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Assessing a minimal executive operation in schizophrenia

Marie-Laure Grillon [a], Marcia K. Johnson [b], Jean-Marie Danion[c], Lydia Rizzo [c], Cécile Verdet [c], Caroline Huron [a,*]

[a] *INSERM 0117, Service Hopitalo-Universitaire de Santé Mentale et Thérapeuthique, Hôpital Sainte-Anne, Université Paris V, Paris, France*
[b] *Department of Psychology, Yale University, Box 208205, New Haven, CT 06520-8205, USA*
[c] *INSERM Unité 666, Clinique Psychiatrique, Hôpitaux Universitaires, Strasbourg, France*

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Abstract

The minimal cognitive operation of thinking of a just-seen stimulus (refreshing) was studied in 24 patients with schizophrenia and 24 normal controls. Verbal response times were measured when participants read a word, read a word immediately again, or refreshed a word just after it was no longer present. Patients showed equal priming as controls in reading a word for the second time and were slower than controls to say a word only in the refresh condition. On a surprise test, participants were asked to recognize the words they had seen previously and to give Remember, Know, or Guess responses according to whether they recognized words on the basis of conscious recollection, familiarity, or guessing. Although patients showed overall poorer recognition memory, the beneficial effect of refreshing on long-term memory accuracy and Remember responses was preserved, whereas they derived less benefit in familiarity from seeing an item twice than from refreshing it. These results suggest that although patients may have some difficulty engaging the refresh process, they show significant long-term memory benefits when induced to do so.

Keywords: Schizophrenia; Psychosis; Cognitive neuroscience; Memory

1. Introduction

Evidence of impaired frontally mediated executive processing in schizophrenia has been broadly reported (for reviews, see Keefe, 2000; Palmer and Heaton, 2000). For example, performance of patients with schizophrenia is disrupted in Wisconsin Card Sorting tasks (recent meta-analysis in Li, 2004), Stroop tasks (review in Perlstein et al., 1998), Tower tasks (e.g., Goldberg et al., 1990; Pantelis et al., 1997; Michel et al., 1998), n-back tasks (e.g., Carter et al., 1998; Glahn et al., 2005; Krieger et al., 2005) and dual tasks (e.g., Bressi et al., 1996; Salamé et al., 1998). On the whole, these tasks are relatively complex. Assuming that they require a combination of simple component processes, it is difficult to identify which specific component process(es) is (are) impaired in patients with schizophrenia when they perform a

* Corresponding author. INSERM 0117, Pavillon Broca, 2 ter rue d'Alésia, 75014 Paris, France. Tel.: +33 1 40 78 86 25; fax: +33 1 45 80 72 93.

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given complex task. For example, the Wisconsin Card Sorting Task minimally involves a combination of selecting one among the three stimulus dimensions (color, shape, or number) as a basis for the sorting rule, noting the common stimulus dimension between the target and the four reference cards to appropriately sort the target card, and updating the rule according the examiner feedback by either refreshing the rule or shifting to a new one to sort the next card. The n-back task involves rehearsing a set of n items, noting whether the current item is a match for the target item, dropping the oldest item and adding the current item to the rehearsal set, perhaps by refreshing it (i.e., updating). As Krieger et al. (2005) suggest, further specifying the component cognitive processes in such complex tasks that are and are not impaired in schizophrenia would be a useful next step.

To clarify the nature of the mechanisms that underlie executive dysfunction in schizophrenia, we have used a component process approach, in which executive functions are broken down into elementary mental operations. Within the Multiple-Entry-Modular memory (MEM) framework (Johnson, 1992; Johnson and Hirst, 1993), mental operations involved in executive processing are defined as reflective processes, which are internally generated, in contrast to perceptual processes, which are stimulus-driven. Reflective component processes include, for example, *refreshing* (thinking of a just-activated representation), *rehearsing* (recycling of information, typically more than one item), *reactivating* (reviving no-longer active representations in a relatively automatic way), and *retrieving* (reviving no-longer active representations through the self-generation of cues). These and other reflective processes are the component processes that can be recruited for strategic encoding of information (e.g., organizing).

