



Neurodevelopmental Disorders

*Lessons learned from autism and open
brain connectome research*

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Senior Research Scientist

Financial disclosure

- Coauthor of the Italian version of the SRS distributed by Organizzazioni Speciali (OS), Italy - Royalties

Neurodevelopmental Disorders

share challenges and opportunities for biomarker discovery

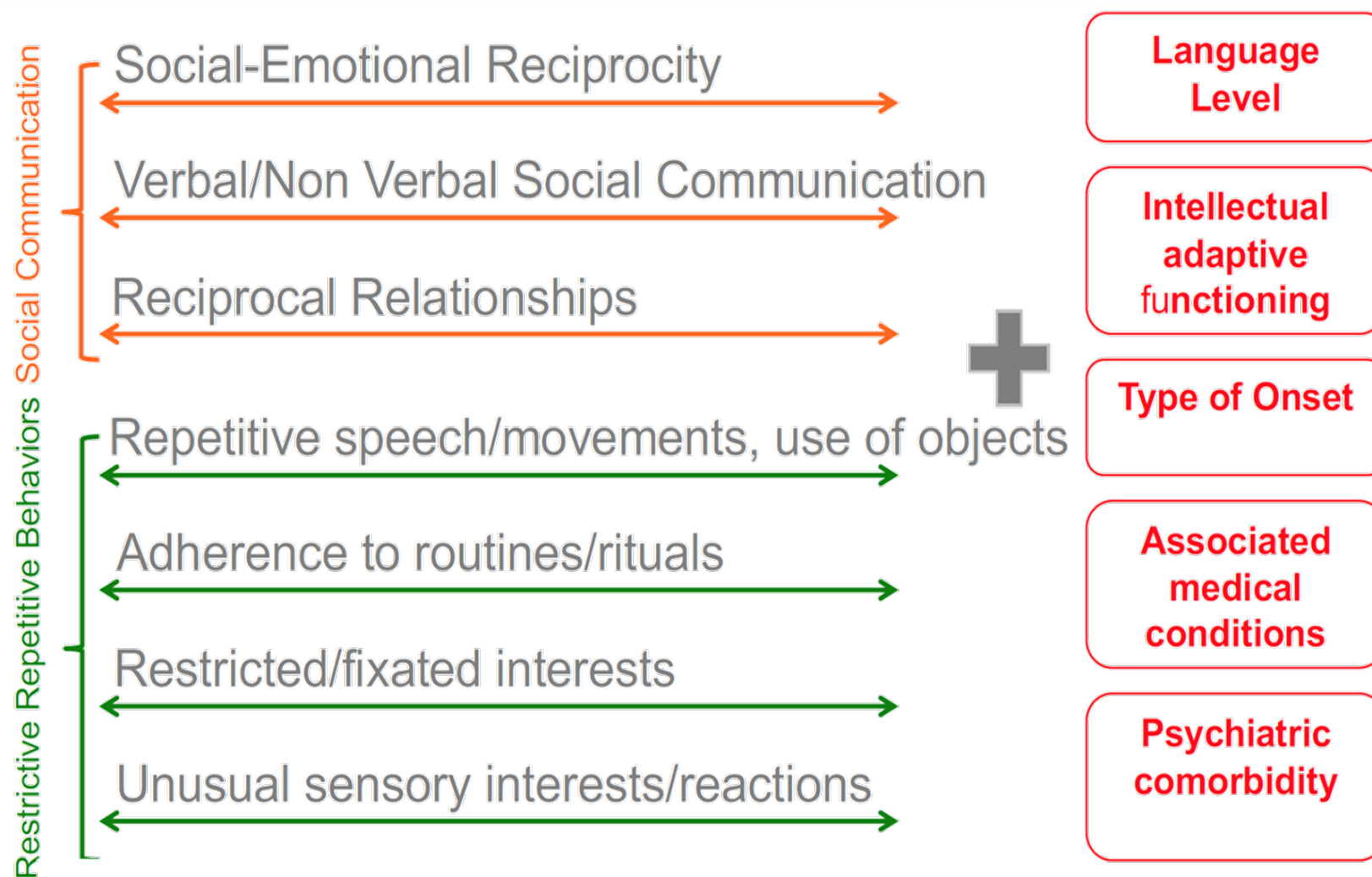


- Attention Deficit/Hyperactivity
- **Autism Spectrum**
- Communication
- Motor
- Specific Learning
- Intellectual Disability

- Childhood onset
- Heterogenous presentations
 - Comorbidity rules
- Multifactorial etiopathogenesis
- Brain connectopathies

- 67% neuropsychiatric disorders onset within the first 20 years of life (e.g., Kessler et al 2005)
- Common disorders of childhood can already be diagnosed in preschoolers (~7%) (e.g., Wichstrom et al 2012)
- Continuity of symptom clusters from preschool-age to childhood/adolescence

Autism heterogeneity- a challenge and an opportunity



Modified from Grzadzinsky Huerta, Lord, 2013

Neurodevelopmental Disorders

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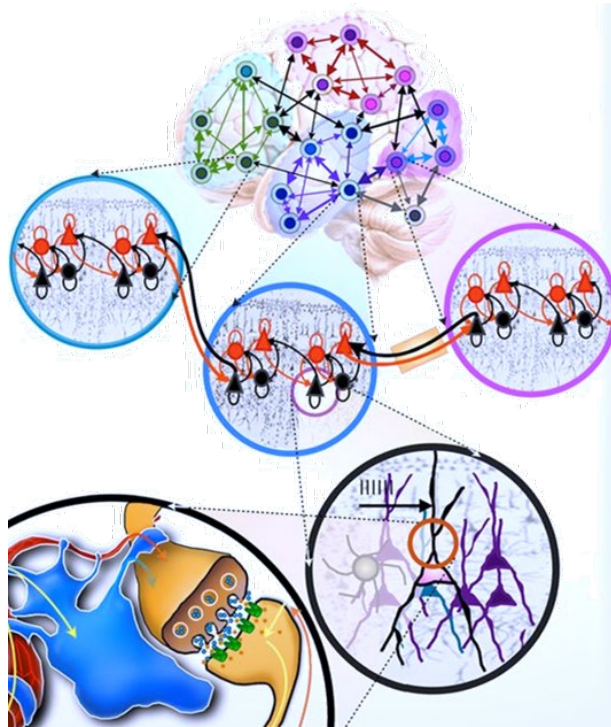


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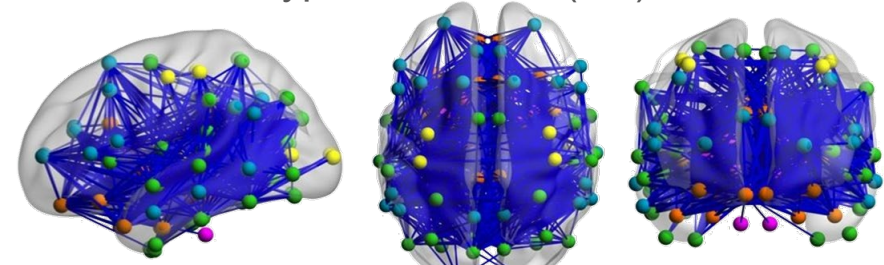
Developmental brain connectopathy



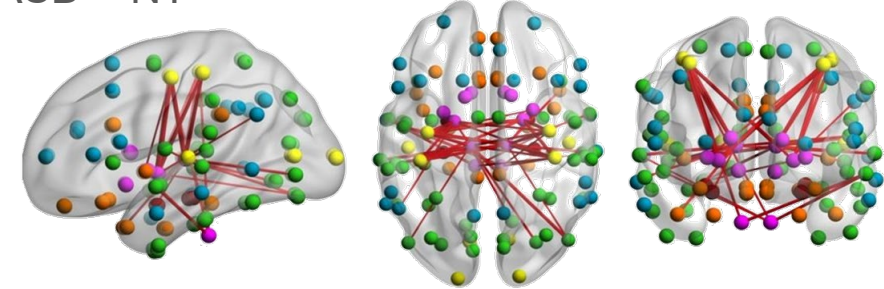
Park and Friston, 2013

Brain connectome: the comprehensive map of brain circuits (i.e., nodes and edges)

Autism < Neurotypical controls (NT)



