Language disorder in schizophrenia as a developmental learning disorder

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Abstract

Receptive language disorder in schizophrenia is hypothesized to represent a learning disorder that involves a neurodevelopmental etiology. It is argued that a preexisting developmental language disorder may characterize a subset of schizophrenia patients. A primary deficit in the temporal dynamics of brain function is assumed to cause receptive language disorder in schizophrenia. This hypothesized core deficit includes both disturbance in the processing of rapid, sequential information and disruptions to patterns of brain activation and synchronization. These timing deficits may alter the way associative connections are formed and/or accessed in semantic memory. It is suggested that abnormalities in second-messenger pathways of subcortical–cortical circuitry offer an etiological nexus for language dysfunction in schizophrenia and developmental dyslexia.

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1. Introduction

Language disorder is increasingly understood to be an important characteristic of schizophrenia. The hypothesis advanced here is that receptive language disorder in schizophrenia represents a learning disorder that involves a neurodevelopmental etiology. It is argued that receptive language disorder may involve a preexisting developmental reading disorder for a subgroup of schizophrenia patients. Whether the language disorder of schizophrenia is equivalent, phenotypically and etiologically, to the language disorder of dyslexia is an open question. Although schizophrenia and dyslexia are separate clinical disorders, independent lines of evidence are suggestive of parallels between their hallmark features, cognitive dysfunction, and potential pathophysiology. To date, these two populations have not been compared directly. It is assumed that a primary disturbance in the temporal dynamics of brain
function causes language dysfunction in both disorders. Development of this hypothesis requires integration of two large and separate research literatures, and, due to length considerations, the review is representative, rather than exhaustive, and controversies are summarized. The primary focus of this treatment concerns the processing of single words. Syntactic processing is not addressed here.

2. The language system in schizophrenia and dyslexia

2.1. Schizophrenia

Language disturbance was among the first clinical features described for schizophrenia (Bleuler, 1911/1950; Kraepelin, 1919/1971) and is considered, by some writers, fundamental to its etiology (Crow, 1997). Speech production abnormalities currently serve as obvious diagnostic symptoms (American Psychiatric Association, 2000). Abnormalities in receptive language processes are also reliably detected for patients and their nonpsychotic family members, including disturbances to word perception, sentence comprehension, and semantic and syntactic processing (for reviews, see Condray et al., 2002; DeLisi, 2001; Minzenberg et al., 2002).

The language dysfunction associated with schizophrenia may involve a neurodevelopmental etiology. Crow et al. (1995) determined that individuals diagnosed with schizophrenia in adulthood were characterized by reading disabilities (word recognition) identified during middle childhood (7 years). Cannon et al. (2002) found receptive language dysfunction during early childhood for individuals who later developed schizophreniform disorder during early adulthood. In contrast, expressive language (speech production) dysfunction during childhood was not associated with adulthood schizophreniform disorder. These longitudinally based findings suggest that receptive language disturbance predates a schizophrenia diagnosis in adulthood and implicate a developmental process for this cognitive disability. Earlier reports of increased rates of dyslexia and reading disability in the children of schizophrenia patients (Fish, 1987; Marcus, 1974; Rieder and Nichols, 1979) are supportive of this interpretation.

2.2. Dyslexia

Developmental dyslexia is the most common of the learning disorders, with prevalence rates ranging from 5% to 17.5% of children accounting for 80% of the individuals who are considered learning disabled (Shaywitz, 1998). This learning disorder appears stable across development. Both cross-sectional and longitudinal data indicate that the reading problems of developmental dyslexia continue into adolescence and adulthood (Jacobson, 1999; Slaghuis et al., 1996).

Traditionally, dyslexia has been defined as a reading disorder that exists within the context of adequate visual acuity, intelligence, and education (for an overview, see Katz et al., 2001). This perspective is reflected in the definition adopted by the International Dyslexia Association:

Dyslexia is one of several distinct learning disabilities. It is a specific language-based disorder of constitutional origin characterized by difficulties in single word decoding, usually reflecting insufficient phonological processing. These difficulties in single word decoding are often unexpected in relation to age and other cognitive and academic abilities; they are not the result of generalized developmental disability or sensory impairment. Dyslexia is manifest by difficulty with different forms of language, often including, in addition to problems with reading, a conspicuous problem with acquiring proficiency in writing and spelling. (Lyon, 1995, p. 9)

In other views, dyslexia represents a syndrome that can include a range of additional cognitive and behavior dysfunction (Frith, 1999; Galaburda, 1999), such as the positive symptoms of psychosis proneness (Richardson, 1994) and working memory (Plaza and Guitton, 1997) and attention (Duncan et al., 1994; Hari and Renvall, 2001) deficits. This heterogeneous pattern thus parallels the familiar gestalt for schizophrenia.

