Toward Understanding Girls with Autism: A Scientist & Father’s Perspective

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How do we understanding intentions?

Pelphrey et al. (2003) *Journal of Neuroscience*
Pretend

Props

SIT ON TABLE

EARPLUGS

HEADPHONES

HELMET ON

Picture
schedules

Pixar

Prizes!
Neural Signatures of Autism

• **State markers**: dysfunction in children with ASD relative to siblings and typical children.
• **Trait markers**: shared dysfunction in siblings and children with ASD
• **Compensatory mechanisms**: enhanced activity unique to siblings
State: ASD < TD & ASD < US
Trait: US < TD & ASD < TD
Compensatory: US > TD & US > ASD

Kaiser et al. (2010) *Proceedings of the National Academy of Sciences*
Can we see autism’s signature in the individual brain?
Classification Analysis

- In each ROI:
  - Trained classifier on Discovery cohort brain responses
  - Predict the diagnostic categories of the Replication cohort

- Significance assessment
  - Permutation testing
    - 1001 permutations
  - FDR control for multiple comparisons
A weak response to biological motion is a marker of autism in boys (but not girls!)

Björnsdotter et al., *JAMA: Psychiatry*, 2016
Autism Center of Excellence: Girls Network

- 250 Boys with ASD
- 250 TD boys
- 250 Girls with ASD
- 250 TD girls
- Unaffected siblings: ½ boys and ½ girls:
- 400

Total $N = 1400$
Sex differences in brain response to coherent versus scrambled biological motion

- **ASD♀ > ASD♂**
  - Female with ASD shows a greater response to coherent biological motion compared to male with ASD.
  - Key regions included: dmPFC, vmPFC, thalamus, precuneus, and amygdala.

- **ASD♀ > TD♀**
  - Female with ASD shows a greater response compared to female with TD.
  - Key regions include: dmPFC, vmPFC, thalamus, and precuneus.

- **TD♂ > TD♀**
  - Male with TD shows a greater response compared to female with TD.
  - Key regions include: precuneus and vmPFC.

- **ASD♀ > ASD♂**
  - Female with ASD shows a greater response compared to male with ASD.
  - Key regions include: pSTS, Crus I, and SPL.

- **Population Frequency**
  - Male ASD liability threshold: Mean + 2.1SD
  - Female ASD liability threshold: Mean + 2.7SD

- **Sex Differences**
  - Female: ♀
  - Male: ♂
  - dmPFC: dorsomedial prefrontal cortex
  - FFG: fusiform gyrus
  - ITG: inferior temporal gyrus
  - pSTS: posterior superior temporal sulcus
  - vmPFC: ventromedial prefrontal cortex

- **Cerebellar view**
  - Right Crus I
  - Left Vilb

- **Right temporo-occipital view**
  - Left Crus I
  - Right Crus I

- **Left temporo-occipital view**
  - Left Crus I

- **Left frontal view**
  - Right Crus I

- **Caudate**
- **Putamen**
- **Left amygdala**
- **Left thalamus**
- **Paracingulate**
- **Left thalamus**
- **Right thalamus**
- **dmPFC**
- **vmPFC**
- **Precuneus**
- **Paracingulate**
Girls

- tactile
- language
- social cognition
- meaning
- comprehension
- anxiety
- phonological awareness
- nonverbal cues
- attention
- emotion regulation
- self referential
- object sounds
- speech production
- retrieval
- somatosensory
- speech perception
- evaluation
- motor control
- auditory
- execution
- pain
- default mode
- recognition
- person perception
- social perception
- recall
- memory

Boys

- meaning
- language
- motion
- identity
- comprehension
- person perception
- recognition
- phonological strategy
- sounds
- priming
- recall
- spatial attention
- nonverbal cues
- retrieval
- visuospatial cues
- auditory
- visual
- biological
- social perception
- self referential
- social cognition
- speech perception
- biological
How do we translate basic science into real-world tools aimed at “target engagement”? 
Identify social and cognitive functions and their neural and genetic substrates.

Link individual differences in neural and genetic substrates to autism symptoms.

Translate basic science into treatment protocols aimed at “target engagement”.

Test efficacy in blinded randomized controlled trials.

Roll out of evidence-based treatments.
IMPRECISION MEDICINE
For every person they do help (blue), the ten highest-grossing drugs in the United States fail to improve the conditions of between 3 and 24 people (red).

1. ABILIFY (aripiprazole)
   Schizophrenia

2. NEXIUM (omeprazole)
   Heartburn

3. HUMIRA (adalimumab)
   Arthritis

4. CRESTOR (rosuvastatin)
   High cholesterol

5. CYMBALTA (duloxetine)
   Depression

6. ADVAIR DISKUS (fluticasone propionate)
   Asthma

7. ENBREL (etanercept)
   Psoriasis

8. REMICADE (infliximab)
   Crohn’s disease

9. COPAXONE (glatiramer acetate)
   Multiple sclerosis

10. NEULASTA (pegfilgrastim)
    Neutropenia

Based on published number needed to treat (NNT) figures. For a full list of references, see Supplementary Information at go.nature.com/4dr781.

If you have met one person with autism...
Pivotal Response Training (PRT)
Change in Behavior: Social Responsiveness Scale (SRS)

Yang et al. (in press) Nature: Translational Psychiatry
Change in brain, driving change in behavior

Yang et al. (in press)
*Nature: Translational Psychiatry*
Neuro-prediction of treatment response

Yang et al. (in press)
*Nature: Translational Psychiatry*
Can we boost brain responses before treatment?
Intranasal Oxytocin – Social Judgments

Gordon et al. (2013) *Proceedings of the National Academy of Sciences*
Neural Prediction of VR Treatment Response in Young Adults

VR Platform

- Real-Time Interaction
- Individual-Driven Avatars
- Real Life Context & Environments
- Voice Modulation
- Face Emotion Capture

Training Objectives

- Recognizing Others
  - Starting a conversation
  - Casual conversation
- Personal Response
  - Job interview, developing a friendship, dating
- Self-Assertion
  - Work dilemmas, confronting a friend
Treatment outcomes

Verbal and Non-verbal Emotion Recognition, WAIS-IV & WMS-IV(ACS)-Social Perception (SP) subtests

Social Responsiveness Scale (SRS)

Friendship network metrics

Neuroimaging
Brain Activation to Biological Motion Predicts Success in Virtual Reality Social Cognition Training for Adults!

$r = .77, p < .001$

$N = 17$, threshold: $Z > 3.6$ (voxel), $p < .05$ (cluster)
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