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ORIGINAL PAPER

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Directed forgetting in schizophrenia

Prefrontal memory and inhibition deficits

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Abstract Schizophrenia is associated with cognitive deficits in the domains of working memory, strategic memory and other executive functions. In the current study we used a computerised and item-cued variant of the directed forgetting (DF) task to assess inhibitory processes in verbal memory. Twenty-five patients with schizophrenia and a group of matched controls were tested. Recognition memory was better for to-be-remembered (TBR) than for to-be-forgotten (TBF) words in both patients and controls. As compared to healthy controls the patients with schizophrenia showed overall memory deficits and difficulties to inhibit memories as indicated by a significant group by cue interaction and a smaller DF effect. The DF effect was associated with disease duration but not with symptom severity. Memory-related inhibition problems are difficult to assess in patients with schizophrenia and might be related to fronto-temporal disconnection.

Key words directed forgetting · inhibition · memory · prefrontal · schizophrenia

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Introduction

Dysregulation of the prefrontal cortex, its connections with temporal and subcortical structures and their dopaminergic modulation are the cornerstones of schizophrenia pathophysiology (Robbins 1990; Andreasen et al. 1998; Braver et al. 1999; Friston 1999; Goldman-Rakic 1999; Müller and Gruber 1999; Kapur 2003). Cognitive deficits are considered to be the core of the disorder by some authors (e. g. Elvevåg and Goldberg 2000) and innovative treatment strategies aim to improve cognitive deficits (Meltzer 1999; Green et al. 2000; Keefe et al. 2003). Card sorting, continuous performance and verbal fluency tasks are most frequently used in schizophrenia research to investigate executive und working memory functions (Heinrichs and Zakzanis 1998; Johnson-Selfridge and Zalewski 2001; Nieuwenstein et al. 2001; Bokat and Goldberg 2003). Long-term memory has been investigated with various list and paired associates learning tasks (Aleman et al. 1999). Memory problems in schizophrenia are typically caused by inefficient use of strategies at encoding or retrieval (Iddon et al. 1998; Cirillo and Seidman 2003). Strategic memory deficits are correlated with reduced working memory capacity (Stone et al. 1998). Prefrontal inhibitory deficits have been demonstrated using Stroop interferences (Cohen and Servan-Schreiber 1992; Barch et al. 1999), attentional focusing procedures (Ferman et al. 1999) and memory tasks with distractors (Elvevåg et al. 2000; Weiss et al. 2002).

In everyday life situations patients with schizophrenia often have problems to focus on relevant information and cannot ignore meaningless details. Incongruity and incoherence were associated with bad performance on the Stroop task (Liddle and Morris 1991) and failures to inhibit inappropriate responses on the Continuous Performance Task (Frith et al. 1991).

Executive control processes that inhibit unwanted encoding and retrieval can be tested experimentally (Aron et al. 2004). The directed forgetting (DF) task in-

vestigates subsequent memory for items (e. g. words) that had to be remembered (TBR) or forgotten (TBF) as indicated by a cue. Recall and recognition of TBR items are normally better than for TBF items; this is the so-called "DF effect". Variants of the DF task have been used for more than 25 years in normal subjects and clinical populations (Johnson 1994; MacLeod 1998; Anderson and Green 2001). The item-by-item cueing method can be combined with a delay between each item and cue, which has the advantage of temporary rehearsal of both TBR and TBF items (Basden and Basden 1996). Patients with complex-partial seizures of temporal lobe origin (without neurosurgical treatment) showed overall memory deficits and DF related retrieval problems (Fleck et al. 1999) and patients with right frontal lesions were unable to inhibit TBF words (Conway and Fthenaki 2003).

The aim of our study was to further investigate inhibitory processes in memory in a group of medicated and clinically stable patients with schizophrenia as compared to healthy controls using a computerised version of the item-cued DF task. According to the model of impaired fronto-temporal information processing in schizophrenia similar deficits as seen in patients with prefrontal and temporal lesions were predicted.