3. Type of receptive language deficit in schizophrenia and dyslexia

Memory research during the past decade has been largely directed to identifying unique systems of memory (e.g., procedural, perceptual, semantic, work-
ing, episodic), with the assumption being that such systems should show relative functional independence and distinct underlying neural circuitry (for reviews, see Schacter and Tulving, 1994; Schacter et al., 2000; Squire and Zola-Morgan, 1991; Squire and Zola, 1998). Two of the systems proposed may play key roles in the language disorders of schizophrenia and dyslexia: perceptual representation system (orthography and phonology of words) and semantic memory (meaning of words). Semantic memory represents factual knowledge about the world. Semantic memory is plastic and dynamic and it creates an ongoing record of an individual’s learning and experience. Language is one medium for the contact between environment, learning, and semantic memory. The logical extension of this circumstance is that the relation between receptive language function and clinical presentation will reflect that complex interplay between environment, learning, and memory. It is now clear that schizophrenia is associated with disturbance to semantic memory function, although it is not yet fully understood whether this dysfunction is due to deficient encoding, storage, access, or response selection processes, and/or some combination of those functions. The data are suggestive, although preliminary, with respect to perceptual memory disturbance. The opposite pattern of knowledge exists for dyslexia; abnormality of perceptual representations is the most consistently delineated disturbance for developmental dyslexia, while semantic memory function is not as well characterized.

3.1. Schizophrenia disorder

3.1.1. Semantic memory

Semantic memory deficits are a robust finding for schizophrenia. The cumulative behavioral and psychophysiological evidence indicates that word meaning is represented and/or accessed differently for many schizophrenia patients (for reviews of the behavioral literature, see Aleman et al., 1999; Minzenberg et al., 2002). Much of the psychophysiological evidence is based on the N400 component of the scalp-recorded event-related brain potential (ERP), which provides an electrophysiological index of semantic memory activation that occurs prior to an overt behavioral response. The N400 regularly occurs within a time window of 250–500 ms post-stimulus onset and, based on studies using intracranial recordings, reflects activity from multiple brain areas, including inferotemporal cortex, superior temporal sulcus, medial temporal lobe, hippocampus, and ventrolateral prefrontal cortex. Until recently, the prevailing view of N400 has been that it reflects on-line semantic integration processes with implications for working memory function. Currently, N400 is also viewed as a reflection of the ease with which access of long-term semantic memory occurs, with increases in N400 amplitude suggesting increased difficulty during semantic memory access. (For a review and analysis of the N400 language literature, see Kutas and Federmeier, 2000.)

Findings based on the N400 suggest that schizophrenia patients do not clearly distinguish among words based on their semantic features. For healthy individuals, access of long-term semantic memory is facilitated by previous learning experience and meaning. Words that follow semantically associated words (apple orange) are recognized more accurately and quickly than words which appear after unassociated words (potato violin). This well-established phenomenon, known as the semantic priming effect, is clearly reflected in the N400. The pattern typically observed for healthy individuals involves an enhanced N400 amplitude to semantically unrelated words compared to the N400 amplitude elicited to semantically related words (N400 unrelated > N400 related words). In contrast, the general findings for schizophrenia show a similar or equivalent N400 response to related and unrelated words. For example, healthy individuals would show an enhanced N400 response to a dog–canoe pairing, compared to their N400 response to a dog–cat pairing. In contrast, patients’ N400 response to the dog–canoe pairing would appear more similar to their N400 response to the dog–cat pairing. Table 1 summarizes findings from studies identified in the literature in which schizophrenia patients and controls were compared for N400 elicited by semantic and repetition priming paradigms (Medline, keywords ‘N400’ and ‘schizophrenia’, English language). In the majority of studies, the presence of schizophrenia was associated with N400 responding during semantic processing that differed from that observed for controls.
Table 1
Summary of N400 priming studies comparing schizophrenia patients and controls

