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Disrupted memory inhibition in schizophrenia

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Abstract

A feature of schizophrenia is disrupted executive function leading to learning difficulties and memory problems. In two experiments we measured the ability of patients with schizophrenia to suppress irrelevant parts of acquired information by intentional (executive) and autonomic (non-executive) strategies. In the first experiment using directed forgetting by lists patients were found to be unable to intentionally suppress recently acquired episodic memories. In a second experiment using a procedure that induces inhibition automatically schizophrenic patients showed levels of inhibition comparable to those of normal controls. These findings indicate that in schizophrenia memory is most impaired in tasks that load heavily on control or executive processes.

Keywords: Schizophrenia; Directed forgetting; Selective practice; Prefrontal inhibition; Executive function

1. Introduction

Patients diagnosed with schizophrenia show a range of neurocognitive deficits including memory malfunctions (McKenna et al., 1990; Saykin et al., 1991). Indeed, it has been frequently shown that patients with schizophrenia perform poorly on immediate and delayed verbal learning tasks, such as the Rey Auditory Verbal Learning Test or the Wechsler Memory Scale (Aleman et al., 1999; Heinrichs and Zakzanis, 1998; see Cirillo and Seidman, 2003 for a review). Patients with schizophrenia are sensitive to interference and contextual change between learning and recall and the degree of memory impairment has not been found to be related to medication or duration of illness (Sevan-Schreiber et al., 1996; Torres et al., 2004). It seems that patients within the schizophrenia spectrum are compromised in their ability to disregard irrelevant information. This observation is supported by findings demonstrating that patients with schizophrenia produce less release from proactive interference and show a usually high intrusion error rate of items from earlier sets (Chan et al.,

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2004; Sitskoorn et al., 2002). Moreover, studies of executive system functions have found schizophrenic patients to be disinhibited on executive tasks such as negative priming, Stroop, and the Go/No-Go motor inhibitory task (Perlstein et al., 1998; see Palmer and Heaton, 2000). Taken together these findings all point to a dysexecutive profile in which malfunctioning control processes leave processing sequences open to interference by related but task-irrelevant information. In short, the pattern shows attenuation in the effectiveness of centrally controlled inhibitory processes.

Inhibitory processes can be triggered intentionally in an explicit, conscious, attempt to avoid or suppress unwanted or irrelevant information, or they may be triggered implicitly, nonconsciously, as part of a processing sequence. Note that what is important here is the way in which inhibitory processes are triggered or initiated, there is no suggestion that the processes themselves could come under direct intentional control. Also note that there is no suggestion either that executive or control processes are conscious, we assume along with all other theorists in the area that executive processes are nonconscious but that some of their outputs may occasionally enter consciousness and that they can be initiated by conscious intentions. Thus, a person might, for example, consciously and intentionally attempt to avoid thinking about a memory or a memory may be inhibited from entering consciousness by nonconscious, incidental, process (Barnier et al., 2007; Barnier et al., 2004; Racsmány and Conway, 2006).

Two experimental paradigms that have been widely used to explore intentionally and incidentally triggered inhibition and these are, respectively, direct forgetting (DF) and retrieval practice (RP). The DF procedure has been most extensively investigated by Bjork and colleagues (see Bjork, 1989; Bjork et al., 1998). In the list-method of DF participants are explicitly instructed to intentionally forget a previously learned list. The forget instruction is then followed by a second to-be-learned list (see MacLeod, 1998 for a detailed review of list- and item DF). The critical contrast that defines the DF effect and which has been observed in many studies is lower List 1 memory performance following a forget instruction compared to List 1 memory performance following a remember instruction, (Bjork and Bjork, 1996; Conway et al., 2000). The single study of directed forgetting in patients with schizophrenia found that produced a significant DF effect, although their forgetting performance was somewhat weaker than that of control group (Müller et al., 2005). This study, however, used an item-by-item DF task, in which items are followed by an R or an F instruction. Item DF effects are considered to be mediated by rehearsal strategies rather than by inhibitory processes (Basden and Basden, 1998) and, therefore, not directly relevant to the present goal of investigating intentional and incidental inhibition. Nonetheless, we note that these patients were able to alter their rehearsal strategies, in order to produce an item DF effect, and that indicates at least partly preserved executive function.

