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fMRI reveals Neuroanatomical Dissociations during Semantic Integration in Schizophrenia

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Abstract

Background—Schizophrenia symptoms can be conceptualized in terms of a breakdown of a balance between (a) activating, retrieving and matching stored representations to incoming information (semantic memory-based processing), and (b) fully integrating activated semantic representations with one another and with other types of representations to form a gestalt representation of meaning (semantic integration). Semantic memory-based processes are relatively more dependent on inferior frontal and temporal cortices, while more demanding integrative processes additionally recruit the DLPFC and sometimes parietal cortices. We used fMRI to determine whether the modulation of temporal/inferior frontal cortices and the DLPFC can be neuroanatomically dissociated in schizophrenia, as semantic integration demands increase. Integration demands were manipulated by varying the nature (concrete versus abstract) and the congruity (incongruous versus congruous) of words within sentences.

Methods—Sixteen right-handed schizophrenia patients and sixteen healthy volunteers, matched on age and parental socio-economic status, underwent event-related fMRI scanning while they read sentences. BOLD effects were contrasted to words within sentences that were (a) concrete versus abstract, and (b) semantically incongruous versus congruous with their preceding contexts.

Results—In both contrasts, large networks mediating the activation and retrieval of verbal and imagistic representations were normally modulated in patients. However, unlike controls, patients failed to recruit the DLPFC, medial frontal and parietal cortices to incongruous (relative to congruous) sentences, and failed to recruit the DLPFC to concrete (relative to abstract) sentences.

Conclusions—As meaning is built from language, schizophrenia patients demonstrate a neuroanatomical dissociation in the modulation of temporal/inferior frontal cortices and the DLPFC.

Keywords

schizophrenia; semantic; language; fMRI; context; prefrontal cortex; DLPFC; temporal cortex

Introduction

Deriving an accurate representation of meaning requires us to strike a fine balance between two types of semantic processes: (a) activating, retrieving and matching stored semantic information with incoming material (semantic memory-based processes), and (b) fully integrating activated semantic representations with one another and with other types of activated representations to derive a gestalt meaning (semantic integration). Both mechanisms are used to construct the meanings of words and whole sentences. Semantic activation, retrieval and matching are thought to be most reliant on temporal and inferior frontal cortices, while more demanding semantic integrative processes additionally engage more superior dorsolateral prefrontal cortices (DLPFC), sometimes together with parietal cortices. This study used fMRI to demonstrate a neuroanatomical dissociation in the modulation of temporal/inferior frontal cortices and the DLPFC in schizophrenia, as meaning is built from language.

Encountering all types of words leads to the retrieval and activation of stored lexico-semantic representations, reflected by activity within left-lateralized temporal and inferior frontal cortices (1,2). In addition, words with concrete meanings activate 'imagistic' representations to a greater degree than abstract words (3). This is reflected by widespread activity, distributed across bilateral ventromedial temporal, orbitofrontal and occipito-parietal cortices, known to subserve perceptual processing of real-world objects (4–6). Therefore, to derive a full representation of concrete word meaning, activated verbal and imagistic perceptual semantic representations must be integrated and, in some cases, undergo additional manipulation, such as mental imagery (7,8). These additional demands of integrating and manipulating the meaning of concrete, relative to abstract, words may be reflected by the increased recruitment of the DLPFC to concrete words (4,5).

Comprehending the meaning of whole sentences also engages semantic memory-based processes in which incoming relationships between content words are matched against relationships that are prestored within semantic memory (9,10) – operations that are again mediated by inferior frontal, and sometimes temporal, cortices (11–13). In addition, integrative processes are engaged, whereby activated semantic and syntactic representations are combined to determine 'who does what to whom' in a sentence. This semantic-syntactic integrative activity is also thought to be mediated within left-lateralized inferior frontal and temporal cortices (14,15). However, when integration demands are particularly high, additional regions, including the DLPFC and parietal cortices, are recruited (13).

In schizophrenia, there is evidence from semantic priming studies that patients' automatic activation of lexico-semantic representations is normal and, in thought-disordered patients, even increased ((16–20); reviewed in (21,22)). Behavioral studies also suggest that many aspects of semantic memory organization are normal in schizophrenia (23), and that patients can successfully retrieve semantic information, so long as appropriate semantic cues are provided (24,25). Neuroanatomically, activity within the inferior frontal cortex is generally preserved during deep semantic encoding (26,27), and functional connectivity between temporal and inferior frontal cortices may be increased (28). Abnormal increases in activity within temporal-occipital cortices have been reported in patients when processing indirectly related (versus unrelated) word-pairs (29), during semantic (versus shallow) verbal encoding

(27), and when completing sentences given highly predictable contexts (versus reading the same single word) (30).

In contrast to this normal or increased semantic memory-based activity in schizophrenia, evidence from behavioral and event-related potential (ERP) studies suggests that patients are relatively impaired when required to integrate activated semantic representations with one another or with other types of activated representations. There is evidence for such impairments at the level of both words and whole sentences. For example, under non-automatic experimental conditions, patients fail to fully integrate semantic representations of prime and target words, leading to relatively reduced semantic priming effects ((31); reviewed in (21)). And, during sentence comprehension, patients show abnormally reduced electrophysiological responses when semantic-syntactic integration demands are increased (32–36)[1].

Despite this behavioral and ERP evidence for a dissociation between (a) preserved or increased activity in association with semantic memory-based processing, and (b) decreased activity with increased integration demands in schizophrenia, there have been no attempts to determine how this dissociation plays out at a neuroanatomical level. In paradigms probing the maintenance and use of contextual information using simple non-verbal stimuli, clear functional dissociations between activity within the DLPFC and other regions have been described in schizophrenia (37–39). The goal of this study was to determine whether patients show such neuroanatomical dissociations when semantic integration demands are increased, as meaning is built from language. We aimed to dissociate activity within temporal-inferior frontal networks from activity within the DLPFC in schizophrenia in two ways: first, by manipulating the concreteness of individual words within sentences, and second, by manipulating the semantic congruity of a sentence-final word with its preceding context. These factors – Concreteness and Congruity – were fully crossed, such that each participant viewed sentences composed of concrete and abstract words, in which the final words were either congruous or incongruous with their preceding stems (Table 1; see (40) for a similar design).

We predicted that, in both contrasts (concrete versus abstract and incongruous versus congruous sentences), patients would show normal activation, retrieval and matching of verbal and perceptual semantic representations, reflected by normal modulation of occipito-temporal and inferior frontal cortices (26,27). Based on our previous fMRI study using semantically related word-pairs (29), we also considered the possibility that patients would show inappropriate increases in activity within inferior temporal and fusiform cortices to the congruous sentences, which contained more semantically related words than the incongruous sentences. Critically, based on behavioral and ERP findings at the level of words (21,22,31) and sentences (32–36), we predicted that patients would be relatively impaired in semantic integrative processes, and that this would be reflected by a failure to recruit the DLPFC to concrete (versus abstract) and to incongruous (versus congruous) sentences.

Methods

Materials

Two-hundred-and-forty 10-word congruous sentences, half primarily containing concrete words and half containing abstract words, matched on frequency and number of letters, were constructed (Table 1). The sentences were divided into two counterbalanced lists. Incongruous

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[1]Such increased semantic-syntactic integration demands may occur when a dominant meaning of a homograph contradicts the incongruous meaning of the entire sentence context (34), when a word is semantically associated with a previous word but the entire context dictates an incongruous meaning (33), or when an incongruous word occurs at the end of a sentence (35,36) where, during 'wrap-up' of final sentence meaning, comprehenders will generally make additional attempts to make sense of a sentence. Note that, depending on the type of word that is to be integrated and its position in the sentence, the abnormally attenuated electrophysiological response in schizophrenia may manifest either as a reduction of the N400 effect (34–36), or of the later P600 effect (33).

abstract and concrete sentences were generated by pseudo-randomizing the final words of the congruous abstract and concrete sentences respectively. Each list contained 60 sentences in each sentence type. Although each of the 240 sentence stems and final words appeared only once per list, across lists, they each appeared in both the congruous and incongruous sentences.

