

Interactive report

# Gating of information flow within the limbic system and the pathophysiology of schizophrenia<sup>1</sup>

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## Abstract

Although first thought of as a dopaminergic disorder, there is little direct evidence to support a primary pathology in the dopamine system as the etiological factor in schizophrenia. In contrast, evidence is amassing in support of a cortical disturbance in this disorder; one consequence of which is a disruption in the cortical regulation of subcortical dopamine systems. Our studies show that the hippocampus plays a major role in this interaction, in that, along with the dopamine system, it provides a gating influence over information flow from the prefrontal cortex at the level of the nucleus accumbens. Moreover, chemically-induced disruption of the development of the hippocampus and entorhinal cortex were found to lead to pathophysiological changes in these interactions in the limbic system of adult rats. Therefore, schizophrenia is proposed to be a developmentally-related disorder, in which disruption of the hippocampal influence over the limbic system during ontogeny results in a pathological alteration of corticoaccumbens interactions in the adult organism. © 2000 Elsevier Science B.V. All rights reserved.

*Keywords:* Schizophrenia; Nucleus accumbens; Prefrontal cortex; Hippocampus; Amygdala; Dopamine; Glutamate

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## 1. Introduction — the dopamine hypothesis of schizophrenia

For years, investigators have examined the human brain in a search for the etiology of schizophrenia using pharmacological and anatomical approaches. Nonetheless, only recently have these studies begun to yield information of relevance to advancing our understanding of this complex disorder. One of the initial models of schizophrenia that has been fruitful in this quest relates to the involvement of the neurotransmitter dopamine (DA). This model, which has become known as the DA hypothesis of schizophrenia, is based on several pieces of compelling evidence. Among these is the finding that drugs that increase DA release within the brain will mimic several aspects of the schizophrenic psychosis in normals, and will exacerbate the psychotic symptoms in patients with schizophrenia [5,59,113]. Moreover, all drugs currently in use that are effective at treating schizophrenia block DA receptors within the brain [22,29,106]. This evidence led to the hypothesis that schizophrenia may be due to a hyperdopaminergic state [120].

Upon closer examination, the simplest form of the DA model proved to be inadequate to account for the pathophysiology of this complex disorder. Thus, although drugs such as amphetamine will mimic at least the paranoid type of schizophrenia and exacerbate positive symptoms [3,4], this is accompanied by a substantial increase in DA turnover in the brain (i.e., up to 35-fold in animal studies, [112]). In contrast, despite substantial efforts, there is little evidence for a marked increase in DA turnover in the brains of patients with schizophrenia [11,99,119]. Furthermore, although antipsychotic drugs will rapidly block DA receptors within minutes of their administration [105] and can readily reverse amphetamine psychosis, the maximal therapeutic effects are not achieved in patients with schizophrenia unless these drugs are administered for weeks [60]. This would not be consistent with a simple DA receptor blocking action, since one would predict that the maximal DA antagonism should be achieved with acute administration, whereas after repeated treatment the induction of compensatory changes in the DA system (e.g., receptor up-regulation, increase in DA synthesis, etc.) should offset the effects of the antipsychotic drug, necessitating higher dose administration. In contrast, evidence shows that once a therapeutic response is achieved, it is not necessary to increase the dose of the antipsychotic drug in order to maintain therapeutic efficacy.

One explanation for the requirement of repeated antipsychotic drug administration in the treatment of schizophrenia is the time-dependent induction of DA neuron inactivation, known as depolarization block [19,49,50]. Whereas such a condition may indeed down-regulate DA system responsiveness by preventing the DA neurons from becoming activated by potentially pathological levels of excitatory input [50], it is clear that this treatment does not

restore the system to 'normal'. Instead, antipsychotic drug-induced depolarization block appears to be an offsetting deficit introduced into what may be an otherwise normal DA system in order to compensate for the pathophysiological insult in the brain of the schizophrenic [46,47]. This raises the question as to what is the primary site of pathophysiology that can lead to such a pervasive brain disturbance? This evidence may be derived from more recent studies of metabolic activation and imaging within the brain of the schizophrenic patient.

## 2. Evidence for cortical involvement in the pathophysiology of schizophrenia

Several studies have suggested that, instead of being a neurochemical disturbance within the DA system, schizophrenia may instead represent a dysfunction in cortical systems using the neurotransmitter glutamate. This was founded on initial studies suggesting that the schizophrenia patient exhibited a tonic decrease in activity within the prefrontal cortex [9,20,39,72,73], particularly in those patients with prominent deficit syndrome [116]. This condition was termed hypofrontality. However, more recent investigations have provided contradictory evidence, suggesting that hypofrontality does not exist in the brain of the schizophrenia patient [53]. In contrast, the prefrontal cortex of afflicted individuals tends to show a diminished activation compared to controls [2,9] during tasks that require prefrontal cortical activity, such as working memory tasks [45]. Indeed, the poor performance of schizophrenia patients on working memory tasks that require frontal cortical involvement (e.g., the Wisconsin Card Sort task, [37,44]) is accompanied by a failure to activate the PFC metabolically [9]. Moreover, insults that disrupt the PFC in human subjects are reported to produce a condition with characteristics similar to that observed in the deficit state of schizophrenia [83]. However, in spite of this evidence, reports of gross structural disturbances of the PFC that are of sufficient magnitude to disrupt behavior have not been made in patients with schizophrenia [110,123].

