GABA and Socio-Communicative Abilities in High-Functioning Adults with Autism Spectrum Disorder

Lawrence Fung, M.D., Ph.D.
Stanford University
INTRODUCTION
“Imitation Game”
Brain

Social Behavior
Questions

• What are the **brain regions** responsible for altered **social behavior** in individuals with autism?

• What **causes** these brain regions to function differently in individuals with autism?
• **Question**: What are the brain regions responsible for altered social behavior in individuals with autism?

• **Hypothesis**: The Thalamocortical Circuits are responsible for altered social behavior in individuals with autism.
• **Question**: What *causes* the Thalamocortical Circuits to function differently in individuals with autism?

• **Hypothesis**: Mechanisms responsible for modulating *excitation / inhibition* balance causes differences in Thalamocortical Circuits in individuals with autism.
Aims

• **Aim 1**: Determine the abnormalities in GABA levels in thalamocortical networks in adults with ASD using proton magnetic resonance spectroscopy (MRS).

• **Aim 2**: Characterize the distribution of GABA$_A$ receptors in adults with ASD using positron emission tomography (PET).

• **Aim 3**: Examine the effects of GABA$_A$ receptor densities and GABA levels in the thalamus and left dorsolateral prefrontal cortex (DLPFC) on socio-communicative abilities.
METHODS
Hybrid PET-MR Scanner (General Electric)

MRS voxel in Thalami
Neuropsychological Assessments

– IQ:
  • Stanford Binet Version 5 (SB5)

– Autism Spectrum Disorder Diagnosis
  • Autism Diagnostic Observational Schedule (ADOS)
  • Autism Diagnostic Inventory – Revised (ADI-R)

– Social interaction abilities:
  • Ritvo Autism Asperger’s Diagnostic Scale (RAADS)
  • Autism Quotient (AQ)
  • Social Responsiveness Scale (SRS-2)

– Emotion regulation:
  • Berkeley Expressivity Questionnaire (BEQ), Aberrant Behavioral Checklist – Irritability (ABC-I)

– Sensory aberrations:
  • Sensory Profile Questionnaire (SPQ)

– Repetitive behaviors:
  • Repetitive Behavior Scale (RBS-R)
## Participant Demographics and Partial Neuropsychological Testing Results

<table>
<thead>
<tr>
<th></th>
<th>ASD</th>
<th>TD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.0 ± 8.7</td>
<td>27.4 ± 7.5</td>
<td>.675</td>
</tr>
<tr>
<td>Gender</td>
<td>16 M / 9 F</td>
<td>17 M / 9 F</td>
<td>--</td>
</tr>
<tr>
<td>FSIQ</td>
<td>102.9 ± 17.6</td>
<td>113.0 ± 12.3</td>
<td>.035</td>
</tr>
<tr>
<td>AQ</td>
<td>32.0 ± 6.7</td>
<td>17.9 ± 8.6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>RAADS total</td>
<td>128 ± 35.1</td>
<td>50.3 ± 41.6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SRS total</td>
<td>68.1 ± 9.8</td>
<td>51.0 ± 9.8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BEQ – Negative Emotionality</td>
<td>22.1 ± 8.9</td>
<td>21.2 ± 6.0</td>
<td>.656</td>
</tr>
<tr>
<td>BEQ – Positive Emotionality</td>
<td>18.9 ± 5.7</td>
<td>21.2 ± 5.2</td>
<td>.142</td>
</tr>
<tr>
<td>BEQ – Impulse Strength</td>
<td>29.8 ± 9.3</td>
<td>26.0 ± 8.1</td>
<td>.132</td>
</tr>
<tr>
<td>BEQ – Emotional Expressivity</td>
<td>70.8 ± 20.0</td>
<td>68.4 ± 16.1</td>
<td>.638</td>
</tr>
</tbody>
</table>
AQ Scores

[Box plot showing AQ scores for ASD and TD groups, with separate boxes for Female and Male gender categories.]
RAADS Scores
Aim 1: GABA levels in Male Participants

**Thalami: TD > ASD**

- $p = .015^*$

**Left DLPFC: ASD > TD**

- $p = .030^*$
- $p = .007^{**}$
Aim 2: GABA$_A$ Receptor Binding Potential

- Lack of Group differences in BP$_{ND}$’s of all voxels of interest
Aim 3: Correlations between GABA levels and Primary Social Functioning Measures – TD Participants ONLY

• No significant correlations

\[
R = -0.295 \\
\text{p} = 0.379
\]

\[
R = -0.017 \\
\text{p} = 0.961
\]
Aim 3: Correlations between GABA levels and Primary Social Functioning Measures – ASD Participants ONLY

\[ R = -0.569 \]
\[ p = 0.027^* \]
Aim 3: Correlations between GABA Levels and Primary Social Functioning Measures – **MALE Participants ONLY**

- **RAADS_Social Relatedness**
  
  \[ R = -0.584 \]
  
  \[ p = 0.004^{**} \]

- **RAADS_Sensory Motor**
  
  \[ R = -0.540 \]
  
  \[ p = 0.009^{**} \]

- **RAADS_Total Score**
  
  \[ R = -0.554 \]
  
  \[ p = 0.008^{**} \]

- **AQ Score**
  
  \[ R = -0.449 \]
  
  \[ p = 0.041^{*} \]
Aim 3: Correlations between GABA levels and Primary Social Functioning Measures – Male ASD Participants ONLY

R = -0.799
p = .003**

R = -0.710
p = .022*
Summary

• Region-specific differences in GABA levels between ASD and TD
  – Thalami: TD > ASD
  – Left DLPFC: ASD > TD
• No apparent differences in GABA\textsubscript{A} receptor density between ASD and TD.
• Correlations between GABA levels and socio-communicative function
  – In Male ASD, lower GABA levels in the thalami correspond to more socio-communicative deficits
  – In TD controls, GABA levels in the thalami do not correlate with socio-communicative function
Acknowledgments

Stanford Psychiatry
• Ryan Flores, BS
• Rachel Schuck, BA
• Leila Chew
• Deanna Shinsky, BA
• Matthew Sacchet, PhD
• Antonio Hardan, MD
• Ruth O’hara, PhD
• Jennifer Philips, PhD

Stanford Radiology
• Harsh Gandhi, BS
• Dawn Holley, BS
• Praveen Gulaka, PhD
• Jun-Hyung Park
• Bin Shen PhD
• Fred Chin, PhD
• Dan Spielman, PhD
• Meng Gu, PhD
• Shyam Srinivas, MD, PhD
• Greg Zaharchuk, MD, PhD

Funding:
• AACAP Pilot Research Award
• Mosbacher Family Fund
• NIMH K08MH111750
• General Electric Healthcare

General Electric Healthcare
• Mehdi Khalighi, PhD

Stanford University
THANK YOU!