Neural basis of autobiographical memory retrieval in schizophrenia†
Christine Cuervo-Lombard, Cédric Lemogne, Fabien Gierski, Céline Béra-Potelle, Eric Tran, Christophe Portefaix, Arthur Kaladjian, Laurent Pierot and Frédéric Limosin

Background
Autobiographical memory retrieval is impaired in schizophrenia.

Aims
To determine the neural basis of this impairment.

Method
Thirteen patients with schizophrenia and 14 healthy controls performed an autobiographical memory retrieval task based on cue words during functional magnetic resonance imaging. Patients were selected on the basis of their ability to perform the task and all participants received training.

Results
Although patients and controls activated a similar brain network during autobiographical memory retrieval, patients displayed decreased activation in several of these regions, including the anterior cingulate cortex, left lateral prefrontal cortex, right cerebellum and ventral temporal area (K > 10, P < 0.001, uncorrected). In addition, activation of the caudate nucleus was negatively correlated with retrieval performance in controls but positively correlated with performance in patients.

Conclusions
The autobiographical memory retrieval brain network is impaired in schizophrenia. Patients with schizophrenia display decreased activation of the cognitive control network during retrieval, possibly due to aberrant functioning of the dorsal striatum.

Declarations of interest
C.L. has received speakers fees from AstraZeneca, Bristol-Myers Squibb, Euthérapie, Lundbeck, Sanofi Aventis and Pfizer. C.B.-P. has received speakers fees from Bristol-Myers Squibb. E.T. has received speakers fees from Bristol-Myers Squibb, Euthérapie, Janssen-Cilag and Lundbeck. A.K. has received speakers fees from AstraZeneca, Euthérapie, Janssen-Cilag, Lilly and Lundbeck. F.L. has received consulting/speakers fees from Bristol-Myers Squibb, Euthérapie, Janssen-Cilag and Lilly.

Participants
Seventeen men with a DSM-IV-TR17 diagnosis of paranoid schizophrenia were approached to take part in the study. They were either out-patients or in-patients recruited just before discharge and all were deemed to be clinically stable by their psychiatrist (i.e. needing no further adjustment to their treatment). None had any psychiatric comorbid conditions. Thirteen patients were selected on the basis of their ability to complete the verbal tests of the third edition of the Wechsler Adult Intelligence Scale18 and the autobiographical memory task (see below). Patients were mildly to moderately ill, according to their mean scores on the Positive and Negative Syndrome Scale (PANSS),19 and all were receiving medication (Table 1). The mean dose of antipsychotics was equivalent to 375 mg/day (s.d. = 203) of chlorpromazine.20

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Fourteen healthy men were recruited from the community through advertisements and matched with the patients for age and level of education. None had any current or past psychiatric diagnosis, according to the Mini International Neuropsychiatric Interview 5.0 for DSM-IV Axis I disorders,21 or any first-degree relative with psychosis and none were on medication. Patients and controls did not differ in age, level of education or verbal abilities (Table 1).

All participants were screened for a history of head trauma, neurological disorder, substance-related disorder, electroconvulsive therapy or claustrophobia. Participants also conformed to...
standard health and safety regulations regarding the use of magnetic resonance imaging (MRI). All participants were right-handed, according to the Edinburgh Handedness Inventory, and were native French speakers. This study was approved by the local ethics committee and all participants gave their written informed consent after receiving a complete description of the study.

**Experimental design**

During the fMRI session, 25 cue words and 25 control words were presented in a pseudorandomised order such that words of each type (cue vs. control) followed each other equally often. The cue words (for example chat (cat), école (school), voiture (car)) were French nouns selected from previous studies on the basis of their frequency in the spoken language and their ability to elicit vivid mental images. They were displayed for 12 s and followed by a fixation cross for 4 s. This fairly long duration was chosen to allow patients and controls sufficient time to recall a specific event for each cue word and to prevent mind-wandering. All the stimuli were shown on an MRI-compatible monitor (white text, black background) viewed by participants via a mirror mounted on the head coil. We used E-Prime software for Windows (Psychology Software Tools, Sharpsburg, Pennsylvania, USA, www.pstnet.com/) to present the stimuli and collect reaction times. Responses were made on an MRI-compatible response pad. For autobiographical memory retrieval, the participants had to press the button under their right middle finger as soon as a memory was fully formed in their mind. For the control words, they had to press the button under the appropriate finger (i.e. index or middle).

