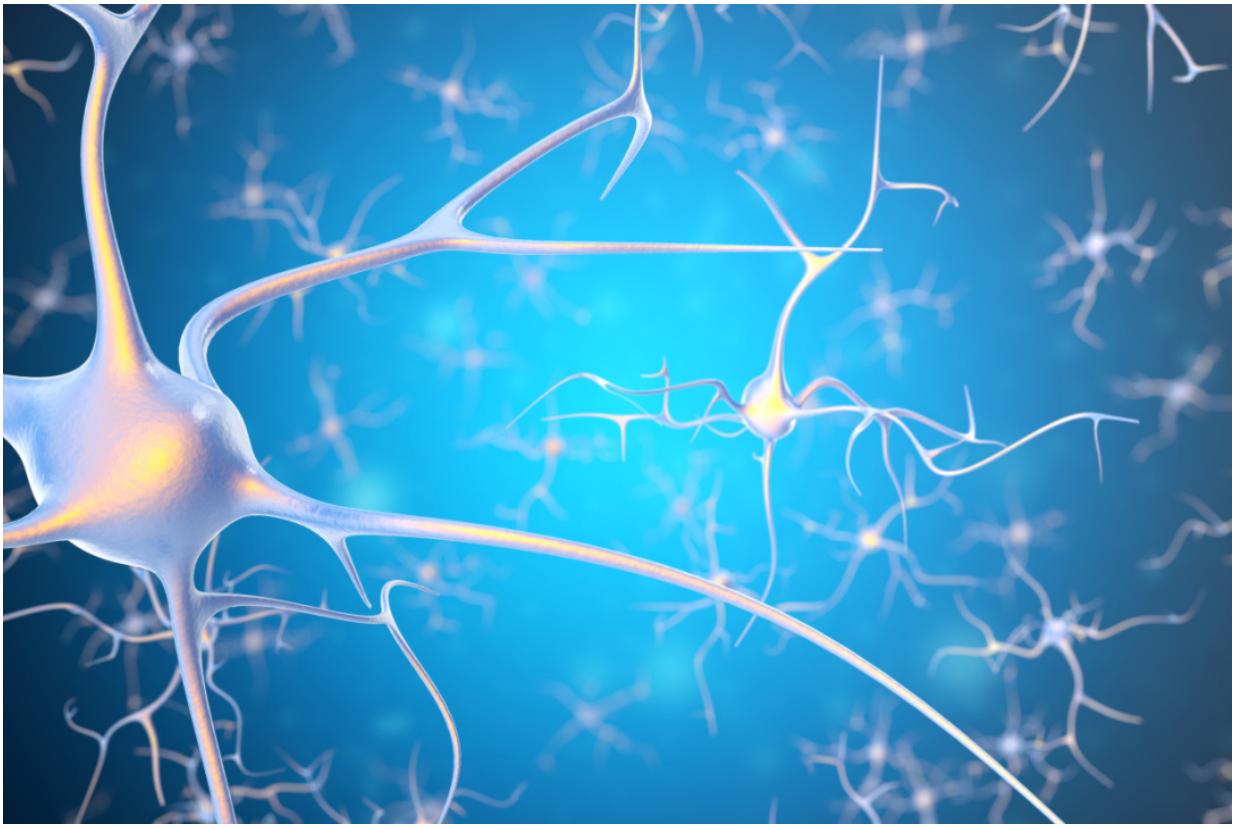
Alcoholism may be caused by dynamical dopamine imbalance

March 10 2017



Credit: National Research University Higher School of Economics

An international research collaborative has identified potential alcoholism mechanisms associated with altered dopaminergic neuron response to complex dynamics of prefrontal cortex neurones affecting

dopamine release.

Interacting neuronal populations in the cerebral cortex generate electrical impulses (called action potentials) that are characterized by specific spatial and temporal patterns of neural firing (or complex neural dynamics). These firing patterns depend on the intrinsic properties of individual neurones, on the neural network connectivity and the inputs to these circuits. The basis for this computational study is the experimental evidence for a specific population of prefrontal cortex neurones that connects via excitatory synapses to dopaminergic and inhibitory ventral tegmental area (VTA) neurons. Thus, the structure of neural firing in the prefrontal cortex can directly affect dopamine cell response and dopamine release.

Boris Gutkin leads the Theoretical Neuroscience Group at the HSE Centre for Cognition and Decision Making. One of the group's research areas focuses on neurobiological processes leading to substance abuse and addiction—specifically, on detecting links between the neurobiological mechanisms of a drug's action and observable behavioural reactions. In particular, the researchers use mathematical modeling to examine specific characteristics of dopaminergic neurone firing patterns and dynamics that can lead to addiction.

