HERITABLE RESTING STATE FUNCTIONAL CONNECTIVITY

F. Xavier Castellanos, Xi-Nian Zuo, & Michael P. Milham
NYU & Nathan Kline Institute

Margaret Wright, Nicholas Martin, Katie McMahon, Greig de Zubicaray, Ian Hickie
Queensland Institute for Medical Research; University of Queensland Centre for Advanced Imaging

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Why study twins?

- Challenge for the field
  - Matrix elements for the human connectome?
  - Human brain “Periodic Table of the Elements” of phenotypes, including addiction risk

- Biology - Genetic factors
  - Causality

Brain Structure is Strongly Influenced by Genes

TABLE I
STRUCTURAL BRAIN PHENOTYPES IN HEALTHY PERSONS WITH HIGH HERITABILITY
(h^2 BETWEEN 0.70 AND 0.99)

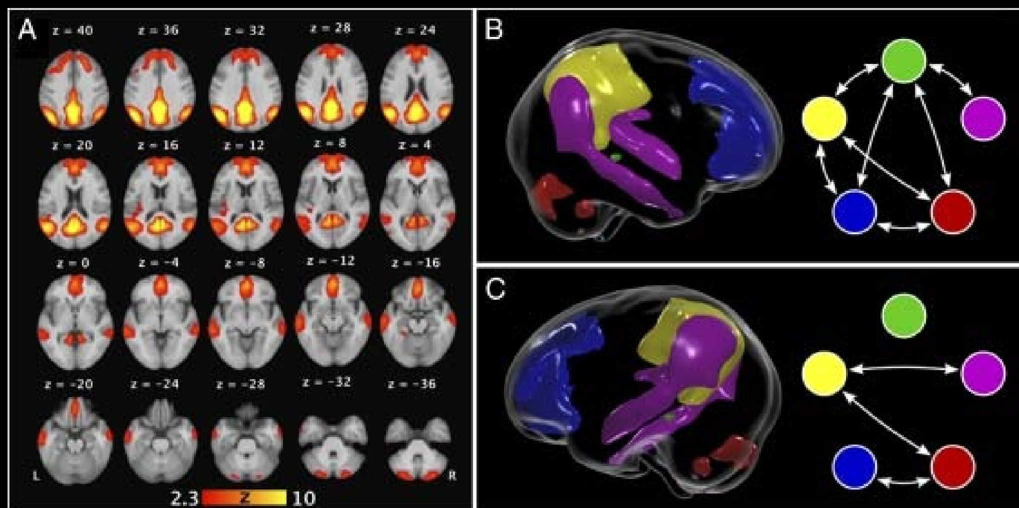
Brain structure	Heritability of brain structure (h^2, ICC or λ)	Sample size and age, gender, whenever different	Study ID
Cranial, intracranial volume	0.91	74 MZ, 71 DZ twin pairs (all M, 68–79 years)	Carmelli *et al.* (1998)[a]
	0.88	54 MZ, 58 DZ twin pairs, 34 siblings	Baaré *et al.* (2001a)[a]
	0.80	44 MZ, 40 DZ twin pairs (all M, 68–78 years)	Sullivan *et al.* (2001)[a]
	0.938	1881 individuals: 1330 genetically related (±60 years)	Atwood *et al.* (2004)[a]
Total brain volume	0.94	10 MZ (±34 years), 9 DZ (±23 years) twin pairs	Bartley *et al.* (1997)[a]
	0.97	23 MZ (12 M), 23 DZ (16 M) twin pairs, all reading disability, C (NRD) = 9 MZ (4 M), 9 DZ (4 M) twin pairs	Pennington *et al.* (2000)[b]
	0.90	54 MZ, 58 DZ twin pairs, 34 siblings	Baaré *et al.* (2001a)[a]
	0.99	12 MZ, 12 controls (all M)	White *et al.* (2002)[b]
	0.89	90 MZ (52 M, 38 F), 37 DZ (22 M, 15 F) twin pairs, 158 unrelated singletons (±11.5 years)	Wallace *et al.* (2006)[a]
	0.91	107 MZ and DZ twin pairs (±9 years)	Peper *et al.* (2009)[a]
Gray matter volume	0.82	54 MZ, 58 DZ twin pairs, 34 siblings	Baaré *et al.* (2001a)[a]
	0.99	12 MZ, 12 controls (all M)	White *et al.* (2002)[b]
	0.82	54 MZ, 58 DZ twin pairs, 34 siblings	Posthuma *et al.* (2002b)[b]
	0.82	90 MZ (52 M, 38 F), 37 DZ (22 M, 15 F) twin pairs, 158 unrelated singletons (±11.5 years)	Wallace *et al.* (2006)[a]
	0.91	107 MZ and DZ twin pairs (±9 years)	Peper *et al.* (2009)[a]
	0.55–0.85	49 MZ, 65 DZ twin pairs (±28 years)	Hulshoff Pol *et al.* (2006)[a]