Immediately after leaving the scanner, participants had to describe each of their memories with as much detail as possible regarding the content of the event (what), where it took place (where) and any temporal information about it (when). They then had to indicate their age at the time of the event (i.e. encoding age) and the emotional valence of the memory on a 10 cm visual scale (ranging from ‘most unpleasant’ to ‘most pleasant’). In addition, they had to indicate their subjective state of consciousness during autobiographical memory retrieval for each aspect of the memory (i.e. what, where and when). The participants gave either a ‘Remember’ response if they recollected phenomenological aspects such as perceptions, thoughts or feelings that were experienced at the time of the event, a ‘Know’ response if retrieval was achieved without any such recollection or a ‘Guess’ response if retrieval was doubtful. A recollection score ranging from zero to three was calculated for each memory, based on the total number of ‘Remember’ responses for the three different aspects (i.e. what, where and when). No memory and thus no conscious recollection was rated zero. Finally, the participants were fully debriefed.

To ensure that the participants were able to perform the autobiographical memory retrieval task properly, including the remember/know paradigm, we ran a training session in a quiet room 1 week before the fMRI session and after a full explanation of the task. This training session featured a list of seven cue words that were not used in the subsequent fMRI session. The participants had to recall a specific event for each cue word and

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**Table 1  Sociodemographic and clinical characteristics of participants**

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 13)</th>
<th>Controls (n = 14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years: mean (s.d.)</td>
<td>30.7 (5.3)</td>
<td>30.1 (5.0)</td>
<td>0.784</td>
</tr>
<tr>
<td>Education level, years:</td>
<td>11.8 (2.3)</td>
<td>12.1 (1.4)</td>
<td>0.761</td>
</tr>
<tr>
<td>mean (s.d.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal Comprehension Index (WAIS-III), mean (s.d.)</td>
<td>98.7 (15.4)</td>
<td>98.7 (12.0)</td>
<td>0.997</td>
</tr>
<tr>
<td>Information</td>
<td>10.1 (4.1)</td>
<td>9.0 (2.0)</td>
<td>0.400</td>
</tr>
<tr>
<td>Similarities</td>
<td>10.3 (2.7)</td>
<td>11.4 (3.5)</td>
<td>0.357</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>8.9 (3.2)</td>
<td>9.0 (1.9)</td>
<td>0.879</td>
</tr>
<tr>
<td>Onset of illness, years:</td>
<td>20.2 (3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (s.d.)</td>
<td>10.5 (3.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness, years: mean (s.d.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive and Negative Syndrome Scale, mean (s.d.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive score</td>
<td>12.9 (3.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative score</td>
<td>23.0 (4.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global psychopathology score</td>
<td>31.6 (5.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>67.5 (6.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotropic drugs, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>8 (61.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>3 (23.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2 (15.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyamemazine</td>
<td>1 (7.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>5 (38.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>3 (23.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital and housing status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living as a couple</td>
<td>1 (7.7)</td>
<td>8 (57.1)</td>
<td></td>
</tr>
<tr>
<td>Single, living alone</td>
<td>4 (30.8)</td>
<td>5 (35.7)</td>
<td></td>
</tr>
<tr>
<td>Single, living with family</td>
<td>6 (46.2)</td>
<td>1 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Single, living in a therapeutic home setting</td>
<td>2 (15.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>1 (7.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working in a normal setting</td>
<td>2 (15.4)</td>
<td>14 (100)</td>
<td></td>
</tr>
<tr>
<td>Working in a therapeutic setting</td>
<td>1 (7.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not working</td>
<td>9 (69.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

WAIS-III: Wechsler Adult Intelligence Scale (3rd edn).

a. One patient was taking both clonazepam and cyamemazine, the latter being used as an anxiolytic.

b. Three patients were taking paroxetine (20 mg/day), one fluoxetine (20 mg/day) and one venlafaxine (112.5 mg/day).

c. Two patients were taking clorazepate (40 and 60 mg/day) and one prazepam (40 mg/day).
immediately and describe each memory (see above). To 

familiarise the participants with the MRI environment (MRI table, screen, response pad) and the experiment’s timing constraints, a 

second training session took place at the beginning of the fMRI 

session, when participants were already on the MRI table. Two 

other cue words and three control words were used.

