Data Aggregation, Synthesis and Replication: Why Resting State fMRI Is and Is Not Ideal

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Child Mind Institute

nki

1000 Functional Connectomes Project

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What Makes R-fMRI the "Low-Hanging Fruit" for Data Aggregation?

- Bypasses potential sources of variation associated with task probes
- Commonly included as an add-on in task activation studies
  - decreases perceived value
  - Increases willingness to share
- Striking similarity in networks observed across laboratories

What Makes R-fMRI Less Than Ideal for Aggregation

Yan et al., 2013b

Table 1
Factors can introduce unintended variations in fMRI measurement.

Category	Factor
1. Acquisition-related variations	Scanner make and model (Friedman and Glover, 2006b), sequence type (spiral vs. echo planar; single-echo vs. multi-echo) (Klarhofer et al., 2002), parallel vs. conventional acquisition (Feinberg et al., 2010; Lin et al., 2005), coil type (surface vs. volume, number of channels, orientation), repetition time, number of repetitions, flip angle, echo time, and acquisition volume (field of view, voxel size, slice thickness/gaps, slice prescription) (Friedman and Glover, 2006a)
2. Experimental-related variations	Participant instructions (Hartstra et al., 2011), eyes-open/eyes-closed (Yan et al., 2009; Yang et al., 2007), visual displays, experiment duration (Fang et al., 2007; Van Dijk et al., 2010)
3. Environment-related variations	Sound attenuation measures (Cho et al., 1998; Elliott et al., 1999), attempts to improve participant comfort during scans (e.g., music, videos) (Cullen et al., 2009), head-motion restraint techniques (e.g., vacuum pad, foam pad, bite-bar, plaster cast head holder) (Edward et al., 2000; Menon et al., 1997), room temperature and moisture (Vanhoutte et al., 2006).
4. Participant-related variations	Circadian cycle (Shannon et al., 2013), prandial (Haase et al., 2009), caffeine (Rack-Gomer et al., 2009), and nicotine status (Tanabe et al., 2011), sleepiness/arousal (Horovitz et al., 2008), sleep deprivation (Samann et al., 2010), scanner anxiety (de Bie et al., 2010), and menstrual cycle status (for women) (Protopopescu et al., 2005)

Lessons Learned From the FCP/INDI Experience

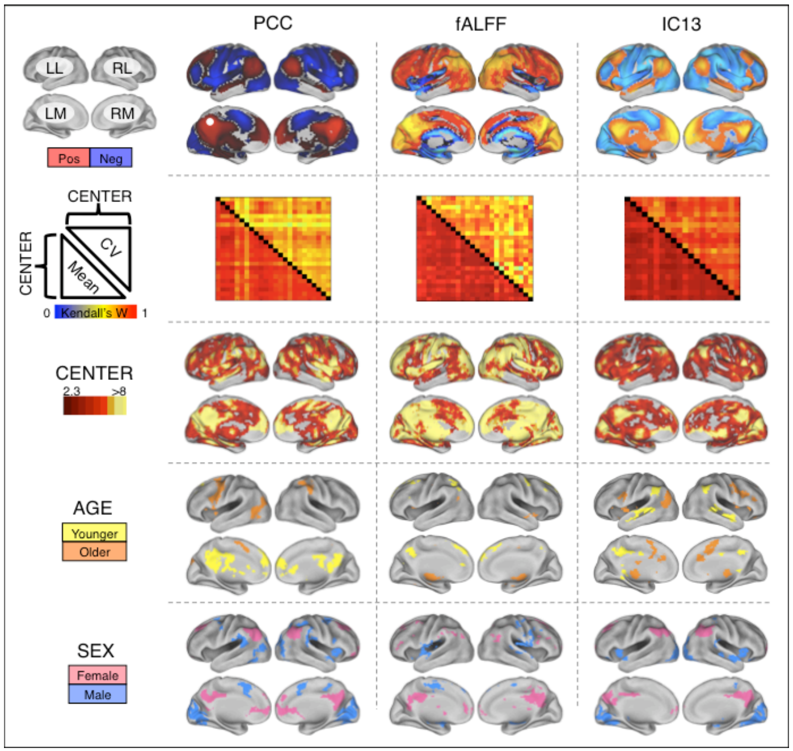
http://fcon_1000.projects.nitrc.org

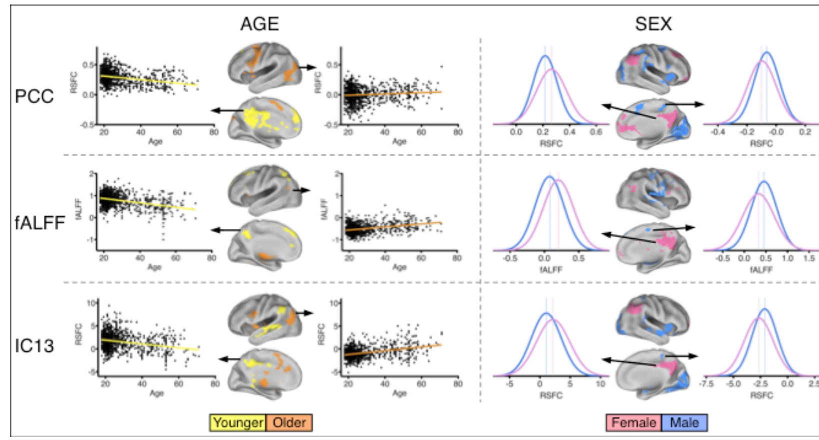
#1

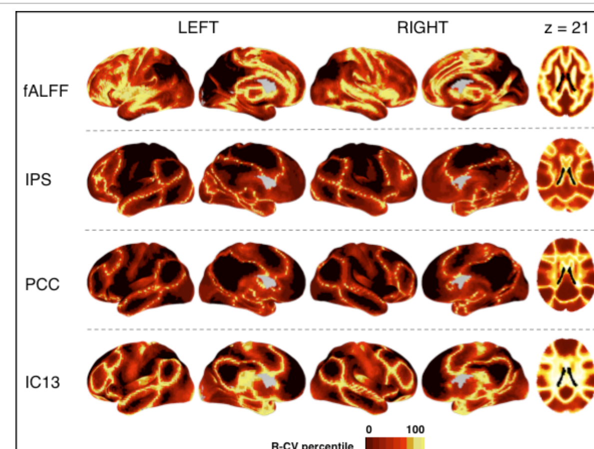
Aggregate R-fMRI Data Analysis is Possible

Toward discovery science of human brain function

Bharat B. Biswal[a], Maarten Mennes[b], Xi-Nian Zuo[b], Suril Gohel[a], Clare Kelly[b], Steve M. Smith[c], Christian F. Beckmann[c], Jonathan S. Adelstein[b], Randy L. Buckner[d], Stan Colcombe[e], Anne-Marie Dogonowski[f], Monique Ernst[g], Damien Fair[h], Michelle Hampson[i], Matthew J. Hoptman[j], James S. Hyde[k], Vesa J. Kiviniemi[l], Rolf Kötter[m], Shi-Jiang Li[n], Ching-Po Lin[o], Mark J. Lowe[p], Clare Mackay[c], David J. Madden[q], Kristoffer H. Madsen[f], Daniel S. Margulies[r], Helen S. Mayberg[s], Katie McMahon[t], Christopher S. Monk[u], Stewart H. Mostofsky[v], Bonnie J. Nagel[w], James J. Pekar[x], Scott J. Peltier[y], Steven E. Petersen[z], Valentin Riedl[aa], Serge A. R. B. Rombouts[bb], Bart Rypma[cc], Bradley L. Schlaggar[dd], Sein Schmidt[ee], Rachael D. Seidler[ff,u], Greg J. Siegle[gg], Christian Sorg[hh], Gao-Jun Teng[ii], Juha Veijola[jj], Arno Villringer[ee,kk], Martin Walter[ll], Lihong Wang[q], Xu-Chu Weng[mm], Susan Whitfield-Gabrieli[nn], Peter Williamson[oo], Christian Windischberger[pp], Yu-Feng Zang[qq], Hong-Ying Zhang[ii], F. Xavier Castellanos[b,j], and Michael P. Milham[b,1]



