Objects, Space & Numbers

Space and Time are very abstract concepts that have “scale” but no actual values attached to them.

- we use mental “units” to break them up meaningfully
- have to learn “how” much is a(n): inch/second, foot, hour
- numbers were invented to describe “how many” units

What if your “mental units” don’t match parts of the real world accurately?

- space/time estimates will be wrong, numbers won’t make sense
- “digital camera” analogy of mental representation -> Crowding

This explanation guides the design for novel interventions

- if only we can find $$ to build them. Grant to NIH in 2 weeks
“Crowding” & Attentional Resolution

From Cavanagh, 2004
Crowding makes it hard to see one of the children in the street

Whitney & Levi, 2011
Spatiotemporal Resolution

In “real life” we use attention to integrate information over space and time:
- to track where we and other things are
- to estimate distance and duration
- to navigate

We can measure amount resolution reduction:
- is 3 a “crowd”, or 2?
Spatiotemporal Resolution

All kids in study accurately track fewer than 3 targets.

- **Dynamic crowding** reduces capacity in 22q11.2DS to lower than TD.

Less spatiotemporal information available for mental processes.
Spatial/Temporal Resolution

Now considerable evidence (Bavelier & others) that FP-POV action games enhance spatial & temporal resolution

- in college aged players (VGPs)
- and N-GVPs trained 10 hours

Direct transfer to kids with 22q11.2?

Existing games don’t target ONLY at spatial/temporal processing

- Submitting grant with proof of concept prototype game
- baseline data from current being collected now
- plan to assess training effect

- then develop/test full game +/- neurotherapeutic medications
Brain Structure & Circuitry

Well-defined brain circuits typically process attentional information:
- Many components are atypical in 22q11.2DS.
- Many are in the midline & mesial regions of the brain.
- Some critical ones are early-developing subcortical regions.

Genetic influence might create suboptimal attentional circuits:
- Their "dysfunction" could impair typical development.
- Weaker cortical circuits for cognitive function might result.

Are there "dysconnectivity" subgroups with different functioning?
Connectivity should be a responsive target for intervention!
SLF: “easy” brain (TD)

88.2% “fibers” track expected path

Michelle Y. Deng Ph.D.
Volume of Interest BOX (7x7x7mm)

x = -31 from the lateral edge of the brain to the most lateral point of the parieto-occipital sulcus
y = -24 from the central sulcus to the most superior point of the parieto-occipital sulcus
z = 31 from beneath the superior longitudinal fasciculus to the top of the brain
(AC-PC aligned) Tsang et al. 2009

13.2% “fibers” track expected path

Michelle Y. Deng Ph.D.
Attention, Arousal & Behavior

Attention functions to select among competing, salient inputs
- salience changes dynamically and is driven internally & externally
  - External:
    - what teacher is writing on the board
    - what the kid next to me is doing
  - Internal:
    - how much do I want/need to understand this math?
    - how much does math make me make head/tummy hurt?
    - *how much yummier does that cookie look when dieting?*

Stress & Anxiety alter arousal & arousal alters salience
- threshold for what enters consciousness drops (survival)
- suddenly more things are competing for (impaired) attention
- “spotlight of attention” is pulled in multiple directions
- nothing is attended long/deeply enough for learning

Explains significant proportion of ADHD Dx?
Michelle Y Deng, Ph.D.
### Discovering Population “Clusters” from Clinical Data

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
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<tbody>
<tr>
<td>CARDIAC</td>
<td>normal</td>
<td>isolated ASD, VSD, PDA, valve</td>
<td>TOF, truncus, aortic arch</td>
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<tr>
<td>HEME</td>
<td>normal</td>
<td>-</td>
<td>abnormal</td>
</tr>
<tr>
<td>RENAL/GU</td>
<td>normal</td>
<td>hernia/cryptorchidism</td>
<td>structural abnormality</td>
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<tr>
<td>CLEFT. PALATE</td>
<td>none</td>
<td>submucous</td>
<td>overt</td>
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<tr>
<td>VPI</td>
<td>normal</td>
<td>abnormal-no surgery</td>
<td>abnormal-surgery corrected</td>
</tr>
<tr>
<td>G.tube</td>
<td>normal</td>
<td>-</td>
<td>abnormal</td>
</tr>
<tr>
<td>FTT</td>
<td>normal</td>
<td>-</td>
<td>abnormal</td>
</tr>
<tr>
<td>autoimmune</td>
<td>normal</td>
<td>-</td>
<td>abnormal</td>
</tr>
<tr>
<td>other infection</td>
<td>normal</td>
<td>-</td>
<td>abnormal</td>
</tr>
<tr>
<td>seizures</td>
<td>normal</td>
<td>febrile seizure</td>
<td>non-febrile seizure, epilepsy</td>
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<tr>
<td>hypocalcemia</td>
<td>normal</td>
<td>-</td>
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</tr>
<tr>
<td>thyroid</td>
<td>normal</td>
<td>-</td>
<td>abnormal</td>
</tr>
<tr>
<td>growth hormone</td>
<td>normal</td>
<td>-</td>
<td>abnormal</td>
</tr>
<tr>
<td>MEDS</td>
<td>normal</td>
<td>vitamins, Miralax, albuterol</td>
<td>serious medical condition</td>
</tr>
<tr>
<td>SURGERY</td>
<td>none</td>
<td>minor (PE tube, hernia)</td>
<td>major (e.g. Cardiac)</td>
</tr>
</tbody>
</table>
Discovering Population “Clusters” from Clinical Data

