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Many ways to forget – Neurophysiology of directed forgetting mechanisms in schizophrenia

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ABSTRACT

Numerous studies have shown dysfunctional mechanism of interaction between bottom-up emotional and top-down cognitive processes in persons with schizophrenia (SCZ). During the emotional directed forgetting (DF) paradigm participants have to apply volitional mechanisms to resist automatic emotional enhancement of the memory. Here we sought to compare mechanisms underlying emotional DF in SCZ and in healthy persons (HC). Eighteen SCZ and eighteen HC completed a DF paradigm with neutral and negative pictures. EEG was recorded during study and test phase of the task. We analyzed both the behavioral outcomes and event-related potential components, indicating emotional enhancement of memory (Late Positive Potential elicited by pictures) and DF strategies (N2/P3 elicited by forget/remember cues during study-phase; "old/new" and "reversed old/new" effects during test-phase of the task). Directed forgetting effects and emotional enhancement of memory were observed in both groups, even despite overall lower recognition rates in SCZ. Furthermore, cue presentation elicited similar pattern of N2/P3s in SCZ and in HC. However, "reversed old/new" effect was observed only in HC for negative stimuli. Patients may show similar reaction to affective stimuli as healthy controls during the emotional DF task. However, further investigation is needed to elicit the specific mechanisms underlying the DF strategies in SCZ.

1. Introduction

Schizophrenia is a severe psychiatric disorder marked with both cognitive (Reichenberg and Harvey, 2007) and emotional abnormalities (Taylor et al., 2012). Recent studies have shown that interaction of cognitive and emotional processing is associated with dysfunctional patterns of cognitive control over the emotional distraction in patients with schizophrenia (SCZ). While in healthy persons (HC) interference control linked to the increased prefrontal activation is seen while coping with highly arousing emotional distractors (Dolcos et al., 2011), SCZ fail to deploy such automatic inhibitory strategy to reduce the impact of affective distractors on the cognitive performance (Anticevic et al., 2011; Diaz et al., 2011). Furthermore, this effect is also evident for volitional top-down cognitive strategies, which have been shown to minimize emotional arousal in HC (Foti and Hajcak, 2008), but not in SCZ (Horan et al., 2013; Strauss et al., 2013, 2015).

Emotional directed forgetting paradigm is well known experimental procedure to study the opposing processes that take place when bottom-up enhancement of memory by emotional stimuli is countered by volitional strategies aimed at suppression of encoding processes (Anderson and Hanslmayr, 2014). During the directed forgetting (DF) paradigm, a participant is presented with a number of stimuli shown in a series. In an *item-variant* of the DF task, each stimulus is followed by an explicit instruction informing the participant whether this stimulus ought to be remembered (TBR items) or forgotten (TBF items). In a *list-variant* of the DF task a series of stimulus is presented before the instruction is shown. Most of the DF studies found higher rates of TBR compared to TBF items being either recalled or recognized during a subsequent test session (Titz and Verhaeghen, 2010). This effect is usually interpreted in terms of an instructed modulation of stimulus

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encoding. Two possible mechanisms were suggested to explain the directed forgetting effects. The first one called "selective rehearsal" refers to TBR items being additionally processed after the presentation of the *Remember* cue, while TBF items are just passively forgotten. This effect has been linked to an increased parietal P3 for *Remember* compared to *Forget* cues (Hsieh et al., 2009; Hauswald et al., 2011; Yang et al., 2012; Brandt et al., 2013) and to enhanced activity of medial temporal lobe memory system for TBR items (Reber et al., 2002; Bastin et al., 2012). The second mechanism termed "active suppression" postulates that forgetting of TBF is an active inhibitory mechanism rather than just passive process (Anderson and Hanslmayr, 2014). In support of this explanation, a number of studies have found that the presentation of *Forget* cues results in an increased activation of frontal structures (Wylie et al., 2008; Bastin et al., 2012) and more negative frontal N2 component (van Hooff and Ford, 2011; Yang et al., 2012; Patrick et al., 2015). Furthermore, while "old/new" effect (increased ERPs for successfully encoded material compared to new material) was documented for correctly encoded TBR items, "reversed old/new" (decreased ERPs for successfully inhibited material compared to new material) effect was observed for successfully suppressed items during the test phase of the task (Nowicka et al., 2009).

Presentation of emotionally charged stimuli may be particularly challenging for directed forgetting mechanisms. Emotional enhancement of memory (EEM) is now a well-established phenomenon, which can be attributed to the amygdalar modulation of the hippocampal activity (Dolcos et al., 2011). Increased recollection of emotional compared to neutral material has been observed in a majority of EEM studies reviewed by the Murty et al. (2010). This effect is linked to the activation of a broad neural network, which includes structures associated with increased automatic bottom-up processing of affective stimuli (amygdala, hippocampus, ventral visual stream), but also fronto-parietal areas, which are known to contribute to the top-down control. Enhanced memory for affective stimuli was also linked to increased amplitudes of late ERPs observed during the presentation of emotional stimuli (Palomba et al., 1997; Dolcos and Cabeza, 2002; Michalowski et al., 2014).

