Familiarity and recollection processes in patients with recent-onset schizophrenia and their unaffected parents

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Abstract

Episodic memory deficits are present in patients with schizophrenia (SZ) and their unaffected relatives and could be considered as a cognitive indicator of genetic vulnerability to SZ. The present study, involving patients with SZ as well as their parents, used experimental tasks specifically designed to disentangle the contribution of familiarity and recollection processes to episodic memory. The performance of patients with SZ ($n=26$) and their unaffected parents ($n=35$) was compared with that of healthy control groups matched on socio-demographic variables (controls of patients, $n=26$; controls of parents, $n=35$) on two memory tasks assessing recollection and familiarity. The first task was designed to investigate item recognition and memory for item-spatial context associations whereas the second targeted item-item associations. The results revealed an overall episodic memory deficit in patients with SZ, encompassing both familiarity and recollection, while unaffected parents showed a dysfunction restricted to the recollection process. Our study highlights differences and similarities in the source of the episodic memory deficit found in patients with SZ and their unaffected parents, and it suggests that recollection could act as a cognitive endophenotype of SZ. The results also suggest that use of experimental tasks represents a promising method in the search of cognitive endophenotypes in SZ.

Keywords

Episodic memory; Binding; Endophenotype; Relatives; Genetic epidemiology

1. Introduction

The identification of susceptibility genes for schizophrenia (SZ) has been complicated by the role of environmental factors, the genetic heterogeneity of SZ and its polygenic transmission. Endophenotypes, which are defined as measurable traits related to an illness (e.g. biochemical, neuroanatomical, or cognitive), can be helpful in identifying susceptibility genes because they are thought to possess a simpler genetic etiology than SZ (Cannon, 2005). According to the Consortium on the Genetics of Schizophrenia, the key cognitive

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functions of attention, working memory and episodic memory meet the criteria for selecting an endophenotype (Gur et al., 2007; for criteria, see Gottesman and Gould, 2003). Among these potential candidate endophenotypes, episodic memory — memory for personally experienced events that are embedded in a particular spatial and temporal context (see Tulving, 1985) — may be particularly promising because it is the cognitive process that is most impaired both in patients with SZ (Saykin et al., 1991; Heinrichs and Zakzanis, 1998) and in their unaffected relatives (Sitskoorn et al., 2004; Maziade et al., 2009).

Episodic memory can be assessed via recall or recognition tasks, both of which involve an encoding phase but differ in the level of support provided at retrieval. There are two well-established theories of recognition. First, the dual-process model holds that performance on recognition tasks reflects two distinct processes, namely recollection and familiarity (Atkinson et al., 1973; Tulving, 1985; Jacoby, 1991; Mandler, 1991; Yonelinas, 1994). *Recollection* refers to the retrieval of specific information about an event while *familiarity* reflects an appraisal of perceptual similarity with something previously encountered. For example, familiarity would support the recognition of someone previously met, but without conscious recollection it is not possible to know who this person is, and when and where this person was met. In an experimental context, recollection is assumed to support recall, in addition, of recognition judgment about the association between different elements (e.g. item-item associations), different aspects of an event (e.g. item-temporal, spatial or physical context associations) or reality monitoring (i.e. attribution of a memory to an internal source — someone else). In contrast, familiarity is sufficient to judge whether the target information was previously encountered. Familiarity seems to be an automatic memory process requiring less cognitive resource than recollection and individuals would resort to familiarity as a backup process whenever recollection fails (see Yonelinas, 1994). The alternative view, referred to as the signal detection model, states that recognition memory is based on the strength of a memory signal in relation to a decision criterion. Whereas an earlier version of this model stated that familiarity is sufficient to make a judgment about the previous occurrence of a stimulus (high-threshold theory), a more recent version holds that the memory strength consists of the additive combination of familiarity and recollection (unequal-variance signal-detection model [UVSD]; for a discussion, see Wixted, 2007). Whereas the UVSD model seems to adequately predict performance in many circumstances, a considerable body of evidence demonstrates that familiarity and recollection are differentially affected by some experimental manipulations supporting the assumption that these processes are distinct and dissociable (for a discussion, see Yonelinas, 2002; Diana et al., 2006).

