Team-based Basic Neuroscience: Brain-Wide Approaches To Working Memory, Learning, and Autism

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NJ-ACTS Symposium
January 28, 2020

Support: NIH R01-MH115750, NIH U19-NS104648
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Support: NIH R01, program R01, U19, R21; Nancy Lurie Marks Foundation…and we are hiring! sswang@princeton.edu

Postdoctoral and staff positions are available to study nonmotor cerebellar function, sensitive periods, and autism mechanisms.
Circuits of coGnitive Systems

**Working memory**, the capacity to temporarily hold multiple pieces of information in mind for manipulation, is central to almost all cognitive abilities. Many mental diseases, including Alzheimer’s, schizophrenia, dementia, bipolar depression, autism, and attention deficit/hyperactivity disorder, involve working memory.

**BRAIN CoGS** is a 7-lab NIH-funded project, based at Princeton and UC Davis, that aims to determine how the brain produces decisions based on working memory. We are using a coordinated effort across all our labs to observe, map, perturb, and model brain circuits with state-of-the-art technologies. Our goal is for this work to lead to a major advance in basic science, that will in turn provide critical clues to therapeutic approaches.

https://www.braincogs.org/
A cerebellum-dependent evidence-accumulation task

Inactivation of crus I reduces accuracy

Deverett, Koay, Oostland & Wang (2018) *eLife*
Neural correlates of accumulating evidence are widespread (though why?)

Cerebellum

Strong evidence

Weak evidence

Cues begin

0.5 s

5% ΔF/F

Striatum

Normalized firing rate

Time from stimulus onset (s)

strong

preferred

weak

null

strong

Neocortical disruption impairs performance

Pinto et al., 2019, Neuron

...and for ventral tegmental area see Engelhard et al. (2019) Nature

Yartsev et al., 2018, eLife
Bidirectional paths broadly link forebrain and cerebellum

Wang, Kloth, and Badura (2014) *Neuron*
Anterograde tracing reveals paths from crus I to multiple thalamic nuclei

Tom Pisano and Zahra Dhanerawala
Whole-brain c-Fos mapping reveals a match with viral tracing.
Brain-wide c-fos activation scanning reveals specific functional networks.
Autism Defined

- Aloneness
- Sameness
Among environmental causes, cerebellar injury has the largest known risk ratio for autism spectrum disorder.

- Autistic identical twin: >50x
- Cerebellar injury at birth: 36x
- Autistic fraternal twin: 10x
- Romanian orphanage: 8.0x
- Premature ≥9 weeks: 7.3x
- Interbirth interval <1 year: 3.4x
- Hurricane strike zone: 3.0x
- Emigrating pregnant: 2.3x
- Parent with mental illness: 2.0x
- Father older than 40: 1.4x
- Mother older than 35: 1.3x
- General population: 1.0x
- MMR vaccine: 0.9x

Wang, Kloth, and Badura (2014) Neuron
Dendritic spine maturation: proliferation - pruning

Typical spine development

Disrupted spine pruning in autism

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A

Log conceptual age (years)

0.1  1  10  100

Study

- Agapino and Bloom, 1967
- Anderson et al., 1966
- Banchi et al., 2015
- Blue and Prensky, 1983
- Boulle et al., 2016
- Brother et al., 1979
- Bourgeois et al., 1990
- Bourgeois et al., 1999
- Craig, 1975
- Cruz–Martin et al., 2010
- De Felipe et al., 1997
- De Groot and Vanon, 1978
- Gelato and Greenshaw, 2005
- Gonzales-Burgos, 2008
- Gunzler et al., 2002
- Hulata and Zhang, 2009
- Hultsch and Courter, 1987

B

Human control subject Human autism patient

7-8 y  15-18 y

Log conceptual age (days)

100  1000  10000

Group

- Control
- ASD

C

Control mouse Tsc1 CKO mouse

20 d  30 d

Spine density (Spines/10 μm)

Log conceptual age (days)

1.25  2.5  5  10  15  20

Group

- Control
- ASD

Genotype

- Arg1 CKO
- Arg1 KO
- Tsc1 CKO
- Tsc1 KO
- Tsc2 KO
- Tsc2 KO
- Tsc2 KO
Imaging spine dynamics while perturbing cerebellar activity
requires a “Crystal Episkull”

Protocol dependent from animal’s age. General outline:

1. **Etch** upper layer of compact bone (Surface enlargement, etchant gel, 2-4 min);
2. **Bone demineralization** (Calcium chelator or decalcifying acid, 20-30 min);
3. **Match RI and prevent recalcification** (Visible-light curable glue with low viscosity)
Crystal episkull enables spine imaging

PSF 0.5x0.5x2.5 µm

PSF 2x2x8 µm
Lab projects (January 2020)

- Probe cerebellar paths to thalamus (dorsomedial and reticular nuclei) for contributions to evidence accumulation
- Image the same Purkinje-cell dendrites in head-fixed and freely moving mice
- Cerebellar influences on neocortical plasticity (chemo- and opto-genetic)
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