# Scientists identify brain circuitry responsible for anxiety in smoking cessation

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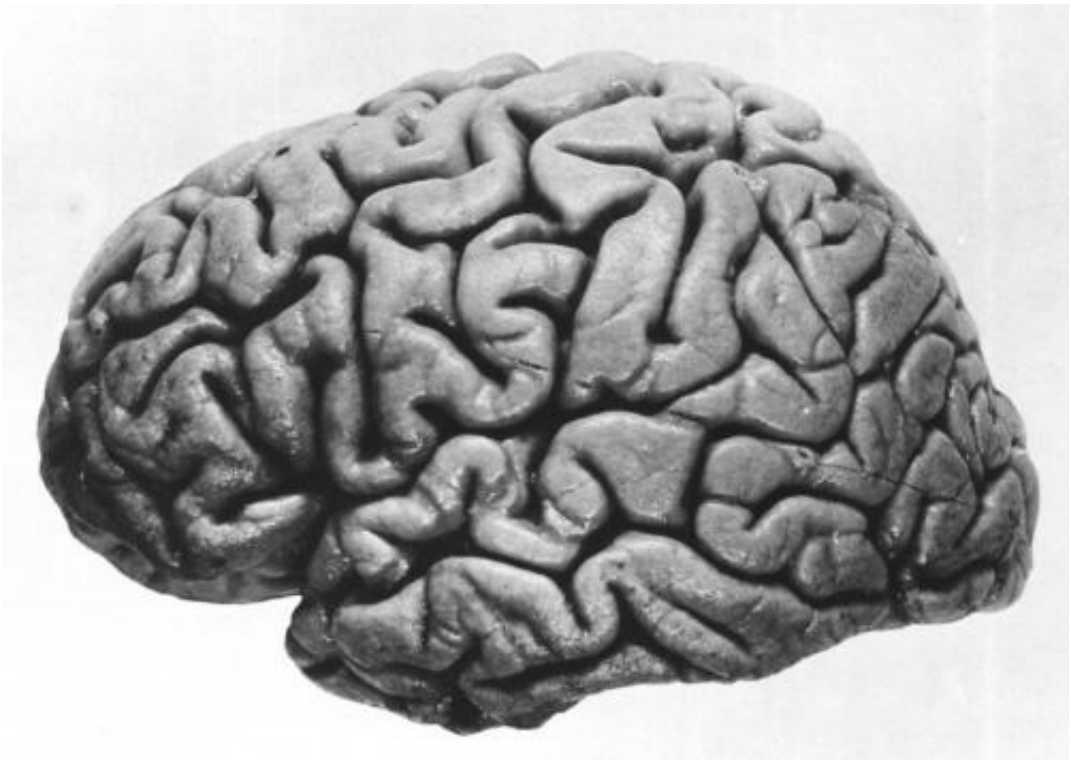

Left hemisphere of J. Piłsudski's brain, lateral view. Credit: public domain

In a promising breakthrough for smokers who are trying to quit, neuroscientists at the University of Massachusetts Medical School and The Scripps Research Institute have identified circuitry in the brain responsible for the increased anxiety commonly experienced during withdrawal from nicotine addiction.

"We identified a novel circuit in the brain that becomes active during nicotine withdrawal, specifically increasing anxiety," said principal investigator Andrew Tapper, PhD , associate professor of psychiatry. "Increased anxiety is a prominent nicotine withdrawal symptom that contributes to relapse in smokers attempting to quit."

The study yielded several discoveries about interconnected brain mechanisms that induce anxiety during nicotine withdrawal—and possible ways to derail these mechanisms in order to treat, or even prevent the especially troublesome symptom.

Experiments leading to the multiple, related findings were conducted over several years by the laboratories of Dr. Tapperand Paul Gardner, PhD, professor of psychiatry at UMMS; and collaborator Olivier George, PhD, assistant professor in the Committee on Neurobiology of Addictive Disorder at The Scripps Research Institute of La Jolla, Cal. Lead author was Rubing Zhao-Shea, MD, research assistant professor of psychiatry at UMMS.

Published online by *Nature Communications* on April 21, the study's main finding is that a brain region called the interpeduncular nucleus is activated and appears to cause anxiety during nicotine withdrawal. Investigators were intrigued to learn that the sub region of the interpeduncular nucleus, which is activated and linked to anxiety during withdrawal, is distinct from another sub-region, previously identified by Tapper, where physical nicotine withdrawal symptoms such as headaches, nausea and insomnia originate.

Anxiety is an affective symptom often likely to thwart smokers' attempts to quit. The newly discovered sub region offers a distinct target for dampening the affective symptoms of nicotine withdrawal.

Also newly identified is the fact that input from neurons in two other

brain regions converge onto the interpeduncular nucleus to stimulate anxiety-provoking neurons. Surprisingly, the ventral tegmental area, which is traditionally associated with the rewarding or pleasurable effects of abused drugs, activates neuron receptors through corticotropin releasing factor, a protein neurotransmitter released in response to stress. Also surprising, neurons in the medial habenula stimulate interpeduncular nucleus neurons by releasing glutamate, the major excitatory neurotransmitter in the brain, an effect that is increased by corticotropin releasing factor receptor activation.

"Both of these inputs are important. We could alleviate anxiety during nicotine withdrawal by either preventing corticotropin releasing factor synthesis in the ventral tegmental area, or by silencing the medial habenula inputs into the interpeduncular nucleus," said Tapper.

Investigators were able to alleviate anxiety in mice by quieting the activity of those activated neurons, suggesting the same might be possible for humans.

"There are already drugs that block the CRF receptor that contributes to activation of these anxiety-inducing neurons," Tapper noted. "These receptors have previously been linked to anxiety and depression, so our findings may also have implications for anxiety disorders in general."

Next steps for this productive research collaboration will be expanding the scope of scientists' understanding of the interactions between anxiety, stress, reward, and withdrawal from addictive substances.

"We're now exploring whether the circuitry that we identified is involved in stress-induced anxiety in general, or specific to nicotine withdrawal-induced anxiety," Tapper said. "We're also exploring if this circuitry is engaged with other drugs of abuse."

**More information:** *Nature Communications*, nature.com/articles/doi:10.1038/ncomms7770