MR imaging of autism: Mining for biomarkers

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Brain
Development
Imaging
Laboratory

www.sci.sdsu.edu/bdil

SDSU Center for Clinical and Cognitive Neuroscience

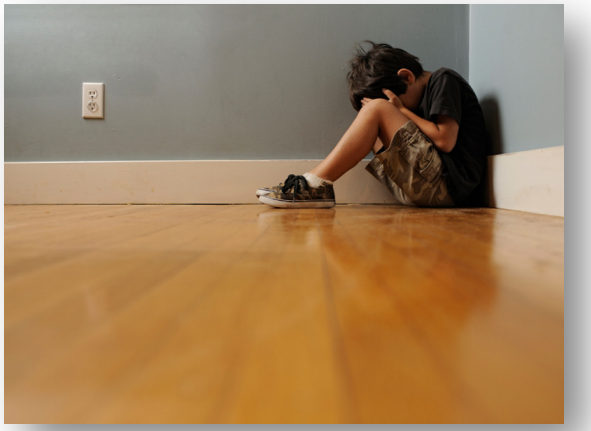
(Originally: "Area of Excellence")

slhs.sdsu.edu/ccn/

- Founding faculty:
  - Karen Emmorey, Tracy Love, Lew Shapiro (SLHS)
  - Sarah Mattson, Ed Riley, Ralph-Axel Müller (Psych.)
- New core faculty (cluster hire):
  - Alyson Abel-Mills (SLHS), Ksenija Marinkovic (Psych.)
- Affiliates
  - N. Amir, I. Fishman, P. Gilbert, D. Goble, P. Holcomb, K. Moon, I. Nip, K. Midgley, C. Murphy, F. Valafar
- Populations:
  - Deafness & use of sign language
  - Dyslexia
  - Aphasia
  - Fetal alcohol syndrome
  - ADHD
  - Autism
  - Anxiety disorders
  - Parkinson's
  - Alzheimer's
  - Huntington's

Autism

- Neurodevelopmental disorder
  - High prevalence
    - 1/88 for whole spectrum (CDC, 2012)
    - 1/38 (Kim et al. 2011)!
  - Diagnosed in terms of consensus-based array of ***behavioral*** criteria
- DSM-IV: Impairments or delays
  - Social interaction
    - Eye contact
    - Peer relations
  - Communication
    - Language delay (or total lack)
    - Inadequate or stereotyped use of language
  - Restricted and repetitive behaviors
    - Preoccupation with specific objects
    - Hand flapping etc.

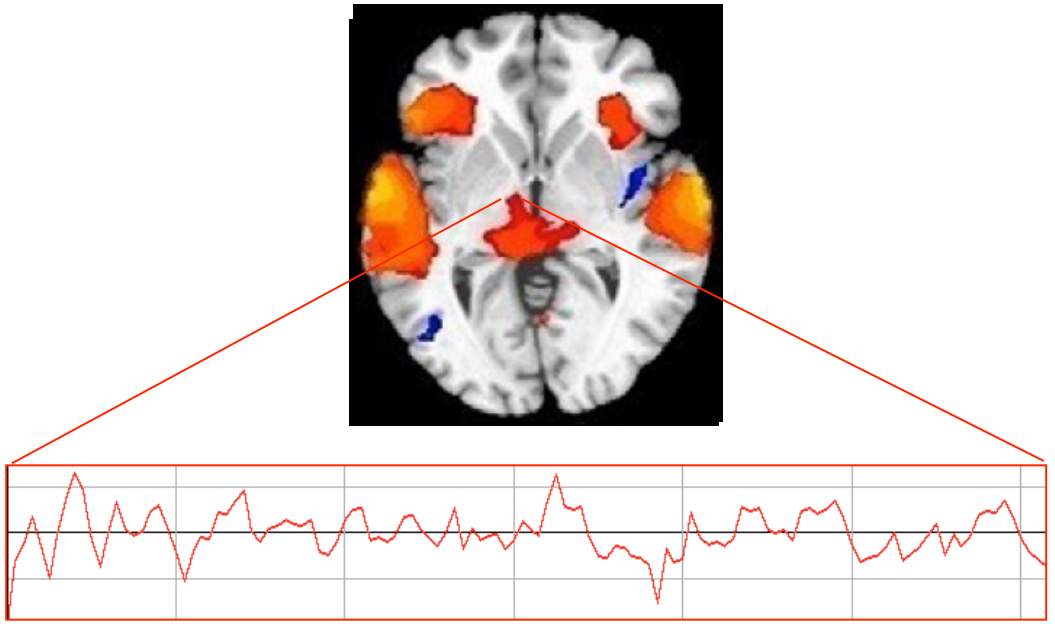


An example of a multimodal autism study

	~# features per pt
• MRI	
• Functional MRI	10,000
• Functional connectivity MRI	100,000
• High-resolution anatomical MRI	1,000
• E.g.: White matter volume, regional cortical thickness	
• Diffusion weighted MRI/tractography	4,000
• Several indices of white matter integrity, tract organization	
• Restriction spectrum imaging	1,000
• Several indices of cortical architecture	
• MR spectroscopy	200
• Measures of brain metabolites	
• Physiological measures	600
• Heart rate, breathing	
• EEG	
• Power spectra at frequencies of interest (e.g., gamma)	500
• MEG	
• Event-related	200
• Coherence in different frequency bands	1000
• Questionnaires	200
• Medical history	
• Sensory profiles	
• Sociocommunicative, executive, etc.	
• Behavior-based measures	200
• Diagnostic scores	
• Neuropsychological tests	
• Performance data from fMRI task or other	
• **For study including 120 participants**	**>14,000,000**

fMRI: Tip of the activity iceberg

- 180-450 time points per scan
- ~100,000 brain voxels
- 120 participants
- Billions of measurements for fMRI alone
- Massive data reduction in conventional activation analysis

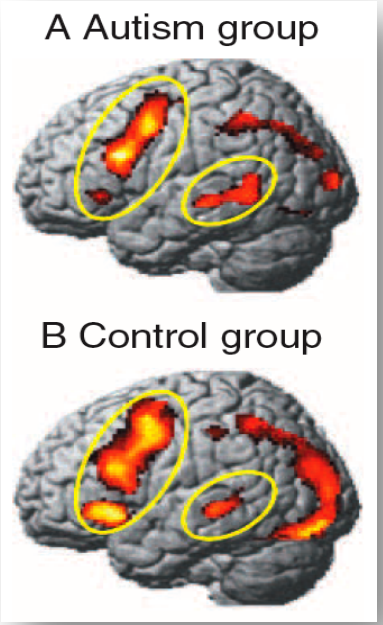


Cluster size (μl)	Peak Talairach coordinates			Peak *t* value	Location of peak activation (approximate Brodmann area)
	x	*y*	*z*		
4568	−13	−17	15	8.9	Left thalamus
	−16	−6	13	8.0	Left lentiform nucleus
4336	−34	17	17	12.5	Left inferior frontal (44/45)
2608	−4	17	39	9.3	Left cingulate (32)
2336	−24	2	52	9.5	Left middle frontal (6)
1752	−9	−58	−2	7.7	Left lingual (19)