Participants

Sixteen patients meeting DSM-IV criteria for schizophrenia (41) (confirmed using the SCID (42)), receiving stable doses of atypical antipsychotics, were recruited from the Lindemann Mental Health Center, Boston. Sixteen demographically-matched volunteers on no medication, without histories of psychiatric disorders (42), were recruited by advertisement. All participants were native, primarily monolingual English speakers who had not learned any other language before age five. All were right-handed (43,44), without histories of head trauma, neurological disorder, substance abuse within six months, or substance dependence. Written consent was obtained following the guidelines of the Partners Healthcare Institutional Review Board. Clinical assessments were carried out within two weeks of scanning. Demographic and clinical data are summarized in Table 2.

Stimulus presentation and task

A typical 8-sec trial is depicted in Figure 1. Participants decided whether or not each sentence made sense by pressing one of two buttons on a response box (using their left hand, with fingers counterbalanced). Sentence trials were pseudo-randomly presented amongst fixation trials (20%) in which subjects fixated on a "+" (for variable durations: 1975–17975sec), allowing efficient deconvolution of the hemodynamic response (45).

MRI Data acquisition

Imaging took place on a 3 Tesla MR scanner (Siemens Trio). Participants underwent two high-resolution 3D structural scans (spoiled GRASS sequence; 128 sagittal slices, 1.33mm thickness, TR: 2530 ms, TE: 3.3msec, flip angle: 7 degrees, bandwidth: 199 Hz, in-plane resolution: 1×1.33 mm), followed by T1-weighted anatomic images (30 slices, 3mm thickness, skip 1 mm) and a T2-weighted image acquired in plane with the functional images to assist in manual registration of functional and structural data.

During functional scanning, each participant viewed sentences in one list, divided over six functional runs, each lasting 414sec during which T2*-weighted echoplanar (EP) images were acquired (30 slices, 203 images/slice, 3mm thickness, skip 1mm, in-plane resolution of 3.125 mm, 30\grad axially), using a gradient echo sequence (TR: 2sec; TE: 30 msec; flip angle: 90 \grad).

Behavioral data analysis

Percentages of errors and reaction times (RTs) to each sentence type (collapsed across items) were entered into $2 \times 2 \times 2$ repeated-measures ANOVAs with Group (patients versus controls) as a between-subject factor and Concreteness (concrete versus abstract) and Congruity (incongruous versus congruous) as within-subject factors. Analyses were repeated after logarithmic transformation and revealed the same pattern of findings unless otherwise noted. Alpha was set to 0.05.

MRI Data analysis

Following motion correction, each participant's two high-resolution structural scans were averaged to increase the signal:noise. The resulting volume was reconstructed using semi-automatic procedures (FreeSurfer) to yield a model of each individual's cortical surface (46–49). To average functional data across subjects (see below), each subject's cortical surface was

morphed/registered to an average spherical surface representation that optimally aligned sulcal and gyral features across subjects (49,50).

Functional images were motion corrected using the AFNI alogarithm (51,52). There was no significant difference in the total (vector) translation between controls (mean ± SD: 3.1 ± 1.1mm; range: 1.7–5.8mm) and patients (mean ± SD: 2.6 ± 0.8mm; range: 1–3.8mm), $p = 0.15$. Following spatial smoothing (3-D Gaussian filter: 6mm FWHM) and intensity normalization, the functional images were analyzed with a General Linear Model (GLM) using the FreeSurfer Functional Analysis Stream. The HRF for each condition was modeled using three components, each constituting a canonical HRF (53), convolved with a box-car of an appropriate length. The first component, modeled as a single regressor, lasted from the onset of the trial until the onset of the critical sentence-final word (5500 msec). The second component lasted from the onset of the critical sentence-final word until the onset of the "?" (550 msec) and was modeled separately for each of the four sentence types. The third component lasted from the offset of the critical word until the end of the trial (i.e. the decision: 1950 msec) and was again modeled as a single regressor. Mean offset and linear trend regressors were also included to remove low-frequency drift.

These GLM parameter estimates were resampled onto each individual's inflated cortical surface, iteratively smoothed (equivalent to a 3D kernel of approx. 8.5mm FWHM), and resampled onto the average cortical spherical representation. The regression weights of the second canonical HRF component (capturing the hemodynamic response to the sentence-final word) were used to construct statistical maps using a $2 \times 2 \times 2$ mixed model with Group (patient versus controls) as a between-subjects factor and Concreteness (concrete versus abstract) and Congruity (incongruous versus congruous) as within-subjects factors. Only 'highest order' effects are reported, i.e. clusters reported as showing main effects for a particular factor are those that failed to reach significance on any interactions involving that factor, and clusters reported as showing two-way interactions failed to show three-way interactions.

To correct for multiple comparisons, clusters covering at least 300mm^2, with a corrected threshold for rejection of the null hypothesis of $p < 0.05$, were identified on the basis of a Monte-Carlo simulation (54). Within-group maps were generated to examine sources of effects; clusters overlapping with those showing main effects or interactions are also reported at both cluster-level significance and at a less conservative uncorrected threshold ($p < 0.01$).

Maps were generated using all trials. Analyses were repeated using only correctly-answered trials and showed the same pattern of findings.

Results

Behavioral data

As shown in Table 3 and Table 4, both groups were more accurate and faster to judge the acceptability of the concrete than the abstract sentences, but these differences were greater in patients than controls (Group by Concreteness interactions). There were no overall differences in accuracy or RTs of acceptability judgments between the incongruous and congruous sentences (no main effects of Congruity), and this pattern did not differ between groups (no

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[2] In the RT data, there was no main effect of Congruity. This may be because, to reduce the neural effects of the motor response, participants were asked to delay their button presses until the "?" cue appeared after the sentences. Thus, potential RT differences between the incongruous and congruous sentences at the point of the sentence-final word may not have been detected. There was, however, an interaction between Congruity and Concreteness due to longer RTs to incongruous than congruous abstract sentences. Abstract sentences were generally harder to comprehend than concrete sentences (reflected by the main effect of Concreteness), and participants' acceptability decisions at the point of incongruous abstract sentence-final words are therefore more likely to have occurred after the "?" appeared.

Group by Congruity interactions). Concreteness by Congruity interactions, however, reflected participants' relatively more accurate and faster judgments of abstract congruous than abstract incongruous sentences, but no such difference was observed for concrete sentences. This pattern did not differ between groups (no Group by Concreteness by Congruity interactions). As expected, patients were generally less accurate and slower than controls in judging all sentences (main effects of Group).

fMRI data

Concreteness: main effects and interactions—In both groups, sentence-final concrete words were associated with significantly more activity than sentence-final abstract words across bilateral orbitofrontal, inferior/ventral/medial temporal cortices, and occipito-parietal cortices (main effects of Concreteness, Table 5A, Figure 2). Abstract sentence-final words, however, were associated with more activity within a left-lateralized superior/middle temporal and inferior frontal network (Table 5B, Figure 3). Within bilateral superior/middle prefrontal cortices, there were Group by Concreteness interactions (Table 6, Figure 4). This area encompassed Brodmann Areas 8/9/46, and is henceforth referred to as the DLPFC; here, controls showed relatively more activity but patients showed relatively less activity to concrete (versus abstract) sentence-final words. These interactions remained significant when premorbid IQ (that differed slightly between the two groups, Table 2) was entered as a potentially confounding covariate, and when analyses were repeated using a subset of the patients and controls (n=12 in each group) matched on premorbid IQ.

Analyses were repeated using a two-component model in which the first component (modeled separately for the four conditions) lasted the duration of the entire sentence until the onset of the "?". This analysis yielded the same pattern of findings, demonstrating that these findings could be generalized to all content words of the sentences (rather than just the sentence-final word).

