Strategy for Semantic Association Memory (SESAME) training: Effects on brain functioning in schizophrenia

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\section*{A R T I C L E   I N F O}

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\section*{A B S T R A C T}

Self-initiation of semantic encoding strategies is impoverished in schizophrenia and contributes to memory impairments. Recently, we observed that following a brief training, schizophrenia patients had the potential to increase the self-initiation of these strategies. In this study, we investigated the neural correlates underlying such memory improvements.

Fifteen schizophrenia patients with deficits in self-initiation of semantic encoding strategies were enrolled in a Strategy for Semantic Association Memory (SESAME) training. Patients underwent a memory task in an fMRI scanner. Memory performance and brain activity during the task were measured pre- and post-training, and changes following training were assessed. We also investigated if structural preservation measured by the cortical thickness of the left dorsolateral prefrontal cortex (DLPFC) predicted memory improvement post-training.

Memory training led to significant improvements in memory performance that were associated with increased activity in the left DLPFC, during a task in which patients needed to self-initiate semantic encoding strategies. Furthermore, patients with more cortical reserve in their left DLPFC showed greater memory improvement.

Our findings provide evidence of neural malleability in the left DLPFC in schizophrenia using cognitive training. Moreover, the brain-behavioural changes observed in schizophrenia provide hope that memory performance can be improved with a brief intervention.

1. Introduction

Episodic memory deficits represent a core feature of schizophrenia and are related to poorer functional outcomes (Green et al., 2000, 2004). Hence, finding ways to improve episodic memory in schizophrenia is critical. Thus far, available pharmacotherapy has not been shown to have a clear impact on memory impairments in this population (Barch, 2010; Genevsky et al., 2010; Minzenberg and Carter, 2012). This may in part explain why during the past decade, there have been several studies on the use of psychological cognitive remediation therapies (CRT) for schizophrenia patients. Meta-analyses have reported a small to moderate positive effect of these CRT programs on episodic memory (McGurk et al., 2007; Wykes et al., 2011). While this suggests that patient’s episodic memory ability could be malleable, the neural correlates that support these improvements remain unknown.

Interestingly, CRT programs that explicitly teach the use of effective strategies in patients have been associated with better functional outcomes (Wykes et al., 2011). These CRTs were designed to target various cognitive deficits and to provide patients with effective strategies that can have positive implications, both in therapy and in everyday life. Taking this into consideration, we recently developed a brief cognitive training to improve a specific mnemonic strategy impaired in schizophrenia (Guimond and Lepage, 2016), namely the self-initiation of semantic encoding strategies. In other words, our training encourages the spontaneous use of semantic features to help memorize relationships between different pieces of information in episodic memory. It is well known that schizophrenia patients have specific difficulties in the self-initiation of semantic encoding strategies (Brebin et al., 2004;...
It remains to be determined whether improvements in memory performance are associated with changes in neural activity. Such a change would suggest that diminished or abnormal neural activity, often observed in schizophrenia and associated with suboptimal response to cognitive challenges, can be restored with a specific type of cognitive training. The left dorsolateral prefrontal cortex (DLPFC) plays a critical role in the ability to self-initiate semantic encoding strategies in healthy controls (Hawco et al., 2013a, 2013b). In a recent study, we also reported lower activity in this brain region related to poor self-initiation of these strategies in schizophrenia patients (Guimond et al., 2017). The goal of the current study was to investigate the impact on memory and brain activity of a brief Strategy for Semantic Association Memory (SESAME) training program, with a group of schizophrenia patients with deficits in the self-initiation of semantic encoding strategies. We hypothesized that, after the training, patients will use more efficient semantic encoding strategies, and that this will be associated with increased activity in brain regions subserving such memory processes, including the left DLPFC. Finally, we also investigated if pre-treatment structural preservation in the left DLPFC area (cortical reserve; Keshavan et al., 2011), could predict greater memory improvements following the training.

2. Methods

2.1. Participants

Exclusion criteria for all participants consisted of: (1) lifetime history of other medical or neurological conditions that may alter cognition; (2) family history of hereditary neurological disorders; (3) substance dependence diagnosis within the last three months; (4) depression, as confirmed by a score of 8 or higher on the Calgary Depression Scale; and (5) contraindication for MRI scanning. 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; (2) had been treated for a minimum of four years; and (3) between the ages of 18 – 50 years.