The present study used a paradigm intended to engage the simplest reflective process, as characterized in the MEM framework, that is, *refreshing* just-activated information (Johnson et al., 2002). Patients with schizophrenia and controls read aloud as quickly as they could unrelated words presented one after another on a computer screen. Critical words were presented once (*read* condition), immediately repeated (*repeat* condition), or followed by a dot signaling the participants to think of the just-previous word and to say it again (*refresh* condition). Verbal response times were compared across conditions. This first phase was followed by a surprise recognition memory test in which previously presented words were randomly mixed with new words. Previous research has shown that refreshing benefits long-term old–new recognition memory in healthy young adults (Johnson et al., 2002). In the present study, in order to investigate phenomenal qualities associated with recognized items that had been only perceived or that had been refreshed, subjects were instructed to make a *remember* response if recognition was accompanied by the conscious recollection of some specific feature of the item's presentation (where it was, what they thought, etc.) and to make a *know* response if recognition was associated only with feelings of familiarity (Tulving, 1985; Gardiner et al., 1996). This remember-know procedure assesses differences in the qualities of memory, specifically whether a memory includes specific details from the original event (which participants should assign a "remember" rating) or is only a feeling of familiarity (which participants should assign a "know" response). The procedure has been previously used in patients with schizophrenia and found an impairment in remember but not in know responses (Huron et al., 1995; Danion et al., 1999; Huron and Danion, 2002; Huron et al., 2003).

Our main goal was to study whether a mental process as elementary as thinking briefly of a just-activated representation is impaired in schizophrenia. We hypothesized that schizophrenia might compromise even the most elementary reflective operations, in which case we should observe a disruption of refreshing (i.e., patients should be slower to refresh, less accurate, or both). This outcome would be evidence against the alternative possibility that executive dysfunction in schizophrenia occurs only under the more reflectively demanding conditions that typically have been studied (e.g., when multiple component processes must be combined, or a prepotent response must be overcome).

Our second goal was to investigate the impact of refreshing on long-term memory in patients. Indeed, patients with schizophrenia typically perform more poorly than normal subjects on long-term memory tests, particularly when the information to be encoded has to be organized in a strategic way. This suggests that long-term memory might be disproportionately impaired in schizophrenia as reflective processing demands increase. However, it has been shown that

differences between patients and controls are reduced when the experimenter specifies the cognitive operations that participants should perform at encoding to organize the information (Koh et al., 1976; Larsen and Fromholt, 1976; McClain, 1983; Harvey et al., 1986; Gold et al., 1992). This suggests that patients do not spontaneously initiate the appropriate reflective processing but can effectively use it when they are induced to engage it. Therefore, depending on whether patients have difficulty either engaging or executing the refreshing operation, two different hypotheses seemed reasonable about the impact of an impairment in refreshing on long-term memory. If patients are disrupted in engaging the refreshing operation but can execute it, we might expect that their memory performance benefits from refreshing to the same extent as controls. In contrast, if patients are disrupted in executing the refreshing operation (i.e., the refresh operation is less effective), their long-term memory performance might benefit less from refreshing compared with controls.

2. Methods

2.1. Subjects

Twenty-four French-speaking patients (16 men, 8 women) comprising 20 outpatients and four inpatients participated in the study. Their mean age was 34.1 (S.D.=6.5) years, and their mean educational level was 10.9 (S.D.=2.5) years. Their mean duration of illness was 9.8 years (S.D.=6.1), their mean total duration of hospitalization was 15.0 weeks (S.D.=16.2), and their mean number of hospitalizations was 2.9 (S.D.=2.6). All patients fulfilled the DSM-IV criteria for chronic schizophrenia as determined by consensus of the current treating psychiatrist and two senior psychiatrists belonging to the research team. Global psychiatric symptoms were assessed by means of the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham, 1962, mean score=44.52, S.D.=14.17) and positive and negative symptoms were measured by the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987, mean score=68.20, S.D.=21.84). Patients with histories of traumatic brain injury, epilepsy, alcohol and substance abuse, or other diagnosed neurological conditions were excluded from the study. All patients were clinically stabilized. Twenty-three patients were on maintenance antipsychotic medication (13 on conventional neuroleptics, and 10 on atypical antipsychotics), administered in a standard dose (mean chlorpromazine-equivalent dose=310±112 mg per day, 241 mg and 400 mg for conventional neuroleptics and atypical antipsychotics, respectively), and combined with an anti-Parkinsonian treatment for five patients. One patient was not receiving any medication. Patients treated with antidepressants, benzodiazepines or mood stabilisers were excluded.

