Theme: Brain, Behavior and Development

Translational Research in the UCLA IDDRC

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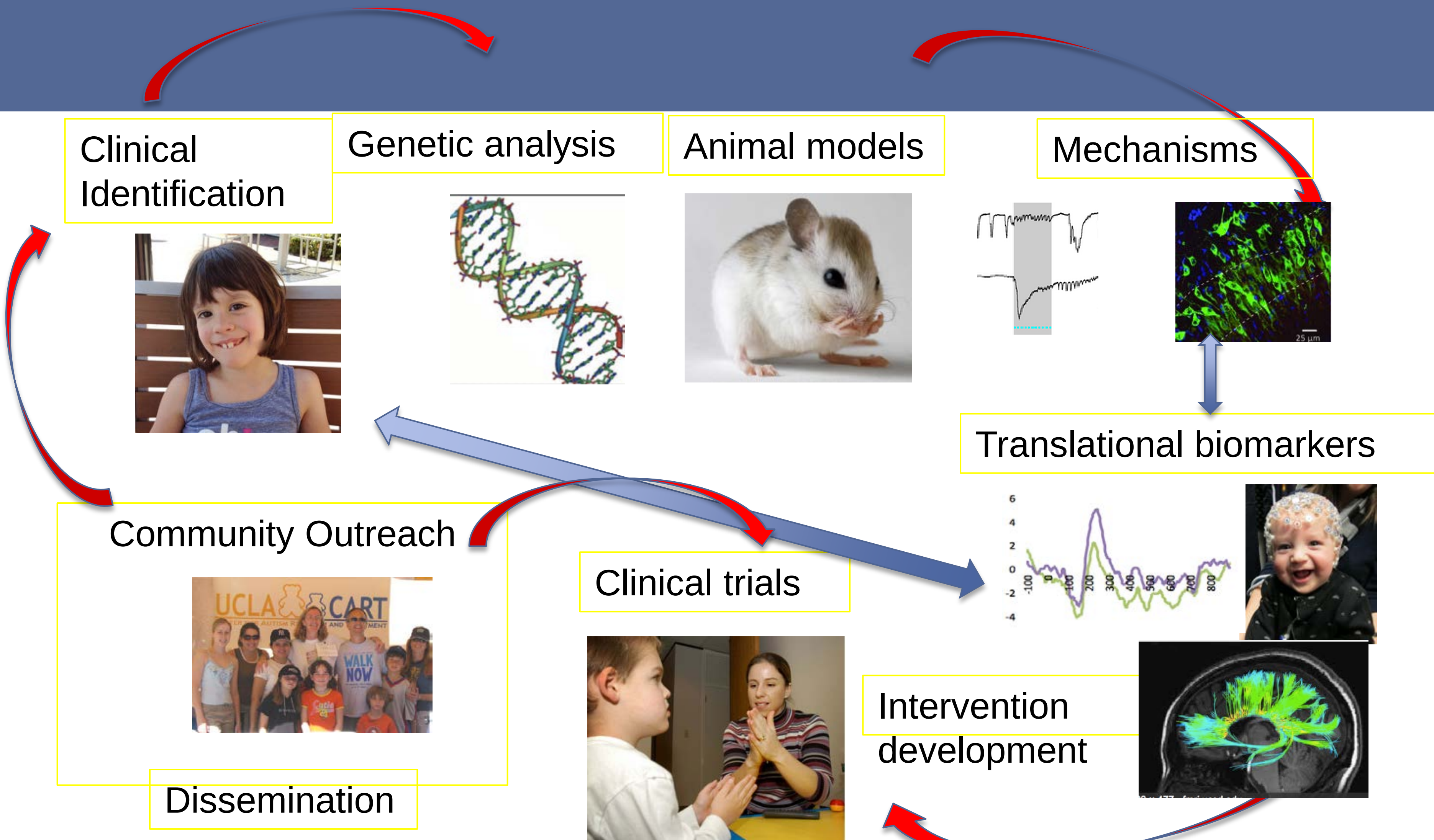
Disclosures

- none

Outline

- Model for Translational Research in Developmental Disorders
- Programs and Resources in the IDDRC for conducting collaborative research
- Translational work in Autism Spectrum Disorders

Interactive Model of Translational Research



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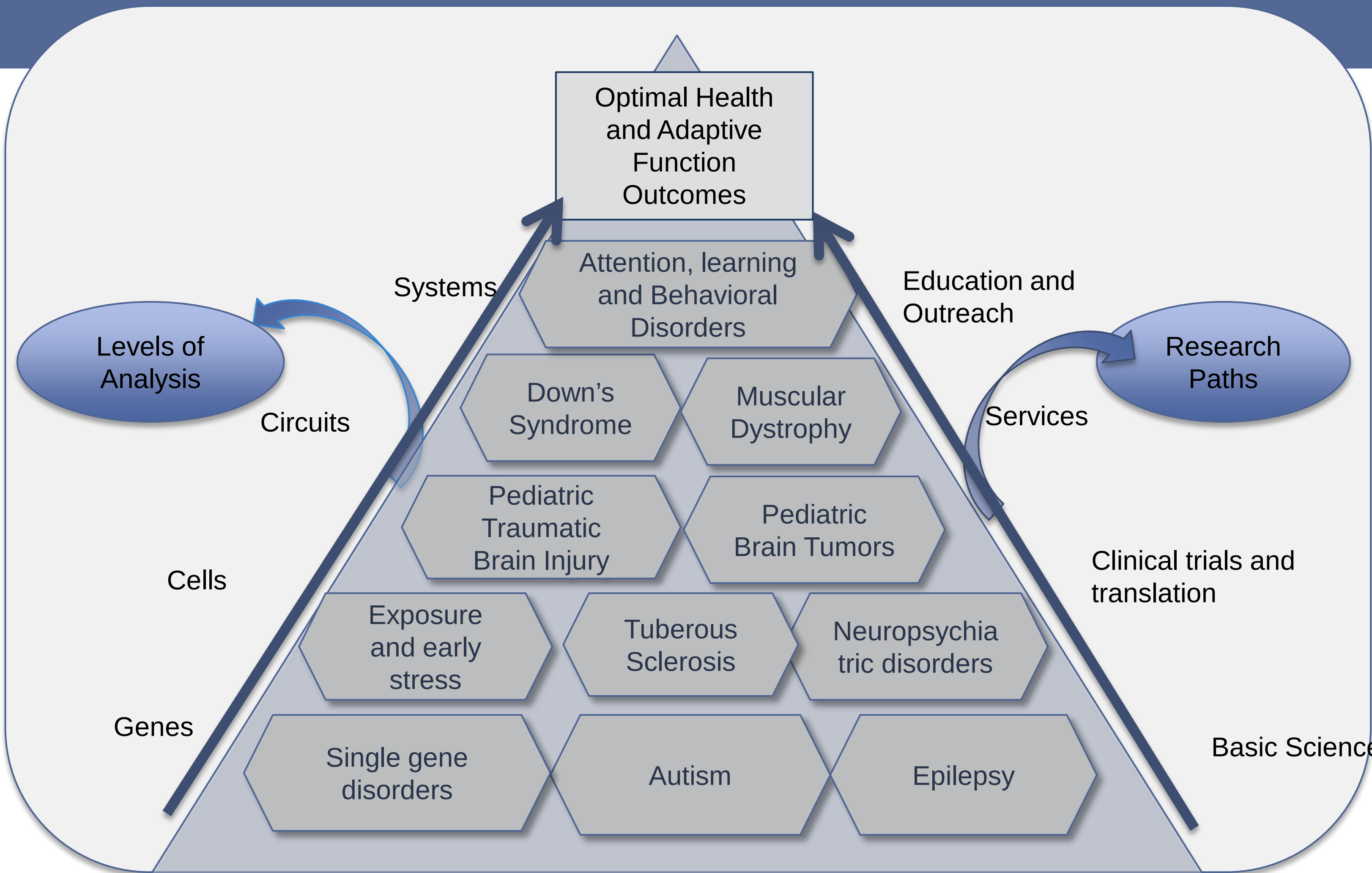
IDDRC Collaborative Research Groups



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IDDRC Core Structure

Core A: Administration, Education and Outreach

- Administrative infrastructure for IDDRC faculty; create of internal, external advisory boards
- Oversight, management, utilization evaluation and QA for all cores
- Educational and outreach activities
- Integration with the UCLA UCEDD (Tarjan Center)
- **Provide vouchers for core utilization by new users**

Core B: Genetics, Genomics and :

- Performing, analyze, and interpret genetics and genomics experiments including:
  - Sequencing
  - gene expression
  - epigenetics
- Provide informatics infrastructure to store, access, and query genetic and genomic data

