Progress in Neuropsychopharmacology & Biological Psychiatry 111 (2021) 110347

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Event-related potentials associated to N-back test performance in schizophrenia

Antonio Arjona-Valladares [a,*], Sabela Fondevila-Estévez [b], Inés Fernández-Linsenbarth [a], Álvaro Díez [a], Francisco Javier Ruiz-Sanz [c], Alberto Rodríguez-Lorenzana [d], Vicente Molina [a,e,*]

[a] Psychiatry Department, School of Medicine, University of Valladolid, Av. Ramón y Cajal, 7, 47005 Valladolid, Spain
[b] Dpto. Psicobiología y Metodología en Ciencias del Comportamiento Facultad de Psicología, Campus de Somosaguas (UCM), Centro UCM-ISCIII para la Evolución y Comportamiento Humanos, Spain
[c] Psychiatry Service, Palencia University Hospital, Spain
[d] Universidad de Las Américas, Quito, Ecuador
[e] Psychiatry Service, Clinical University Hospital Valladolid, Spain

ARTICLE INFO

Keywords:
Schizophrenia
Event-related potentials
N-back task
Task demands
Attentional/cognitive load

ABSTRACT

Mapping of Event-Related Potentials (ERP) associated with auditory and visual odd-ball paradigms has shown consistent differences between healthy controls and schizophrenia patients. It may be hypothesized that higher task attentional/cognitive demand will result in larger differences in these paradigms, which may help understanding the substrates of cognitive deficits in this syndrome. To this aim, we performed an EEG study comparing the effects of increasing the attentional/cognitive load of an auditory N-back task on the Event-Related Potential in 50 subjects with schizophrenia (11 first episodes) and 35 healthy controls. We considered a post-target window of 1000 ms to explore possible between groups differences in N100, P300, and Late Slow Wave (LSW), and compared these components between 0-back ('lower attentional/cognitive load) and 1-back ('higher attentional/cognitive load') conditions. Our results showed that N100 and LSW amplitude increase from 0- to 1-back condition was significantly larger in healthy controls compared to schizophrenia patients. Furthermore, LSW amplitude difference between 0- and 1-back conditions positively correlated with performance in the behavioral cognitive assessment. Taken together, these results support that higher task attentional/cognitive load (0-back *vs.* 1-back condition) increase N100 amplitude differences and reveal new findings related to the LSW component in schizophrenia.

1. Introduction

In schizophrenia, attentional and working memory (WM) impairments have been consistently reported (Obiols, 1992; Docherty et al., 1996; Lee and Park, 2005; Diwadkar et al., 2011; Gold et al., 2017). Studies using Event-Related Potentials (ERPs) as possible markers of the underlying processes have helped to understand the neural substrates of these deficits (Pfefferbaum et al., 1989; Wagner, 1999; Shelley et al., 1999; Jeon and Polich, 2001; Sabeti et al., 2011; Spironelli et al., 2019). In this sense, differences in P1, N1, N2, and P2 components related to the attentional/sensory perception/encoding of the stimuli prior to evaluation of their significance have been reported in schizophrenia patients (Ogura et al., 1991; Bahramali et al., 1998; O'Donnell et al., 2004; Luck and Gold, 2008; Yeap et al., 2008; Salisbury et al., 2009, 2019). Moreover, regarding to WM processing, differences in the latency and amplitude of components associated with late memory phases, such as P300 or Late Slow Wave (LSW), have been observed (Barrett et al., 1986; McCarley et al., 1997; Ford, 1999; Jeon and Polich, 2003; Galletly et al., 2005; Haenschel et al., 2007; Qiu et al., 2014; Turetsky et al., 2015). The lower amplitude of these later components in schizophrenia patients could reflect an impairment in the contextual evaluation/updating of previous significant stimuli in WM.

Over the past several decades the N-back task has been a useful paradigm to investigate the underpinnings of attentional and WM processing (Kirchner, 1958). Previous ERP studies have used this paradigm to explore different brain disorders. Fraga et al. (2018), studying early

* Corresponding author.
E-mail addresses: aarjona@us.es (A. Arjona-Valladares), sbfondevila@gmail.com (S. Fondevila-Estévez), ineslinsenbarth@gmail.com (I. Fernández-Linsenbarth), a.diez@uva.es (Á. Díez), fruiz@saludcastillayleon.es (F.J. Ruiz-Sanz), aa.rodriguez@udlanet.ec (A. Rodríguez-Lorenzana), vicente.molina@uva.es (V. Molina).

https://doi.org/10.1016/j.pnpbp.2021.110347
Received 4 October 2020; Received in revised form 20 April 2021; Accepted 6 May 2021
Available online 11 May 2021

diagnosis of mild cognitive impairment and Alzheimer's disease, observed a reduced P450 amplitude in the execution of the non match 1-back task. Zhang et al. (2018a), using the 2-back task with positive, negative and neutral contents, reported that depressed patients showed smaller occipital P100 for positive material and larger parietal late positive potential irrespective of the valence of the words.

The present study tries to provide new data about the possible ERPs differences in schizophrenia associated with the inclusion of a higher attentional/cognitive load in an auditory N-back task (*e.g.* 0- *vs.* 1-back condition). The amplitudes of three post-target ERP components (N100, P300, and LSW) are compared between schizophrenia patients and Healthy Controls (HC) during two N-back conditions: 0-back ('lower attentional/cognitive load') and 1-back ('higher attentional/cognitive load'). Our initial hypothesis would be that the performance of an auditory 1-back task will demand higher cognitive resources to perceive/evaluate/update the context/stimuli value in comparison to the performance of an auditory 0-back task. This higher cognitive request will be associated with larger amplitude differences in the post-target N1, P300, and LSW components between HC and patients.

2. Materials and methods

2.1. Sample

Fifty schizophrenia patients (39 stable chronic and 11 first episode) and 35 Healthy Controls (HC), all with normal hearing skills, participated in the study. Patients were diagnosed by two expert psychiatrists (VM and FRS) according to the Diagnostic and Statistical Manual of Mental Disorders (5th edition). Exclusion criteria were; (i) neurological illness, (ii) history of cranial trauma with loss of consciousness, (iii) current substance abuse (except nicotine or caffeine), (iv) intelligence quotient (IQ) lower than 70 and (v) any psychiatric treatment (for controls) or diagnosis different from schizophrenia.