In line with these observations reduced directed forgetting effects were observed for negative stimuli (Hauswald et al., 2011; Nowicka et al., 2011; Bailey and Chapman, 2012; Brandt et al., 2013). It is believed that directed forgetting of negative stimuli is possible, yet it engages broader network of brain structures than directed forgetting of neutral material (Nowicka et al., 2011). More laborious inhibition of encoding for negative compared to neutral stimuli may be reflected in larger N2 amplitudes for *Forget* cues presented after negative compared to neutral stimuli (Yang et al., 2012). In another DF study, ERPs associated with "selective rehearsal" and "active suppression" predicted successful directed forgetting of neutral but not negative stimuli (Hauswald et al., 2011).

While there is a solid body of evidence for decreased directed forgetting for neutral material in SCZ (Müller et al., 2005; Racsmány et al., 2008; Soriano et al., 2009; Patrick and Christensen, 2013; Patrick et al., 2015), only a handful of studies analyzed the processes associated with directed forgetting of affective stimuli in patients, suggesting either a specific reduction of DF effects for affective material (Patrick and Christensen, 2013) or general reduction of DF mechanisms in patients (Patrick et al., 2015). However, both of the studies were based on the verbal material, while it has been suggested that arousal and valence effects on ERP response may be differential for affective words and pictures, especially for negatively-valenced material (Bayer and Schacht, 2014).

To address the abovementioned issues, the current study aims to examine the neurophysiological correlates of processes associated with directed forgetting of affective stimuli in SCZ by using negative and neutral complex visual stimuli. In line with previous findings of intact processing of affective stimuli in schizophrenia (Llerena et al., 2012), we expect to find similar processes associated with self-reported (elevated arousal ratings from participants), behavioral (increased automatic learning) and neurophysiological (increased LPP) response to negative stimuli in both groups. However, due to the large body of literature suggesting decreased prefrontal control over emotional distractors in patients with schizophrenia (Horan et al., 2013; Strauss et al., 2013, 2015), we believe that reduced prefrontal inhibition will be reflected in reduced behavioral DF effects for negative pictures and decreased neurophysiological markers of active suppression (N2 during study phase, "reversed old/new" effect during test phase), rather than selective rehearsal (P3 during study phase) markers in SCZ.

2. Methods and materials

2.1. Participants

Eighteen patients aged 18–55 diagnosed with schizophrenia according to ICD-10 were recruited from inpatients of the Third Department of Psychiatry of the Institute of Psychiatry and Neurology in Warsaw, Poland. To be eligible to participate in the study patients had to be on a stable antipsychotic treatment (at least of two weeks of stable medication regimen). Patients with neurological disorders, any history of head trauma or comorbid psychiatric disorders were excluded from participation in the study. Additional exclusion criteria included treatment with benzodiazepines and antihistamines. None of the patients in the sample has been treated with anticholinergics. Due to the specific impact of both mania (Fleck et al., 2005) and depression (Cottencin et al., 2008) on the directed forgetting, we did not include patients with schizoaffective disorder in the sample. Patients' diagnosis was confirmed by reviewing the available documentation, furthermore each patient has been screened for inclusion and exclusion criteria by a qualified psychiatrist (AW, MJ). Each patient was also assessed with a Positive and Negative Symptoms Scale (Kay et al., 1987). Eighteen healthy volunteers were recruited from community sample as a control group. We aimed at matching the healthy comparison group with patients' group with regard to age and gender. Participants from healthy comparison group reported no history of psychiatric or neurological hospitalizations or current psychiatric or neurological treatment. Protocol of the study was approved by Institute of Psychiatry and Neurology Bioethics Committee.

Demographic and clinical characteristics of the sample of participants are visualized in Table 1. No differences in age or gender were found between the samples used to analyze behavioral data and ERPs in the study phase analysis ($n = 36$) nor the test phase ($n = 28$), for which 4 patients and 4 controls were excluded from the sample due to the insufficient ($n < 10$) number of trials in any of the categories of interest from the test phase.

2.2. Material selection

The set of stimuli consisted of images taken from the Nencki Affective Picture System (NAPS, Marchewka et al., 2014), the International Affective Picture System Lang and Flickr, which is an image and video hosting website. For Flickr images only those under the Creativity Commons license were used. During the task participants were presented with 480 pictures among which 240 were high-arousing negative (NEG) and 240 were low-arousing neutral stimuli (NEU). Sixty NEU and sixty NEG were presented during the study phase as TBR items, while another sixty NEU and sixty NEG were presented as TBF items. During the test phases additional 120 NEU and 120 NEG items were presented as new items. All categories were overall matched for the content they depicted with the same proportion of social (e.g. people, faces) and non-social (e.g. animals, objects) pictures across the categories. The content of the both neutral and negative pictures was also balanced between the study- and test-phase of the task. The order of the trials was pseudorandomized to avoid presentation of more than two consecutive trials from the same category. For the details of the

Table 1
Basic demographic and clinical characteristics of the participants.

	SCZ M [SD]	HC M [SD]	
Gender	15 M - 3 F	12 M - 6 F	n.s.
Age (years)	30.7 [8.0]	26.2 [8.5]	$t = 1.7$ n.s.
Edu (years)	12.4 [2.1]	14.8 [1.5]	$t = 3.7$***
PANSS Pos	12.6 [4.9]	–	
PANSS Neg	20.4 [5.8]	–	
PANSS Gen	30.1 [7.6]	–	
CPZ (mg)	515 [382]	–	
Treatment	monotherapy $n = 11$ (amisulpride - 1; aripiprazole - 2; flupenthixol - 1; quetiapine - 1; olanzapine - 4; risperidone - 2); polytherapy $n = 7$ (aripiprazole/olanzapine - 5; haloperidol + clozapine - 1; flupenthixol + clozapine - 1)	–	

M – mean; SD – standard deviation; SCZ – patients with schizophrenia, HC – control group; PANSS – Positive and Negative Syndrome Scale; CPZ – chlorpromazine equivalent; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

material selection please refer to Marchewka et al. (2016) from which the task has been adapted.

