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Suppression From Afar: Striatal D2 Receptors Temper Inhibition in Cortex

11 July 2011. Altering dopamine signaling in one region of the brain can have substantial repercussions elsewhere, according to a study published online on July 5, 2011, in the Proceedings of the National Academy of Sciences. The laboratories of Wen-Ju Gao at Drexel University in Philadelphia, Pennsylvania, and Eric Kandel at Columbia University in New York joined forces to examine the synaptic consequences of overexpressing D2 dopamine receptors in the striatum of mice. They turned up a deficit in GABAergic transmission in the prefrontal cortex—a result that links two disparate findings in schizophrenia and suggests that impaired cognition stems from overactive dopamine signaling in the striatum.

The work explores the synaptic repercussions in mice engineered to overexpress D2 receptors specifically in the striatum, as found in schizophrenia. This mouse model debuted in 2006 with a study that found cognitive and motivational deficits in these D2 receptor-overexpressing (D2R-OE) mice (see [SRF related news story](#)). This suggested that hyperactive dopamine signaling—widely viewed as causing psychosis—may also spur the cognitive and negative symptoms of schizophrenia ([Simpson et al., 2010](#)). The new study adds heft to this idea by finding decreased GABAergic signaling in the prefrontal cortex, a region important for cognition and which also shows decreases in GABA-related molecules in postmortem studies of schizophrenia.

Turning down inhibition from afar

Because D2R-OE mice show deficits in prefrontal cortex-dependent tasks, including those measuring working memory and incentive motivation (see [SRF related news story](#)), first author Yan-Chun Li and colleagues made brain slices of the medial prefrontal cortex. Using whole-cell patch clamp recordings to detect the currents impinging upon layer V pyramidal neurons, the researchers found that spontaneously occurring inhibitory post-synaptic currents (sIPSCs) in D2R-OE mice occurred half as often and were about half the size of those recorded in control littermates. These changes were not accompanied by frequency or amplitude differences in miniature IPSCs (mIPSCs), which reflect the state of the pre-synaptic vesicle release machinery or post-synaptic receptors, respectively. The inherent excitability of layer V pyramidal cells was also unchanged in D2R-OE mice. Together, these results point to a suppression of inhibitory signals in the medial PFC in D2R-OE mice.

In contrast, the researchers found evidence for enhanced excitatory neurotransmission. The spontaneously occurring excitatory post-synaptic currents (sEPSCs) in D2R-OE mice occurred about twice as frequently as those in control littermates, though they were the same size, and no difference in mEPSCs was detected.

Blunted sensitivity to dopamine

The PFC receives some of the far-reaching dopamine projections of the brain, and previous studies have found that dopamine can modulate inhibitory synaptic transmission there. This prompted the researchers to check whether the subdued inhibitory transmission found in D2R-OE mice would be

similarly sensitive to dopamine. The results, though complicated, suggest that the inhibitory signals are somewhat impervious to dopamine. In control mice, the lowest concentration of dopamine increased the size of IPSCs evoked by stimulating the neuron's synaptic inputs, whereas two higher concentrations decreased IPSC size. This pattern was not matched in D2R-OE mice: the lowest concentration of dopamine had no effect on IPSC size, whereas a higher effect increased IPSC size, and the highest concentration had no effect.

Further experiments explored whether D1 or D2 receptors were behind this change in dopamine sensitivity. While a D1 receptor agonist similarly modulated IPSCs in both kinds of mice, a D2 receptor agonist decreased the IPSC size in controls only, and was ineffective in D2R-OE mice. This suggests that, in addition to a decrease in inhibitory synaptic transmission in the PFC, these inhibitory signals are not as open to modulation, both of which could contribute to cognitive defects.

Explaining action at a distance

These abnormalities in the PFC could reflect a developmental program gone awry as a result of too many D2Rs in the striatum. Alternatively, it could stem from aberrant striatal signaling in adulthood, which could influence signaling in the PFC through a network of connections. To get at this, the researchers removed the extra D2 receptors in young adult animals by feeding them doxycycline for two weeks, which turned off the promoter driving D2R overexpression. This reversed the synaptic signal changes in D2R-OE mice, which had both spontaneous IPSCs and EPSCs that were no different from controls. This argues that aberrant dopamine signaling in the striatum reverberates throughout a mature network of connections in the brain to influence signaling in the PFC.

Similarly, the motivation deficits found in D2R-OE mice reverse upon doxycycline treatment; however, the working memory and conditional associative learning do not. This suggests that the synaptic changes documented here in the PFC may contribute more to the motivation deficits and less to the cognitive impairments found in these animals.

