Distractor filtering and its electrophysiological correlates in schizophrenia

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HIGHLIGHTS

• Patients with schizophrenia process distracting information less efficiently and are more distractible.
• Event-related theta synchronization was not modulated by the salience of distracting information in patients as opposed to healthy controls.
• Salience of distractors modulated event-related alpha desynchronization in both groups, although less strongly in patients.

ABSTRACT

Objective: Patients with schizophrenia are characterized by compromised working memory (WM) performance and increased distractibility. Theta synchronization (especially over the frontal midline areas) is related to cognitive control and executive processes during WM encoding and retention. Alpha event-related desynchronization (ERD) is associated with information processing and attention.

Methods: Participants (35 patients and 39 matched controls) performed a modified Sternberg WM task, containing salient and non-salient distractor items in the retention period. A high-density 128 channel EEG was recorded during the task. Theta (4–7 Hz) and fast alpha (10–13 Hz) event-related spectral perturbation (ERSP) were analyzed during the retention and encoding period.

Results: Patients with schizophrenia showed worse WM performance and increased attentional distractibility in terms of lower hit rates and increased distractor-related commission errors compared to healthy controls. Theta synchronization was modulated by condition (learning vs. distractor) in both groups but it was modulated by salience only in controls. Furthermore, salience of distractors modulated less the fast alpha ERD in patients.

Conclusions: Our results suggest that patients with schizophrenia process salient and non-salient distracting information less efficiently and show weaker cognitive control compared to controls.

Significance: These differences may partly account for diminished WM performance and increased distractibility in schizophrenia.

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1. Introduction

Besides clinical symptoms, most patients with schizophrenia suffer from some degree of cognitive deficit as well (Morice and Delahunty, 1996). Cognitive deficits emerge in the early stages of the disease, before the appearance of clinical symptoms (Rossi et al., 2016), and may be present even in childhood (Javitt, 2007). These are stable in time, strongly affecting the every-day functioning of the patients (Green and Nuechterlein, 1999). Cognitive disturbances have been proved to be better predictors of disease outcome than e.g. positive symptoms (Javitt, 2007). A wide range of cognitive functions are affected in schizophrenia, including sensory processing (Brenner et al., 2009; Dias et al., 2013; Hong et al., 2012), attention (Carter et al., 2010; Giakoumaki et al., 2011), memory (Forbes et al., 2009; Leavitt and Goldberg, 2009), planning

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functioning (Enriquez-Geppert et al., 2014). Previous research suggests that dysfunctional executive control of cognitive control allocation, and inefficient phasic up-regulation of a distributed fronto-parietal network that mediates executive functions (Cavanagh et al., 2012; Enriquez-Geppert et al., 2014; Sauseng et al., 2009). Cognitive control-related theta – low frequency and high amplitude (4–7 Hz) – oscillations are associated with the communication between and coordination of distant brain areas (Basar-Eroglu et al., 2008; Cavanagh and Frank, 2014; Cavanagh et al., 2012). Cognitive control-related theta is mostly measured over fronto-central areas (around Fz and Cz electrode sites), in the literature referred to as frontal-midline theta (Choi et al., 2016; Enriquez-Geppert et al., 2014; Inanaga, 1998; Schmiedt et al., 2005). According to previous results, the medial prefrontal cortex (mPFC), the anterior cingulate cortex (ACC) (Hsieh and Ranganath, 2014) and the midline cingulate cortex (MCC), hub-like areas have been identified as the main sources of these oscillations (Cavanagh and Frank, 2014). Theta ERS over fronto-central electrode sites is associated with the functioning of a distributed fronto-parietal network that mediates executive functions (Enriquez-Geppert et al., 2014; Sauseng et al., 2010). An elevated fronto-midline theta is induced by tasks that involve conflict-related processes (Cavanagh and Frank, 2014; Cohen and Donner, 2013), and in general, by tasks that require executive functions (Cavanagh et al., 2012; Enriquez-Geppert et al., 2014; Töllner et al., 2017).

Frontal-midline theta is regarded as an electrophysiological correlate of cognitive control allocation, and inefficient phasic up-regulation of theta oscillations is related to dysfunctional executive functioning (Enriquez-Geppert et al., 2014). Previous research suggests that dysfunctional executive control would not or less strongly modulate theta ERS in patients relative to controls, as patients tend to have difficulties in executive functioning.

