nections in the beta2-range, revealing pathological rigidity. During task performance, the differences in coherence patterns between these two groups were insignificant.

As we see from the above, the results obtained in the coherence study showed dramatic results: the absence of interhemispheric connections in both patient groups in comparison with the norm at the frequency 20–40 Hz (beta2) in all conditions. At the same time there were no significant differences between the two patient groups.

Typical connections study. In the normal group in rest condition, there were two interhemispheric and three intrahemispheric connections at the frequency 38 Hz. During the task, the number of connections at this frequency increased to four interhemispheric and five intrahemispheric ones, with the predominant inclusion of areas of the left hemisphere. In patients with positive symptoms in the rest condition, in the beta2-range interhemispheric connections were absent. In comparison with the norm, in this group there were significantly more connections of temporal areas with other ones. During task performance in patients with positive symptoms, typical interhemispheric connections in the beta2-range were also absent.

In patients with negative symptoms, in the beta2-range (20–40 Hz) typical connections were revealed only in the left hemisphere. The interhemispheric connections were absent in both situations.

The comparison between the patients with positive and negative symptoms during task performance revealed in the beta2-range (20–40 Hz) a sort of "parity" in the number of significant differences between these groups, but patients with negative symptoms had more connections in medial areas, including interhemispheric ones, and patients with positive symptoms had more connections in the temporal areas.

The greatest departure of schizophrenics from the norm was revealed at the frequency 35–40 Hz: In the norm there were many typical interhemispheric connections, while in schizophrenics there were no interhemispheric connections at this frequency. Instead, a new pathological system seems to have evolved in patients – the system of connections at a frequency (29 Hz) significantly lower than normal.

Conclusions. 1. In both groups of schizophrenic patients there is phase shift instability, revealed by the coherence method. This instability causes functional disconnections between the hemispheres in the beta2-rhythm, this rhythm being important for cognitive functions and consciousness.

2. In both groups of patients, the number of typical connections was decreased in comparison with the norm. In patients with negative symptoms, this number was greater than in the other patient group, but on account of lower frequency connections.

3. All the abovementioned deficiencies observed in schizophrenic patients may be at least partly connected with NMDA-hypofunction.

Synchronous dynamics for cognitive coordination: But how?

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Abstract: Although interesting, the hypotheses proposed by Phillips & Silverstein lack unifying structure both in specific mechanisms and in cited evidence. They provide little to support the notion that low-level sensory processing and high-level cognitive coordination share dynamic grouping by synchrony as a common processing mechanism. We suggest that more realistic large-scale modeling at multiple levels is needed to address these issues.

The main hypothesis advanced by Phillips & Silverstein (P&S) is that synchrony of fast rhythms (e.g., gamma or beta rhythms) can explain "cognitive coordination" throughout the cortex at multiple levels of processing, and that schizophrenia results from a breakdown of this coordination. These dynamics, in turn, are hypothesized to be regulated by NMDA-receptor activity, which is thought to be reduced in schizophrenia. The evidence presented by P&S mainly derives from studies of context in perceptual processing, and P&S suggest that the principles at this level can be extended to higher level cognitive processing throughout the cortex. They hypothesize that synchrony of high-frequency rhythms across cell assemblies is sufficient as an explanatory mechanism for a dynamic grouping that underlies cognitive coordination at multiple levels. But is this consistent with the evidence? Furthermore, while the P&S hypothesis is appealing in its parsimony, it is not clear that synchrony is necessary to explain the phenomena described. In the debate on the role of rhythms in the cortex, it has been argued, including by one of the authors (Phillips & Singer 1997a), that no rhythmic patterns are necessary for synchronization to occur (Roy et al. 2001).

How appropriate is it to assume a unified process across multiple levels, such as low-level perception and cognitive coordination of high-level processes? In general, there is little explanation in the target article of specific mechanisms that make use of synchrony that might support the authors' view. Rather, supporting evidence is drawn for each of the parts of the argument, but little is done to induce a "Gestalt": How, exactly, do all the pieces fit together? Does "coordination" of perceiving the parts of an object as a whole equate with selecting an appropriate answer to a simple perceptual matching task, and does the latter require the same type of coordination that is needed for playing chess or for daydreaming? If so, then which components of each task are bound by the dynamic grouping, and in what order? Synchronous gamma band activity has been proposed to serve a role in binding components of a percept into a unified whole, and most of the evidence cited by P&S draws on this literature. This, in itself, is not coordination, in the more common sense of the word. Coordination implies sequences of actions in some useful order in time, and certainly, higher-order cognitive processes require coordination in this sense. No satisfactory definition is given to the term "coordination," and no explanation is given here of how the proposed synchronous mechanisms could mediate the necessary transitions between states for coordination to occur.

A large part of the authors' argument revolves around the role of NMDA both in mediating the synchronous behavior across multiple levels, and in the lack of this coordination in schizophrenia. Yet it is widely believed that dopamine plays a significant role in control of processing in the frontal cortex, but not in early sensory and association regions of the cortex. This fact already suggests potentially different basic mechanisms. With respect to schizophrenia, virtually all antipsychotics have dopamine receptor binding action. Although the evidence for NMDA-receptor involvement in schizophrenia is compelling (Holcomb et al. 2001; Medoff et al. 2001; Tamminga 1998), it is not clear that it alone can explain the disease, since NMDA partial agonists seem to be most effective in treating negative symptoms (van Berckel et al. 1996), and mainly in conjunction with other, more standard antipsychotics. Recent theories of schizophrenia have rather emphasized the likely role of multiple interacting receptor systems in this disease. One theory that might involve the type of dynamics proposed by P&S is in studies of the regulation of dopamine by NMDA-receptor activity. Specifically, there is evidence that NMDA-receptor-based mechanisms may regulate the flow of dopamine from the ventral tegmental area (VTA) to the prefrontal cortex (PFC) in a reciprocal interaction which depends on a temporal pattern of activity in the VTA (Svensson 2000).

A bursting pattern of activity at 5 Hz (near the alpha-rhythm) in the VTA caused dopamine release to the PFC, while nonbursting spiking at the same mean rate did not. This dynamic behavior was found to depend on NMDA-receptor activation by afferents

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