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# An Introduction to Translational Neuroscience Approaches to Investigating Autism

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*Carolina Institute for Developmental Disabilities*

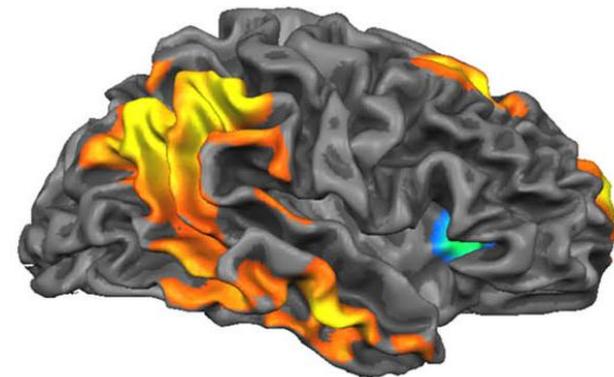
# Outline

- 1) Brief overview of translational neuroscience approaches including strengths and limitations
- 2) Overview of eyetracking methods & select autism findings
- 3) Overview of electrophysiology methods & major autism findings
- 4) Overview of fMRI methods & select autism findings

# Translational Neuroscience

Research designed to understand biological substrates of psychological / perceptual / cognitive / motor / emotional processes.

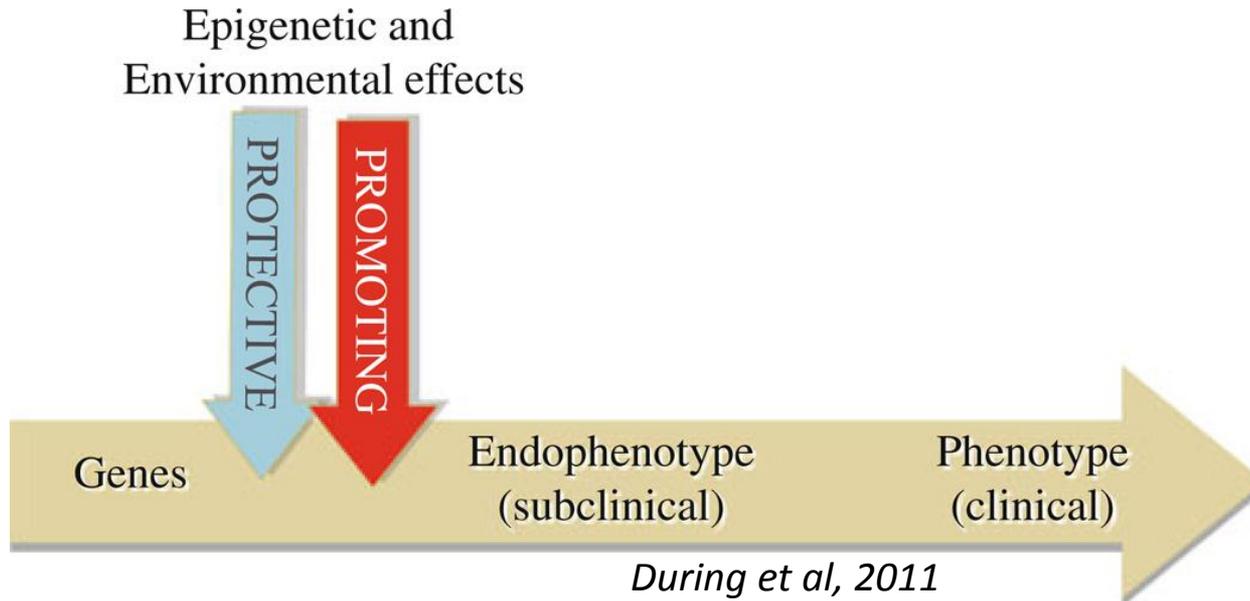
Typically uses specialized equipment to measure activity in the brain, ANS, or skelotomotor system.

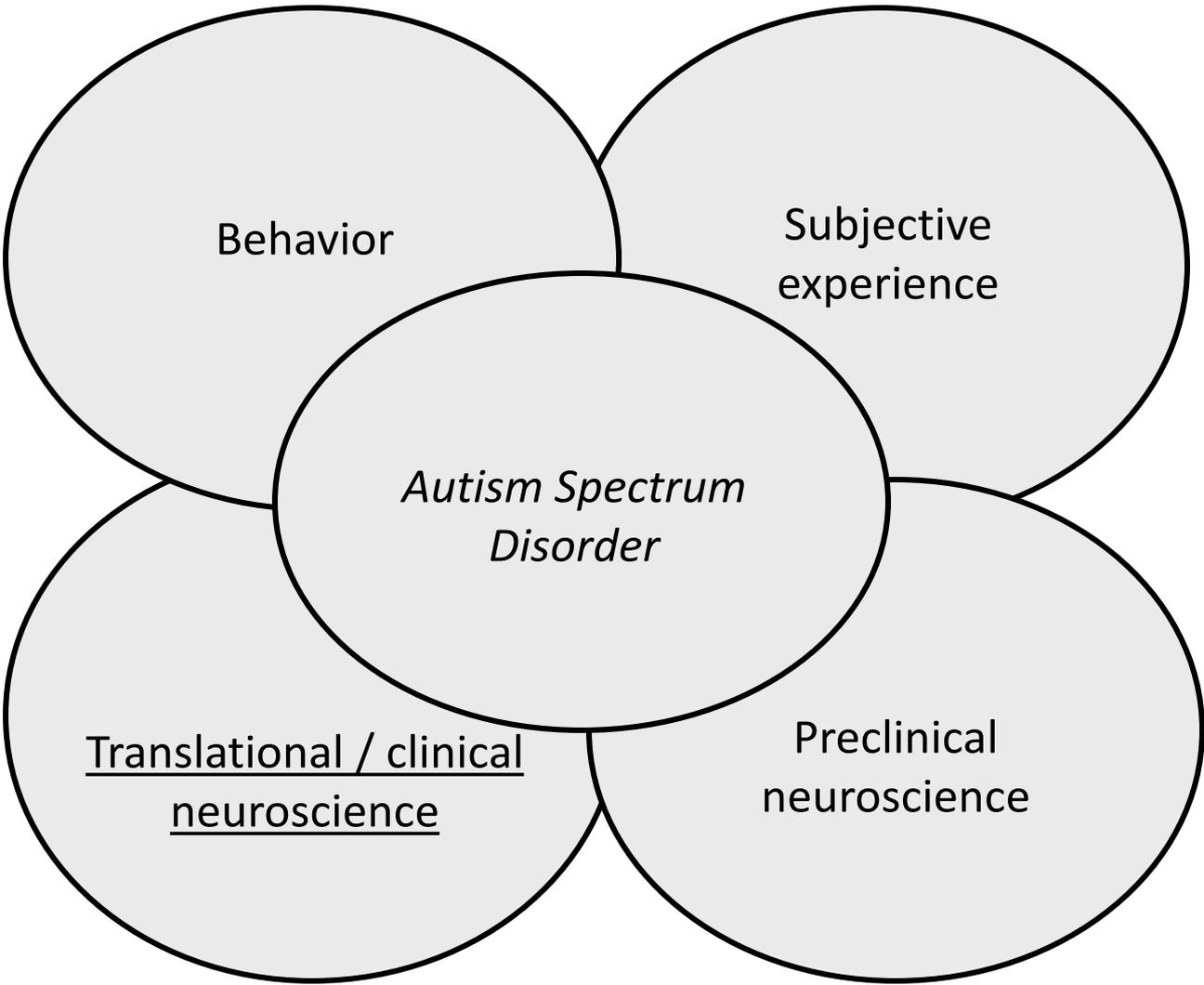


# Why Translational Neuroscience?

Translational neuroscience measure “**endophenotypes**”, intermediate traits that lie on the developmental pathway from genes to phenotype.

Such traits may be more proximal to etiology (e.g., genes) than downstream behavioral phenotypes, and thus may provide measures of causal mechanisms of psychiatric disorder.





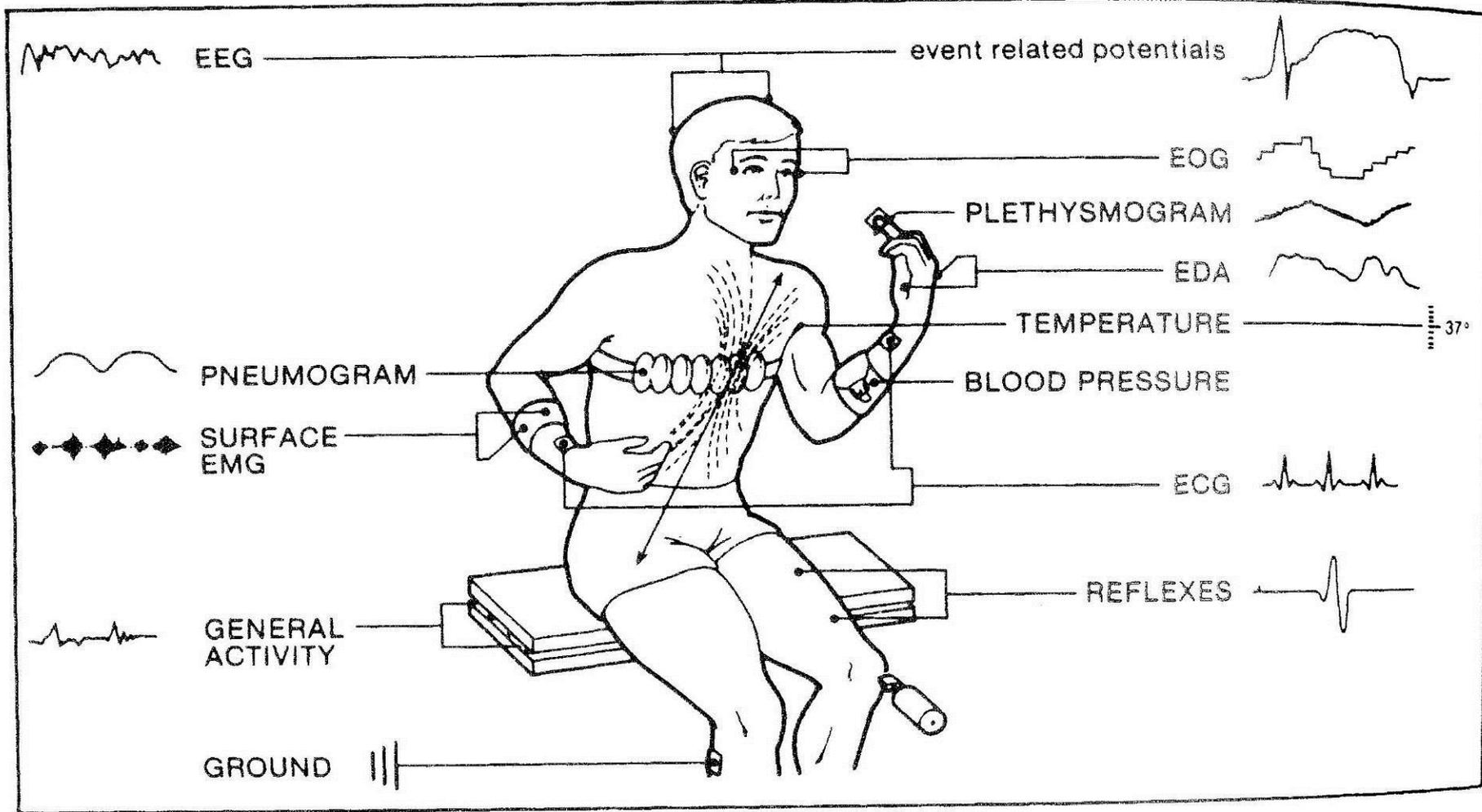
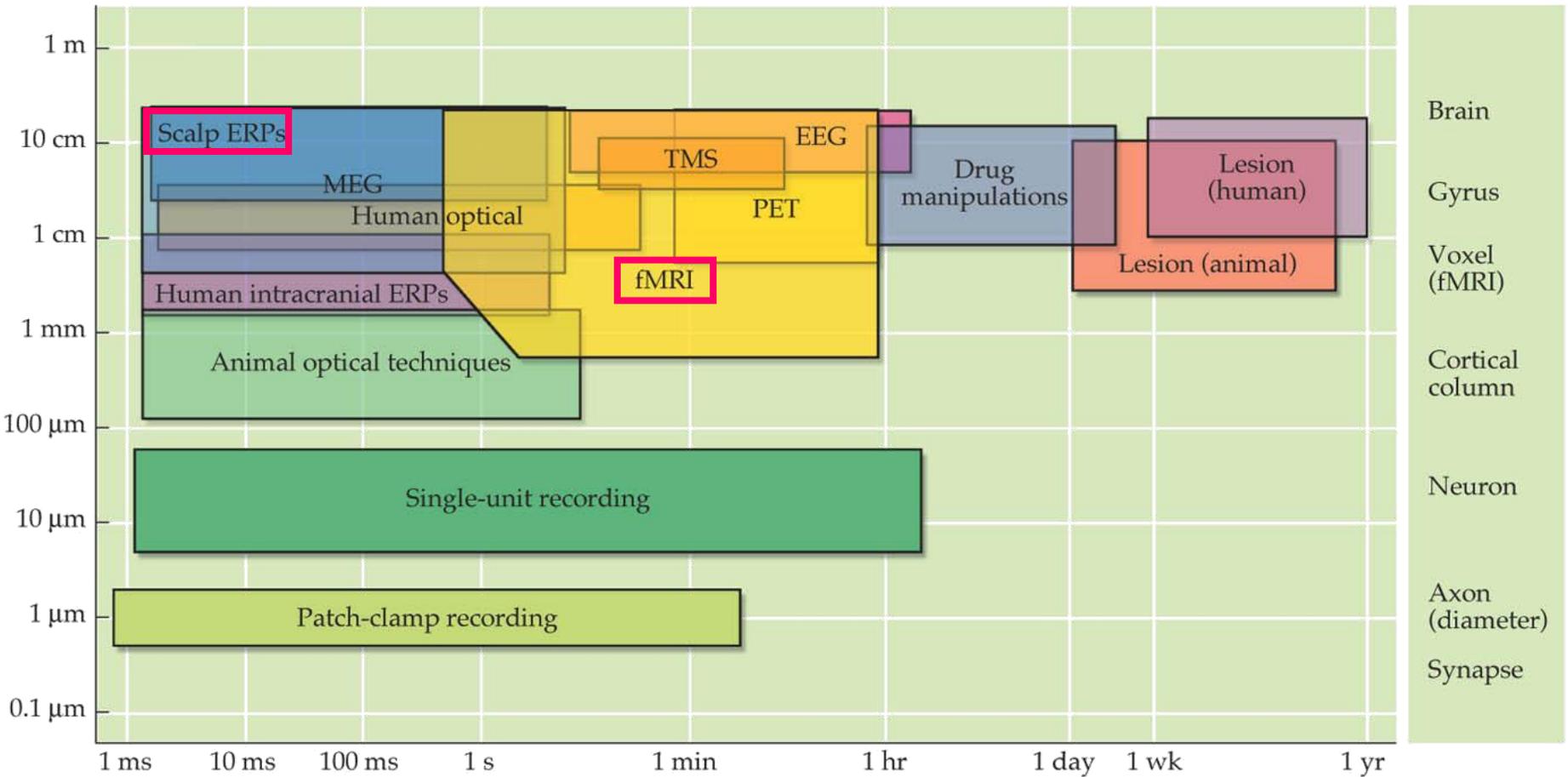


Figure 4.12. Commonly used measures in psychophysiological research. (Adapted with permission from J. Pillard, *Psychophysiologie du comportement*, Vol. 3, © Presses Universitaires de France, 1966, and reprinted in C. H. M. Brunia, *Activation*. In J. A. Michon, Eg G. J. Eijkman, & Len F. W. Klkerk (Eds.), *Handbook of psychonomics*, Vol. 1, © Amsterdam, North-Holland, 1979.)

