Cerebellum, autism, and sensitive periods

Sam Wang, Aleksandra Badura and Tom Pisano
The Cerebellum, Sensitive Periods, and Autism

Samuel S.-H. Wang,1,* Alexander D. Kloth,1 and Aleksandra Badura1

Neuron 83, August 6, 2014

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Article level metrics

104

Score in context

- Puts article in the top 5% of all articles ranked by attention
- Very good compared to other articles of same age & journal (94th percentile)
- Very good compared to articles of the same age (98th percentile)

Mentioned by

- 7 news outlets

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So far Altmetric has seen 7 stories from 7 outlets.

- **EurekAlert!**
  - Early cerebellum injury hinders neural development, possible root of autism
  - EurekAlert!
  - (Princeton University) Princeton University researchers offer a new theory that an early-life injury to the cerebellum disrupt...
  - 2014-09-02T04:00:00+00:00

- **MedicalXpress**
  - Early cerebellum injury hinders neural development, possible root of autism
  - MedicalXpress
  - A brain region largely known for coordinating motor control has a largely overlooked role in childhood development that could re...
  - 2014-09-02T17:03:41+00:00

- **HealthCanal**
  - Early cerebellum injury hinders neural development, possible root of autism, theory suggests
  - Health Canal
  - A brain region largely known for coordinating motor control has a largely overlooked role in childhood development that could re...
  - 2014-09-02T17:03:41+00:00
Many mouse autism models show cerebellar learning deficits

<table>
<thead>
<tr>
<th>MOUSE MODEL</th>
<th>ASD-like?</th>
<th>Probability</th>
<th>LEARNING</th>
<th>PERFORMANCE</th>
<th>GENE EXPRESSION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amplitude</td>
<td>Peak time</td>
<td>Rise time</td>
</tr>
<tr>
<td>Mecp2^{R308Y}</td>
<td>yes</td>
<td>unchanged</td>
<td>decrease</td>
<td>later</td>
<td>slower</td>
</tr>
<tr>
<td>Shank3+/ΔC</td>
<td>yes</td>
<td>decrease</td>
<td>decrease</td>
<td>earlier</td>
<td>faster</td>
</tr>
<tr>
<td>L7-Tsc1</td>
<td>yes</td>
<td>decrease</td>
<td>decrease</td>
<td>unchanged</td>
<td>unchanged</td>
</tr>
<tr>
<td>Cntnap2/-</td>
<td>yes</td>
<td>decrease</td>
<td>unchanged</td>
<td>unchanged</td>
<td>unchanged</td>
</tr>
<tr>
<td>patDp/+</td>
<td>yes</td>
<td>decrease</td>
<td>unchanged</td>
<td>unchanged</td>
<td>unchanged</td>
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<tr>
<td>Cntnap2+/−</td>
<td>no</td>
<td>unchanged</td>
<td>unchanged</td>
<td>unchanged</td>
<td>unchanged</td>
</tr>
</tbody>
</table>

Piochon, Kloth et al. (2014) *Nature Communications*
Kloth et al. in review
### Why cerebellum?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autistic identical twin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellar injury at birth</td>
<td></td>
<td>36x</td>
</tr>
<tr>
<td>Autistic fraternal twin</td>
<td></td>
<td>10x</td>
</tr>
<tr>
<td>Romanian orphanage</td>
<td></td>
<td>8x</td>
</tr>
<tr>
<td>Premature ≥9 weeks</td>
<td></td>
<td>7.3x</td>
</tr>
<tr>
<td>Interbirth interval &lt;1 year</td>
<td></td>
<td>3.4x</td>
</tr>
<tr>
<td>Hurricane strike zone</td>
<td></td>
<td>3.0x</td>
</tr>
<tr>
<td>Emigrating pregnant</td>
<td></td>
<td>2.3x</td>
</tr>
<tr>
<td>Parent with mental illness</td>
<td></td>
<td>2.0x</td>
</tr>
<tr>
<td>Father &gt;40 years old</td>
<td></td>
<td>1.4x</td>
</tr>
<tr>
<td>Mother &gt;35 years old</td>
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<td>1.3x</td>
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<tr>
<td>General population</td>
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<td>1.0x</td>
</tr>
<tr>
<td>MMR vaccine</td>
<td></td>
<td>0.9x</td>
</tr>
</tbody>
</table>

**Diagram:**
- **Thalamus**
- **Cerebellar nucleus**
- **Purkinje cells**
- **Granule cells**
- **Forebrain areas**
- **Cerebellar cortex**
- **Pontine nuclei**
Tests for cerebellar roles in cognitive and social behavior

1. Cellular imaging of cerebellar network activity
2. Subregion-specific perturbations
3. Transsynaptic pathway tracing
4. Developmental shaping of distant brain circuits
Multisensory processing in the cerebellum

2-photon microscope
- Pulsed IR
- Scan lens
- Tube lens
- Dichroic mirror
- Detector
- XY scan mirrors
- Objective

Cerebellum
- Purkinje cell
- Granule cell layer
- Climbing fibers
- Parallel fibers
- Mossy fibers
- (multisensory inputs)

To Deep Nuclei
What cerebellar regions keep cognitive development on track?

DREADDs - Designer Receptors
Exclusively Activated by Designer Drugs

Adapted from Farrell, 2011, Frontiers in Integrative Neuroscience

Inject DREADDs
>P56: Behavioral tests +CNO

Group 1
Group 2

PUP (P0-P21) JUVENILE (P21-P56) ADULT (>P56)

Inject DREADDs
CNO

DREADD
CNO
activity
neuron silenced
Stereotyped Behavior: Grooming and Y-maze Reversal

Wild-Type Grooming Components, adapted from Kalueff et al, 2007

Acquisition

Reversal Day 1

Reversal Day 2
Sociability: Three-Chamber Test

Captured Still Image from Video Recording: Lobule Vermis-Injected Mouse Social Chamber Test
Tests for cerebellar roles in cognitive and social behavior

1. Cellular imaging of cerebellar network activity

2. Subregion-specific perturbations

3. Transsynaptic pathway tracing

4. Developmental shaping of distant brain circuits
Clearing techniques

ARTICLE

Structural and molecular interrogation of intact biological systems

Kwanghun Chung1,2, Jenedle Wallace1, Sung-Yon Kim1, Sandhya Kalyanasundaram2, Aaron S. Andalman1,2, Thomas J. Davidson1,2, Julie L. Mitrakos1, Kelly A. Zaloucousky1,2, Joanna Marts1, Aleksandra K. Doniuss1, Sally Pak1, Hannah Bernstein1, Charu Ramakrishnan1, Logan Grossnick1, Viviana Gradinaru1 & Karl Deisseroth1,2,3,4

Figure 2 | Intact adult mouse brain imaging. Imaging was performed in
Wang laboratory

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