Kaymaz & van Os, 2009

Brain Function is also Heritable

- Cognitive strategy (language-based vs. numerical) strongly influenced by genes
  - Koten et al., 2009
- N-back working memory heritability (h^2) ~ 14-30%, NS
  - Blokland et al., 2008
- Small-world networks in RS-EEG – 46-89% of variability in clustering coefficient and 37-62% of path-length are heritable
  - Smit et al., 2008
- Default Network (ICA) significantly heritable (h^2 = .42) in extended pedigrees – Glahn et al., 2010

Initial Report of Genetic Contributions to Intrinsic Brain Function – Glahn et al., 2010



Heritability estimates for regions within the default mode

Region*	Functional connectivity Heritability†	Functional connectivity *P* value‡	Gray-matter density Heritability†	Gray-matter density *P* value‡
Posterior cingulate/precuneus	0.423 (0.17)	4.4×10^{-3}	0.623 (0.16)	6.8×10^{-5}
Medial prefrontal cortex	0.376 (0.15)	3.8×10^{-3}	0.631 (0.15)	5.3×10^{-6}
Left temporal–parietal region	0.331 (0.19)	3.1×10^{-2}	0.387 (0.21)	3.1×10^{-2}
Right temporal–parietal region	0.420 (0.16)	3.5×10^{-3}	0.365 (0.21)	3.4×10^{-2}
Left cerebellum	0.104 (0.13)	2.0×10^{-1}	0.493 (0.15)	4.9×10^{-4}
Right cerebellum	0.304 (0.16)	1.6×10^{-2}	0.596 (0.14)	1.6×10^{-5}
Cerebellar tonsil	0.219 (0.19)	1.1×10^{-1}	0.271 (0.16)	3.2×10^{-2}
Left parahippocampal gyrus	0.273 (0.14)	1.7×10^{-2}	0.420 (0.18)	7.5×10^{-3}

*Bolded figures are significant at 5% FDR.
†Estimated heritability, h2 (SE).
‡*P* value for the heritability estimate.

Study Goals

- Determine heritability of commonly used metrics of intrinsic brain function
  - Regional voxel-wise measures
    - Regional Homogeneity (ReHo), fALFF, VMHC
  - Relational (RSFC) measures
    - DN seeds (Andrews-Hanna et al. 2010)
    - Exploratory seed sets (BG, ACC, Precuneus)
  - Network measures (pending)
    - Small world properties, degree centrality

