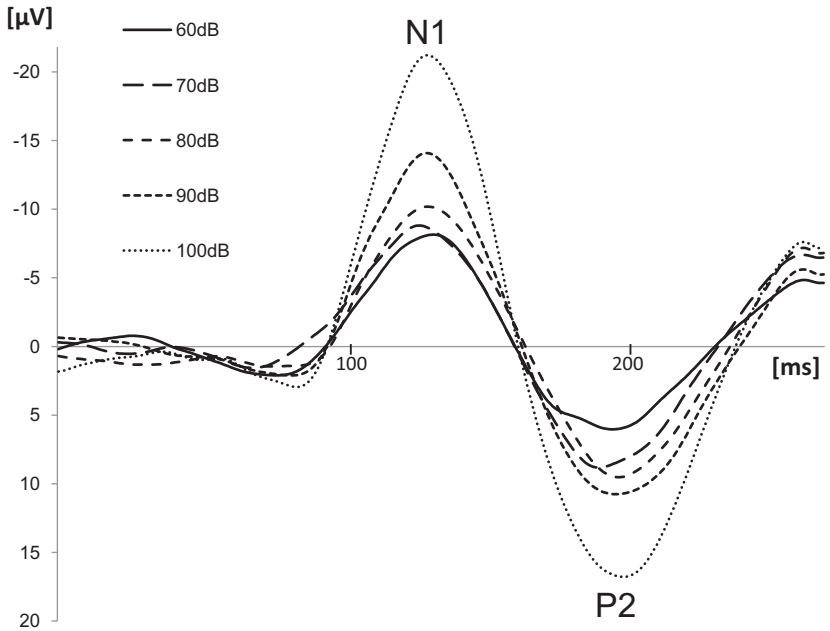

Fig. 1. Example of auditory evoked potentials (AEP) in a single subject taken from the Cz electrode.

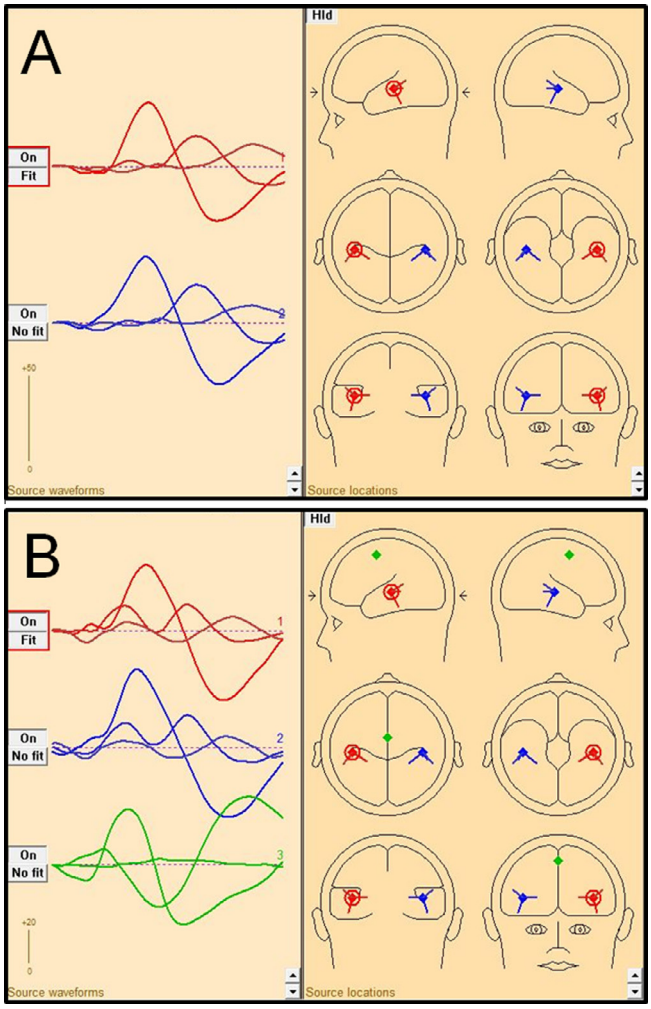

Fig. 2. Examples of the N1/P2 source model with (A) two (for the low intensities 60/70/80 dB) and (B) three (for the high intensities 90/100 dB) regional sources and corresponding dipole strength.

