ORIGINAL ARTICLE

Increased Temporal and Prefrontal Activity in Response to Semantic Associations in Schizophrenia

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Context: Loosening of associations has long been considered a core feature of schizophrenia, but its neural correlate remains poorly understood.

Objective: To test the hypothesis that, in comparison with healthy control subjects, patients with schizophrenia show increased neural activity within inferior prefrontal and temporal cortices in response to directly and indirectly semantically related (relative to unrelated) words.

Design: A functional neuroimaging study using a semantic priming paradigm.

Setting: Lindemann Mental Health Center, Boston, Mass.

Participants: Seventeen right-handed medicated outpatients with chronic schizophrenia and 15 healthy volunteers, matched for age and parental socioeconomic status.

Interventions: Functional magnetic resonance imaging as participants viewed directly related, indirectly related, and unrelated word pairs and performed a lexical decision task.

Main Outcome Measures: Event-related functional magnetic resonance imaging measures of blood oxygenation level–dependent activity (1) within a priori temporal and prefrontal anatomic regions of interest and (2) at all voxels across the cortex.

Results: Patients and controls showed no behavioral differences in priming but opposite patterns of hemodynamic modulation in response to directly related (relative to unrelated) word pairs primarily within inferior prefrontal cortices, and to indirectly related (relative to unrelated) word pairs primarily within temporal cortices. Whereas controls showed the expected decreases in activity in response to semantic relationships (hemodynamic response suppression), patients showed inappropriate increases in response to semantic relationships (hemodynamic response enhancement) in many of the same regions. Moreover, hemodynamic response enhancement within the temporal fusiform cortices to indirectly related (relative to unrelated) word pairs predicted positive thought disorder.

Conclusion: Medicated patients with chronic schizophrenia, particularly those with positive thought disorder, show inappropriate increases in activity within inferior prefrontal and temporal cortices in response to semantic associations.

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ABNORMALITIES IN ASSOCIATIVE connections between words and concepts have long been considered core to schizophrenia.[1] At their most extreme, such abnormalities manifest clinically as positive thought disorder—unintelligible language that is dominated by associations between individual words at the expense of whole themes.[2-4] When first described by Bleuler,[1] however, "loosening of associations" was conceived not only as a clinical phenomenon but also as a clue to understanding the neurocognitive mechanisms underlying schizophrenia. In this study we used functional magnetic resonance imaging (fMRI) to demonstrate abnormal increases in temporal-prefrontal brain activity in response to semantic associations in schizophrenia.

Target words preceded by semantically related words are processed faster than those preceded by semantically unrelated words.[5,6] This is known as *semantic priming*. It is also known that behavioral semantic priming has a neural correlate: the attenuation of a specific elec-

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trophysiologic response (the N400) to primed vs unprimed targets.[7,8] Semantic priming is thought to reflect the operation of different cognitive processes that make differential contributions depending on experimental conditions and on the semantic relationship between prime and target. For example, when the interval between prime and target (the stimulus onset asynchrony) is short, semantic priming is usually explained by an automatic spread of activation through semantic memory[9,10] that can facilitate the processing of both targets that are directly related to their prime, eg, lion-tiger,[6] and that are indirectly linked to their prime through an unseen mediator word, eg, lion-(tiger)-stripes.[11-15] When the stimulus onset asynchrony is long, some automatic spread of activation can still occur, but processing is dominated by controlled processes that take time to develop and that are under strategic control, such as the generation of predictions[16] and attempts to match the semantic relationship between prime and target.[17] While these controlled processes are effective in facilitating the processing of directly related targets, leading to robust direct priming, they are less effective in facilitating processing of indirectly related targets where, in many trials, the relationship between the prime and target is not obvious (discussed by Neely[6]). This is why, when subjects engage in such controlled processes, indirect semantic priming is usually not seen[11,12,15,18-20] or else is less robust than direct priming.[21]

Patients with schizophrenia can show normal, increased, or decreased semantic priming in comparison with healthy control subjects.[22] Under automatic conditions, direct semantic priming is usually normal,[23-31] but it can be increased in patients with positive thought disorder,[32-35] and indirect priming is consistently increased in association with positive thought disorder.[29-31,33] Under controlled conditions, some studies report no differences between patients and controls in direct[36,37] or indirect[33] priming, but others report reduced direct priming in patients relative to controls.[28,38-42] Many explanations, some mechanistic, have been offered to account for these discrepancies. Increased direct and indirect priming under automatic conditions in thought-disordered patients has been taken as evidence of a wider (and perhaps faster) automatic spread of activation,[29-31,33] while reduced direct priming under controlled conditions in schizophrenia has been interpreted as reflecting an impairment in the effective use of semantic matching or predictive strategies to facilitate the processing of directly related targets.[28,38] The literature on this subject, however, remains contradictory. Functional neuroimaging techniques may give new insights into what is occurring at a neural level during semantic priming in chronic schizophrenia.

In healthy individuals, functional neuroimaging studies of priming show 2 main patterns of hemodynamic modulation. The most common is hemodynamic response suppression,[43] the decrease in the hemodynamic response to primed relative to unprimed targets. This decrease in hemodynamic activity patterns with the decrease in reaction time and the N400 amplitude to primed relative to unprimed targets, and is usually interpreted as reflecting the *consequence* of priming: the reduced neural activity required to process primed targets.[44] Hemodynamic response suppression has been reported in the left inferior prefrontal cortex and/or in various regions within the temporal cortex in both repetition[45,46] and direct semantic[47-54] priming paradigms. Sometimes, however, *increases* in hemodynamic activity in response to primed relative to unprimed targets are observed: hemodynamic response enhancement.[43] Hemodynamic response enhancement is seen in temporal-prefrontal regions in association with repetition priming[43,55-57] and has also been reported (together with temporal-prefrontal response suppression) in other regions in association with semantic priming.[48,49] It has been conceptualized as reflecting the *mechanism* of priming: the cognitive processes that occur to a greater degree on primed relative to unprimed words.[43] Depending on experimental conditions, it has been interpreted as indexing the spread of activation itself[55,58] or controlled semantic matching processes.[49]

In the present study, we measured hemodynamic activity as patients with schizophrenia and demographically matched healthy controls viewed directly related, indirectly related, and unrelated word pairs presented in pseudorandom order, using a long stimulus onset asynchrony to encourage controlled processing. We predicted that healthy controls would show direct behavioral priming and that this would be associated with hemodynamic response suppression, particularly within inferior prefrontal cortices that are thought to mediate controlled semantic processes.[59-61] We expected that controls would not show indirect behavioral priming[11,12,15,18-20] or prefrontal hemodynamic response suppression. However, because neurophysiologic indirect priming can occur in the absence of behavioral indirect priming,[19] we did not rule out the possibility that the hemodynamic response might detect the effects of a more implicit spread of activation within the temporal cortices[62-64] that was not reflected behaviorally.

