Neuromodulation of Attention in Schizophrenia

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Schizophrenia has long been thought to be characterized by a profound disturbance of attention. As early as 1919 in his classic Praecox and Paraphrenia, Kraepelin wrote of the peculiar mixture of over- and under-attention in patients with schizophrenia, which he described as:

“It is quite common for them to lose both inclination and ability on their own initiative to keep their attention fixed for any length of time. The patients digress, do not stick to the point, let their thoughts wander without voluntary control in the most varied directions. On the other hand the attention is often rigidly fixed for a long time, so that the patients stare at the same point, or at the same object, continue the same line of thought, or do not let themselves be interrupted in some definite piece of work. Further it happens that they deliberately turn away their attention from those things to which it is desired to attract it, turn their backs when spoken to and turn away their eyes if anything is shown to them. But in the end there is occasionally noticed a kind of irresistible attraction to casual external impressions.”

The prescience of Kraepelin’s description was that like William James he understood the heterogeneity of attention or the “varieties of attention” ——- the many functions and mental operations that are subsumed under the psychological construct of attention. Kraepelin’s writing suggested that schizophrenia-related attentional impairments could be characterized on a number of relevant dimensions of contemporary models of attention, ranging from automatic and involuntary to controlled and conscious. In this sense, schizophrenia, perhaps unlike any other disease, illustrates the distributed nature of attention in the human brain, and how disease-related cognitive impairment may originate from a relatively subtle disturbance in either one or more attention brain systems.

What might be the neural underpinnings of the schizophrenic attentional disturbance? Schizophrenia lacks the type of definitive neuropathological signature that has been established for other brain diseases, such as Alzheimer’s disease or Parkinson’s disease. It is, however, almost invariably thought to have a pronounced effect on brain chemistry, especially on two critical neurotransmitter systems: dopamine and glutamate. The properties and dynamics of these systems, specifically as they relate to modulation and amplification of neuronal circuits, may very well be linked to the properties and functions ascribed to the psychological construct of attention. Consider that dopamine represents one of the most prominent modulatory neurotransmitters of the central nervous system, which is invariably disrupted by schizophrenia. Consider also that schizophrenia often produces a state of excessive dopamine in some brain sites and reduced dopamine in other brain regions, a condition that may be best characterized by disease-related dysregulation of dopamine. Consider finally that disturbances in dopaminergic transmission have been linked to problems with various aspects of attention and working memory, and disturbances in these cognitive domains are often central to the disease.

Glutamate represents another important neurotransmitter, one putative function of which is to constrain activation of local neuronal circuits by recurrent inhibition. In fact, glutamatergic antagonists selectively disrupt recurrent inhibition. These antagonists, as for example the N-methyl-D-aspartate (NMDA) glutamatergic receptor antagonists, also produce psychotomimetic effects, which are thought to mimic many of the classic symptoms of schizophrenia. These NMDA receptor antagonists, most notably phencyclidine (PCP) or ketamine, have provided a compelling pharmacological model for many of the positive and negative symptoms of schizophrenia. Of added interest is that the mechanisms by which these NMDA receptor antagonists produce psychotomimetic effects have been closely linked to dopaminergic transmission.

In this paper, we first present a neuropsychological model of attention that serves as a heuristic framework to examine how schizophrenic impairments in specific attentional processes might originate from a disease-related disturbance in neurotransmission. Here we emphasize the attentional sequelae of putative dopaminergic dysregulation from various levels of description, ranging from that of basic signal processing of neuronal circuits to networks and systems levels of cognition and brain organization. In addition, from in vitro “realistic” cellular models, we consider evidence that glutamatergic-mediated
recurrent inhibition may represent an important property of neuronal circuitry, which promotes the essence of attention, that is signal and informational selectivity, but which also might be compromised by schizophrenia.

Neuropsychology of attention

A heuristic model. Neuropsychological models are often derived from observations of the effects of localized lesions on various aspects of cognition, emotion, and behavior. These models typically place less emphasis on how these lesions might have affected neurotransmission, and the putative neuropsychological sequelae of these neurochemical effects. This of course is hardly surprising given that neurotransmitters and neuropharmacological agents, such as dopamine antagonists, affect multiple sets of receptors in distinct and sometimes opposite ways so that only tentative inferences about location and mode of action can be made. In the absence of a clear understanding of location and mode of action of selective neurotransmitters, any inferences about their potential contributions to function will be even more difficult to elucidate and to support. Moreover, the relationship between function and neurochemistry may also be more dynamic and widely distributed throughout the brain than many of the brain–behavior relationships that are often the concern of traditional neuropsychology.

