Behavioral deficits and related *in vivo* electrophysiological recordings in a mouse model of schizophrenia with genetic reduction of dysbindin-1 and D2L

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The pathophysiology of schizophrenia and its treatment have been consistently linked to dysregulation of dopaminergic neural transmission and in particular of dopamine D2 receptor pathways. The D2 gene codes for a short form (D2S) and a long form (D2L) of the D2 receptor. Interestingly, recent results indicate that functional genetic variants in the D2 gene might modulate schizophrenia-related phenotypes by modifying the D2S/D2L ratio. Levels of dystrobrevin-binding protein 1 gene expression and its protein dysbindin 1 (dys1) are significantly reduced in patients with schizophrenia. This reduction of dys1 impacts cognitive abilities and leads to up-regulation of D2 receptors on the neural surface. Based on this biological evidence, we generated a novel mouse model with reduced expression of both D2L and dys1. We then predicted that synergistic effects of a reduced dys1 expression and an increased D2S/D2L ratio in the same subject might alter dopamine/D2 signaling, thus triggering cognitive- and schizophrenia-relevant symptoms.

Executive function deficits are core enduring symptoms in schizophrenia; thus, we tested our dys1/D2L genetically modified mice in a modified version of the 5-choice serial reaction time task. This test revealed increased impulsivity in dys1/D2L 2-het mice. Dys1, D2L and dys1/D2L 2-het mice showed also deficits in visuospatial attention. Furthermore, testing in our novel automated task able to measure attentional set-shifting in mice revealed that mice with reduction of dys1 have a selective impairment on extradimensional shift (EDS) abilities, while mice with a reduction of D2L show deficits in reversal learning. Dys1/D2L 2-het mice exhibited more severe deficits and were not able to reliably perform the test. To investigate possible underlying deficits in neuronal activity, we implanted microelectrode arrays for extracellular recording of multi-unit activity in the mPFC of our mutant mice and recorded neuronal activity while they performed the attentional set-shifting task. Dys1 het mice showed a reduced number of activated neurons in the first trials of the EDS stage, while learning the rule of this stage, compared to wild-type mice. These results suggest that the behavioral deficits observed in the dys1 het mice in the EDS may be possibly due to altered firing activity in the mPFC.

Taken together, these results begin to unravel the role of a genetic interaction between dys1 and D2L in cognitive and schizophrenia-related deficits.