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Greater neuronal responses during automatic semantic processing in schizophrenia

Lisa B. Wilson^a, Donald C. Rojas^a, Shireen Shatti^a, and Jason R. Tregellas^{a,b}

^aDepartment of Psychiatry, University of Colorado Denver, Aurora

^bDenver VA Medical Center, Research Service, Denver, Colorado, USA

Abstract

A core feature of schizophrenia is a disturbance of associative processes. To date, no functional MRI studies have investigated semantic priming in schizophrenia under experimental conditions that measure automatic, as opposed to strategic, processing. The present study's focus was to investigate hemodynamic responses during indirect semantic priming at a short stimulus onset asynchrony (i.e. 350 ms), conditions which are considered to be a particularly sensitive measure of automatic spreading activation during semantic processing and of the associative disturbances in schizophrenia. Seventeen individuals with *DSM-IV*, schizophrenia and 15 comparison participants underwent functional scanning while performing a lexical decision task on directly related, indirectly related, unrelated, and word/nonword pairs. A random-effects region of interest analysis within a priori temporal and frontal regions was performed. Whereas comparison individuals exhibited hemodynamic suppression in response to priming, individuals with schizophrenia exhibited hemodynamic enhancement. Relative to the comparison group, these enhancements were observed in the left fusiform and superior temporal gyri for indirectly related word pairs relative to unrelated pairs. Greater priming-related responses within temporal regions may reflect increased and prolonged automatic spreading activation during semantic processing in schizophrenia.

Keywords

functional magnetic resonance imaging; fusiform gyrus; schizophrenia; semantic priming; superior temporal gyrus

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Correspondence to Lisa B. Wilson, Department of Psychiatry, University of Colorado Denver, 13001 East 17th Place, Aurora, CO 80045, USA, Tel: + 1 303 724 4992; fax: + 1 303 724 3594; lisa.wilson@ucdenver.edu.

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Conflicts of interest

There are no conflicts of interest.

Introduction

From its earliest descriptions, a disturbance of associative processes has been regarded as a core feature of schizophrenia [1]. Bleuler, who coined the term schizophrenia, observed heightened associations between words at the expense of overall themes in the discourse of his patients. These associations were often indirect wherein two words were related through another unspoken mediating word. Bleuler considered these indirect associations to be particularly significant to schizophrenia's symptomatology and believed that the disturbances in general arose from a yet to be discovered brain pathology.

Towards an understanding of this hypothesized brain pathology, recent investigations of the associative disturbances in schizophrenia have utilized functional magnetic resonance imaging (fMRI) in combination with semantic priming paradigms. Semantic priming refers to the influence of semantic context on word recognition speed such that a target word is recognized more rapidly when preceded by a semantically related than by a semantically unrelated prime word [2]. Experimental conditions, in particular the stimulus onset asynchrony (SOA) (i.e. interval between prime and target onset), are thought to influence the type of lexical-semantic processing underlying the priming effect. At short SOAs (i.e. 400 ms or less), priming is generally explained by an automatic spread of activation through semantic memory, whereas at longer SOAs, processing is thought to be dominated by controlled mechanisms.

To date, three fMRI studies of semantic priming in schizophrenia have been undertaken [3–5], which reported attenuated modulation of hemodynamic responses as well as enhanced hemodynamic enhancement in left temporal and frontal cortices in response to semantic priming. However, these studies utilized long SOAs (i.e. 650ms) so could not disentangle the contributions of automatic processes to the priming-related hemodynamic response differences observed in individuals with schizophrenia. Unlike previous studies, the present fMRI study of semantic priming in schizophrenia used a short SOA (i.e. 350ms) in order to investigate the initial, automatic stages of semantic processing. Furthermore, since indirect priming at short SOAs has been suggested to be a sensitive measure of the associative disturbances in schizophrenia [6], we hypothesized that individuals with schizophrenia would exhibit increased hemodynamic responses relative to comparison individuals for indirect priming within temporal regions reflecting increased and prolonged automatic spreading of activation during semantic processing.

Materials and methods

Participants

The study included data from 17 individuals with *DSM-IV*, schizophrenia (14 men, three women, mean age 39.4 ± 10.1 years) and 15 comparison individuals (nine men, six women, mean age 33.8 ± 10.6 years). All individuals were right-handed with English as their first language. Schizophrenia diagnoses were confirmed with the Diagnostic Instrument for Genetic Studies (DIGS) [7], and all individuals with schizophrenia were administered the Brief Psychiatric Rating Scale (BPRS) [8]. Of the 17 individuals with schizophrenia included in the study, 14 were treated with atypical, two with typical, and one with both

atypical and typical antipsychotics. The average chlorpromazine-equivalent antipsychotic dose across the 16 individuals for whom we had dosage information for was 33.81 mg/day. All individuals signed informed consent consistent with the guidelines of the Colorado Multiple Institution Review Board.