Dopamine, a neurotransmitter released by dopaminergic neurons in the brain, is a chemical that plays a key role in the internal brain reward system that drives learning of motivated behavior. By acting within the reward systems in the brain (e.g. the ventral tegmental area found deep in the mid-brain; the striatum, responsible for selecting correct actions and the prefrontal cortex that controls voluntary goals and behaviors), it signals either unexpected reward or anticipation of reward resulting from a particular action or event. Thus, dopamine provides positive reinforcement of behaviours that lead to these rewards, causing them to be repeated. Conversely, where a particular action fails to produce the

expected positive effect or is followed by an unpleasant event, dopamine release decreases sharply, leading to frustration and an unwillingness to repeat the behaviour in question.

Many dopamine neurons produce these learning signals by emitting rapid bursts of spikes when the animal receives more reward than expected or pausing when there is less than expected. In order to govern the learning correctly, the number of bursts (and the dopamine released) must be proportional to the discrepancy between the received and the expected reward (for example if one expects to get 50 euros for his work, but gets 100; the dopamine activity should be proportional to 50; when one expects 50 but gets 500; the activity should signal a number proportional to 450). Hence the bigger the mismatch, the stronger the response. Yet another subgroup of dopamine neurons simply signals when stimuli are important for behaviour or not giving binary all-or-none responses. These binary signals then drive orienting or approach to the important behaviors. So the two dopamine cell populations have different response modes: the analogue learning signal or the all-or-none importance alert.

Two Modes of Neurone Activity

Recent research by Gutkin's group conducted jointly with scientists from Indiana University and the RAN Institute of Applied Physics suggests potential mechanisms of alcohol's effect on dopaminergic neuronal activity. Their paper, "Dopamine Neurons Change the Type of Excitability in Response to Stimuli," published in *PLOS One*, features a computational model of dopamine (DA) neurone activity, describing its key properties and demonstrating that the DA neurone's response mode can vary depending on the pattern of the synaptic input (including that from the prefrontal cortex).

When in the first mode, the amount of dopamine released by the DA neurones reflects the learning signal propotional to the difference

between what an animal or human expects and what they actually receive as a result of a certain action. When in the second DA neurone mode, dopamine release serves as a reference binary signal indicating whether or not a certain event is important. Thus, the results of the computational study imply that dopamine neurons may not be two distinct populations, but are capable of switching flexibly from one response mode to another depending on the nature of the signals they receive.

In a related study, "Contribution of synchronized GABAergic neurons to dopaminergic neuron firing and bursting," published in the *Journal of Neurophysiology*, the same group suggests that in addition to direct links between DA and prefrontal cortex neurones, indirect neural inputs from the prefrontal cortex via inhibitory (GABAergic) VTA neurones should be considered. In particular, the researchers found that signals from the prefrontal cortex can cause GABAergic neurones to synchronise, producing a strong inhibitory effect on DA neurons. The study found that in some cases, such inhibitory effects can lead to paradoxical results—instead of suppressing DA neurone firing and thus decreasing dopamine release, they can multiply DA firing frequency leading to higher dopamine release and positive reinforcement.

What It Means for Our Understanding of Alcoholism

Experimental evidence suggests that alcohol is capable of modifying DA neurone firing patterns, both indirectly via prefrontal cortex and inhibitory VTA neurones, and directly by acting on DA neurones per se. Based the current findings, the researchers hypothesise what mechanisms may be involved.

The VTA has about 20,000 DA neurones in a non-alcoholic person. Some of these serve to signal that a certain stimulus has importance, while the rest transmit the error signal. A certain balance between the two types of signals is essential for good judgment and proper behaviour.

Alcohol disrupts the balance by changing both the pattern of neural activity in the prefrontal cortex and DA neurone properties. This change may bias more neurons to signal importance as opposed to the error. So under the influence of alcohol, any stimulus associated with alcohol is treated by DA neurones as having behavioural and motivational importance, regardless of whether or not it matches the anticipated outcome, while in the absence of alcohol, neural firing would normally be consistent with the expected and received reinforcements.

This effect may be the reason why alcoholics may eventually develop a narrower than normal range of behavioural responses, motivating them to seek out alcohol. In doing so, they are either unaware of potential consequences of their actions or, even if they can anticipate such consequences, this awareness has little or no effect on their behaviour. According to surveys, most alcoholics understand that they may lose their home and family and even die from binge drinking, but this rarely stops them. To properly assess the consequences of drinking, their prefrontal cortex needs to integrate and learn to properly represent the negative expectations from this behaviour, supported by reinforcement learning signals from DA neurones. This may not happen, however, because alcohol (like other mood-altering substances) can affect both the neural activity in the addict's prefrontal cortex and their DA neurones directly, blocking the learning.

Finding a way to balance out the dopamine function in the addicted brain and to elicit adequate neural responses to environmental stimuli even while under the influence could offer hope to people with substance abuse problems.

More information: Ekaterina O. Morozova et al, Dopamine Neurons Change the Type of Excitability in Response to Stimuli, *PLOS Computational Biology* (2016). DOI: 10.1371/journal.pcbi.1005233

Ekaterina O. Morozova et al. Contribution of synchronized GABAergic neurons to dopaminergic neuron firing and bursting, *Journal of Neurophysiology* (2016). DOI: 10.1152/jn.00232.2016