Huron and his collaborators (Huron et al., 1995) were among the first to experimentally investigate recollection and familiarity processes in SZ using the remembered-know procedure designed by Tulving (1985). Typically, participants are required to give a “remember” response when recognition is accompanied by a rich memory representation (e.g. including spatial, temporal, perceptual or affective information). Alternatively, participants give a “know” response if recognition is based on a “feeling-of-knowing” state, without recollection. A majority of the studies using this paradigm found that impaired recognition performance in patients with SZ was associated with a reduced level of “remember” responses, and therefore that performance was largely based on familiarity

(Huron et al., 1995; Danion et al., 1999; van Erp et al., 2008; for a discussion, see Danion et al., 2007). Item and associative recognition tasks are also commonly used in combination to circumscribe the defective processes underlying episodic memory deficits (familiarity and/or recollection). For example, an *item recognition task* requires distinguishing between old items (items previously studied) and new items (items never previously studied). In such a task, recollection will lead to correctly recognizing the old items, but familiarity can also be useful because only the old items are familiar. An *associative recognition task* requires distinguishing between intact and rearranged associations. Here, all the items are familiar so the judgment about the association can only be based on recollection. In sum, associative recognition can only be supported by recollection, whereas both processes can be useful for item recognition. Thus, a lower performance on both item and associative recognition tasks would suggest that recollection as well as familiarity processes are affected in SZ, while a deficit limited to the associative recognition task would indicate a selective impairment of the recollection process. Meta-analyses of studies of recognition memory (item and associative recognition tasks) revealed that people with SZ have impaired performance on both tasks (Achim and Lepage, 2003; Pelletier et al., 2005). The recollection deficit could be a potential endophenotype of SZ, as it has been found in adolescents with psychosis, in prepsychotic patients, in remitted and acutely ill patients (with and without auditory hallucinations) but also in unaffected first-degree relatives (Bartok et al., 2005; Waters et al., 2006; Brunelin et al., 2007; Doré et al., 2007). In accordance with many studies on memory function in unaffected relatives, the performance of relatives on the task tapping the recollection process is intermediate between that of healthy controls and that of patients with SZ (Whyte et al., 2005; Trandafir et al., 2006).

The main objective of our study was to determine whether deficits in recollection, familiarity, or both underlie the episodic memory dysfunction found in patients with SZ and their unaffected parents. We used two experimental tasks, each assessing different types of association, namely item-item associations and item-spatial context associations. In line with the aforementioned results on item and associative recognition in SZ, we expected a significant impairment on both recollection and familiarity processes in patients with recent-onset SZ. A deficit of smaller magnitude and restricted to the recollection process was expected in unaffected relatives. To our knowledge, this is the first study to simultaneously examine recollection and familiarity processes within the same experiment in patients as well as their unaffected first-degree relatives. Also, the present study allows us to establish whether the recollection deficit is generalized or restricted to specific types of associations. Finally, the combination of experimental tasks targeting precise cognitive processes along with the inclusion of a group of unaffected relatives, giving access to the genetic vulnerability to SZ without the confounding factors usually related to the illness, will increase the specificity of an eventual deficit.

2. Method

2.1. Participants

Our clinical sample included 26 recent-onset (i.e. <5 years since the first contact with psychiatric services) and clinically stabilized patients meeting DSM-IV criteria for SZ

($n=22$) or SZ spectrum psychotic disorders¹ (schizophreniform disorder, $n=3$; delusional disorder, $n=1$). All patients were taking a second-generation antipsychotic as their primary medication (see Table 1 for socio-demographic and clinical characteristics of the samples). Thirty-five of their unaffected parents were included in the study (for 9 patients, both parents agreed to participate). Patients were recruited from the Clinique Notre-Dame des Victoires (affiliated to the Centre Hospitalier Robert-Giffard, Québec city), which receives patients with recent-onset psychotic disorders. The comparison group comprised 26 participants individually matched for age and gender to the patients and 35 individuals matched for gender, age and education level to the parents. The healthy control groups were recruited through advertisements in local newspapers, dental and medical offices. The local ethics committee approved this study. All participants provided their written informed consent after a detailed description of the research protocol and were compensated for study participation.