The comparison group comprised 24 normal subjects (16 men, 8 women) matched with the 24 patients for sex, age, and educational level. The normal subjects had no history of alcoholism, drug abuse, or neurological or psychiatric illness and did not take any drugs. Their mean age was 33.2 (S.D.=6.5) years, and their mean educational level was 10.8 (S.D.=2.4) years. The groups did not differ significantly in age ($F=0.24$, $df=1, 46$, $P=.63$) or education ($F=0.08$, $df=1, 46$, $P=0.77$). The mean intelligence quotient (IQ) as assessed with a short form of the Wechsler Adult Intelligence Scale-Revised (Crawford et al., 1992) was significantly lower in patients ($m=92.8$, S.D.=17.8) than in control subjects ($m=104.5$, S.D.=13.4, $F=6.61$, $df=1, 46$, $P<0.01$).

The protocol was approved by the ethical committee of Strasbourg. All participants provided informed written consent after the procedure had been fully explained.

2.2. Materials

A set of 180 common French two-syllable nouns, each between 4 and 10 letters in length, with a mean word frequency of 46.24 per million and a neutral affective value, was selected from the Brulex database. This word set was randomly divided into five subsets of 36 items each, which did not differ in mean word frequency or mean number of letters ($F<1$). Each subset was presented equally often in each experimental condition of the first phase and as new words in the recognition task.

2.3. Procedure

During phase 1, stimuli were displayed on a computer screen at a 2.5-s rate (2 s on, 0.5 s inter-

stimulus interval). In each of the 108 trials, participants read a first word aloud. This word disappeared and was either followed by a new word in the read condition (36 trials), by the same word in the repeat condition (36 trials), or by a dot (•) that signalled participants to think of the word that preceded the dot and to say it aloud in the refresh condition (36 trials). Therefore, the number of responses given by participants was equal across conditions, but each read trial involved two different words whereas repeat and refresh trials involved a single word, either presented twice or presented once and refreshed once. Read, refresh and repeat trials were pseudo-randomly mixed. All participants received exactly the same instructions. They were asked to say aloud the words as fast as possible without being explicitly instructed to be accurate. They were not informed of the subsequent recognition test. Response times were collected via a voice key. Responses were also recorded on audiotape; trials in which the voice key was triggered by erroneous responses, coughs, or other extraneous sounds were discarded. The mean proportions of responses omitted for patients with schizophrenia and control subjects were, respectively, 0.01 and 0.00 on first presentation of any item and 0.01 and 0.00 on the critical (read, repeat, refresh) items.

During a 15-min interval separating phases 1 and 2, subjects were given a set of oral and then typed instructions regarding the general test procedure, and Remember, Know and Guess responses. The instructions were closely based on those of Gardiner et al. (1996). A Remember response was defined as conscious awareness of some aspect of what had happened or had been experienced when the word was presented. Examples included an association with another list word, an image that came to mind, something about the physical appearance or the position of the word, something of personal significance in autobiographical memory, or something that had happened in the room. A Know response was described as the knowledge that an item had appeared in the study list but without any conscious recollection, the recognition being based primarily on feelings of familiarity. A Guess response corresponded to words that elicited neither the experience of remembering nor of knowing, but that might have appeared during the learning phase. The subjects were then asked to read the typed instructions carefully. They were informed that they could refer to the typed instructions during the test phase as often as they needed to. Before the test phase, all subjects received a practice test to check whether they had correctly understood the instructions and to familiarise them with the general test procedure. The subjects were tested on six words that had been presented just before phase 1, randomly intermixed with six new words. Subjects were asked to explain their responses.

Phase 2 was a recognition task consisting of 180 items (the 144 items[1] presented in phase 1 and 36 completely new items) presented in a different random order for each subject. Each word on the test list appeared on the screen until the subjects pressed the button for a Yes response if they recognized the word as having occurred during the learning phase or a No response if they did not recognize the word. If the response was Yes, the subjects then pressed one of three other buttons labelled Remember, Know and Guess. Then the next word appeared. If the response was No, the next word appeared immediately.