The authors note at least two ways by which D2R overexpression in the striatum may alter PFC function. Altered activity in the striatum could result in altered activity in the PFC via a domino effect through a pathway traveling from the striatum, to the pallidum (the basal ganglia output), to the thalamus, and then to the cortex. Alternatively, D2R overexpression in the striatum could alter dopamine release in the PFC via dopamine-containing ventral tegmental neurons, which receive striatal inputs. However it happens, the results illustrate the far-reaching effects of a fairly specific manipulation, and suggest that the cognitive and negative symptoms of schizophrenia may stem from a primary defect in the striatum, rather than the cortex.—Michele Solis.

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Li YC, Kellendonk C, Simpson EH, Kandel ER, Gao WJ. D2 receptor overexpression in the striatum leads to a deficit in inhibitory transmission and dopamine sensitivity in mouse prefrontal cortex. *Proc Natl Acad Sci U S A*. 2011 Jul 5.

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Comment by: [Barbara K. Lipska](#)

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Kellendonk et al. have reported that transient and selective overexpression of dopamine D2 receptors in the mouse striatum during development has long-term effects on cognitive function mediated by the prefrontal cortex. This is an important study providing further elegant evidence that disturbed function of the subcortical dopamine system may affect dopamine functioning in the entire circuitry and have important adverse behavioral consequences. It is unclear, however, whether this mouse model provides us with new clues about the pathophysiology of schizophrenia. A hyperdopaminergic hypothesis of schizophrenia originated from pharmacological studies showing that dopamine D2 antagonists have antipsychotic efficacy and dopamine agonists, such as amphetamine or apomorphine, can induce psychosis ([Randrup and Munkvad, 1974](#); [Snyder, 1972](#)). This hypothesis has been supported recently by clinical data from brain imaging studies with D2 receptor ligands showing higher presynaptic dopamine terminal activity in at least acutely psychotic patients when challenged with amphetamine or at baseline ([Abi-Dargham et al., 2000](#); [Hietala et al., 1994](#)). Accordingly, amphetamine or apomorphine-induced hyperactivity and stereotypy in rodents have been postulated as psychosis-like behaviors and such pharmacological models have been widely used for screening antipsychotic drugs. Currently, all antipsychotic drugs on the market act by reducing D2 signals in brain, most by functioning as antagonists of D2 receptors. It is also clear, however, that although these drugs are beneficial, they do not cure the disease. It is also increasingly clear that although there is considerable evidence about the role of the dopaminergic system in the pathophysiology of schizophrenia, genetic association and linkage between schizophrenia and the genes encoding dopamine receptors or transporter remain weak ([Daniels et al., 1995](#); [Kojima et al., 1999](#)). Thus, dopamine abnormalities may not be at the core of pathophysiology. The exploration of genetic models beyond the dopamine system may perhaps prove more fruitful for capturing many aspects of this devastating illness.

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Comment by: [Stephen J. Glatt](#)

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The development of animal models is a critical need in the realm of schizophrenia research. Current models relying on lesions or pharmacological manipulations may be relatively nonspecific, and thus, less than optimal for unraveling the underlying pathophysiology of the disorder. Models in which specific key candidate genes are up- or down-regulated may be better models because the effects can be more subtle and, as in this study, a very specific behavioral deficit may result. Ultimately, many genes, including DRD2, may be involved in discrete aspects of the illness, and when those gene deficiencies co-occur in certain individuals, schizophrenia may manifest. This study developed and validated a model, but the study itself is a model for how such studies should be done.

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Comment by: [Daniel Weinberger, SRF Advisor](#)

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The study by Kellendonk and colleagues from Eric Kandel's lab at Columbia is a landmark piece of science in a number of respects. Transgenic overexpression of D2 receptors in the mouse striatum is a novel model of how a developmental perturbation in striatal dopaminergic signaling has long-term implications for processing of information through critical brain circuits involved in learning and memory. The model may also have implications for understanding abnormalities of the function of this circuit in schizophrenia. There is ample evidence from clinical and from postmortem studies that cortical-striatal circuits are involved as part of the pathophysiology of schizophrenia. The work of Ann Marie Thierry and colleagues in Paris in the 1970s first drew attention to the fact that cortical function impacted on the striatal dopamine system ([Thierry et al., 1973](#)). A ground-breaking study of [Pycock et al.](#) (1980) showed that DA depletion in the prefrontal cortex affected DA parameters in the striatum, by increasing specifically DA turnover and D2 receptor expression. They were the first to report an inverse relationship between cortical and subcortical DA activity, a finding that has been reproduced in a broad variety of studies in rodents, nonhuman primates, and in humans (e.g., [Jaskiw et al., 1990; 1991; Deutch, 1993; Saunders et al., 1998; Bertolino et al., 1999; 2000; Meyer-Lindenberg et al., 2002; 2005](#)). The mechanism of this effect is still uncertain, but likely involves the anatomical connectivity between prefrontal cortex and brainstem DA neurons, which involve a tonic inhibitory brake, such that normal prefrontal cortical function translates into tonic inhibition of DA neurons that project to the striatum ([Carr and Sesack, 2000](#)). Thus, prefrontal cortex is in a position to release that brake and increase DA-related reinforcement of environmental stimuli, when circumstances dictate an appropriately DA response, as might be expected during learning and memory. It is tempting to conclude from these various experiments over 30 years that the prefrontal

