Prefrontal activity and impaired memory encoding strategies in schizophrenia

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**Abstract**

Schizophrenia patients have significant memory difficulties that have far-reaching implications in their daily life. These impairments are partly attributed to an inability to self-initiate effective memory encoding strategies, but its core neurobiological correlates remain unknown. The current study addresses this critical gap in our knowledge of episodic memory impairments in schizophrenia. Schizophrenia patients ($n=35$) and healthy controls ($n=23$) underwent a Semantic Encoding Memory Task (SEMT) during an fMRI scan. Brain activity was examined for conditions where participants were a) prompted to use semantic encoding strategies, or b) not prompted but required to self-initiate such strategies. When prompted to use semantic encoding strategies, schizophrenia patients exhibited similar recognition performance and brain activity as healthy controls. However, when required to self-initiate these strategies, patients had significant reduced recognition performance and brain activity in the left dorsolateral prefrontal cortex, as well as in the left temporal gyrus, left superior parietal lobule, and cerebellum. When patients were divided based on performance on the SEMT, the subgroup with more severe deficits in self-initiation also showed greater reduction in left dorsolateral prefrontal activity. These results suggest that impaired self-initiation of elaborative encoding strategies is a driving feature of memory deficits in schizophrenia. We also identified the neural correlates of impaired self-initiation of semantic encoding strategies, in which a failure to activate the left dorsolateral prefrontal cortex plays a key role. These findings provide important new targets in the development of novel treatments aiming to improve memory and ultimately patients’ outcome.

Introduction

Memory impairments have been established as strong predictors of poor clinical and functional outcome in schizophrenia (Lepage et al., 2014), with episodic memory as one of the most impaired forms of memory in this illness (Aleman et al., 1999; Danion et al., 2007; Lepage, 2007). The inability to self-initiate effective memory strategies in the absence of direct prompts represents a critical factor leading to deficient episodic memory in schizophrenia (Bonner-Jackson and Barch, 2011). Previous behavioral studies have suggested that schizophrenia patients have specific deficits in self-initiating semantic encoding strategies, but are capable of being and benefiting from strategies when prompted to use them (Brebin et al., 2004; Chan et al., 2000; Fiszdon et al., 2006; Hazlett et al., 2000). The self-initiation of semantic encoding strategies is a process in which individuals evaluate semantic relationships between information when such an evaluation is not prompted or directly required for the task. Intriguingly, individuals with frontal lobe lesions also show similar self-initiation impairments (Gershberg and Shimamura, 1995; Hirst and Volpe, 1988). It is therefore plausible that such deficits in schizophrenia may have a similar underlying neural component involving the prefrontal cortex (PFC).

Isolating the specific pattern of brain activity related to the self-initiation of encoding strategies in schizophrenia is challenging. Previous functional magnetic resonance imaging (fMRI) studies

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have succeeded in isolating the neural correlates of different types of encoding when patients were prompted to use deep versus shallow encoding (Bonner-Jackson et al., 2005). These studies suggest that patients may activate similar regions in the PFC as healthy controls when they are oriented towards deeper encoding strategies. However, given that the deficit in schizophrenia appears to relate to spontaneously self-initiating such strategies, rather than to making use of strategies when prompted, there is still a need to disentangle the relationship between the PFC and deficits in the self-initiation process. Recently, our group developed a task to address this issue and investigate the self-initiation of semantic encoding strategies in healthy controls (Hawco et al., 2013). Participants were presented triads of objects with varying numbers of semantic relationships, and were asked either to evaluate these semantic relationships or to perform a size judgment of the objects (in which case any elaborative semantic encoding was not in response to an external cue but instead internally self-initiated). They observed that the dorsolateral PFC (DLPFC) plays a key role in the self-initiation of semantic encoding strategies in healthy controls, along with the parietal cortex.

