



Negev Autism Center



מרכז זלוטובסקי למדעי העצב
Zlotowski Center for Neuroscience

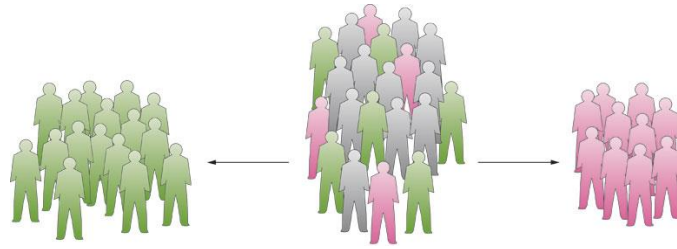
One carbon metabolic pathway deficiency increases risk for autistic-like behavior in mice.

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Faculty of Health Sciences**

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HYPOTHESIS

Maternal and child low activity of one carbon metabolism (genetic or environmental) predispose the developing brain to ASD.

Genetic: polymorphism in genes encoding for enzymes of C1 metabolism
Environmental: in-utero environment, lactation, nutrition including food selectivity, GI..

Objectives

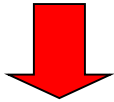
Test of hypothesis
(mouse)



Regional Autism Database.
(human)



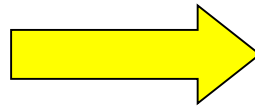
MTHFR deficiency, Evaluation of outcome and origin. (behavioral and molecular pathways and markers)



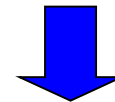
Optimization of dietary intervention to Reduce behavioral, molecular and epigenetic outcome. Search for Markers.



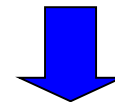
Adjustment of diet to genotype, age, sex



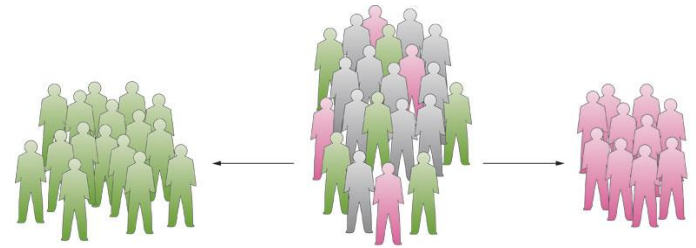
Regional Autism Database (obstetrics, gynecology, neonatology, psychiatric, genetic, bio-bank)



Evaluation of risk factors and C1 metabolism involvement (in the database)



Genotype dependent adjustment of supplementation to reduce the risk for ASD and attenuate the symptoms in affected children.

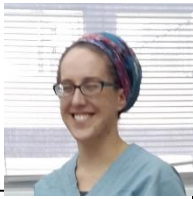


Aim I

To develop personalized intervention for two target populations:

- 1) Pregnant women with compromised one carbon metabolism to reduce the risk for autism among their newborns.
- 2) Autistic patients with one carbon metabolism imbalances.

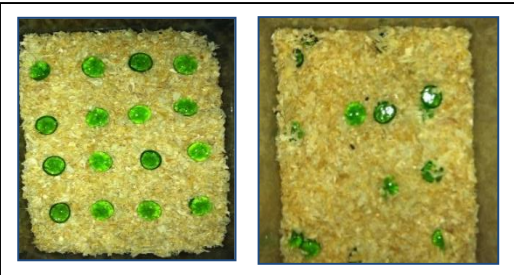
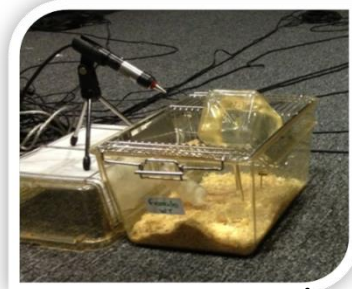
Behavioral Phenotyping