ASD > NT



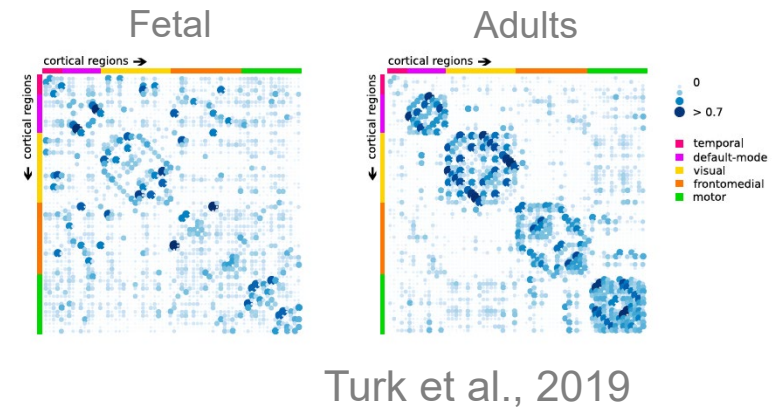
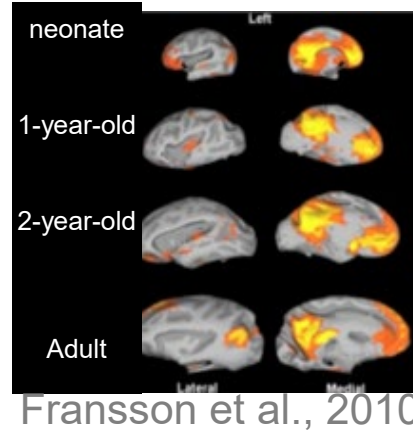
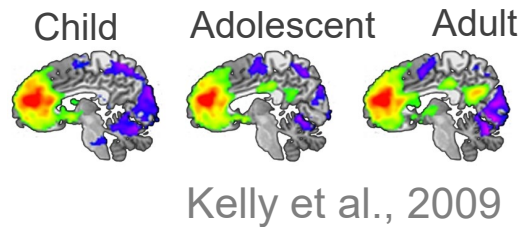
● Unimodal ● Subcortical ● Paralimbic
● Heteromodal ● Primary SM ● Limbic

Di Martino, et al., Milham, 2014

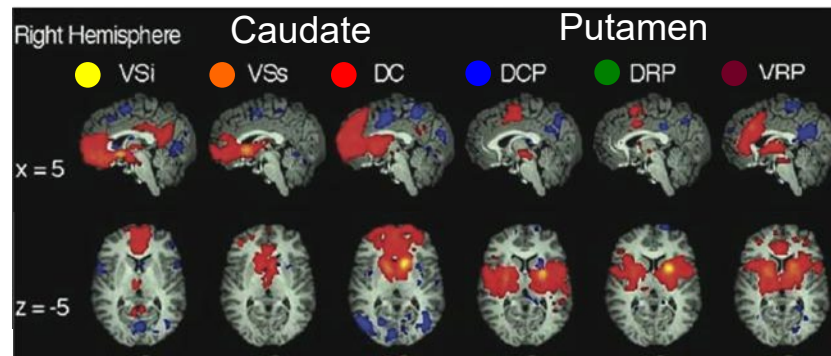
A mosaic of dysconnections: ASD-related increased and decreased connectivity varying by functional circuitry

