Serotonin booster leads to increased functional brain connectivity, shows study

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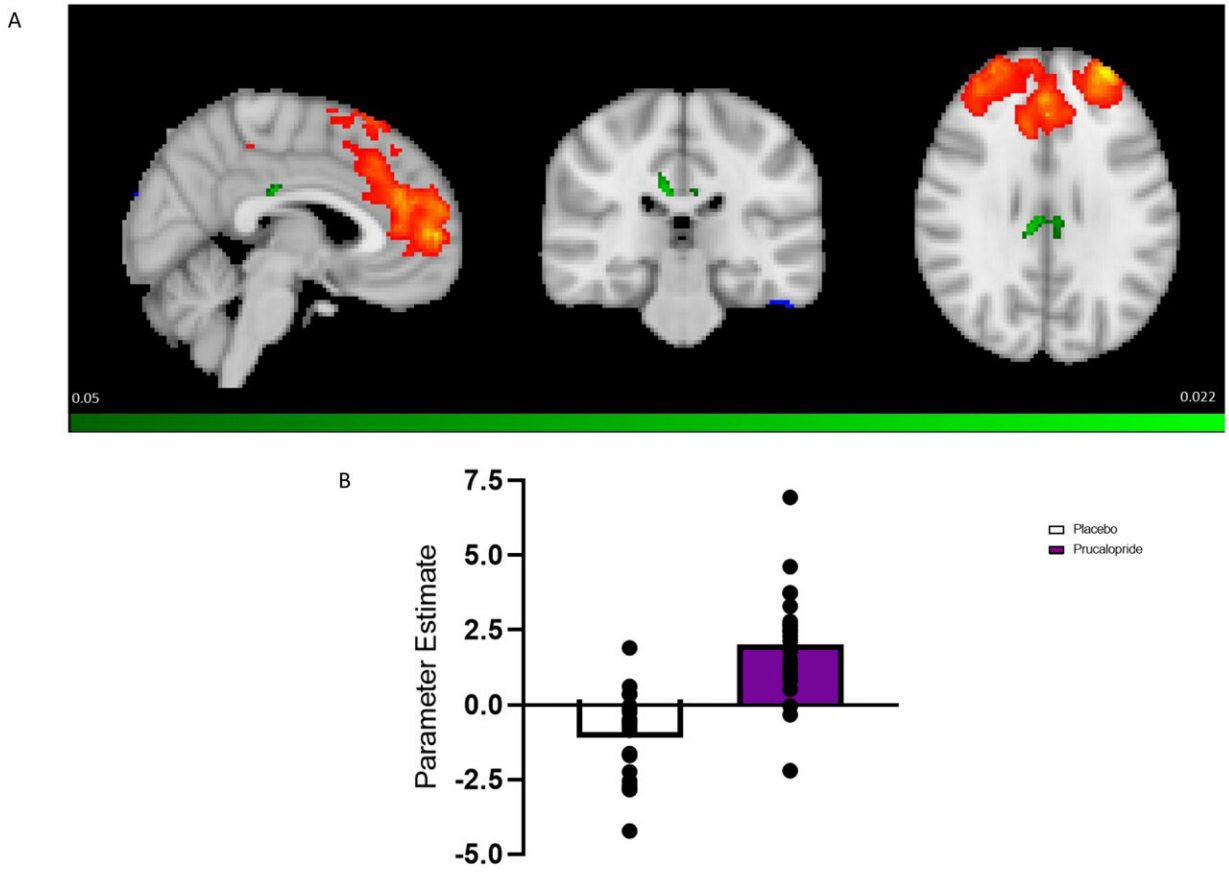

This figure shows that the healthy participants who received prucalopride had greater functional connectivity between key cognitive regions (the posterior / anterior cingulate cortices) and a major cognitive network (the central executive network). That is, they appeared to be strengthening their connectivity within cognitive networks. Credit: *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* (2023). DOI: 10.1016/j.bpsc.2023.03.014

Cognitive deficits accompany mood disorders and other psychiatric conditions, often with debilitating effects. Limited treatments currently exist, but studies in animals and humans have pointed to drugs such as the laxative prucalopride that activate serotonin receptors as a potential therapeutic for the symptoms. It has remained unclear, however, how the medication affects resting brain activity.

Now, a new study in *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* examines the drug's effects in healthy human adults.

Serotonin receptors and the 5-HT_4-type receptors in particular are found in areas throughout the brain, including the frontal cortex, basal ganglia, and hippocampus, that are known to mediate cognitive function and regulate mood. Serotonin receptors are the primary targets of antidepressant medications, but resolving mood disturbances often does not resolve cognitive symptoms.

The researchers enlisted 50 healthy volunteers, half of whom received a six-day course of prucalopride, a highly selective agonist of the 5-HT_4 type serotonin receptor, whereas the other half of the participants received a placebo. Participants underwent scanning with functional magnetic resonance imaging, including a "resting scan," in which they relaxed in the scanner.

Lead author Angharad de Cates, Ph.D., MRCPsych, at the University of Oxford, said of the work, "Our previous studies on prucalopride demonstrated that even at low clinical doses it can improve cognition and memory in healthy volunteers. This latest research provides a neurological mechanism by which this might occur."

Participants who received the medication displayed more functional connectivity in their resting-state (rsFC) between major cognitive networks. This included more rsFC between the central executive

network, a brain network used for processing thoughts, and the posterior and anterior cingulate cortex (ACC), brain areas that regulate information processing and attention in the brain.

There was also more rsFC between regions of the ACC and the lateral occipital cortex, a region that helps us pay attention to objects that matter. In addition, medicated participants compared to placebo controls showed decreased rsFC in the default mode network, a brain network that is activated during mind wandering.

Dr. de Cates added, "This provides further evidence that prucalopride is having an effect in areas of the brain that improve cognitive function—both by increasing and reducing connectivity between specific brain regions as required."

Susannah Murphy, Ph.D., Associate Professor and joint senior author of the study, said, "Appropriate connectivity between and within these brain networks is needed to think properly, and this connectivity has been shown to be abnormal in depression. Here, the participants taking prucalopride had better scores on cognitive tests the day of the scan compared to the placebo participants. That suggests that the changes in rsFC that we saw with prucalopride may serve as a 'signature' of a drug that improves cognition."

Dr. Murphy continued, "Untreated cognitive problems have a significant impact on the quality of life of people with depression. This study adds to the growing evidence base that drugs affecting the 5-HT_4 serotonin receptor hold promise as a novel way to treat depression and cognitive impairment."

Catherine Harmer, Ph.D., Professor of Cognitive Neuroscience and joint senior author of the study, said, "This study adds to the evidence base that the common laxative treatment prucalopride can have important

effects in the brain, particularly affecting circuits which are important for learning and memory. Together with previous data, this suggests that this drug might be useful as a pro-cognitive treatment in disorders such as depression."

Cameron Carter, MD, Editor of Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, said of the work, "These data, showing modulation of resting state connectivity in the brain by the $5HT_4$ receptor agonist and putative cognitive enhancer prucalopride, add to previous evidence that the agent modulates brain systems that are engaged during focused, higher cognitive activity and might have therapeutic potential."

More information: Angharad N. de Cates et al, 5-HT4 receptor agonist effects on functional connectivity in the human brain; Implications for pro-cognitive action, *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* (2023). DOI: 10.1016/j.bpsc.2023.03.014

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