2.3. Task design

The current study used the item-variant of the directed forgetting paradigm. During the first phase of the task (study phase) each trial started with a presentation of picture for 1000 ms, followed by fixation cross (1500–2000 ms). Then cue was presented in a verbal form ("REMEMBER" or "FORGET") for 1000 ms, followed by fixation cross (1500–2000 ms). During the break between the study and the test phases (ca. 10 min) the EEG setup was re-checked while participants were informed to relax. No buffer task was used. During the second part of the task (test phase) each trial started with a presentation of the picture for 1000 ms followed by a fixation cross for 500 ms After that question mark was presented for 2500 ms. Participants were instructed to respond if the presented picture had been presented during the study phase by pressing one of the response pad buttons during the presentation of the question mark. If no response was given, next trial was started. Upon completion of the directed forgetting procedure, participants were asked to provide arousal and valence ratings of the 480 stimuli with Self-Assessment Manikin Scale (Bradley and Lang, 1994).

2.4. EEG recording

EEG activity was recorded during the task performance with a 64-channel Ag/Cl NeuroScan QuikCap connected to NeuroScan SynAmps2 (Compumedics, Australia) amplifier. Impedances were kept below 5 k Ω. Recording was digitized at 1000 Hz with 0.1–100 Hz bandpass filter. Two continuous recordings were archived during the task, one from study phase and one from test phase. Standard preprocessing included 256 Hz resampling, re-reference to linked mastoids and FiR 0.1–30 Hz filtering. ICA decompositions were used to remove eye-blink artifacts from the recording. Preprocessed recording was epoched into 1200 ms event-locked trials, with 200 ms prestimulus correction. For the study phase two types of trials were extracted: trials with picture presentation (NEU or NEG), and cue-trials (*Remember* NEG, *Remember* NEU, *Forget* NEG, *Forget* NEU). For the test phase epochs were locked into 4 types of the trials depending of the behavioral performance: TBR_R trials (TBR items recognized as "old"), TBF_R (TBF items recognized as "old"), CR (new items classified as "new"), TBF_F (TBF items classified as "new"), separately for NEG and NEU pictures. Due to the low number of trials (<10 in most participants) false alarms (new items classified as "old") and TBR_F (TBR items classified as "new") were not subjected to further analysis. During the last step of the preprocessing ± 100 μV artifact removal was performed. Data for the test-phase analyses were extracted from 28 participants with at least 10 trials per condition that survived artifact correction. Remaining number of trials in Table S1 in Supplementary Materials.

Late Positive Potential during the study phase has been examined as a mean ERP value in the 450–1000 ms window after the presentation of the affective stimuli averaged over the midline centro-parietal (CPz) and parietal (Pz) sites in NEU and NEG trials. In line with previous studies, which analyzed the neural mechanisms underlying the directed forgetting of neutral and negative images (Yang et al., 2012), response to cues has been analyzed over the nine electrodes (F3-Fz-F4-C3-Cz-C4-P3-Pz-P4). N2 was extracted as the most negative point in the 200–350 ms post-cue window for each participant, while P3 was extracted as the most positive point in the 300–450 ms post-cue window. Analysis of the centro-parietal ERP component from the test phase was performed on the amplitudes averaged over the two midline effects where amplitudes of the ERPs were maximal for (i) peak activity in the 250–450 ms window and (ii) mean activity in the 500–800 ms window (CPz and PZ – see Fig. 2 for topographical distribution of the scalp activity in the time window). Electrode selection for the LPP and test-phase ERPs was dictated by the topographical distribution of the activity, while the inclusion of the site and laterality of the electrodes for the cue-related ERPs was literature driven (Yang et al., 2012). EEG preprocessing and analysis were carried out with EEGlab (Delorme and Makeig, 2004) and ERPlab (Lopez-Calderon and Luck, 2014) toolboxes.

2.5. Statistics

Behavioral performance was assessed with regard to the percentage of to-be-remembered (TBR) and to-be-forgotten (TBF) pictures recognized as "old" during the test phase of DF task. Mixed model ANOVA with Cue (*Remember* vs. *Forget*) and Stimuli (Neutral vs. Negative) as a within-subject factors and Group (HC vs. SCZ) as a between-subject factor was used to analyze the results.

Percentage of false alarms (new stimuli classified as previously seen) has also been computed. It has been then used to calculate signal detection theory (SDT) sensitivity (d') and criterion (c) (Macmillan et al., 2005). The first of these parameters (d') informs about the ability to distinguish previously seen material from new items, with higher d' being indicative for more efficient discriminatory abilities. Second of the parameters (criterion) is associated with decision making process regarding the classification of stimuli as either "old" or "new": lower criterion values informs about more liberal threshold for qualifying the stimuli as previously seen. Because TBF items are subjected to active suppression mechanisms, only a TBR rate was used as a hit rate for SDT calculations. SDT parameters, as well as valence and arousal ratings of affective pictures were analyzed with ANOVA with a Stimuli as a within-subject and Group as a between-subject factor.

