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Auditory brainstem response (ABR) profiling in schizoaffective disorder

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Original Article

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Abstract

Objective: The aim of the study was to assess whether the auditory brainstem response (ABR) profiling test for schizophrenia (SZ) would recognise schizoaffective disorder (SZA) patients as SZ or not. *Method:* Male and female SZA patients ($n = 16$) from the psychosis unit at Uppsala University Hospital were investigated. Coded sets of randomised ABR recordings intermingled with patients with SZ, adult attention-deficit hyperactivity disorder (ADHD) and healthy controls were analysed by an independent party blinded to clinical diagnoses. *Results:* The ABR profiling test for SZ was positive in 5/16 patients (31%) and negative in 11/16 patients (69%) with SZA. A surprising finding was that 4/16 (25%) SZA patients were positive for the ABR profiling test for ADHD. *Conclusion:* With the ABR profiling test, a minority of patients with SZA tested positive for SZ. In contrast, a majority (85%) of patients with SZ in a previous study tested positive. These preliminary results leave us ignorant whether SZA should be regarded as a SZ-like disorder or a psychotic mood disorder and add to the questions regarding the validity of this diagnostic entity. However, the ABR profiling method is still in its infancy and its exploration in a range of psychiatric disorders is warranted.

Significant outcomes

- The auditory brainstem response (ABR) profiling test for schizophrenia (SZ) was positive in 5/16 patients and negative in 11/16 patients with schizoaffective disorder (SZA).
- The ABR profiling test for adult attention deficit hyperactivity disorder (ADHD) was positive in 4/16 patients and negative in 12/16 patients with SZA.

Limitations

- There was a limited number of study participants.
- Test–retest reliability of the ABR profiling tests for SZ and ADHD have not been ascertained.
- Absence of information on the ABR profiling tests in major depressive and manic episodes.

Introduction

Utilising new techniques of analysing digitised auditory brainstem response (ABR) waveforms, gender-specific ABR profiling has permitted identification of patients with schizophrenia (SZ) versus healthy controls and versus adult attention-deficit hyperactivity disorder (ADHD) patients with high sensitivity and specificity (Källstrand *et al.*, 2016). A separate study with blind evaluation of the ABR profiling methods obtained similar results (Juselius Baghdassarian *et al.*, 2018). Thus, the ABR profiling test for SZ differentiated patients with SZ versus healthy controls with an accuracy of 90.5% receiver operating characteristic curve (ROC area 0.92) and versus patients with ADHD with an accuracy of 88.0% (ROC area 0.94).

Schizoaffective disorder (SZA) is an uninterrupted period of illness during which there is a major depressive, manic or mixed episode concurrent with symptoms that meet criterion A for SZ (DSM-IV TR) (Washington, 2000). The depressive and bipolar subtypes are based on the mood component. Differential diagnoses are mood disorders with psychotic features, psychotic disorder due to general medical condition, delirium, dementia and substance-induced psychotic disorder. The nosological validity of SZA as a separate diagnosis is questioned and the diagnostic reliability is low (Jäger *et al.*, 2010; Santelmann *et al.*, 2015). Diagnostic shift over time is common (Fusar-Poli *et al.*, 2016; Santelmann *et al.*, 2016). SZA may reflect the co-occurrence of SZ and a mood disorder (Abrams *et al.*, 2008), whereas others suggest a dimensional approach with SZA on a continuum between SZ and bipolar disorder

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(Keshavan *et al.*, 2011). Lake and Hurwitz (2006, 2007) have argued that the various subtypes of SZA are psychotic mood disorders.

The aim of the present study was to assess whether the ABR profiling method for SZ would recognise patients with SZA as SZ or not.

