The Future of Neuropsychiatric Diagnoses

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Nathan Kline Institute for Psychiatric Research

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Stockholm

I declare no financial conflicts of interest.

Summary

- The purposes/functions of diagnoses
- We all agree that categorical diagnoses are limited in revealing mechanisms
- The future of diagnosis depends on uncovering pathophysiological mechanisms
- Hypothesis-driven approach
- Data-driven approaches

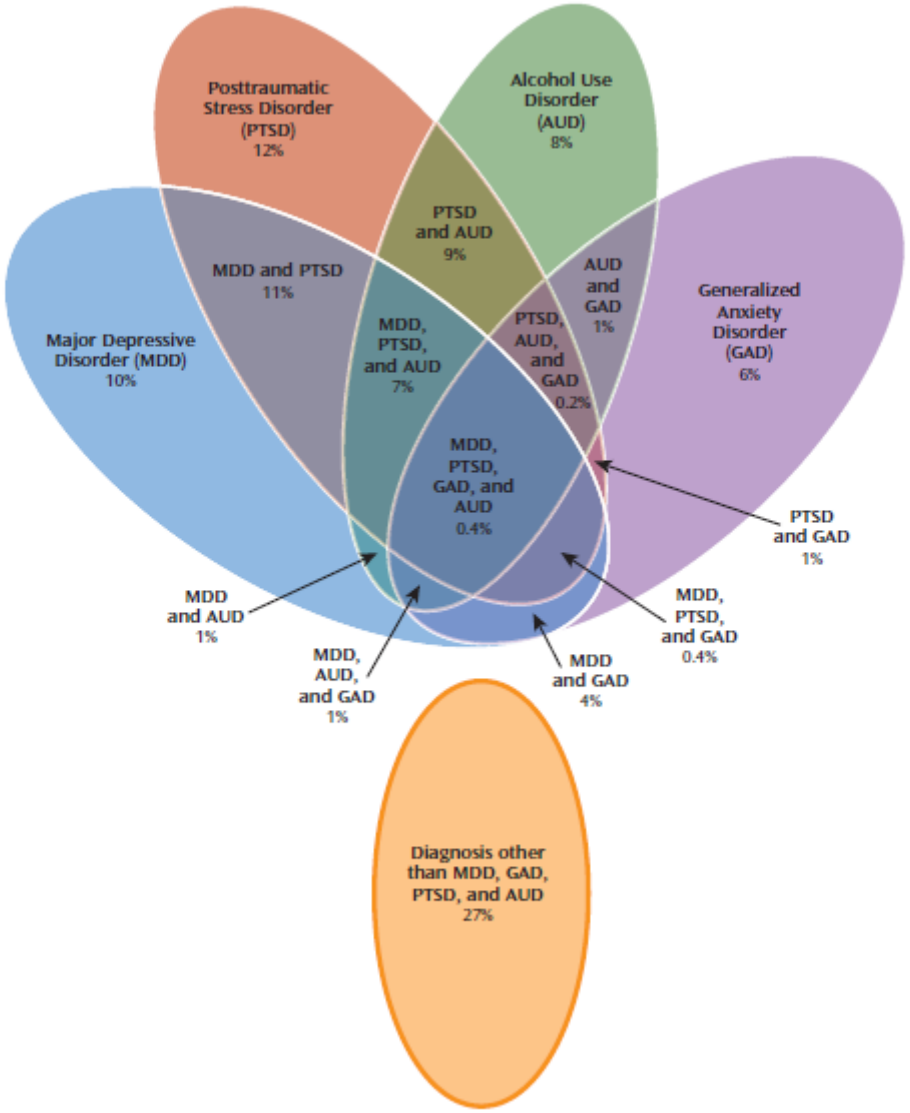
Essential Functions of Diagnoses

- *Sine qua non*: Harmonization
  - Inter-rater reliability
    - Major achievement of DSM-III+
      - Still mostly moderate
      - In DSM-5 pediatric field trials
        - Very good to questionable:
          - » Kappa for ADHD = 0.61
          - » Kappa for ASD = 0.69
          - » Kappa for MDD = 0.28
          - » Kappa for DMDD= 0.25

Desirable Functions of Diagnoses

- Organizing phenomenology
  - Familiality
  - Longitudinal course
- Predict
  - Outcomes
  - Optimal treatment(s)
    - Whether to medicate or not…

FIGURE 1. Comorbidity of Major Depressive Disorder, Posttraumatic Stress Disorder, Alcohol Use Disorder, and Generalized Anxiety Disorder[a]



Regier et al., 2013

ESSENCE-Q-REV (Gillberg C 2012)

Name of child:	

Age:		Completed by:	
Sex:		Date:	

Please take a few minutes to read and check the following items.

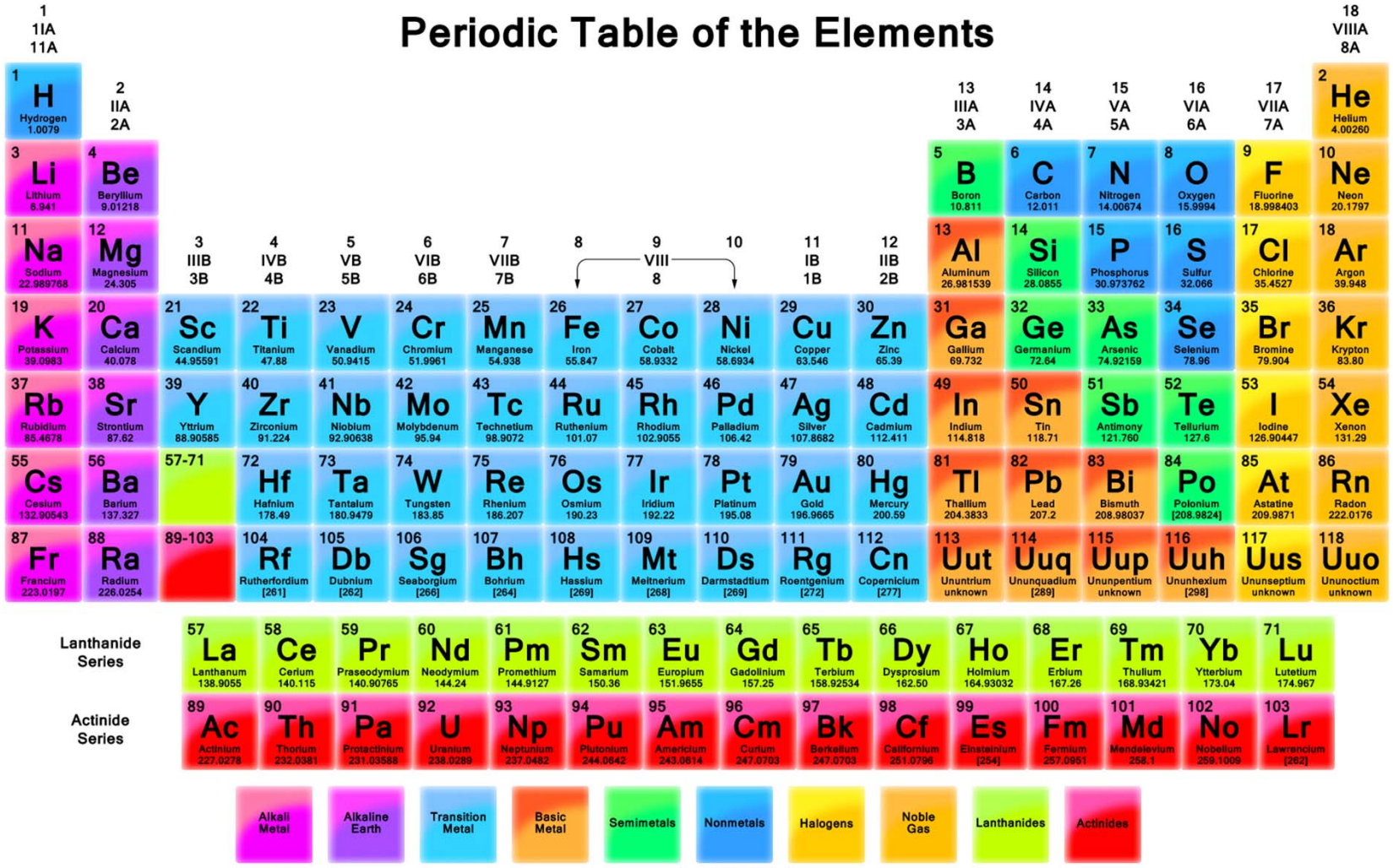
- **Y= Yes**
- **M/AL = Maybe/A little**
- **N= No**

Have you (or anybody else, who?_____) been concerned for more than a few months regarding child´s

1. General development ☐
2. Motor development/ milestones ☐
3. Sensory reactions (e.g. touch, sound, light, smell, taste, heat, cold, pain) ☐
4. Communication/language/ babble ☐
5. Activity (overactivity/passivity) or impulsivity ☐
6. Attention/concentration/ "listening" ☐
7. Social interaction/interest in other children ☐
8. Behaviour (e.g. repetitive, routine insistence) ☐
9. Mood (depressed, elated/manic, extreme irritability, crying spells) ☐
10. Sleep ☐
11. Feeding ☐
12. "Funny spells"/ absences ☐

If Y or M/AL to any of the above, please elaborate briefly here:

The Future of Psychiatric Diagnoses



What are the relevant linear dimensions of phenotypic variation?