Exclusion criteria for all participants were (1) a history of alcohol or substance abuse/dependence in the 6 months preceding the study, (2) a history of a neurological illness, (3) a history of a head injury with a loss of consciousness greater than 5 min, (4) current use of benzodiazepine medication on a daily basis, (5) IQ lower than 70, and (6) age less than 18 or greater than 60 years. In addition, we excluded controls and parents with a personal history of psychotic or bipolar disorder, as assessed with the Structured Clinical Interview for DSM-IV (SCID) or with a cluster A Axis II disorder (paranoid, schizoid or schizotypal personality) as assessed with the SCID-II-Q. We excluded controls if such a diagnosis was suspected in any of their first-degree relatives.

2.2. Clinical measures and IQ estimation

The severity of symptoms was rated by psychiatrists using the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987). IQ was estimated with the vocabulary, and Block Design subtests of the Wechsler Adult Intelligence Scale (WAIS-III, see Jeyakumar et al., 2004).

2.3. Experimental procedure

Two experimental tasks were specifically designed to disentangle the contribution of familiarity and recollection processes to the episodic memory deficit. The first task targeted item-spatial context association whereas the second examined item-item association.

2.3.1. The item-spatial context association task (first task)—This task included two parts, each starting with an encoding session followed by a recognition session (similar to the one used in Rizzo et al., 1996). The first part assessed memory for individual items and the second part assessed associative memory. A schematic representation of this task is presented in Fig. 1.

2.3.1.1. Material and procedure: Three lists of 30 six-letter long infrequently used French words (printed frequency of 5, 6 or 7 per million, see Baudot, 1992) were formed. Words were randomly presented on a grid of 72 rectangles (9×8). A computer controlled the

¹These disorders are manifestations of the same underlying genetic vulnerability (Kendler et al., 1995).

selection of words and locations with the requirement that the selected locations be spaced by a minimum of three rectangles within each recognition trial.

For the first part (*item recognition*), the 30 words from the first list were presented in different locations on the grid. Each word appeared on the screen for 2 s and was followed by another word from the same list 3 s later (inter-stimulus interval (ISI)= 5 s). Participants were instructed to read aloud and remember each word. After a retention interval of 5 min, a self-paced (i.e. without temporal limit) three-alternative forced-choice recognition test was used to evaluate item recognition. For each of the 10 item-recognition trials, a previously learned word (target) was presented along with two new words (lures) drawn from the second 30-word list and participants had to indicate which word has been presented previously. Participants could answer on the basis of a rich memory representation of the target item (recollection) or on a feeling-of-knowing state (familiarity).

During the second part (*associative recognition*), the 30 words belonging to the third list were shown the same way as in the first part. Participants were instructed to read aloud and memorize the words and their location on the grid. Two test phases (also self-paced) whose sequence was counterbalanced between participants followed after a 5-min retention interval. In the first test phase, termed “*location task*”, 10 series of three words (all 30 words from the encoding phase) were presented below the grid simultaneously with one location in the grid being colored in black. Participants had to indicate which of the three words was in this location during the study phase. The three words were equally familiar because all had been seen during the study phase, so participants could only answer on the basis of their ability to associate the word with its location in the grid (*recollection*). In the second test phase, called the “*relocation task*”, 10 series of three black rectangles were shown in the grid simultaneously with one word below the grid. Participants had to indicate which rectangle was occupied by the word during the study phase. Here, only the correct location was familiar to the participants, as the two others had never contained any word during the study phase. Consequently, participants could answer on the basis of the association between the word and its location (*recollection*), but if this association could not be remembered, they could resort to *familiarity* with one location over the other two locations.