LPP amplitudes were analyzed with ANOVA with Stimuli (Neutral vs. Negative) as within-subject factor and Group (HC vs. SCZ) as a between-subject factor. Cue-related ERP N2 and P3 amplitudes recorded during the study phase were analyzed with an ANOVA with Cue (*Remember* vs. *Forget*), Stimuli (Neutral vs. Negative), Site (Frontal, Central, Parietal) and Laterality (Left, Midline, Right) as within-subject

factors and Group (HC vs. SCZ) as a between-subject factor. Test phase ERP component was analyzed with Type (TBR_R, TBF_R, CR, TBF_F) and Stimuli (Neutral vs. Negative) as within-subject factors and Group (HC vs. SCZ) as a between-subject factor. All of the analyzes were Greenhouse-Geisser corrected.

Finally, to investigate the relationship between the study phase ERPs and subsequent recognition performance we have additionally investigated the correlations between (1) LPP enhancement to negative vs. neutral stimuli and memory sensitivity to neutral and negative stimuli; (2) N2 amplitudes to Forget cues and recognition of TBF items and (3) P3 amplitudes to Remember cues and recognition of TBR items.

3. Results

3.1. Behavioral ratings

NEG pictures were rated as more arousing ($F(1,32) = 45.1$ $p < 0.001$ $\eta_p^2 = 0.59$ CI(95%) = [0.32;0.72] NEG (M ± SD): 3.9 ± 1.8 vs. NEU: 2.6 ± 1.6) and more negative ($F(1,32) = 96.6$ $p < 0.001$ $\eta_p^2 = 0.75$ CI(95%) = [0.57;0.83] NEG: 3.7 ± 0.8 vs. NEU: 5.4 ± 0.9) than NEU. No between-group differences or interactions were found in affective ratings (Arousal: SCZ: NEG: 4.1 ± 2.0 vs. NEU: 2.9 ± 1.7; HC: NEG: 3.7 ± 1.6 vs. NEU: 2.3 ± 1.4; $F(1,32) < 1.0$ n.s.; Valence: SCZ: NEG: 3.6 ± 1.0 vs. NEU: 5.4 ± 1.4, HC: NEG: 3.8 ± 0.5 vs. NEU: 5.4 ± 0.3; $F(1,32) < 1.0$ n.s.).

3.2. Behavioral results of DF task

Recognition rates of the stimuli are visualized in Fig. 1.

Recognition rates: For the recognition scores main effects of Stimuli ($F(1,34) = 123.3$ $p < 0.001$ $\eta_p^2 = 0.78$ CI(95%) = [0.63;0.85]), Cue ($F(1,34) = 5.0$ $p < 0.05$ $\eta_p^2 = 0.13$ CI(95%) = [0;0.33]) and Group ($F(1,34) = 10.9$ $p < 0.01$ $\eta_p^2 = 0.24$ CI(95%) = [0.04;0.45]) were found with higher recognition for NEG than for NEU pictures (NEG: 65 ± 17% vs. NEU: 52 ± 17%), for *Remember* than for *Forget* cues (*Remember*: 60 ± 17% vs. *Forget*:57 ± 18%) and for HC than for SCZ (HC: 70 ± 13% vs. SCZ: 50 ± 17%). Marginally significant Stimuli by Cue interaction was also observed ($F(1,34) = 4.2$ $p = 0.0499$ $\eta_p^2 = 0.11$ CI(95%) = [0;0.31]). Further analysis of this effect revealed that Cue effects were observed for NEG (TBR: 68 ± 17% vs. TBF: 64 ± 19% $t(33) = 3.4$ $p < 0.01$), but not for NEU (TBR: 52 ± 19% vs. TBF: 52 ± 17% $t(33) < 1$ n.s).

False alarms: Main effect of Stimuli was observed for false alarms ($F(1,34) = 28.3$ $p < 0,001$; $\eta_p^2 = 0.45$ CI(95%) = [0.20;0.62]), with higher rate of FA for NEG than for NEU (NEG: 15 ± 12% vs. NEU: 10 ± 9%). Stimuli by Group interaction ($F(1,34) = 6,3$ $p < 0,05$ $\eta_p^2 = 0.16$ CI(95%) = [0;0.36]) was also observed with higher discrepancy between NEG and NEU in SCZ (NEG: 18 ± 14% vs. NEU: 11 ± 11%) than in HC (NEG: 12 ± 9% vs. NEU: 9 ± 8%). In both groups, false alarm rate was lower than recognition of TBR items (HC: $t(17) = 17.0$; SCZ: $t(17) = 9.9$) and TBF items (HC: $t(17) = 16.8$; SCZ: $t(17) = 9.0$).

Sensitivity: Main effects of Stimuli ($F(1,34) = 5.7$; $p < 0.05$ $\eta_p^2 = 0.14$ CI(95%) = [0;0.35]) and Group ($F(1,34) = 15.8$ $p < 0.001$ $\eta_p^2 = 0.32$ CI(95%) = [0.08;0.51]) were observed with higher d' for NEG than for NEU (NEG: 1.2 ± 0.5 vs. NEU:1.1 ± 0.5) and in HC than in SCZ (HC: 1.4 ± 0.4 vs. SCZ: 0.9 ± 0.4).

