memory (*28*)]. In each case, computational models have demonstrated that double-dissociations of behavior can result from complex interactions within a single, interactive, nonlinear system (for example, along the red and yellow arrows in the figure) in response to the effects of lesions and/or the demands of particular behavioral tasks [see (*29*, *30*) for similar arguments]. It should be noted, however, that although computational modeling can establish the viability of alternatives to modularity, empirical evidence is required to establish their validity. The Haxby *et al.* data provide an important and exciting step in this direction. However, it remains to be determined whether the distributed pattern of activity that they observed is in fact necessary for face perception. Modularists might argue that such activity is the result of, or incidental to, processing in the face module. In other words, it is not enough to show that patterns of activity outside a putative module correlate with behavior—it must be shown that they are causal.

We have considered how modular and distributed theories might, in their purest forms, account for the existing findings. Of course, prudence dictates that neither extreme is likely to be correct. Indeed, we can think of pure modularity and undifferentiated distributed representation as the Scylla and Charybdis of cognitive neuroscience, between which the field must carefully navigate. On the one hand, we must avoid running aground on simplified notions of modularity. This would risk a form of "neophrenology," or naïve localizationism, that fails to respect the true complexity of the brain. On the other hand, we must avoid being consumed by irreducible forms of distributed representation that cannot be analyzed in terms of fundamental principles. It is, after all, the job of science to reduce the complexity of nature to a more comprehensible form. We can imagine a variety of possible intermediate or alternative positions: a heterogeneous mix of special purpose modules and more distributed general mechanisms; representations that appear modular at one scale but distributed at finer scales; or representational structure that does not divide along the lines of common stimulus categories (such as faces versus objects) but rather is organized along more complex or abstract dimensions.

As the Haxby and Downing studies illustrate, neuroimaging has begun to contribute important new data regarding neural organization. Such efforts, combined with other neuroscientific techniques, promise ever more detailed sources of information about the nature of neural processing and representation. However, we suspect that meaningful advances will require equally dramatic progress in elaborating theories. We are likely to find that more detailed theories will naturally fall on intermediate ground between the purest forms of modularity and distributed representation. Dealing with the complexity that increasing detail introduces will no doubt require the assistance of more formal methods of theory building, such as computational modeling and mathematical analysis.

References

1. J. Fodor, *Modularity of Mind* (MIT Press, Cambridge, MA, 1983).
2. G. E. Hinton, J. A. Anderson, *Parallel Models of Associative Memory* (Erlbaum, Hillsdale, NJ, 1981).
3. J. J. Hopfield, *Proc. Natl. Acad. Sci. U.S.A.* **79**, 2554 (1982).
4. D. E. Rumelhart, J. L. McClelland, *Parallel Distributed Processing: Explorations in the Microstructure of Cognition* (MIT Press, Cambridge, MA, 1986), vols. 1 and 2.
5. P. E. Downing *et al.*, *Science* **293**, 2470 (2001).
6. J. V. Haxby *et al.*, *Science* **293**, 2425 (2001).
7. R. Epstein, N. Kanwisher, *Nature* **392**, 598 (1998).
8. N. Kanwisher *et al.*, *J. Neurosci.* **17**, 4302 (1997).
9. N. Kanwisher *et al.*, *Neuroreport* **10**, 183 (1999).
10. F. Tong *et al.*, *Cognit. Neuropsychol.* **17**, 257 (2000).
11. J. Bodamer, *Arch. Psychiatr. Nervenkr.* **179**, 6 (1947).
12. J. C. Meadows, *J. Neurol. Neurosurg. Psychiatry* **37**, 489 (1974).
13. M. J. Farah *et al.*, *Neuropsychologia* **33**, 661 (1995).
14. T. Allison *et al.*, *J. Neurophysiol.* **71**, 821 (1994).
15. C. G. Gross *et al.*, *J. Neurophysiol.* **35**, 96 (1972).
16. S. Yamane *et al.*, *Exp. Brain Res.* **73**, 209 (1988).
17. M. E. Hasselmo *et al.*, *Behav. Brain Res.* **32**, 203 (1989).
18. D. I. Perrett *et al.*, *Exp. Brain Res.* **86**, 159 (1991).
19. D. I. Perrett *et al.*, *Exp. Brain Res.* **47**, 329 (1982).
20. R. E. Kettner *et al.*, *Neuroscience* **8**, 2938 (1988).
21. D. H. Hubel, *Nature* **299**, 515 (1982).
22. I. Gauthier *et al.*, *Nature Neurosci.* **3**, 191 (2000).
23. M. Moscovitch *et al.*, *J. Cognit. Neurosci.* **9**, 555 (1997).
24. A. Caramazza, *Brain Cognit.* **5**, 41 (1986).
25. M. J. Farah, J. L. McClelland *J. Exp. Psychol. Gen.* **120**, 339 (1991).
26. D. C. Plaut *et al.*, *Psychol. Rev.* **103**, 56 (1996).
27. M. J. Farah *et al.*, *Psychol. Rev.* **100**, 571 (1993).
28. J. D. Cohen, D. Servan-Schreiber, *Psychol. Rev.* **99**, 45 (1992).
29. R. C. O'Reilly, M. J. Farah, *Cognit. Neuropsychol.* **16**, 1 (1999).
30. D. C. Plaut, *J. Clin. Exp. Neuropsychol.* **17**, 291 (1995).