To examine dynamic relationships of function and neurochemistry, we apply a neuropsychological model of attention that emphasizes three levels of description: circuits, networks, and systems. These levels differ in terms of scale, content, and function. At the most basic level, attention is seen as enhancing signal processing of local neuronal circuits by constraining and amplifying content–free activation. Bound by both time and space, these local circuits are organized to form distributed networks that support symbol processing. Network communication is facilitated by attention, which is often represented and simulated by idealized synapses of connectionist models. These networks in turn help form wide–scale neural computational systems of perception, memory, language and other higher–order cognitive modules in which the role of attention is to insure the fidelity of computational contents. Thus in this model, brain and function are composed of constituent operations and processes that are supported by discrete local circuits that act in concert to form widely–distributed networks and large–scale systems. Attention and its derivative cognition emerge as a product of intricate relationships between and among brain circuits, networks, and systems, all of which may be modulated and reconfigured by neurochemical dysregulation.

Normal attentional effects. Among the most influential of the various conceptual and operational definitions of attention is one that views attention as a limited source of general resources, energy, electricity, effort, or fuel for cognition. Subsequent iterations of these so–called energetic models of attention have emphasized local domain–specific resource pools that are dedicated to supporting distinct functions, such as verbal and spatial cognition. In the past decade, the energetic view of attention has gained considerable neurological validity, with several neuroimaging studies of both animals and humans clearly demonstrating selective and specific attention effects on neural circuits. These studies have largely shown that attention selectively modulates neuronal response by either facilitating or sharpening firings of already activated cells or by suppressing or inhibiting neighboring deactivated cells. Interestingly, catecholamines have been shown to exert similar modulatory effects on target neurons, and these effects have often been referred to as “potentiation” of excitation or inhibition. As summarized by Servan–Schreiber and Cohen, “… norepinephrine and dopamine appear to produce a sharpening of the behavior of the cell —– a potentiation of its response to the same stimuli.” (p. 127).

These attention effects are therefore distinct from those that might be linked to arousal. Attention unlike arousal modulates only those circuits that are activated in response to specific information processing demands, as for example stimulus encoding or perceptual discrimination. It therefore exerts a specific effect unlike the nonspecific effect of arousal. Moreover, attention effects extend beyond neuronal circuitry to brain networks and systems that support high–level cognition. As cognition become more intensive or demanding, attention is called to help drive the computational machinery. For example in a functional MRI study of sentence comprehension, Just et al. demonstrated that the increasing linguistic complexity of sentences produced a proportionate increase of activation of
the classical left hemisphere language system in healthy controls

**Dopamine dysregulation and schizophrenic attention**

Attention therefore represents a critical concept of neuropsychology of schizophrenia that is especially well suited to the study of dopamine dysregulation in schizophrenia. The evidence is less direct, but still quite convincing for the regulation of attention by various neurotransmitter systems, with dopamine being one of the most important. For example, studies of healthy subjects administered catecholamine (e.g., dopamine) antagonists have demonstrated attention disturbances that are remarkably similar in form to those of medicated schizophrenic patients. In these studies, subjects performed a well-known visual attention task in which facilitation and inhibition are isolated (Posner, 1980). The striking finding of these studies was that both medicated schizophrenics and healthy controls administered catecholamine antagonists showed evidence of a similar pattern of attention disturbance. In both studies, subjects showed relatively faster reaction time (RT) to visually cued targets, but failed to show the expected slowing in RT to unpredictable, unexpected, visual targets preceded by invalid cues. This reflected a fairly distinctive pattern of facilitation and inhibition of attention, one that differed from that observed in neurological patients with posterior parietal lobe damage using the identical RT paradigm.

**Facilitation and inhibition.** These findings therefore suggested normal facilitation of attention by a valid cue, but abnormal inhibition of attention by an invalid cue for both schizophrenic patients and healthy subjects administered catecholamine antagonists. In addition, in relation to normal controls, medicated schizophrenic patients showed slightly, but not statistically faster RT validly cued targets --- an unexpected finding that may be indicative of hyper-facilitation. As with many drug studies with humans, however, these results failed to establish a selective and specific relationship between abnormal inhibition of attention and dopaminergic transmission. In fact, healthy subjects showed a similar pattern of results when administered either noradrenergic or dopaminergic antagonists. More recent studies, though, have suggested noradrenergic agents might be less important to specific facilitation or inhibition of attention and more important to maintaining a general level of alertness so as to reduce lapses in attention. The significance of these studies then is that they provide indirect evidence of an attention disturbance in schizophrenia characterized by an imbalance of facilitation and inhibition that may correspond with the disease-related dysregulation of catecholamines, especially dopamine.