Memory specificity assessment

The specificity of each memory (transcribed verbatim) was 

assessed by two independent raters (C.C.L. and Sarah Barrière) 

on a four-point scale: 4 for a highly specific event located in time 

and place, described with numerous details; 3 for a specific event 

located in time and place, but not detailed; 2 for a repeated event; 

1 for a vague event; 0 for no memory or only general information 

about a theme. One of the raters (Sarah Barrière) was masked to 

the diagnosis. Cohen’s kappa coefficient indicated substantial 

inter-rater agreement (κ = 0.94, P < 0.001). Every conflicting rating 

was re-examined until a consensus was reached. For each patient, 

a mean specificity score was computed. Together with the 

recollection score, this specificity score was used to index 

individual autobiographical memory retrieval performances.

MRI data acquisition

Imaging was conducted with a 3T whole-body MRI scanner with 

an eight-channel head coil. Head motions were minimised with a 

forehead strap and comfortable padding around the participant’s 

head. For each participant, a T1-weighted anatomical image, 

oriented parallel to the anterior commissure-posterior commissure 

axis was first acquired with a fast-field echo (FFE) sequence 

(T1-FFE; repetition time (TR) = 253 ms; echo time (TE) = 2.30 ms; 

flip angle: 80°; 32-axial slices; slice thickness: 4.50 mm; no gap; 

field of view (FOV) = 240 × 240 × 240 mm³; matrix: 268 × 214; 

acquisition voxel size: 0.43 × 0.43 × 4.5 mm³). Functional data 

were acquired in ascending slice order with a two-dimensional 

(2D) T2*-weighted echo-planar imaging (EPI) sequence sensitive 

to blood oxygen level-dependent (BOLD) contrast in the same axial 

plane as the T1-weighted structural images (2D T2*-FFE–EPI; 

TR = 2000 ms; TE = 33 ms; flip angle: 90°; 32-axial slices; slice 

thickness: 4.5 mm; no gap; matrix: 80 × 80; FOV = 240 × 240 

mm²; acquisition voxel size: 3 × 3 × 4.5 mm³). The functional 

volumes were collected during a single functional session (330 

volumes). Finally, a high-resolution T1-weighted anatomical image 

was acquired with a three-dimensional (3D) turbo-field echo 

(TFE) sequence (3D T1-TFE, TR = 8.2 ms; TE = 3.73 ms; flip angle: 

8°; 160 axial slices; slice thickness: 1 mm; FOV = 240 × 240 

mm²; matrix: 240 × 240; acquisition voxel size: 1 × 1 × 1 mm³).

MRI image pre-processing

The fMRI data were analysed with Statistical Parametric Mapping 

(SPM8; Welcome Department of Cognitive Neurology, Institute of 


MRicro software for Windows (www.mccauslandcenter.sc.edu/ 

mricro/mricro) was used for image conversion. Five initial brain 

volumes were discarded from the analyses to eliminate the 

non-equilibrium effects of magnetisation. Functional EPI–BOLD 

images were spatially realigned to the first volume. There were 

no patient or control images with excessive head movements 

(>2 mm or >2°). Interpolation was used to minimise timing 

trends between slices. These images were then anatomically 

normalised to the Montreal Neurological Institute (MNI) 

template and smoothed with an isotropic Gaussian kernel of 

8 mm full-width at half maximum. A high-pass filter was 

implemented, using a cut-off period of 128 s, to remove low-

frequency drift from the time series.

fMRI statistical analysis

Individual analyses were performed with a fixed-effect model, 

whereas group analyses were performed with a random-effect 

model. For each participant, we computed an individual statistical 

parametric map based on the general linear model and an event-

related approach.28 Since our main hypothesis was predicated on 

previous fMRI studies of episodic retrieval, in which search 

processes may prevail over other processes such as mental imagery, 

our primary aim was to investigate the search component of 

autobiographical memory retrieval. We thus computed a 

convolution of each stimulus onset with the canonical haemo-

dynamic response function to create regressors of interest. Motion 

parameters (three translations and three rotations) determined 

from the initial realignment procedure were included as regressors 

of non-interest. Statistical parametric maps of t-statistics were 

calculated to identify voxels with event-related signal changes. 