PERSPECTIVES: NEUROBIOLOGY

Dopamine's Reversal of Fortune

Randy D. Blakely

Dopamine (DA) is one of the most important neurotransmitters in brain neural circuits that carry information about movement. The death of dopaminergic neurons in one component of this motor circuitry, the substantia nigra (SN), causes the movement disorder Parkinson's disease (PD). Proteins in the presynaptic membranes of dopaminergic neurons called DA transporters (DATs) are often thought of as the janitorial staff of synaptic transmission, mopping up excess DA released at synapses. This all makes sense in the brain's striatum, where there is a high density of dopaminergic synapses and where so much presynaptic DAT is present that imaging the density of DATs can be used to chart the progression of PD (*1*). According to Falkenburger *et al.* (*2*), reporting on page 2465 of this issue, the story gets complicated back in the SN, where DATs participate in synaptic transmission in a completely different way.

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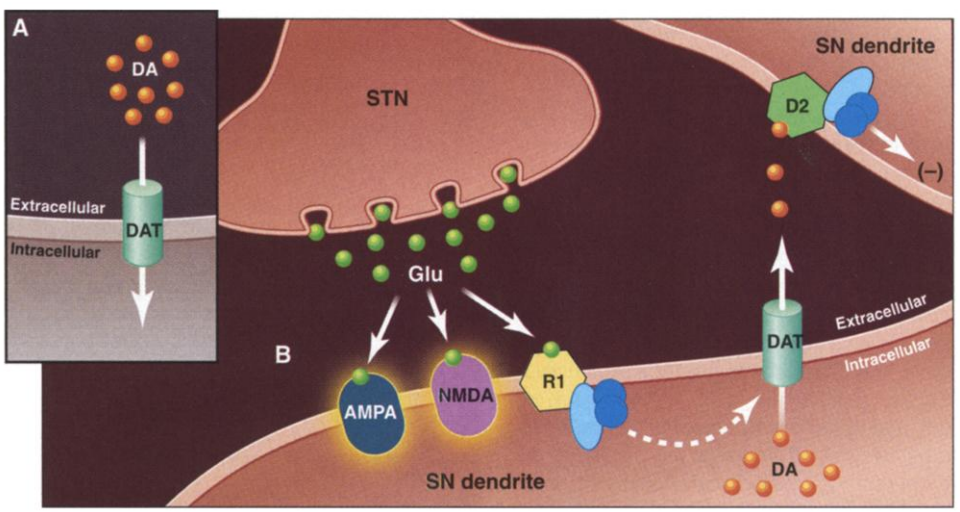
In the SN, where the cell bodies of neurons lie, few dopaminergic axons with conventional synapses are evident. Instead, dopaminergic cell bodies extend alternative processes, termed dendrites, that receive inputs from other regions of the brain. After collecting all the information coming into their dendrites, dopaminergic neurons integrate input signals to determine how much DA to release from their axon terminals, which are miles away in molecular terms. If these dendrites are passive recipients of incoming information, why then are they filled with the enzyme to make DA, tyrosine hydroxylase, and why do they contain large amounts of DAT (*3*)? It is possible that the protein trafficking machinery of dopaminergic neurons is simply inefficient and that some tyrosine hydroxylase and DAT winds up in the dendrite, a sorting error of minimal importance.