In schizophrenia, on the basis of previous neuroimaging studies that collapsed across different types of semantic association,[65-71] we predicted abnormal modulation of activity within both temporal and prefrontal cortices. More specifically, we hypothesized that patients would be less efficient in their use of semantic matching and predictive strategies to prime directly related targets and might therefore fail to attenuate inferior prefrontal neural activity in response to directly related (relative to unrelated) word pairs. If, integrated over the course of seconds, the net neural activity in response to directly related word pairs remained less than to the unrelated word pairs, this would predict prefrontal hemodynamic response suppression (although less suppression than in controls). If, however, the net neural activity to directly related word pairs exceeded that to the unrelated word pairs, this would predict prefrontal hemodynamic response enhancement. In the case of indirectly related word pairs, we expected that patients, like controls, would fail to show behavioral priming or an attenuation of activity within the prefrontal cortices. However, if patients, particularly those with positive thought disorder, showed an increase in the spread of activation within the temporal cortices, this might be picked up hemodynamically, even in the absence of behavioral indirect priming differences between patients and controls.[72] Again, if the net neural activity in response to in-

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Table 1. Demographic and Psychopathologic Data of Healthy Controls and Patients With Schizophrenia*

Measure	Subject Group: Controls (n = 15)	Subject Group: Patients (n = 17)
Sex, No. of participants		
Male	13	15
Female	2	2
Race/ethnicity No. of participants		
Non-Hispanic white	10	11
African American	3	6
Hispanic	2	0
Age, y	41.6 (11.40)	45.1 (9.55)
Hollingshead index	3.1 (0.74)	3.4 (1.27)
Premorbid verbal IQ	114.5 (10.25)	105.0 (11.25)
Use of anticholinergics, No. of participants+/–	NA	1
CPZ equivalent	NA	480 (320)
Duration of illness, y	NA	19 (11)
PANSS score		
Global	NA	62.0 (7.65)
Positive	NA	13.4 (4.54)
Negative	NA	18.8 (4.93)

Abbreviations: CPZ, chlorpromazine; NA, not applicable; and PANSS, Positive and Negative Syndrome Scale.[76]
*Data are expressed as mean (SD) unless otherwise specified.

directly related word pairs remained less than that to unrelated word pairs, this would predict temporal hemodynamic response suppression, but if activity to the indirectly related word pairs exceeded that to unrelated word pairs, this would predict temporal hemodynamic response enhancement.

We tested these hypotheses in 2 complementary ways. First, we generated hemodynamic time courses by averaging activity at each repetition time (TR) across all voxels within a priori temporal and inferior prefrontal regions of interest (ROIs). This gave us the power to detect abnormal modulation of activity averaged across large regions where we predicted group differences, without assumptions about the shape of the hemodynamic responses. Second, we generated cortical statistical maps that had more power to detect more localized changes. This provided a more unbiased and comprehensive assessment of group differences at all voxels across the cortical surface.

METHODS

PARTICIPANTS

Twenty-three patients who met *DSM-IV* criteria for schizophrenia[2] (confirmed by means of the Structured Clinical Interview for *DSM-III-R*[73] and chart examination), receiving stable doses of atypical antipsychotics, were initially recruited from the Lindemann Mental Health Center, Boston, Mass. Eighteen demographically matched volunteers receiving no medication, without histories of psychiatric disorders,[73] were recruited by advertisement. All participants were native, primarily monolingual English speakers who had not learned any other language before age 5 years. All were right-handed,[74,75] without histories of head trauma, neurologic disorder, substance abuse within 6 months, or substance dependence. Written consent was obtained following the guidelines of the Massachusetts General Hospital Human Subjects Research Committee. Psychopathology was assessed by a psychiatrist (G.R.K.) within 2 weeks of scanning; there were no medication changes between this assessment and scanning. Two patients failed to complete scanning, 3 patients could not perform the task inside the scanner at all, and 1 control's behavioral performance was at chance. One patient and 2 controls were excluded because of scanning artifacts.

Demographic and psychopathological data of the 17 patients and 15 controls included in the final analyses are summarized in **Table 1**. Patients and controls were matched closely on sex and race/ethnicity distributions, and there was no significant difference between the groups in age ($P=.36$). The patient and control groups showed no significant difference on parental socioeconomic status ($P=.57$), as determined by Hollingshead index scores,[77] although patients had a slightly lower premorbid IQ ($P<.02$) as assessed by the North American Adult Reading Test.[78]

STIMULI AND TASK

One hundred fifty triplets (eg, lion-tiger-stripes) were gathered from previous indirect priming studies[11,12,14] or developed for the current study by means of the University of South Florida free association norms,[79] the Edinburgh Associative Thesaurus,[80] and stimuli from previous direct priming studies. Words were counterbalanced across 3 lists so that, across all subjects, the same targets were viewed in all 3 conditions and the same primes were viewed in the directly related and unrelated conditions. Thus, each participant viewed 50 directly related word pairs, 50 indirectly related word pairs, and 50 unrelated word pairs in 1 of 3 counterbalanced litst. Fifth word-nonword pairs were added to each of these lists. The number of letters and the frequency[81] of primes were matched across the 4 conditions. More details and a sample stimulus set are provided in **Table 2**.

A pilot study established that healthy individuals generated the mediator word when given both prime and target but not when they were just given the prime. A second pilot study demonstrated that indirectly related word pairs were rated as less related than directly related word pairs on a 5-point scale.

After scanning, all subjects were asked to make binary decisions about whether the word pairs they had viewed were related or unrelated: both patients and controls classified approximately 50% of the indirectly related word pairs as related and 50% as unrelated. The relatedness proportion for the whole experiment was therefore approximately 0.5. The nonword ratio (the number of word-nonword pairs divided by word-nonword pairs plus unrelated pairs)[17] was 0.4.

Each trial began with the prime (500 milliseconds), a blank screen (300 milliseconds), a target (500 milliseconds), and then another blank screen (300 milliseconds). Subjects decided as quickly and as accurately as possible whether the target was a real English word or a nonword (lexical decision) by pressing 1 of 2 buttons with the index and middle fingers of their left hand (counterbalanced across subjects). Between word pairs, a question mark appeared (1100 milliseconds) followed by a blank screen (300 milliseconds). The 4 trial types appeared in pseudorandom order, interspersed among 100 visual fixation trials (fixate on a plus sign for variable durations of 1000-8000 milliseconds; mean, 3000 milliseconds) to aid deconvolution of the hemodynamic response.[82]

MRI DATA ACQUISITION

Subjects underwent 2 structural scans on a 1.5-T scanner (Siemens Medical Solutions, Iselin, NJ), each constituting a 3-di-

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Table 2. Stimuli Construction and Examples

Condition	Construction	Example	Frequency, Mean (SD)	Word Length, Mean (SD) No. of Letters
Directly related	Word pairs were categorically related (eg, "cat-mouse"), associatively related (eg, "tiger-stripes"), or functionally related (eg, "hammer-nail")	Tiger-stripes	Prime: 70 (133) Target: 101 (431)	Prime: 5 (1) Target: 5 (1)
Indirectly related	Targets were categorically, associatively, or functionally related to the primes of the corresponding directly related word pairs but not to their own primes	Lion-stripes	Prime: 75 (253) Target: 101 (431)*	Prime: 5 (1) Target: 5 (1)*
Unrelated	A target from the directly related condition was paired with a prime of another related word pair from another list	Chair-stripes	Prime: 70 (133)* Target: 101 (431)*	Prime: 5 (1)* Target: 5 (1)*
Word-nonword	The same word-nonword pairs were added as fillers to each list; nonword targets were phonologically permissible letter strings derived from words that were unrelated to their primes	Lion-soble	Prime: 74 (121) Target: NA	Prime: 5 (1) Target: 5 (1)

Abbreviation: NA, not applicable.
*These values are identical to those of the directly related word pairs because of how the stimuli were counterbalanced.

mensional magnetization prepared rapid gradient echo (MPRAGE) sequence (128 sagittal sections, 1.3-mm thickness; TR, 7.25 milliseconds; echo time, 3 milliseconds; flip angle, 7°; bandwidth, 195 Hz/pixel; in-plane resolution, 1.3 × 1 mm). During fMRI on a 3.0-T head-only scanner (Allegra; Siemens Medical Solutions), participants viewed word pairs over 3 runs (each 4 minutes 10 seconds) during which 125 images were acquired by means of a T2*-weighted gradient-echo pulse sequence (TR, 2 seconds; echo time, 25 milliseconds; flip angle, 90°) with 33 transverse sections covering the whole brain (125 images per section, 3-mm thickness, 0.9 mm between sections). The in-plane resolution was 3.13 × 3.13 mm (64 × 64 matrix, 200 mm field of view). Head motion was minimized with pillows and a forehead strap.