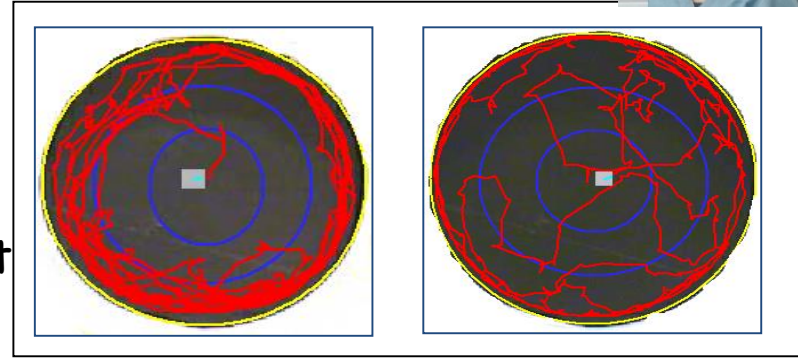
Repetitive behavior



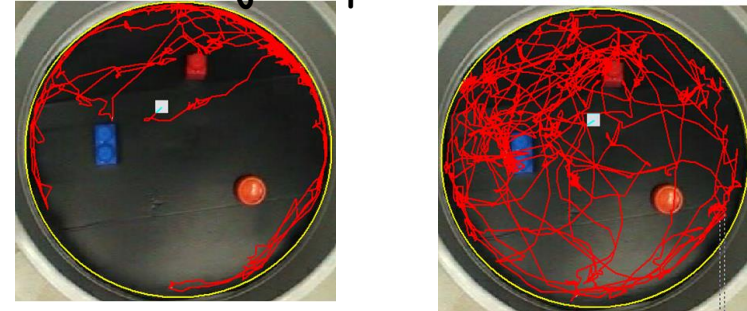
Vocalization in social context



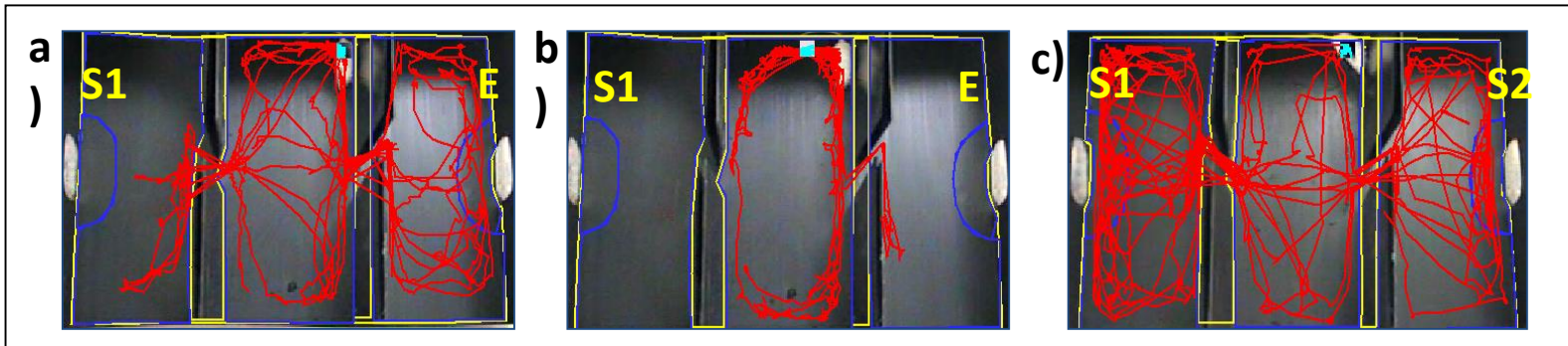