The RP procedure has been extensively studied by Anderson and colleagues (Anderson et al., 1994; Anderson and Spellman, 1995; see for a recent review Norman et al., 2007). In the RP procedure participants study a list containing words grouped into categories. The study phase is followed by the RP phase in which participants practice recalling selected items from the study list. This yields three types of items: Rp+ items are items which have been rehearsed, Rp− items which were studied items but which not themselves been rehearsed but which originate from categories that contain an Rp+ item, and finally Nrp items which are from studied categories from which no items have been rehearsed. The standard finding is that Rp+ items are remembered to a high level, Nrp items to a reliably lower level, with Rp− items showing poorest recall. The explanation is that this effect arises because of the effect of recalling Rp+ items during the practice phase is to automatically inhibit Rp− items (see Racsmány and Conway, 2006). Importantly, a recent study (Nestor et al., 2005) using the RP procedure with 15 patients diagnosed with schizophrenia and found a normal RP effect.

The aim of the present study is then to compare these two inhibitory procedures, DF and RP, in a patient group diagnosed with schizophrenia. We expect RP performance in this group to be in the normal range and show the standard inhibitory pattern as, indeed, previous studies have found, (Müller et al., 2005; Nestor et al., 2005). If this is the case then it demonstrates that at least some incidental, automatic, inhibitory processes are intact and function normally in this group. In contrast, we predict that in DF where initiating inhibition is intentional and effortful and requires the normal functioning of executive processes then a standard pattern of inhibition will not be observed. This is because executive function in schizophrenic spectrum disorder is comprised, as it is in brain damaged patients with frontal lobe lesions who also do not show a normal pattern of directed forgetting (Conway and Fthenaki, 2003).

2. Experiment 1

2.1. Method

2.1.1. Participants

A total of thirty patients with a diagnosis of schizophrenia defined by DSM-IV (American Psychiatric

Association, 1994) and ICD-10 criteria for research (World Health Organization, 1993) took part in the experiments. Patients were selected from the outpatient clinic of the Department of Psychiatry, University of Szeged. All patients were in an early stage of the illness, currently in a stable inter-episodic state, and under antipsychotic medication. The thirty control subjects were recruited from hospital staff and community volunteers. They were evaluated with a modified structured interview (Mini International Neuropsychiatric Interview). Control participants with a personal history of psychiatric disorder or a family history of psychotic and affective spectrum disorders, history of neurological illness, any medical illness known to affect brain structure, head injury with loss of consciousness for more than 30 min, clinically significant substance abuse within the last 6 months, or any medical illness that could significantly constrain neurocognitive functions were excluded. All participants were 18 to 50 years of age, minimum 8 years in education (primary school), and able to give informed consent. The patients were excluded if they had previously undergone electroconvulsive therapy or were subject of clinically significant substance abuse.

2.1.2. Clinical and neuropsychological measures

Clinical symptoms were assessed by psychiatrists using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1991), and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982). The demographic and clinical characteristics are shown in Tables 1 and 2.

Widely used neuropsychological tasks were employed to measure working memory and executive functions. We measured verbal working memory capacity with the Digit Span Task (Racsmány et al., 2005), we used the Visual Patterns Test (VPT, Della Sala et al., 1997) for measuring visuo-spatial working memory capacity. We assessed executive functions with the Wisconsin Card Sorting Test (WCST, Heaton et al., 1993).

2.1.3. Procedure

Participants were tested individually. They were told that they were participating in an experiment on memory

Table 1
Demographic characteristics of the subjects

	Patients		Control	
	Mean	SD (+/−)	Mean	SD (+/−)
Age	31.1	9.8	32.6	9.4
Education (years)	11.1	1.8	12.2	1.9
Full scale IQ WAIS-H	103.4	14.8	109.1	11.2

Standard deviations are presented in parentheses.