Model Research Project: Dup15q
PI: S. Jeste, P. Golshani

Core C: Cell, Circuit and Systems

- hESC,hISPC culture and differentiation
- Organoid Modeling
- Electrophysiology
- Optogenetics

Core D: Structural and Functional Visualization :

- Light and confocal microscopy access, analysis and training
- Build and develop technology for one photon miniaturized fluorescent microscopes for live imaging neural activity
- Optogenetic image analysis with Clarity, with technical development and optimization
- Animal and Human MRI protocol development and image analysis

Core E: Clinical translation

- Recruitment, clinical trial design implementation, and regulatory approvals
- Biostats support
- Cognitive and behavioral phenotyping
- Collect and database information on biospecimens
- Test putative biomarkers for diagnosis and treatment

and Innovation Institute

Translational Research in Autism

- Gene identification
- Expression
- Effects on neurodevelopment-animal models
- Common variation in genes- effects on human brain
- Animal model of intervention
- Behavioral and pharmacological Treatment, translational biomarkers

Candidate Genes for Autism

Table 23.4.3 Evidence scores for promising and for probable ASD genes[a] (modified from [3], with permission)

Gene	Total score	Syndrome/ mutations	Replicated association	Analysis of variant	Mouse model	Other evidence
Promising						
AVPR1A	1	0	0	0	1	No
CACNA1G	1	0	1	0	0	No
DISC1	1	0	0	0	1	No
DOCK4	1	0	1	0	0	Involved in regulation of hippocampal dendrite morphology
ITGB3	1	0	1	0	0	No
MDGA2	1	0	1	0	0	No
PRKCB1	1	0	1	0	0	No
AHI1	2	2	0	0	0	No
ASMT	2	0	1	0	0	ASD-associated variant also associated with melatonin levels
BZRAP1	2	0	1	0	0	Ca^{2+}-dependent modulator of synaptic transmission
CACNA1H	2	0	1	1	0	No
CNTN4	2	2	0	0	0	No
EN2	2	0	1	0	1	No
GRIK2	2	0	1	0	0	Homozygous mutation results in nonsyndromic MR
SCN2A	2	0	1	1	0	No
SLC25A12	2	0	1	0	0	Associated with neurite outgrowth; up-regulated ASD brain
Probable						
MET	3	0	1	1	0	Expression reduced in brains of cases versus controls
NRXN1	3	2	0	0	0	Interacts functionally with neuroligins
OXTR	3	0	1	0	1	Expression reduced in blood of cases versus controls
SHANK3	3	2	0	0	0	Modulates glutamate-dependent reconfiguration of dendritic spines
SLC6A4	3	0	1	1	0	Clinical benefit from inhibitors; variation linked to gray matter volume
CACNA1C	4	2	0	1	0	Linked to PI3K signaling along with PTEN / TSC1 / TSC2
CADPS2	4	2	0	1	1	No
CNTNAP2	4	2	1	0	0	Downstream target of FOXP2
DHCR7	4	2	0	1	0	Hypocholesterolemia in a proportion of probands
FMR1	4	2	0	1	1	No
NLGN3	4	2	0	1	1	No
NLGN4X	4	2	0	1	1	No
GABRB3	5	2	1	0	1	Expression is dysregulated in PDDs
PTEN	5	2	0	1	1	Linked to PI3K signaling along with TSC1 / TSC2 / CACNA1C
MECP2	5	2	0	1	1	MECP2 deficiency causes reduced expression of UBE3A and GABRB3
TSC1	5	2	0	1	1	Regulates dendrite morphology and function of glutamatergic synapses
TSC2	5	2	0	1	1	Regulates dendrite morphology and function of glutamatergic synapses
UBE3A	5	2	0	1	1	Expression is dysregulated in PDDs
RELN	6	2	1	1	1	Levels reduced in brains of cases versus controls

Based on Abrahams and Geschwind *Nature Reviews Genetics* 2008

- Risk genes share pathways
- Involved in cell adhesion, signaling, synaptogenesis, neural migration, dendritic growth: ie, all processes involved in fetal brain development and neurons forming connections

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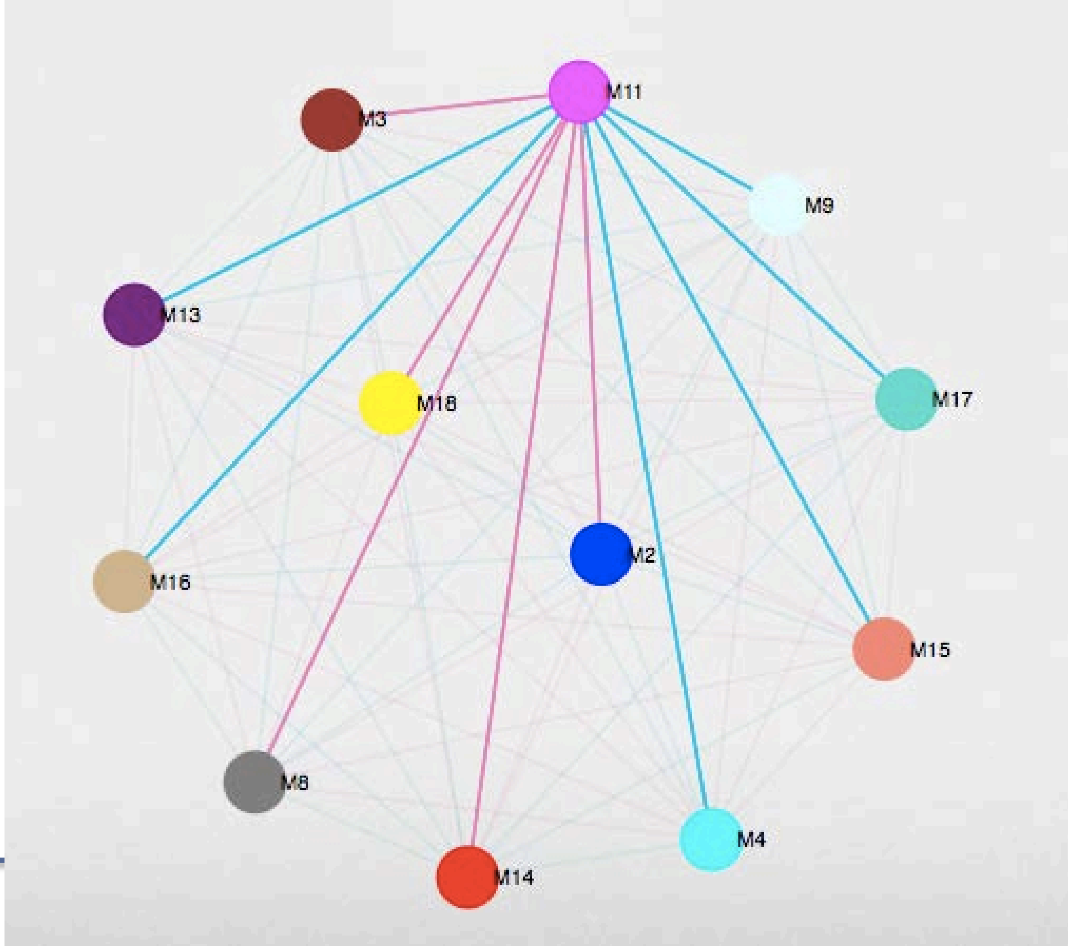
Integrative Functional Genomic Analyses Implicate Specific Molecular Pathways and Circuits in Autism

Parikshak NN, Luo R, Zhang A, Won H, Lowe JK, Chandran V, Horvath S, **Geschwind** DH. Cell. **2013** Nov 21;155(5):1008-21.