Investigating the neural correlates of semantic encoding strategies in schizophrenia patients will address a critical gap in our knowledge of their episodic memory deficits and in turn, could help identify therapeutic targets for the development of novel memory treatments to improve patients’ outcome. Indeed, being able to self-initiate strategies for improving memorization is essential in daily life. As a result improving patients’ self-initiation can have a strong positive impact on their level of functioning within the community. With these goals in mind, the current study was designed to investigate the neural correlates of impaired self-initiation of semantic encoding strategies in schizophrenia. We used an associative episodic memory task inspired by Hawco et al., 2013 and recently validated to target this process in schizophrenia patients (Guimond and Lepage, 2016). Using event-related fMRI, we examined brain activity during associative encoding in schizophrenia patients and healthy controls: (1) when they were prompted to use semantic encoding strategies with the encoding question, and (2) when they were required to self-initiate these strategies; that is, when the encoding orienting question was not a semantic cue. We propose a model that accounts for improvements in performance attributable to semantic relatedness. We hypothesized that patients and healthy controls would have similar recognition performance and brain activity when prompted to use semantic strategies, but patients would exhibit reduced recognition performance and brain activity in the DLPFC when required to self-initiate semantic encoding strategies. Finally, we examined the impact of patients’ inherent capacity to self-initiate such strategies on neural activity by dividing the group into two subgroups based on their level of self-initiation. We hypothesized that patients with greater difficulties in self-initiation would show lower brain activity in the DLPFC.

Methods and materials

Participants

Forty-four patients with enduring schizophrenia were recruited from inpatient and outpatient clinics at the Douglas Mental Health University Institute (Montreal, QC, Canada). To be eligible, patients (1) fulfilled criteria for a schizophrenia spectrum disorder, as confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders and medical chart review; and (2) had been treated for a minimum of four years. Twenty-seven healthy controls were recruited within the Institute’s catchment area using advertisements. Participants were between the ages of 18–50 years. Exclusion criteria are detailed in SA1. After exclusion, data from 23 healthy controls and 35 patients were kept for further analyses. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki, the Douglas Mental Health University Institute’s Research Ethics Board approved the study, and all participants provided informed written consent.

Clinical and demographic assessment

All participants were assessed with the Edinburgh Handedness Inventory (Oldfield, 1971), the Hollingshead two-factor index of social position to determine the parental socioeconomic status (Hollingshead, 1965) and either the SCID-I (patient version) to confirm diagnosis for patients or the SCID-NP (non-patient version) to confirm status as healthy controls (First, 1998). Clinical symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b). Medication history was obtained via self-reports and verified when necessary with the treating psychiatrist. All participants were also assessed at baseline with the Wechsler Abbreviated Scale of Intelligence (WASI) (Hays et al., 2002) to confirm that their IQ was greater than 70.

Experimental task

All participants completed the Semantic Encoding Memory Task (SEMT), developed to assess self-initiation of semantic encoding strategies in associative episodic memory with schizophrenia individuals (Guimond and Lepage, 2016). During the encoding phase of the SEMT, participants were presented with 128 pairs of objects (Fig. 1A). Importantly, participants were explicitly instructed to commit to memory each pair of objects, and were told they will need to remember which objects were paired together. Moreover, for half of the pairs, participants were required to answer a semantic question (indicated by the cue ‘Category?’), and for the other half they were required to answer a visualization question (indicated by the cue ‘Bigger?’). It is important to note that both encoding strategies questions oriented the participant towards ‘deep’ encoding of the stimuli, as both require extraction of feature information from each object and extrapolation of either their meaning (‘Category?’) or their real-life size (‘Bigger?’). Half of the pairs belonged to the same semantic category and the remaining half belonged to different categories, which led to four different encoding conditions (see Fig. 1C). We expected participants to use semantic encoding strategies for the condition where both objects were semantically related and they were explicitly prompted to use these strategies (the ‘Category?’ cue). The condition targeting the self-initiation of semantic encoding strategies was created when both objects were from the same semantic category and the orienting question involved a size judgment (the ‘Bigger?’ cue). In this condition, participants were not prompted to use the semantic information, but could still benefit from self-initiating semantic encoding strategies to better encode the object pair. Additional information about the task design is provided in SA1.

