Tuning the engine of cognition: A focus on NMDA/D1 receptor interactions in prefrontal cortex

Abstract

The prefrontal cortex of the primate frontal lobes provides the capacity for judgment which can constantly adapt behavior in order to optimize its outcome. Adjudicating between long-term memory programs and prepotent responses, this capacity reviews all incoming information and provides an interpretation dependent on the events that have just occurred, the events that are predicted to happen, and the alternative response strategies that are available in the given situation. It has been theorized that this function requires two essential integrated components, a central executive which guides selective attention based on mechanisms of associative memory, as well as the second component, working memory buffers, in which information is held online, abstracted, and translated on a mental sketchpad of work in progress. In this review, we critically outline the evidence that the integration of these processes and, in particular, the induction and maintenance of persistent activity in prefrontal cortex and related networks, is dependent upon the interaction of dopamine D1 and glutamate NMDA receptor signaling at critical nodes within local circuits and distributed networks. We argue that this interaction is not only essential for representational memory, but also core to mechanisms of neuroadaptation and learning. Understanding its functional significance promises to reveal major new insights into prefrontal dysfunction in schizophrenia and, hence, to target a new generation of drugs designed to ameliorate the debilitating working memory deficits in this disorder.

Keywords: Prefrontal cortex; Primate; Schizophrenia; Dopamine; Glutamate; D1 receptor; NMDA receptor; Sensitization; Working memory

Article Outline

Biological substrates of working memory

1.1. Working memory concept

The way in which working memory is viewed is not specific to a single process but has been used to explain many adaptive behaviors such as recall of a recent item, remembering baited arms in a maze, or the location of a submerged platform (Bartus and Johnson, 1976, Chambers et al., 1996 and Pouzet et al., 1999). One of the stricter definitions of short-term memory puts its extent down to seconds (Brozoski, Brown, Rosvold, & Goldman, 1979) whereas others can broaden the time scale to minutes (Phillips, Ahn, & Floresco, 2004). However, one of the important facets of working memory is that it is not just a delay between a stimulus and a response, but that it entails an employment of a buffer for information that can be swapped in and out and processed on in order to guide an appropriate response (Baddeley, 1996, Baddeley and Hitch, 1974 and Goldman-Rakic, 1987). In fact, there are two key aspects of working memory that distinguish it from simple short-term memory: the first involving selective attention that permits access to the buffer, otherwise known as the central executive, and the second involving a persistence of neuronal activity whereby a neural representation of information is maintained (Baddeley, 1992 and Dias et al., 1996). Thus, working memory conjoins higher order attentional processes with the capacity for representational memory. While there have been multiple attempts to segregate these two aspects in relation to regional cortical function, it is clear that they must act in unison for successful execution of a working memory task. Hence, in order for information to be represented it must first carry with it a signal of salience that then enables the generation of the persistent neuronal activity that underlies that representation. Therefore, learning is critical for working memory in shaping the decision making aspect of whether a stimulus or information contained within a stimulus is important or not. As we will discuss in this review, both dopaminergic transmission, particularly via the D1 receptor, and glutamatergic transmission, via the *N*-methyl-d-aspartate (NMDA) receptor, are essential to these processes. Moreover, we will argue that it is the interaction between D1 and NMDA receptor signaling that forms a fundamental neural substrate for working memory. In fact, there are many lines of evidence that implicate the importance of these signaling pathways to cognition and their dysfunction is thought to be core to many psychiatric disorders such as schizophrenia, where cognitive function is an important indicator of outcome (McGurk and Meltzer, 2000, Liddle, 2000, Lysaker et al., 1996, Smith et al., 1999a and Smith et al., 1999b).

1.2. Dependency on neuronal activity

Functional magnetic resonance imaging (fMRI) has been used to study the time course of neuronal activity in delayed response tasks requiring varying degrees of working memory load. In humans, it has been shown that the region of the middle frontal gyrus, analogous to Area 46 in the nonhuman primate (Walker, 1940), is active throughout the delay period of a task in which the subject must remember a particular stimulus location (Leung, Gore, & Goldman-Rakic, 2002). In fact, rather than the blood oxygen level dependent (BOLD) signal reflecting just the encoding or retrieval of a particular location, it was found that activity in this region was maintained throughout the early, middle, and late epochs of an 18-s delay

period. Thus, while many metabolic processes may contribute to the observed signal, the obvious conclusion can be drawn that neurons in this region are firing throughout the entire delay period in order to subserve the working memory process.

As implicated by the notion that persistent activity serves as a representation of stimulus information, it is clear that actual neuronal firing and the consistency of action potential production is an obvious manifestation of the working memory process. This neuronal activation is not just important for representational memory *per se*, but also for the initial response to a stimulus or external signal that is capable of initiating subsequent persistent activity. Therefore, the physiological investigation of working memory processes in prefrontal as well as other cortical areas has been well-served by extracellular recording studies in awake nonhuman primates performing cognitive tasks, where neuronal activity can be directly recorded. Nevertheless, it is important to recognize at the outset that there are first prevailing conditions that can influence the generation of persistent activity and there are also a number of distinct subthreshold synaptic and membrane-dependent processes that are critical for both the generation and persistence of representational neuronal activity which we will attempt to unravel below. One enigmatic feature of neuronal activity involved in the working memory process is the contribution of dopaminergic neuron firing. While there can be little doubt from the studies of Schultz and colleagues (Ljungberg et al., 1991 and Schultz et al., 1993) that dopamine cells fire in relation to the presentation of the stimuli used in many working memory tasks, it has been hypothesized that it is only the tonic level of dopamine that has any real influence on prefrontal neuronal firing and indeed, that it is actually the glutamate that is co-released from these neurons that is responsible for the initiation of persistent neuronal activity (Lavin et al., 2005). Hence, within our current hypotheses of the mechanisms responsible for persistent neuronal activity in working memory, there are several major issues which need to be addressed. These we will try to pinpoint in this review with the intention of highlighting the critical experiments that are necessary to advance our knowledge of the biology of working memory and to improve the treatments developed for those suffering from cognitive deficits.

1.3. Lesion studies in human and nonhuman primates

The inspiration to study working memory and its biological origins comes from early descriptions of the effects of frontal lobe lesions in both humans and monkeys. The first clues to frontal lobe function came from patients who suffered from lesions of different regions who manifested dramatic alterations, not only in their reasoning and judgment, but also in aspects of their memory. In particular, a number of such patients have shown an inability to successfully hold information in mind for brief periods, with a consequential tendency to be preoccupied with immediate events and a paucity in the ability to plan activities. This apparent mnemonic deficit was examined formally in the monkey by Jacobsen (1935), who first studied monkeys with prefrontal lesions in a delayed response task and found impairments in what he termed “immediate” or “recent” memory. Such impairments were more recently studied in humans by Ghent, Mishkin, and Teuber (1962) following frontal lobe injury and it was confirmed that humans with lesions in analogous regions of the frontal lobe did indeed exhibit deficits in a form of short-term representational memory. Once it became recognized that representational memory played a key role in both planning and decision-making aspects of behavior an intense effort was initiated, which is still under way, to further our understanding of how this form of memory is used to guide behavior and to discover its neurobiological basis. A major landmark in this understanding was formulated in psychological terms by Baddeley in the concept of working memory—a process by which

selected items of information are maintained in a temporary buffer in order to successfully direct a future response (Baddeley & Hitch, 1974). Thus, it has now been shown in nonhuman primates that interruption of prefrontal function in the region of the principal sulcus by ablation, excitotoxic damage, or cooling results in profound impairments in performance on delayed response tasks that are considered to depend upon working memory itself (Bauer and Fuster, 1976, Butters et al., 1971, Collins et al., 1998, Fuster, 1997, Goldman-Rakic, 1987, Levy and Goldman-Rakic, 1999 and Passingham, 1985). The finding that the dorsolateral prefrontal cortex (DLPFC) plays such a key role in this function has stimulated a wide range of experiments on the nature of the functions in which it is involved. Of particular note, it is now clear that there is an intimate relation between the functions of DLPFC and the frontal eye fields (FEF) in the voluntary control of eye movements—one of the highest orders of cognitive processing in primates (Goldberg & Bruce, 1986). The relation of these two regions in frontal function has been determined to be to a large extent the result of the parallel information conveyed from posterior parietal cortex as part of the dorsal visual stream involved in the processing and utilization of spatial information (Gattass et al., 1990 and Ungerleider and Haxby, 1994). Therefore, as we will discuss, a wide variety of working memory tasks utilizing spatial stimuli have been exploited to elucidate the neural networks and cellular circuits involved in the process of generating the mnemonic activity that underlies the capacity to hold important items of information "on-line" (Goldman-Rakic, 1990).

1.4. Distributed networks and the prefrontal engine

While there is a solid core of evidence that DLPFC has a pivotal role in spatial working memory, there is still much to be discovered and significant controversy as to the extent of the cognitive processes in which this region is involved and the circuitry that operates across the entire brain in working memory tasks. Thus, neuronal activity in posterior parietal cortex is virtually identical to that in DLPFC in the oculomotor delayed response task (ODR) (Chafee & Goldman-Rakic, 1998) and activity in the inferotemporal cortex bears a strong resemblance to that found in ventrolateral prefrontal cortex (VLPFC)/inferior convexity (Fuster et al., 1985, O Scalaidhe et al., 1997 and Wilson et al., 1993). These findings imply that the information held in working memory is not necessarily stored in prefrontal cortex (PFC) *per se*, but rather there is a functional link up between prefrontal and other association cortices that maintain aspects of sensory information. As such, there may be fundamental differences in the operations of PFC in the mnemonic representation of spatial location as opposed to working memory for object features. Since there are highly evolved cortical mechanisms for the extraction, encoding, and recognition of object features in the temporal lobe, it could be argued that it would be redundant for PFC to be involved in any further processing of this information. In contrast, pinpoint information on spatial location might be expected to be much more readily processed within prefrontal circuitry and, therefore, far more integral to the functions of DLPFC. This hypothetical viewpoint is supported by the strong relation between DLPFC and the FEF as particularly exemplified by evidence from nonhuman primate studies (Cavada and Goldman-Rakic, 1989, Funahashi et al., 1990, Funahashi et al., 1991 and Selemon and Goldman-Rakic, 1988). However, it is not supported by a number of fMRI studies in the human and certain neurophysiological studies in the nonhuman primate which emphasize the processing in which different regions of PFC are involved as opposed to the type of information being processed (Glahn et al., 2002, Goldman-Rakic, 2000, Levy and Goldman-Rakic, 1999, Levy and Goldman-Rakic, 2000, Miller, 2000, Nystrom et al., 2000, Rao et al., 1997 and Rowe et al., 2000). It is important to note that the difficulty in exacting the nature of a particular process or the actual nature of

particular information has contributed to divergence in the conceptualization of dorsolateral prefrontal function. For example, whereas in somatosensory cortex processing can be attributed to both convergent and divergent neural circuits that convey critical details of sensory information including type and location, processing in PFC is frequently conceptualized in terms of rules, abstractions, and central executive function. Such concepts are hard to assign to exact neuronal substrates whether manifested by the functional characteristics of firing by a population of neurons or by alterations in the BOLD signal as measured by fMRI. It is therefore of critical importance in the research to be as specific as possible as to the spatial nature of the stimuli used in working memory tasks and the process being tested in order to further our understanding of dorsolateral prefrontal function. In the strictly spatial domain, the relation between inferior/posterior parietal and prefrontal processes is clearly evident (Buckner et al., 1996, Chafee and Goldman-Rakic, 1998 and Cohen et al., 1997). An important insight into this relation was gleaned from the transcranial magnetic stimulation study of Priori, Bertolasi, Rothwell, Day, and Marsden (1993) where it was demonstrated that stimulation over posterior parietal cortex in the human interrupted the encoding of spatial stimuli and visually guided saccades whereas stimulation over prefrontal in a delayed response version of the task was capable of interrupting memory-guided saccades. This finding is consistent with those from ablation studies which indicate that visually guided saccades are preserved in nonhuman primates with DLPFC lesions even though mnemonically guided saccades are abolished (Funahashi, Bruce, & Goldman-Rakic, 1993). Another prime example of the closeness of prefrontal function to sensory processing in parietal cortex is given by Constantinidis, Franowicz, and Goldman-Rakic (2001) who showed that the strength of the sensory stimuli used in the ODR had an important bearing on the encoding of that information during the delay period of the task. Therefore, while processes such as rule abstraction or object discrimination may have an important influence on dorsolateral prefrontal function, the direct nature of spatial information processing in this critical region is of paramount importance to understanding how it works.