BrainSpan developmental RNA-seq data to examine cortically expressed proteins during development.
Weighted Gene Coexpression Network Analysis, identifying modules of anatomically co-expressed genes.
17 co-expressed modules



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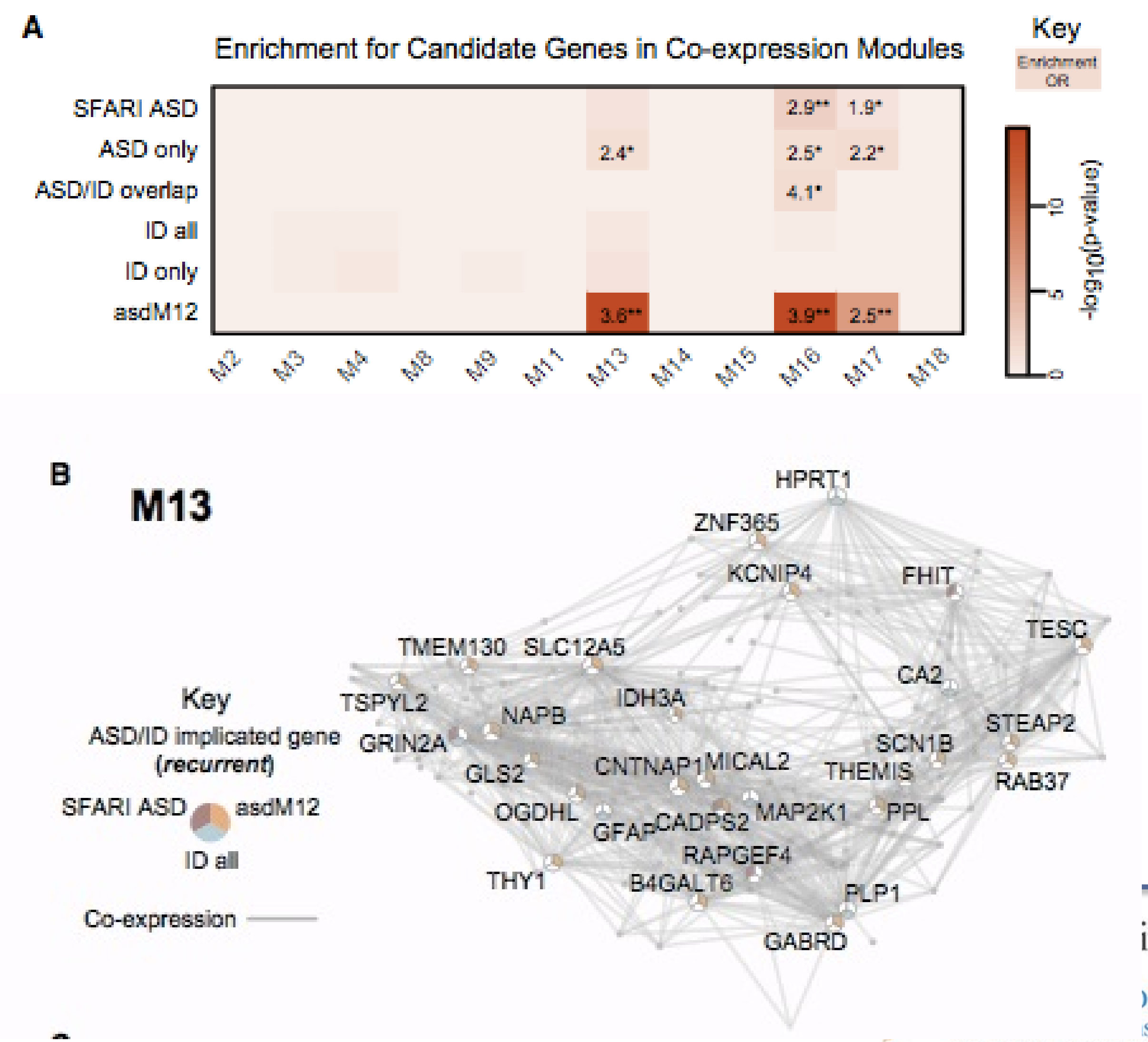
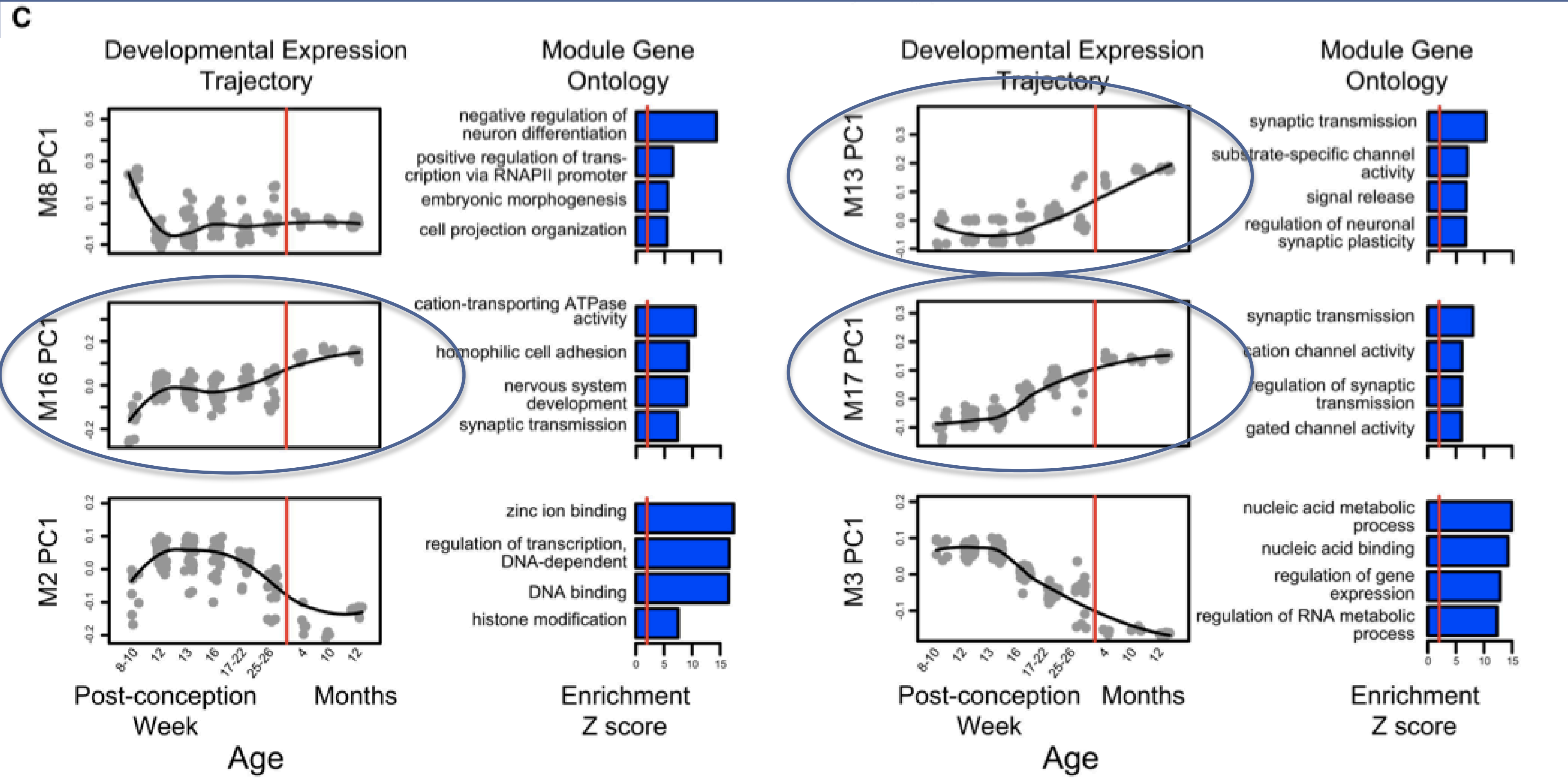
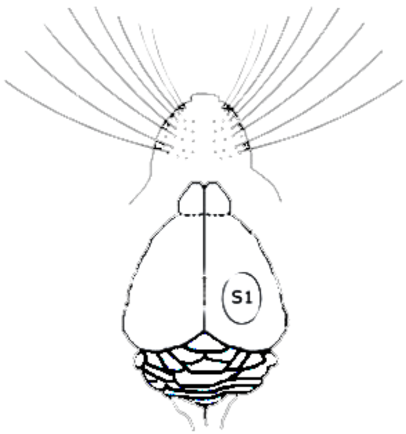
Modular Expression and Network Analysis of ASD-risk genes Of Note: These modules are ASD specific; not enriched in Intellectual Disability

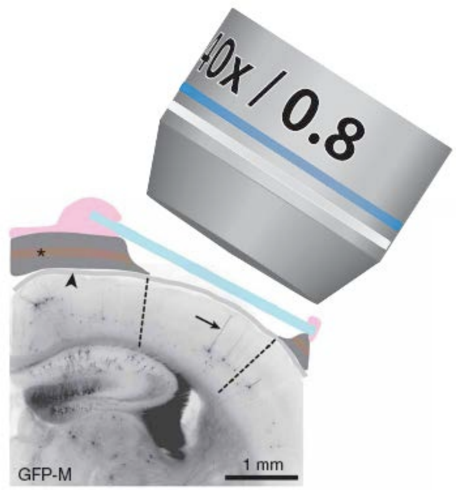


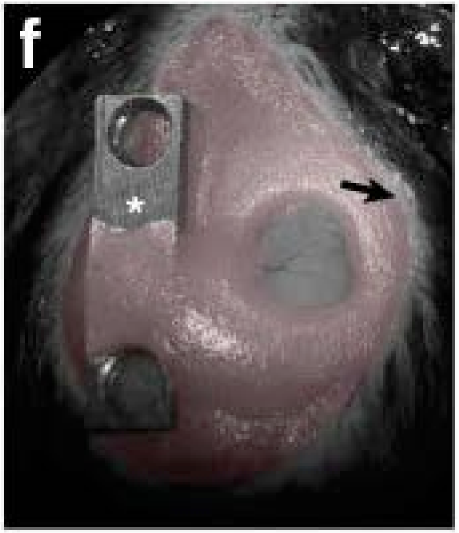
Sample Transcriptome modules and developmental expression trajectories