between groups were analyzed using ANOVA (LDAEP_Cz) resp. MANOVA (LDAEP from DSA, left and right source), corrected *post hoc* with the Games-Howell procedure. Age could not be entered as covariate because it differed significantly between groups (Miller and Chapman, 2001). As information about substance use was not given for all subjects, we performed only an explorative analysis, comparing users vs. non-users with student's *t*-tests. To investigate the relationship between LDAEP and demographic and clinical data, Pearson's *r* were calculated. Because of the assumed effect of medication on clinical symptoms, correlations with clinical data were computed only in the at-risk group without medication. We restricted those correlations to symptoms related to psychosis proneness measured by SPIA (7 scales) and SIPS (4 scales) as well as to depression (HAMD total score) and hypomania (HCl total score) in order to reduce the bias inherent to multiple testing. *p*-Values below 0.05 were regarded as statistically significant and below 0.1 as statistical trends.

3. Results

LDAEP scores evaluated using both DSA separately for each hemisphere and surface electrode Cz are given in Table 3 for the whole group. Variances were greater in LDAEP using DSA than in LDAEP at Cz. The variations of the N1/P2-amplitudes as a function of the loudness, as estimated with both DSA and Cz are plotted in Fig. 3.

Table 3
Loudness Dependence of Auditory Evoked Potentials (LDAEP) using dipole source analysis and single electrode estimation at Cz in the healthy control (HC), at-risk-bipolar (HR-BIP), high-risk (HR-SZ) and ultra-high-risk (UHR-SZ) groups (given as mean and standard deviation).

	HC	HR-BIP	HR-SZ	UHR-SZ
N	47	27	74	86
LDAEP left[a]	.77 (1.01)	.73 (.80)	.88 (.79)	.87 (.93)
LDAEP right[a]	.67 (.97)	.73 (.71)	.88 (.84)	.82 (.83)
LDAEP Cz[b]	.23 (.14)	.18 (.09)	.24 (.17)	.23 (.13)

[a] Using dipole source analysis (nAm/10dB).
[b] Using single electrode estimation (μV/10dB).

3.1. LDAEP estimated with dipole source analysis

The LDAEP estimated with DSA in both hemispheres (Table 3) did not differ between groups (Pillai's trace: $V = .012$, $F(6,458) = .47$, p = n.s.). Men did not differ from women. Age did not correlate with LDAEP from DSA.

3.1.1. Medication

The LDAEP values differed in subjects without medication ($n = 122$) compared to subjects with medication ($n = 65$, antipsychotic or antidepressant drugs or both), but this difference did not reach significance. *t*-Tests revealed a trend for a lower LDEAP from the right hemisphere in unmedicated subjects from the HR-BIP group ($t(8.7) = -2.0$, $p = .078$) and from the HR-SZ group ($t(72) = -1.9$, $p = .084$) compared to medicated subjects from these groups. Within subjects without medication, LDAEP from DSA did not differ significantly between groups (Pillai's trace, $V = .025$, $F(6,328) = .70$, p = n.s.). LDAEP from DSA in the right hemisphere correlated with CPZe ($r = -.40$, $p < .05$; $n = 34$ subjects taking neuroleptics).

3.1.2. Substance use: alcohol and cannabis

Within the whole at-risk group (HR-Bip, HR-SZ, UHR-SZ, $n = 187$) as well as among unmedicated subjects from the at-risk group ($n = 122$), the LDAEP was generally stronger in alcohol users

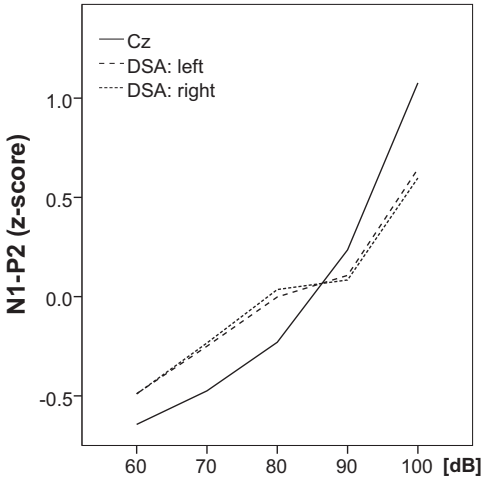

Fig. 3. Peak-to-peak amplitudes of N1–P2 (*z*-values) estimated at Cz and with dipole source analysis (DSA) in the left resp. right hemisphere plotted against loudness (dB) within the whole sample ($n = 234$).

compared to alcohol non-users, but this difference did not reach significance. LDAEP of cannabis users did not differ significantly from cannabis non-users.