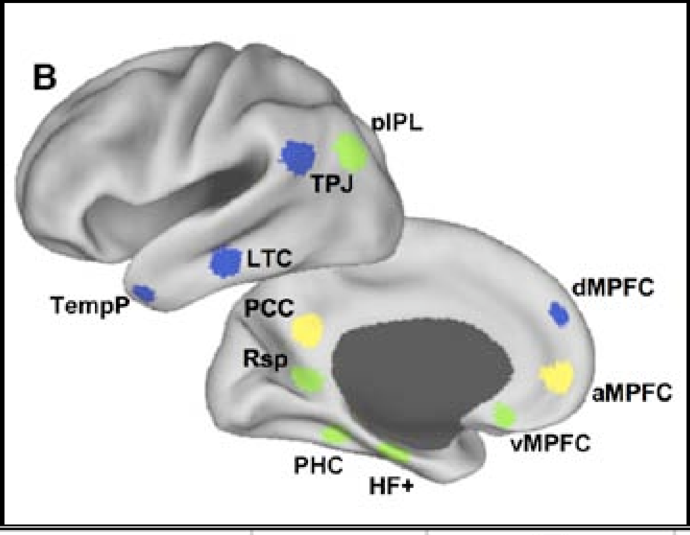
Participants & Imaging

- Sample
  - 79 MZ twins pairs
  - 84 DZ twins pairs
  - Age: 22.7 ± 3.1 yrs
- Image acquisition
  - 4T fMRI scanner in University of Queensland, Brisbane
  - Scan condition: rest
  - Scan duration: 145 time points, TR = 2.1s

Methods

- Falconer heritability
- (A) $H^2 = 2*(\text{corr}[MZ_{t1}, MZ_{t2}] - \text{corr}\ [DZ_{t1}\ \ DZ_{t2}]) = 2*(MZr - DZr)$ with upper-bound = $\text{corr}\ [MZ_{t1}\ \ MZ_{t2}]$;
- (C) = $2*DZr - MZr$;
- (E) = $1 - MZr$;
- Voxel-wise heritability analyses within a gray matter mask ($p \geq 25\%$)
- Account for age/sex/registration quality in regression

Default Network RSFC



Region		BA	x	y	z
PCC-aMPFC Core					
Anterior medial prefrontal cortex	aMPFC	10,32	-6	52	-2
Posterior cingulate cortex	PCC	23,31	-8	-56	26
dMPFC Subsystem					
Dorsal medial prefrontal cortex	dMPFC	9,32	0	52	26
Temporal parietal junction	TPJ	40,39	-54	-54	28
Lateral temporal cortex	LTC	21,22	-60	-24	-18
Temporal pole	TempP	21	-50	14	-40
MTL Subsystem					
Ventral medial prefrontal cortex	vMPFC	11,24,25,32	0	26	-18
Posterior inferior parietal lobule	pIPL	39	-44	-74	32
Retrosplenial cortex	Rsp	29,30,19	-14	-52	8
Parahippocampal cortex	PHC	20,36,19	-28	-40	-12
Hippocampal formation	HF+	20,36	-22	-20	-26