The resulting t-statistics were transformed to z-score maps of 

normal unit distribution. As regards the main effect of the task 

(i.e. autobiographical memory retrieval vs. control), we used a 

family-wise error (FWE) corrected threshold of P < 0.05. To look 

for between-group differences in the brain regions actually 

involved in autobiographical memory retrieval, we first defined 

an inclusive mask including all regions activated during retrieval 

in either patients or controls, separately, with a statistical 

threshold of P < 0.05, FWE-corrected.29 We then looked for 

between-group differences within these regions, combining an 

extent threshold of 10 voxels, with a statistical threshold of 

P < 0.001, uncorrected.

Results

Behavioural results

The groups did not differ on the quantity of memories, their 

specificity or the recollection scores. Nor did they differ on 

remoteness, encoding age or emotional valence (Table 2). 

Discrepancies between behavioural responses during fMRI and 

the post-scanning assessment revealed that 8 participants (5 

patients, 3 controls) forgot at least once to press the button after 

recalling a personal event, whereas 14 participants (6 patients, 8 

controls) pressed it at least once even though they had not recalled 

a personal event. Behavioural responses and reaction times were 

thus discarded from subsequent analyses.

fMRI results

A priori analyses

Regardless of group, autobiographical memory retrieval activated 

an extensive brain network including the cortical midline structures, 

left lateral prefrontal cortex, left angular gyrus, medial and lateral 

temporal lobes, occipital lobes and cerebellum (Table 3 and Fig. 1). 

To identify the regions activated in both patients and controls, we 

performed a conjunction analysis with a conjunction null 

hypothesis (i.e. an ‘AND’ conjunction29), which yielded a smaller 

number of activation clusters (Table 4).

Since we were primarily interested in examining between-group 

differences in the regions actually involved in autobiographical 

memory retrieval, we then performed a conjunction analysis with a 

global null hypothesis (i.e. an ‘OR’ conjunction) to identify 

regions that were activated during retrieval in either patients or 

controls.29 This map was used as an inclusive mask to look for 

between-group differences. Although none of these regions was
more activated in patients than controls ($P > 0.001$, uncorrected), several of them were less activated in patients than controls, including some cortical midline structures (i.e. the anterior cingulate cortex and the precuneus), the left lateral prefrontal cortex, left medial temporal lobe, occipital lobe, cerebellum and a midbrain region extending to the lateral ventral tegmental area (Table 5 and Fig. 2). Adjusting for autobiographical memory retrieval performances yielded similar results except for the left medial temporal lobe, whose activation was no longer significant when adjusting for either specificity or recollection, and the precuneus, whose activation was no longer significant when adjusting for specificity (see online Tables DS1 and DS2).

We then looked for between-group differences at a whole-brain level, using a more stringent statistical threshold to avoid type I errors due to multiple comparisons. This analysis revealed four clusters of activation corresponding to the left lateral ventral tegmental area (16 mm$^3$, MNI coordinates: $-12$, $-20$, $-16$; $z(125) = 4.93$, $P < 0.05$, FWE-corrected), the right cerebellum (48 mm$^3$, MNI coordinates: $20$, $-38$, $-28$; $z(125) = 4.86$, $P < 0.05$, FWE-corrected) and the caudate nuclei (48 mm$^3$, MNI coordinates: $-10$, $18$, $4$; $z(125) = 4.85$; and 64 mm$^3$, MNI coordinates: $10$, $18$, $4$, $z(125) = 4.80$, $P < 0.05$, FWE-corrected) (Fig. 3(a)).

**Post hoc analyses**

Although the lateral ventral tegmental area and the cerebellum clusters were among the between-group differences that had previously been found within the global null conjunction mask, the caudate nuclei clusters were not. To examine how these two clusters were functionally related to autobiographical memory retrieval, we performed a series of post hoc analyses.
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retrieval, we looked for correlations between their mean beta values and retrieval performances (i.e. specificity and recollection). The activation of the left caudate nucleus tended to be positively correlated with retrieval performances in patients (specificity: $r = 0.705$, $P = 0.007$; recollection: $r = 0.589$, $P = 0.034$), but negatively with performances in controls (specificity: $r = -0.508$, $P = 0.063$; recollection: $r = -0.367$, $P = 0.196$), thus yielding significant group $\times$ specificity ($z = 3.289$, $P < 0.001$) and group $\times$ recollection ($z = 2.273$, $P = 0.023$) interactions (Fig. 3(b)). A similar pattern was observed in the right caudate nucleus, although neither the group $\times$ specificity ($z = 1.694$, $P = 0.090$) nor the group $\times$ recollection ($z = 1.242$, $P = 0.214$) interaction reached significance. There was no significant correlation between retrieval performances and the activation of the other regions characterised by between-group differences during retrieval.