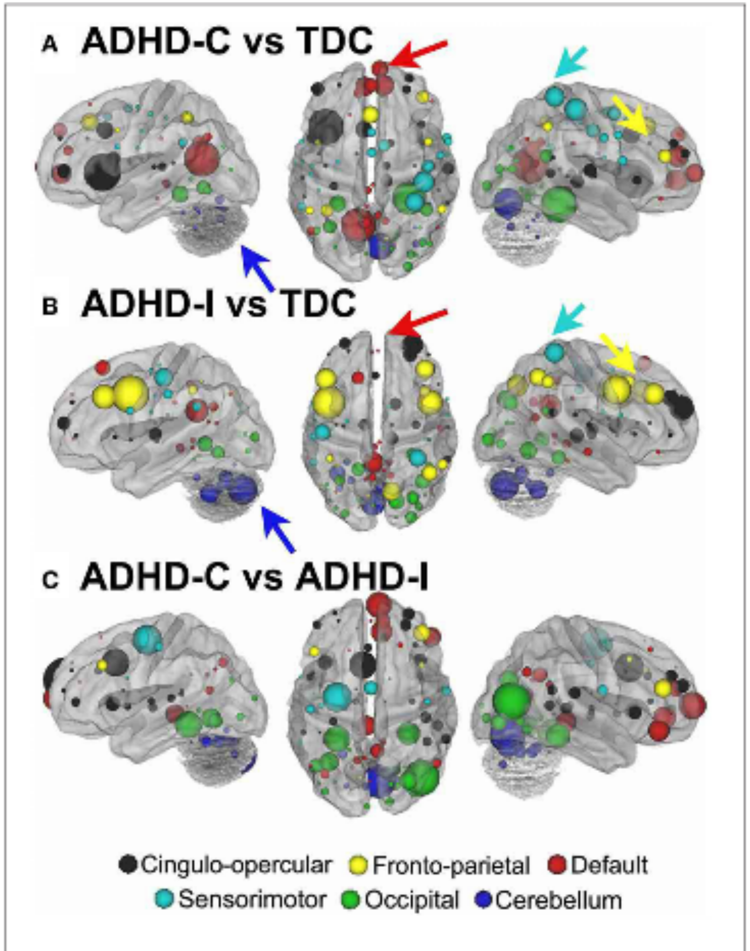




Analysis scripts available at
http://fcon_1000.projects.nitrc.org

Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data

Damien A. Fair[1,2]*, Joel T. Nigg[1,2], Swathi Iyer[1,2], Deepti Bathula[1,2,3], Kathryn L. Mills[1,2], Nico U. F. Dosenbach[4], Bradley L. Schlaggar[4], Maarten Mennes[5], David Gutman[5], Saroja Bangaru[5], Jan K. Buitelaar[6], Daniel P. Dickstein[7], Adriana Di Martino[5], David N. Kennedy[8], Clare Kelly[5], Beatriz Luna[9], Julie B. Schweitzer[10], Katerina Velanova[9], Yu-Feng Wang[11,12], Stewart Mostofsky[13,14], F. Xavier Castellanos[5,15] and Michael P. Milham[15,16]*