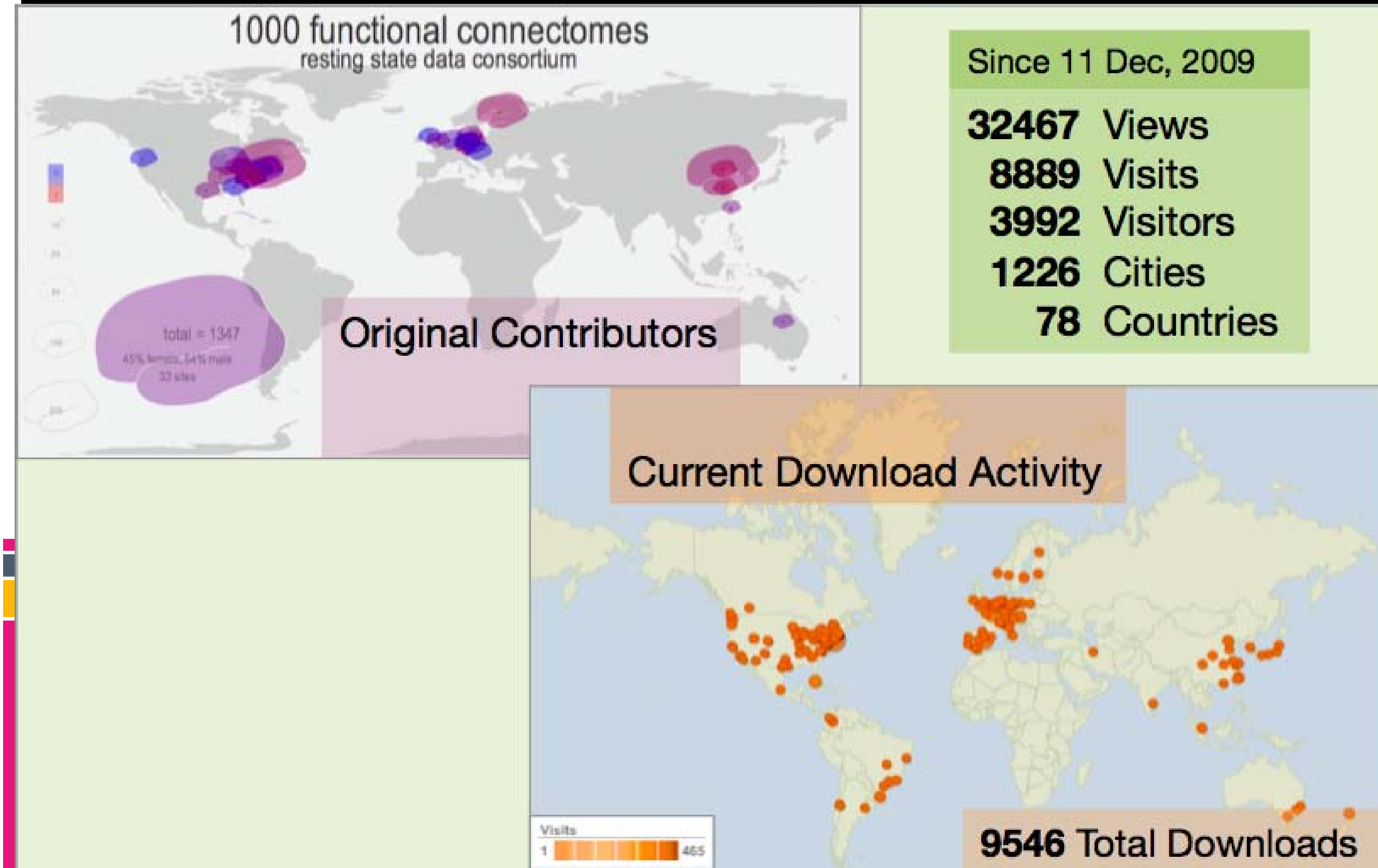
Andrews-Hanna, et al., 2010

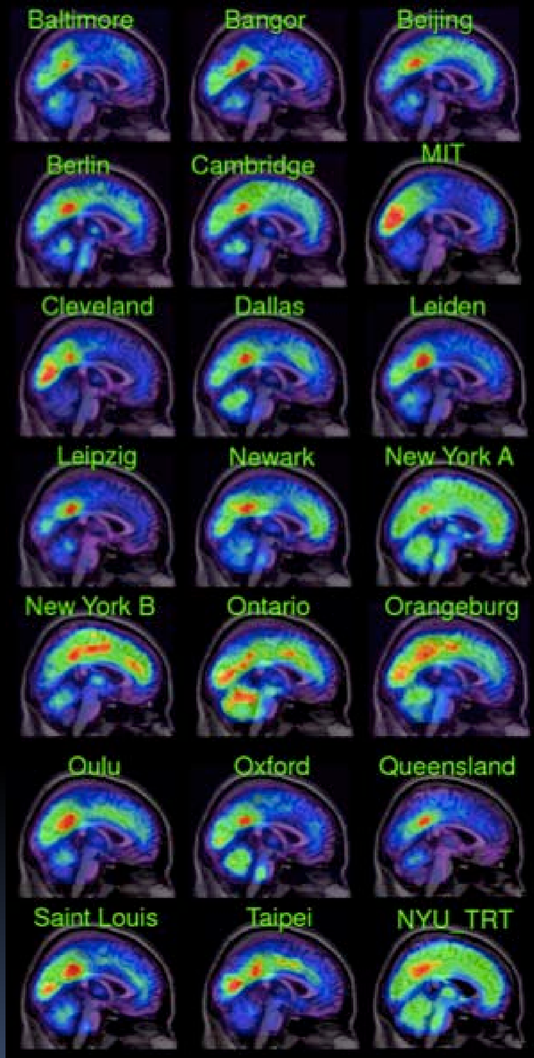
Default Network Falconer Heritability

Conclusions

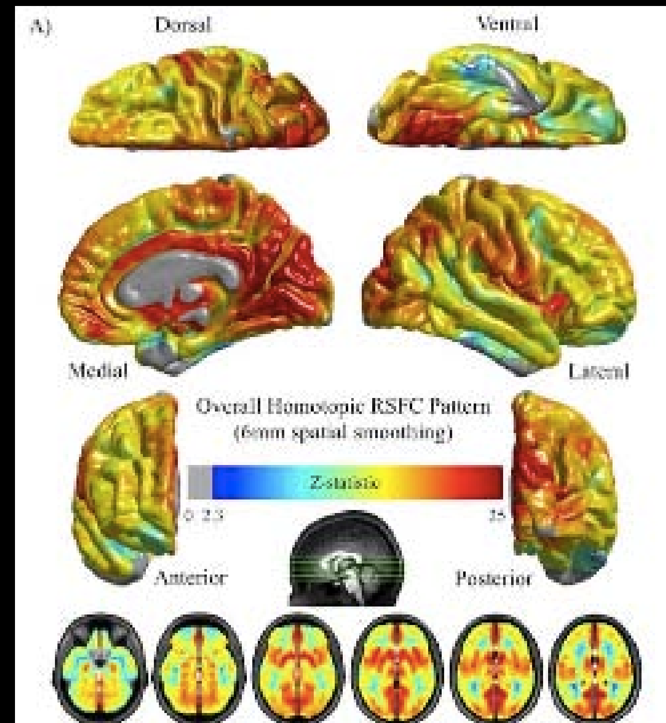
- Spontaneous/intrinsic brain activity as indexed by BOLD is strongly influenced by genes
  - Survives covariance for highly heritable structural effects (gray matter density)
- Heritable relationships (RSFC, ReHo, VMHC) and voxel-wise properties (fALFF) are 'well behaved'
  - Provide spatial hypotheses for GWAS & brain gene expression analyses
  - Candidate nodes/elements for assembling functional & structural connectomes & for network analyses
- Basis for massive discovery-science approaches to understand addiction risk & sequelae

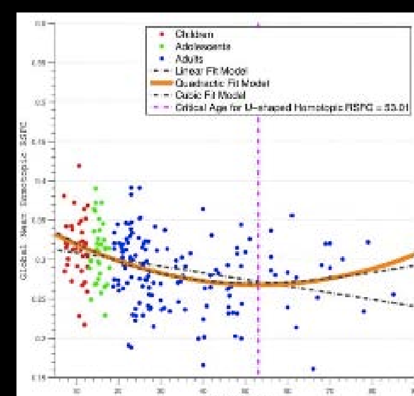
Data-Sharing Progress to Date





Tomasi & Volkow, 2010; PNAS





Zuo et al., in press; J Neuroscience

Next Steps Towards Discovery Science?

