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

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cognitive coordination. It has been demonstrated that the relationship between synchronous Gamma activity and cognitive coordination is modulated by phasic arousal of specific cortical regions (Sheer 1984). Grossberg (1984) argued that psychosis can be conceptualised as the expression of an opponent process in which arousal is gated by slowly accumulating neurotransmitters. In this case the inverted-U properties of under- and overarousal may be represented clinically as the compensatory syndromes of Psychomotor Poverty (hyposynchronisation, decreased cholinergic modulation) and reality distortion (hypersynchronisation, increased dopamine modulation) syndromes, respectively. P&S suggest that computational modeling provides an important way forward in elucidating interactions of NMDA activity with other neurotransmitter systems. A numerical simulation of whole-brain neurophysiology developed by our group has demonstrated that enhanced Gamma activity emerges from an increase of gain-related parameters of the thalamo-cortical feedback loop and associated cortical arousal (Rennie et al. 2000). The reliance of this approach on physiological parameters offers a quantitative means to examine neurotransmitter function in relation to synchronous brain activity.

Authors' Response

Cognitive coordination and its neurobiological bases: A new continent to explore

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Abstract: The additional arguments and evidence supplied by the commentaries strengthen the hypothesis that underactivity of NMDA receptors produces impaired cognitive coordination in schizophrenia. This encourages the hope that though the distance from molecules to mind is great, it can nevertheless be traversed. We therefore predict that in this decade or the next molecular psychology will be seen to be as fundamental to our understanding of mind as molecular biology is to our understanding of life.

R1. Introduction

The commentaries raise many relevant issues, provide new and important evidence, and offer many valuable insights. The range of disciplines from which the commentators come is a testament to the generality of the issues discussed. Overall, we see them as supporting the general perspective proposed, but asking for further clarification, detail, and evidence. We strongly agree this is needed, as we see cognitive coordination, its neural bases, and their malfunctions, not as a small and well-known territory, but as a vast continent that remains largely unexplored.

Section R2 discusses comments concerning the underlying conceptual framework. Sections R3 to R8 discuss cognitive coordination, and its relation to other aspects of schizophrenia; R9 discusses NMDA hypofunction; R10 discusses the relevance of high-frequency rhythms; R11 discusses the role of computational theory and computational models. Finally, section R12 discusses implications for treatment.

R2. The basic conceptual framework

R2.1. Terminology

"Cognitive coordination" refers to the family of interactions that modify neuronal signals without changing what they mean. "Meaning" refers to features detected within perceptual systems, to particular movements within motor systems, and to the semantic contents of thoughts, plans, and memories. We assume that interactions that change the time at which signals occur do not change their meaning. Dysfunctions of timing as discussed by **Condray & Steinhauer** are therefore prima facie examples of a disorder in cognitive coordination. Similarly, interactions that affect salience by modulating response amplitude do not change the meaning of the signals that they make more salient. This conception is expressed formally using information theory as cited in the target article. As **Grossberg** clearly saw, we emphasise two distinct but interdependent classes of cognitive coordination, that is, contextual disambiguation and dynamic grouping. "Context" is activity that affects the processing of signals without changing what they mean. Information theory has been used in psychophysical paradigms designed to distinguish modulatory interactions from those that determine the semantic content of the signals modulated (Phillips 2001; Phillips & Craven 2000). This is one way of clarifying the core construct of cognitive coordination as requested by **MacDonald**. In the psychophysical experiments of Phillips and Craven (2000) evidence for driving interactions was easier to find than evidence for coordinating interactions. This should alleviate MacDonald's concern that coordination may be so ubiquitous that it is difficult to test. The central point here is that coordination is identified with interactions between variables, not with tasks as a whole. The importance of such "process-oriented" approaches to the study of cognition and its dysfunctions is discussed in detail by Knight and Silverstein (2001).

We therefore assume that "amplification" and "attenuation" must be distinguished from "excitation" and "inhibition." The former are conditional upon the latter because the latter determine whether there is something to be modulated. Though obvious to many, this distinction is often overlooked.

"Grouping" is the specification of a subset of signals on which to perform some operation. "Prespecified grouping" is that which is specified without knowing the realized values of the variables grouped. In perceptual systems it determines the features to which cells are sensitive. "Dynamic grouping" is that which can be specified only after the realized values are known, that is, after the stimulus has been received in perceptual systems (Watt & Phillips 2000). "Dynamically embedded grouping" specifies groups within groups, that is, embedded levels of grouping where the embedding cannot be prespecified. **Tagamets & Horwitz** argue that "coordination" refers to sequences of actions, and should not be used to refer to perceptual organization. They seem to be in a minority on this, as the other commentators use the term in the way we do.

At the synaptic level, we have used the terms RF (receptive field) and CF (contextual field) to distinguish inputs involved in the two classes of interaction. Local processors

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