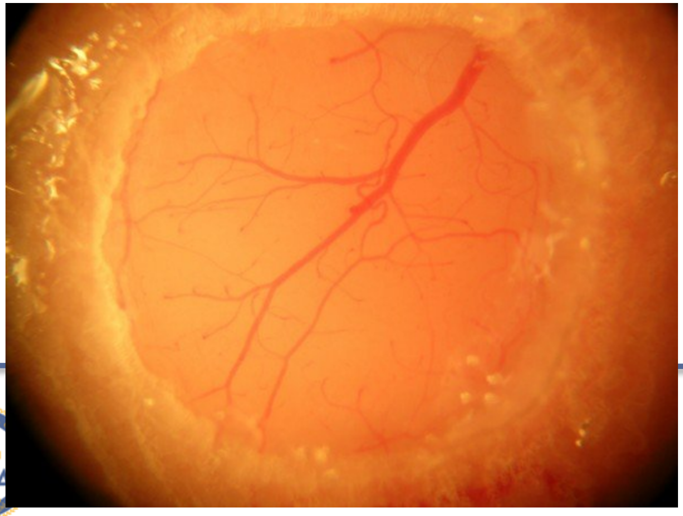


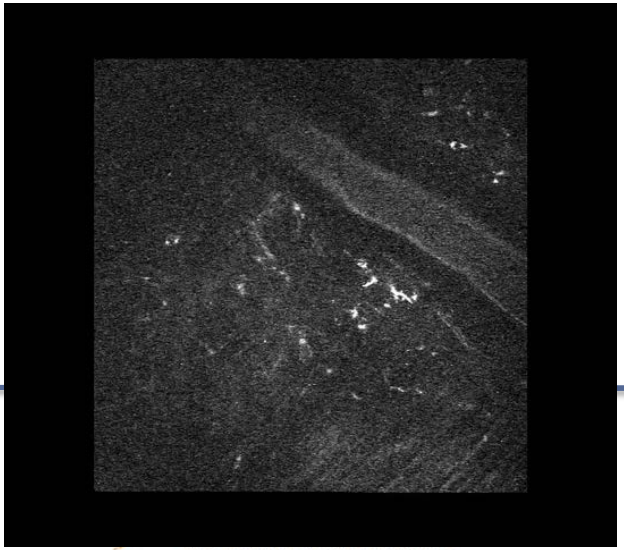
Chronic in vivo imaging in mouse cortex is used to track changes in cortical dendrites before and after Pten KO
J. Trachtenburg Lab, UCLA







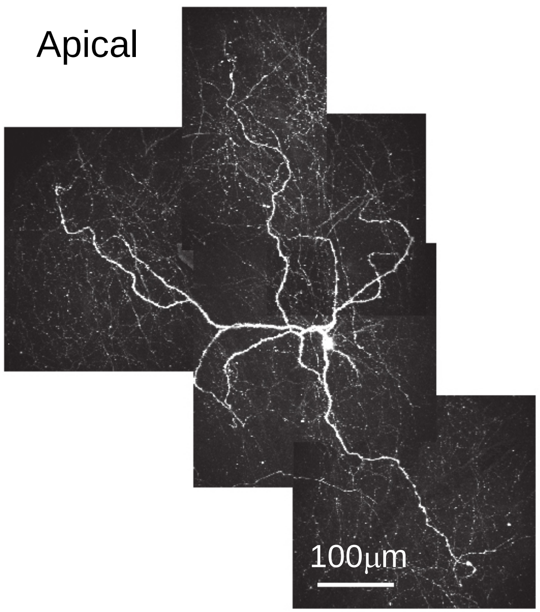




Dendritic growth is restricted to the apical dendrites

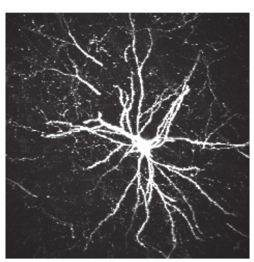
Pten KO

Apical

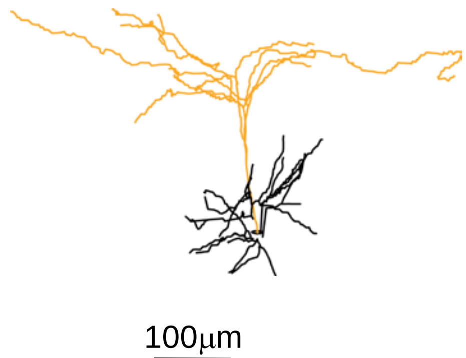


Pten KO

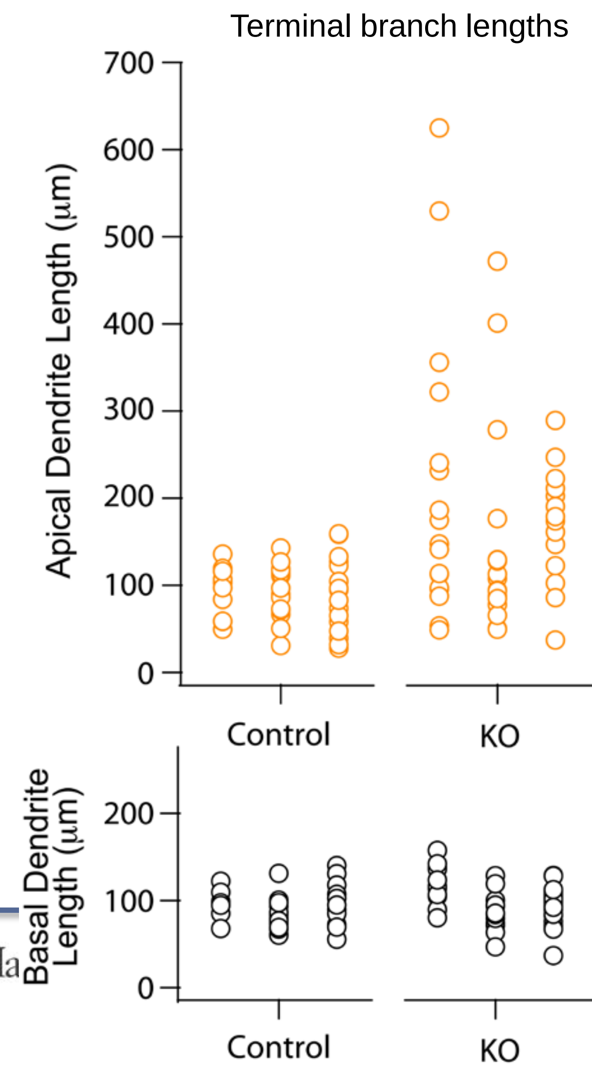
Basal



Pten KO



Control



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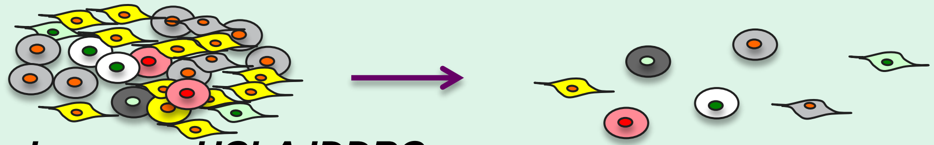
Calcium Imaging

Single Cell Transcriptome Analyses (SC-RNA-seq &WGCNA):

Medicine for Heterogeneity:



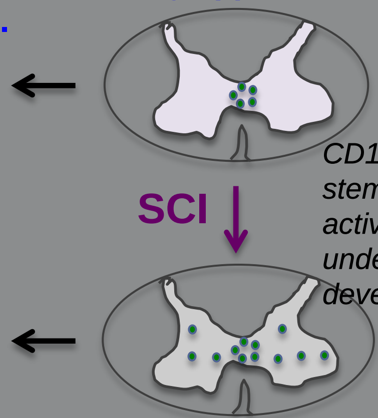
Cell. *2015 May 21;161(5):1175-86.* ***Sun's group, UCLA IDDRC***

Revealing CD133+ ependymal quiescent adult neural stem cells lining the whole ventricular surface of the CNS express VEGF receptor and can be activated by VEGF to manifest stem cell activities in regions, which were not previously considered to be neurogenic e.g. the 4th ventricle, ***revealing a endogenous stem cell source for neural repair.***

Single Cell RNA-seq

To study cell lineage development using ROSA-reporter mice

e.g. CD133 stem cell activation and lineage differentiation after spinal cord injury (SCI), which can be easily applied to other lineage studies.