Alpha oscillations are linked to multiple functions (Başar et al., 1997). Event-related fast alpha (10–13/14 Hz) synchronization/desynchronization (ERS/ERD) has been indicated as being more closely linked to memory operations, while slow alpha (8–10 Hz) is more strongly associated with general alertness/vigilance and attention processes (Klimesch et al., 2006; Wianda and Ross, 2019). Bearing this distinction in mind, a number of researchers have examined slow and fast alpha oscillations separately or examined fast alpha oscillations selectively (Bachman et al., 2008; Fujimoto et al., 2012; Higashima et al., 2007; Koh et al., 2011; Petsche et al., 1997; Wianda and Ross, 2019). According to the inhibition-timing hypothesis (Klimesch et al., 2007), event-related alpha synchronization (i.e. stronger alpha power compared to baseline alpha activity) has a top-down inhibitory function, while event-related alpha desynchronization indicates release from inhibition, and detailed information processing. Previous research show, during WM encoding, alpha ERD takes place (Wianda and Ross, 2019). In contrast, during the retention stage, after encoding, alpha ERS is present, enabling maintenance of mental representations and protecting them from interference caused by processing of irrelevant external stimuli (Bonnefon and Jensen, 2012; Heinz and Johnson, 2017; Jensen et al., 2002; Payne et al., 2013; Sauseng et al., 2009). However, this gating function of alpha oscillations works successfully only in cases when the type and the exact timing of distractors are predictable and these appear only for a short time (Bonnefon and Jensen, 2012; Heinz and Johnson, 2017; Myers et al., 2015; Wianda and Ross, 2019), but if it is not the case, encoding of distractor items takes place, accompanied by an alpha ERS, as a bottom-up attentional system gets involuntarily activated (Myers et al., 2015; Schroeder et al., 2018; Vissers et al., 2016). Magnitude of the alpha ERS is modulated by the salience of distractors, i.e. it is larger during encoding of salient distractors (Schroeder et al., 2018), that is supposed to be related to deeper processing of these distractor items and increased distractibility (Schroeder et al., 2018).

Plenty of evidence suggest that inhibition-related alpha ERS seems to be dysfunctional in schizophrenia (Bachman et al., 2008; Fujimoto et al., 2012; Gaspar et al., 2011; Kayser et al., 2014; Magosso et al., 2019; Rojas, 2019), however little is known about alpha ERD in response to different distractor stimuli during WM retention, where release from inhibition (alpha ERD) seems to cause interference, reflected in heightened error rates (Bonnefon and Jensen, 2012; Schroeder et al., 2018). Therefore, we hypothesized that patients with schizophrenia would show a more pronounced fast alpha ERD after distractors (reflecting an elevated level of distractibility).
abuse in the past 3 months, no history of head injury with loss of consciousness for more than ten minutes.

Patients were recruited from the Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary. The Semmelweis University’s Regional, Institutional Scientific and Research Ethics Committee gave ethical approval to the study. All patients gave written informed consent and met the criteria for schizophrenia based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (American Psychiatry Association, 1994). Psychiatric symptoms on the PANSS (Positive and Negative Syndrome Scale) (Kay et al., 1987) were rated by trained psychiatrists. At the time of testing all patients took antipsychotic medication. The average Chlorpromazine equivalent dose (Gardner et al., 2010) was 465.62 mg/day ($N = 32, SD = 332.83$).

2.2. EEG stimuli and procedures

The examination took place in a dimly lit, sound-attenuated room. During EEG recording, subjects performed a modified version of the Sternberg task (Sternberg, 1966), a widely used paradigm to assess WM performance (Karrasch et al., 2006; Vergauwe and Cowan, 2014). The original task was adjusted in order to investigate the effect of distractors on WM performance and brain activity during the retention period. The stimuli consisted of white, green and blue letters (Arial font, point size 50), that were presented on a computer screen at approximately 50 cm with Presentation 13.0 software (Neurobehavioral Systems, Inc.; Albany, CA).

Each trial consisted of three stages: encoding, retention (involving distractor filtering) and retrieval (Fig. 1). At the beginning of each trial, six randomly selected white consonants appeared serially in the middle of the screen for 1200 ms, separated by a blank screen for 1350–1450 ms. The complete set of consonants used in the task was the following: B, C, D, F, G, H, J, K, L, M, N, P, R, S, T, V, Z. During the retention period, two green-colored distractors were presented in a randomized order for 3000–3200 ms, separated by a blank screen for 1350–1450 ms: a green exclamation mark (weak distractor) and a green consonant (strong distractor) that was not part of the previous learning sequence. Type and the exact timing of the appearance of distractors were randomized. During retrieval, in each trial, two blue-colored consonants appeared on the screen sequentially. Subjects were instructed to indicate whether the probe letter (item appearing during retrieval) was part of the learning sequence by clicking the mouse buttons (yes-right / no-left). The order of the distractors and response assignment were counterbalanced across 72 trials.