Evidence has accumulated to suggest that deficits in other cortical regions may play a role in the pathophysiology of schizophrenia. For example, studies of schizophrenia patients revealed morphological alterations within the amygdala [6,100] as well as a decrease in metabolism in limbic-related cortical areas that are connected reciprocally with the amygdala [116]. In particular, disruptions of neuronal function within the amygdala and anterior cingulate cortex are proposed to encompass a particular set of symptoms in schizophrenia, such as attentional deficits, blunted affect, and the inability to respond appropriately to social situations. These types of symptoms are analogous to those that occur with lesions of the amygdala in non-human primates, and resemble the behavioral deficits observed in humans with lesions of the anterior cingulate,

which is interconnected with the amygdala [33,63,101]. There has also been recent evidence that implicates hippocampal dysfunction in schizophrenia. Among this evidence are reports of cellular organizational disturbances in the hippocampus of schizophrenics [27,64] as well as a decrease in hippocampal volume [15] that is particularly prominent in the afflicted cohort of twins discordant for schizophrenia [115]. However, in contrast to the pathophysiological consequences that are observed upon pharmacological manipulation of the DA system or the PFC, lesions that involve the ventral hippocampus in adult animals does not produce a state that resembles the psychopathological disturbances observed in schizophrenia.

In contrast, recent studies by Lipska, Weinberger and colleagues suggest that the important variable with respect to the pathophysiology of schizophrenia is the developmental period during which the hippocampal pathology takes place. Therefore, even though lesions of the ventral hippocampal region performed in adult animals fails to produce schizophrenia-like alterations in limbic system function, disruption of this brain region in neonatal rats causes these behavioral alterations to emerge after the rat reaches the adult stage [74]. The behavioral alterations produced by these neonatal ventral hippocampal lesions include hyperlocomotion and increased responsiveness to stress and amphetamine. Such responses resemble those observed after prefrontal cortical lesions made in adult animals [1,57,125].

Why does a neonatal lesion within the hippocampal structure lead to an emergence of dysfunction within the prefrontal cortical-accumbens DA system in the adult? It is not likely that these deficits are a direct result of hippocampal damage, given that hippocampal lesions in adults do not lead to these types of behavioral profiles. Thus, it is not obvious how hippocampal pathology in the neonate (which otherwise has a higher capacity for compensatory changes; [18]) causes a transformation in adult corticoaccumbens-mediated behaviors. Among several explanations is the possibility that the neonatal hippocampal damage may trigger compensatory changes within systems that depend on a normal hippocampal input. In fact, studies have suggested that glutamatergic transmission is necessary for the induction of several types of time-dependent modifications to occur within dopaminergic systems [34,61]. Therefore, damage to the hippocampus in neonates may induce a functional reorganization within the limbic system as a means of compensating for this pathology.

### 3. Relevance of the nucleus accumbens to schizophrenia

Among the limbic structures that have been investigated, the nucleus accumbens continues to attract the interest of researchers studying the neurobiological bases of schizophrenia for several reasons. With respect to neuroanatomy, the nucleus accumbens receives glutamatergic

afferent input from each of the cortical regions that have been associated with schizophrenia, including the paleocortex (amygdala), archicortex (hippocampus) and neocortex (PFC) [7,25,40,77,84,108], in addition to a significant input from the ventral tegmental area DA neuron population [8,122]. The nucleus accumbens neurons send projections to the ventral pallidum [54], which in turn sends efferents to the thalamus, including a major projection to the mediodorsal nucleus of the thalamus [67,128]. The mediodorsal thalamic nucleus is the region of the thalamus that is interconnected with the PFC [118], and is thought to regulate its activity. The mediodorsal thalamus itself has a dopaminergic innervation [8,28,52], which we have shown will facilitate oscillatory activity within this thalamic region [69]. The nucleus accumbens also exhibits substantial alterations in response to repeated administration of antipsychotic drugs, including intercellular dye coupling [88,95], the expression of mRNA [78], and the induction of immediate early genes [32,103]. The selectivity of classical and atypical antipsychotic drugs for these actions and the delayed onset of these antipsychotic drug-induced responses is cited as evidence that the nucleus accumbens may be a primary site of therapeutic action of antipsychotic drugs [50], given the temporal correspondence between these actions and the delayed therapeutic response of schizophrenia patients to antipsychotic drug administration [60].