1.5. Neuronal correlates of working memory

Critical insights into the cellular substrates subserving working memory in PFC have come from studies of neuronal activity in nonhuman primates performing delayed response tasks. As first demonstrated by Kubota and Niki (1971) in delayed alternation and by Fuster and Alexander (1971) in spatial delayed response, neurons in primate DLPFC appear to encode the location of a target in space that is used to guide a response at the end of the delay period in the task. At around the same time that recording in delayed response originated in PFC, Wurtz and Goldberg (1972) discovered neurons in the superior colliculus that responded prior to saccade initiation in an oculomotor task. When this was examined in FEF, a critical node in the network involved in control of eye movements, neurons were found in this region whose firing anticipated a forthcoming saccade during a delay period (Bruce & Goldberg, 1985). At one and the same time, applying the ODR task to the study of DLPFC function and recognizing that neuronal activity during delayed response tasks was representative of working memory, Goldman-Rakic (1987) and colleagues (Funahashi et al., 1989, Funahashi et al., 1990 and Funahashi et al., 1991) were able to reveal the cellular substrate of working memory and multiple neuronal processes involved (Goldman-Rakic, 1990). Thus, it was found that neurons in Areas 46 and 8a, in the region of the caudal principal sulcus, showed spatially tuned delay activity, or “memory fields” with particular neurons encoding selective target locations by firing maximally for preferred directions and minimally for nonpreferred directions of the opposite region in the visual field. Neurons bearing memory fields frequently also show responses to the sensory stimulus itself (cue activity) and the initiation

of the saccadic response (presaccadic activity), while other neurons show such cue and/or presaccadic responses without mnemonic activity. Thus, multiple aspects of working memory appear to be encoded by prefrontal neurons which enable the transitions from sensory information through a transient storage process to guidance of the appropriate response. In the monkey, it was shown that the delay activity remained reasonably accurate in guiding saccades over delays of five or more seconds (Funahashi et al., 1989), an indication perhaps that the persistent activity of particular neurons could maintain neural representation of a stimulus over meaningful periods of behavior consistent with the fMRI findings of Leung et al. (2002). Given the impact of multiple neuropsychiatric and neurological disorders, such as schizophrenia or Parkinson's Disease (PD) on working memory, the ability to generate persistent activity, while maintaining its spatial tuning, has become one of the most critical issues for neuroscience research. As the principal neurons of PFC are pyramidal cells, it might be expected that these neurons bear primary responsibility for working memory processing. In fact, fast-spiking, putative interneurons in this region bear very similar functional characteristics to their neighboring pyramidal cells exhibiting isodirectional tuning of cue, delay, and presaccadic responses (Rao, Williams, & Goldman-Rakic, 1999). Thus, it is evident that it is not only excitatory components arising from connections between pyramidal cells, but also inhibitory components arising from GABAergic interneurons that are involved in the neural circuitry that generates and maintains spatially tuned delay activity. As we will discuss here, the significance of the NMDA contribution to the excitatory components (Lisman et al., 1998 and Wang, 1999) and dopaminergic modulation of both components (Durstewitz, Seamans, & Sejnowski, 2000a) appear to be critical to our understanding of prefrontal function in working memory as well as its disruption in mental disorders.

2. Dependency on dopamine receptor function

2.1. Dopamine depletion studies

Studies in the nonhuman primate, using a wide variety of experimental manipulations, have established a critical role for dopamine in working memory particularly in relation to prefrontal function. The importance of dopamine in this region was first demonstrated in a seminal study by Brozoski and colleagues (1979). 6-Hyroxydopamine (6-OHDA) lesions of DLPFC produced a profound delay-dependent deficit in delayed alternation performance of nonhuman primates that was ameliorated by subsequent administration of levodopa (l-dopa). In the nonhuman primate, repeated administration of the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has been employed to model the core symptoms of PD including both motoric and cognitive deficits (e.g., Kolata, 1983 and Langston et al., 1984). Interestingly, while low dose MPTP treatment produces persistent deficits in working memory, it results in only transient motor symptoms reminiscent of the disorder (Fernandez-Ruiz et al., 1995, Fernandez-Ruiz et al., 1999, Schneider and Roeltgen, 1993, Schneider et al., 1994a, Schneider et al., 1994b, Schneider and Pope-Coleman, 1995, Schneider et al., 1999 and Schneider et al., 2003). Similar to the findings for 6-OHDA, acute administration of l-dopa effectively alleviates deficits in working memory, as measured by performance on the spatial delayed response task, in MPTP-treated nonhuman primates (Fernandez-Ruiz et al., 1999). In humans, studies of PD patients on and off l-dopa have also pointed to a critical role for dopamine in PFC for successful performance of spatial working memory tasks. Lange and colleagues (1992) first demonstrated that withdrawal from l-dopa replacement therapy for more than 13 h in PD patients induced deficits in spatial working memory which were reversed one hour after reinstatement of treatment. Moreover, findings from imaging studies

have shown that l-dopa treatment in patients with PD serves both to normalize regional cerebral blood flow (rCBF) and to focus (BOLD) the extent of prefrontal cortical activation recruited during a working memory task (Cools et al., 2002 and Mattay et al., 2002). This restitution of normal prefrontal function was found to be correlated with a reduction in errors as compared to the same patients 12 h off l-dopa in the fMRI study, but was also manifested despite no significant deficit compared to controls in the rCBF study. Taken together, these findings were amongst the first to indicate that (i) a minimum level of dopamine transmission is required in DLPFC for cellular mechanisms in this region to function normally, and (ii) pharmacologically induced elevations of dopamine signaling above this level may further improve prefrontal function sufficiently to enhance spatial working memory performance: i.e., elevations in dopamine signaling can have "cognitive-enhancing" actions. Further insights into the essential role for dopamine in PFC in working memory stem from recent research on genotypic variations such as the met/val polymorphism of the gene encoding catechol-*O*-methyltransferase (COMT) which is thought to influence the prevailing level of dopamine in PFC. Substitution of valine for methionine in this gene results in augmented catabolism of dopamine and hence, reduced dopaminergic transmission (Weinberger et al., 2001). As might be predicted from the above findings from lesion and PD studies, individuals with greater load of the val allele demonstrated a greater extent of cortical recruitment visualized by the BOLD signal with increasing working memory load. This sign of potentially reduced efficiency of prefrontal function as measured by fMRI was associated with worse performance in comparison with subjects carrying a higher load of the met allele (Egan et al., 2001 and Goldberg et al., 2003). In accord with these findings, amphetamine (AMPH) administration has been shown to reduce cortical efficiency at the highest memory load in the N-back task, a test of working memory capacity, in subjects with the met/met genotype (Mattay et al., 2003) and coincidence of this genotype with the dopamine transporter (DAT) 10 repeat allele yields the most focused BOLD response in subjects performing a working memory task (Bertolino et al., 2006). Given this evidence for the influence of prevailing dopamine levels on the putative indices of efficiency of prefrontal cortical function, it has been postulated that dopaminergic transmission may modulate neuronal circuitry in this region in a manner which augments signal while attenuating noise. This hypothesis has been supported by the findings of Winterer et al. (2006) which showed that both PFC and associated neural circuitry carry diminished signal and elevated noise in subjects with the val/val genotype performing an oddball task that recruits these regions.

2.2. Involvement of the D1 receptor family: Localization of function

Dopaminergic innervation of the cortex in the primate shows a number of apparent differences from that in the rodent (Williams & Goldman-Rakic, 1998). Perhaps the greatest development of the dopamine system in evolution has been the dramatic elevation of D1 receptor abundancy in PFC. As Lidow and colleagues (1991) discovered, the D1 receptor family outnumbers that of the D2 receptors by more than 20 to 1 in the DLPFC of nonhuman primates. Thus, it is not surprising that signaling via the D1 receptor subtype may play the prominent role in modulating neuronal activity in this region which subserves spatial working memory. Decisive evidence for this supposition was provided by the findings of Sawaguchi and Goldman-Rakic, 1991 and Sawaguchi and Goldman-Rakic, 1994 who revealed that direct microinjections of D1, but not D2, receptor antagonists into DLPFC interrupted performance of memory-, but not visually-, guided saccades. This finding indicated for the first time that the D1 receptor was pivotal to the essential cellular mechanisms of spatial working memory residing in this region and as such highlighted the potential for deleterious consequences of a lack of dopamine signaling through this receptor for working memory, in

particular, but more importantly for cognition in general. Further, it is important to note that the mnemonic scotomas induced by localized direct application of D1 antagonists into DLPFC produce working memory deficits comparable to those produced by microlesions performed in this same region (Funahashi et al., 1993). Thus, a virtually total blockade of D1 receptors over an area of multiple cubic millimeters, potentially involving more than a million neurons in multiple layers can eradicate the function of a prefrontal cortical region in a qualitatively similar manner to a focused electrolytic lesion. This *in vivo* evidence from nonhuman primates performing a precise spatial working memory task indicates that a certain level of D1 receptor signaling is required in order to produce a functional output from prefrontal pyramidal cells. This is presumably dependent on occupancy by endogenous dopamine which suggests that a minimal level of prevailing dopamine is required for sufficient facilitation of prefrontal neurons, consistent with the findings of Brozoski et al. (1979). In a seminal study by Williams and Goldman-Rakic (1995), it was discovered that local iontophoretic application of the selective D1 antagonist, SCH39166, at a dose just above threshold for effect, resulted in enhancement of neuronal memory fields by increasing firing selectively for the preferred direction of pyramidal cells during the delay period of the ODR task. Notably, they further found that iontophoretic application of the D1 antagonist at higher ejection currents actually abolished memory fields. These findings led them to propose the inverted-U hypothesis of dopaminergic transmission in primate PFC. Specifically, it was hypothesized that dopaminergic signaling within DLPFC must fall within a limited, 'optimal' range for successful performance on working memory tasks, i.e., either suboptimal or supraoptimal signaling should impair cognition, as would occur with the natural aging process or following acute AMPH administration, respectively (Arnsten et al., 1994, Lidow et al., 1998, Goldman-Rakic, 2000 and Williams and Castner, 2006). An example of the inverted-U hypothesis in action can be seen in the previously unpublished data shown in Fig. 1. During the earliest iontophoretic experiments in primate DLPFC, less selective D1 antagonists were tested which frequently accentuated memory fields by attenuating the activity of neurons for their nonpreferred directions as well as their background activity itself. One such example is shown in Fig. 1 for SCH 23390 which was found to produce a reduction in neuronal firing which actually increased the signal-to-noise ratio of the cell's firing for its preferred direction and, hence, augmented this cell's tuning. Such data for this and other D1 antagonists which also have affinity for 5-HT_{2A} and/or α1 receptors highlights the caution with which results for pharmacological studies using these compounds must be viewed. Indeed, as described by Sawaguchi (2001), iontophoretic application of SCH23390 at currents between 20 and 100 nA typically results in sufficient reduction of neuronal firing to attenuate memory fields of prefrontal neurons.

Full-size image (68K)

Fig. 1. Accentuation of a memory field by iontophoretic application of a D1 antagonist. Activity in the control condition is shown for both preferred (left) and nonpreferred (right) directions of the cell, as raster plots of consecutive trials (top) and the summed histogram (bottom) for the cue (C), delay (D), and response (R), periods of the ODR task. This cell has a relatively high baseline firing rate, as evident for the nonpreferred direction such that the activity for the preferred direction is hard to distinguish from the noise. Upon application of SCH23390 at 25 nA, the baseline activity of the cell dropped drastically, but the task-related activity of the neuron became relatively more discernable. The signal-to-noise ratio of the delay activity for the preferred direction relative to the nonpreferred direction was increased

more than threefold. The enhancement of spatially tuned delay activity was even more pronounced immediately after the drug application was ceased. Nevertheless, this result is both quantitatively and qualitatively different from the enhancement of memory fields obtained with the selective D1 antagonist, SCH39166 (Williams & Goldman-Rakic, 1995).