# Temporal vs Spatial Resolution



# Questions Addressed

Neural Mechanisms of Pathophysiological Processes

*e.g., Describe brain function in children with ASD*

Genetics & Vulnerability Models

*e.g., Describe brain function in first-degree relatives*

Intervention Research (but be careful)

*e.g., What are the effects of treatment on brain function?*

Classification/Diagnosis/Subtyping (DSM-6 and beyond)

# Advantages of an endophenotypic approach

- Directly measure neurobiological processes
  - *Window into disease mechanism*
  - Decreased reliance on verbal reports
  - Sensitive to processes that are outside of awareness or are subthreshold
  - Well suited for studies addressing chronometry of responses

# Limitations of an endophenotypic approach

- Signal-to-noise limitations
  - e.g., sensitivity to electrical artifacts or motion
- Signal processing is time- and labor-intensive
- Questionable external and face validity
- Limited use in naturalistic context
- Psychometric issues (test-retest stability, construct validity, reliability).
- Not the gold-standard; not “unbiased”; verbal reports and behavior should not be overlooked.

# 1. Eyetracking



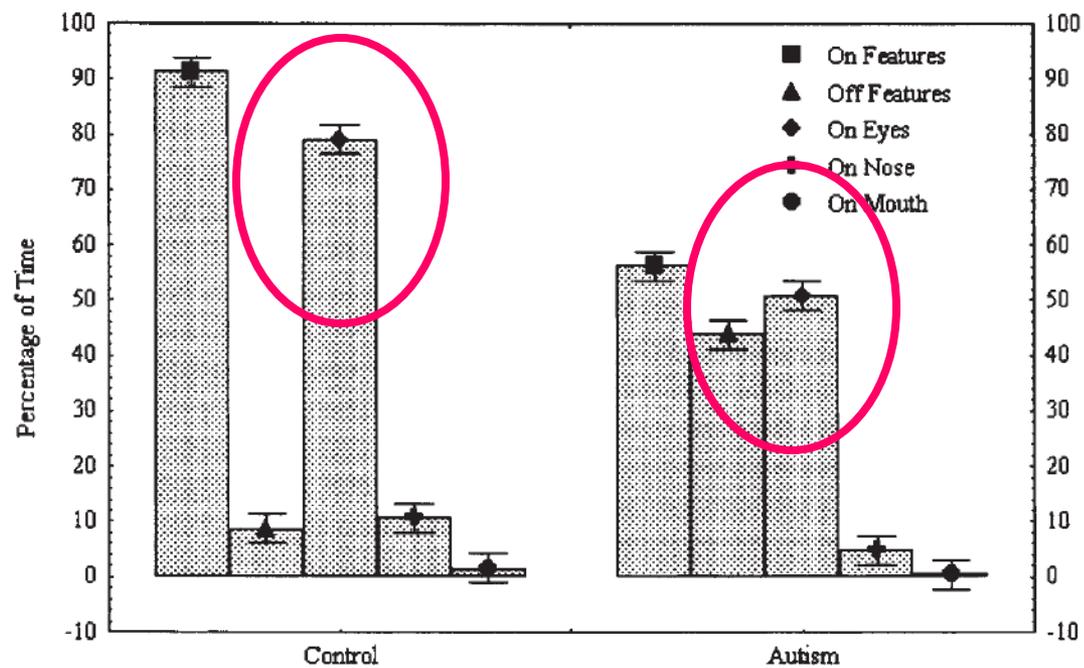
# Visual Scanning of Faces in Autism

Kevin A. Pelphrey,<sup>1,2,4</sup> Noah J. Sasson,<sup>1</sup> J. Steven Reznick,<sup>1</sup> Gregory Paul,<sup>3</sup>  
Barbara D. Goldman,<sup>1</sup> and Joseph Piven<sup>2,3</sup>

Autistic Group



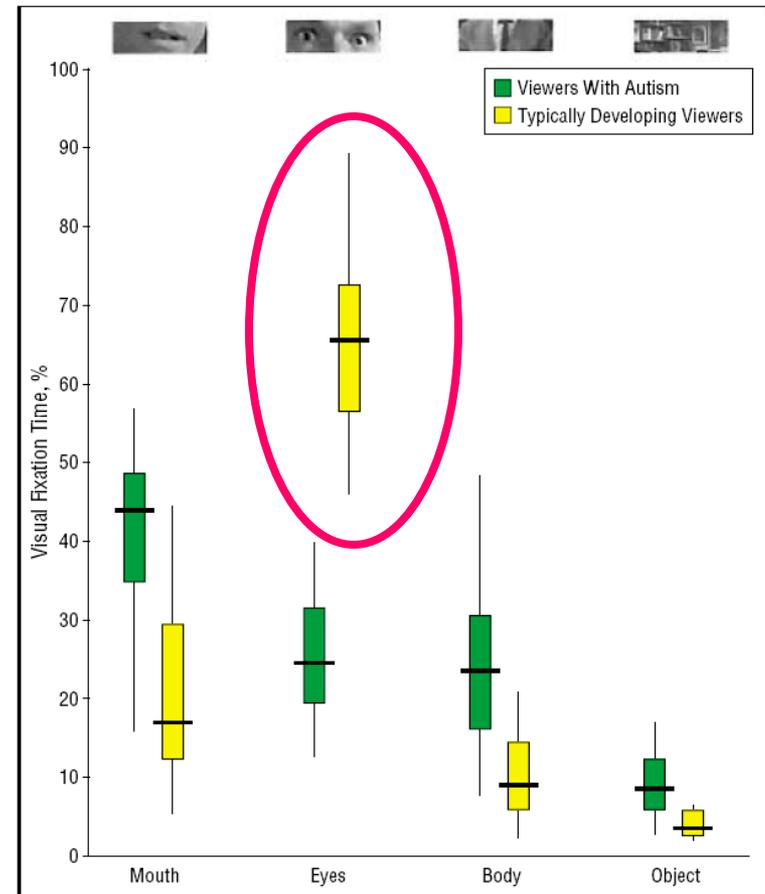
Control Group



# Visual Fixation Patterns During Viewing of Naturalistic Social Situations as Predictors of Social Competence in Individuals With Autism

Ami Klin, PhD; Warren Jones, BA; Robert Schultz, PhD; Fred Volkmar, MD; Donald Cohen, MD

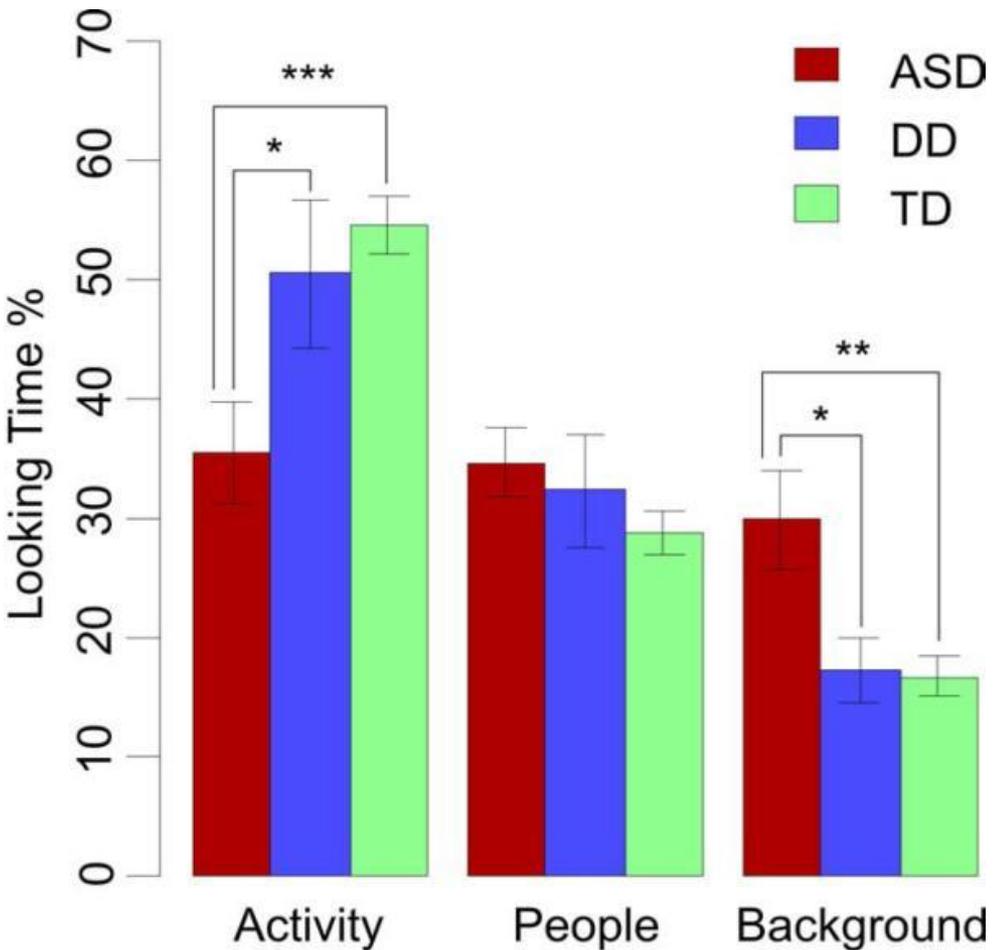
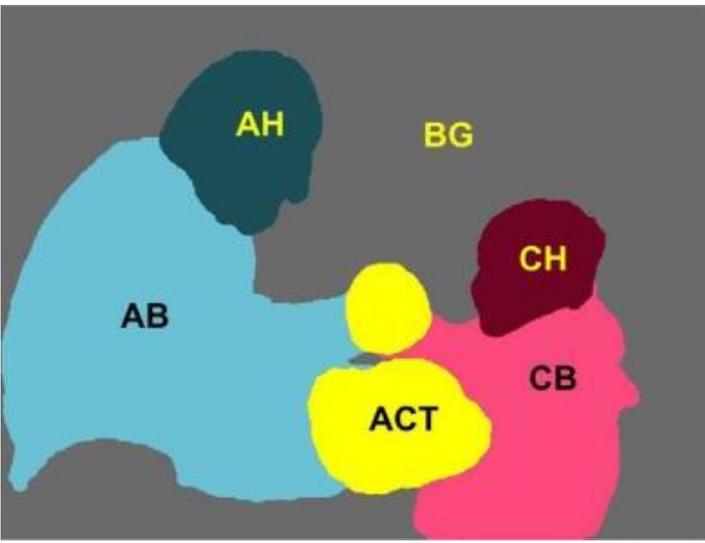
ARCH GEN PSYCHIATRY/VOL 59, SEP 2002



