Hope for the hopeless: dopamine circuits modulate depression-related symptoms

By [redacted]

Which specific dopaminergic pathways modulate common depression symptoms? *Tye et al., 2013* uses optogenetics to dissect distinct dopamine neuronal circuits that promote or inhibit depression-related symptoms of hopelessness and anhedonia.

Have you ever seen a goldfish in a plastic bag? A patient once described her struggle with depression to be similar to that of the goldfish. Through the transparent barrier she could see that there was nothing wrong in particular with her environment, yet she could not liberate herself from the bag, and what's worse, her bag had a hole in it, too small to escape from, but large enough to deplete the limited amount of water around her (pers. obs.).

This patient is describing two all-consuming symptoms of depression: anhedonia, or the inability to experience pleasure, and hopelessness, or the acceptance of impending doom despite potential positive outcomes of exerting effort *(Deisseroth, 2014)*. How can these behaviors be modulated to alleviate the symptoms of depression? Moreover, are there specific neuronal pathways that cause depression-related symptoms? The idea that neurochemicals in the brain are responsible for the imbalances in depressed patients is widely accepted, but precisely how certain neurotransmitters affect specific circuits of the brain has only recently been explored (*Tye et al., 2013*).

Evidence suggests that current depression treatments have several pitfalls. Firstly, certain patients experience a significant lag time between the use of treatment and the effects of treatment (*Tye et al., 2013*). Secondly, these therapies are not guaranteed to be effective (*Tye et al., 2013*). Thirdly, depression treatments often cause debilitating side effects (*Tye et al., 2013*). This last point emphasizes the importance of bridging the gap between current depression therapy—treating the brain as "neurochemical soup"—and potential treatments that target specific brain circuits involved in depression-enabling behaviors (*Tye et al., 2013*).

Using behavioral, pharmacological, optogenetic, and electrophysiological methods, *Tye et al., 2013* studied the causal relationship of midbrain dopamine neurons and the onset and

dissipation of the depressive symptoms anhedonia and hopelessness or lack of motivation. To induce symptoms commonly found in depressed patients, the researchers began by optogenetically inhibiting the ventral tegmental area (VTA) dopamine neurons (*Tye et al., 2013*). The VTA is the area in which dopamine producing neurons reside and extend to other parts of the brain, these neurons can be modulated bidirectionally through activation and inhibition of dopamine neurons (Fig. 1). Previous studies have shown that under chronic stress, a depressed rodent will underperform escape behaviors, but that performance is restored after antidepressant intervention, such as activating dopaminergic neurons (*Tye et al., 2013*). To test motivation, the rodents were exposed to a chronic stressor—either the tail-suspension test (TST) or the forced-swim test (FST), and the ratio of time spent trying to escape (high motivation) to the time spent passive (low motivation), indicated the rodent's motivation level (*Tye et al., 2013*). When the neuronal membrane was hyperpolarized and the dopamine neurons were optogenetically inhibited, the rodents showed decreased motivation to escape (*Tye et al., 2013*). In an open-field-test (OFT), absent of a chronic stressor, the rodents did not show decreased locomotion, thus indicating a difference in motivation rather than differences in movement capability (*Tye et al., 2013*). As the study suggests, the change in motivation by activating or inhibiting VTA dopamine neurons indicates that specific dopaminergic pathways are responsible for depression-related behaviors (*Tye et al., 2013*). The reversal of the depression symptom is especially significant because it emphasizes firstly that normal behaviors can be restored, and secondly, that treatments would be more effective and efficient if they targeted specific pathways rather than the brain as a whole. Additionally, the rodents did not exhibit other side effects besides what is being modulated (motivation level), further indicating that the intolerable side effects in present day depression treatment can be alleviated if precise pathways are the targets of treatment.