Positive, negative, and total symptoms were scored from patients using the 'Positive and Negative Syndrome Scale' (PANSS) (Kay et al., 1987). Cognitive data were collected from patients and HC using; (i) the 'Wechsler Adult Intelligence Scale-III' (WAIS-III) (Wechsler, 1997); (ii) the Spanish version of the 'Brief Assessment in Cognition in Schizophrenia Scale' (BACS) (Keefe et al., 2008; Segarra et al., 2011), which scores performance in verbal memory (list learning), working memory (digit span), motor speed (token motor task), verbal fluency (categories), attention and processing speed (symbol coding), and executive function and problem solving (Tower of London); and (iii) the 'Wisconsin Card Sorting Test' (WCST: percentage of perseverative errors) (Chelune and Baer, 1986). Sociodemographic, behavioral, cognitive and clinical data are shown in Table 1.

All participants gave their written informed consent after receiving full printed information. The ethical committees of the participating hospitals endorsed the study.

2.2. Electroencephalographic recording and processing

EEG data were recorded through a 64-channel EEG system (BrainVision., Brain Products GmbH). Active electrodes were placed in an elastic cap using the international 10–20 system (FP1, FP2, F7, F8, F3, F4, Fz, FC5, FC6, FC1, FC2, T7, T8, C3, Cz, C4, CP5, CP6, CP1, CP2, TP9, TP10, P7, P8, P3, P4, Pz, O1, O2, Oz, AF7, AF3, AFz, F1, F5, FT7, FC3, FCz, C1, C5, TP7, CP3, P1, P5, PO7, PO3, POz, PO4, PO8, P6, P2, CPz, CP4, TP8, C6, C2, FC4, FT8, F6, F2, AF4, AF8). The impedance was maintained under 5 kΩ and a sampling frequency of 500 Hz was used. EEG recordings were initially referenced over Cz electrode and subsequently re-referenced off-line to the average mastoid ((TP9 + TP10)/2). Data were preprocessed using EEGLAB v13.6.5b (Delorme and Makeig, 2004) and Matlab R2015b (MathWorks Inc., MA, USA). Processing included a low pass filter of 70 Hz and a high pass filter of 0.05 Hz (Luck and Hillyard, 1994). Eye movements, blink, and muscle artifacts were rejected with an Independent Components Analysis (ICA) (Delorme et al., 2007). Trials contaminated with artifacts were automatically detected and rejected if their amplitude exceeded a statistical based local adaptive threshold (Bachiller et al., 2015). As a consequence, the mean of artifact-free trials during 1-back condition was slightly lower in patients (mean = 47.84, SD = ±7.61) compared to HC (mean = 52.34, SD = ±2.57). The artifact-free trials were averaged on each subject to obtain the evoked activity to the target stimulus onset. After visual exploration of the post-target ERP waveforms and topographies depicted in Fig. 1, one early fronto-central component (N100 (latency: 100–140 ms, electrodes: AF7, AF3, AFz, AF4, AF8, F5, F3, F1, Fz, F2, F4, F6, FC5, FC3, FC1, FCz, FC2, FC4, FC6, C5, C3, C1, Cz, C2, C4, C6, CP3, CP1, CPz, CP2, CP4)), one centro-parietal deflection (P300 (latency: 320–420 ms, electrodes: C3, C1, Cz, C2, C4, CP5, CP3, CP1, CPz, CP2, CP4, CP6, P7, P5, P3, P1, Pz, P2, P4, P6, P8, PO7, PO3, POz, PO4, PO8, O1, Oz, O2) and one central Late Slow Wave (latency: 600–1000 ms, electrodes: F1, Fz, F2, FC5, FC3, FC1, FCz, FC2, FC4, FC6, C5, C3, C1, Cz, C2, C4, C6, CP5, CP3, CP1, CPz, CP2, CP4, CP6, P1, Pz, P2)) were analyzed.

Table 1
Demographic, clinical and cognitive data in schizophrenia patients and Healthy Controls (HC).

	Patients ($n = 50$)	HC ($n = 35$)
Age	37.64 (11.96)	33.51 (11.16)
Sex (male:female)	27:23	17:18
CPZ equivalents (mg/d)	421.22 (291.28)	NA
Duration (months)	98.20 (119.12)	NA
Education (years)	15.31 (3.30)	17.05 (1.92)
Positive symptoms (PANSS)	12.36 (3.97)	NA
Negative symptoms (PANSS)	16.38 (7.85)	NA
Total symptoms (PANSS)	54.00 (17.85)	NA
Total IQ (WAIS)	93.77 (13.17)***	116.66 (11.64)
Verbal memory (BACS)	37.54 (11.30)***	54.51 (5.40)
Working memory (BACS)	17.54 (5.02)***	23.11 (2.56)
Motor speed (BACS)	58.86 (17.81)***	82.55 (14.59)
Verbal fluency (BACS)	20.57 (5.17)***	30.07 (3.34)
Processing speed (BACS)	45.27 (11.29)***	70.03 (11.69)
Problem solving (BACS)	16.90 (3.75)**	19.22 (2.43)
% perseverative errors (WCST)	15.29 (10.45)**	8.64 (4.44)
0-back – Reaction times (ms)	519.16 (180.67)	490.57 (138.27)
1-back – Reaction times (ms)	516.68 (166.59)**	429.20 (119.26)
0-back – Artifact free epochs	93.50 (13.74)	96.57 (8.38)
1-back – Artifact free epochs	47.84 (7.61) **	52.34 (2.57)

Data are stated as mean (SD). Antipsychotic doses were converted to chlorpromazine (CPZ) equivalents. Sz: Schizophrenia, HC: Healthy Controls, CPZ: Chlorpromazine, PANSS: Positive and Negative Syndrome Scale, IQ: Intelligence Quotient, WAIS: Weschler assessment of intelligence scale, BACS: Brief Assessment of Cognition in Schizophrenia, WCST: Wisconsin card sorting test. Significant differences with respect to HC are shown for Sz patients: $*p < .05$, $**p < .01$, $***p < .001$.