After the encoding task, participants performed a forced-choice recognition task (Fig. 1B) and were required to choose which second-object (among 4) presented on the right side of the screen was paired with the first-object on the left side of the screen during encoding. By only presenting previously seen objects, potential confounds from familiarity (e.g., I have not seen that object before, so can reject it as a possible choice) were avoided.
Behavioral analysis

To evaluate accuracy of participants on the encoding task, we performed a repeated measure $2 \times 2$ ANOVA with group as a between factor and the orienting encoding question (Bigger? vs. Category?) as the within-group factor. Solely for the behavioral encoding analyses, three healthy controls and two patients were excluded (see details in SA1).

For recognition performance during the SEMT, a $2 \times 2 \times 2$ ANOVA was performed to analyze main effects of the orientation question (Bigger? vs. Category?), semantic relatedness (unrelated vs. related), group (patients vs. healthy controls), and their interaction. To isolate the effect of self-initiation of semantic encoding strategies on task performance, planned paired $t$-test comparisons were then conducted for each group separately to determine any significant differences between the two conditions when both objects were related dependently on the encoding question. As a secondary analysis, we performed the same paired $t$-test comparisons, separating patients with “poor” and “good” self-initiation.

fMRI and statistical analyses

Data were analyzed using a general linear model (GLM), in which individual conditions were modeled with the canonical hemodynamic response function implemented in Statistical Parametric Mapping (SPM8, Welcome Department of Cognitive Neurology, London, UK). Scanning parameters and preprocessing details are described in the SA1. A subject-specific fixed-effects model was used to estimate the effect of each event during encoding, and the motion parameters were entered as covariates in the model. Seven event types were labeled and included in the model: a single event type for the first object of each pair, four event types for each encoding condition, time locked to the presentation of the second object, and two event types for the onset of the encoding questions. Second-level, random-effect analyses were then performed to measure the activity related to the use of semantic encoding strategies with two specific contrasts time-locked to the onset of the second objects of each pair (when participants started encoding the association between the two objects sequentially presented, see Fig. 1A.)

The first contrast isolated the activity related to semantic encoding strategies (objects semantically related > objects unrelated) when the participants were prompted by the encoding question “Category?”. The second contrast isolated the activity related to the self-initiation of semantic encoding strategies by contrasting objects semantically related to objects unrelated when participants were not prompted to use this strategy (the encoding question was ‘Bigger?’). Within-group analyses were performed separately for controls and patients for each of these contrasts (and its inverse) by means of a random-effects model. The neural correlates of prompted and self-initiated semantic encoding strategies were examined with a whole-brain analysis. Finally, between-group effects were examined with 2-sample $t$-tests by means of a random-effects model. In an attempt to strike a balance between...
the risk of false-positives (Eklund et al., 2016) and false-negatives (Lieberman and Cunningham, 2009) we applied a cluster extent threshold determined by a non-parametric Monte Carlo simulation to correct for multiple comparisons (Slotnick et al., 2003). For within-group analyses, statistical significance was defined at the cluster level, using an uncorrected p-value of 0.001 at the single voxel level. Results of a Monte-Carlo simulation with 10,000 iterations indicated that a cluster of 114 contiguous voxels in the normalized image corresponded to a cluster significance of p < 0.05, corrected for multiple comparisons. Due to the reduction in the degrees of freedom for the between-group analysis, we used a p-value of 0.005 at the single voxel level, and using the same Monte-Carlo simulation approach as above, a cluster comprised of 171 resampled contiguous voxels was established as the threshold to attain significance at p < 0.05, corrected (see details in SA1).