Non-invasive connectome profiling by R-fMRI

Sensitive to development

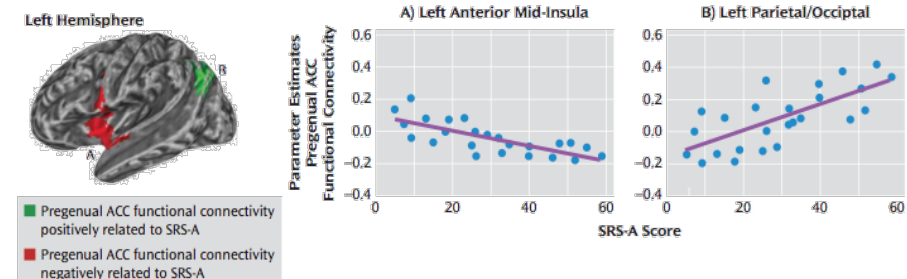


In vivo circuit dissection



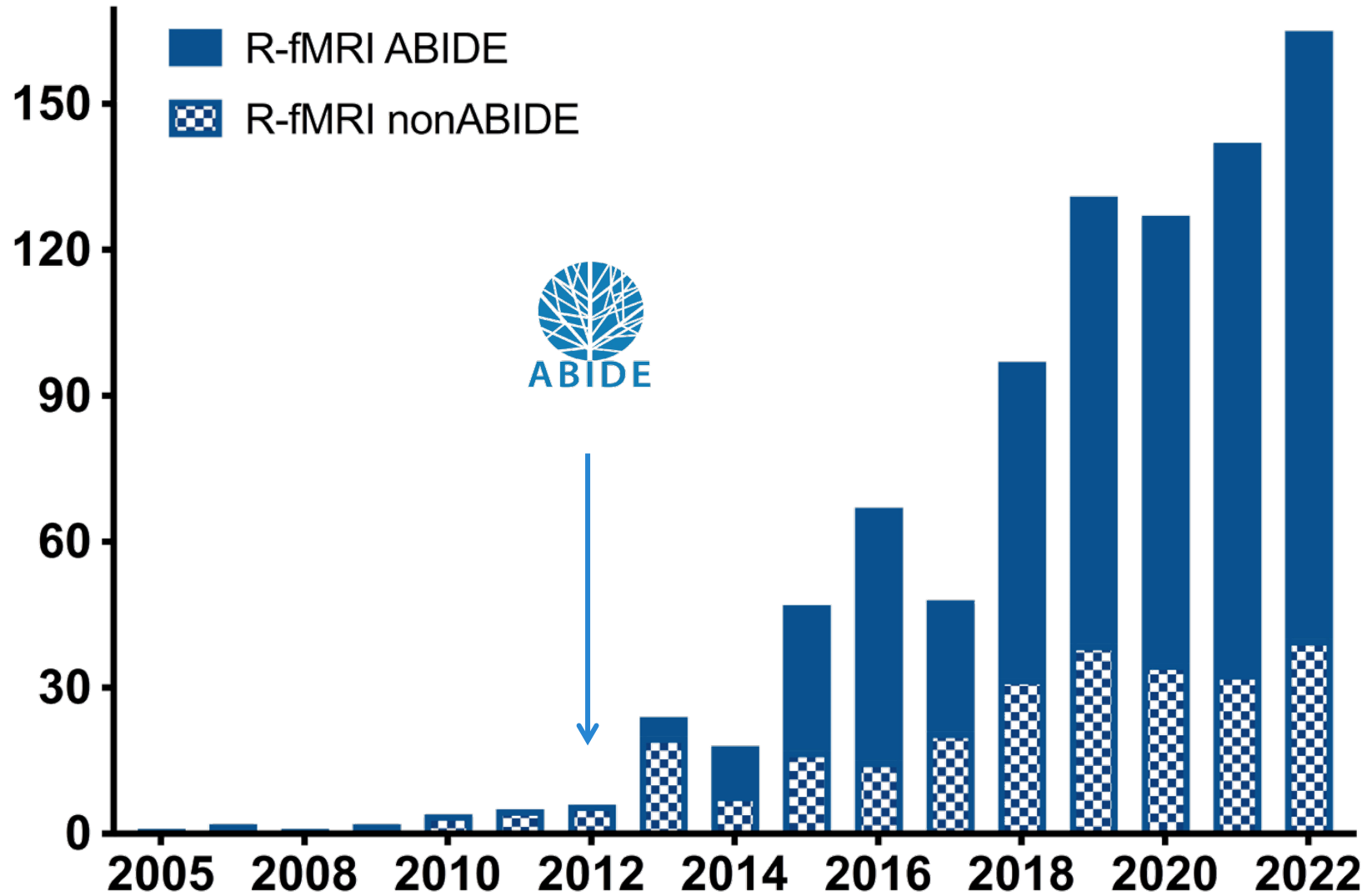
Di Martino et al. 2008

Captures inter-individual variability

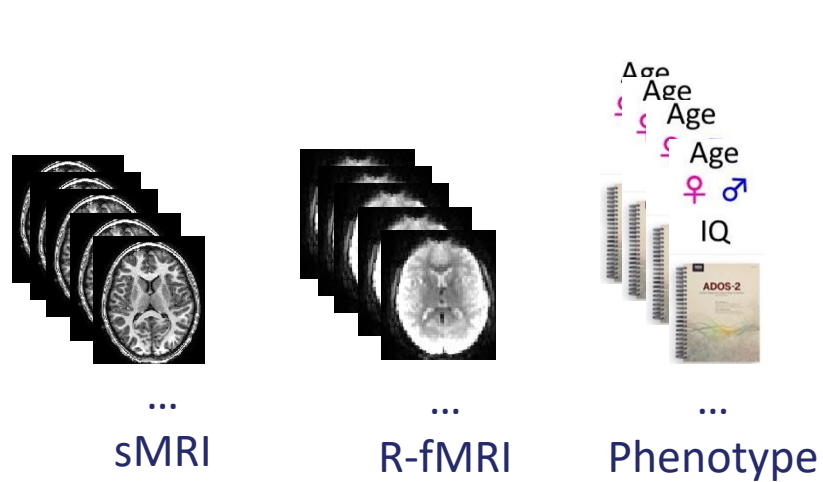


Di Martino et al., 2009

Resting-state fMRI (R-fMRI) in Autism



Autism Brain Imaging Data Exchange - open data sharing



ABIDE I

Released August 2012

N Sites=17

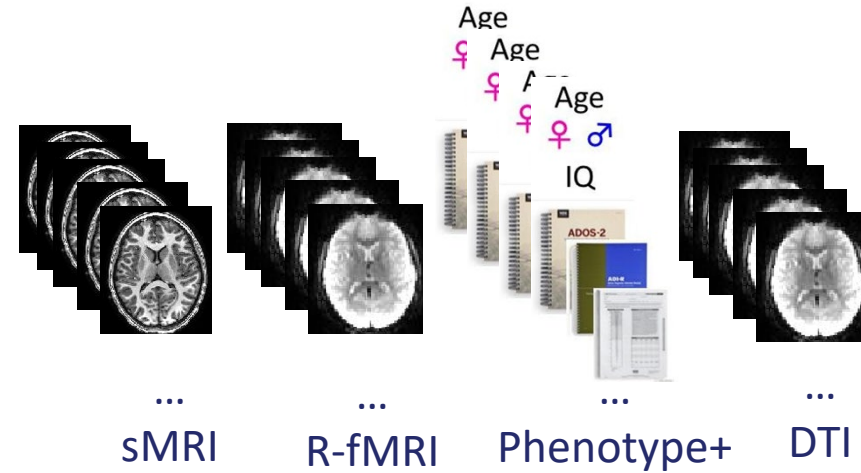
N Collections=20

N Individuals=1112

ASD n=539, TDC n=573

Grass rooted

Di Martino et al., Mol Psych, 2013



ABIDE II

Released June 2016

N Sites=17 (8 from ABIDE I)

N Collections=18 add long

N Individuals=1114

ASD n=521, TDC n=593

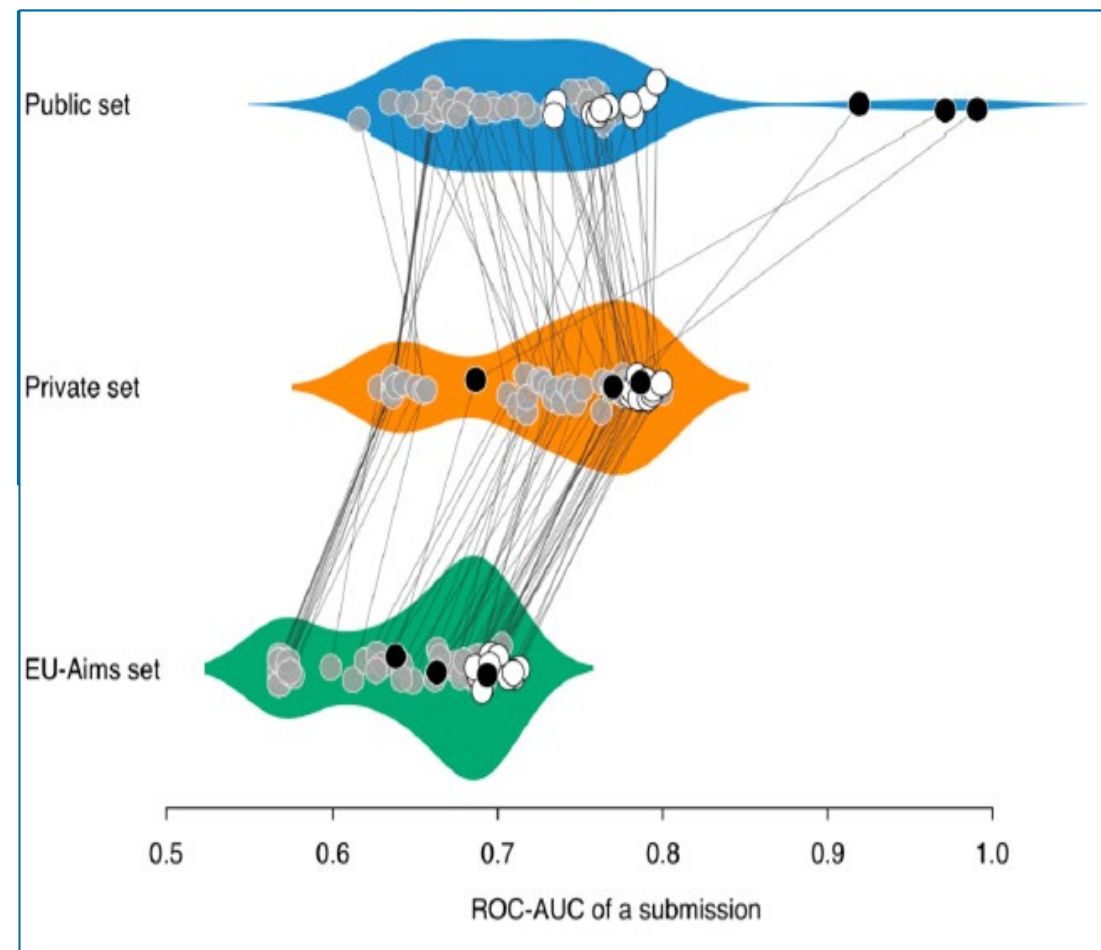
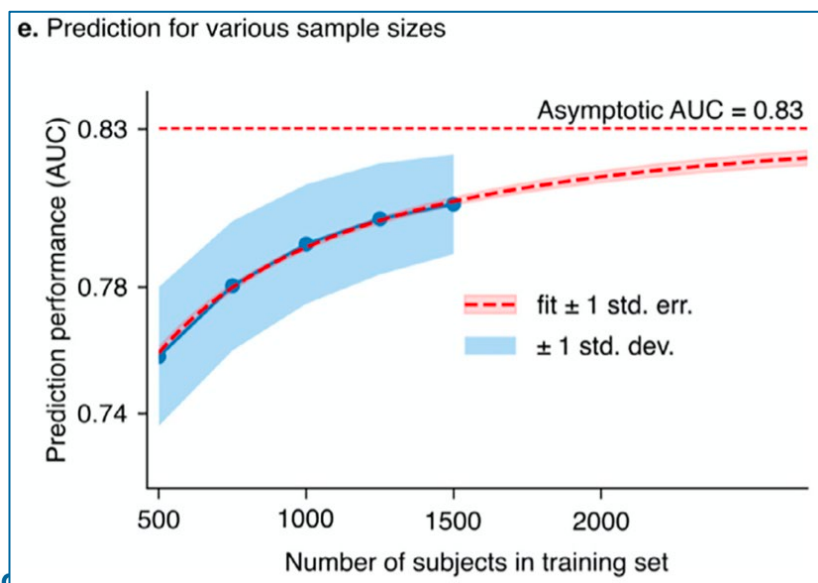
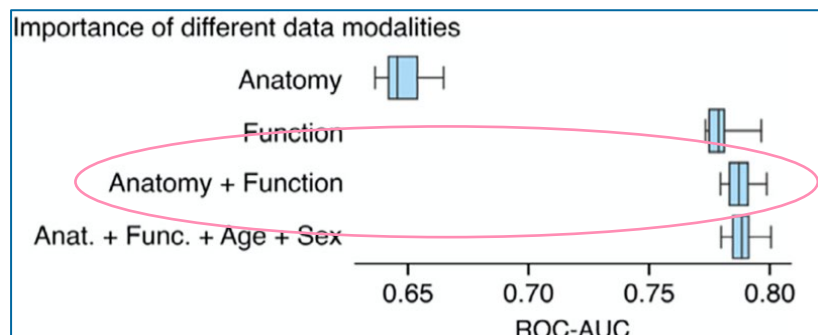
NIMH R21MH107045

Di Martino et al., Sci Data, 2017

Insights from an autism imaging biomarker challenge: Promises and threats to biomarker discovery