To summarize and clarify, blockade of D1 receptors by D1 antagonists has dose-dependent effects on the spatially tuned delay activity of pyramidal cells. High doses (inferred from the iontophoretic ejection current) attenuate firing sufficiently to diminish or abolish memory fields, presumably by reducing D1 receptor stimulation to a level below the minimum required to produce facilitation of pyramidal cells subserving the spatial working memory process. This finding at the cellular level is therefore consistent with the findings at the behavioral level for the deleterious effects of local depletion of dopamine or microinjection of D1 antagonists on spatial working memory performance. Conversely, the enhancement of pyramidal cell memory fields by a modest level of D1 receptor blockade and their attenuation by application of a D1 agonist suggests that the level of prevailing dopamine may be higher than optimal for the signal strength of memory fields at least for a substantial proportion of the population. These latter findings therefore infer that D1 receptor stimulation does not just produce facilitation of pyramidal neurons but also invokes inhibitory mechanisms in prefrontal circuits and thus, the signal strength of pyramidal cell memory fields reflects a balance between facilitatory and inhibitory mechanisms to which D1 receptor stimulation contributes, dependent of the level of prevailing dopamine in PFC. As we discuss below, this balance is critical for understanding the influence of dopamine on working memory and reflects a multitude of signaling mechanisms that are influenced by the D1 receptor. These mechanisms have been studied in detail *in vitro* and they have been reviewed by us previously in detail (Williams & Castner, 2006).

Studies on the effects of systemic injections of D1 agonists on working memory in dopamine-deficient states in nonhuman primates have had a significant impact not only by solidifying the importance of D1 signaling in performance of cognitive tasks that recruit DLPFC, but also in highlighting this receptor family as a key target for drug development related to the treatment of cognitive deficits in disorders such as schizophrenia. Coincident with the natural aging process in both human and nonhuman primates, there is a loss of dopaminergic signaling in PFC that encompasses reduced dopamine D1 and D2 receptor binding, dopamine cell loss, as well as indices of dopamine turnover (Bannon and Whitty, 1997, de Keyser et al., 1990, Goldman-Rakic and Brown, 1981, Harada et al., 2002, Henby and Trojanowski, 2003, Ma et al., 1999, Naoi and Maruyama, 1999, Rinne et al., 1990 and Wang et al., 1998). Not surprisingly, one of the core cognitive functions sensitive to age-related decline is that of working memory (Arnsten et al., 1994, Bachman and Farde, 2001, Bachevalier et al., 1991, Bartus et al., 1978a, Bartus et al., 1978b, Nieoullon, 2002, Moore et al., 2003, Rapp and Amaral, 1989 and Volkow et al., 1998). Both the partial D1 agonist, SKF38393, and the full D1 agonists, dihydrexidine, SKF81297, and A77636, when administered acutely to aged monkeys have been shown to produce significant improvements in performance on a working memory task (Arnsten et al., 1994 and Cai and Arnsten, 1997). Providing further support for the inverted-U hypothesis, it has been found that the cognitive enhancing properties of full D1 agonists administered systemically are dose-dependent such that high doses are actually deleterious to cognition in aged monkeys. While systemic administration of D1 antagonists have been found to impair spatial working memory performance at sufficiently high doses,

D1 blockade can also reverse cognitive deficits induced by environmental or pharmacological stressors which elevate prefrontal dopamine transmission (Arnsten and Goldman-Rakic, 1998, Morrow et al., 2000, Murphy et al., 1996a and Murphy et al., 1996b). Similar to the findings for aged monkeys, acute administration of dihydrexidine to serial low dose MPTP-treated monkeys ameliorates their spatial working memory deficits (Schneider et al., 1994b). However, the partial D1 agonist, SKF 38393, had no effect on delayed response performance in this model (Schneider et al., 1994a). Together with the findings for aged animals above, this evidence suggests that attempts to ameliorate cognitive deficits arising from hypodopaminergia may succeed or fail according to the status of dopamine signaling that remains in different conditions. As pointed out by Ramos et al. (2003), D1 signaling via cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) appears to become supersensitive with aging, such that fine tuning of D1 signaling with a partial D1 agonist is clearly beneficial in aged monkeys, but fails to have this cognitive enhancing effect in the MPTP-treated monkey due to the paucity of D1 signaling normally maintained by endogenous dopamine (Schneider et al., 1994a). Thus, unlike the aged animal, signaling through the D1 receptor may actually be run down in animals that are rendered chronically hypodopaminergic via neurotoxins. However, there is evidence that even under such conditions D1 signaling may be reinstated in association with restoration of function via a mechanism which is potentially critical for neuroplasticity on the one hand and for effective cognitive strategies on the other. Thus, Criswell, Mueller, and Breese (1989) demonstrated that repeated, intermittent treatment of neonatally 6-OHDA-lesioned rats with D1 agonists could produce a long-lasting amplification of the ability of an acute D1 agonist challenge to ameliorate behavioral deficits. This phenomenon of D1 priming yielding "behavioral sensitization" to a subsequent challenge bears a strong resemblance to the classic behavioral sensitization induced by psychomotor stimulants, particularly indirect dopamine agonists, such as AMPH and cocaine (e.g., Robinson and Becker, 1986 and Kalivas and Stewart, 1991) to be discussed later in this review. This revelation has opened a new path for research on restoration of function in dopamine-deficient states. Exploiting this process, we investigated whether repeated, intermittent D1 stimulation with the full D1 agonist, ABT-431, could restore cognitive function in animals rendered D1-deficient in PFC as a result of chronic and continuing haloperidol treatment (Castner et al., 2000a, Castner et al., 2000b, Lidow and Goldman-Rakic, 1994 and Lidow et al., 1997). Remarkably, not only did this intermittent D1 regime ameliorate spatial working memory deficits during the treatment period, but this cognitive restoration persisted for more than 1 year following cessation of D1 therapy despite ongoing haloperidol administration. Taken together, these findings implicate D1 receptor signaling as having a critical role in neuroadaptive mechanisms relevant to the functions of PFC and working memory. As remarkable, the doses of the D1 agonist required to induce this apparent cognitive sensitization were in the order of 10–100 ng/kg which presumably yields only a fractional increase in signaling through the receptor. As such, the minute changes induced by each administration of the agonist must have invoked a process in which there was an incremental feedback response to further stimulation, presumably an important part of which was the prevailing dopamine levels in PFC. The significance of endogenous dopamine for this effect is evident in data we have from aged monkeys treated with chronic haloperidol. In four aged monkeys, we found that the dose of haloperidol required to induce a cognitive deficit was substantially higher, up to 0.42 mg/kg/day, than that required for the young adults described above. In fact, two of the four failed to show a deficit even at this dose which was designed to approximate a high end clinically therapeutic dose. In the two aged monkeys that did show a haloperidol-induced cognitive deficit, we used the same intermittent, D1 regimen as that published for young adults and found that even in the face of endogenous age-related dopamine depletion and haloperidol administration we were able to dramatically reinstate and

enhance spatial working memory performance (Fig. 2). Notably, the D1-stimulated cognitive recovery in these two aged females subsided at approximately 1 year after the initiation of the treatment regimen (9 months after cessation of D1 treatment) and we were able to reinstate working memory performance in these animals by repeating the D1 treatment regime despite ongoing haloperidol administration. Therefore, it can be concluded that the available endogenous dopamine and the receptor signaling that it maintains is critically involved in facilitating the mechanisms of sensitization recruited by repeated D1 agonist administration. This means that in the serial low-dose MPTP-treated model where cognitive deficits persist in the absence of motor symptoms, there is likely to be sufficient compensatory mechanisms involved which maintain some aspects of dopamine receptor signaling in order for the full D1 agonists to exert their beneficial effects. Supporting this notion, Castner and Goldman-Rakic (2004) employed the D1 sensitizing regimen to substantially enhance spatial working memory in aged monkeys but notably found that this same regimen in young monkeys failed to enhance and actually significantly impaired performance in one of these animals. Importantly, similar to the findings for the chronic haloperidol-treated young monkeys, cognition was enhanced in the aged animals for at least 1 year follow cessation of the D1 regime. Thus, despite endogenous dopamine depletion repeated, intermittent administration of a D1 agonist can recruit a mechanism akin to sensitization which can be exploited to benefit cognitive performance. This raises the question as to whether the incremental feedback in the signaling mechanisms invoked by D1 agonist administration is mediated primarily through pathways other than cAMP and PKA such that the deleterious consequences of increased signaling through the latter pathways in aged animals is avoided. Moreover, this D1-related neuroadaptive mechanism may represent a critical tool for the development of novel therapeutic strategies designed specifically to treat cognitive deficits in patients with schizophrenia who are thought to suffer from prefrontal hypodopaminergia (Abi-Dargham et al., 2002, Daniel et al., 1991, Guo et al., 2003 and Weinberger et al., 1988). Of relevance to the hypothesized glutamatergic dysfunction in schizophrenia (Coyle, 2006 and Tamminga, 1998), Criswell, Mueller, and Breese (1990) found that pretreatment with the noncompetitive NMDA antagonist, MK-801, prior to D1 agonist administration prevented the behavioral sensitization induced by D1 priming in neonatally 6-OHDA-lesioned rats. This finding is an important insight into the relation between D1 and NMDA receptor signaling which we explore below.

Full-size image (87K)

Fig. 2. Mean percent correct performance on spatial delayed response is shown for two aged female rhesus monkeys across test sessions for seven different experimental treatment conditions including baseline (a), chronic escalating doses of haloperidol up to 0.35 mg/kg/day (b), repeated, intermittent coadministration of ABT-431 (0.00001 interleaved with 0.0001 mg/kg; IM 30 min. prior to cognitive testing; see Castner et al., 2000a and Castner and Goldman-Rakic, 2004 for details) (c), post-D1 testing period with continued administration of haloperidol (d), performance at approximately 1 year post D1 treatment (e), reinstatement of cognitive enhancement under continued haloperidol treatment by replicating the original D1 agonist regime (f), and performance across sessions after completion of the second round of D1 therapy under continued haloperidol administration (g). Animals performed at a stable baseline prior to chronic administration of haloperidol, until a dose of 0.35 mg/kg of haloperidol was administered upon which performance deteriorated rapidly. Adjuvant D1 therapy progressively improved performance to their original baseline level and

performance remained stable until approximately 1 year after starting the first D1 regime, despite continued administration of haloperidol. Around 1 year, performance of these two animals was consistently lower than baseline. Thus, the D1 regime was repeated a second time which resulted again in a significant reinstatement of cognition to levels above baseline performance and this improved performance was maintained out to several months after cessation of the adjuvant D1 treatment.

3. Dependency on NMDA receptor function

3.1. Ketamine studies in human and nonhuman primates

Following the discovery that the psychotropic drug, phencyclidine (PCP), could produce psychotic-like symptoms in otherwise healthy subjects (for review see Javitt and Zukin, 1991 and Steinpresis, 1996) and exacerbation of these symptoms in patients with schizophrenia (for review see Tamminga, Holcomb, Gao, & Lahti, 1995), the significance of deficiencies in NMDA transmission for prefrontal function and working memory came to the forefront for research in this field. The property of PCP to act as a noncompetitive NMDA antagonist appears to be a common factor for compounds that can have deleterious consequences for cognition. One such drug, ketamine, commonly used as a short-acting anesthetic, has been widely exploited to study the effects of such noncompetitive NMDA blockade on prefrontal function and cognition in both human and nonhuman primates. In a seminal study, Krystal and colleagues (1994) discovered that administration of ketamine at subanesthetic doses was capable of producing both disorders in perception as well as in frontal cortical function, as measured by the Wisconsin Card Sorting Task (WCST) and the delayed recall task. A later study by Adler, Goldberg, Malhotra, Pickar, and Breier (1998) suggested that the deficits induced by ketamine in working memory were associated with a concomitant induction of formal thought disorder. In a recent study comparing the effects of ketamine with those of AMPH, Krystal and colleagues (2005a) have shown that AMPH coadministration is capable of ameliorating ketamine-induced impairment of delayed recall while both ketamine and AMPH produced thought disorders. Further, ketamine has been shown to not only impair spatial working memory, but acquisition of a spatial learning task and ketamine-induced schizophrenia-like symptoms in healthy volunteers were related to deficits in spatial learning (Rowland et al., 2005a). The finding of this study that retrieval of previously learned information was not impaired by ketamine is in contradiction to the conclusions of Ghoneim, Hinrichs, Mewaldt, and Petersen (1985), who reported that ketamine induced impairments in both immediate and delayed recall. The above studies in humans suggest, therefore, that the most profound effects of ketamine are on the PFC and associated circuitry involved in both acquisition and performance of tasks involving working memory. Indeed, Vollenweider et al., 1997a and Vollenweider et al., 1997b have reported a hyperfrontality following ketamine administration in healthy volunteers as manifested by increased regional cerebral glucose metabolism (rCMglu) in a number of distributed brain regions. This increased metabolism was associated with psychotic-like symptoms. Elevated metabolism in PFC has also been described in FDG-PET studies of patients with schizophrenia. Thus, ketamine, or more precisely the (*S*)-enantiomer of ketamine, appears to induce a significant aberration of frontal cortical function, associated with positive-like symptoms, both of which parallel the aberrations described in patients. Indeed, 6 weeks of risperidone treatment administered to medication naïve patients with schizophrenia has been associated with a reduction of rCMglu in left lateral frontal cortex and in the medial frontal cortex (Ngan, Lane, Ruth, & Liddle, 2002). Moreover, the degree to which metabolism was reduced in medial frontal cortex was correlated with the extent to which positive symptoms were reduced. Of note, chronic

ketamine abuse in humans has been found to be associated with a significant upregulation of D1 receptor binding in DLPFC (Narendran et al., 2005) similar to that observed in medication free/naïve patients with schizophrenia (Abi-Dargham et al., 2002).