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample</th>
<th>Medication status of patients</th>
<th>Paradigm (task, overt behavioral response, semantic conditions, timing parameters)</th>
<th>Results for N400 priming effect (Diagnosis×Semantic condition interaction)</th>
</tr>
</thead>
</table>
| Bobes et al., 1996 | Cross-cultural | Medicated | Semantic relationship, OBR-Y, Semantic Priming-PP, each stimulus presented only once, stimulus duration=1 s/subjектs initiated each trial | Mean integrated N400 (µV): Diagnosis×semantic condition (p<0.02)  
N400 (µV) at Cz:  
Associated: Sz>C (p<0.01)  
Unassociated: Sz=C  
Diagnosis×culture×semantic condition (p=n.s.)  
N400 peak latency @ Cz:  
Main effect-diagnosis: Sz>C (p<0.01) |
|                   | Cuba   |                  |                                                                                   |                                                                                |
|                   | 20 patients (7 males) |                  |                                                                                   |                                                                                |
|                   | 20 controls (13 males) |                  |                                                                                   |                                                                                |
|                   | China  |                  |                                                                                   |                                                                                |
|                   | 20 patients (10 males) |                  |                                                                                   |                                                                                |
|                   | 20 controls (10 males) |                  |                                                                                   |                                                                                |
| Condray et al., 2003 | 37 inpatients (males), 34 controls (males) | 30 medicated (haloperidol only) 21 unmedicated (Note: 14 patients were tested twice; once during each medication condition.) | Lexical Decision Task, OBR-Y, Semantic Priming-WW, each stimulus presented only once, SOAs=350 and 950 ms (prime duration=100 ms, blank-screen ISIs=250 and 850 ms, target duration=1200 ms) | Mean integrated N400 (µV) at midlines:  
Diagnosed patients versus Controls:  
Diagnosis×semantic condition×electrode (p<0.01)  
Fz and Cz: Sz=C (p=n.s. for both sites)  
Pz and Oz: Sz<C (p<0.01 for both sites)  
Unmedicated patients versus Controls:  
Diagnosis×semantic condition (p=0.001)  
Sz: Semantic condition (F<1)  
C: Semantic condition (p<0.001)  
N400 μV difference waveform (Unassoc minus Assoc) at midlines:  
Main effect of diagnosis: Sz>C (p≤0.05) |
|                   |                   |                  |                                                                                   |                                                                                |
| Grillon et al., 1991 | 14 outpatients (males), 14 controls | Medicated | Semantic relationship, OBR-Y, Semantic priming-WW, each stimulus presented only once, SOA=1020 ms (prime duration=289 ms, target duration=289 ms) | N400 (µV) difference waveform (Unassoc minus Assoc) at midlines:  
Main effect of diagnosis: Sz>C (p<0.02) |
| Hokama et al., 2003 | 17 outpatients/1 inpatient (9 males), 18 controls (9 males) | Unmedicated | Lexical Decision Task, OBR-Y, Semantic priming-WW (Japanese), prime or S1 words served as S1 stimuli for all word/nonword pairs, and all S1–S2 pairs were presented twice, SOA=1500 ms (prime duration=500 ms, blank-screen ISI=1000 ms, target duration=until behavioral response occurred or 1500 ms elapsed) | N350 peak (µV):  
Diagnosis×semantic condition (p=n.s.)  
N400 (µV) difference waveforms (Unassoc minus Assoc versus Nonword minus Assoc):  
Main effect-diagnosis (p=0.01)  
Main effect-semantic condition (p=n.s.)  
Diagnosis×semantic condition (p=n.s.)  
Mean integrated N400 (µV) at midlines:  
Diagnosis×semantic condition (p<0.01):  
Associated words: Sz>C (p<0.02)  
N400 (µV) difference waveform (Unassoc minus Assoc):  
Main effect-diagnosis (p<0.001) |
<p>| Kostova et al., 2003 | 38 patients (28 males), 24 controls (9 males) | Medicated | Lexical Decision Task, OBR-Y, Semantic priming-WW, each stimulus presented only once, SOA=450 ms (prime duration=200 ms, blank-screen ISI=250 ms, target duration=1200 ms) |                                                                                   |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Design</th>
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<th>Results</th>
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<tr>
<td>Koyama et al., 1994</td>
<td>28 patients (19 males), 14 medicated</td>
<td>Lexical Decision Task, OBR-Y, Semantic priming-WW, kanji characters (Japanese), prime or S1 words served as S1 stimuli for all word/nonword pairs, and all S1–S2 pairs were presented twice, SOA=1500 ms (prime duration=500 ms, ISI=1000 ms, target duration=until behavioral response occurred or 1500 ms)</td>
<td>N370 peak (µV): No significant main or interaction effects involving the diagnosis factor, N370 peak latency at Cz: Main effect of diagnosis: S&gt;C (p&lt;0.001)</td>
<td></td>
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<tr>
<td>Mathalon et al., 2002</td>
<td>18 patients (17 males), Medicated</td>
<td>Picture-Word verification, OBR-Y, Semantic priming-PW, each prime was presented four times, SOA=325 ms (prime duration=250 ms, ISI=75 ms, target duration=until behavioral response occurred)</td>
<td>Mean integrated N400 (µV): Diagnosis x semantic condition (p&lt;0.05) Associated: Sz=C (p=n.s.) Unassociated: Sz=C (p&lt;0.05) N400 peak latency at Pz: Sz=C (p&gt;0.5)</td>
<td>Mean integrated N400 (µV) at midline (Fz, Cz, Pz) sites: 300–400 ms window: Diagnosis x repetition condition (p&lt;0.05): Sz: Effect of repetition (p=n.s.) C: Effect of repetition (p&lt;0.01) N400-immediate&lt;N400-no N400-immediate&lt;N400-delay 400–500 ms window: Diagnosis x repetition condition (p&lt;0.01): Sz: Effect of repetition (p&lt;0.01) N400-immediate&lt;N400-no C: Effect of repetition (p&lt;0.001) N400-immediate&lt;N400-no N400-immediate&lt;N400-delay</td>
</tr>
<tr>
<td>Matsumoto et al., 2001</td>
<td>20 patients (13 males), Medicated</td>
<td>Semantic categorization, OBR-Y, Repetition priming-W (no, immediate, or delay repetition), kana characters (Japanese), SOAs=2200 and 3200 ms (stimulus duration=200 ms, ISIs=2000 and 3000 ms)</td>
<td>Mean integrated N400 (µV): (a) Words versus Nonwords: Semantic categorization (a) for words versus nonwords, and (b) during Repetition priming-W (no, immediate, or delay repetition), OBR-Y, kana characters (Japanese) and unpronounceable foreign letters, SOAs=2100 and 3100 ms (stimulus duration=100 ms, ISIs=2000 ms and 3000 ms)</td>
<td>Mean integrated N400 (µV): (a) Words versus Nonwords: Diagnosis x semantic condition (p=n.s.) (b) Repetition Priming: Diagnosis x repetition condition (p&lt;0.01): Reduced N400 (µV)-Immediate: C&gt;Sz N400 peak (µV): Diagnosis x semantic condition (p&lt;0.001): Idiomatic: Sz&gt;C (p&lt;0.05) Literal: Sz=C (p=n.s.) Nonsense: Sz=C (p=n.s.)</td>
</tr>
</tbody>
</table>

OBR-Y=overt behavioral response—yes; Semantic Priming-WW=Word (prime)–Word (target); Semantic Priming-PP=Picture (prime)–Picture (target); Semantic Priming-PW=Picture (prime)–Word (target); SOA=stimulus onset asynchrony: time interval between the onset of stimulus 1 and onset of stimulus 2; ISI=interstimulus interval; Sz=schizophrenia patients; C=normal/healthy controls.
3.1.2. Interconnectivity of semantic representations: excessive versus insufficient?