Congruity: main effects and interactions—Across all participants, bilateral inferior frontal cortices were recruited to the incongruous relative to congruous sentence-final words (main effects of Congruity, Table 7, Figure 5). In addition, a network that included bilateral DLPFC (BA 8/9), the left inferior parietal lobule, medial frontal (including anterior cingulate) cortices, as well as the right middle temporal cortex and bilateral anterior fusiform gyri, showed significant Group by Congruity interactions. In most of these regions (except for the right middle temporal and fusiform cortex), controls showed more activity to incongruous (versus congruous) sentence-final words, and in all these regions, patients showed relatively less activity to incongruous (versus congruous) sentence-final words (Table 8, Figure 6). All these interactions remained significant when premorbid IQ was entered as a covariate and when analyses were repeated using the IQ-matched subset of patients and controls.

There was an interaction between Congruity and Concreteness within bilateral medial superior frontal cortices, due to increases in activity to abstract incongruous (versus congruous) sentence-final words, but no such differences in comparing concrete incongruous and congruous sentence-final words, across all participants (Table 9). There were no interactions between Group, Concreteness and Congruity.

Correlations with clinical features—As described above, Group interacted independently with (a) Concreteness and (b) Congruity within bilateral superior DLPFC. Within the patient group, the difference in hemodynamic activity between concrete and abstract words within the left DLPFC inversely correlated with both total positive symptoms (Spearman's rho: -0.6, p < 0.04) and total negative symptoms (Spearman's rho: -0.6, p < 0.038), and, within the right DLPFC, inversely correlated with patients' difficulty in abstract thinking (Spearman's rho:

-0.6, p < 0.02). The difference in hemodynamic activity between incongruous and congruous sentences within the left or right DLPFC did not correlate with any symptoms. Medication dosage did not correlate with differences in hemodynamic activity within the DLPFC for either the concrete versus abstract or the incongruous versus congruous comparisons, ps > 0.5.

Discussion

We investigated the neural underpinnings of building meaning from language in schizophrenia by contrasting words within sentences that were (a) concrete versus abstract, and (b) semantically incongruous versus congruous with their preceding contexts. In both these contrasts, widespread temporal-occipital and inferior frontal cortices showed similar patterns of modulation in patients and controls. However, whereas controls recruited bilateral DLPFC (and parietal cortices) to incongruous (versus congruous) sentences, and recruited bilateral DLPFC to concrete (versus abstract) sentences, patients showed the opposite pattern of modulation in both contrasts.

Neuroanatomical dissociations in effects of Concreteness

Both patient and control groups showed more activity to concrete, relative to abstract, sentences within a large, bilateral network distributed across ventromedial temporal, occipitoparietal and orbitofrontal cortices. This replicates previous findings in healthy individuals using single words presented outside a sentence context (4,5,55). This network is likely to have reflected the activation of non-verbal 'imagistic' representations of concrete words (3) – representations of percepts and affordances that are represented by such words (6,56). Also, consistent with previous findings in healthy individuals (4,5,57), both groups showed more activity to abstract, relative to concrete, sentences words within a more localized left-lateralized network, distributed across inferior frontal and lateral temporal cortices. This suggests that both groups accessed and retrieved verbal representations of abstract words. In both groups, the superior behavioral performance (fewer errors and shorter RTs) in judging the acceptability of concrete, relative to abstract, sentences may have arisen either because participants' implicit access to imagistic representations of concrete words facilitated processing, or because the increased lexico-semantic retrieval demands of abstract words slowed processing (58).

Controls and patients, however, showed strikingly different patterns of hemodynamic modulation within bilateral superior DLPFC. In controls, the increased DLPFC recruitment to concrete, relative to abstract, sentences is again consistent with previous studies in healthy individuals using words outside a sentence context (4,5). Its activity may have reflected the demands of integrating verbal and non-verbal representations of meaning that are activated by concrete words (see (59) for evidence for a role of the DLPFC in relational binding), as well as further elaborative semantic processing, such as imagery, of the concrete sentences (7,8). Such additional integrative and elaborative semantic activity to concrete, relative to abstract, words may contribute to their superior recall in memory paradigms (3) (and, indeed, activity within the DLPFC during encoding predicts the success of later recognizing words that are cued by their corresponding pictures (60)).

In patients, we suggest that the failure to recruit the DLPFC to concrete, relative to abstract, sentences reflected a failure to fully integrate activated verbal and non-verbal representations. Rather, the increased activity within this region to abstract, relative to concrete, sentences may have reflected patients' relative inefficiency in processing abstract concepts whose meanings are unsupported by imagistic representations. Consistent with this interpretation, patients performed worse than controls in judging the acceptability of the abstract relative to the concrete sentences (Group by Concreteness interactions in accuracy and, less robustly, in RTs) and, within the patient group, the degree of abnormal modulation within the right DLPFC correlated with patients' clinically-assessed difficulties with abstract thinking.

Neuroanatomical dissociations in effects of Congruity

Both patient and control groups showed increases in activity to all incongruous, relative to all congruous, sentences within bilateral inferior frontal cortices[2]. Such increases are likely to have reflected increased semantic memory-based processing, i.e. participants' increased and prolonged efforts to retrieve and match stored semantic material with the semantic relationships between incoming content words within incongruous, relative to congruous, sentences (11–13,61,62).

Controls also showed increased recruitment of bilateral superior DLPFC, the left inferior parietal lobule and bilateral medial frontal and medial parietal cortices to the incongruous, relative to the congruous, sentence-final words – a network that we have previously reported as more active to semantic anomalies when semantic-syntactic integration demands are particularly high (13). Although the functional roles of each of these regions are debated (see (13) for a discussion of alternative hypotheses), additional recruitment of this network in the present study can be broadly interpreted as reflecting the increased semantic-syntactic integration and reanalysis demands required to integrate sentence-final incongruities[3].

Patients failed to recruit this DLPFC/medial frontal/parietal network to the incongruous sentence-final words (indeed, in some of these regions, activity fell below that to the congruous sentences). We suggest that this failure reflects an impairment in patients' engagement of additional integrative and reanalysis processes to the sentence-final incongruities – an interpretation that is consistent with ERP studies reporting a normal modulation of waveforms in schizophrenia to semantic incongruities that are detectable through semantic memory-based processing (33,63,64), but reduced modulation of components when there are additional demands to integrate semantic and syntactic information ((33–36,65) and see footnote 1). This interpretation is also consistent with findings of an fMRI study that reported abnormally reduced activity within the DLPFC as patients produced syntactically more complex (versus less complex) sentences (66) – a situation where demands for integrating word meaning and syntactic structure are again increased.

Patients were generally successful in judging the incongruous sentences as unacceptable and the congruous sentences as acceptable. We suggest that their relatively intact behavioral performance was driven by normal semantic memory-based retrieval and matching processes, mediated within inferior frontal cortices; sentence-final words of the incongruous sentences were generally less semantically related to their preceding content words than those of the congruous sentences, explaining why semantic memory-based mechanisms would lead to successful behavioral judgments[4]. Indeed, there was some indirect evidence that implicit semantic memory-based activity within temporal cortices may have even been increased in patients: consistent with previous studies demonstrating inappropriate recruitment of temporal cortices to indirect and predictable semantic relationships (29,30), patients showed abnormally increased activity within right-sided middle/inferior temporal and fusiform regions to the congruous, relative to incongruous, sentences. This may have reflected some hyperactivity to semantically-associated congruous sentence-final words. This interpretation, however, remains speculative and future experiments directly manipulating semantic association within sentences should explore this hypothesis further.

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[3]Activity within the left inferior frontal cortex is also likely to mediate semantic-syntactic integration processes in both congruous and incongruous sentences; our assumption here is that more superior frontal and parietal cortices are additionally engaged when integration demands are particularly high on semantically anomalous sentence-final words.

[4]Although such a semantic memory-based mechanism would be successful in interpreting the types of sentences used in this study, such a strategy would be inadequate in other situations where semantic-syntactic integration and reanalysis is necessary for successful interpretation. For example, a pure semantic memory-based analysis would fail to determine that an anomalous sentences containing semantically associated content words (e.g. "At breakfast the eggs would eat…") is implausible. Indeed, there is some evidence that patients' accuracy in judging the acceptability of such sentences is selectively impaired (32,33).