### 4. The cellular basis for hippocampal-PFC-DA interactions

As a way of integrating the above observations, current models into the pathophysiology of schizophrenia suggest that this disorder is not due to a primary pathology within the dopaminergic system. Instead, an emerging concept is that the DA system may be relatively normal, but is subjected to a dysregulation as a consequence of the abnormal control by cortical glutamatergic afferents, e.g., [21,46]. We have examined the mechanisms that may contribute to this type of pathological cortical modulation of subcortical DA system function using correlated *in vivo* and *in vitro* intracellular recording techniques. Using this approach, we have assessed the functional interaction of several of these major components believed to play a role in the pathophysiology of schizophrenia.

#### 4.1. PFC innervation of accumbens neurons *in vitro* — modulation by dopamine

DA appears to exert a multitude of actions within the nucleus accumbens [117,127]. Among these actions are a direct, potent depression of nucleus accumbens neuron excitability [79,89]. Moreover, DA appears to also depress excitatory afferent input arising from PFC, amygdala, and hippocampus [86,98,126]. The interaction of DA with PFC afferents is of particular interest, in that DA was found to

exert a tonic presynaptic inhibitory influence on PFC-evoked responses on accumbens neurons, although the pharmacological nature of this response was atypical [86]. Specifically, we found that administration of the D2 agonist quinpirole (1–20  $\mu$ M) to accumbens slices in vitro attenuated the amplitude of cortical afferent stimulation-evoked EPSPs in 40% of accumbens neurons tested. Moreover, the D2-specific antagonist sulpiride increased EPSP amplitude in most of the cells tested. The response to sulpiride suggested that the EPSP was inhibited by tonic levels of DA in the tissue. This was supported by the observation that, in slices obtained from DA-depleted animals, sulpiride failed to induce changes in the amplitude of the EPSPs, whereas quinpirole produced a highly significant suppression of EPSP amplitude in every cell tested. These results indicate that DA modulates the response of accumbens neurons to corticoaccumbens fiber stimulation via D2 receptors. Furthermore, these D2 receptors appear to be located presynaptically on the cortical afferent terminals, since this action of DA was not accompanied by changes in membrane potential, input resistance, or time constant, and was not modified by changes in the membrane potential. Although DA terminals have not been found to synapse directly onto glutamatergic afferents, ultrastructural studies show that these terminals land in close proximity to each other on single dendritic spines of accumbens neurons [109]. These data provide support for the presence of a tonic basal level of D2 receptor stimulation in the accumbens slice preparation.

In addition, stimulation of DA receptors and stimulation of cortical afferent fibers were both found to exert potent and regionally-selective modulation of the incidence of dye coupling in the accumbens core and shell regions, as well as in the dorsal striatum [85,90,94]. Furthermore, the increase in dye coupling produced by cortical afferent stimulation was found to be mediated by a nitric oxide-dependent process [91]. This dye coupling is thought to indicate the presence of electrical coupling mediated by gap junctions between nearby neuronal dendrites. Intercellular coupling is proposed to be an important mechanism for modulation of neuronal interaction at the network level. For this reason, it is significant that it can be modulated in a regionally-selective manner by repeated administration of antipsychotic drugs [88,96] or amphetamine [96,97]. Therefore, DA was found to exert multidimensional actions within the nucleus accumbens that occur over several levels of integration.

#### 4.2. Gating of PFC afferent input within the accumbens by the hippocampus and the amygdala

As described above, the PFC input to the accumbens appears to be regulated presynaptically by the DA system. The corticoaccumbens system is also subject to gating influences by other afferents to the nucleus accumbens as well. In particular, evidence garnered from in vivo intra-

cellular recording studies revealed that the hippocampus exerts a potent modulatory control over PFC afferent activation of neurons in this brain region. Thus, accumbens neurons recorded intracellularly in vivo exhibited substantial levels of spontaneous activity consisting of spontaneous EPSPs, plateau depolarizations, and spike discharge [87]. Moreover, the plateau depolarizations caused the membrane potential of the accumbens neurons to alternate between two clearly identifiable states: a hyperpolarized, non-firing state and a depolarized state during which the neuron fired action potentials (Fig. 1). Therefore, these neurons exhibited a bistable steady-state membrane potential. This depolarization appears to be driven by afferents from the hippocampus subiculum. Thus, although most of the neurons in the nucleus accumbens exhibited excitatory potentials in response to stimulation of the fornix, in cells that exhibited spontaneous bistable states fornix stimulation evoked a unique response. This response consisted of either a long-lasting transition to the depolarized state or a prolonged EPSP/plateau potential with a duration of 40–60 msec followed by a repolarization. This could also be readily induced by delivering a train of stimulus pulses to the fornix. However, if the fimbria/fornix is transected, none of the accumbens neurons recorded exhibited this bistable membrane potential. Similarly, injection of the local anesthetic lidocaine onto the fimbria/fornix induced a reversible suppression of the bistable state [87]. Therefore, the hippocampal subiculum appears to be the drive that causes nucleus accumbens neurons to exhibit the bistable state.