An important question concerns whether the semantic memory deficit in schizophrenia is due to an excessive or an insufficient degree of connectivity among semantic representations. In the excessive-connectivity condition, semantic memory would be expected to operate according to an ‘everything-is-related’ principle. An ‘everything-is-unrelated’ rule would be expected for the case of insufficient connectivity. For semantic priming paradigms, the available evidence for N400 suggests that the pattern of semantic connectivity is modulated by variations in timing parameters and pharmacological regimen (Bobes et al., 1996; Condray et al., 2003; Kostova et al., 2003; Mathalon et al., 2002; Strandburg et al., 1997). At rapid presentation rates (SOAs < 400 ms), an ‘everything-is-related’ rule or excessive connectivity appears to operate (N400 to unassociated words: patients < controls; N400 to associated words: patients = controls). That is, patients’ N400 response to unassociated words is more similar to both groups’ N400 response to associated words. At longer presentation rates (SOAs > 400 ms), an ‘everything-is-unrelated’ principle or insufficient connectivity seems to hold (N400 to associated words: patients > controls; N400 to unassociated words: patients = controls). That is, patients’ N400 response to associated words is more comparable to both groups’ N400 response to unassociated words. Dopaminergic modulation by pharmacological regimen does not appear to alter the nature of the relation between timing and semantic connectivity so much as it seems to affect its degree or magnitude. Of potential importance, much longer presentation rates (SOAs = 1.5 s) were used in the two studies that failed to observe significant group differences for the N400 semantic priming effect (Koyama et al., 1994; Matsuoka et al., 1999). Findings collectively suggest that the influence of temporal contiguity on learning and memory is altered in

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1 The N400 semantic priming effect was significantly reduced for schizophrenia patients, compared to normal controls, during both medicated and drug-free phases (Condray et al., 2003). Different patterns of N400 responding to associated and unassociated words are apparent across presentation rates (collapsing across electrode and expectancy conditions), and differences in dopaminergic tone across pharmacological conditions appear to amplify rather than alter these patterns. For the rapid presentation rate (SOA = 350 ms), the N400 (µV) mean amplitudes (± S.E.M) for the comparison based on medicated patients showed reduced activation to unassociated words for patients [controls = 0.60 (0.43); medicated patients = 0.34 (0.46)] and similar activation to associated words [controls = 0.86 (0.48); medicated patients = 0.97 (0.51)]. The N400 mean amplitudes for the comparison based on unmedicated patients also showed reduced activation to unassociated words for patients [controls = 0.60 (0.45); unmedicated patients = 0.26 (0.58)] and more comparable activation to associated words [controls = 0.86 (0.48); unmedicated patients = 0.51 (0.62)]. In contrast, for the long presentation rate (SOA = 950 ms), the N400 mean amplitudes for the comparison based on medicated patients showed enhanced negativity to associated words for patients [controls = 3.56 (0.49); medicated patients = 2.82 (0.52)] and similar activation to unassociated words [controls = 2.02 (0.46); medicated patients = 2.34 (0.49)]. The N400 mean amplitudes for the comparison based on unmedicated patients also showed enhanced negativity to associated words for patients [controls = 3.56 (0.51); unmedicated patients = 1.26 (0.65)] and more comparable activation to unassociated words [controls = 2.02 (0.47); unmedicated patients = 1.64 (0.60)].
schizophrenia. Because associations are more likely formed when events occur in spatial and temporal proximity, disruptions to temporal processes (see Section 4) may influence the way in which associative connections are formed and/or accessed (for discussion regarding contiguity as a necessary versus sufficient condition, see Lachnit, 2003; Underwood, 1983).

The findings for N400 from semantic priming paradigms indicate that schizophrenia patients, as a group, show an atypical pattern of semantic memory access. In its most severe form, however, this disturbance may characterize only a subgroup of schizophrenia patients. As shown in Table 2, deficit or impaired responding may characterize between 20% and 40% of schizophrenia patients, reduced responding may occur for 5–10% of patients, and responding within the normal range may be seen for approximately 50% of patients. Comparable inter-subject variability was reported by Grillon et al. (1991). The subgroup distinctions reflected in Table 2 have important implications for etiology and treatment. Firstly, the proportion of patients showing deficit or impaired semantic processing is comparable across medication conditions, thereby implicating a stable trait. Secondly, the patterns of relationship between the N400 semantic priming response, intelligence, and clinical symptoms suggest that semantic memory impairment in schizophrenia does not reflect a negative symptom phenomenon. Moreover, semantic memory access in schizophrenia appears to require a multifactorial model that includes, minimally, language and timing parameters, subgroup membership (impaired versus normal responding), pharmacological condition, and clinical symptomatology (Condjay, unpublished data).

