Peeling the onion: NMDA dysfunction as a unifying model in schizophrenia

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Abstract: *N*-methyl-d-aspartate receptor (NMDAR) dysfunction plays a crucial role in schizophrenia, leading to impairments in cognitive coordination. NMDAR agonists (e.g., glycine) ameliorate negative and cognitive symptoms, consistent with NMDAR models. However, not all types of cognitive coordination use NMDAR. Further, not all aspects of cognitive coordination are impaired in schizophrenia, suggesting the need for specificity in applying the cognitive coordination construct.

Although neuropsychological dysfunction in schizophrenia has been extensively characterized, the majority of studies have focused on anatomical, rather than neurophysiological, characterizations. The article by Phillips & Silverstein (P&S) highlights the critical but long neglected need to peel away the layers that separate overt behavior from underlying neurophysiological mechanisms, and then to build new conceptualizations of schizophrenia from the bottom up.

The pattern of neuropsychological dysfunction in schizophrenia, in general, fits poorly with predictions of dopamine models. The review by P&S highlights an important alternative hypothesis wherein a single ongoing deficit in *N*-methyl-d-aspartate receptor (NMDAR) transmission could account for both the symptomatic and the neuropsychological features of the disorder. Deficits in perceptual organization are particularly difficult to shoehorn into dopamine theories of the disorder. In contrast, this type of deficit is an expected and anticipated consequence of NMDAR dysfunction. The review by P&S points out an intermediate mechanism, impaired cognitive coordination that labels a class of interaction contributing to cognitive dysfunction in schizophrenia.

Basic support for the NMDAR models of schizophrenia comes from the observation that phencyclidine (PCP), ketamine, and other NMDAR antagonists induce symptoms that closely resemble negative and cognitive symptoms of schizophrenia. Moreover, the pattern of dysfunction induced by NMDA antagonists closely resembles the pattern observed in schizophrenia. For example, the AX-type Continuous Performance Task (AX-CPT) is a test designed to evaluate working memory/executive dysfunction (Cohen & Servan-Schreiber 1992). In this task, subjects respond to a specific sequence of letters (*A* followed by *X*) presented sequentially on a computer screen while ignoring all other sequences. We (Javitt et al. 2000) have observed, as have others (Cohen et al. 1999a), that stabilized patients with chronic schizophrenia show persistent deficits in the ability to inhibit responses following presentation. In a parallel study performed by Umbricht and coworkers (Umbricht et al. 2000), an identical pattern was observed following ketamine administration to normal volunteers (Fig. 1).

In both cases, deficits were observed only in the AX (correct detection) and BX (invalid cue) conditions. Neither persons with schizophrenia nor ketamine volunteers showed false alarms to invalid targets, indicating a selective deficit in executive processing rather than a generalized performance deficit. Further, in both cases, the magnitude of deficit was similar at short and long ISI (Interstimulus interval), indicating that deficits were a result of deficits of encoding the go/no-go contingency, rather than failure in information retention. The difference in pattern is critical since dopaminergic mechanisms, in general, are involved in information retention, whereas NMDAR mechanisms are involved in initial encoding. The pattern of dysfunction in schizophrenia, following stabilization, thus corresponds to the pattern induced by ketamine challenge in normals and the pattern predicted by basic conceptualizations of NMDAR function.

Most recently, Javitt et al. (2001) have also investigated the ability of an NMDAR agonist, glycine, to reverse AX-CPT deficits in schizophrenia (Fig. 2). In our study, AX-CPT performance was evaluated prior to and following 6 weeks of treatment with either glycine ($n = 5$) or placebo ($n = 6$) added to typical or atypical antipsychotics. Patients showed significant improvement in negative and cognitive symptoms during treatment with glycine but not placebo (Javitt et al. 2001). A parallel improvement in BX errors was observed in the AX-CPT. During glycine treatment, a significant reduction in BX errors was observed at both short ($p = .06$) and long ($p < .03$) ISI. In contrast, rates of BX errors during placebo treatment were unaffected, leading to significant between-group difference in improvement at both short ($p < .05$) and long ($p < .03$) ISIs. The effects of glycine on AX-CPT were over and above any degree of improvement that had occurred during antipsychotic stabilization. Therefore, P&S are correct that deficits in working memory/executive processing, as measured with tests such as the AX-CPT, may reflect underlying NMDAR dysfunction.