During the session, we made sure that participants understood the instructions and stayed alert during the examination, in order to avoid the possible distorting effect of extended eye closure on the EEG (especially alpha) activity (Barry et al., 2007). For this purpose, participants completed the task in six blocks (each consisting of 12 trials) separated by a 3-minute rest period.

2.3. EEG recording and processing

EEG was recorded from DC (i.e. a direct current-based EEG system was used) with a low-pass filter at 100 Hz using a high-density 128-channel BioSemi ActiveTwo amplifier (Metting van Rijn et al., 1990). Electrode caps used during the experiment had an equidistant-layout and covered the whole head. EOG electrodes were placed below the left and above the right external canthi in order to monitor eye movements. Data were digitized at a sampling rate of 1024 Hz. Both built-in and self-developed functions as well as the freeware EEGLAB toolbox (Delorme and Makeig, 2004) in the Matlab (MathWorks, Natick, MA) development environment were used for subsequent off-line data analyses. Scalp EEG was re-referenced to the common average potential measured from all electrodes and filtered off-line between 0.5 and 45 Hz using zero-phase shift forward and reverse IIR Butterworth filter.

Epochs from 500 ms pre-stimulus to 3000 ms post-stimulus (and 1200 ms post-stimulus, as learning of individual items took place for shorter time) were extracted from the continuous EEG. EEG data were corrected for the pre-stimulus baseline in order to analyze changes of alpha oscillations in the weak and strong distractor condition. As far as theta responses were compared between three conditions (learning, and weak and strong distrac-

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**Modified Sternberg task**

6 blocks/ 12 trials

| + | R | T | Z | V | B | P |
|---|---|---|---|---|---|---|

1000-1500 ms

1200 ms, ISI: 1350-1450 ms

3000-3200 ms (randomized order)

1200 ms

**Fig. 1.** The modified Sternberg working memory task. Each trial consisted of three stages: encoding, retention (involving distractor filtering) and retrieval. At the beginning of each trial, six randomly selected white consonants appeared serially on the screen for 1200 ms, separated by a blank screen for 1350–1450 ms. During the retention period, two green-colored distractors were presented in a randomized order for 3000–3200 ms, separated by a blank screen for 1800–2000 ms: a green exclamation mark (weak distractor) and a green consonant (strong distractor) that was not part of the previous learning sequence. Type and the exact timing of the appearance of distractors were randomized. During retrieval, in each trial, two blue-colored consonants appeared on the screen sequentially. Subjects had to indicate whether the letter was part of the learning sequence by clicking the mouse buttons (yes-right / no-left).
tor condition), in order to avoid the effect of possible differences in tonic changes of theta (differences in pre-stimulus theta power before retention vs. encoding), the period before the appearance of the first stimulus in the encoding phase (e.i. the beginning of the trial) was used as a baseline in each condition. Bad channels were removed after visual inspection. Muscle and ocular artifacts (detected by EOG) were removed by ADJUST (Mognon et al., 2011), an automatic artifact detection algorithm based on ICA (Independent Component Analysis) method. In addition, epochs with a voltage exceeding ± 100 μV on any channel were rejected from the analysis.

After artifact rejection, the average number of trials was 64.56 (SD = 9.78) for the weak distractor, 64.79 (SD = 9.75) for the strong distractor condition, 390.18 (SD = 53.53) for the learning condition in the control group, 55.91 (SD = 11.20) for the weak distractor, and 56.08 (SD = 11.15) for the strong distractor condition, 358.66 (SD = 64.74) for the learning condition in patients, respectively. For the analysis of the effect of distractors on fast alpha ERSP during the retention period we selected 4 scalp regions (frontal, central, right parieto-occipital, left parieto-occipital) on the basis of previous studies (Fodor et al., 2020, 2018; Wianda and Ross, 2019), while theta ERSP was analyzed in 2 regions (midline frontal and central) (Enriquez-Geppert et al., 2014; Inanaga, 1998).

2.4. EEG data analysis

Stimulus-related theta (4–7 Hz) and fast alpha (10–13 Hz) activity changes were measured by the ERSP, providing a time–frequency domain representation of the mean change in spectral power (measured in dB) compared to baseline activity (Makeig et al., 2004). A major advantage of the technique is that it is able to capture event-related evoked as well as induced oscillatory activity. Unlike evoked responses, induced activity is not phase-locked to the stimulus, thus it is averaged out from the ERPs. While distractor filtering is a time-consuming process, involving cognitive control-related functions (Basar-Eroglu et al., 2008; Choi et al., 2016; Fujimoto et al., 2012; Geng, 2014; Schmiedt et al., 2005), that modulate specifically the induced oscillatory activity (Tong and Thakor, 2009), similarly to previous studies we applied the ERSP approach in our analysis.