Nestor et al. provided a more direct test of the hypothesis of dopaminergic-attention dysregulation in schizophrenia by comparing neuroleptic-withdrawn and medicated (conventional) patients on a relatively precise, experimentally controlled measure of sustained visual attention. The task, a version of the continuous performance task (CPT), presented perceptually degraded numbers (0–9), rapidly and singly, with zero as the pre-designated, infrequent target to which the subject made a speeded response. This task has been demonstrated to be superior to other conventional versions of the undegraded CPT that are often marred by ceiling effects in healthy controls apparently because of the ease with which undegraded targets are identified. Moreover, in relation to convention forms of the undegraded CPT, only the degraded CPT distinguished children at risk for schizophrenia from other contrast groups, including hyperactive children with attention deficit disorders.

When comparing neuroleptic-withdrawn and medicated schizophrenic patients on this same degraded CPT, Nestor et al. found that both groups showed evidence of attention abnormalities, although the neuroleptic-withdrawn patients showed more pronounced deficits. In particular, in relation to the medicated patients, the neuroleptic-withdrawn patients showed significantly reduced perceptual sensitivity and a more rapid decline in perceptual sensitivity over time on task, with the latter interpreted as evidence of problems maintaining a selected area of focus. By contrast, both groups showed similar responses on a measure of response bias considered to be unrelated to attention processes. Thus, these findings provided evidence of a fairly specific schizophrenic abnormality in sustained attention, which requires the effective balance of facilitation and inhibition, and which might be improved but not normalized by anti-psychotic agents.
More recently, Salo Robertson, and Nordahl\textsuperscript{35} provided additional evidence of dopaminergic involvement in the schizophrenic attention disturbance. These researchers compared selective attention of 12 unmedicated schizophrenic outpatients and 16 matched controls on a Stroop task. They found that both groups showed the expected Stroop–interference effect, as reflected, for example by slower response time to naming the ink color of the word RED printed in green ink. Salo et al. also examined the phenomenon known as negative priming, which holds that a previous distractor–turned–target will produce slower response times than a novel target. The idea is that the build–up of inhibition to the previous distractor–turned–target slows response time. Negative priming therefore provides a measure of the degree of efficiency of prior selection, even though it serves to interfere with current selection. It represents one of the few instances where schizophrenic patients might be viewed as outperforming controls by showing less interference, presumably because of reduced inhibition of a previous distractor. In fact, Salo et al demonstrated reduced negative priming in these unmedicated patients in relation to normal controls. Moreover, the results also suggested that some patients actually responded faster to those stimuli that were prior distractors, a pattern resembling a hyper–priming effect in schizophrenia that has been reported using other types of cognitive paradigms.\textsuperscript{36,37,38} Taken together, these results suggested a schizophrenic pattern of attention marked by hyper–facilitation and hypo–inhibition.

**Symbol processing and attention.** Attention effects extend beyond the signal processing level of neuronal circuits to the network levels of cognition and brain organization. In connectionist models that are intended to emulate information–processing characteristics of distributed neural networks, attention serves to modulate information processing, causing a shift in responsiveness of units in competing processing pathways.\textsuperscript{39} Words are represented as networks of interconnected nodes, with each node (e.g., phonological, semantic, orthographic) corresponding to an idealized neuron and each link corresponding to an idealized synaptic weight.\textsuperscript{40} Attention is thought to modulate synaptic weights that connect local circuits that form distributed networks. Effective neuronal computation and network communication depend on effective and efficient modulation of synaptic weights.

Nelson et al.\textsuperscript{41} applied a connectionist network model to study word recall in healthy subjects. They proposed that the activation and recall of a word is a function of both the size and degree of connectivity of its network. In so doing, they developed a word recall paradigm to isolate the effects of network size and connectivity on associative memory in healthy subjects. The paradigm consisted of four types of words: 1) high connectivity–small network size (e.g., waves, wife, zoo), 2) low connectivity–small–network size (e.g., cap, clock, hive); 3) high connectivity–large network size (e.g., bottle, cloth, flute); and 4) low connectivity–large network size (e.g., blood, party, rabbit). In the Nelson et al. studies, subjects first study a list of words consisting of equal proportions of these four types, followed by a cued recall test in which word cues and targets are equated on both connectivity and network size. In several carefully controlled experiments Nelson and colleagues have consistently found best recall performance for words of high connectivity–small network (e.g., wife cued by spouse), followed by low connectivity–small network (e.g., clock cued by time), then by high connectivity–small network size (e.g., bottle cued by cork), and last by low connectivity–large network (e.g., party cued by birthday).