Methods

Male ($n = 7$) and female ($n = 9$) SZA patients, diagnosed with the Structured Clinical Interview for diagnostic and statistical manual of mental disorders (DSM) IV Disorders axis I and II (SCID-I and -II) (Klein *et al.*, 1994; First *et al.*, 1996; First *et al.*, 1997; Herlofson, 1999) from the psychosis unit at Uppsala (First *et al.*, 1996, 1997; Herlofson, 1999) University Hospital, were investigated between October 2009 and May 2012. In summary, surface electrodes were applied behind the participant's left and right ear, and a ground electrode and a reference electrode placed on the vertex and forehead, respectively. A set of 13 patented sounds were presented to both ears with the stimuli in phase over the headphones. The output from each test session resulted in 26 unprocessed analogue ABR recordings (13 sounds times 2 ears) which together with information on sex, age and handedness were coded and sent to SensoDetect AB, Lund, Sweden in sequential order dependent on time of inclusion in the study intermingled with patients with SZ, ADHD and healthy controls. No clinical information on symptoms or diagnosis was provided. The proprietary gender-specific ABR profiling methods that used (Källstrand *et al.*, 2016) were the same as those described in Juselius Baghdassarian *et al.* (2018). The above methods had previously identified sets of 10–17 traits (markers) that characterised the SZ group versus the adult ADHD group versus no-diagnosis controls in female and male patients, respectively. Based on these traits which correspond neuroanatomically to different parts of the auditory pathways, a SZ index (0–100) and an ADHD index (0–100) were calculated for each study participant indicating percentage similarity with either of the diagnostic groups. A disease index >50 rendered the study participant an 'ABR profiling diagnosis' of SZ or ADHD, respectively. A disease index <50% was regarded as no such diagnosis. The results were returned to Uppsala University Hospital in a code-breaking session to match clinical data against the final ABR profiling results, that is, diagnostic indices for SZ and ADHD in males and females, respectively.

Written informed consent was obtained from the study participants prior to their inclusion in the study in accordance with the conditions for approval of the study by the Regional Ethical Review Board, University of Uppsala (2009/114).

Results

Sixteen out of 16 registrations were available for analysis. The results are shown in Table 1.

Patient characteristics

At inclusion, all SZA participants (seven males and nine females, median age 25.5 years, range 19–42 years) were on antipsychotic medication: aripiprazole ($n = 1$), aripiprazole+olanzapine ($n = 2$), clozapine ($n = 6$), clozapine+ quetiapine ($n = 1$), olanzapine+haloperidol ($n = 1$), paliperidon ($n = 1$), quetiapine(=3), ziprasidon ($n = 1$). The median daily dose expressed as chlorpromazine equivalents (cpz eq/d) was 343 mg. Six participants were on antipsychotics only, while seven combined with antidepressants and three with mood stabilisers. Regarding SZA subtypes, seven participants were of the depressive type, eight of the bipolar or mixed type and one unspecified type. All participants but one (f 06) were in remission regarding psychotic symptoms as characterised by clinical global impression - severity scale (CGI) severity of illness scores (Guy, 1976) and global assessment of functioning - scale (GAF) scores (Pedersen *et al.*, 2007; Pedersen and Karterud, 2012). Two participants (f 02 and f 03) had personality disorders. The median Audit score (Saunders *et al.*, 1993; Babor *et al.*, 2001) was 1 (range 0–6). There were three tobacco users, one left-handed and six participants with any lifetime otology problems excluding tinnitus. The median duration of illness was 3.5 years, (range 1–18 years) which was calculated from the first psychosis diagnosis noted in medical charts.

ABR profiling results

The ABR profiling method for SZ using the disease index of ≥50% identified 5/16 (31%) as positive and 11/16 (69%) patients with SZA as negative for SZ. The ABR profiling method for ADHD using a disease index of ≥50% identified 4/16 (25%) as positive and 12/16 (75%) patients with SZA as negative for ADHD. There was no obvious relationship between ABR profiling diagnoses and subtype of SZA. Similarly, there were no obvious differences between participants with an ABR profiling diagnosis of SZ and those without in mean severity of illness as measured by CGI or GAF or dose of antipsychotic drugs. There were no differences between participants with an ABR profiling diagnosis of ADHD and those without in mean severity illness or dose of antipsychotic drugs.

Discussion

The present investigator-initiated blinded study explores the gender-specific ABR profiling methods for SZ and ADHD by Källstrand *et al.* (2016) in DSM IV-TR patients with SZA diagnosed with the SCID-I and SCID-II.

The major finding of the present study is that the ABR profiling test of SZ was positive for only 31% and negative for 69% in the group of patients with SZA. In contrast, the results from the previous study by Juselius Baghdassarian *et al.* (2018) showed that 22/26 (85%) of patients with clinical SZ were positive and 4/26 (15%) negative for SZ using ABR profiling. In a group of 58 healthy controls, 4 (7%) were false positives and 54 (93%) were true negatives for SZ, and in a group of 24 patients with ADHD, 2 (8%) were false positives and 22 (92 %) were true negatives for SZ.