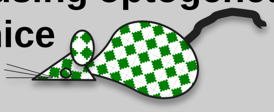


CD133+ ependymal stem cells are activated and undergoing lineage development

To reveal the molecular programs underlying lineage differentiation in normal & injury environment

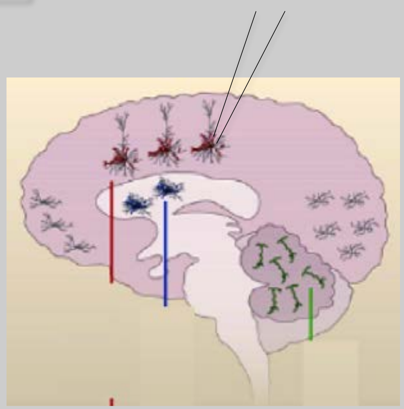
Single Cell RNA-seq

To study the molecular logic for neural circuitry wiring and function using optogenetically labeled mice



Electrical recording

coupled



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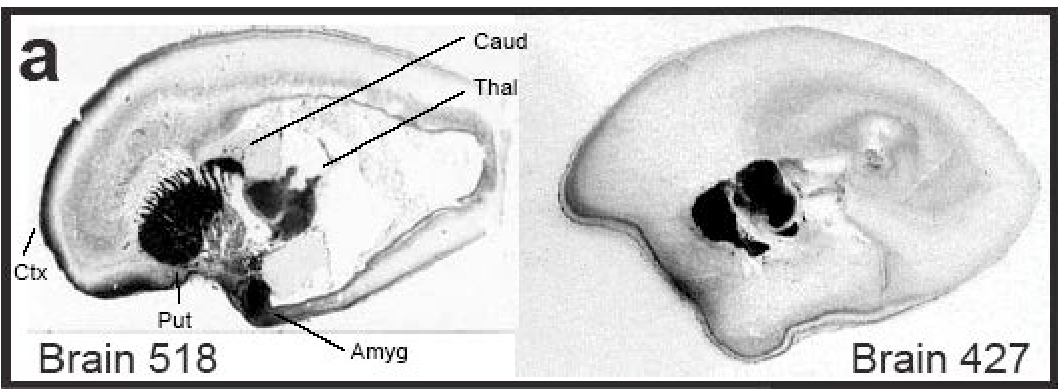
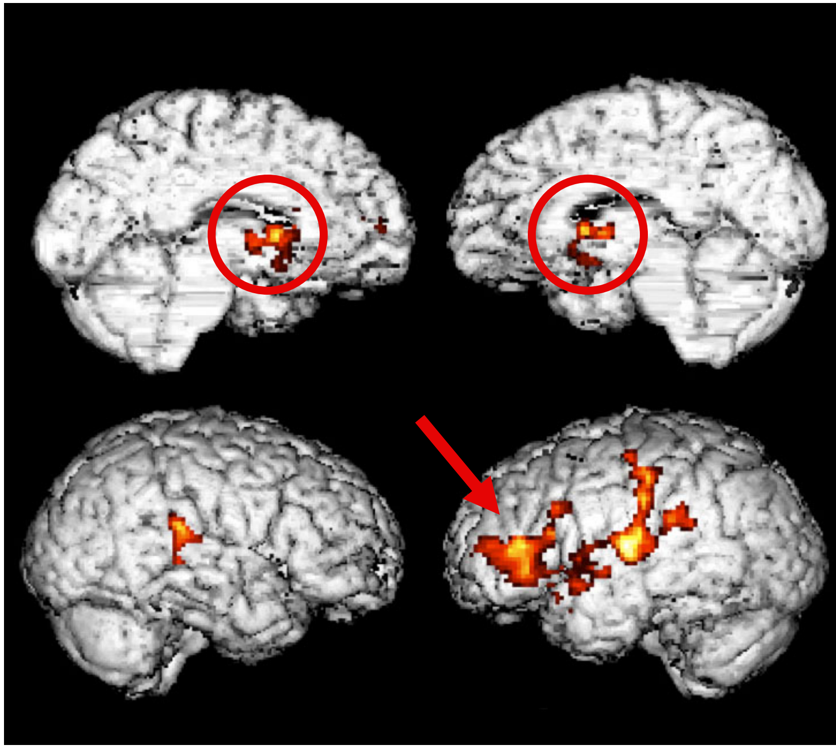
Expression of CNTNAP2 gene compared to language learning differences between TD and

Fetal expression of CNTNAP2 in frontal cortex and basal ganglia





Courtesy Brett Abrahams

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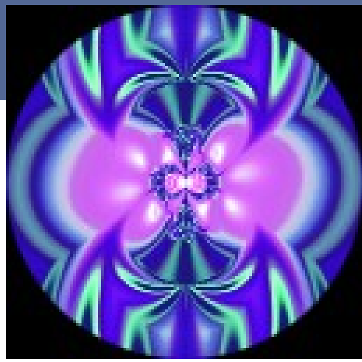
Implicit Learning-Social Reward



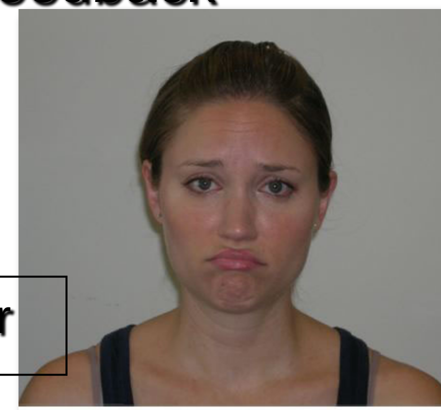
Response

"1"
or
"2"

Social
Feedback

That's Right!

Or

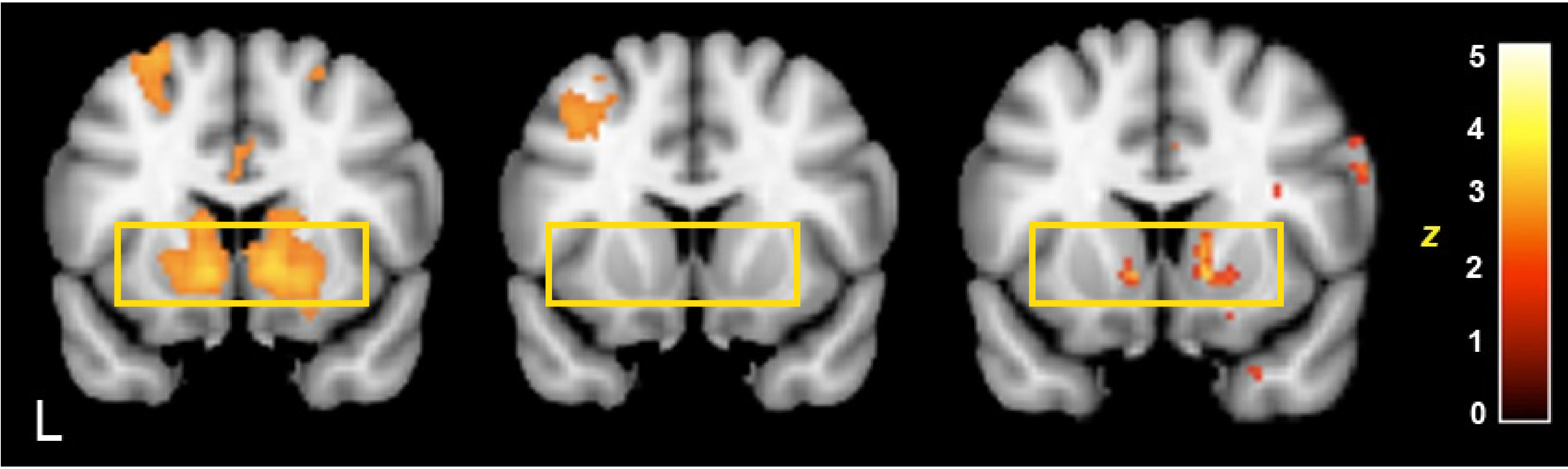


That's Wrong

- Stimulus-response association is only probabilistic-seems random to subject
- Evidence of learning across trials which we can measure

Reward Centers (ventral striatum)

