from the PFC. Although dynamic interactions are very much a part of this theory, both the qualitative behavior and the temporal scale are inconsistent with the fast-frequency mechanisms proposed by P&S. Low-frequency rhythms such as alpha are thought to synchronize loosely at best (Kopell 2000). Although on the surface this could be viewed as coordination that is mediated by NMDA-induced temporal patterns of activity, it is difficult to assess whether this scheme would fit into the scheme proposed by P&S; there is a lack of any specific mechanism in the target article.

The proposal of P&S emphasizes the critical interplay between computational modeling and experimental observation. Although we agree that combining modeling and experimental observation is essential if one is to begin to understand complex cognitive processes and their dysfunction, we have argued (Horwitz et al. 1999; Tagamets & Horwitz 1998) that, to understand the neural substrates mediating cognitive tasks (and brain disorders), it is necessary to embed the specific assumptions one makes into a neurobiologically realistic model and to simulate neural data at multiple levels (e.g., single unit, fMRI) that can be compared with quantitative experimental data. In the case presented by P&S, such a model would have defective NMDA-receptors, and one would attempt to show that the model is deficient in performing tasks on which schizophrenic patients show deficits, and also, that the model results in simulated neural activity similar to that seen in schizophrenic patients (e.g., hypofrontality in an appropriate fMRI study). It is at this level of analysis that one can start to determine the neural basis of the disruption of normal cognition that one finds in schizophrenic patients.

The type of hypothesis proposed by P&S should be viewed as the beginning stage for a neurobiologically realistic physiologic theory aimed at elucidating the neural basis of the thought disorder associated with schizophrenia, not as a theory itself.

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## Combating fuzziness with computational modeling

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**Abstract:** Phillips & Silverstein's ambitious link between receptor abnormalities and the symptoms of schizophrenia involves a certain amount of fuzziness: No detailed mechanism is suggested through which the proposed abnormality would lead to psychological traits. We propose that detailed simulation of brain regions, using model neural networks, can aid in understanding the relation between biological abnormality and psychological dysfunction in schizophrenia.

In the last decades, the sciences studying brain and behavior have started to converge. The paper by Phillips & Silverstein (P&S) is a good example of this tendency. In it, the cognitive and behavioral symptoms of schizophrenia are tied to a putative dysfunction of the NMDA-receptor. The vast differences in scale that are bridged in the process are both the strong-point and the weakness of this paper. On the one hand, such an explicit bridge is necessary to link an identified neuropathology to observed cognitive or behavioral impairments in a testable way. On the other hand, because of a shortness of relevant data, the cellular and network mechanisms that might lead from NMDA-receptor dysfunction to the symptoms associated with the disorder largely remain obscure.

Nevertheless, P&S's viewpoint focuses attention on a thus far poorly understood issue in schizophrenia research, namely, the remarkable similarities between effects induced by NMDA-receptor blockers such as PCP and schizophrenia symptoms. The mechanisms underlying these effects are of considerable importance, both with respect to disorder pathogenesis and in relation to drug therapy. P&S present various evidence that suggest a role of NMDA-receptors in at least some of the symptoms of schizophrenia. This link is most convincing with respect to deficits on perceptual tasks. The authors discuss in detail what paradigms are affected in this domain, and how deficits in these tasks are related to the concepts of cognitive coordination and dynamic grouping. It is also in this field (in auditory perception) that they present the sole direct evidence linking NMDA-receptor blockage to a decrease in contextual modulation (Javitt et al. 1996).

With respect to the cognitive symptoms discussed in the article, the distance from the neurochemical level is so great that some vagueness is necessarily introduced. In these issues both the step from NMDA to cognitive coordination, and that from cognitive coordination to symptomatology, are not wholly transparent. For example, P&S argue that NMDA-receptors typically carry information from outside the receptive field of the cell. However, in higher order areas, the notion of receptive field may be problematic. Still, the authors suggest a distinction can be made between what neurons "transmit information about," and information that is merely modulating. It would seem to us that such distinctions are clear-cut only in lower order sensory or motor areas, where the relation between environmental stimuli and neuronal representations is relatively straightforward. How such distinctions are to be applied to, for example, hippocampal structures with their multiple recurrent circuits, is unclear.

Another problem is that the exact nature of the putative NMDA abnormality in schizophrenia remains undefined. NMDA-receptors have been associated primarily with learning (Newcomer & Krystal 2001). Although the authors show that some symptoms in schizophrenia cannot be caused by LTP deficits, we wonder why learning would not be affected, and how LTP deficits would fit in their story.

At the cognitive level, the concept of "cognitive coordination" is thus used in a rather loose way. It seems that anything and nothing can be a reflection of cognitive coordination. As a consequence, the predictions of the theory at the cognitive level are unclear. This suggests that it would perhaps be more fruitful to consider a link of NMDA-receptors and contextual modulation within the limited domain of sensory tasks. Although this would greatly limit the generality of the theory, it would have the benefit of making it relatively clear-cut what types of transmission are thought to be affected by NMDA abnormalities, and how that relates to behavioral effects. Loss of generality would thus be made up by gains in testability.

In more general terms, the closing of the gap between brain and behavior might benefit from models that are explicit about how an observed neuropathology, in a particular brain region, might affect network function, and how this, in turn, may result in particular symptoms. As stressed by P&S, simulation of brain circuits using computational techniques can be a great aid in this process, provided that one is explicit about the substrate that is modeled.

There are already several examples of such an approach (Andrew 2000; Braver et al. 1999; Meeter et al. 2002; Monchi et al. 2002). The study by Andrew (2000) showed how dopamine upregulation, simulated as an increase in excitability in frontal cortex neurons, produced perseverance errors on a simulated Wisconsin Card Sort Test, as also found in patients with schizophrenia. As another example, in our own work we relate specific wiring abnormalities in the parahippocampal gyrus with the pattern of memory deficits observed in schizophrenia (Meeter et al. 2002; Talamini et al., in preparation). The architecture of our network incorporates the broad features of medial temporal lobe anatomy, while the simulated neuropathology is derived from a considerable body of evidence that suggests reduced connectivity in the input-output regions of the hippocampus (Harrison & Eastwood



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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



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