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

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 and working memory functions (Heinrichs and Zakzanis 1998; Johnson-Selridge 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. 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 permuted 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.