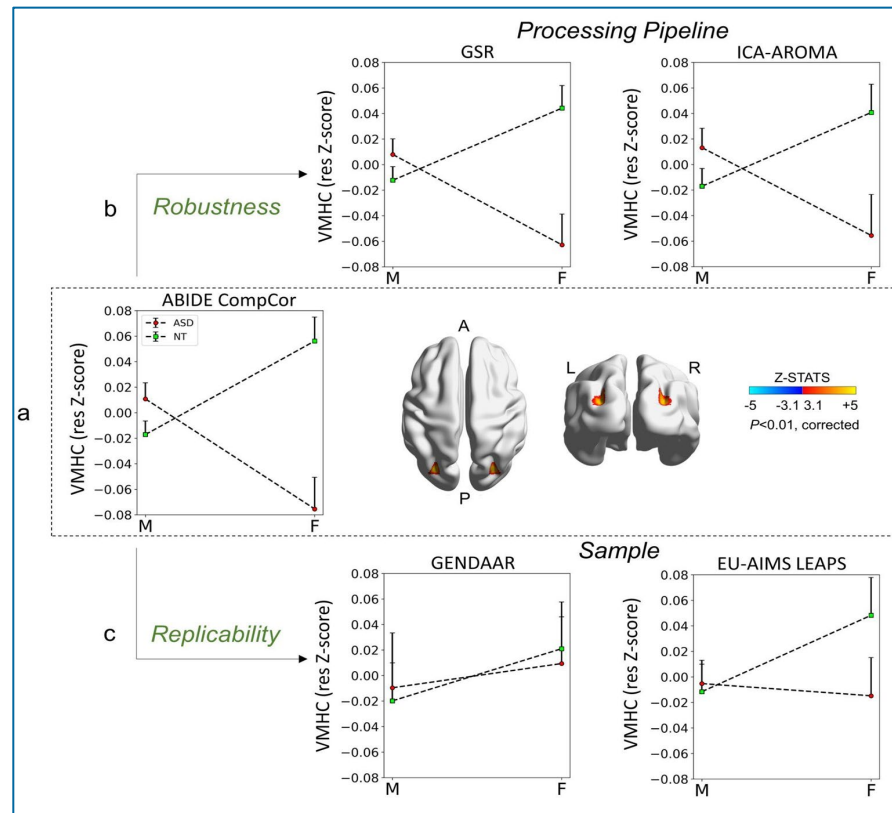
Nicolas Traut^{a,i,†}, Katja Heuer^{a,d,i,†}, Guillaume Lemaître^{b,c,†}, Anita Beggiato^{a,k}, David Germanaud^e, Monique Elmaleh^f, Alban Bethegnies^g, Laurent Bonnasse-Gahot^l, Weidong Cai^j, Stanislas Chambon^p, Freddy Cliquet^a, Ayoub Ghriss^h, Nicolas Guigui^e, Amicie de Pierrefeu^e, Meng Wang^{n,o}, Valentina Zantedeschi^m, Alexandre Boucaud^{b,c}, Joris van den Bossche^{b,c}, Balázs Kegl^q, Richard Delorme^{a,k}, Thomas Bourgeron^a, Roberto Toro^{a,+}, Gaël Varoquaux^{b,r,+,*} Neuroimage, 2022

- MRI powerful and reliable for ASD
- MRI modality matters
- Sample size improves accuracy
- Overfitting and sample variations threat discovery

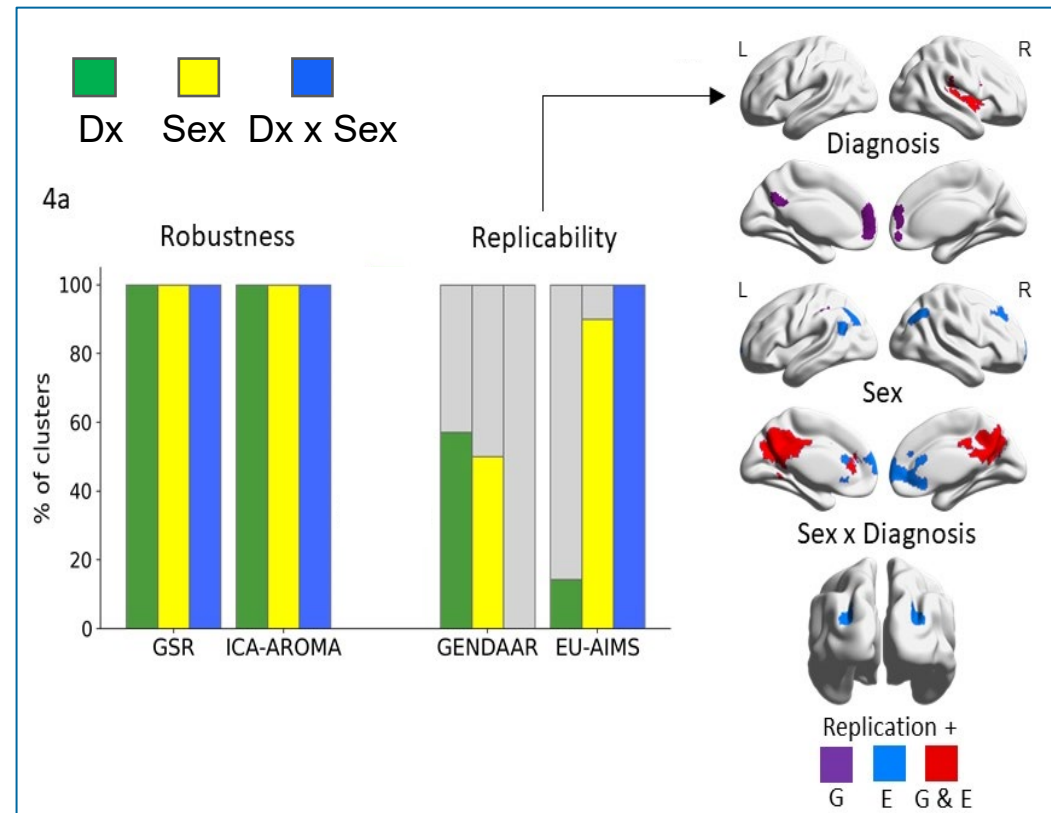


Towards robust and replicable sex differences in the intrinsic brain function of autism

Dorothea L. Floris^{1,2†}, José O. A. Filho^{3†}, Meng-Chuan Lai^{4,5,6,7,8}, Steve Giavasis³, Marianne Oldehinkel², Maarten Mennes¹, Tony Charman⁹, Julian Tillmann^{9,20}, Guillaume Dumas^{10,21}, Christine Ecker^{11,12}, Flavio Dell'Acqua^{11,13}, Tobias Banaschewski¹⁴, Carolin Moessnang¹⁵, Simon Baron-Cohen⁷, Sarah Durston¹⁶, Eva Loth^{11,13}, Declan G. M. Murphy^{11,13}, Jan K. Buitelaar^{1,2,17}, Christian F. Beckmann^{1,2,18}, Michael P. Milham^{3,19} and Adriana Di Martino^{3*}

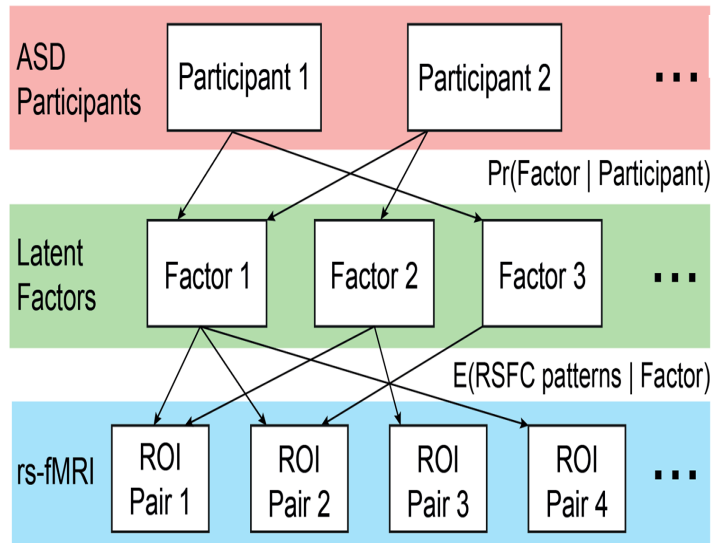


- Diagnostic differences common across the sexes, ASD-specific sex differences
- Results robust to varying analytical choices
- Replicability vary by R-fMRI metric, effects, sample size and sample