2.3. N-back working memory paradigm

Each participant performed two consecutive auditory N-back tasks (first task: 0-back condition, second task: 1-back condition) with eyes closed. During the 0-back condition, a random series of 600 tones with an interstimulus interval (ISI) of 1500 ms was presented. The tones (duration 50 ms, rise and fall time 5 ms and intensity 90 dB) were divided into *target* (500 Hz tone, probability 0.2), *distractor* (1000 Hz tone, probability 0.2), and *standard* (2000 Hz tone, probability 0.6) tones. Participants were instructed to press a button when detecting the *target* tone. The 1-back condition was composed of a random series of 270 tones divided into *target* (500 Hz tone, probability 0.5), and *standard* (2000 Hz tone, probability 0.5) tones (ISI: 1500 ms). In this case, participants were instructed to press the button when detecting the *target* tone only if it was immediately preceded by another *target* tone. For both modalities *target* tones were considered 'attended' tones when followed by a button press, and only 'attended' target tones were considered for subsequent ERP analyses. Artifact free epochs were averaged and

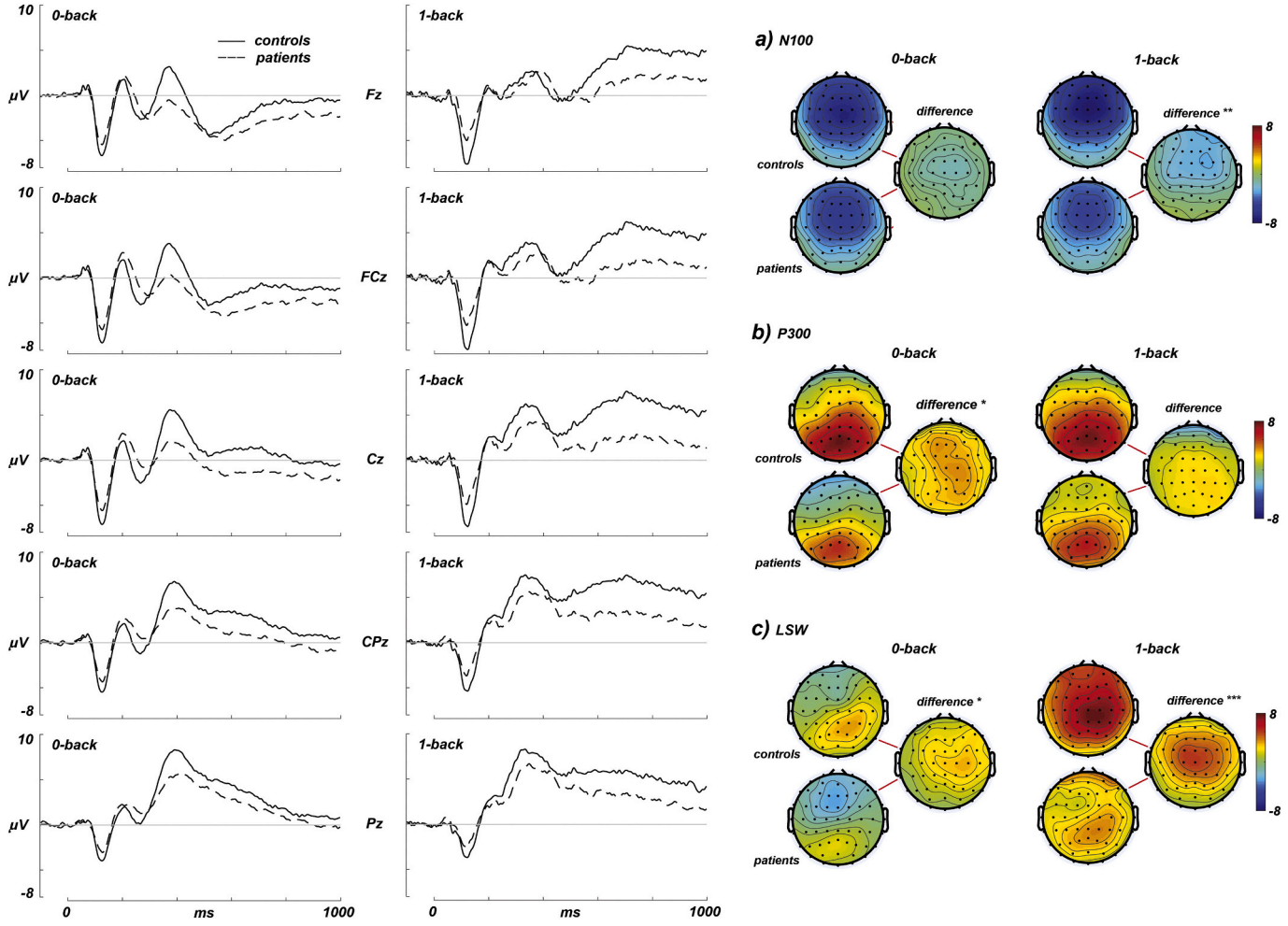

Fig. 1. *On the left side*: averaged evoked responses in each group comparing 0-back and 1-back conditions. Midline electrodes. *On the right side*: topographical maps obtained in Sz patients and HC during 0-back and 1-back conditions. (a) Mean amplitude of N100 latency. (b) Mean amplitude of P300 latency. c Mean amplitude of LSW latency.

indicated in Table 1.

2.4. Data analysis

Sociodemographic, behavioral, cognitive, and clinical differences between patients and HC were examined using Chi squared or Student's *t*-tests (Table 1).

A Principal Components Analysis (PCA), which extracted factors summarizing cognitive scores (BACS and WSCT), was performed to reduce the number of comparisons. More details about the individual factor scores were included in Table 3.

ERP data were analyzed with repeated measures ANOVA on averages of trials. There were three factors: group (divided in two conditions: patients and HC), task (divided in two conditions: 0-back and 1-back) and electrode. The mean amplitude values of each component were compared; (i) between tasks (0-back and 1-back) within each group (patients and HC) and (ii) between groups within each task. Finally, interactions were explored to compare each component amplitude difference from 0- to 1-back condition between groups. The *p* values were corrected with the Greenhouse-Geisser when necessary, and effect sizes were assessed using partial eta-squared values (SPSS Statistics for Windows, Version 23.0. Chicago: SPSS Inc.).

In a second step, we assessed the cognitive correlates of the ERP differences. A curvilinear regression analysis was performed with N100, P300 and LSW amplitudes as predictors of (i) behavioral performance (RTs); (ii) cognitive factor scores (summarizing BACS () and WSCT performance); (iii) positive and negative symptoms (PANSS); (iv) and treatment dose in mg/d of chlorpromazine equivalents. Previous regressions were performed joining patients and HC to maximize the statistical power.

3. Results

There were no significant group differences (patients *vs.* HC) in age, sex or education (years). Cognitive scores showed generalized deficits in patients in comparison to HC (Table 1).

