reduced NMDA-channel activity on inhibitory cells outweighs underactivity due to reduced NMDA-channel activity on glutamatergic cells. This is compatible with evidence for cases of schizophrenia both with and without progressive degeneration (Benes & Coyle 1998).

5. When patients experience verbal hallucinations they do not know that the words they experience are due to activity in those other parts of their cognitive system that generate things to be said (Frith 1992). Such hallucinations are possible because the sub-systems that instantiate the phonological and semantic forms of words can be activated by input from any of several different sources, some internal, some external. To signal the origin of activity within them on any particular occasion, that activity must be dynamically linked to the activity from which it arose on that occasion. Failure of this dynamic linking could produce the strange experience of having words in mind, but not as part of a larger pattern of activity that links them to their origin in other brain regions on that occasion. Verbal activity might then be experienced as coming from outside the self, and delusional beliefs might then reflect attempts to account for this experience.

6. Silverstein and Palumbo (1995) describe similarities between schizophrenia and nonverbal perceptual-organization-output disability, which is a severe form of nonverbal learning disability thought to fall within the autism spectrum (Rourke 1982). They suggest that this disorder also involves impaired stimulus organization mechanisms, and that studies of such disorders could compliment high-risk studies in the attempt to uncover the aetiology of schizophrenia. Furthermore, some learning disabled individuals have deficits in backward masking (Blackwell et al. 1983) and span of apprehension tasks (Tarnowski et al. 1986), which are often thought to be vulnerability markers for schizophrenia. Thus, there is evidence of common cognitive impairments in schizophrenia and some other neurodevelopmental disorders. It is not the case that all of these populations perform similarly simply by virtue of a general intellectual impairment. Certain developmental disorders exhibit a very different pattern of cognitive deficits. For example, patients with Williams Syndrome show increased rather than decreased global processing (Pani et al. 1999), when tested on the same perceptual organization task as used with schizophrenic patients by Silverstein et al. (1996a). Much may therefore be gained by comparing these disorders using relevant process-oriented designs (Knight 1992; Knight & Silverstein 1998).

7. Discussing the role of the thalamus in the pathophysiology of schizophrenia, Patterson (1987) concludes "If one were to single out a brain structure that displayed the possibility for central 'timing' functions in brain, it would most likely be the thalamus." The basal ganglia are also often implicated in schizophrenia (Robbins 1990). Graybiel (1997) argues that just as they contribute to the coordination of motor output so they may also contribute to the coordination of cognitive activity. She argues that in both cases this coordination involves dynamic binding through the synchronization of firing patterns so as to produce appropriate and precisely timed sequences of activity. In their review of the functional architecture of the basal ganglia, Alexander and Crutcher (1990) conclude that "the functional integration that is widely assumed to occur within these circuits may prove to be based less upon the spatial convergence of functionally disparate pathways than upon the temporal coincidence of processing within pathways whose functional segregation is rather strictly maintained" (p. 270). All these views are highly consonant with that proposed here. One function of the limbic system is thought to include putting things in context while maintaining their individual identities, so that too, may involve the formation of contextual associations that are implemented in part by NMDA-receptors, which are particularly dense in the hippocampus.

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The ketamine model for schizophrenia

Murray Alpert and Burt Angrist

Department of Psychiatry, NYU School of Medicine, New York, NY 10016.
murray.alpert@nyu.edu

Abstract: This commentary compares clinical aspects of ketamine with the amphetamine model of schizophrenia. Hallucinations and loss of insight, associated with amphetamine, seem more schizophrenia-like. Flat affect encountered with ketamine is closer to the clinical presentation in schizophrenia. We argue that flat affect is not a sign of schizophrenia, but rather, a *risk factor* for chronic schizophrenia.

The Phillips & Silverstein (P&S) target article provides striking evidence for the explanatory power of drug models of psychotic psychopathology, although the paper is broader than the ketamine story, touching on clinical, cognitive, electrophysiologic, neuroanatomic, and other domains. We will focus on the clinical aspects of drug models of psychosis and compare ketamine with amphetamine, with some consideration of hallucinatory processes and loss of insight. In addition, we will touch on questions related to the role of flat affect. The target article should facilitate empirical study of important questions such as differences between ketamine and competing drug models.

At present, a number of drugs tied to different neurotransmitters have been shown to provoke psychotic symptoms. Early on, LSD produced considerable interest because of the tiny dose required for an induction. It was possible to imagine that a metabolic error could produce an endogenous intoxicant. Mescaline attracted interest because of its structural similarity to dopamine, and the authority of the transmethylation hypothesis. Neither LSD nor mescaline produced a clinical presentation that had the "look and feel" of schizophrenia. It appeared that different transmitters might provide some specificity for the different psychoses: Prolonged exposure to steroids could produce states that mimicked manic psychoses, and a ditran induction shared characteristics with the alcohol-withdrawal psychoses (Alpert et al. 1970).

The amphetamine model psychosis provides the "look and feel" of paranoid schizophrenia and nests nicely with the dopamine hypothesis of schizophrenia. Because of the risk of cardio-toxic effects, the rate of dosing of amphetamine must be slow, and the rate and duration of dose increase may be important for the amphetamine model (Alpert & Friedhoff 1980). Many of these issues appear accessible to empirical study within the conceptual framework of the P&S article. The amphetamine model seems more attractive than ketamine for a number of reasons. A model should demonstrate a schizophrenic presentation without altering consciousness, and ketamine is an anesthetic. It has a narrower range of action below a threshold for clouding.

In addition, the hallucinatory phenomena with ketamine are less compelling: The hallucinations are more mixed with illusions and there is a shift to visual compared with auditory changes. In surveys of hallucinations in schizophrenic patients (Alpert & Silvers 1970), about 50% of the patients reported auditory hallucinations and about 20% reported visual hallucinations, and all of the patients with visual hallucinations also had auditory ones. Schizophrenic hallucinations are primarily verbal, of high intelligibility, and give the impression of "thoughts becoming audible." The alcoholic auditory hallucinations resemble "sounds becoming

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.