The ERSP method generalizes the narrow-band measures of event-related synchronization and desynchronization introduced by Pfurtscheller and Aranibar(1977) and includes both phase-locked and non-phase-locked contributions. The principle of calculating the ERSP is to compute the power spectrum of the EEG signal from a sliding time window. For n trials, if Fk(f,t) is the power of trial k at frequency f and time t, the ERSP value is calculated as:

$$ERSP(f,t) = \frac{1}{N} \sum_{k=1}^{N} |F_k(f,t)|^2$$

The analysis was performed on epochs extending from 500 ms before to 3000 ms and 1200 ms after stimulus onset to compare oscillations in the different conditions within the 1.5–30 Hz frequency range. The sliding window was 400 ms wide, and it was applied 200 times with an average step size of 15.4 ms (and 7.11 ms). While no zero padding was applied and the width of the sliding window was 400 ms, the analyzed time interval lasted from 282 ms before to 2782 ms (and 1133 ms) after stimulus onset, however these presentations (figures) comprise information from the whole time interval from 500-3000 ms. Dynamical changes in oscillatory activity were studied by computing ERSPs for each trial, then averaging them separately for weak distractor and strong distractor and learning condition. The ERSP time–frequency matrices were baseline corrected by the average power calculated from the 500 to 200 ms pre-stimulus baseline for the assessment of the modulatory effect of learning and distractor saliency to oscillatory activity during learning and the retention period. ERSP values within the analyzed frequency ranges were averaged.

Based on the literature on WM and distractor filtering (Fujimoto et al., 2012; Gaspar et al., 2011; Heinz and Johnson, 2017; Schmiedt et al., 2005; Schroeder et al., 2018), and two previous studies of our research group with similar design (Fodor et al., 2020, 2018), we selected later time windows for the analysis of theta and fast alpha ERSP: 350–550 ms and 500–700 ms post-stimulus, respectively. Mean ERSP values were calculated by averaging across electrodes within the above mentioned scalp regions to further attenuate noise and get more robust results.

2.5. Statistical analysis

Behavioral results of the two groups were compared with Mann-Whitney test because of a strong deviation from normal distribution. The different effects on theta and fast alpha oscillations in the analyzed conditions were tested by repeated measures mixed linear models (PROC MIXED) of group (patient vs. control) × condition (learning vs. strong vs. weak distractor in case of theta / strong vs. weak distractor in case of alpha) × region (2 regions in case of theta / 4 regions in case of alpha), Post-hoc pairwise contrasts (t-tests) were conducted to investigate the interactions. Since post-hoc comparisons were evaluated over multiple regions, the Bonferroni correction method was used to control for multiple comparisons. Associations between behavioral results, theta and fast alpha ERSP were assessed by Pearson and Spearman correlation coefficients. Before correlation analysis, distractor commission error rates and overall commission error rates were logarithmically transformed. Effect sizes were estimated based on Cohen’s d index (Cohen, 1977; Lenhard and Lenhard, 2017; Wolf, 1986).

3. Results

3.1. Behavioral results

Response accuracy (percentage of hits) of the healthy subjects was significantly higher than that of schizophrenia patients (Mcontrols = 88.5%, SD = 12.2, Mdncontrols = 93.1%, MPatients = 75.7%, SD = 15.7, Mdnpatients = 77.8%, Z = -3.98, p < 0.0001, Cohen’s d = 1.0) (Fig. 2, Table 1).

Schizophrenia patients made significantly more “distractor commission errors” (the type of error when a participant mistakenly identifies the previously presented strong distractor as a member of the memory sequence) than controls (Mcontrols = 4.2%, SD = 5.4, Mdncontrols = 2.8%, MPatients = 10.0%, SD = 2.1, Mdnpatients = 8.4%, Z = -4.40, p < 0.0001, Cohen’s d = 1.2). Patients also made significantly more non-target-related (NT) commission errors (this type of error occurs when a participant mistakenly identifies an item that was not presented previously as a member of the memory sequence) than controls (Mcontrols = 3.3%, SD = 4.2%, Mdncontrols = 2.0%, MPatients = 6.4%, SD = 6.5%, Mdnpatients = 4.0%, Z = -2.35, p = 0.019, Cohen’s d = 0.56) (Fig. 2, Table 1).