Patients included in this study were recruited from inpatient and outpatient clinics at the Douglas Mental Health University Institute (Montreal, QC, Canada), through their psychiatrist or case manager, and were taking part in a larger study investigating neural correlates of insight in patients with enduring schizophrenia (Emami et al., 2016). More specifically, the current study focused on a subgroup of patients who also participated in a previous memory study (Guimond et al., 2017) and who demonstrated a deficit in self-initiation of semantic encoding strategies. A total of 17 out of the 35 patients in Guimond et al. (2017) exhibited poor self-initiation of semantic encoding strategies and were then selected for the training in the current study following the same selection procedure as in Guimond and Lepage (2016). To be selected, a participant had to show a decrease in performance (of at least 10%) in the condition where they needed to self-initiate semantic encoding strategies compared to the condition where they were helped by the orientation question. From these 17 patients, one patient did not complete the training due to admission to an intensive rehabilitation program, and another was excluded from the analyses as the participant fell asleep in the scanner post-training. Hence, 15 patients with difficulties in the self-initiation of semantic encoding strategies completed the training and were included in the analyses presented in this manuscript. The Douglas Mental Health University Institute’s Research Ethics Board approved the study and all participants provided informed written consent.

2.2. Clinical, demographic, and neuropsychological assessment

All participants were assessed with the Edinburgh Handedness Inventory (Oldfield, 1971), the Hollingshead two-factor index of social position (Hollingshead, 1965), and either the SCID-I for DSM-IV (patient version) to confirm each patient’s diagnosis or the SCID-I (non-patient version) to confirm status as healthy controls. 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. The Hamilton Anxiety Scale (HAS) (Riskind et al., 1987) and the Calgary Depression Scale (CDS) (Addington et al., 1993) were administered to all participants. Patients’ negative and positive 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). Patients’ current medication was obtained via self-reports and confirmed when necessary with the treating psychiatrist. Research staff not involved with the current intervention performed the clinical assessments.

Standardized memory assessments were performed at baseline and post-training (using an alternate version). All participants completed the first five trials of the California Verbal Learning Test (CVLT-II; List A or B) to objectively assess their use of semantic clustering (Delis et al., 1987). Importantly, only the first five trials were administered to the participants to prevent prompting the use of semantic encoding strategies with the name of the categories. The Brief Visuospatial Memory Test–Revised (BVMT-R) was used as a control measure for the practice effect, as well as a measure of the training specificity (Benedict et al., 1996). Indeed, the training specifically targeting semantic associative encoding was expected to increase memory performance on the CVLT-II, but not on the BVMT-R.

2.3. Semantic Encoding Memory Task (SEMT)

Following these tests, participants completed the Semantic Encoding Memory Task (SEMT, see Guimond and Lepage, 2016, and Guimond et al., 2017). Participants were instructed to memorize 128 pairs of items; half of the pairs were related (same category) and half were unrelated. In addition, for half of the encoding trials, participants needed to indicate whether both items were from the same category or not (as cued by ‘Category?’); for the other half, they needed to indicate which item was bigger in real life (as cued by ‘Bigger?’). Each of the four different encoding conditions contained 32 pairs of items and were pseudo-randomized in 6 different versions of the task. Importantly, an effort was made to have one object of each pair that was bigger than the other. We also interchanged the encoding question (Category? or Bigger?) in different versions of the task. Hence, there were always two versions sharing the same pairs of objects, but presented with a different question. After encoding, participants performed a forced-choice recognition task, where they selected which item on the right side of the screen (among 4 previously shown during the encoding) was paired with the item on the left side of the screen during encoding. After the training, participants performed a version of the task containing different pictures than the version they did before the training.

The encoding condition targeting self-initiation of semantic encoding strategies resides in the juxtaposition of semantically-related objects and the orientation question not cueing semantic strategies (i.e., ‘Bigger?’, see Fig. 1). In this condition, participants were not explicitly cued to use semantic information but needed to self-initiate semantic encoding strategies to facilitate the encoding of the pair of items. Our design is based on the assumption that participants who can self-initiate semantic encoding strategies during the SEMT have similar performance when both items to memorize are from the same category irrespective of the encoding cue (‘Category?’ or ‘Bigger?’) (see Guimond et al., 2017).
2.4. Subjective Strategies Encoding Questionnaire

After the recognition task, participants filled out a Subjective Strategies Encoding Questionnaire to investigate their use of self-initiation of semantic encoding strategies. This questionnaire asked to what extent participants thought they used three different encoding strategies (repetition, visualisation, and semantic strategies; see Supplementary Material 2). In order not to bias or prompt the participants into using a specific strategy, given that they would perform another version of the task after the training, they were told that there were no wrong or correct answers, and that all strategies could have been used or not during the encoding task.

