verbal." The hallucinating schizophrenic differs from the nonhallucinator in regard to cognitive style and semantic processing (Alpert et al. 1976). Amphetamine-associated hallucinations are phenomenologically like those in schizophrenia.

In their Figure 2, P&S suggest horizontal and vertical neuroanatomic geometric models of neurotransmitter interactions for psychopathologic disturbances. It has been shown that sensory transduction of auditory sharpening mechanisms (lateral inhibition) may be affected by alcohol exposure in alcohol-withdrawal psychoses (Alpert & Bogorad 1975). Similar processes may occur in schizophrenia, and could be accessible to psychophysical examination. In addition, hallucinators differ from nonhallucinating schizophrenics in regard horizontal organization of cognitive processing (Alpert & Martz 1977). The P&S model provides a reasonable context for investigation of these issues.

The loss of insight and other behavioral effects with amphetamine can be very impressive. Among Angrist's amphetamine subjects, one was reluctant to report his auditory hallucinations for fear that he would be locked away in a psychiatric hospital. He had predicted at baseline that he would experience verbal hallucinations as part of the amphetamine experience. When they occurred, he thought that he was becoming schizophrenic. Another subject spoke of "setups and traps" and rejected our attempts to reassure him. He was convinced that a gang was coming to the ward to get him. A third subject felt that he had received special enlightenment and had become a "prophet." He preached to the ward for about an hour (Angrist 1972; Angrist & Gershon 1970). Loss of insight appears to be a direct, primary effect of the amphetamine induction, not the subjects' reaction to their perplexing subjective experiences. These important aspects of the induction do not appear to be duplicated in the ketamine model.

A ketamine induction, perhaps more than amphetamine, is associated with affective flattening. Although the DSM IV (Diagnostic and Statistical Manual IV, of the American Psychiatric Association) has added flat affect as a diagnostic criterion for schizophrenia, this may be an error. Flat affect appears early in life, perhaps years before schizophrenia appears (Knight & Roff 1985), and may diminish at the time of an acute schizophrenic episode. Similarly, flat affect is reduced in cocaine abuse while hallucinations and delusions are markedly increased (Serper et al. 1995; 1996). Emotions appear to be intact in schizophrenics with flat affect (Alpert et al. 2000), and flat affect can be conceptualized as a disturbance in motor expression. Flat affect may worsen in treatment with typical neuroleptics but respond to treatment with atypical antipsychotic drugs, even while other psychotic signs remain. For these reasons, flat affect does not appear to be coherent with diagnostic signs for a schizophrenic episode. It may be conceptualized as a risk factor for schizophrenia rather than a sign of schizophrenia. Further, flat affect may represent a condition involving lowered dopamine turnover. The role of flat affect in ketamine model psychosis may represent complex interactions with dopamine. The P&S article will help to clarify the actions of neurotransmitters in psychosis.

Where the rubber meets the road: The importance of implementation

Deanna M. Barch and Todd S. Braver

Department of Psychology, Washington University, St. Louis, MO 63130.
dbarch@artsci.wustl.edu **http://iac.wustl.edu/~ccpweb/**
tbraver@artsci.wustl.edu

Abstract: Phillips & Silverstein argue that a range of cognitive disturbances in schizophrenia result from a deficit in cognitive coordination attributable to NMDA receptor dysfunction. We suggest that the viability of this hypothesis would be further supported by explicit implementation in a computational framework that can produce quantitative estimates of the behavior of both healthy individuals and individuals with schizophrenia.

Phillips & Silverstein (P&S) put forth an interesting and provocative hypothesis as to the ways in which NMDA receptor dysfunction might lead to disturbances in cognitive coordination in schizophrenia. They do an elegant job of synthesizing psychological, computational, and neurobiological perspectives on the cognitive coordination construct and its underlying mechanisms. We are grateful that P&S acknowledge our own work (with Jonathan Cohen and colleagues) as trying to achieve similar goals with regard to understanding cognition in schizophrenia (Braver et al. 1999). P&S contrast their hypotheses to our theory, which suggests that one of the core cognitive deficits in schizophrenia is a dysfunction in the ability to represent and maintain context information, as a result of a disturbance in dopamine function in prefrontal cortex. P&S highlight a potentially more fundamental mechanism of context processing (cognitive coordination in their model) that involves the NMDA-receptor and computational processing within, as well as between, cortical modules. As such, P&S suggest that deficits in the kinds of cognitive control mechanisms that are central to our theory could arise from disturbances in basic mechanisms that may be involved in processing throughout the entire brain. This contrasts with our theory, which focuses on processing mechanisms that more selectively involve dopamine interactions with prefrontal cortex, and on the cognitive capabilities that depend on such interactions. We have argued that disturbances in such mechanisms among individuals with schizophrenia give rise to relatively selective cognitive deficits that are most severe under particular task conditions.