Secondary analyses

We investigated potential individual differences in schizophrenia patients relating to their level of self-initiation of semantic encoding strategies. We performed a post-hoc analysis in which we separated our patient group into two subgroups, based on the presence of a deficit in self-initiation of semantic encoding. For consistency purposes, we followed the procedure we have developed and published (Guimond and Lepage, 2016), where the presence of "poor" self-initiation of semantic encoding was defined with an index of self-initiation deficit corresponding to a decrease in recognition accuracy of related pairs for the self-initiated condition relative to the prompted condition of at least 10%. This approach controls for overall memory performance while indexing differences in performance when semantic encoding is self-initiated. Considering our a priori hypothesis about the PFC, the significant clusters in the PFC from the within-group analysis in healthy controls were defined as our regions of interest (ROIs). Motivated by the idea that these regions were typically activated in healthy controls, we investigated the extent by which both subgroups of patients (with "poor" and "good" self-initiation of semantic encoding strategies) were using these brain regions. To do so, we compared differences in brain activity in these ROIs (related vs. unrelated, separately for when semantic encoding strategies were prompted, and self-initiated) in healthy controls compared to the two subgroups of patients. Using FSL (Jenkinson et al., 2012), we extracted the mean HRF beta value of these ROIs for all participants. Univariate ANOVAs in SPSS were performed using these beta values to investigate significant between-group differences, and if appropriate, post-hoc independent t-tests were performed, using Bonferroni correction, to further explore differences between each pair of groups.

Moreover, for each of these ROIs, we plotted the index of self-initiation deficit in SEMT that we used to split the group of patients and the HRF betas values for all participants. Exploratory bivariate correlations in SPSS were then performed between these two variables. Finally, we also explored possible correlations between this index of self-initiation deficit in SEMT with positive and negative symptoms in patients.

Results

Clinical and demographic data

As can be observed in Table 1, groups were equivalent on all demographic and clinical measures.

Behavioral results

Accuracy for the encoding questions asked to healthy controls ('Bigger?': mean = 83%, SD = 11%, 'Category?': mean = 87%, SD = 8%) and patients ('Bigger?': mean = 82%, SD = 13%, 'Category?': mean = 89%, SD = 8%) demonstrate participants were able to correctly perform the task. Participants performed significantly better when the question was 'Category?' compared to 'Bigger?', F(1, 51) = 12.27, p < 0.01, with no significant between-group effect, F(1, 51) = 0.05, corrected for multiple comparisons. Due to the reduction in the degrees of freedom for the between-group analysis, we used a p-value of 0.005 at the single voxel level, and using the same Monte-Carlo simulation approach as above, a cluster comprised of 171 resampled contiguous voxels was established as the threshold to attain significance at p < 0.05, corrected (see details in SA1).