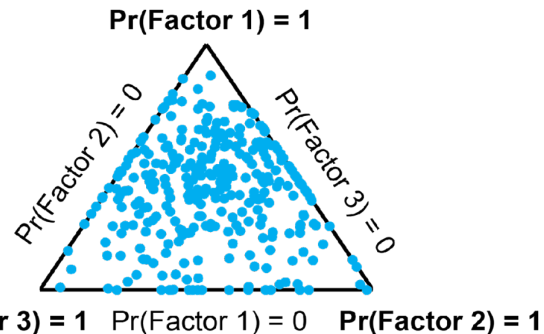


Neurosubtyping

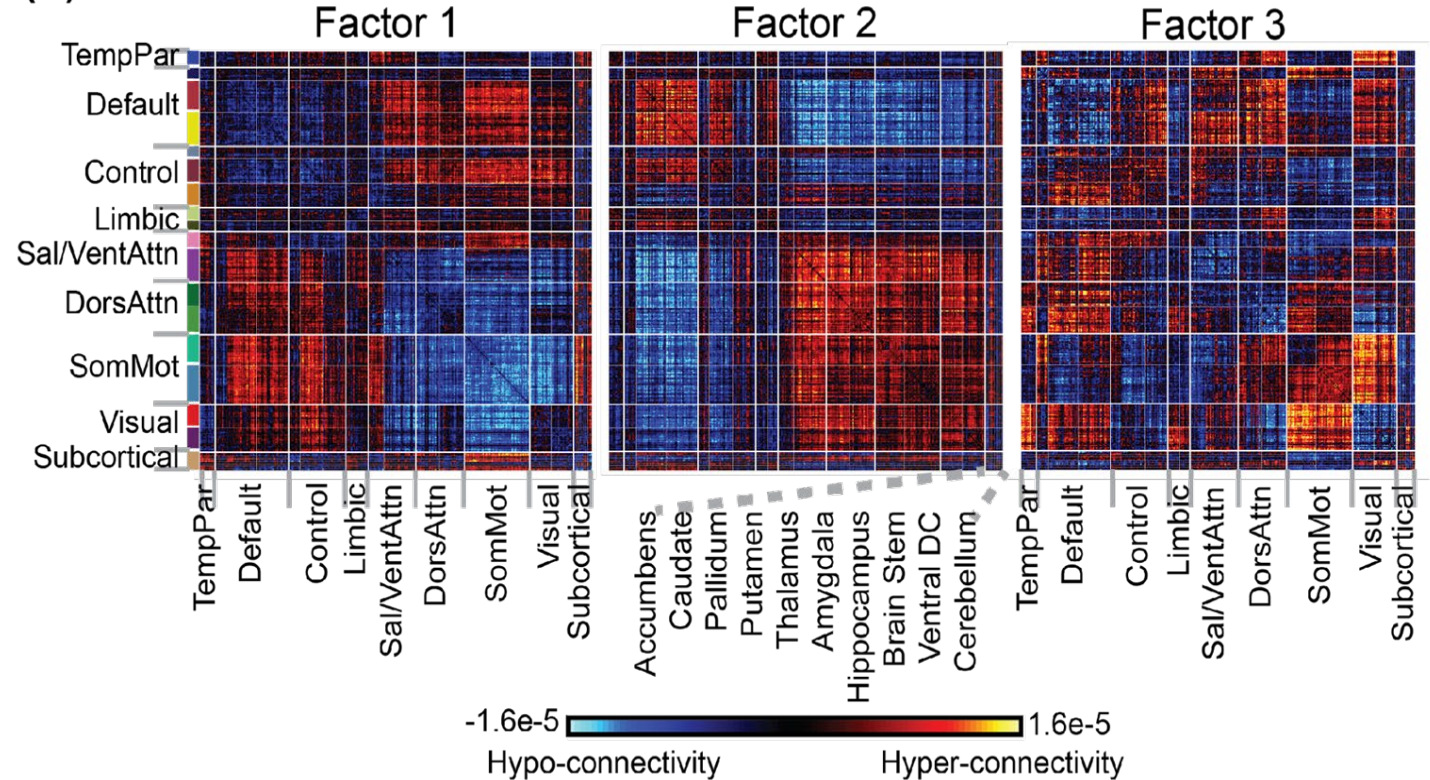
Mosaic of latent brain connectopathy factors - i.e., neurosubtypes



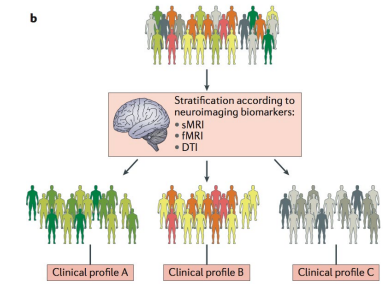
Yeo et al 2016; Sun et al 2017



(C)



Tang, Sun, Floris, Zhan Di Martino, Yeo., Biol Psych 2020



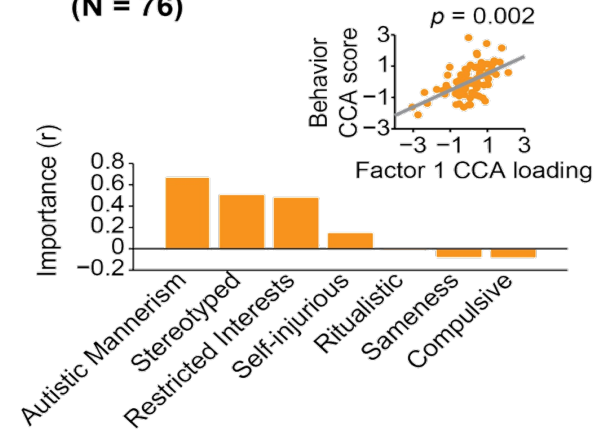
Loth et al, 2016

Phenotypic depth and harmonization have lagged in clinical neuroscience research

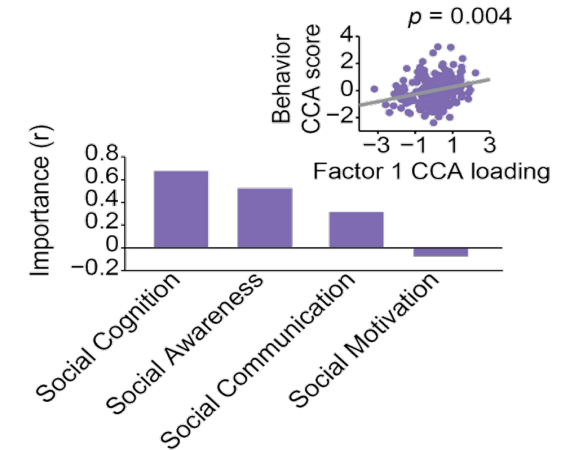


- Across sites depth of multiple phenotyping is limited beyond diagnostics and IQ
- Need prospective harmonized protocols
 - wider and deeper (items-levels) phenotypic data

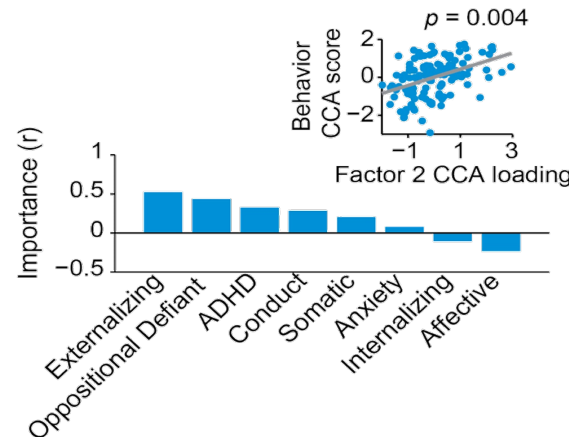
(A) Factor 1 associated with restricted/repetitive behaviors (N = 76)



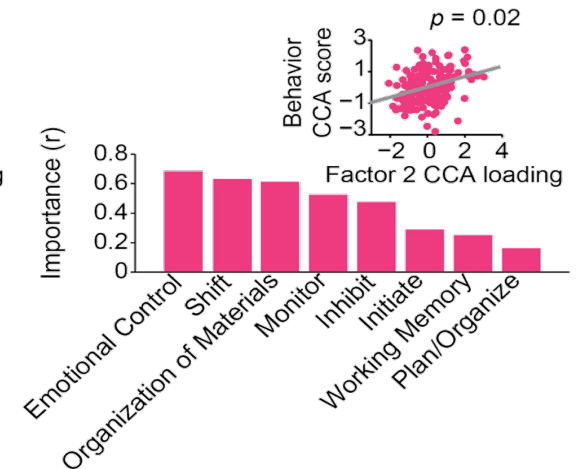
(B) Factor 1 associated with social impairment (N = 200)



(C) Factor 2 associated with externalizing problems (N = 123)



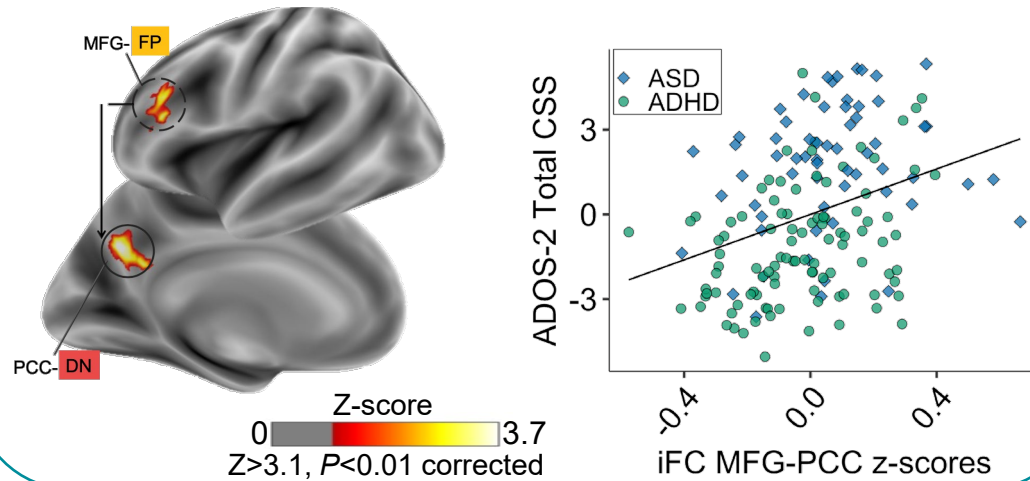
(D) Factor 2 associated with executive dysfunction (N = 171)