Similarly, anhedonia was analyzed using a sucrose-preference test in which a greater number of licks for a spout delivering water indicated greater anhedonia and greater licks for 1% sucrose showed less anhedonia (*Tye et al., 2013*). The group that experienced

hyperpolarization of the neuronal membrane and dopamine neuron inhibition via halorhodopsin, a light activated ion pump, licked the sucrose-secreting spout much less than the control group (*Tye et al., 2013*). This illustrated the symptom of dampened pursuit of pleasure commonly found in depressed patients. Once the dopamine neurons no longer were optogenetically inhibited, the depressive symptom of anhedonia was reversed (*Tye et al., 2013*). Despite the caveats of genetic manipulation in humans, optogenetics does show attractive results in stifling depression-related symptoms. For those struggling with depression, targeting VTA dopamine neurons, whether pharmacologically, electrophysiologically, or perhaps even optogenetically in the future can provide some relief from anhedonia and hopelessness by rescuing high motivation and hedonic behaviors.

Depressed patients often become depressed after long-term exposure to a stressor (*Tye et al., 2013*). To model time-intensive chronic mild stress (CMS) similar to those depressed patients, the researchers subjected the rodents to mild stressors twice a day for eight to twelve weeks (*Tye et al., 2013*). Illuminating a light activated ion channel, channelrhodopsin-2 (ChR2), excited VTA dopamine neurons on command (*Tye et al., 2013*). As in the short-term stress experiment, the rodents underwent the tail-suspension test to measure level of motivation and the sucrose-preference test to measure anhedonia (*Tye et al., 2013*). The CMS rodent group exhibited significantly lower motivation and escape behavior than the control or for the ChR2 activated, CMS exposed group (*Tye et al., 2013*). In the OFT, neither the control nor experimental group had statistically significant differences in locomotor activity, or in other words, both groups showed normal movements in a stress free environment (*Tye et al., 2013*). Moreover, the sucrose-preference test revealed that the groups exposed to CMS without ChR2 activation and the group with inhibited VTA dopamine neurons licked the sucrose spout less, thus indicating decreased sucrose preference, whereas those who were not exposed to CMS or had excitation of dopamine neurons licked the sucrose spout more, thus exhibiting increased sucrose preference (*Tye et al., 2013*). Once more, a decreased proportion of sucrose licks

indicates the anhedonic symptom of depression. Taken together, these results suggest that VTA dopaminergic neurotransmission bidirectionally affects motivation and anhedonia.

Because of the ubiquity of dopaminergic pathways within the brain, depression therapies should target the specific circuits of the brain that are associated with depression-related behaviors, since these drugs can produce different effects in various parts of the brain. The ventral striatum, specifically the nucleus accumbens (NAc) showed increased reactivity to VTA dopamine neuron activation and inhibition (*Tye et al., 2013*). Previous research suggested that during forced-swim tests, optogenetically activated neurons projected from the VTA to the medial prefrontal cortex (mPFC) and dorsal raphne nucleus (DRN) increased high motivation activity (*Deisseroth, 2014; Warden et al., 2012*). As seen in Tye et al. 2013, no significant changes in locomotion were seen in the OFT after neuronal activation, again indicating that the difference in group escape behavior in the stress tests were due to changes in motivation levels (*Deisseroth, 2014*). The significance of these results conveys that depression-related symptoms in depressed patients derive from dopaminergic pathways in specific brain circuits (Fig. 1). Additionally, this indicates the importance of revising the action of current depression therapies, especially pharmacologically, in which the current drugs on the market target various pathways of the brain, indiscriminately.

As the studies suggest, the downfalls of modern day depression treatment could be averted if the brain is not perceived as “neurochemical soup,” but rather as a system of precise pathways that induce depression-like behaviors. *Tye et al., 2013* specifically bridges this gap by showing the bidirectional modulation of depression-associated symptoms in the ventral tegmental area and the nucleus accumbens. Similarly, *Deisseroth, 2014* provides compelling evidence by presenting the effects of prefrontal dopamine neuron modulation on depression-like behavior such as motivation or hopelessness and anhedonia. In summary, the bidirectional modulation of depression related symptoms by manipulation of dopamine pathways predicts a promising future for depressed patients who wish to return to their hopeful and hedonic selves.