2.3.2. The item-item association task (second task)—This task was inspired by the well-established pair learning task (e.g. Kelley and Wixted, 2001). In addition to assessing episodic memory and its underlying processes, this task allows examining whether decisions are biased, that is, if participants respond either ‘old’ or ‘new’ in a systematic manner (liberal vs. conservative decision criterion).

2.3.2.1. Material and procedure: Stimuli were 160 words of four to eight letters. The words had high imagery ratings (i.e. were easily represented mentally; values ranging from 4 to 5 on a scale of 1–5, see Bonin et al., 2003) and a low frequency in the French language (average printed frequency of 60.4/million, S.D.=23.8, see Baudot, 1992). Two lists of 40 word pairs were formed; the sequence of presentation of the lists was counterbalanced between participants. For each list, 30 word pairs were used in the study phase and the remaining 10 pairs served as “new pairs” during the test phase. The words within each pair had no obvious semantic relationship to each other. In the initial study phase, 30 pairs of

words were consecutively presented on the screen. They were onscreen for 5 s followed by a white screen for 3 s (ISI=8 s). Participants were instructed to read aloud and remember each word pair. In the test phase, 30 word pairs were consecutively presented on the screen. Among them, 10 were identical to the pairs presented during the study phase (old pairs), 10 were never seen during study phase (new pairs), and 10 were formed of words previously presented in a different pairing (rearranged pairs). For each pair, the participant had to click on “OLD” if he recognized a pair shown during the study phase (old pairs) or click on “NEW” if he did not (corresponding to both new and rearranged pairs).

Hits for old pairs (i.e. old pairs correctly recognized as “old”) and correct rejections for new and rearranged pairs (i.e. new and rearranged pairs correctly recognized as “new”) were first considered. Hits for old pairs and correct rejections for new pairs could be supported either by recollection or by familiarity whereas the rejection of rearranged pairs could only be based on recollection. We calculated two indices of discrimination (A')²: (1) A' for old versus rearranged pairs (reflecting the recollection process), (2) A' for old versus new pairs (reflecting the recollection process or familiarity as a backup). This index ranges from 0 for null discrimination to 1 for maximal discrimination. We also assessed the decision criterion (B'') (Snodgrass and Corwin, 1988), which is an index of response bias, and was calculated for old versus rearranged pairs. This index ranges from -1 to +1, negative values indicating a liberal response bias, i.e. a tendency to respond “old” more often than “new”, and positive values indicating a conservative response bias, i.e. a tendency to respond “new” more often than “old”.

3. Results

3.1. Item-spatial context association task

Performance of all participants on the three memory tasks of the item-spatial context association paradigm (item, location and relocation) is reported in Fig. 2. To compare the patients with SZ or the unaffected parents to their respective control group, two separate analyses of variance (ANOVAs) were conducted with the number of correct responses for the three memory tasks as a within-subject factor and group as a between-subject factor. An alpha level of 0.05 (two-tailed) was used for all statistical tests. All analyses were performed using SPSS software (SPSS 11.0 for Microsoft Windows).

As expected, the overall performance of patients was lower than that of their controls as confirmed by the main effect of Group, $F(1,50)=7.19$, $P<0.05$. There was also a significant effect of Memory tasks, $F(1,50)=145.39$, $P<0.01$. However, the Group by Memory tasks interaction was not significant, suggesting that the lower performance in patients was not specific to one memory task ($F<1$, $P=0.91$). Indeed, the effect sizes (Cohen's d) were all in the medium range for the item ($d=0.64$), location ($d=0.44$), and relocation tasks ($d=0.55$). Given that healthy controls had higher IQ than SZ patients (see Table 1), we entered IQ as a covariate and observed that all differences remained statistically significant (Table 2).

²Formulas for the calculation of A' and B'' . We have corrected all hits (H) and false alarms (FA) rates by adding 0.5 to each frequency and dividing by $N-1$, where N is the number of trials, as recommended by Snodgrass and Corwin (1988). $A' = 0.5 - [(H-FA)/(1+H-FA)]/[4H(1-FA)]$. $B'' = [H(1-H) - FA(1-FA)]/[H(1-H) + FA(1-FA)]$. The results obtained were corrected given the proportion of targets over non-targets (0.33/0.67).