The percentage of distractor related errors was calculated as follows: distractor error ratio (%) = (distractor related errors / all errors) * 100. We found that the ratio of distractor related errors was higher among patients relative to controls (Mcontrols = 52.2%, SD = 26.3%, Mdncontrols = 55.3%, N = 39; MPatients = 67.9%, SD = 16.2%, Mdnpatients = 65.5%, N = 34: Z = -2.51; p = 0.01; Cohen’s d = 0.74) (Fig. 2, Table 1).
Fig. 2. Behavioral results in the group of patients with schizophrenia (SCH) and healthy controls (HC). A: Hit rate, i.e. accuracy is the ratio of correct answers (hits / responses). B: Commission error rate is the ratio of false alarms (false alarms / responses). This type of error occurs when an item (distractor [i.e. lure] or non-target) is mistakenly identified as a target. False alarm = commission error C: Ratio of distractor-related commission errors among all commission errors (distractor related errors / false alarms). Asterisks mark significant differences.

Table 1
Results of the Modified Sternberg working memory task.

|                         | Schizophrenia patients | Healthy controls | Mann-Whitney U test | Cohen's d |
|-------------------------|------------------------|------------------|---------------------|-----------|
|                         | M          | SD      | Mdn        | M          | SD      | Mdn        | z-value | p-value |           |
| Hit-rate                | 75.7       | 15.7    | 77.8       | 88.9       | 12.2    | 93.1       | -3.98   | <0.0001 | 1.0       |
| Distractor (D) commission errors | 10.0     | 2.1     | 8.4        | 4.2        | 5.4     | 2.8        | -4.40   | <0.0001 | 1.2       |
| Non-target-related (NT) commission errors | 6.4      | 6.5     | 4.0        | 3.3        | 4.2     | 2.0        | -2.35   | <0.02    | 0.56      |
| Ratio of distractor-related commission errors (D/NT*100) | 67.9     | 16.2    | 65.5       | 52.2       | 26.3    | 55.3       | -2.56   | <0.01    | 0.74      |
3.2. Theta (4–7 Hz) ERSP (time window: 350–550 ms post-stimulus)

A positive ERSP response (ERS, Event-related synchronization) was found within the selected time window, i.e. 350–550 ms after stimulus presentation (learning and strong and weak distractor condition) in the theta frequency range (4–7 Hz), in the context of a global tonic theta power decrease (Fig. 3).

The main effect of group on the theta ERS was not significant ($F$ (1,72) = 0.35, $p$ = 0.55), but significant main effects of condition ($F$ (1,72) = 78.1, $p$ < 0.0001; learning < weak distractor < strong distractor) and region ($F$ (2,72) = 609.3, $p$ < 0.0001; frontal > central) were found. The interactions of region × condition ($F$ (2,72) = 12.7, $p$ < 0.0001) and condition × group ($F$ (2,72) = 3.4, $p$ < 0.05) were both statistically significant, while interactions of region × group ($F$...
(1.72) = 0.10, p = 0.75) and region \times \text{distractor type} \times \text{group} (F(2,72) = 1.40, p = 0.25) were not significant (Fig. 3).

Further analyzing the condition \times group interaction we found that theta synchronization to learning items was decreased compared to weak (t_{control} = -7.54, df = 72, p < 0.0001; Cohen’s d = -1.95, 95% CI [-2.5, -1.4], t_{patient} = -7.35, df = 72, p < 0.0001; Cohen’s d = -1.6, 95% CI [-2.1, -1.1]) and strong distractors (t_{control} = -9.98, df = 72, p < 0.0001; Cohen’s d = -2.2, 95% CI [-2.8, -1.7], t_{patient} = -6.8, df = 72, p < 0.0001; Cohen’s d = -1.8, 95% CI [-2.3, -1.2]) in both groups. In controls theta ERS to strong distractors was increased relative to weak distractors (t = -3.5, df = 72, p < 0.001; Cohen’s d = -2.6, 95% CI [-3.1, -2.0]) while there was no similar difference in patients between weak and strong distractors (t = 0.07, df = 72, p = 0.95; Cohen’s d = 0.02, 95% CI [-0.54, 0.58]).

3.3. Fast alpha (10–13 Hz) ERSP (time window: 500–700 ms post-stimulus)

A negative ERSP response (ERD, Event-related desynchronization) was found within the selected time window, i.e. 500–700 ms after stimulus (strong [salient] or weak [non-salient] distractor) presentation in the “fast” alpha frequency range (10–13 Hz), compared to baseline alpha activity (Fig. 4).