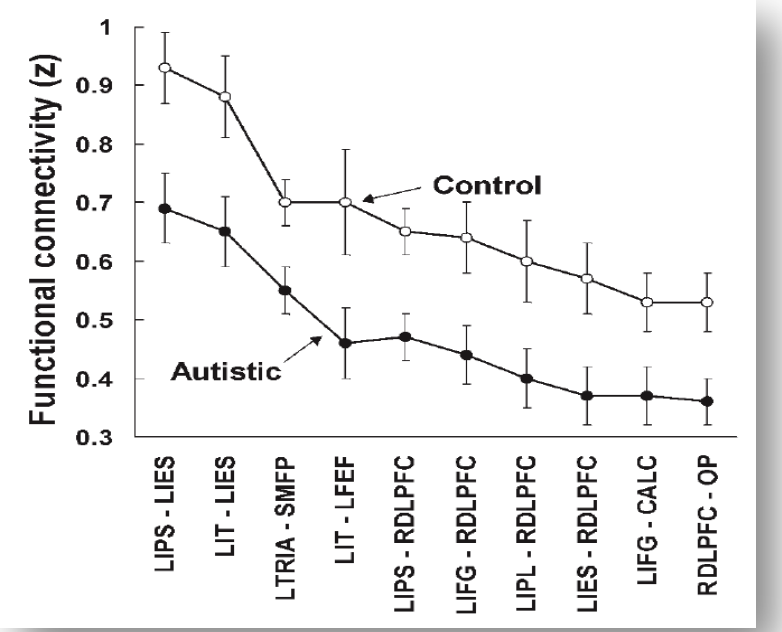
fcMRI: Focus on regions of interest…

Just et al. (2004)

Activations for sentence comprehension



Reduced functional connectivity



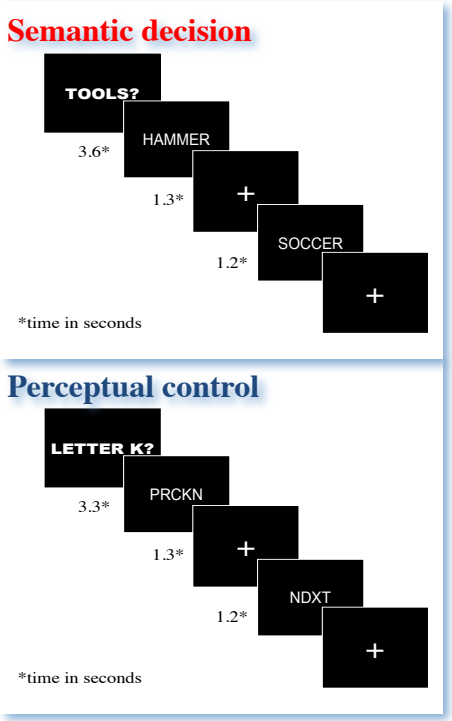
Underconnectivity findings from <u>same group</u>:

- Just et al. (2006): Executive (Tower of London)
- Cherkassky et al. (2006): Rest (default mode network)
- Kana et al. (2006, 2007): Sentence comprehension; response inhibition
- Koshino et al. (2008): Nonverbal working memory
- Mason et al. (2008), Kana et al. (2009): Theory of mind
- Damarla et al. (2010): Visuospatial
- Mizuno et al. (2012): Perspective-taking

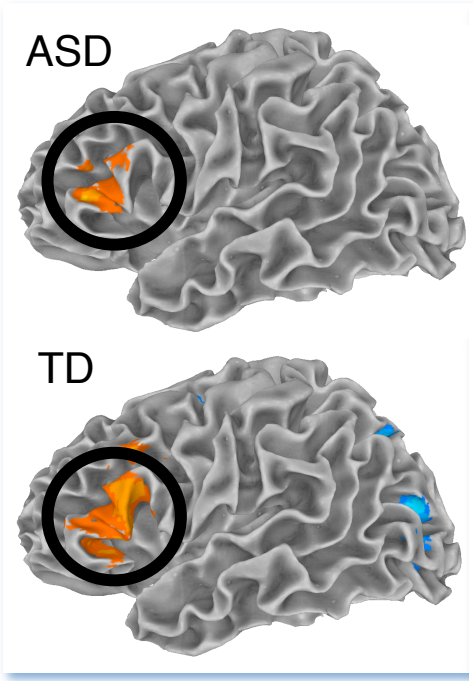
… and from <u>other groups</u>:

- Villalobos et al. (2005): Visuomotor coordination
- Bird et al. (2006): Selective visual attention
- Kleinhans et al. (2008): Face processing
- Lee et al. (2009): Response inhibition
- Mostofsky et al. (2009): Finger movement
- Solomon et al. (2009): Cognitive control

