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Researchers find direct human evidence for a neural circuit that may help better understand a mystery of Parkinson’s Disease

Researchers at UC Santa Barbara have uncovered direct human evidence for a neural circuit that may explain paradoxical kinesia. It’s a phenomenon often associated with individuals with Parkinson’s Disease, in which they perform smooth, swift and complex actions despite the impairment of their motor circuitry.

“There has been evidence in nonhuman primates that there might be this circuit that may bypass the traditional closed-loop motor circuit,” said Elizabeth Rizor, a postdoctoral scientist in the Department of Psychological & Brain Sciences, and co-lead author of a study that appears in the Proceedings of the National Academy of Sciences.

Neuroanatomical tracing studies in these subjects revealed evidence of an alternative circuit, but until now “no one had ever really dived into it in the human brain,” she said. A better understanding of this lesser-known circuitry can lead to “foundations for context-based therapeutic interventions,” according to the paper.

A neurological ‘back door’

In people with Parkinson's Disease, a closed-loop neural circuit that runs from the dorsal putamen located deep in the forebrain to the motor cortex on the surface of the frontal lobe and back again is impaired, resulting in slow, jerky or absent movement. Yet, cases exist in which these patients can also catch a ball, ride a bike, even play musical instruments. This paradoxical kinesia is typically tied to moments of stress and situations of high emotion and motivation. Once the situation resolves, the threat passes or the reward is obtained, the patient goes back to their previous state.

"As humans, we face these motivations constantly," said co-lead author Neil Dundon, formerly a project scientist in the lab of UCSB neuroscience professor emeritus Dr. Scott Grafton. The idea, Dundon continued, has been that another neural pathway is activated in these high-motivation scenarios.

"This circuit is essentially a back door to the motor system in highly salient moments that might allow movement to be

facilitated," Dundon said. That open loop circuit begins at the amygdala, a structure located in the middle of the brain that is associated with arousal and emotion; links to the ventral

putamen, which is typically associated with affective — emotion or mood-related — processes, as opposed to motor processes; and ends at the motor cortex.

To prove the physical existence of this back door, and whether and how it responds to incentive conditions, the researchers and their collaborators conducted two experiments, in cohorts of healthy subjects using magnetic resonance imaging to scan their brains under different conditions.

"The first one was with ultra-high field imaging," Rizor said. "We really wanted to get a good look at these small areas deep in the brain and these sub areas of the putamen, the dorsal and ventral putamen." Because the dorsal putamen tended to be damaged in cases of

Parkinson's, the hypothesis was that the signal could be routed toward the ventral putamen in more arousing situations, she said. Previous research in animal models

using a modified rabies virus to trace backward through neural pathways revealed evidence of this lesser-known connection, she added; the researchers wanted to find it in the human brain. Controlling for the signal activity in the dorsal putamen, they found that the ventral putamen was actively connected to the cingulate motor cortex, a

region of the brain that links motivation to action.

The second experiment, involving functional MRI scans, required the subjects to participate in incentivized motor-based tasks to see which and how the open and closed-loop neural circuits are engaged. The subjects underwent 300 trials that involved a timed joystick task that required speed and accuracy. The trials awarded prizes on a reward (jackpot) incentive, a loss avoidance (punishment) incentive and a standard incentive.

“We were able to see when they started moving the joystick and how quickly their movements started,” Dundon explained. “And then we were able to ask what brain regions are active more when that movement goes more quickly? Are there regions that are correlated with movement initiation speed that are more relevant in these high-reward or high punishment scenarios?”

Their initial assumption was that for the standard incentive task, which gave a smaller reward relative to the “jackpot” and “punishment” incentives, the normal, closed loop circuit would be associated with movement speed, and then in cases of higher reward, the open loop circuit would become more relevant for movement.

What they found instead was a bit more nuanced. Both closed and open-loop circuits were correlated with movement initiation speed during the standard reward condition. In the jackpot condition, the closed-loop circuit became less relevant, while the open loop remained coupled with movement initiation. In the subjects, this translated to faster movement initiation, but more false starts.

“You’ve got these regions of the sensory motor circuit that are really important for getting timing and precision right,” Dundon explained. “And when they downregulate in a highly salient moment, you’ll move more quickly but you’ll be a little less accurate with that movement.”

In the punishment scenario, where subjects aimed to avoid losing money, both the open and closed-loop circuits became less relevant, and other brain regions became associated with movement, particularly the subthalamic nucleus, a structure located deep in the brain that is associated with slowing or stopping movement.

“It didn’t mean that in the punishment scenario, none of the open and closed loop motor areas were working,” Rizor clarified. “It just means that specifically this slower and more cautious reaction time is coupled with a different kind of network.”

Armed with these insights, the next steps for the researchers involve recruiting individuals with Parkinson’s disease and conducting similar experiments in that patient population. Though the results seem to provide a promising research direction, the work is still at a very basic stage, according to the researchers, with the hope that the insights gained could provide the foundation for some future protocols.

“This is very much about starting with basic understanding of how connections function and work in the brain in various contexts and increasing our general understanding,” Rizor said.

Research in this project was also conducted by Joanne E. Stasiak, Jingyi Wang, Taylor Li, Kiana Subugo, Christina Villanueva, Parker Barandon, Viktoriya Babenko, Renee Beverly-Aylwin, Alexandra Stump, Tyler Santander and Regina Lapate at UCSB; and Andreea C. Bostan at the University of Pittsburgh.

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