3.1.3. Psychopathology

Within the unmedicated subjects ($n = 122$), LDAEP from DSA (left) correlated with SPIA 'Disturbances in experiencing the self and surroundings', $r = .21$, $p < .05$. The LDAEP did not correlate with other scales from SPIA nor with SIPS. There was no correlation with HAMD and HCl scores.

3.2. LDAEP estimated at Cz

In the whole sample ($n = 234$), the LDAEP estimated at Cz (Table 3) did not differ significantly between groups, $F(3,230) = 1.16$, p = n.s. Men did not differ from women. Age correlated negatively with LDAEP ($r = -.21$, $p = .002$).

3.2.1. Medication

The LDAEP at Cz did not differ significantly between medicated ($n = 65$) and unmedicated ($n = 122$) subjects from the at-risk group (HR-BIP, HR-SZ, UHR-SZ). However, the LDAEP in unmedicated HR-BIP subjects ($n = 19$) was significantly lower than in HR-BIP subjects taking medication ($t(25) = -2.24$, $p < .05$). Within the unmedicated subjects, there was a trend indicating an effect of group on LDAEP at Cz ($F(3,165) = 2.25$, $p = .085$). *Post hoc* tests revealed that HR-BIP subjects had a lower LDAEP than subjects from the HR-SZ (−.09, 95% CI (−.17, −.02), $p = .01$) and the UHR-SZ (−.09, 95% CI (−.16, −.03), $p < .005$) groups (see also plots in Fig. 4). There was no correlation with CPZe.

3.2.2. Substance use: alcohol and cannabis

Within the whole at-risk group, the LDAEP at Cz was significantly stronger in alcohol users ($n = 83$) compared to alcohol non-users ($n = 70$), $t(151) = -2.25$, $p < .05$ but this difference was not significant within the unmedicated group (users $n = 56$ vs. non users $n = 41$). As for LDAEP estimated by DSA, LDAEP at Cz in cannabis users did not differ significantly from cannabis non-users.

3.2.3. Psychopathology

Within the unmedicated subjects ($n = 122$), LDAEP at Cz correlated with SIPS negative symptoms ($r = .18$, $p < .05$). The LDAEP did not correlate with other scales from SIPS nor with SPIA. There was no correlation with HAMD and HCl scores.

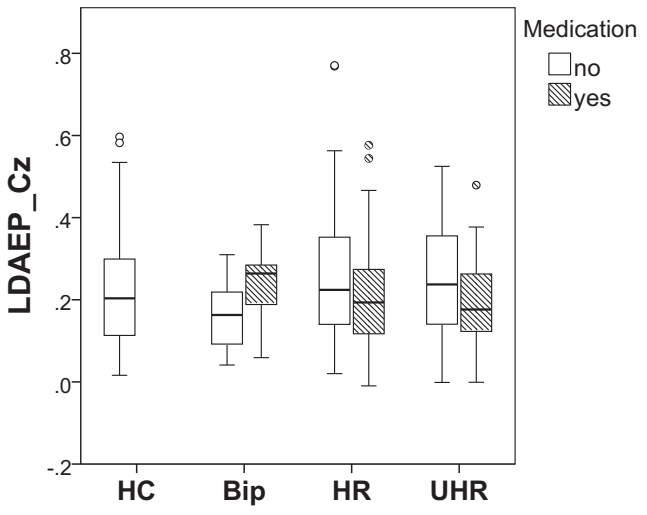

Fig. 4. Boxplots of Loudness Dependence of Auditory Evoked Potentials (LDAEP) estimated at Cz in healthy controls (HC), unmedicated subjects of the at-risk-bipolar (HR-BIP), high-risk (HR-SZ) and ultra-high-risk (UHR-SZ) groups.

4. Discussion

The aim of the present study was to investigate the LDAEP as an indicator for a putative dysfunction of serotonergic neurotransmission in subjects at risk for schizophrenia (HR-SZ and UHR-SZ) and bipolar disorders (HR-BIP). The two methods of AEP analysis (estimation at Cz vs. with DSA) lead to both similar and slightly differing results.

