will then shed new light on cognitive coordination in schizophrenia.

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Mechanisms of disrupted language comprehension in schizophrenia

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Abstract: Mechanisms that contribute to perceptual processing dysfunction in schizophrenia were examined by Phillips & Silverstein, and formulated as involving disruptions in both local and higher-level coordination of signals. We agree that dysfunction in the coordination of cognitive functions (disconnection) is also indicated for many of the linguistic processing deficits documented for schizophrenia. We suggest, however, that it may be necessary to add a timing mechanism to the theoretical account.

The notion that aberrations in sensory-perceptual and attentional processing contribute to higher-order cognitive dysfunction in schizophrenia was apparent to the first clinicians that studied the disorder. Development of behavioral and neurophysiological methodologies in the past four decades has provided neurobiological links to those observations. Phillips & Silverstein (P&S) provide a careful and compelling integration of such studies, beginning with the experimental evidence indicating consistent difficulties in perceptual grouping and organization which cannot be explained by inattention alone.

P&S describe the interference of perceptual discriminations that is indicative of failures of Gestalt organization. We agree that similar integrative and organization failures may contribute to schizophrenia patients' deficits in language comprehension, and that the types of rhythmic activity (i.e., gamma band oscillations) that P&S emphasize as relevant for primary perceptual integration are likely to be significant for language function. We emphasize, however, the importance of a timing mechanism for any theoretical account of language dysfunction in this disorder. We will direct our comments to the relevance of both mechanisms (cognitive coordination and temporal processing) for language function in schizophrenia.

First, our data on receptive syntax processes in schizophrenia (Condray et al. 2002) are consistent with a formulation of the type advocated by P&S. Compared with controls, patients exhibited reduced accuracy (i.e., not knowing who did what to whom) about object-relative sentences ("*The senator that the reporter attacked admitted the error.*"). More important, receptive syntax and general intelligence were correlated in controls; these functions were not associated in patients. Recent additional analyses of those data illustrate P&S's argument regarding the failure of higher-order coordination of functions that may be more locally specialized. An initial multiple regression analysis determined comprehension accuracy was predicted by a model that included the variables temporal processing accuracy (intelligibility of rapid speech) and a diagnosis *x* semantic knowledge (WAIS-R Vocabulary subtest score) interaction term [Model: $R^2 = .32$, Adjusted $R^2 = .30$, $F_{2,50} = 11.88$, $p < .001$. Predictors: temporal processing (t-test = 3.21, $p = .002$); diagnosis *x* semantic knowledge (t-test = 2.94, $p < .01$)].

Table 1 presents the results of the separate regression analyses conducted for each group to increase understanding about the significant interaction. Findings show different patterns of association for the two groups: For patients, temporal processing predicted comprehension accuracy, but semantic knowledge did not; for controls, the reverse was true. Overall, the cumulative patterns obtained for patients' receptive syntax performance are generally consistent with P&S's assumption of a failure to coordinate cortical activity within and between cognitive sub-systems. These data suggest the additional importance of temporal processing for patients' language comprehension.

Table 1 (Condray & Steinhauer). *Summary of separate multiple regression analyses for variables predicting comprehension accuracy for schizophrenia patients and normal controls*

R^2 Adj.	R^2 F-ratio	df	p beta	SE beta	*t*test p
Patients (n=32)	.22	.16	4.02	2.29	.03
Variables					
Temporal Processing	.64	.25	2.63	.014	
Semantic Knowledge	.03	.02	1.06	.30	
Controls (n=21)	.59	.54	12.92	2,18	<.001
Variables					
Temporal Processing	.92	.46	1.99	.061	
Semantic Knowledge	.10	.03	4.13	.001	

