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THE AUDITORY N1 IN SCHIZOPHRENIA: COMPARATIVE ANALYSIS WITH A MONOAURAL STIMULI PARADIGM

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SUMMARY

The auditory N1 component has been gaining interest as a possible biomarker in schizophrenia (SCZ). N1 to right (RE) and left ear (LE) amplitudes and latencies were assessed using a monoaural auditory oddball paradigm in 12 SCZ subjects and 15 matched healthy controls (M=40.1±8.53 and 39.4±7.73, respectively). T-student test revealed no differences between RE and LE stimulation for N1 amplitude and latency to both groups. However, there were differences in peak-to-peak N1 amplitudes between the two groups for both LE (t=-3.067; ρ=0.003) and RE (t=-2.794; ρ=0.007). These findings strengthen auditory N1 has an electrophysiological biomarker for schizophrenia.

Key words: *auditory N1 – schizophrenia - monoaural stimuli – AERPs - biomarker*

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INTRODUCTION

Schizophrenia (SCZ) is a clinically heterogeneous syndrome, meaning that no symptoms are pathognomonic for this disorder. In the spectrum of SCZ, diagnostic frameworks still distinguish between schizophrenia, schizoaffective disorder, schizophreniform disorder, and psychosis. The differential diagnosis for these disorders depends on the presentation of certain positive and negative symptoms during the active stage of the disease, which can lead to changing diagnosis overtime (Lopez-Castroman et al. 2019, McCarley et al. 1991). Due to this interindividual variability, the diagnosis relies on well-established criteria regarding the intensity and duration of major signs and symptoms (American Psychiatric Association 2013), namely: delusions; hallucinations; disorganized thinking (speech); grossly disorganized or abnormal motor behaviour (including catatonia). Considering the heterogeneity of the biological mechanisms of SCZ, adding a biomarker in diagnostic protocols would bring a more objective and definite answer to the study of this disorder (Weickert et al. 2013).

The use of auditory event-related potentials (AERPs) as a diagnostic tool for SCZ and its clinical applicability (e.g. to understand central processing) has been the target of several studies. Evidence from AERPs has provided increasingly well-founded and detailed results due to the evolution of equipment and paradigms, as well as the exponential increase in interest in diagnostic tools for mental health (Rosburg et al. 2008, Sumich et al. 2014, Weickert et al. 2013).

The auditory N1 reflects sensory / perceptual processes and an apparent early synchronization between primary and secondary auditory cortices (Tomé et al. 2015). In studies that resorted to an auditory oddball paradigm, N100 amplitude was reduced in patients with SCZ in comparison to controls both in frequent and rare trials, although there were no significant differences in latency peaks (Kayser et al. 2001, Laurent et al. 1999). Moreover, typical and atypical antipsychotic medication does not seem to significantly affect amplitude nor latency (Rosburg et al. 2008).

No studies found following a literature review regarding auditory N1 in SCZ used a monoaural stimulation design. Consequently, the main goal of this study is to describe putative alterations regarding auditory N1 properties following a monoaural stimulation paradigm in SCZ patients when compared to healthy controls. This will provide valuable information about bilateral auditory processing in this population and develop further insights regarding N1 as an electrophysiological SCZ biomarker.

SUBJECTS AND METHODS

Twelve subjects with SCZ/schizoaffective disorder diagnosis were recruited from a psychosocial rehabilitation facility - ANARP (11 male; M=40.1 years; SD=8.53) and compared with a matched control group of 15 healthy participants (13 male; M=39.4 years; SD=7.73). The following clinical information was collected to characterize the SCZ group: length of illness in years (19.1±9.54); lifetime psychiatric admissions

(2.5±1.54), years since last admission (10.8±10.5); overall functioning according to the Personal and Social (57.2±12.7). There were no statistically significant differences between the groups for age (t=0.245; p=0.809), and gender (χ^2=0.169; p=1.000).

The experimental procedures followed the principles of the Declaration of Helsinki and were approved by the Ethics Committee from the School of Health – Polytechnic of Porto. Data collection was also authorized by ANARP and all participants gave their written informed consent.

Regarding the SCZ group, all participants had an established diagnosis of schizophrenia spectrum disorder according to the DSM-V (no comorbid substance-related and addictive disorders), no medication changes in the last month and no psychiatric admission in the last 3 months. In the control group, participants had no first-degree relatives with serious mental disorders as well as no use of psychotropic medication or history of any mental disorder in the last 2 years. Furthermore, all participants had normal hearing (125-8000Hz tested with pure tone average <20 dB, according to BIAP 1997), no otologic surgery in the last 6 months, no history of neurological disorders, and were within a 18-60 age-range.

Participants underwent a hearing assessment by the same audiologist, performing an otoscopy (*mini-Heine 2000* otoscope) and pure-tone audiometry (*Otometrics Madsen Astera* audiometer). During AERP acquisition (EEG recording 0.05-100 Hz bandwidth; 4 channel bio-amplifier *Eclipse EP25 Interacustics*®), participants were presented with an active auditory oddball paradigm: a block of monaural tone-burst stimulus (1000 Hz frequent stimulus at 70 dB SPL; 3000 Hz rare stimulus at 80dB SPL), with 1 stimulus per second, and 600 trials per ear. For each ear, 80% of trials were frequent and 20% rare.