The main effect of group on the fast alpha ERD was not significant (F(1,72) = 0.8, p = 0.38), while significant main effects of distractor type (F(1,72) = 54.5, p < 0.0001; strong > weak) and region (F(3,72) = 27.9, p < 0.0001; frontal = central < left parieto-occipital) were found. The interactions of region \times distractor type (F(3,72) = 15.9, p < 0.0001) and distractor type \times group (F(1,72) = 5.2, p < 0.05) were both statistically significant, while interactions of region \times group \times region (F(3,72) = 0.9, p = 0.43) and region \times distractor type \times group (F(3,72) = 1.1, p = 0.34) were not significant (Fig. 4).

Overall, fast alpha ERD after presentation of strong distractors was increased compared to the weak distractors (t = -7.4, p < 0.0001). Further analyzing the distractor type \times group interaction, results of the post hoc analyses show that strong distractors elicited larger fast alpha ERD response than weak distractors, both in controls (t = -7.0, df = 72, p < 0.0001; Cohen’s d = 1.6, 95% CI [1.2, 1.98]) and in patients (t = -3.5, df = 72, p = 0.0008; Cohen’s d = 0.9, 95% CI [0.55, 1.3]), but in controls the difference was more pronounced.

3.4. Correlations between behavioral results, clinical symptoms and electrophysiological data

There were no statistically significant correlations between theta or fast alpha ERSP and behavioral results in either of the two groups, in the strong distractor condition. However, there was a positive correlation between the severity of the patients’ negative symptoms (according to PANSS-N subscale [Kay et al., 1987]) and fast alpha ERSP after strong distractors, i.e. patients with stronger negative symptoms tended to show weaker alpha ERD in the frontal (r = 0.36, p < 0.05) and central (r = 0.36, p < 0.05) areas, after presented with strong distractors.

Furthermore, theta ERS, induced by distractors (weak and strong) over both the midline frontal (t_{patients\_weak} = -0.35, p < 0.005; t_{patients\_strong} = -0.335, p < 0.05) and central (t_{patients\_weak} = -0.35, p < 0.005; t_{patients\_strong} = -0.34, p < 0.05) area was correlated negatively with age in the patient group, while no similar correlation was found in controls (t_{frontal\_weak} = -0.03, p = 0.85; t_{frontal\_strong} = -0.14, p < 0.41; t_{central\_weak} = -0.03, p = 0.845; t_{central\_strong} = -0.13, p = 0.42).

Electrophysiological data did not show any correlation with Chlorpromazine equivalent dose.

4. Discussion

In the present study, participants performed a verbal WM task, where memory load consisted of 6 serially appearing consonants. The task also included distractor items (strong: a consonant and weak: an exclamation mark) in the retention period, enabling the task to test the efficiency of the central executive component of WM as well. At the end of each trial, participants had to respond whether the presented consonant was part of the memory sequence or not. Stimuli were presented visually.

4.1. Behavioral results

Results show that schizophrenia patients’ WM performance was significantly worse compared to controls, they had lower hit rate. Furthermore, patients produced higher distractor-related and unrelated false alarm rate, however the difference between groups was much higher for distractor related errors (Cohen’s d = 1.2 vs. 0.6). In order to further explore the relationship of errors with distractors, the percentage of distractor related errors was also compared between groups. We found the ratio of distractor related errors was significantly higher among patients (Cohen’s d = 0.8). This is in accordance with previous research on WM in schizophrenia reporting that the diminished WM performance in patients with schizophrenia is caused by various disturbances in attentional filtering and memory processes (Forbes et al., 2009; Lee and Park, 2005; Perry et al., 2001).

In fact, a number of factors – not addressed in the study – could have also affected the results, including even e.g. anxiety and motivational factors. But given that the ratio of distractor related errors among false alarms is larger in patients as compared to controls it is an indication that salient distractors specifically worsened patients’ WM performance.

4.2. Theta ERS

In order to gain more insight into the differences in the processing of distractor items during the retention period, we chose to examine event-related theta and fast alpha reactivity. As far as every patient received antipsychotic medication, we also tested the potential effects of medication on the results. Chlorpromazine equivalent dose did not show any correlation with EEG data or WM performance. A phasic increase of theta synchronization over fronto-central electrode sites is generally observed in tasks that require executive processes such as flexible action selection and overcoming automatic processing (Basar-Eroglu et al., 2008; Cavanagh and Frank, 2014; Cavanagh et al., 2012; Schmiedt et al., 2005). Frontal-midline theta is argued to reflect the realization of the need for cognitive control (Cavanagh et al., 2012), and it has a gating function, suppressing task-irrelevant information (Sauseng et al., 2010). Furthermore, task demands (Hsieh and Ranganath, 2014; Klimesch, 1999; Schmiedt et al., 2005; Wang et al., 2018) as well as performance (Enriquez-Geppert et al., 2014) are positively related to enhanced theta ERS.