The visual N400 elicited by semantic processing paradigms typically has a centro-parietal maximum in healthy individuals; data are therefore shown for the ERP recorded at the parietal site (Pz). The small proportion of patients showing enhanced or hyper-priming may be due, in part, to the type of related word pairs used in this study, most of which were selected from corpora of discrete free word association norms based on respondents reporting the first word they thought of for each stimulus (prime) word. Word pairs based exclusively on indirect associations (e.g., lemon sweet) may produce hyper-priming in a larger proportion of patients (e.g., Spitzer et al., 1993).

Schizophrenia patients tested during haloperidol maintenance therapy did show improvement in N400 responding, but the improvement was restricted to anterior scalp (Fz) (Condjay et al., 2003).

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4 Intelligence (WAIS-R Full-Scale IQ) did not differ between patients with impaired and normal N400 responding [FSIQ (M/SD) for medicated patients: N400-impaired=88.9 (8.9), N400-normal=91.7 (6.4), F1,15=1.1; FSIQ (M/SD) for unmedicated patients: N400-impaired=95.0 (10.7), N400-normal=89.9 (7.3), F1,15=1.35, p>0.10].

Ratings of clinical symptoms (means/S.D.s) show differences between the medicated patients with impaired and normal N400 responding for BPRS Thinking Disturbance [impaired=6.2 (2.6), normal=4.3 (1.7): F1,22=5.12, p<0.05] and BPRS Psychosis [impaired=13.9 (3.4), normal=11.3 (2.7): F1,22=4.35, p<0.05]. However, the two subgroups did not differ for BPRS symptoms of paranoia, mood, or overall psychological disturbance, or for SANS negative symptomatology [Paranoia: impaired=4.4 (0.9), normal=4.3 (0.9); Anxiety and Depression: impaired=5.9 (2.2), normal=5.9 (2.2); Emotional Withdrawal and Motor Retardation: impaired=5.8 (1.3), normal=7.7 (3.5); BPRS Total: impaired=42.9 (8.4), normal=41.3 (10.1); SANS Total: impaired=7.1 (2.4), normal=8.5 (4.6)]. Clinical symptomatology did not differ significantly between the unmedicated patients with impaired and normal N400 responding [Thinking Disturbance: impaired=5.7 (1.3), normal=6.8 (5.1); Paranoia: impaired=5.4 (2.1), normal=6.8 (3.9); Psychosis: impaired=13.9 (2.7), normal=16.4 (9.6); Anxiety and Depression: impaired=6.5 (3.7), normal=5.0 (1.9); Emotional Withdrawal and Motor Retardation: impaired=6.1 (2.4), normal=6.9 (2.3); BPRS Total: impaired=45.6 (9.7), normal=47.1 (15.8); SANS Total: impaired=7.1 (1.9), normal=10.0 (5.0)].

The two subgroups of schizophrenia patients were characterized by different patterns of relationship between clinical symptoms and their N400 responding to words presented at a rapid rate. For the medicated patients with impaired N400 responding, a relationship was observed between N400 amplitude elicited by unassociated words and symptoms of paranoia (rho=−0.79, p=0.01), indicating that reduced N400 amplitude, which represents atypical responding, was related to increased paranoia. For the unmedicated patients with impaired N400 responding, overall psychological disturbance (BPRS Total symptoms) was correlated with N400 amplitude elicited to both associated words (rho=−0.71, p<0.05) and unassociated words (rho=−0.79, p<0.05), suggesting that reduced N400 amplitude was correlated with greater overall psychological disturbance. For medicated patients with normal N400 responding, a relationship was observed between the magnitude of the N400 priming effect (unassociated minus associated words) and symptoms of anxiety and depression (rho=−0.55, p<0.05), suggesting that reduced N400 priming was correlated with increased mood symptomatology. For the unmedicated patients with normal N400 responding, N400 amplitude elicited by unassociated words was negatively correlated with symptoms of paranoia (rho=−0.67, p=0.05), suggesting that for this subgroup, enhanced N400 amplitude, representing typical responding, was related to increased...
paranoia. Negative clinical symptomatology (SANS) was not significantly correlated with N400 responding for either of the two subgroups receiving either of the pharmacological regimens.

Thus, intelligence did not differ between the two subgroups of patients defined on the basis of their N400 responding to rapidly presented language (impaired versus normal). However, these subgroups did differ for clinical symptoms during haloperidol maintenance therapy. Moreover, the subgroups showed different patterns of relationship between N400 responding and clinical symptoms, and these patterns varied between medicated and unmedicated conditions. The most striking example of this latter effect involves the relation between paranoia and N400, the interpretation of which requires a series of conceptual linkages that are presently indirect in nature. Firstly, the clinical concept of paranoia includes an enhanced vigilance of the environment with the expectation of potential harm to self. Secondly, an argument was previously advanced that visual-system transient (magnocellular)-channel function, which is biased toward stimuli of short latency (rapid rate), comprises part of an evolutionary-based “early warning system” serving orienting and attention functions (Breitmeyer and Ganz, 1976). This assumption provides a link between the processing of rapidly presented language and the conceptual rudiments of clinical paranoia. Thirdly, the patterns of association for schizophrenia patients between clinical paranoia and their N400 response to rapidly presented language provide an empirical link.

