PERSPECTIVES

NEUROSCIENCE

Illuminating anhedonia

Optogenetics and fMRI reveal the brain circuitry of anhedonia

By **Trevor W. Robbins**

The mesolimbic dopamine (DA) system is part of the brain's reward circuitry (see the figure). It controls an individual's responses to rewards such as food, social interactions, and money, and is therefore an important determinant of motivation. Midbrain DA neurons projecting to the striatum are causally involved in reward-like processes. Less clear is how another apparent target of midbrain DA neurons, the ventromedial prefrontal cortex (vmPFC), may contribute to the reward system. On page 41 of this issue, Ferenczi *et al.* (*1*) report using a unique combination of optogenetic tools and functional magnetic resonance brain imaging (fMRI) in conscious rats to investigate the underlying mechanisms of the competitive relationships of these two brain regions over striatal function and reward-like behavior. The findings have implications for understanding and treating affective symptoms in disorders such as depression, schizophrenia, and addiction.

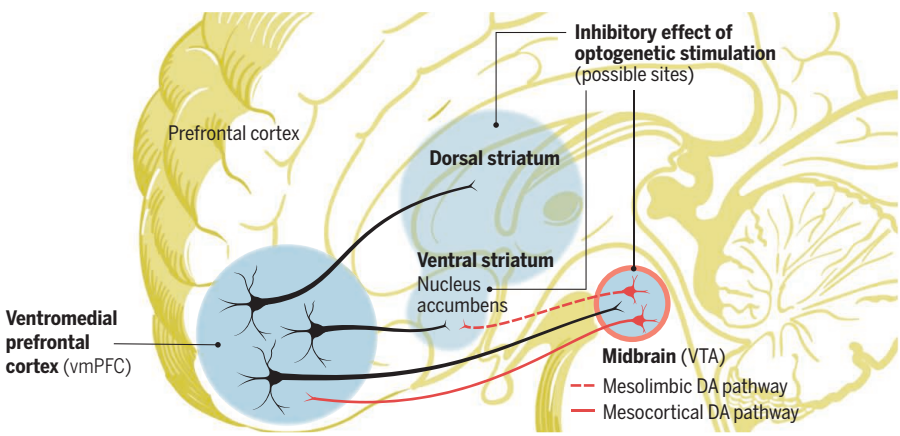
Evidence of a reward system was derived from experiments in rats some 40 years ago and has been confirmed by recent studies showing that rodents will choose to receive optogenetic stimulation of midbrain DA neurons [which were engineered to be activated by light (*2*)]. The findings have been paralleled in humans by fMRI; thus, the anticipation of reward evokes increased activity in the human ventral striatum. This correlated with indirect measures (from positron emission tomography) of DA release in the striatum (*3*). Exposure to both primary rewards (e.g., pleasant tastes and sights) and conditioned or symbolic rewards (such as money) leads to increased activity in the vmPFC (*4*). It is therefore paradoxical that hyperactivity of this region has also been linked in humans to anhedonia, the inability to feel pleasure (*5*, *6*). Removing this hyperactivity has been a target for various antidepressant treatments, including pharmacotherapy, cognitive therapy, and deep brain stimulation. Ferenczi *et al.* asked whether the effect of enhancing midbrain DA neuron activity is blunted by influences from the rat medial PFC.

DA-containing midbrain neurons in the rat were exposed to laser light (via implanted optic fibers) to activate ion channels (opsins) that were either inhibitory or excitatory. Stimulation via excitation acted as a reward, as rats chose to turn on such stimulation. Stimulation also produced an increased blood oxygen level–dependent (BOLD) fMRI response in the striatum, just as would have been predicted from prior human studies. Moreover, this activation of the striatum was DA-dependent, as exposure to DA receptor antagonists blocked both the rewarding effects and the BOLD signature.

A key question is the precise physiological nature of this potent rewarding effect; there are at least two reasons for thinking it may not always be equivalent to other forms of reward. Stimulant drugs such as cocaine are presumed to produce their rewarding effects, at least partly, by increasing tonic (background) levels of striatal DA rather than by increasing phasic DA release in the striatum as a consequence of mesolimbic DA neuron activity. In the study of Ferenczi *et al.*, phasic stimulation of midbrain DA neurons not only activated regions of the dorsal and ventral striatum, but also activated regions of the cerebral cortex (the retrosplenial cortex), although surprisingly not the vmPFC itself, as has been shown in studies of natural reward anticipation and feedback in humans (*4*).