Exploration and anxiety



Object preference

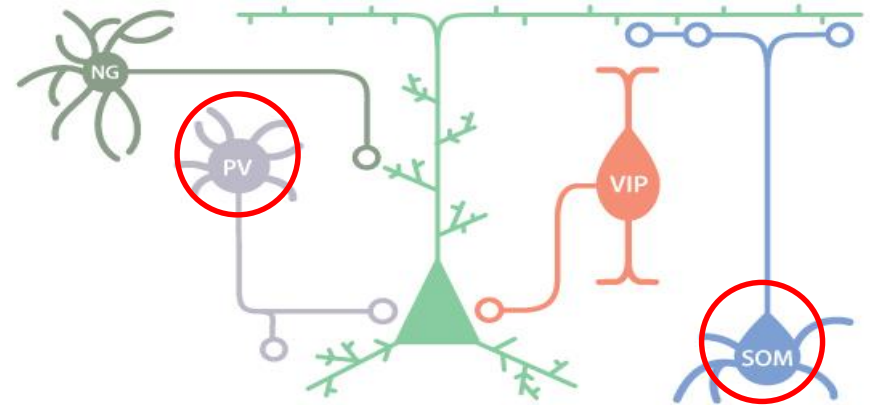
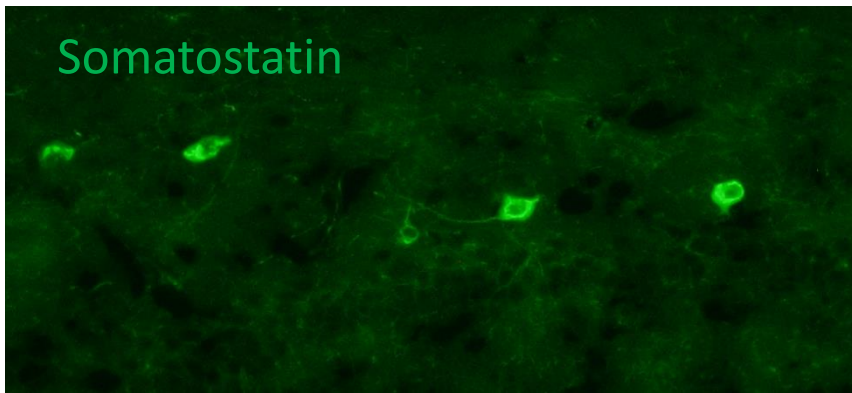
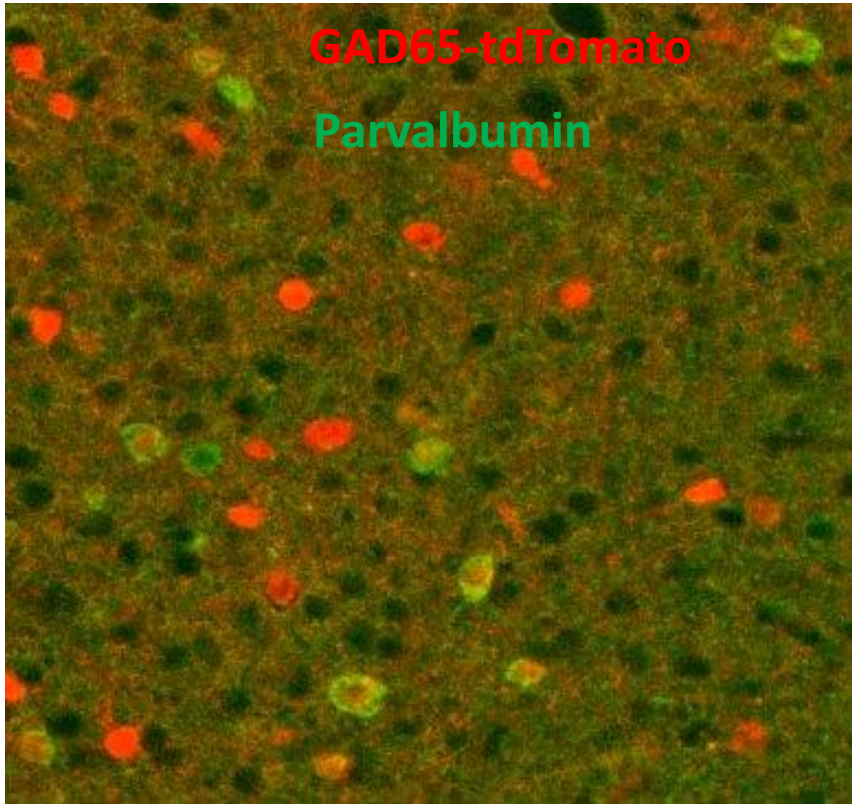