The relation between paranoia and the N400 response to rapidly presented language also has implications for the connectivity of semantic representations in schizophrenia. At rapid presentation rates, an excessive connectivity or “everything-is-related” rule appears to operate, with patients’ N400 response to unassociated words more similar to both groups’ N400 response to associated words (see Section 3, Table 1). The relationship for the medicated impaired-N400 subgroup showed that reduced N400 amplitude to unassociated words, representing atypical responding, was correlated with increased symptoms of paranoia. Excessive connectivity during semantic memory access is therefore implicated for clinical paranoia. The suggestion that this pattern may be unique to a subset of patients is supported by the relationship observed for the unmedicated normal-N400 subgroup, with enhanced N400 amplitude to unassociated words, representing typical responding, correlated with increased paranoia. Finally, these variable relationships between N400 responding and paranoia occurred within the context of similar levels of paranoia symptomatology; the impaired- and normal-N400 subgroups did not differ for paranoia.

In summary, the subgroup patterns identified generally indicate that a multifactorial model is required for semantic memory access in schizophrenia, including, minimally, language and timing parameters, subgroup membership (impaired versus normal), clinical symptomatology, and pharmacological condition.

3.1.3. Nonassociative memory: repetition effects

The effect of word repetition on the N400 is atypical in schizophrenia. Repetition of words produces a reduction in the amplitude of N400 in healthy individuals (see Kutas and Federmeier, 2000), and this effect is attenuated and delayed for schizophrenia patients compared to controls (Matsumoto et al., 2001; Matsuoka et al., 1999). Mere repetition of semantic stimuli, however, does not eliminate the group difference for the N400 semantic priming effect (Hokama et al., 2003; Mathalon et al., 2002; Strandsburg et al., 1997). Attenuated and delayed repetition priming may indicate that nonassociative language learning (habituation) is compromised in schizophrenia. Whether this represents an alteration in its basic features or merely a weakening of its influence is unknown. Whether and/or how compromised non-associative learning influences long-term associative memory in schizophrenia is an important question.

3.1.4. Sentence processing

The effects of sentence-level processing on N400 also indicate alterations in semantic memory processes for schizophrenia patients. Sentence processing involves multiword semantic contexts plus syntactic elements, the latter of which are beyond the scope of the present paper. However, a few general comments are in order. A commonly used sentence-processing paradigm is the semantic congruity task for which participants read sentences that are varied with respect to the semantic fit of sentence constituents (e.g., The pizza was too hot to eat versus drink) (Kutas and Hillyard, 1980). The N400 semantic congruity effect (N400 semantically incongruous>N400 congruous words) is the typical pattern observed for healthy individuals. Comparisons of the N400 congruity effect for schizophrenia patients and healthy controls have yielded inconsistent results with significant group differences observed in many (Adams et al., 1993; Mitchell et al., 1991; Niznikiewicz et al., 1997; Ohta et al., 1999; Salisbury et al., 2002; Sitnikova et al., 2002), but not all (Andrews et al., 1993; Kuperberg et al., 2004; Nestor et al., 1997; Ruchsw et al., 2003) studies. These studies reflect a range of experimental tasks (sensibility judgements, reading for memory tests and main ideas), sentence-constituent foci (final words, initial nouns, mid-sentence verbs), and types of context bias (probability constraints, homographs biased for dominant versus subordinate meaning). In combination, findings are suggestive of variable N400 responses, including normal and abnormal, which appear to be modulated...
by the size (single-, multiword), locus (global, immediate), and type of bias (dominant, subordinate meaning) of the available context (in particular, see approaches used by Kuperberg et al., 2004; Sitnikova et al., 2002).

3.1.5. Perceptual representation system

The degree to which perceptual representations of words (orthography and phonology) are disrupted in schizophrenia is unsettled. Greater impairment to semantic memory, compared to phonological memory, has been suggested based on results from word fluency tests (Bokat and Goldberg, 2003; Gourovitch et al., 1996). However, subgroup differences have also been reported, with schizophrenia patients characterized by greater severity of thought disorder showing comparable levels of phonological and semantic dysfunction (Goldberg et al., 1998). Moreover, differential phonological processing across presentation rates (rapid versus long) has been observed, with the most dramatic difference occurring under the rapid rate between controls and patients with thought disorder (Spitzer et al., 1994). Reduced accuracy during a simple syllable counting task (single- and two-syllable words) (Weiss et al., 2002) is also suggestive of disturbance to perceptual representations. Such findings, in combination, indicate that phonological and orthographic skills in schizophrenia warrant closer investigation.

3.2. Developmental dyslexia

Abnormality of perceptual representations is the most consistently delineated disturbance for developmental dyslexia. The majority of dyslexics show substantially reduced ability to read pseudowords (e.g., nonword letter strings such as glix, sebwag, blomtek) (for reviews, see Rack et al., 1992; Van Orden et al., 2001). The correlation reliably obtained between sound segmentation skill and later reading ability suggests that this phonology-to-orthography competence may play an important role in developing reading proficiency (Rack et al., 1992). Perceptual representations of words are likely multicomponential, however, and differential patterns of deficits (e.g., various combinations of speech perception, phoneme awareness, and morphology processing disturbance) may distinguish subgroups within the developmental reading disorders population (Joanisse et al., 2000).