3.1. Analyses of event-related potentials

The comparisons of ERP data are summarized in Table 2 (mean amplitude values/differences). Waveforms and topographies of N100, P300 and LSW during 0- and 1-back conditions are depicted in Fig. 1.

3.1.1. Group and task interactions

A three-factors repeated measures ANOVA was performed on the voltage data of each component (N100, P300 and LSW). Factors were: *task* (0-back, 1-back), *group* (patients, HC) and *electrode*. The results showed a significant *task x group* interaction in N1 ($F_{1,34} = 8.59$, $p = .006$, $\eta_p^2 = 0.20$) and LSW ($F_{1,34} = 5.14$, $p = .030$, $\eta_p^2 = 0.13$), due to a larger amplitude increase in both component from 0- to 1-back

Table 2
ERP mean amplitude values/differences in schizophrenia patients and Healthy Controls (HC).

a)

	Patients ($n = 50$)	HC ($n = 35$)
0-back – N1 amplitude (μV)	−3.43 (2.14)	−4.37 (1.52)
1-back – N1 amplitude (μV)	−3.10 (1.89)	−5.14 (1.94)
0-back – P300 amplitude (μV)	2.42 (3.46)	4.70 (4.31)
1-back – P300 amplitude (μV)	3.61 (3.43)	5.16 (3.53)
0-back – LSW amplitude (μV)	−0.79 (3.27)	0.71 (2.56)
1-back – LSW amplitude (μV)	2.19 (3.46)	5.19 (2.85)

b)

	Higher amplitude from 0-back to 1-back condition	Higher amplitude in HC compared to Sz patients	Amplitude difference from 0-back to 1-back condition
N1	HC*	1-back task**	HC > Sz patients**
P300	SZ patients**	0-back task*	———————
LSW	Sz patients***	0-back task*	
	HC***	1-back task***	HC > Sz patients*

a: Data are stated as mean (SD). N1, P300, and LSW mean amplitudes are referred to selected groups of electrodes (see materials and methods section). b: Significant differences with respect to controls are shown for Sz patients: *$p <$ .05, **$p <$ .01, ***$p <$ .001.

Table 3
Individual factor scores and PCA factor score in schizophrenia patients and Healthy Controls (HC).

	Patients ($n = 50$)	HC ($n = 35$)
Verbal memory	54.51 (5.4)	37.27 (11.29)
Working memory	23.11 (2.56)	17.51 (5.07)
Motor speed	82.55 (14.59)	58.51 (17.87)
Verbal fluency	30.07 (3.34)	20.3 (4.89)
Attention and processing speed	70.03 (11.69)	45.46 (11.35)
Executive functions	19.22 (2.43)	17 (3.75)
Wisconsin test	8.64 (4.44)	15.29 (10.45)
PCA factor scores	−0.59 (0.79)	0.94 (0.33)

Data are stated as mean (SD).

condition in HC compared to patients.

To summarize, N100 and LSW amplitude increases from 0- to 1-back condition were significantly larger in HC as compared to patients. In contrast, P300 amplitude did not show between groups differences related to attentional/cognitive load increase (Table 2 and Fig. 1).

3.2. Cognitive and clinical correlates

Smaller RTs in 1-back condition were positively correlated with an increase of P300 ($R^2 = 0.152$, $p = .001$) and LSW ($R^2 = 0.117$, $p = .004$) amplitudes (Supplementary Fig. 1).

PCA of cognitive scores yielded one single factor (eigenvalue 4.033) explaining 57.61% of the total variance, and showed positive contributions from BACS scores and negative contributions by perseverative errors in WSCT.

The whole sample showed significantly direct associations between cognitive performance and the following ERP amplitudes: N100 in 0-back ($R^2 = 0.074$, $p = .023$; Fig. 2a), N100 in 1-back ($R^2 = 0.170$, $p < .001$; Fig. 2b), P300 in 0-back ($R^2 = 0.104$, $p = .006$; Fig. 2d), P300 in 1-back ($R^2 = 0.122$, $p = .003$; Fig. 2e), LSW in 1-back ($R^2 = 0.232$, $p < .001$; Fig. 2h). Cognitive scores were also directly associated to LSW amplitude difference between 0- and 1-back condition ($R^2 = 0.103$, $p = .007$; Fig. 2i).

N100, P300, and LSW amplitude differences between tasks did not show significant associations to cognitive performance when both samples were analyzed separately (Supplementary Figs. 2 and 3). There were also not significant associations of ERP amplitudes and positive/negative symptoms or antipsychotic doses in schizophrenia patients (Supplementary Fig. 4).

4. Discussion

The aim of this study is to compare the ERP amplitude changes from 0-back ('lower attentional/cognitive load') to 1-back ('higher attentional/cognitive load') condition between schizophrenia patients and HC. Results showed that the HC group presented higher amplitude than patients in N100 during 1-back; P300 during 0-back; and LSW during both 0- and 1-back conditions. Furthermore, the ERP amplitude increase in N100 and LSW components from 0- to 1-back condition was larger in HC compared to patients.

According to our results, the amplitude increase in LSW from 0- to 1-back condition was associated with cognitive performance (Fig. 2i), indicating that the neural processes underlying such an increase might relate to those involved in cognition. This would be coherent with the larger LSW increase from 0- to 1-back condition in HC and the cognitive deficits in patients. Additionally, P300 and LSW amplitudes negatively correlated with RTs in 1-back condition (Supplementary Fig. 1), reflecting that both components would be associated with the RT benefit generated by the previous cue stimulus (Zhao et al., 2013).

Regarding the cognitive performance of the schizophrenia group, the scores presented in this study (Fig. 2) could give the impression that schizophrenia patients have a ceiling effect. In this line, recent analyzes (Planchuelo-Gómez et al., 2020) have shown that this ceiling effect does not happen in the whole population of schizophrenia patients. Instead, there seem to be at least two subgroups of patients across schizophrenia and bipolar disorder based on neuroanatomy differences, showing only one of these two subgroups a cognitive performance similar to the healthy control group.