Social interactions - Sociability and social preference



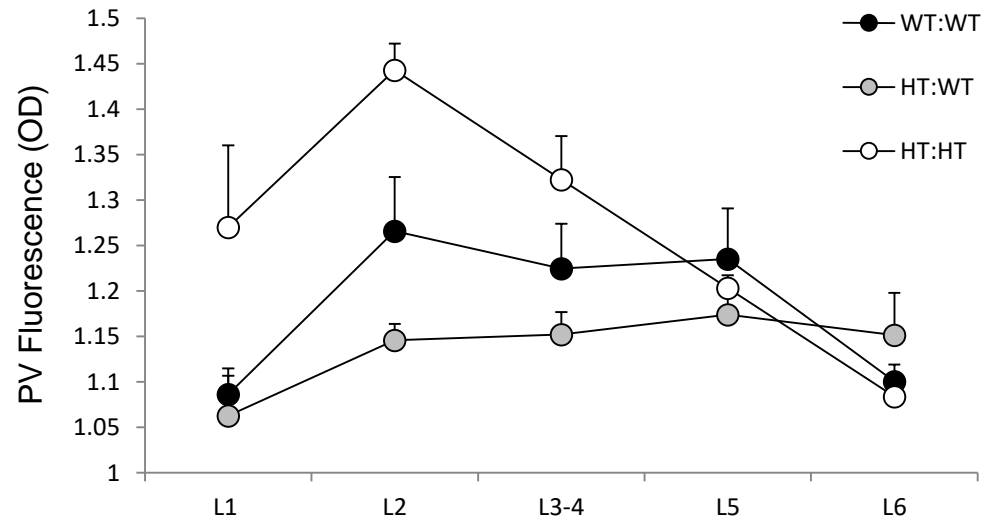
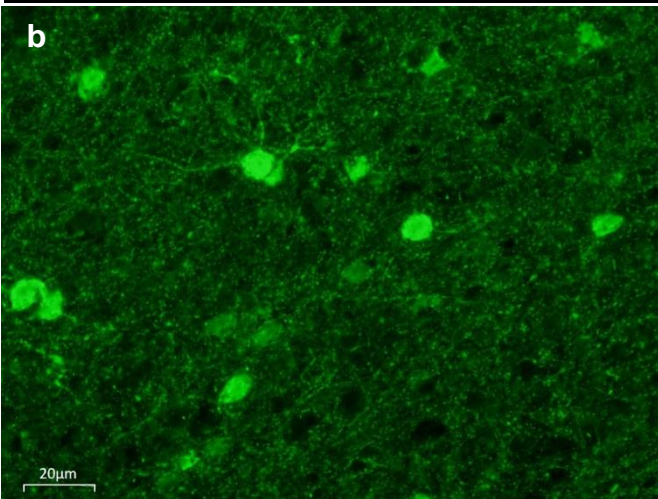
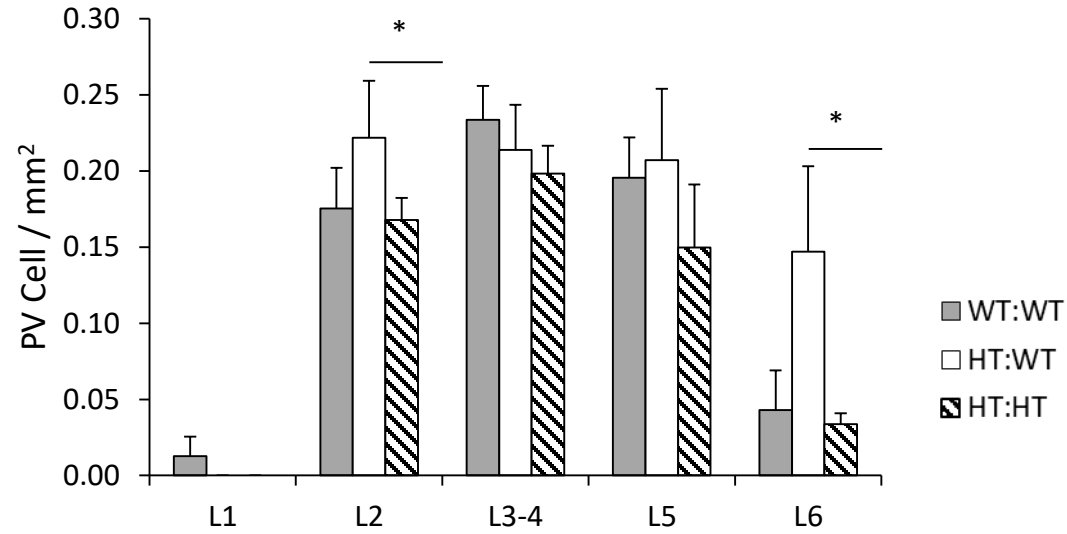
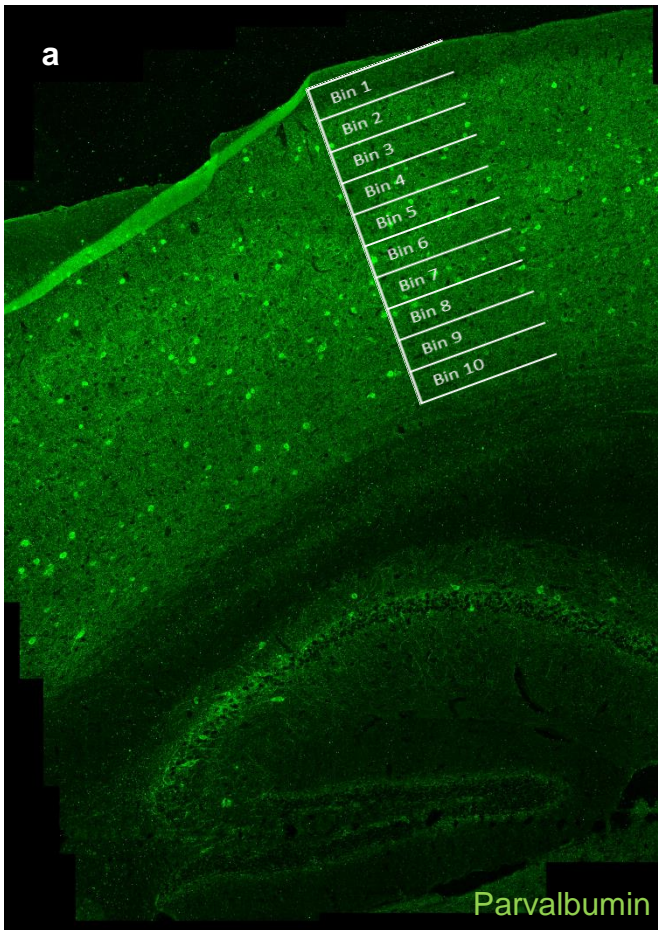
Age \ Sex	Variable	Female		Male	
	Genotype	Maternal	Offspring	Maternal	Offspring
Neonatal P4-P17 Developmental milestones	<i>Weight and morphogenesis</i>	delay	no effect	delay	no effect
	<i>Geotaxis</i>	delay	early	delay	early
	<i>Rotarod</i>	no effect	no effect	delay	no effect
	<i>Nest finding</i>	delay	early	delay	early
	<i>Cliff avoidance</i>	no effect	delay	no effect	delay
Adult - P80 ASD core symptoms	<i>Repetitive behavior (Marble Burying and Nest building)</i>	effect (direction not clear)	repetitive behavior	repetitive behavior	no effect
	<i>Restricted interest (Object preference)</i>	no restricted interest	no effect	restricted interest	no effect
	<i>Social - Social preference</i>	no effect	no effect	no effect	social deficit
	<i>Social -Social novelty preference</i>	no effect	no effect	social deficit	social deficit
Adult - P80 Behavior associated with ASD	<i>Aggressive Social interaction – Resident intruder</i>	aggressiveness	aggressiveness	aggressiveness	aggressiveness
	<i>Recognition memory – Object recognition</i>	no effect	poor performance	poor performance	poor performance
	<i>Anxiety – anxiety index</i>	no effect	increased anxiety	increased anxiety	decreased anxiety

