2001; Hemby et al. 2002). The model's performance on a number of episodic memory tasks is compared with scores from patients with schizophrenia on the same tasks. Thus, the model is constrained at various levels of architecture and performance, and correspondences between both model and brain, and model and behavior are explicit. This facilitates verification or falsification of hypotheses, while derivation of new predictions can occur in an unambiguous way.

This type of analysis may also be appropriate for studying the role of NMDA currents in schizophrenia, as proposed by P&S. As the behavioral effects of abnormalities in these currents will probably depend on the wiring architecture of the region, network characteristics in the areas underlying the function of interest will need to be considered. For example, a computational model of auditory cortex may show how NMDA-receptor anomalies could produce deficits in sensory processing. Computational modeling thus allows the investigation of concrete deficits produced by concrete abnormalities in the brain.

Guarding against over-inclusive notions of "context": Psycholinguistic and electrophysiological studies of specific context functions in schizophrenia

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Abstract: Phillips & Silverstein offer an exciting synthesis of ongoing efforts to link the clinical and cognitive manifestations of schizophrenia with cellular accounts of its pathophysiology. We applaud their efforts but wonder whether the highly inclusive notion of "context" adequately captures some important details regarding schizophrenia and NMDA/glutamate function that are suggested by work on language processing and cognitive electrophysiology.

Schizophrenia is an enigmatic disorder associated with impairments in the structure and function of many interdependent neurocognitive systems. The neural and cognitive manifestations of schizophrenia are wildly heterogeneous, nevertheless significant advances have been made in understanding its biology and psychology. Phillips & Silverstein's (P&S's) thesis builds upon recent advances in linking cognitive dysfunction in schizophrenia to the NMDA/Glutamate system, and we applaud their efforts. However, similar to other comprehensive views of schizophrenia (e.g., Cohen & Servan-Schreiber 1992), we wonder whether their over-inclusive view of "context" adequately captures some important subtleties regarding neurocognitive dysfunction in schizophrenia.

In the domain of language, for example, the channel through which thought disorder in schizophrenia is most apparent, context may affect processing at any number of functional levels, thus clouding the notion of what constitutes a "primary" or "receptive field" input. These levels include the encoding of the auditory speech signal (or printed word), the activation of lexical entries, the retrieval of semantic information, how semantic information gets bound into episodic memory, and so on. Moreover, a given context may exert independent and separable effects in normal language processing that are differentially impaired in schizophrenia patients and following ketamine administration in normals (thus interfering with the NMDA/glutamate system directly). Such examples, to be reviewed, are problematic for global notions of "context" because they suggest that context processing is not unitary but rather a collection of processes, only a subset of which may be impaired in schizophrenia or arise from NMDA/glutamate function.

Language contexts exert facilitative and inhibitory effects on semantic activation that are differentially impaired in schizophrenia. We examined whether schizophrenia patients differentially use context to facilitate priming of contextually relevant meanings, and to inhibit priming of contextually irrelevant meanings (Titone et al. 2000) using a semantic priming method. Participants listened to moderately or strongly biased sentences that contained ambiguous words (e.g., bug), and saw targets presented for a lexical decision response (i.e., word/nonword judgment) that were semantically related to dominant (e.g., insect) or subordinate (e.g., spy) meanings. Sentence contexts always favored the subordinate, or less frequent meaning; therefore, priming to subordinate targets was always contextually appropriate and priming to dominant targets was always contextually inappropriate.

Similar to the perceptual closure data cited by P&S, schizophrenia patients differed from controls only for moderately biased but not strongly biased contexts. For strongly biased subordinate contexts, both schizophrenia patients and controls used context to selectively prime subordinate meanings, and thus to appropriately inhibit dominant meanings. For moderately biased subordinate contexts, however, only controls selectively primed subordinate meanings. In contrast, schizophrenia patients significantly primed both meanings, which indicates that they used the context to appropriately enhance subordinate meaning activation but not to inhibit dominant meaning activation (see also Chapman et al. 1976; Done & Frith 1984 for similar results; see Titone et al. 2002 for evidence of schizophrenia-related priming impairments for ambiguous idioms). These data suggest that context may produce multiple effects simultaneously – the activation of relevant semantic representations and the inhibition of irrelevant semantic representations. Further, these distinct effects of context may be selectively disrupted in schizophrenia.