Stemming from its pronounced effects on PFC in humans, its potential viability as a model relevant to schizophrenia, and its potential for abuse, the acute ketamine model has been exploited in nonhuman primates to further investigate its putative deleterious consequences for cognition. Taffe, Davis, Gutierrez, and Gold (2002b) found that acute ketamine (1.0–1.78 mg/kg) administration impaired the performance of rhesus monkeys on tasks designed to test working memory and visual recognition memory, serial self-ordered spatial search and delayed match-to-sample, respectively. These investigators have further confirmed that acute ketamine induces deficits in recognition memory by testing monkeys under the same paradigm on a task requiring visuo-spatial paired-associates learning (Taffe, Weed, Gutierrez, Davis, & Gold, 2002a). Further evidence for the utility of acute ketamine to model cognitive symptoms akin to those found in patients with schizophrenia comes from the work of Stoet and Snyder (2006) where they demonstrated that acute ketamine administration in monkeys not only impairs overall accuracy but also the animals ability to ignore task irrelevant stimuli on a Stroop-like task. Moreover, using an oculomotor paradigm, Condy, Wattiez, Rivaud-Pechoux, and Gaymard (2005) showed that acute ketamine impairs performance on an antisaccade task in nonhuman primates by increasing error rate and antisaccade latency—deficits similar to those found in patients with schizophrenia. In ongoing studies in our laboratory, we have found that acute ketamine profoundly impairs spatial working memory performance of young adult rhesus monkeys, as assessed by spatial delayed response (Roberts et al. Society for Neuroscience Astracts 2006). The acute nature of the deficits induced and its parallel to those in humans make this an ideal model for evaluating potential novel cognitive enhancers designed to target cognitive deficits in patients with schizophrenia.

3.2. Acute and subchronic PCP

Both acute and subchronic administration of another noncompetitive NMDA antagonist, PCP, have been widely exploited in nonhuman primates to model key symptoms relevant to schizophrenia. Specifically, acute PCP impairs both spatial and object working memory in nonhuman primates (Baron and Wenger, 2001 and Rupniak et al., 1991). Further, acute PCP also produces pronounced impairments on multiple tasks included in an operant test battery for nonhuman primates with deficits encompassing aspects of short-term memory and color and position discrimination (Paule, 1994). Javitt and colleagues have shown that acute PCP also induces deficits in prepulse inhibition akin to those shown by patients and that these deficits can be ameliorated by pretreatment with the atypical antipsychotic clozapine (Linn and Javitt, 2001 and Linn et al., 2003). These researchers have also demonstrated another commonality between the acute PCP model and patients with schizophrenia, particularly both are characterized by deficits in P1 and N1 aspects of auditory event related potentials (ERP) at long interstimulus intervals (Javitt et al., 2000 and Shelley et al., 1999). Subchronic PCP regimens in nonhuman primates have been used to model positive- and negative-like symptoms of schizophrenia as well as cognitive deficits related to prefrontal cortical dysfunction. Linn, O'Keeffe, Schroeder, Lifshitz, and Javitt (1999) found that repeated administration of PCP to monkeys was associated with increased scanning and psychomotor depression. Using a 14 day subchronic PCP administration regime in vervets, Jentsch et al., 1997, Jentsch et al., 1999a and Jentsch et al., 2000 showed pronounced impairments in performance on an object retrieval detour task for up to 4 weeks post-PCP and the magnitude of an individual's impairment was correlated with the degree of reduction in dopamine

transmission in PFC. Notably, they also reported a significant reduction in dopamine transmission in striatum following repeated PCP treatment and previous studies have shown that performance on this task relies upon the integrity of corticostriatal connections. They were, however, able to ameliorate deficits on the object retrieval task induced by PCP by acute administration of either clozapine or a D4 antagonist (Jentsch et al., 1997 and Jentsch et al., 1999b). While subchronic PCP has been considered one of the leading nonhuman primate models of schizophrenia, several factors must be taken into account in evaluating the utility of this model for targeting cognitive dysfunction in schizophrenia. Specifically, the nature and persistence of cognitive deficits induced by these regimens is unclear as evidenced by the amelioration of the PCP-induced deficit in object retrieval performance by 28 days after cessation of subchronic treatment (Jentsch, Roth, & Taylor, 2000). Further, it is also not known as to whether there are enduring alterations in either D1 or NMDA receptor signaling in the model reminiscent of putative alterations in these systems in patients with schizophrenia. Finally, there is evidence for PCP-induced neurotoxic consequences that are inconsistent with the neuropathological changes in the disorder (Arnold, 2000, Harrison, 1999, Lewis and Gonzalez-Burgos, 2000, Selemon and Rajkowska, 2003 and Selemon et al., 1995).

3.3. Acute and subchronic MK-801

Similar to PCP, there have been a series of investigations in the nonhuman primate examining the cognitive consequences of both acute and subchronic administration of the selective, noncompetitive NMDA antagonist, MK-801. When administered acutely, MK-801 has been shown to impair performance on a delayed matching-to-sample task, a test of visual recognition memory, in a dose-dependent manner, together with significant increases in the animals' response biases (Ogura & Aigner, 1993). Acute MK-801 induces more selective impairments in the performance of monkeys on an operant battery than acute PCP does, i.e., MK-801 disrupts learning and time perception to a greater extent than short-term memory and color and position discrimination (Frederick et al., 1995 and Paule, 1994). Specifically, in this model deficits on delayed matching-to-sample are only observed following higher doses of MK-801 which also induce significant reductions in responding (Buffalo, Gillam, Allen, & Paule, 1994). It is of note though that in a recent study, Tsukada et al. (2005a) found that acute intravenous administration of MK-801 (at doses of 0.03, 0.1, and 0.3 mg/kg) significantly impaired the performance of monkeys on the classic ODR task, suggesting that similar to other noncompetitive NMDA antagonists, MK-801 within a given dose range is capable of inducing impairments in spatial working memory. Several investigators have examined the consequences of subchronic dosing with MK-801 for cognition in rhesus monkeys. Popke, Allen, Pearson, Hammond, and Paule (2001) reported that MK-801 administered chronically in a low dose (0.1 mg/kg, b.i.d.) or a high dose (1.0 mg/kg; b.i.d.) over a 2 year period to juvenile monkeys did not impair short-term memory, as measured by delayed matching-to-sample, but transiently (first 6 months) impaired acquisition of a task designed to assess color and position discrimination. Given the contrast in these findings with those discussed above for acute MK-801, the question is raised as to whether over such a prolonged administration period tolerance develops to the cognitive-impairing aspects of this compound. In the recent study by Tsukada and colleagues (2005a), however, they found that twice daily administration of a low dose of MK-801 (0.03 mg/kg; IM) over 13 days produced marked impairments in the monkeys ability to perform the ODR task and this deficit was shown up to 15 h following the last dose of MK-801. Furthermore, the deficit in spatial working memory induced by subchronic low dose MK-801 was associated with D1 upregulation in PFC as measured by PET and reduced dopaminergic/glutamatergic

transmission as measured by microdialysis. On the basis of the hypothesis that the vast majority of patients with schizophrenia smoke as a means of self-medication, Tsukada and colleagues (2005b) examined the consequences of acute nicotine administration on chronic MK-801-induced changes in prefrontal function. Consistent with this hypothesis, the nicotine treatment restored prefrontal dopamine levels and normalized the D1 receptor binding potential in conjunction with a partial improvement in spatial working memory performance. This latter finding suggests that nicotine receptor stimulation is capable of producing a substantial change in the state of dopaminergic signaling in PFC that arises from a hypoglutamatergic condition. Similar to PCP, it is yet to be determined whether the alterations in prefrontal function brought about by subchronic treatment with MK-801 are actually enduring phenomena or a reflection of withdrawal processes, however, the effectiveness of nicotine in this model supports its potential for the study of cognitive enhancers in schizophrenia and a hypothesized dependence of working memory on normal interactions between dopamine and glutamate receptor transmission.

3.4. Relation to dopamine

It is clear from the above findings that both subchronic PCP and MK-801 treatments produce multiple effects which concord with the known neurobiological aberrations in schizophrenia and in both cases result in significant dopamine depletion in PFC. Therefore, through a mechanism requiring an enduring change of state NMDA receptor antagonism has a critical influence on dopamine function in cognition. This evidence points out that an underlying primary deficit of NMDA transmission in schizophrenia may be the root cause of dopamine dysregulation in the disorder and may also be the primary perpetrator in the disruption of prefrontal function. Several key observations, however, are not entirely consistent with this hypothesis. For example, as regards the hypodopaminergia in PFC and cognitive deficits induced by PCP, the latter was reversible by acute administration of two drugs known to act via blockade of dopaminergic receptors, i.e., clozapine and a D4 antagonist—both of which likely exerted at least some portion of their beneficial cognitive consequences by increasing dopaminergic transmission in PFC (e.g., Ichikawa et al., 2001 and Youngren et al., 1999). Furthermore, clozapine was able to reverse deficits in PPI induced by acute PCP (Linn et al., 2003). Moreover, just as AMPH partially reverses the ketamine-induced deficit in delayed recall (Krystal et al., 2005a), it has also been observed that lamotrigine, mGLur2 agonists, and AMPA antagonists are capable of partially reversing working memory deficits induced by acute ketamine (Anand et al., 2000, Krystal et al., 2005b and Moghaddam et al., 1997), inferring that, at least in part, at the dose ranges of ketamine administered in these studies, the cognitive deficits arise from a hyperglutamatergic state that exerts its deleterious effects via the AMPA receptor. As noted above, acute MK-801 also induces a hyperglutamatergic state and deficits in both cognition and pre-pulse inhibition (PPI) (Keith, Mansbach, & Geyer, 1991). The attenuation of PPI by MK-801 can be reversed by a combination of acute clozapine and nicotine administration (Levin, Petro, & Caldwell, 2005). In addition, MK-801-induced working memory impairments in rats, as tested by the radial arm maze, can be reversed by a combination of idazoxan and raclopride at doses which produce a similar degree of occupancy at α2 and D2 receptors, respectively (Marcus et al., 2005). This combination of dopamine and adrenoreceptor stimulation has been shown to elevate dopamine levels in rodent PFC (Hertel, Fagerquist, & Svensson, 1999). Thus, from multiple lines of evidence involving a number of animal models, there is a strong indication that the dopaminergic system can exert a powerful regulation over glutamatergic transmission that has important implications for cortical function and cognition. In fact, there is substantial data *in vitro* for such regulation which will be discussed in detail below, but for now we wish to

highlight the significance of this regulation from data obtained *in vivo*. Just as the mGLUR2 agonist has been shown to attenuate glutamate release via a presynaptic mechanism, there is also clear evidence from paired cell patch recordings in PFC that D1 receptor stimulation can dramatically attenuate excitatory postsynaptic currents (EPSCs) induced by action potential generation in the presynaptic neuron (Gao et al., 2001 and Gonzalez-Burgos et al., 2002). This suppressive action of D1 receptor stimulation may contribute to the ability of a D1 antagonist to actually enhance memory fields in prefrontal neurons. As shown in Fig. 3, we have been able to demonstrate this effect *in vivo* by measuring the cross-correlation of spiking in pairs of primate prefrontal pyramidal cells. Iontophoretic application of A77636 leads to an attenuation of the peak in the correlogram which is representative of a reduction in the functional connectivity between the two cells at an ejection current of 25 nA. This effect occurs with little reduction in the background activity (top panel). Conversely, iontophoresis of the selective D1 antagonist, NNC2210, can be seen to unmask functional connectivity between another pair of cells, as demonstrated by an emergence of a clear peak in the correlogram despite little increase in the background activity of the cells (bottom panel). These data show that D1 receptor regulation of glutamate transmission within prefrontal local circuits may contribute to the enhancement of memory fields by a D1 antagonist and the reversal of this effect by a D1 agonist, as demonstrated by Williams and Goldman-Rakic (1995).