BEHAVIORAL DATA ANALYSIS

The percentages of lexical decision errors were entered into repeated-measures one-way analyses of variance (ANOVAs). A′ scores (a nonparametric measure of signal detection[83]) were also calculated for each subject. Reaction times to correctly answered word targets were entered into both *subjects analyses* (repeated-measures ANOVAs with subjects as a random effect, collapsing over items, F1) and *items analyses* (repeated-measures ANOVAs with items as a random effect, collapsing over subjects, F2). The α level was set to .05. Analyses were repeated after logarithmically transforming the data and yielded the same pattern of results.

INDIVIDUAL MRI ANALYSIS

The 2 structural scans for each participant were averaged, after motion correction, to create a single high signal-to-noise volume, avoiding confounds of poor scan quality or low signal. The surface representing the gray-white border was reconstructed and inflated to yield a representation of the cortical surface[84-86] by means of FreeSurfer software developed at the Martinos Center, Charlestown, Mass (http://surfer.nmr.mgh.harvard.edu/).

Functional images were motion corrected by means of the AFNI (analysis of functional neuroimages) algorithm.[87,88] There was no significant difference in the total (vector) translation between patients (mean ± SD, 1.07 ± 0.58 mm) and controls (mean ± SD, 0.96 ± 0.44 mm) ($P = .55$). Images were corrected for temporal drift, normalized, and spherically smoothed with a 3-dimensional spatial filter (full-width half-maximum, 8.7 mm). A finite impulse response model was used to selectively average the hemodynamic response to correctly answered trials every 1 second (as stimuli were allowed to onset on half as well as the full 2-second TR)[89] by means of the FreeSurfer Functional Analysis Stream.

GROUP fMRI ANALYSIS

ROI-Based Analysis

Seven a priori inferior prefrontal and temporal ROIs where we predicted group differences were anatomically defined[90,91] on individual cortical surfaces using automated parcellation methods[92,93] (see **Figure 1** and **Figure 2** for details). These ROIs were selected because they were known (1) to show structural deficits in morphometric studies of schizophrenia,[103,104] (2) to be involved in normal semantic processing, and (3) to be abnormally modulated in fMRI studies of semantic processing in schizophrenia (example references are given for each ROI in the legends to Figures 1 and 2). We also examined 4 control cortical ROIs (the left and right calcarine fissures and central sulci), as well as several subcortical ROIs (the right and left thalamus, nucleus accumbens, globus pallidus, caudate, and putamen) where we did not predict group differences. These anatomic regions were further constrained by means of an omnibus functional mask constituting any activity (at $P < .05$, positive and negative polarities) from 3 through 6 seconds in any contrast including fixation. By excluding voxels within each ROI that showed no activity to any condition, this mask increased the signal-to-noise ratio but was unbiased with respect to examining the contrasts of interest. Finite impulse response parameter estimates were mapped and averaged across all voxels within each ROI at each poststimulus delay, averaged across subjects, and plotted to generate hemodynamic time courses.

Voxel-Based Analysis

The cortical surface of each individual was morphed/registered to an average spherical surface representation to align sulci and gyri across subjects.[105,106] This structural spherical transform was used to map the finite impulse response parameter estimates at each voxel in each individual into a common spherical coordinate system[105,106] on which the data were then smoothed using an iterative nearest-neighbor averaging procedure (equivalent to applying 2-dimensional gaussian smoothing with 8-mm full-width half-maximum) and then averaged within and between groups.

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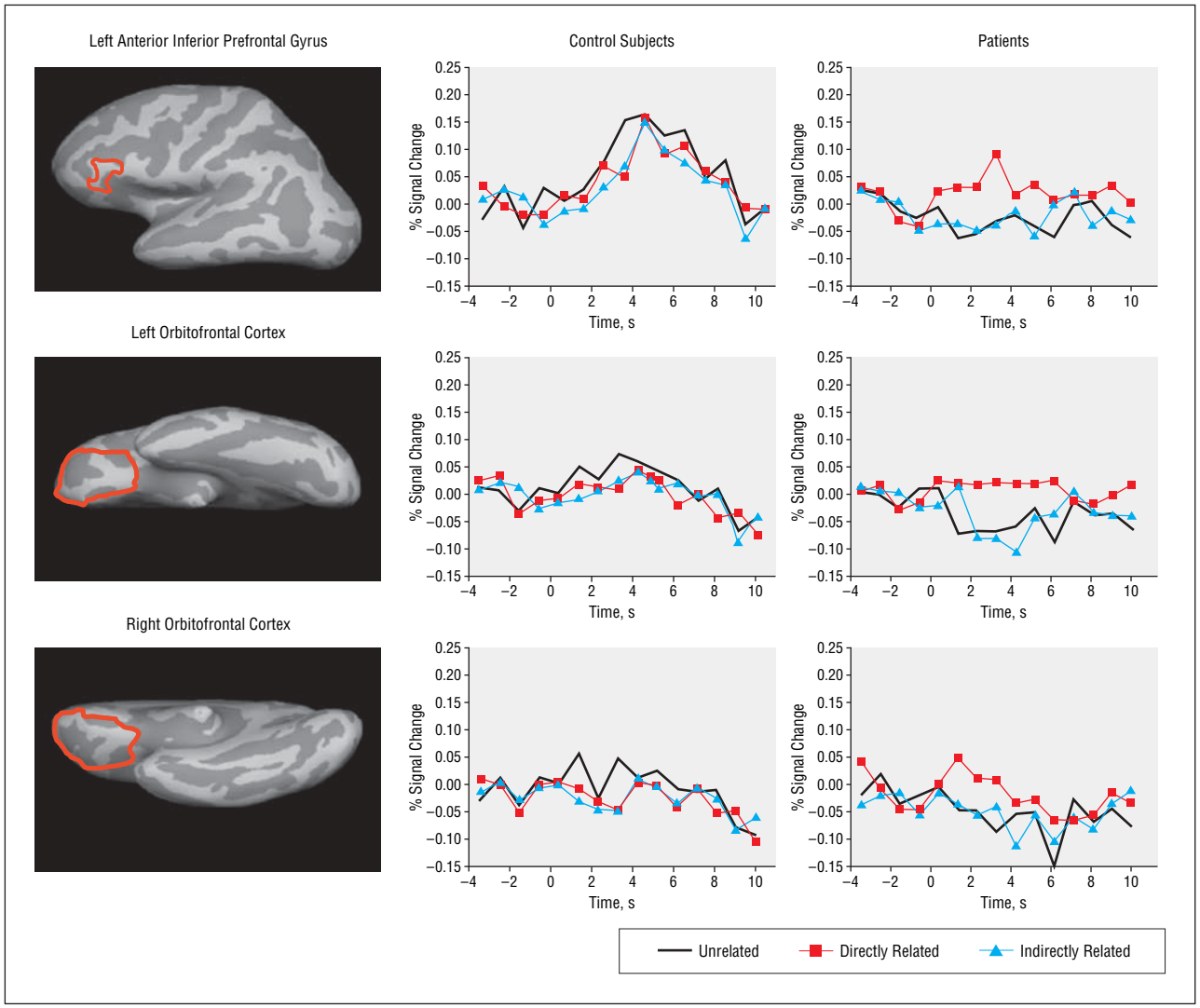

Figure 1. Left, Three prefrontal regions of interest (ROIs) illustrated on maps of average folding patterns of the cortical surface, with gyral and sulcal folds shown in light and dark gray, respectively. The left anterior inferior prefrontal gyrus constitutes pars triangularis and pars orbitalis (Brodmann areas 45 and 47), which previous studies have implicated in normal semantic processing[48,50,52-54,59-61] and which are abnormally modulated in patients with schizophrenia.[67,69,94] The left and right orbitofrontal cortices constitute the fronto-orbital gyri and orbital sulci (Brodmann areas 10 and 11), which have also been implicated in aspects of normal semantic processing[58,95,96] and which are abnormally modulated in schizophrenia.[70] Right, Hemodynamic time courses within these ROIs.

fMRI STATISTICAL ANALYSES

ROI-Based Analysis

The percentage blood oxygenation level–dependent (BOLD) signal change in each individual was averaged across all voxels within each ROI and across 3 to 6 seconds (encompassing the peak hemodynamic response) and was entered as a single dependent variable in repeated-measures ANOVAs. For each a priori ROI, α was set to .05. For the 2 control cortical ROIs and subcortical ROIs, α was set to .003 (Bonferroni corrected for 14 comparisons).