Frontal-midline theta has a role in the communication of remote brain areas, mPFC and MMC or ACC – highly functionally connected areas – were identified as its main sources (Cavanagh and Frank, 2014; Cavanagh et al., 2012). According to the literature, theta oscillations may be connected to a fronto-parietal network or to prefrontal-hippocampal interactions (Hsieh and Ranganath, 2014; Sauseng et al., 2010). According to previous results, frontal-midline theta is often found to be diminished in schizophrenia and schizophrenia spectrum disorder (Choi et al., 2016; Schmiedt et al., 2005), or may show altered topography in patients, possibly reflecting dysfunc-
tional executive processing in them (Basar-Eroglu et al., 2008). Diminished theta synchronization in patients can probably be related to functional disconnectivity in schizophrenia (Reinhart et al., 2015; Sauseng et al., 2010).

In our study we analyzed event-related theta synchronization in a later time window, as previous studies suggest that filtering out distracting stimuli is a time-consuming process (Tong and Thakor, 2009). We chose to examine the late theta response because it is regarded as the electrophysiological correlate of cognitive control. Late theta is most prominent at fronto-central and central areas, whereas the early (evoked) theta response is known to have a more posterior distribution, and it is linked to perceptual processes in WM tasks (Deiber et al., 2007). As regards the results, we found a global tonic decrease in theta power in relation to the baseline (the beginning of the trial). Phasic theta synchronization after distractors was higher as compared to that after learning stimuli in both groups. Higher theta ERS after distractors may reflect the realization of the need for cognitive control, in order to overcome automatic processing of distractor items (Cavanagh et al., 2012). Furthermore, as far as suppression of salient distractors is supposed to be more difficult – and also more important, as they can interfere with items previously encoded – we expected

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**Fig. 4.** A: Grand average event-related fast alpha spectral perturbations (ERSP) in the strong and weak distractor condition in the two groups (500–700 ms time window highlighted in grey). B: Scalp topography of averaged event-related fast alpha spectral perturbations (ERSP) in the strong and weak distractor condition (500–700 ms time window).
that strong distractors would induce a higher theta response as opposed to weak ones in healthy controls. In accordance with our hypothesis, theta ERS was further modulated by the salience of distractors in controls, but the salience of distractors failed to modulate the magnitude of theta response in patients, i.e. theta synchronization around the analyzed time window showed a secondary peak after salient distractors but only in controls. This result may indicate dysfunctional control processes during filtering in patients with schizophrenia, but also, it can be a result of a deficit in salience detection (Brenner et al., 2009; Katthagen et al., 2018).

Correlational results of our study indicate, that theta ERS (both in the frontal and central region) after distractors (both salient and non-salient) was negatively related to age in patients with schizophrenia, but not in controls. Evidence suggest that aging leads to compromised WM performance (decreased ability to maintain information in memory), and lower ability to regulate theta oscillations in response to varying cognitive demands (Kardos et al., 2014).

4.3. Fast alpha ERD

According to the inhibition-timing hypothesis, alpha ERD reflects increased excitability of the cortex (Klimesch et al., 2007). It occurs during WM encoding (Wianda and Ross, 2019). It was also found that fast (10–13/14 Hz) alpha oscillations are specifically related to memory processes and stimulus encoding (Bachman et al., 2008; Klimesch et al., 2006; Wianda and Ross, 2019), and is supposed to reflect the functioning of a network involved with the processing of different stimuli (Koh et al., 2011).

Previous research on alpha ERS in WM maintenance confirms its involvement in proactive but not in reactive filtering (Myers et al., 2015). If distractors are unpredictable, or if these are present during the whole retention period, encoding of distractor stimuli takes place, as reflected by alpha ERD (Myers et al., 2015; Vissers et al., 2016). Following salient distractors, the alpha ERD tends to be even larger, which shows deeper processing of salient distractors that causes interference (Schröder et al., 2018). Distractors appeared in the center of attention and exact timing and type of distractors could not be predicted in the present study. As a result, fast alpha ERD, peaking around 500–700 ms post-stimulus was found in the retention period, reflecting stimulus encoding processes.