In the SN, however, researchers have long realized that dopaminergic synapses are formed *between* dendrites, and that drugs and physiologic stimuli cause substantial DA release from dendrites in vivo (*4*–*6*). Moreover, DA receptors exist on the cell bodies and dendrites of dopaminergic neurons, and direct application of DA to these structures alters the excitability of dopaminergic neurons (*7*). What then is the source of DA released from dendrites, and how do DATs participate in this release?

To address this question, Falkenburger *et al.* first sought to show that physiologically triggered DA is released from the dendrites of SN dopaminergic neurons in rat brain slices in vitro. When they stimulated the subthalamic nucleus (STN), a brain region with major input to the SN, they detected DA (or a DA-like substance) in the extracellular fluid surrounding the SN dendrites. They wondered whether this DA could have

been released from vesicles that fused with the dendritic membrane and whether DATs would clean up the excess DA released. Surprisingly, when calcium was omitted from the experiment—a maneuver that should stop vesicular release in its tracks—DA release continued. Furthermore, when DAT antagonists were added to the preparation, DA release was squelched (whereas extracellular DA would have increased if the DA had been released at synapses instead of dendrites). These findings imply that SN dendrites may not use their DATs simply to inactivate released DA after thalamic stimulation. Rather, SN dendritic DATs appear to contribute directly to the release of DA, in essence running backwards, exporting instead of importing DA (see the figure).



Putting transporters into reverse. DATs on SN dopaminergic neurons export as well as import DA. (**A**) DATs are thought to be involved in the elimination of extracellular DA after its release at synapses between neurons. (**B**) However, the finding that there is modulated efflux of DA from the dendrites of SN dopaminergic neurons suggests that DATs may be able to export as well as import DA (*2*). Glutamate, a neurotransmitter released by subthalamic (STN) afferent neurons that input to the SN, triggers efflux of DA from the dendrites. This DA then acts as a dendrite-to-dendrite messenger by binding to D2 receptors to reduce membrane excitability (denoted by minus sign). The pathway for glutamate-triggered DA efflux may involve G protein–coupled receptors (possibly mGluR1 subtype) because evidence for DA efflux is found in the presence of agents that block other glutamate receptor subtypes (AMPA and NMDA).

But how does such transporter reversal occur? DA influx is driven by the energetically favorable movement of cotransported ions, specifically Na^+ and Cl^-, carried together with DA by DATs (*8*). Hydrolysis of adenosine triphosphate (ATP) supports DA transport only indirectly, as it is the fuel that sustains ion pumps such as the Na^+/K^+ dependent ATPase. Inward transport of DA also involves the movement of net positive charge into the cell, and thus a negative membrane potential facilitates DA influx. Conditions that affect the amount of ATP, alter ion gradients, or depolarize the membrane prevent DA influx and can even lead to transporter reversal (efflux). During reduced blood flow (ischemia), there is efflux of the neurotransmitters glutamate and norepinephrine in brain and heart tissue, respectively, which may contribute to subsequent pathology (*9, 10*). Indeed, it is expected that all transporters will exhibit efflux to some degree if the driving forces are significantly altered. What Falkenburger *et al.* demonstrate is that DA efflux occurs under more physiological circumstances: after high-frequency stimulation of excitatory inputs to the SN.