Open questions and Conclusions

An open question is whether patients' abnormal pattern of activity in both contrasts (concrete versus abstract, and incongruous versus congruous sentences) reflected a single neurocognitive deficit. The absence of a three-way interaction between Group, Concreteness and Congruity argues against this hypothesis[5]. Moreover, whereas reduced activity to concrete (versus abstract) words within the left DLPFC correlated with positive and negative symptom severity (although not medication dosage) within the patient group, this was not true of the contrast between incongruous and congruous sentences, possibly because semantic-syntactic integration and reanalysis was relatively less dependent on this single region.

Nonetheless, it is still possible that an abnormality in a more basic cognitive operation contributed independently to the abnormal modulation of activity seen in each contrast. One obvious candidate for such an operation is the maintenance and/or manipulation of information within working memory – a process long known to be impaired (67), correlated with language comprehension deficits (68,69), and associated with abnormal DLPFC modulation (37–39, 70,71) in schizophrenia. There is evidence that working memory operations subserved by the DLPFC play a role in relational binding between activated representations of single concepts (72), providing a mechanism by which a working memory deficit in schizophrenia could contribute the abnormal DLPFC modulation to concrete (versus abstract) words. And, although there has been debate as to whether integration processes during sentence comprehension are language-specific (73), recent evidence in healthy individuals suggests that they may engage at least some domain-general working memory mechanisms (74). Future studies should determine whether DLPFC dysfunction in schizophrenia, indexed using general working memory paradigms, predicts DLPFC dysfunction during the construction of higher-order meaning.

In conclusion, as meaning is built from language in schizophrenia, large networks mediating the retrieval and activation of verbal and imagistic representations are spared (and some may even show increased activity in response to semantically associated material). However, when demands for integrating multiple different activated representations together are increased, patients fail to recruit the DLPFC (and sometimes also medial frontal and lateral/medial parietal cortices). In healthy individuals, semantic memory-based and integrative mechanisms both contribute to language processing and are highly interactive (10). We suggest that abnormalities in schizophrenia are best conceived of as a disturbance in the *balance* between these mechanisms. As meaning is built from language, patients may be relatively more dependent on semantic memory-based processes at the expense of integrative processes (10). This imbalance may contribute to intrusions of internal semantic representations at the expense of forming accurate representations of meaning of the external world in schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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[5]The presence of an interaction between Congruity and Concreteness in the medial superior frontal gyrus, mirroring the behavioral interaction, suggests that some common neurocognitive mechanism may have been engaged in these two contrasts, but this did not differ between patients and controls.

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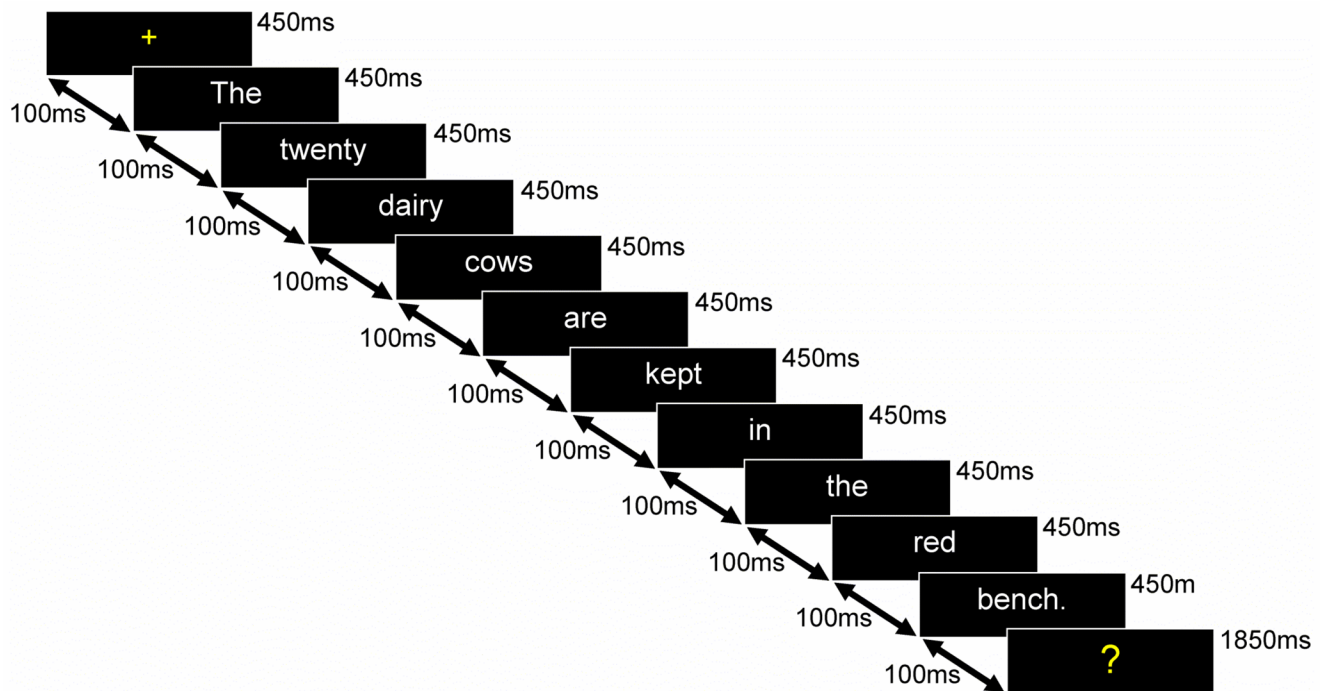**Figure 1. Depiction of a single trial**
Each trial began with a centered yellow fixation followed by each word (450msec, ISI:
100msec). The sentence-final word was followed by a response cue ("?"), giving subjects
1850msec (ISI: 100msec) to respond before the next trial began. The sentence shown is a
concrete incongruous sentence. See Table 1 for examples of sentences presented in the other
three conditions.

Main Effect of Concreteness: Concrete > Abstract

Figure 2. Cortical statistical maps comparing the hemodynamic response to concrete and abstract sentence-final words, across patients and controls (main effects of Concreteness in the absence of any interactions involving Group)

Yellow-red: more activity to concrete than to abstract words. Blue: more activity to abstract than concrete words (shown again in Figure 3). These maps were generated by contrasting the second component of the HDR to each sentence type (lasting 550msec, from the onset of the critical sentence-final word until the onset of the "?"). They are therefore likely to reflect differences in neurocognitive activity at the point of sentence-final word, as well as during decision making (see (11) and (13) for Discussion). Hemodynamic time courses show activity in patient and control groups within each of these clusters at each TR. On the time axes, zero refers to the onset of the trial as a whole. The critical events – the sentence-final words – began 4950msec into the trial. All clusters circled are significant at a cluster-level p < 0.05. Cluster numbers correspond directly to the regions reported in Table 5A.