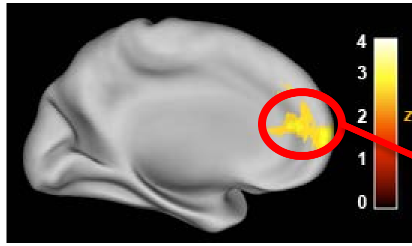
Typical **Autism** **Typical > Autism**



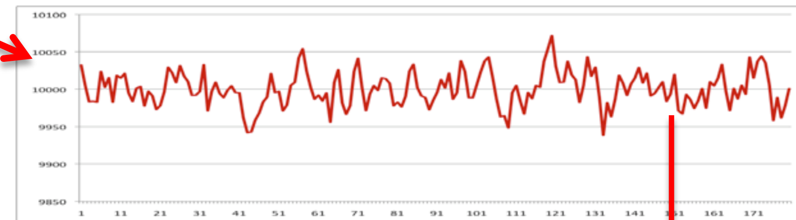
Only TD children show activity in ventral striatum
Increased Learning-related changes in Dorsal Striatum in TD

Functional Connectivity Analysis

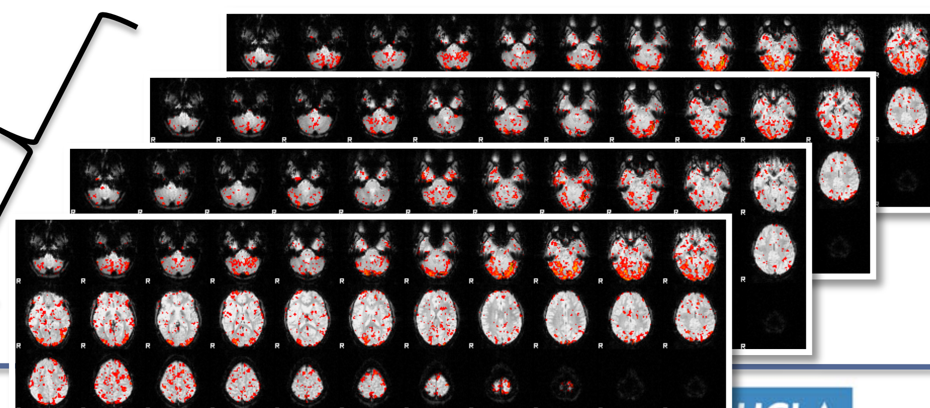
1) Remove task and noise from data using general linear model



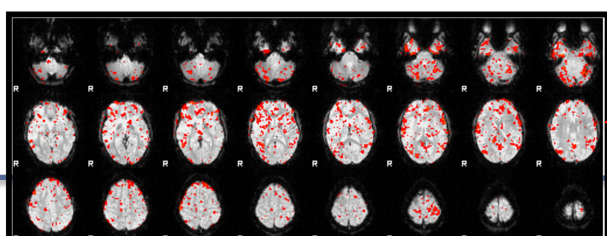
2) Extract seed timeseries



3) Enter time series into correlation analysis within subjects



4) Average within groups and compare across groups to get final maps



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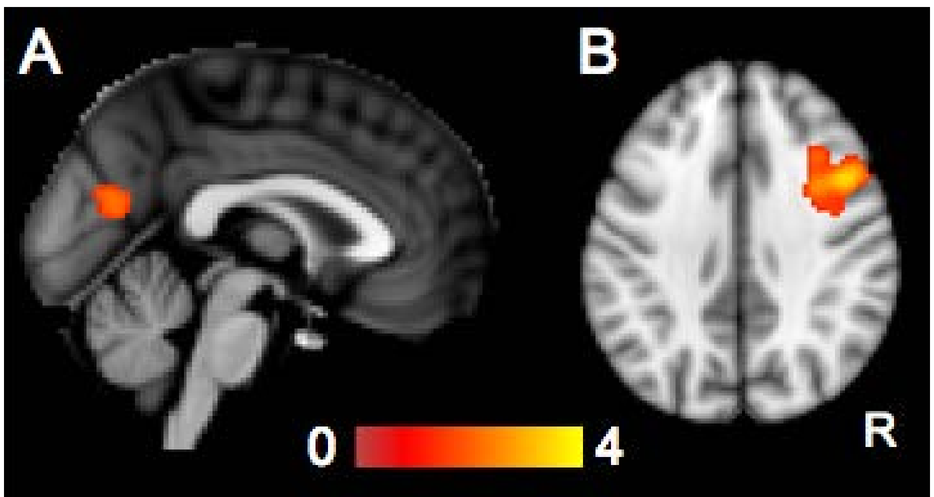
We can relate abnormal growth of connections in animal models to connections in humans

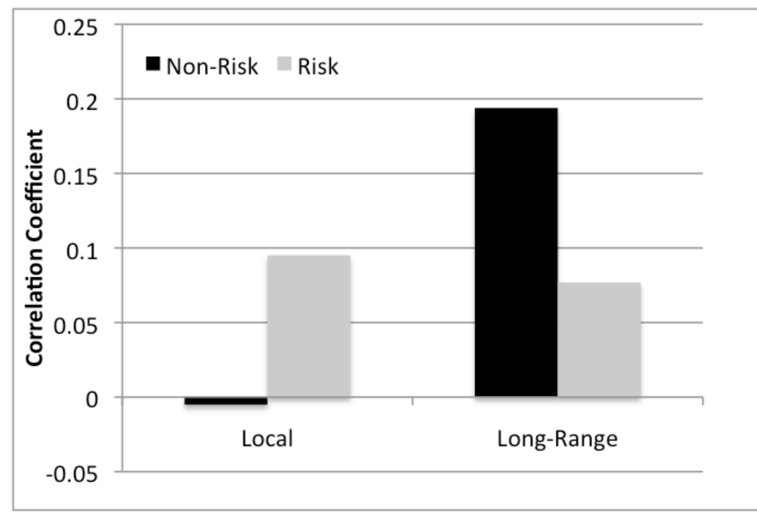
CNTNAP2 Risk carriers have stronger local and weaker long-range connectivity than non-risk



[redacted]

[redacted]

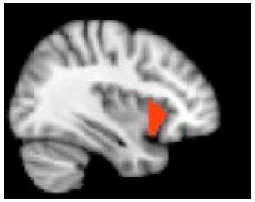
Maximum correlation coefficient within regions for genetic groups

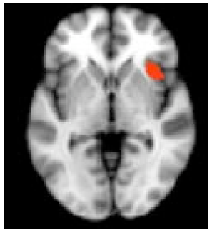


OXTR and Functional Connectivity in the Salience Network in ASD

Leanna Hernandez et al, submitted

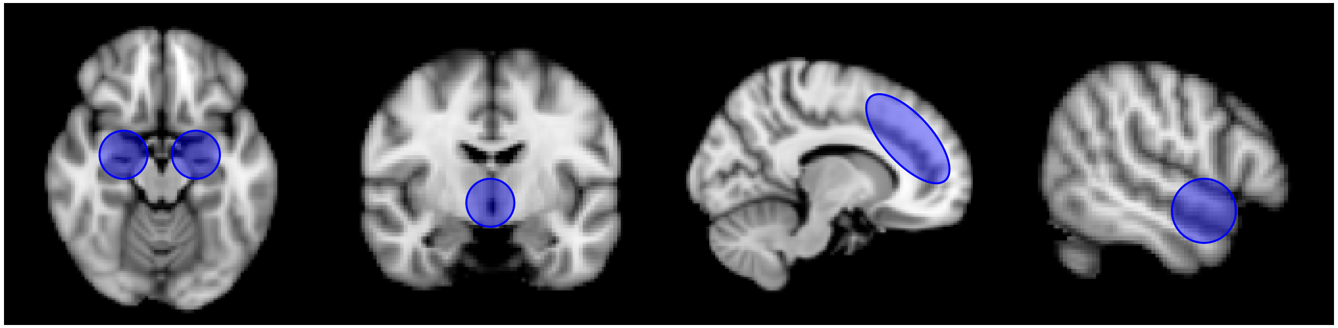
- Network of brain regions including the anterior insula and medial frontal cortex important for marking the most relevant information in the environment (Seeley et al. 2007)





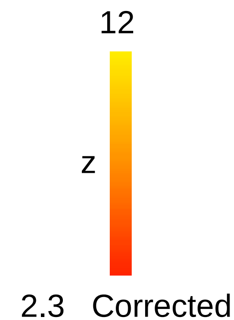
- Hub region: Right anterior insula (AI) (Uddin et al. 2009)
  - AI: Consistently hypoactivated in individuals with ASD during social cognitive tasks (Di Martino et al. 2009)