There is substantial evidence that the plateau depolarizations of the bistable state were driven by hippocampal subicular afferents. First, there is known to be a substantial glutamatergic innervation of the accumbens derived from the fimbria/fornix that originates in the ventral subiculum [13,14,30,40,62]. This is consistent with the rapid excitation observed upon stimulation of the fimbria/fornix, which resembles responses obtained by ventral subicular stimulation [13], rather than the slower modulatory actions that would be produced by activation of monoaminergic afferents in the fimbria/fornix [107]. Furthermore, the rhythmic activity of the plateau depolarizations resembles hippocampal theta-like activity [71,87]. Finally, stimulation of nearby structures (e.g., thalamus) evoke markedly different responses than those observed with fimbria/fornix stimulation.

In contrast, stimulation of PFC afferents evoked only a brief excitatory response that, in itself, exhibited a low probability of triggering spike discharge in accumbens neurons. In contrast, if a hippocampal stimulation-evoked plateau discharge was evoked first, subsequent stimulation of the PFC afferent readily evoked spike discharge in the nucleus accumbens neuron. Thus, activation of the subicular input caused the bistable neuron to shift to a depolarized state, during which PFC afferents are capable of triggering spike discharge (Fig. 1). This interaction appears

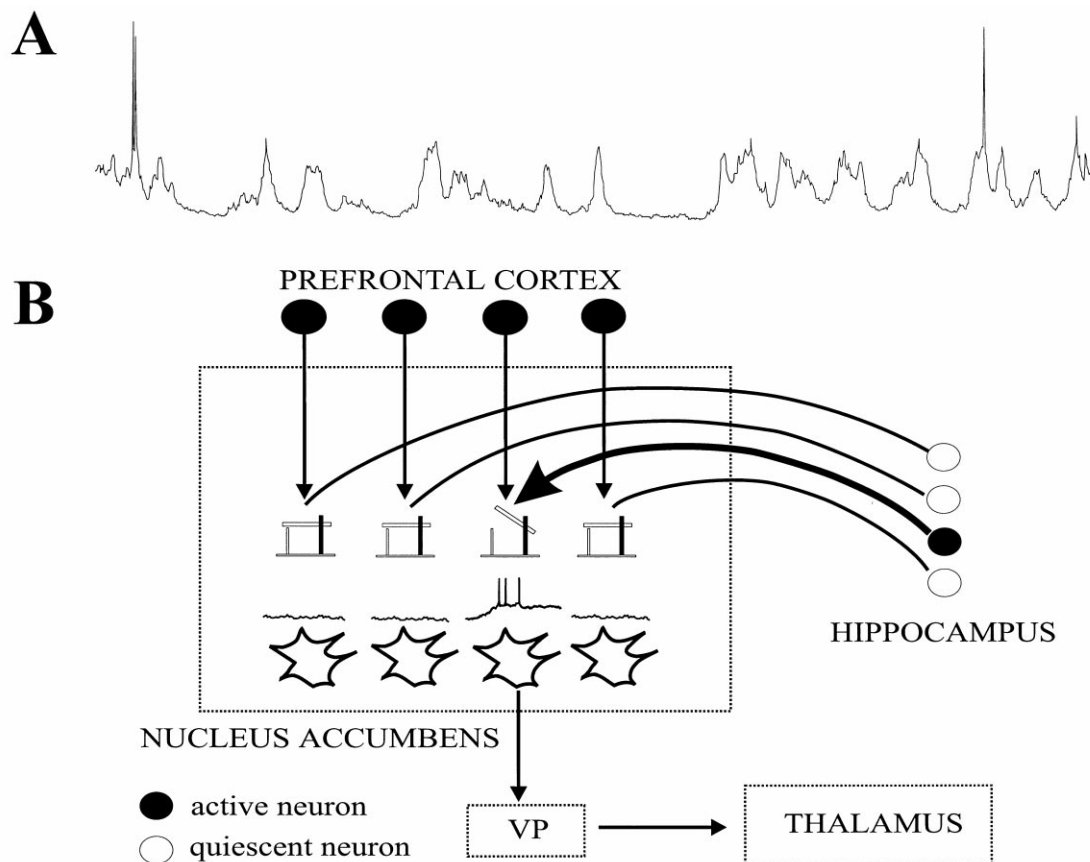


Fig. 1. Hippocampal gating of information flow from the prefrontal cortex via modulation of nucleus accumbens neuronal activity. (A) In vivo intracellular recording illustrating the bistable membrane state of neurons in the nucleus accumbens. The membrane potential of these neurons alternates between a hyperpolarized, inactive state and a depolarized plateau during which action potentials are generated. Our studies revealed that the subiculum of the hippocampus is responsible for driving the depolarized state in these neurons. Moreover, afferent input from the prefrontal cortex is capable of triggering action potentials only when the accumbens neuron is in the depolarized state. (B) A model of hippocampal gating of prefrontal cortical input. Spontaneously active prefrontal cortical cells (filled circles) provide afferent stimulation to each of the four nucleus accumbens neurons illustrated. In contrast, a limited afferent