Criterion: Main effect of Stimuli ($F(1,34) = 165.0$ $p < 0.001$ $\eta_p^2 = 0.83$ CI(95%) = [0.70;0.88]) with higher response bias for NEG than for NEU (NEG: 0.3 ± 0.4 vs. NEU: 0.7 ± 0.4).

3.3. ERP results

3.3.1. Study phase

Picture presentation: LPP for NEG was larger than for NEU (NEG: 3.1 ± 3.2 μV vs. NEU: 1.7 ± 2.5 μV $F(1,34) = 28.7$ $p < 0.01$ $\eta_p^2 = 0.46$ CI(95%) = [0.20;0.62]). No effect of Group or interaction between the factors were observed.

Cue presentation: N2: Main effect of the Cue was observed ($F(1,34) = 6.6$ $p < 0.05$ $\eta_p^2 = 0.16$ CI(95%) = [0.01;0.37]) with more negative N2 to *Forget* (0.6 ± 3.0 μV) than to *Remember* (1.3 ± 2.8 μV) cues. Main effect of the Site was observed with more positive amplitudes from frontal to parietal sites ($F(2,34) = 52.3$ $p < 0.001$ $\eta_p^2 = 0.75$ CI(95%) = [0.57;0.83]). Furthermore, an interaction between the Site and Laterality ($F(4,34) = 5.1$ $p < 0.01$ $\eta_p^2 = 0.38$ CI (95%) = [0.07;0.52]) was observed with laterality effects observed over frontal (Left > Midline $t(35) = 2.4$ $p < 0.05$; Left > Right $t(35) = 2.2$ $p < 0.05$) and parietal (Left > Midline $t(35) = 2.2$ $p < 0.05$; Right > Midline $t(35) = 3.6$ $p < 0.01$), but not central sites. Finally, three-way interaction between Emotion, Site and Laterality ($F(4,34) = 3.1$ $p < 0.05$ $\eta_p^2 = 0.27$ CI(95%) = [0.0;0.42]) was observed - greater N2 was observed for negative than neutral cues over the right parietal channel, ($t(35) = 2.1$, $p < 0.05$). No emotion effect was observed for other channels (*ts* < 1, n.s.). Cue-related waveforms on Fz and Pz are presented in a Supplementary Figure 1.

P3: Main effect of the Cue ($F(1,34) = 23.3$ $p < 0.001$ $\eta_p^2 = 0.41$ CI (95%) = [0.15;0.58]) was observed with larger P3 for *Remember* than for *Forget* cues. Main effect of the Site was observed with more positive amplitudes from frontal to parietal sites ($F(2,34) = 37.4$ $p < 0.001$ $\eta_p^2 = 0.69$ CI(95%) = [0.47;0.78]). Furthermore, interaction between the Site and Laterality was observed ($F(4,34) = 5.7$ $p < 0.01$ $\eta_p^2 = 0.40$ CI(95%) = [0.09;0.54]), with Laterality effects over central

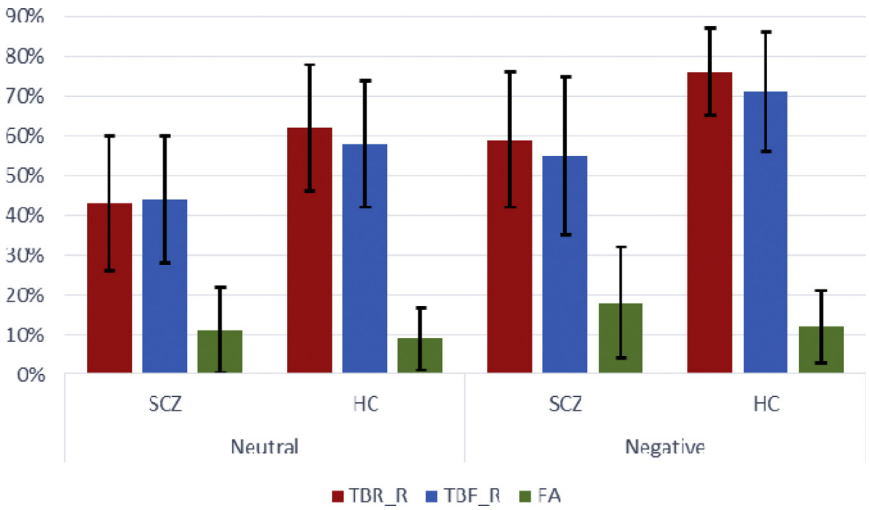

Fig. 1. Behavioral scores of DF task. Each bar represents percentage of the given type of responses during the DF test phase. Error bars are for standard deviations. SCZ – patients with schizophrenia, HC – healthy controls, TBR_R – to-be-remembered items classified as "old"; TBF_R – to-be-forgotten items classified as "old"; FA – new items classified as "old".

(Right < Midline $t(35) = 2.6$ $p < 0.05$), but not parietal or frontal sites.

Correlational analyses: LPP enhancement to NEG vs NEU images was significantly correlated to the memory sensitivity to NEG items during the test phase of the task ($r = 0.37$ $p < 0.05$). No correlations were observed between N2 amplitudes to Forget cues and recognition of TBF items. Recognition of NEU TBR items was significantly correlated with P3 to Remember cues presented after NEU items (Cz: $r = 0.33$ $p < 0.05$; Pz: $r = 0.36$ $p < 0.05$).