- High throughput datasets are crucial for successful implementation of discovery science
  - Brain genomics
  - Markers of psychiatric illness & addiction risk
  - Dilemma: wait for even better imaging methods, or move forward?
- Recruit/encourage widespread involvement of the scientific community

Current Goal

- To make the aggregation and sharing of well-phenotyped datasets a cultural norm for the imaging community.
  - Make comprehensive phenotypic information available with imaging datasets to facilitate sophisticated data-mining.
  - Shift from retrospective to prospective data sharing (e.g., weekly, monthly, or quarterly).
  - Dynamic ‘self-organizing’ network of investigators pushing technologies and approaches

International Neuroimaging Data-sharing Initiative (INDI)

International Neuroimaging Data-sharing Initiative (INDI)

- To enhance the 1000 FCP by including comprehensive phenotypic data.
- To help establish a common protocol for sharing phenotypic/metadata via the FCP.
- To initiate open, prospective data-sharing for the neuroimaging community (e.g., weekly, monthly, or quarterly uploads of data).

Initial Retrospective Data-Sharing Commitments

SAMPLE	CONTRIBUTORS	RELEASE DATE	SAMPLE INFO	Phenotypic Data
ADHD-200	Jan Buitelaar Xavier Castellanos Damien Fair Bea Luna Michael Milham Stewart Mostofsky Joel Nigg Julie Schweitzer Katerina Velanova Yu-Feng Zang	1/1/11	~200 ADHD ~200 TDC (ages 7-14)	Psychiatric assessment resul dimensional measures
Beijing	Yu-Feng Zang	10/15/10	Community Sample	IQ+
NYU Institute for Pediatric Neuroscience	Clare Kelly Xavier Castellanos Michael Milham	11/1/10	30 cocaine dependent 30 healthy controls (ages 18-50)	Psychiatric assessment resul symptom severity measures questionnaires
TRAIN-30	Art Kramer, Michelle Voss, Kirk Erickson, Ruchika Prakash	Spring, 2011	30 young adults trained 20 hours each on a complex video game	Phenotypic Data - age, gend performance (learning data) the video game

Initial Prospective Data-Sharing Commitments

SAMPLE	CONTRIBUTORS	RELEASE DATE/ FREQUENCY	SAMPLE INFO	Phenotypic Data
Baylor College of Medicine	Cameron Craddock Stephen LaConte The Neuro Bureau	1/1/11 25+ Quarterly	Psychiatrically Screened Sample	Various dimensional psychiatric scales & behavioral performance measures
Beijing	Yu-Feng Zang	12/1/10 5-10 Weekly	Community Sample	Various dimensional psychiatric scales & behavioral performance measures
Berlin Mind and Brain Institute	Daniel Margulies Arno Villringer The Neuro Bureau	1/1/11 25+ Quarterly	Community Sample	Health/activity screening information and cognitive/affective trait scales
Harvard-MGH	Randy Buckner	1/1/11 50+ Quarterly	Community Sample	Extended demographic information and a mix of trait/performance measures, as well as personality assessments.
Kennedy Krieger Institute	Stewart Mostofsky	1/1/11 15-20 Quarterly	Psychiatrically Screened Sample (ages 8-12)	Demographic information, psychiatric diagnostic interview, psychiatric/ behavioral questionnaires, cognitive testing (IQ/achievement), executive function measures, motor function measures
MPI-Leipzig	Daniel Margulies Arno Villringer The Neuro Bureau	1/1/11 25+ Quarterly	Community Sample	Psychological questionnaires (e.g., PANAS, PDI, DSQ)
NKI-Rockland	Bharat Biswal Xavier Castellanos David Guilfoyle Matthew Hoptman Dan Javitt Bennett Leventhal Larry Maayan Maarten Mennes Michael Milham Kate Nooner Nunzio Pomara	10/1/10 5-10 Weekly	Psychiatrically Evaluated Sample (ages 6-90)	Intelligence testing, psychiatric diagnostic interview, executive function performance measures, dimensional psychiatric scales and laboratory results
NYU Institute for Pediatric Neuroscience	Xavier Castellanos Adriana Di Martino Clare Kelly Maarten Mennes Michael Milham	11/1/10 3-5 Weekly	Psychiatrically Screened Sample (ages 6-55)	Psychiatric diagnostic interview, cognitive testing (IQ/achievement), psychiatric/ behavioral questionnaires
Valencia Spanish Resting State Network	Xavier Castellanos Erika Proal Maria de la Iglesia-Vaya	Early 2011 5-10 Weekly	Community; clinically indicated studies	Clinical indication for MRI scans; diagnostic codes