# Limited activity monitoring in toddlers with autism spectrum disorder

BRAIN RESEARCH 1380 (2011) 246-254

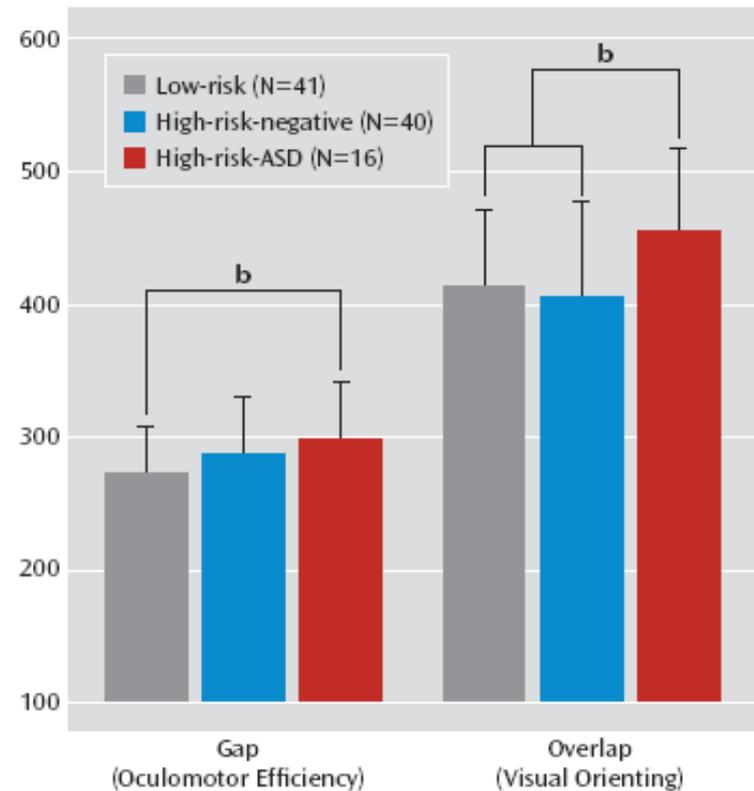
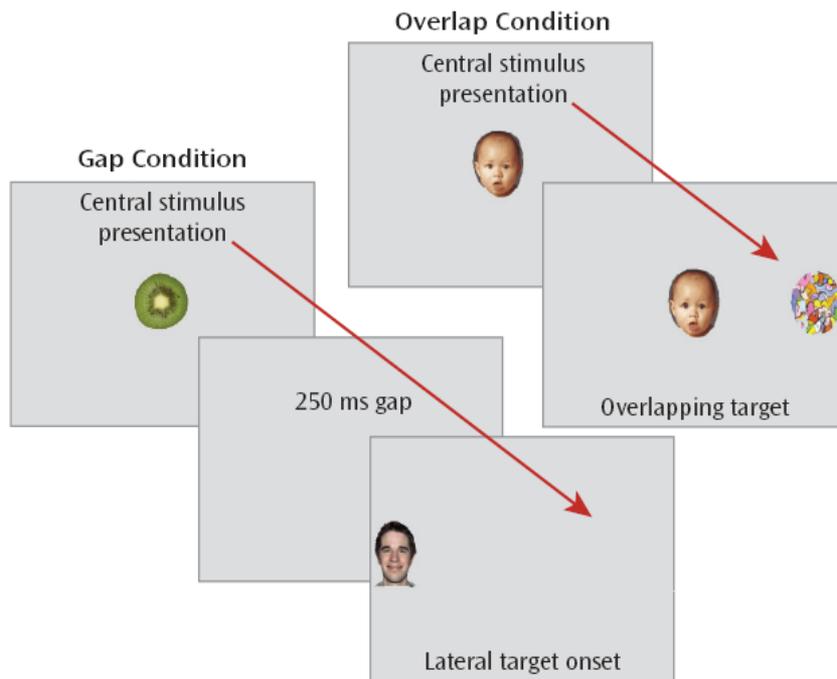
Frederick Shic<sup>a,\*</sup>, Jessica Bradshaw<sup>a</sup>, Ami Klin<sup>a</sup>, Brian Scassellati<sup>b</sup>, Katarzyna Chawarska<sup>a</sup>



# White Matter Microstructure and Atypical Visual Orienting in 7-Month-Olds at Risk for Autism (Am J Psychiatry 2013; 170:899–908)

Elison et al (IBIS Network)

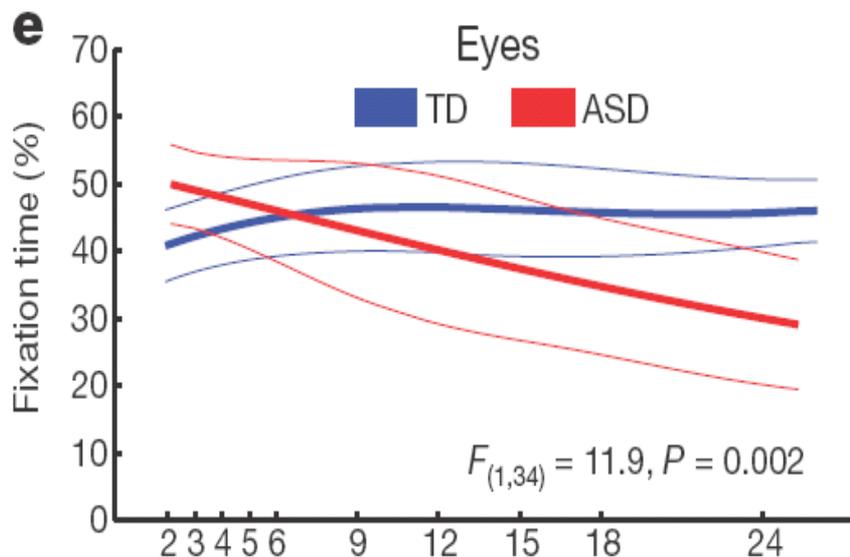
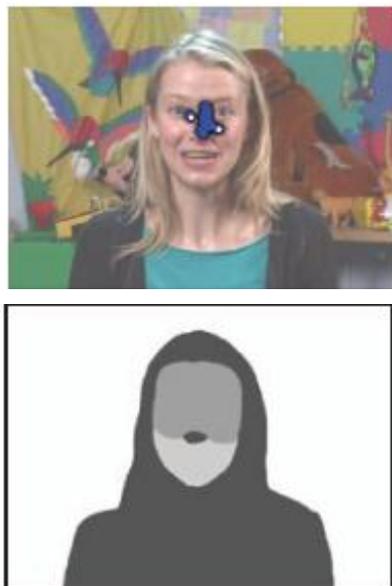
FIGURE 1. The Modified Gap/Overlap Procedure<sup>a</sup>



# Attention to eyes is present but in decline in 2–6-month-old infants later diagnosed with autism

Warren Jones<sup>1,2,3</sup> & Ami Klin<sup>1,2,3</sup>

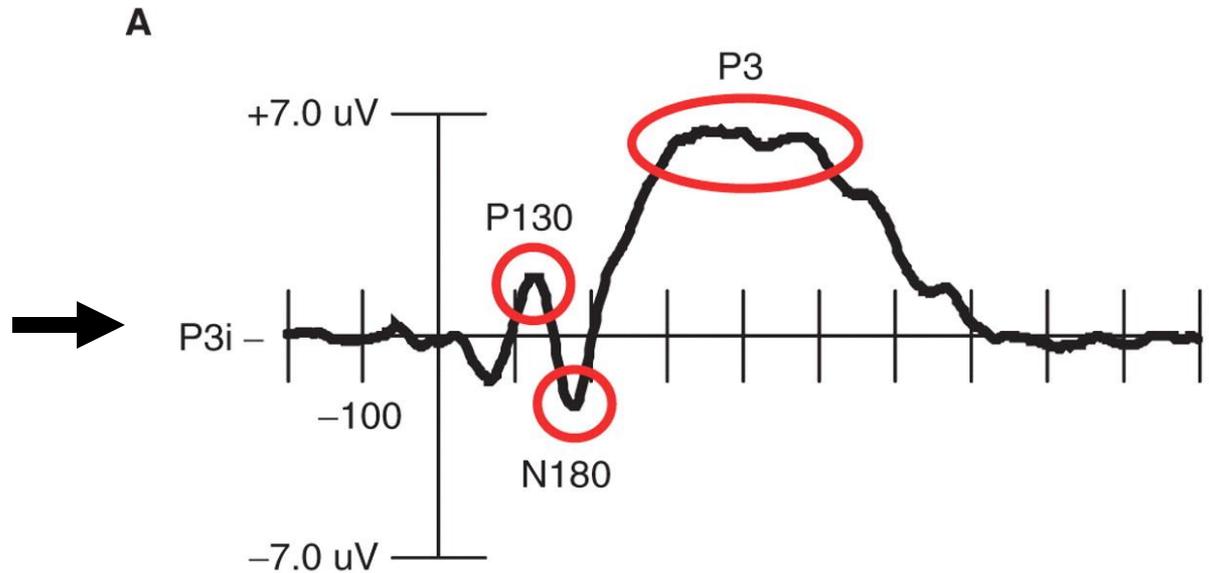
[doi:10.1038/nature12715](https://doi.org/10.1038/nature12715)



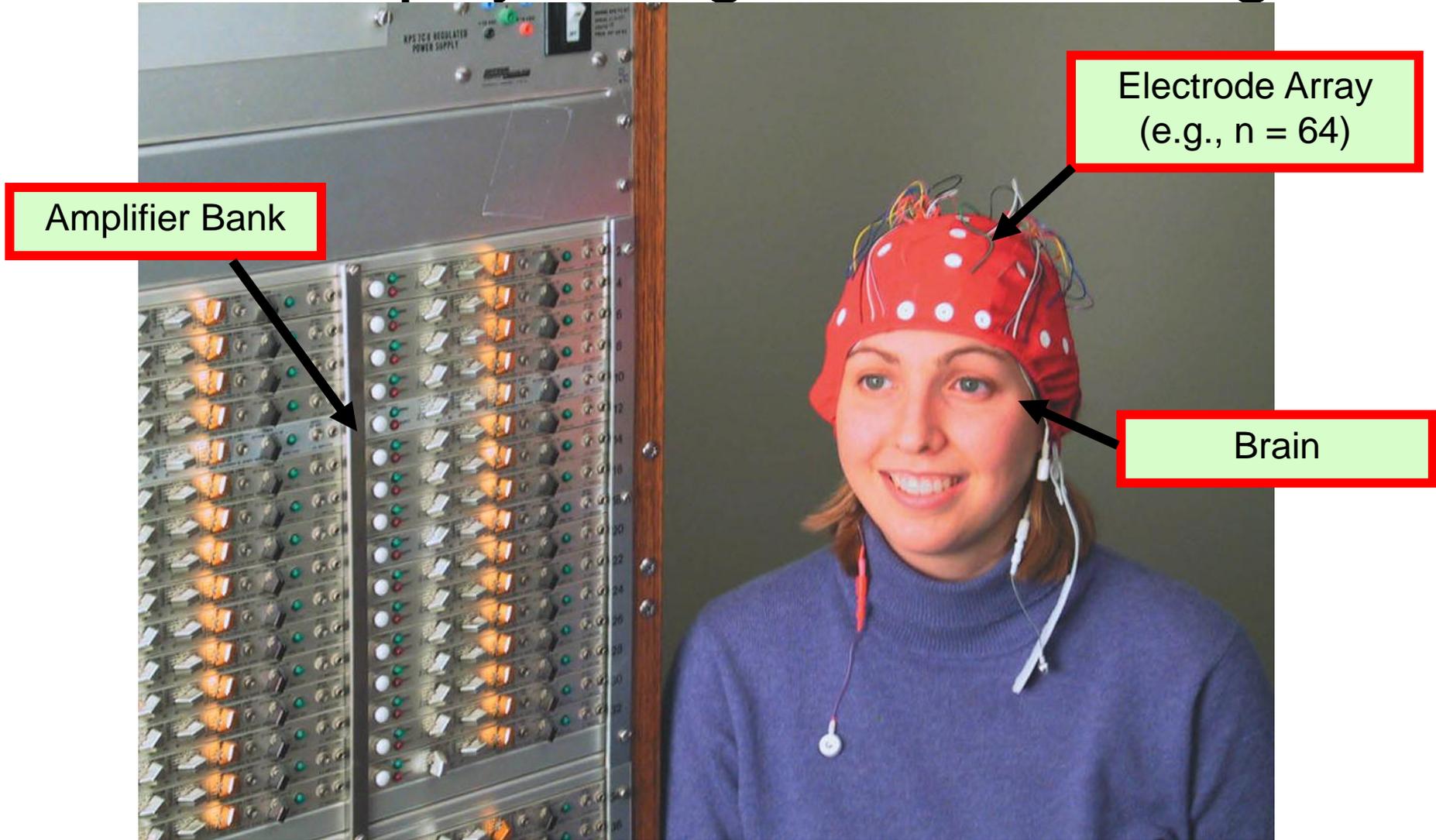
- Infants later diagnosed with ASDs showed decline in eye fixation from 2 - 6 months old
- Suggests a developmental window when disrupted social process may canalize social development.

# 2. Scalp-recorded electrophysiology

*Electroencephalography (EEG) & event-related potentials (ERPs)*



# Electrophysiological Recording



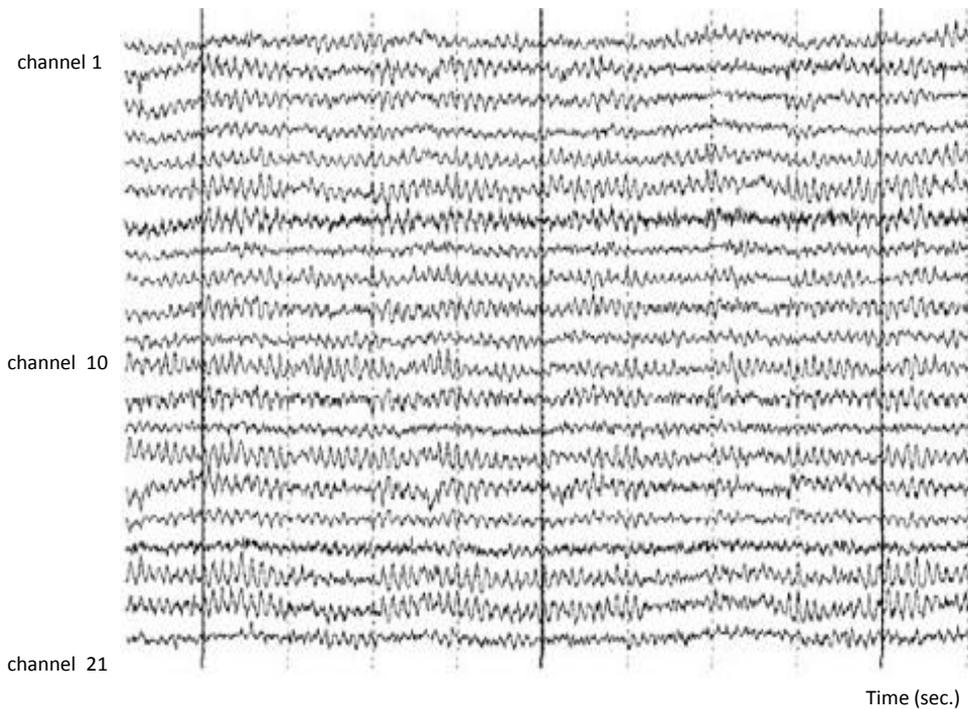


Collected by placing sensors (or electrodes) onto the scalp



Number of sensors can vary from a couple to over 300

*10 seconds of typical EEG activity  
from 21 channels recorded from a healthy adult*