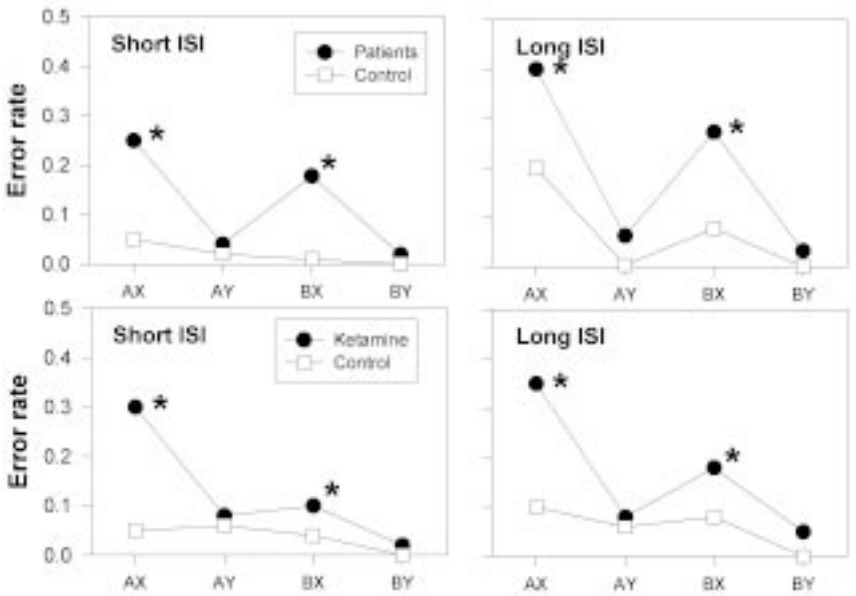


Figure 1 (Javitt). Performance of schizophrenia patients (top row) and ketamine-treated normal controls (bottom row) on the AX-type continuous performance task (AX-CPT). Note increased rates of omission (AX) errors, and increased false alarm rates only to BX-type trials in both groups. Schizophrenia data is from Javitt et al. 2000. Ketamine challenge data is from Umbricht et al. 2000. *$p < .05$

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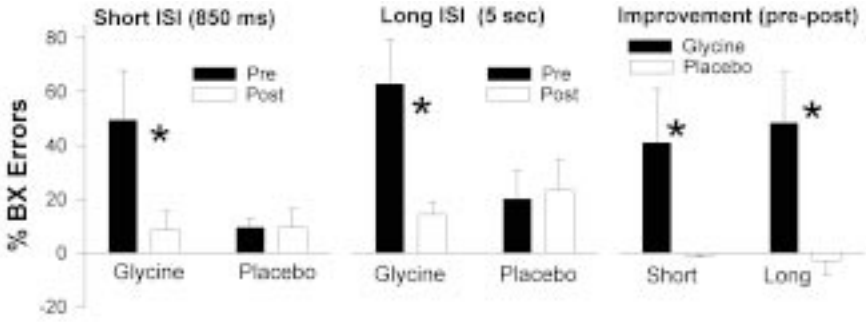


Figure 2 (Javitt). Rates of BX errors on the AX-type continuous performance task (AX-CPT) in patients with schizophrenia prior to and following treatment with glycine (an NMDA agonist) or placebo. Note decrease in BX error rate from pre- to post-treatment at both short (left panel) and long (center panel) interstimulus intervals (ISI) following treatment with glycine but not placebo. This improvement was significantly greater in the glycine, than placebo, group (right panel). *$p < .05$

Although we agree with P&S about the role of NMDAR dysfunction in schizophrenia, we are concerned that "cognitive coordination," while broader than the previous conceptualizations such as "executive processing" or "working memory," still does not capture both the breadth and specificity of NMDAR-related phenomena in schizophrenia. For example, NMDARs play a crucial role in regulating subcortical dopamine systems (Balla et al. 2001; Kegeles et al. 2000). While this type of interaction does not fit easily within the "cognitive coordination" rubric, it is nevertheless a critical mechanism whereby a single neurochemical deficit, NMDAR dysfunction, could lead to complex dopaminergic dysfunction such as is observed in schizophrenia.