Voxel-Based Analysis

Group × relatedness interactions at each voxel across the cortical surface were identified by constructing statistical maps showing BOLD activity (summed across the 3- to 6-second time epoch) that differed significantly between patients and controls (using unpaired, 2-tailed *t* tests and a random effects model) for comparisons of interest. Within-group statistical maps determined the polarity of modulation (response suppression or enhancement) within the patient and control groups.

To correct for multiple comparisons for all voxels across the surface, clusters covering at least 300 mm^2, with a corrected threshold for rejection of the null hypothesis of $P<.05$, were identified on the basis of a Monte Carlo simulation.[107] In addition, we report smaller clusters that were activated at a less conservative uncorrected threshold of $P<.01$ because many of these smaller clusters fell within our a priori temporal and prefrontal ROIs and had peak *P* values of less than .001, meeting Bonferroni criteria for a correction for multiple comparisons of voxels falling within these ROIs.

Correlations With Symptoms

Hemodynamic priming effects in each patient within each a priori ROI were computed by subtracting BOLD activity (averaged across all voxels within the ROI and across 3 to 6

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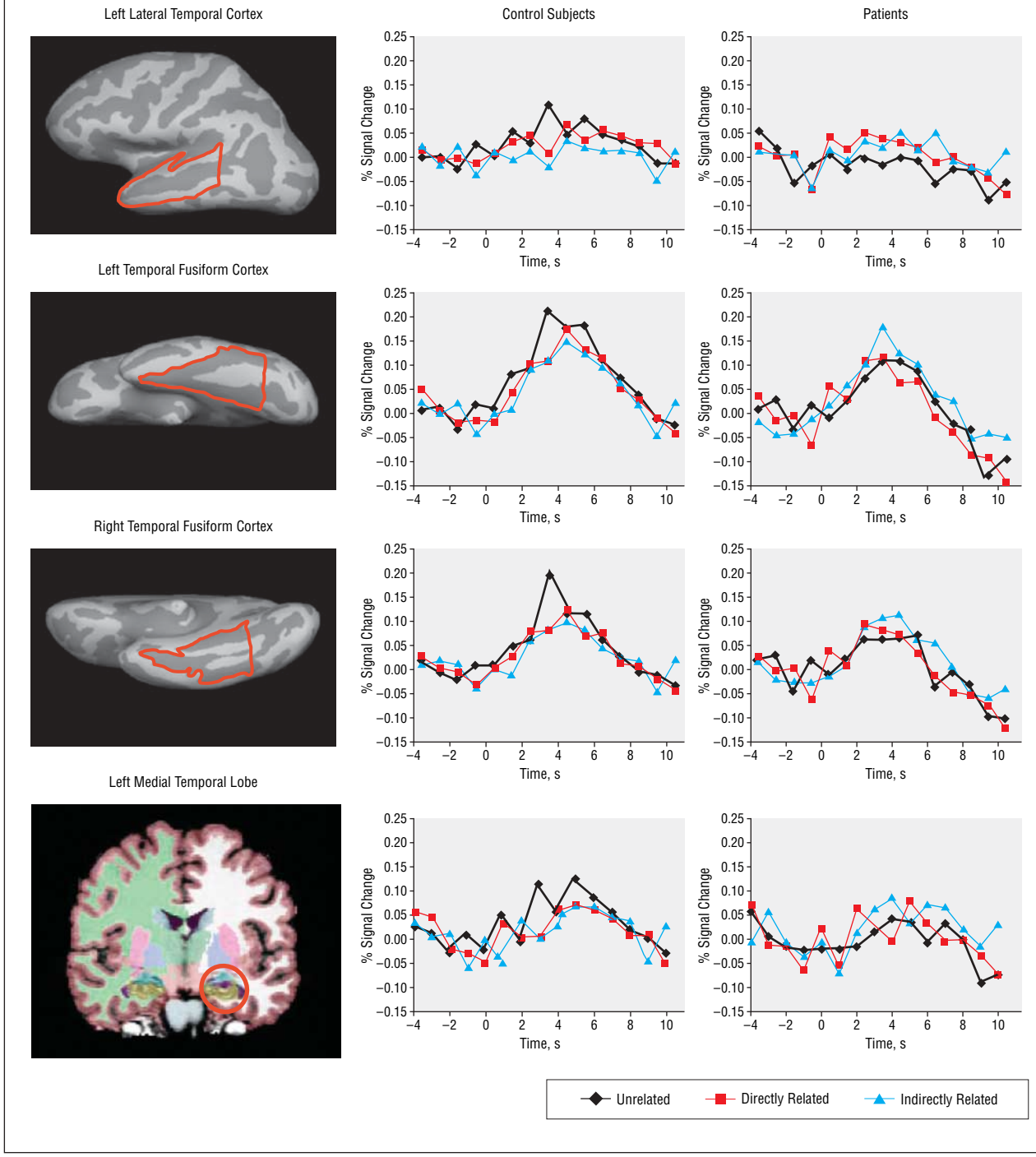

Figure 2. Left, Top 3 images show cortical temporal regions of interest (ROIs) on maps of average folding patterns of the cortical surface, with gyral and sulcal folds shown in light and dark gray, respectively. The left lateral temporal cortex constitutes the left superior temporal gyrus, the left superior temporal sulcus, and the left middle temporal gyrus (Brodmann areas 22, 42, and 21), which previous studies have implicated in normal semantic processing[50-53] and which are abnormally modulated in patients with schizophrenia.[69,70,94,97,98] The left and right temporal fusiform cortices constitute temporal fusiform gyri and adjacent collateral and occipitotemporal sulci (Brodmann areas 37 and 20), which have been implicated in normal semantic processing[49,54,58,62,99] and which are abnormally modulated in schizophrenia.[97,100] In the bottom image, the left medial temporal lobe constitutes the left hippocampus-amygdala complex (circled), which has been implicated in normal semantic processing[99,101,102] and which is abnormally modulated in patients with schizophrenia.[65,68,70,71,94] Right, Hemodynamic time courses within these ROIs.

seconds) to directly or indirectly related word pairs from BOLD activity to unrelated word pairs. In each a priori ROI, Pearson correlations were conducted between these hemodynamic effects and medication dosage and Positive and Negative Syndrome Scale measures of conceptual disorganization, hallucinations, delusions, and negative symptoms. The α level was set to .05 for our a priori hypothesis that severity of conceptual disorganization would correlate with hemodynamic modulation in response to indirectly related (relative to unrelated) word pairs within temporal ROIs. For correlations with each of the other 5 variables, α was set to .001 (Bonferroni corrected for correlations in each of 7 ROIs).

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Table 3. Accuracy*

Condition	Subject Group: Controls	Subject Group: Patients
Directly related	3 (7)	4 (5)
Indirectly related	3 (6)	7 (1)
Unrelated	3 (7)	10 (12)
Nonwords	6 (8)	20 (21)

*Mean percentage errors on lexical decision in each condition in the patient and control groups, with SDs in parentheses.