cortex regulates the reward/reinforcement effects of DA neurons based on experiential context. The studies beginning with Thierry showed that when prefrontal function was disturbed, DA activity was no longer appropriately regulated. The study of Kellendonk et al. is consistent in terms of the circuitry involved with these earlier studies, but instead of creating an abnormality at the level of the prefrontal cortex and disrupting regulation of the DA reward system, they changed DA function directly in the striatum and their behavioral readout suggested that abnormal function of prefrontal cortex was a result. The “yin-yang” relationship again was reproduced, but now starting with the yang rather than the yin. The yang-based mechanism of the striatal effect on cortical function and cortical DA turnover is likely complex, including via striatal feedback to mesencephalic DA neurons that project to cortex and via striatal projections through thalamus back to prefrontal cortex.

The findings of Kellendonk et al. illustrate how critical prefronto-centric circuitry is, especially during development, for the elaboration of behaviors and biochemical phenomena related to schizophrenia. Their important finding that restoring normal DA function in the striatum did not restore prefrontal cognition indicates that it was no longer a matter of acute excess D2 activity in the striatum that accounted for the cognitive abnormalities. Presumably, in developmentally wiring the circuitry in and out of prefrontal cortex, abnormal information processing through the striatum (which feeds back to prefrontal cortex and presumably formats cortical information for frontally mediated action) changes the wiring diagram, producing more trait-like functional abnormalities. Trait-like changes in prefrontal function and molecular biology related to early developmental perturbations of other prefronto-centric neuronal systems implicated in schizophrenia, for example, temporal-limbic inputs to prefrontal cortex, also have been described (see [Lipska and Weinberger, 2000](#), for review).

Finally, the study has important implications for neurobiologic models of phenomena associated with schizophrenia. PET studies of patients with schizophrenia suggest that, to the extent that striatal DA activity may be increased ([Abi-Dargham et al., 1998](#)), it is a state phenomenon, linked to active psychosis. On the other hand, evidence of abnormal cortical DA activity and function is more trait-like and persists between periods of florid psychosis. The persistent changes in cortical function independent of fluctuations in striatal D2 expression may provide some parallels to the clinical phenomena. It is surprising that these animals showed no deficits in activity or in prepulse inhibition of startle, both of which have been interpreted as measures of excess DA activity and as animal correlates of psychosis. The failure to observe these phenomena may be related to species differences—here mice as compared to earlier models with rats—or it may reflect relatively more selective overexpression of D2 receptors in the dorsal striatum. This latter finding is of interest as recent studies from Laurelle and colleagues at Columbia, using high-resolution PET imaging, have found that increased DA activity in patients with schizophrenia may also involve preferentially the dorsal striatum. The changes in DA measures in the cortex also bear interesting relationships to those found in patients with schizophrenia. The transgenic mice showed no change in markers of cortical DA innervation, which has been reported in schizophrenia ([Akil et al., 1999](#)), but they did show reduced cortical DA turnover, evidence of which also has been reported in schizophrenia ([Weinberger et al., 1988](#)). During D2 overexpression, D1 receptor sensitivity appeared to be increased, but during normalization of D2 overexpression, D1 receptors in prefrontal cortex appeared to be functionally subsensitive. These variations in cortical DA function may correspond to apparent reduced cortical DA activity as a trait characteristic and enhanced cortical DA activity as a correlate of acute psychosis ([Winterer and Weinberger, 2004](#)).

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Comment by: [Ricardo Ramirez](#)

Submitted 28 February 2006

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I read the paper by Simpson et al. from Kandel's group with much interest. It seems that the dopamine hypothesis of schizophrenia has many lives and appears and reappears in many forms. This latest reincarnation combines hyperdopaminergia with the neurodevelopmental hypothesis of the disorder. My initial enthusiasm, however, waned upon closer reading of the paper.

It seems that the various conclusions reached are not wholly supported by the results. The prefrontal cognitive deficits of the D2 mice seem to be extremely subtle. It is difficult to infer specific impairments of working memory performance solely from acquisition effects. The D2 mice require more trials to reach criteria, but how do the mice perform once these criteria are met? To be sure, schizophrenia patients present with learning impairments, but their working memory deficits are persistent and ever present. It is interesting that high-order "executive functions" as measured by attentional set-shifting (e.g., intra- and extra-dimensional shifts) are spared in these mice, given that these depend on the rodent medial frontal cortex and are modulated by dopamine as well ([Birrell and Brown, 2000](#); [Tunbridge et al., 2004](#)). Thus, contrary to what has been reported, these mice show normal behavioral flexibility. We are thus left with mice whose prefrontal function, at least behaviorally, is relatively intact.