Molecular Psychiatry (2013), 1–9

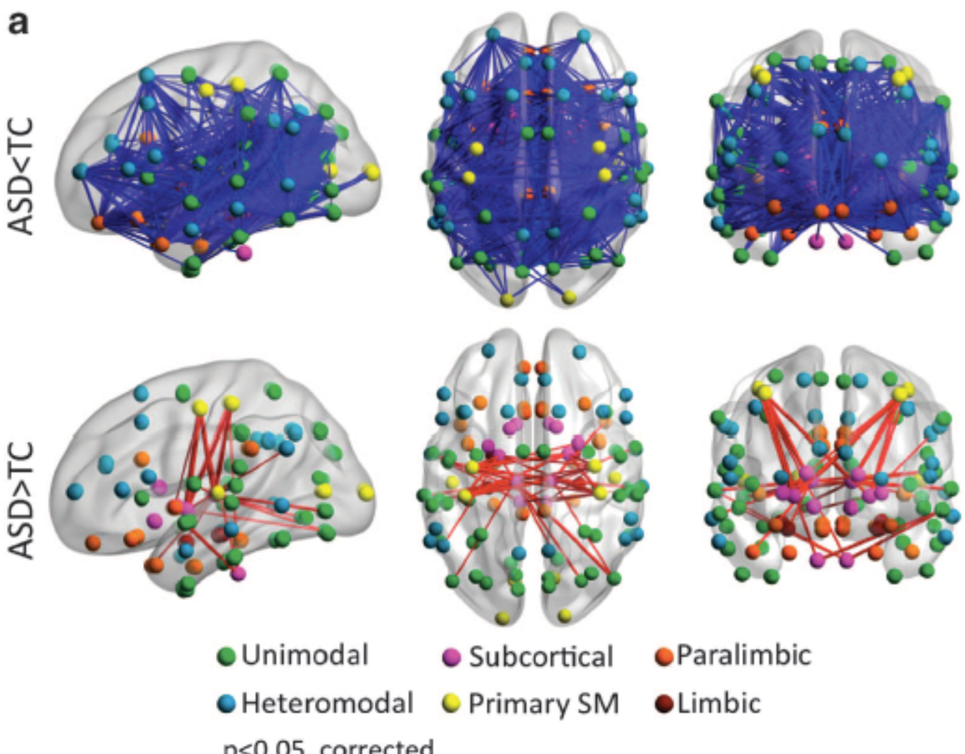
www.nature.com/mp

ORIGINAL ARTICLE

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

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

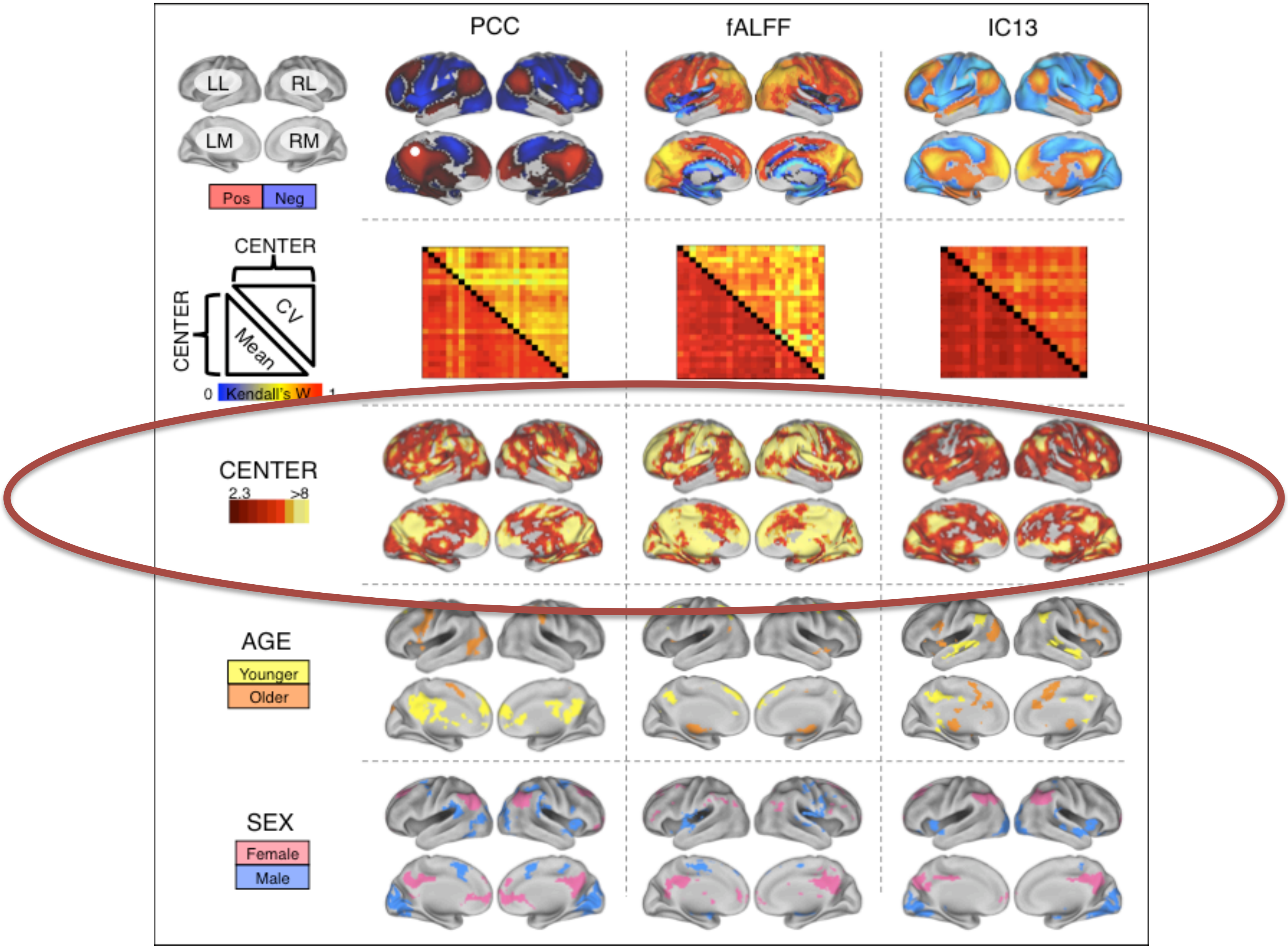
a



b

Functional Divisions	Primary SM		Unimodal		Heteromodal		Paralimbic		Limbic		Subcortical	
ASD vs.TC	*Hypo*	*Hyper*	*Hypo*	*Hyper*	*Hypo*	*Hyper*	*Hypo*	*Hyper*	*Hypo*	*Hyper*	*Hypo*	*Hyper*
	n (%)		*n (%)*		*n (%)*		*n (%)*		*n (%)*		*n (%)*	
Primary SM	6 (13%)											
Unimodal	88 (20%)		276 (29%)									
Heteromodal	32 (13%)		166 (16%)		57 (21%)							
Paralimbic	34 (19%)		147 (19%)		104 (24%)		57 (37%)					
Limbic	7 (18%)		14 (8%)		7 (7%)		14 (19%)		1 (17%)			
Subcortical		20 (17%)		18 (3%)		1 (0%)	10 (5%)	1 (0%)		1 (2%)	2 (3%)	
Total n (%)	**167 (16%)**	20 (2%)	**691 (18%)**	18 (0%)	**366 (15%)**	1 (0%)	**366 (20%)**	1 (0%)	**43 (11%)**	1 (0%)	12 (1%)	**41 (3%)**

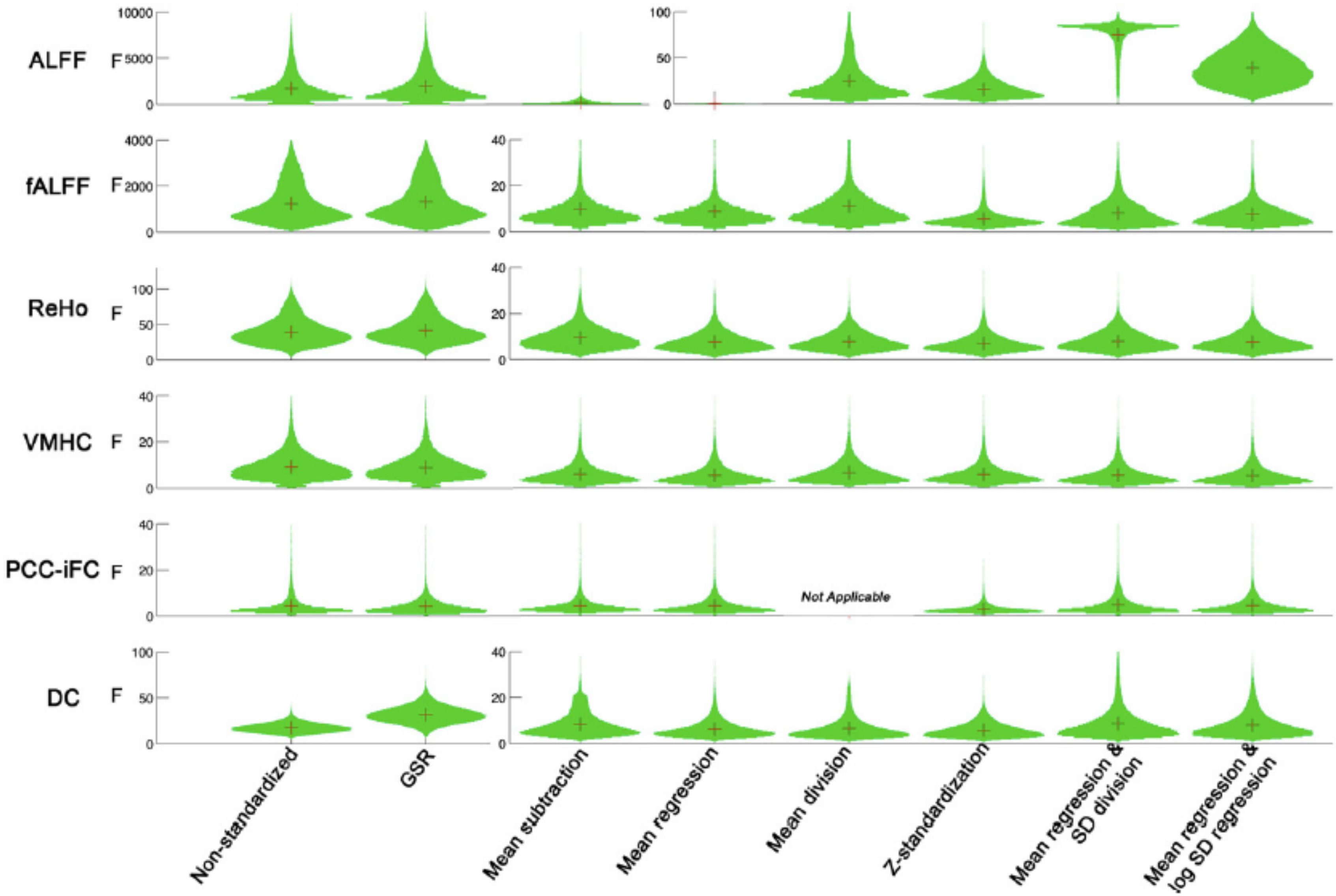
#2
Site-Related Variation is Very Real
(and potentially addressable post-hoc)



Biswal et al., 2010

Standardizing the intrinsic brain: Towards robust measurement of inter-individual variation in 1000 functional connectomes

Chao-Gan Yan [a,b,c], R. Cameron Craddock [a,b], Xi-Nian Zuo [d], Yu-Feng Zang [e], Michael P. Milham [a,b,*]



Standardizing the intrinsic brain: Towards robust measurement of inter-individual variation in 1000 functional connectomes

Chao-Gan Yan [a,b,c], R. Cameron Craddock [a,b], Xi-Nian Zuo [d], Yu-Feng Zang [e], Michael P. Milham [a,b,*]