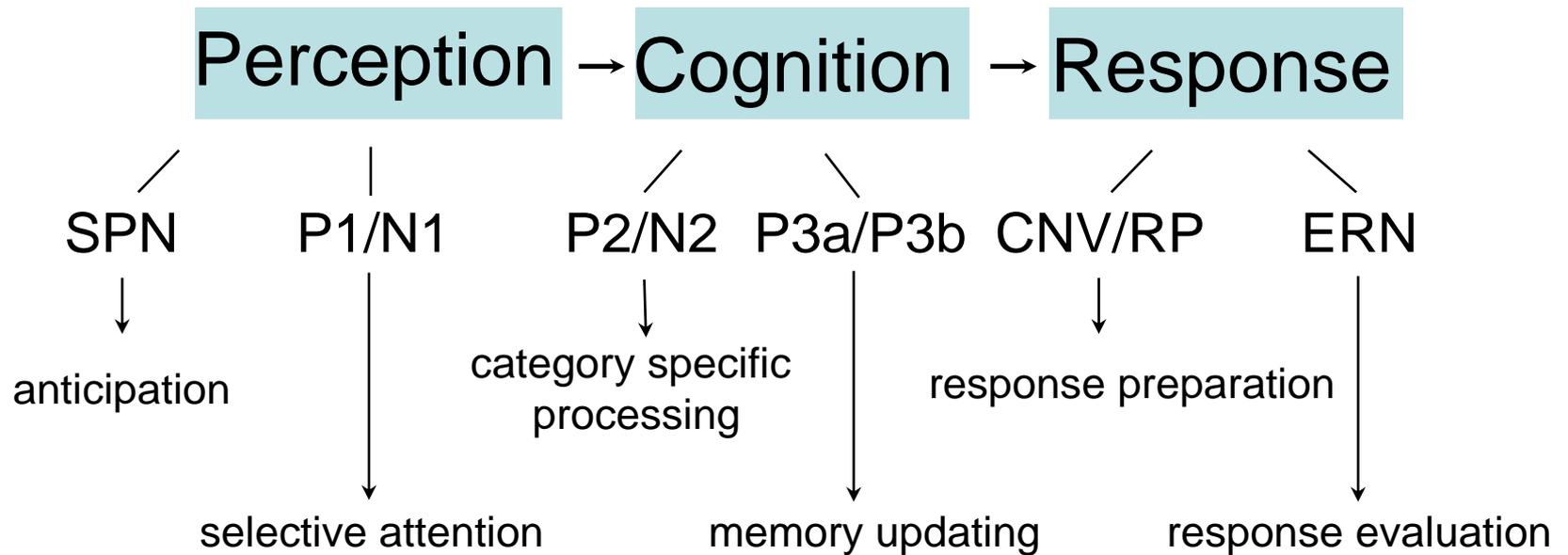
**Advantages:**

*EEG is a direct measure of  
brain activity*

*EEG has a very high time  
resolution (in ms range)*

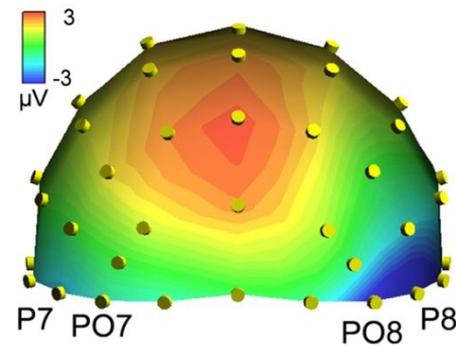
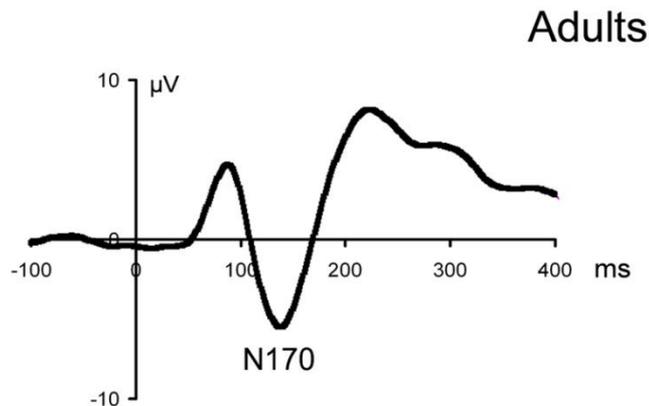
*EEG is relatively cheap*

# ERPs & information processing



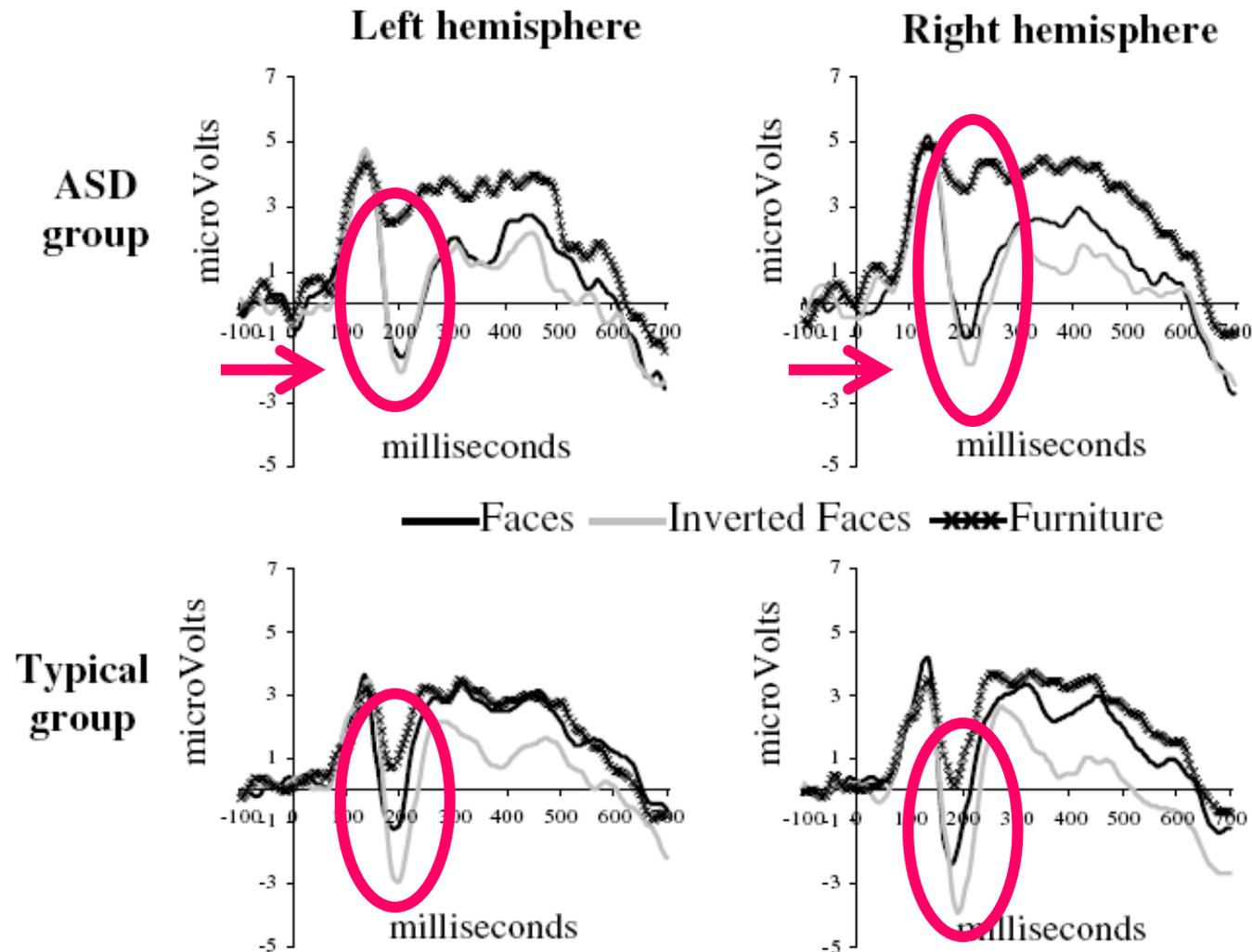
# ERPs of face processing in autism

- Face sensitive component (N170)
  - One of the earliest stages of face processing (by 3 months)
  - Structural encoding (recognizes a face as a face)
  - Sensitive to inversion & decomposition effects
- Also other components (e.g., N290, P400 and negative slow waves).



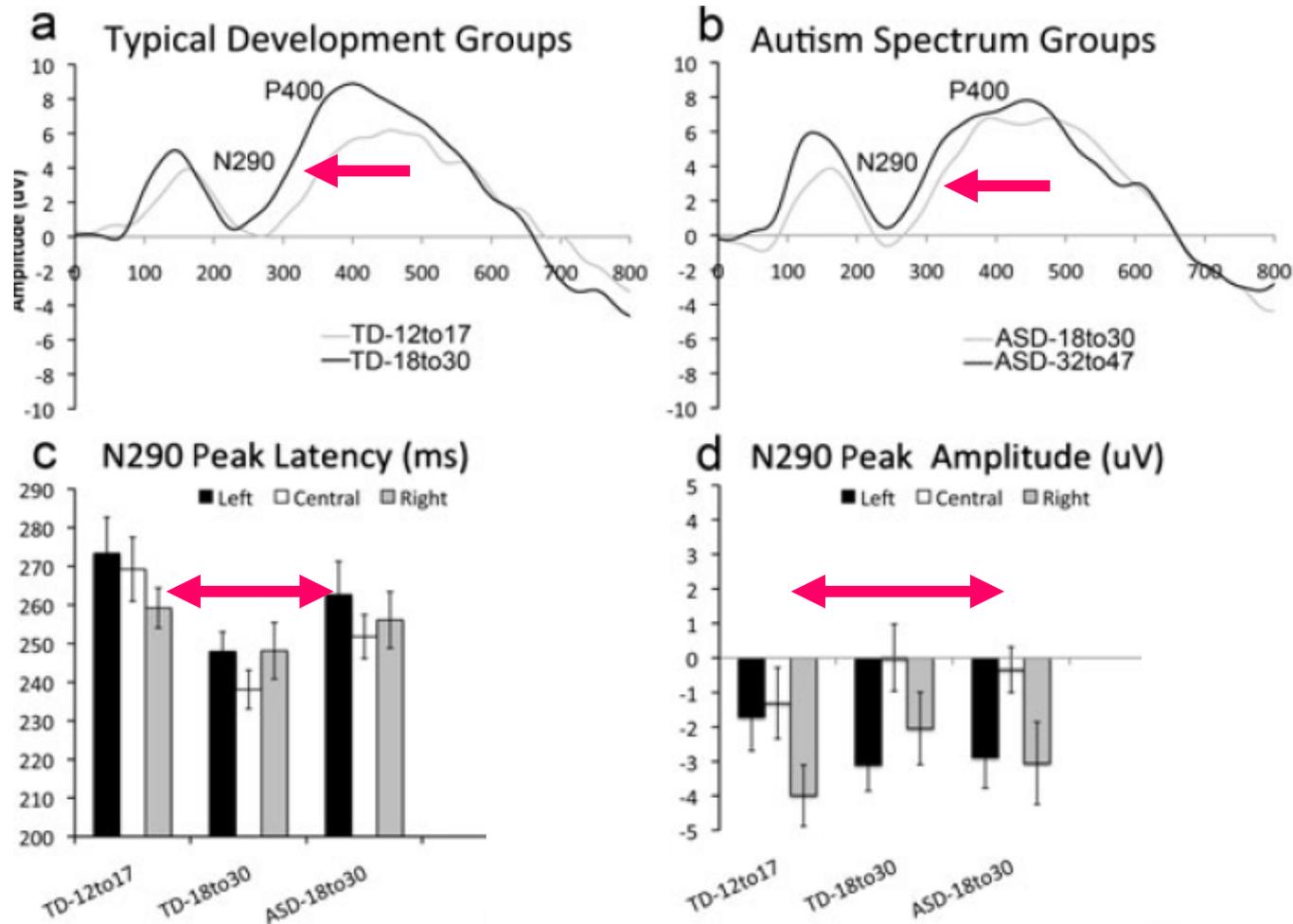
# ERPs of faces encoding in autism (N170)

(Upright vs inverted faces in adults → delayed N170 in ASD (15-42 yo))



# ERPs of face recognition in autism (N290)

Familiar vs unfamiliar faces in 18-47 month olds (Webb et al, 2011).