input from the hippocampus (one filled circle, dark arrow) causes only one of the accumbens neurons to enter the depolarized state. Only the accumbens neuron in this depolarized state is capable of passing prefrontal cortical information through to the ventral pallidum and on to the thalamocortical system. In this way, the hippocampus opens a 'gate' in the accumbens to allow passage of only a subset of information arriving from the prefrontal cortex.

therefore to act as a gate, in which the hippocampal input is required to 'arm' the gate to respond to subsequent input arriving from the PFC. This would thereby enable information to flow from the PFC through the accumbens and ventral pallidum, and on to activate thalamocortical circuits. In particular, such a system would enable the PFC to activate afferents to the mediodorsal nucleus, thereby reinforcing activity within a loop circuit determined by the hippocampal gate.

This gate also is affected by drugs which are known to be psychotomimetic agents. Thus systemic administration of the D1 agonist SKF38393 combined with the D2 agonist quinpirole was found to decrease the frequency at which the membrane potential exhibited transitions to the depolarized state (i.e., from 1 Hz to 0.5 Hz; O'Donnell and Grace, in preparation). In addition, systemic administration of phencyclidine (PCP) caused a marked attenuation of the spontaneous occurrence of depolarizing plateau

potentials. Moreover, this effect appears to be mediated via an action outside of the subiculum, since direct injection of PCP into the subiculum failed to attenuate the bistable state [93]. Given that the bistable state is necessary for gating of the PFC throughput in the nucleus accumbens, this decrease in the bistable state frequency would result in a functional blockade of prefrontal cortical throughput in the accumbens.

In addition to gating by the subiculum, we have examined the ability of the amygdala to gate PFC throughput in the nucleus accumbens as well. Using in vivo intracellular recordings, we found that stimulation of the amygdala caused a brief depolarization of nucleus accumbens neurons [87]. Moreover, if a stimulus train delivered to the basolateral amygdala preceded stimulation of the PFC, there was a facilitation in the probability of PFC stimulation to evoke an action potential in accumbens neurons [81]. This potentiation was found to depend on the interval