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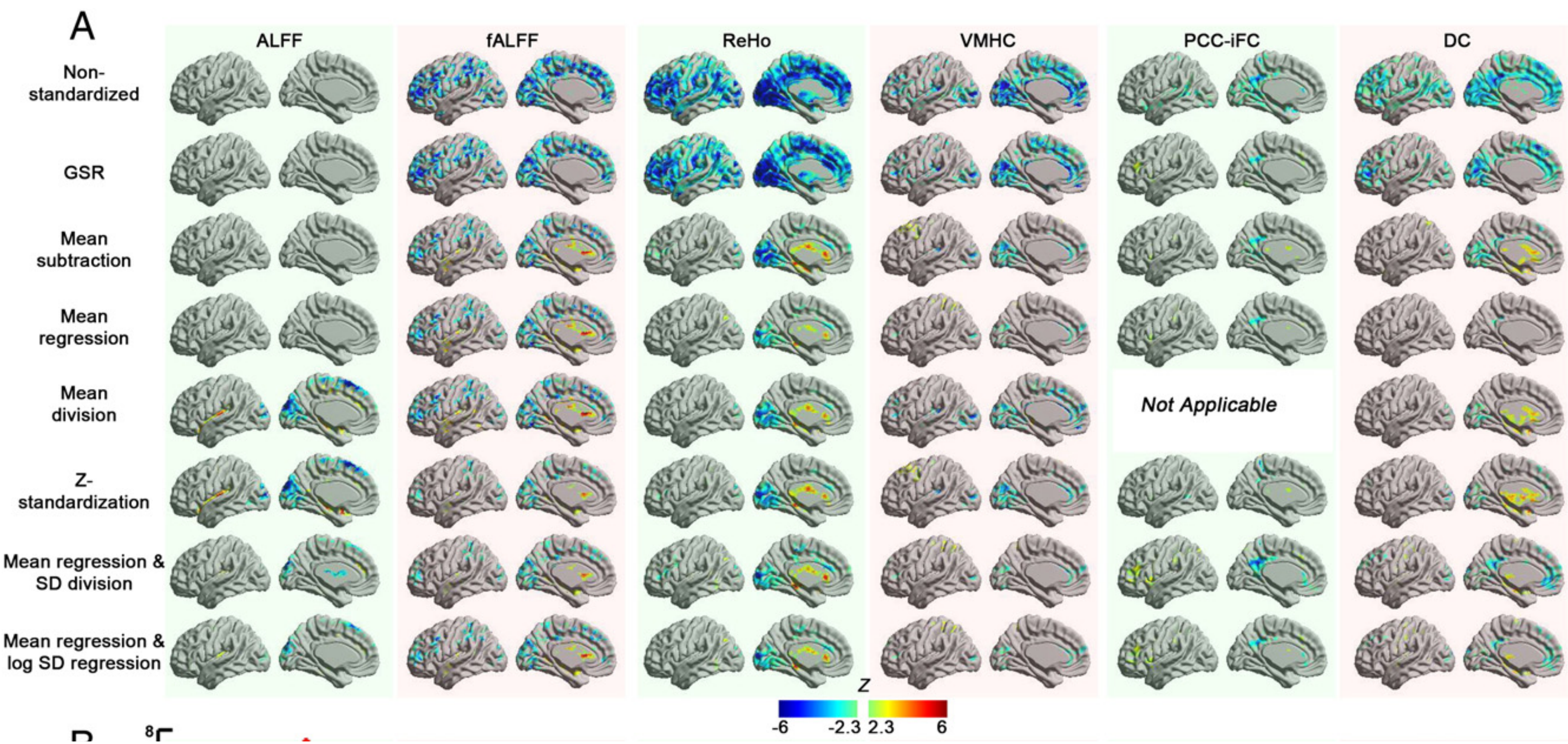
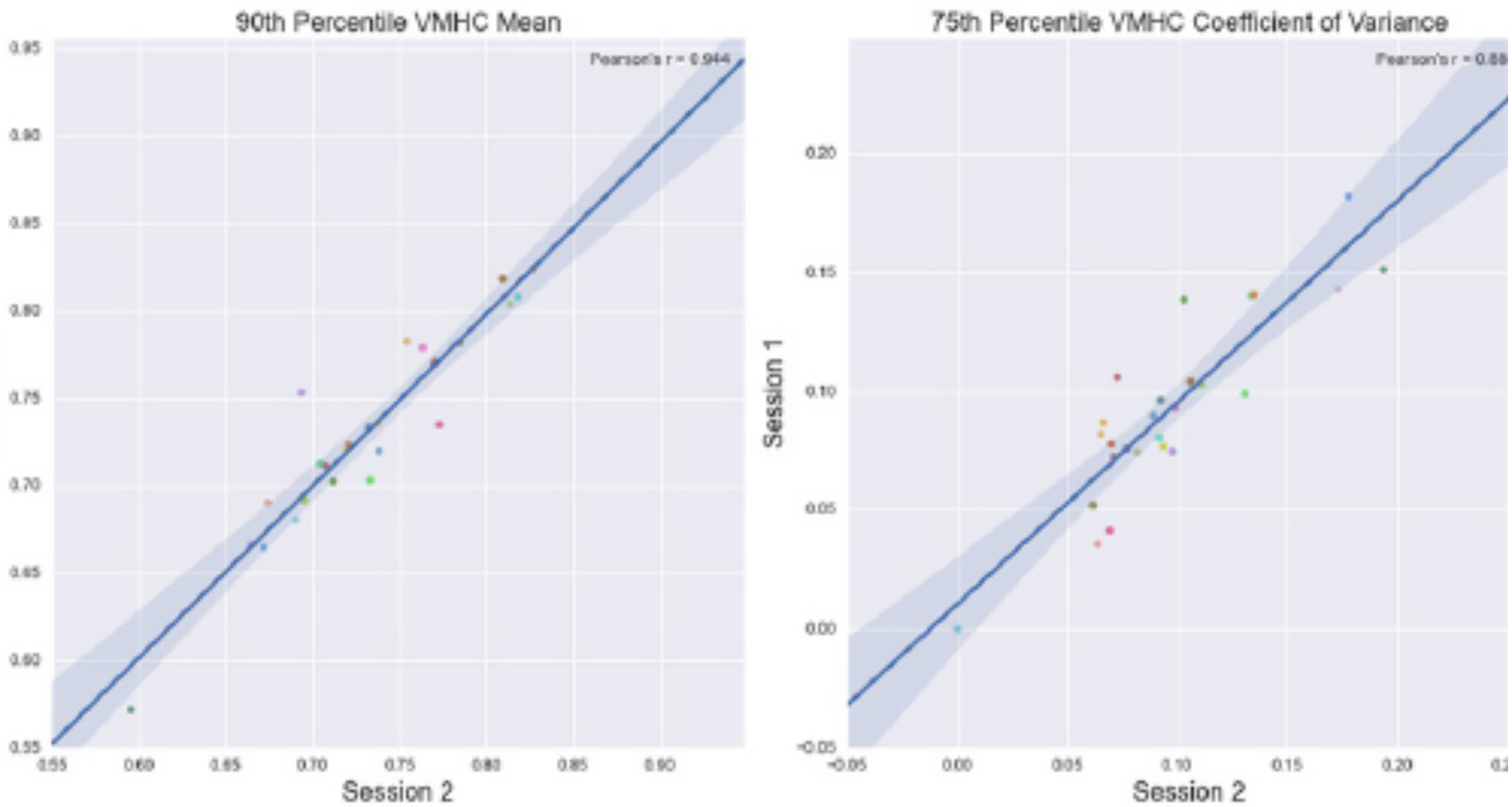
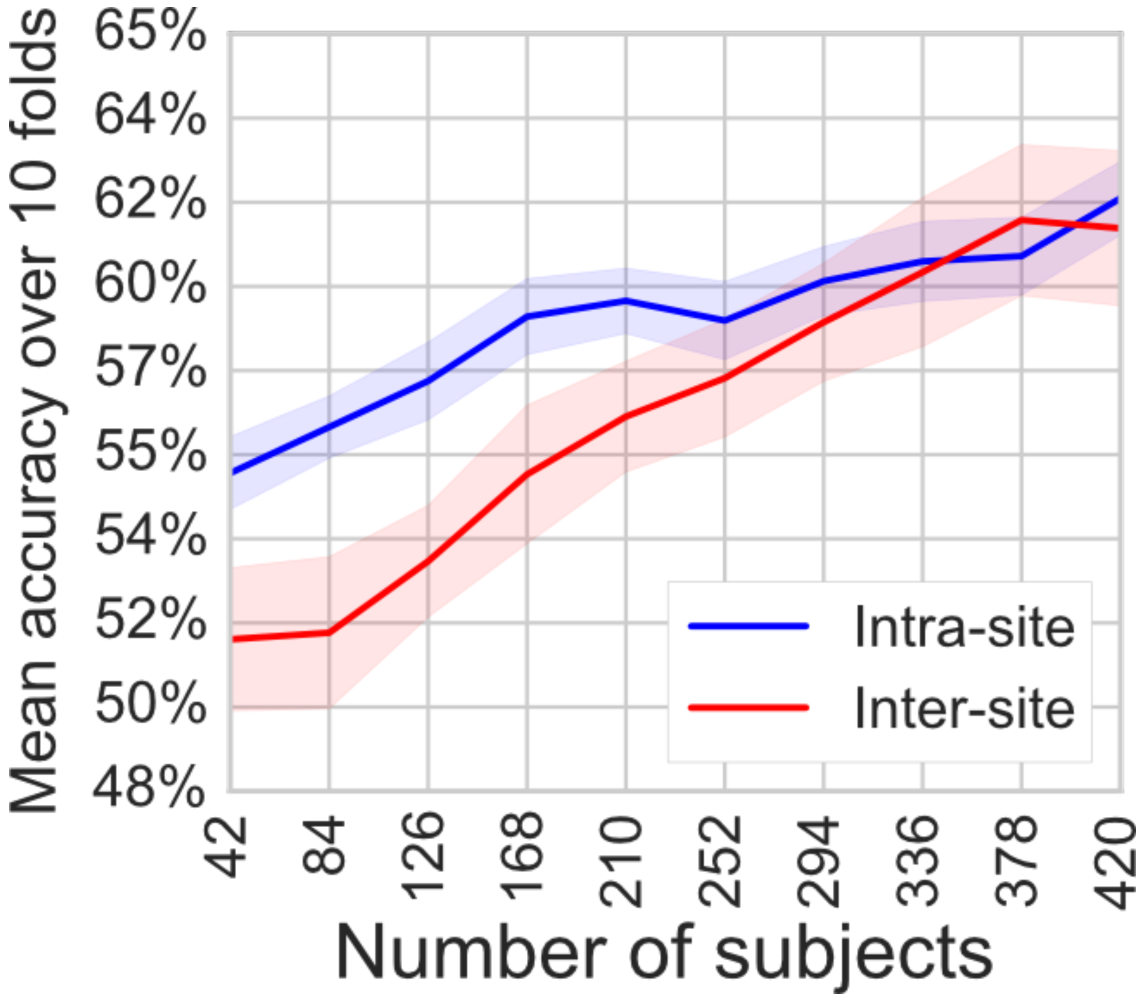