22q (n=37) General Clinical Index K-mean Three Group

These two components explain 35.14% of the point variability.

<table>
<thead>
<tr>
<th></th>
<th>group1</th>
<th>group2</th>
<th>group3</th>
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</thead>
<tbody>
<tr>
<td>CARDIAC</td>
<td>2.0</td>
<td>2.0</td>
<td>0.3</td>
</tr>
<tr>
<td>MEDS</td>
<td>1.3</td>
<td>0.7</td>
<td>0.7</td>
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<tr>
<td>SURGERY</td>
<td>2.0</td>
<td>1.9</td>
<td>1.0</td>
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<tr>
<td>HEME</td>
<td>0.6</td>
<td>0.4</td>
<td>0.3</td>
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<tr>
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<td>0.1</td>
<td>1.1</td>
<td>0.3</td>
</tr>
<tr>
<td>CLEFT. PALATE</td>
<td>0.3</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>VPI</td>
<td>1.0</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>G.tube</td>
<td>0.0</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>FTT</td>
<td>1.1</td>
<td>0.4</td>
<td>0.6</td>
</tr>
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<td>0.3</td>
<td>0.7</td>
<td>0.0</td>
</tr>
<tr>
<td>other infection</td>
<td>2.0</td>
<td>0.0</td>
<td>0.3</td>
</tr>
<tr>
<td>seizures</td>
<td>0.7</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>hypocalcemia</td>
<td>1.7</td>
<td>0.0</td>
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<tr>
<td>thyroid</td>
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<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>growth.hormone</td>
<td>0.3</td>
<td>0.0</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Michelle Deng, Kathy Angkustsiri, Danielle Harvey
Discovering Population “Clusters” from Clinical Data

22q (n=37)

Step 2:
PCA to 1st: see individual plots on the first two principal components
2nd: see how the variables are clustered, and the weight of contribution
3rd: notice that there looks like a tided subgroup (where I put a circle)

Ask question here:
Is it any potential subgroups here? To answer this, K-mean is used in the next slide
The 22q11.2DS Puzzle

Genetics
- heart, immune, brain

Trauma
- surgery, illness, loss

Cognition
- academic, social, practical

Community
- family, school, friends

Affect
- stress, fear, anxiety

Biology
- regulation, expression

OUTCOMES
- behavioral, psychiatric
  - educational, vocational
  - interpersonal, romantic
  - parenting
Summary

Now able to integrate many research area for translation/intervention

- representational changes underlying cognitive impairments
- **allostatic load** of challenges & neurobiological stress/anxiety response modulate coping success (+/- family/community supports)
- cognitive control changes & common schizophrenia-related symptoms in adolescence may be risk/protection factors
- medical history & other subtyping explorations may identify further ideas about potential outcomes

ALL of these will be affected by background genes, experience etc

- but combined basic & clinical research are starting to indicate ways to explain, treat and perhaps alter outcomes
Thanks

MOST important: Kids who participated & their families!!

Majority of the work presented here was done by:

- Margie Cabaral, Freddy Bassal, Heather Shapiro, Ling Wong, Elliott Beaton Ph.D., Siddarth Srivastava Ph.D., Michelle Deng Ph.D., Joel Stoddard, M.D., Danielle Harvey, Ph.D., Kathy Angkustsiri M.D., Nicole Tartaglia M.D., Ingrid Lecklitter Ph.D., Janice Enriquez Ph.D.

With important contributions from:

- Brian Avants Ph.D., Tracy Riggins Ph.D., Yukari Takarae Ph.D., Gary Zhang Ph.D., Marisol Mendoza M.A., Leeza Kondos & others
- UC Davis Center of Excellence in Developmental Disabilities
Integrating Cognition, Emotion & Psychiatry for Treatment in 22q11.2DS

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