Overall, performance of unaffected parents was not significantly lower than that of their controls, Group effect, $F(1,68)=1.29$, $P=0.25$. There was a significant effect of Memory tasks, $F(1,68)=253.13$, $P<0.01$. The key interaction of Group by Memory tasks was significant, indicating that the impairment was specific to one memory task, $F(1,68)=4.07$, $P<0.05$. Indeed, post hoc independent t -tests revealed that parents had a significantly lower performance on the location task, $t(68)=2.31$, $P<0.05$, $d=0.56$, but neither on item, $t(68)=2.53$, $P=0.67$, $d=0.09$, nor relocation tasks, $t(68)=1.61$, $P=0.94$, $d=0.01$.

3.2. Item-item association task

Performance of all groups on measures of the item-item association task (hits to old pairs, correct rejection of rearranged pairs and corrected rejection of new pairs) is shown in Fig. 3. Two separate ANOVAs (patients with SZ versus controls and unaffected parents versus controls) were carried out with these three specific measures as a within-subject factor and group as a between-subject factor. Moreover, independent t -tests were performed to compare the patients to their controls and the unaffected parents to their controls.

The patient group had a significantly lower global index of performance (percentage of correct responses), $t(48)=3.96$, $P<0.01$, $d=1.12$. Comparisons on the specific measures of the item-item association task revealed a significant Group effect, $F(1,48)=18.18$, $P<0.01$; patients had a lower level of performance than controls. We also observed a significant Measure effect, $F(1,48)=37.54$, $P<0.01$, suggesting that performance level was not similar across hits to old pairs, correct rejection of rearranged pairs and corrected rejection of new pairs (correct rejection of new pairs > hits to old pairs > correct rejection of rearranged pairs). However, the Group by Measure interaction did not reach significance, $F(1,48)=2.17$, $P=0.13$, which means that the lower performance in patients was not specific to one measure of the item-item association task. The effect sizes varied from medium (correct rejection of new pairs, $d=0.53$; hits to old pairs, $d=0.56$) to large (correct rejection of rearranged pairs, $d=0.83$). Again, all differences remained statistically significant when we entered IQ as a covariate. Independent t -tests on the indices of discrimination (A') revealed that patients showed a poorer distinction of old versus rearranged pairs (A' ; patients: 0.66 ± 0.20 ; controls: 0.82 ± 0.13 ; $t(48)=3.50$, $P<0.01$), and also of old versus new pairs (A' ; patients: 0.87 ± 0.08 ; controls: 0.92 ± 0.05 ; $t(48)=2.61$, $P<0.05$). There was no significant difference between groups on the decision criterion (B'' ; patients: -0.08 ± 0.35 ; controls: -0.13 ± 0.38 ; $t(48)=-0.48$, $P=0.63$).

The group of unaffected parents also showed a lower global index of performance (percentage of correct responses) than their controls, $t(66)=2.47$, $P<0.05$, $d=0.59$. Comparisons on the specific measures of the item-item association task revealed a significant Group effect, $F(1,66)=6.09$, $P<0.05$, a significant Measure effect, $F(1,66)=70.66$, $P<0.01$, as well as a significant Group by Measure interaction, $F(1,66)=15.78$, $P<0.01$. Post-hoc independent t -tests showed a significant difference only for the correct rejection of rearranged pairs, which reflects the recollection process, $t(66)=4.33$, $P<0.01$, $d=1.06$. Independent t -tests on the indices of discrimination revealed that parents had difficulty in distinguishing between old and rearranged pairs (A' ; parents: 0.67 ± 0.22 ; controls: 0.80 ± 0.15 ; $t(66)=2.76$, $P<0.01$) but not between old versus new pairs (A' ; parents:

0.91 ± 0.06 ; controls: 0.89 ± 0.06 ; $t(66) = -1.12$, $P = 0.26$). There was a significant difference between groups concerning the decision criterion; parents had a tendency to respond “old” more often than “new” (B''); parents: -0.19 ± 0.25 ; controls: -0.03 ± 0.37 ; $t(66) = 2.14$, $P < 0.05$) for old versus rearranged pairs.