An open science resource for establishing reliability and reproducibility in functional connectomics

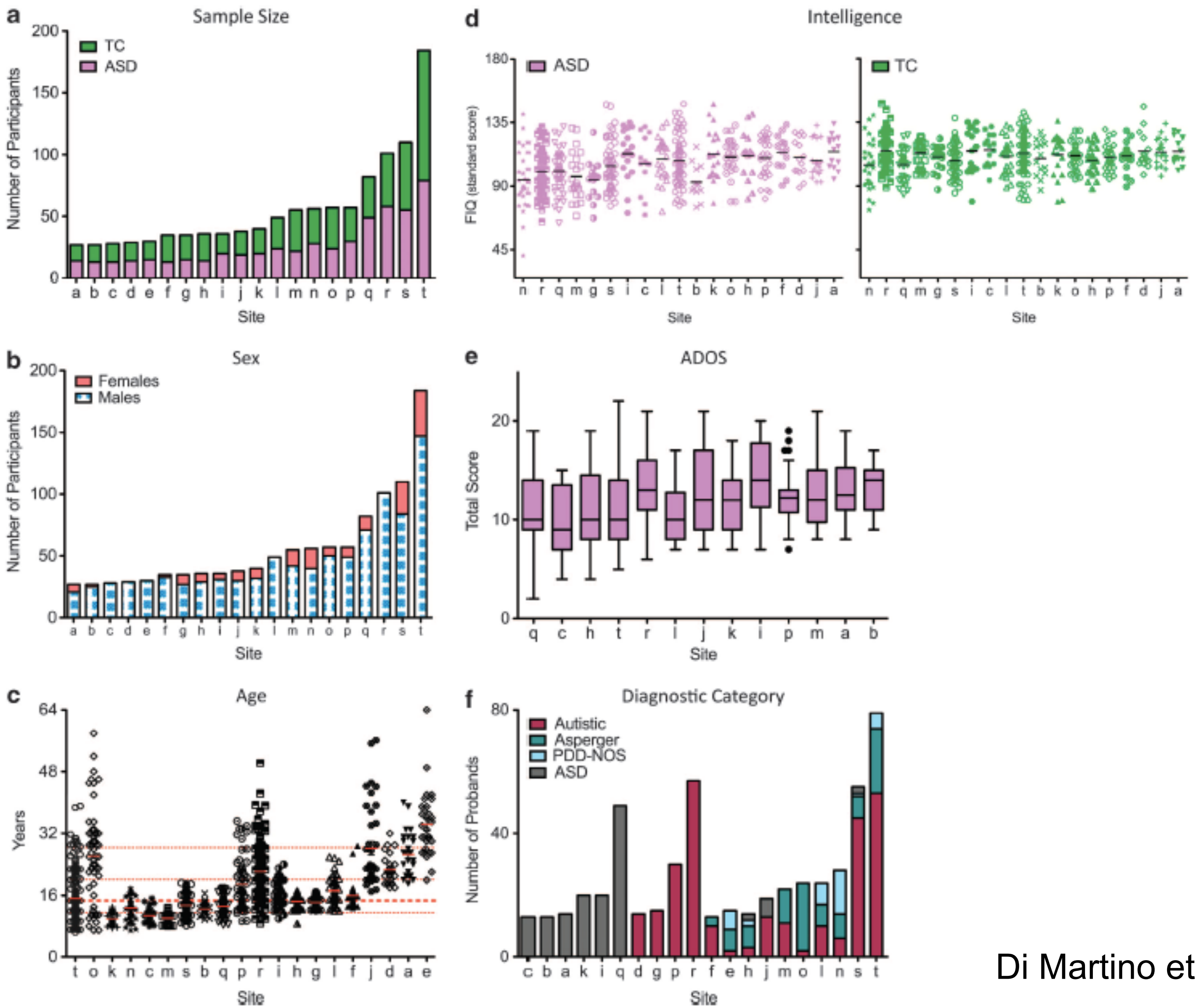
Xi-Nian Zuo[1,2,*], Jeffrey S. Anderson[3], Pierre Bellec[4], Rasmus M. Birn[5], Bharat B. Biswal[6], Janusch Blautzik[7], John C.S. Breitner[8], Randy L. Buckner[9], Vince D. Calhoun[10], F. Xavier Castellanos[11,12], Antao Chen[2], Bing Chen[13], Jiangtao Chen[2], Xu Chen[2], Stanley J. Colcombe[11], William Courtney[10], R. Cameron Craddock[11,14], Adriana Di Martino[12], Hao-Ming Dong[1,15], Xiaolan Fu[1,16], Qiyong Gong[17], Krzysztof J. Gorgolewski[18], Ying Han[19], Ye He[1,15], Yong He[20], Erica Ho[11,14], Avram Holmes[21], Xiao-Hui Hou[1,15], Jeremy Huckins[22], Tianzi Jiang[23], Yi Jiang[1], William Kelley[22], Clare Kelly[12], Margaret King[10], Stephen M. LaConte[24], Janet E. Lainhart[5], Xu Lei[2], Hui-Jie Li[1], Kaiming Li[17], Kuncheng Li[25], Qixiang Lin[20], Dongqiang Liu[13], Jia Liu[20], Xun Liu[1], Yijun Liu[2], Guangming Lu[26], Jie Lu[25], Beatriz Luna[27], Jing Luo[28], Daniel Lurie[11,14], Ying Mao[29], Daniel S. Margulies[18], Andrew R. Mayer[10], Thomas Meindl[7], Mary E. Meyerand[30], Weizhi Nan[1,15], Jared A. Nielsen[3], David O'Connor[11,14], David Paulsen[27], Vivek Prabhakaran[31], Zhigang Qi[25], Jiang Qiu[2], Chunhong Shao[32], Zarrar Shehzad[11,14], Weijun Tang[33], Arno Villringer[34], Huiling Wang[35], Kai Wang[1,15], Dongtao Wei[2], Gao-Xia Wei[1], Xu-Chu Weng[13], Xuehai Wu[29], Ting Xu[1,11,14], Ning Yang[1,15], Zhi Yang[1], Yu-Feng Zang[13], Lei Zhang[1,15], Qinglin Zhang[2], Zhe Zhang[1,15], Zhiqiang Zhang[26], Ke Zhao[1], Zonglei Zhen[20], Yuan Zhou[1], Xing-Ting Zhu[1,15] & Michael P. Milham[11,14]