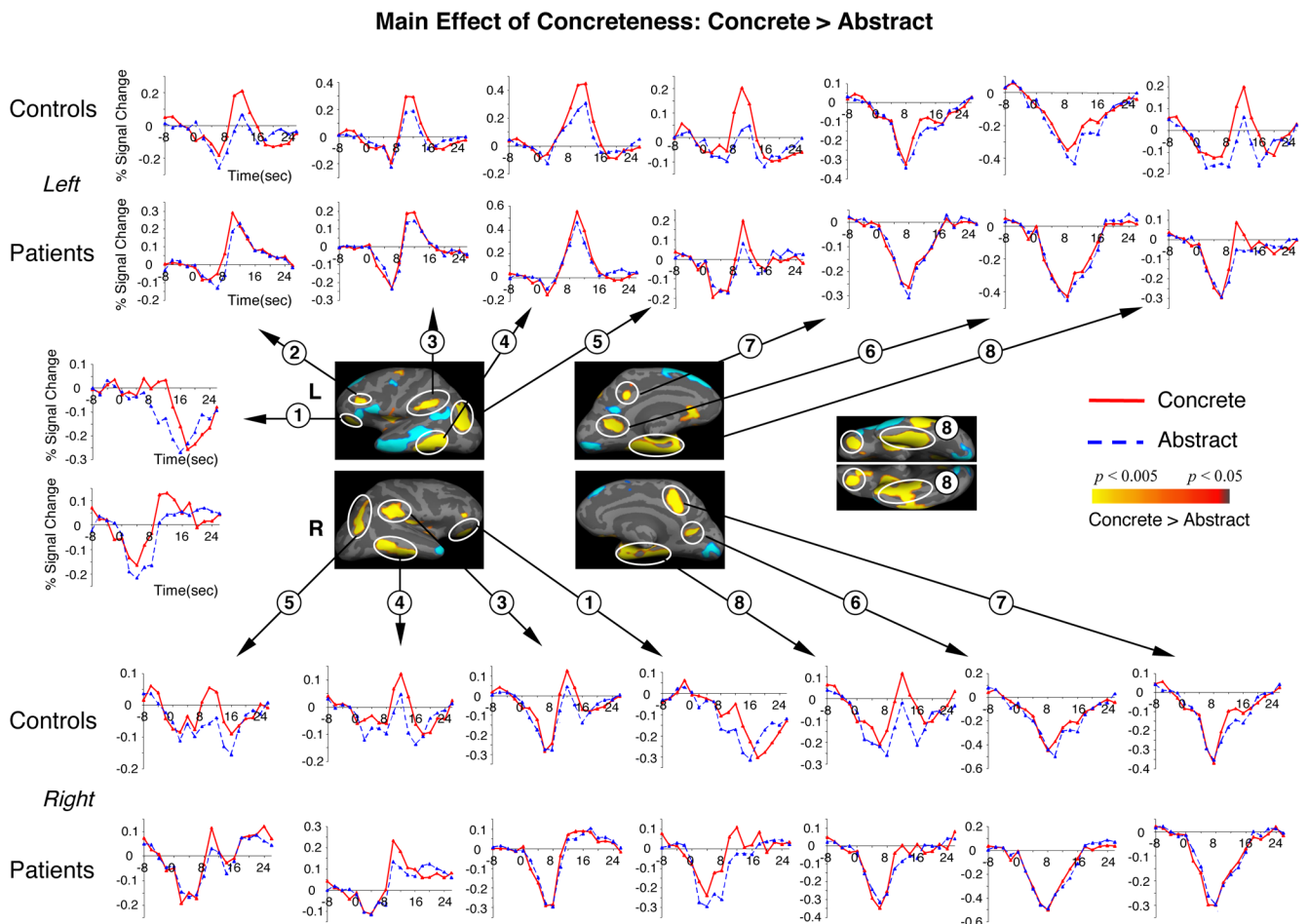## Main Effect of Concreteness: Abstract > Concrete

Figure 3. Cortical statistical maps comparing the hemodynamic response to concrete and abstract sentence-final words, across patients and controls (main effects of Concreteness in the absence of any interactions involving Group)
Blue: more activity to abstract than to concrete words. Hemodynamic time courses show activity in patient and control groups within each of these clusters at each TR (on the time axes, zero refers to the onset of the whole trial). All clusters circled are significant at a cluster-level $p < 0.05$. Cluster numbers correspond directly to the regions reported in Table 5B.

Group x Concreteness Interaction
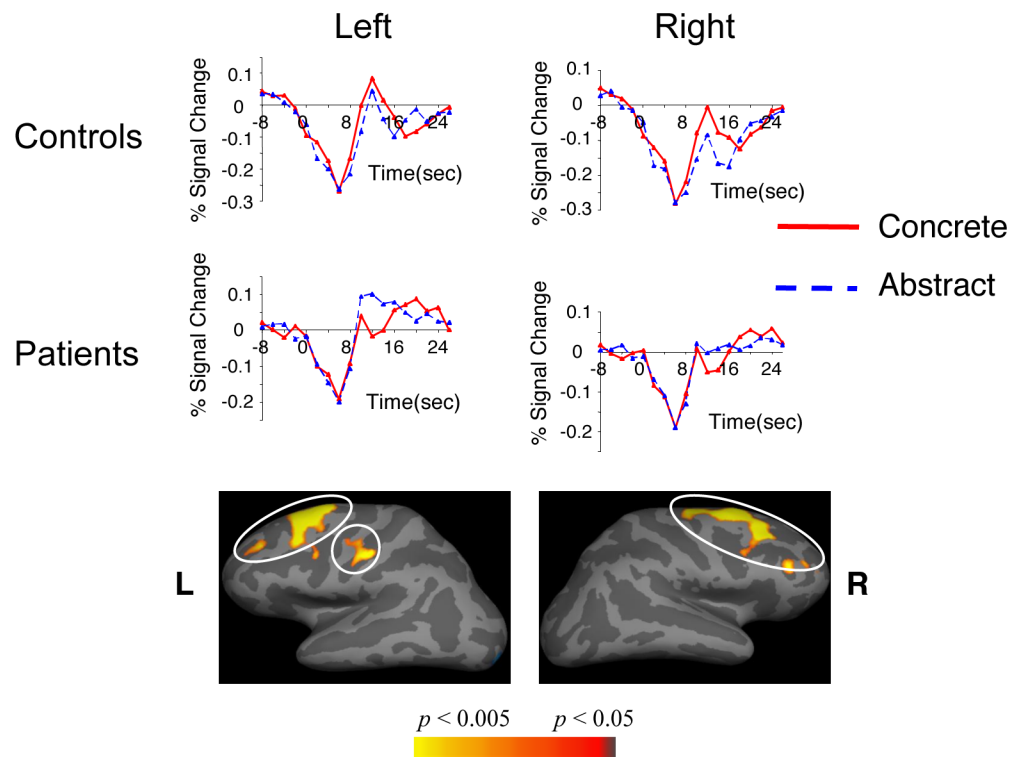
Figure 4. Group by Concreteness interactions: areas showing different patterns of modulation between patients and controls in comparing concrete and abstract sentence-final words
Hemodynamic time courses show activity in patient and control groups within each of these clusters at each TR (on the time axes, zero refers to the onset of the whole trial). All clusters circled are significant at a cluster-level $p < 0.05$. Cluster numbers correspond directly to the regions reported in Table 6.
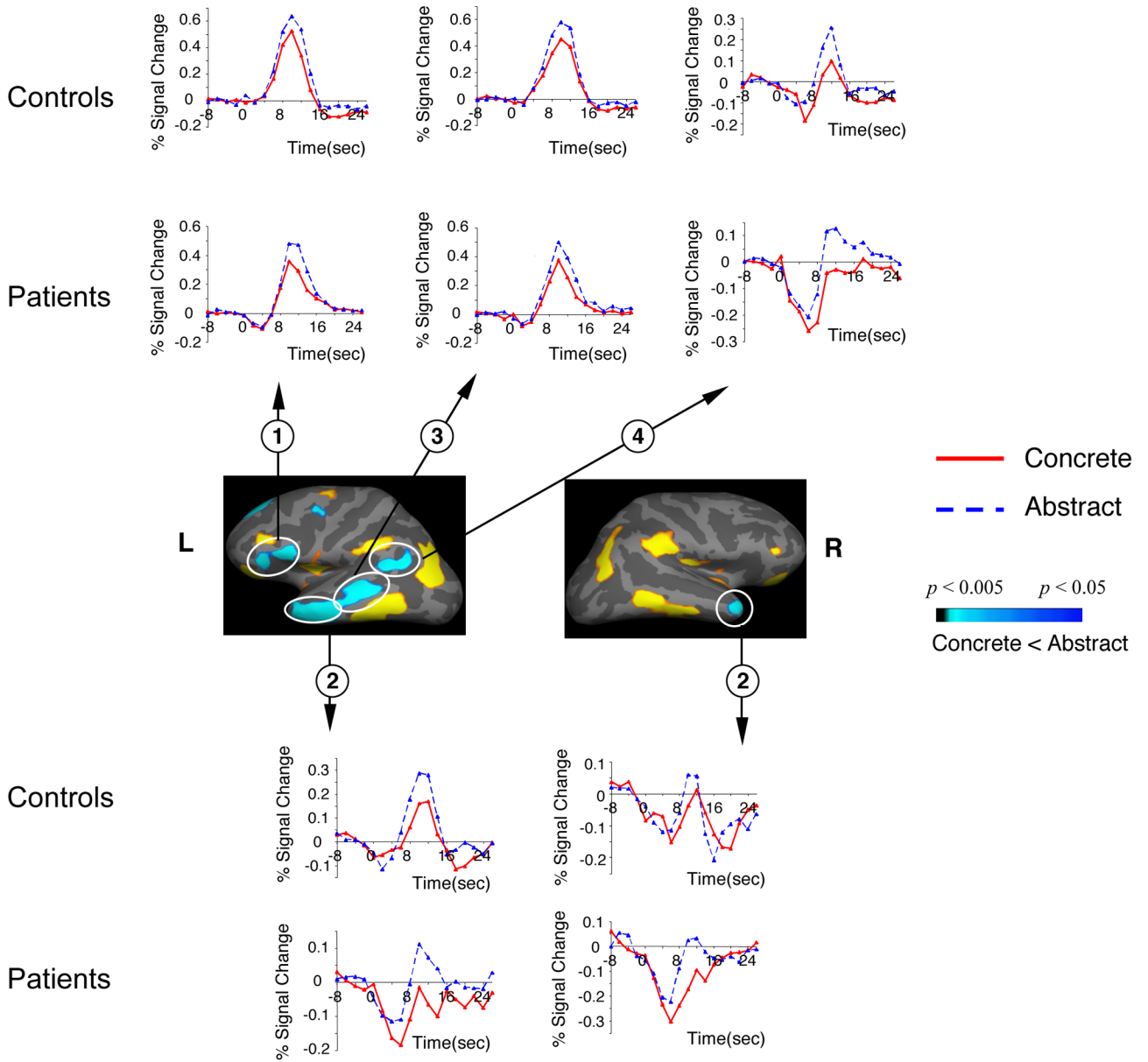
Main Effect of Congruity
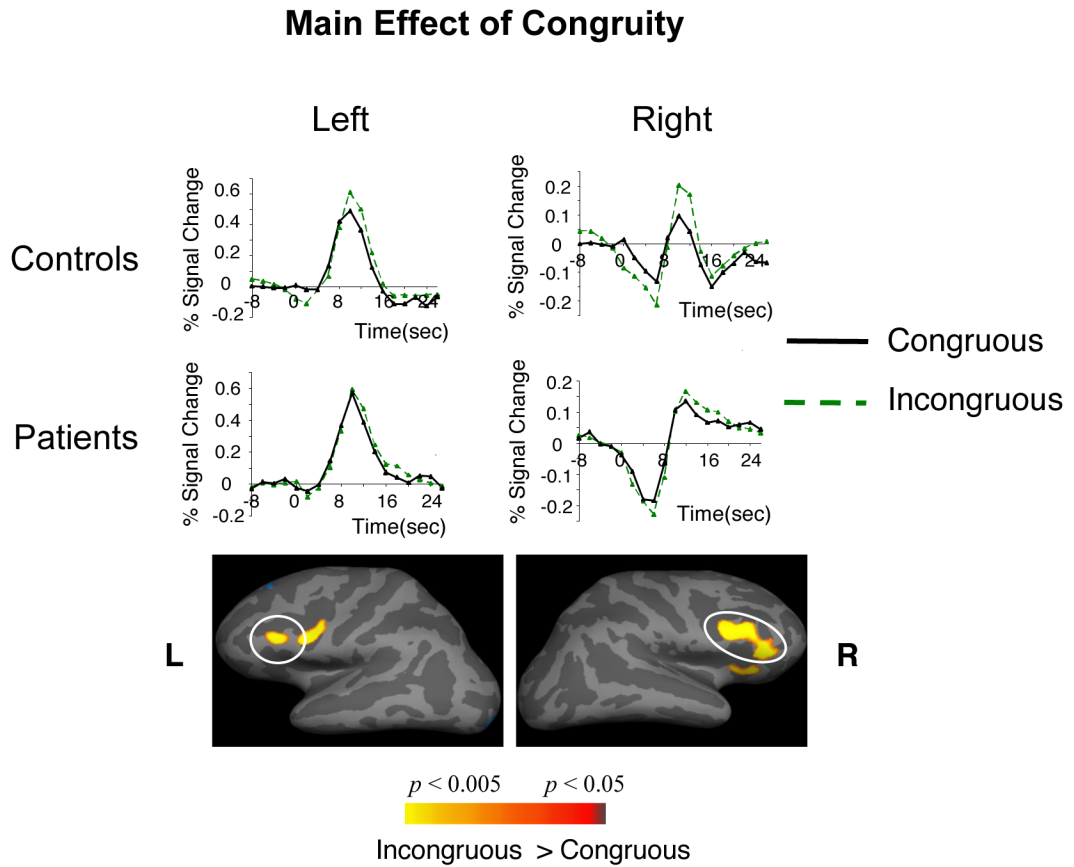
Figure 5. Cortical statistical maps comparing the hemodynamic response to incongruous and congruous sentence-final words, across patients and controls (main effects of Congruity in the absence of any interactions involving Group)