Methods

Subjects

Twenty-five patients with schizophrenia were investigated (9 women, 16 men; mean age 37.9 ± 11.9 (20–58) years, 13.9 ± 1.5 (12–16) years of education). All patients were recruited at the Department of Psychiatry, University of Leipzig, Germany, and met ICD-10 research criteria for schizophrenia as confirmed by a diagnostic checklist (Janca and Hiller 1996). Seventeen patients had a paranoid form (F20.0), five an undifferentiated schizophrenia (F20.3) and three suffered from post-schizophrenic depression (F20.4). Main exclusion criteria were an age under 18 or over 60 years and severe psychiatric or medical comorbidity. Symptoms of schizophrenia at the time of neuropsychological testing were evaluated with the positive and negative symptoms scale (PANSS) (Kay et al. 1987) by two experienced and trained psychiatrists (TB, UM); a mean PANSS total score of 59.4 ± 12.7 (range 42–85) was rated. Mean duration of illness was 9.9 ± 9.6 (0–29) years and six patients suffered from a first psychotic episode. Mean length of current (or last) inpatient treatment was 49.4 (range 5–198) days. Mean global clinical impression (CGI) score on the day of release was 2.9 (as compared to 6.3 on admission), and the general assessment of functioning (GAF) score was 58.3 (as compared to 43.5 on admission). All patients were on stable antipsychotic medication, twelve were treated with atypicals only (clozapine, olanzapine, risperidone or quetiapine) and thirteen with conventional drugs (haloperidol or flupentixol) alone or in combination.

Twenty-five control subjects matched for age, sex and education were selected mainly from the volunteer panel of the Max Planck Institute of Cognitive Neuroscience. They had no present or previous neuropsychiatric diseases. All subjects were native German speakers. The study protocol was approved by the Ethics Committee of the University of Leipzig (reg. no. 923) and written consent was obtained from all participants. Patients and volunteers had sufficient capacity to give informed consent.

Study design

The study had a control group design in order to compare the performance on cognitive tasks of patients with those of matched controls. Cognitive tasks were always administered in the same order; short breaks between tasks were allowed. The computerised DF task was performed in a quiet laboratory room. All patients were on stable antipsychotic medication and tested at the end of or shortly after hospital treatment on two consecutive days, one for the prefrontal screening battery and the next for the DF task. Only patients who did understand and follow the instructions were included for the DF task.

Cognitive screening battery

The cognitive screening battery comprises tests of working memory and executive functions, namely the digit spans forward and backward, the digit ordering span, a reading span, letter and category fluency and the modified card sorting task, as previously described in our studies of patients with Parkinson's disease and frontal lobe lesions (Müller et al. 2000; Werheid et al. 2002). There was no formal testing of declarative memory functions with standardised neuropsychological tests; however, the DF task comprises control conditions for recall and recognition memory. To estimate verbal intelligence we used the MWT-A (Mehrfach Wortschatz Test, Version A), a German equivalent of the National Adult Reading Test (NART).

Directed forgetting task

The DF task was programmed using the ERTS (Experimental Run Time System; BeriSoft Cooperation, Frankfurt/Main, Germany) software package. It was adapted from studies by Zacks et al. (1996) and Ullsperger et al. (2000) for the use in a patient population. In order to make the task easier and shorter we used fewer words. As previously described, this task has two separate parts, one with stimulus presentation (study phase) and another for old-new recognition (test phase).

In the study phase 3 blocks of 30 words each (5 nouns per category) were presented; 180 words were taken from 18 categories (see appendix to Ullsperger 2000) and balanced for number of syllables, typicality, frequency as well as recency and primacy effects. The emotional valence of the stimulus words was balanced by the use of four parallel and permutated sets of words. The presentation of each word was followed by a short delay of 2.5 seconds and afterwards a cue that indicates whether the item is to be remembered (TBR) or to be forgotten (TBF). At the end of each block subjects were instructed to write down as many TBR words as possible (immediate recall).