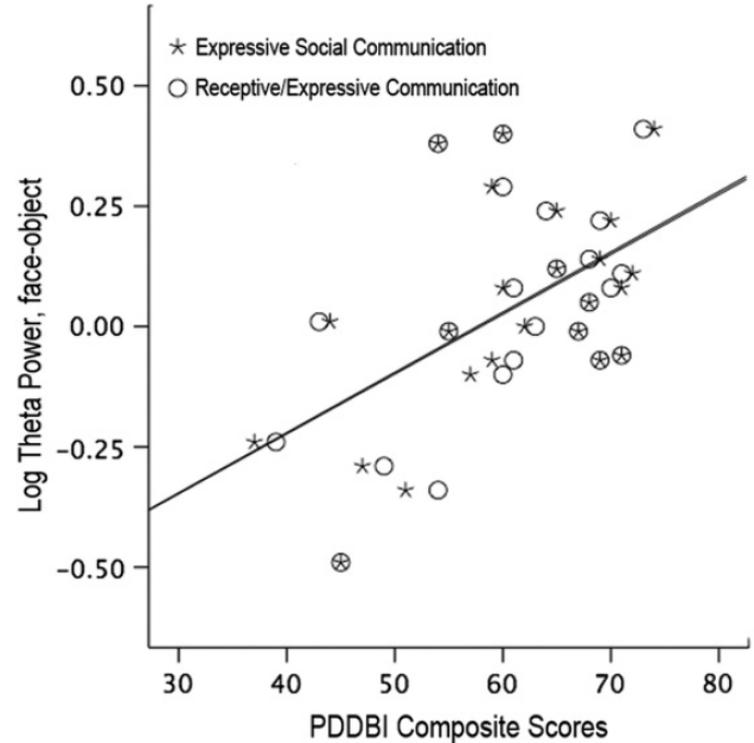
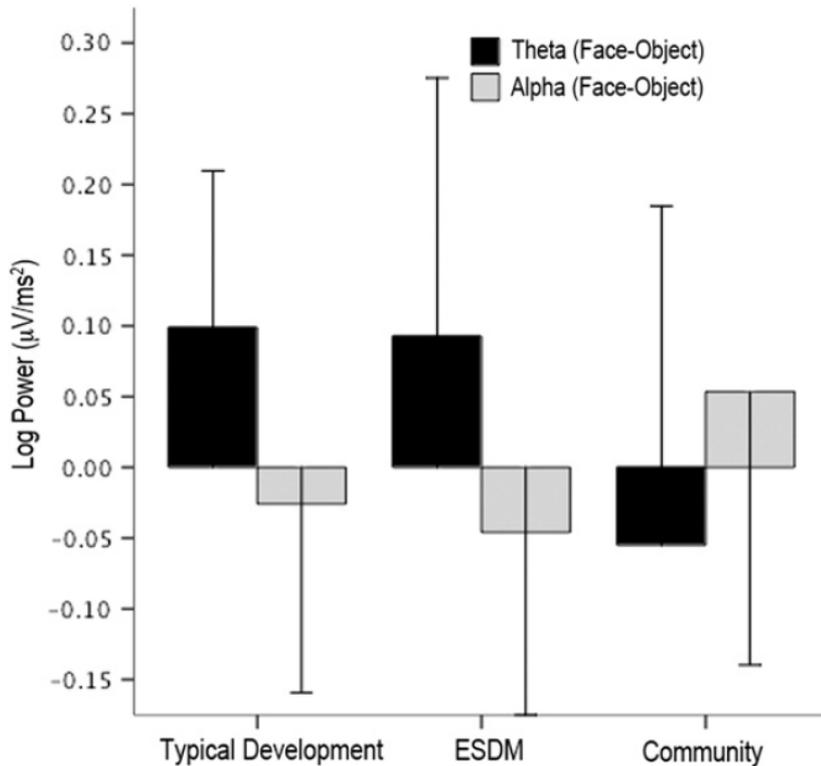


# Early Behavioral Intervention Is Associated With Normalized Brain Activity in Young Children With Autism

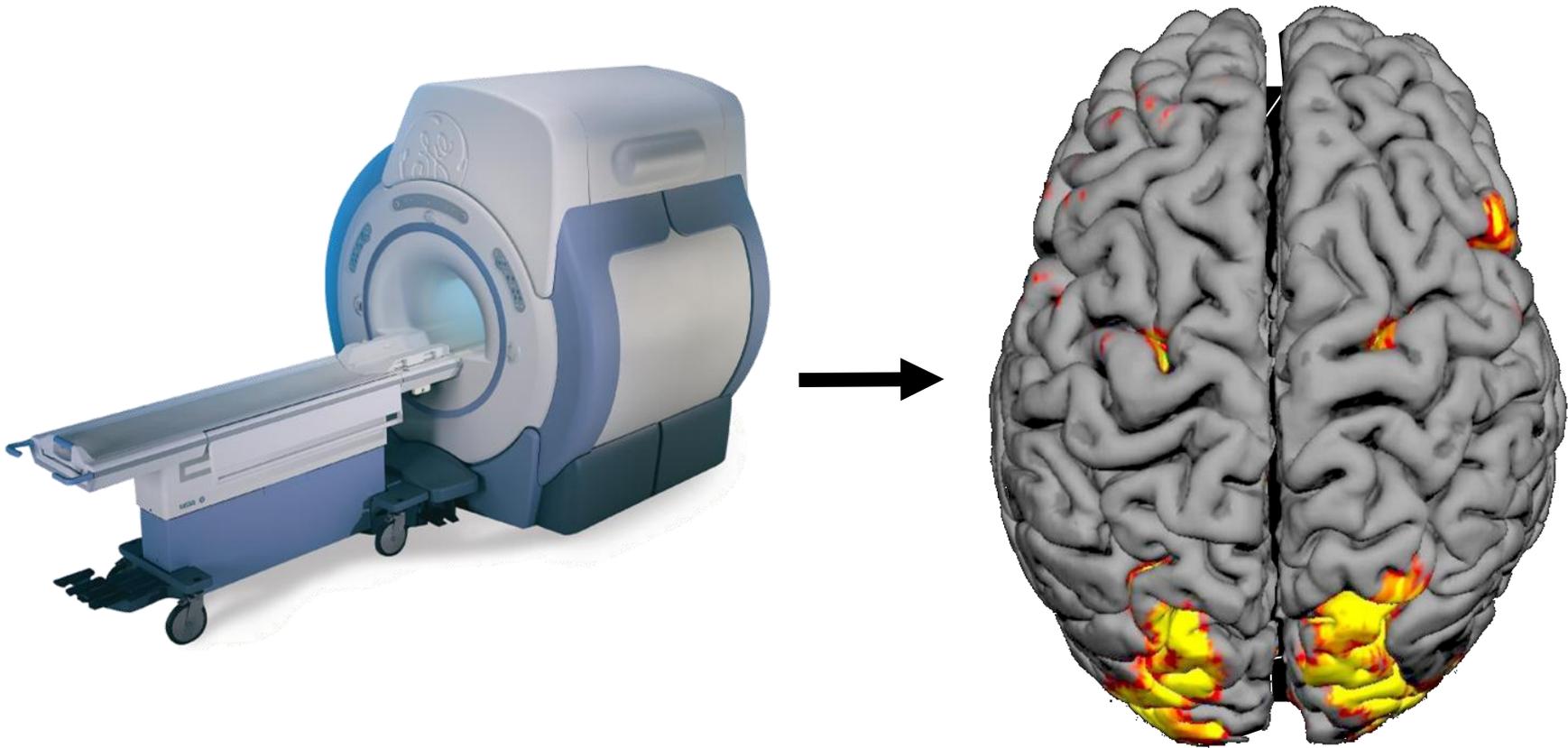
Geraldine Dawson, Ph.D., Emily J.H. Jones, Ph.D., Kristen Merkle, B.S., Kaitlin Venema, B.S., Rachel Lowy, B.S., Susan Faja, Ph.D., Dana Kamara, B.S., Michael Murias, Ph.D., Jessica Greenson, Ph.D., Jamie Winter, Ph.D., Milani Smith, Ph.D., Sally J. Rogers, Ph.D., Sara J. Webb, Ph.D.

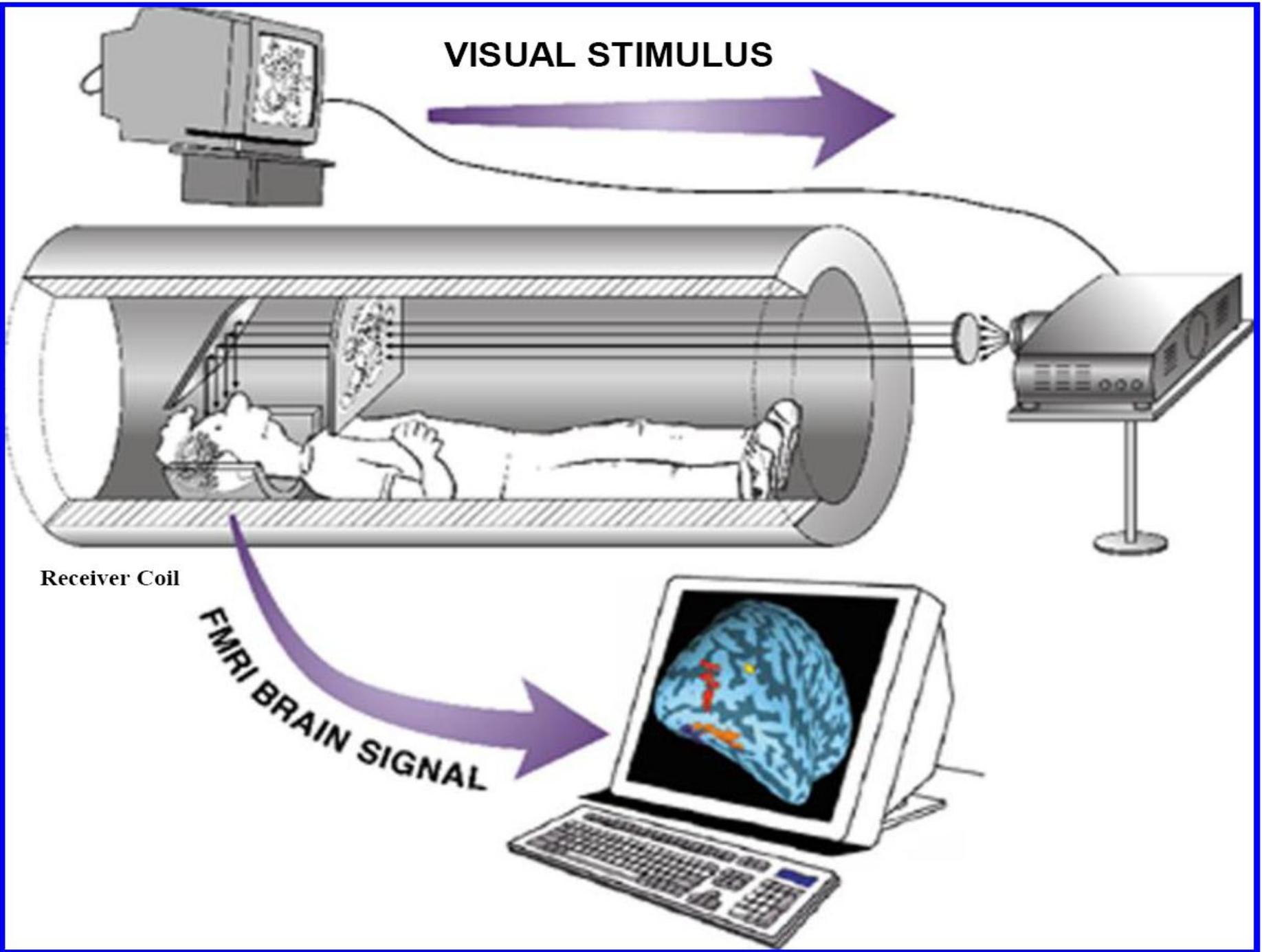
JAACAP, 2012

EEG & ERP to faces & objects in 4-6 year old who received ESDM vs TAU for 2 years.



# 3. Functional Neuroimaging (fMRI)





# Synopsis of MRI

**M:** Put subject in strong magnetic field

**R:** Transmit radio waves into subject, turn off transmitter, receive radio waves emitted by subject's brain. This is the MR signal.

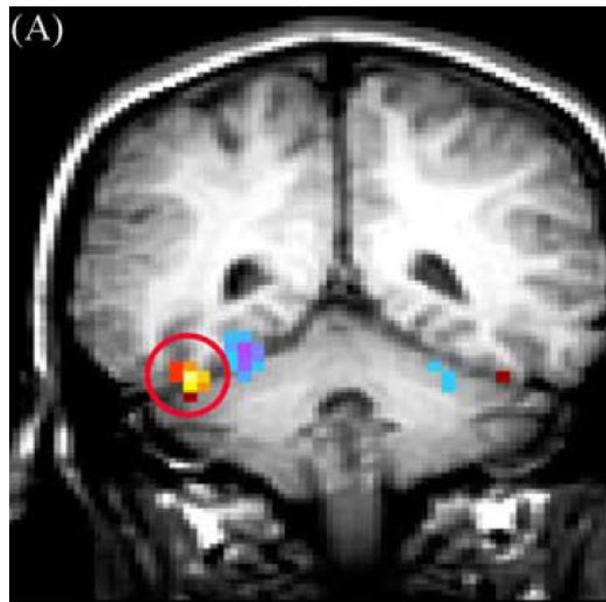
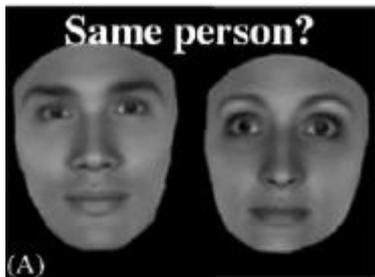
**I:** Translate the emitted MR signal into brain images.



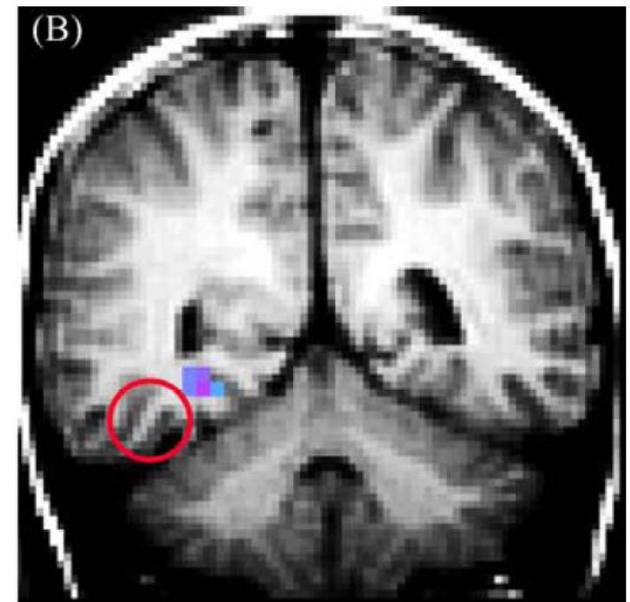
# fMRI of Autism: Face Processing

“Fusiform Face Area” is responsive to faces in typical development (Kanwisher, 1997)

Activation of FFA is disrupted in autism (Schultz, 2005 and >20 other studies)