Hemodynamic time courses show activity in patient and control groups within each of these clusters at each TR (on the time axes, zero refers to the onset of the whole trial). All clusters circled are significant at a cluster-level p < 0.05. Cluster numbers correspond directly to the regions reported in Table 7.

Group x Congruity Interaction
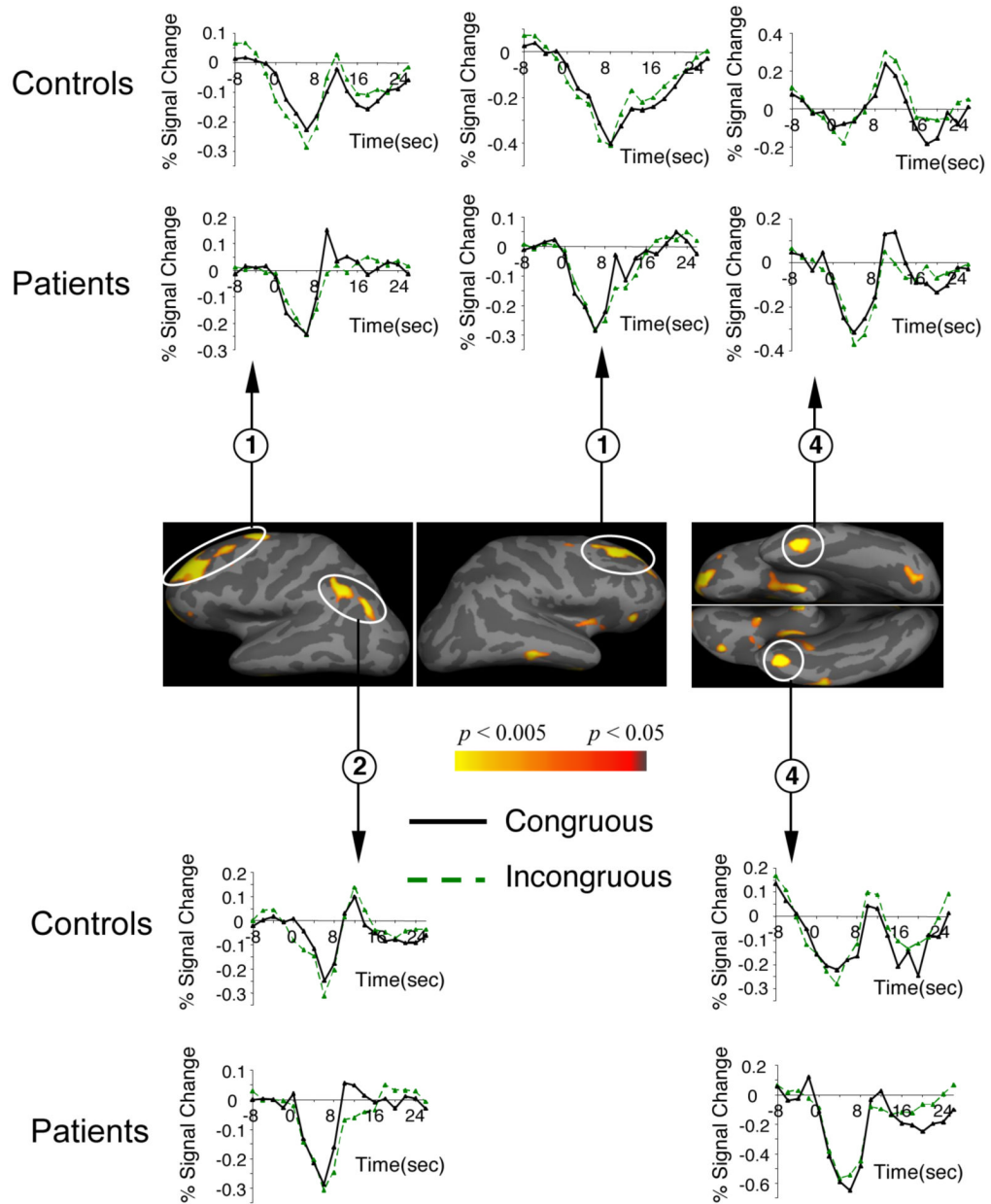
Figure 6. Group by Congruity interactions: areas showing different patterns of modulation between patients and controls in comparing incongruous and congruous sentence-final words
Hemodynamic time courses show activity in patient and control groups within each of these clusters at each TR (on the time axes, zero refers to the onset of the whole trial).
All clusters circled are significant at a cluster-level p < 0.05. Cluster numbers correspond directly to the regions reported in Table 8.