- Linearity as a necessary simplifying assumption
- A priori hypotheses-based
  - Example: Variability in ADHD → Default network interference hypothesis
- Data-driven discovery science
  - Examples: Intelligence correlates and brain functional connectivity
  - C4A in schizophrenia

DSM-5 ADHD

Hyperactive/Impulsive Symptoms

Often…

- fidgets or squirms
- can't stay seated
- restless (subjective in adolescents)
- loud, noisy, diff playing quietly
- always "on the go"
- talks excessively

- blurts out
- impatient
- intrusive

6 or more present over 6 months;

5 if age ≥ 17 y

DSM-5 ADHD

Inattention Symptoms

Often …

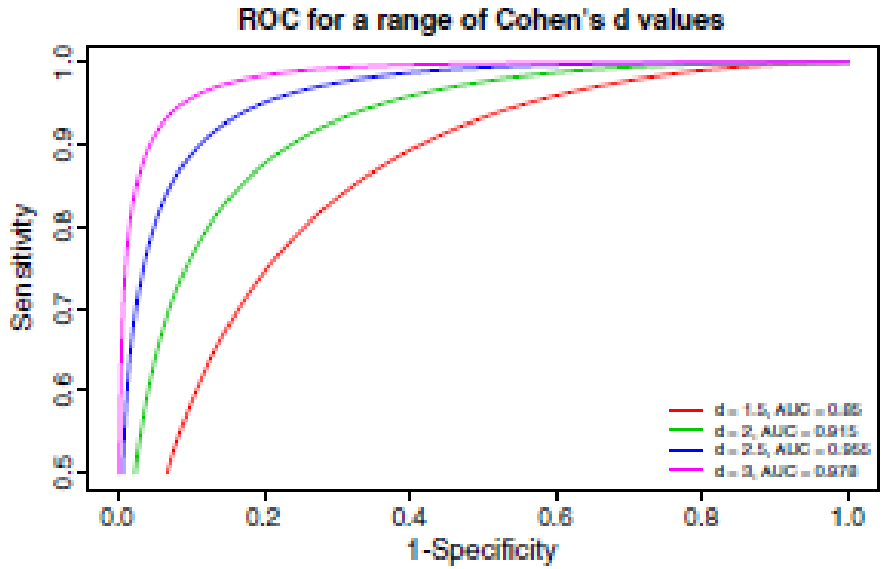
- careless errors, inattention to detail
- sustains attention poorly
- *appears* to not listen
- poor follow through on obligations
- disorganized
- avoids/dislikes sustained mental effort
- loses needed objects
- easily distracted
- forgetful

6 or more present over 6 months;

5 if age ≥ 17 y

Diagnosing ADHD

- Fundamentally subjective
  - Like all psychiatric syndromes…
- Neuropsychological tests have failed to yield **large** effect size measures (Cohen's d ≥ 2)



Castellanos et al. 2013

Inconsistency & ADHD

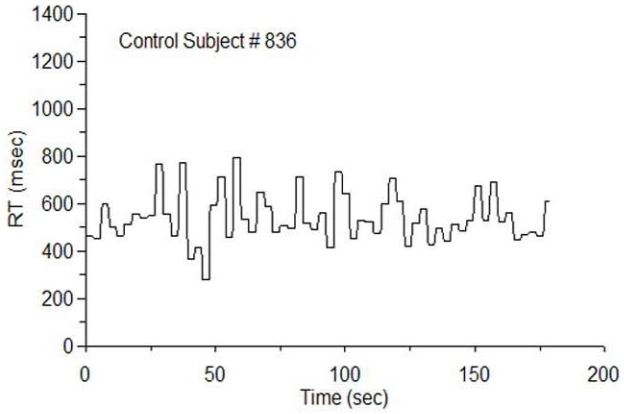
Leth-Steenson 2000; Kuntsi 2001; →

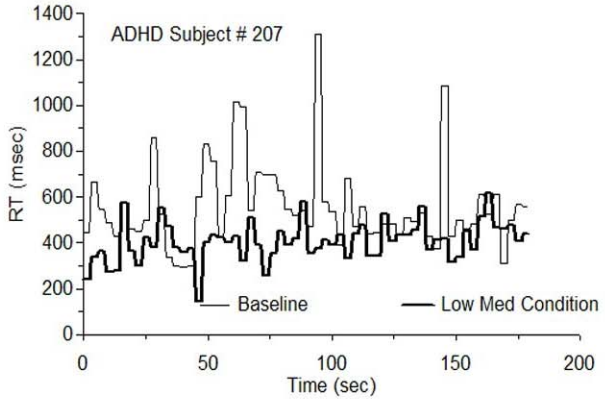
- "…the most striking clinical characteristics of ADHD include the transient but frequent lapses of … attention, and the moment-to-moment variability and inconsistency in performance….
- Response variability is ubiquitous … across a variety of … reaction-time tasks, laboratories and cultures."

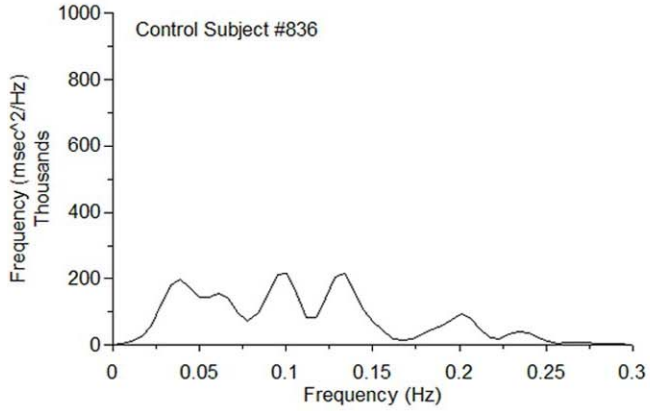
Castellanos & Tannock, 2002

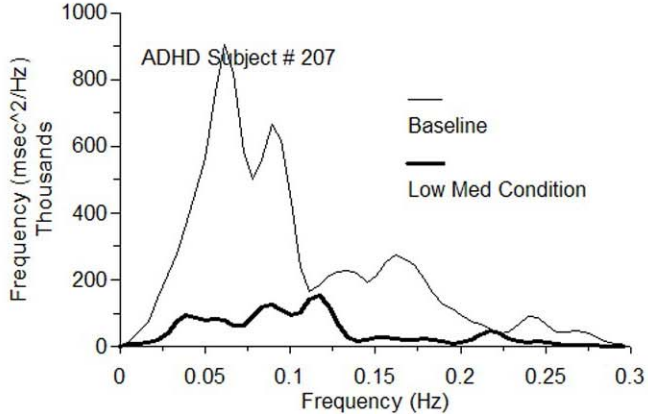
Varieties of Attention-Deficit/Hyperactivity Disorder-Related Intra-Individual Variability

F. Xavier Castellanos, Edmund J.S. Sonuga-Barke, Anouk Scheres, Adriana Di Martino, Christopher Hyde, and Judith R. Walters





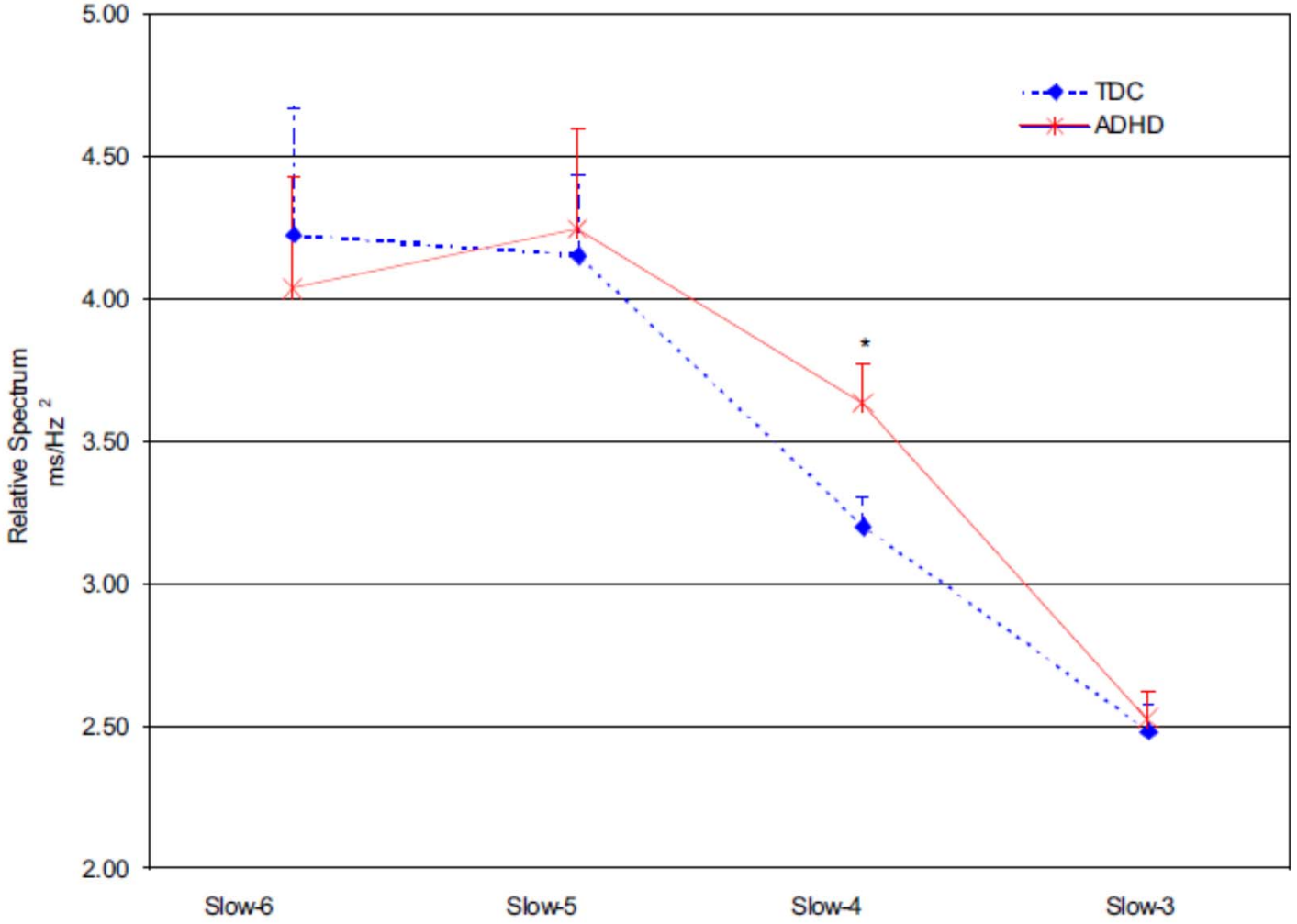




Biological Psychiatry, 2005

Decomposing Intra-Subject Variability in Children with Attention-Deficit/Hyperactivity Disorder

Adriana Di Martino, Manely Ghaffari, Jocelyn Curchack, Philip Reiss, Christopher Hyde, Marina Vannucci, Eva Petkova, Donald F. Klein, and F. Xavier Castellanos