Table 2
Clinical and neuropsychological characteristics of the subjects

	Mean	SD (+/−)
Age at onset (years)	23.5	6.8
Duration of illness (years)	7.5	7.1
Relapses	4.5	4.7
PANSS		
Positive	11.4	5.5
Negative	16.4	6.2
Global	29.8	11.1
Total	57.6	19.9
SANS		
Affective	1.6	1.1
Alogia	1.5	0.9
Avolition	1.5	1.2
Anhedonia	2.1	1.2
Attention	1.4	1.1
WCST		
Categories	2.8	2.4
PE%	28.8	18.7
CLR%	37.8	26.6
Digit span	5.7	1.1
VPT	6.4	1.6

Standard deviations are presented in parentheses.

with the aim to test their ability to recall words. The experiment was conducted in four phases: a list learning phase, a distracter phase, a free-recall phase, and a cued-recall phase. Words were presented visually on separate sheets of papers. After the words of the first list (7 words) had been presented, participants were instructed to stop. At this point participants in the forget-instruction-condition (F-condition) were given the following forget instruction: The list you have just learned was a practice list to familiarize with the experimental procedure. You should now forget these words, try to put them out of your mind. The real experimental list will be presented now. In the remember-instruction condition (R-condition) the same procedure was followed, but instead of the forget instruction, participants received a remember instruction: That is the end of List 1. You must try to keep those words in mind while you learn the second list which will be presented now.

Following the forget or remember instructions, the second list was presented. After all words had been studied participants were given a 5-minute simple arithmetic filler task. This was followed by the free-recall test. Participants were provided with paper and pen and asked to try to recall as many words as they could from both lists. They were asked to start at the top of the page and write each recalled word under the previous word. In order to reduce the role of output interference we followed the recall instruction of Conway et al. (2000 Experiment 7): participants were required to recall List 1 words first and then List 2 words. Following the free-recall participants took part in a stem-cued-recall test. They were given printed list containing the first two letters of the words of first and second lists in a randomised order, and completed the stems for the previously studied words. Each subject took part both in F and R conditions and the order of conditions was counterbalanced among participants. Four lists were constructed from a pool of twenty eight (Hungarian) words of moderate to high frequency (Füredi and Kelemen, 1989). The order of presentation of the lists was counterbalanced for each participant in both conditions.

2.1.4. Results and discussion

A 2 x 2 x 2 (group x instruction x list) mixed analysis of variance (ANOVA) was conducted on individual free-recall rates. The main effect of group was significant $F(1,58)=482.9$, $p<0.001$, the main effect of instruction was not significant $F(1,58)=2.7$, $p>0.1$, and the main effect of list was also not significant $F(1,58)=2.8$, $p>0.1$. More interesting was that we found highly significant interaction between instruction and list $F(1,58)=19.42$, $p<0.001$, and also a powerful interaction between group, instruction, and list $F(1,58)=10.7$, $p<0.001$. Together this pattern shows a strong and reliable directed forgetting effect for the control group but no effect for the patient group. As can be seen from Table 3 the forget instruction had no effect on patients' performance, the only detectable change is a small, non-significant reverse directed forgetting effect in which patients recalled more List 1 words in the forget than in the remember conditions. We calculated an inhibitory index for each participant by subtracting F1 (List 1 in F-condition) performance from R1 (List 1 in R-condition) performances. As can be seen from Table 3 the inhibition score is negative for the patient group showing a reverse effect of the forget instruction.

An identical 2 x 2 x 2 (group x instruction x list) analysis of variance (ANOVA) was carried out with the stem-cued-recall rates. The pattern of results was the same as for the previous the list-cued-recall task, the main effect of group was significant $F(1,58)=14.75$, $p<0.001$, the main effect of instruction was not significant $F(1,58)=1.7$, $p>0.1$, and the main effect of list was also not significant $F(1,58)=0.57$, $p>0.1$. However, we found again a significant interaction between instruction and list $F(1,58)=8.4.42$, $p<0.01$, and also a powerful interaction between group, instruction, and list $F(1,58)=6.2$, $p<0.01$.

An inhibitory index was again calculated by subtracting List 1 performances in the forget condition from List 1 performance in the remember condition. As can be seen from Table 3 patients with schizophrenia did not produce inhibition at all in either recall test and their inhibitory index was negative reflecting a rebound effect. A one-way ANOVA was carried out on individual's inhibitory indexes which yielded significant differences between groups both for the free-recall $F(1,58)=8.51$, $p<0.01$ and for the stem-cued-recall tasks $F(1,58)=7.34$, $p<0.01$. Overall this pattern of data demonstrates that patients with schizophrenia are not able to intentionally inhibit previously acquired information.