4. Discussion

The purpose of this study was to determine whether impairment in familiarity, recollection, or both could be related to the episodic memory deficit found in patients with SZ and their unaffected relatives. Our findings, as revealed by the two recognition tasks testing item-spatial context and item-item associations, are threefold. First, patients with SZ and their unaffected relatives showed poorer performance compared with their healthy controls on variables reflecting recollection (i.e. location recognition, correct rejection of rearranged pairs and A' for old versus rearranged pairs). Although unaffected parents had a more liberal decision criterion than controls on the task assessing item-item association, the lower performance observed on this task did not seem to be related to non-specific processes (e.g. expectancy, motivation or fatigue) because it was restricted to the discrimination of old versus recombined pairs. Consequently, the liberal bias could reflect a lower confidence level related to an impairment of the recollection process. Second, the presence of a recollection deficit for both experimental tasks suggests that the impairment is universal. Indeed, in addition to previously reported deficits for the recollection of an item and its temporal context (Elvevag et al., 2000; Waters et al., 2004), we observed deficits for an item and its spatial context as well as item-item associations. Third, patients with SZ also demonstrated difficulty in dealing with the familiarity process (e.g. poor item recognition and discrimination for old versus new pairs), whereas their unaffected parents showed no difference from healthy controls. In accordance with the latter finding, we also observed the often-reported increased rate of false alarms in patients compared with healthy controls (correct rejection of new pairs³, $d' = 0.87$) but not for their unaffected parents (Brebion et al., 1999; Moritz et al., 2003; Weiss et al., 2004). In sum, our results indicate that patients suffer from a significant deficit in episodic memory that encompasses both recollection and familiarity processes while their unaffected parents seem to suffer from a memory deficit selective to recollection. Given the generalized cognitive impairment described in SZ patients (Heinrichs and Zakzanis, 1998; Fioravanti et al., 2005), the presence of deficits in both processes was not unexpected. However, the fact that patients and unaffected parents shared impairment on recollection and that familiarity deficits were specific to patients raised the possibility of some specificity associated with the genetic vulnerability to SZ, which is further discussed below.

One limitation of the current study is related to sampling. The composition of our samples could have slightly increased the magnitude of the effect sizes observed. Indeed, our sample of individuals with SZ included only male patients, who may present more severe cognitive deficits than female patients (Leung and Chue, 2000). Thus, the extent to which these results apply to female patients would require further investigation. In addition, the group of unaffected relatives was mostly composed of females (68.60%), who may have more severe

³High level of false alarms results in a low level of correct rejection of new pairs.

memory deficits than male relatives (Kremen et al., 1997). Among our sample of unaffected parents, males and females did not significantly differ on measures reflecting the recollection process, which suggests that this possible gender effect did not lead to a significant overestimation of effect size in relatives. Another concern with regards to our methodology is that the design did not allow linking the deficit to a specific memory stage (encoding versus retrieval). However, imaging studies revealed abnormal patterns of brain activation in patients with SZ compared with controls during both encoding and retrieval (Achim and Lepage, 2005), suggesting that the deficits herein reported probably resulted from dysfunctions at both these stages.