As in Johnson et al. (2002), a control experiment was conducted in a subsequent session to assess whether the performance of patients with schizophrenia was disrupted by the need to switch from reading words to responding to a symbol. All subjects performed this task. The procedure was exactly the same as in phase 1 of the previous task except that the refresh condition, in which a dot (•) signalled subjects to say a previously seen word, was replaced with a plus condition in which subjects were asked to respond 'plus' whenever the + appeared. Four new lists of 36 words with the same characteristics as those used in the previous task were used.

2.4. Data analysis

Mean response times for phase 1 and corrected recognition scores (hits minus false alarms) for phase 2 computed separately for read, repeat, and refresh

[1] The items comprised 72 words from the read trials, 36 words from the repeat trials, and 36 words from the refresh trials. The recognition data presented here are for the 36 target words from the read trials corresponding to those from repeat and refresh trials. (Performance of the two sets of read items did not differ significantly.)

conditions were normally distributed. These scores were subjected to an analysis of variance (ANOVA) with repeated measures with group (patients with schizophrenia versus controls) as a between-subjects factor, and condition of presentation (read, repeat, refresh) as a within-subject factor. For the control task, a similar analysis was conducted on mean response times with read, repeat and plus as conditions of presentation. The results on the control task provided no evidence of an impaired ability to respond to a symbolic cue in response times of the patients with schizophrenia on the plus trials relative to the read trials; that is, there was no interaction between group and condition ($F=1.16$, $df=2,92$, $P=0.30$). Thus, the control task is not further discussed.

To investigate the experience associated with recognition memory, proportions of Remember, Know and Guess responses were calculated separately for each type of item condition (read [presented once], repeated, refreshed) by dividing the number of responses given by the number of trials in this condition ($n=36$). Corrected proportions were obtained by subtracting the proportion of false recognitions of new items from the proportion of correct recognitions of critical items. These proportions were subjected to an ANOVA with group (patients with schizophrenia versus controls) as a between-subjects factor, and condition of presentation (read, repeat, refresh) and response type (remember, know, and guess) as within-subject factors. Whenever the result of an interaction was significant, post-hoc analyses (Fisher LSD) were carried out to localize differences. In the group of patients with schizophrenia, correlations were calculated between task performance (response times, recognition scores), on the one hand, and measures of psychiatric symptoms and dose of neuroleptic and anticholinergic drugs, on the other. The alpha level was set at $P<0.05$.

3. Results

3.1. Phase 1

Neither patients nor controls made any errors in Phase 1. Fig. 1 shows the time to say words in Phase 1. An ANOVA carried out on mean response times resulted in a group effect ($F=10.59$, $df=1$, 46, $P<0.01$), a condition effect ($F=59.6$, $df=2$, 92, $P<0.01$), and a significant interaction between group and condition ($F=3.54$, $df=2$, 92, $P<0.04$). Both patients with schizophrenia and controls read a word faster if they had read it before ($ts>6.20$, $Ps<0.001$). This repetition priming effect was of similar magnitude in both groups: 82 and 89 ms in patients and controls, respectively. In addition, although the mean response times were not significantly different between groups in the read or repeat

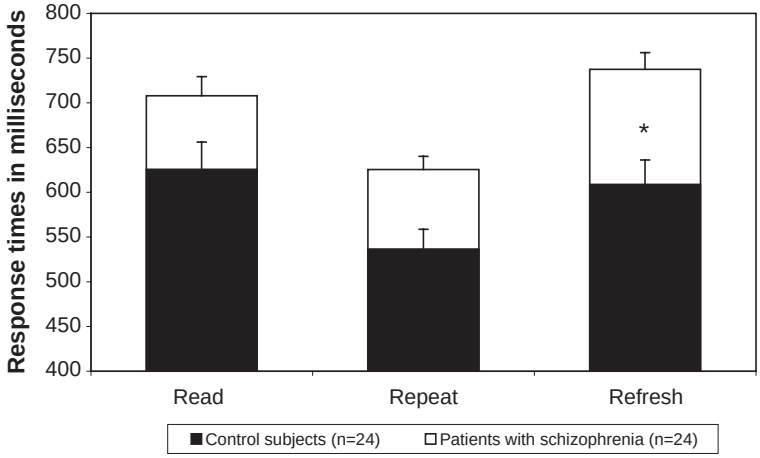

Fig. 1. Phase 1 response times in patients with schizophrenia and control subjects on read, repeat, and refresh trials. Bars indicate standard errors. *Significant difference between patients with schizophrenia and control subjects, $P<0.05$.