Table 3
Mean percentages of memory performances in Experiment 1

	Patients		Control	
	Mean	SD (+/−)	Mean	SD (+/−)
Recall of F1 words	35.7	17.1	42.8	24.3
Recall of F2 words	31.4	21,4	62.9	19.9
Recall of R1 words	34.3	18.6	61.4	20
Recall of R2 words	24.3	17.4	40	22.1
Inhibitory index for list-cued recall (R1 − F1)	−9.6	18.2	18.4	13.3
Stem-cued recall of F1	55.7	19.2	62.9	21.1
Stem-cued recall of F2	54.3	19.8	72.9	19.7
Stem-cued recall of R1	51.4	20.1	72.7	19.6
Stem-cued recall of R2	45.7	21.1	62.6	19.4
Inhibitory index for stem-cued recall (R1 − F1)	−6.1	14.1	10.4	11.2

Standard deviations are presented in parentheses.
F1 = List 1 words in the forget condition; F2 = List 2 words in the forget condition; R1 = List 1 words in the remember condition; R2 = List 2 words in the remember condition.

3. Experiment 2

The aim of this second experiment was to establish whether those patients who produced no inhibition in DF task were nonetheless able to produce inhibition in the RP task. Such a result would replicate the main findings of Nestor et al. (2005), and confirm our hypothesis that patients with schizophrenic spectrum disorder cannot initiate inhibition intentionally but are able to initiate inhibition when it is an incidental part of a task.

3.1. Method

3.1.1. Procedure and materials

The same patients and controls who took part in Experiment 1 took part in the present experiment and the data was collected from participants individually. The order of the DF and RP experiments was counterbalanced among participants; there was minimum one day delay between the two experiments. The RP procedure was conducted in four phases, following the procedure of Racsmány and Conway (2006): Study Phase, RP Phase, Distracter Phase, and a surprise cued-recall phase. Ten categories were used two of which were fillers. Each category consisted of twelve exemplars from each of eight target categories forming two subsets (six items) with moderate to high frequency words drawn from two published Hungarian frequency norms (Kónya and Pintér, 1985; Füredi and Kelemen, 1989). We created two subsets from the eight target categories and designated an equal number of items as practiced and nonpracticed categories. The practiced and nonpracticed exemplars were counterbalanced as well. In the study phase participants saw category-exemplar pairs on a screen and were told to try to remember the category examples as best as they could. Each category-exemplar pair was presented in uppercase letters at the centre of the screen for 5 s. When participants had completed the learning phase, the experimenter distributed practice booklets. Each page in the booklet contained one of the category names they had seen previously and the first two letters of one of the members of that category which they had to complete. Their task was to complete the exemplar fragment with one of the words they had studied earlier. Participants were told that some of the examples might be tested more than once but in every case they should complete the word stem with a word studied previously (note that only a single response was possible for each word stem). After the RP phase booklets were collected and participants were given an unrelated mathematical task for 12 min. Finally, participants were given recall booklets with the name of one of the previously studied categories on the top of each page. Participants had 10 min to recall as many examples as they could, and they had to keep the order of categories as they were arranged in the booklet. Order of presentation of category cues was counterbalanced over participants.

3.1.2. Result and discussion

A 2 x 3 (group x item type) mixed analysis of variance was performed on individual recall percentages. The main effect of group was significant $F(1,58)=44.143$, $p<0.001$. The main effect of list was also significant $F(1,58)=241.2$, $p<0.001$, however and more importantly there was no significant group by item type interaction $F(1,58)=2.1$, $p>0.1$. To detect specific effects of RP in both groups separate one-way analyses of variance on item types (Rp+, Rp−, Nrp items) were conducted for both the patient and the control groups. The findings replicated the results of Anderson et al. (1994), and a reliable effect of item type was observed, $F(1, 29)=165.1$, $p<0.001$ for the control group. Planned comparisons showed that the recall of Rp+ items was significantly higher than that of Nrp items, $F(1,29)=12.7$, $p<.001$, confirming the benefits of practice on subsequent recall. The recall of Rp− items was found to be significantly lower than that of Nrp items, $F(1,29)=5.8$, $p<.001$, indicating inhibition of these items.