Biological Psychiatry, 2008

THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY

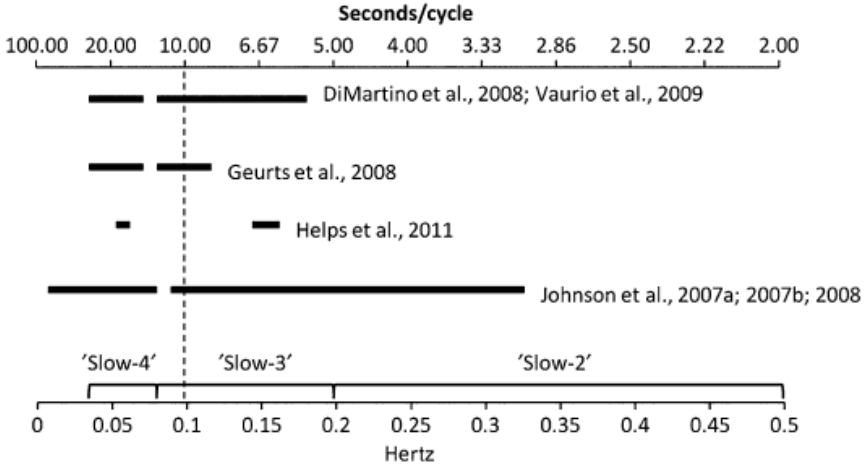
ACAMH

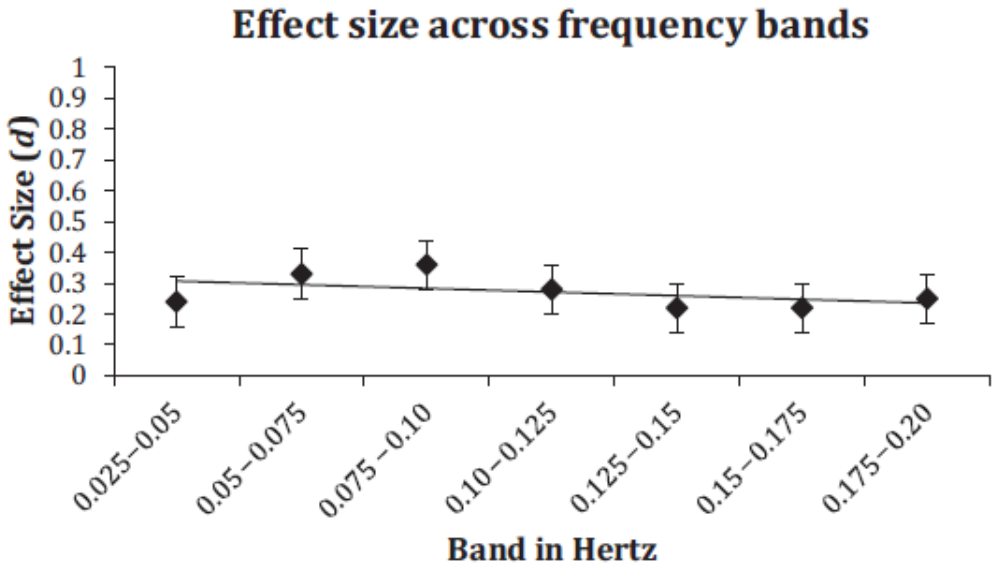
Journal of Child Psychology and Psychiatry 54:5 (2013), pp 536–544 doi:10.1111/jcpp.12028

Is reaction time variability in ADHD mainly at low frequencies?

Sarah L. Karalunas,[1] Cynthia L. Huang-Pollock,[2] and Joel T. Nigg[1]

[1]Oregon Health & Science University, Portland, OR; [2]Psychology Department, Pennsylvania State University, University Park, PA, USA





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Castellanos & Tannock, 2002

Reaction time variability in ADHD: A meta-analytic review of 319 studies

Michael J. Kofler [a,*], Mark D. Rapport [b], Dustin E. Sarver [b], Joseph S. Raiker [b], Sarah A. Orban [b], Lauren M. Friedman [b], Ellen G. Kolomeyer [b]

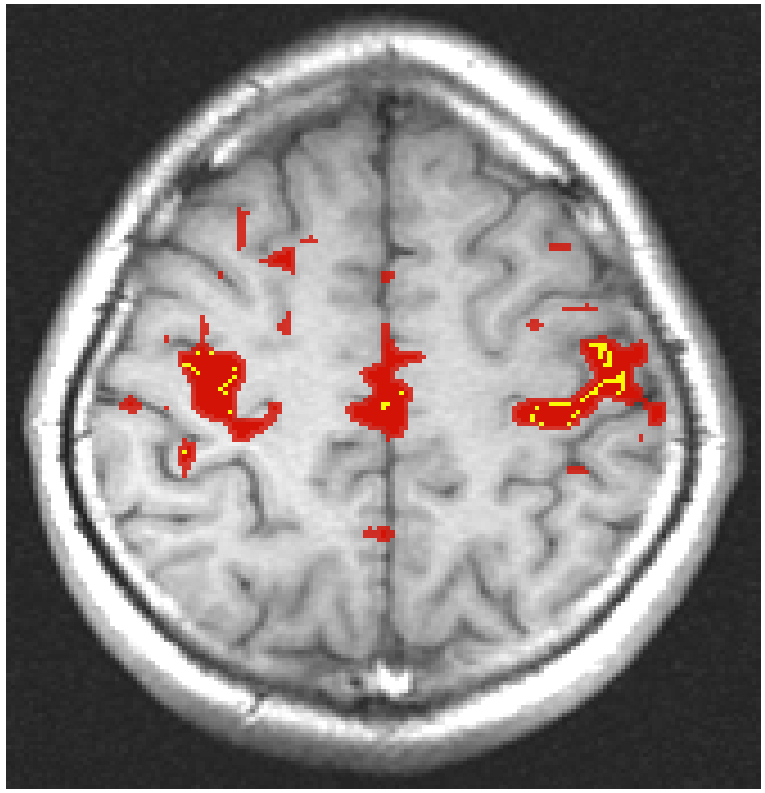
Clinical Psychology Review 2013

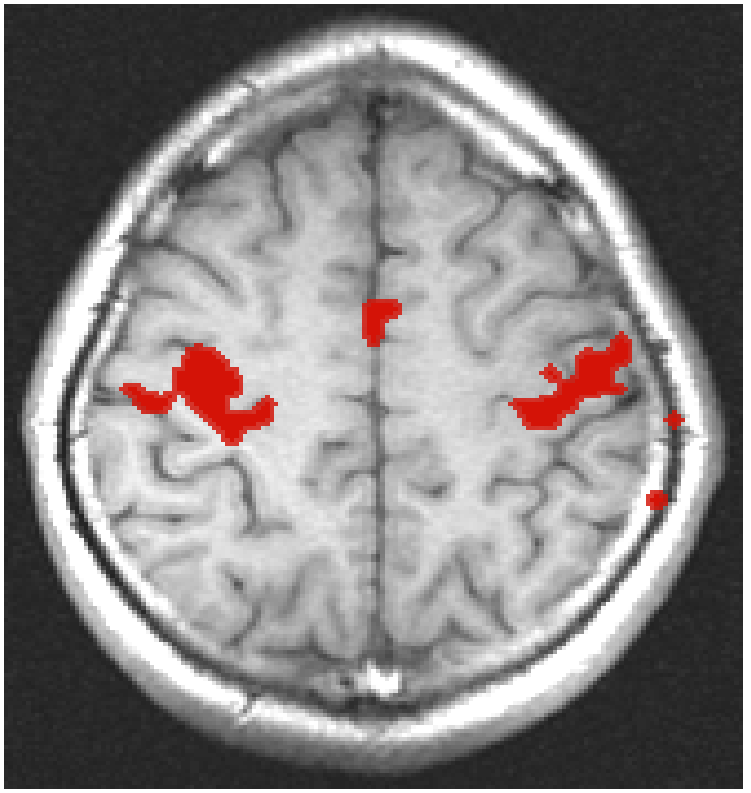
Functional Connectivity in the Motor Cortex of Resting Human Brain Using Echo-Planar MRI

Bharat Biswal, F. Zerrin Yetkin, Victor M. Haughton, James S. Hyde

Functional Connectivity at Rest

Finger-tapping task





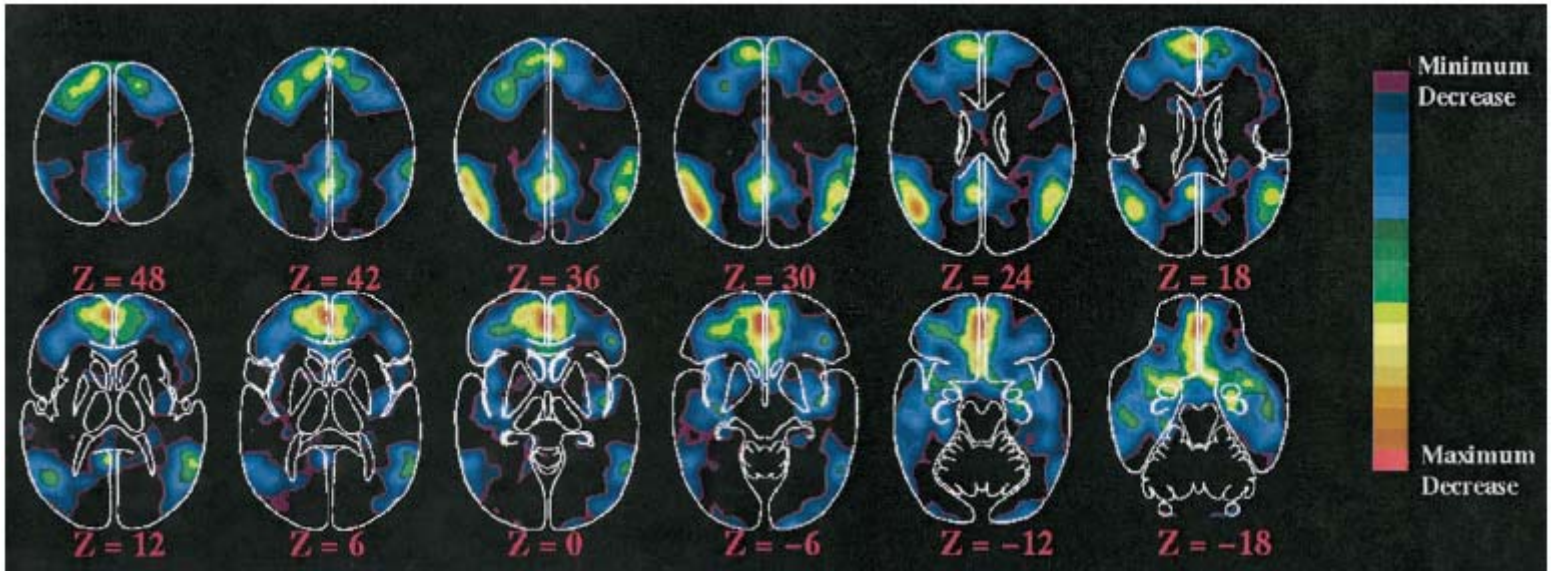
4164 GS cites on 2016.02.05

Biswal et al., 1995

PNAS 2001

A default mode of brain function

Marcus E. Raichle*†, Ann Mary MacLeod*, Abraham Z. Snyder*, William J. Powers‡, Debra A. Gusnard*§, and Gordon L. Shulman‡