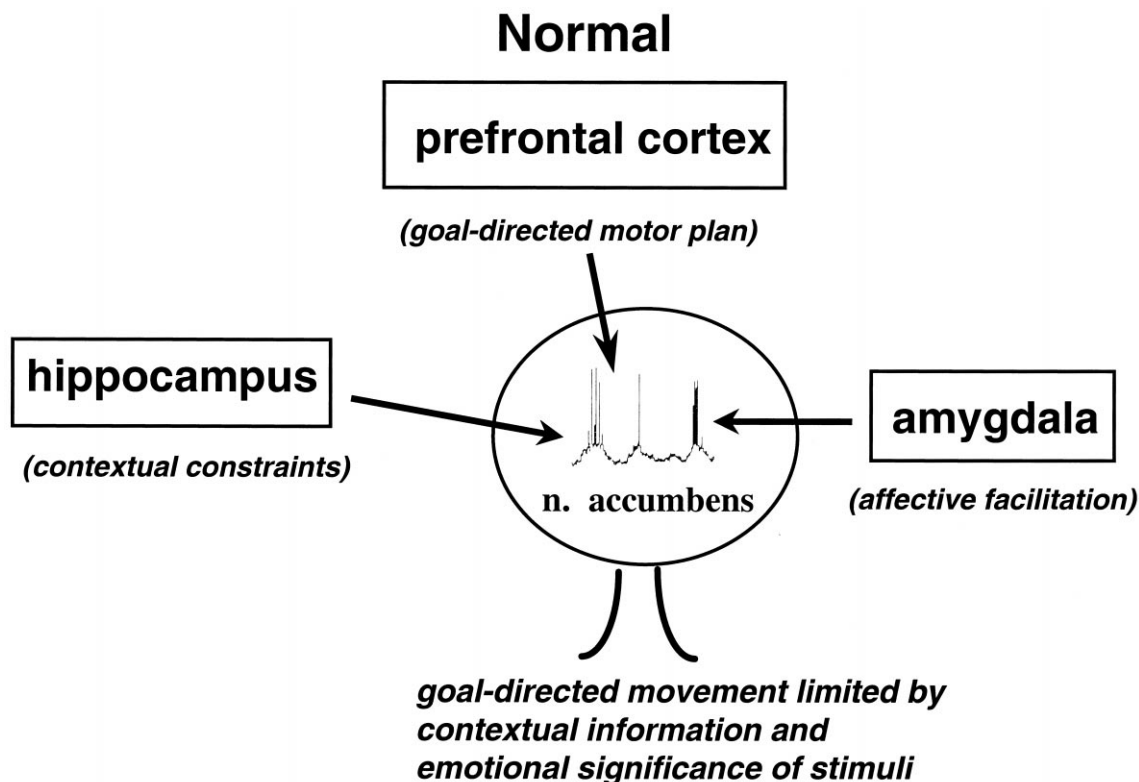


Fig. 2. The accumbens is a site in which limbic structures have overlapping input with the dopamine system. In this model, the prefrontal cortex provides multiple motor plans by which it drives goal-directed behavior. The most effective plan is then selected within the nucleus accumbens via the facilitatory effects of hippocampal and amygdalar influences. This selection occurs via the ability of the hippocampus and amygdala afferents to facilitate the response of accumbens neurons to the specific prefrontal cortical input chosen. Under normal conditions, the hippocampus selects behavioral output based on the current context of the situation or past experiences with the stimulus. However, should a stimulus with a high affective valence (e.g., a threatening object) come into play, the amygdala can over-ride the hippocampal influence, and instead direct behavior in a manner that can effectively deal with the threatening stimulus. The motor plan that is selected by these interactions is then passed via the ventral pallidum to the mediodorsal thalamus where, via a return loop to the prefrontal cortex, the selected motor plan can be enacted.

between amygdala activation and PFC stimulation, in that the facilitation only occurred if the amygdala was activated between 7 and 30 msec prior to PFC stimulation. Therefore, as with the subiculum, the amygdala appears to be capable of gating PFC throughput at the level of the accumbens. However, in the case of the amygdala, this gating appears to be more of a brief response that is likely to be related more to event-related phenomena.

What are the functions of such gates? An evaluation of the literature suggests that the hippocampal subiculum is involved in modulating stimuli with respect to context. Thus, several studies have implicated the subiculum in context-dependent fear conditioning, and potentially other types of context-related events [58]. Given the literature suggesting that schizophrenics show deficits in tasks that contain context-related information [24,31,114], this is consistent with a primary pathology in schizophrenia involving the ventral hippocampus and its ability to gate context-dependent information at the level of the accumbens [51]. In contrast, the amygdala has been associated with stimuli related to emotion or affective state [35,70]. Given the brief duration of the facilitation produced by

amygdala stimulation, the amygdala is proposed to gate information based on its affective valence. Therefore, under normal conditions, a person may be focused on a task based on its context, which is driven by hippocampal facilitation of information flow in the accumbens only when the information conforms to the present context. However, should a threatening stimulus be presented, the amygdala should be capable of producing an over-ride of the context information at the level of the accumbens, instead facilitating those prefrontally-directed responses that are related to escape. This would enable the organism to respond to the threatening stimulus even if it is not congruent with the current context (Fig. 2; [51]).

### **5. Potential role for DA in modulating synaptic interactions in the nucleus accumbens — the tonic/phasic model of DA system regulation**

As reviewed above, evidence indicates that there are sufficient levels of DA in the extracellular fluid to produce a tonic inhibition of PFC afferent input to accumbens

