Functional Magnetic Resonance Imaging Reveals Neuroanatomical Dissociations During Semantic Integration in Schizophrenia

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Background: Schizophrenia symptoms can be conceptualized in terms of a breakdown of a balance between 1) activating, retrieving, and matching stored representations to incoming information (semantic memory-based processing) and 2) 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, whereas particularly demanding integrative processes additionally recruit the dorsolateral prefrontal cortex (DLPFC) and sometimes parietal cortices. We used functional magnetic resonance imaging (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 vs. abstract) and the congruity (incongruous vs. congruous) of words within sentences.

Methods: Sixteen right-handed schizophrenia patients and 16 healthy volunteers, matched on age and parental socioeconomic status, underwent event-related fMRI scanning while they read sentences. Blood oxygen level dependent (BOLD) effects were contrasted to words within sentences that were 1) concrete versus abstract and 2) 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 control subjects, 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.

Key Words: Context, DLPFC, fMRI, language, prefrontal cortex, schizophrenia, semantic, temporal cortex

Deriving an accurate representation of meaning requires us to strike a fine balance between two types of semantic processes: 1) activating, retrieving, and matching stored semantic information with incoming material (semantic memory-based processes), and 2) 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, whereas particularly demanding semantic integrative processes additionally engage more superior dorsolateral prefrontal cortices (DLPFC), sometimes together with parietal cortices. This study used functional magnetic resonance imaging (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 might 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

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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 might be increased (28). Abnormal increases in activity within temporal-occipital cortices have been reported in patients when processing indirectly related (vs. unrelated) word-pairs (29), during semantic (vs. shallow) verbal encoding (27), and when completing sentences given highly predictable contexts (vs. 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 nonautomatic 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 1) preserved or increased activity in association with semantic memory-based processing and 2) 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 with simple nonverbal 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 vs. abstract and incongruous vs. 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). On the basis of 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, on the basis of 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 demanding semantic integrative processes and that this would be reflected by a failure to recruit the DLPFC to concrete (vs. abstract) and to incongruous (vs. congruous) sentences.

Table 1. Examples of Sentences

Sentence Type	Example
Concrete Congruous	During the rain storm he carried a large golf umbrella.
Concrete Incongruous	The twenty dairy cows are kept in red bench.
Abstract Congruous	Although she strove for perfection she continued to make mistakes.
Abstract Incongruous	Her outer expressions were completely blank and revealed no equality.

In the example, critical sentence-final words are underlined.

Methods and Materials

Materials

Two-hundred-and-forty 10-word congruous sentences, one-half primarily containing concrete words and one-half containing abstract words, matched on frequency and number of letters, were constructed (Table 1 and Table 1 in Supplement 1). The sentences were divided into two counterbalanced lists. Incongruous 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 with the SCID [42]), receiving stable doses of atypical antipsychotic drugs, were recruited from the Lindemann Mental Health Center, Boston. Sixteen demographically matched volunteers, receiving no medication and 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) and 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 2 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 in Supplement 1. Each trial began with a centered yellow fixation followed by each word (450 msec, interstimulus interval: 100 msec). The sentence-

[1]Such increased semantic-syntactic integration demands might 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 might manifest either as a reduction of the N400 effect (34-36) or of the later P600 effect (33), reviewed in (22).