Table 1

Sentence type and examples	No. of content words per sentence	Cloze probability y of congruous sentences	Frequency of content words per sentence	Concreteness rating of all content words, per sentence	Concreteness rating of sentence-final words	Min and Max Concreteness Rating Final word
Concrete *Congruous:* During the rain storm he carried a large golf umbrella. *Incongruous:* The twenty dairy cows are kept in the red bench.	5.48 ± 0.96	0.74 ± 0.19	138.22± 107.89	5.43 ± 0.42	6.30 ± 0.42	5.00, 6.89
Abstract: *Congruous:* Although she strove for perfection she continued to make mistakes. *Incongruous:* Her outer expressions were completely blank and revealed no equality.	5.48 ± 1.06	0.69 ± 0.21	162.57 ± 145.95	3.64 ± 0.47	2.94 ± 0.70	1.22, 4.78
P Value	0.974	0.103	0.144	< 1 E -20	< 1 E -20	

Means are shown with standard deviations in brackets. In the examples, critical sentence-final words are underlined.

Values for cloze probability and concreteness ratings (on a scale of 1–7) were derived in normative studies ratings in two separate groups of healthy participants who did not participate in the fMRI experiment. Frequencies (per million) were taken from Frances & Kucera (75).

Table 2

Demographic and psychopathological data of healthy controls and patients with schizophrenia

	Subject Group	
Parameter	Controls (n=16)	Patients (n=16)
Gender (M/F)	11/5	12/4
Race (C/AA)	12/4	13/3
Age (years)	44.4 (5.9)	45.9 (8.0)
Hollingshead Index	3.0 (1.3)	3.2 (1.1)
Premorbid verbal IQ	116.2 (9.4)	105 (14.2)
CPZ equivalent	-	395 (223)
Duration of illness (years)	-	20.3 (7.7)
PANSS positive (total)		10.8 (6.1)
PANSS negative (total)		16.9 (8.4)

Patients and controls matched closely in gender and race/ethnicity distributions and there was no significant difference between the groups in age (p = 0.55). The patient and control groups showed no significant difference on parental socioeconomic status (p =0.5), as determined by Hollingshead Index scores (76), although patients had a lower premorbid IQ (p < 0.03) as assessed by the North American Adult Reading Test 77 (NAART).

Abbreviations: M = Male; F = Female; C = Caucasian; AA = African-American; CPZ = chlorpromazine; PANSS: Positive and Negative Syndrome Scale. (78.)

Table 3

	Controls	Patients	Controls	Patients
		Concrete		Abstract
Congruous % errors	3.1 (2.5)	10.9 (8.6)	3.1 (3.6)	15.5 (14.3)
Incongruous % errors	2.8 (3.3)	8.2 (7.7)	10.7 (8.3)	20.8 (9.9)
Congruous (RTs)	937.3 (152.2)	1130.1 (159.2)	972.9 (151.5)	1137.2 (141.3)
Incongruous (RTs)	902.6 (182.7)	1105.6 (165.8)	1016.1 (163.3)	1150.9 (121.3)

Mean percentage of errors and reaction times across the four sentence types, with standard deviations in brackets. Note that an error to a congruous sentence is a false negative (classifying it as incongruous) and an error to an incongruous sentence is a false positive (classifying it as congruous).

Table 4

Behavioral data

		Accuracy			Reaction times	
	DOF	F	p	DOF	F	p
Group × Congruity × Concreteness	1, 30	0.003	p=.96	1, 30	1.52	p=.22
Congruity × Concreteness	1, 30	24.39	p<.0001 ****	1, 30	13.05	p<.001 ***
Group × Congruity	1, 30	0.96	p=.33	1, 30	0.11	p=.74
Group × Concreteness	1, 30	8.49	p<.01 **	1, 30	6.49	p<.05 *
Concreteness	1, 30	64.51	p<.0001 ****	1, 30	28.19	p<.001 ***
Congruity	1, 30	4.20	p<.05 *	1, 30	0.001	p=.97

*
  $p<.05$

**
  $p<.01$

***
  $p<.001$

****
  $p<.0001$

Note: For reaction time data, the Group × Concreteness interaction did not remain significant when analyzed using a log transform or when correct responses only were examined.

Table 5

Main effects across all participants: Concrete sentences versus abstract sentences

Table 5A: CONCRETE VERSUS ABSTRACT

No.	Region	Lat.	BA	Main effect of Concreteness: Concrete > Abstract			Controls: Concrete > Abstract			Patients: Concrete > Abstract		
				Area mm²	Tal. x, y, z	p	Area mm²	Tal. x, y, z	p	Area mm²	Tal. x, y, z	p
1	Orbito frontal cortex	L	11	800	−21 24 −13	$2.2e^{-6}$	775	−21 25 −11	.00049	368	−21 24 −11	.00046
		R	11	1040	20 26 −15	$1.8e^{-7}$	592	19 28 −19	.00017	526	21 29 −18	$8.1e^{-5}$
2	Inferior frontal sulcus	L	46/45	429	−36 34 11	.0002	799	−38 36 10	.00012		NS	
		R		451	39 40 −4	.0001	781	40 38 7	.00024		NS	
3	Supramarginal gyrus/ Postcentral gyrus	L	40/1	930	−54 −26 36	$5.0e^{-6}$	781	−53 −32 37	.00047	1320	−60 −23 21	.00063
		R		1471	57 −21 31	$5.4e^{-5}$	1035	55 −26 27	.00037	357	60 −19 33	.00096
4	Middle/Inferior temporal gyrus (posterior)	L	21	1700	−53 −42 −5	$4.07e^{-9}$	1490	−54 −47 2	$6.9e^{-5}$	958	−54 −44 1	.00032
		R		1650	58 −37 −2	$9.33e^{-5}$	309	55 −47 3	.00135	520	56 −42 −1	.00157
5	Angular gyrus/Middle occipital gyrus	L	39/19	1670	−37 −65 32	$2.0e^{-7}$	1382	−39 −72 31	.00076	90	−46 −77 30	$6.3e^{-6}$
		R		1483	46 −67 30	.0003	1278	46 −68 30	.00313		NS	
6	Precuneus	L	31	579	−12 −60 16	$2.0e^{-5}$	246	−12 −60 15	^.00631	327	−10 −60 15	.00245
7	Post. Cingulated gyrus	L	31/23	334	−11 −32 35	$5.0e^{-5}$	523	−12 −31 36	.00032		NS	
		R		803	12 −34 37	.0002	916	12 −34 42	$4.6e^{-5}$		NS	
8	Parahippocampal gyrus/Medial fusiform	L	36	3000	−27 −25 −20	.0009	1600	−26 −27 −20	.0015	2229	−27 −29 −16	.00182
		R		2000	25 −25 −19	.0005	890	22 −8 −28	.0046	968	28 −26 −18	.00479