4.1. Auditory N100

Auditory N100 is considered a pre-attentive component associated with the detection of changes in the surrounding environment. This early negativity has been studied with attentional paradigms (designed to analyze the neural correlates of deviant/attended stimulus perception and processing) and would be reflecting both orienting of attention and processing of the stimulus attributes (Hillyard et al., 1973; Hung et al., 2001; Inui et al., 2010; Arjona et al., 2017). Despite current evidence on this early component, there is not a clear consensus regarding the meaning of its amplitude reduction in schizophrenia (see Rosburg et al. (2008) for a critical review). Based on previous literature, our results would indicate that the N100 amplitude increase from 0- to 1-back condition in HC, but not in patients, may be due to a higher expectancy (or 'short term expectation') generated by the previous cue stimulus during 1-back in comparison to 0-back condition (in which deviant stimulus arrival can be at any time: 'long term expectation') (Table 2 and Fig. 1). In other words, the absence of N100 amplitude increase from 0- to 1-back condition in schizophrenia patients may suggest a possible deficit in the capacity to generate a higher/short term state of expectation.

4.2. P300 component

P300 is a positive wave generated between 300 and 500 ms after target stimulus perception, whose amplitude is higher in response to unexpected/salient stimuli compared to frequent ones (Polich, 2007). There is some agreement in considering it as a reflection of attentional resource allocation and working memory updating (Duncan-Johnson and Donchin, 1980; Beydagi et al., 2000; Kumaran and Maguire, 2007; Zhang et al., 2018b). Our results corroborated the reduced P300 amplitude in schizophrenia during 0-back condition (probably reflecting the attentional/WM impairments), but not during 1-back (due to the amplitude increase from 0- to 1-back only in patients) (Table 2 and

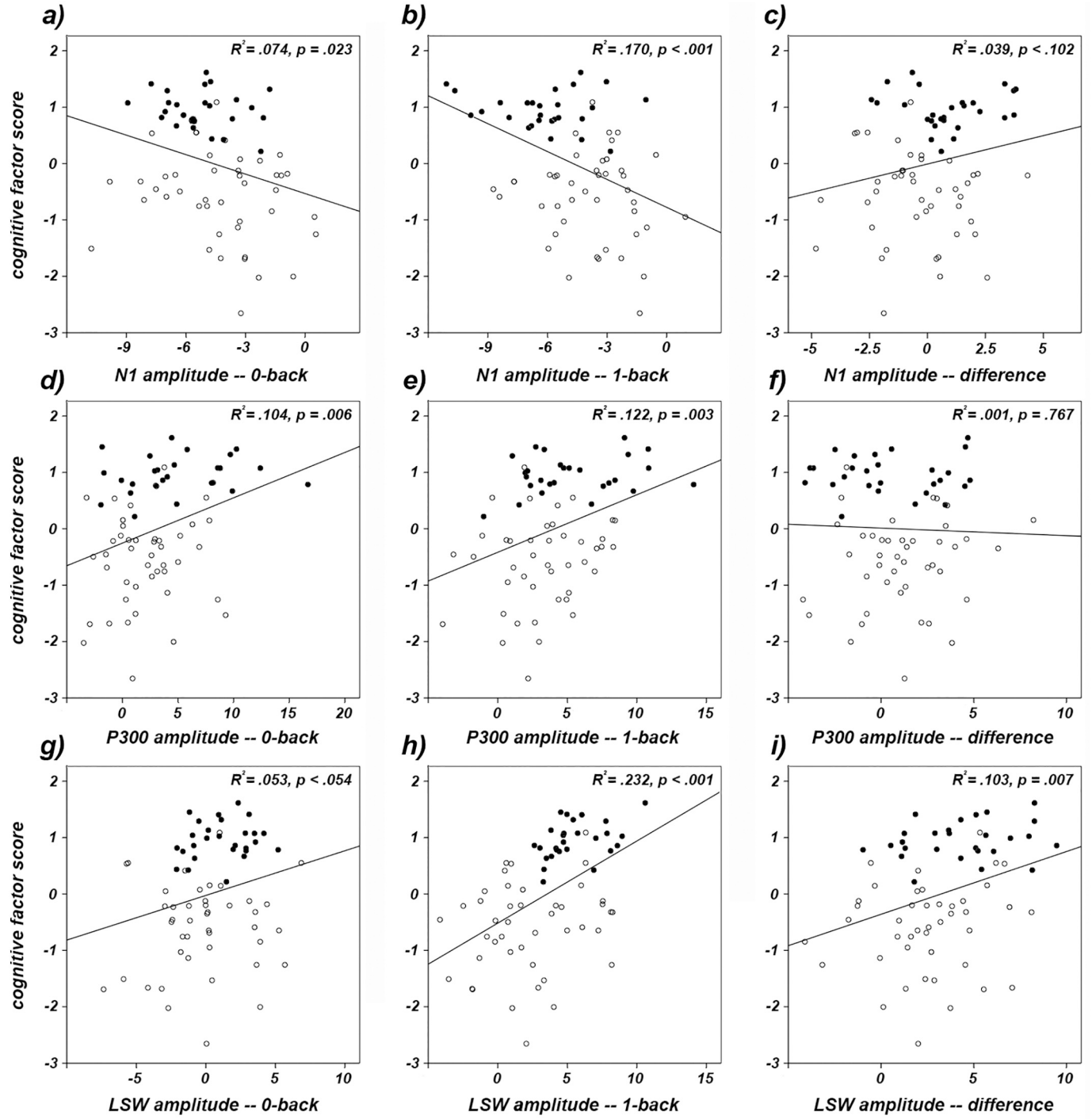

Fig. 2. Associations between ERP amplitudes and cognitive performance. White and black dots depict Sz patients and HC respectively. (a–c) Scatterplot showing the associations between N100 amplitude and cognitive performance. Notice the significant correlation in 0-back and 1-back conditions. (d–f) Scatterplot showing the associations between P300 amplitude and cognitive performance. Notice the significant correlation in 0-back and 1-back conditions. (g–i) Scatterplot showing the associations between LSW amplitude and cognitive performance. Notice the significant correlation in 1-back condition and for the amplitude difference between both conditions.

Fig. 1). Considering that P300 amplitude would be related to the 'surprise' generated by the target stimulus onset and the subsequent WM updating process, the smaller P300 amplitude increase in HC during 1-back condition may be consequence of the higher expectancy (consistent with the greater N100 amplitude in 1-back) generated by the previous cue stimulus about the target stimuli arrival.