A critical issue that these investigators address is whether DAT-mediated efflux of DA, although measurable with sensitive carbon fiber electrodes, is too insignificant to influence the excitability of nigral dopaminergic neurons. It is conceivable that nigral excitability is so dominated by the glutamate released after subthalamic stimulation that the effects of DA efflux are inconsequential. This does not appear to be the case, because application of the DA receptor (D2 subtype) antagonist sulpiride further enhances glutamatergic responses. This finding suggests that DA efflux, mediated by DATs, acts on dendritic DA (D2) receptors to limit excitation of dopaminergic neurons. Moreover, analysis of the electrophysiological responses recorded by Falkenburger *et al.* reveals additional complexities in DAT reversal. If the opening of glutamate-gated channels or membrane depolarization is responsible for DA efflux, why then do we see physiological evidence of evoked DA efflux when ionotropic glutamate receptors are blocked?

The authors note that G protein–coupled glutamate receptors (mGluR1 subtype) may trigger DAT reversal (*2*). Evidence exists that specific isoforms of protein kinase C (PKC) are required for amphetamine-elicited DAT reversal (*11*), and mGluR1 receptors are known to be coupled with PKC pathways (*12*). Robust PKC activation with phorbol esters causes DAT internalization (*13, 14*), but such regulation would actually limit the process by removing carriers from the cell surface. Quick's group (*15*) examined PKC-modulated interactions of the synaptic membrane protein syntaxin with the GAT1 transporter for the neurotransmitter γ-aminobutyric acid (GABA). They showed that transporters can be altered directly as well as indirectly through regulation of their interactions with syntaxin. Intriguingly, the evoked DA efflux observed by Falkenburger *et al.* is more rapid than could be accounted for by syntaxin-mediated trafficking. Given that DATs have been found in a complex with protein phosphatase 2A (*16*), it is possible that phosphorylation of transporters by PKC or their dephosphorylation by phosphatases switches DATs between influx and efflux modes. Such a sequence of events would be similar to the mGluR1-triggered dephosphorylation and activation of potassium channels (*17*). Further analysis of signaling between mGluR1 and DATs is needed to understand the physical basis of efflux stimulation and how transporters switch between influx- and efflux-competent states.

Beyond the admittedly heightened awareness of flux reversal among transporter biologists, why should neuroscientists care whether dendrites signal between themselves with DA released by transporters or from vesicles? One reason is that there exist a number of DAT antagonists that are used clinically (buproprion, methylphenidate) and abused socially (cocaine). Dendritic DATs are also evident on DA neurons in the ventral tegmental area (*18*), a region involved in addiction, suggesting that evoked DA efflux could contribute to psychostimulant modulation of reward circuits. The degree to which the actions of these drugs involve suppression of DAT-mediated DA efflux in dendrites as well as reuptake blockade at axon terminals will need to be clarified.

Once the mechanism for glutamate-triggered DA efflux in the SN is understood, perhaps we can also find ways to therapeutically modulate DA efflux in PD. For example, the authors remind us that too much extracellular DA, like too much glutamate, can be a bad thing. Excess extracellular DA can kill neurons because of its propensity to oxidize and activate cellular apoptotic programs (*19, 20*). In PD, the subthalamic neurons are disinhibited and their excessive firing could trigger the nigral dendrites to produce harmful amounts of DA, creating additional stresses on themselves and their

neighbors. Blocking DAT-mediated DA release could thus be neuroprotective in the early stages of the disorder. We should not be surprised to see the ideas of Falkenburger *et al.* generalized to other transporters and pathways. Schwartz has shown that GABA transporters in the retina release GABA in response to electrical stimulation (*21*). Serotonin efflux triggered by MDMA ("ecstasy") is a well-known facet of this psychostimulant's action (*22*). The glycine required to allow glutamate stimulation of *N*-methyl-D-aspartate receptors may arise from transporter-mediated glycine efflux (*10*). More ideas regarding how transporter-dependent neurotransmitter efflux shapes the excitability of neurons and influences pathology will undoubtedly come to mind as neuroscientists become more forward-thinking in embracing transporter reversal.