Table 4. Reaction Times*

	Subject Group: Controls	Subject Group: Patients
Subjects analysis		
Directly related	826 (165)	891 (221)
Indirectly related	838 (180)	904 (233)
Unrelated	842 (167)	930 (241)
Items analysis		
Directly related	812 (176)	885 (184)
Indirectly related	827 (182)	896 (216)
Unrelated	835 (186)	909 (218)

*Mean reaction times (in milliseconds), with SDs in parentheses. In the subjects analysis, reaction times in each subject were averaged over all correctly answered items. In the items analysis, reaction times to each correctly answered word-pair item were averaged over all subjects.

RESULTS

BEHAVIORAL DATA

Accuracy

An ANOVA including all conditions showed a significant group × condition interaction, $F_{3,90}=3.68$, $P=.04$, that resulted because patients made more errors in response to nonwords than to each type of word target (all $t>2.08$, all $P<.05$), but controls did not show differences across conditions, $F_{3,42}=1.50$, $P=.24$ (**Table 3**). An ANOVA that excluded the word-nonword pairs did not show a significant group × relatedness interaction ($F_{2,60}=2.51$, $P=.1$) or a significant main effect of group ($F_{1,30}=2.42$, $P=.13$). A′ scores in all subjects in all conditions were more than 0.8, suggesting that there were no response biases.

Reaction Times

Patients showed overall longer reaction times than did controls, reflected by significant effects of group on the items analyses (although not the subjects analyses) (**Table 4** and **Table 5**). However, there were no significant differences between controls and patients in direct or indirect priming, reflected by the absence of group × relatedness interactions. Across all participants, direct priming was significant on both subjects and items analyses (Table 5), but indirect priming did not reach significance on the subjects or items analyses (Table 5).

fMRI DATA

ROI-Based Analyses

Group × relatedness interactions reached or approached significance in all a priori ROIs (**Table 6**) and remained significant when premorbid IQ (which differed slightly between the 2 groups; Table 1) was entered as a potentially confounding covariate ($P<.05$).

In comparing directly related and unrelated word pairs (Table 6), ANOVAs showed significant group × relatedness interactions in all prefrontal ROIs but in none of the temporal ROIs except for the left lateral temporal cortex. Follow-up comparisons showed less hemodynamic activity in response to directly related than to unrelated word pairs (hemodynamic response suppression) in the control group, which reached or approached significance only in the prefrontal ROIs (Figure 1, **Table 7**). Patients, however, showed a significantly greater hemodynamic response to directly related than to unrelated word pairs (hemodynamic response enhancement) in the left anterior inferior prefrontal gyrus and the left orbitofrontal cortex (Figure 1, Table 7).

In comparing indirectly related and unrelated word pairs (Table 6), ANOVAs showed significant group × relatedness interactions in all temporal ROIs but in no prefrontal ROIs. Follow-up comparisons showed significant hemodynamic response suppression in all temporal ROIs in controls (Figure 2, Table 7). Patients, however, showed either no modulation of activity or hemodynamic response enhancement that reached or approached significance in all temporal ROIs (Figure 2, Table 7).

There were no significant group × relatedness interactions in the 4 control cortical ROIs or in the right and left thalamus, nucleus accumbens, globus pallidus, caudate, or putamen (all $P>.10$).

Voxel-Based Analyses (Cortical Statistical Maps)

Voxel-based analyses generally confirmed the results of the ROI analyses by demonstrating robust group × relatedness interactions that arose because of hemodynamic response suppression in controls and reduced hemodynamic response suppression or hemodynamic enhancement in patients in response to directly related (relative to unrelated) word pairs within inferior prefrontal regions (**Figure 3**, **Table 8**) and to indirectly related (relative to unrelated) word pairs within temporal regions (**Figure 4**, **Table 9**). At less conservative significance thresholds, however, the group × relatedness interaction maps also showed some modulation in response to directly related (relative to unrelated) word pairs within temporal cortices and to indirectly related (relative to unrelated) word pairs in prefrontal cortices, suggesting that these distinctions in localization were not absolute.

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Table 5. ANOVAs: Behavioral Reaction Times

	2 × 3 ANOVA, Directly Related vs Indirectly Related vs Unrelated		2 × 2 ANOVA, Directly Related vs Unrelated		2 × 2 ANOVA, Indirectly Related vs Unrelated	
	Subjects	Items	Subjects	Items	Subjects	Items
Group	$F_{1,30} = 1$, $P = .32$	$F_{1,291} = 71.9$, $P < .001$	$F_{1,30} = 1.2$, $P = .29$	$F_{1,293} = 48.4$, $P < .001$	$F_{1,30} = 1.1$, $P = .31$	$F_{1,294} = 43$, $P < .001$
Relatedness	$F_{2,60} = 4.43$, $P = .02$	$F_{2,582} = 2.5$, $P = .09$	$F_{1,30} = 6.6$, $P = .02$*	$F_{1,293} = 5.2$, $P = .02$*	$F_{1,30} = 3.9$, $P = .06$†	$F_{1,294} = 1.2$, $P = .28$†
Group × relatedness	$F_{2,60} = 1.0$, $P = .36$	$F_{2,582} = 0.2$, $P = .82$	$F_{1,30} = 1.1$, $P = .3$	$F_{1,293} = 0.03$, $P = .86$	$F_{1,30} = 2.4$, $P = .14$	$F_{1,294} = 0.2$, $P = .65$

Abbreviation: ANOVA, analysis of variance.

*In controls, direct priming was significant on the items analysis ($t_{295} = 1.9$, $P < .05$) but did not reach significance on the subjects analysis ($t_{14} = 1.43$, $P = .1$). Behavioral data collected from a larger sample of controls (n = 36) outside the scanner by means of exactly the same paradigm, however, did show a significant behavioral direct priming effect on the subjects analysis ($t_{35} = 2.8$, $P < .009$). In patients, there was significant direct priming on both the subjects analysis ($t_{16} = 2.18$, $P < .045$) and the items analysis ($t_{294} = 0.6$, $P = .05$).

†In controls, there was no indirect priming effect on the subjects analysis ($t_{14} = 0.63$, $P = .54$) or the items analysis ($t_{295} = 1.13$, $P = .26$). In patients, the indirect priming effect was significant on the subjects analysis ($t_{16} = 2.41$, $P < .03$), but not on the items analysis ($t_{295} = 0.70$, $P = .48$).

Table 6. ANOVAs: Group × Relatedness Interactions for Averaged BOLD Activity Within Prefrontal and Temporal ROIs

	3 × 2 ANOVA, Directly Related vs Indirectly Related vs Unrelated (*df* = 1,60)		2 × 2 ANOVA, Directly Related vs Unrelated (*df* = 1,30)		2 × 2 ANOVA, Indirectly Related vs Unrelated (*df* = 1,30)	
	F	*P* Value	F	*P* Value	F	*P* Value
Prefrontal regions						
Left anterior inferior prefrontal gyrus	4.57	.02	13.04	.001	1.65	.21
Left orbitofrontal cortex	6.03	.007	7.48	.01	0.47	.40
Right orbitofrontal cortex	3.42	.04	5.71	.02	1.62	.21
Temporal regions						
Left lateral temporal cortex	7.51	.002	6.51	.01	13.3	.001
Left temporal fusiform cortex	3.10	.06	3.13	.09	8.02	.008
Right temporal fusiform cortex	3.61	.04	0.40	.53	9.32	.005
Left medial temporal lobe	4.63	.02	2.53	.12	14.49	.001
Right medial temporal lobe	3.08	.06	2.30	.14	7.74	.009

Abbreviations: ANOVA, analysis of variance; BOLD, blood oxygenation level–dependent; ROI, region of interest.