The observation of an episodic memory deficit in patients with SZ and their unaffected relatives is consistent with previous studies using classical neuropsychological tasks (Heinrichs and Zakzanis, 1998; Snitz et al., 2006; Trandafir et al., 2006). Moreover, the rather generalized impairment found in patients is in accordance with the results of the meta-analysis, which concluded that recollection and familiarity processes are impaired in SZ (Achim and Lepage, 2003; Pelletier et al., 2005). The absence of a deficit in the process of familiarity in unaffected parents can be taken as evidence for dual-process models, which posit that familiarity and recollection processes are distinct and dissociable (the inverse pattern, i.e. familiarity impairment along with a preservation of the recollection process, has been described in Davidson et al., 2006 and Bowles et al., 2007). Two further assumptions of these models are that familiarity and recollection processes are initiated in parallel (e.g. Jacoby, 1991; Mandler, 1991) and that one can resort to familiarity if recollection fails (Yonelinas, 1994). When these assumptions are taken into account, our pattern of results suggests that patients fail to rely on familiarity as an effective backup process, while unaffected parents can make adequate use of familiarity-based judgment. The profile of deficits found in patients was also consistent with the results of a recent meta-analysis of imaging studies (Achim and Lepage, 2005) which provides evidence that, when performing tasks that promote high levels of recollection, people with SZ show an underactivation of the hippocampus, a region implicated in recollection, along with an overactivation in the parahippocampal gyrus region, assumed to be involved in familiarity assessment. Moreover, smaller hippocampal volume has been reported in unaffected relatives compared with controls; the hippocampus, of course, is a region consistently found to be implicated in recollection (Seidman et al., 2002; Boos et al., 2007).

Using experimental tasks designed specifically to characterize the defective processes underlying the episodic deficit, the present study has allowed us to underline similarities and also differences in the source of the episodic memory deficit found in patients with SZ and their unaffected relatives (i.e. recollection versus familiarity). The observed recollection deficit was of similar magnitude for patients and their unaffected parents whereas previous studies using a global score of performance derived from classical neuropsychological tasks highlighted deficits of smaller magnitude in relatives (Whyte et al., 2005; Trandafir et al., 2006). Although these differences in magnitude may stem from stochastic variations, it is possible that the lesser severity of the deficit on global scores found in unaffected relatives could be explained by their capacity to resort to familiarity when recollection fails, whereas patients could not benefit as much from this backup process. The use of global score in

previous studies, as opposed to the experimental approach used herein, could have masked the presence of a specific form of memory alteration (see Fig. 4).

As we mentioned above, the pattern of similarities and differences in episodic memory alterations observed in the current study in patients with SZ versus their relatives may relate to genetic versus environmental etiological factors of SZ. Indeed, it is plausible that some neural system deficits in SZ would be genetically mediated whereas others would be subject to nongenetic causes or gene–environment interactions (Cannon, 2005). In light of this etiological hypothesis and along with the postulate that familiarity and recollection could be dissociated (dual-process model), we suggest that the impairment of recollection could result from the inherited vulnerability for SZ because this deficit is found both in patients and their unaffected relatives, while the familiarity deficit could be modulated by nongenetic influences or gene–environment interaction because it seems to be only associated with the full disorder. Of course, we cannot totally rule out the possibility that there is a small alteration of familiarity in unaffected relatives. Given that the recollection deficit is associated with SZ and is more prevalent in unaffected family members than in the general population, this selective deficit could be a candidate for genetic studies. The item-item association task allowed us to adequately distinguish patients and their unaffected parents from healthy controls (patients, $d=0.94$ and parents, $d=1.05$). The use of experimental tasks could eventually help to delineate the memory profile of closely related disorders (e.g. SZ and bipolar disorders - BP). As the episodic memory impairment reported in patients with BP is not as severe as that of patients with SZ (Goldberg, 1999), one could make the assumption that the episodic deficit of patients with BP could be attributable to a selective impairment of recollection with a preservation of the familiarity process.

In conclusion, three lines of evidence support recollection as a candidate endophenotype. First, the recollection deficit is found in both patients with a recent-onset SZ and their unaffected parents. Second, the magnitude of the recollection deficiency is similar for both groups. Third, the deficit is robust and is found for different types of associations. The results of the present study suggest that use of experimental tasks represents a promising method in the search for cognitive endophenotypes in SZ.

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Fig. 1.
Schematic representation of the experimental task assessing item-context association.

Fig. 2.
Mean number of correct responses for the three conditions of the item-spatial context association task for SZ patients (left panel) and unaffected parents (right panel).

Fig. 3. Number of correct responses (hits and correct rejection) for measures of the word pair task for SZ patients (left panel) and unaffected parents (right panel).