Distinct ERPs associated with context processing are differentially impaired in schizophrenia subtypes and following ketamine administration. At least two event-related-potential (ERP) components may be relevant to context processing and NMDA accounts of schizophrenia. One deflection, the N400, is evoked by stimuli that are meaningful in everyday life, such as words, sentences, objects, or faces. For most authors, the N400 indexes the integration of stimulus meaning into an unfolding context (Halgren & Smith 1987; Holcomb 1993; Rugg et al. 1988), or the inhibition of inappropriate knowledge (Debruille 1998; Debruille et al. 1996). A second component, the P600 (a member of the P3b family; Kutas et al. 1977), is also evoked by stimuli that are meaningful in everyday life. Its amplitude is larger for stimuli that are subsequently recalled (Kutas 1988; Neville et al. 1986), and as the amount of information that is *consciously* extracted from a stimulus configuration increases (Donchin & Coles 1988). Therefore, the P600 potential may be related to the formation of an episodic memory event, or stimulus "binding."

Within P&S's framework, both the N400 and the P600 qualify as context-sensitive potentials. The N400 appears to be abnormal in schizophrenia (Koyama et al. 1991; Niznikiewicz et al. 1999; Sitnikova et al. 2002), especially as thought disorder or cognitive disorganization increases (Andrews et al. 1993). P600 amplitude is also smaller in schizophrenia patients than in controls, although schizophrenia patients who frequently experience reality distortion (i.e., hallucinations and delusions) show significantly larger (i.e., relatively more intact) P600 amplitudes than schizophrenia patients who do not experience prominent reality distortion (Guillem et al. 2001; 2003). Thus, the P600 effect is consistent with P&S's interpretation of gamma in schizophrenia, which is also thought to reflect episodic binding and is less impaired in schizophrenia patients who frequently experience reality distortion.

Although these N400 and P600 results fit with P&S's framework, the available evidence regarding these potentials and ketamine clouds the picture. Ketamine produces significant amplitude reductions in one of the most important sources of the N400, the antero-medial temporal lobe (AMTL) generator (Grunwald et al. 1999). Thus, the N400 findings are consistent with P&S's notion

of an NMDA-dependent relationship between cognitive disorganization in schizophrenia and contextual coordination. However, ketamine does not alter the AMTL generator of the P600 (Grunwald et al. 1999). Thus, context functions related to the inhibition of mental representations (i.e., N400) are impaired in schizophrenia, and associated with ketamine-induced MNDA/glutamate system damage. In contrast, context functions related to episodic memory formation and binding (i.e., P600), although impaired in schizophrenia, may not be associated with ketamine induced NMDA/glutamate system damage.

Recommendations. Although the studies reviewed here are preliminary, we hope they serve as examples of why pathophysiological models of schizophrenia should move beyond overly inclusive views of context and context-mediated effects, however tempting they may be. Only by decomposing the specific neurocognitive processes involved in any one "context" task, as well as understanding the interrelationships between critical processes involved across tasks, will the precise relationship(s) emerge between cellular and higher-level cognitive mechanisms that produce the intriguing pattern of cellular and cognitive deficits found in schizophrenia. Given the computational sophistication of P&S's contextual coordination approach, we hope they continue to pursue more precise linkages between specific context functions, NMDA/glutamate system function, and cognitive processing abnormalities in schizophrenia.

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High-frequency synchronisation in schizophrenia: Too much or too little?

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Abstract: Phillips & Silverstein's focus on schizophrenia as a failure of "cognitive coordination" is welcome. They note that a simple hypothesis of reduced Gamma synchronisation subserving impaired coordination does not fully account for recent observations. We suggest that schizophrenia reflects a dynamic compensation to a core deficit of coordination, expressed either as hyper- or hyposynchronisation, with neurotransmitter systems and arousal as modulatory mechanisms.