Full-size image (10K)

Fig. 3. D1 modulation of functional connectivity between prefrontal pyramidal cells. (a) Cross-correlograms of spike-timing for a pair of pyramidal cells recorded simultaneously at the same site. The timing of spikes in the putative postsynaptic neuron are shown relative to the occurrence of spikes in the putative presynaptic neurons (time zero). In the control condition (left), a clear short latency peak in spiking was observed which is consistent with a monosynaptic excitatory connection between the two cells. This local excitatory connection was virtually abolished by application of the D1 agonist A77636, with only a modest decrease in the background activity of the postsynaptic cell (right). (b) The cross-correlograms for another pair of pyramidal cells showed no evidence of functional connectivity in the control condition but a clear short-latency peak in spiking was unmasked by application of the D1 antagonist NNC 22-0010 (NNC2210), a close analog of SCH23390. These findings demonstrate the functional D1 receptor modulation of a local feedforward excitatory connection *in vivo* which reflects the presynaptic inhibition of spike-induced glutamate release found *in vitro*. Note: the small gap in spikes at time zero results from the inability to differentiate spikes occurring virtually simultaneously when recorded by the same electrode.

4. Nexus of dopamine/glutamate interactions

4.1. The molecular basis of D1/NMDA receptor interactions

Pointers to the significance of interaction between dopaminergic and glutamatergic transmission came from apparently disparate lines of evidence at cellular and behavioral

levels. Chiodo and Berger (1986) demonstrated that iontophoretic application of dopamine at currents that produced little or no inhibition of firing of neostriatal neurons in rodents led to an increase in glutamate-evoked excitation and GABA-induced inhibition. Ejection of dopamine at higher currents dramatically reduced glutamate-evoked excitation, while still augmenting the inhibitory response to GABA. Hu and Wang (1988) found that iontophoresis of D1 agonists at low ejection currents (5 nA) could also facilitate excitatory responses to glutamate and Hu and White (1997) later confirmed this interaction of dopamine and glutamate transmission, discovering that activation of both D1 and D2 receptors were required for this effect. On the other hand, models of behavioral sensitization revealed that MK-801 could block the sensitization produced by amphetamine (Criswell et al., 1990 and Karler et al., 1989), despite the fact that repeated administration of MK-801 is capable of producing sensitization itself (Wolf & Khansa, 1991). Specific aspects of the interaction between D1 and NMDA receptors were brought to light by Cepeda and colleagues (1993) who showed that stimulation of D1 receptors facilitated NMDA receptor currents in rat striatal slices while D2 receptor stimulation had, if anything, the opposite effect, in addition to attenuating responses evoked by non-NMDA glutamate receptor agonists. The D1 agonist potentiation of NMDA-induced current could be substantially reduced by L-type calcium (Ca^{2+}) channel blockers, concomitant with the finding that a D1 agonist could also augment barium (Ba^{2+}) currents in neostriatal neurons. This provided the first strong evidence that modulation of intracellular calcium levels might be critical for D1 stimulation to exert its potentiating effects on NMDA-mediated glutamatergic transmission. Further, Cepeda et al. (1999) showed that this interaction is not limited to corticostriatal glutamatergic transmission, but also includes glutamatergic transmission within the cortex itself as demonstrated in ex situ tissue from children with catastrophic epilepsy. Since there has been so much speculation as to the specific functional roles of the D1 versus the D5 receptor, it is of great interest to note that the D1 receptor-related facilitation of NMDA currents was not observed in D1 deficient mice (Levine et al., 1996). We will come back to further evidence for this receptor subtype specificity below. In keeping with the evidence that the cAMP/PKA pathway is a major signaling route for the D1 receptor, Greengard and colleagues have shown that PKA-induced dephosphorylation of the dopamine associated phosphoprotein of molecular weight equal to 32 kDa (DARPP-32) leads to facilitation of the NMDA receptor (Blank et al., 1997) and this effect is mediated by potent inhibition of protein phosphatase 1 (PP-1) which normally dephosphorylates the NR-1 subunit of the NMDA receptor (Snyder, Fienberg, Huganir, & Greengard, 1998). Flores-Hernandez et al. (2002) demonstrated the significance of this D1 signaling cascade for facilitation of NMDA currents in dissociated striatal neurons revealing that this facilitation was indeed dependent upon PKA, DARPP-32, and PP-1. Tseng and O'Donnell (2004) have gone on to show that the synergism of D1/NMDA receptor interaction is dependent not only upon PKA but also upon intracellular calcium in pyramidal cells of rat PFC. At the same time, Chen, Greengard, and Yan (2004) showed that extracellular calcium was required for the calcium-mediated facilitation of the NMDA receptor and interference with protein kinase C (PKC) signaling could also attenuate D1 receptor potentiation of NMDA currents in PFC. Thus, there appear to be at least two critical signaling pathways involved in the D1/NMDA receptor interaction, the first being through PKA, DARPP-32, and PP-1 and the second one resulting from elevation of intracellular calcium levels involving an interaction between the PKA and PKC signaling pathways. However, direct coupling of NMDA and D1 receptors at the molecular level may be just as important to their synergism (Cepeda & Levine, 2006). One such mechanism involves the trafficking of receptors into the plasmalema. As shown by Scott et al. (2002), NMDA receptor activation increases recruitment of D1 receptors into the plasmalemma of dendritic spines in primary cultures of striatal neurons and this translocation can be reversed by an

NMDA receptor antagonist or by removal of calcium. As a result of this mechanism, NMDA receptor stimulation produces a large rise in the abundance of spines containing the D1 receptor and this translocation has been demonstrated to result in increases adenylyl cyclase activity in isolated membranes. In a further study, Scott et al. (2006) uncovered a calcium-independent NMDA-stimulated increase in D1 receptor-containing spines in striatum. Part of this mechanism may be attributed to the formation of D1/NMDA heteroreceptor complexes, effectively trapping subsets of D1 receptors that diffuse within the plasma membrane. Thus, acute elevations of glutamatergic transmission can produce a increased D1 receptor function at the level of dendritic spines, whereas hypoglutamatergia or lack of NMDA receptor stimulation may result in significant loss of this function. Therefore, the self-supporting roles, or synergy, between the D1 and NMDA receptor forms a focal point for mechanisms of synaptic plasticity, learning, and memory. Much of this synergism has been demonstrated in vitro in slices of rodent or primate PFC. For example, Seamans, Durstewitz, Christie, Stevens, and Sejnowski (2001) have shown that D1 receptor stimulation enhances the NMDA-mediated components of excitatory postsynaptic currents (EPSCs) of layer V pyramidal cells via a postsynaptic mechanism. This facilitation may contribute to the lack of depression in the excitatory postsynaptic potential (EPSP) due to increased depolarization through the NMDA receptor component of EPSCs. Stemming from the theory that NMDA-mediated states of depolarization amongst a coordinated ensemble of neurons permits cohesion of cell firing driven by recurrent excitation (Durstewitz et al., 2000b and Lisman et al., 1998), it can be postulated that support of sustained synaptic inputs by the synergistic actions of NMDA and D1 receptor stimulation may play a key role in the generation of persistent activity in PFC.

5. Functional aspects of dopamine and NMDA receptor actions in cognition

5.1. State-dependent action receptors of NMDA up-states

One potential manifestation of the synergistic action on sustained synaptic inputs between D1 and NMDA receptor stimulation is the generation of up-states as originally described in striatum and then PFC (Lewis and O'Donnell, 2000, West and Grace, 2002 and Wilson and Kawaguchi, 1996). Periods of up-states, as measured by a relative depolarization of neurons over a period of hundreds of milliseconds, are associated with periods when the cell shows increased excitability to its excitatory inputs. It has been hypothesized that these up-states are generated by a combination of recurrent excitatory and inhibitory inputs arising within local circuits (McCormick et al., 2003 and Shu et al., 2003). In tandem with the depolarization, synaptic barrages and noise can contribute to an increased probability of firing. As such the up-states provide a functional substrate for persistent activity which can be rapidly initiated and terminated by specific synaptic inputs to the neuron. Lewis and O'Donnell (2000) have shown that stimulation of the ventral tegmental area (VTA) containing mesocortical dopamine neurons (Thierry, Blanc, Sobel, Stinus, & Golwinski, 1973) in the rodent had differential effects upon prefrontal cortical activity dependent upon the presence of up-states in the neurons. When burst firing was simulated by a train of stimulation in the VTA, a long-lasting switch of membrane potential to the up-state was observed which could be blocked by a D1 receptor antagonist. Moreover, oscillations in local field potentials of the VTA are synchronized with up-states in PFC and transient block of VTA activity leads to disruption of up-states and loss of LFPs in PFC (Peters, Barnhardt, & O'Donnell, 2004). These findings suggest that there is a critical relation between the local circuits generating up-states in PFC and their dopaminergic modulation arising from the mesencephalon. In addition to these findings, Seamans and colleagues (Lavin et al., 2005) have suggested that there are two

modes by which dopamine neuron firing may have an influence on up-states and the excitability of neurons in PFC. The first is the generation of a fast postsynaptic potential postulated to be mediated by glutamate and the second is a long-term potentiation of firing in response to transient dopamine release. Since the phasic firing of dopamine neurons has been hypothesized to reflect a temporal prediction error in reward (Hollerman & Schultz, 1998), these findings were used to suggest that the fast inputs arising from glutamate may reflect a salient signal whereas the prolonged modulation of firing may reflect a state-dependent change in prefrontal cortical circuitry. While these predictions provide a fascinating new route for investigating prefrontal function, it must be recognized that VTA stimulation is not synonymous with temporal reward prediction error and that prefrontal cortical circuitry in the absence of a demanding cognitive process may lack specific glutamatergic excitatory inputs which may be normally make a substantial contribution for promoting transitions to increased excitability in the functional organism. Thus, it remains an open question as to whether the phasic firing of dopamine neurons contributes to a salience-related signal in PFC. In striatum, the phasic firing of dopamine neurons resulting from stimulation of the median forebrain bundle for periods as brief as 125ms (yielding just 6 cycles of a sinusoidal stimulation) can invoke a robust phasic peak of firing in striatal neurons (Williams and Millar, 1990a and Williams and Millar, 1990b). Similar activation of striatal neurons by phasic MFB stimulation has been shown to be highly attenuated by systemic administration of a D1 antagonist (Gonon, 1997). Thus, it is proposed here that synergism between dopaminergic and glutamatergic inputs arriving on prefrontal neurons in relation to the onset of a stimulus requiring working memory processing is a vital component in the generation of persistent activity that can subserve the neural representation of the stimulus, dependent on context. In other words, we suggest that there is normally a phasic dopamine input on to PFC cells that enables NMDA receptor dependent transitions in to a state of increased excitability which promotes mnemonic activity. In this model, co-release of glutamate from dopaminergic neurons would be anticipated to increase the cell's responsiveness to the immediately following dopamine receptor activation and the dopamine release itself would lead to synergistic support of activation resulting from sufficiently strong and cohesive sensory inputs and promotion of any ensuing persistent activity that is NMDA-dependent. However, just as transition to up-states can be switched on or off at any second, and just as attention to any stimulus can be relevant at one moment and irrelevant the next, the D1 support of NMDA transmission is temporally constrained such that it can be terminated by specific synaptic inputs. One illustration of how this might work is the ODR task itself, where illumination of the central fixation stimulus does not accurately predict the timing of reinforcement at the end of the trial since the animal can take varying periods of time to actually fixate on the stimulus. However, illumination of the peripheral cue stimulus does provide this temporal prediction, which is contingent on its association in long term memory with a learned motor response—a saccade—to the remembered target location. This phasic response of dopamine neurons would be predicted from the findings of Schultz and colleagues (1993) who investigated conditioned and unconditioned dopamine neuron activity in the acquisition of a delayed response task. Moreover, results from the same study also predict some conditional firing of dopamine neurons in response to the extinction of the fixation stimulus at the end of the delay period, as this acts as a "Go" signal for the animal to make the appropriate saccade, and which therefore closely predicts time to reinforcement. As noted by Schultz and colleagues, dopamine neurons do not show elevated or burst firing during the delay period itself which indicates (1) that dopamine neuron firing is particularly important to the initiation of persistent activity and (2) that the supposition by Seamans et al. that phasic activation of dopamine neurons produces a prolonged change in state of PFC local circuits may equate to a dopamine-mediated support of delay activity subsequent to phasic

dopamine release. Indeed, the firing induced by phasic stimulation has been shown to result in activation of striatal neurons for several seconds in the anesthetized rat (Gonon, 1997 and Williams and Millar, 1990a).