Same Rules for Sharing as FCP…

- Local IRB/ethics board approval
- User registration required to access data
- All data will be completely anonymized
- Please be sure to cite the website and specify the datasets included in your study
- Unrestricted usage of all FCP datasets
- Use FCP data at your own discretion and caution
- Report any data concerns to the FCP forums located on NITRC

The Nathan-Kline/Rockland Sample

Assessment Protocol

PROCEDURES COMPLETED BY ALL PARTICIPANTS
Demographics
Medication Form
Test Meal
Based Diagnostic Interview (KSADS/SCID)
Autism Spectrum Screening Questionnaire (ASSQ)
IQ Screening (WASI)
Physical measures (blood pressure, heart rate, height, weight and waist and hip measurements)
fasting blood draw (metabolic panel, hemogram, genetics)
Eating Questionnaire
Social Responsiveness Scale (SRS)
Delis-Kaplan Executive Fucntion System (D-KEFS)
Repetitive Behavior Scale-Revised (RBS-R)
6 minute walk
Achenbach System of Empirically Based Assessment (Child Behavior Checklist, Youth Self Report, Adult Self Report, Older Adult Self Report)

ASSESSMENTS TO BE COMPLETED BY ADULTS (AGE 18+)
Cognitive Appraisal of Risky Events (CARE)
Fagerstrom Test for Nicotine Dependence
Phsyical Activity Scale for the Elderly (PASE)
UPPS Impulsive Behavior Scale
State Traint Anxiety Inventory (STAI)
Trauma Symptom checklist for Adults
Beck Depression Inventory--II (BDI)

ASSESSMENTS TO BE COMPLETED BY CHILDREN (AGE 6-18)
Behavior Assessment System for Children –Second Edition (BASC-2)
Vineland Adaptive Behavior Scales-Revised
Adolescent Risk-taking Questionnaire (ARQ)
Fagerstrom Tolerance Questionnaire for Adolescents
Multidimensional Anxiety Scale for Children (MASC)
Trauma Symptom Checklist for Children (TSC-C)
Children’s Depression Inventory (CDI)

The Nathan-Kline/Rockland Sample

Imaging Protocol

- R-fMRI Scan
  - 3.0T Siemens Tim Trio
  - 3.0 mm isotropic voxel size, .3 mm inter-slice gap
  - TR = 2.5 sec
  - Scan Duration = 10 minutes
  - 32 channel coil
- DTI
  - 2.0 mm isotropic voxel-size
  - 64 directions
  - bVal = 1000

ADHD-200

- Anticipated Release Date: Jan 3, 2011
- 200+ children (ages 7-14) and 200 TDC collected across 4 or more sites
- Competition proposed for 2011 OHBM meeting in Quebec City
  - Feature identification
  - Diagnostic classification

What Can You Do for INDI?

- Contribute your data
  - Previously published datasets
    - Release some or all of the phenotypic information – your call, but simple rule is, the more the better!
  - Unpublished datasets
    - You set the upload schedule.
    - Release some or all of the phenotypic information – your call, but simple rule is, the more the better!
- Contribute your scripts/code
  - 817 downloads of FCP scripts since 3/10/10
- http://fcon_1000.projects.nitrc.org

Thanks

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Adriana Di Martino
Clare Kelly

NYU Child Study Center
NYU LANGONE MEDICAL CENTER

THE UNIVERSITY OF SYDNEY

nki

The Young & Restless Beach-side Gala Ball

THE UNIVERSITY OF QUEENSLAND AUSTRALIA

Queensland Institute of Medical Research

The NEURO BUREAU