6371 GS cites on 2016.02.05

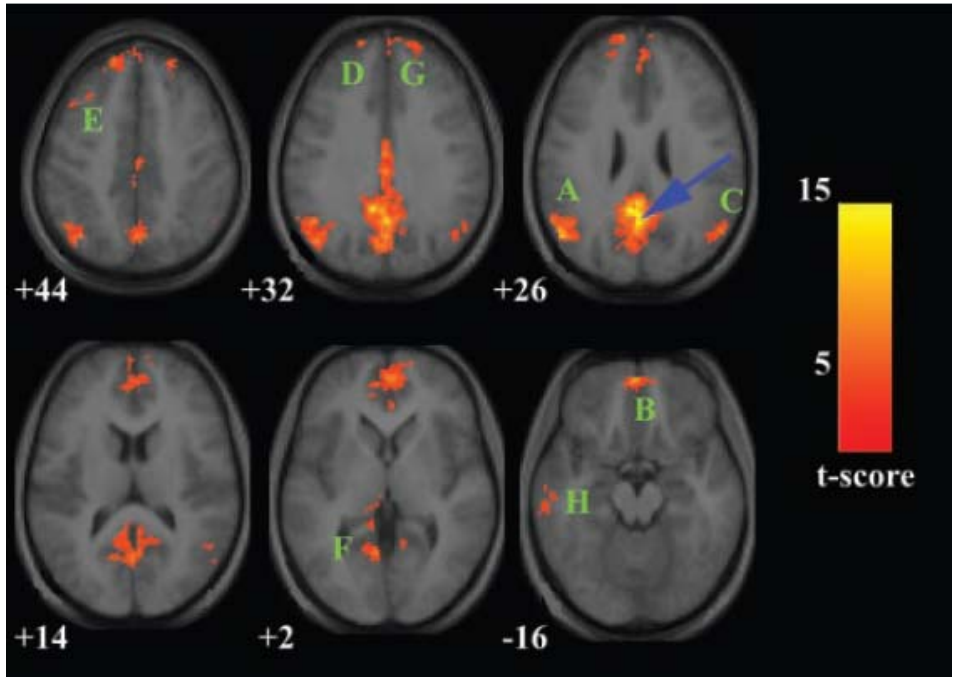
Functional connectivity in the resting brain: A network analysis of the default mode hypothesis

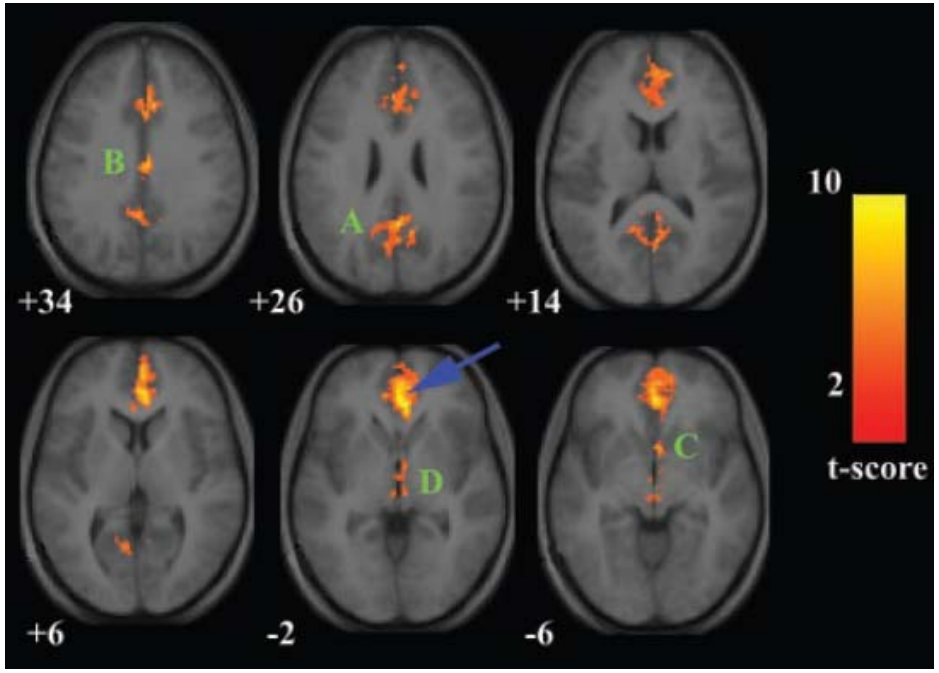
PNAS 2003

Michael D. Greicius*†‡, Ben Krasnow*, Allan L. Reiss*§¶, and Vinod Menon*§¶

Departments of *Psychiatry and Behavioral Sciences and †Neurology and Neurological Sciences, §Program in Neurosciences, and ¶Stanford Brain Research Center, Stanford University School of Medicine, Stanford, CA 94305-5719

Edited by Marcus E. Raichle, Washington University School of Medicine, St. Louis, MO, and approved November 12, 2002 (received for review August 21, 2002)



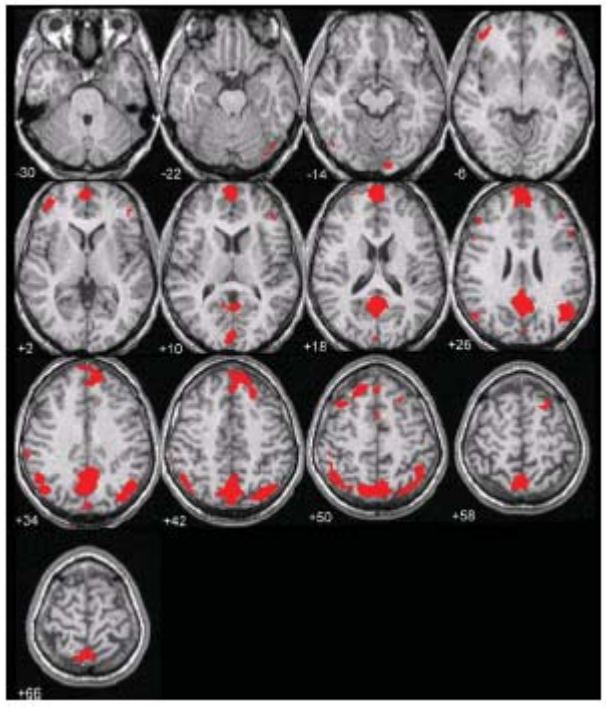


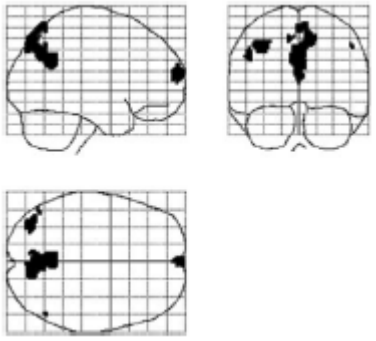
◆ Human Brain Mapping 26:15–29(2005) ◆

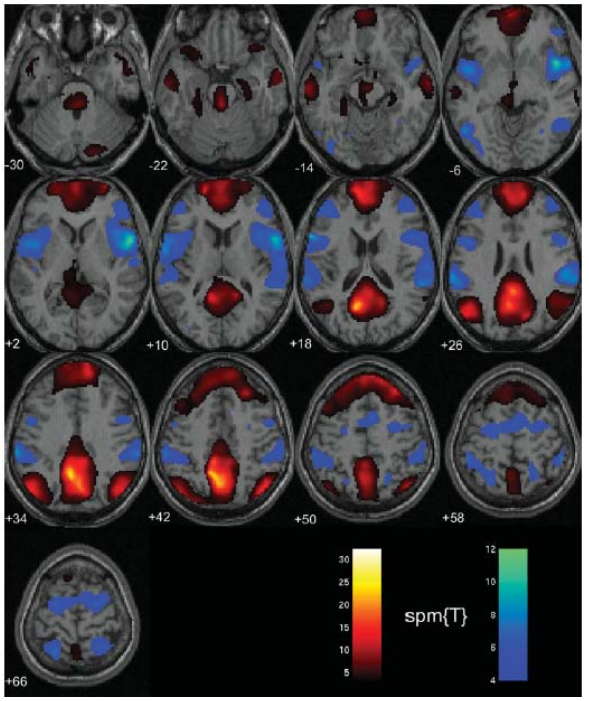
Spontaneous Low-Frequency BOLD Signal Fluctuations: An fMRI Investigation of the Resting-State Default Mode of Brain Function Hypothesis

Peter Fransson*

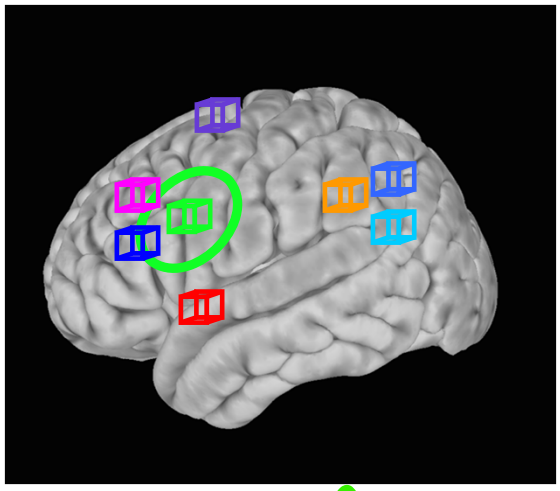
MR Research Center, Cognitive Neurophysiology, Department of Clinical Neuroscience, Karolinska Institute/Karolinska University Hospital, Stockholm, Sweden