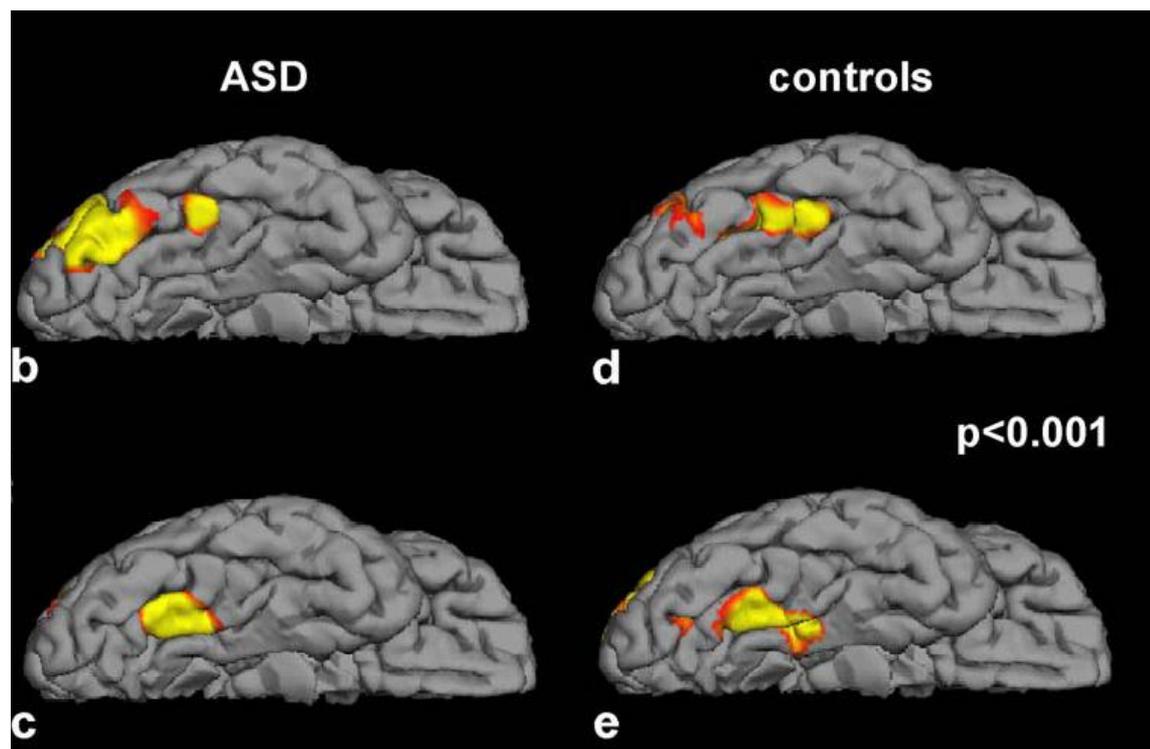
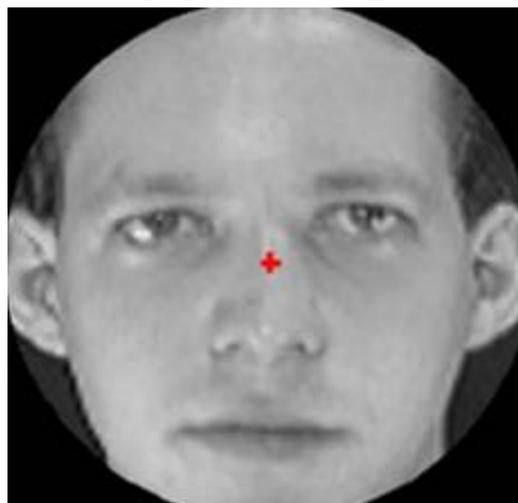
TD



ASD

## Activation of the fusiform gyrus when individuals with autism spectrum disorder view faces

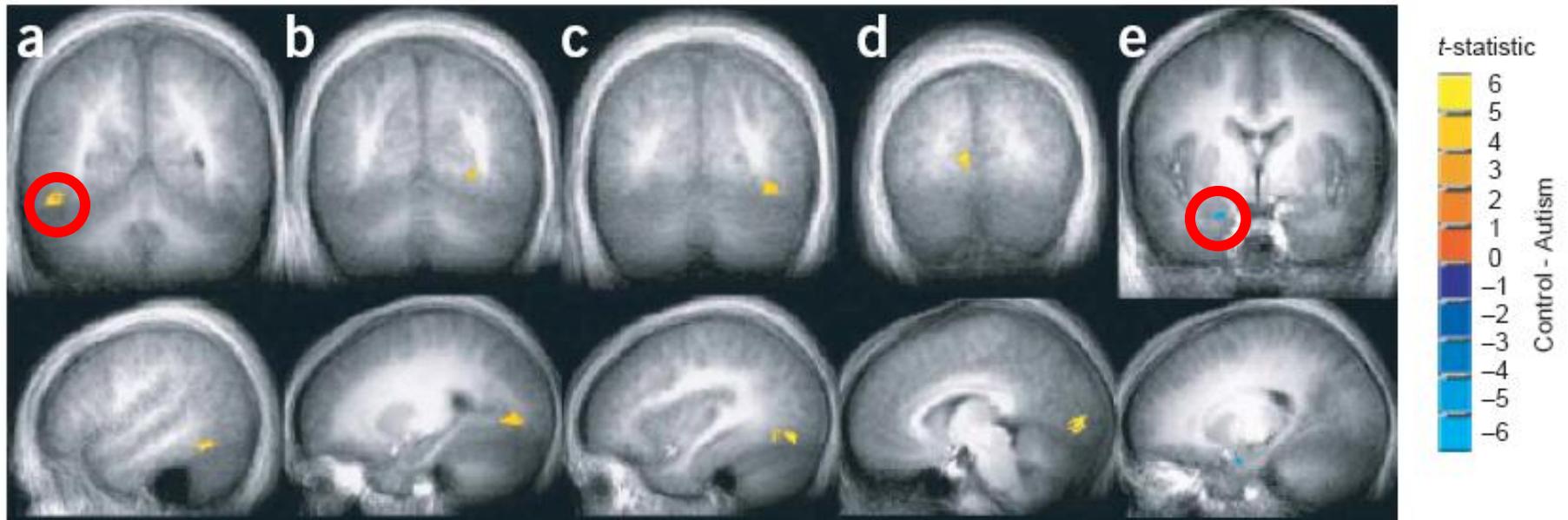
Nouchine Hadjikhani,<sup>a,\*</sup> Robert M. Joseph,<sup>b</sup> Josh Snyder,<sup>a</sup> Christopher F. Chabris,<sup>c</sup> Jill Clark,<sup>a</sup> Shelly Steele,<sup>b</sup> Lauren McGrath,<sup>b</sup> Mark Vangel,<sup>a</sup> Itzhak Aharon,<sup>a</sup> Eric Feczko,<sup>d</sup> Gordon J. Harris,<sup>d</sup> and Helen Tager-Flusberg<sup>b</sup>



# Gaze fixation and the neural circuitry of face processing in autism

nature  
neuroscience

Kim M Dalton<sup>1,2</sup>, Brendon M Nacewicz<sup>2</sup>, Tom Johnstone<sup>2</sup>, Hillary S Schaefer<sup>2</sup>, Morton Ann Gernsbacher<sup>1,3</sup>,  
H H Goldsmith<sup>1,3</sup>, Andrew L Alexander<sup>1,2,4</sup> & Richard J Davidson<sup>1-4</sup>



↑  
*Underactive "Face Area"*

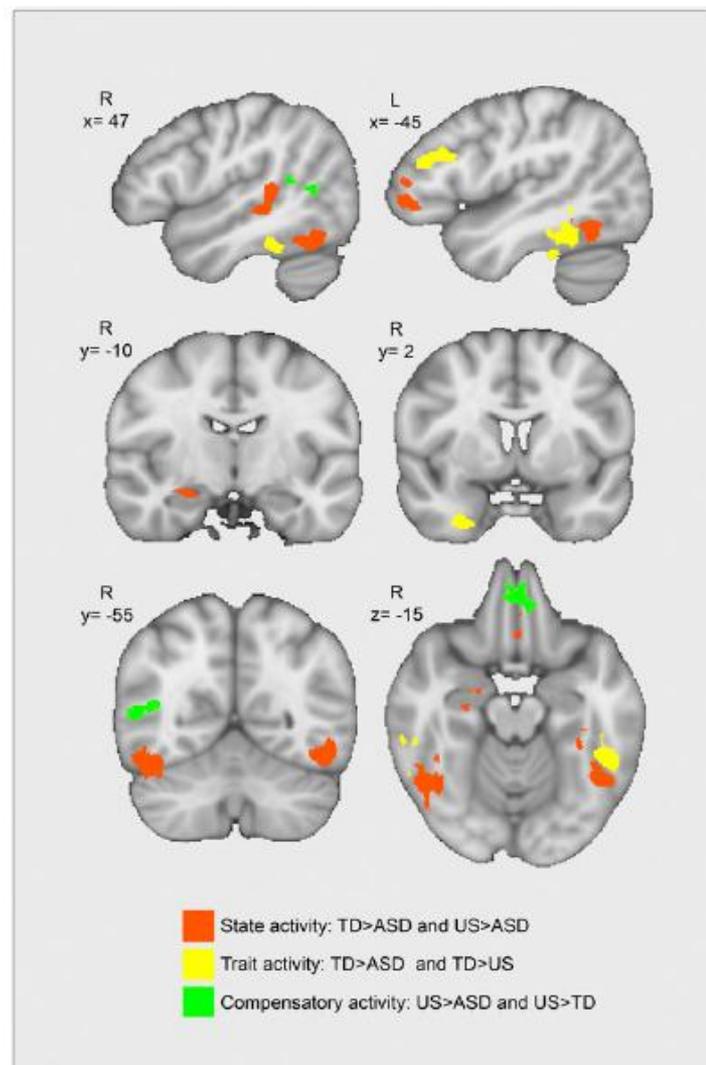
↑  
*Overactive Amygdala*

# Neural signatures of autism

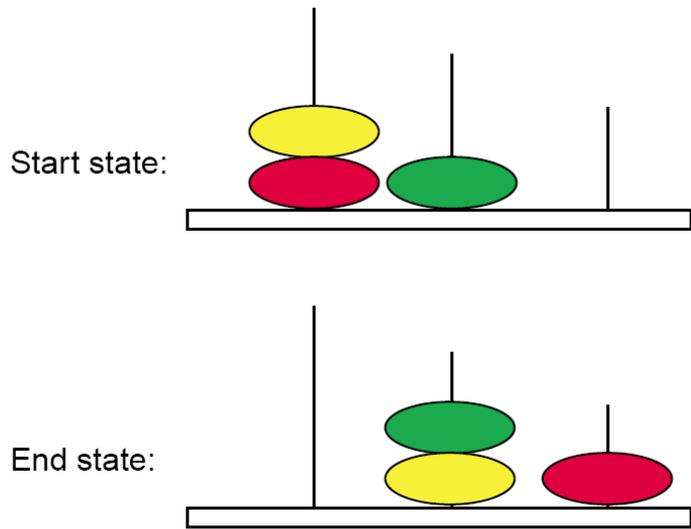
Martha D. Kaiser<sup>a</sup>, Caitlin M. Hudac<sup>a</sup>, Sarah Shultz<sup>a,b</sup>, Su Mei Lee<sup>a,b</sup>, Celeste Cheung<sup>a</sup>, Allison M. Berken<sup>a</sup>, Ben Deen<sup>a</sup>, Naomi B. Pitskel<sup>a</sup>, Daniel R. Sugrue<sup>a</sup>, Avery C. Voos<sup>a</sup>, Celine A. Saulnier<sup>a</sup>, Pamela Ventola<sup>a</sup>, Julie M. Wolf<sup>a</sup>, Ami Klin<sup>a</sup>, Brent C. Vander Wyk<sup>a</sup>, and Kevin A. Pelphrey<sup>a,b,1</sup>

<sup>a</sup>Yale Child Study Center, Yale School of Medicine, New Haven, CT 06520, and <sup>b</sup>Department of Psychology, Yale University, New Haven, CT 06520

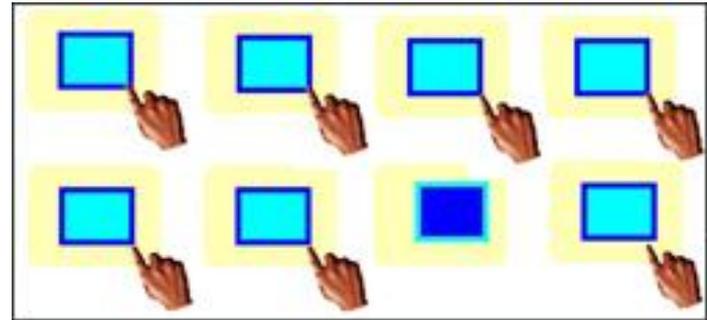
Measure	TD	US	ASD
Sex, males: females, n	12:5	9:11	20:5
Age, years, (range)	10.9 (3.1) [4.6–16.7]	11.3 (2.8) [6.6–16.9]	11.8 (3.6) [4.0–17.7]
SRS, total raw score	23.7 (14.5)	18.9 (15.3)	98.7 (23.5)



# fMRI of Autism: Cognitive Control



Tower task

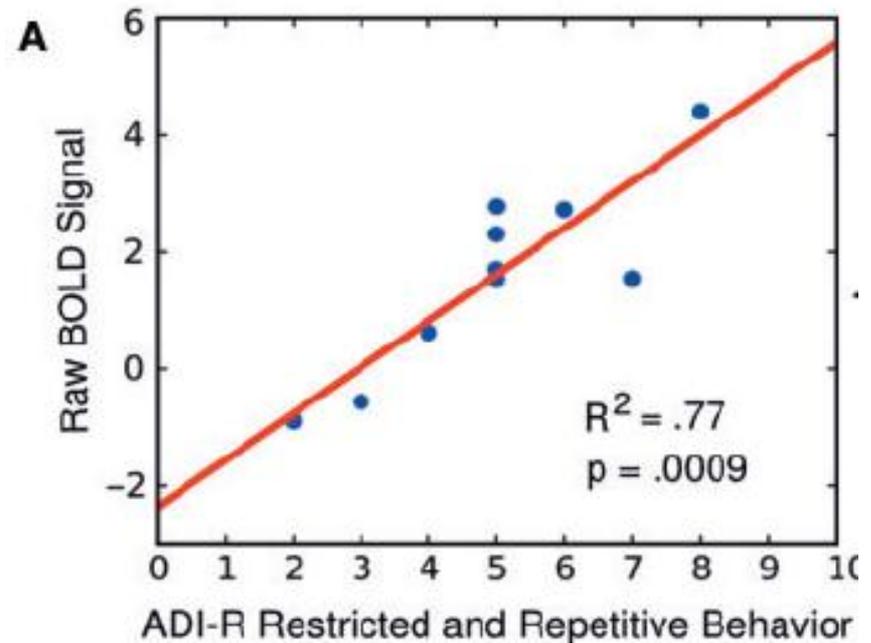
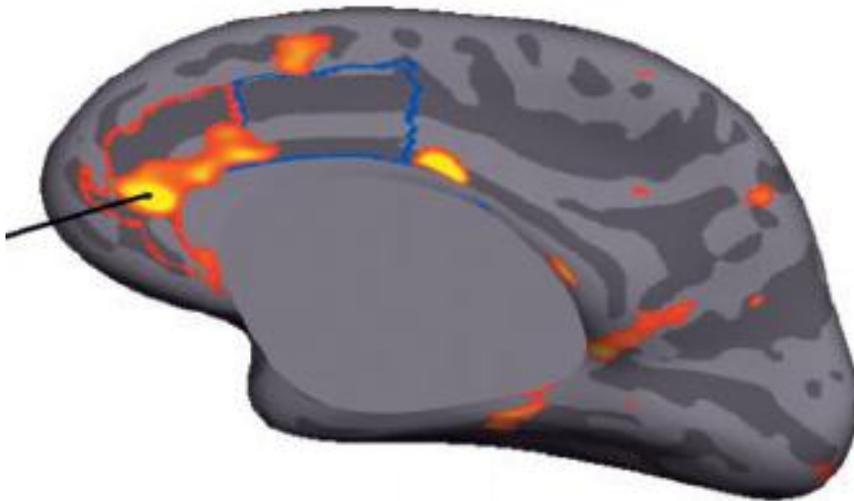


Go/NoGo task

Linkages to restricted & repetitive behaviors in autism due to functions of frontostriatal brain systems.