- Seed-based Salience Network Connectivity:
  - Seed the AI; relate activity in amygdala, hypothalamus, dorsal anterior cingulate cortex, superior temporal pole (Seeley et al. 2007)

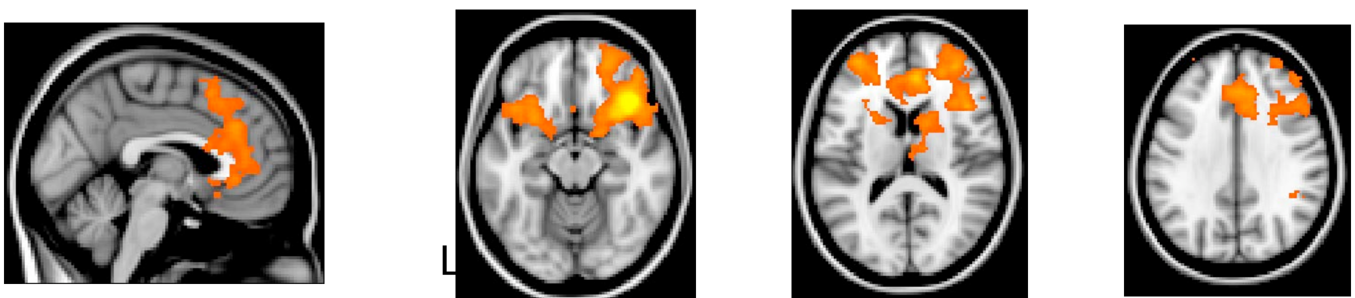


Right Anterior Insula - Whole Brain Connectivity

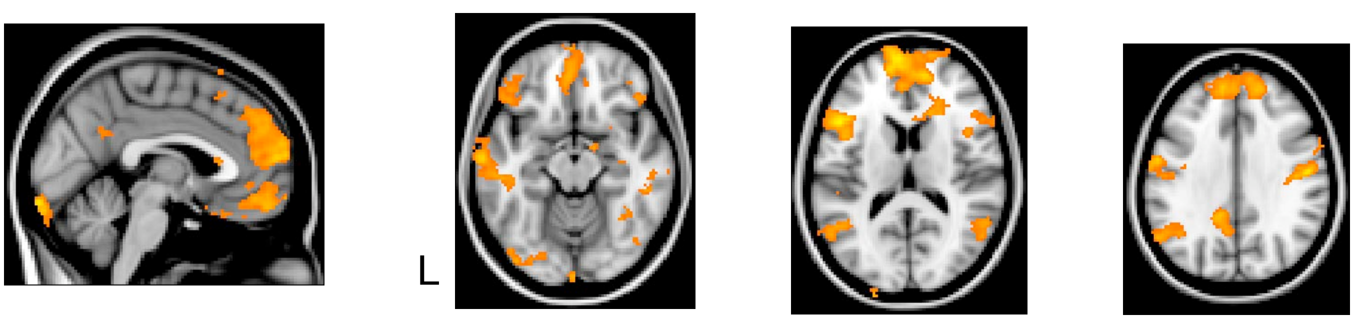
GG “Non Risk”



AA “Risk” + AG “Intermediate”



GG “Non Risk” > AA “Risk” + AG “Intermediate”



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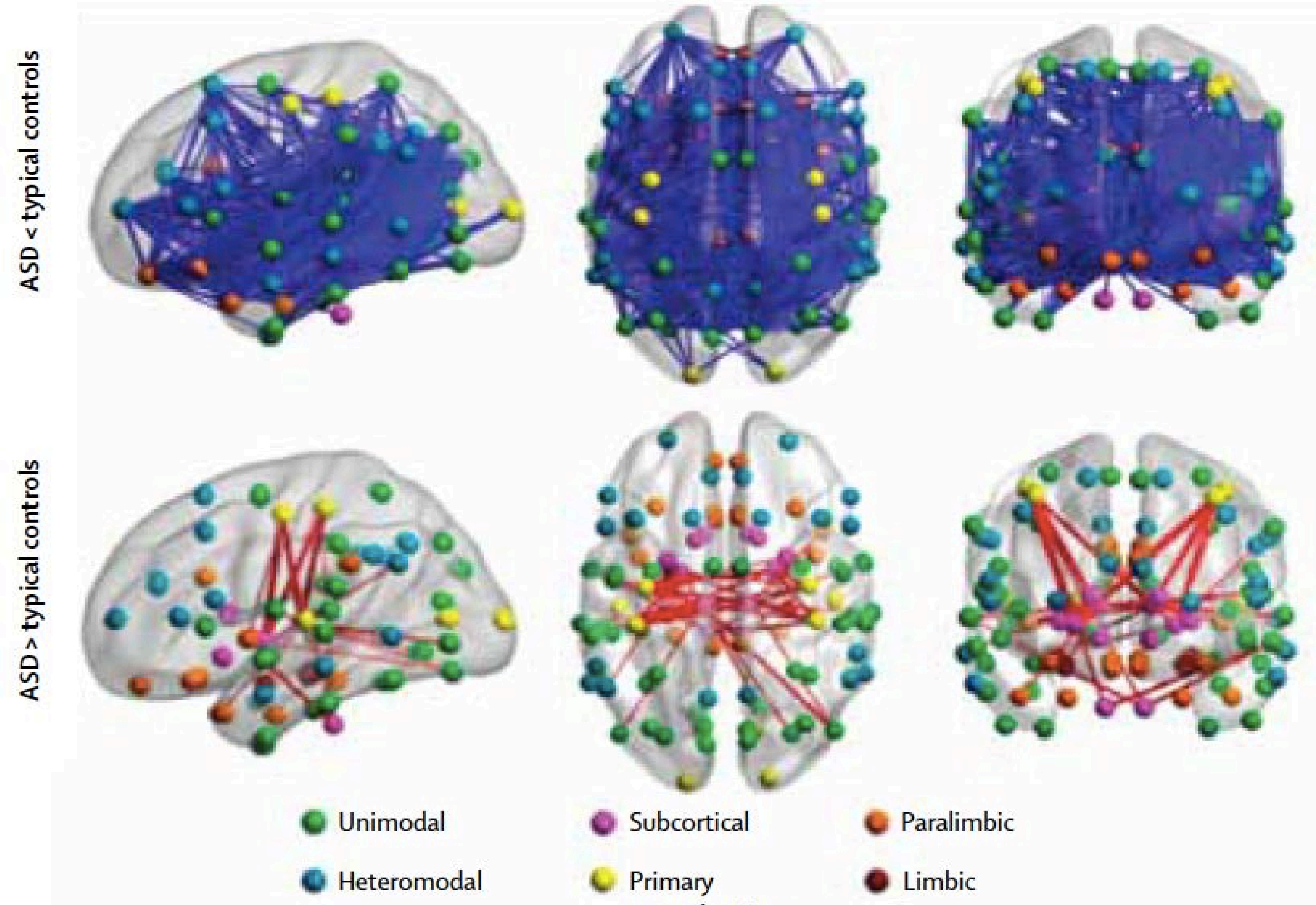
Connectivity in a multi-site sample DiMartino et al, 2014