While the salience-related firing of dopamine neurons in relation to a conditioned stimulus that temporally predicts reward and requires an instrumental response is a reasonably well-established concept, there still remains an important distinction between the probability of reinforcement and the quantity and nature of the reward itself. As shown by Watanabe (1996), prefrontal neurons, even within the principal sulcus region, are powerfully influenced by contingencies of the rewards given at the end of a trial and such information can be as strong an influence on neuronal activity as task specific information. In fact, although neuronal activity related to spatial working memory is more likely to be involved in the expectancy of reward, Watanabe, Hikosaka, Sakagami, and Shirakawa (2005) showed that many prefrontal neurons have more memory-related activity for preferred as opposed to nonpreferred rewards and preferred rewards produce better task performance in the monkeys. Thus, reward contingency provides a motivational guidance for behavior which is integrated with that executed by working memory at the level of PFC. However, the monitoring of outcome and expectation of reward integrates systems beyond just the fundamental signal provided by dopamine neuron firing. This is evident from the findings of Leon and Shadlen (1999) who showed that, when a signal was provided that indicated increased magnitude of reward, the delay activity corresponding to the preferred direction in space in an oculomotor task was enhanced in PFC but not in the frontal eye fields (FEF). Since, as these authors point out, the DLPFC and FEF have rather equivalent dopaminergic innervation from the midbrain, the differential influence of reward contingency on neurons in these two regions can not be readily explained by dopamine neuron firing. Rather, a key distinction on the functional input to these two regions lies in the known projections from ventrolateral regions of orbitofrontal cortex to the region of the principal sulcus and not to the region of the FEF (Cavada and Goldman-Rakic, 1989, Cavada et al., 2000, Ongur and Price, 2000 and Selemon and Goldman-Rakic, 1988). These same regions of orbitofrontal cortex have been highly implicated in the processing the valence signal of predicted rewarding/aversive events (Beaver et al., 2006, Hikosaka and Watanabe, 2000, Hikosaka and Watanabe, 2004, Jensen et al., 2006, Roberts, 2006, Roesch and Olson, 2004, Rolls, 2000 and Schultz et al., 2000).

In liaison with orbitofrontal cortex, the anterior cingulate cortex (ACC) also plays a critical role in monitoring outcome but one that is more tuned to the assessment of whether a particular response is appropriate, given the expectation of reward in a particular context (see Rushworth, Walton, Kennerle, & Bannerman, 2004, for review). This role has been postulated to involve a signaling of the degree of conflict between the response being made and the likelihood of obtaining the best outcome (Carter, Botvinick, & Cohen, 1999). An alternative, but not entirely distinct hypothesis is that ACC is a central node in the circuitry used for error detection, as manifested by the error-related negative potential (ERN; Gehring & Fencsik, 2001). In this respect, ERN recorded by scalp electrodes has been shown to be abnormally low in patients with schizophrenia, despite abnormally large potentials related to commission of correct responses and evidence from other potentials of error awareness (Alain et al., 2002 and Mathalon et al., 2002). Holroyd and Coles (2002) were among the first to develop a computational model for the generation of the ERN which includes the input from the reward prediction error provided by the mesocortical dopamine system. It is therefore of interest to note that a significantly reduced ERN has been found in otherwise high functioning elderly subjects, and this may be directly explained from the model by an attenuation in the phasic firing of dopamine neurons (Nieuwenhuis et al., 2002). Consistent

with this hypothesis, Zirnheld et al. (2004) have shown that haloperidol administration can lead to an impairment in learning associated with a reduction in ERN. As yet, there are no direct data on the role of NMDA transmission in the functions of ACC; however, as shown by Vollenweider et al., 1997a and Vollenweider et al., 1997b, ketamine induces increased metabolic activity of ACC in healthy human subjects in association with induction of psychosis-like symptoms (see also Rowland et al., 2005b). It has also been found that ketamine-induced increases in rCBF in ACC in patients with schizophrenia which show an acute exacerbation of their psychotic symptoms in response to the drug (Lahti et al., 1995 and Holcomb et al., 2005). Moreover, the ketamine-induced psychosis-like symptoms in healthy human volunteers are negatively correlated with dopamine efflux in ACC and DLPFC, as measured by D2/D3 radioligand binding, despite the fact that there is no significant change in the level of dopamine release in these regions (Aalto et al., 2005). This result would not be predicted from a D2 antagonist—typical antipsychotic—approach to treatments of symptoms, particularly those exacerbated by ketamine administration. Thus, it is interesting to note that patients withdrawn from antipsychotic medication for 3 weeks or more show a significant increase in metabolism in ACC (Holcomb et al., 1996 and Miller et al., 1997). High frequency trains of stimulation to the VTA in the rat have been shown to produce a transition in membrane potential to prolonged depolarization and a frequency-dependent intense persistent firing in ACC neurons (Onn & Wang, 2005). This effect was attenuated by systemic administration of a D1 agonist and abolished by acute dopamine depletion, indicating an important role for dopamine receptor stimulation, particularly of the D1 family subtype, for this activation of ACC. Taken together, these findings indicate that there is an interaction between D1 and NMDA receptor function at the level of ACC which is likely to have a substantial impact on central executive and working memory functions, in close relation to DLPFC. Specific studies are required to determine the extent to which local interactions between D1 and NMDA receptor transmission influence the error and conflict-related processes in this region.

5.2. The neuronal basis for D1/NMDA receptor actions in cognition

While the evidence for a critical interaction of NMDA and D1 receptors on cortical neuronal activity is well substantiated, it remains to be determined as to how this interaction leads to selective mnemonic activity that is highly tuned to the information being represented. To better understand this issue, it is important to recognize that the influence on the activity of both pyramidal cells and interneurons must operate in a concerted manner based on local circuit function within PFC and the extrinsic circuits/networks with which it communicates. Within the local circuits themselves, there are functional nodes related to cell phenotype and structural components related to radially arranged aggregations of neurons and their dendrites as well as the afferents/efferents that they receive. Beginning with the major cellular phenotype, there are multiple aspects of D1 receptor modulation which can interact with both NMDA signaling and the depolarization state of pyramidal cells. A number of these aspects were first described by Yang and Seamans (1996) for layer V pyramidal cells. These researchers showed that dopamine acting via D1 receptors facilitated EPSPs in these cells and potentiated L-type calcium channel conductances, while at the same time attenuating N- and P-type calcium conductances primarily associated with inputs from distal dendrites on to the apical trunk. Surmeier and colleagues (1995) were able to confirm this D1 modulation of calcium ion channels in rat neostriatal neurons, and demonstrated that the D1 modulation of L-type channel conductances in these cells facilitates their firing provided the cells were at a sufficiently depolarized membrane potential (Hernandez-Lopez, Bargas, Surmeier, Reyes, & Galarraga, 1997). Thus, increased NMDA channel opening with membrane depolarization

can be indirectly supported by the D1 receptor influence on calcium conductance. In addition, a dopamine D1-mediated potentiation of the persistent inward sodium conductance (INaP) which can normally facilitate firing in these neurons has been identified obtained in slices from rat PFC (Gorelova and Yang, 2000 and Yang and Seamans, 1996). However, this finding was not observed in acutely isolated rat PFC neurons and it remains to be seen if this enhancement of INaP by D1 stimulation depends on indirect or as yet unknown signaling mechanisms that may not be present in an isolated neuron preparation (Maurice, Tkatch, Meisler, Sprunger, & Surmeier, 2001). From their observations, Yang and colleagues (1999) posited a model of how D1 modulation tunes the signal throughput of pyramidal cells in layer V and how this tuning might be altered in schizophrenia. In this model, D1 stimulation would facilitate those EPSPs arriving at the soma and increase the likelihood to reach threshold for spiking such that for any given input to this region D1 stimulation would produce a greater output, with presumably a greater frequency response for the neuron. At the same time, they proposed a filtration mechanism which acts in conjunction with the signal amplification process. They describe this filter as mediated by the attenuation of calcium influx through high threshold calcium ion channels, gating inputs from the distal dendrites. The significance of this filter would then be that original excitatory inputs from afferents to the distal dendrites would have to be sufficiently strong (and presumably summative) in order to undergo amplification in the perisomatic region. Such a filtration mechanism could be posited to be more selective to inputs on a particular dendritic branch or more widespread inputs to the distal dendrites in general. On the other hand, it could also be posited to be preferentially selective for inputs where there is a strong association between D1 and NMDA receptors and where AMPA receptors may be more abundant on postsynaptic sites. Thus, the trapping of D1 receptors in the neck of dendritic spines could be important for this selection (Scott et al., 2006). In addition, the functional recruitment of AMPA receptors to the membrane would also contribute to this effect.

This possibility has been revealed by a recent study in primary cultures of rat PFC neurons in which it was found that D1 stimulation results in trafficking of GluR1-containing AMPA receptors to the membrane surface via a PKA-dependent mechanism (Sun, Zhao, & Wolf, 2005). However, it was only with subsequent NMDA receptor stimulation that GluR1 subunits became translocated into synapses from an extrasynaptic pool. Thus, a conjunction of signaling through the D1 and NMDA receptors can lead to additional signaling from afferent inputs to PFC pyramidal cells which enables fast synaptic transmission. This particular aspect of the interaction between D1 and NMDA receptors highlights an important role in a powerful mechanism of synaptic plasticity, one we shall come back to later when we discuss the relevance of the interaction to learning and neuroadaptive processes in the brain. We are currently studying *in vivo* mechanisms that may support the *in vitro* evidence for a functional filtration of glutamatergic inputs to prefrontal pyramidal cells. The *in vitro* data described above suggest that elevations of D1 receptor stimulation would attenuate firing that results from glutamatergic inputs on to distal dendrites. We have directly tested this mechanism of modulation by iontophoretic application of D1 agonists and antagonists in a cyclic manner, interleaved with brief (5 s) pulses of glutamate application. As shown in the example of Fig. 4, the periodic pulsatile application of glutamate induces brief bursts of spiking in pyramidal cells which are reasonably consistent over time. Upon interleaved application of the D1 agonist, A77636, there is a delayed, but robust, attenuation of the glutamate-evoked activity which persists long after cessation of D1 agonist application (top panel). Conversely, in another neuron in which the same pulsatile glutamate application was tested (bottom panel), interleaved iontophoresis of the D1 antagonist, SCH39166, actually produced a potentiation of the glutamate-evoked bursts in spiking. As pointed out in the study

of dorsal horn neurons by Millar and Armstrong-James (1982), spikes evoked by glutamate iontophoresis can be recorded along the dendritic tree of a neuron at large distances from the soma and, in fact, there are hot spots for such glutamate-evoked activity. We have observed a similar finding *in vivo* and, indeed, we believe that the glutamate-evoked activity that we have recorded was frequently obtained at a distance of tens, if not hundreds, of microns from the soma as we are able to track these spikes and their potential waveform over considerable distances *in vivo*. Therefore, the actions of D1 receptor stimulation we have seen may be affecting glutamatergic inputs at locations high up and above the apical dendrite of the neuron, if not in the distal dendrites themselves. This means that we may well have detected a functional corollary of D1-mediated blockade of calcium ion channels, presumably N- and P-type, *in vivo*. Note that (1) any presynaptic influence of the D1 agonist on endogenous glutamate release would be completely overwhelmed by the postsynaptic action of the exogenous glutamate, and (2) we do not expect that the D1 agonist would increase GABAergic inputs sufficiently to attenuate glutamate-evoked firing, since preliminary data using the specific $GABA_A$ antagonist, SR9553, does not show reversal of the D1 effect. Moreover, D1 agonists usually have to be applied, continuously, and close to fast-spiking cells in order to affect their activity (usually as an increase in spiking). As quantified by Krimer, Jakab, and Goldman-Rakic (1997), there are multiple appositions of tyrosine hydroxylase-containing nerve terminals on the apical and distal dendrites of pyramidal cells in PFC, and thus, there is a clear potential for dopamine to exert modulation of high threshold calcium conductances at this level in the neuron (Seamans et al., 1997 and Young and Yang, 2004).