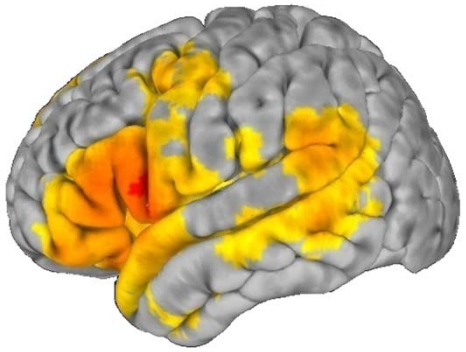


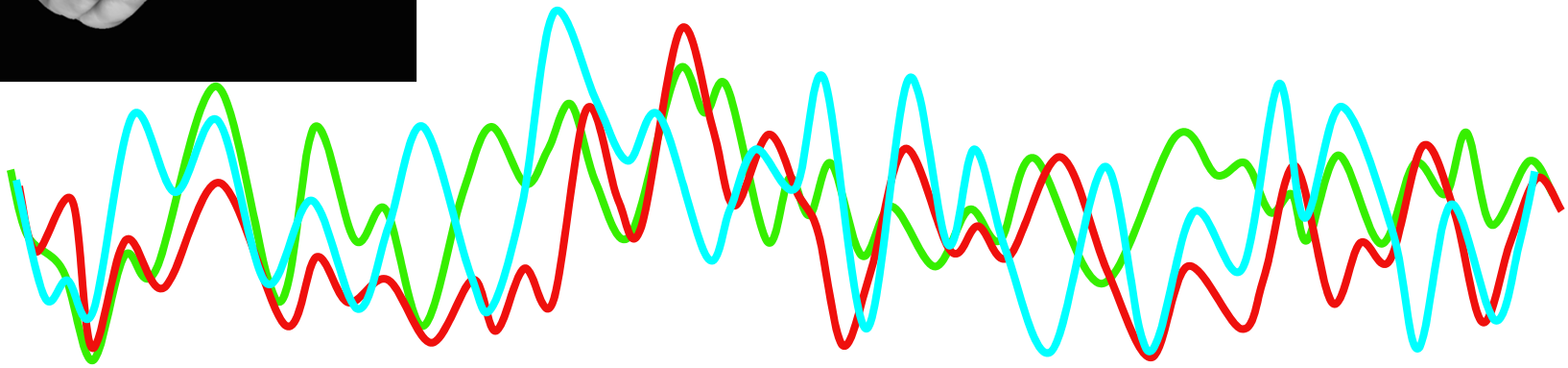


Untitled (2008) Daniel Margulies & Chris Sharp
http://vimeo.com/9871689



Correlation Analysis



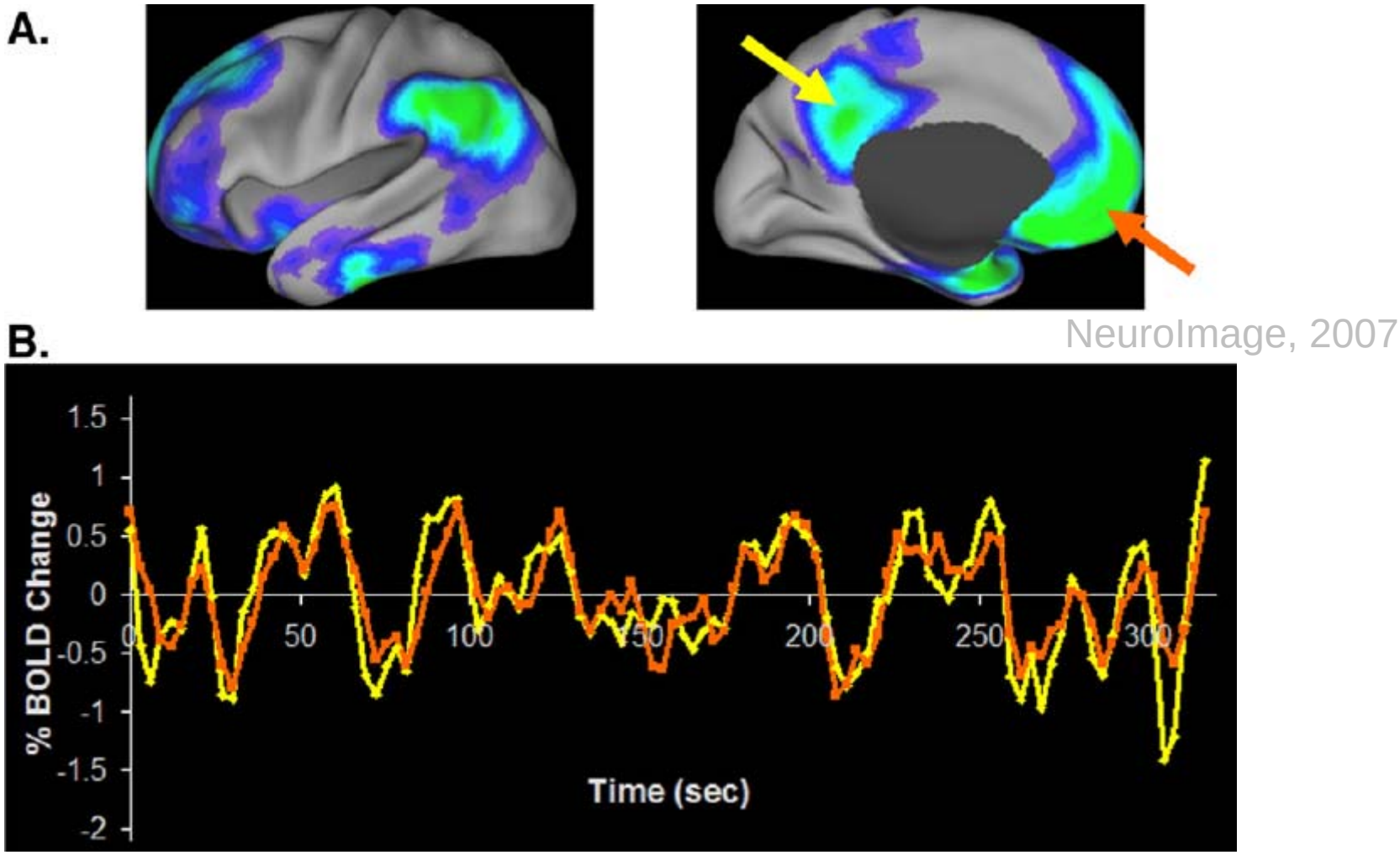


How do we study the brain's intrinsic architecture?

Functional Connectivity

A default mode of brain function: A brief history of an evolving idea

Marcus E. Raichle[a,b,c,*] and Abraham Z. Snyder[a,b]

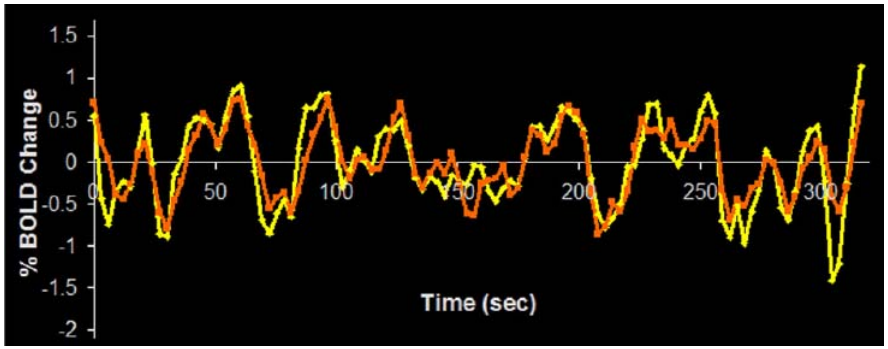


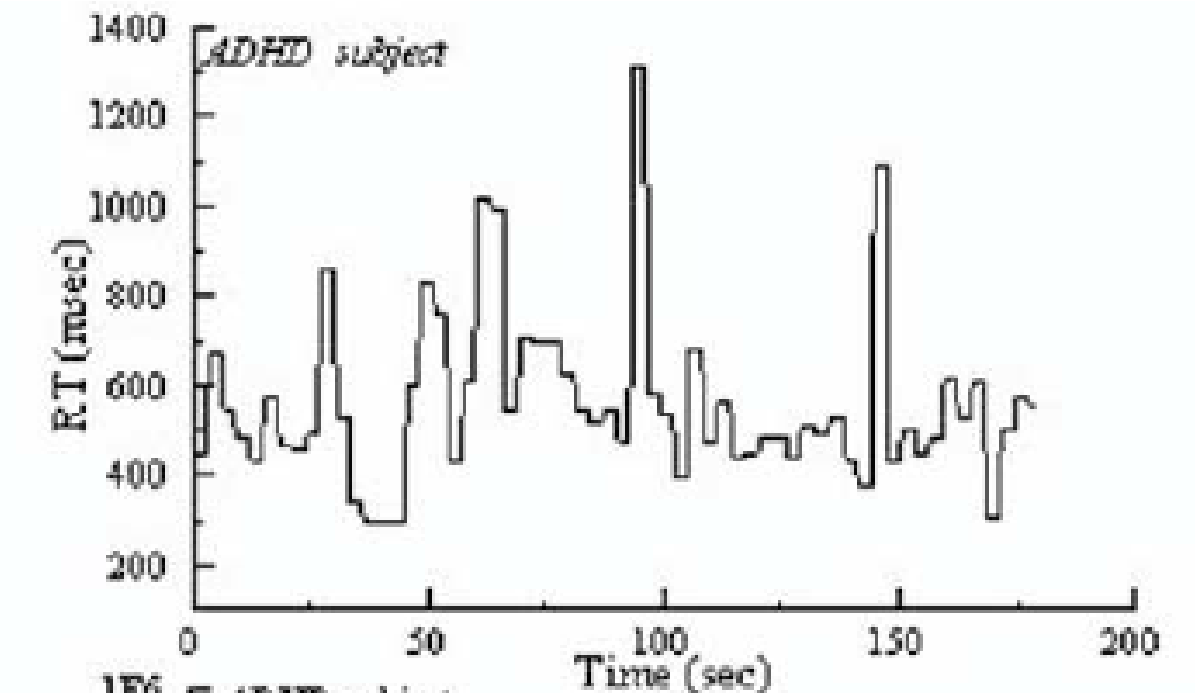
NeuroImage, 2007

A default mode of brain function

Marcus E. Raichle*†, Ann Mary MacLeod*, Abraham Z. Snyder*, William J. Powers‡, Debra A. Gusnard*§, and Gordon L. Shulman‡