2.5. Strategy for Semantic Association Memory (SESAME) training

SESAME consists of two one-hour training sessions conducted over two weeks that focuses on enriching self-initiation of semantic memory encoding strategy use. At the start of the first session, a meta-memory presentation introduced the objective of the training, during which the therapist helped participants to understand the training content. The presentation was partly inspired by the meta-cognitive training of Moritz et al. (2010), and required participants to reflect on their own memory processes: how does memory work, why do we forget information, how can we improve our memory, etc. Then, the training began by explicitly teaching how to use semantic information from different stimuli to organize information into groups more easily. Participants first practiced with a task following explicit instructions and cues to help categorize different items. Second, they were asked to apply these strategies within different memory tasks. Four distinct tasks have been created with different types of stimuli: visual (memorize items in different rooms), auditory (food verbally ordered in a restaurant), and verbal (grocery lists and word pairs). Participants were performing two of these tasks during the first session, and the four tasks during the second session.

After the first session, as homework, participants were asked to find an example where the strategies learned could be used to improve memory in daily life; this was discussed at the end of the second training session. Also, at the end of both sessions, time was allocated for a bridging discussion where participants provided feedback about the activities and the therapist questioned participants about how applying efficient semantic encoding strategies could be useful in their daily life. The intervention was delivered individually by one of the authors (S.G.) and supervised by a licensed neuropsychologist (M.L.). The sessions took place in a quiet room at the Douglas Mental Health University Institute, Montreal, QC, Canada. The training is detailed in Supplementary Material 3 of Guimond and Lepage (2016).

2.6. Behavioural analyses

To evaluate the performance of patients during the encoding of the SEMT as a function of time point (pre- vs. post-training), orientation question (Bigger? vs. Category?), and their interaction, a $2 \times 2$ repeated measures analysis of variance (ANOVA) was performed. Then, to evaluate the performance of patients during the recognition of the SEMT as a function of time point (pre- vs. post-training), orientation question (Bigger? vs. Category?), semantic relatedness (unrelated vs. related), and their interaction, a $2 \times 2 \times 2$ repeated measures ANOVA was used. Planned paired $t$-test comparisons were then conducted to determine significant recognition performance differences (pre- and post-training) for each condition of the SEMT, using a Bonferroni correction. Participants’ subjective evaluation of their use of semantic encoding strategies for the self-initiation condition after having completed the recognition task was also investigated using paired $t$-tests (pre- and post-training).

Differences pre- and post-training for the corrected total recall and semantic clustering (chance-adjusted) of the first 5 trials of the CVLT-II, as well as the delayed recall and recognition indices of the BVMTR were investigated using paired $t$-test comparisons. Considering the small sample size, we also included a standardised mean effect size (Cohen’s $d$) to the pre- and post-training $t$-tests. All behavioural analyses were conducted using SPSS version 20 (SPSS, Chicago, IL, USA).

2.7. fMRI 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 parameter and preprocessing details are described in Supplementary Material 1. 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. Item-1, Item-2, and the orienting questions were entered in the model, but all contrasts were time-locked at the onset of Item-2, thus when participants were encoding the association between the two.

Second-level random-effect analyses were performed to measure the activity time-locked at the beginning of Item-2 presentation with a whole-brain analysis, and conducted separately in our group of patients for the two timepoints: pre- and post-training. The contrast we used to isolate the activity related to the self-initiation of semantic encoding strategies, we compared the brain activity when participants encoded items (semantically related > unrelated) when they were not cued to use this strategy (the orienting question was ‘Bigger?’). The inverse contrast was also explored (semantically unrelated > related). We used a whole-brain paired $t$-test to observe significant change in activity after the training using these contrasts. 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 using $p < .05$ corrected (Slotnick et al., 2003)(see details in Supplementary Material 1). For visualisation purpose, we used FSL (Jenkinson et al., 2012) to extract the mean HRF.
beta values of the significant clusters from the whole-brain analyses for each timepoint.

2.8. Cortical thickness analyses

Cortical thickness was analyzed using the CIVET processing pipeline (version 1.1.10; Montreal Neurological Institute at McGill University, Montreal, Quebec, Canada). T1-weighted images were registered to the ICBM152 nonlinear template with a 9-parameter linear transformation (Collins et al., 1994). The T1s were then corrected for inhomogeneities (Sled et al., 1998) and classified into different tissue types (Zijdenbos et al., 2002). Deformable models were used to create white and gray matter surfaces for each hemisphere separately (Kim et al., 2005; MacDonald et al., 2000). From these surfaces, the distance between the white and gray surfaces was measured (Lerch and Evans, 2005) and was subsequently blurred using a 20-mm surface-based diffusion blurring kernel in preparation for statistical analyses (Lerch et al., 2008).

