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

Disorganized schizophrenia have little or no trouble with Negative symptoms, and in fact can be impulsive, aggressive, and unpredictable with potential for violence. It would be important to know under what conditions prefrontal dopamine and glutamate levels do interact. The suggestion has also been made, that hypofrontal glutamate activity causes excessive mesolimbic phasic dopamine reactivity, producing psychotic symptoms (Grace 1991).

Data. The clinical research evidence linking the construct of cognitive coordination to frank thought disorder is not as strong as it needs to be to be conclusive. Disorganized symptoms were found to be associated with exposure to NMDA-antagonists in humans, but so were Psychotic symptoms (delusions and hallucinations) and Negative symptoms. Contextual disambiguation is heavily relied on as an overarching proxy for cognitive coordination, stressing the fact that both information per se, and the meaning of the signals, are embedded in context. Experimental operationalization of cognitive coordination depended heavily on the perceptual-grouping method. Although it is quite clearly indicated that perceptual-grouping scores were correlated with scores of disorganization and associative thought disturbance, there is a possible tautology in other citations which use language perception and production as indicators of cognitive coordination.

Stimulus configuration studies (Rudy & Sutherland 1989; Sutherland & Rudy 1989) developed a method of studying acquisition of associated stimuli in rodents (light or tone, or light plus tone). Although the original focus of interest was primarily the role of hippocampus in learning and memory, there is a connection indicated by the authors in their consideration of the influence of contextual constraints on long-term memory formation. A possible source of controlled experimental data may exist if this method were used to assess the effects of PCP-like substances on configural stimulus acquisition in rats.

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Cognitive coordination deficits: A necessary but not sufficient factor in the development of schizophrenia

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Abstract: The Phillips & Silverstein model of NMDA-mediated coordination deficits provides a useful heuristic for the study of schizophrenic cognition. However, the model does not specifically account for the development of schizophrenia-spectrum disorders. The P&S model is compared to Meehl's seminal model of schizotaxia, schizotypy, and schizophrenia, as well as the model of schizophrenic cognitive dysfunction posited by McCarley and colleagues.

Since Meehl's (1962) address to the American Psychological Association, investigators have conjectured that a failure of inhibition at the cellular level is associated with a failure of inhibition at the cognitive level. In Meehl's model, a genetic diathesis produces schizotaxia, an integrative neural defect in the CNS of preschizophrenic individuals. In combination with social learning influences, the genetically determined defect of schizotaxia, gives rise to a latent personality organization known as schizotypy. According to Meehl's (l962; l989) model, all individuals who possess schizotypy would be expected to show some evidence of aberrant information processing.

Like others (cf. McCarley et al. l999), Phillips & Silverstein (P&S) invoke advances in neuroscience to account for the information-processing deficits observed in schizophrenia. P&S assert that hypoactivity in the NMDA glutamate receptor channels serves as the mechanism for cognitive dysmetria. There is considerable overlap between the P&S theory of cognitive coordination and the McCarley et al. (l999) model of cognitive dysfunction. Both models discuss NMDA receptor blockage as a fundamental mechanistic factor in the underlying cognitive deficits of schizophrenia. The latter model also ties in event-related potential (ERP) findings, most notably those pertaining to the N100 component, which indicate that schizophrenia-spectrum subjects show contextual processing abnormalities. While McCarley et al. have focused primarily on temporal cortical regions, P&S propose that the anatomical substrates of the cognitive coordination deficit are more global, including, but not limited to, the prefrontal cortex.

The authors' conceptualization of a failure in cognitive coordination maps on very nicely to Meehl's construct of schizotaxic cognitive slippage, which he proposed could account for the cognitive, clinical, and behavioral symptoms associated with schizophrenia. However, the cognitive impairments that characterize schizophrenia are necessary but not sufficient for the development of schizophrenia. In Meehl's model, a key aspect is an underlying genetic diathesis for the disorder. The P&S model is distinctly lacking a behavioral genetics perspective. Explicitly relating a specific genetic diathesis for schizophrenia to NMDA-channel hypoactivity might link the disruptions on the cellular level not only to disruptions on the cognitive and phenomenological levels, but also to a schizophrenia-spectrum outcome.

According to Meehl, there are various outcomes for schizotaxia; these outcomes might include aberrant personality traits and/or laboratory test performance, schizophrenia-spectrum disorders such as schizotypal personality disorder and schizoaffective disorder, and schizophrenia. In the P&S model, the ways in which schizophrenia arises from a failure in cognitive coordination are not explicated. The failure in cognitive coordination that is posited in the P&S model accounts for various psychotic conditions, including, but not limited to, frequently observed phenocopies of schizophrenia, such as PCP-psychosis. Although P&S compare the effects of NMDA-antagonists to the impairments observed in schizophrenia, the same impairments could be noted in non-schizophrenia patients who suffer from psychosis. Thus, the P&S model appears to fall short in accounting for the ways in which the neural bases of cognitive disorganization lead specifically to schizophrenia and/or schizophrenia-spectrum disorders.

One positive aspect of the P&S model is that it incorporates a neurodevelopmental perspective. However, one corollary of a neurodevelopmental model of schizophrenia is that signs of the underlying liability for schizophrenia should precede the manifestation of schizophrenia symptoms. Schizotypal traits are more common among first-degree relatives of schizophrenia patients (Gottesman l991) and other individuals at increased risk for the later development of schizophrenia (Kwapil l998). In our lab, we have observed that schizotypal individuals are more likely than nonschizotypal controls to display deficits similar to the ones observed in schizophrenia patients, namely, cognitive slippage (Gooding et al. 2001), disinhibition as measured by an anti-saccade task (Gooding l999), increased perseverative errors on the Wisconsin Card Sorting Test (Gooding et al. 1999), and subtle working memory impairments (Tallent & Gooding 2000), as well as smooth-pursuit eye-tracking deficits (Gooding et al. 2000). Findings that such individuals also show evidence of NMDA-receptor channel hypoactivity and/or higher levels of endogeneous NMDA-receptor blocker, N-acetyl-aspartyl-glutamate (NAAG), would buttress support for the P&S model.

We also assert that the cognitive coordination deficit described by P&S does not adequately capture the cognitive signature of schizophrenia. Inhibition is broadly defined to include the following processes: deliberate controlled suppression of prepotent responses; decrease in activation of some nodes (as in connectionist