Table 7. Planned *t* Tests Within Patient and Control Group in Prefrontal and Temporal ROIs

	Controls (*df* = 14)		Patients (*df* =16)	
	t	*P* Value	*t*	*P* Value
Prefrontal regions		Unrelated ≥ Directly Related		
Directly Related ≥ Unrelated				
Left anterior inferior prefrontal gyrus	2.05	.06	3.06	.007
Left orbitofrontal cortex	1.92	.08	2.24	.04
Right orbitofrontal cortex	2.48	.03	1.58	.13
Temporal regions		Unrelated ≥ Indirectly Related		
Indirectly Related ≥ Unrelated				
Left lateral temporal cortex	2.91	.01	2.47	.03
Left temporal fusiform cortex	3.64	.003	1.24	.23
Right temporal fusiform cortex	2.95	.01	1.91	.08
Left medial temporal lobe	2.84	.01	2.51	.02
Right medial temporal lobe	3.22	.006	0.83	.41

Abbreviation: ROI, region of interest.

Correlations Between Psychopathology and Averaged BOLD Activity Within ROIs

As predicted, within the patient group, conceptual disorganization correlated with modulation to indirectly related (relative to unrelated) word pairs in the left ($r = -0.51$, $P < .05$) and right ($r = -0.55$, $P < .03$) temporal fusiform ROIs (**Figure 5**). There were no other significant correlations between (1) hemodynamic modulation to directly related or indirectly related (relative to unre-

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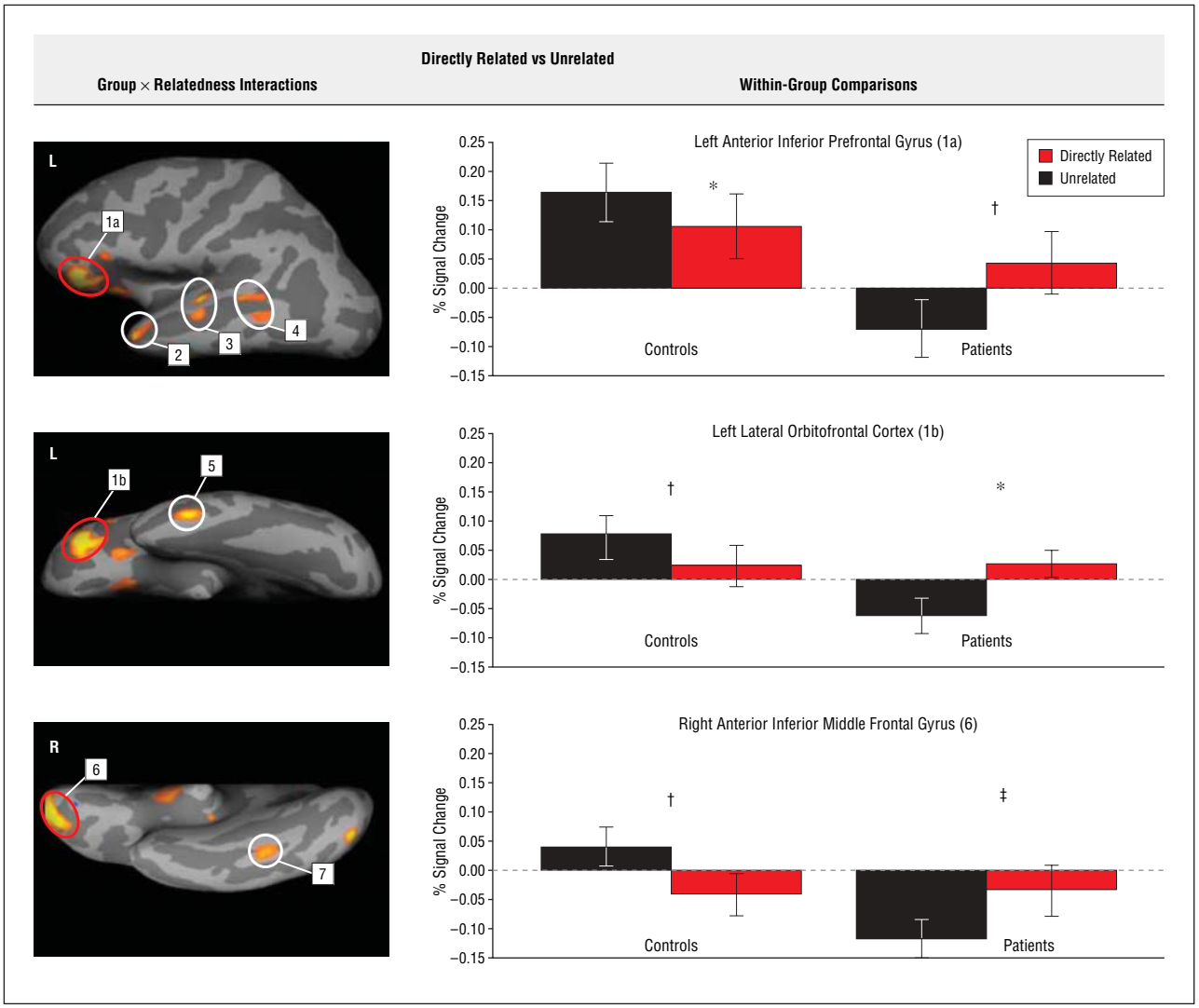

Figure 3. Left, Group × relatedness cortical maps comparing activity to directly related and unrelated word pairs. Red circles (in prefrontal regions) indicate clusters that reached significance corrected for multiple comparisons across the whole cortex (cluster level, $P<.05$). White circles (in temporal regions) illustrate clusters that reached a voxel-wise significance level of $P<.01$ (uncorrected). Cluster numbers correspond directly to those in Table 8. Right, Activity in the patient and control groups averaged over all voxels within clusters. In prefrontal clusters that showed significant group × relatedness interactions, controls showed response suppression while patients showed response enhancement. *$P<.001$. †$P<.05$. ‡$.1>P>.05$.

lated) word pairs and (2) hallucinations, delusions, negative symptoms, or medication dosage, in this or any other ROI (all $P>.10$).

COMMENT

Patients and controls showed different patterns of hemodynamic modulation to directly and indirectly semantically related (relative to unrelated) word pairs. Controls showed hemodynamic response suppression while patients showed less response suppression and sometimes even response enhancement in many of the same regions. In both patient and control groups, the most robust modulation of activity occurred within inferior prefrontal cortices to directly related (relative to unrelated) word pairs and within temporal regions to indirectly related (relative to unrelated) word pairs. However, the voxel-based analyses indicated that these distinctions in localization were not complete, suggesting that any neurocognitive distinctions in the processing of these 2 types of semantic relationships (discussed subsequently) were also not absolute. Within the patient group, the degree of response enhancement within the temporal fusiform cortices to indirectly related (relative to unrelated) word pairs correlated with severity of positive thought disorder. As in other recent studies examining the neural correlates of semantic processing in schizophrenia,[69,71,72] these hemodynamic abnormalities occurred in the absence of behavioral differences between patients and controls, suggesting that the hemodynamic responses may have been a more direct and sensitive measure of underlying neural abnormalities than behavior.