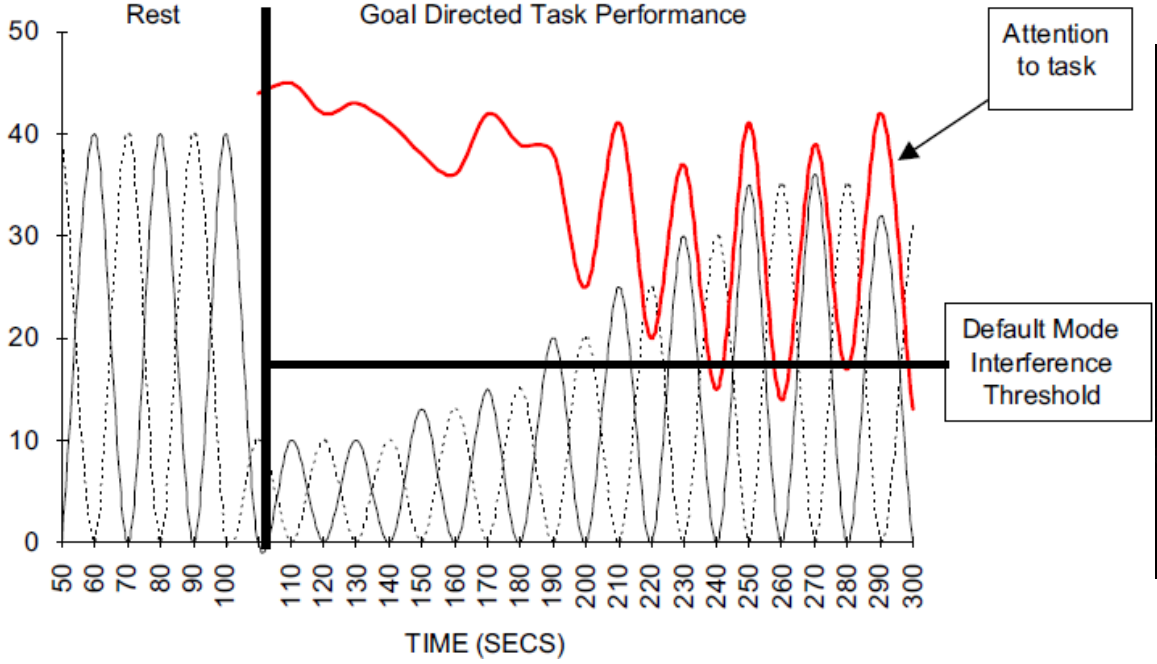
PNAS 2001

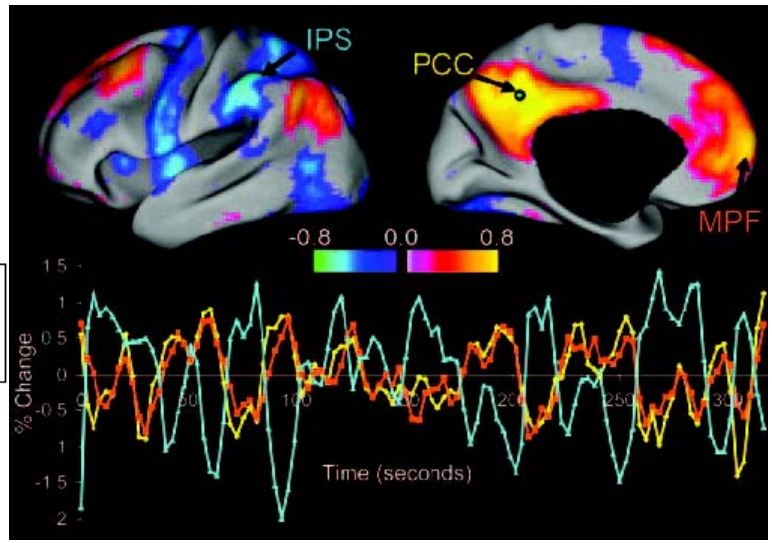

% BOLD Change
1.5
1
0.5
0
-0.5
-1
-1.5
-2
0
50
100
150
200
250
300
Time (sec)


ADHD subject
RT (msec)
1400
1200
1000
800
600
400
200
0
50
100
150
200
Time (sec)

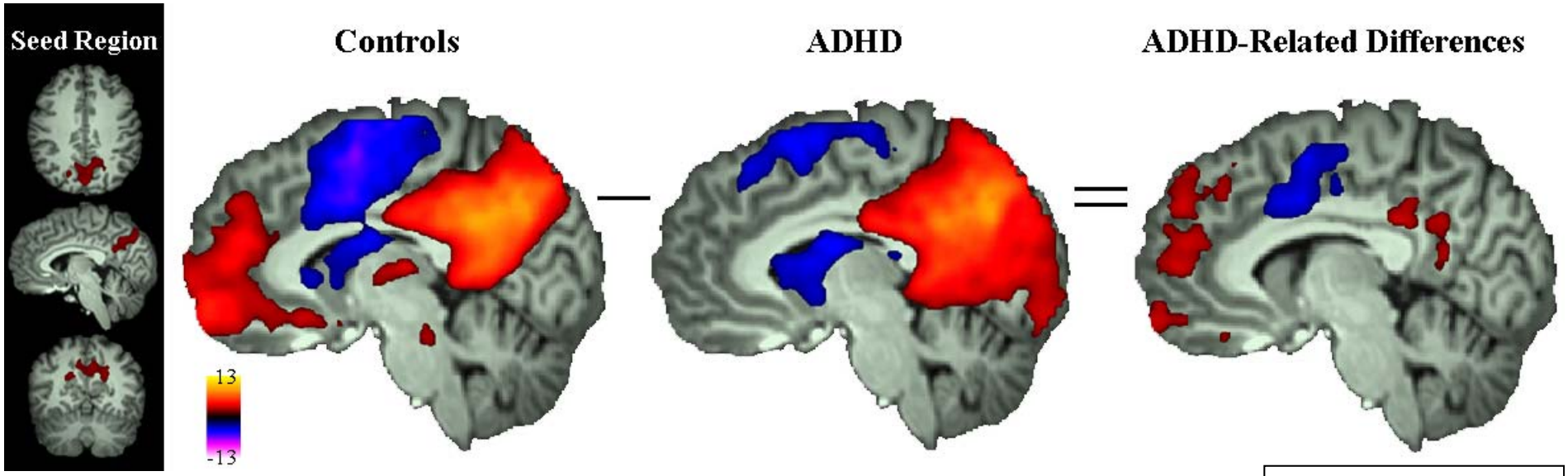
Sonuga-Barke & Castellanos, 2007

- Hypothesized that lapses of attention result from interference or poor coordination between default network and executive control networks
  - frontoparietal, dorsal attention and ventral attention





Castellanos et al., Biological Psychiatry, 2008



p <.05 corrected

The **precuneus** is involved in 'high-level integration between posterior association processes and anterior executive functions' (Cavanna & Trimble, Brain, 2006); functional circuits linking dACC to precuneus and PCC may represent 'small-world network' long-range connections that should be considered as a candidate locus of dysfunction in ADHD.

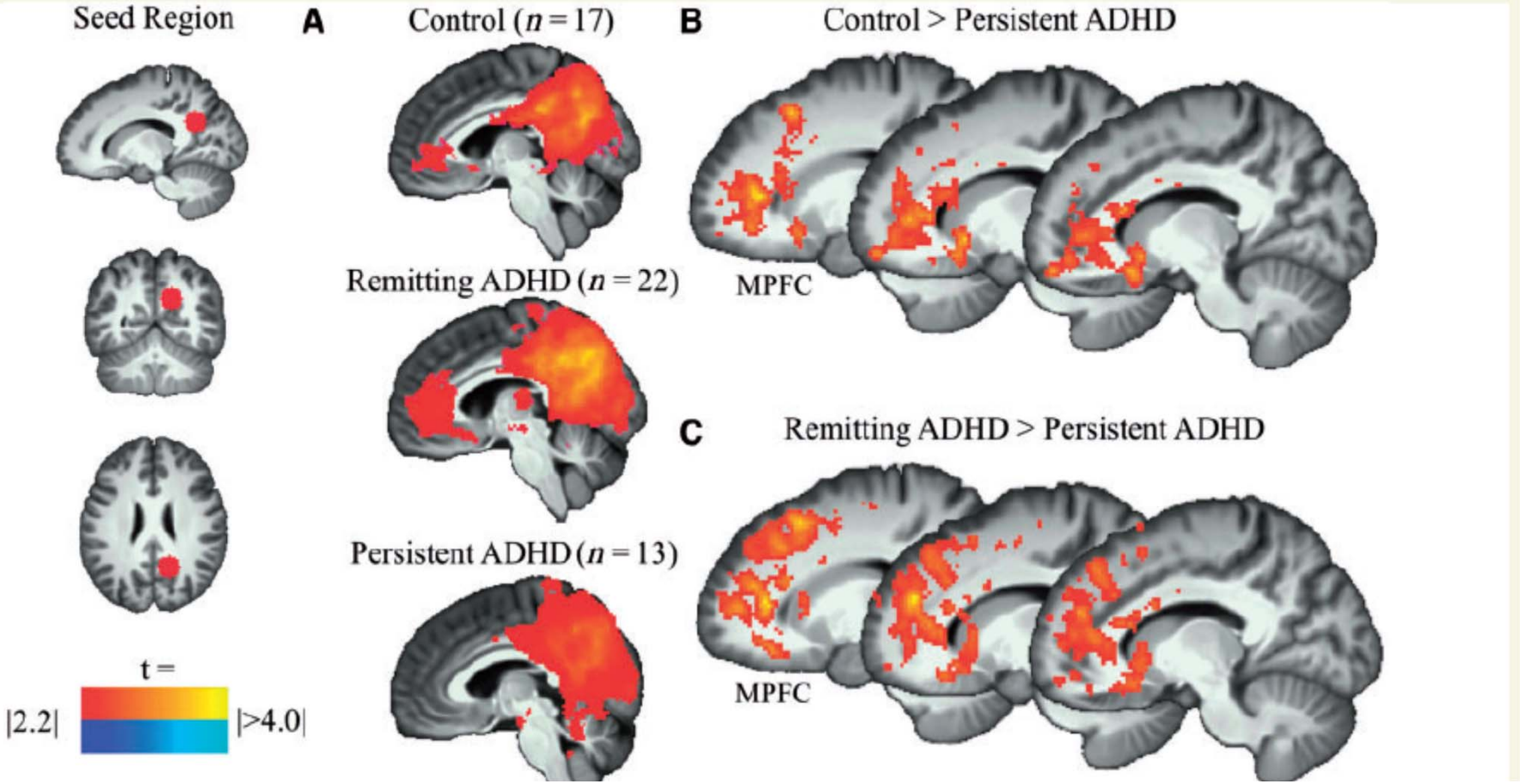
doi:10.1093/brain/awu137 Brain 2014: 137; 2423–2428 | 2423

BRAIN
A JOURNAL OF NEUROLOGY

REPORT

Brain differences between persistent and remitted attention deficit hyperactivity disorder

Aaron T. Mattfeld,[1,2] John D. E. Gabrieli,[1,2] Joseph Biederman,[3,4] Thomas Spencer,[3,4] Ariel Brown,[3,4] Amelia Kotte,[3,4,5] Elana Kagan[3,4] and Susan Whitfield-Gabrieli[1,2]



http://fcon_1000.projects.nitrc.org/indi/adhd200

N = 285 ADHD

N = 491 Typically Developing Controls

Ages 7-21 years old

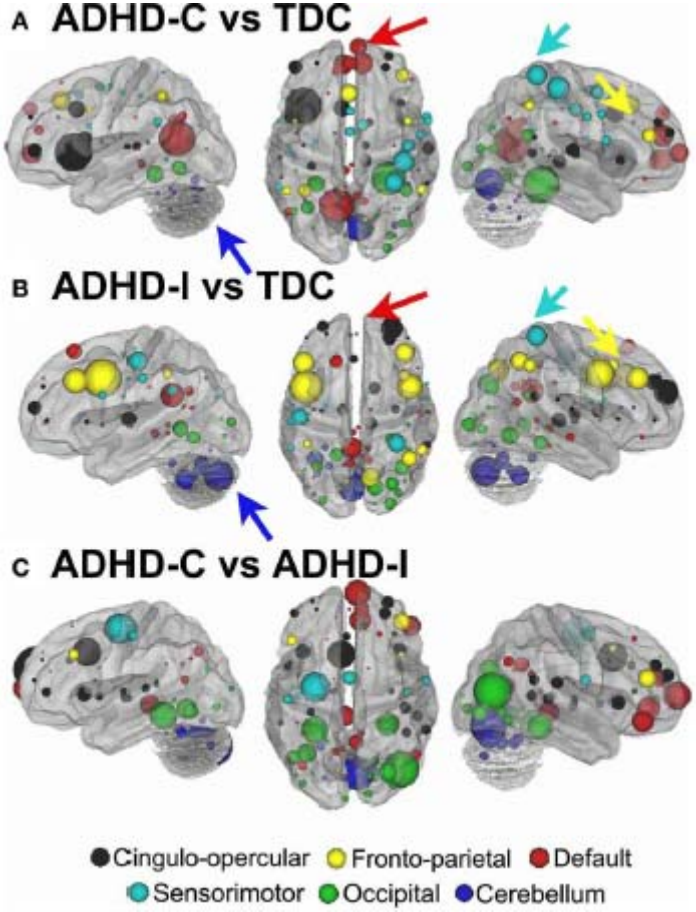
Released March 1, 2011

frontiers in
SYSTEMS NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 04 February 2013
doi: 10.3389/fnsys.2012.00080