| Table 1 |
| --- | --- | --- |
| **Demographic and clinical data.** | **Controls (N = 23)** | **Patients with “good” self-initiation (N = 18)** | **Patients with “poor” self-initiation (N = 17)** |
| **Mean** | **SD** | **Range** | **Mean** | **SD** | **Range** | **Mean** | **SD** | **Range** |
| **Age** | 33.78 N | 8.17% | 22–50 | 32.22 N | 7.01% | 24–48 | 33.06 N | 8.8% | 22–49 |
| Gender | | | | | | | | | |
| Male | 18 | 78 | 16 | 89 | 14 | 82 | | | |
| Female | 5 | 22 | 2 | 11 | 3 | 18 | | | |
| Parental socioeconomic status (SES) | | | | | | | | | |
| Lower | 4 | 17 | 0 | 0 | 1 | 6 | | | |
| Lower-middle | 6 | 26 | 6 | 33 | 6 | 35 | | | |
| Middle | 6 | 26 | 6 | 33 | 5 | 29 | | | |
| Upper-middle | 6 | 26 | 1 | 6 | 1 | 6 | | | |
| Upper | 1 | 4 | 0 | 0 | 2 | 12 | | | |
| Handiness category | | | | | | | | | |
| Right | 18 | 78 | 12 | 67 | 14 | 82 | | | |
| Ambidextrous | 1 | 4 | 1 | 6 | 1 | 6 | | | |
| Left | 3 | 13 | 5 | 28 | 2 | 12 | | | |
| Duration of illness (years) | 10.83 | 5.31 | 4–19 | 8.59 | 3.30 | 3–16 | 8.35 | 3.30 | 3–16 |
| Total SANS without attention | 17.5 | 10.05 | 0–33 | 23 | 11.66 | 1–43 | 20 | 11.66 | 1–43 |
| Total SAPS | 17.94 | 21.66 | 0–85 | 12.59 | 8.94 | 0–24 | 12 | 8.94 | 0–24 |
| Calgary depression | 2.28 | 2.23 | 0–7 | 2.47 | 3.61 | 0–13 | 2.31 | 3.61 | 0–13 |
| Hamilton anxiety scale | 5.44 | 4.64 | 0–16 | 5.59 | 5.42 | 0–21 | 5.49 | 5.42 | 0–21 |
| Medication (mg chlorpromazine) | 717.16 | 624.28 | 166.25–2043 | 617.84 | 390.09 | 148.8–1500 | 717.16 | 624.28 | 166.25–2043 |

Note: Antipsychotic doses were converted to chlorpromazine equivalents according to the literature (Jensen and Regier, 2010; Leucht et al., 2014; Woods, 2003) to allow for comparison between patient subgroups. Medication information is missing for 3 patients, handedness information is missing for one healthy control, and SES scores are missing for 6 patients due to missing/un-reported data on years of education completed by these patients’ parents.
During the recognition task, patients had significantly lower recognition performance than healthy controls across all conditions, \( F(1, 56) = 18.55, p < 0.001 \). We observed two significant two-way interactions between groups and the relatedness of the pairs, \( F(1, 56) = 22.82, p < 0.001 \), and between the relatedness of the pairs and the encoding questions, \( F(1, 56) = 4.58, p < 0.05 \). To break down these interactions, we used planned paired \( t \)-tests to determine any significant difference between the two conditions were both objects were related, depending on the encoding question, for each group separately. When both objects were semantically related, patients had significant lower performance when the encoding question was ‘Bigger?’ (mean = 73%, SD = 10%) compared to ‘Category?’ (mean = 79%, SD = 9%), \( t(34) = -4.00, p < 0.001 \), while healthy controls had similar performance regardless of encoding question (‘Bigger?’: mean = 81%, SD = 8%; ‘Category?’: mean = 83%, SD = 7%). \( t(22) = -1.67, p = 0.11 \). This interaction effect confirms the presence of a significant difficulty in self-initiating semantic encoding strategies observed in patients (see Fig. 2A).

When the patient group was divided into two subgroups (“poor” and “good”) self-initiation of semantic encoding strategies respectively, only patients with “poor” self-initiation had significantly lower performance when both objects were related and the question was ‘Bigger?’ (mean = 67%, SD = 10%) compared to when it was ‘Category?’ (mean = 81%, SD = 8%), \( t(16) = -11.45, p < 0.001 \). The “good” self-initiation group showed a similar pattern of performance to what was observed in healthy controls (‘Bigger?’: mean = 77%, SD = 7%; ‘Category?’: mean = 76%, SD = 10%), \( t(17) = 0.75, p = 0.46 \) (see Fig. 2B).

