



# F42. CHONDROTIN-6 SULFATE CLUSTERS: ASSOCIATION OF SYNAPTIC DOMAINS AND REGULATION OF SYNAPTIC PLASTICITY DURING FEAR LEARNING

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**Background:** Duplication at 16p11.2, affecting approximately 30 genes, has consistently been associated with increased risk of schizophrenia (Psychiatric Genomics Consortium, 2017. *Nat Genet* 49: 27). We currently have little understanding of how this CNV impacts on brain and neurotransmitter system function. Here we use a mouse model of 16p11.2 duplication (7DUP mice, Horev et al. 2011. *PNAS*. 108: 17076) to determine the impact of this CNV on cerebral metabolism. In addition, we characterize in vivo glutamate and monoamine neurotransmitter system function by challenging these animals acutely with ketamine and d-amphetamine, respectively.

**Methods:** 7DUP mice and littermate controls were treated with ketamine (25mg/kg), d-amphetamine (5mg/kg), or saline (2ml/kg). n=11 (6 male, 5 female) for each genotype per treatment group. Cerebral metabolism was determined by <sup>14</sup>C-2-deoxyglucose functional brain imaging (Dawson et al., 2015. *Transl Psychiatry*. 5:e569). Data were analysed using repeated measures ANOVA with post-hoc Tukey's HSD.

**Results:** 7DUP mice show significant constitutive hypometabolism in the thalamic reticular nucleus, mesolimbic system, and in neuromodulatory brain regions. Hypometabolism was also seen in the striatum of female, but not in male, 7DUP mice. 7DUP mice were also found to show hypermetabolism in the hippocampus, amygdala, and cerebral cortex. The impact of ketamine on cerebral metabolism is attenuated in 7DUP mice with sex specific effects, being evident in the mesolimbic and neuromodulatory system of males, whereas the attenuation is present in the hippocampus and striatum in female mice. By contrast, 7DUP mice showed an exaggerated response to d-amphetamine. Again, these effects were influenced by sex, with the exaggerated response being significantly more widespread in males than in females.

**Discussion:** 7DUP mice show altered constitutive cerebral metabolism in brain regions implicated in schizophrenia, including hippocampal and temporal cortex hyperactivity. In addition, 7DUP mice demonstrate a reduced response to ketamine, supporting NMDA receptor hypofunction as a result of 16p11.2 duplication. This effect is consistent with the glutamate hypofunction hypothesis of schizophrenia. By contrast, 7DUP mice show an exaggerated response to d-amphetamine, supporting monoamine neurotransmitter system dysfunction as a consequence of 16p11.2 duplication. Intriguingly, each of these effects differs in male and female mice, suggesting that the phenotypic impact of 16p11.2 duplication is influenced by sex. These data provide new insight into the mechanisms through which 16p11.2 duplication increases the risk of developing schizophrenia.

#### F42. CHONDROTIN-6 SULFATE CLUSTERS: ASSOCIATION OF SYNAPTIC DOMAINS AND REGULATION OF SYNAPTIC PLASTICITY DURING FEAR LEARNING

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**Background:** Emerging evidence from our group and others has brought the brain extracellular matrix (ECM) to the forefront of investigations on brain disorders. Our group has shown that organized perisynaptic ECM aggregates, i.e. perineuronal nets (PNNs) are decreased in several brain regions in people with schizophrenia (SZ) and bipolar disorder (BD). PNNs were detected by their expression of specific chondroitin sulfate proteoglycans

(CSPGs), main components of the ECM, thought to play a key role in synaptic regulation during development and adulthood. Our studies have also shown that glial cells expressing CSPGs are altered in these disorders, suggesting a link between glial cell and PNN abnormalities. Finally, we have recently shown that novel CSPG structures, bearing a distinct CS-6 sulfation pattern and named CS-6 glial clusters, are decreased in the amygdala of people with SZ and BD. The morphology and function of CS-6 glial clusters is not currently known, but evidence from rodents and on the role of CSPGs in regulating synaptic functions strongly suggest that they may affect synaptic plasticity. We tested this hypothesis using a combination of human postmortem and rodent brain studies.

**Methods:** High Resolution electron microscopy was used to investigate the ultrastructural organization of CS-6 glia clusters. A transgenic mouse model expressing green fluorescent protein in a subset of excitatory pyramidal neurons was used to investigate dendritic spines association with CS-6 glia clusters. Mice were exposed to a single session of auditory fear conditioning for a total of 15 minutes. Animals were euthanized 4 hours after behavioral test. Multiplex immunocytochemistry was used to visualize CS-6 clusters.

**Results:** In human tissue, we show that CS-6 glia clusters are widespread in several brain regions, including the amygdala, entorhinal cortex, thalamus and hippocampus. Ultrastructural results show that CS-6 glia clusters are formed by CS-6 accumulations surrounding several dendrites. CS-6 expression was detected in astrocytes surrounding the dendrites, particularly in astrocytic endfeet enveloping dendritic spines, and within spines postsynaptic densities. Following auditory fear conditioning, marked changes of CS-6 glia clusters were observed in hippocampus regions dentate gyrus (g>1.5) and CA2 (g>1.5) and basolateral amygdala (g>1).

**Discussion:** These findings suggest that CS-6 glia clusters may represent segregated microdomains, dynamically regulated during learning and contributing to the modulation of synaptic regulation machinery. Specifically, we postulate that astrocytes synthesize CS-6 CSPG and secrete it through their endfeet around dendrites, modulating structural plasticity of dendritic spines. These results suggest a relationship between the abnormalities in CSPGs expression and alteration in dendritic spines, two pathological landmarks observed in postmortem brains of people with SZ and BD.

#### F43. POTENTIATION OF INHIBITORY NEUROTRANSMISSION IN THE TREATMENT OF RECENT-ONSET SCHIZOPHRENIA BY MODIFICATION OF DEVELOPMENTAL PRUNING OF PREFRONTAL CIRCUITRY

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**Background:** The overt symptoms and deficits of schizophrenia (SZ) typically emerge during late adolescence and early adulthood, followed by a period of post-onset functional deterioration. This peri-onset period temporally coincides with the final maturation of the prefrontal cortex (PFC), which is characterized by a process of extensive pruning of synaptic connectivities. Developmental maturation of inhibitory neurotransmission may play a key role in regulating the onset and duration of peri-adolescent synaptic pruning. We hypothesize that a deficit in the developmental increase in inhibitory neurotransmission may disturb the PFC synaptic pruning process and hence contribute to the onset and the functional deterioration that is characteristic of the early course of SZ. Enhancement of inhibitory neurotransmission may therefore restore the integrity of PFC neural circuitry, which may then lead to lasting improvements in cognitive deficits and clinical symptoms.