We\textsuperscript{42} recently used the same associative memory paradigm\textsuperscript{41,43} to examine how connectivity and network size might modulate word recall in schizophrenia. In our study, schizophrenic patients and normal comparison subjects first studied each of the 32 words presented singly, followed by a cued recall test. The comparison subjects showed the expected effects, with the best recall for words of high connectivity–small network size, followed by words of low connectivity–small network size, then by words of high connectivity–large network size, and finally by words of low connectivity–large network size. By contrast, for the patients, regardless of network size, recall improved substantially for words of high connectivity and declined dramatically for words of low connectivity. These findings suggested that schizophrenia might selectively compromise the associative links that bind networks. In connectionist models, these associative links are intended to emulate idealized synaptic weights, which are thought to be modulated by attention. These results therefore suggested that the associative disturbance of schizophrenia, long considered a hallmark of the disease since the time of Bleuler, might very well be related to an attention failure in the modulation of idealized synaptic weights.

**NMDA Modulation of Recurrent Inhibition: A Cellular Mechanism of Schizophrenic**
Attention Disturbance?

Attention influences processing throughout the various levels of the central nervous system, from the relatively low level of neuronal circuits, to distributed networks, to wide-scale brain systems. Single-cell attention effects produce selective and specific facilitation or inhibition of dedicated neuronal circuits. The precise cellular mechanisms by which facilitation and inhibition operate are unknown, although both psychological and physiological models have converged on recurrent inhibition as critically important to the integrity of neural circuitry and cognitive architecture.

Recurrent inhibition represents a key element of neural circuitry that serves to maintain and contain activation. For example, a simplified version of a neural circuit consists of a projection neuron, a target neuron, and an inhibitory inter-neuron. Recurrent inhibition of the circuit occurs when activation from the projection neuron to the target neuron is constrained by the inhibitory inter-neuron that is typically thought to be GABAergic. By preventing the collateral spread of activation, recurrent inhibition ensures that activation is largely contained within the circuit. Analogous mechanisms are thought to operate in computation models of cognition. Indeed, efficient and effective cognition depends in large part on the capacity of the information processing architecture to maintain stability by reducing activation. Whereas recurrent inhibition insures stability of neuronal circuits, an analogous role for activation reduction in cognition has long been ascribed to attention, the principal function of which is to enhance informational selectivity by resolving competition through facilitation and inhibition. Its effects are thought to extend well beyond signal processing, and recurrent inhibition might be critical to competition and selection in higher order cognition, such as perception and associative memory.

In vitro simulations. Grunze and colleagues examined recurrent inhibition of local hippocampal circuits in region CA1of the rat brain. In their biophysical simulations of neuronal circuitry, they examined the effects of NMDA antagonists, known for their psychotomimetic and cognitive-imparing effects that are thought to be central to the pathophysiology of schizophrenia. Grunze et al. first demonstrated that activated projection neurons excited GABAergic inhibitory inter-neurons, which in turn inhibited other projection neurons within the circuit. They further demonstrated that this recurrent inhibition of the circuit by these inhibitory inter-neurons emerged as a result of effective modulation of glutamatergic NMDA receptors. Moreover, Grunze et al. showed that the now effectively self-contained circuit produced long-term potentiation, the sine qua non of cellular learning.

These researchers next manipulated these circuits by introducing NMDA antagonists, such as ketamine. Recurrent inhibition dampened if not evaporated, and the once effectively constrained circuit activation became fraught with asynchronous reverberation and random perturbations. In addition, when Grunze and colleagues partially blocked recurrent inhibition with NMDA antagonists, the circuit showed evidence of the type of cognitive disturbances in humans that are often produced by NMDA antagonists and are generally viewed as central to schizophrenia. Specifically, the circuit no longer could distinguish among patterns that had overlapping elements. These results thus suggested that a known psychotomimetic drug, ketamine, disrupted recurrent inhibition, and the ensuing aberrant spread of excitation reduced the perceptual sensitivity (signal to noise ratio) of the local circuit to make fine pattern discriminations.

Ketamine is known to disrupt both dopamine and glutamate transmission, and single exposure to ketamine or related phencyclidine may produce cognitive, affective, and behavioral disruptions similar to those that accompany schizophrenia. As a result, these drugs have provided a compelling neuropharmacological model of schizophrenia. That these agents disrupted neuronal recurrent inhibition may provide a specific cellular mechanism for the disturbances in cognition and attention that they invariably produce. Moreover, that virtually all computational models of cognition include analogous mechanisms of inhibition renders these biophysical simulations all the more relevant to developing realistic neuropharmacological-neuropsychological models of schizophrenia. Finally, recurrent inhibition provides a specific cellular model that sheds light on how attention effects of facilitation and inhibition might be mediated by neurotransmission.