The two main gyri forming the left DLPFC, namely the left dorsolateral superior frontal gyrus and the left middle frontal gyrus, were defined as ROIs using the cortical parcellations available in the Automated Anatomical Labeling atlas (AAL) (Tzourio-Mazoyer et al., 2002) by using the intersection of atlas regions and the cortical surface. Mean cortical thickness values for these ROIs were then extracted using the SurfStat package (Worsley et al., 2009) in MATLAB (Mathworks, Inc.), using the AAL atlas. Using SPSS, we then performed partial correlation analyses between the mean cortical thickness in these ROIs and the percentage of improvement at the task following the training, entering age and sex as covariates.

2.9. Effect of medication

Post-hoc correlations were performed to explore possible relationships between the amount of antipsychotic medication used by patients, as measured by chlorpromazine equivalents, and the significant change observed in memory performance and brain activity, as well as the measure of cortical thickness in the DLPFC at baseline. We also explored potential effect of typical and atypical antipsychotics intake on the improvement on the SEMT post-training, using an independent t-test comparison.

3. Results

3.1. Demographical and clinical results

Table 1 shows the demographical and clinical data of all participants (schizophrenia (n = 13), schizoaffective disorder (n = 1), and psychosis not otherwise specified (n = 1)).

<table>
<thead>
<tr>
<th>Demographic and clinical data</th>
<th>Schizophrenia patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean = 32.13, SD = 8.58, Range = 22–49</td>
</tr>
<tr>
<td>SANS (without attention) total</td>
<td>Mean = 22.53, SD = 12.39, Range = 1–43</td>
</tr>
<tr>
<td>SAPS total</td>
<td>Mean = 11.93, SD = 9.25, Range = 0–24</td>
</tr>
<tr>
<td>Calgary Depression Scale</td>
<td>Mean = 2.53, SD = 3.78, Range = 0–13</td>
</tr>
<tr>
<td>Hamilton Anxiety Scale</td>
<td>Mean = 5.2, SD = 4.92, Range = 0–21</td>
</tr>
<tr>
<td>Medication (mg chlorpromazine)</td>
<td>Mean = 611.44, SD = 385.80, Range = 148.80–1500</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>Mean = 8.13, SD = 3.04, Range = 3–16</td>
</tr>
</tbody>
</table>

Note: SES is missing for one patient because he could not remember how many years his parents went to school, and we could not calculate the SES score. Medication information is also missing for one patient.

3.2. Behavioural results

Accuracy for the encoding questions before training (mean = 84%, SD = 6%) and after the training (mean = 88%, SD = 9%) demonstrate that patients could correctly perform the task. A repeated measures ANOVA in the group of patients at pre- and post-training revealed a significant interaction between the orientation question and the timepoint, F1, 14 = 9.31, p = 0.006. Post-hoc t-tests revealed that patients had similar performance when answering the question ‘Category?’; pre- (mean = 88%, SD = 7%) and post- (mean = 88%, SD = 7%) training, t1, 14 = .11, p = .92 but significant pre- (mean = 80%, SD = 12%) and post- (mean = 88%, SD = 6%) differences for the question ‘Bigger?’ t1, 14 = 3.22, p = .006.

The repeated measures ANOVA (with pre- and post- measures) on recognition performance revealed a significant main effect of the training, F1, 14 = 5.53, p = .034, and a significant interaction between the orientation question and the timepoint, F1, 14 = 10.22, p = .006. Paired t-tests performed to investigate the specific pre- and post-training effect on each condition showed a significant increase in performance only in the condition where participants had to self-initiate semantic encoding strategies (when both objects were related and the orienting question was ‘Bigger?’; see left panel Fig. 2; mean pre = 67%, SD pre = 10%, mean post = 79%, SD post = 10%), t1, 14 = 3.99, p = .001, d = 1.2.

These behavioural results are also concordant with the subjective report that participants gave regarding their use of semantic encoding strategies (see right panel Fig. 2). Indeed, for the condition when participants needed to self-initiate semantic encoding strategies, patients reported a trend of using semantic encoding strategies more often after the training compared to before, t1, 14 = −1.91, p = .07, d = −.49.