3.3.2. Test phase

Early effects: Main effect of Type ($F(3,24) = 6.8$ $p < 0.01$ $\eta_p^2 = 0.46$ CI(95%) = [0.10;0.61]) and interaction between the Type and Stimuli ($F(3,24) = 5.3$ $p < 0.01$ $\eta_p^2 = 0.40$ CI (95%) = [0.05;0.56]) were observed. For NEG stimuli TBR_R items elicited larger ERP amplitudes than new items (TBR_R vs. CR: $t(27) = 2.6$ $p < 0.05$). For NEU stimuli all types of the "old" items elicited larger ERP amplitudes compare to new items (TBR_R: $t(27) = 3.8$ $p < 0.1$; TBF_R: $t(27) = 6.1$ $p < 0.001$; TBF_F: $t(27) = 5.4$ $p < 0.001$). Furthermore, unsuccessfully suppressed stimuli (TBF_R) elicited larger amplitudes than TBR_R items ($t(27) = 2.4$ $p < 0.05$).

Late effects: Main effect of Stimuli ($F(1,26) = 12.5$ $p < 0.01$ $\eta_p^2 = 0.32$ CI(95%) = [0.06;0.54]) was observed with higher ERP amplitudes for NEG (3.7 ± 4.0 μV) than for NEU (2.8 ± 3.2 μV). Main effect of Type ($F(3,24) = 8.0$ $p < 0.01$ $\eta_p^2 = 0.50$ CI (95%) = [0.14;0.64]) and interaction between the Type and Stimuli ($F(3,24) = 3.9$ $p < 0.05$ $\eta_p^2 = 0.26$ CI(95%) = [0.01;0.42]) were also observed for test-phase component. Furthermore, Type by Stimuli interaction was modulated by the Group ($F(3,24) = 3.9$ $p < 0.05$ $\eta_p^2 = 0.26$ CI(95%) = [0.01;0.42]). The investigation of the three-way interaction revealed that "reversed old/new effect" was observed only for NEG stimuli in HC, with all types of the stimuli eliciting larger ERP component amplitudes than TBF_F items (TBR_R: $t(13) = 3.4$ $p < 0.01$; TBF_R: $t(13) = 3.4$ $p < 0.01$; CR: $t(13) = 3.9$ $p < 0.01$). However, classic "old/new effect" was found in SCZ for NEG stimuli (TBR_R vs. CR: $t(13) = 2.6$ $p < 0.05$; TBF_R vs. CR: $t(13) = 2.2$ $p < 0.05$) and in HC for NEU stimuli (TBR_R vs. CR: $t(13) = 2.7$ $p < 0.05$; TBF_R vs. CR: $t(13) = 3.7$ $p < 0.01$). Finally, in SCZ only observed effects for NEU were associated with unsuccessfully suppressed stimuli (TBF_R) eliciting larger amplitudes than any other type of the stimuli (TBR_R vs. TBF_R: $t(13) = 2.7$ $p < 0.05$; TBF_R vs. CR: $t(13) = 5.4$ $p < 0.001$; TBF_R vs. TBF_F: $t(13) = 3.4$ $p < 0.01$). The pattern of the results is visualized in Fig. 2.

4. Discussion

This study was aimed to explore the neurophysiological and behavioral patterns associated with emotional directed forgetting in patients with schizophrenia (SCZ) and in healthy controls (HC). Furthermore, it is the first study with SCZ to use pictorial stimuli to examine behavioral and ERP data in an emotional DF paradigm and it is the first such study to also examine test phase ERP data. Pictorial stimuli has been shown to be more efficient in eliciting negativity bias compared to other types of the stimuli (Bayer and Schacht, 2014), thus use of this type of stimuli could provide new insights in the mechanisms of top-down, cognitive control mechanisms over emotionally salient information in patients with schizophrenia.

In line with our initial hypothesis, both groups have shown similar behavioral (emotional enhancement of memory) and neurophysiological (increased LPP to negative stimuli) markers of the response to affective stimuli, as well as P3 modulation to Remember cues. Overall worse memory performance was found in patients. Still, contrary to our hypothesis, similar effects of directed forgetting were observed in both groups. Furthermore, only weak support was observed for reduced frontal inhibition during DF task: no between-group differences were found in N2 modulation during the study phase, however some between-group differences were observed in the pattern of ERPs observed during the study phase of the task.

Behavioral and neurophysiological findings from the current study provide varying degree of support for three concurrent mechanism which might underlie effects of emotion and cue on the learning of the stimuli in participants. Firstly, our results provide evidence for intact emotional enhancement of the memory in patients with schizophrenia. This effect was reflected both in better recognition of NEG than NEU pictures, but also in more successful "old/new" discrimination for NEG than for NEU pictures in the test phase. Interestingly, increased d' was observed for NEG pictures, even though more liberal response criterion was also found for this particular type of stimuli. At the neurophysiological level, similar effects were elicited by the presentation of NEG pictures in both groups with increased LPP amplitude during the presentation of NEG pictures observed both in SCZ and in HC. Elevated LPP to emotional stimuli has previously been linked to emotional enhancement of memory (Palomba et al., 1997; Dolcos and Cabeza, 2002; Michalowski et al., 2014). Furthermore, LPP enhancement to NEG stimuli was associated with higher sensitivity during the recognition of the NEG stimuli during the test phase of the task.