Semantic memory function in developmental dyslexia is not as well characterized, although the available ERP studies show distinctions between dyslexics and normal readers. Using a picture-word priming design, Stelmack and Miles (1990) observed reduced N400 amplitude to unassociated words in boys with reading disorder compared to boys classified as normal readers. This finding parallels the pattern obtained for schizophrenia patients during picture-word priming by Mathalon et al. (2002). Disturbance in the contextual integration of sentence constituents may also characterize developmental reading disability. Compared to normal readers, children with developmental language impairment showed enhanced N400 amplitude to open class words (nouns, verbs, adjectives) within sentences (Neville et al., 1993). In that same study, ERP waveforms for the language-impaired children showed enhanced negativity to both semantically incongruous and congruous sentence endings, while normal readers showed the typical N400 semantic congruity effect. In a study of the effects of presentation rate (SOAs=100 versus 700 ms) on the N400 congruity effect, adults with developmental dyslexia, compared to normal readers, showed increased N400 amplitude, but only under the slower rate (Robichon et al., 2002). These results are generally suggestive of atypical activation during semantic processing for individuals with developmental reading disorder.

4. Dyschronia hypothesis: a general mechanism for language disorder in schizophrenia and dyslexia

It is hypothesized here that a primary deficit in the temporal dynamics of brain function may cause receptive language disorder in schizophrenia. This deficit is assumed to involve both disturbance in the processing of rapid, sequential information and disruptions to patterns of brain activation and synchronization. As a result of these timing deficits, alterations likely occur in the formation and access of associative connections in long-term semantic memory. The rationale for this hypothesis is based on known mechanisms for language and memory
processes and converging findings for schizophrenia. Firstly, language processing is rate-dependent. The optimal rate for reading prose is estimated to be ~300 words per minute (5 words/s or 1 word/200 ms), with systematic declines in understanding occurring at faster rates (Carver, 1982). Moreover, speech is based on acoustic signals that unfold rapidly (e.g., 40 ms for formant transitions) (Fitch et al., 1997), which has implications for memory representations based on phonology. Secondly, cellular mechanisms of memory function (e.g., long-term potentiation and depression) are timing and rate-dependent (see Kandel, 2000; Sjöström et al., 2001). Thirdly, strong converging evidence is suggestive of a generalized deficit in temporal dynamics for schizophrenia. Reduced perception of event duration (stimulus duration \( \leq 1 \) s) has been documented for schizophrenia patients (Elvevag et al., 2003). Early auditory processing of small bits of information (clicks) is also atypical in schizophrenia (failure to suppress the P50 response) (Freedman et al., 1996), and a relationship has been observed between this sensory gating failure and behavior (response time) during a semantic priming lexical decision task (Vinogradov et al., 1996). An important aspect of this latter relationship is the apparent link between associative and nonassociative learning processes. Moreover, as detailed above, the available evidence for the N400 suggests that interconnectivity of lexical representations in semantic memory is modulated by timing parameters. One limitation of the psychophysiological literature has been that the presentation rates used are longer (SOAs \( \geq 325 \) ms) than the optimal reading rate (SOAs=200 ms). To date, the most stringent version of the timing deficit hypothesis for language function (rates \( < 100 \) ms) has been tested only for bits of linguistic information (behavioral responding to backward masking of single letters: Braff and Saccuzzo, 1985; Butler et al., 2002; Green et al., 1994). Tests are required for word-level stimuli using rates that correspond to the optimal reading rate and faster.

A temporal processing deficit has also been proposed for developmental dyslexia (the dyschronia hypothesis of Llinas, 1993; Tallal, 1999), and considerable evidence indicates that this type of processing is compromised for individuals with reading disorder (Eden et al., 1995; Rey et al., 2002; Tallal, 1999; Temple et al., 2000). Deficient timing skills for music in dyslexics (Overy et al., 2003) lend support to a generalized deficit interpretation, although its precise role in developmental reading disability has not been determined.

Candidate pathways and mechanisms hypothesized to account for the temporal processing deficit(s) associated with schizophrenia and dyslexia include dysfunction of subcortical–cortical pathways, high-frequency oscillations, and second-messenger pathways.

4.1. Magnocellular pathway dysfunction

The behavioral performance deficit observed for schizophrenia patients during the backward masking of rapid, sequential visual stimuli (single letters) may involve a complex functional pathophysiology and not merely a slow rate of processing. The transient/sustained neural channel model of Breitmeyer and Ogmen (2000), based on the parallel and complementary pathways of the visual system, has been suggested as a heuristic (Braff et al., 1991). One possibility is that the backward masking deficit is due to an overreactive transient (magnocellular) channel that interrupts sustained (parvocellular) channel function (Green et al., 1994). A magnocellular deficit theory has also been proposed for dyslexia (Stein, 2001). Postmortem tissue abnormalities detected in the magnocellular pathway of lateral geniculate nuclei (Livingstone et al., 1991) provide the strongest evidence, although specific functional tests have produced mixed results (Amitay et al., 2002; Demb et al., 1997, 1998; Hayduk et al., 1996; Kronbichler et al., 2002; Livingstone et al., 1991).

4.2. Cerebellar pathway dysfunction

Timing functions may also be influenced by pathways in the cerebellum. Although traditionally associated with control and coordination of movement, recent findings implicate additional functional roles for this region, including language and cognition (Ghez and Thach, 2000; Leiner et al., 1995) and time-based processing (reviewed in Condray and Glasgow, 2003). Structural and functional alterations in cerebellum regions have been
reported for both schizophrenia patients (Andreasen et al., 1996; Katsetos et al., 1997) and dyslexics (Rae et al., 2002). Moreover, activation (fMRI) to rapid, nonlinguistic acoustic stimuli has been shown to differ between controls and dyslexics in prefrontal cortex and cerebellum (Temple et al., 2000).

