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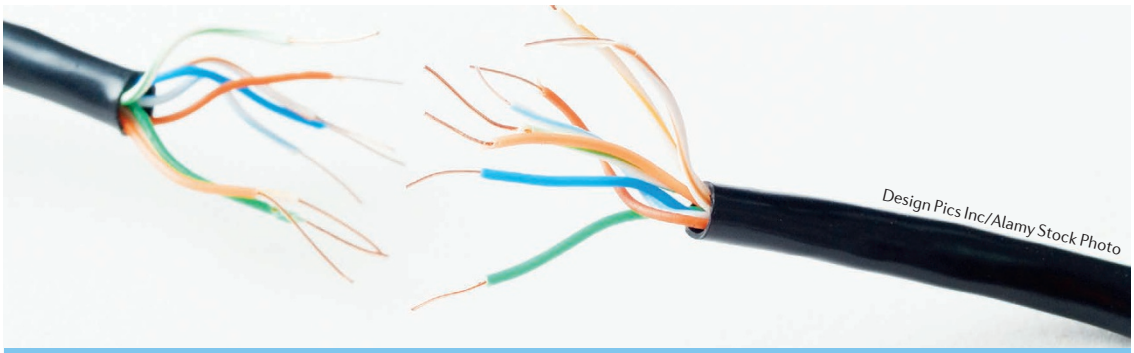

PSYCHIATRIC DISORDERS

Splitting depression apart

> Optogenetic activation of $PV^{VP \rightarrow VTA}$ neurons in naive mice induced social withdrawal

Depression is associated with several different symptoms, including helplessness, social withdrawal and anhedonia. However, whether separate circuitries underlie each of these behavioural components of depression is not known. Now, Knowland *et al.* show that, in a mouse model of depression, increases in the activity of parvalbumin-expressing (PV^+) neurons in the ventral pallidum (VP) that project to the lateral habenula (LHb) or the ventral tegmental area (VTA) may underlie behavioural signs of despair and social withdrawal, respectively.

PV^+ VP neurons had been identified previously, but not extensively characterized. Here, the authors examined the projections of PV^+ VP neurons using various virus and optogenetic approaches. They found that PV^+ neurons in the VP project to either the VTA or the LHb, but not to both. Moreover, genetic labelling and patch-clamp recordings revealed that PV^+ VP neurons projecting to the LHb ($PV^{VP \rightarrow LHb}$ neurons) are excitatory, whereas $PV^{VP \rightarrow VTA}$ neurons comprise a mixture of inhibitory and excitatory neurons. In addition, trans-synaptic tracing revealed that $PV^{VP \rightarrow LHb}$ neurons and $PV^{VP \rightarrow VTA}$ neurons preferentially receive inputs from different brain structures. Together, these observations suggest that $PV^{VP \rightarrow LHb}$ neurons and $PV^{VP \rightarrow VTA}$ neurons are distinct subpopulations.

Given that the VP is a crucial node in both reward-related and aversion-related circuits, the authors investigated the role of PV^+ VP neurons in the chronic social defeat stress (SDS) model of depression. Mice exposed to SDS were separated into 'susceptible' and 'resilient' cohorts based on their tests of depressive-like behaviours, including helplessness in the tail suspension test, anhedonia in the sucrose preference test and social withdrawal. Examination of PV^+ VP neurons in acute slices from these mice revealed that SDS increases the excitability of $PV^{VP \rightarrow LHb}$ neurons (reflected by more-frequent spiking and fewer inhibitory postsynaptic potentials) in susceptible mice, but not in resilient mice, and that treatment with the antidepressant fluoxetine ameliorated this effect. Relatedly, $PV^{VP \rightarrow VTA}$ neurons in resistant or treated mice showed decreased excitability compared with those in susceptible or control animals. Thus, SDS-susceptible animals show increased PV^+ VP neuron activity.

Next, the authors asked whether attenuating PV^+ VP neuron could enhance SDS resilience. Indeed, reducing the activity of PV^+ VP neurons (through targeted expression of a hyperpolarizing channel) in mice subsequently subjected to SDS reduced helplessness and social withdrawal, although it did not prevent anhedonia. Optogenetic activation of $PV^{VP \rightarrow VTA}$ neurons in naive mice induced social withdrawal. Optogenetic or chemogenetic inhibition of $PV^{VP \rightarrow LHb}$ neurons in SDS mice reduced measures of helplessness but did not affect social avoidance. Conversely, inhibition of $PV^{VP \rightarrow VTA}$ neurons in SDS mice rescued social interaction but did not change levels of helplessness. Therefore, these two subpopulations are necessary for separate components of depression-like behaviour.

Overall, these results demonstrate that two major components of depression-like behaviour — social avoidance and helplessness — are mediated by different VP circuits.

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ORIGINAL ARTICLE Knowland, D. *et al.* Distinct ventral pallidal neural populations mediate separate symptoms of depression. *Cell* **170**, 284–297 (2017)