Inhibitory neurons in the Prefrontal cortex and cingulate cortex

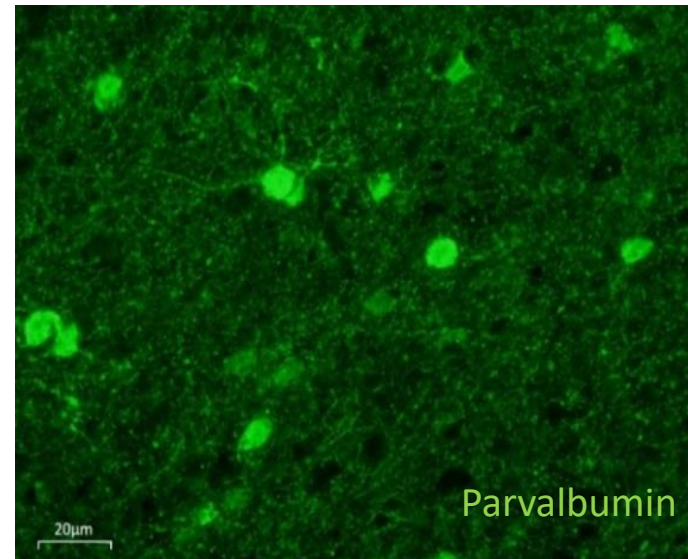
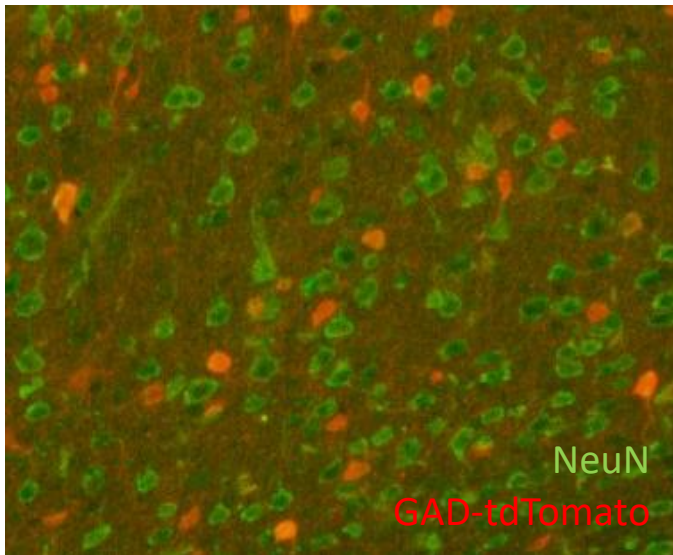
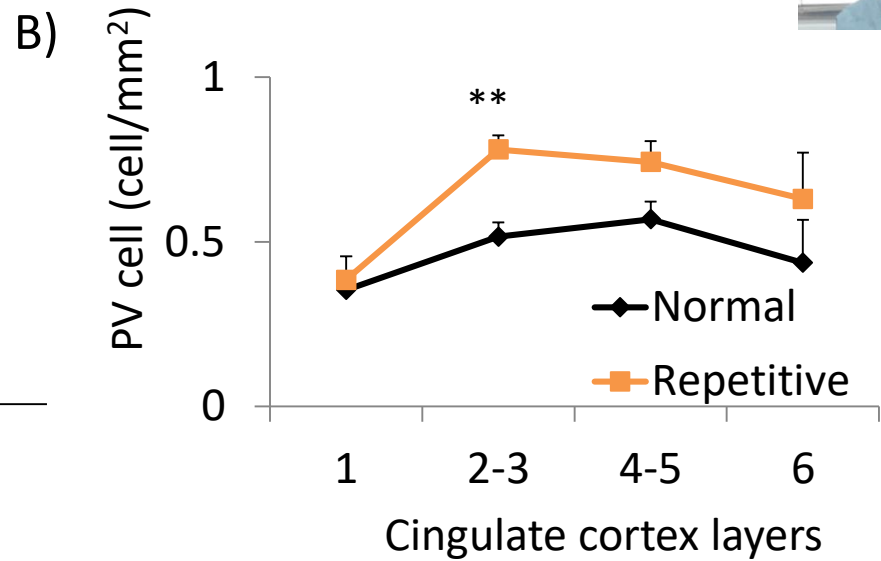
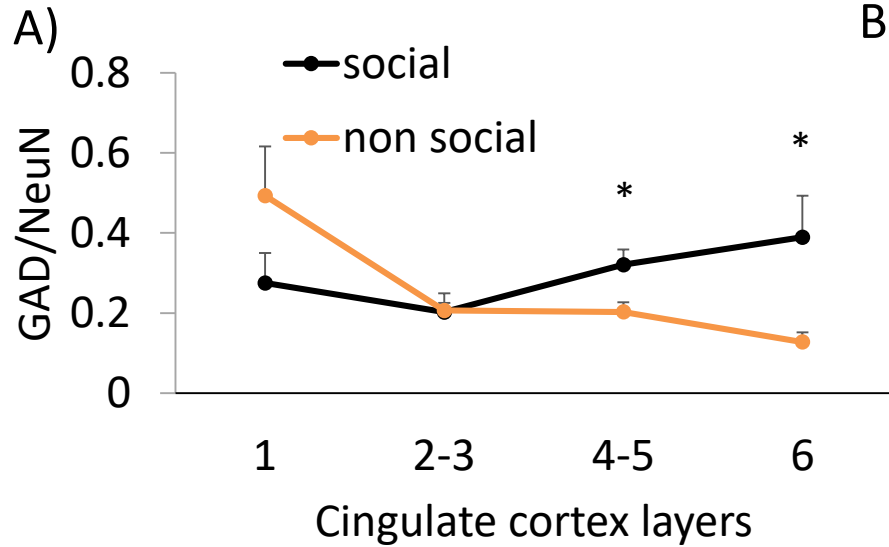