After a delay of 10 minutes, normally filled with conversation, the new instruction was given. We used a written instruction that was read aloud and paraphrased by the experimenter to make the point of a change of instruction as clear as possible. The test phase consisted of 180 words that were successively presented; half of them had been shown in the study phase and the other half were new, but semantically related "lures". Using a forced dual-choice procedure the subjects had to decide whether a word was "old" or "new" by pressing one of two keys. All words presented in the study phase had to be classified as old, irrespective of whether they were TBR or TBF. Reaction times (RT) were recorded and the decision time was terminated with a beep after 3 seconds. The entire DF task lasted about one hour.

Data analysis

Performance data were analysed by ANOVA using individual and group means of error rates. Reaction times (RTs) were analysed using individual median values of correct answers to correct for outliers. Normal distribution was assessed and the Greenhouse-Geisser conservative *F*-test was used to interpret the ANOVA where necessary. Post hoc contrasts were evaluated by *t*-test. Correlations with psychopathology and other cognitive tasks were evaluated by an exploratory analysis using Spearman's rho, because some psychopathological parameters were not normally distributed.

Results

Demographic and clinical data

There were no significant differences between patients and controls with regard to age, sex and years of education (Table 1); however, most patients were unemployed or on a pension scheme.

Cognitive screening

Patients with schizophrenia showed significantly poorer performance in most of the tasks of the cognitive screening battery with the exception of digit spans forward, which served as a control condition for working memory tasks with higher manipulative demands. Differences in letter fluency and intelligence (MWT-A) did not reach statistical significance when multiple correlations where taken into consideration. Abnormally low MWT-A scores (≤15) were seen in three patients and can be explained by motivational deficits. Detailed results of this battery in a larger sample of patients are reported elsewhere, together with an analysis of medication effects (Müller et al. in press).

Directed forgetting

There were highly significant DF effects in the recognition part, i. e. fewer TBF words were classified as "old" (Table 2), in the overall group ($F_{1,48} = 182.6$, $p < 0.001$) as well as in patients ($F_{1,24} = 65.8$, $p < 0.001$) and controls ($F_{1,24} = 117.7$, $p < 0.001$). A significant interaction of group (patient vs controls) and cue (remember vs forget) effects ($F_{1,48} = 8.5$, $p = 0.005$) indicates disease-dependent differential processing of TBR and TBF words. This interaction remained significant when controlled for verbal intelligence and age by analysis of covariance ($F_{1,48} = 6.5$, $p = 0.014$), but not when immediate recall performance was considered as a covariate. The absolute DF effect (recognition of TBR minus TBF items) was significantly smaller in the patients as compared to controls ($F_{1,48} = 8.4$, $p = 0.006$), but not the proportionate DF effect (Table 2). Overall memory performance was significantly worse in patients with schizophrenia as compared to healthy controls, both in the immediate recall and delayed recognition of TBR words. The group by cue ANOVA for RTs showed a significant cue effect ($F_{1,48} = 19.6$; $p < 0.001$) with slower reactions to TBF words, but no significant group effect or interaction. No effect of treatment with conventional as compared to atypical antipsychotics on any parameter of the DF task was observed.

Table 1 Subject demographics (mean, standard deviation in parenthesis; range)

	Patients (n = 25)	Controls (n = 25)	F	p
Age (years)	37.9 (11.9); 21–56	39.3 (13.9); 19–58	0.1	> 0.10
Gender	9 female: 16 male	10 female: 15 male	0.1	> 0.10
Verbal IQ (MWT-A)	28.9 (6.3); 12–35	31.6 (2.2); 27–35	4.3	0.043
Years of education	13.9 (1.5); 12–16	14.3 (1.5); 13–16	0.9	> 0.10

Table 2 Performance of patients with schizophrenia (n = 25) and control subjects (n = 25) in the Directed Forgetting task (group means, standard deviations in parenthesis)

