Exploring Brain Connectivity in Autism and Sensory Processing Disorders
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Elysa Marco MD, UCSF Associate Professor of Neurology, Psychiatry & Pediatrics
Pratik Mukherjee, MD PhD Professor of Radiology

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  - Simons Foundation
  - NIMH
  - Families around the world: SPD.UCSF.EDU

By the end of this talk, we hope you will:

- Deeply question the utility and veracity of labels as diagnoses
- Understand the emerging findings of altered connectivity in children with neurodevelopmental disorders with a focus on information (sensory) processing differences in “autism” and “SPD”

DSM 5 Autism Spectrum Disorder- The Shifting Label

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following:

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day).
3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).
4. Hyper- or hypo-reactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

http://www.autismspeaks.org/what-autism/diagnosis/dsm-5-diagnostic-criteria
Genetics and Sensory Processing
(and/or Autism and/or ADHD and/or Language disorder and/or schizophrenia and/or bipolar)

- Copy Number Variations: 16p11.2

Absence of autism
It’s been suggested that people with this deletion do not have autism, but they have not necessarily had formal testing for autism. Autism is still a clinical diagnosis based on specific behaviour patterns (Battaglia 2007). Two unique members have a diagnosis of an autistic spectrum disorder (Bailiff 2007; Hempel 2009; Unique).

He has been labelled as having autistic traits, mainly sensory integration such as disliking loud noises and certain textures, liking routine, but not crowds - 7 years

Unique Website: www.rarechromo.org
The Cognitive and Behavioral Phenotype of the 16p11.2 Deletion in a Clinically Ascertained Population. Hanson, F et al Biol Psychiatry 2014

Why the and/or’s?

Table 2: Frequency of DSM-IV Psychiatric Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Child Carrier</th>
<th>Adult Carrier</th>
<th>Noncarrier Child</th>
<th>Noncarrier Adult</th>
<th>Carrier vs.</th>
<th>Carrier vs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phonomotor Processing</td>
<td>44 (98%)</td>
<td>0 (0%)</td>
<td>0</td>
<td>0</td>
<td>&lt; .0001</td>
<td>0.002</td>
</tr>
<tr>
<td>Development</td>
<td>49 (98%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>&lt; .0001</td>
<td>0.003</td>
</tr>
<tr>
<td>Language Disorders</td>
<td>38 (98%)</td>
<td>1 (13%)</td>
<td>0</td>
<td>0</td>
<td>&lt; .0001</td>
<td>0.034</td>
</tr>
<tr>
<td>Enuresis (307.0)</td>
<td>16 (21%)</td>
<td>2 (3%)</td>
<td>0</td>
<td>0</td>
<td>0.0002</td>
<td>0.03</td>
</tr>
<tr>
<td>Autism Spectrum Disorders</td>
<td>20 (26%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.01</td>
<td>0.22</td>
</tr>
<tr>
<td>ADHD</td>
<td>16 (19%)</td>
<td>0 (0%)</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
<td>0.22</td>
</tr>
</tbody>
</table>

- Copy Number Variations: 16p11.2 CNV
Genetics and Sensory Processing (and/or Autism)

- Triplet Repeat Disorders: Fragile X

How can genetics guide treatment and Prognosis?

- Fragile X
  - mGLUR5 = STX209 (Arbaclofen)?
- GABA
  - Specialized Clinics with screening of family members
  - Investigate for associated conditions
- Arghef9
  - GABA, GABA, GABA
- 16p11.2
  - Focus on articulation and praxis
  - Focus on specific aspects of cognitive control
  - Meds?
  - Seizures?

Brain Injury/Structural malformation and Sensory Processing (and/or Autism)

- Fetal Alcohol Syndrome (other exposures)
- Prematurity
- Stroke
- Infection
- Agenesis of the Corpus Callosum
- Migraine?
Brain Injury: Prematurity

Posterior Brain Regions: Multisensory & Interhemispheric

What did we find?