conditions ($t_s < 1.67$, $P_s > 0.10$), patients with schizophrenia were significantly slower than controls to say the previously presented word on refresh trials ($t = 2.42$, $P < 0.02$). Patients with schizophrenia were slower to refresh than to read a word ($t = 2.21$, $P = 0.03$) whereas, in controls, the mean response times did not differ between refresh and read conditions ($t = 1.27$, $P = 0.21$).

In addition to the control experiment previously described, we conducted an analysis of the main experimental data to assess whether an impaired ability to alternate between two tasks might account for the results. The task switches between the read and repeat conditions, in which participants are required to read a word, and the refresh condition, in which participants are instructed to say a word in response to a dot. We compared the mean response time between the switch trials when alternating between two tasks and the no switch trials when performing the same task twice in succession (see, for instance, Meiran et al., 2000, for similar analyses). Thus, the time to say a word in response to a dot was compared between refresh trials that were preceded by a read or repeat trial (a switching condition, mean number = 12.2 among 16 trials) and refresh trials that were preceded by another refresh trial (a no switching condition, mean number = 3.8 among 16 trials). An ANOVA carried out on mean response times showed a group effect ($F = 11{,}74$, $df = 1$, 46, $P = 0.001$), but no condition (switching versus no switching) effect and no interaction between group and condition ($F_s < 2.36$, $P_s > 0.13$). These results argue against a task-switching cost in the present paradigm: neither patients nor controls were slower in a switching condition (mean RT = 736 ms and 605 ms, for patients and controls, respectively) than in a no switching condition (mean RT = 772 ms and 627 ms for patients and controls, respectively).

3.2. Recognition memory task

3.2.1. Overall recognition performance

An ANOVA carried out on corrected recognition scores showed a significant group effect ($F = 15.29$, $df = 1$, 46, $P < 0.001$) and a significant condition effect ($F = 13.73$, $df = 2$, 92, $P < 0.0001$), but no interaction between group and condition ($F = 0.69$, $df = 2$, 92, $P = 0.50$). The pattern of results was exactly the same when uncorrected recognition scores, d′, and A′ values were used in the analyses. The main group effect indicated that, overall, patients with schizophrenia recognized fewer words than controls. The main condition effect together with the lack of a significant interaction indicated that despite their lower recognition performance, patients with schizophrenia benefited from refreshing an item in comparison with reading it, as did controls. This improvement of performance occurred to the same extent in both groups — the mean recognition score of refreshed items minus the mean recognition score of read items was 0.06 for patients with schizophrenia and 0.07 for controls ($t = 0.34$, $P = 0.73$) (Table 1).

3.2.2. Phenomenal experience: remember, know, and guess responses

An ANOVA on proportions of remember, know, and guess responses showed that all main effects were significant ($F_s > 13.25$, $P_s < 0.003$), and there was a

Table 1
Mean (SD) proportions of yes, remember, know, guess responses to read, repeat, refresh, and new words in patients with schizophrenia and control subjects

Word type	Patients with schizophrenia ($n = 24$)				Control subjects ($n = 24$)			
	Yes	Remember	Know	Guess	Yes	Remember	Know	Guess
Read	0.59 (0.19)	0.19 (0.16)	0.23 (0.18)	0.17 (0.13)	0.71 (0.11)	0.29 (0.19)	0.31 (0.21)	0.11 (0.09)
Repeat	0.61 (0.19)	0.27* (0.21)	0.21# (0.13)	0.13* (0.10)	0.76 (0.09)	0.34* (0.22)	0.35 (0.23)	0.07* (0.06)
Refresh	0.64 (0.21)	0.25* (0.22)	0.27# (0.16)	0.12* (0.11)	0.78 (0.10)	0.37* (0.24)	0.33 (0.23)	0.08* (0.10)
New	0.19 (0.20)	0.02 (0.03)	0.07 (0.09)	0.10 (0.11)	0.15 (0.10)	0.03 (0.05)	0.06 (0.06)	0.06 (0.06)