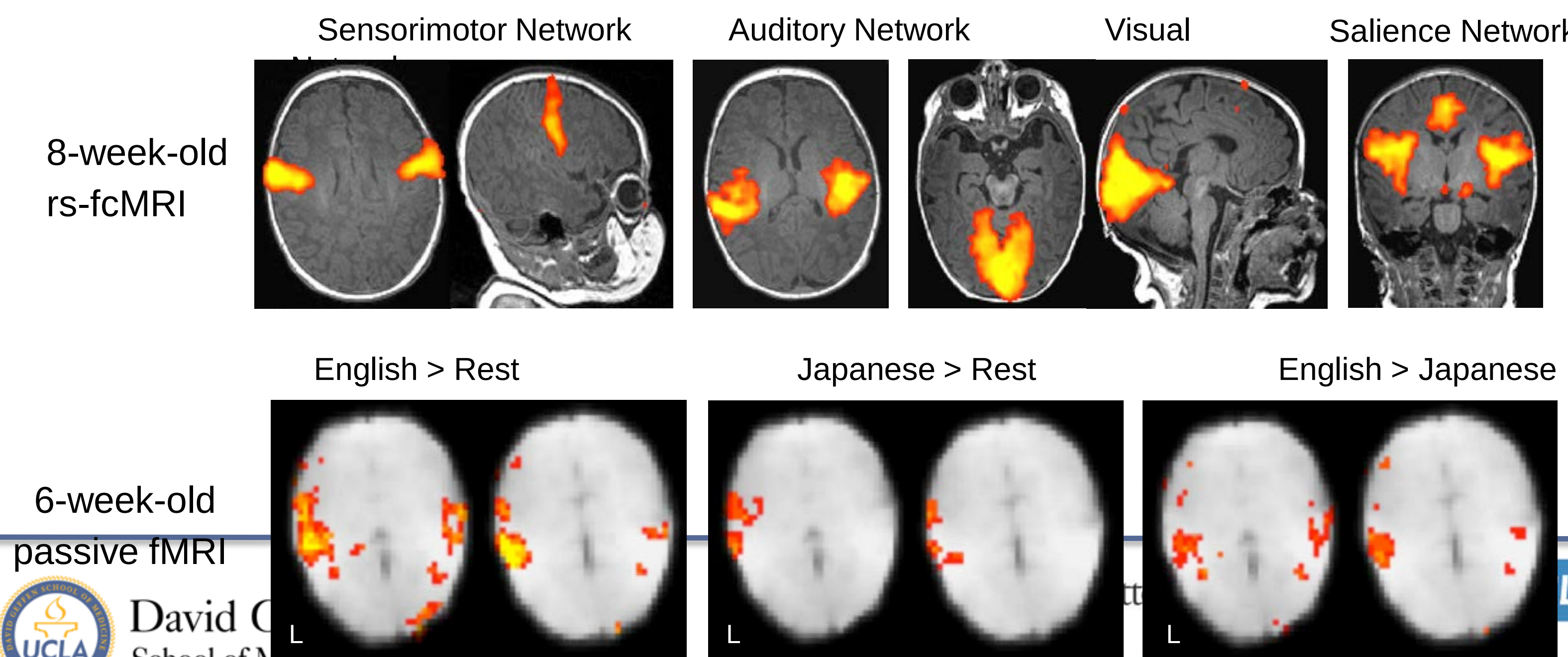


Starting early

Longitudinal studies in high-risk infants

Examine trajectories of brain and behavioral development

Intervene in high-risk toddlers to change trajectory

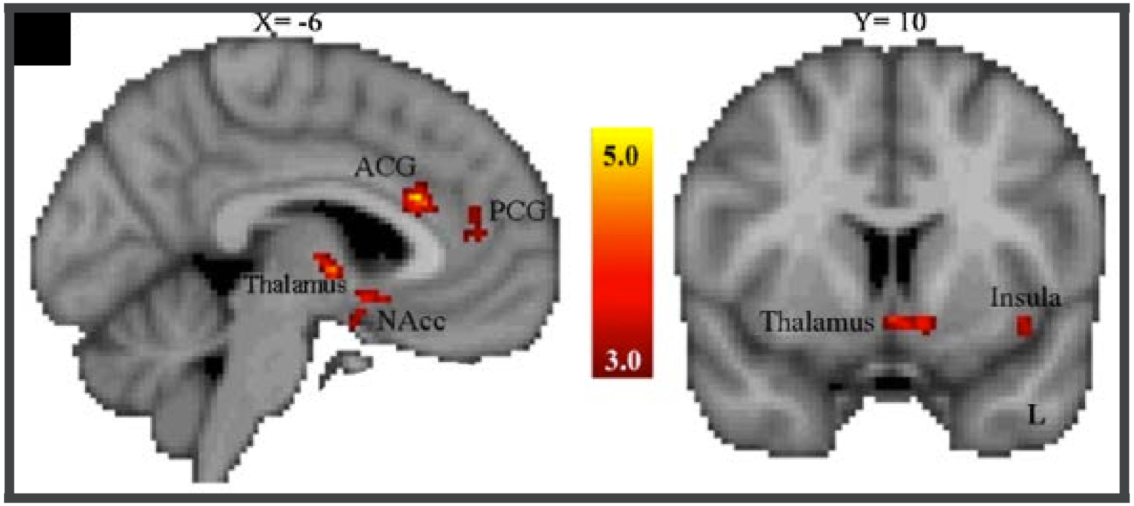


Treatment Trials

- Animal models of intervention
- Early intervention with joint attention/symbolic play (Kasari)
- Medication trials for minimally verbal (McCracken)

Relate animal findings to human findings

- Variations in the gene confer autism risk.
- Ongoing studies administer oxytocin to children with autism

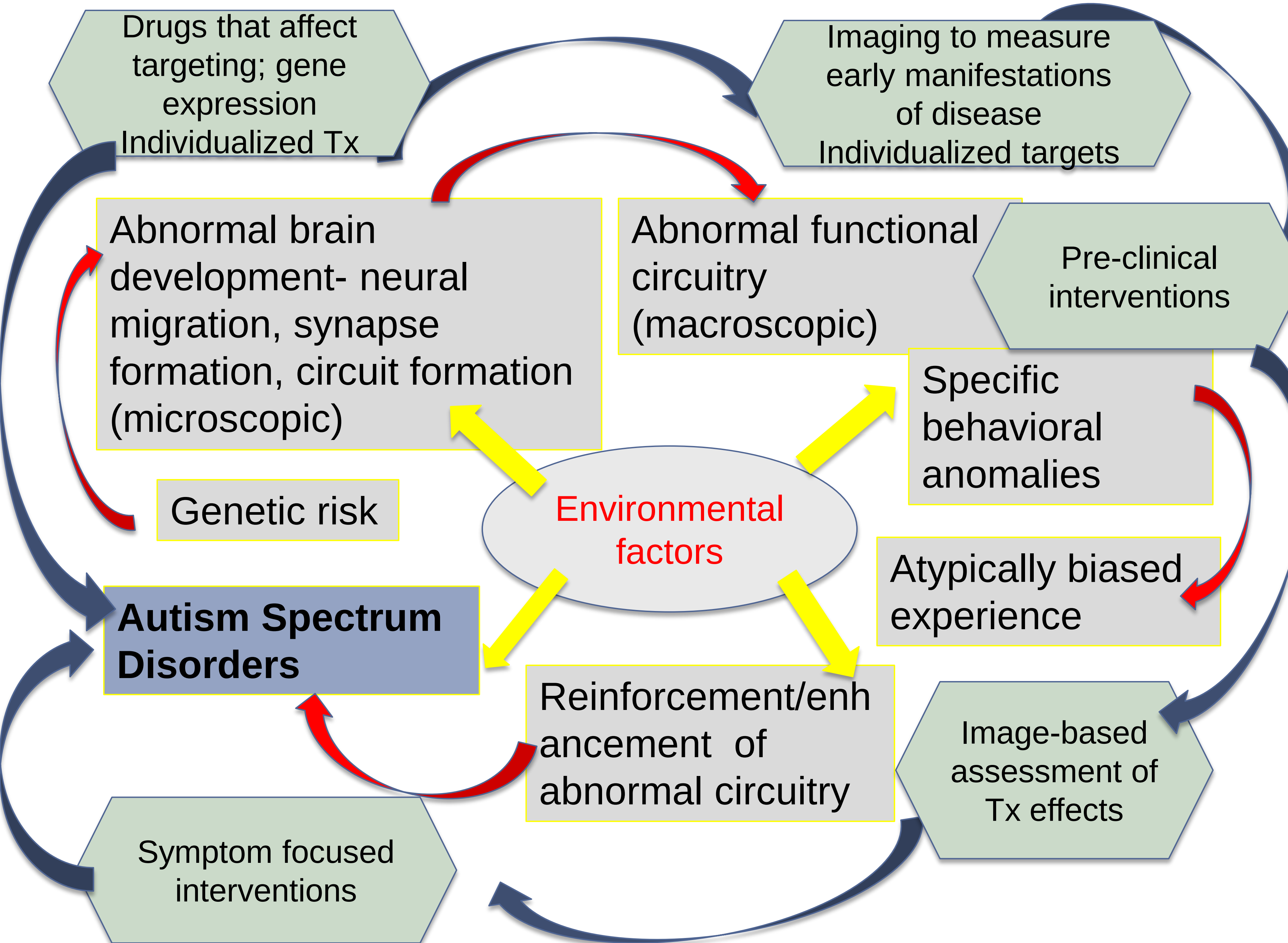


Reduced brain activity for normal adults in reward centers (Nacc) in OXTR risk gene carriers (Damiano et al 2014)

“wild type”

knockout

CNTNAP2 Mice treated with OXTR



Drugs that affect targeting; gene expression Individualized Tx
Imaging to measure early manifestations of disease Individualized targets
Abnormal brain development- neural migration, synapse formation, circuit formation (microscopic)
Abnormal functional circuitry (macroscopic)
Pre-clinical interventions
Specific behavioral anomalies
Genetic risk
Environmental factors
Atypically biased experience
Autism Spectrum Disorders
Reinforcement/enhancement of abnormal circuitry
Image-based assessment of Tx effects
Symptom focused interventions

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