Finally, to rule out the potential role of antipsychotic drugs and look for clinical correlations, we performed regression analyses among the patients only, using the between-group differences as an inclusive mask. There was no significant correlation with either the PANSS subscales or the chlorpromazine equivalent dose at a threshold of $P < 0.001$, uncorrected. Using a very lenient statistical threshold to avoid type II errors, we found a negative correlation between the chlorpromazine equivalent dose and the activation of the left medial temporal lobe (72 mm$^3$, MNI coordinates: $-22$, $-20$, $-22$; $z(11) = 2.13$, $P < 0.05$, uncorrected).

Discussion

Main results

This study investigated whether the neural basis of autobiographical memory retrieval differs between patients with schizophrenia and healthy controls. As expected, because patients were selected according to their ability to perform the autobiographical

Table 5 Brain regions displaying greater activation in controls than patients ($k \geq 10$, $P < 0.001$, uncorrected) among those regions activated during autobiographical memory retrieval in either controls or patients ($P < 0.05$, family-wise error corrected)

<table>
<thead>
<tr>
<th>Brain regions</th>
<th>mm$^3$</th>
<th>z-score at peak voxel</th>
<th>MNI coordinates at peak voxel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>Frontal inferior gyrus (L)</td>
<td>720</td>
<td>4.48</td>
<td>-54</td>
</tr>
<tr>
<td>Ventral tegmental area (L)</td>
<td>104</td>
<td>4.40</td>
<td>-10</td>
</tr>
<tr>
<td>Anterior cingulate cortex (L)</td>
<td>408</td>
<td>4.05</td>
<td>-2</td>
</tr>
<tr>
<td>Frontal inferior gyrus (R), insula (R)</td>
<td>232</td>
<td>3.95</td>
<td>34</td>
</tr>
<tr>
<td>Cerebellum (R)</td>
<td>232</td>
<td>3.89</td>
<td>40</td>
</tr>
<tr>
<td>Cerebellum (L)</td>
<td>184</td>
<td>3.65</td>
<td>16</td>
</tr>
<tr>
<td>Anterior cingulate cortex (R)</td>
<td>232</td>
<td>3.62</td>
<td>4</td>
</tr>
<tr>
<td>Precuneus (L)</td>
<td>136</td>
<td>3.60</td>
<td>0</td>
</tr>
<tr>
<td>Parahippocampal gyrus (L)</td>
<td>88</td>
<td>3.47</td>
<td>-22</td>
</tr>
<tr>
<td>Calcarine sulcus (L), lingual gyrus (L)</td>
<td>256</td>
<td>3.41</td>
<td>-8</td>
</tr>
</tbody>
</table>

MNI, Montreal Neurological Institute; L, Left; R, Right.
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memory retrieval task, the retrieval performances measured after the scan were similar in both groups. However, we were not able to measure retrieval performances during the scan. Consistent with previous studies with healthy individuals, patients and controls activated a similar brain network during retrieval, including the cortical midline structures, left lateral prefrontal cortex, left angular gyrus, medial temporal lobes, occipital lobe and cerebellum. Compared with controls, patients with schizophrenia displayed reduced activation in several of these regions, including two cortical midline structures (i.e. the anterior cingulate cortex and precuneus), the left lateral prefrontal cortex, left medial temporal lobe, occipital lobe, right cerebellum and left lateral ventral tegmental area. Apart from the decreased activation of the left lateral prefrontal cortex, which was expected a priori, the other findings should be interpreted with caution because of the uncorrected statistical threshold. In addition, a whole-brain analysis with a more stringent statistical threshold revealed between-group differences outside these regions, especially in the caudate nuclei.

Given the functional neuroanatomy of autobiographical memory retrieval in healthy individuals, the present results may reflect a global impairment of retrieval in patients with schizophrenia, encompassing strategic search (left lateral prefrontal cortex, anterior cingulate cortex, right cerebellum), self-referential processing (cortical midline structures), conscious recollection (medial temporal lobe, precuneus) and visual imagery (precuneus, occipital lobe). Apart from the left medial temporal lobe and the precuneus, between-group differences remained significant when adjusting for individual retrieval performances.