Stimuli design, task procedure, and behavioral data analyses

A total of 192 prime-target pairs were developed using the South Florida free association norms [9], the Edinburgh Associative Thesaurus [10], the MRC Psycholinguistic Database [11], and stimuli from previous priming studies [12–14]. The pairs were divided equally into the following four conditions: directly related (e.g. salt–pepper), indirectly related (e.g. lion–stripes), unrelated (e.g. star–drill), and word/nonword (e.g. cheek–sporg). Primes and targets were matched across conditions on frequency (mean 44.6 ± 17.6), concreteness (mean 579.2 ± 13.6), and number of letters (mean 4.9 ± 0.2). Stimuli were also independently scored for degree of relatedness on a scale of 1–7 (i.e. 1=unrelated, 7=directly related) by 23 healthy adults, who did not partake in the study. Mean relatedness scores were 6.1 ± 0.4 for directly related, 3.4 ± 0.7 for indirectly related, and 1.2 ± 0.3 for unrelated stimuli.

Participants performed a lexical decision task (i.e. decide if target is a word or nonword) by pressing a button for words only. Stimuli were presented via MR-compatible goggles as follows: 400 ms fixation, 250 ms prime, 100 ms blank screen, 250 ms target, and 3000 ms blank. The task consisted of two runs of 16 blocks each. Each block consisted of eight word pairs: five pairs of one condition intermixed with two word/nonword pairs, and one pair of another condition. Condition intermixing was used to minimize the likelihood that individuals developed block-related strategies. Rest blocks of equivalent duration were included. Stimuli were pseudorandomized with the order maintained across participants.

Statistical analyses of behavioral data were performed using SPSS, version 11 (SPSS Inc., Chicago, Illinois, USA) at P -value less than 0.05. Percentage accuracy was entered into a 4×2 analysis of variance (i.e. condition by group), and mean reaction times were entered into a 3×2 analysis of variance (i.e. condition by group). Post-hoc comparisons were conducted using the least significant difference pairwise multiple comparison test.

Magnetic resonance imaging data acquisition and analyses

Imaging data was acquired with a 3T GE MR system (General Electric, Milwaukee, Wisconsin, USA) using a standard quadrature head coil and a gradient-echo T2* Blood Oxygenation Level Dependent (BOLD) technique. A total of 32 slices were attained with a TR of 2000 ms.

Data were analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK). Following exclusion of the first four images for saturation effects, each individual's functional data was realigned to the first volume, normalized using unified segmentation [15], and smoothed at 8mm full-width at half-maximum. All trials belonging to each condition were separately convolved with the canonical hemodynamic response function using the general linear model (e.g. direct trials within a direct block as well as those intermixed within the indirect and unrelated blocks). Modeling the data on an individual trial

basis rather than as blocks resulted in the inclusion of only corresponding trials in each condition. Contrasts of interest were: (a) direct versus unrelated, (b) indirect versus unrelated, and (c) indirect versus direct.

To account for both within-group and within-subject variance, a random-effects analysis was implemented. Parameter estimates for each individual's first-level analysis were entered into second-level one-sample and two-sample *t*-tests. Region of interest (ROI) analyses were carried out wherein the mean response for all voxels in each ROI was determined using the MarsBaR toolbox (MRC Cognition and Brain Sciences Unit, Cambridge, UK) [16]. Based on the previous fMRI semantic priming studies of schizophrenia [3–5], the following ROIs, defined as the corresponding labeled region within the Automated Anatomical Labeling atlas, [17] were included: (a) left fusiform gyrus (FG), (b) left middle temporal gyrus (MTG), (c) left superior temporal gyrus (STG), and (d) left inferior frontal gyrus (IFG).

To investigate correlations between symptoms and hemodynamic responses, a regression analysis with the BPRS subscale scores for conceptual disorganization and the first-level contrasts for the direct relative to the unrelated condition and the indirect relative to the unrelated condition was performed.

Results

Behavioral data

Reaction times for two comparison individuals were not recorded because of a program error, so behavioral data are reported for 17 individuals with schizophrenia and 13 comparison individuals. For percentage accuracy, there was a significant main effect of condition [$F(1.49, 41.72) = 9.98$, $P = 0.001$], but both the main effect of group and the condition by group interaction were not significant. Post-hoc tests indicated poorer accuracy for both groups for the word/nonword condition relative to the three other conditions ($P < 0.05$). For reaction times, there was a significant main effect of condition [$F(2, 56) = 21.31$, $P < 0.001$] and main effect of group [$F(1, 28) = 6.39$, $P = 0.02$], but a nonsignificant condition by group interaction. Post-hoc tests indicated that reaction times to the direct and indirect conditions were faster than the unrelated condition ($P < 0.001$), suggesting that both groups exhibited direct and indirect priming effects. Post-hoc tests indicated that in all conditions, individuals with schizophrenia responded 99.44 ms slower than comparison individuals ($P < 0.05$) (Table 1).

Functional magnetic resonance imaging

Comparison individuals exhibited priming-induced hemodynamic suppression (i.e. greater hemodynamic responses for unprimed stimuli) in the left inferior frontal gyrus and the STG. In addition, comparison individuals exhibited greater hemodynamic response suppression for indirect relative to direct stimuli within the STG. In comparison, individuals with schizophrenia exhibited priming-induced hemodynamic response enhancement within the FG for both direct and indirect priming. Group comparisons revealed greater hemodynamic responses in individuals with schizophrenia than comparison individuals in the FG and STG for indirect priming (Table 2 and Fig. 1).