In controls, the decrease in hemodynamic activity in response to directly related (relative to unrelated) word pairs is consistent with the decrease in reaction time and the N400 in response to directly related (relative to unrelated) target words described in numerous behavioral[6,108] and electrophysiological[7,8] studies. Hemodynamic response suppression is also consistent with

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Table 8. Directly Related vs Unrelated Clusters Activated Across the Cortex*

Region	Group × Condition Interactions: Cluster No.	BA	Area, mm²	*P* Value	Talairach (x, y, z)	Within-Group Comparisons†: Controls, Unrelated > Related (Suppression)	Patients, Related > Unrelated (Enhancement)
Left anterior inferior prefrontal gyrus‡	1a	47	736	<.001§	–51, 25, –12	‖	§
Left lateral orbitofrontal cortex‡	1b						
Left anterior middle temporal gyrus	2	21	188	.003‖	–43, 3, –28	NS	‖
Left middle superior temporal gyrus and sulcus	3	21/22	165	.002‖	–57, –19, –8	NS	‖
Left posterior superior temporal sulcus and middle temporal gyrus	4	21	152	.008‖	–51, –35, 1	NS	‖
Left inferior temporal sulcus and gyrus	5	20	199	.002‖	–49, –22, –28	‖	‖
Right anterior inferior middle frontal gyrus	6	11	1199	<.001§	15, 55, –10	§	§
Right fusiform gyrus	7	37	116	.004‖	37, –53, –8	‖	NS
Right anterior superior temporal gyrus	8	22	86	.01‖	55, 8, –4	§	§

Abbreviations: BA, Brodmann area; NS, no significant activation in this region at cluster-level threshold of $P<.05$, corrected across the whole cortex.

*Cluster numbers 1 through 7 correspond directly to cluster labels in Figure 3. Talairach coordinates of peak activation and approximate BA locations correspond to the local minimum *P* values for each cluster of activated vertices on the cortical surface.

†Within-group comparisons in both controls and patients also showed response suppression at an uncorrected voxel level of $P<.01$ within the right cuneus, BA 19 (Talairach coordinates: controls, 3, –72, 28; patients, 5, –83, 29).

‡In a group × relatedness interaction map comparing directly related and indirectly related word pairs, these clusters showed significantly more activation in response to directly related word pairs than to indirectly related word pairs (cluster level, $P<.05$ corrected).

§Cluster reached a cluster-level significance of $P<.05$ corrected across the whole cortex.

‖Voxels within cluster reached a voxel-level significance of $P<.01$ uncorrected across the whole cortex.

previous functional neuroimaging studies in healthy individuals that report reduced hemodynamic responses to directly related (relative to unrelated) word pairs in prefrontal[48,50,52-54] and temporal[49-54] cortices. In the present study, in which the long stimulus onset asynchrony biased toward controlled processing, the localization of the most robust suppression to the inferior prefrontal cortices, particularly the left anterior inferior prefrontal gyrus, is consistent with the known role of these regions in controlled semantic processing.[59-61]

The hemodynamic response suppression primarily within temporal cortices in response to indirectly related (relative to unrelated) word pairs in controls is particularly interesting because, consistent with previous electrophysiologic findings,[19] it occurred in the absence of a significant indirect behavioral priming effect. Nonsignificant behavioral indirect priming under controlled conditions is consistent with most[11,12,15,18-20] (although not all[33]) previous studies. Whereas semantic matching and predictive processes serve to facilitate the processing of directly related (relative to unrelated) targets, these controlled processes might not be so effective in priming targets whose semantic relationships with their primes are not obvious or easily predictable.[6] If, as suggested earlier, inferior prefrontal cortices mediate such controlled processes, this would explain why prefrontal hemodynamic response suppression in response to indirectly related word pairs was minimal. A failure of the prefrontal cortices to semantically match or predict indirect semantic relationships, however, may have allowed time for a spread of activation to build up and attenuate activity within the temporal cortices that are implicated in the storage of word representations and their more implicit activation.[62-64]

Patients showed less hemodynamic response suppression than did controls and sometimes even more hemodynamic activity in response to directly related and indirectly related word pairs than to unrelated word pairs. Such seemingly paradoxical hemodynamic "response enhancement" in temporal and prefrontal cortices has been observed in healthy individuals in fMRI studies of repetition priming of words and objects, particularly under masked priming conditions.[55,56] It has been conceptualized as reflecting activity that occurs selectively on primed but not unprimed targets and may reflect the mechanism, rather than the result, of priming. Magnetoencephalography studies suggest that an initial increase in neural activity in response to primed (relative to unprimed) words precedes a later phase of robust neural response suppression.[58,109] Because the hemodynamic response integrates neural activity over seconds, and targets are generally viewed for much longer than required for recognition, fMRI is more likely to pick up this second phase of neural response suppression than early neural enhancement, except when suppression is curtailed such as when the prime is masked.[55,56] Given this potential explanation in healthy controls, one way of explaining the hemodynamic increase in response to related (relative to unrelated) words in patients is that it reflected an abnormal increase or prolongation of this early phase of neural enhancement that outweighed any later neural response suppression.

Hemodynamic response enhancement in response to directly and indirectly related (relative to unrelated) word pairs in patients occurred primarily in inferior prefrontal and temporal cortices, respectively—the same regions where controls showed response suppression. Thus, these increases or prolongations of neuronal activity in patients might have reflected increases or prolongations of the particular cognitive processes these regions subserved, eg, increased or prolonged semantic matching to directly related (relative to unrelated) word

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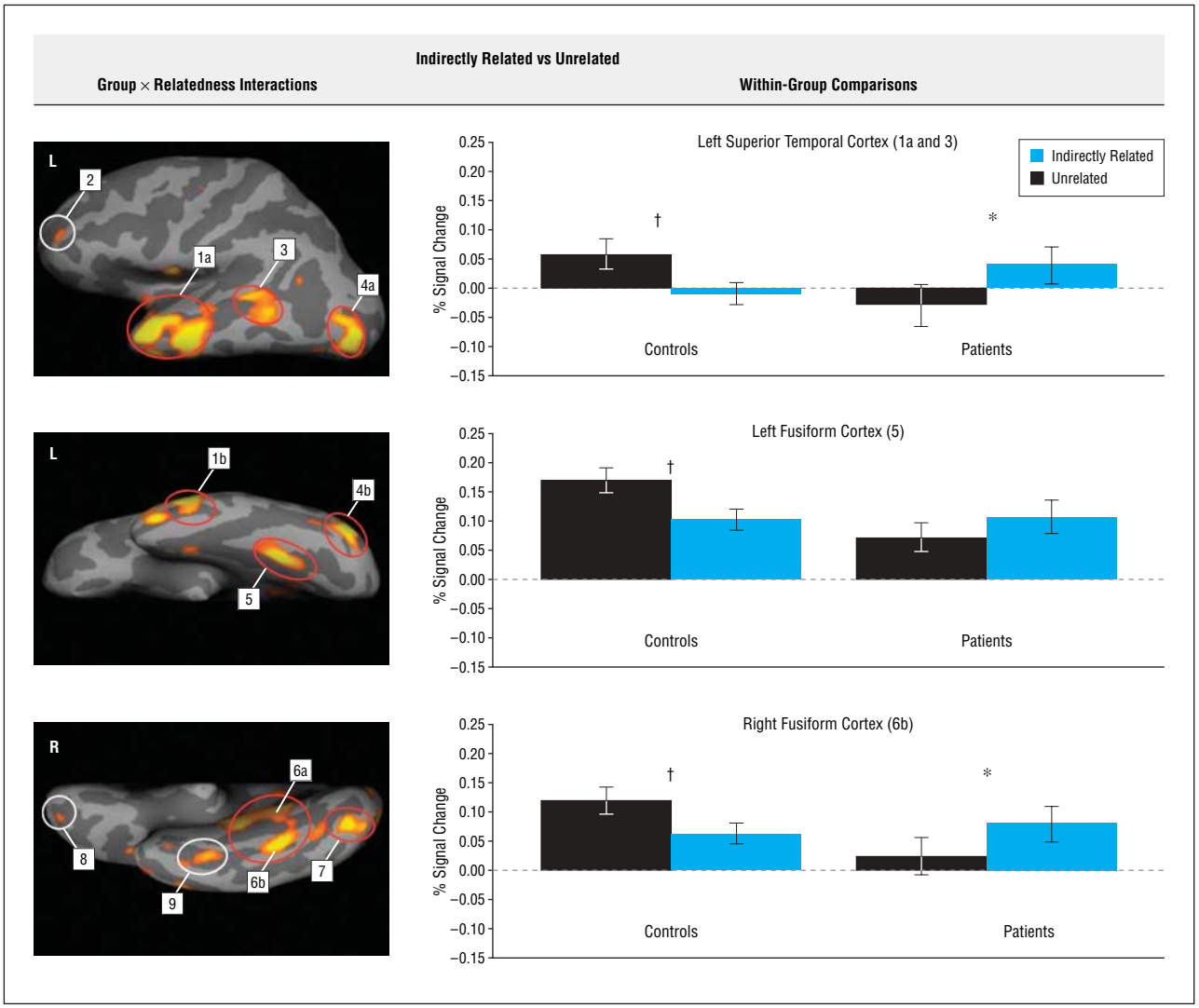