Against our expectation, we found no statistically significant difference in LDAEP-strengths between HR-BIP and healthy control subjects. However, we found with both methods indications for an effect of medication: the LDAEP estimated with DSA tended to be weaker in subjects from the HR-BIP group without medication than in subjects with medication. The same trend was observed in the HR-SZ group. This is in line with previous studies discussing the effect of pharmacologic treatment as a modulator for the LDAEP (Ostermann et al., 2012). The weaker LDAEP in the HR-BIP group obtained with DSA was replicated by the estimation at Cz. Looking *post hoc* at group differences among the subjects without medication, we found that the HR-BIP group showed a weaker LDAEP at Cz than both the HR-SZ and the UHR-SZ groups. The association of a week LDAEP – i.e. a high serotonergic neurotransmission – with bipolar disorders was shown in previous reports (Lee et al., 2012; Ostermann et al., 2012; Park et al., 2010).

Given the inverse relationship between LDAEP and serotonin, the present result may indicate a difference in neurotransmission between subjects at risk for bipolar disorders and subjects at risk for schizophrenia. This is in line with other findings reporting distinct physiological deficits between these disorders (Thaker, 2008) and with reports on structural and functional dissimilarities in the brain, e.g. showing a reduction of the temporal lobe in schizophrenia (Wright et al., 2000) versus an increased temporal lobe volume in bipolar disorders (Harvey et al., 1994) or activation differences in several brain regions between these disorders (Whalley et al., 2012). Murray et al. (2004) speculate that, within a predisposition to psychosis in general as a common basis for both disorders, differences in brain structure and functions observed in patients with schizophrenia versus bipolar disorders may be partly determined by differing genetic influences and environmental factors, i.e. that schizophrenia would be related to more (neuro-)developmental impairments than bipolar disorders. However, studies on altered serotonergic neurotransmission in patients at risk mental state, especially at risk for bipolar disorders, are lacking. This may be due to the fact that changes in the action of brain neurotransmitters, especially serotonin, are more difficult to measure in humans than structural abnormalities (Juckel, 2014). Furthermore, potential risk criteria for bipolar disorder are still not well investigated. Due to the large overlap between schizophrenic and bipolar disorders (e.g. genetic risk and psychotic symptoms) today most early recognition programs for psychosis additionally also take potential risk factors for bipolar disorder into account (Bechdolf et al., 2014; Brietzke et al., 2012; Theodoridou et al., 2014). Therefore, different inclusion criteria and outcome definitions, as well as uncontrolled treatment that patient might receive, may account for inconsistent findings.

Against our expectation and in contrast to some previous studies (Gudlowski et al., 2009; Juckel et al., 2003, 2008a; Park et al., 2010), we found no difference in LDAEP-strengths between subjects at risk for schizophrenia and healthy control subjects. However, this is in line with Ostermann et al. (2012) who report no difference of LDAEP between patients with schizophrenia or schizoaffective disorder and healthy controls.

In the schizophrenia spectrum as well as in other major psychiatric disease dimensions, it is assumed that heterogeneity of different disease mechanisms can lead to the observed psychopathology which by similarity of clinical presentation is subsumed under the same disease classification. Especially different neuromodulatory dysregulations – such as dopaminergic, cholinergic or serotonergic dysregulation of NMDA-mediated synaptic plasticity – are hypothesized to lead to the development of psychotic symptoms (Stephan et al., 2009). A serotonergic dysregulation would therefore only be present in one part of this sample of at risk subjects. And the potential effect on LDAEP would therefore be statistically diluted by the other subjects with other predominant neurotransmitter dysregulations that are not captured by LDAEP. This hypothesis might provide an explanation for the missing group differences between schizophrenia risk groups and healthy controls.

Nevertheless, there was a correlation between negative symptoms as measured with SIPS (McGlashan et al., 2001) and the LDAEP at Cz in the unmedicated risk group. It is discussed that 'negative symptoms' of schizophrenia, including problems with motivation, social withdrawal, diminished affective responsiveness, contribute more to poor quality of life than do positive symptoms. This is in line with Wyss et al. (2013) who reported a stronger LDAEP related to predominant negative symptoms within a sample including only medicated patients with predominant negative symptoms meeting the diagnostic criteria for chronic paranoid schizophrenia. As individuals commonly experience negative symptoms at the beginning of a prodrome (Larson et al., 2011), an under-regulated serotonergic system might be related to the origin of negative symptoms.

Other precursors of schizophrenia are described as disorders of personal relationships which result, along with other influences, from basic difficulties in self-other differentiation (Strauss et al., 1974). There is evidence that a conversion to psychosis in schizophrenia risk subjects is associated with higher scores on 'disturbances in experiencing the self and surroundings' (Schultze-Lutter et al., 2007b). The correlation of this scale with the LDAEP suggests that this may be related to a serotonergic dysregulation.