Phillips & Silverstein (P&S) present a welcome focus on large-scale coordinating mechanisms, as a complement to spatially localised brain functions. From this perspective, schizophrenia deficits in cognitive coordination stem primarily from reduced NMDA activity. The focus on NMDA-hypofunction suggests an associated emphasis on reduced coordination. It is noted that high frequency (40-Hz) Gamma activity is related to NMDA-receptor activity, as well as to dynamic organisation and coordination. From this context, the authors present the logical first-pass hypothesis that Gamma activity will be reduced in schizophrenia. Although they cite core supporting studies, P&S also point to observations of abnormally enhanced Gamma activity that suggest a more complex hypothesis.

We have recently reported a series of studies on Gamma activity in schizophrenia (for a review, see Lee et al. 2003b), examining both Gamma power and Gamma phase synchrony. While we observed a consistent reduction in Gamma activity in groups of both chronic and first-episode subjects, a more specific pattern of abnormalities has emerged in relation to distinct syndromes. Disorganisation is associated with the most disturbed profile of Gamma activity across task-relevant and task-irrelevant stimuli. It is associated with widespread increases in synchrony for task-relevant stimuli (Lee et al. 2003c). By contrast, Disorganisation is associated with a reduction in Gamma power frontally for task-irrelevant stimuli (Gordon et al. 2001). An opposing and more spatially localised pattern has been revealed for Psychomotor Poverty (primarily left hemisphere hypofunction) and Reality Distortion (primarily right hemisphere hyper-function) in relation to both Gamma synchrony and Gamma power (Gordon et al. 2001; Lee et al. 2003c).

We suggest that the widespread enhancement of Gamma synchrony with Disorganisation is synonymous with the authors' observation that disturbances in perceptual organisation (reflecting a failure of cognitive 'binding') increase specifically with severity of Disorganisation. The target article does not present specific predictions concerning the other syndromes. We speculate that Psychomotor Poverty and Reality Distortion might represent an attempt to compensate for a core deficit in synchronisation associated with the clinical syndrome of Disorganisation, in terms of either under or over-binding of stimuli. By contrast, Disorganisation might reflect a fundamental inability to locate a state of compensation and is therefore expressed as the most disrupted pattern of binding, to both task-relevant and task-irrelevant stimuli. From this view, the "compensatory" syndromes may be conceptualised in terms of "hyposynchronisation" (distinct reduction in binding and information processing shut-down associated with Psychomotor Poverty) or "hypersynchronisation" (abnormal increase in binding and over-processing associated with Reality Distortion). This speculation is consistent with functional disconnection models of schizophrenia which associate positive schizophrenia symptoms with "hyperconnectivity" and negative symptoms with "hypoconnectivity."

Is such a dynamical compensation view compatible with the NMDA-hypofunction model? We propose a number of interacting mechanisms, consistent with the authors' suggestion that the consequences of both direct and indirect neurotransmitter function may produce the diversity of schizophrenia symptoms. NMDA-hypofunction could account for general hypersynchronisation in Disorganisation, via the effects of glutamatergic activity which has a widespread cerebral distribution (Javoy-Agid et al. 1989). The authors note that NMDA-antagonists such as ketamine have been shown to produce Disorganisation in a dose-dependent manner. Ketamine also produces excessive glutamatergic activity, which in turn leads to enhanced synchronous Gamma activity. Enhanced dopamine activity (associated more closely with Reality Distortion (Oades et al. 1994) has also been related to excessive Gamma activity. Dopaminergic effects appear to be more regionally localised than NMDA-glutamatergic effects, and modulate task-relevant selective attention in particular, consistent with the regionally localised and task-related hypersynchronisation in Reality Distortion (Ahveninen et al. 2000). By contrast, we speculate that hyposynchronisation in Psychomotor Poverty may reflect cholinergic activity, given that anticholinergic agents produce a reduction in Gamma activity, and that clozapine (antipsychotic medication that is a partial cholinergic agonist) improves cognitive deficits that are most apparent in this syndrome (Allen et al. 1993). Bearing in mind the complexity of receptor subtypes, these speculations raise the possibility that abnormal regulation of dopamine or cholinergic activity may represent longer time-scale neuromodulatory attempts to cope with a Disorganisation-related deficit in NMDA activity.

In addition, we suggest that arousal may act as a dynamic regulator of the interactions between these neurochemical effects and