References

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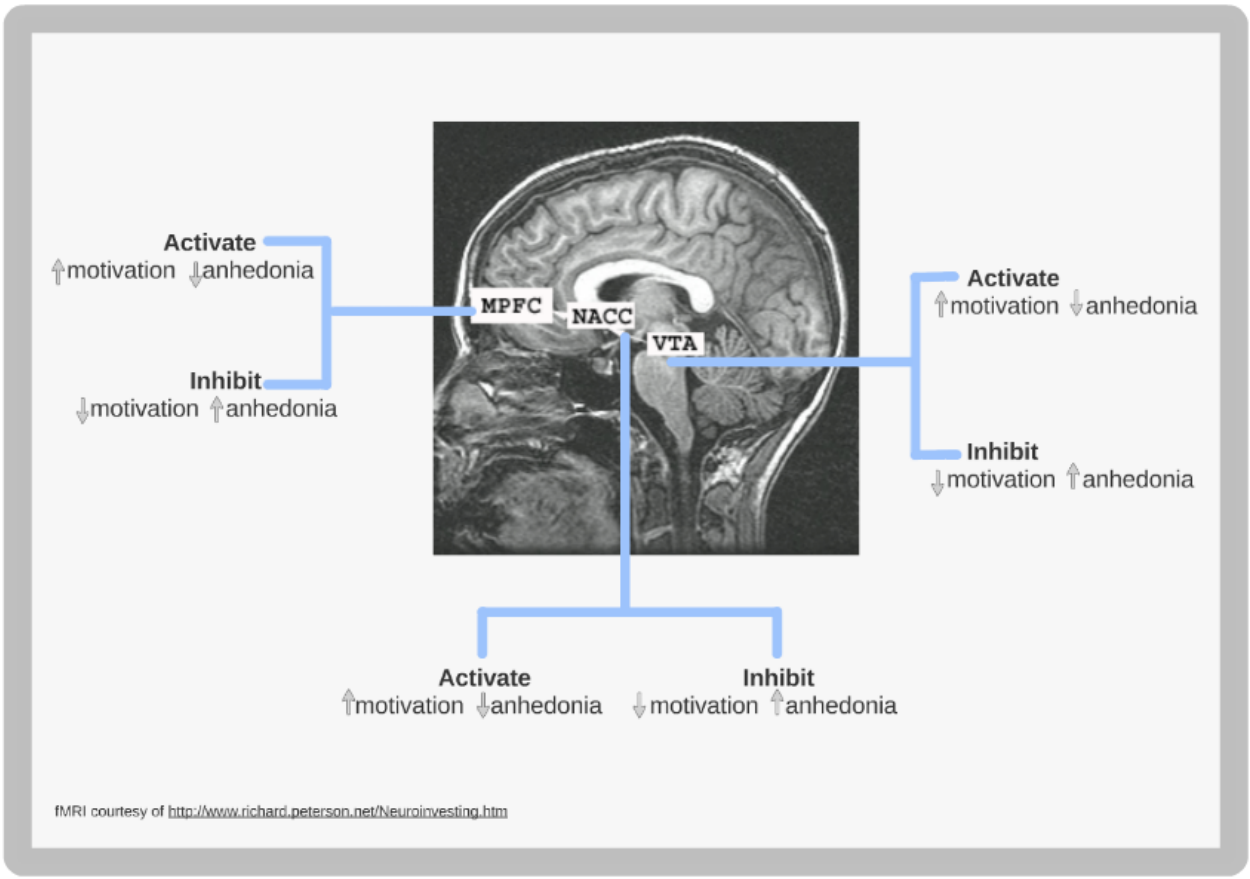

Figure 1 fMRI of sagittal brain shows the ventral tegmental area (VTA), nucleus accumbens (NAc), and medial prefrontal cortex (mPFC) thought to be major *in vivo* dopaminergic pathways in the reward and motivation systems. Activation of VTA, NAc, and mPFC dopamine neurons resulted in greater motivation in the tail-suspension test (TST) or the forced-swim test (FST), and increased sucrose preference indicating decreased anhedonia. Inhibition of the NAc and mPFC dopamine neurons extending from the VTA showed greater passivity in TST or FST, and lower sucrose preference, therefore conveying decreased motivation and increased anhedonia. Modulating dopaminergic pathways in the prefrontal cortex shows bidirectional alteration of depression-related symptoms in specific brain circuits.