Participants also significantly increased their level of semantic clustering over the first 5 trials of the CVLT-II (Chance-Adjusted), t1, 14 = −2.38, p = .03, d = −.62, with a trend towards increased total recall t1, 14 = −1.78, p = .09, d = −.46. No significant improvements were reported on the BVMT-R for the delayed recall, t1, 14 = −1.10, p = .28, d = −.28.

3.3. fMRI results

At baseline, no significant activation was observed in the group of patients when we compared the encoding of related versus unrelated pairs of items (and its inverse). Interestingly, after the training, we observed significantly greater brain activation in the bilateral DLPFC (BA 9), as well as in the right inferior parietal lobule (BA 40) when patients encoded semantically related items relative to unrelated (see Fig. 3, and Table S1 in Supplementary material 1).

The whole-brain analysis using paired t-test to isolate the significant brain activity changes as a function of the training showed a significant increase in brain activity in the left DLPFC after the training, when patients were self-initiating semantic encoding strategies (see Fig. 4, and Table S2 in Supplementary material 1).

3.4. Cortical thickness results

Cortical thickness analysis demonstrated that patients with greater...
3.5. Effect of medication

Post-hoc analyses revealed no significant association with antipsychotic medication dose on any changes observed in memory performance or brain activity, nor on the cortical thickness at baseline (p > .3). No significant difference on memory performance was observed between patients using only atypical antipsychotics (n = 7) compared to those using only typical antipsychotics, or a combination of both (n = 8) (p = .51).

4. Discussion

We observed that schizophrenia patients could improve their episodic memory performance, and exhibit changes in brain functioning following SESAME. Not only were schizophrenia patients able to increase self-initiation of semantic encoding strategies after the training (as observed on the CVLT-II and the SEMT), but also, these improvements were reflected at the level of brain activity, specifically within the left DLPFC. Previous findings of hypoactivity in the left DLPFC may be better accounted for by the patient’s inability to initiate encoding strategies (Lepage et al., 2006; Ragland et al., 2012, 2009). In line with this, we recently observed that schizophrenia patients with lower self-initiation of semantic encoding strategies also have lower brain activity in this region (Guimond et al., 2017). The current study provides novel evidence that implementing such strategies appears to increase brain activity within this clinical population. Furthermore, these results bring hope to the treatment of episodic memory deficits in schizophrenia, and posit the left DLPFC as a specific target for future interventions.

Our behavioural results confirm that schizophrenia patients with specific deficits in the self-initiation of semantic encoding strategies have the capacity to improve this ability. Other studies have also shown that schizophrenia patients are able to increase their level of semantic clustering when instructed to regroup the words in categories during the encoding task, or when they received the name of the categories shortly prior to carrying out the task (Chan et al., 2000; Fiszdon et al., 2006). Importantly, in the present study, as well as in Guimond and Lepage (2016), which described a behavioural study using the same intervention, patients not only used these strategies when they were cued to do so, but they also learned to spontaneously self-initiate those strategies following a brief cognitive training. Cues that indicate which strategies to use when memorizing information in daily life are quite rare, thus being able to self-initiate strategies for improving memorization is essential and adaptive. As a result, improving patients’ self-initiation could also have a positive impact on their level of functioning within the community.

The left DLPFC plays a key role in the self-initiation of semantic encoding strategies in healthy controls and in the deficits observed in schizophrenia (Guimond et al., 2017; Hawco et al., 2013a, 2013b). Our findings show evidence of neural malleability of the left DLPFC in schizophrenia patients accompanied by enhanced memory encoding function of this brain region, when provided with the proper training. This is in line with results from two recent meta-analyses reporting increased activity in the prefrontal cortex following CRT in schizophrenia (Ramsay and MacDonald, 2015; Wei et al., 2016). However, the studies included in these meta-analyses observed PFC activity changes mainly during tasks targeting working memory or executive function. Increased PFC activation following CRT has also been observed with improvement in cognitive control (Keshavan et al., 2017) and affect recognition (Habel et al., 2010; Hooker et al., 2013). With our current study, we show for the first time a similar increase in PFC activity following specific improvement in semantic encoding strategies during associative memory task.

Moreover, CRT is usually provided over a long period of time, requiring sustained motivation from the patients. Brief and specialized modules, such as the training presented in this study, represent a novel and useful approach that could be added to existing CRT protocols. In the current study, it took only two sessions of training to observe significant changes in the left DLPFC, which is very promising. The fact that we selected only patients with an initial deficit of self-initiation might have contributed to this effective intervention response. CRT commonly trains patients across multiple cognitive domains (McGurk et al., 2007; Wykes et al., 2011), and our results suggest that greater consideration of individual cognitive profiles could possibly improve the efficacy of these treatments (Wykes and Spaulding, 2011).