Furthermore, behavioral results of the study revealed an impact of the cue on the later recognition of stimuli, with TBR being recognized at higher rate than TBF items during the test phase. Despite these similarities, patients displayed significantly lower learning ability, with overall worse recognition of TBR and TBF items and decreased ability to discriminate between "old" and "new" stimuli during test phase. Memory and learning deficits are well-documented in SCZ (Reichenberg and Harvey, 2007), however to address the possibility of SCZ not engaging adequately during the task, especially given at-chance level of responses for NEU pictures in SCZ, the recognition level of "old" and "new" stimuli was compared in SCZ. While the recognition of NEU in SCZ did not exceed chance level, post-hoc analyses revealed that the percentage of recognized TBR items (TBR_R) and TBF items (TBF_R) was significantly higher than the percentage of new stimuli classified as previously seen (false alarms, FA). This finding limits the possibility that results of this study may be due to the erratic responding style in SCZ. Still, the fact that the effects of the cue were observed only for negative material, should be treated with cautiousness, as it may be linked to the psychometric confound among SCZ patients (MacDonald & Kang, 2006), which limits the possibility to interpret any differential findings for NEU and NEG stimuli in the current study.

At the neurophysiological level, in line with our initial hypothesis the analysis of the ERPs elicited by cues revealed increased posterior positivity during TBR presentation in both groups. This effect is believed to indicate selective rehearsal processes with elevated posterior positivity starting around 300 ms after *Remember* cue presentation being found in a number of previous studies (Hsieh et al., 2009; Hauswald et al., 2011; Yang et al., 2012; Brandt et al., 2013). Higher amplitudes of P3 were also observed during study phase of DF task for cues associated with subsequent intentional (recognition of the TBR stimuli during the test phase) than unintentional remembering (recognition of TBF stimuli) during test phase (Yang et al., 2012). Enlarged positive wave for *Remember* cues is thus believed to reflect additional effort associated with operations aimed at enhancement of encoding of TBR stimuli ("selective rehearsal"). Furthermore, an association between the P3 amplitudes to Remember cues presented after the NEU stimuli and subsequent recognition of NEU TBR items, which suggest that "selective rehearsal" may underlie directed forgetting effects for this type of the stimuli.

When it comes to the neurophysiological markers of the "active suppression", only limited support for reduced prefrontal inhibition was found in patients with schizophrenia. Firstly, during the study phase of the task, increased N2 during *Forget* cue presentation was observed in participants. Previous studies have linked this effect to the active suppression of encoding mechanism, which may be crucial for successful

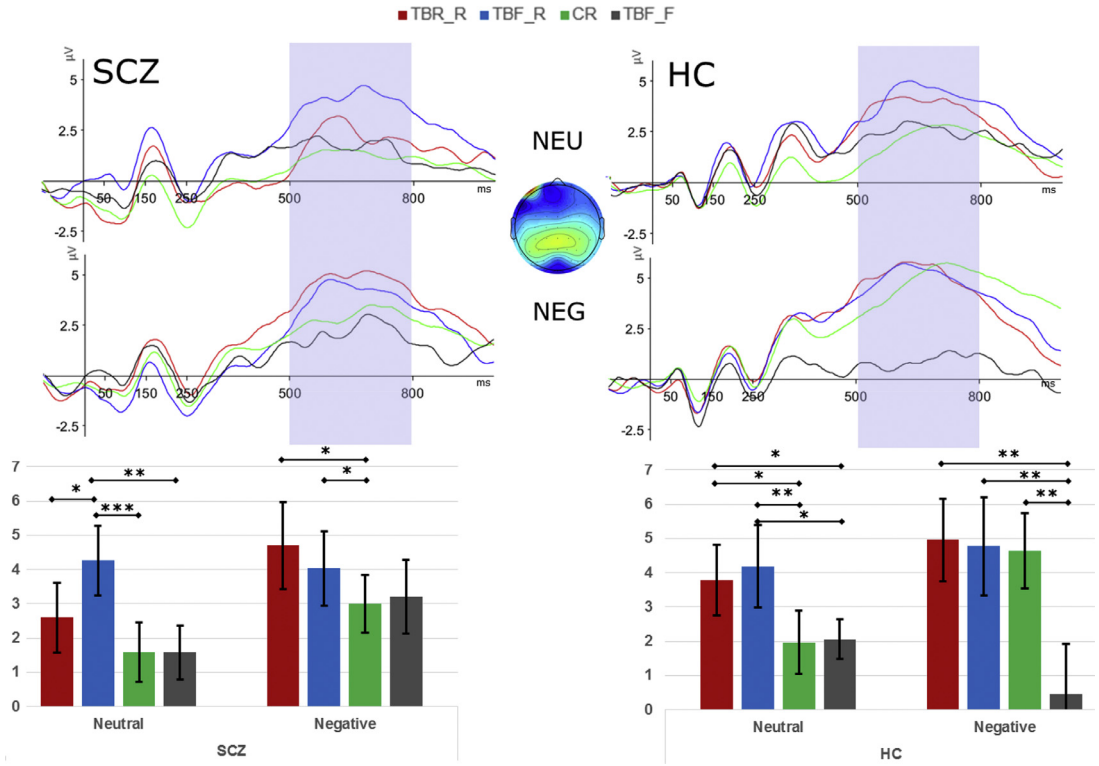

Fig. 2. Mean amplitude in the 500–800 ms window after picture onset during the test phase of DF paradigm. SCZ – patients with schizophrenia, HC – healthy controls, TBR_R – to-be-remembered items classified as "old"; TBF_R – to-be-forgotten items classified as "old"; CR – new items classified as "new", TBF_F - to-be-forgotten items classified as "new". Waveforms present averaged activity on CPz and Pz.