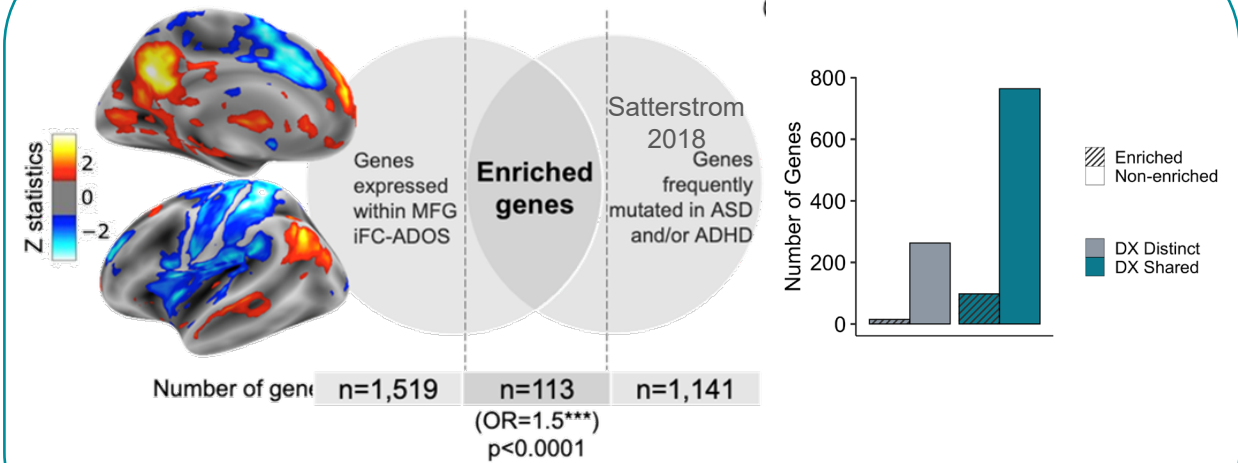
Targeting inter-individual differences – transdiagnostic

N=166; n=103 ADHD, N=63 ASD; 6-12 years, 116 males

Internetwork connectivity relates to clinician-based symptom severity



Shared Transcriptomics

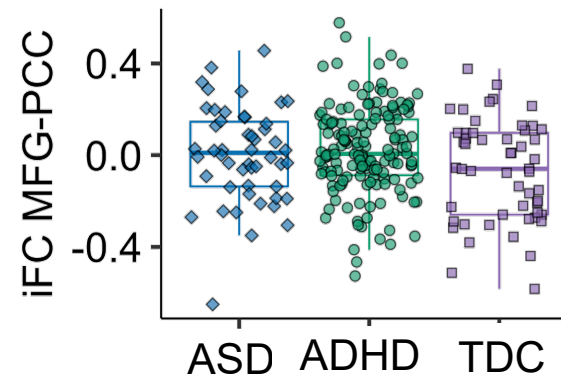


Exploring replicability

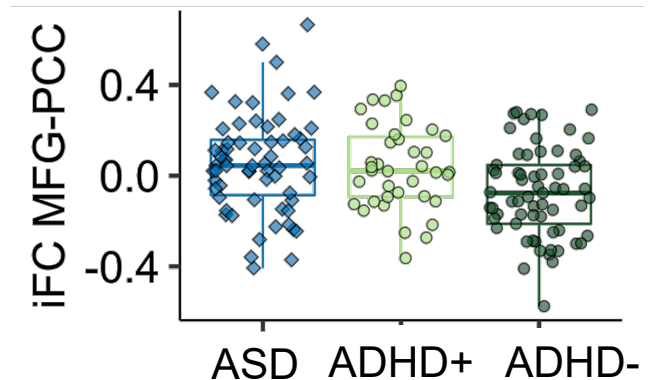
Data Descriptor: An open resource for transdiagnostic research in pediatric mental health and learning disorders Healthy Brain Network

Lindsay M. Alexander¹, Jasmine Escalera², Lei Ai³, Charissa Andreotti¹, Karina Febre¹, Alexander Mangone¹, Natan Vega-Potler¹, Nicolas Langer^{1,2}, Alexis Alexander¹, Meagan Kovacs¹, Shannon Litke¹, Bridget O'Hagan¹, Jennifer Andersen¹, Batya Bronstein¹, Anastasia Bui¹, Marijane Bushey¹, Henry Butler¹, Victoria Castagna¹, Nicolas Camacho¹, Elisha Chan¹, Danielle Citera¹, Jon Clucas¹, Samantha Cohen¹, Sarah Dufek¹, Megan Eaves¹, Brian Fradera¹, Judith Gardner¹, Natalie Grant-Villegas¹, Gabriella Green¹, Camille Gregory¹, Emily Hart¹, Shana Harris¹, Megan Horton¹, Danielle Kahn¹, Katherine Kabotyanski¹, Bernard Karmel¹, Simon P. Kelly¹, Kayla Kleinman¹, Bonhwang Koo¹, Eliza Kramer¹, Elizabeth Lennon¹, Catherine Lord¹, Ginny Mantello¹, Amy Margolis¹, Kathleen R. Merikangas¹⁰, Judith Milham¹¹, Giuseppe Minniti¹, Rebecca Neuhaus¹, Alexandra Levine¹, Yael Osman¹, Lucas C. Parra¹, Ken R. Pugh¹², Amy Racanello¹, Anita Restrepo¹, Tian Saltzman¹, Batya Septimus¹, Russell Tobe^{1,13}, Rachel Waltz¹, Anna Williams¹, Anna Yeo¹, Francisco X. Castellanos^{14,15}, Arno Klein¹, Tomas Paus^{1,16,17}, Bennett L. Leventhal^{1,18}, R. Cameron Craddock^{1,19}, Harold S. Koplewicz¹ & Michael P. Milham^{1,13}

Independent sample – HBN (n=232)

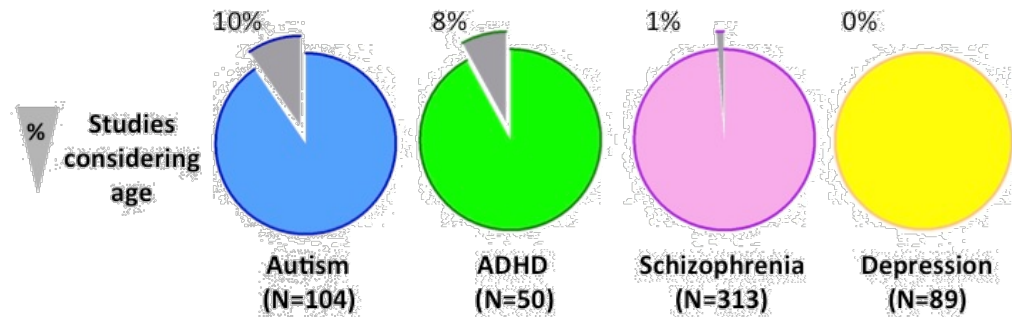


Primary sample (n=166)