	Patients	Controls	F	p
Recall of TBR words				
Correct recall (%)	35.4 (12.5)	69.6 (13.3)	75.0	**< 0.001**
Intrusion errors (%)	1.2 (1.1)	2.7 (2.6)	6.3	0.017
Recognition of TBR words				
Correct "old" classification (%)	58.4 (21.1)[a]	81.3 (13.8)[a]	20.7	**< 0.001**
RTs (ms)	942 (199)	840 (155)	4.1	0.049
Recognition of TBF words				
Correct "old" classification (%)	37.1 (17.5)[a]	48.3 (19.0)[a]	4.7	0.035
RTs (ms)	1007 (270)	950 (158)	0.8	> 0.10
DF effect				
absolute	21.5 (12.8)	33.1 (15.2)	8.4	**0.006**
proportionate	0.630 (22.4)	0.586 (19.7)	0.5	> 0.10
Recognition of lures				
Correct "new" classification (%)	76.4 (14.8)	80.7 (13.3)	1.2	> 0.10
RTs (ms)	980 (182)	954 (179)	0.3	> 0.10

[a] significant group (patients *vs* controls) by cue (remember *vs* forget) interaction; *DF* directed forgetting (absolute DF effect = $\text{recognition}_{TBR} - \text{recognition}_{TBF}$; proportionate DF effect = $\text{recognition}_{TBF}/\text{recognition}_{TBR}$); *RT* reaction time; *TBR/TBF* to-be-remembered/to-be-forgotten

Correlations with other cognitive and clinical parameters

An exploratory analysis revealed a distinct pattern of correlations between DF parameters, other cognitive measures and clinical parameters (Table 3). The DF effect, i. e. the difference of recognition of TBR and TBF items, was significantly correlated with disease duration, the longer the disease the smaller the DF effect. Recognition of TBR words was positively correlated with verbal intelligence and the digit ordering span. There were no significant correlations between any DF parameter and auditory hallucinations or other psychopathological parameters (PANSS subscores or symptom clusters as derived from factor-analytic PANSS studies (Cameron et al. 2002)). In the overall group the recall of TBF words (so-called "intrusion errors") was positively correlated with age ($p = 0.001$). Immediate recall was highly correlated with recognition of TBR ($p < 0.001$) and TBF words ($p = 0.003$) and the absolute DF effect ($p = 0.002$) in our sample.

Discussion

We have shown that patients with schizophrenia are able to intentionally forget words that had to be maintained in short-term memory. As compared to healthy controls, the patients showed, however, a smaller absolute DF effect and less efficient differential processing of TBR and TBF words as indicated by a significant cue by group interaction. Our data indicate that both learning of TBR and forgetting of TBF words are impaired in patients with schizophrenia (Fig. 1).

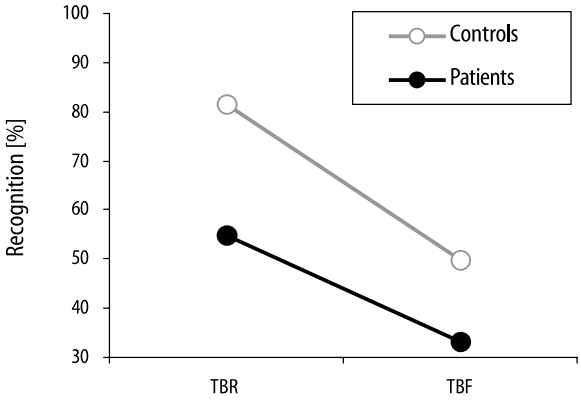

Fig. 1 Recognition (hit rate for correct "old" classification) of to-be-remembered (TBR) and to-be-forgotten (TBF) words in the directed forgetting (DF) task in patients with schizophrenia and healthy controls

This result of a relative impairment of memory inhibition is different from findings in a small group of patients with right frontal lesion who showed normal learning performance and an inverted DF effect with better memory for TBF as compared to TBR words using a list variant of the DF task (Conway and Fthenaki 2003). Two other recent studies in patients with frontal brain lesions or traumatic brain injury could, however, not replicate these findings (Andres and van der Linden 2002; Schmitter-Edgecombe et al. 2004). Minimal and inverted DF effects in clinical studies can also be explained by difficult to control problems with switching from one instruction in the study phase ("forget TBR items") to another in the test phase ("recall or recognise TBR and TBF items").