directed forgetting (Anderson and Hanslmayr, 2014). Additionally, another study which utilized picture based directed forgetting task, has observed that study-phase trials for which subsequent directed forgetting (classifying stimuli presented with *Forget* cue as new) was observed were associated with a more frontal negativity than trials for which unintentional forgetting (classifying stimuli presented with *Remember* cue as new) was later observed (Yang et al., 2012). While similar pattern of ERPs was observed in both groups during the study phase of the task, between-group differences, which may be linked to active inhibition mechanisms, were found in test-phase ERPs. One previous neurophysiological study analyzed ERPs observed during the test phase of DF task (Nowicka et al., 2009). Authors found that during DF test phase, in addition to the "old/new effect" associated with successful encoding of previously studied information, a "reversed old/new effect" which is indicative for successful inhibition of TBF items may be observed in a 500–750 ms time window. In the current study "reversed old/new effect" which may be indicative of inhibitory mechanisms was observed only in HC for NEG with successful suppression of NEG TBF items being associated with a larger negative deflection than any other type of stimuli, including correctly classified new pictures. Interestingly classic "old/new effect" was observed during the test phase for NEU pictures in healthy controls and for NEG pictures in SCZ. However, only effect which has been observed for NEU stimuli in patients was linked to unsuccessfully suppressed TBF items eliciting larger magnitude of test-phase ERPs than any other type of stimuli, including successfully encoded TBR items.

Taken together, our findings suggest that, while patients with schizophrenia may present overall worse memory performance, patients with schizophrenia may present similar behavioral directed forgetting effects, and neurophysiological markers of emotional memory enhancement and selective rehearsal during the emotional directed forgetting task. Furthermore, both groups have shown markers suggesting „active suppression" during the study phase of the task, though some differences in ERP patterns were found during the test phase of the task. This latter effect may be linked to the fact that effective application of the top-down control to inhibit encoding of the material may be more effortful than other mechanisms underlying DF effects, especially when it comes to negative stimuli. A neuroimaging study by Nowicka et al. (2011) compared the networks activated by the intention to forget neutral and negative pictures. A much broader network of both anterior and posterior brain structures was engaged by the intention to forget emotional images, while only a cluster of activation (lingual gyrus) was found for Forget cues presented after neutral pictures (Nowicka et al., 2011). Successful directed forgetting of emotional images was related to activations in fronto-parietal cognitive control network compared to unintentional forgetting, with no similar effects observed for neutral images. Thus, test-phase ERPs may suggest that patients may have been less successful in implementing active inhibitory strategies, even despite neurophysiological markers suggesting both groups using similar mechanisms during the study-phase of the task. This interpretation may be further corroborated by the fact that correlations were found between behavioral results and neurophysiological markers of emotional memory enhancement and selective rehearsal, but not active suppression mechanisms. This may also explain failure of previous non-emotional studies to find any DF effects in SCZ (Müller et al., 2005; Racsmány et al., 2008; Soriano et al., 2009). However, the discrepancies between the results of the current study, and previous DF studies in SCZ may also have arisen from the type of the material used, with the current study being the only one based on the pictorial, instead of verbal, stimuli. In conclusion, the results of the current study suggest that even though SCZ may be able to present DF effects, patients may have been less successful in implementing active inhibitory strategies.

While a number of insights into DF processes in HC and SCZ can be inferred from these results, a few important limitations of the study can be pointed out. Firstly, both groups differed in the number of years of education and while we have run exploratory analyses and found no correlations between years of education and directed forgetting effects

neither at the whole-sample level nor in any of the groups, this could still affected our results. Moreover, a procedure of the study was considerably long with over two hours for the EEG preparation procedures and DF task and another session for stimuli assessment. Therefore, it could not have been expanded with a neuropsychological assessment, which could be informative for baseline memory dysfunction in SCZ. While this may be seen as a major limitation of the study, memory deficits are well established in patients. At the same time, there is still discussion if patients show intact response to affective stimuli (Anticevic and Corlett, 2012), thus we decided to collect only latter data to avoid drop-outs due to the length of the procedure. Secondly, due to the response-dependent character of the ERPs in the test-phase of the task, the number of the trials averaged for each category varied largely between the specific ERPs (please see Table S1 in Supplementary Data), which could affect this part of the analyses. Furthermore, the paradigm used only neutral and negative stimuli, while a number of studies have shown that SCZ might present abnormal reactivity to positive stimuli. Thus, further studies on DF in SCZ should also include this type of stimuli. Furthermore, the current study included only inpatients, who may be more symptomatic compared to outpatients. Thus, even though no relationship was observed between experimental data and PANSS scores, the generalizability of the results for the patients' sample is limited. Future DF studies in SCZ should include both inpatients and outpatients and analyze DF capacity in a symptom clusters of patients rather than in a SCZ group as a whole, as it has been previously suggested that specific type of psychopathology may be differentially linked to directed forgetting abilities (Patrick et al., 2015).

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.02.057.

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