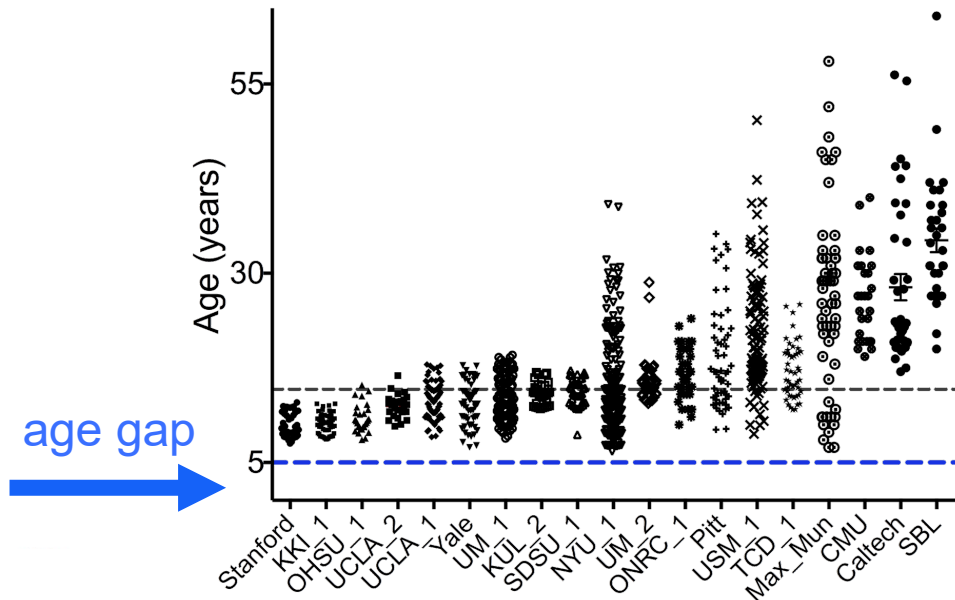


Remaining challenges

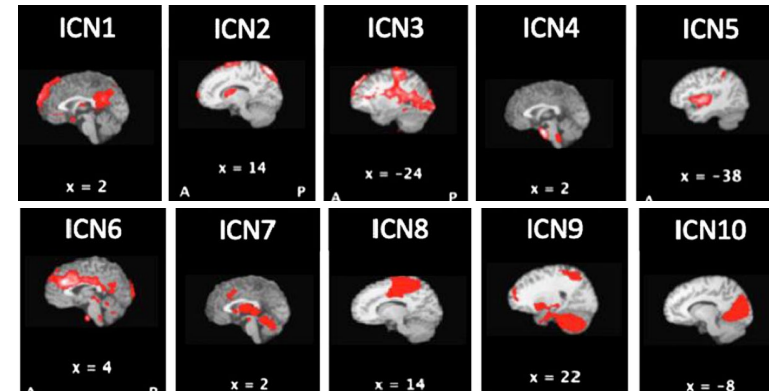
Developmental perspective to developmental disorders



Di Martino et al., Neuron 2014



- Longitudinal approaches are needed to assess traits vs state-related biomarkers
- Focus on younger ages
 - e.g., IBIS >> infants likely to develop autism
- Natural sleep resting state fMRI is feasible



Manning et al 2013

Pre-Prisma 3T



Summary and moving forward

- Aggregation of openly-shared increasingly large MRI dataset is **feasible** and **necessary** to facilitate:
 - Replicability assessments (should be the norm)
 - Leverage heterogeneity
 - *A priori* focus on known sources of variation (e.g., sex at birth, comorbidity...) and underrepresented subgroups
 - Neurosubtyping
 - Inter-individual variability across dimensional metrics
 - Connectome-based fMRI markers are promising candidate for Multimodal BioM discovery but clinical utility of BM depends on phenotyping depth
 - Need for harmonization efforts focusing on reliable and specific measures
 - Measurement-invariance analyses
- Transdiagnostic and longitudinal large-scale efforts needed

Acknowledgments

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Michael P Milham

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Bethany Vibert

Bennet Leventhal

NYU Child Study Center

F Xavier Castellanos

Eva Petkova



**Child Mind
Institute**

Transforming Children's Lives

childmind.org

UCLA

Cathy Lord

NKI

Stan Colcombe

UCSF

Somer Bishop

University of Singapore

Thomas Yeo

MNI, MIC

Boris Bernhardt

ABIDE Consortium



IIT

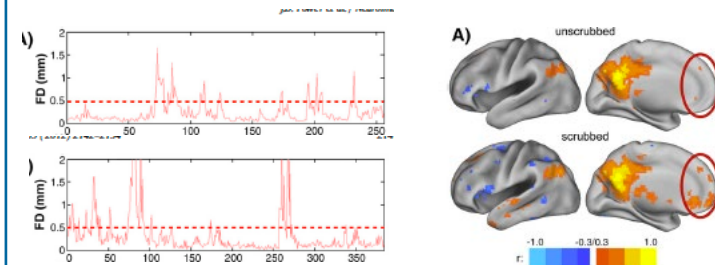
Alessandro Gozzi

Michael Lombardo

Drawbacks and proposed solutions...

Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion

Jonathan D. Power^{a,*}, Kelly A. Barnes^a, Abraham Z. Snyder^{a,b},
Bradley L. Schlaggar^{a,b,c,d}, Steven E. Petersen^{a,b,d,e}



A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics

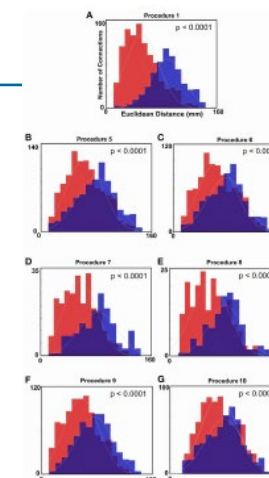
Chao-Gan Yan^{a,b,c}, Brian Cheung^b, Clare Kelly^c, Stan Colcombe^a, R. Cameron Craddock^{b,d},
Adriana Di Martino^c, Qingyang Li^b, Xi-Nian Zuo^e, F. Xavier Castellanos^{a,c}, Michael P. Milham^{a,b,*}

Mitigating head motion artifact in functional connectivity MRI

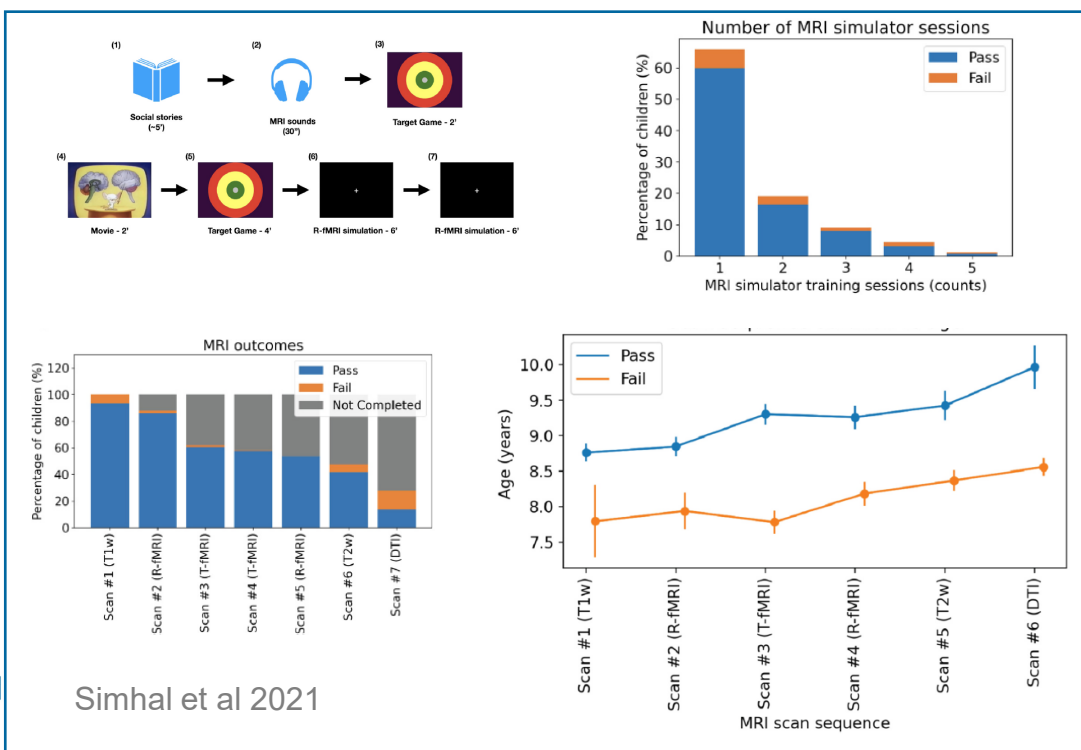
Rastko Ciric¹, Adon F. G. Rosen¹, Guray Erus², Matthew Cieslak^{1,2}, Azeez Adebimpe^{1,2},
Philip A. Cook³, Danielle S. Bassett⁴, Christos Davatzikos^{2,3}, Daniel H. Wolf^{1,2},
Theodore D. Satterthwaite^{1,2*}

An evaluation of the efficacy, reliability, and sensitivity of motion correction strategies for resting-state functional MRI