4.3. Late slow wave

Analyzes of late ERP components associated with the cognitive processing of auditory target-stimulus have been widely reported (Ruchkin and Sutton, 1983; Rushby et al., 2005; Guo et al., 2010). Despite the variety of tasks related to long latency slow waves, comparisons suggest that these deflections may reflect further perceptual and conceptual operations (beyond the activity underlying P300

component), and its amplitudes would be related to task demands (Ruchkin et al., 1980; Parasuraman et al., 1982; Pinal et al., 2014). Enhanced LSW amplitude has been reported in stimulus detection, recognition, and localization because of increasing task difficulty. Matching of linguistic stimulus and semantic/abstract memorization also showed a correlation between task complexity and LSW amplitude (Sanquist et al., 1980; Neville et al., 1986; Rösler et al., 1986). LSW attenuation in schizophrenia patients is observed with target detection tasks and relates to impairments in executive functions as WM (Roth et al., 1981; Galletly et al., 2005). The present results showed that LSW amplitude increased from 0- to 1-back condition in patients and HC, being this increase significantly larger in the HC group (Table 2 and Fig. 1). Besides, our data revealed a positive association of cognitive scores with LSW amplitude in 1-back (Fig. 2h) and LSW amplitude difference between 0- and 1-back conditions (Fig. 2i). Together, these results corroborate the relation between LSW amplitude and task cognitive demand, and support that the higher task complexity (from 0- to 1-back condition) accentuates the LSW amplitude difference between HC and schizophrenia patients. Furthermore, the relevance of the smaller LSW increase in patients is supported by the association between such an increase and the behavioral cognitive performance.

4.4. Conclusions

According to our initial hypothesis, higher attentional/cognitive load (from 0- to 1-back condition) generated larger amplitude differences in N100 and LSW components between schizophrenia patients and HC. Besides, LSW amplitude difference from 0- to 1-back condition was positively associated with cognitive performance.

4.5. Limitations

Among the main limitations of our study, sample size is relatively small and most of the patients were in a stable chronic state. Moreover, although the antipsychotic doses seemed not to produce a relevant effect on ERP amplitudes, all patients were under a stable treatment. Finally, the specificity of our findings cannot be assessed without further studies including other groups of patients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2021.110347.

Funding source

This study has been supported by the Consejería de Educación Junta de Castilla y León VA057P17 (Universidad de Valladolid), and the Instituto de Salud Carlos III PI18/00178 (Hospital Clínico Universitario de Valladolid).

Author statement

We herein acknowledge that each author has reviewed and approved the manuscript and no substantial portion of the study has been published or is under consideration for publication elsewhere. The support obtained for this study comes exclusively from public research funding.

Contributors

V. Molina and A. Arjona were responsible for the study design, statistical analysis and drafting the manuscript. A. Arjona, A. Díez, S. Fondevila and I. Fernández were responsible for data extraction. V. Molina, F.J. Ruíz and A. Rodríguez were responsible for accessing the schizophrenia patient sample.

Ethical statement

We have read and agreed with the journal's ethical standards. We declare that all experiments on human participants were conducted in accordance with the Declaration of Helsinki and all procedures were carried out with the adequate understanding and written consent of the participants. We certify that formal approval to conduct the experiments described have been obtained from the review board of the University Hospital of Valladolid and could be provided upon request.

Declaration of competing interest

All authors had access to all data of the study. The authors have no conflicts of interest to declare.

Acknowledgements

Authors thank the schizophrenia patients and control subjects who donated their time and effort to participate in this study.

References

Arjona, A., González, J.G., Gómez, C.M., 2017. Event related potentials changes associated with the processing of auditory valid and invalid targets as a function of previous trial validity in a Posner's paradigm. Neurosci. Res. 115, 37–43. https://doi.org/10.1016/j.neures.2016.09.006.

Bachiller, A., Poza, J., Gómez, C., Molina, V., Suazo, V., Hornero, R., 2015. A comparative study of event-related coupling patterns during an auditory oddball task in schizophrenia. J. Neural Eng. 12, 016007 https://doi.org/10.1088/1741-2560/12/1/016007.

Bahramali, H., Gordon, E., Li, W.M., Rennie, C., Wright, J., Meares, R., 1998. Fast and slow reaction times and associated Erps in patients with schizophrenia and controls. Int. J. Neurosci. 95 (3–4), 155–165. https://doi.org/10.3109/00207459809003337.

Barrett, K., McCallum, W., Pocock, P., 1986. Brain indicators of altered attention and information processing in schizophrenic patients. Brit. J. Psychiat. 148 (4), 414–420. https://doi.org/10.1192/bjp.148.4.414.

Beydagi, H., Özesmi, Ç., Yilmaz, A., Süerd, C., Ergenoglu, T., 2000. The relation between event related potential and working memory in healthy subjects. Int. J. Neurosci. 105 (1–4), 77–85. https://doi.org/10.3109/00207450009003267.

Chelune, G.J., Baer, R.A., 1986. Developmental norms for the Wisconsin Card Sorting test. J. Clin. Exp. Neuropsychol. 8, 219–228. https://doi.org/10.1080/13854049308401516.

Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J. Neurosci. Methods 134 (1), 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009.

Delorme, A., Sejnowski, T., Makeig, S., 2007. Enhanced detection of artifacts in EEG data using higher-order statistics and independent component analysis. NeuroImage 34 (4), 1443–1449. https://doi.org/10.1016/j.neuroimage.2006.11.004.

Diwadkar, V.A., Goradia, D., Hosanagar, A., Mermon, D., Montrose, D.M., Birmaher, B., et al., 2011. Working memory and attention deficits in adolescent offspring of schizophrenia or bipolar patients: comparing vulnerability markers. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 35 (5), 1349–1354. https://doi.org/10.1016/j.pnpbp.2011.04.009.

Docherty, N.M., Hawkins, K.A., Hoffman, R.E., Quinlan, D.M., Rakfeldt, J., Sledge, W.H., 1996. Working memory, attention, and communication disturbances in schizophrenia. J. Abnorm. Psychol. 105 (2), 212–219. https://doi.org/10.1037/0021-843X.105.2.212.

Duncan-Johnson, C.C., Donchin, E., 1980. The relation of P300 latency to reaction time as a function of expectancy. Prog. Brain Res. 54, 717–722. https://doi.org/10.1016/S0079-6123(08)61693-3.

Ford, J.M., 1999. Schizophrenia: the broken P300 and beyond. Psychophysiology 36, 667–682. https://doi.org/10.1111/1469-8986.3660667.

Fraga, F.J., Mamani, G.Q., Johns, E., Tavares, G., Falk, T.H., Phillips, N.A., 2018. Early diagnosis of mild cognitive impairment and Alzheimer's with event-related potentials and event-related desynchronization in N-back working memory tasks. Comput. Methods Prog. Biomed. 164, 1–13. https://doi.org/10.1016/j.cmpb.2018.06.011.

