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Researchers identify protein necessary for behavioral flexibility

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Researchers have identified a protein necessary to maintain behavioral flexibility, which allows us to modify our behaviors to adjust to circumstances that are similar, but not identical, to previous experiences. Their findings, which appear in the journal *Cell Reports*, may offer new insights into addressing autism and schizophrenia—afflictions marked by impaired behavioral flexibility.

Our stored memories from previous experiences allow us to repeat certain tasks. For instance, after driving to a particular location, we recall the route the next time we make that trip. However, sometimes circumstances change—one road on the route is temporarily closed—and we need to make adjustments to reach our destination. Our behavioral flexibility allows us to make such changes and, then, successfully complete our task. It is driven, in part, by protein synthesis, which produces experience-dependent changes in neural function and behavior.

However, this process is impaired for many, preventing an adjustment in behavior when faced with different circumstances. In the Cell Reports study, the researchers sought to understand how protein synthesis is regulated during behavioral flexibility.

To do so, they focused on the kinase PERK, an enzyme that regulates protein synthesis. PERK is known to modify eIF2alpha, a factor that is required for proper protein synthesis. Their experiments involved comparing normal lab mice, which possessed the enzyme, with those that

lacked it.

In their study, the mice were asked to navigate a water maze, which included elevating themselves onto a platform to get out of the water. Normal mice and those lacking PERK learned to complete this task.

However, in a second step, the researchers tested the mice's behavioral flexibility by moving the maze's platform to another location, thereby requiring them to respond to a change in the terrain. Here, the normal mice located the platform, but those lacking PERK were unable to do so or took significantly more time to complete the task.

A second experiment offered a different test of the role of PERK in aiding behavioral flexibility. In this measure, both normal and mutant mice heard an audible tone that was followed by a mild foot shock. At this stage, all of the mice developed a normal fear response—freezing at the tone in anticipation of the foot shock. However, the researchers subsequently removed the foot shock from the procedure and the mice heard only the tone. Eventually, the normal mice adjusted their responses so they did not freeze after hearing the tone. However, the mutant mice continued to respond as if they expected a foot shock to follow.

The researchers sought additional support for their conclusion that the absence of PERK may contribute to impaired behavioral flexibility in human neurological disorders. To do so, they conducted postmortem analyses of human frontal cortex samples from patients afflicted with schizophrenia, who often exhibit behavioral inflexibility, and unaffected individuals. The samples from the control group showed normal levels of PERK while those from the schizophrenic patients had significantly reduced levels of the protein.

"A rapidly expanding list of neurological disorders and

neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and Fragile X syndrome, have already been linked to aberrant protein synthesis," explained Eric Klann, a professor in NYU's Center for Neural Science and one of the study's co-authors. "Our results show the significance of PERK in maintaining behavioral flexibility and how its absence might be associated with schizophrenia. Further studies clarifying the specific role of PERK-regulated protein synthesis in the brain may provide new avenues to tackle such widespread and often debilitating neurological disorders."

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