90th Percentile VMHC Mean
Pearson's r = 0.944
Session 2
75th Percentile VMHC Coefficient of Variance
Session 1
Session 2



Abraham et al., Varoquaux, in prep

#3
Site-Related Variation Goes Well Beyond Imaging Protocols



Di Martino et al., 2010

General Information:

- Demographic Questionnaire (DEMOS)
- Edinburgh Handedness Questionnaire (EHQ)
- Hollingshead Four-Factor Index of Socioeconomic Status: (SES-Adult, Child)
- Medical History Questionnaire-Adult, Child
- Medical Conditions
- Medication Form
- PhenX (13+)
- Sex Role Identity Scale (13+)
- Sexual History (13+)
- Sexual Orientation Scale (13+)

Physical Measures:

- Actigraphy
- Bike Test
- Blood Collection: chemistry profile, lipid profile, thyroid profile, CBC with differential, lead level, genetics, pregnancy test
- Urine Sample (Drug Test)(11+)
- Height/Weight
- Hip/Waist Measurements
- Ishihara's Test for Color Deficiency
- Grip Strength
- The Grooved Pegboard Test
- MRI Mock Scan
- MRI Scan
- MRI Incidental Finding Report
- Tanner Staging (TANN)(6-17)
- Vital Signs

Cognitive Tasks:

- Attention Network Test (ANT) (Child, 6-12)(Adult, 12+)
- Penn's Computerized Neurocognitive Battery (CNB)
- Delis-Kaplan Executive Functioning System (D-KEFS)(8+)
- Wechsler Abbreviated Scale of Intelligence (WASI-II)
- Wechsler Individual Achievement Test – Second Edition Abbreviated (WIAT-IIA)
- Digit Span (Forward and Backward)(Child, 6-17)(Adult, 18+)
- Rey Auditory Verbal Learning Test (RAVLT)(8+)

Diagnostic Assessments:

- Adult ADHD Clinical Diagnostic Scale (ACDS)(18+)
- Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-PL)(6-17)
- Structured Clinical Interview for DSM-IV – Non Patient Edition (SCID-NP)(18+)

Behavioral Measures:

- The High-Functioning Autism Spectrum Screening Questionnaire (ASSQ)(6-17)
- Behavior Assessment System for Children, 2nd Edition – Parent Rating Scale (BASC -2, 6-11), (BASC – 2, 12–17)
- The Behavioral Indicator of Resiliency to Distress (BIRD)
- Yale-Brown Obsessive Compulsive Scale (CY-BOCS, 6-17), (Y-BOCS, 18+)
- Conners Adult ADHD Rating Scale – Self Report, Short Version (CAARS-S:S)(18+)

Behavioral Measures Continued:

- The Child Behavior Checklist – Parent Report Form (CBCL), Youth Self-Report (YSR)(11-17), Adult Self Report (ASR)(18-59), Older Adult Self Report (OASR)(60+)
- The Children's Behavior Questionnaire (Very Short Form) – (CBQ-VSF), The Early Adolescent Temperament Questionnaire (Revised) Parent Report (EATQ-R)(9-15), Adult Temperament Questionnaire (ATQ)(16+)
- The Children's Depression Inventory 2 (CDI-2)(7-17), Beck Depression Inventory (BDI – II)(18-64), Geriatric Depression Scale (GDS)(65-85)
- The Comprehensive Addiction Severity Index for Adolescents (CASI-A)(11+)
- The Children's Eating Behavior Questionnaire (CEBQ)(6-11), Tanner Three-Factor Eating (TFEQ)(12+)
- The Cognitive Failures Questionnaire (CFQ) (6+)
- The Cambridge-Hopkins Restless Legs Syndrome (Version 2) (CHRLS)(13+)
- The Conners ADHD Rating Scale 3 - Parent Short Form (6+)
- The Conners ADHD Rating Scale 3 – Youth Short Form (8-17)
- The Domain-Specific Risk-Taking Scale (DOSPERT)(18+)
- Dot Probe
- Eating Disorder Examination Questionnaire (EDEQ)(13+)
- Fagerstrom Test for Nicotine Dependence (FTND)(18+)
- Modified Fagerstrom Tolerance Questionnaire – Adolescents (FTQA)(13-17)
- Inventory of Callous-Unemotional Traits – Parent Version (ICUP); Youth Self-Report (ICUY)(13+)
- International Physical Activity Questionnaire (IPAQ)(15+)
- Interpersonal Reactivity Index (IRI)(13+)
- Multidimensional Anxiety Scale for Children (MASC)(8-17)
- MRI Mind Wandering Questionnaire (MRIQ)(13+)
- NEO Five Factor Inventory (NEO-FFI-3)(12+)
- NIDA Quick Screen V1.01(11+)
- The 21-Item Peters et al. Delusions Inventory (PDI-21)(13+)
- Pittsburgh Sleep Quality Index (PSQI)(13+)
- Positive and Negative Affect Schedule-Short Form (PANAS-S)
- Repetitive Behaviors Scale – Revised (RBS-R)(6-17)
- Satisfaction Survey (Adult, Child)(12+)
- Social Networking Questionnaire (22-85)
- Social Responsiveness Scale (SRS) - Parent Report (6-17)
- State Trait Anxiety Inventory (STAI)(18+)
- Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behavior Scale (SWAN)(6-17)
- Trauma Symptom Checklist for Adults (TSC-40)(18+), Trauma Symptom Checklist for Children (TSC-C)(8-17)
- UCLA PTSD Reaction Index (UCLA-Parent) (UCLA-Youth)(8+)
- UPPS-P Impulsive Behavior Scale (18+)
- Yale Global Tic Severity Scale (YGTSS)(6+)
- Youth Risk Behavior Surveillance System YRBSS-MS (11-13), YRBSS-HS (14-21)

Behavioral Measures, Real-Time Neurofeedback Only

- Affect Intensity Measure (AIM)
- Ruminative Response Scale (RRS)
- Rapid Visual Information Processing Assessment (RVIP)
- Penn State Worry Questionnaire (PSQW)
- Pereservative Thinking Questionnaire (PTQ)
- Emotional Regulation Questionnaire (ERQ)
- Short Imaginal Process Inventory (SIPI)
- Meditation Questionnaire