Galletly, C.A., Clark, C.R., Mcfarlane, A.C., 2005. Clozapine improves working memory updating in schizophrenia. Eur. Neuropsychopharmacol. 15 (6), 601–608. https://doi.org/10.1016/j.euroneuro.2005.03.001.

Gold, J.M., Robinson, B., Leonard, C.J., Hahn, B., Chen, S., McMahon, R.P., et al., 2017. Selective attention, working memory, and executive function as potential independent sources of cognitive dysfunction in schizophrenia. Schizophr. Bull. 44 (6), 1227–1234. https://doi.org/10.1093/schbul/sbx155.

Guo, J., Gao, S., Hong, B., 2010. An auditory brain–computer interface using active mental response. IEEE Trans. Neural Syst. Rehabilitation Eng. 18 (3), 230–235. https://doi.org/10.1109/TNSRE.2010.2047604.

Haenschel, C., Bittner, R.A., Haertling, F., Rotarska-Jagiela, A., Maurer, K., Singer, W., Linden, D.E.J., 2007. Contribution of impaired early-stage visual processing to working memory dysfunction in adolescents with schizophrenia. Arch. Gen. Psychiatry 64 (11), 1229. https://doi.org/10.1001/archpsyc.64.11.1229.

Hillyard, S.A., Hink, R.F., Schwent, V.L., Picton, T.W., 1973. Electrical signs of selective attention in the human brain. Science. 182 (4108), 177–180. https://doi.org/10.1126/science.182.4108.177.

Hung, J., Jones, S.J., Vaz Pato, M., 2001. Scalp potentials to pitch change in rapid tone sequences. Exp. Brain Res. 140, 56–65. https://doi. https://doi.org/10.1007/s00221010100783.

Inui, K., Urakawa, T., Yamashiro, K., Otsuru, N., Nishihara, M., Takeshima, Y., Keceli, S., Kakigi, R., 2010. Non-linear laws of echoic memory and auditory change detection in humans. BMC Neurosci. 11, 80. https://doi.org/10.1186/1471-2202-11-80.

Jeon, Y.W., Polich, J., 2001. P300 asymmetry in schizophrenia: a meta-analysis. Psychiatry Res. 104 (1), 61–74. https://doi.org/10.1016/S0165-1781(01)00297-9.

Jeon, Y.W., Polich, J., 2003. Meta-analysis of P300 and schizophrenia: patients, paradigms, and practical implications. Psychophysiology 40, 684–701. https://doi.org/10.1111/1469-8986.00070.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (panss) for schizophrenia. Schizophr. Bull. 13, 261–276. https://doi.org/10.1093/schbul/13.2.261.

Keefe, R.S., Harvey, P.D., Goldberg, T.E., Gold, J.M., Walker, T.M., Kennel, C., Hawkins, K., 2008. Norms and standardization of the Brief Assessment of Cognition in Schizophrenia (BACS). Schizophr. Res. 102 (1–3), 108–115. https://doi.org/10.1016/j.schres.2008.03.024. Epub 2008 May 20. 18495435.

Kirchner, W.K., 1958. Age differences in short-term retention of rapidly changing information. J. Exp. Psychol. 55 (4), 352–358. https://doi.org/10.1037/h0043688.

Kumaran, D., Maguire, E.A., 2007. Which computational mechanisms operate in the hippocampus during novelty detection? Hippocampus 17, 735–748. https://doi.org/10.1002/hipo.20326.

Lee, J., Park, S., 2005. Working memory impairments in schizophrenia: a meta-analysis. J. Abnorm. Psychol. 114 (4), 599–611. https://doi.org/10.1037/0021-843X.114.4.599.

Luck, S.J., Gold, J.M., 2008. The construct of attention in schizophrenia. Biol. Psychiatry 64, 34–39. https://doi.org/10.1016/j.biopsych.2008.02.014.

Luck, S.J., Hillyard, S.A., 1994. Electrophysiological correlates of feature analysis during visual search. Psychophysiology 31 (3), 291–308. https://doi.org/10.1111/j.1469-8986.1994.tb02218.x.

McCarley, D., O'Donnell, B., Niznikiewicz, M., Salisbury, D.F., Potts, G.F., Hirayasu, Y., Nestor, P., Shenton, M., 1997. Update on electrophysiology in schizophrenia. Int. Rev. Psychiat. 9, 373–386.

Neville, H.J., Kutas, M., Chesney, G., Schmidt, A.L., 1986. Event-related brain potentials during initial encoding and recognition memory of congruous and incongruous words. J. Mem. Lang. 25, 75–92. https://doi.org/10.1016/0749-596X(86)90022-7.

Obiols, J.E., 1992. Sustained attention deficit in young schizophrenic and schizotypic men. Psychol. Rep. 71 (8), 1131. https://doi.org/10.2466/PR0.71.8.1131-1136.

O'Donnell, B.F., Vohs, J.L., Hetrick, W.P., Carroll, C.A., Shekhar, A., 2004. Auditory event-related potential abnormalities in bipolar disorder and schizophrenia. Int. J. Psychophysiol. 53, 45–55. https://doi.org/10.1016/j.ijpsycho.2004.02.001.

Ogura, C., Nageishi, Y., Matsubayashi, M., Omura, F., Kishimoto, A., Shimokochi, M., 1991. Abnormalities in event-related potentials: N100, P200, P300, and slow waves in schizophrenia. Jpn. J. Psychiatry. Neurol. 45, 57–65. https://doi.org/10.1111/j.1440-1819.1991.tb00506.x.

Parasuraman, R., Richer, F., Beatty, J., 1982. Detection and recognition: concurrent processes in perception. Percept. Psychophys. 31, 1–12. https://doi.org/10.3758/BF03206196.

Pfefferbaum, A., Ford, J.M., White, P.M., Roth, W.T., 1989. P3 in schizophrenia is affected by stimulus modality, response requirements, medication status, and negative symptoms. Arch. Gen. Psychiatry 46, 1035–1044. https://doi.org/10.1001/archpsyc.1989.01810110077011.

Pinal, D., Zurrón, M., Díaz, F., 2014. Effects of load and maintenance duration on the time course of information encoding and retrieval in working memory: from perceptual analysis to post-categorization processes. Front. Hum. Neurosci. 8, 165. https://doi.org/10.3389/fnhum.2014.00165.