There are some limitations of this study that have to

Table 3 Nonparametric (Spearman's) correlations between DF performance, other cognitive and clinical parameters in patients with schizophrenia (n = 25)

	Immediate recall		Recognition		DF effect
	TBR	TBF	TBR	TBF	
Disease duration	−0.43*	−0.06	−0.36	−0.11	**−0.50****
PANSS					
Auditory hallucinations	0.05	0.06	0.05	0.10	−0.04
Positive	−0.27	−0.03	−0.21	−0.12	−0.26
Negative	−0.22	0.22	−0.03	−0.04	0.00
Disorganisation	−0.05	−0.10	0.03	0.10	−0.16
Verbal intelligence (MWT-A)	0.46*	0.22	**0.51****	0.47*	0.22
Digit spans					
Forward	0.43*	0.10	0.39	0.13	0.46*
Backward	0.25	−0.10	0.30	0.07	0.38
Ordering	0.48*	−0.05	**0.53****	0.34	0.46*
Reading span	0.38	0.35	0.48*	0.43*	0.26
Fluency					
Letter	0.36	0.24	0.20	0.23	0.03
Category	0.29	−0.05	0.13	0.12	0.08
WCST					
Categories	0.20	−0.10	0.19	−0.10	0.44*
Perseverations	−0.20	−0.14	−0.11	0.10	−0.30
Age (overall group)	−0.19	**0.50****	−0.30*	−0.12	−0.20

* $p < 0.05$; ** $p < 0.01$

be considered in detail: First, the main finding of reduced absolute DF effects and the interaction between group and cue have to be interpreted carefully; however, floor effects are an unlikely explanation for low recognition of TBF words in patients with schizophrenia, given the general bias towards "new" classifications (around 60 % vs 40 % for "old" over all conditions). Second, the lack of convincing correlations with positive symptoms (especially distracting auditory hallucinations) or other psychopathological parameters might weaken the clinical relevance of our findings; however, the combination of deficits in working memory, recognition memory and memory-related inhibition has important implications for occupational and social functioning and rehabilitation of patients with schizophrenia.

Since we completed our study two other groups have communicated results of studies using different variants of the DF task in schizophrenia. Sonntag et al. (2003) tested 21 clinically stabilised, French patients with an item version of the DF task. Their recognition task consisted of 48 old and 48 new distractor words typed on four sheets of paper; each word had to be classified as "remember", "know" or "guess". The absence of a DF effect in their patients is indicating a problem of memory inhibition; however, the lack of an immediate recall makes it difficult to differentiate problems with instruction comprehension from DF deficits. Menon et al. (2004) reported impaired source memory in 31 patients with schizophrenia and no differences between delusional and non-delusional patients. They used an item version of the DF task with computerised stimulus presentation. The recognition procedure was similar to the study of Sonntag et al. (2003). Stimulus presentation differed from our paradigm in so far as the cue was shown with the stimulus still present, which makes a differential encoding strategy more likely than memory-related inhibition. The findings of all three DF studies in schizophrenia are converging; however, our task with computerised stimulus presentation in both parts and immediate recall provides better control of instruction comprehension and involved cognitive processes. If inhibitory processes in memory are partially disturbed in schizophrenia the question rises, whether this is part of a more general inhibition or memory deficit?

