Central role played by the claustrum in cognitive deficits observed in neurodevelopmental disorders

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Cognitive symptoms are a core feature of neurodevelopmental disorders (NDD) such as autism spectrum disorder and schizophrenia. The dopaminergic system modulates cognitive functions, and its malfunction is central to many theories regarding the pathophysiology of these disorders. NR4A2 is a risk gene for several NDD and encodes a nuclear receptor essential for the specification and maintenance of the dopaminergic phenotype in midbrain neurons. However, NR4A2 is also highly expressed in glutamatergic projection neurons of the claustrum (CLA), a subcortical nucleus that is highly reciprocally connected to the neocortex, particularly to frontal areas implicated in cognitive functions. We investigated whether cognitive deficits could arise from claustral rather than dopaminergic dysfunction in Nr4a2 knockout mice. Physiological responses were monitored in genetically identified populations of glutamatergic neurons in the CLA and the medial prefrontal cortex (mPFC) during cognitive tasks. Mutant mice displayed cognitive unflexibility, which was associated with reduced neuronal activity and impaired ensemble dynamics in both circuits. Surprisingly, claustral-specific manipulations of either NR4A2 function or neuronal excitability in adult wild-type mice were sufficient to mimic both the neurophysiological and the behavioral deficits observed in the mutants. More importantly, re-expressing Nr4a2 or increasing excitability in claustral neurons of adult mutant mice corrected both CLA and mPFC neurophysiology and restored cognitive flexibility. In conclusion, the claustrum is a critical brain nucleus whose dysfunction in some NDD can impair mPFC physiology, leading to cognitive deficits. It may therefore represent a novel therapeutic target to improve cognitive symptoms in some NDD, even during adulthood.