Nooner et al., 2012

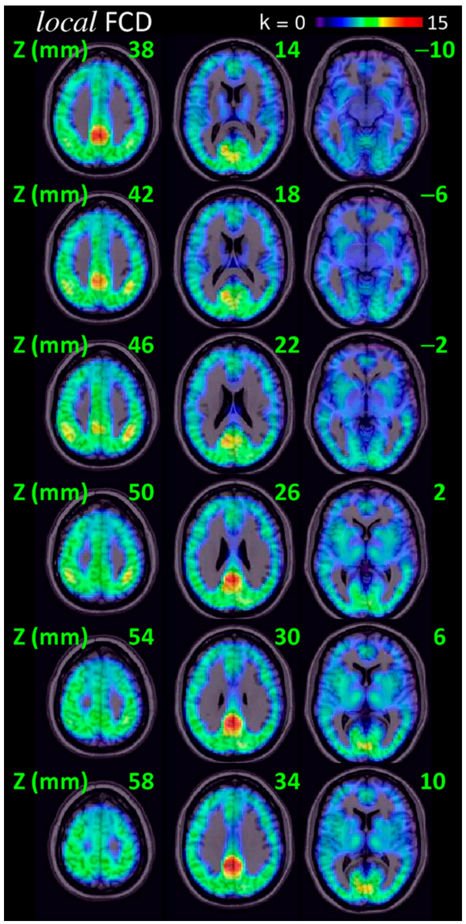
#4
Aggregation Promotes Replication

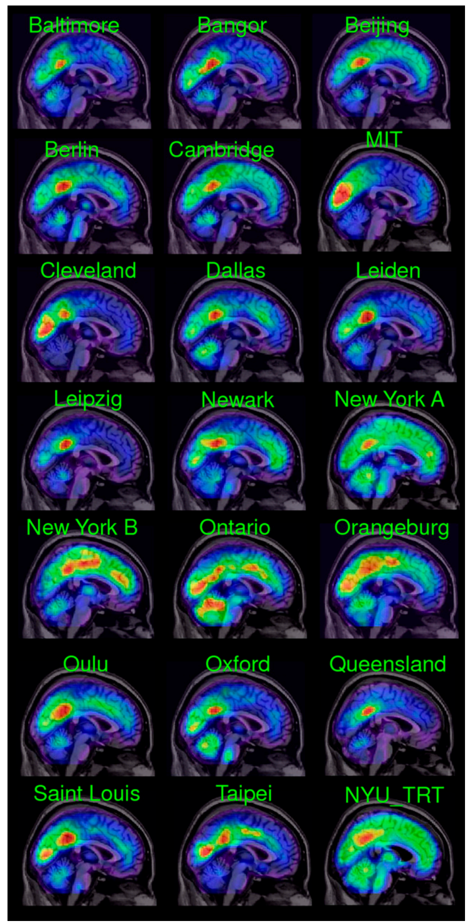
Functional connectivity density mapping

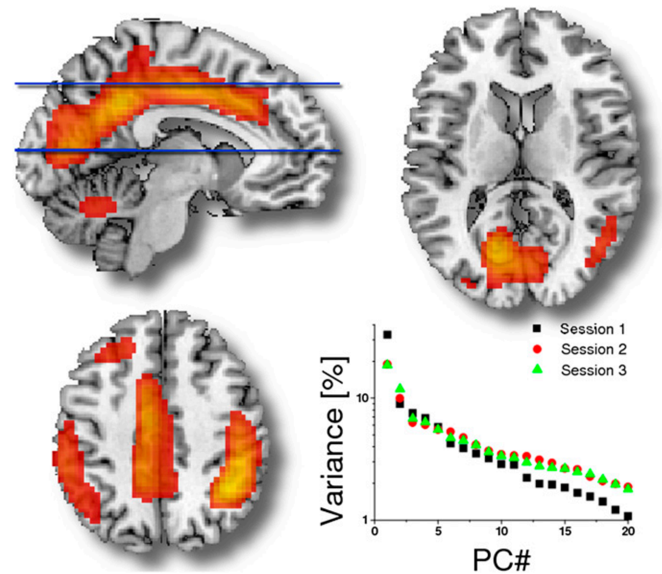
Dardo Tomasi[a,1] and Nora D. Volkow[a,b]

[a]National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD 20892; and [b]National Institute on Drug Abuse, Bethesda, MD 20892

Edited by Robert Desimone, Massachusetts Institute of Technology, Cambridge, MA, and approved April 21, 2010 (received for review February 4, 2010)







Developmental Effects S/P Volume Censoring and Mean FD Matching

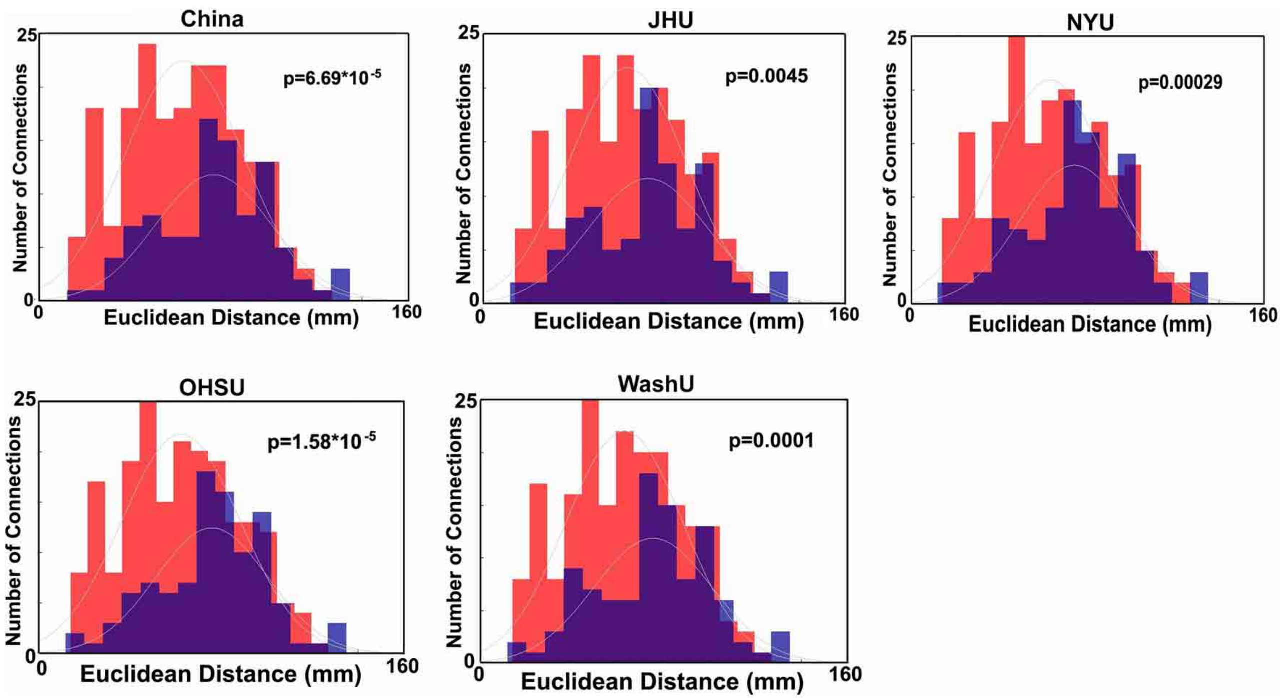


FIGURE A2 | Site-by-site histograms of Euclidean distance for functional connections identified in the whole group analysis that get stronger with age and those that get weaker with age (FDR corrected) using procedure 8.

Fair et al., 2012

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,*]

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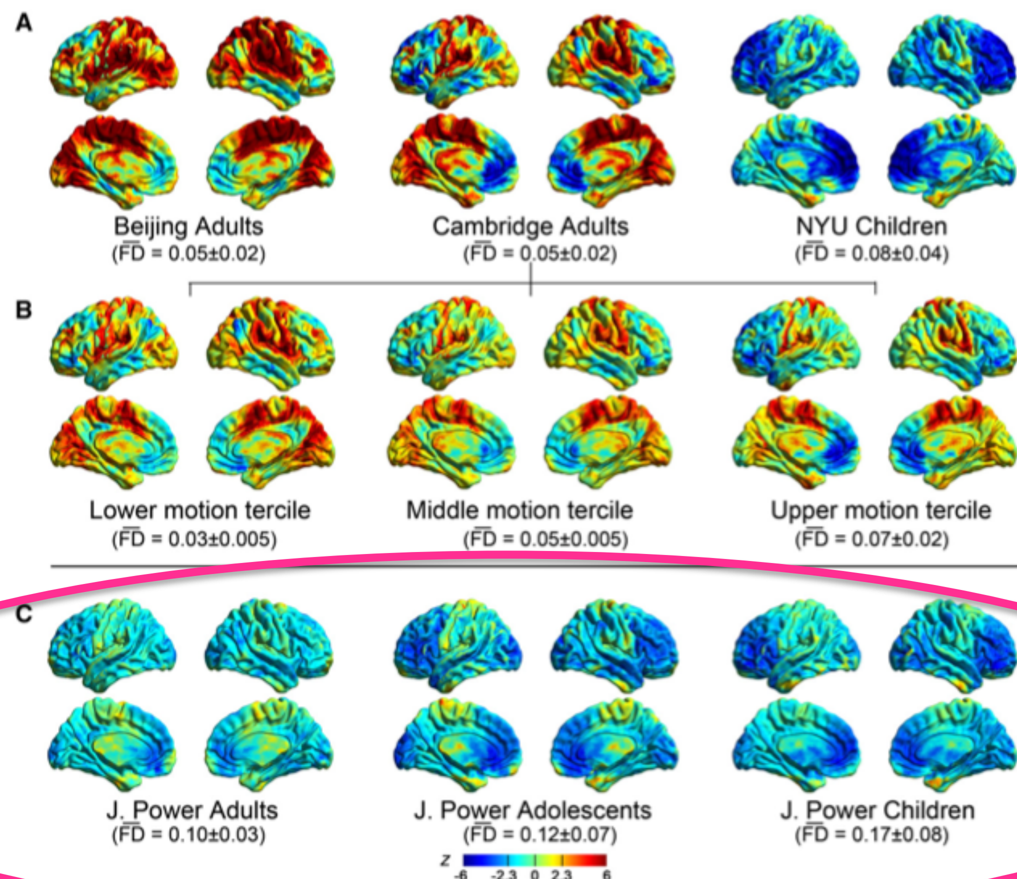
[b] *Center for the Developing Brain, Child Mind Institute, New York, NY, USA*
[c] *The Phyllis Green and Randolph Cowen Institute for Pediatric Neuroscience, New York University Child Study Center, New York, NY, USA*
[d] *Virginia Tech Carilion Research Institute, Roanoke, VA, USA*
[e] *Key Laboratory of Behavioral Science, Laboratory for Functional Connectome and Development, Magnetic Resonance Imaging Research Center, Institute of Psychology, Chinese Academy of Sciences, Beijing, China*