With regard to substance use, both AEP analysis methods revealed a stronger LDAEP in alcohol users as compared to alcohol non-users, although this effect was significant only with LDAEP at Cz in the whole group, i.e. including medicated and unmedicated subjects. Alcohol has been shown to have serotonergic effects (Ollat et al., 1988). Subjects tending to a hyposerotonergia may rather use alcohol to regulate deficits in serotonergic neurotransmission (Ballenger et al., 1979; Heinz et al., 2005; Preuss et al., 2000; Sellers et al., 1992). According to other studies (Roser et al., 2009; Tuchtenhagen et al., 2000), we found no association of LDAEP with cannabis-use.

Finally, age correlated negatively with LDAEP at Cz, according to previous studies (Hegerl et al., 1994; Ostermann et al., 2012; Pogarell et al., 2004). In line with a decrease in LDAEP, increased alterations of serotonergic responsivity with age have been reported (e.g. McBride et al., 1990; Tauscher et al., 2001).

Slightly differing results for LDAEP from DSA compared to LDAEP at Cz may be due to the divergence caused by the heterogeneity of the sample on one hand and on the other hand by the AEP analysis method per se, as illustrated by Fig. 1 (for a comparison of the methods see Hagenmuller et al., 2011). Wyss et al. (2014) propose that data measured at Cz may arise from different underlying generators than data derived from DSA. Moreover, it is still unclear whether other neurotransmitter systems are also modulating the LDAEP (Juckel et al., 2008a) and if serotonin is primarily related to pathophysiology or secondarily affected by other processes (Breier, 1995), e.g. by a dysfunction in dopaminergic transmission (Abi-Dargham, 2007; Grace, 1993; Howes et al., 2012). Little is known about the effects of other neurotransmitter systems on the LDAEP. Nevertheless, a recent dopamine challenge trial (Hitz et al., 2012) failed to show an association between the LDAEP and acute dopaminergic influence, in line with other findings (O'Neill et al., 2008, 2006).

We are aware that many antipsychotic and in particular antidepressant drugs have an impact on the serotonergic system and thereby could affect the LDAEP. Therefore, we compared medicated and unmedicated subjects statistically and we were able to show a correlation between chlorpromazine-equivalent (CPZe) and LDAEP activation in the right hemisphere. That is why we explored effects separately for the group of at-risk subjects who received no medication. Most of the significant results were actually found in unmedicated subjects.

Some limitations have to be taken into consideration. Firstly, group sizes were not equal and variances were comparably large. This could have weakened the power of statistical testing. However, we presume that the remarkable sample size ($n = 234$) and the quality of data provided trustable results. As the effect sizes of the correlations are small (mostly below $r = 0.3$), these have to be interpreted with caution. Secondly, the UHR-SZ group was significantly younger than the other groups (HR-SZ, HR-BIP, HC). This may be caused by the association of a higher risk to develop schizophrenia and an earlier onset of the illness. The younger UHR-SZ showed no statistically different LDAEP compared to the control (and to the HR-SZ) group. Unfortunately in the present case, the effects of group and age cannot be statistically disentangled (Miller and Chapman, 2001). But taking into account that the LDAEP declines with age, one can hypothesize that the UHR-SZ group may actually even had weaker LDAEP than the control group if they had the same age. Another limitation of the study is that 3 subjects of our HR-BIP group only had depressive symptoms without fulfilling any other inclusion criteria. We decided to include even subjects who only have depressive symptoms, since many patients with bipolar disorder report retrospectively that they had depressive symptoms prior to manifest bipolar disorder. Unfortunately, it cannot be excluded that these subjects are only at risk for unipolar depressive disorder instead of bipolar disorder.

5. Conclusion

Taken together, our results did not reveal differences in LDAEP between healthy controls and subjects at risk for bipolar disorders or for schizophrenia. This does not necessarily stands in contradiction to results on clinically manifest or chronic bipolar disorders resp. schizophrenia, but suggests that an altered LDAEP may not be measurable until the onset of the illness. However, it could be possible that the development of bipolar disorders may be due to a different pathogenic mechanism than the development of schizophrenia.

To the best of our knowledge, this is the first examination of the LDAEP in subjects at risk for bipolar disorder. Further research is needed in order to ascertain if alterations of serotonergic transmission, as they appear in clinically manifest bipolar disorders, are also detectable in subjects at-risk, as this was previously suggested.

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