Ferenczi *et al.* used a clever optogenetic stimulation method to drive an asynchronous enhancement of medial PFC hyperexcitability in awake rats, thereby mimicking states in human patients with depression; increased BOLD responses in the vmPFC to happy (but not sad) stimuli have been correlated with anhedonia ratings (*5*, *6*). Hyperexcitability of the medial PFC suppressed sucrose preference in the rat, but not drinking per se, and curtailed social interaction without affecting general locomotor activity, suggestive of a specific inhibitory effect of medial PFC on reward-motivated behavior. The same medial PFC hyperexcitability also suppressed the striatal responses to optically stimulated DA neurons in the midbrain, and abolished a behavioral preference for the place associated with midbrain DA neuron stimulation.

More generally, the state of medial PFC hyperexcitability elicited greater connectivity between the medial PFC, lateral orbitofrontal cortex (OFC), and ventral striatum by enhancing synchronous firing. This greater synchronous connectivity correlated with reduced sucrose preference (through mechanisms that are still obscure). This is reminiscent of the discovery of greater connectivity of the subgenual cingulate cortex with nodes of the "default network," including the OFC, the thalamus, and the precuneus in depressed patients (*5*) and of the association of vmPFC activity with anhedonia during the processing of positive emotional information in nonclinical individuals (*6*). Whether this



Reward circuitry. Shown are approximate anatomical relationships in the human brain between the midbrain dopamine (DA) pathways from the ventral tegmental area (VTA) to the nucleus accumbens (part of the ventral striatum) and the vmPFC, and reciprocal influences (mediated by glutamate) of the vmPFC. The vmPFC includes the medial orbitofrontal cortex and parts of the ventral cingulate cortex, including the subgenual cingulate cortex. Ferenzi *et al*. show that the rewarding effects of optogenetic stimulation of the VTA were counteracted by optogenetically-induced hyperexcitability of the vmPFC to mimic behavioral anhedonia-like symptoms in rats, presumably via descending pathways to the subcortical regions including the striatum and VTA.

ILLUSTRATION: K. SUTLIFF/*SCIENCE*

Department of Psychology and Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge CB2 3EB, UK. E-mail: twr2@cam.ac.uk

is true of other patient groups exhibiting anhedonia, including schizophrenia (*7*), is, however, less clear.

The findings of Ferenczi *et al.* highlight PFC hyperactivity as a causal inhibitory influence on reward-related behavior in the rodent mediated via the striatum. This contrasts with a more traditional view of the importance of PFC hypoactivity in human and experimental animal models, in which hypoactivity may cause a lack of control over subcortical structures such as the striatum and amygdala. It would be interesting to use optogenetics to compare the effects of medial PFC hyperexcitability with those of medial PFC silencing on measures of reward-related behavior in the rodent model. Other PFC-subcortical interactions potentially mediate a broader range of symptom dimensions, including anxiety and impulse control. It may be overly simplistic to relate only symptoms of anhedonia to depression; other motivational symptoms such as apathy and reward prediction, as well as negative affective bias, may also contribute to this phenotype (*8*).

Some explanation is still required for the origin of the vmPFC hyperexcitability in depression, as well as the striking paradox that although a hyperactive vmPFC is correlated with the mood state of anhedonia, this structure actually mediates responses to reward in humans (*5*–*7*). An initial step may be to determine whether such BOLD-related reward signals also occur in the rat vmPFC. A recent study, however, using amperometric O_2 measures as a proxy BOLD response, reported that transient signals in the medial PFC were more related to negative than to positive reward signals (*9*), so this question may represent another important translational focus.