Wickremasinghe, Rogers, Johnson & Marco; PAS 2012; Former Preterm Infants Exhibit Abnormal Sensory Behavior

<table>
<thead>
<tr>
<th>QUADRANTS</th>
<th>N</th>
<th>% with scores &gt;2 SD* from the mean</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Registration</td>
<td>91</td>
<td>24</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sensory Seeking</td>
<td>85</td>
<td>11</td>
<td>0.02</td>
</tr>
<tr>
<td>Sensory Sensitivity</td>
<td>90</td>
<td>10</td>
<td>0.03</td>
</tr>
<tr>
<td>Sensory Avoiding</td>
<td>87</td>
<td>11</td>
<td>0.01</td>
</tr>
<tr>
<td>SECTIONS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auditory Processing</td>
<td>99</td>
<td>12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Visual Processing</td>
<td>96</td>
<td>2</td>
<td>0.19</td>
</tr>
<tr>
<td>Tactile Processing</td>
<td>86</td>
<td>10</td>
<td>0.02</td>
</tr>
<tr>
<td>Vestibular Processing</td>
<td>102</td>
<td>13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Oral Sensory Processing</td>
<td>88</td>
<td>9</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Demopoulos, Arroyo, Dunn, Sherr, Marco (Neurolopsychology, in revision) Individuals with agenesis of the corpus callosum show sensory processing differences as measured by the Sensory Profile.
How can understanding brain injury/structural differences guide treatment:

- AgCC:
  - Focus on registration-increasing intensity and salience of sensory input
  - Focus on auditory processing
  - Slow it down
  - Consider excitation as well as inhibition-keep one hand busy when working on the other.

- Prematurity
  - Increase the stimulus intensity
  - Focus on Auditory-Visual Integration!

Environment (Experience over Time)

- Sensory Deprivation v. Engagement/Experience
- Trauma/Conflict v. Comfort
- Screen Time: passive v. active, addictive v. stimulating
- Skill practice and Success

Charting our course:

- 2014 Updates on sensory processing and neuroimaging assessment

But first, What does a child neurologist and pediatric neuroradiologist mean by sensory processing:
How are the sensory domains organized and Connected?

- Structural
  - CT
  - MRI
  - DTI
- Functional
  - MEG
  - fMRI

How do we look into our kids’ brains?

Biological Basis For SPD using DTI
- TBSS Data Driven Approach SPD boys 8-12y compared to Controls

With a focus on sensory processing: we recruited, evaluated, and scanned kids with SPD...
- Right handed boys
  - SPD n=16
  - Controls n=25
- Age Matched
  - 8 to 11 years old
- FSIQ matched
  - SPD mean 113 (100-131)
  - Control mean 115 (97-130)
Then, we looked for lesions...

<table>
<thead>
<tr>
<th>Group</th>
<th>SPD (n=16)</th>
<th>Controls (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corpus Callosum</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decreased White matter</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grey Matter Injury</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Posterior Fossa Cyst</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Next, we looked for volume...

<table>
<thead>
<tr>
<th>Free Surfer</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cortex</td>
<td>.87</td>
</tr>
<tr>
<td>Intracranial</td>
<td>.63</td>
</tr>
<tr>
<td>Total White</td>
<td>.49</td>
</tr>
<tr>
<td>Left White</td>
<td>.58</td>
</tr>
<tr>
<td>Right White</td>
<td>.42</td>
</tr>
<tr>
<td>Left Cortex</td>
<td>.94</td>
</tr>
<tr>
<td>Right Cortex</td>
<td>.81</td>
</tr>
</tbody>
</table>

Free Surfer: Total Cortex = .87

So finally, we looked at white matter integrity using diffusion tensor imaging (DTI)

Fractional Anisotropy & Radial Diffusivity

Based on water movement under the influence of a gradient:
- FA: Degree of directionality
- RD: Rate of movement perpendicular to the WM tract
The differences were striking!

