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...
to be distinguished from the preattentive processing function(s) measured with the mismatch negativity (MMN) paradigm, the latter being associated with increased cortical activity elicited by stimulus novelty (Picton et al. 2000), as opposed to decreased activity due to stimulus redundancy.

In the terminology of (P&S), the conditioning click in the traditional sensory gating paradigm modifies the salience and subsequent neural processing of the test click. This is consistent with the phenomenological constraints of cognitive coordination. However, do the neural mechanisms that mediate sensory gating involve coordinating activity of gamma-band oscillations through NMDA-receptors, as specified in the physiological portion of P&S’s cognitive coordination model?

Regarding oscillations in the gamma-band, there is substantive evidence that neuronal oscillatory activity in the 20–50 Hz range—which is known to be abnormal in schizophrenia patients (Kwon et al. 1999)—is involved in the generation of middle latency auditory evoked potentials (Basar et al. 1987). In the context of sensory gating, the results of a preliminary investigation by Clementz et al. (1997) involving 10 schizophrenia patients and 10 controls suggested a possible link between the magnitude of gamma-band response and P50 suppression. However, a more recent study of 20 patients and 20 controls concluded that low frequency activity (<30 Hz) is a more important contributor to the suppression of middle latency evoked potentials in response to repetitive stimulation (Clementz & Blumenfeld 2001). For example, evoked potentials shown in both reports suggest that the 20–50 Hz oscillations evoked by the conditioning click expire before the test click occurs. Given this, it is difficult to imagine how gamma-band oscillations could serve to “coordinate” the contextual relationship between the first and second clicks.

To date, the only evidence that NMDA-channels might play a role in sensory gating comes from pharmacological studies in a rodent model. Adler et al. (1986) demonstrated that sensory gating is disrupted in rats when an NMDA-antagonist—phencyclidine (PCP)—is administered. However, a subsequent investigation concluded that this effect does not occur through NMDA-receptor blockade, but rather by an indirect pathway involving a noradrenergic mechanism (Miller et al. 1992). More recently, two studies were conducted to determine whether NMDA-channels might still be important for sensory gating in humans (Oranje et al. 2002; van Berckel et al. 1998). Both studies showed that ketamine, another NMDA antagonist, does not disrupt sensory gating as measured by the paired click paradigm. Although glutamatergic neurotransmission appears to be involved in the generation of wave P50, other neurotransmitter and receptor systems—particularly nicotinic-cholinergic—play a more central role in the suppression of this wave during the paired-click paradigm (Adler et al. 1998b).

In summary, evidence to support the claim that sensory gating is mediated by the physiological mechanisms described in the cognitive coordination model of P&S is lacking. On the other hand, sensory gating deficits could still play a role in cognitive coordination dysfunction. As summarized by P&S, and originally proposed by Venables (1964), the inculcation that would result from an inability to filter out irrelevant sensory stimulation could lead to cognitive fragmentation. Based on this idea, a fruitful theoretical approach would be to model the mechanism by which unselected and overwhelming input signals could disrupt the subsequent formation of laterally-connected cortical networks that are central to the cognitive coordination framework.

Theory of mind in schizophrenia: Damaged module or deficit in cognitive coordination?

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Abstract: Schizophrenics exhibit a deficit in theory of mind (ToM), but an intact theory of biology (ToB). One explanation is that ToM relies on an independent module that is selectively damaged. Phillips & Silverstein’s analyses suggest an alternative: ToM requires the type of coordination that is impaired in schizophrenia, whereas ToB is spared because this type of coordination is not involved.

Phillips & Silverstein (P&S) document how schizophrenic patients exhibit deficits that may be explained by impaired cognitive coordination. The specific phenomena they discuss involve paradigms that engage perceptual and low-level semantic processes. Can this line of analysis also account for specific deficit patterns in higher cognitive and social-cognitive functioning in schizophrenia?

We summarize here work of our own and by others on the abilities of schizophrenic patients to handle “naïve theories” in two contrasting domains: Theory of mind (ToM) and theory of biology (ToB). ToM is defined as the ability to attribute mental states to the self and to others, to predict and explain their behavior with reference to mental states (Premack & Woodruff 1978). Several recent studies examined ToM in schizophrenia, and all indicate that ToM is damaged in the acute phase (e.g., Doody et al. 1998; Frith & Corcoran 1996) but returns to normal in periods of remission (Drury et al. 1998). This is a specific deficit that cannot be accounted for by IQ or memory. As is well-known, a similar specific deficit is found in the case of autism, where it is also permanent (Baron-Cohen 1995). The relation between schizophrenia and autism was pointed out by Frith (1992), who speculated that there is a common cognitive failing in these two conditions: Autists never develop a ToM, whereas schizophrenics attempt to exercise a lost capability.

One way of testing ToM in schizophrenia uses a nonverbal paradigm, where subjects are presented with cartoons (Sarfati et al. 1997). Each cartoon strip contains three pictures, depicting a character performing some activity. Understanding these strips requires deriving the mental state and goals of the character. After studying the cartoon strip, subjects are presented with three additional pictures, one of which provides a suitable ending to the story. Another filler depicts a common, everyday activity, performed by the character, and the third is very similar to the last picture in the strip. Neither of them is related to the context of the mental states of the character as established by the strip. In a variant of the task which involved an absurd filler (Sarfati et al. 1999) virtually no patients selected that option. This indicates that the patients do attempt to make sense of the task, and the paradigm makes it possible to identify the compensatory strategy used by schizophrenic patients. Lacking understanding of what the character is up to, schizophrenic patients who are not disorganized tended to select the picture that is visually similar to the last picture. Disorganized patients and manic patients tend to select familiar everyday activities, regardless of their resemblance to the preceding pictures.

We replicated these findings, and complemented them with the more common set of stories used to test ToM (Frith & Corcoran 1996). These stories involve understanding cheating and false beliefs, either “first-order beliefs,” requiring distinguishing the beliefs of characters from the true state of affairs, or “second-order beliefs,” about others’ beliefs. These stories are read aloud, and simple drawings help the subjects follow and remember the plots. Schizophrenics performed significantly worse than the control groups (both normals and affective-disorders hospitalized patients).