While several studies failed to show specific inhibition deficits in patients with schizophrenia using negative priming (Moritz et al. 2000; Roesch-Ely et al. 2003) or variants of the Stroop task (Fuentes et al. 2000; Henik et al. 2002), there is some similarity between our results and the findings of Waters et al. (2003), who found inhibitory deficits in patients with schizophrenia using the Inhibition of Currently Irrelevant Memories task, which has previously revealed specific inhibitory deficits in patients with medial orbitofrontal lesions and confabulations (Schnider and Ptak 1999). The DF task has the advantage to explicitly (and not only incidentally) investigate declarative memory and memory-related inhibitory processes. The computerised item-cued version of the DF task that we were using allows to study and to separate learning and forgetting processes; however, it does not allow disentangling different types of inhibitory processes in memory, i. e. at encoding or retrieval of TBR or TBF stimuli. Auditory hallucinations did not correlate with DF performance in our study. This is different from the study of Waters et al. (2003), who argued that patients might be distracted from memory processing by hallucinations.

The observed correlation of the DF effect with disease duration in our study can be regarded as a disease specific finding; however, neither DF nor other neurocognitive parameters were associated with symptom severity as measured by PANSS scales (Simon et al. 2003). Correlations with clinical and psychopathological parameters require further investigation in larger samples of patients in order to understand the relevance of memory related inhibition deficits in schizophrenia. Correlation of intrusion errors and age is in agreement with studies of DF in aging: Elderly subjects showed an increased rate of intrusion errors and a reduced DF effect in item-cued studies with words (Zacks et al. 1994; Andrés et al. 2004; Dulaney et al. 2004) and action descriptions (Earles and Kersten 2002). Prefrontal cognitive deficits in elderly subjects can be related to progressive degeneration of ascending dopamine neurons (Müller et al. 2000; Volkow et al. 2000; Kaasinen and Rinne 2002). In spite of highly interfering stimuli (categorically ordered nouns) the rates of intrusion errors were generally low in our study; this indicates that our subjects understood and followed the instruction of the study part.

The pattern of correlations between DF parameters and span tasks supports the view of a critical involvement of the prefrontal cortex in memory inhibition (Zacks and Hasher 1994; Conway and Fthenaki 2003). The lack of specific correlations with memory for TBF words does not contradict the idea of a special involvement of the right inferior prefrontal cortex in memory-related inhibitory processes (Aron et al. 2004). Further evidence from brain imaging studies is summarised to elucidate the neuronal mechanisms underlying DF processing that might be impaired in schizophrenia: Two brain mapping studies with event-related potentials (ERP) found differential effects of TBR and TBF words on regional brain activity. In subjects with efficient directed forgetting the "forget" cue resulted in an enhanced positive activity over the frontal cortex (Paz-Caballero et al. 2004) and in the recognition phase we found late right frontal activity differences after TBR as compared to TBF words; these effects were different from depth of processing differences and may indicate an involvement of the prefrontal cortex in retrieval inhibition (Ullsperger et al. 2000). Evidence for a specific involvement of the right inferolateral prefrontal cortex in memory inhibition comes from a recent event-related fMRI study that was using a "think/no-think" procedure (Anderson et al. 2004). Studies with fMRI have consistently shown an involvement of both hippocampal and prefrontal regions in impairments of declarative mem-

ory processes in patients with schizophrenia (Heckers et al. 1998; Barch et al. 2002; Hofer et al. 2003; Jessen et al. 2003; Weiss et al. 2003). Disturbances in the interaction between prefrontal and temporal mechanisms are essential for the frontotemporal disconnection hypothesis of schizophrenia (Friston 1999) and might be directly investigated in a future fMRI study with the DF task. Detailed neuronal correlates of DF and other inhibitory processes have to be investigated with further neuroimaging studies in healthy volunteers and patients.

In summary, using an item-cued and computerised variant of the DF task we found that memory-specific inhibition was less efficient in a group of medicated and clinically stable patients with schizophrenia. Deficits in the DF task might be related to dopaminergic abnormalities in the prefrontal cortex and frontotemporal disconnection. Further neuroimaging and pharmacological studies will help to elucidate cognitive processes and detailed neurobiological mechanisms involved in DF.

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