Planchuelo-Gómez, Á., Lubeiro, A., Núñez-Novo, P., Gomez-Pilar, J., de Luis-García, R., del Valle, P., et al., 2020. Identificacion of MRI-based psychosis subtypes: replication and refinement. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 100, 109907. https://doi.org/10.1016/j.pnpbp.2020.109907.

Polich, J., 2007. Updating P300: an integrative theory of P3a and P3b. Clin. Neurophysiol. 118, 2128–2148. https://doi.org/10.1016/j.clinph.2007.04.019.

Qiu, Y., Tang, Y., Chan, R.C.K., Sun, X., He, J., 2014. P300 aberration in first-episode schizophrenia patients: a meta-analysis. PLoS One 9 (6), e97794. https://doi.org/10.1371/journal.pone.0097794.

Rosburg, T., Boutros, N.N., Ford, J.M., 2008. Reduced auditory evoked potential component N100 in schizophrenia – a critical review. Psychiatry Res. 161 (3), 259–274. https://doi.org/10.1016/j.psychres.2008.03.017.

Rösler, F., Clausen, G., Sojka, B., 1986. The double-priming paradigm: a tool for analyzing the functional significance of endogenous event-related brain potentials. Biol. Psychol. 22 (3), 239–268. https://doi.org/10.1016/0301-0511(86)90029-3.

Roth, W.T., Pfefferbaum, A., Kelly, A.F., Berger, P.A., Kopell, B.S., 1981. Auditory event-related potentials in schizophrenia and depression. Psychiatry Res. 4 (2), 199–212. https://doi.org/10.1016/0165-1781(81)90023-8.

Ruchkin, D.S., Sutton, S., 1983. Positive slow wave and P300: Association and disassociation. In: Gaillard, A.K.W., Ritter, W. (Eds.), Tutorials in ERP Research: Endogenous Components. North Holland, Amsterdam, pp. 233–250.

Ruchkin, D.S., Sutton, S., Kietzman, M.L., Silver, K., 1980. Slow wave and P300 in signal detection. Electroencephalogr. Clin. Neurophysiol. 50, 35–47. https://doi.org/10.1016/0013-4694(80)90321-1.

Rushby, J.A., Barry, R.J., Doherty, R.J., 2005. Separation of the components of the late positive complex in an ERP dishabituation paradigm. Clin. Neurophysiol. 116 (10), 2363–2380. https://doi.org/10.1016/j.clinph.2005.06.008.

Sabeti, M., Moradi, E., Katebi, S., 2011. Analysis of neural sources of P300 event-related potential in normal and schizophrenic participants. Adv. Exp. Med. Biol. 696, 589–597. https://doi.org/10.1007/978-1-4419-7046-6_60.

Salisbury, D.F., Collins, K.C., McCarley, R.W., 2009. Reductions in the N1 and P2 auditory event-related potentials in first-hospitalized and chronic schizophrenia. Schizophr. Bull. 36 (5), 991–1000. https://doi.org/10.1093/schbul/sbp003.

Salisbury, D.F., Kohler, J., Shenton, M.E., McCarley, R.W., 2019. Deficit effect sizes and correlations of auditory event-related potentials at first hospitalization in the schizophrenia spectrum. Clin. EEG Neurosci. 51 (4), 198–206. https://doi.org/10.1177/1550059419868115.

Sanquist, T.F., Rohrbaugh, J.W., Syndulko, K., Lindsley, D.B., 1980. Electrocortical signs of levels of processing: perceptual analysis and recognition memory. Psychophysiology 17, 568–576. https://doi.org/10.1111/j.1469-8986.1980.tb02299.x.

Segarra, N., Bernardo, M., Gutierrez, F., Justicia, A., Fernadez-Egea, E., Allas, M., Safont, G., Contreras, F., Gascon, J., Soler-Insa, P.A., Menchon, J.M., Junque, C., Keefe, R.S., 2011. Spanish validation of the brief assessment in cognition in schizophrenia (bacs) in patients with schizophrenia and healthy controls. Eur. Psychiatry 26, 69–73. https://doi.org/10.1016/j.eurpsy.2009.11.001.

Shelley, A.M., Silipo, G., Javitt, D.C., 1999. Diminished responsiveness of ERPs in schizophrenic subjects to changes in auditory stimulation parameters: implication for the theories of cortical dysfunction. Schizophr. Res. 37, 65–79.

Spironelli, C., Romeo, Z., Maffei, A., Angrilli, A., 2019. Comparison of automatic visual attention in schizophrenia, bipolar disorder, and major depression: evidence from P1 event-related component. Psychiatry Clin. Neurosci. 73 (6), 331–339. https://doi.org/10.1111/pcn.12840.

Turetsky, B.I., Dress, E.M., Braff, D.L., Calkins, M.E., Green, M.F., Greenwood, T.A., et al., 2015. The utility of P300 as a schizophrenia endophenotype and predictive biomarker: clinical and socio-demographic modulators in COGS-2. Schizophr. Res. 163 (1–3), 53–62. https://doi.org/10.1016/j.schres.2014.09.024.

Wagner, A.D., 1999. Working memory contributions to human learning and remembering. Neuron 22 (1), 19–22. https://doi.org/10.1016/S0896-6273(00)80674-1.

Wechsler, D., 1997. WAIS-IH: Wechsler Adult Intelligence Scale, Third ed. The Psychological Corporation, San Antonio, TX.

Yeap, S., Kelly, S.P., Sehatpour, P., Magno, E., Garavan, H., Thakore, J.H., Foxe, J.J., 2008. Visual sensory processing deficits in schizophrenia and their relationship to disease state. Eur. Arch. Psychiatry Clin. Neurosci. 258 (5), 305–316. https://doi.org/10.1007/s00406-008-0802-2.

Zhang, H., Chang, L., Chen, X., Ma, L., Zhou, R., 2018a. Working memory updating training improves mathematics performance in middle school students with learning difficulties. Front. Hum. Neurosci. 12, 154. https://doi.org/10.3389/fnhum.2018.00154.

Zhang, D., Xie, H., He, Z., Wei, Z., Gu, R., 2018b. Impaired working memory updating for emotional stimuli in depressed patients. Front. Behav. Neurosci. 12 https://doi.org/10.3389/fnbeh.2018.00065.

Zhao, X., Zhou, R., Fu, L., 2013. Working memory updating function training influenced brain activity. PLoS One 8 (8). https://doi.org/10.1371/journal.pone.0071063.