*Significant differences ($P < 0.05$) in responses for repeated and refreshed words in comparison with responses for read words.
#Significant difference ($P < 0.05$) between repeated and refreshed words.

significant interaction between condition and response type ($F=9.41$, $df=2, 92$, $P<.001$), and between condition, response type and group ($F=2.54$, $df=4, 184$, $P<0.04$). These interactions indicated that the pattern of remember, know and guess responses varied across condition and between groups. Separate analyses were conducted for remember, know, and guess responses to clarify the results (Table 1).

For remember responses, an ANOVA on corrected scores resulted in a condition effect ($F=18.13$, $df=2, 92$, $P<0.0001$), no significant group effect ($F=2.11$, $df=1, 46$, $P=0.15$), and no interaction between group and condition ($F=1.31$, $df=2, 92$, $P=0.27$). Both groups reported more remember responses for words that were repeated or refreshed than presented once ($ts>2.72$, $Ps<0.008$). These results indicated that conscious recollection as measured by remember responses benefited as much from experiencing a word twice versus once for patients with schizophrenia as for controls.

An ANOVA carried out on know responses revealed no significant main effect ($F_s<3.36$, $P_s>0.07$), but a significant interaction between group and condition ($F=5.09$, $df=2, 92$, $P<0.008$). This interaction was due to the fact that patients with schizophrenia assigned fewer know responses to repeated than refreshed words ($t=-3.27$, $P=0.001$), whereas controls did not ($t=0.90$, $P=0.37$)[2].

As in the analysis on remember responses, the ANOVA on corrected proportions of guess responses showed a condition effect ($F=6.76$, $df=2, 92$, $P<0.002$), but no group effect ($F=0.08$, $df=1, 46$, $P=0.78$), and no significant interaction between condition and group ($F=0.19$, $df=2, 92$, $P=0.83$). Both patients and controls reported more guess responses for words that were presented once than for words that were repeated or refreshed ($ts>2.03$, $Ps<0.05$).

As indicated by these separate ANOVAs, the interaction between condition, response type and group observed in the global analysis can be attributed to the fact that repeating and refreshing a word had the same effect in patients and controls for remember, but not know responses.

[2] Separate analyses of variance for patients with schizophrenia and for control subjects on know responses showed a condition effect in patients ($F=5.93$, $df=2,46$, $P=0.005$) but not in controls ($F=2.19$, $df=2, 46$, $P=0.12$).

3.3. Secondary analyses

Patients were matched with normal subjects for sex, age, and education level, but not for IQ. This raises the question of whether the pattern of results observed in patients is related to IQ. To investigate this issue, we excluded from the analysis the three patients with an IQ lower than 70 and the three normal subjects with an IQ higher than 130. Secondary analyses were carried out on a subgroup of 21 patients whose IQ (mean=96.81, S.D.=14.98) was not statistically different from that of 21 comparison subjects (mean=100.71, S.D.=9.37; $t=1.01$, $P=0.32$). They displayed exactly the same results as those carried out on the whole group for both the mean response times and the recognition scores. This indicates that the difference in response pattern of the whole group of patients compared with the controls was not the consequence of differences in IQ.

Response times and recognition memory performance were neither significantly correlated with measures of psychiatric symptoms from the BPRS and PANSS, nor with drug dose ($Ps>0.38$). In addition, when patients taking anticholinergic drugs were excluded, the pattern of response times and recognition scores was unchanged.