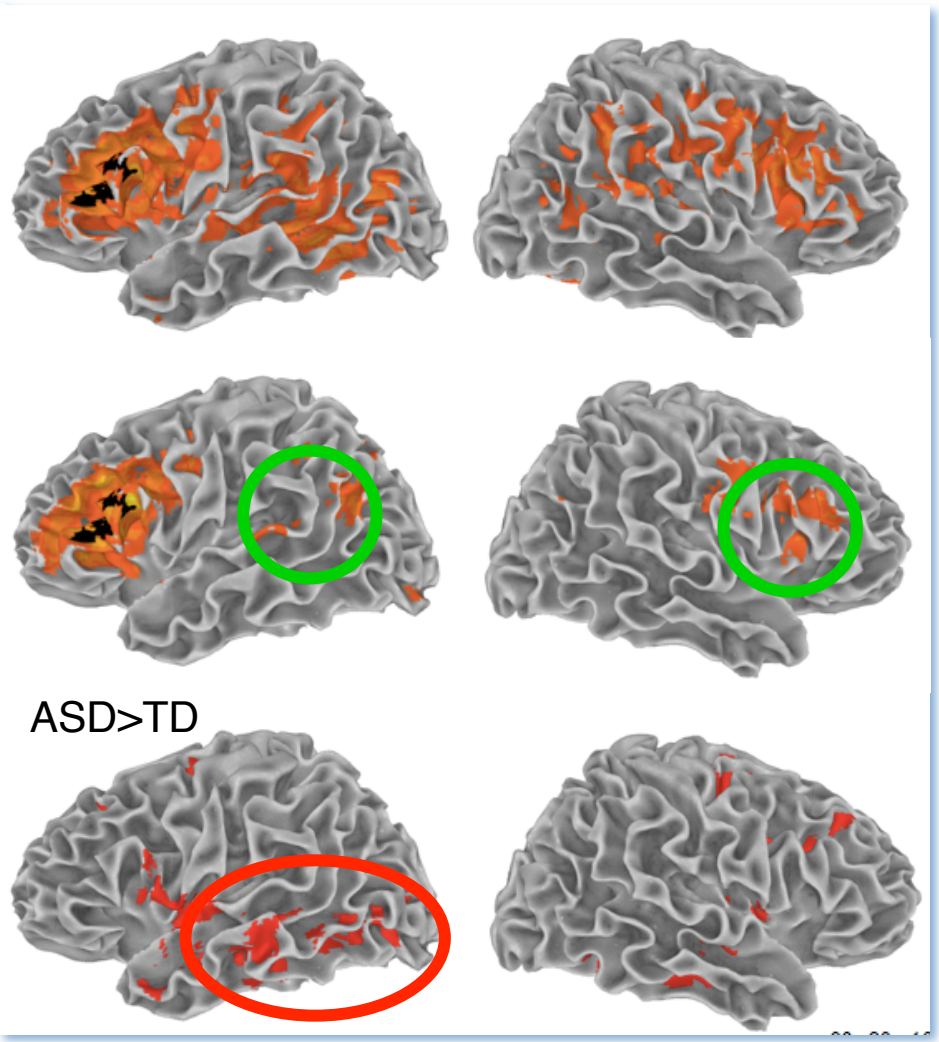
… may be missing the bigger picture



Activations for semantic decision



Functional connectivty for LIFG seed

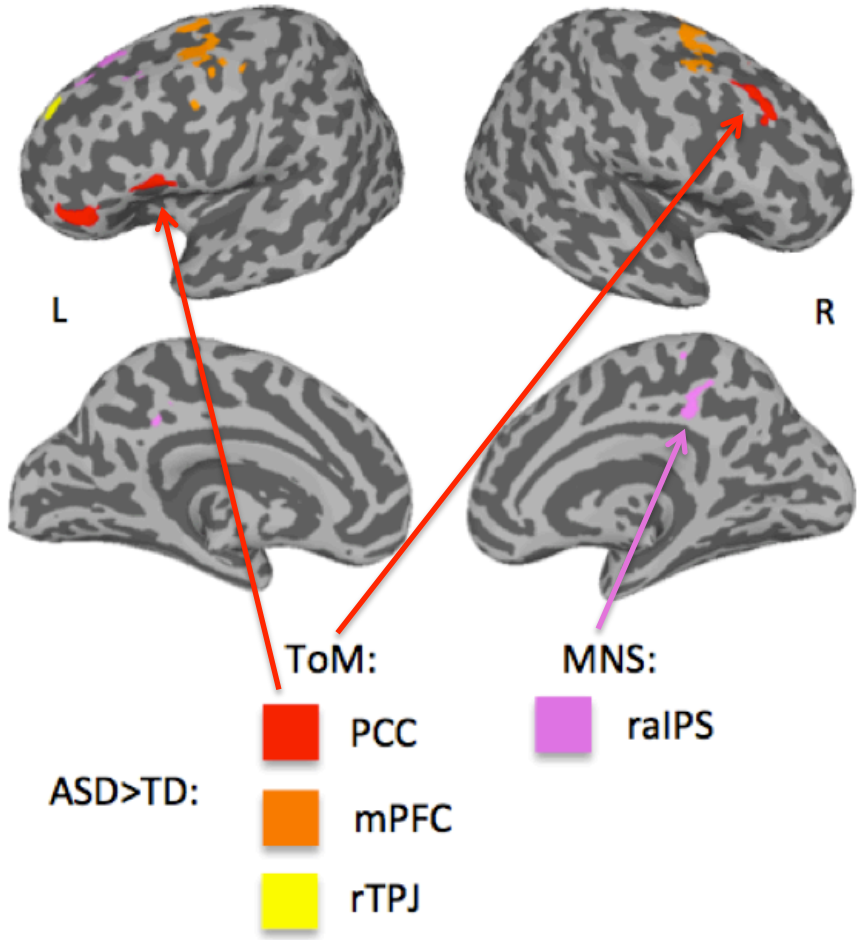


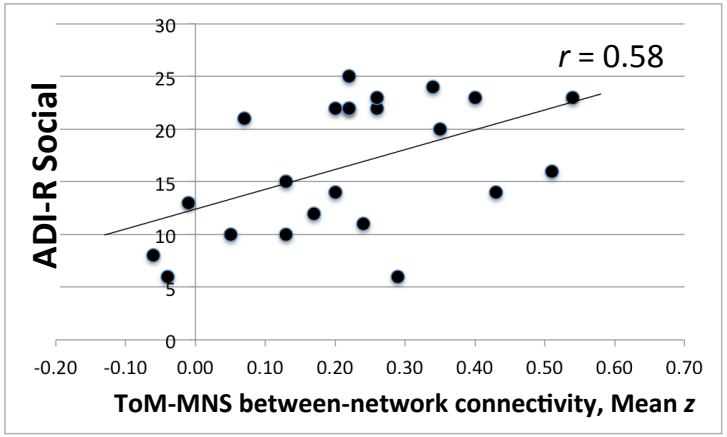
IFG: Less consistent local activity, but diffusely increased BOLD correlation

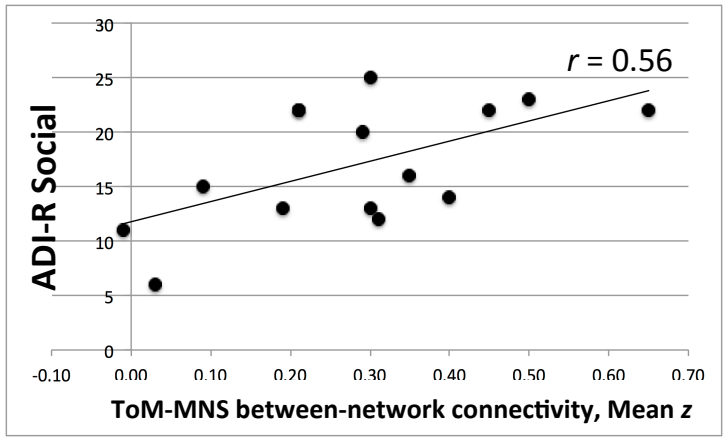
M. Shen et al. *NeuroImage* (2012)

ASD: Cross-talk rather than underconnectivity?

- Overconnectivity *between* mentalizing network and mirror neuron system in ASD
  - Between-network "cross-talk" correlated with sociocommunicative impairment

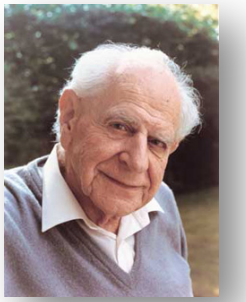






I. Fishman et al., *JAMA Psychiatry* 2014

Popper or not?



