Researchers find new altered neural circuits in Huntington's disease

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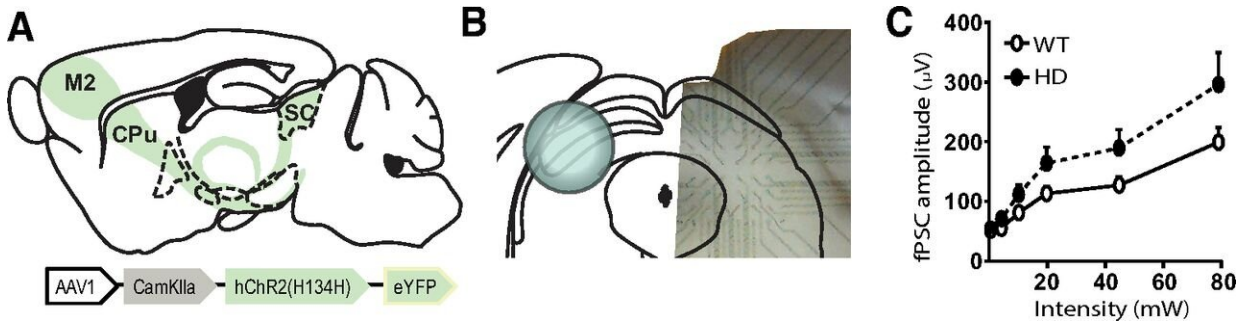

Optogenetic stimulation of M2 cortex terminals in the SC evoked similar electrophysiological responses in WT and HD mice. A, Schematic representation of AAV-CamKII-ChR2-YFP construct injection at M2 cortex. B, Representative MEA location in coronal slices containing the SC with axons from M2 cortex expressing ChR2. C, Amplitude of fPSC triggered by increasing light intensities in the SC of WT and HD mice. Data are mean ± SEM (WT n = 7 and HD n = 8 mice; 21-week-old mice). Credit: *The Journal of Neuroscience* (2023). DOI: 10.1523/JNEUROSCI.1172-22.2023

Huntington's disease is a genetically-based neurodegenerative disorder that causes motor, cognitive and psychiatric disorders in the affected individuals. Understanding the alterations in the neural circuits in this disorder is essential in order to design therapeutic approaches. In the case of patients, this disease is associated with the dysfunction of some neuronal pathways in the brain, specifically the corticostriatal circuitry.

Now, a study published in *The Journal of Neuroscience* has identified new alterations in other neural circuits in mice models, used to study this pathology which significantly alters the lives of patients.

An inherited disorder that affects neurons in the brain

Huntington's disease is a rare, inherited disease that usually manifests in adults aged between 35 and 50, although there are also some juvenile forms of the disease. It is caused by a mutation in the gene called IT15 or HTT, which codes for huntingtin protein (HTT). Historically, the motor disorder that was most commonly associated with the disorder was chorea—which causes abnormal, involuntary movements—but there are also other non-motor disorders that often appear earlier.

This disorder is associated with dysfunction of corticobasal circuits in the brain. In a previous study, published in the journal *eLife* (2020), the team characterized one of the neural circuits involved in the development of the disease in animal models: the connection from the secondary motor cortex (M2) to the dorsolateral striatum nucleus (DSL).

In patients, the most affected brain area from the beginning of the disease is the premotor cortex—the M2 cortex in mice—which is involved in cognitive functions and perceptual processes. In the case of animal models, the M2 is associated with motor learning deficits. Moreover, this cortical area is known to be able to project neuronal axons to various brain regions beyond the striatum nucleus.

Now, this study has identified for the first time that the M2 cortex sends different axonal projections to another anatomical structure in the brain—the superior colliculus (SC). These projections are deeply impaired and could be linked to the disease symptomatology.

As part of the study, the functional magnetic resonance imaging revealed the reduced functional connectivity between the left M2 cortex and all the brain regions analyzed in mice models of the disease. By applying other innovative methodologies to monitor and modulate neural activity —ontogeny, electrophysiology, photometry and chemogenetics—the team discovered that the lack of M2 cortex activity could be responsible for the altered responses in Huntington's disease.

Identifying the different alterations and functions of the M2 cortex circuitry—beyond the cortico-striatal pathway— provides data that are crucial to further analyze the symptoms of Huntington's disease and other neurodegenerative pathologies (Parkinson's disease, etc.). Also, a deeper understanding of the role of the superior colliculus and its neural circuits—involved in many neurological disorders such as Huntington's—may provide new insights into delaying the onset and severity of the symptoms in motor disorders.

More information: Sara Conde-Berriozabal et al, M2 Cortex Circuitry and Sensory-Induced Behavioral Alterations in Huntington's Disease: Role of Superior Colliculus, *The Journal of Neuroscience* (2023). DOI: 10.1523/JNEUROSCI.1172-22.2023

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