Within-group results

When healthy controls were prompted (‘Category?’) and encoded objects that were semantically related compared to unrelated, they exhibited significantly increased activation in the left DLPFC (BA 9), the left medial frontal gyrus (BA 10), the left supramarginal gyrus (BA39/40) and the right cerebellum (Fig. 3 and ST1). The inverse contrast showed significant increased activation in the left postcentral gyrus (BA 5) when both objects were unrelated. When healthy controls self-initiated (‘Bigger?’) and encoded objects that were semantically related compared to unrelated, they showed significant increased activity in the left superior frontal gyrus (BA 8/6), the left ventrolateral PFC (VLPFC, BA 47), the left parietal lobule (BA 7/39), the right inferior parietal lobule (BA 40), the left inferior temporal gyrus (BA 37), and the right cerebellum, and trending significant increased activity in the left DLPFC (BA 46), and the right inferior temporal gyrus (BA 37) (Fig. 3 and ST1). The inverse contrast showed significant increased activation in the right precuneus (BA 7) when both objects were unrelated.

Schizophrenia patients significantly activated the left middle frontal gyrus (BA 9/10/46), the left medial frontal gyrus (BA 9) and the bilateral cerebellum to a greater extent when they were prompted to use semantic encoding strategies with ‘Category?’ and, when the objects were semantically related, compared to unrelated. No significant differences were observed for the inverse contrast. When patients self-initiated (‘Bigger?’), only a cluster in the medial frontal gyrus (BA 6) was significantly more activated when both objects were related compared to unrelated (Fig. 3 and ST2). The inverse contrast showed significant increased activation in the cerebellum when both objects were unrelated.

Between-group results

The between-group analyses showed significant differences in brain activation for healthy controls and schizophrenia patients, but only for the contrast isolating the self-initiation of semantic encoding strategies (see Fig. 4 and ST3).

When self-initiating (‘Bigger?’) healthy controls had significant increased activity in left DLPFC (BA 10/46), left superior parietal lobule (BA 7), left inferior temporal gyrus, and cerebellum bilaterally compared to schizophrenia patients. Examination of the Beta values in these regions shows controls had greater activity for related trials, while patients did not show differences in activity for related or unrelated. Significant increased activations in healthy controls were also observed in subcortical regions (the left thalamus and the right caudate nucleus).

Group comparison revealed significant increased activation in schizophrenia patients in the left medial frontal gyrus (BA 6), the bilateral cingulate gyrus (BA 32), the bilateral lingual gyrus (BA 19), and the right fusiform gyrus (BA 37), and trending significant increased activation in the right medial frontal gyrus (BA 6), and the left precuneus (BA 7/31), compared to healthy controls when participants were self-initiating (‘Bigger?’). The examination of the HRF beta values suggests these differences were mainly driven by greater deactivations of these brain regions in healthy controls when they were encoding two objects semantically related versus unrelated (see SF1). This indicated that these effects were driven by differences in activity between conditions in the control groups, while patients again did not differentiate related and unrelated trials.

Secondary results

The brain regions in the PFC that were significantly more activated when healthy controls were prompted to use semantic encoding strategies, or self-initiated these strategies, are presented.

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**Fig. 2.** Semantic Encoding Memory Task (SEMT): Hit rate for each condition. Panel A: Comparison between healthy controls and schizophrenia patients. Panel B: Comparison between the two subgroups of patients with “poor” (Scz -) and “good” (Scz +) self-initiation of semantic encoding strategies. Scz – Schizophrenia patients, HC – Healthy controls, Error bars – standard deviation.
in the left panel of Fig. 5. No significant between-group differences were observed when participants were prompted to use semantic encoding strategies (‘Category?’), $F_{(2, 55)} = 0.77, p = 0.47$. However, we observed significant group differences in the two ROIs related to the self-initiation of semantic encoding strategies (‘Bigger?’) (BA 46: $F_{(2, 55)} = 3.97, p = 0.025$; BA 47: $F_{(2, 55)} = 7.23, p = 0.002$), but only between healthy controls, and the subgroup of patients with “poor” self-initiation ($p < 0.05$).