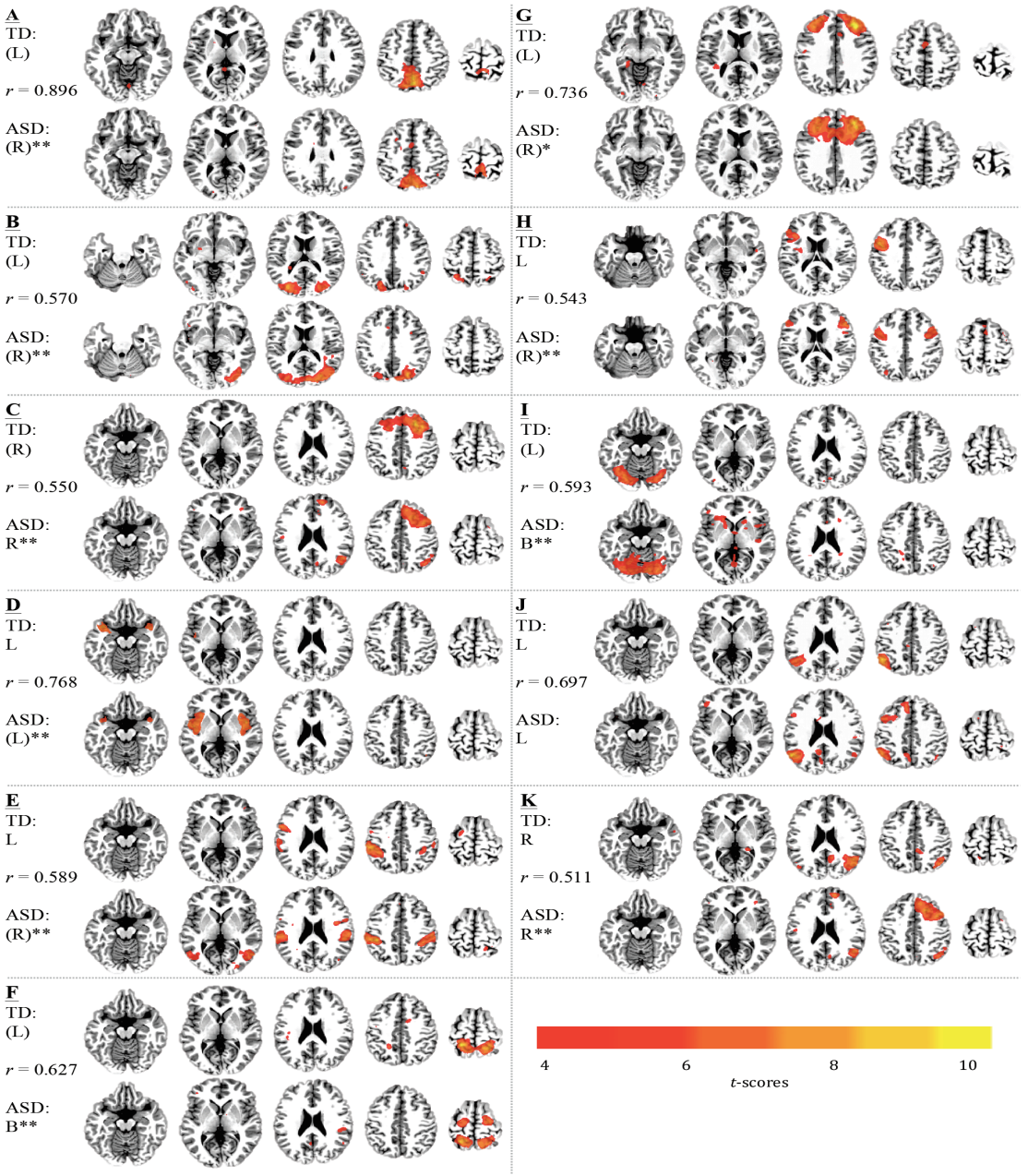
- Hypotheses for ASD are “cheap”
  - *Some* supportive evidence for virtually any pet idea
- No strong hypotheses for *unique* biomarkers

  => Need for data-driven approaches

Data-driven approaches: ICA

- 17 non-noise components (=functional networks)
  - Matched to components from previous TD studies (Smith et al., 2009; Laird et al., 2011)
- 10 show group differences in asymmetry index
- Exclusively: **rightward** shift in ASD

Cardinale et al.
(*JAMA Psychiatry*, 2013)



Diagnostic classification

- Machine learning
  (Random Forest)
  - Low-motion subsample
    - (selected from ABIDE)
    - N=252
  - 220 ROIs (Power et al., 2011)

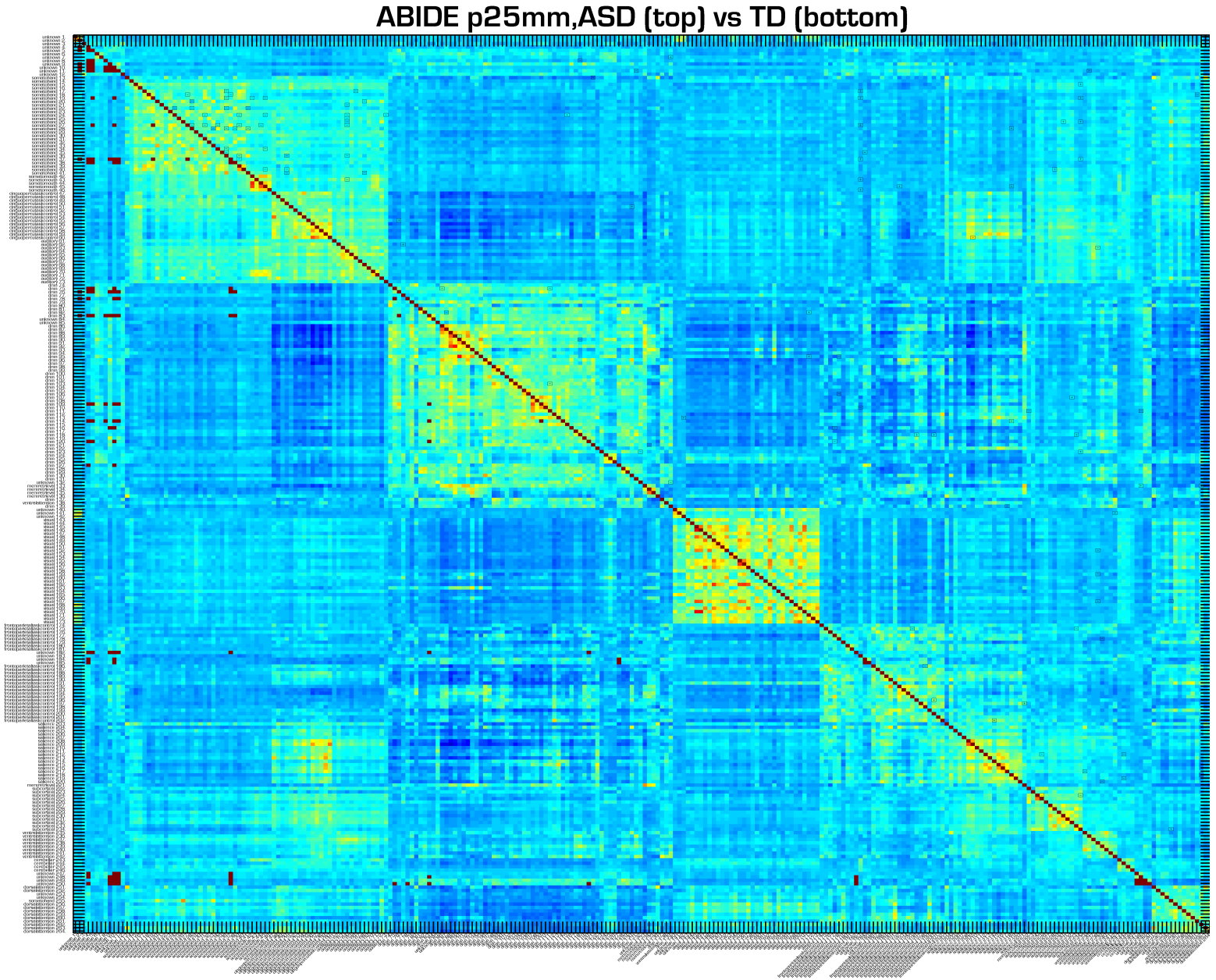
    => 24090 features
  - Selection of 100 most informative features
  - Classification accuracy
    - 90.9%
    - "Out of bag" (validation sample) error: 9.1%