Table 4
Mean percentages of memory performances in Experiment 2

	Patients		Control	
	Mean	SD (+/−)	Mean	SD (+/−)
Recall of Rp+ words	57.5	19.1	80	11.9
Recall of Rp− words	15.8	15,8	30	14.25
Recall of Nrp words	20.4	16.8	44.2	13
Inhibitory index (Nrp − Rp−)	4.6	10.3	12.2	11.2

Standard deviations are presented in parentheses.

Importantly the same pattern of results was present in the patient group where the main effect of item type was significant $F(1, 29)=91.6$, $p<0.001$. Planned comparisons showed that the recall of Rp+ items was significantly higher than that of Nrp items, $F(1,29)=11.9$, $p<.001$, showing that the patients too benefited from retrieval practice. The critical finding was, however, that recall of Rp− items was significantly lower than that of Nrp items, $F(1,29)=5.3$, $p<.01$, indicating the standard inhibitory effect. As in Experiment 1 inhibition scores were calculated and the patient group scores although showing the standard inhibitory effect (see Table 4) were nonetheless reliably lower than those of the control group, $F(1,58)=6.69$, $p<0.01$. Thus, normal but weaker inhibition was found in the patient's with schizophrenic spectrum disorder.

4. General discussion

The present study demonstrates that patients with schizophrenia are not able to intentionally forget items from a previously acquired list, and compared to controls patients produced no DF effect. Patients with schizophrenia are not then able to intentionally initiate inhibition. In marked contrast our patients produced a strong and reliable inhibitory effect in the RP procedure (a finding highly consistent with Nestor et al., 2005). Despite this normal pattern of recall in the RP procedure the general level of their inhibitory index was somewhat lower than that of control subjects, perhaps indicating a more widespread memory problem, in addition to problems with intentional forgetting.

Over the two experiments the pattern of performance is very similar to that reported by Conway and Fthenaki (2003) in a group of patients with frontal and temporal lobe lesions. Frontal patients produced an inverted DF effect and normal RP effect (as did the patients in the present study), while temporal lobe patients produced the reverse pattern. Conway and Fthenaki (2003) argue that the actual process of inhibition is the same in both kinds of task and it is the way this process is triggered that differs. In DF inhibition is intentionally elicited by active thought avoidance, a process carried out mainly by networks of the lateral prefrontal cortex and its connections (Anderson et al., 2004; Bunge et al., 2001; Aaron et al., 2004; Wylie et al., in press). Although prefrontal cortex may also have an important role in successful inhibition in RP paradigm, hippocampal and temporal networks can apply inhibitory processes without top-down executive control (see Norman et al., in press, for an interesting neural network model of this).

We suggest then that the pattern of performance by the patients with schizophrenia in DF may be a sign of disrupted frontal function possibly associated with attenuation of fronto-temporal pathways that, under normal circumstances, would mediate inhibition of recently acquired knowledge. In contrast, the intact, albeit somewhat weaker, inhibitory pattern in RP may reflect functioning medial temporal lobe inhibitory processes. In this case the practice phase induces inhibition by establishing retrieval competition between practiced items and unpracticed items from the same category that compete for recall during the category cued practice phase. In this way a pattern of activation and inhibition is created over the contents of a memory of the study list, with some items highly active (Rp+), some active but at a lower level (Nrp), and some inhibited (Rp−). It is this pattern that mediates recall (see Racsmány and Conway, 2006) and leads to the normal pattern of cued recall in the patients and controls.

In conclusion, the present experiments indicate that possible disrupted executive functions may considerably weaken the ability of patients with schizophrenic spectrum disorder to intentionally avoid recent memories and, perhaps, other cognitions too. This can occur even when other incidentally initiated inhibitory processes appear to function relatively normally. The wider consequences for schizophrenic cognition more generally are negative and one implication is that of weakened intentional control of a wide range of recently acquired material.

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Contributors

Authors Racsmány and Conway designed the study, undertook the statistical analysis and wrote the manuscript. Author Garab managed the experimental work. Authors Janka, Kurimay, Cimmer and Szendi managed the psychiatric and neuropsychological diagnosis. Author Pléh managed the literature searching. All authors contributed to and have approved the final manuscript.

Conflict of interest

Hereby all authors declare that they have no conflicts of interest.

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