Conclusion
Schizophrenia disrupts the intimate balance between facilitation and inhibition, leading to a dysregulation of attention.\textsuperscript{18} It affects both low and high levels of information processing, influencing basic abilities of visual perception to complex computations of reasoning and judgement. The effects of the schizophrenic attention disturbance are seen on neuropsychological tasks that require conscious, effortful processes related to, for example, working memory, such as digit span exercises. These effects are also evident on basic psychophysical tasks such as visual masking that largely involve mental computations that may be considered pre–attentive and unconscious.\textsuperscript{37} Moreover, the dysregulation of attention may lead to the faulty percepts that often characterize schizophrenic thought. For example, hyper–facilitation and hypo–inhibition might result in special significance being attributed to incidental details, irrelevant associations, coincidences, or sensory experiences. All of these phenomena would remain dormant or be otherwise dismissed by a regulated and balanced attention system.

There is no one neurotransmitter system that is responsible for the many functions and properties related to attention. Even by narrowing attention to those processes that selectively and specifically facilitate and inhibit neuronal circuits fails to provide any strong leads as to the specific dynamics of its underlying neurotransmission. Dopamine, for example, is generally thought to act as an inhibitory neurotransmitter, although its role will depend on a host of other factors including its interaction with other neurotransmitters, anatomical projections, and sites of action. Dopaminergic and related glutamatergic neurotransmitter systems are nonetheless central to the expression of the disease, close to representing the neurochemical signature that the disease has historically lacked. The empirical evidence reviewed above suggested that dopaminergic dysregulation might very well be critical to the disruption of the balance of specific attentional functions of facilitation and inhibition in schizophrenia. These attentional effects may in turn operate across various levels of brain organizations —– from signal processing of local neuronal circuits, to word association of neural networks, to thought and reasoning of large–scale neural systems. Moreover, these abnormal attention effects may emerge from a failure of glutamatergic–mediated recurrent inhibition of discrete but widely distributed neural circuits. The foregoing description awaits further empirical scrutiny, but represents a foundation for developing verifiable and falsifiable neuropsychological model of schizophrenic dysregulation of attention that has been considered a cardinal characteristic of the disorder since the time of Kraepelin.\textsuperscript{1}

References


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Questions for "Neuromodulation of Attention in Schizophrenia"

1. Schizophrenia has long been thought to be characterized by a profound disturbance of what function?
   A) attention
   B) motivation
   C) arousal
   D) digestion

   Answer: A

2. What are the critical neurotransmitter systems affected by schizophrenia?
   I) serotonin
   II) dopamine
   III) glutamate
   IV) ketamine

   A) I, II, & III
   B) I & II
   C) II & III
   D) II, III, & IV

   Answer: C

3. What pharmacological substances cause schizophrenia-like symptoms?
   I) ketamine
   II) phencyclidine (PCP)
   III) NMDA receptor antagonists
   IV) glutamatergic receptor agonists

   A) I & II
   B) II & III
   C) II, III, & IV
   D) I, II & III

   Answer: D

4. What view describes attention as a limited source of general resources, electricity, effort, or fuel for cognition?
   A) endothermic
   B) energetic
   C) evolutionary
   D) orthogonal

   Answer: B

5. What do results suggest when catecholamine antagonists are administered to both schizophrenia patients and healthy subjects?
   I) abnormal facilitation of attention by a valid cue
II) normal facilitation of attention by a valid cue
III) abnormal inhibition of attention by an invalid cue
IV) normal inhibition of attention by an invalid cue

A) I & III
B) I & IV
C) II & III
D) II & IV

Answer: C

6. Which test of attention distinguished children at risk for schizophrenia from other contrast groups, including hyperactive children with attention deficit disorders?

A) Degraded Continuous Performance Test
B) Rorshack Ink Blot Test
C) Undegraded Continuous Performance Test
D) Scholastic Aptitude Test

Answer: A

7. What phenomenon holds that a previous distractor-turned-target will produce slower response times than a novel target?

A) psychopathology
B) positive priming
C) negative priming
D) premonition

Answer: C

8. Which of the following is characteristic of “recurrent inhibition”?

I) It occurs when activation from the projection neuron to the target neuron is constrained by the inhibitory inter-neuron that is typically thought to be GABAergic
II) It ensures that activation is largely contained within the circuit
III) It might be critical to competition and selection in higher order cognition
IV) It increases instability in neuronal circuits

A) I & IV
B) I, II, & III
C) I, II, & IV
D) II & IV

Answer: B