	ASD (n=126)	TD (n=126)	
Gender (M/F)	108 / 18	95 / 31	
	M ± SD (range)	M ± SD (range)	*p*
Age (years)	17.3 ± 6.0 (8.2 - 35.7)	17.1 ± 5.7 (6.5 - 34)	0.8
Motion (RMSD; mm)	.06 ± .02 (.02-.1)	.06 ± .02 (.02-.1)	0.92
Non-verbal IQ	106.9 ± 17 (37-149)	106.3 ± 12.8 (67-155)	0.8
ADOS_total	12 ± 4 (4-22)	N/A	

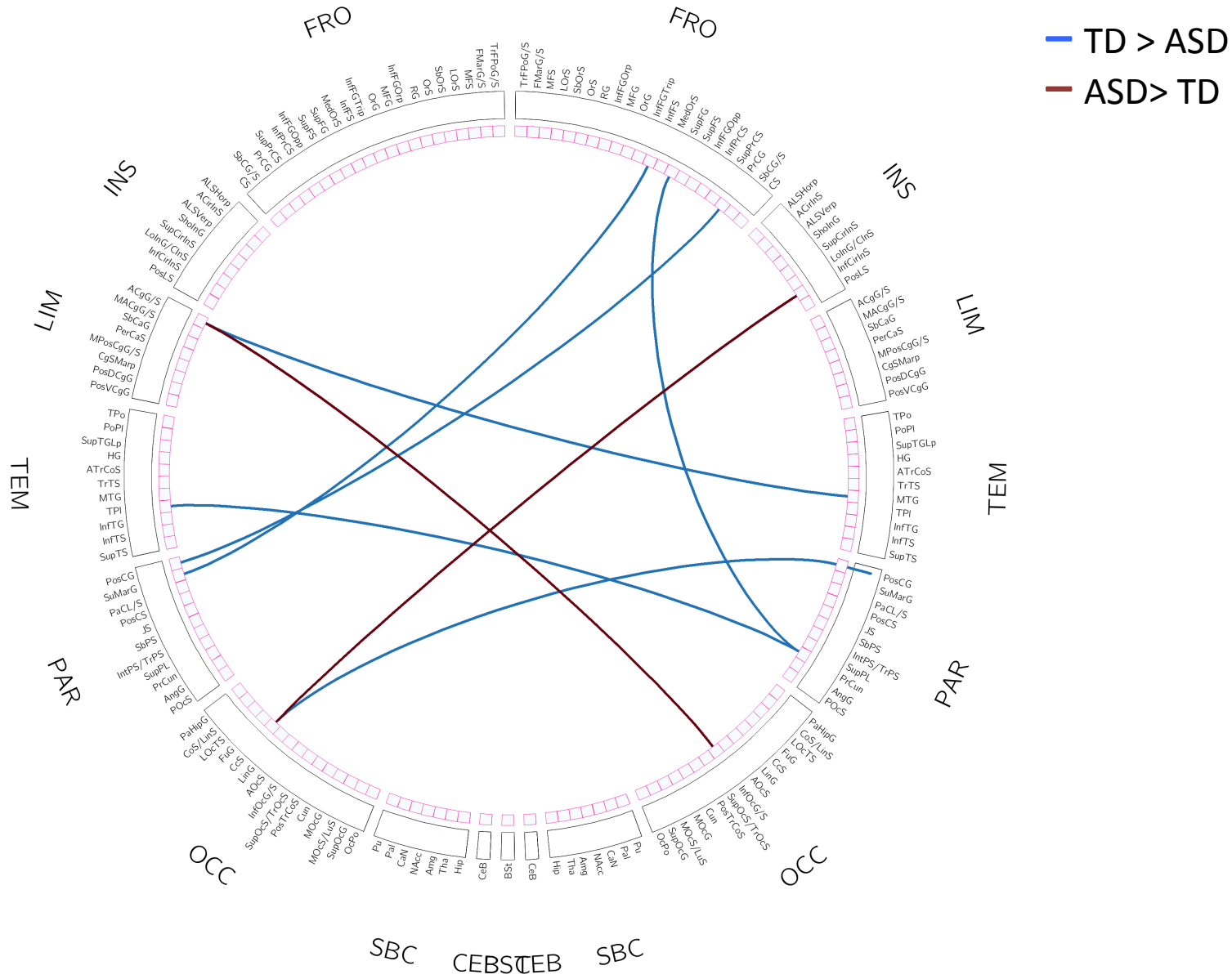
C. Chen et al. (under review)