Full-size image (64K)

Fig. 4. D1 modulation of pyramidal cell activity evoked by exogenous glutamate. Given the presynaptic modulation of glutamatergic transmission by D1 receptor signaling, it can be postulated that the response of a cell to exogenous glutamate application is a direct result of postsynaptic activation. Thus, we applied glutamate (10 mM, pH 8.0, 40–50 nA) in order to examine D1 modulation of glutamate-evoked activity at the postsynaptic level. (a) Spike trace of mean firing rate of a pyramidal cell recorded over a period of over 20 min. Regular bursts of activity were evoked via cyclic application of brief pulses of glutamate (which avoid any saturation or depolarization block). Interleaved application of the D1 agonist A77636 (in 15 s periods finishing 1s before each glutamate pulse) led to a dramatic reduction in the evoked burst after a delay of more than 2 min. This suppression of evoked response showed signs of only a very slow recovery. (b) Glutamate-evoked bursts in another pyramidal cell. Application of the D1 antagonist SCH39166 led to a gradual increase in the burst amplitude after a delay of minutes. Evoked activity was still discernibly high at the beginning of the recovery period but showed some signs of reduction within 10 min. Subsequent application of A77636 resulted in a gradual reduction of burst amplitude. These data suggest that there is an endogenous dopaminergic tone that modulates the postsynaptic response to glutamate through D1 receptor activation but activity can become even further suppressed by elevations in D1 receptor stimulation.

Another critical part of prefrontal circuitry that is modulated by the D1 receptor and has an important potential for interaction with the NMDA receptor is found in the local circuit interneurons themselves. It has been shown that D1 stimulation potentiates local feed forward excitatory inputs on to a subpopulation of fast-spiking GABAergic interneurons (Gorelova, Seamans, & Yang, 2002). In this study, dopamine was found to induce membrane depolarization and increase excitability in rat prefrontal cortical neurons *in vitro*. This depolarization could be mimicked by a D1 agonist and one mechanism that was shown to partly account for this effect was a D1-mediated suppression of a voltage-independent potassium current. In slices from primate PFC, dopamine, via the D1 receptor, can increase the excitability of fast-spiking interneurons, but not other populations of interneurons that show adaptation in their firing (Kroner, Krimer, Lewis, & Barrionuevo, 2006). In addition, Gao and Goldman-Rakic (2003a) demonstrated that dopamine, acting on D1 receptors, could directly enhance the excitability of a subgroup of fast-spiking cells, such that a single EPSP could induce spiking at a precise latency. From these findings, it is evident that D1 receptor facilitation of feedforward excitation of fast-spiking interneurons within local circuits can provide an important mechanism for temporally precise high frequency inhibitory inputs to pyramidal cells within the circuit. Evidence for the functional significance of this D1 effect was found by Gonzalez-Islas and Hablitz (2001) who demonstrated that D1 receptor stimulation could result in a large increase in IPSCs, not only in pyramidal cells but also in interneurons in cortical slices. These findings are also consistent with the finding that stimulation of the VTA by local injection of NMDA produces an increase in firing in this type of neuron in PFC (Tseng et al., 2006). It has long been considered that the activity of parvalbumin-containing fast-spiking interneurons in neocortex is highly dependent upon NMDA receptor-mediated glutamatergic inputs. One of the first demonstrations of this NMDA-dependency was obtained from intracellular recordings of entorhinal cortex *in vitro* which revealed that the enduring excitation of these cells by synaptic activation was predominantly NMDA receptor-dependent (Jones & Buhl, 1993). Kawaguchi (1993) found similar evidence for the NMDA-dependency of interneurons in PFC and further demonstrated that the conjunction of local stimulation with induced depolarization could produce repetitive firing in fast-spiking interneurons that was blocked by an NMDA receptor antagonist. It should be noted, however, that in direct paired cell recordings, unitary EPSPs and EPSCs evoked by action potentials in the presynaptic pyramidal cell, were found to be primarily AMPA-receptor mediated in fast-spiking neurons of the rat neocortex in vitro (Angulo, Rossier, & Audinat, 1999). Although it was found that depolarization of the postsynaptic cell increased the NMDA component of EPSCs, the combined effects of repetitive stimulation and depolarization were not tested. From the evidence above, it can be seen that dopamine modulates the activity and signal processing of both pyramidal cells and fast-spiking neurons in PFC. As we will discuss below, the perisomatic inhibition provided by the fast-spiking neurons, primarily of the basket cell phenotype, is a critical regulator of firing and persistent activity in the pyramidal cells and may represent an important site of dysfunction in schizophrenia.

5.3. Presynaptic mechanisms regulating PFC circuits

Earlier we described an aspect of D1 modulation which regulates the functional circuitry within PFC via presynaptic mechanisms. Thus, as already noted, activation of the D1 receptor presynaptically inhibits glutamate release on terminals of pyramidal cells which synapse on neighboring cells of the same type. This site of action of D1 modulation is highly significant for two reasons. First, it may be an important site for amelioration of cognitive deficits and other symptoms that might arise from an acute hyperglutamatergic state whether induced

pharmacologically or otherwise. In this respect, D1 agonists may exert actions on prefrontal circuitry that could parallel those of mGLUR2 metabotropic glutamate receptor agonists. It is therefore interesting to note that the mGLUR2 agonist, LY354740, can ameliorate working memory deficits induced by ketamine in a dose-dependent manner (Krystal et al., 2005b). Second, D1 receptor signaling at this site may provide a profound regulatory control over the inclusion of pyramidal cells into an active recurrent, excitatory network. This form of regulation essentially increases the necessity for pyramidal cells to be in a depolarized state, or up-state, in order to enter and remain within these networks. It remains to be seen how far this presynaptic mechanism interacts with the modification of presynatic spike—induced postsynaptic currents by terminal membrane fluctuations that propogate along the axons of prefrontal pyramidal cells (Shu, Hasenstaub, Duque, Yu, & McCormick, 2006). In addition to this regulation of recurrent excitatory circuitry, the D1 receptor also exerts a precise control over the recurrent inhibitory circuitry that operates in synergy with the pyramidal cell networks. In keeping with this notion, D1 receptor activation has been shown to have a presynaptic influence at the terminals of GABAergic interneurons projecting to nearby pyramidal cells (Gao & Goldman-Rakic, 2003a), suppressing inhibitory inputs from fast-spiking interneurons. However, the enhancement of inhibition between other interneuronal subtypes and pyramidal cells induced by dopamine was not found to result from a presynaptic D1 action (Gao, Wang, & Goldman-Rakic, 2003b). These findings highlight the differential circuitry influenced by dopamine whereby D1 receptor action can have a different influence on inhibition in the perisomatic region as opposed to the peridendritic region of pyramidal cells.

5.4. The role of synchronization

The multiple sites of action for D1 receptor signaling in this circuitry allows for an integral modulation of critical recurrent signaling networks which are almost certainly essential for the generation of persistent activity in prefrontal neurons and for the process of working memory. It can be computed under such circumstances that the precise timing of action potentials in fast-spiking neurons has a critical influence on the transition to or from up-states in pyramidal cells within the same active circuitry, enabling a spatially and temporally coordinated series of events to occur within the circuit for generation and destruction of a discrete mnemonic representation (Constantinidis, Williams, & Goldman-Rakic, 2002). On this point, Kawaguchi (2001) investigated the firing patterns in cortical neurons that result from an NMDA receptor-dependent synchronized activation state induced by reduction of extracellular Mg^{2+}. In this preparation, a synchronization of firing was found between pairs of pyramidal cells, between pyramidal cells and fast-spiking interneurons, and between pairs of these interneurons. Fast-spiking neurons fired fastest during the initial bursts of activity, reaching frequencies up to 400 Hz, and continued to fire at high frequencies for several seconds. Pyramidal cells began firing at high frequency during the burst period, and then after a brief period of inhibition, continued to fire at relatively high frequency which eventually began to oscillate and fail. These findings show that NMDA-dependent shifts in depolarization can have dramatic effects on firing in both pyramidal cells and interneurons, but their spiking is synchronized and in this way pyramidal cells can continue to fire for tens of seconds despite ongoing GABAergic inputs. As we have already described above, stimulation of the VTA can also produce prolonged firing states in prefrontal pyramidal cells and therefore, it can be expected that a synergism between depolarization supported NMDA receptor signaling and phasic dopamine transmission provides an ideal circumstance for the generation of representational persistent activity. The role of the fast-spiking neuron in this process has been the subject of a number of computational models. Some models ascribe the

function of fast-spiking activity to the suppression of background activity and activity related to interfering stimuli, while leaving the generation and maintenance of persistent activity to the recurrent excitatory networks (Durstewitz & Seamans, 2002). However, other models give fast-spiking activity a far more central role. For example, in one model that examined the degree of synchrony of inhibitory inputs in local networks it was observed that spiking in the model neurons became more coherent with their synaptic input and could yield an increased firing rate (Tiesinga, Fellous, Salinas, Jose, & Sejnowski, 2004). This effect was greatest when oscillations in the input network were in the gamma frequency range. Consistent with this prediction, Miller and Wang (2006) have described the generation of an inhibitory signal, or "inhibitory feedback control" that enables the active comparison of incoming sensory information with the contents of that already held in working memory. They found that synchronized firing of fast-spiking neurons within the gamma range at 40 Hz was optimal for this process. Given the significance of the attentional processes ascribed to gamma oscillations in the cortex (Lee, Williams, Breakspear, & Gordon, 2003), it becomes evident that synchronized firing within the gamma frequency range may be critical for the transition of state in prefrontal circuitry that can generate mnemonic persistent activity and interactions between D1 and NMDA receptor signaling may provide both the ignition and fuel for this process. Finally, it should be acknowledged that working memory is not just provided for by the strength of delay activity, but also requires a tuning of that activity to accurately reflect the information being encoded. We have previously shown that local fast-spiking interneurons provide significant isodirectional inhibition to neighboring pyramidal cells which plays a critical role in shaping their spatially tuned activity and memory fields (Rao et al., 1999 and Rao et al., 2000). Moreover, we have defined this interaction to be structurally constrained in relation to microcolumnar elements in PFC. It will therefore be essential to ascertain in future research the significance of synchronization for this isodirectional inhibition and the exact contribution of D1/NMDA interactions to its generation.

5.5. Role in synaptic plasticity and learning

Both dopamine neuronal activity and NMDA-dependent changes in the state of neuronal excitability have been implicated in learning processes and the synaptic plasticity that underlies them. The relevance of the "reward-related" activity of dopamine neurons to learning has been a subject of intense scrutiny by Schultz and colleagues. In one of their first predictive models (Guigon, Dorizzi, Burnod, & Schultz, 1995), they posited that dopamine neuron firing contributed to activity-dependent changes in synaptic transmission that enabled the development of long-term memory for recruitment of working memory processes. A critical part of this learning arose from the ability of reward contingency to enable sustained activity in prefrontal neurons. Hence, we are able to see the relevance of the reward contingency studies by Watanabe (1996) and others to the adaptive nature of prefrontal function. An essential component of this influence of reward contingency arises from the reward prediction error encoded by dopaminergic neurons (Hollerman & Schultz, 1998). These cells fire when reward is received unexpectedly, either at random, or at the very outset of learning a new task. As learning proceeds, and rewards become more predictable in parallel with increased frequency of correct responses, so the response of dopaminergic neurons to the actual reward dwindles. At the same time, the original cue stimulus which guides the response of the animal, now increasingly predicts reinforcement and recruits dopamine neuron firing as a result. Moreover, in accord with learning theory, the response of dopamine neurons and the learning of behavioral responses to conditioned stimuli were shown to be dependent on the presence of reward prediction errors and not on the simple

association between stimulus and reward (Waelti, Dickinson, & Schultz, 2001). Thus, the occurrence of errors in relation to an emitted behavior elicits a critical dopamine signal during the learning process. These aspects of dopamine signaling may have important conjunctions with those of NMDA receptor signaling during learning. Any given stimulus, in the right context (as guided by long-term memory), may have a considerable transient influence over neuronal activity in the forebrain. Thus, for example, simple spatial stimuli and complex objects can evoke a seemingly sensory response in DLPFC and the inferior convexity in nonhuman primates (Suzuki and Azuma, 1983 and Wilson et al., 1993). These sensory responses could be phasic and/or tonic in nature and occurred while the animals performed simple eye fixation tasks. Hence, conditions are ideal within PFC for transitions in state that may convert this sensory information into a mnemonic representation. In other words, it is reasonable to expect that such sensory responses are capable of producing depolarizations in prefrontal neurons sufficient to facilitate NMDA receptor transmission. Assuming that this state, at least partially, remains when dopamine neurons fire in relation to an unexpected reward, then a conjunction between this state of prefrontal neurons and their phasic dopaminergic input has the potential to modify synaptic transmission related to the stimulus over a number of consecutive presentations. This would suggest that there is a dopaminergic influence on NMDA-mediated synaptic plasticity, attributable to D1 receptor signaling. In fact, there is direct evidence for this specificity of action on layer V pyramidal cells in PFC (Young & Yang, 2005). It has been demonstrated that stimulated release of dopamine, evoked by brief tetanic stimulation, acts via D1 receptors to promote short-term potentiation of relatively low frequency synaptic inputs from layer V, and to suppress post-tetanic potentiation of relatively high frequency synaptic inputs from layer III, presumably via presynaptic inhibition of glutamate release. Moreover, the NMDA receptor-dependent LTP produced in PFC by high frequency tetanic stimulation of the hippocampus has been shown to require concomitant stimulation of D1 receptors in association with the stimulated release of dopamine (Gurden, Takita, & Jay, 2000). From the evidence reviewed above, the postsynaptic calcium-dependent facilitation of NMDA receptor currents by D1 stimulation, combined with (i) the NMDA-mediated trapping of D1 receptors and depolarization-dependent translocation to the synapse, and (ii) recruitment of AMPA receptors to the membrane by a D1/NMDA receptor interaction, represents one of the most powerful mechanisms for synaptic plasticity in the central nervous system. When this mechanism is coupled to conditional dopamine neuron firing it may provide a fundamental neuroadaptive substrate for learning and memory, as may have already been detected for the appetitive instrumental learning that is dependent on the potentiation of basolateral amygdala-evoked firing of n. accumbens neurons by D1 and NMDA receptors (Floresco et al., 2001 and Smith-Roe and Kelley, 2000).