Decreased activation of the cognitive control network

One may argue that focusing on discrete brain regions rather than distributed networks is unlikely to capture the core processes that underlie our findings. First, the neural signature of autobiographical memory retrieval is not unique. Second, schizophrenia is thought to be characterised by a lack of coordinated activation of segregated neural networks rather than by the aberrant activation of any given region. Among healthy individuals, the neural basis of episodic memory retrieval are thought to involve three segregated yet interacting networks. First, the so-called ‘default-mode network’, including the precuneus and the medial temporal lobe, may underlie self-referential processing and conscious recollection. Second, a dorsal frontoparietal network, including the anterior cingulate cortex and the lateral prefrontal cortex, may underlie increased top–down cognitive control, such as that triggered by difficulty achieving retrieval goals. Third, a ventral frontoparietal network may underlie bottom–up salience processing, as a complementary system for guiding memory searches.

Our results suggest that autobiographical memory retrieval in schizophrenia can be mainly characterised by decreased activation of a cognitive control network involving the left lateral prefrontal cortex, dorsal anterior cingulate cortex and right cerebellum, which is functionally and anatomically connected to the left lateral prefrontal cortex. Since our autobiographical memory task was based on generative retrieval (i.e. an effortful constructive process) rather than direct retrieval (i.e. an automatic process triggered by a specific cue provided during a pre-scan interview), we believe that our study specifically addressed the controlled aspects of autobiographical memory retrieval. Our results may thus highlight a lack of top–down cognitive control during retrieval, making patients with schizophrenia less able to perform goal-directed memory searches.

Aberrant activation of the dorsal striatum

Auch healthy individuals, the dorsal striatum, including the caudate nuclei, plays a critical role in strategy shifting, through prediction error signalling (i.e. signalling a discrepancy between expected and actual outcome). In the context of memory search, prediction errors during free recall may indicate when to shift from automatic (bottom–up) to controlled (top–down) retrieval strategies. In the present study, encoding age, remoteness and valence did not predict between-group differences. Moreover, the activation of the left caudate nucleus during autobiographical memory retrieval was inversely correlated with autobiographical memory performances in patients and controls. Increased activation in controls was
associated with lower retrieval performances, suggesting that a relative failure of retrieval may have triggered increased cognitive control. In contrast, increased activation in patients was associated with higher autobiographical memory retrieval performances, suggesting that it may represent a partially successful compensatory mechanism. This aberrant dorsal striatum activation may account for the decreased activation of the cognitive network during retrieval in schizophrenia. This hypothesis is consistent with the similar pattern of activation observed in the lateral ventral tegmental area, whose erratic dopaminergic outputs to the striatum may mediate aberrant prediction error in schizophrenia. 31,38

**Limitations**

Several limitations should be acknowledged. First, our sample was fairly small and included only male patients who were selected according to their verbal abilities, thus limiting the generalisability of our results. In addition, all the patients were taking anti-psychotic drugs, which may have influenced our results to some extent. However, although we found a weak negative correlation between the chlorpromazine equivalent dose and the activation of the left medial temporal lobe, we found no correlation within the cognitive control network. Second, our results may partially reflect processes shared with other cognitive functions that are impaired in schizophrenia, such as episodic memory retrieval or executive functions. 39 Third, we were not able to measure autobiographical memory performances during the scan or verify the veracity of the reported memories. Fourth, as we did not include psychiatric patients as controls, we cannot be sure that our findings are specific to schizophrenia. For instance, there is evidence that autobiographical memory retrieval is also impaired in major depression. 57 Fifth, our experimental design may have magnified the role of top–down attention, as it focused on generative retrieval. 1 Further studies are therefore needed to examine the role of bottom–up processes, as well as their interplay with top–down processes during autobiographical memory retrieval in patients with schizophrenia. Finally, our study lacked a measure of global functioning that could have been used to examine the functional correlates and clinical significance of our results.

**Implications**

Given the role of autobiographical memory in the pursuit of long-term goals and social cognition, 1 this autobiographical memory retrieval impairment may contribute to poor social outcomes associated with schizophrenia. 12 Future studies will need to confirm these preliminary results among unmedicated and female patients and translate these results into therapeutic interventions such as cognitive remediation.
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Data supplement

**Fig. DS1**  Brain regions activated during autobiographical memory retrieval regardless of group ($P<0.05$, family-wise error corrected) displayed on a 1 mm isotropic version of the Montreal Neurological Institute 152 standard brain.