References

1. M. J. Kuhar *et al.*, in *Neurotransmitter Transporters: Structure, Function, and Regulation*, M. E. A. Reith, Ed. (Humana, Totowa, NJ, 1997), pp. 297–314.
2. B. H. Falkenburger, K. L. Barstow, I. M. Mintz, *Science* **293**, 2465 (2001).
3. M. J. Nirenberg *et al.*, *J. Neurosci.* **16**, 436 (1996).
4. C. J. Wilson *et al.*, *Exp. Brain Res.* **30**, 161 (1977).
5. A. Cheramy *et al.*, *Nature* **289**, 537 (1981).
6. P. M. Groves, J. C. Linder, *Exp. Brain Res.* **49**, 209 (1983).
7. M. L. Pucak, A. A. Grace, *Crit. Rev. Neurobiol.* **9**, 67 (1994).
8. G. Rudnick, in *Neurotransmitter Transporters: Structure, Function, and Regulation*, M. E. A. Reith, Ed. (Humana, Totowa, NJ, 1997), pp. 73–100.
9. A. Schömig *et al.*, *Eur. Heart J.* **12**, 38 (1991).
10. D. Attwell *et al.*, *Neuron* **11**, 401 (1993).
11. L. Kantor, M. E. Gnegy, *J. Pharmacol. Exp. Ther.* **284**, 592 (1998).
12. V. A. Skeberdis *et al.*, *Neuropharmacology* **40**, 856 (2001).
13. H. Melikian, K. Buckley, *J. Neurosci.* **19**, 7699 (1999).
14. G. M. Daniels, S. G. Amara, *J. Biol. Chem.* **274**, 35794 (1999).
15. S. L. Deken *et al.*, *Nature Neurosci.* **3**, 998 (2000).
16. A. L. Bauman *et al.*, *J. Neurosci.* **20**, 7571 (2000).
17. M. Levy *et al.*, *J. Biol. Chem.* **273**, 6495 (1998).
18. M. J. Nirenberg *et al.*, *J. Neurosci.* **17**, 4037 (1997).
19. Y. Luo *et al.*, *Mol. Pharmacol.* **56**, 254 (1999).
20. D. Offen *et al.*, *Adv. Neurol.* **80**, 265 (1999).
21. E. A. Schwartz, *Science* **238**, 350 (1987).
22. G. Rudnick, S. C. Wall, *Proc. Natl. Acad. Sci. U.S.A.* **89**, 1817 (1992).

PERSPECTIVES: ASTRONOMY

A Stellar Merry-Go-Round

Thierry Montmerle

Imagine a giant torus, like a tire tube, filled with hot gas and rotating around a star like a merry-go-round. This is what astronomers have recently found in detailed modeling studies of the light signatures of several stars. The signatures were obtained by widely different techniques, including absorption in the ultraviolet (UV) (*1*), optical spectrophotometry and emission of x-rays (*2*), and analysis of radio waves (*3*).