We are excited by the prospect of a theory of cognition in schizophrenia that attempts the same integration of psychological, computational, and neurobiological perspectives that we have tried to incorporate in our work. An especially exciting prospect is the suggestion by P&S that their mechanism could account for deficits among individuals with schizophrenia, both on high-level cognitive tasks and in more basic sensory and perceptual domains. If this were true, it would constitute an advance upon our own theory, which is admittedly more constrained in terms of the phenomena for which it attempts to account. Phillips and colleagues have conducted computational studies demonstrating that NMDA-receptors have properties (i.e., their voltage-dependence) that allow these receptors to help organize processing and learning. However, a more convincing demonstration of the explanatory power of the P&S model would be to explicitly demonstrate that a disturbance in the same mechanism could lead to changes in both high-level cognitive processing and sensory/perceptual (e.g., Gestalt grouping phenomena).

P&S refer to a distinction between computational theory and computational modeling. Their theory seems to be rooted in the former approach. In contrast, our work has focused on the latter approach, using simulations of specific cognitive tasks. We would advocate that explicit simulations of cognitive tasks provide an useful means by which to compare and contrast theories such as ours and that of P&S. In particular, simulations of actual cognitive tasks enable quantitative estimates of the success with which a model can account for the relevant behavioral phenomena. Such estimates provide an objective metric by which to evaluate competing models. For example, one would judge the P&S model to be a more successful model of cognition in schizophrenia than our own if, in addition to accounting for sensory/perceptual phenomena, the P&S model could also account for the behavior of individuals with schizophrenia on tasks such as our AX version of the Continuous Performance Task (a task that our theory suggests is highly dependent on integrity of context processing functions) with the same degree of success that our model can.

Such explicit implementation may also help to identify task conditions that would help arbitrate between competing theories. For example, our simulation work has suggested that deficits in context processing among individuals with schizophrenia should be amplified under conditions in which context needs to be actively maintained in working memory and/or used to inhibit dominant response tendencies that are not appropriate for the task at hand.

A number of empirical studies provide support for these model predictions (e.g., Barch et al. 2003; Cohen et al. 1999b; Javitt et al. 2000; Servan-Schreiber et al. 1996; Stratta et al. 1998). However, it is not clear from the level of description provided by P&S whether their theory would also predict that such factors should influence the severity of cognitive deficits in schizophrenia. It is also possible that simulations of specific cognitive tasks in the P&S framework would identify other conditions that are especially dependent on their proposed NMDA-receptor mechanism. In our experience we have found that the process of simulating empirical phenomena forced us to refine and elaborate our initial conceptual hypotheses in ways that we could not have predicted ahead of time.

In summary, we are intrigued by the theory put forth by P&S and encourage the authors to take this theory to the next level by providing an explicit computational implementation that can be compared with competing theories.

A wide-spectrum coordination model of schizophrenia

Hendrik Pieter Barendregt

Nijmeegse Instituut voor Informatica en Informatiekunde, 6500 GL Nijmegen, The Netherlands. **henk@cs.kun.nl** **http://www.cs.kun.nl/~henk**

Abstract: The target article presents a model for schizophrenia extending four levels of abstraction: molecules, cells, cognition, and syndrome. An important notion in the model is that of coordination, applicable to both the level of cells and of cognition. The molecular level provides an "implementation" of the coordination at the cellular level, which in turn underlies the coordination at the cognitive level, giving rise to the clinical symptoms.

The model of schizophrenia presented by Phillips & Silverstein (P&S) can be depicted as follows:

$$\text{NMDA}\downarrow \Rightarrow \text{neur. coord.}\downarrow \Rightarrow \text{cogn. coord.}\downarrow \Rightarrow \text{schiz.}\uparrow$$

This requires some explanation from the following dictionary:

NMDA	N-methyl-D-aspertate glutamate receptor activity
neur. coord.	neuronal coordination
cogn. coord.	cognitive coordination
schiz.	schizophrenia symptoms
$X\downarrow$	*X* decreases
$X\uparrow$	*X* increases

In somewhat more detailed terms, the model states the following. If the activity of NMDA glutamate receptors in the cortex is below normal, then neural coordination within and between cortical regions is decreased; this in turn implies decreased cognitive coordination, such as disambiguation and dynamic grouping; this then will be the direct cause of the symptoms of schizophrenia, such as impairments of perception, preattentive sensory gating, selective attention, working memory, and long-term memory. The authors choose to focus on disorganization.