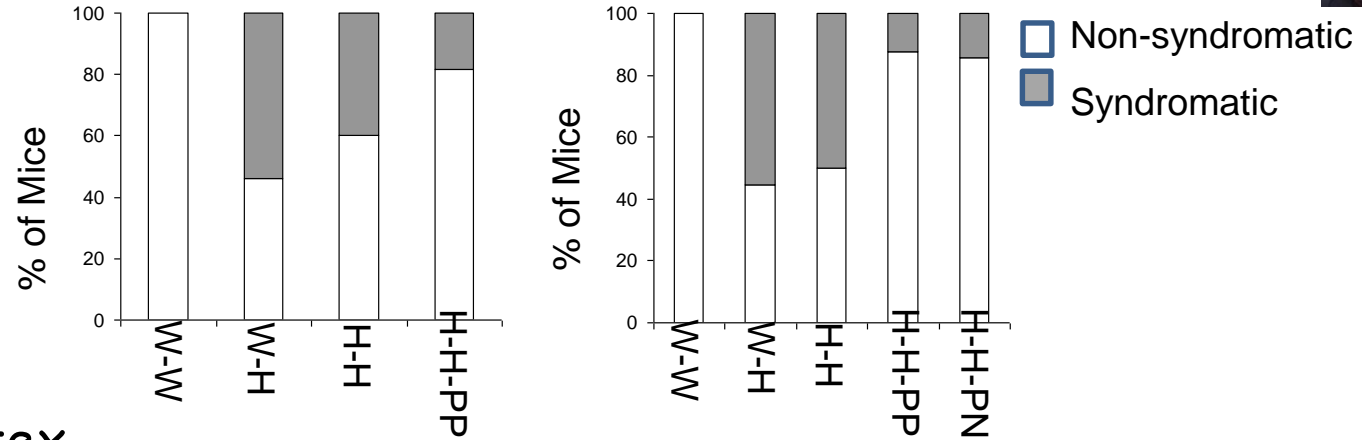
Altered laminar distribution of PV neurons in the cingulate cortex