Another important aspect of the current study, is the investigation of cortical reserve as a neural predictor of improvement following the training. The concept of cortical reserve in schizophrenia is relatively recent. While previous studies on schizophrenia have showed that cortical alteration in the PFC could predict poor outcome following antipsychotic drug treatment (Prasad et al., 2005; Kasparek et al., 2009), only one study investigated the impact of cortical reserve on outcome following CRT (Keshavan et al., 2011). In this study, Keshavan et al. (2011) observed that broad cortical surface area and gray matter volume at baseline predicted greater improvement on social cognition after one year of CRT. Interestingly, our findings show that patients with greater pre-training cortical reserve in the left DLPFC had greater improvement at the SEMT following a brief training. Together, these
results suggest that cortical reserve could help predict outcomes following various cognitive interventions in schizophrenia. Further studies should particularly investigate the role of cortical reserve in key brain structures targeted by the treatment, as it has the potential to facilitate the development of personalized intervention for patients (Keshavan et al., 2011, 2014; Kurtz, 2012).

Increases in PFC activity following brief semantic encoding training have also been observed in elderly adults (Kirchhoff et al., 2012), in patients with prefrontal cortex lesions (Miotto et al., 2013), and in patients with traumatic brain injury (Lepping et al., 2015). Taking these recent studies into consideration, it is possible that semantic encoding strategies may improve memory performance and alter PFC activity in multiple clinical populations. A better understanding of the neural correlates of memory improvements in schizophrenia could thus provide a potential new target for the development of cognitive treatments across other clinical conditions.

While our findings suggest a positive impact of SESAME on the brain in schizophrenia, future studies will need to evaluate lasting efficacy, and whether it improves patient’s functional outcome. Moreover, the interpretation of the results should be appreciated considering the current limitations, including the relatively small sample size and the lack of proper control group for the intervention. A randomized controlled trial investigating durable change of SESAME and potential impact on functional outcomes, with a larger sample size and enough power to use more stringent control of false-positive results (Eklund et al., 2016) is warranted in future work. Some could also argue that using a questionnaire of strategies after the task could have probed the participants to use more strategies the second time. However, different strategies were indicated on the questionnaire (e.g., visualisation, repetition). Hence, it is very unlikely that by itself, the questionnaire could have caused the specific increase in self-initiation of semantic encoding strategies observed post-training. To assess the specificity of the training, we also included a control task (BVMT) in the current design. Our participants only improved their performance on the

Fig. 3. Upper panel: Brain activation in patients observed after the training when they encoded semantically related items compared to unrelated, and the orienting question was not cuing them to use semantic encoding strategies (i.e. ‘Bigger?’). DLPFC = dorsolateral prefrontal cortex, IPL = Inferior parietal lobule. Lower panel: HRF beta values observed in these regions pre- and post-training for each condition of encoding. Error bars represent the standard deviation. HRF = hemodynamic response function.
targeted tasks and conditions, and not on the control task, which increases the confidence that the observed changes were related to the specific training. Finally, episodic memory deficits are also present in early schizophrenia (Czepielewski et al., 2015), and unmedicated first-episode patients (Censits et al., 1997; Hill et al., 2004). Meta-analyses even reveal impairments in memory in individuals at clinical or genetic high-risk of developing psychosis (Valli et al., 2012). Cognitive remediation could be a promising avenue to alleviate cognitive deficits in early course schizophrenia and prodromal individuals (Lewandowski, 2016). In line with this, there is recent evidence for the potential benefits of cognitive training in early course schizophrenia (Eack et al., 2009, 2010; Revell et al., 2015) and high-risk individuals (Hooker et al., 2014). Hence, these individuals are likely to benefit from similar training as SESAME, and future studies should investigate this.

In summary, these novel results suggest that SESAME, a brief intervention, is sufficient to improve the self-initiation of specific memory strategies and alter DLPFC activity in schizophrenia. As mentioned above, episodic memory is a key factor for better functional outcome in this illness. Therefore, treatments showing combined brain-memory improvements could positively impact the daily life of these patients, and should be encouraged.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jpsychres.2017.10.010.

References


Andreason, N.C., 1984a. Scale for the Assessment of Negative Symptoms (SANS). University of Iowa.