A more pressing issue is the controls that were used for the experiments. The authors did not compare D2 mice (carrying both transgenes) with mice carrying the same two transgenes but who did not at any time express the D2 receptor. Instead the authors compared the D2R expressing mice with their littermates who carried no transgene or either the CamKII or D2 transgenes alone. They state that these groups showed no differences, but their control groups were of nine mice, so there is a potential lack of power to detect any differences between these groups. It will be of interest to know whether any of the other striatal D2 overexpressing lines that were created show similar phenotypes. Lacking this information, we cannot be sure that the subtle effect on behavior is not due to the disruption of another gene by the random insertion of the D2 transgene.

This paper is a natural extension of many years of work showing the balance between cortical and subcortical dopamine systems ([Grace, 1991](#)). A brief transient overexpression of striatal D2Rs during development does seem to affect DA function long into adulthood. This mouse model also reflects the long-used strategy of probing those systems thought to underlie the pathophysiology of schizophrenia. These models are of great benefit, but whether they shed any light on the cause or etiology of the disorder is an open question. One would hope that with these now sophisticated genetic tools and the identification of several reliable susceptibility genes (NRG1, DTNBP1, DISC1), more etiologically relevant mouse models can be created.

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Comment by: [Tomiki Sumiyoshi](#), [Philip Seeman](#) ([Disclosure](#))

Submitted 7 March 2006

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Comment by Tomiki Sumiyoshi and Philip Seeman

Kellendonk et al. report various behavioral and neurochemical findings from transgenic mice expressing an increased number of dopamine (DA)-D2 receptors in the striatum, labeled by 3H-spiperone. These mice showed deficits in some aspects of working memory, a cognitive domain associated with the prefrontal cortex function.

This study was prompted by the landmark hypothesis that DA supersensitivity in some of the subcortical brain regions, such as the striatum, constitutes a neurochemical basis for psychotic symptoms of schizophrenia (e.g., [van Rossum, 1966](#); [Seeman et al., 2005](#)). Conventionally, dysregulation of DA-related behaviors, including enhanced locomotor activity and stereotypy, as well as disrupted prepulse inhibition, have been thought to reflect psychosis-related symptoms. However, the D2 receptor transgenic mice did not demonstrate alterations in any of these behavioral measures, although an in vitro assay indicated reduced DA-induced adenylate cyclase activity in these animals. To follow the behavioral changes after challenging the mice with amphetamine or other DA-agonists would have conveyed more information on whether the up-regulated D2 receptors are actually functional.

It is also crucial to determine if there is a shift of D2 receptors to the high-affinity state, or functional state (D2High) ([Seeman et al., 2005](#)), in this animal model of schizophrenia. It is argued that D2High sites may be more relevant to psychotic symptoms than the total density of D2 receptors measured by conventional binding methods, such as that used by Kellendonk et al. with 3H-spiperone as a ligand ([Seeman et al., 2005](#); [Sumiyoshi et al., 2005](#)). In fact, increased proportions of D2High have

been reported in various animal models of psychosis, including those based on the neurodevelopmental hypothesis of schizophrenia ([Seeman et al., 2005](#); [Sumiyoshi et al., 2005](#)).

Kellendonk et al. found that the extra D2 receptors in the striatum were associated with the cognitive disturbances. Since it has been found that overexpression of the catechol-O-methyl transferase (COMT) gene also impairs cognitive function (Chen et al., 2005), further research is needed to determine if the cognitive deficits result from overexpression of these specific genes and not just any gene.

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Comment by: [Patricia Estani](#)

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I agree with Dr Weinberger's comments about the work of Kellendonk et al. In this sense, the cortical, frontal-striatal connections are well-known circuits involved in the development of schizophrenia.

Dr. Weinberger, in 1992, reported studies from limbic-prefrontal circuits, connections involved in schizophrenia pathophysiology ([Weinberger et al., 1992](#)). This work used an inverse experimental methodology (of corroborating the existing relationship between frontal cortex and the striatum) from the methodology commonly used (search for the line-activation in frontal cortex, then see the results in the striatum).

The most outstanding part of the study is one dedicated to the developmental approach. Thus, in the article, it was clear that restoring the normal DA function in the striatum did not restore cognitive functioning. As this article demonstrates, developmental approaches are excellent for the understanding of the neurobiology of schizophrenia.

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