Figure 4. Left, Group × relatedness cortical maps comparing indirectly related and unrelated word pairs. Red circles (in temporal and occipital regions) indicate clusters that reached significance corrected for multiple comparisons across the whole cortex (cluster level, $P<.05$). White circles (in prefrontal regions) illustrate clusters that reached a voxel-wise significance level of $P<.01$ (uncorrected). Cluster numbers correspond directly to those in Table 9. Right, Activity in the patient and control groups averaged over all voxels within clusters. In prefrontal clusters that showed significant group × relatedness interactions, controls showed response suppression while patients showed response enhancement. *$P<.001$. †$P<.05$.

pairs within the prefrontal cortices, and increased or prolonged spreading activation in response to indirectly related (relative to unrelated) targets within the temporal cortices. Increases or prolongations in both types of neurocognitive mechanisms could potentially have resulted from reduced inhibitory activity.[10,17,33] At a neuropathological level, reduced inhibition could arise from a selective loss or dysfunction of inhibitory synapses within the temporal-prefrontal cortices in patients[110,111] that might lead to subtle cortical thinning observed in these regions.[103,112,113] Such potential links between hemodynamic functional activation, neural activity, cognitive abnormalities, and neuropathological abnormalities in schizophrenia are speculative. Nonetheless, they provide hypotheses that can be tested by using complementary techniques such as structural MRI, event-related potentials, and magnetoencephalography.

As predicted, within the patient group, severity of thought disorder predicted the degree of response enhancement to indirectly related words within the ventral temporal fusiform cortices, a finding consistent with the idea that thought disorder is associated with an increased spread of activation in response to indirectly related targets,[21,29-31,33] the role of temporal fusiform regions in generating the N400,[62] and its increased activity in thought-disordered patients during sentence completion[100] and in the production of thought-disordered speech.[97] This finding was specific: there were no other correlations between hemodynamic modulation and any other symptom in the temporal fusiform cortices or in any other ROI.

There are important caveats in generalizing these findings. All patients had chronic schizophrenia, and it will be important to determine whether acutely psychotic patients, who can show different patterns of behavioral priming than those in chronically ill patients,[114] exhibit the same hemodynamic abnormalities. Although in the present study there were no correlations between medication dosage and hemodynamic effects, and although pre-

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Table 9. Indirectly Related vs Unrelated Clusters Activated Across the Cortex*

Region	Group × Condition Interactions: Cluster No.	BA	Area, mm²	*P* Value	Talairach (x, y, z)	Within-Group Comparisons: Controls,† Unrelated ≥ Indirectly Related (Suppression)	Within-Group Comparisons: Patients, Indirectly Related ≥ Unrelated (Enhancement)
Left anterior superior and middle temporal cortex‡	1a (lateral surface) and 1b (ventral surface)	21	1779	<.001§	54, 0, –24	§	§
Left anterior middle frontal gyrus‖	2	46/10	144	.009‖	–37, 48, 1	‖	NS
Left posterior superior temporal sulcus, and middle temporal gyrus‡	3	22/21	346	.004§	–66, –47, 6	‖	‖
Left occipital cortex (middle occipital gyrus)‡	4a (lateral surface) and 4b (ventral surface)	19	1048	<.001§	–51, –80, 7	‖	‖
Left fusiform cortex‡	5	37	392	<.001§	–35, –55, –7	§	NS
Right parahippocampal gyrus	6a	19/30	572	.003§	16, –52, 5	§	NS
Right occipital cortex (lingual gyrus)	7	18	456	.002§	21, –84, –5	§	NS
Right anterior orbitofrontal cortex	8	11	82	.01‖	18, 47, –8	‖	NS
Right fusiform cortex‡	9 (anterior) and 6b (posterior)	20/37	202	.001‖	42, –19, –12	‖	NS
Right anterior superior temporal sulcus and middle temporal gyrus‡	10	22/21	590	<.001§	47, –4, –6	‖	‖
Right insula	11	NA	309	.004§	34, –11, 18	§	NS
Left anterior cingulate gyrus	12	12	10	.01‖	–9, 38, –8	§	NS

Abbreviations: BA, Brodmann area; NA, not applicable; NS, no significant activation in this region at cluster-level threshold of $P<.05$, corrected across the whole cortex.

*Cluster numbers 1 through 10 correspond directly to cluster labels in Figure 4. Talairach coordinates of peak activation and approximate BA locations correspond to the local minimum *P* values for each cluster of activated vertices on the cortical surface.

†The within-group map in controls also showed response suppression (at $P<.01$ voxel-level uncorrected) in the right anterior middle frontal gyrus, BA 10/46 (Talairach coordinates: 36, 47, –2).

‡In a group × relatedness interaction map comparing indirectly related and directly related word pairs, these clusters showed significantly more modulation to indirectly related word pairs than to directly related word pairs (cluster level, $P<.05$ corrected).

§Cluster-level significance, $P<.05$ corrected.

‖Voxel-level significance, $P<.01$ uncorrected across the whole cortex.

vious electrophysiologic[42] and neuroimaging[94] studies on medication-naïve patients have also reported abnormal neural activity during semantic processing, it will be important to replicate these findings on unmedicated patients in their first episode of illness.

In summary, we have demonstrated inappropriate hemodynamic increases in response to directly and indirectly related (relative to unrelated) word pairs within prefrontal and temporal regions, respectively, in chronic schizophrenia. Increases in hemodynamic activity within temporal fusiform cortices in response to indirectly related (relative to unrelated) word pairs predicted positive thought disorder within the patient group. This inappropriate activity may be a neural correlate of the abnormal associative activity conceived by Bleuler[1] as being fundamental to understanding positive thought disorder and schizophrenia psychosis as a whole.

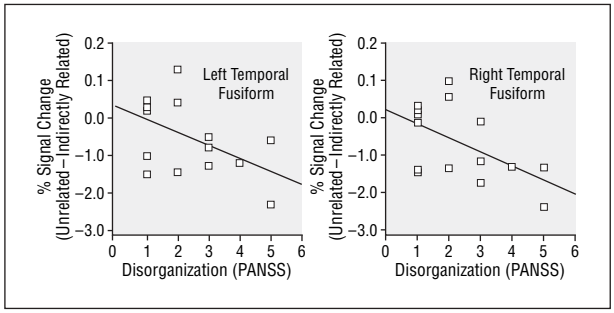

Figure 5. Inverse correlations between conceptual disorganization (on the Positive and Negative Syndrome Scale [PANSS]) and the difference in hemodynamic activity (averaged between 3 and 6 seconds) between the unrelated and indirectly related word pairs in the left and right temporal fusiform regions of interest.

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