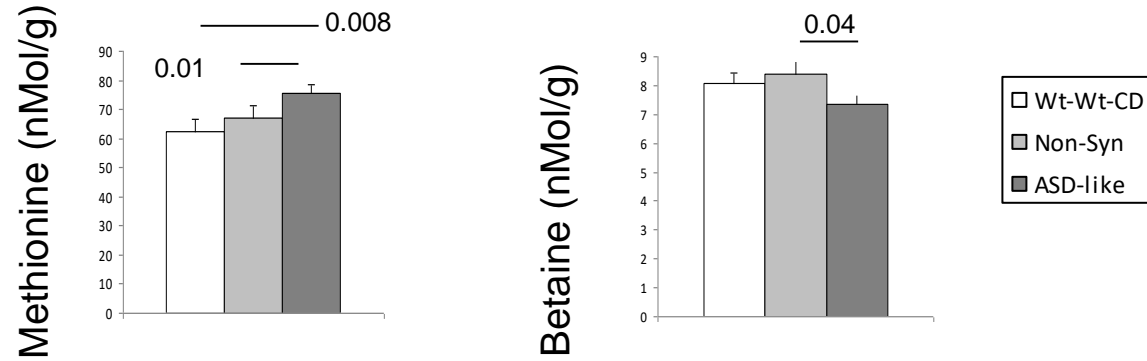
Inhibitory neurons layer acquisition correlate with ASD like phenotype



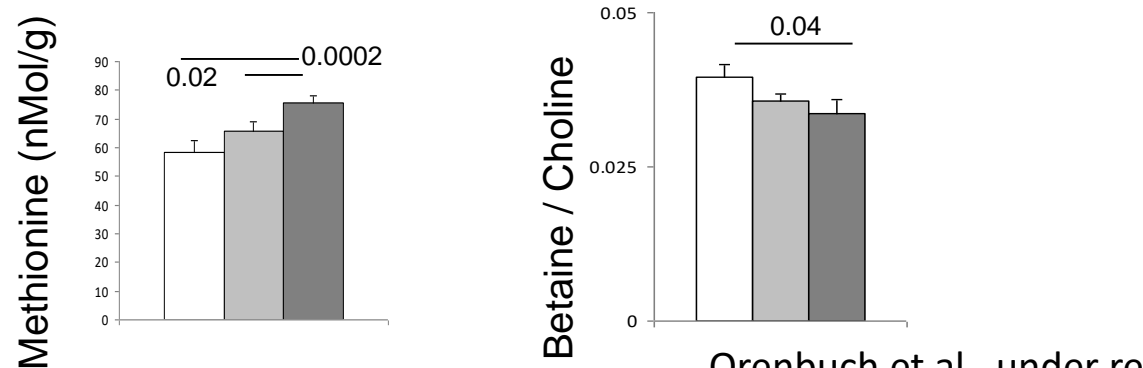
Prenatal intervention reduced autistic-like behavior rates.



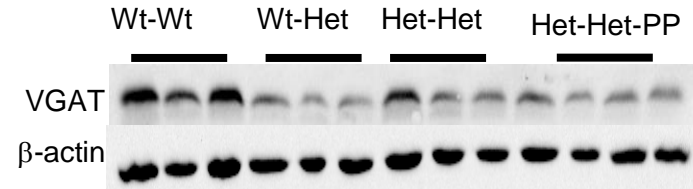
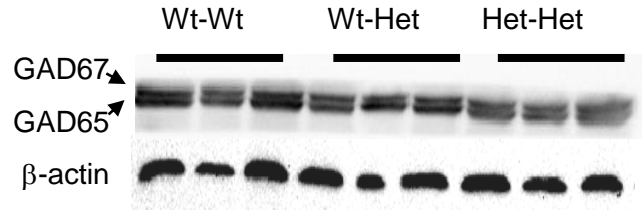
Cerebral Cortex