4.2.1. Dysfunction of high-frequency oscillations

Synchronization of activation in distributed brain regions may be a necessary precondition for establishing integrated cognitive percepts. Rhythmic bursts in the gamma frequency range (~40 Hz), occurring in subcortical and cortical regions, may serve as a key mechanism for achieving cognitive integration (the coherence theory of John, 2001, 2002). Such activity may be important for lexical memory (Pulvermuller, 1999), and recent findings for healthy individuals show that language tasks produce systematic variations in gamma-frequency responding (Braeutigam et al., 2001; Pulvermuller et al., 1996). Using a gamma-driving paradigm (trains of auditory stimuli presented at rates ranging from 20 to 40 Hz), Kwon et al. (1999) observed reduced power for 40-Hz activity at the 40-Hz rate for schizophrenia patients, as well as delays in the timing of this activation pattern. A number of writers have suggested that this type of disturbance may underlie patients’ perceptual and cognitive dysfunction (Condray and Steinhs, 2003; Green et al., 1999; Lee et al., 2003; Phillips and Silverstein, 2003). A similar proposal has been advanced for dyslexia (Llinas, 1993).

4.2.2. Abnormalities in second-messenger pathways

Variations in neuronal membrane structure and function within subcortical–cortical pathways supply an additional potential etiological nexus for schizophrenia and dyslexia. A relationship between schizophrenia and dyslexia was previously suggested based on common abnormalities in cell membrane phospholipids, including dysfunction involving arachidonic acid and docosahexaenoic acid reported for both disorders (Horrobin et al., 1995). How such abnormalities at the cellular level could produce language dysfunction would require a complex, dynamic cascade of events. As one possibility, an interaction of brain fatty acids and second-messenger function that modifies long-term potentiation and synaptic connections could influence the coordinated pattern of excitation and inhibition in subcortical–cortical pathways devoted to language and memory processes.

5. Etiology: is the receptive language disorder associated with schizophrenia actually a preexisting developmental reading disorder?

The proposition advanced here is that a common etiology may underlie the language disorders associated with schizophrenia and dyslexia. While there are no known empirical data that bear directly on

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**Equivalence Hypothesis**

**Developmental Dyslexia**

Perceptual Representation System

Semantic Representation System

**Schizophrenia Disorder**

Perceptual Representation System

Semantic Representation System

Fig. 1. Hypothesized relation between schizophrenia and developmental dyslexia for type of language dysfunction (deficit/; compromised/; double-headed arrow → denotes interaction between representation systems. Perceptual=orthography/phonology; semantic=conceptual/meaning).
this question, several possibilities are evident based on the disturbances to semantic and perceptual memory function reported in the separate literatures for the two disorders. Figs. 1–3 show three competing hypotheses for this idea. Firstly, it is possible that the severe form of language disorder in schizophrenia is actually preexisting developmental dyslexia. That is, the parallels between schizophrenia and developmental dyslexia described above reflect a common phenotype and etiology (equivalence hypothesis depicted in Fig. 1). However, it is also possible that any phenotypic similarities observed are merely superficial and random (non-equivalence or null hypothesis, Fig. 2). In this case, the language disorder associated with schizophrenia is due to deficits in semantic memory; the language disorder associated with developmental dyslexia emerges from deficiencies in the perceptual representation system. A third possibility is that the two disorders share some phenotypic similarities and etiologic pathways, but differ for others (overlapping or mixed hypothesis, Fig. 3). For this case, schizophrenia would involve a primary disturbance in semantic memory representations and a secondary disturbance in perceptual representations; developmental dyslexia would be characterized by a primary disturbance in perceptual representations and a secondary disturbance in semantic memory representations. At present, the latter possibility, an overlapping or mixed etiology, would seem the more likely, based on the current literatures for each disorder, as well as the literature concerning pure double dissociations as ideals, rather than realities, of nature (see Van Orden et al., 2001). Direct comparisons of the two populations are required to evaluate these possibilities.
These possibilities have implications for intervention strategies. If the severe language disorder observed for a subset of schizophrenia patients represents a developmental learning disorder, intervention strategies used for developmental dyslexia may have utility for schizophrenia. For example, behavior training administered to dyslexic children (8–12 years), which included nonlinguistic and acoustically modified linguistic stimuli, produced improvement in reading performance and increased activation in multiple brain regions (Temple et al., 2003). Moreover, an association was observed between reading improvement and the magnitude of increased activation in left temporo-parietal cortex. Word identification and phonics training also produced significant gains in reading performance for children (7–13 years) with severe reading disability (Lovett et al., 2000). Whether the severe reading disability identified in a subset of adult schizophrenia patients would be responsive to cognitive remediation strategies is an important question. Identification of individuals at familial risk for such disability during childhood could play a role in early intervention.

6. Summary

It was hypothesized that receptive language disorder in schizophrenia represents a learning disorder that involves a neurodevelopmental etiology. It was argued that a preexisting developmental reading disorder may characterize a subset of schizophrenia patients. This hypothesis includes the assumption that a primary or core deficit in the temporal dynamics of brain function produces receptive language disorder in both schizophrenia and dyslexia. Investigation of these possibilities will advance our theories of schizophrenia.

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