BPRS scores were not collected for three individuals with schizophrenia, so correlations were examined for 14 individuals with schizophrenia. No significant correlations with the subscale score for conceptual disorganization and priming-related hemodynamic responses were observed.

Discussion

The present study was designed to identify cortical regions reflecting increased automatic obligatory semantic processing in individuals with schizophrenia by utilizing a priming paradigm with a short SOA. As hypothesized, direct group comparisons revealed priming-induced hemodynamic response enhancement in individuals with schizophrenia relative to comparison individuals for indirect priming at this short SOA in temporal regions including the FG and the STG. This general finding of priming-induced hemodynamic response enhancement in individuals with schizophrenia is consistent with previous studies of semantic priming in schizophrenia, although at long SOAs [3–5], and suggest that temporal regions may be particularly relevant to the associative disturbances in schizophrenia. This is in line with Kuperberg *et al.* (2007), who reported that increased activation in temporal fusiform cortices in response to indirect semantic priming at a long SOA correlated with severity of positive thought disorder in their schizophrenia sample. Furthermore, the left STG is one of the most consistently reported regions of abnormality in structural brain studies of schizophrenia, with volume changes found to correlate with symptoms of auditory hallucinations and thought disorder (for reviews see [18,19]). An interpretation of these enhancements reflecting a possible enhanced obligatory spread of activation within semantic memory is also provided by MEG studies, which have demonstrated early repetition priming-induced increases in activation in left poster-ventral regions that were suggested to reflect automatic access to lexical representations in typically developing individuals [20,21].

As hypothesized, individuals with schizophrenia exhibited increased hemodynamic responses relative to comparison individuals for indirect priming within temporal cortical regions. However, this study has several limitations and should be considered preliminary. Due to the relatively small sample size, the study was not powered for whole-brain analyses. Therefore, we performed ROI analyses, which were based on a priori hypotheses. In addition, all individuals with schizophrenia were medicated, and it would be important to replicate these findings in unmedicated patients at time of first-episode onset. Regarding replication, this study is the first study examining semantic priming in individuals with schizophrenia at a short SOA. As such, it clearly warrants replication.

Conclusion

As the first fMRI study to use a short SOA to investigate semantic priming in schizophrenia, the present findings do suggest that indirect priming at short SOAs may be a sensitive measure of the associative disturbances observed in schizophrenia as they have been proposed to be. These initial automatic stages of semantic processing are less influenced by complex cognitive processes. As such, they may be more easily interpreted in the context of the basic pathophysiology of schizophrenia. The exacerbated responses observed in

schizophrenia may, for example, reflect a fundamental neuronal deficit such as the failure of inhibitory interneurons that has been proposed as a core feature of the illness [22,23]. Whether or not this deficit causes or is but one feature of semantic priming differences observed in schizophrenia cannot be determined from the current study. These results suggest, however, that similar responses observed in previous studies using longer SOAs may have been driven at least in part by the hyperactivity observed in early automatic semantic processing.

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Fig. 1. Greater hemodynamic responses were observed in the left fusiform and superior temporal gyri in schizophrenia ($N=17$) relative to comparison individuals ($N=15$) for indirect priming. Hemodynamic responses for individual participants, in terms of percent signal change relative to the global mean for the average of all voxels in each region of interest (ROI).

Table 1Behavioral results for comparison ($N=13$) and schizophrenia ($N=17$) individuals

Conditions	Percentage correct		Reaction time (ms)	
	Comparison individuals	Schizophrenia individuals	Comparison individuals	Schizophrenia individuals
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Direct	97.4 $\pm$ 7.4	98.5 $\pm$ 2.9	515.1 $\pm$ 65.3	621.2 $\pm$ 135.6
Indirect	96.6 $\pm$ 7.5	98.3 $\pm$ 3.1	530.1 $\pm$ 64.6	616.9 $\pm$ 110.9
Unrelated	97.0 $\pm$ 4.6	97.6 $\pm$ 4.3	558.7 $\pm$ 78.9	664.2 $\pm$ 144.4
Nonword	92.5 $\pm$ 7.3	94.6 $\pm$ 7.1	NA	NA

Table 2Functional magnetic resonance imaging results for comparison ($N=15$) and schizophrenia ($N=17$) individuals

	t	P
Comparison individuals		
Unrelated > Direct		
Left inferior frontal gyrus	2.38	0.02
Unrelated > Indirect		
Left superior temporal gyrus	3.15	0.004
Direct > Indirect		
Left superior temporal gyrus	1.77	0.05
Schizophrenia individuals		
Direct > Unrelated		
Left fusiform gyrus	2.93	0.01
Indirect > Unrelated		
Left fusiform gyrus	2.02	0.03
Schizophrenia > Comparison individuals		
Indirect > Unrelated		
Left fusiform gyrus	1.96	0.03
Left superior temporal gyrus	1.72	0.05