A surprising finding was that 4/16 (25%) patients were positive using the ABR profiling test for ADHD. Among 58 healthy controls in the study by Juselius Baghdassarian *et al.* (2018), 5 (9%) were false positives and among 26 patients with SZ only 1 (4%) was a false positive.

There were no indications of ADHD symptoms in the patients with SZA disorder scoring positive for ADHD. However, no specific assessment methods for ADHD were used.

The main finding that most patients with SZA scored negative for SZ using the ABR profiling method adds to the questions regarding the validity of this diagnostic entity, that is, whether SZA should be included in studies of SZ or kept separate. However, the ABR profiling method is still in its infancy, and its exploration in a range of psychiatric disorders is warranted.

Limitations of the present study are the modest number of patients and lack of data on test–retest reliability of the ABR

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Table 1. Study participants, individual data (*x* = plus mood stabiliser; *= plus antidepressant)

Code m = male, f = female	Age	CGI	GAF symptoms	GAF function	AUDIT	Anti-psychotics chlorpromazine eq/day	Tinnitus any time	Clinical diagnosis (SCID) SZA type	SZ index %	ADHD index %	ABR profiling diagnosis
SZA m 01	24	3	53	53	0	225*	No	295.70B Depressive type	62	66	Schizophrenia + ADHD
SZA m 02	26	1	78	85	1	100	No	295.70A Bipolar type	30	0	Neither
SZA m 03	23	4	52	65	3	700*	No	295.70B Depressive type	12	66	ADHD
SZA m 04	27	5	60	50	5	225*	No	295.70A Bipolar type	6	41	Neither
SZA m 05	42	5	54	50	1	450x	No	295.70A Bipolar type	44	32	Neither
SZA m 06	41	1	80	85	2	600	No	295.70A Bipolar type	40	66	ADHD
SZA m 07	28	2	60	64	2	200	Yes	295.70B Depressive type	51	24	Schizophrenia
SZA f 01	25	4	55	61	0	300x	Yes	295.70B Depressive type	0	2	Neither
SZA f 02	23	4	51	57	6	550	No	295.70A Mixed type	95	34	Schizophrenia
SZA f 03	25	5	55	50	0	500	Yes	295.70A Mixed type	0	7	Neither
SZA f 04	22	4	58	62	0	75*	Yes	295.70B Depressive type	44	22	Neither
SZA f 05	29	1	87	85	0	350*	Yes	295.70A Mixed type	12	2	Neither
SZA f 06	23	5	40	43	1	425x	No	295.70A Bipolar type	64	11	Schizophrenia
SZA f 07	19	4	45	45	6	600*	No	295.70B Depressive type	14	11	Neither
SZA f 08	38	5	45	49	0	133	No	295.70 Unspecified type	51	1	Schizophrenia
SZA f 09	33	4	57	53	2	337*	No	295.70B Depressive type	25	63	ADHD

profiling methods. The SZ and ADHD profiling methods used have not been studied in patients with major depressive or manic episodes. We could not compare our results with the ABR waveforms from a previous study in bipolar disorder (Sköld *et al.*, 2014) due to a different apparatus and methods being used in that investigation. Studies of patients on and off medication on ABR profiling are warranted. State versus trait issues need to be investigated.

Conclusion

With the ABR profiling test for SZ, a minority, that is, 5/16 (31%), of patients with SZA disorder tested positive. In contrast, 22/26 (85%) of patients with SZ tested positive. These preliminary results leave us ignorant whether SZA should be regarded as a SZ-like disorder or a psychotic mood disorder in congruence with previous discussions (cf Introduction). It cannot be excluded that some patients with SZA disorder are mainly SZ-like, whereas others are suffering from psychotic mood disorders.

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Authors' contributions. The present study was part of the study on ABR profiling in SZ and adult ADHD at Uppsala University Hospital(2009–2012) and planned by the author and the co-author. First draft of the manuscript made by Eva Juselius Baghdassarian was critically revised by the co-author. Both the author and the co-author have approved the final version of the paper.

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Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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