Future work may contrast the effects of hypo- and hyper-PFC function and distinguish whether both of these influences can occur concurrently in parallel PFC-striatal circuitry involving distinct PFC sectors with potentially different, even opposing (*10*), functions. This research cannot proceed until controversies regarding evolutionary relationships of the PFC in rodent and primate brains are fully resolved, which in turn may have to await the development of optogenetic tools that can be deployed more readily in nonhuman primates. ■

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CELL SIGNALING

Seeing mTORC1 specificity

Structural information reveals how a multiprotein complex responds to amino acid abundance

By **Gwen R. Buel** *and* **John Blenis**

Cells must sense their environment to determine whether conditions are suitable for growth. Despite the physiological importance of a multiprotein complex called mammalian/mechanistic target of rapamycin complex 1 (mTORC1) in this process, a detailed molecular understanding of its assemblage and regulation of its serine-threonine kinase function have proven difficult to elucidate. On page 48 of this issue, Aylett *et al.* (*1*) help uncover the molecular underpinnings of mTORC1, while on pages 43 and 53, Wolfson *et al.* (*2*) and Saxton *et al.* (*3*), respectively, make strides in determining how mTORC1 is regulated by the amino acid leucine.

> ***"The studies...help to clarify an important aspect of mTORC1 regulation."***

mTORC1 exists as a dimer of two mTOR molecules along with its accessory proteins, but it has been unclear how the mTORC1 component called regulatory-associated protein of mTOR (Raptor) fits into the structure and promotes substrate specificity (*4*). Aylett *et al.* used cryo–electron microscopy to resolve the structure of mTORC1, and combined this with crystallographic studies of Raptor to better understand the function of mTORC1 components. They found, as shown before (*4*), that mTORC1 exhibits the shape of a bumpy doughnut, with twofold rotational symmetry. Additionally, Aylett *et al.* show that the backbone is continuous from one mTOR subunit to the next, and that Raptor binds at the junctions of the two mTOR molecules, appearing to stabilize the dimer as a piece of tape would hold together two pieces of overlapping wrapping paper.

Another partial structure of mTOR previously revealed that the catalytic site of mTOR is found deep in a cleft, which is thought to allow access to selected substrates (*5*). The structure determined by Aylett *et al.* shows that Raptor makes this cleft even smaller, suggesting that Raptor may play an important role in limiting access to substrates. Additionally, the authors provide a model as to how Raptor may select substrates containing a TOR signaling (TOS) motif (*6*). Raptor has homology to cysteine-aspartic proteases (CASPases), including a domain that these enzymes use to bind a conserved aspartate-containing motif on substrates. It is known that TOS motifs are important for recruitment of some substrates to mTORC1 *(6),* and the authors hypothesized which region of Raptor may bind TOS motifs based on the homology to CASPases. They found that this region in Raptor is located at the base of the active-site cleft, likely allowing for Raptor to position substrates.

Given the importance of the structural support and substrate specificity that Raptor provides for mTORC1, it would be interesting to see if rapamycin-insensitive companion of mTOR (Rictor) has the same role in mTORC2 or if the complex achieves these feats by other means. mTORC2 promotes cell growth and survival partially through activation of mTORC1, and Rictor is an accessory component comparable to Raptor. Another question is how the new structural information might explain how mTORC1 recognizes targets that do not contain a TOS motif. Additionally, the mechanisms by which the protein called Ras homology enriched in brain (Rheb) binds to and activates mTORC1 are still unclear. Rheb is a member of the Ras superfamily of guanosine triphosphatases (GTPases) and is tethered to endomembranes by a lipid anchor. The higher-resolution structure of mTORC1 might enable future studies to better answer these questions.

Although much can be learned about the function and regulation of mTORC1 from the structure of mTORC1 itself, a plethora of signaling molecules come into contact with mTORC1 directly or indirectly to regulate its activity, and focusing on those proteins can help elucidate mTORC1 function as well. Wolfson *et al.* and Saxton *et al.* looked at a family of proteins called Sestrins, which the authors show can sense leucine and correspondingly regulate mTORC1. Sestrins were initially implicated in regulating oxidative stress, cell metabolism, and life span (*7*). Sestrins 1 and 2 were first connected to mTORC1 signaling through their ability to activate

[1]*Department of Pharmacology, Meyer Cancer Center, Weill Cornell Medical College, New York, NY 10065, USA. E-mail: job2064@med.cornell.edu*