Similarly, in our studies of sensory processing, my colleagues and I have demonstrated that despite having severe bottom-up deficits, patients show minimal top-down deficits. Thus, in the auditory system, patients show elevated tone-matching thresholds but no increase in distractibility (Rabinowicz et al. 2000). Similarly, in the visual system, patients require greater detail before they can identify fragmented images but show relatively normal benefit from stimulus repetition or verbal cueing (Doniger et al. 2001). Both bottom-up and top-down elements of these tasks require cognitive coordination. Therefore, the need for coordination between brain regions, of itself, does not seem to predict which class of functions will be impaired in schizophrenia.

In the visual system, perceptual organization deficits, such as those observed by Silverstein and others, most likely arise because of impaired magnocellular input in dorsal stream visual areas (Butler et al. 2001), giving rise to impaired recurrent processing within the ventral stream object recognition areas as described by Schroeder and others (Schroeder 1995). Contrast gain within the magnocellular system is a process that explicitly depends upon NMDAR-mediated nonlinear amplification mechanisms (Kwon et al. 1992). Other aspects of cognitive coordination may or may not, depending on the specific underlying brain substrates. Current literature suggests that those aspects of cognitive coordination that depend upon NMDAR activation are impaired in schizophrenia. Those that are unaffected by NMDAR antagonists (e.g., ketamine, PCP), in contrast, appear to be unimpaired. Therefore, while the cognitive coordination construct adds to our understanding of mediating mechanisms in schizophrenia, it is NMDAR involvement that serves as the necessary and sufficient condition for predicting patterns of cognitive dysfunction in schizophrenia.

Is sensory gating a form of cognitive coordination?

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Abstract: Neurophysiological investigations of the past two decades have consistently demonstrated a deficit in sensory gating associated with schizophrenia. Phillips & Silverstein interpret this impairment as being consistent with cognitive coordination dysfunction. However, the physiological mechanisms that underlie sensory gating have not been shown to involve gamma-band oscillations or NMDA-receptors, both of which are critical neural elements in the cognitive coordination model.

As evidence to support a unified model of cognitive dysfunction in schizophrenia, Phillips & Silverstein (P&S) interpret "sensory gating" abnormalities as a form of impaired cognitive coordination. To qualify as such, however, sensory gating must satisfy phenomenological and physiological requirements. It would be hard to argue that sensory gating *isn't* a form of cognitive coordination as delineated by P&S, as any sensory stimulus can modify the context of any other stimulus, provided they are proximal in space and/or time. The physiological proposition, on the other hand, is more amenable to critical evaluation.

Sensory gating has traditionally been investigated as the reduction in amplitude of middle latency auditory evoked potentials as a result of stimulus repetition. For example, Adler et al. (1982) were the first to demonstrate that wave P50 (also P1 or Pb) diminishes in size from one acoustic click to the next for healthy individuals, but not for those afflicted with schizophrenia. This was demonstrated with a "paired-click" paradigm, in which a pair of clicks (0.5-second interclick interval) was presented every 10 seconds. Sensory gating was quantified as the ratio of P50 amplitude evoked by the second ("test") click of the pair to that evoked by the first ("conditioning") click. The observed impairment in response-suppression, manifest as a test-response/conditioning-response ratio near 1 compared with a ratio near 0 for controls, was suggested to underlie schizophrenia patients' common complaint of an inability to ignore, or "gate out" irrelevant sensory information. The *preattentive* nature of this impairment has recently been supported by sensory gating measurements taken during states of sleep (Kisley et al. 2003).

Sensory gating, as measured with the paired-click paradigm, is to be distinguished from *sensorimotor gating,* in which a warning stimulus tends to reduce the magnitude of startle movement elicited by a loud sound ("prepulse inhibition"). Even though abnormalities in sensorimotor gating have also been reliably demonstrated in schizophrenia, the relevant neural mechanisms differ from those of P50 gating (Braff et al. 2001). Sensory gating is also

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