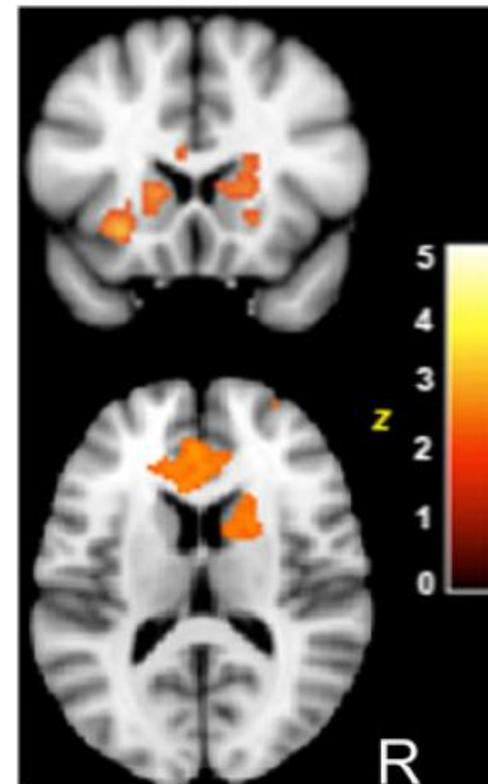
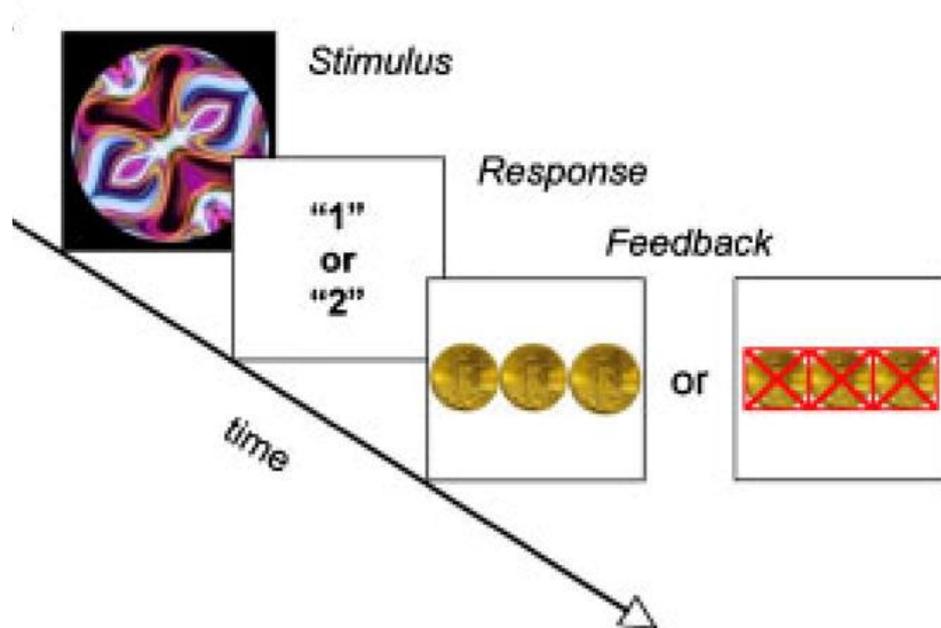
# Response monitoring, repetitive behaviour and anterior cingulate abnormalities in autism spectrum disorders (ASD)

Katharine N. Thakkar,<sup>1</sup> Frida E. Polli,<sup>1,2</sup> Robert M. Joseph,<sup>3</sup> David S. Tuch,<sup>4,5,6</sup> Nouchine Hadjikhani,<sup>4,5,6</sup> Jason J. S. Barton<sup>7,8</sup> and Dara S. Manoach<sup>1,5,6</sup>



## Reward Processing in Autism

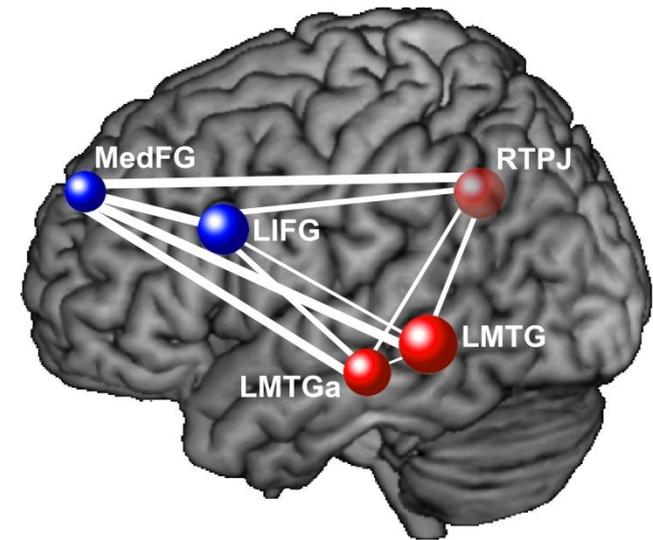
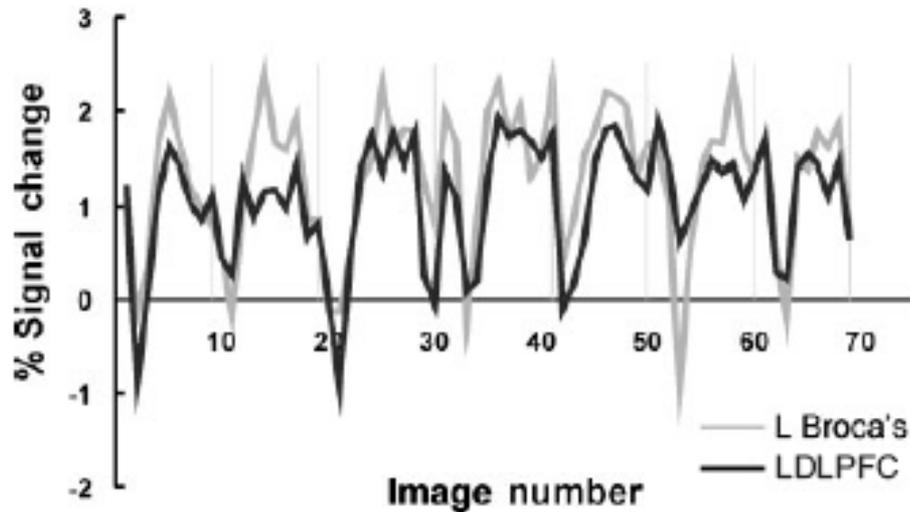
Ashley A. Scott-Van Zeeland, Mirella Dapretto, Dara G. Ghahremani, Russell A. Poldrack, and Susan Y. Bookheimer



**Figure 5.** Between-group differences in response to socially rewarded learning trials. TD>ASD deterministic social rewards vs. rest. MNI coordinates,  $z = 14$ .  $Z > 1.96$ ,  $P < 0.05$  cluster corrected.

# Autism as a Disorder of Functional Brain Disconnectivity

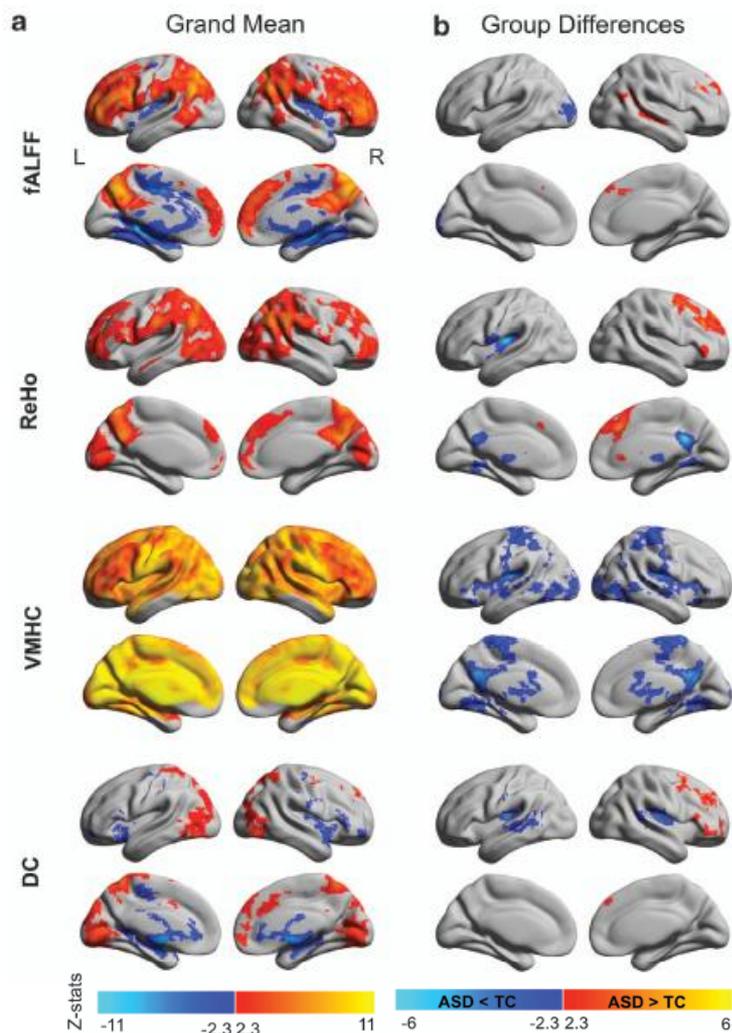
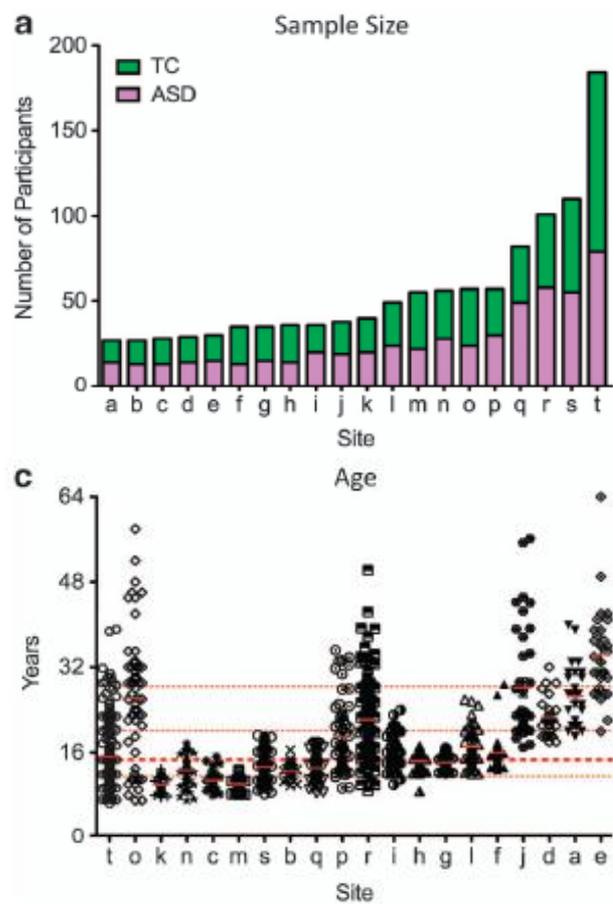
Synchronization of activation across brain regions reflects circuit-level activity (areas that “work together”)