Functional connectivity

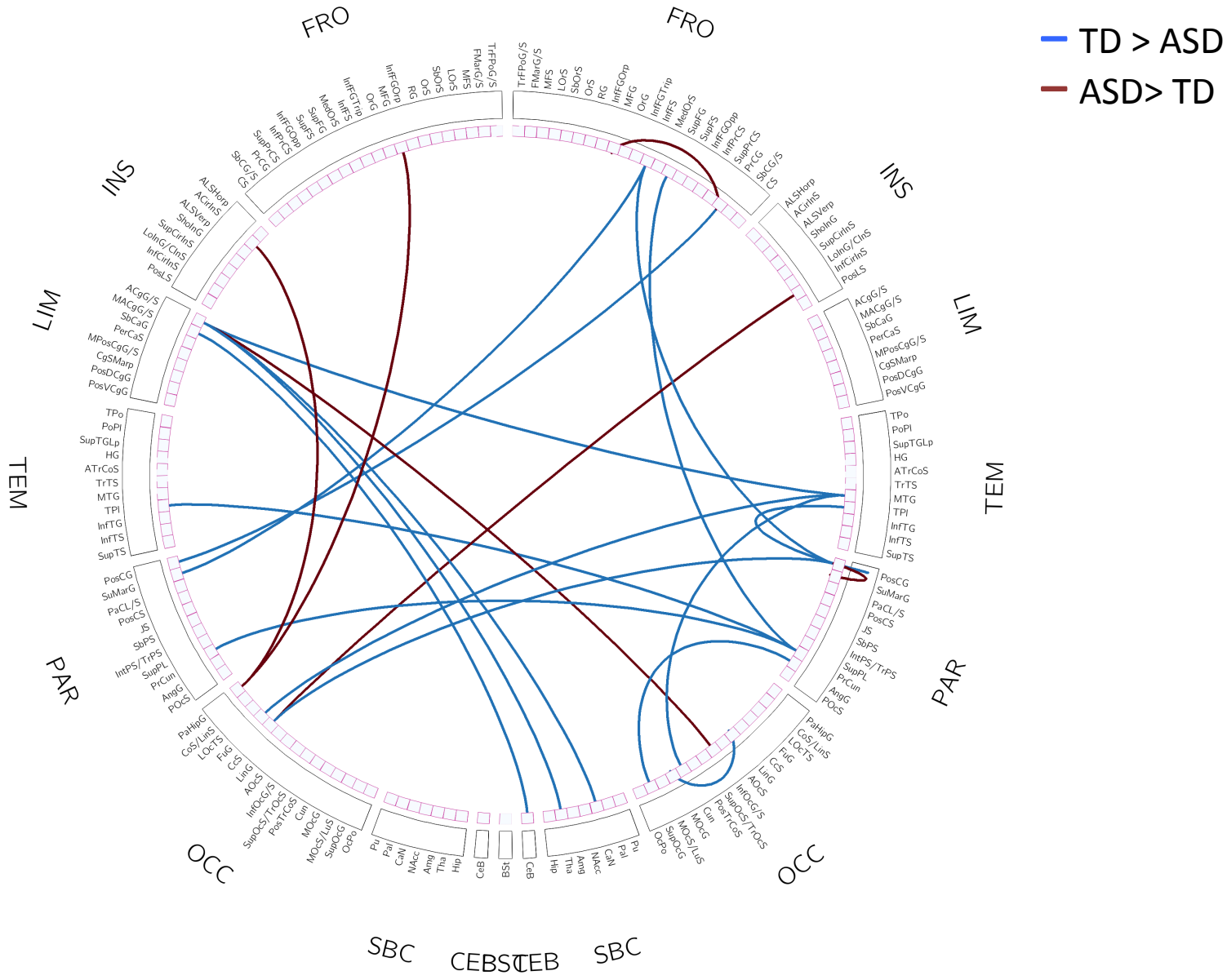
- Matrix of signal correlations between 220*220 regions of interest
- >24,000 features