Moreover, a significant relationship was observed between the index of self-initiation deficit on the SEMT in all our participants, and the HRF beta values from the left DLPFC, $r = -0.35, p = 0.007$. Interestingly, the index of self-initiation deficit on the SEMT in patients also marginally correlated with the negative symptoms scores on the SANS (without attention), $r = 0.31, p = 0.06$.

**Discussion**

Our findings bring a novel perspective to the understanding of memory difficulties in schizophrenia by emphasizing the critical role of impaired self-initiation of elaborate encoding strategies. While previous studies show that patient's memory performance improves when structured encoding strategies are provided (Brebion et al., 2004; Chan et al., 2000; Danion et al., 2007; Fiszdon et al., 2006; Gsottschneider et al., 2011; Hazlett et al., 2000), the actual deficit in self-initiation of these strategies has not been studied extensively. Our behavioral and neuroimaging results provide us with a better picture of this deficit and identify its core neurobiological correlates, which could help guide therapies aimed at improving memory and cognition in schizophrenia.

We propose the DLPFC may play a core part in the self-initiation process of elaborate encoding strategies impaired in schizophrenia. This brain region has been implied in memory deficits in schizophrenia (Lepage et al., 2006; Ragland et al., 2012) as well as in the self-initiation of encoding strategies in healthy controls (Hawco et al., 2013). Impairments in self-initiation of encoding strategies in schizophrenia could be driven by a failure of supportive cognitive control functions which facilitate memory processing. This is in line with a recent study showing deficient cognitive control processes (mediated by the DLPFC) during different encoding tasks in schizophrenia (Ragland et al., 2015). This top-down process is putatively impaired in schizophrenia and requires the coordination of multiple brain regions, including the DLPFC and the parietal cortex (Lesh et al., 2011). Interestingly, these two regions showed reduced brain activity in our schizophrenia sample, emphasizing the potential importance for these regions in memory and cognitive impairments in schizophrenia.

These findings have important clinical implications. Considering that the self-initiation of elaborate encoding strategies plays an important role in memory deficits in schizophrenia, cognitive training emphasizing greater use of cognitive control strategies may be more effective than generalized routine-based memory training. We recently reported preliminary, but promising, evidence that patients with “poor” self-initiation of semantic encoding strategies can improve memory performance following a specific brief training targeting such strategies (Guimond and Lepage, 2016). Greater activity in the left DLPFC could be associated with such improvement, which should be investigated in future studies. These results (Guimond and Lepage, 2016) alongside those of our current study also suggest the importance of tailoring cognitive therapy to the specific deficits observed in each individual. The analysis of the two subgroups of patients based on their level of self-initiation suggests differences in both the nature of the cognitive deficit (with patients with “good” self-initiation showing minimal memory impairment) and the underlying neural changes.
Therefore, patients in the “poor” self-initiation subgroup would be expected to benefit the most from targeted strategy based cognitive training. Properly addressing the memory impairments in these patients is particularly important considering the strong association between verbal episodic memory impairments and functional outcome (Lepage et al., 2014), as well as negative symptoms (Hovington et al., 2013). We also observed that the more difficulties patients presented in self-initiating semantic encoding strategies during the SEMT, the more severe their negative symptoms were. Hence, tailored treatment that could improve semantic encoding strategies in patients and potentially normalize the activity in the left DLPFC could also potentially have a positive impact on patient outcome.

An important strength of the study is that heterogeneity of the patients with respect to their capacity to self-initiate semantic encoding strategies was taken into account. Heterogeneity in cognitive performance in schizophrenia is well documented (Gilbert et al., 2014; Joyce and Roiser, 2007). Nonetheless, most neuroimaging studies comparing groups of patients with healthy controls collapse all patients into a single group, without consideration of potential cognitive differences and how that might affect underlying biology. In the current study, we investigated to which extent patients with either “poor” or “good” self-initiation of semantic encoding strategies used brain regions that were normally recruited by healthy controls. We observed significant differences only between healthy controls and the subgroup of patients with “poor” self-initiation.