4. Discussion

Patients with schizophrenia, although they were equally accurate in refreshing the correct word on refresh trials, were disproportionately slower to refresh a word than controls. This deficit occurred under conditions in which patients with schizophrenia were not significantly slower than controls to read words presented once, suggesting that their longer response times in the refresh condition were not simply due to a general slowness or inattention to the task but at least in part to a specific disruption of refreshing. Furthermore, patients said aloud the same word twice on both repeat and refresh trials, but whereas they were slower to refresh than to read, they were faster to repeat than to read. Therefore, their slowness on refresh trials was not due to the fact that they had to say the same item twice. Evidence that the refresh impairment was not due to an impaired ability to respond to a symbolic stimulus mixed in with words

and used as a cue was provided by the absence of impairment of patients with schizophrenia when they had to say "plus" whenever the symbol "+" occurred. It could be argued that because people may be used to translating "+" to "plus," this condition is not the best control for the ability to respond to a symbolic cue. However, although easy, it does require a switch from the ongoing task of translating letters into words. Moreover, a comparison between refresh trials following refresh trials and refresh trials following read and repeat trials did not show any evidence that task switching was a significant factor in this procedure for either controls or patients with schizophrenia. This finding argues against the idea that the increase in the response times in the refresh condition was due to an impaired task-switching ability in patients with schizophrenia (see also Meiran et al., 2000; Barton et al., 2002; Manoach et al., 2002). Of course, patients might show an impairment in task switching under more demanding conditions.

The issue of speed/accuracy trade-off is also relevant for interpreting response-time measures in between-group comparisons (see Salthouse and Hedden, 2002, for a discussion of this point). In contrast with typical instructions in response-time tasks, participants of our study were required to respond as rapidly as possible, but they were not explicitly told to be accurate. It cannot be ruled out that the responses of patients might have been slower because they were more cautious than controls in trying to avoid errors. However, because saying a just-seen word aloud is an easy task as reflected by the absence of errors in both groups, it seems unlikely that patients were induced by the task to be especially cautious as they might be for more complex response-time tasks. Last, since all patients but one were receiving medication at the time of testing, it could be asked whether drug treatment may have contributed to the refresh deficit. Although a potential effect of medication on performance cannot be rejected, the fact that drug dosage was not significantly related to response times argues against this interpretation. It could be argued that the relatively small sample size limits the weight of this result. However, previous findings suggest that antipsychotic drugs alone cannot account for cognitive impairments of patients with schizophrenia. For instance, cognitive deficits occur before illness onset (Jones et al., 1994; Cornblatt and Keilp, 1994) and in first episode patients with schizophrenia who have never been exposed to medication (Saykin et al., 1994; Hoff et al., 1992) and have also been observed in unaffected siblings (Egan et al., 2001; Saoud et al., 2000). In short, the results of the present study clearly showed that an elementary reflective operation, useful for maintaining or foregrounding just activated information, was disproportionately slower in schizophrenia.

Using functional magnetic resonance imaging (fMRI) to investigate the brain regions underlying the refresh process in young adults, Raye et al. (2002) showed that refreshing was associated with increased refresh-related activity in left dorsolateral prefrontal cortex (PFC) (middle frontal gyrus, BA9). Interestingly, a number of studies suggest a disturbance in the activation of dorsolateral regions of the PFC in patients with schizophrenia (Berman et al., 1986; Weinberger et al., 1986; Weinberger et al., 1988; Andreasen et al., 1992; Berman et al., 1992; Weinberger and Berman, 1996; Volz et al., 1997; Callicott et al., 1998; Carter et al., 1998a; Manoach et al., 1999; Callicott et al., 2000; Barch et al., 2001; Menon et al., 2001; Perlstein et al., 2001), although other regions of PFC are also sometimes disturbed (Weinberger et al., 1986; Weinberger et al., 1988; Weinberger and Berman, 1996; Volz et al., 1997; Stevens et al., 1998). These two sets of findings, those that associate refreshing with activity in dorsolalteral PFC in normal participants and those that show disruptions in dorsolateral PFC in schizophrenia, are consistent with the refresh deficit that we observe in our behavioural study of patients with schizophrenia. Additional neuroimaging studies using a procedure similar to the one in the present study would provide direct information about the brain regions implicated in the disproportionately slower response times for refreshing observed in the present study in patients with schizophrenia. Two hypotheses are plausible: patients might either recruit new regions for refreshing that are not engaged by normal subjects or use the same regions less efficiently (e.g., there is some evidence for the latter in older adults, Johnson et al., 2004).