As a second consideration, we suggest that inclusion of a timing mechanism in theoretical accounts is necessary to explain the full range of language dysfunction in this disorder. Deficits in time-dependent processing as a core feature of schizophrenia have been pursued as an independent line of investigation (for a review of the early literature, see Braff et al. 1991). Findings indicate that schizophrenia is associated with disturbances in the processing of sequential, rapidly presented stimuli, including the disruptions in auditory sensory gating and visual backward masking discussed in the target article. Recognizing that this disturbance may be more complex than a mere slow processing speed, Braff and colleagues suggested that more refined distinctions are necessary, such as Breitmeyer's transient/sustained neural channel model (Breitmeyer & Ganz 1976). That model is based on the parallel and complementary pathways of the visual system, with functional distinctions made on the basis of temporal latency, and temporal and spatial resolution. Backward masking effects are assumed to be a result of the interruption of the slower responding of the sustained channels to the target stimulus by the faster responding of the transient channels to the mask. One hypothesis is that the visual backward masking deficit in schizophrenia is due to an overreactive transient channel that compromises sustained channel function (Green et al. 1994).

Most of the experimental tasks described by P&S involve rapid, sequential presentation of stimuli, but it is not clear whether they subsume a dysfunction of timing under their cognitive coordination mechanism. In combination with our receptive syntax data, considerations regarding semantic memory deficit in schizophrenia include the possibility that some type of timing dysfunction is a key mechanism. In particular, compromised semantic memory, as indexed by semantic priming deficits, may be due to dysfunction in the temporal dynamics of neural channel activation and synchronization. Recent visual backward masking studies have demonstrated that disruptions to patients' perception of rapid, sequential bits of information (single letters) represent a robust phenomenon (Butler et al. 2003; Cadenhead et al. 1997; Green et al. 1999). It is not known, however, if visual backward masking deficit can account for semantic priming disturbance in schizophrenia. Alternatively, it is possible that a temporal processing disturbance alone is sufficient to explain semantic priming dysfunction in this population. This latter type of account has been advanced for theories of dyslexia ("dyschronia": Llinas 1993; cf. the "cognitive dysmetria" for schizophrenia proposed by An-

dreasen et al. 1998). Moreover, researchers pursuing both lines of investigation (dyslexia and schizophrenia) have suggested that processing of rapid, sequential information produces cortical oscillations in the gamma range. Thus, converging lines of inquiry and discussion include emphases on temporal processing and on binding and coherence activity that may be reflected by high-frequency cortical oscillations.

Physiologically, coherent activity of disparate brain regions must occur to process relationships among stimuli. High-frequency electrocortical oscillations in the gamma range (30–50 Hz) have been proposed as one of the key types of binding processes. Pulvermuller (1999) has proposed the importance of this type of activity for semantic memory formation and lexical access. John (2001) has emphasized that electrocortical binding of functions, based on gamma activity and other key oscillatory frequencies, appears to progress from patterns of coherent activity across brain regions to states where there is zero lag in onset of activity in different regions. He refers to this process as *resonance.* Thus, development and learning may underlie the progression to resonance. As noted by P&S, schizophrenia may involve a neurodevelopmental pathogenesis (Marenco & Weinberger 2000). To the extent that brain organization is disrupted during crucial developmental periods, such as the migration of cortical neurons during prenatal development and the synaptic pruning during adolescence, the likelihood of interference in the progression toward resonance would therefore be increased.

We agree with the authors that the normal pattern of interconnectivity among cognitive functions is disrupted in schizophrenia, with some type of disconnection account potentially explaining a range of language disturbances for this population. We wish to emphasize, however, the importance of adding a timing mechanism to theoretical accounts of language dysfunction in schizophrenia.

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Setting domain boundaries for convergence of biological and psychological perspectives on cognitive coordination in schizophrenia

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Abstract: The claim that the disorganized subtype of schizophrenia results from glutamate hypofunction is enhanced by consideration of current subtypology of schizophrenia, symptom definition, interdependence of neurotransmitters, and the nature of the data needed to support the hypothesis. Careful specification clarifies the clinical reality of disorganization as a feature of schizophrenia and increases the utility of the subtype.

The authors make clear at the outset that they are primarily concerned with the "disorganization syndrome" of schizophrenia. More should be said, then, about how the disorganization syndrome fits into the bigger clinical picture of this heterogeneous brain disorder.