neurons [86] as well as to facilitate D1 modulation of dye coupling in the core of the accumbens [85]. In contrast, stimulation of D1 receptors in the accumbens appears to require higher levels of DA agonists [85,89,102]. Indeed, this type of information formed the bases for the development of a hypothesis of schizophrenia based on the presence of two types of DA release [46]. In this model, DA transmission is proposed to occur by way of two processes: a tonic level of DA that is maintained at low (i.e., 20–50 nM; [26,111]) concentrations in the extracellular fluid (ECF) by potent homeostatic regulatory mechanisms, and a phasic DA release into the synaptic cleft that is brief in duration, yet achieves substantially higher concentrations (i.e., hundreds of  $\mu$ M up to mM levels; [42]). Although the tonic DA levels in the ECF are probably too low to act in a similar manner as DA released by spikes intrasynaptically, this concentration is nonetheless adequate to stimulate highly sensitive presynaptic receptors in this region. These include the presynaptic D2 receptors located on the corticoaccumbens terminals as well as the DA autoreceptors located presynaptically on DA terminals, which are reported to have an estimated  $K_d$  of 52 nM [102]. Indeed, a central tenet of this hypothesis is that tonic DA levels mediate an inhibition of spike-dependent DA release [46,48]. In this model, it is proposed that a behaviorally significant event will trigger DA cell burst firing [36,104], which then drives the rapid, high-amplitude phasic DA release into the synaptic cleft. In contrast, the low level tonic DA present in the ECF is proposed to be regulated by glutamatergic afferents [43,46], such as those coming from the PFC, amygdala, and the hippocampus [12,38]. In this model, I proposed that a pathological disruption in one of the glutamatergic afferent systems that innervate the accumbens (e.g., from the hippocampus, amygdala, or PFC) causes a decrease in tonic DA levels. As a result, there would be a potent disinhibition of phasic DA release. In this way, the hyper-responsivity in the DA system, e.g. [16,17,65,66] may be a consequence of a failure of corticoaccumbens glutamate systems to provide a tonic dopaminergic down-modulation of phasic DA system function, causing the system to respond inappropriately to otherwise insignificant stimuli. Although the evidence for presynaptic glutamatergic regulation of DA release is controversial [80], recent studies [121] suggest that DA release can occur via metabotropic glutamate receptors. In synthesis, a pathological interruption of glutamatergic input from afferent cortical systems (e.g., PFC, hippocampus, amygdala) could be responsible for the increase in DA system responsivity in schizophrenia.

## 6. Synaptic plasticity and the impact of neonatal hippocampal lesions on limbic system function in the adult

The evidence reviewed thus far indicates that lesions of the ventral hippocampus in neonatal but not adult rats leads to changes in DA regulation of limbic system-media-

ted behaviors in adult animals. However, the nature of this alteration has not been investigated at the cellular level. Therefore, we used another type of developmental disruption to mimic the pathophysiology of schizophrenia. As described above, studies by Lipska and Weinberger [75,124] demonstrated the importance of developmental disruption of the subiculum in altering the responsivity of the limbic system. We used an approach that utilized a mitotoxin, methyl azoxymethanol acetate (MAM) that arrests cells in the process of division [23]. By adjusting the timing of the administration and the dose of MAM, we were able to administer doses of this drug that produced cytoarchitectural changes in the hippocampus, entorhinal cortex, and prefrontal cortex that were in many ways analogous to what has been observed in schizophrenia.

Thus, administration of MAM to pregnant rats on gestational day (GD) 15–17 caused a dose-dependent disruption in the development of the ventral hippocampal regions and the surrounding perirhinal cortex when the brain was examined after the rat reached adulthood [82]. These animals exhibited an increase in baseline locomotor activity when placed in novel environments, and an enhancement in the locomotor effects of PCP. In particular, there was an enhancement of PCP-induced dyskinesias [41]. Although such behaviors had previously been found with frontal cortical damage in rats, the lack of substantial pathological alterations in the frontal cortex suggests that this was a developmental alteration in frontal cortical function that resulted in such deficits. Indeed, MAM-treated rats also exhibited an attenuation of DA-mediated inhibition of pyramidal cell activity in the PFC *in vivo* [68].

This enhanced response to PCP is interesting in light of the observation that this drug will produce an extended and symptom-specific enhancement of schizophrenia symptoms when administered to schizophrenia patients [76]. This may be related to the fact that this compound is a ‘trapped’ NMDA receptor channel blocker [55], which requires membrane depolarization and NMDA channel opening in order to eject the compound. Therefore, one would expect PCP to exert particularly potent and long-duration action at those glutamatergic synapses that receive a pathologically low level of glutamate stimulation [51,92,93]. This may provide an explanation both for the potent actions in the schizophrenia patient as well as the observation of a long-duration action in the MAM-treated rats.

In addition to the effects on behavior, the MAM-treated rats also exhibited an alteration in the interaction of limbic afferents in the nucleus accumbens. Thus, whereas in control rats amygdala stimulation was found to enhance PFC-evoked spike discharge in the accumbens, in the MAM-treated rat this interaction was significantly altered: instead of facilitating throughput, amygdala stimulation was found to attenuate PFC-evoked spike discharge. Indeed, in the MAM-treated rats amygdala stimulation was found to directly evoke accumbens cell spike discharge

[82]; a response that was rarely observed in the control rats. One hypothesis that could be drawn is that, if the MAM model does indeed resemble the schizophrenic brain, it suggests that schizophrenia patients may respond to stimuli not on the basis of past experience or context (hippocampus) driving a motor plan (PFC), but instead respond to all stimuli based on their affective valence (Fig. 3; [51]). Such a condition may account for the reported flooding of emotions and the inability to discriminate relevant and irrelevant stimuli that are reported to be present in the schizophrenia patient.