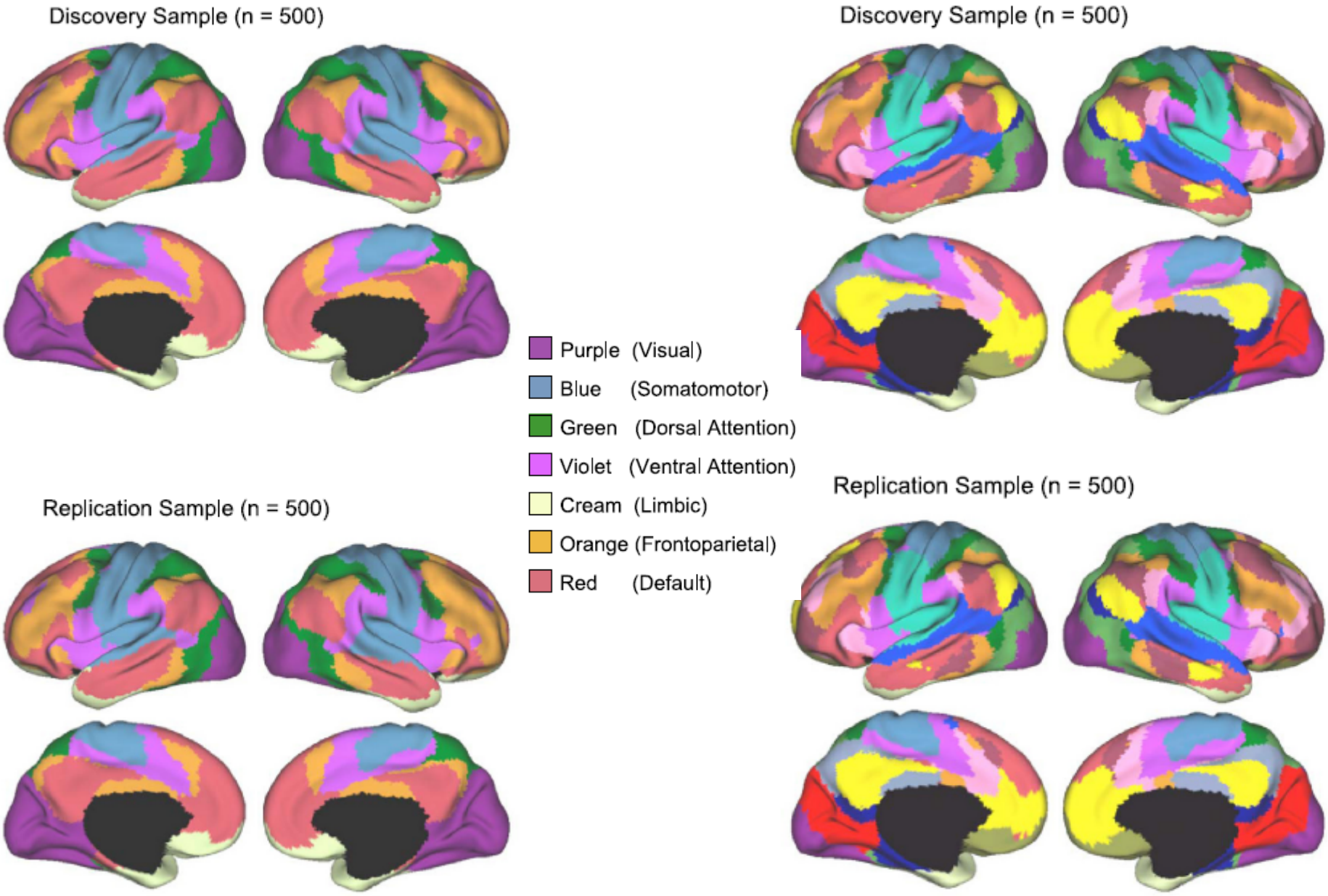
Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data

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]**



- 776 scans → 3 matched groups of 52 (N=156) incl. on low motion
- (A) ADHD-C vs. TDC differ particularly for anterior and posterior nodes of the **default network**; sensorimotor and occipital networks.
- (B) Contrast between ADHD-I and TDC highlights frontoparietal and cerebellar networks.
- (C) Head-to-head contrast between the two subtypes highlights differences in the **anterior** nodes of **default network**, occipital, and sensorimotor networks.

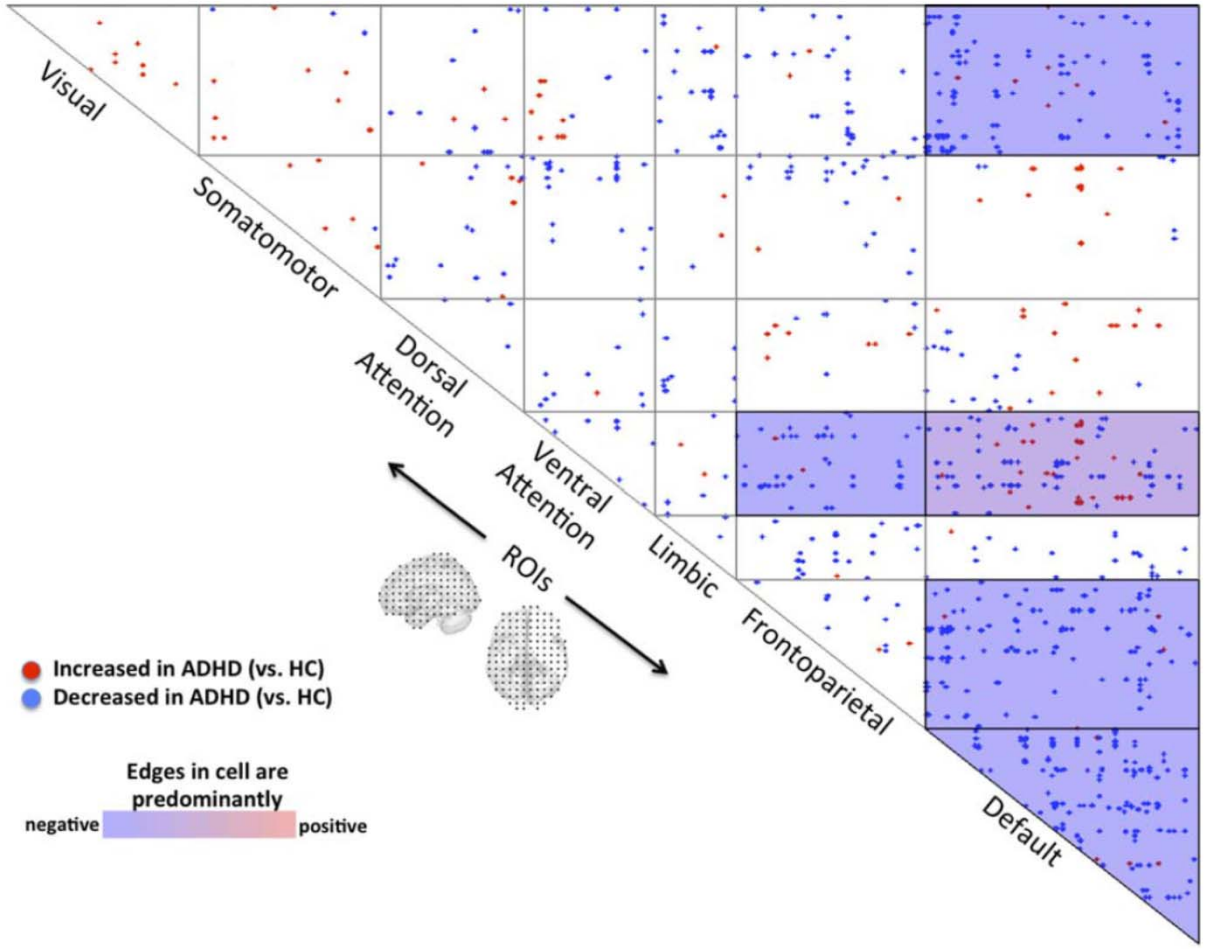
Yeo, Krienen et al., 2011 J Neurophysiology



Disrupted Network Architecture of the Resting Brain in Attention-Deficit/Hyperactivity Disorder

Chandra Sripada,[1]* Daniel Kessler,[1] Yu Fang,[1] Robert C. Welsh,[1,2]
Krishan Prem Kumar,[1] and Michael Angstadt[1]