Recordings were obtained using the following setup: a positive electrode on the vertex (Cz), one ground electrode on the low forehead (Fpz/G) and two negative electrodes placed on each mastoid (M1 and M2). Impedance was kept below 10 kΩ at all sites after an appropriate skin cleaning. Stimuli were presented monaurally for each ear, via closed TDH-39 headphones with alternate polarity. Participants were comfortably seated in an armchair and instructed to stay alert with their eyes-open (focused on a small cross in a white wall), while passively listening to auditory stimuli. Preprocessing included band-pass filtering (0.83-25 Hz) with automatic rejection for ocular artefacts (>70 μV). The N1 was identified as the largest negative peak occurring between 70 and 150 ms. Peak-to-peak amplitude for frequent and rare trials was measured.

Statistical analysis was completed using Statistical Package for the Social Sciences 25.0. Normality (for each group) and homogeneity of variance assumptions were tested using the Shapiro-Wilk and Levene tests, respectively. Independent samples t-tests were used to compare groups regarding N1 latency and amplitude for each ear. Moreover, paired samples t-tests were used to compare N1 latency and amplitude between ears, within each group. Inferential statistics (independent samples t-test and chi-square test) were also used to compare sociodemographic characteristics at baseline. Between-group effect sizes (d) for each measure were computed using G*Power: Statistical Power Analyses v.3.1.9.6 (Faul et al. 2007). Effect sizes were classified according to Cohen (1988) as small (d>0.2), medium (d>0.5) or large (d>0.8).

RESULTS

Statistical findings regarding N100 amplitude and latency are presented in Table 1. There were statistically significant group differences for N1 amplitude in the left earlobe (t=-3.067; ρ=0.003) and right earlobe (t=-2.794; ρ=0.007). More specifically, the control group had a higher N1 amplitude in comparison to SCZ group in both earlobes. However, there were no statistically significant group differences in N1 latency (ρ>0.05). Regarding within-group analysis, there were no significant differences between ears for either N1 amplitude or latency for both groups (ρ>0.05). The effect sizes suggests large differences between groups for N1 amplitude in both the left (d=0.815) and right ears (d=1.519). Conversely, regarding N1 latency, differences between groups were negligible in the left ear (d=0.071) and small in right ear (d=0.342).

Table 1. Between-group (SCZ vs. controls) and within-group (left vs. right ear) analysis for N1 amplitude and latency at Cz position

	SCZ			Control			T-student test for independent samples	
	M (SD)	T test for paired samples t	T test for paired samples ρ	M (SD)	T test for paired samples t	T test for paired samples ρ	t	ρ
LEA (μV)	4.18 (2.69)	0.653	0.527	6.45 (2.88)	-0.426	0.677	-2.097	0.046
REA (μV)	3.77 (1.47)			6.62 (2.21)			-4.002	0.001*
LEL (ms)	82.1 (12.6)	-1.375	0.196	81.2 (12.6)	-0.092	0.928	0.175	0.862
REL (ms)	85.3 (13.7)			81.3 (9.31)			0.901	0.376

*Corrected value for heterogeneity of variance; M - mean; SD – Standard Deviation; ρ – p value; μV – microvolts; ms – milliseconds; LEA – Left Ear Amplitude; REA – Right Ear Amplitude; LEL – Left Ear Latency; REL – Right Ear Latency

DISCUSSION

Findings from this study are consistent with previous reports of reduced N1 amplitude in patients with schizophrenia (Ford et al. 2001, Kayser et al. 2001, Laurent et al. 1999, Rosburg et al. 2008). However, in comparison with previous studies, we selected a monoaural auditory oddball stimulation paradigm which allowed us to assess each cortical pathway (left and right). Our findings suggest a large decrease in N1 amplitude in both ears on the SCZ group, allowing us to postulate that schizophrenia is associated with bilateral temporal lobe damage (as well as damage in frontal lobe zones with supratemporal connections), which interferes in auditory cortical pathways in each side of the brain. Previous imaging studies that demonstrate loss of cortical grey matter and damage in the temporal lobe's structure support our hypothesis (APA 2013, Hajima et al. 2013, Shenton et al. 2001, Vita et al. 2012). Thus, decreased N100 amplitude suggests a deficit in early sensory processing of auditory stimuli or reduced neural resources allocation to auditory processing (Bridwell et al. 2014, Ford et al. 1994, Kayser et al. 2001, Kim et al. 2009, Kogoj et al. 2005, O'Donnell et al. 2004, Rosburg et al. 2008).

Several authors have suggested that the N1 amplitude deficits meet the main criteria to be considered a genetic endophenotype for schizophrenia. However, a few studies, such as Frangou et al. (1997), which compare first-degree relatives of schizophrenia patients with healthy controls, failed to find any significant differences in N1 amplitude. Thus, future studies should explore monoaural paradigms to compare bilateral auditory pathways in first-degree relatives as well as across different psychotic stages (e.g. van Tricht et al. 2011). This could provide more information about the underlying mechanisms of disease progression in schizophrenia. Furthermore, future efforts should also consider N1 measurement using phonetic stimuli.

CONCLUSION

Reduced auditory N100 amplitude is a robust physiological abnormality in schizophrenia. Our study shows that it is possible to find reduced N1 amplitude in both ears using monoaural stimulation. Future studies with larger sample sizes and using phonetic stimuli in a monoaural paradigm could provide new insights into the underlying biology of SCZ.

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Conflict of interest: None to declare.

Contribution of individual authors:

António Mota: study design, literature review, data collection, statistical analysis, first manuscript draft, manuscript revision.

David Tomé: study design, literature review, data collection, first manuscript draft, approval of the final version.

Carlos Campos: literature review, data collection, statistical analysis, first manuscript draft, manuscript revision.

Nuno Rocha: first manuscript draft, manuscript revision.

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