Interestingly, the effect of the refresh operation on long-term memory was preserved in schizophrenia: patients' long-term recognition memory benefited to the same extent as controls from refreshing a word. In addition, the pattern of remember, know and guess

responses did not differ between patients with schizophrenia and controls for the items that had been refreshed. These findings suggest that requiring patients to engage in a specific reflective process such as refreshing during the encoding phase might be a way to improve memory performance and to normalize phenomenal experience associated with recognition in schizophrenia. Previous evidence indicates that episodic memory deficits of patients with schizophrenia are reduced when some control is exercised over the encoding operations to be performed (Koh et al., 1976; Koh and Peterson, 1978; McClain, 1983; Gold et al., 1992) and that patients show a preserved level of processing effect: as is seen in normal subjects, recognition memory of patients is better for information that undergoes deep (i.e., conceptual) versus shallow (i.e., perceptual) processing (e.g., Ragland et al., 2003; Paul et al., 2005). The present results extend these findings by demonstrating that in patients, as in controls, an improvement in recognition-memory performance resulting from engaging in a simple encoding task (refreshing) is associated with a higher level of remember responses. Nevertheless, even if long-term memory benefited from refreshing to the same extent in patients as in controls, which suggests that patients might be impaired in engaging rather than executing the refresh process, the overall recognition performance was lower in patients. Presumably, this difference reflected uncontrolled processing differences between groups. Processing differences might occur at encoding, perhaps especially, as discussed below, on stimulus displays where the item was perceptually present. However, an impairment of processes involved in the consolidation, storage or retrieval phases cannot be ruled out.

Although the levels of remember responses were consistently lower in patients than in controls, these differences were not statistically significant. In contrast, previous studies have found significant decreases in remember responses of patients with schizophrenia (Huron et al., 1995; Danion et al., 1999; Huron and Danion, 2002; Huron et al., 2003). However, experimental conditions of the present study were quite different from those of previous studies that used the remember/know procedure in patients with schizophrenia. In particular, the present study is the only one to use incidental learning and such short presentation times at encoding (2 versus 5 s). Both intentional learning and long encoding times increase the chance that participants, particularly controls, will use organizational strategies, involving combinations of different component processes, in order to memorize the items-to-be-learned. Patients with schizophrenia might fail to spontaneously engage in such strategies. In the present study, increasing control over the processes engaged in by both patients and controls might have reduced the advantage of controls in conscious recollection as measured by remember responses.

Patients with schizophrenia showed a preserved repetition priming effect: patients, to the same extent as controls, read words faster when they were presented for the second time. These results extend previous findings that schizophrenia does not impair performance on implicit memory tasks for which subjects are not required to retrieve material consciously (e.g., Gras-Vincendon et al., 1994). Although the repetition priming effect was intact in schizophrenia, the effect of repetition on long-term memory was impaired: patients, in contrast with controls, derived less benefit from seeing an item twice than from refreshing it. Neuroimaging data could provide information about the mechanisms underlying this decrease in familiarity. For example, patients may show less activation in visual areas than controls, suggesting less sustained attention to the visual stimuli (enough to result in preserved repetition priming, but not to increment a conscious sense of familiarity). Or patients and controls may show equal activation in visual areas, but patients may show less activation in medial temporal regions associated with familiarity (e.g., Davachi et al., 2003).

The present study showed that patients with schizophrenia were impaired in refreshing (i.e., they were slower to think of a just-activated representation). Refreshing is a basic building block of executive function (e.g., Raye et al., under review) and any impairment in it is likely to result in deficits in a wide range of cognitive tasks. Further studies would be useful to determine whether other reflective operations (e.g., rehearsing, reactivating, noting relations) are disrupted in schizophrenia. Patients might be impaired in engaging some reflective processes, such as refreshing, whereas other reflective operations may be intact. In this case, identifying impaired and spared reflective processes will be critical for devel-

oping new therapeutic approaches targeted at remediating disrupted processes or exploiting spared processes. Alternatively, an impairment of control mechanisms that engage and/or monitor other reflective processes (Johnson, 1992; Johnson and Reeder, 1997) might affect all of them and not just a specific reflective operation.

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