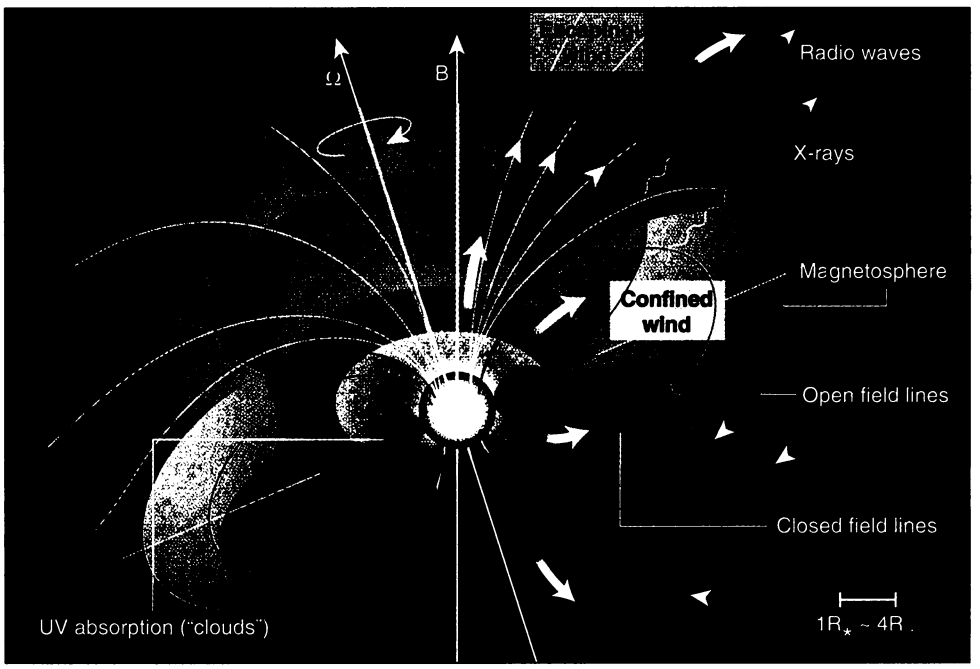
The stars investigated in these studies are special. Called "magnetic stars," they were discovered by Babcock in the 1940s (*4*, *5*). Their magnetic fields typically have field strengths of several kilogauss, although they may reach field strengths of up to 50 kG (100,000 times the Earth's magnetic field). Several indications, especially the rotational periodicity, suggest that the magnetic structure is mainly dipolar and rotates with the star, the magnetic axis being at an angle (sometimes even 90°) to the rotation axis.

Theoretical studies have predicted for some time that gaseous tori should exist around magnetic stars, as a result of the confinement of a stellar wind within a dipolar magnetic structure (see the figure). The confirmation of these predictions is an important step toward understanding the plasma physics of stellar atmospheres in cases where the magnetic field dominates the spatial structure of the gas near the stellar surface.

Stellar magnetism is widespread. The magnetic field of the Sun and Sunlike stars is structured on small spatial scales (much less than the solar radius) and is believed to originate in the dynamo mechanism, which is driven by convective motions in their external layers. However, in stars with masses much larger than the Sun, the external layers are radiative and do not generate magnetic fields. The radiation pressure is so strong that it creates a massive "stellar wind," which leaves the star at very high velocities.

Between these two broad categories lie the so-called intermediate-mass stars (with masses a few times that of the Sun), which are entirely radiative and drive weaker winds. They are quiet stars that should normally not have magnetic fields. How, then, can some of them be magnetic? The answer is still unclear, but it is thought that their magnetic fields are "fossil"; that is, they were initially interstellar and were trapped somehow while the star was forming.

In such stars, the fine-tuning between a strong, dipolar magnetic field and a weak,



The wind environment of a magnetic hot star. In hot stars, UV radiation drives the outer layers into a fast (~1000 km/s) wind. This wind normally leaves the star freely, but if the star has a strong dipolar magnetic field, the wind is "bent" by the magnetic field. The magnetosphere separates two regions: the "escaping wind" region, similar to normal hot stars, and the "confined wind" region, where the wind is forced to collide with itself, producing a shock that heats the gas to x-ray temperatures (several million K). The gas eventually cools, forming a torus of equatorial "clouds." The clouds absorb the stellar UV radiation, producing characteristic signatures in the UV spectrum. At larger distances, high-energy electrons accelerated by the shock emit radio waves. All these emissions have been observed and make up a fairly consistent picture of the environment of a magnetic hot star.

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