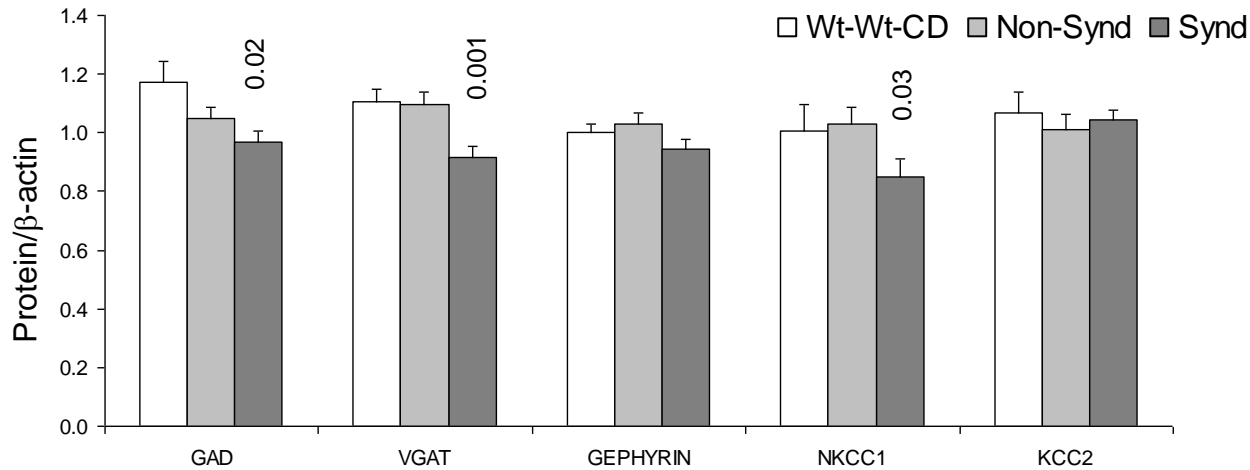
Basal Forebrain



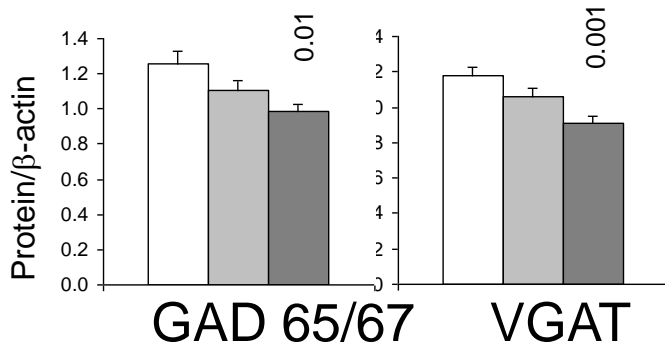
GABA pathway proteins in the cerebral cortex



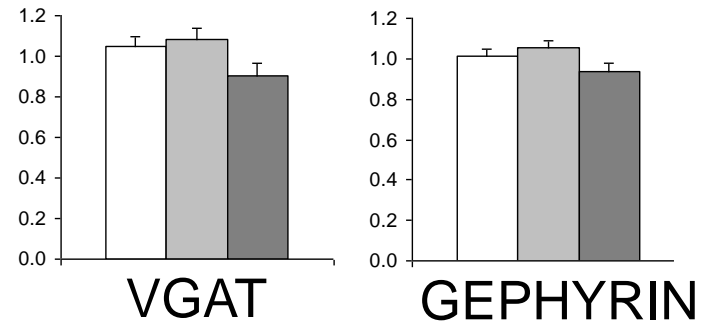
Male & Female



Male



Female



Aim II:

Find the developmental origin and trajectories

Questions:

Who should we "treat" ?

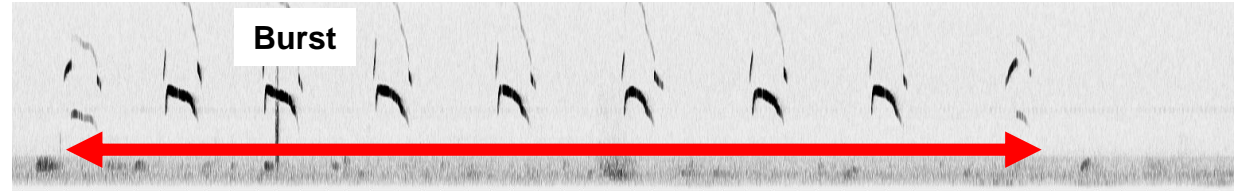
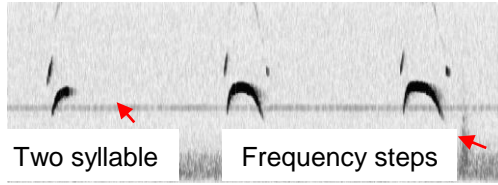
When can we detect first signs of autistic-like behavior?

Which variables in the pups are predictive for later autistic-like behavior in mice?

Characteristics of the pup - mother communication by ultrasonic vocalization calls



Frequency (Hz)



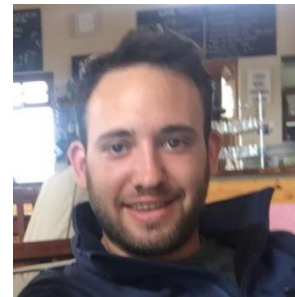
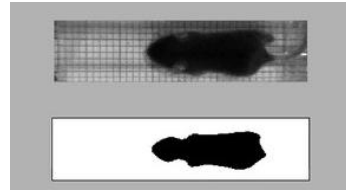
Time (sec)

Sensory sensitivity:

Light

Sounds

Gravity - geotaxis



Origin of impairment in the GABAergic system (implications for treatment)

Test of hypothesis
(mouse)



National Autism Database.
(human)



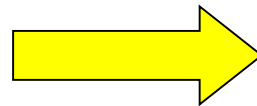
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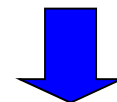
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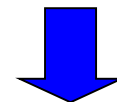
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Evaluation of risk factors and C1 metabolism involvement (in the database)



Genotype dependent adjustment of supplementation to reduce the risk for ASD and attenuate the symptoms in affected children.



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