**Fig. DS2**  Brain regions displaying greater activation in controls than in patients ($P<0.001$, uncorrected; $k=10$) among those activated during autobiographical memory retrieval in either controls or patients ($P<0.05$, family-wise error corrected) displayed on a 1 mm isotropic version of the Montreal Neurological Institute 152 standard brain.

**Fig. DS3**  Greater activation of the caudate nuclei in controls than in patients during autobiographical memory retrieval ($P<0.05$, family-wise error corrected) displayed on a 1 mm isotropic version of the Montreal Neurological Institute 152 standard brain.
Table DS1 Brain regions displaying greater activation in controls than patients ($P<0.001$, uncorrected, $k\geq10$) among those regions activated during autobiographical memory retrieval in either controls or patients ($P<0.05$, family-wise error corrected), adjusting for specificity score

<table>
<thead>
<tr>
<th>Brain regions</th>
<th>mm$^3$</th>
<th>z-score at peak voxel</th>
<th>MNI coordinates at peak voxel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$x$</td>
</tr>
<tr>
<td>Ventral tegmental area (L)</td>
<td>112</td>
<td>4.64</td>
<td>−12</td>
</tr>
<tr>
<td>Frontal inferior gyrus (L)</td>
<td>520</td>
<td>4.36</td>
<td>−54</td>
</tr>
<tr>
<td>Anterior cingulate cortex (L)</td>
<td>216</td>
<td>4.13</td>
<td>−2</td>
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<tr>
<td>Cerebellum (R)</td>
<td>184</td>
<td>3.90</td>
<td>16</td>
</tr>
<tr>
<td>Cerebellum (R)</td>
<td>120</td>
<td>3.69</td>
<td>40</td>
</tr>
<tr>
<td>Frontal inferior gyrus (R), insula (R)</td>
<td>144</td>
<td>3.64</td>
<td>34</td>
</tr>
<tr>
<td>Anterior cingulate cortex (R)</td>
<td>544</td>
<td>3.62</td>
<td>4</td>
</tr>
<tr>
<td>Calcarine sulcus (L), lingual gyrus (L)</td>
<td>328</td>
<td>3.48</td>
<td>−8</td>
</tr>
</tbody>
</table>

MNI, Montreal Neurological Institute; L, Left; R, Right.

Table DS2 Brain regions displaying greater activation in controls than patients ($P<0.001$, uncorrected; $k\geq10$) among those regions activated during autobiographical memory retrieval in either controls or patients ($P<0.05$, family-wise error corrected), adjusting for recollection score

<table>
<thead>
<tr>
<th>Brain regions</th>
<th>mm$^3$</th>
<th>z-score at peak voxel</th>
<th>MNI coordinates at peak voxel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$x$</td>
</tr>
<tr>
<td>Ventral tegmental area (L)</td>
<td>120</td>
<td>4.50</td>
<td>−10</td>
</tr>
<tr>
<td>Frontal inferior gyrus (L)</td>
<td>704</td>
<td>4.37</td>
<td>−54</td>
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<tr>
<td>Anterior cingulate cortex (L)</td>
<td>768</td>
<td>4.07</td>
<td>−2</td>
</tr>
<tr>
<td>Frontal inferior gyrus (R), insula (R)</td>
<td>208</td>
<td>3.94</td>
<td>34</td>
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<tr>
<td>Cerebellum (R)</td>
<td>208</td>
<td>3.83</td>
<td>40</td>
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<tr>
<td>Cerebellum (R)</td>
<td>176</td>
<td>3.60</td>
<td>16</td>
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<tr>
<td>Precuneus (L)</td>
<td>136</td>
<td>3.60</td>
<td>0</td>
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<tr>
<td>Calcarine sulcus (L), lingual gyrus (L)</td>
<td>208</td>
<td>3.38</td>
<td>−8</td>
</tr>
</tbody>
</table>

MNI, Montreal Neurological Institute; L, Left; R, Right.

Cuervo-Lombard et al: Neural basis of autobiographical memory retrieval in schizophrenia

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Christine Cuervo-Lombard, Cédric Lemogne, Fabien Gierski, Céline Béra-Potelle, Eric Tran, Christophe Portefaix, Arthur Kaladjian, Laurent Pierot and Frédéric Limosin
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