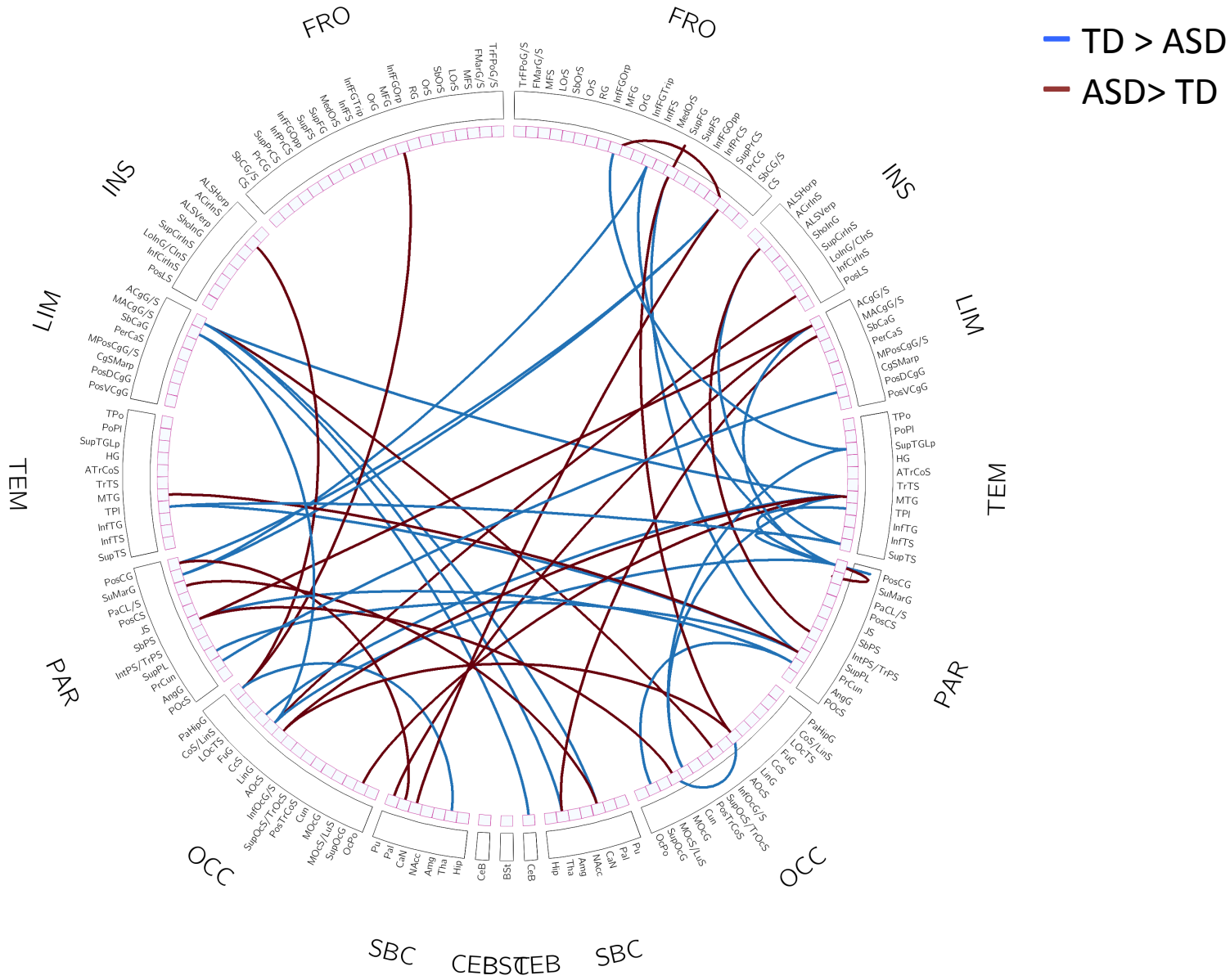
Informative features: Top 10



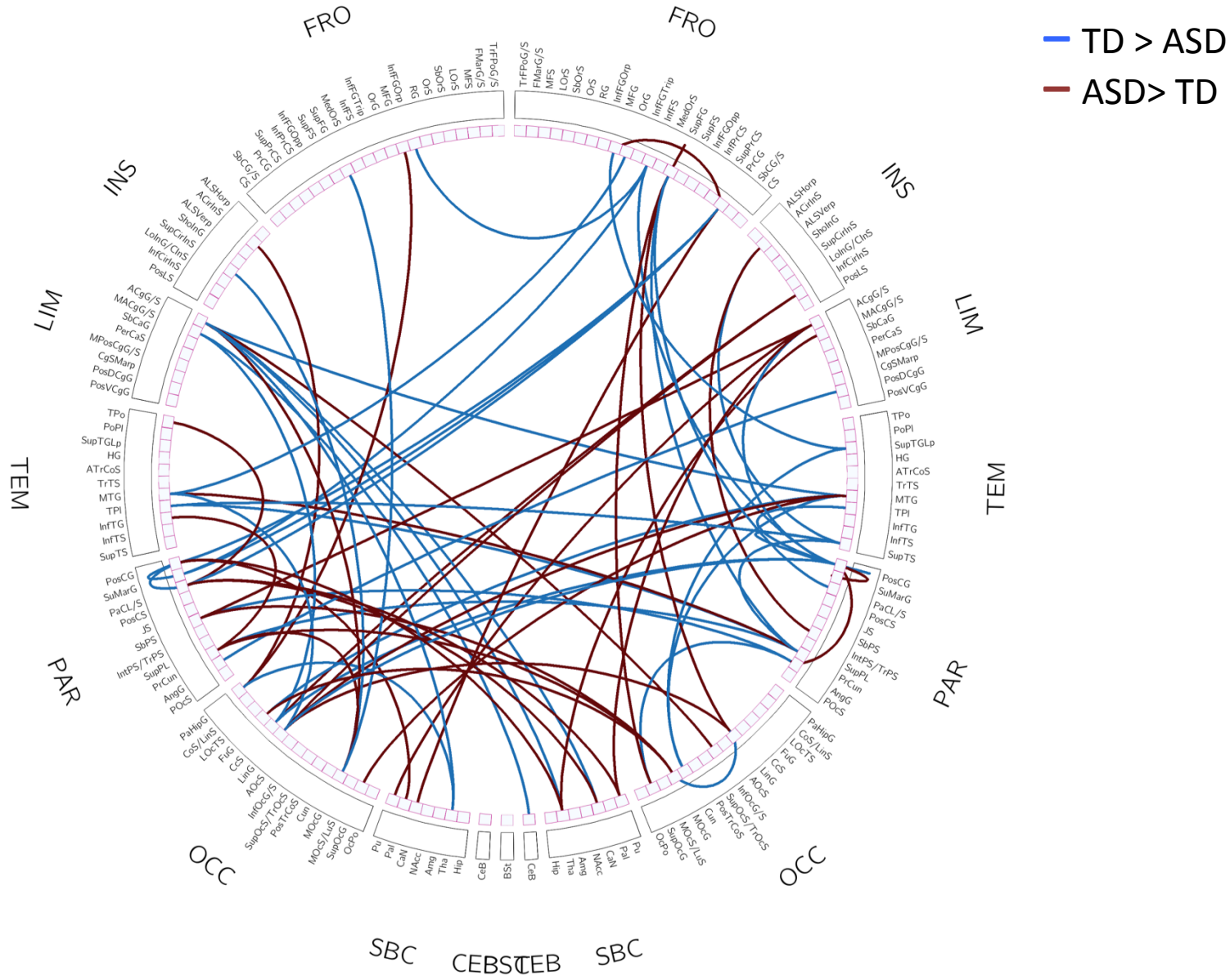
Informative features: Top 25



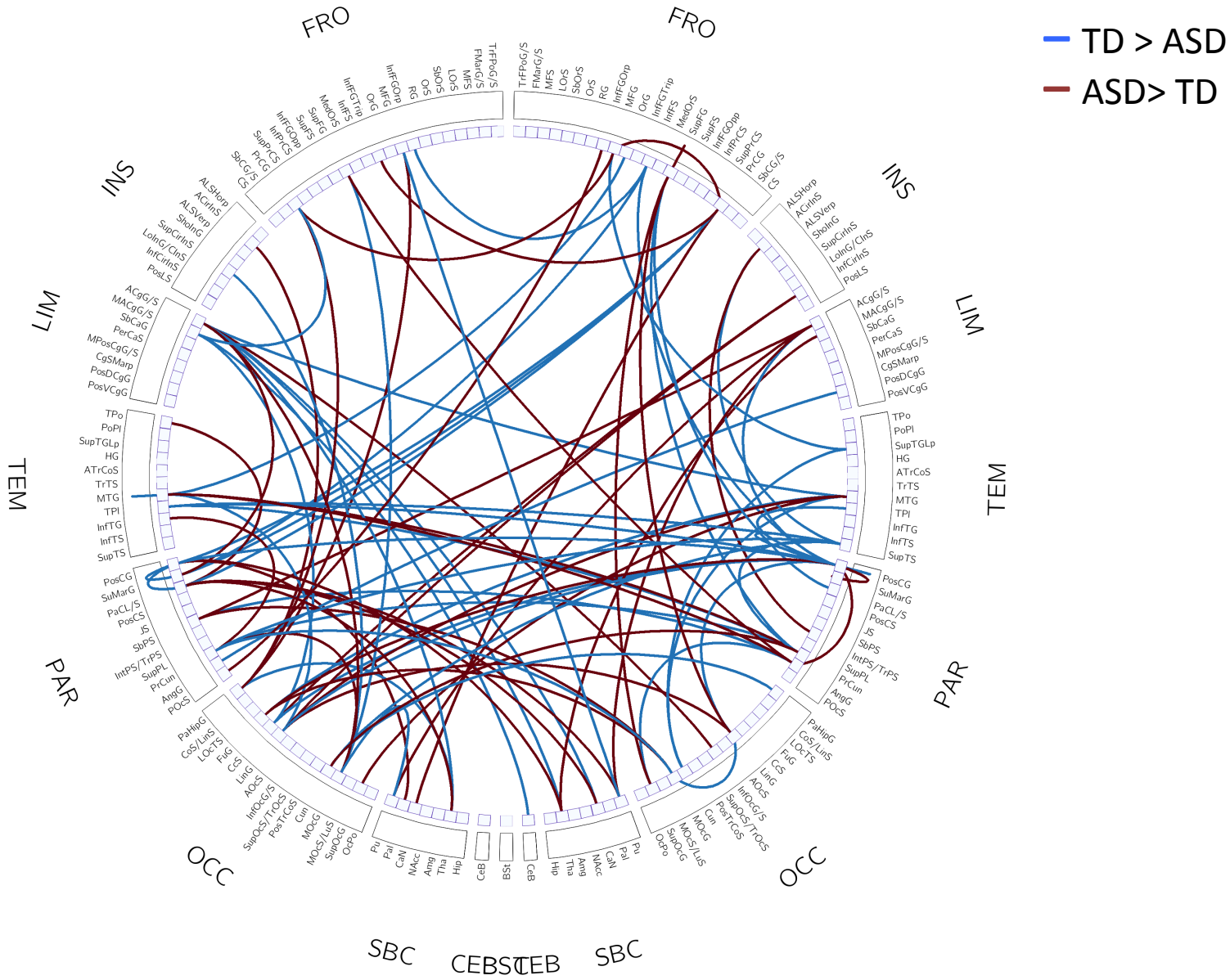
Informative features: Top 50



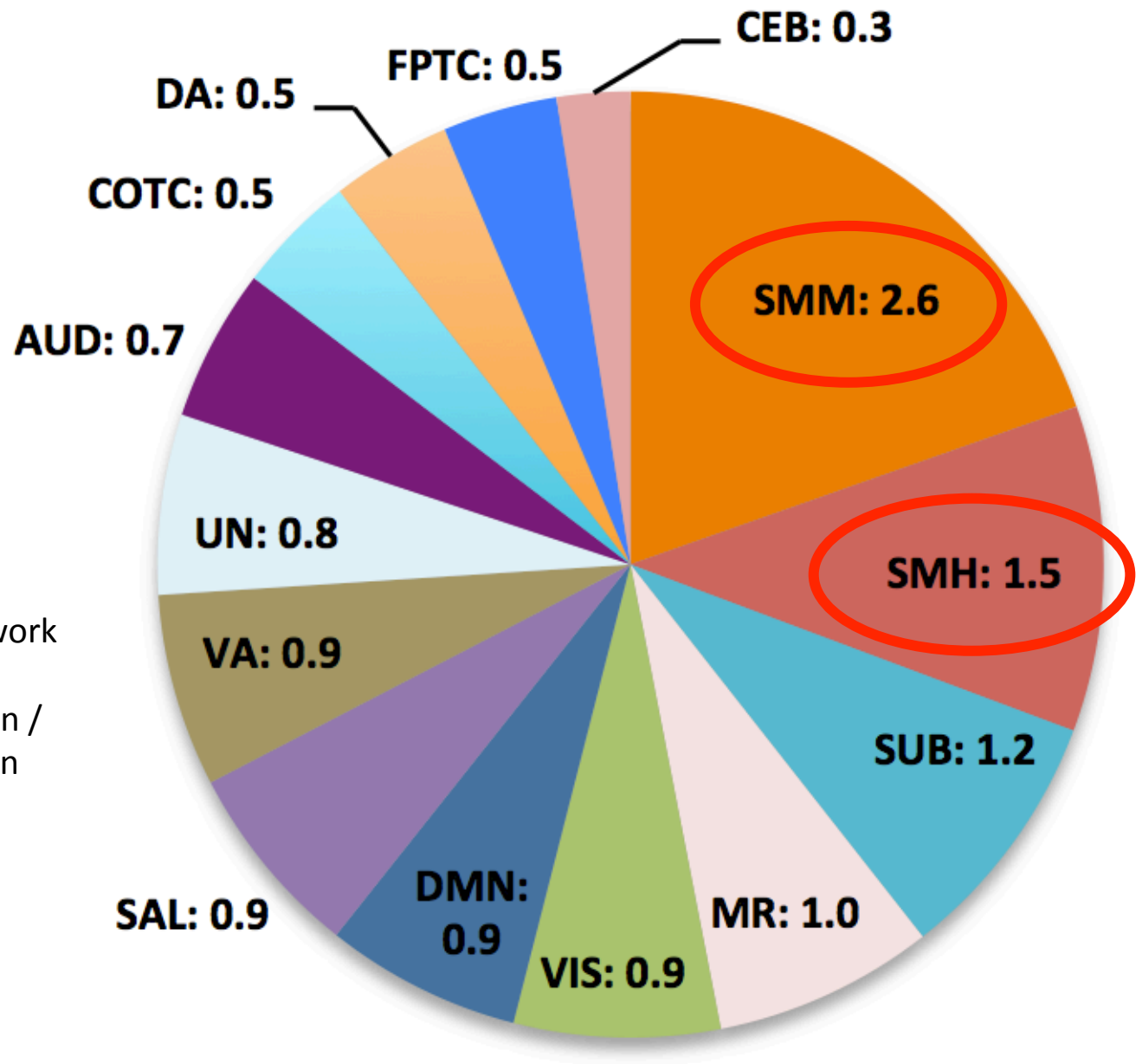
Informative features: Top 75



Informative features: Top 100



Informative ROIs: normalized* numbers per network



*Number of times network ROIs participate in informative connection / total number of ROIs in network

Machine learning for detection of biomarkers

- Issues
  - Large functional dataset only from ABIDE
    - Multisite data sources introduce many factors of variability that are hard to control
  - No solution for validation problem
    - Separate validation sets cannot be fully matched to training sets
      - Unknown subtypes
    - Random Forest: Out of Bag validation
  - Multimodal imaging more likely to capture complex signature of disorder
    - Usually not available for very large samples

Why all this?

- Autistic symptomatology likely due to complex patterns of brain network abnormalities
- Conventional hypothesis-driven techniques have not succeeded in identifying distinct patterns of brain anomalies
- Need for biomarkers of ASD
  - Measures of network connectivity a potential source for such markers
    - Detection requires data-driven methods (e.g., machine learning)
    - Biomarkers may be highly complex
  - Identification of brain-based subtypes of ASD

    = Clusterings of patterns of biomarkers
  - Perspectives:
    - More transparent links between such subtypes and specific genetic (+ environmental) factors
    - Mechanistic models of developmental disturbances
    - Taylored treatments

Thanks!

To parents and participants

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Brain Development Imaging Lab:

- *Faculty*: Inna Fishman, Ruth Carper, Dinesh Shukla
- *Graduate*: Aarti Nair, Chris Keown, Colleen Shen, Angela Abbott, Michael Datko, Afrooz Jahedi, Aina Eill, Leeza Andersen, Sangeeta Nair, Morgan Sullivan, Patti Shih, Brandon Keehn, Michael Gaffrey, Mark Shen, Laurie Brenner, Birgit Öttl, Janae Deyoe, Sarah Noonan, Mark Mulvey, Nick Peterson…
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