Snap25 heterozygous knockout mice as a potential model for ADHD: stress induction and pharmacological challenge
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Purpose of the study
Synaptosomal-Associated Protein of 25 kDa (SNAP25; part of the SNARE complex) is involved in axonal growth and synaptic plasticity, as well as in the docking and fusion of synaptic vesicles in presynaptic neurons necessary for the regulation of neurotransmitter release. In humans, different single nucleotide polymorphisms of SNAP25 have repeatedly been associated with attention deficit hyperactivity disorder ADHD. Heterozygous Snap25 knockout mice thus are a potential model of ADHD.

Results: Stress reactivity
![Figure 1: Corticosterone concentrations in blood plasma after behavioral testing](image)

Results: Locomotor activity
![Figure 2: Distance travelled in 60 minutes in a rectangular Open Field arena, initially (A) and three weeks later (B).](image)

Methods 1
Heterozygous Snap25 knockout mice as well as their wild-type littermates were reared under control conditions or underwent a Maternal Separation procedure for the first 21 days of their lives.

Methods 2
At adult age, Maternal Separation and Control mice were tested using:
- Open Field Test (locomotor activity)
- 5 Choice Serial Reaction Time Task (attention deficits and impulsive behavior)
- Forced Swim Test (depression-like behavior)
- Light dark box (anxiety-like behavior)

After testing mice were sacrificed; blood and brains were taken to test for corticosterone concentration and gene expression, respectively.

Results: Anxiety- and depression-like behavior
![Figure 5: Latency to enter the lit compartment in the Light-dark Box test](image)

Results: Gene expression
![Figure 7: Results from gene expression analysis with qRT-PCR (relative quantities). (A) NOS1 expression in the Striatum (B) and (C) MAO-A and COMT expression in the Frontal Cortex, respectively](image)

Results: Methylphenidate
![Figure 8: Locomotor activity in a 60-min Open Field test after oral Methylphenidate administration (45 mg/kg).](image)

Conclusions
Heterozygous Snap25 knockout mice show some of the behavioral symptoms of ADHD, as for example mild hyperactivity in a familiar environment and difficulties in the correct execution of a given task. The reduced number of rewards eaten directly after a correct response in the SCRTT also reflects impulsive behavior to a certain degree. Depressive-like behavior is not found in the unstressed group, but MS heterozygous mice spent less time struggling in the FST than MS wild-types. In the LDR, MS significantly enhanced anxiety-like behavior in heterozygous animals. Although the exaggerated locomotor activity response to MPH is not to be expected of an ADHD model, the difference in the response between +/+ and +/- mice nonetheless implicates a dysfunction of the catecholaminergic system. The same is true for the differences in MAO-A and COMT expression in the Frontal Cortex. In summary, a heterozygous knockout of Snap25 in mice does not lead to full occurrence of ADHD-like symptoms, but nonetheless results in an endophenotype of increased activity and irritability which, considered together with the changes in gene expression, constitutes another step towards the understanding of not only ADHD, but also other psychiatric disorders.

Supported by the DFG (RTG 1253) by federal and Länder funds
No potential conflict of interest

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