Table 5B. ABSTRACT > CONCRETE

No.	Region	Lat.	BA	Main effect of Concreteness: Abstract > Concrete			Controls: Abstract > Concrete			Patients: Abstract > Concrete		
				Area mm²	Tal. x, y, z	p	Area mm²	Tal. x, y, z	p	Area mm²	Tal. x, y, z	p
1	Inferior frontal gyrus	L	47/45	999	−45 31 −4	$1.8ei^{-5}$	465	−43 31 −4	.0004	988	−48 35 2	.01259
2	Anterior lateral temporal cortex (middle temporal & temporal pole)	L	21/20	1576	−50 −10 −15	$1.6e^{-7}$	851	−57 −6 −19	.00013	1361	−51 −1 −23	.00372
		R	21/38	360	43 14 −27	$3.2e^{-5}$	276	48 7 −28	^.00324	334	40 14 −28	.00174
3	Mid-portion of superior temporal sulcus and middle temporal gyrus	L	22/21	1100	−53 −33 1	$6.3e^{-6}$	320	−56 −41 6	.00126	1221	−50 −40 4	.00065
4	Inferior parietal lobule and Posterior superior temporal sulcus	L	40/22	910	−40 −48 31	$3.0e{-6}$	497	−38 −52 32	.00083	970	−39 −50 34	.00129
5	Cuneus	L	18	491	−9 −93 9	$1.5e^{5}$	943	−5 −93 4	.00087	1230	−9 −92 8	.00186

Table 5B. ABSTRACT > CONCRETE

		Main effect of Concreteness: Abstract > Concrete			Controls: Abstract > Concrete			Patients: Abstract > Concrete	
R	9 11	4 −85 21	.00032	800	6 −90 11	.00056	561	10 −83 2	0.005

No. corresponds directly to cluster labels in Figure 2 (for Table 5A) and Figure 3 (for Table 5B) When clusters or Brodmann Areas (BAs) span over more than one region, both regions/BAs are indicated, separated by a hash sign. Lat.: Laterality. Tal. (Talairach) coordinates. All clusters indicated in *p* column reached cluster-level significance, $p < 0.05$ corrected across the whole cortex, except for those marked with ^ that reached a voxel-wise significance of $p < 0.05$, uncorrected across the cortex. *NS*: non-significant.

Table 6

Group by Concreteness Interactions: Differences between the patient and control groups in hemodynamic modulation to concrete versus abstract sentences.

No.	Region	Lat.	BA	Area mm²	Tal. x, y, z	P	Area mm²	Tal. x, y, z	p	Area mm²	Tal. x, y, z	p
				Group by Concreteness Interactions			**Controls: Concrete > Abstract**			**Patients: Abstract > Concrete**		
1	Superior and middle frontal gyrus	L	8/9/46	2450	−21 24 47	2.7e^{-5}	1364	−18 23 50	.00021	3800	−17 47 27	6.0e^{-5}
		R		2300	31 25 40	.0007	1631	26 7 41	.00071	2151	41 27 21	.00132
2	Post central gyrus	L	1/2	740	−45 −16 34	.0006	728	−44 −16 34	.00015		NS	
3	Precuneus	L	7	649	−2 −62 41	.0007		NS		921	−8 −68 43	6.3e^{-5}

No. corresponds directly to cluster labels in Figure 4. When clusters or Brodmann Areas (BAs) span over more than one region, both regions/BAs are indicated, separated by a hash sign. Lat.: Laterality. Tal. (Talairach) coordinates. All clusters indicated in *p* column reached cluster-level significance of p < 0.05, corrected across the whole cortex, except for those marked with ^ that reached a voxel-wise significance of p < 0.05, uncorrected across the cortex. *NS*: non-significant.

Table 7

Main effects across all participants: Incongruous versus Congruous sentences

No.	Region	Lat.	BA	Area mm²	Tal. x,y,z	p	Area mm²	Tal. x,y,z	p	Area mm²	Tal. x,y,z	p
				Main effect of Congruity Incongruous > Congruous			Controls: Incongruous > Normal			Patients: Incongruous > Normal		
	INCONGRUOUS > NORMAL											
1	Inferior frontal gyrus	L	45	362	−49 25 8	.00065	380	−50 32 10	.00159		NS	
		R		1250	49 22 10	.00018	1782	49 36 8	.00081		NS	
2	Precentral gyrus (inferior)	L	6	527	−43 3 12	.00021	752	−44 3 14	.00129		NS	

No. corresponds directly to cluster labels in Figure 5. When clusters or Brodmann Areas (BAs) span over more than one region, both regions/BAs are indicated, separated by a hash sign. Lat.: Laterality. Tal. (Talairach) coordinates. All clusters indicated in **p** column reached cluster-level significance, p < 0.05 corrected across the whole cortex, except for those marked with ^ that reached a voxel-wise significance of p < 0.05, uncorrected across the cortex. *NS*: non-significant.

Table 8

Group by Congruity Interaction: Differences between the patient and control groups in hemodynamic modulation to incongruous versus congruous sentences.

No.	Region	Lat.	BA	Group by Congruity Interactions			Controls: Incongruous > Congruous			Patients: Congruous > Incongruous		
				Area mm²	Tal. x, y, z	p	Area mm²	Tal. x, y, z	p	Area mm²	Tal. x, y, z	p
1	Middle/superior frontal gyrus	L	8/9	2100	−24 26 36	.00513	182	−19 49 20	^.0234	2633	−16 24 41	.00120
		R	8/9	1650	21 40 30	.00324	408	13 53 20	.00058	1021	21 36 40	.00063
2	Inferior parietal lobule	L	40	1291	−50 −46 47	.002	278	−45 −43 41	^.00229	2111	−45 −52 36	$2.5e^{-5}$
3	Middle temporal gyrus/ inferior temporal sulcus	R	21	311	58 −33 −9	.001		NS		177	57 −32 −12	^.001
4	Fusiform gyrus (anterior)	L	20	380	−49 −21 −27	.0006	72	−42 −18 −26	^.0245	425	−49 −26 −22	.00102
		R	20	395	40 −12 −29	.0006		NS		510	37 −10 −32	.001
5	Precuenus	L	7	1400	−2 −56 42	.00178	428	−11 −71 37	.00047	1287	−4 −62 30	$6.0e^{-5}$
		R	7	380	6 −68 40	.00501	649	13 −63 36	.00031	1033	6 −61 27	$6.46e^{-5}$
6	Ant. cingulated gyrus and medial prefrontal cortex	L	24/32/9/33	3200	−4 25 −5	.00126	608	−8 16 33	.00417	2798	−8 31 −11	.00115
		R	24/32/9/33	335	7 23 24	.00013	359	11 23 22	$1.2e^{-5}$	597	7 26 −9	.00316

No. corresponds directly to cluster labels in Figure 6. When clusters or Brodmann Areas (BAs) span over more than one region, both regions/BAs are indicated, separated by a hash sign. Lat.: Laterality.

Tal. (Talairach) coordinates. All clusters indicated in *p* column reached cluster-level significance of p < 0.05, corrected across the whole cortex, except for those marked with ^ that reached a voxel-wise significance of p < 0.05, uncorrected across the cortex. *NS*: non-significant.

Table 9

Concreteness by Congruity interactions

Region	Lat.	BA	Concreteness by Congruity			Concrete: Incongruous vs congruous			Abstract: incongruous vs congruous		
			Area mm²	Tal. x, y, z	p	Area mm²	Tal. x, y, z	p	Area mm²	Tal. x, y, z	p
Superior frontal gyrus (medial)	L		398	−8 18 46	0.00015		NS		737	−8 18 46	−0.0000 67
	R	8/32	476	7 23 34	0.00035		NS		1008	8 23 38	− 0.0000 58

All clusters indicated in *p* column reached cluster-level significance of p < 0.05, corrected across the whole cortex. *NS*: non-significant.