Subtyping schizophrenia. It is fair to say that heretofore, subtyping schizophrenic disorders has not approached the degree of validity necessary to produce agreement about individual patients among professionals who are practicing in the clinical setting. For cognitive coordination, and its underlying neuropathology, to represent an isolatable subtype with clinical utility, it is necessary to examine current schizophrenic subtypology briefly, and to support a modification of its reformulation with better specification of symptoms.

Conceptualizations of subtypes of schizophrenic disorder from the 1930s to the 1990s used dichotomous categorizations: Type I/Type II, Nondeficit/Deficit, Reactive/Process, and Positive/Negative. The first of each listed pair would be generally characterized by good premorbid function, abrupt onset with an identifiable stressor, flat affect, and fair to good prognosis; the second of the pair is characterized by a baseline of social withdrawal, insidious onset, absent stressors, affective lability, and unfavorable prognosis.

The *Diagnostic and Statistic Manual-IV* (DSM-IV) does not employ any dichotomous classification of schizophrenia. The Axis II, Cluster A personality disorders (Schizotypal, Schizoid, and Paranoid) comprise what was earlier designated as Simple Schizophrenia (Sanislow & Carson 2001). Although paranoid conditions are still viewed as distinct from other psychotic disorders (Blaney 1999), they are widespread throughout the DSM-IV, falling into Cluster A, Delusional Disorder, and Paranoid Schizophrenia. The remaining DSM-IV subtypes of schizophrenia are Disorganized, Catatonic, Undifferentiated (also referred to in current literature as "Mixed"), and Residual. Disorganized thought (and behavior) are choice principle criteria that, when predominant, are sufficient to define the subtype. However, negative symptoms are not placed into classification as a single subtype, but rather are listed as one of the criteria of the choice principle, and so may be associated with any subtype.

Recent studies, in line with the target article, have now established that the dichotomous factor designated "Positive" is better divided into two factors: Psychotic (hallucinations and delusions) and Disorganization. A third factor, Negative symptoms, still emerges. (Suggestions that there is furthermore a fourth dimension – relational – are not as well supported at this time.) Awareness among the authors of the DSM-IV in 1994 evidently was great enough to spur them to include an appendix with "Alternative Dimensional Descriptors for Schizophrenia" that corresponds exactly to the three-factor solution: Psychotic (Hallucinations or Delusions), Disorganized, and Negative.

Symptom definition. The three-factor solution of schizophrenia has the diagnostic effect of separating Disorganized thought from the Psychotic symptoms in one subtype, although one may reasonably hope that this was a de facto outcome of careful observation and diagnostic acumen anyway. The importance of this insight is its etiologic implications. Following the lines of clinical correlation, it appears that Negative symptoms are still associated with the Psychotic as well as the Disorganized subtype. This raises questions about the relationships among the symptom complexes. Negative symptoms could be either a downstream effect of delusions/hallucinations and thought disorder or could be a fundamental deficit that has different outcomes. This is a question to be explored further empirically, for example by using clinical notes. Similarly, one would like to know the comorbidity rates of Negative symptoms with Disorganized and Psychotic subtypes. By the way, it proves a difficult task to find surprisingly simple demographics about the population with schizophrenia, such as the relative prevalence of subtypes. One reference notes 55% Paranoid subtypes among successive admissions with any type of schizophrenia (Hachem et al. 1997), but a prevalence figure for the Disorganized subtype was not found.

Neurotransmitter systems. The authors are well aware that hypofunction of NMDA receptors has effects on other neurotransmitters systems, and note that dysregulation of dopamine in prefrontal cortex, resulting in a chronic decrease of utilization, is produced by NMDA-antagonists. This fact seemingly adds to the basis on which Disorganization symptoms (NMDA-hypofunction) can be separated from Negative symptoms (prefrontal dopamine decreased utilization). The dissociation (or lack of it) of these neurotransmitter system abnormalities is not directly addressed. This harks back to the need, mentioned above, for comorbidity prevalence data, to determine how often a schizophrenic Disorganization syndrome occurs with and without Negative symptoms. Clinical anecdotal perspective suggests that many patients with