Fig. 4.

Effect sizes in classical neuropsychological tasks (Trandafir et al., 2006) and experimental tasks from the current study for unaffected relative. Legend: Experimental task from the current study: EXP 1=location (item-spatial association task); EXP 2=correct rejection of rearranged pairs (item-item association task). Classical tasks (Trandafir et al., 2006): CVLT=California Verbal Learning Test, immediate recall; VR(D) =Visual Reproduction (WMS) delayed recall; VR (I)=Visual Reproduction (WMS) immediate recall; LM(D)=Logical Memory (WMS) delayed recall; LM(I)=Logical Memory (WMS) immediate recall; VPA(I+D)=Verbal Paired Associates (WMS) immediate and delayed recall. The red line represents the cut off for large effect size.

Table 1

Socio-demographic and clinical characteristics.

	SZ patients (<i>n</i> =26)	Controls of patients (<i>n</i> =26)	Parents (<i>n</i> =35)	Controls of parents (<i>n</i> =35)
Proportion of males	100% males	100% males	31.40% males	31.40% males
Age	23.81 (3.41)	23.38 (3.55)	53.14 (4.30)	53.43 (4.35)
Education (years) ^a	13.00 (2.62)	15.50 (2.02)	15.14 (2.91)	15.29 (3.08)
IQ ^a	108.80 (15.29)	120.61 (7.65)	107.08 (9.95)	109.82 (10.86)
Length of illness (months)	37.52 (20.94)	–	–	–
Number of hospitalizations	2.15 (1.75)	–	–	–
PANSS total	58.92 (18.56)	–	–	–
Medication (mg/day)				
Clozapine (<i>n</i> =4)	433.33 (115.47)			
Quetiapine (<i>n</i> =7)	828.57 (427.06)			
Olanzapine (<i>n</i> =6)	19.58 (7.41)			
Risperidone (<i>n</i> =9)	32.22 (12.33)			

Key: Education=number of years corresponding to the highest level of education achieved. IQ was estimated with the Vocabulary, and Block Design subtests of the WAIS-III. Risperidone dosage is given in mg/2 weeks.

Note: Means are given with the standard deviation in parentheses.

^aPatients<controls, *p*<0.05.

Table 2

Means, standard deviation and effect sizes for all the indexes used to assess memory task performance as a function of group.

	SZ patients (n=26)	Controls of patients (n=26)	d	Parents (n=35)	Controls of parents (n=35)	d
Item-spatial association task						
Item recognition ^a	9.00 (1.26)	9.65 (0.69)	0.64	9.45 (0.70)	9.37 (0.97)	0.09
Location ^{a,b}	5.07 (2.19)	5.92 (1.60)	0.44	4.42 (1.92)	5.51 (1.99)	0.56
Relocation ^a	4.80 (1.41)	5.65 (1.64)	0.55	4.96 (1.71)	4.82 (1.97)	0.01
Item-item association task						
Hits to old pairs ^a	7.48 (1.89)	8.48 (1.66)	0.56	8.47 (1.56)	8.09 (1.67)	0.23
CR of rearranged pairs ^{a,b}	5.00 (2.48)	7.08 (2.48)	0.83	4.44 (2.69)	7.12 (2.39)	1.06
CR of new pairs ^a	9.08 (1.07)	9.60 (0.86)	0.53	9.38 (1.07)	9.21 (1.25)	0.14
A' (old vs. rearranged) ^{a,b}	0.66 (0.19)	0.82 (0.13)	1.00	0.67 (0.22)	0.80 (0.15)	0.69
A' (old vs. new) ^a	0.87 (0.09)	0.92 (0.05)	0.71	0.91 (0.06)	0.90 (0.06)	0.16
B'' (old vs. rearranged) ^b	-0.08 (0.35)	-0.13 (0.38)	0.14	-0.19 (0.25)	-0.02 (0.38)	0.53

^aPatients<controls, $P<0.05$.

^bParents<controls, $P<0.05$.