*Line widths reflect magnitude of group differences (Mason et al., 2008)*

# The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism

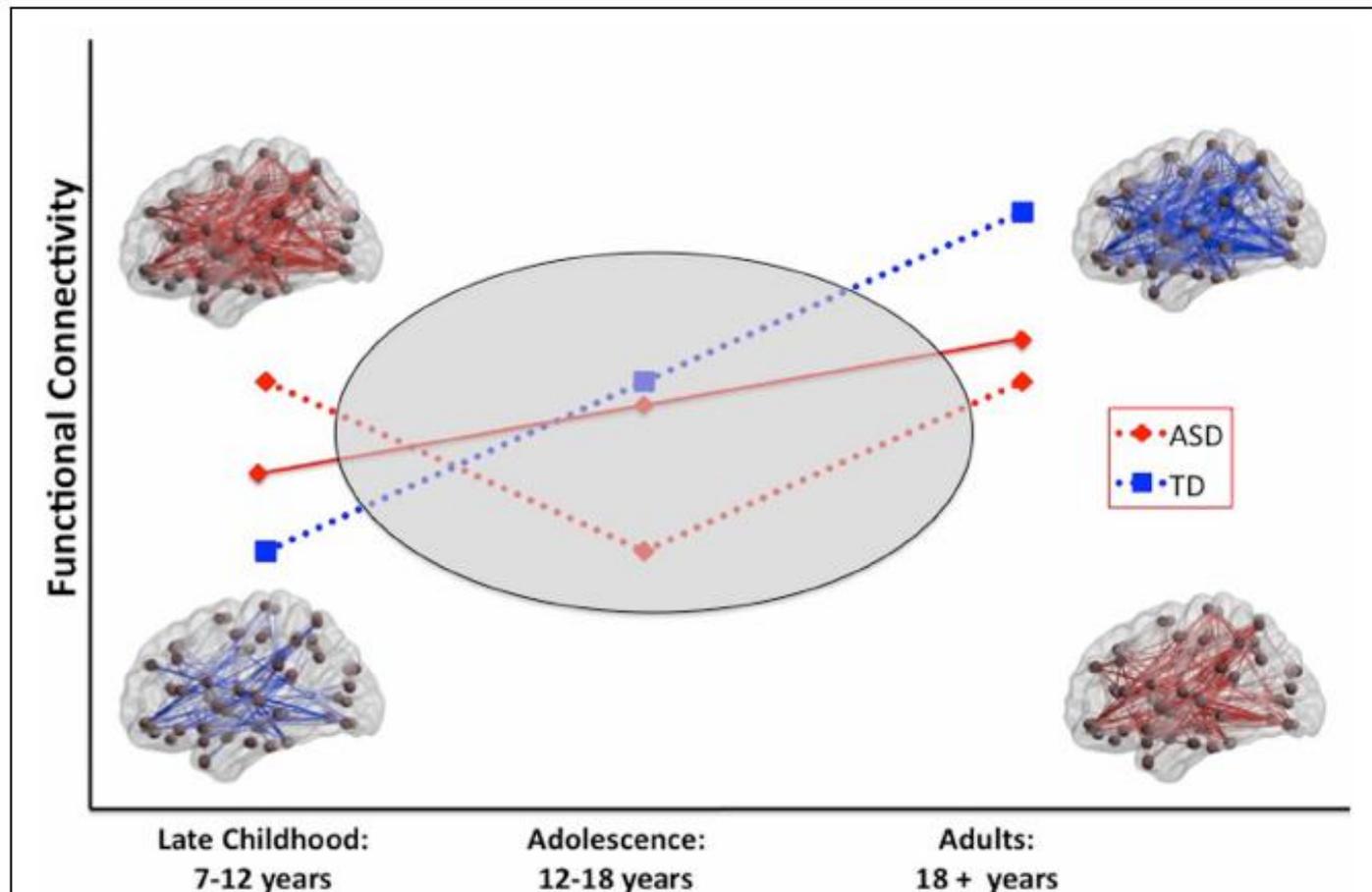
A Di Martino<sup>1</sup>, C-G Yan<sup>2,39</sup>, Q Li<sup>3,39</sup>, E Denio<sup>1</sup>, FX Castellanos<sup>1,2</sup>, K Alaerts<sup>1,4</sup>, JS Anderson<sup>5,6,7,8</sup>, M Assaf<sup>9,10</sup>, SY Bookheimer<sup>11,12,13,14</sup>, M Dapretto<sup>12,13,15</sup>, B Deen<sup>10,16</sup>, S Delmonte<sup>17</sup>, I Dinstein<sup>18,19</sup>, B Ertl-Wagner<sup>20</sup>, DA Fair<sup>21</sup>, L Gallagher<sup>17</sup>, DP Kennedy<sup>22,23</sup>, CL Keown<sup>24</sup>, C Keyers<sup>25,26</sup>, JE Lainhart<sup>27,28</sup>, C Lord<sup>29</sup>, B Luna<sup>30</sup>, V Menon<sup>31</sup>, NJ Minshew<sup>32</sup>, CS Monk<sup>33</sup>, S Mueller<sup>20</sup>, R-A Müller<sup>24</sup>, MB Nebel<sup>34</sup>, JT Nigg<sup>35</sup>, K O'Hearn<sup>30</sup>, KA Pelphrey<sup>10</sup>, SJ Peltier<sup>33</sup>, JD Rudie<sup>12,13,14,15</sup>, S Sunaert<sup>36</sup>, M Thioux<sup>25,26</sup>, JM Tyszka<sup>37</sup>, LQ Uddin<sup>31</sup>, JS Verhoeven<sup>36</sup>, N Wenderoth<sup>4</sup>, JL Wiggins<sup>33</sup>, SH Mostofsky<sup>34,38</sup> and MP Milham<sup>2,3</sup>





# Reconceptualizing functional brain connectivity in autism from a developmental perspective

Lucina Q. Uddin<sup>1\*</sup>, Kaustubh Supekar<sup>1</sup> and Vinod Menon<sup>1,2,3</sup>



**FIGURE 1 | Schematic model of two scenarios that could explain a developmental shift from intrinsic hyper- to hypo-connectivity in ASD.** In scenario 1 (solid red line), the ASD group shows a less steep developmental increase in functional connectivity over the age span compared with the TD group. In scenario 2 (dashed red line), the ASD group shows anomalous patterns of connectivity across the pubertal

period. Resting-state functional connectivity MRI studies provide evidence for widespread hyper-connectivity in children with ASD in contrast to hypo-connectivity observed in adolescents and adults with ASD. To reconcile these findings, it will be necessary to conduct longitudinal studies that span the developmental period surrounding puberty (gray oval). ASD, autism spectrum disorders; TD, typical development.

# Conclusions

## Eyetracking:

Excellent tool for studying the emergence of attentional impairments very early in development.

Decreased visual attention to the social world & eye regions.

## Electrophysiology:

Excellent temporal resolution and suitable for studies of infants.

Decreased amplitude of face processing ERP components.

Initial evidence of sensitivity to early behavioral interventions.

## Functional brain imaging:

Provides information about brain function with good temporal and spatial resolution.

Aberrant activation in brain regions coding for social information (e.g., face processing), cognitive control, and reward valuation.

Emerging evidence of network-level brain disconnectivity.

# Future Directions

- Longitudinal studies to address neurodevelopment and critical risk periods.
- Larger samples (ABIDE; NDAR).
- More psychiatric comparison groups.
- Should consider dimensional impairments across disorders (e.g., RDoC).
- Intervention studies are needed to understand and predict treatment effects.



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Questions?

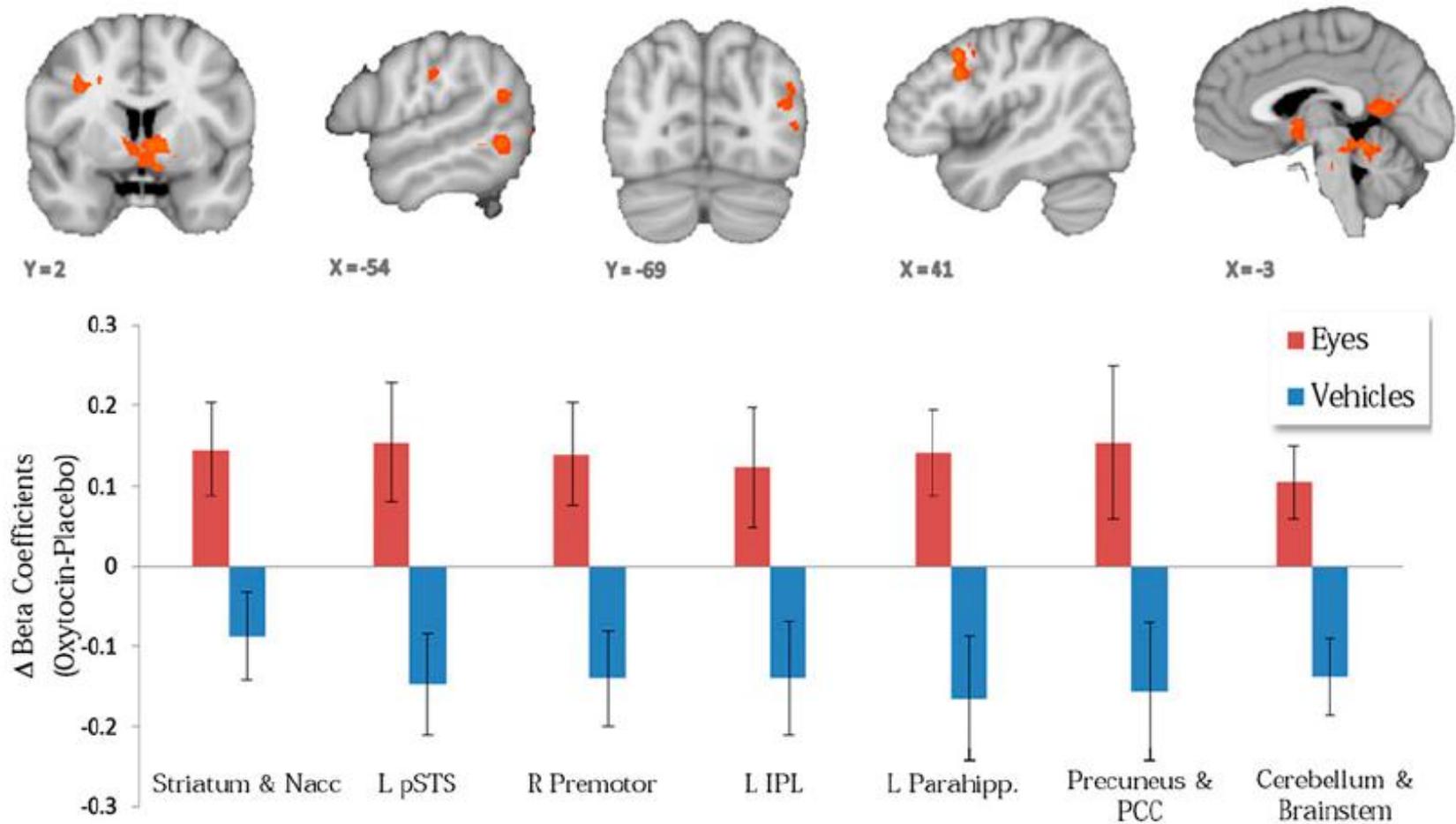
[gabriel\\_dichter@med.unc.edu](mailto:gabriel_dichter@med.unc.edu)

**Additional Slides**

# Oxytocin enhances brain function in children with autism

Ilanit Gordon<sup>a,b,1</sup>, Brent C. Vander Wyk<sup>a</sup>, Randi H. Bennett<sup>a</sup>, Cara Cordeaux<sup>a</sup>, Molly V. Lucas<sup>a</sup>, Jeffrey A. Eilbott<sup>a</sup>, Orna Zagoory-Sharon<sup>c</sup>, James F. Leckman<sup>d</sup>, Ruth Feldman<sup>b,c,d</sup>, and Kevin A. Pelphrey<sup>a</sup>

<sup>a</sup>Center for Translational Developmental Neuroscience, Yale Child Study Center, Yale University, New Haven, CT 06520; <sup>b</sup>Department of Psychology, and <sup>c</sup>The Gonda Multidisciplinary Brain Research Center, Bar-Ilan University, Ramat Gan 52900, Israel; and <sup>d</sup>Yale Child Study Center, School of Medicine, Yale University, New Haven, CT 06520  
[www.pnas.org/cgi/doi/10.1073/pnas.1312857110](http://www.pnas.org/cgi/doi/10.1073/pnas.1312857110)



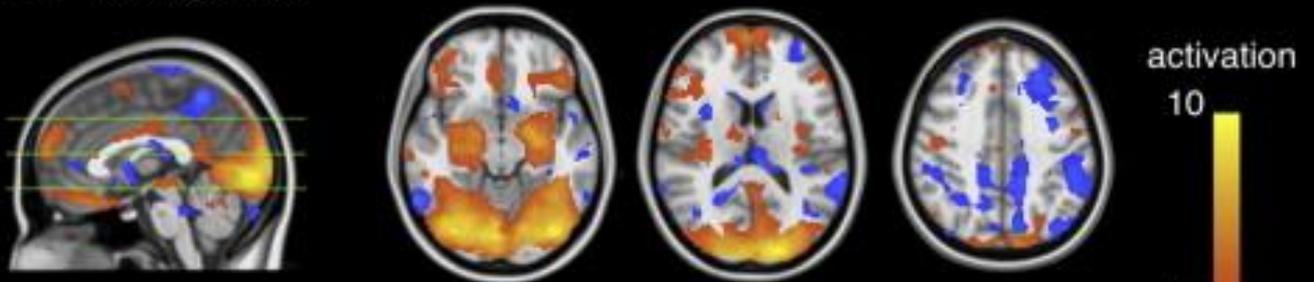
# Autism-Associated Promoter Variant in *MET* Impacts Functional and Structural Brain Networks

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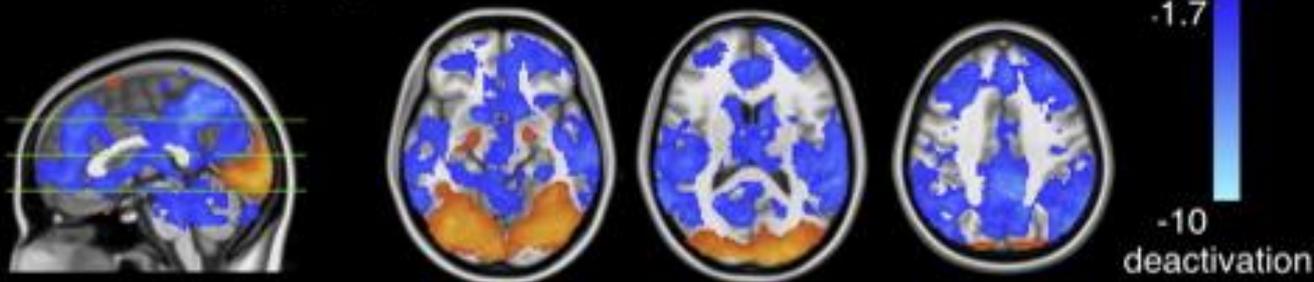
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## A *MET* genotype: fMRI activation maps

CC “risk” group



GG “nonrisk” group



CC “risk” > GG “nonrisk”