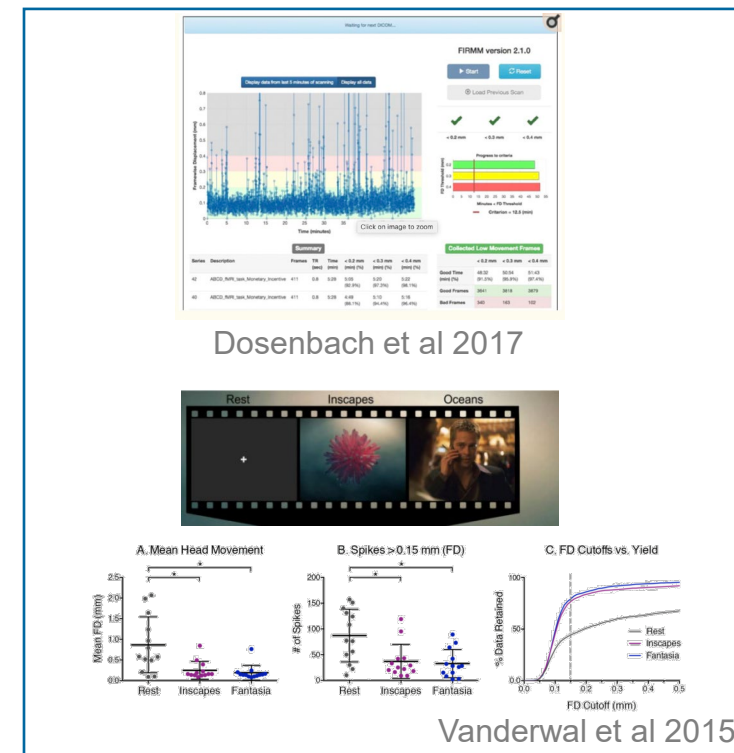
Linden Parkes^a, Ben Fulcher, Murat Yücel, Alex Fornito



Fair et al 2013



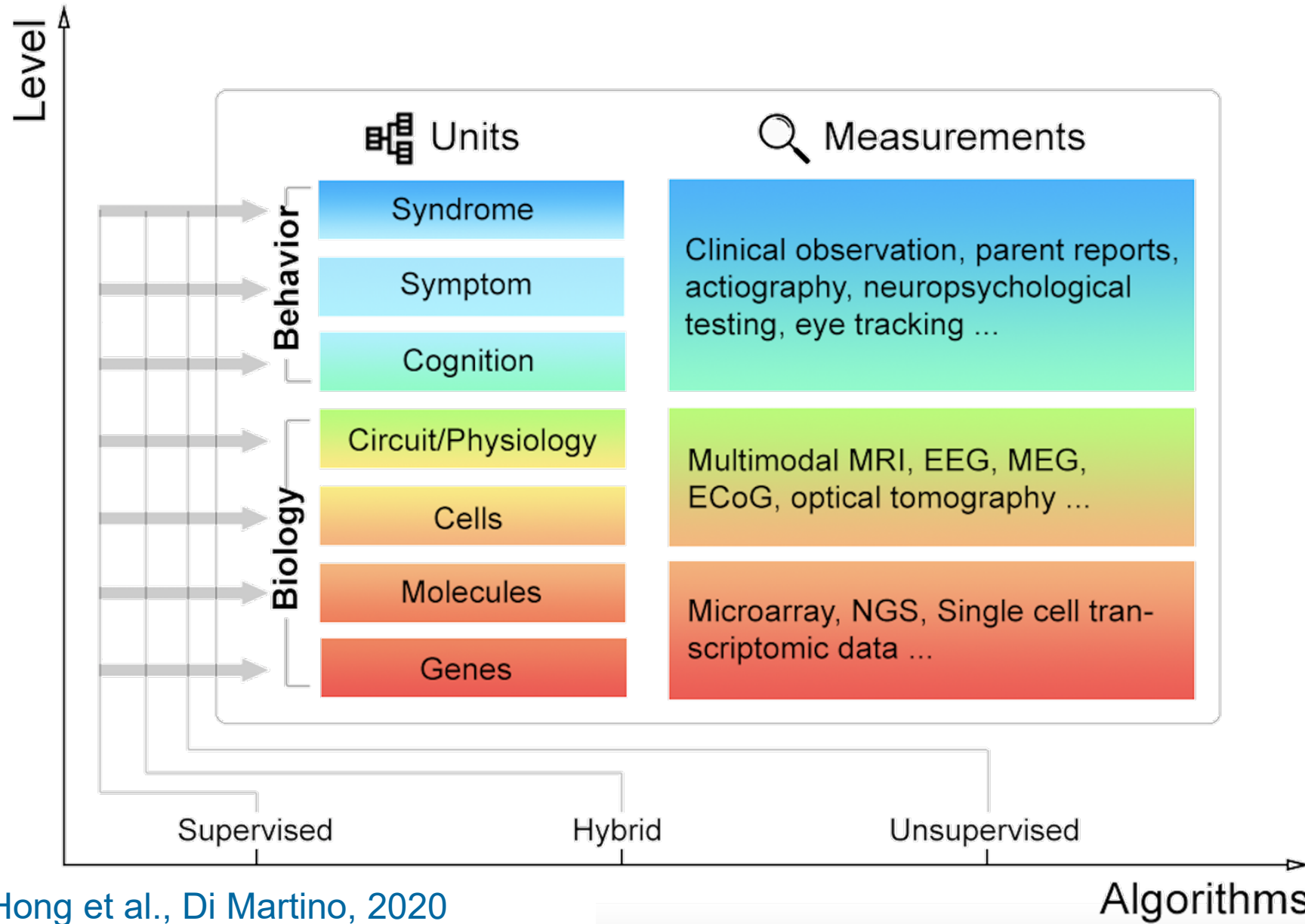
Simhal et al 2021



Dosenbach et al 2017

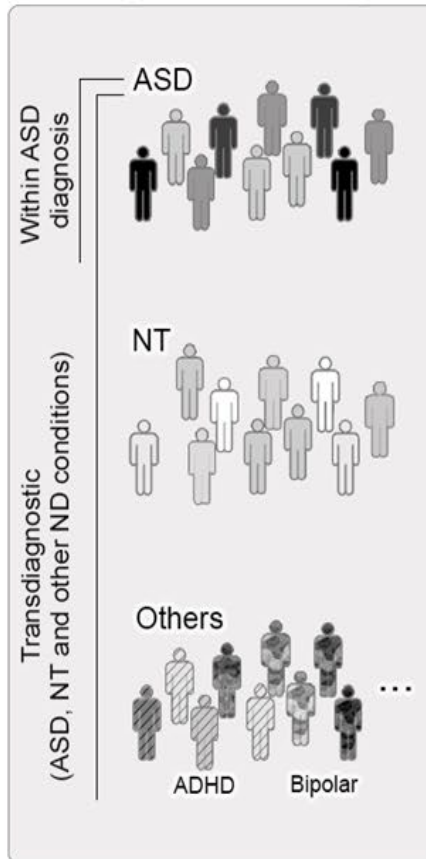
Vanderwal et al 2015

Approaches to Autism

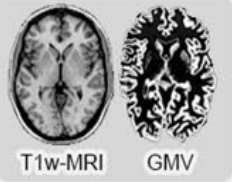


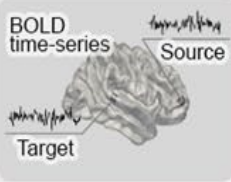
Data driven neurosubtyping in autism

A. Diagnostic samples



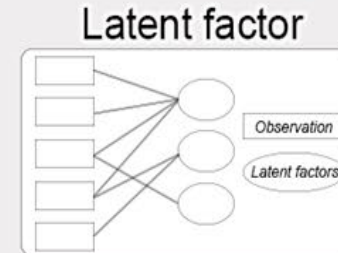
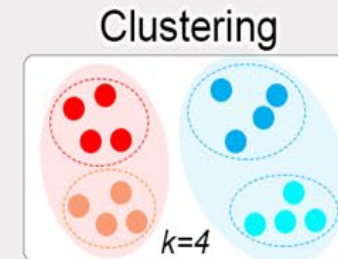
B. Features

- **Feature selection**
 - *A priori* selection
 - Quantitative selection (e.g., Filter, Wrapper methods)
- **Structural**


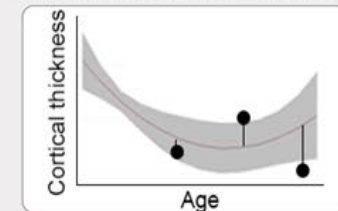
T1w-MRI GMV
- **Functional**


BOLD time-series Source
Target
- **Dimensionality reduction** (e.g. PCA, NMF)
- **Data fusion** (e.g. Multi-viewing learning - SNF, JIVE)
- **Data harmonization** (e.g. Combat, Significance-weighted PCA)

C. Algorithms



Normative modeling



D. Validation

- **Goodness of fit**
 - Silhouette, Davies-Bouldin index
- **Stability**
 - Cross-method validation, Bootstrapping
- **Independent validation**
 - Clinical (e.g., symptom severity - ADOS, ADI-R)
 - Cognitive (neuropsychological scores)
 - Biological (genetics profile - CNV, common/rare variants)
- **Replicability**
 - Bootstrap aggregation (Bagging)
 - Cross-modal validation (e.g., functional connectivity or structural metrics)