The reliance of these phenomena on developmental disruptions may relate to the type of alteration that such lesions may produce. Thus, one potential explanation that may account for these findings is that the homeostatic compensations produced neonatally in response to hippocampal damage are not an attempt to restore functions mediated by the ventral hippocampus directly, but instead are directed toward compensating for the loss of its regulatory influence over other systems. A region in which all of these aforementioned systems overlap is the nucleus accumbens. Within the accumbens, we have provided evidence that the ventral hippocampus potently modulates

PFC excitation of accumbens neurons, and thereby gates PFC information throughput within this structure. Given this condition, one could imagine that damage to this hippocampal gating mechanism would result in an alteration in the other ‘arm’ of this intersection to compensate for this loss of regulation. This is proposed to involve changes in the relationship between the corticoaccumbens glutamatergic input and its modulation by DA. As cited earlier, there is substantial evidence that glutamatergic systems exert potent regulatory control over the induction of long-term compensatory changes in the DA system [34,61]. Therefore, in this model, neonatal damage to the hippocampus results in a reorganization within the corticoaccumbens system and its regulation by DA in order to compensate for this loss of gating. One potentially interesting result would be the attenuation of PFC efferent activity following neonatal hippocampal lesions as a compensation for inadequate gating control over these inputs. Such a consequence could account for both the hypofrontality/decreased PFC activation observed in this disorder [2,9,10,56] as well as provide an explanation for the apparent hyperresponsivity of the DA system based on our tonic-phasic model of DA system regulation [46].

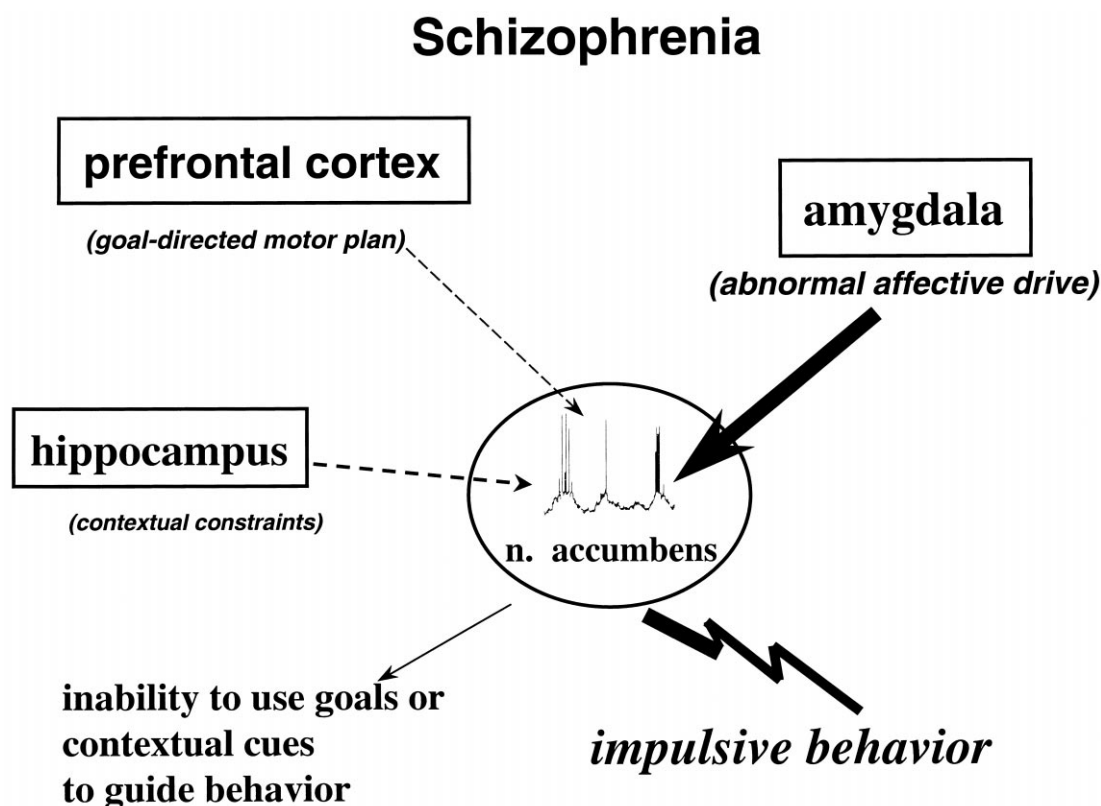


Fig. 3. The model presented in Fig. 2 is altered based on our results using the MAM model to approximate what is proposed to occur in the brain of the schizophrenia patient. In this pathological state, the amygdala not only fails to facilitate prefrontal cortical throughput, but in this condition actually competes with it for driving accumbens cell activity. Therefore, instead of selecting response strategies based on the goal-directed motor plan (prefrontal cortex) as modulated by the current contextual constraints (hippocampus), the system is biased to react exclusively based on the affective valence of the stimulus. As a result, the planned behavior is replaced by impulsive responses based solely on the emotional state of the subject.

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