The way the authors come to their model is as follows: NMDA-antagonists cause schizophrenia-like symptoms; schizophrenia implies impaired cognitive coordination, and vice versa; neural coordination is behind cognitive coordination. The model postulates that the NMDA glutamate channels provide a control for the neural coordination. The rationale behind this is that the NMDA-receptors are voltage-gated, that is, they depend on both the ligand and the right voltage to be opened. So they may indeed be used to coordinate processes (they essentially have the function of an AND-gate in a computer).

One virtue of the model is that it is *wide-spectrum.* It ranges from a molecular mechanism via cellular phenomena, via cognition, to psychiatric symptoms. The model makes predictions about patients suffering from schizophrenia: There is impairment of global, but not local, motion perception; high frequency rhythms (gamma) will be reduced. This implies that the model is falsifiable.

The main virtue of P&S's model is its emphasis on coordination, interaction. In computer science, a notion and theory has emerged that seems relevant here: that is, the notion and theory of communicating systems (see Milner 1999). Although everything happening in a computer may be described by fluctuating bits, the theory of communication forms a convenient level of abstraction. Some bits encode meaningful information to be used later, other bits represent actions that are relevant at the very moment. An interacting communication, the most fundamental concept in the mentioned theory, needs two half-acts, each waiting for the other half to be present simultaneously (like two persons who want to shake hands).[1] All this may be useful for a thorough theoretical underpinning of the way in which coordination is implemented by NMDA glutamate channels.

Although a single model for schizophrenia is presented, this does not imply that it is a homogeneous condition. For, there are many ways in which coordination can be impaired. Also, the effects can vary in severity. The authors give several examples of this and it is also apparent from the computer science theory of communicating systems, mentioned above.

The authors mention how their model is similar to many other theories, though not in all aspects. The theories they put forward regarding the cause of the disconnection between cortical regions are mainly similar to each other, apart from the fact that they do not speak about coordination *within* regions and focus on long term, that is, learning, effects (see Dolan et al. 1999; Friston 1999). P&S do focus in their model on the cortex but mention that other brain regions will also be involved. A paper not mentioned by the authors, in which such an involvement is described, is van Hoof (2002). Van Hoof provides a model of the pathogenesis of schizophrenia, in which the drive and guidance mechanisms in the brain (specific brain regions are mentioned) are said to be underdeveloped (in the terminology of the target article, they do not *coordinate* well). Such intentional aspects fit well with the model of P&S.

The target article ends by stating many open questions. Yet, one puzzle that has been ignored is the claim in Menninger et al. (1963) that some of the schizophrenic patients get "weller than well."

The theory of mobile systems (also see Milner 1999) goes beyond that of communicating ones. The intended model in ICT (Information and Communication Technology) is that of mobile telephones, or Web pages with links. Here, the number of action channels is variable and a communication may create a new channel between other processes. This theory may model very well the way in which cells communicate. In some cases, there is no receptor in a cell for a certain transmitter *T,* but there is for another transmitter T'. Reception of T' will cause the DNA code for the receptor for *T* to be read from the genome, and brought to expression, so that *T* can be received.

NOTES

1. A typical example of a communicating process is a vending machine. It has a slot for coins and one button for coffee and one for tea. The process of the machine is:

$$M = \text{want\_coin}.(\text{ready\_tea-button} + \text{ready\_coffee-button}).M.$$

This means that the machine (M) is waiting for a coin and, after that, for a push on either the tea or the coffee button. Here, the period (.) stands for sequential composition and the (+) for choice. The M is repeated on the right-hand side because we'd like the machine to keep operating. A human that regularly wants to use the machine has the process:

$$H = \text{put\_coin}.(\text{push\_tea-button} + \text{push\_coffee-button}).H.$$

Now, the interaction of the human (H) with the machine (M) is denoted by H‖M. Provided that we postulate that there are communications *c,* such that:

$$\begin{aligned} c(\text{put\_coin},\text{want\_coin}) &= \text{accept\_coin} \\ c(\text{push\_tea-button},\text{ready\_tea-button}) &= \text{pour\_tea} \\ c(\text{push\_coffee-button},\text{ready\_coffee-button}) &= \text{pour\_coffee} \end{aligned}$$

https://doi.org/10.1017/S0140525X03230028 Published online by Cambridge University Press