5.6. Role in sensitization

Sensitization can be defined as the development of an augmented response to a stimulus upon repeated presentations of that stimulus. The response can be detected as behavioral, physiological, or chemical, and the stimulus can be in the form of an actual stimulus, a pharmacological manipulation, or an environmental manipulation such as a stressor. The significance of this phenomenon in primates was made all too apparent in clinical cases of drug addiction, where it was observed that users of psychostimulants showed elevated responses of particular behaviors upon repeated use of a drug (Ellinwood et al., 1973 and Snyder, 1973). When the behavioral aspects of this phenomenon were studied formally in animals, it soon became apparent that administration of psychomotor stimulants in an intermittent, rather than chronic paradigm, using slowly escalating doses, could effectively

mimic the typical binge crash pattern of stimulant abuse in humans taking amphetamines and/or cocaine (Flemenbaum, 1977, Kalivas and Stewart, 1991 and Robinson and Becker, 1986). AMPH sensitization in the rodent, as induced by repeated, intermittent escalating low doses of AMPH over a period of weeks, is characterized by enhanced behavioral responsivity (hyperlocomotion and more 'intense' stereotypic behavior) as well as enhanced dopamine release in nucleus accumbens, stiatum and medial PFC in response to a subsequent acute low dose challenge (Paulson and Robinson, 1995 and Robinson et al., 1985). In the nonhuman primate, we have shown that an analogous repeated, intermittent escalating low dose regimen of AMPH administered over either 12- or 6 weeks produces a robust sensitization of hallucinatory-like behaviors in response to an acute AMPH challenge, as well as long-lasting psychomotor depression and profound cognitive deficits in the absence of a challenge which persist for more than 1 year following cessation of the escalating dose regime (Castner and Goldman-Rakic, 1999, Castner and Goldman-Rakic, 2003, Castner et al., 2000a, Castner et al., 2000b and Castner et al., 2005). In contrast to the findings from the rodent studies, there is actually a significant reduction in dopamine utilization in dorsolateral PFC resulting from AMPH sensitization in the nonhuman primate in association with morphological changes, including reduced spine density in this region (Castner et al., 2005 and Selemon et al., 2006). It is important to note that the latter two findings are consistent with reports of prefrontal cortical dysregulation in patients with schizophrenia (Black et al., 2004, Broadbelt et al., 2002, Garey et al., 1998, Glantz and Lewis, 2000 and Kalus et al., 2000). It could be postulated that the enduring, and often 'seemingly permanent' behavioral sensitization expressed in response to an acute low dose AMPH challenge (as shown out to more than 1 year in the rodent (Paulson, Camp, & Robinson, 1991) and more than three years in the nonhuman primate (Castner & Goldman-Rakic, 1999) also Castner and Goldman-Rakic, unpublished observations may represent the highest form of neuronal plasticity in the primate brain. Therefore, it is not surprising that the induction and maintenance of behavioral sensitization to psychomotor stimulants, such as AMPH and cocaine, is critically reliant upon both D1 and NMDA receptor stimulation. In fact, direct injection of the D1 antagonist SCH23390 into the VTA has been found to diminish the effects of acute amphetamine on locomotor activity and to abolish the development of sensitization to amphetamine (Stewart & Vezina, 1989). Thus the stimulation of local D1 receptors within the VTA appears to be a critical route by which repeated AMPH administration produces a distinct form of neuroadaptation. However, although systemic injection of SCH23390 exerts the same effects, it does not block the sensitization induced by repeated injections of morphine into the VTA (Vezina & Stewart, 1989). Thus, although behavioral sensitization may have common forms of manifestation, it can arise from distinct mechanisms, dependent on the compound being tested. AMPH sensitization has been shown to affect brain regions in addition to the VTA. Direct injection of AMPH into the VTA produces an increased sensitivity of nucleus accumbens neurons to the inhibitory effects of D1 agonists (Hu et al., 2002) and results in a D1 receptor-dependent induction of immediate early gene expression which may contribute to the sensitization process. In addition, a transient period of autoreceptor subsensitivity has been found a few days after repeated amphetamine administration that disappears within a week to 10 days, at which time increased dopamine release is found in nucleus accumbens in response to an amphetamine challenge (Wolf, White, & Hu, 1993). These findings indicate that there are multiple changes that occur in dopamine transmission as a result of repeated amphetamine administration, at least within the mesolimbic system. There is also evidence for considerable changes in glutamatergic transmission. This was first evident in the study of behavioral sensitization in response to repeated administration of a D1 agonist, described as D1 priming, which induced an equal degree of sensitization with treatment intervals ranging between 1 day and 2 weeks (Criswell et al., 1990). Pretreatment with MK-801 blocked D1

priming and raised the suggestion that signaling through D1 and NMDA receptors might contribute to a unique form of neural plasticity which may be significant for learning and mental disorders. It was later shown that intracranial injections of the competitive NMDA receptor agonist D(−)-2-amino-5-phosphonopentanoic acid (AP-5) as a pretreatment for amphetamine administration repeated four times over 12 days prevented sensitization when the injection was placed into the VTA but not into *n*. accumbens. Thus, both D1 and NMDA receptor activation are required in the VTA for repeated doses of amphetamine to induce sensitization. It should be noted, however, that as might be expected for a positive feedback process in the brain, glutamatergic transmission in general plays an important role in the process. Rats pre-exposed to amphetamine in VTA show an elevated degree of locomotor activity in response to a subsequent systemic administration of amphetamine but coinjection with the competitive groups I and II metabotropic glutamate receptor (mGluR) antagonist (RS)-α-methyl-4-carboxyphenylglycine (MCPG) blocks this sensitization. In addition, Karler, Calder, & Turkanis (1991) found that systemic coadministration of the AMPA/kainite receptor antagonist DNQX could also block amphetamine sensitization and this effect was specific to those particular behaviors that showed an exaggerated response to a subsequent amphetamine challenge. Since it has been demonstrated that acute injections of amphetamine (all be it at high doses of 5.0 mg/kg, s.c.) evokes an efflux of glutamate in nucleus accumbens and VTA that takes hours to develop (Xue, Ng, Li, & Wolf, 1996), it is clear that glutamate transmission is centrally involved in the circuitry that generates aspects of behavioral sensitization. Wolf & Xue (1999) were able to show that the amphetamine-induced glutamate efflux in VTA is prevented by pretreatment with either MK-801 or SCH23390 at doses which have been shown in other studies to block the behavioral sensitization to repeated amphetamine administration. Moreover, this behavioral sensitization is also blocked by prior ibotenic acid lesions of medial PFC which lead to a slight reduction of basal glutamate levels in VTA. Therefore, amphetamine-induced glutamate release in the VTA is actually essential to the development of sensitization, and PFC may have a critical role in providing glutamatergic inputs to this region. In fact, amphetamine sensitization appears to produce a temporary supersensitivity of AMPA receptors in VTA such that local injection of an AMPA antagonist at this site produces a greater elevation of both dopamine and glutamate levels in nucleus accumbens and VTA following repeated systemic amphetamine treatment (Giorgetti, Hotsenpiller, Ward, Teppen, & Wolf, 2001). In horizontal slices of the VTA that preserves its afferent pathways from PFC, amphetamine was found to enhance EPSCs evoked by afferent stimulation in a dose-dependent manner, and this effect was mainly dependent on AMPA/kainite receptor activation (Prieto-Gomez et al., 2005). Moreover local injections of either NMDA antagonists or D2 antagonists into the PFC have been shown to block the induction of sensitization to amphetamine (Karler, Bedingfield, Thai, & Calder, 1997).

Finally, it must be noted that MK-801 itself is capable of producing behavioral sensitization which can only be partially blocked by pretreatment with SCH23390 but which does lead to a more rapid rise of dopamine levels in nucleus accumbens and D1 supersensitivity on neurons in that region (Wolf et al., 1993). It can be posited therefore, that behavioral sensitization results from protracted periods of elevated dopaminergic and glutamatergic transmission in VTA and nucleus accumbens that involves prefrontal afferents to the VTA, D1 and NMDA receptor activation, and supersensitivity of AMPA receptors in that region. Thus, the capacity of D1/NMDA interactions to recruit AMPA receptors to the membrane and potentiate depolarized states and persistent firing may be an essential component of neuroadaptive mechanism in the CNS, providing a powerful engine for learning and memory but also conferring the vulnerability that such a process can lead to disruption of prefrontal function in behavioral adaption and its dopaminergic regulation. It should be noted that a signaling

pathway has now been described which pinpoints the significance of this interaction for extracellular signal-regulated kinase (ERK) 1/2, an important regulator of gene expression and cellular mechanisms of plasticity. Both acute and sensitizing administration regimes of the partial D1 agonist SKF38393 have been found to induce a prolonged NMDA receptor-dependent elevation of phosphorylated ERK in layers II/III of medial PFC in rats with neonatal 6-OHDA lesions (Papadeas, Blake, Knapp, & Breese, 2004). In addition, phosphorylated cAMP response element-binding protein (CREB) was detectable in medial PFC but not in other brain regions after D1 sensitization. Similarly, amphetamine has been shown to produce phosphorylation of ERK in the striatum by a combined action at D1 and NMDA receptors and blockade of the ERK pathway attenuates the behavioral sensitization induced by a single administration of psychostimulants (Valjent et al., 2005). These findings led to the suggestion that the ERK pathway acts as a detector of the coincidence between NMDA and D1 receptor stimulation in order to produce long-term adaptation of cell function via CREB control of gene transcription. Thus, dramatic or long term changes in signaling at either or both of these receptors may directly impact adaptive mechanisms of the cell in order to alter its function, or *en mass*, to alter the function of entire regions and networks in the brain.

6. Significance and conclusions

Both the D1 and NMDA receptor have been shown to have a powerful influence on prefrontal function and working memory and their interaction particularly comes into play when neurons become depolarized in relation to afferent stimulation. Their direct interaction not only bolsters synaptic plasticity by recruitment of AMPA receptors but also signals the neuron to adapt to changes in dopaminergic and glutamatergic transmission. Thus the role on this interaction in learning may be paramount, including the temporal prediction error encoded by dopamine neurons, the mismatch between response and potential outcomes encoded by neurons in ACC, and the valence signals to DLPFC signifying the rewards associated with particular events. It is not surprising then, that the persistent activity that is the engine of prefrontal function, and the recurrent excitation and inhibition it depends upon, is highly dependent on the appropriate conjunction of signaling through these two receptors. This dependence is highlighted by the effects of non-NMDA antagonists, not just on working memory itself but also on the coherent guidance of behaviors and the interpretation of events and their relation to each other and to behavior. It is equally evident from the study of D1 agonists and antagonists, under many conditions of altered dopaminergic status, that dopamine acts as an active filter via this receptor, regulating the signal-to-noise ratio of prefrontal neurons in a concentration dependent manner which is tuned to cognitive demands. Implications for changes in the signaling of both receptors in schizophrenia point to the necessity to understand the interaction of their signaling rather than focus on a “glutamate” or “dopamine” hypothesis, and calls for the need to investigate further the role of sensitization in the development of cognitive deficits as well as psychosis and negative symptoms of the disease. We hope then that this review will encourage research that will combine measures of function at many levels from the molecular to human cognition in order to explore the D1/NMDA interaction in tests lasting milliseconds or years. For, just as signaling through these receptors may trigger the recruitment of a neuron into an up-state, it may also switch whole networks in the brain into a permanently altered state

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