**Fig. 4.** Brain regions showing increased activation in healthy controls relative to schizophrenia patients when self-initiating semantic encoding strategies. This is based on the comparison between two conditions, when encoding two semantically related objects compared to unrelated, and the question (“Bigger?”) was not prompting them to do so. Only statistically significant clusters are presented. A) Left dorsolateral prefrontal cortex (DLPFC) B) Left superior parietal lobule C) Left inferior temporal gyrus. Scz – Schizophrenia patients, HC – Healthy controls, Error bars – standard deviations.
No such differences in this brain region were observed in patients who had ‘low to mild’ verbal memory deficits. These results, along with those from the current study, suggest that variability in performance should be taken into consideration in further studies investigating the neurobiology of memory in schizophrenia.

Our results should be appraised in the context of limitations. First, the cognitive construct of self-initiation is challenging to study. In the current study, healthy controls demonstrated increased recognition equally in both ‘Bigger?’ and ‘Category?’ conditions when objects were semantically related, suggesting they are in fact using the encoding strategy targeted by this study in the absence of an external cue. Thus, we have extrapolated this as evidence for the presence of self-initiated cognitive processing. Critically, patients performed worst in the ‘Bigger?’ condition for related trials, which strongly suggests they were making less use of semantic information to facilitate encoding when they were not externally prompted to consider such information. However, schizophrenia patients also showed an improvement for related over unrelated pairs. This suggests that on average, patients exhibited a deficit in self-initiation, but this cognitive process was not entirely absent. Another limitation to consider is the preponderance of patients in our sample taking medication. Therefore, caution should be exercised when generalizing these results to unmedicated schizophrenia patients, or individuals in the early phase of their illness. Another point to mention is that schizophrenia can negatively affect semantic networks (Chen et al., 1994), and thereby cause difficulties in detecting similarities among objects (Brebion et al., 2004). However, in light of our present results, patients did not significantly differ from healthy controls when cued to use efficient strategies. Moreover, there is no clear support for altered or deficient semantic priming in schizophrenia (Pomarol-Clotet et al., 2008). Therefore, it is unlikely this impacted our results. Some could also argue that participants used the notion of category, prompted during the encoding, to guide their decisions during recognition trials. However, this effect is unlikely to be an explanatory factor of participants’ performance during the task, because 50% of the trials with the ‘Category’ encoding question terminate in a negative outcome (i.e. presented objects were unrelated). Hence, cues probing information about the category of presented objects may have had opposing effects, such that some trials served to facilitate performance, while others interfered with performance. Considering the relatively high level of successful recognition in both conditions (‘Bigger’ or ‘Category’) involving...
objects from the same category, it seems unlikely that these results were obtained by chance performance. Finally, although our focus resided on the difficulties to self-initiate semantic encoding strategies in schizophrenia, these patients also had lower memory performance than healthy controls when the objects were semantically unrelated. This suggests that their deficits in associ- 
itive episodic memory cannot be solely explained by impairment in semantic encoding strategies. Therefore, further studies should investigate the impact of other encoding strategies possibly impaired in schizophrenia, which could account for their diffi-
culties in encoding pairs of unrelated objects.

In summary, schizophrenia patients have difficulties in self-
initiating semantic encoding strategies in associative episodic memory, for which the left DLPFC plays a critical role. Nonetheless, patients can benefit from prompting during the encoding of semantically related pairs, and activate similar brain regions as healthy controls. The current results provide critical new insights into the interpretation of encoding strategies deficits in schizo-
phrenia, and have important clinical implications for the develop-
ment of novel and targeted memory treatments.

Disclosures

All authors reported no biomedical financial interests or poten-
tial conflicts of interest.

All authors contributed to the design of the study. SG undertook all statistical analyses and wrote the first draft of the manuscript. All authors significantly contributed to the interpretation of the data and to the revisions of the manuscript, and have approved the final article.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://
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