Q: how does decreased FA relate to auditory behavior?  
A: better connection = more typical behavior

Q: how does decreased FA relate to multisensory behavior?  
A: better white matter = more typical behavior

Sensory Profile- Auditory

Sensory Profile- Multisensory

Sensory Profile- Attention
What is found in autism?

From: J Psychiatry Neurosci. 2011 January; 36; Pervasive microstructure abnormalities in autism: A DTI study

Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Diagnosis</th>
<th>Age Matched</th>
<th>PIQ Matched</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td></td>
<td>ASD</td>
<td>7 ± 1.7</td>
<td></td>
<td>113</td>
</tr>
<tr>
<td>2nd</td>
<td>HARDI Probabilistic Streamline Tractography Hypothesis Tract Based Approach</td>
<td>SPD 8-12y compared to Controls</td>
<td>ASD 8-12y compared to Controls</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

How do they compare?
- Both ASD and SPD groups show decreased FA in basic sensory perception and integration tracts (SPD > ASD)

So we added a group of boys with autism...and Shin (like Charlie Sheen) Chang!

- Right handed boys
- SPD n=16
- ASD n=15
- Controls n=23
- Age Matched
  - Between 8 to 12 years old
- PIQ matched
  - SPD mean 116
  - ASD mean 102
  - Control mean 113
- WMIQ:
  - SPD: 104
  - ASD: 100
  - Control: 108
How are they different?

- The ASD group is more affected in the face processing and auditory tracts.

& does this relate to the real world?

- Tract strength is correlated with auditory processing performance (SPD>ASD).

& does this relate to the real world?

- Tract strength is correlated with working memory performance (SPD>ASD).
& does this relate to the real world?

- Tract strength is correlated with social skills (driven by the ASD group)

Take home message:

- Children with SPD and ASD show decreased connectivity in basic (posterior) sensory tracts
- Children with ASD are more affected in facial recognition and language tracts
- These changes in connectivity correlate with working memory and social behavior across diagnosis

From structure to Function:
How do neurons talk to each other?

How can you measure electrical activity?
Functional imaging with magnetoencephalography

- Milli-second & milli-meter cortical activity resolution (w/ MRI co-registration)
- Non-invasive
- Well tolerated
- Resting Paradigms and Activity based Paradigms

Minimal group differences by clinical autism diagnosis

Bringing the bedside to the scanner...

Two groupings: Clinical Autism Diagnosis and Tactile Sensitivity
What we have learned:

- Phenotype must guide our Neurotype analysis; not the label
- We see EARLY differences at the level of primary cortex

Interventions:
Our goal (like yours!) is to build both areas of strength and areas of challenge (Visuomotor and Attention)

So how do we move from the scanner back to the bedside?

1. Use scanning tools to IDENTIFY & MEASURE neural deficits in individuals & CREATE personalized sensory based intervention approach
2. Provide objective measures of intervention EFFICACY
Develop tablet based tools for assessment and training (paired with neuroimaging)!

Many Hands:
- Bay Area SPD providers
- The kids and their parents!
- SPD MEG/DTI Team
  - Srikanth Nagarajan
  - Pratik Mukherjee
  - Elliott Sherr
  - Leighton Hinkley
  - Carly Demopoulos
  - Annie Aitken
  - Shivani Desai
  - Ashley Antovich
  - Julia Harris
  - Susannah Hill
  - Richard Hill
- Angelina Jocson
- Kasra Khatibi
- Anne Bernard
- Monica Arroyo
- Heidi Kirsch
- Anne Findlay
- Suzanne Honna
- Julia Owens
- Shin Chang
- EVO Team
  - Adam Gazzaley
  - Joaquin Anguera
  - Shivani Desai
  - Ashley Antovich
  - Cammie Rolle
  - Johno Gibbons
- MAC
  - Bruce Miller
  - Joel Kramer
  - John Neuhaus
- Sensory Processing Foundation
  - Lucy Miller
  - Sarah Schoen
- Autism Neurodevelopment Program
  - Bryna Siegel
  - Robert Hendren
  - Lauren Weiss