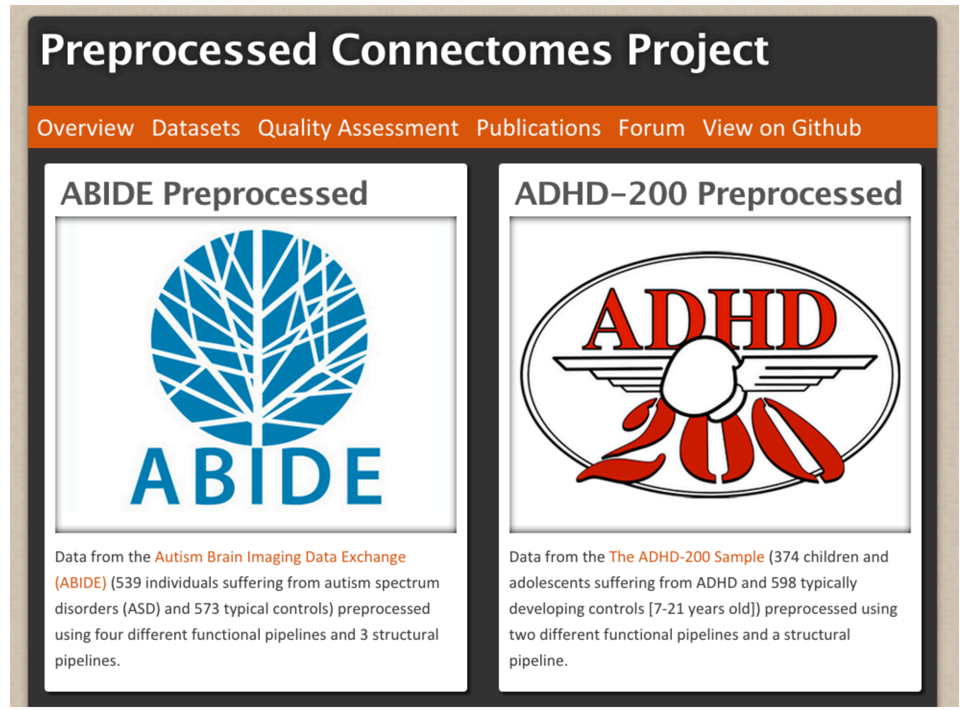


Harmonization Needs Beyond Aggregation: Preprocessing

- Lack of consensus regarding optimal preprocessing (Craddock et al., 2013)
  - Nuisance signal correction
    - Physiologic signals
    - Motion signals
    - Scanner artifacts
  - Registration approaches/algorithms
  - Temporal filtering
  - Slice-timing

Preprocessed INDI Data in the Cloud

- Available through S3 Bucket generously provided by AWS
- Raw INDI will be available soon



indi
International Neuroimaging Data-Sharing Initiative

http://preprocessed-connectomes-project.github.io/

Craddock et al., in prep

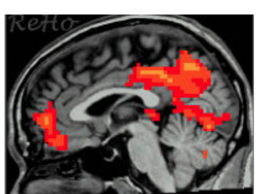
ABIDE Preprocessed

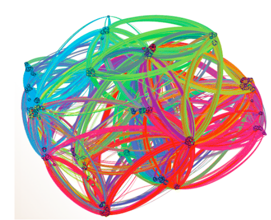
Overview Download Pipelines Quality Assessment View on Github

ABIDE
Autism Brain Imaging Data Exchange
PREPROCESSED

The Preprocessed Connectomes Project (PCP) is pleased to announce the public release and open sharing of preprocessed neuroimaging data from the Autism Brain Imaging Data Exchange (ABIDE). A consortium of the International Neuroimaging Datasharing Iniative (INDI), ABIDE is a collaboration of 16 international imaging sites that have aggregated and are openly sharing neuroimaging data from **539 individuals suffering from ASD** and **573 typical controls**. These 1112 datsets are composed of structural and resting state functional MRI data along with an extensive array of phenotypic information.

Data from ABIDE was preprocessed by five different teams using their preferred tools. Functional preprocessing was performed using: the Connectome Computation System (CCS), the Configurable Pipeline for the Analysis of Connectomes (CPAC), the Data Processing Assistant for Resting-State fMRI (DPARSF) and the NeuroImaging Analysis Kit. Due to the controversies surrounding bandpass filtering and global signal regression, four different preprocessing strategies were performed with each pipeline: all combinations of with and without filtering and with and without global signal correction. To limit the variance between outputs to just preprocessing, statistical derivatives for each pipeline and strategy were calcualted by the CPAC software. Structural preprocessing and calculation of cortical measures was performed using three different pipelines: ANTS, CIVET, and FreeSurfer. Refer to the links on the left for more information about the different pipelines and derivatives.

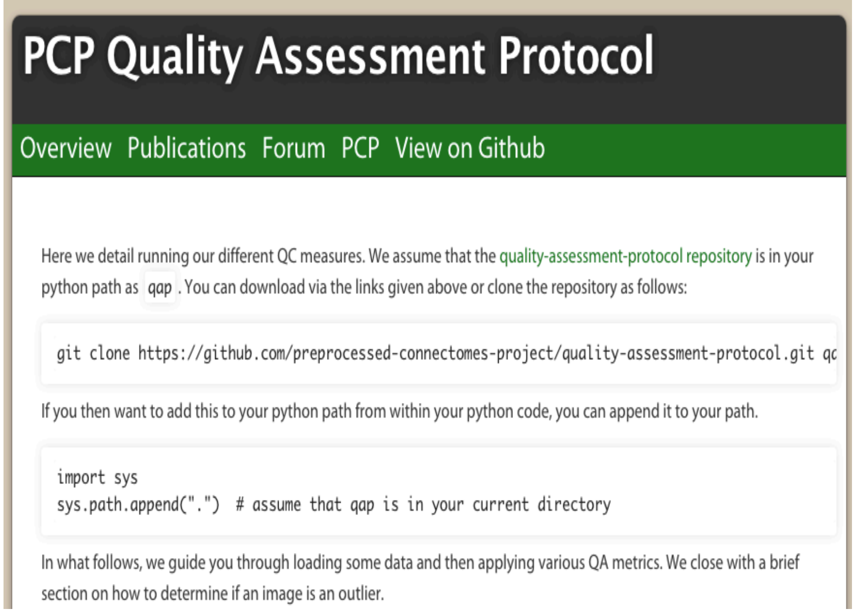




Craddock et al., in prep

PCP Quality Assessment Protocol

- Spatial Measures
  - Contrast to Noise Ratio
  - Entropy Focus Criterion
  - Foreground to Background Energy Ratio
  - Smoothness (FWHM)
  - % Artifact Voxels
  - Signal-to-Noise Ratio
- Temporal Measures
  - Standardized DVARS
  - Median distance index
  - Mean Functional Displacement
  - # Voxels with FD > 0.2m
  - % Voxels with FD > 0.2m



http://preprocessed-connectomes-project.github.io/quality-assessment-protocol/

Craddock et al., in prep

Beyond Aggregation: Synthesis

- Analytic Variation
  - A growing plethora of approaches
  - Even for same approach, marked variation can exist
    - Seed-based correlation approaches
    - Parameter specification
      - ICA
      - Graph theoretical approaches
      - Cluster analysis
- Reporting variations
  - Inherent to all of fMRI

Editorial

Toward a Meta-Analytic Synthesis of the Resting-State fMRI Literature for Clinical Populations

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That’s all Folks!