In the present study, we found no between group difference in the magnitude of fast (10–13 Hz) alpha ERD after the appearance of distractors. Our results indicate that the magnitude of fast alpha ERD was modulated by the salience of the distractors in both groups: an increased fast alpha ERD was found following salient distractors – due to longer duration – as compared to following non-salient ones; weak distractors seem to permit faster resynchronization of alpha, whereas strong distractors evoke a longer period of desynchronization, reflecting stronger interference. A difference in the strength of this modulatory effect was found between study groups: salience of distractors less strongly modulated fast alpha ERD in the patient group, that can be associated with less deep processing of salient distractors in patients compared to healthy controls. Although, this seems to be a conflicting result, it can be related to disrupted stimulus classification and cognitive resource allocation in patients with schizophrenia (Koh et al., 2011; Sharma et al., 2011). A possible explanation to these results is that there is a causal relationship between increased alpha ERD modulation and increased theta synchronization indicating that controls can respond to increased distraction with stronger cognitive control.

While fast alpha ERD after strong distractors did not show any relationship with behavioral distractibility in the present study, it correlated with negative symptom severity: the more serious the patient’s negative symptoms were, the smaller fast alpha ERD magnitudes were present after salient distractors in both frontal and central regions. This result can probably be linked to the well-studied relationship between frontal dysfunction – “hypofrontality” – and negative symptoms of schizophrenia (Semkovska et al., 2001).

Previous research suggest that a general dysregulation of alpha oscillations can be observed in schizophrenia. According to the literature, altered alpha reactivity – reflecting the inefficiency of the shifting between the state of inhibition and information processing – is present in patients with schizophrenia, often resulting in decreased amplitudes of alpha ERS/ERD in patients (Abeles and Gomez-Ramirez, 2014; Fujimoto et al., 2012; Gaspar et al., 2011; Higashima et al., 2007; Rojas, 2019) and also in individuals at ultra-high risk of schizophrenia (Kayser et al., 2014; Koh et al., 2011). However, in a study by Bachman et al. (2008), larger fast (upper) alpha reactivity (ERD/ERS) was found in patients during WM encoding and maintenance. The authors argue, that their results are related to reduced neural efficacy in schizophrenia. In our research, we came to different results as we found no difference in the overall strength of alpha ERD after distractors between the two groups. It was the salience of the items that seemed to less strongly modulate the alpha response in patients, resulting in perhaps shallower, less detailed processing of salient distractor items. This may be a result of disrupted functioning of networks that mediate stimulus classification and resource allocation (Koh et al., 2011; Sharma et al., 2011).

Lack of correlations between behavioral performance and the analyzed EEG-measures suggest that other factors – not considered in the present study – probably also affect WM performance and false alarm rate in patients with schizophrenia. Although, it is not known, which component of WM (encoding, maintenance or retrieval) is the most strongly affected in schizophrenia, most likely these are all affected to some degree. A limitation of the study is that EEG data of the patients with schizophrenia were slightly noisier compared to controls as they had a smaller number of artifact-free epochs.

Finally, it should be noted that schizophrenia is an illness with diverse symptoms and the degree of cognitive deficits in patients vary as well. However the small sample size of our present study did not allow us to divide patients into smaller subgroups (and only few patients showed severe cognitive deficit in our sample), but we think that based on the literature the analysis of alpha modulation would also be interesting in different subsamples of patients (Boutros et al., 2019; Cerquera et al., 2017; Gjini et al., 2020), and it should be considered in further studies involving larger sample sizes.

5. Conclusion

According to behavioral results, schizophrenia patients have worse working memory performance, higher rates of false alarms (here referred to as “commission errors”) in general, and more specifically they showed increased attentional distractibility in terms of distractor related commission errors compared to healthy controls. Results also revealed that salience of distractors did not modulate theta ERS in patients unlike healthy controls and it modulated fast alpha ERD less strongly in patients compared to controls. Based on these findings, it can be concluded that altered processing of distractor stimuli – difficulties in stimulus classification and allocation of cognitive control – reflected by EEG-data and behavioral results in the present study, may contribute to the observed deficiencies in working memory performance in patients.
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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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contribution statement

Melinda Becske created the first version of figures and wrote the first draft of the manuscript. Csilla Marosi, participated in the execution of measurements, and contributed to the writing of the methods and results sections. Hajnalka Molnár participated in the execution of measurements, and contributed to the creation of the figures. László Tombor contributed to the study design, programming the experiments and to the writing of the methods section. Zsuzsanna Fodor undertook the statistical analyses of the EEG data and gave supervision during the whole study including writing the manuscript. Gábor Csukly designed the study, wrote the protocol, supervised the statistical analyses and gave supervision during the whole study including writing the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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