HBM, 2014



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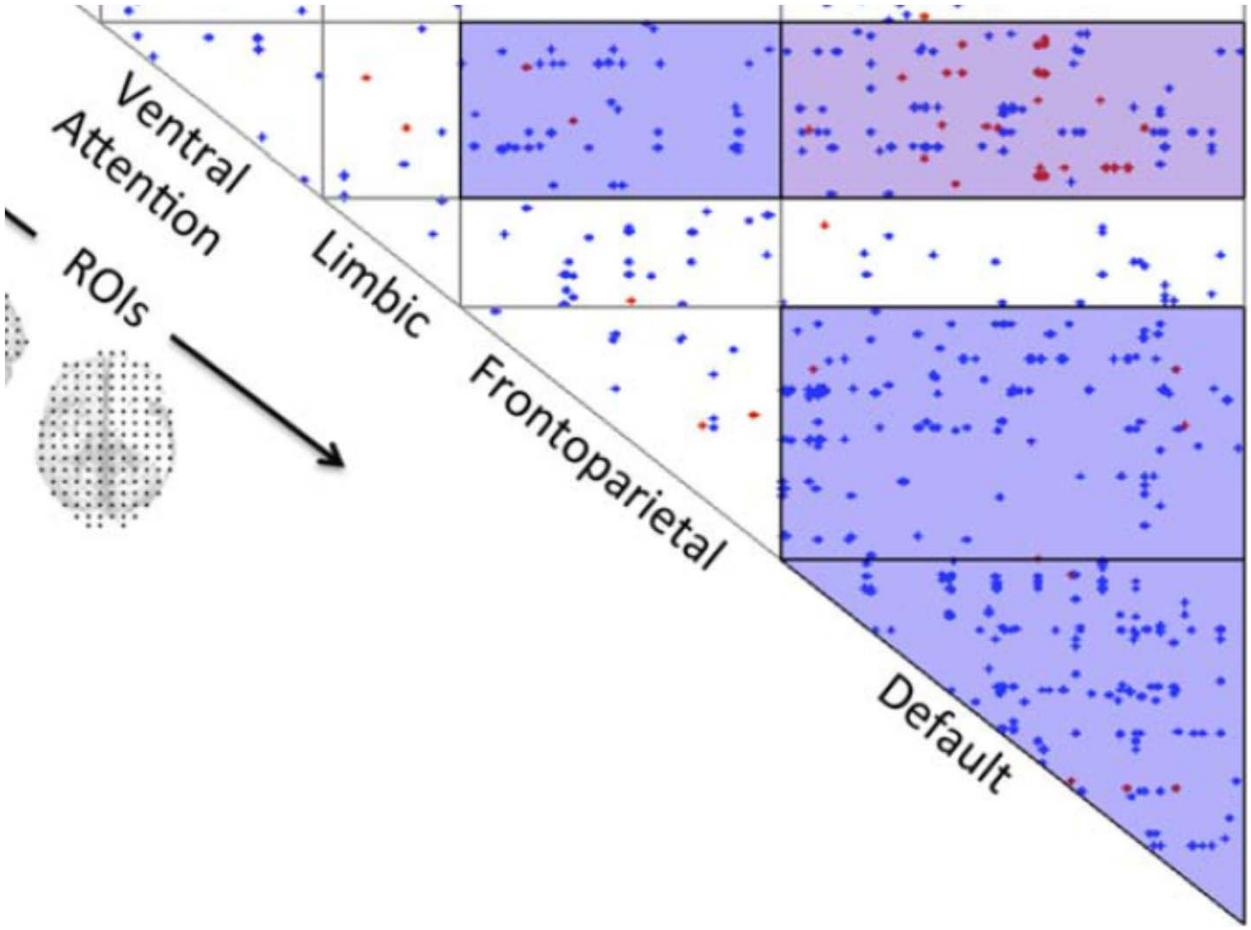

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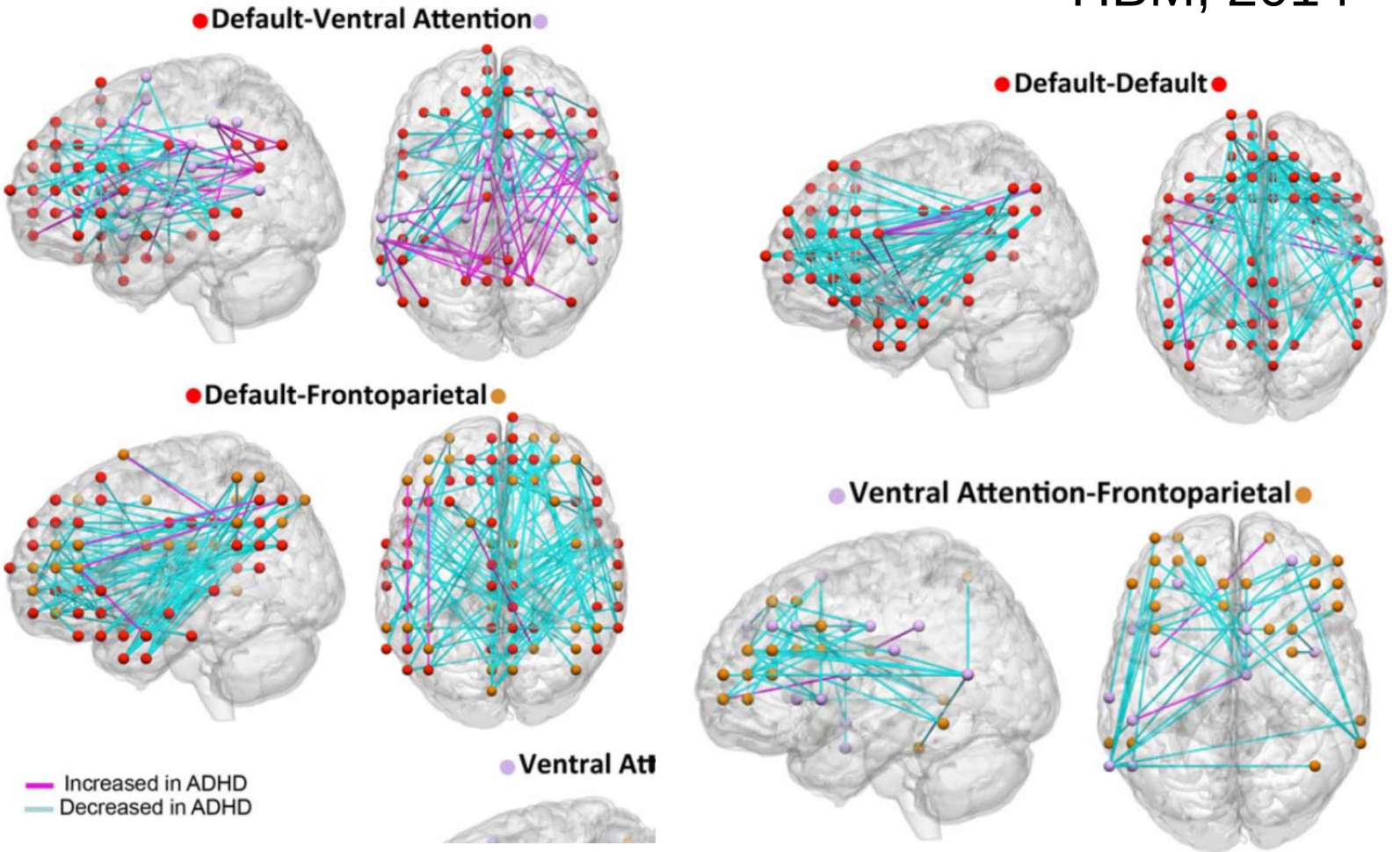

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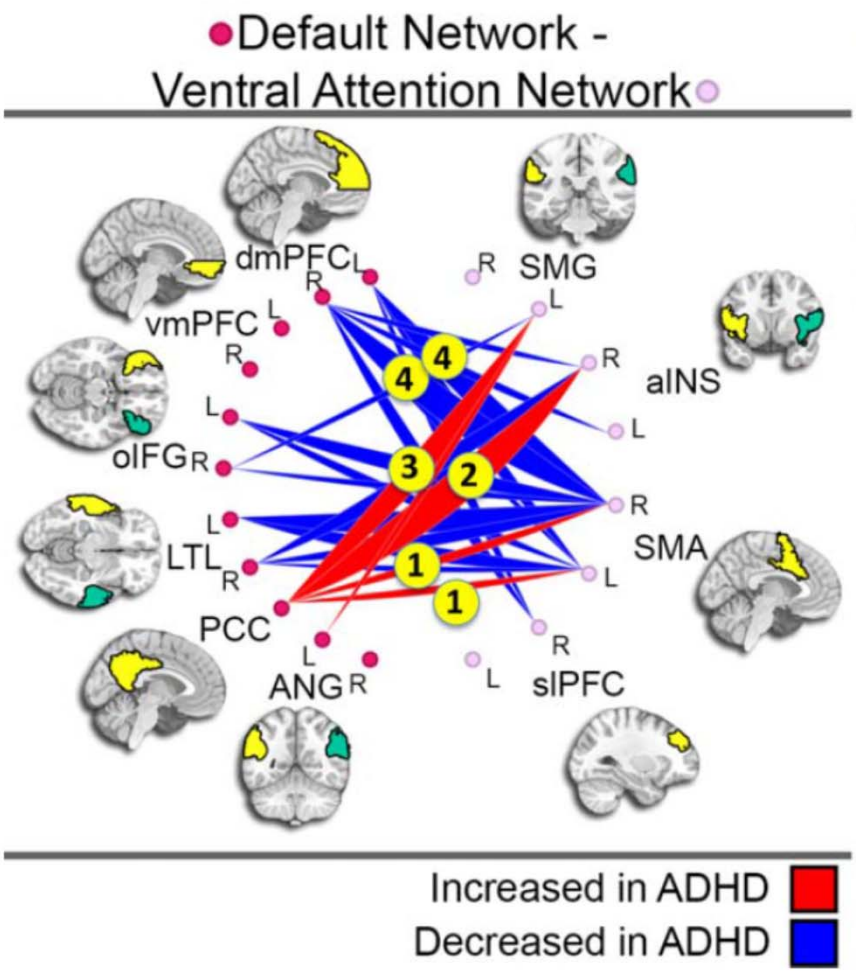
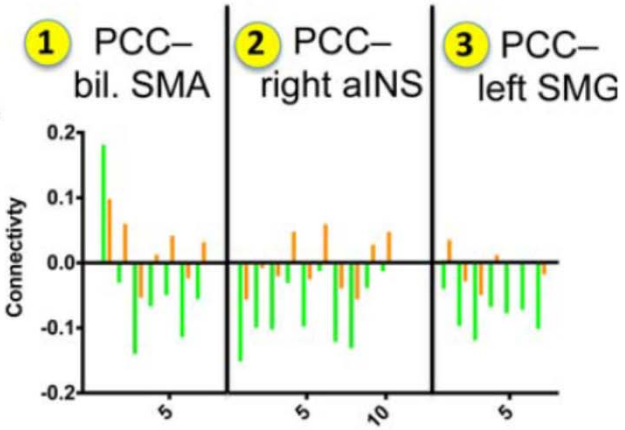
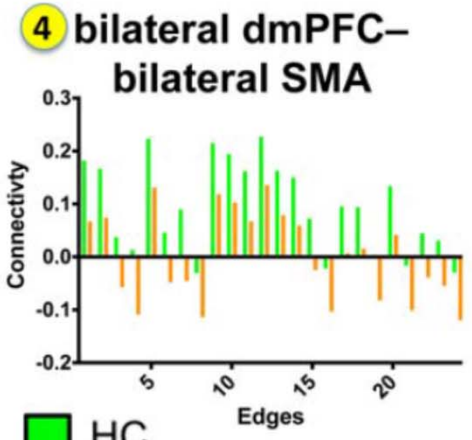
HBM, 2014





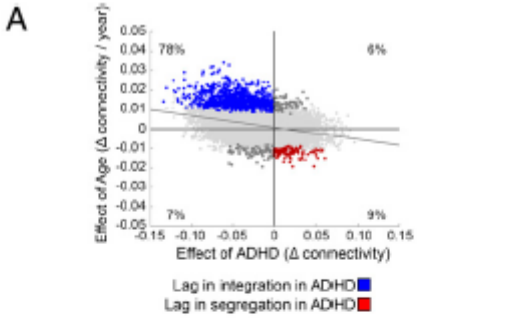


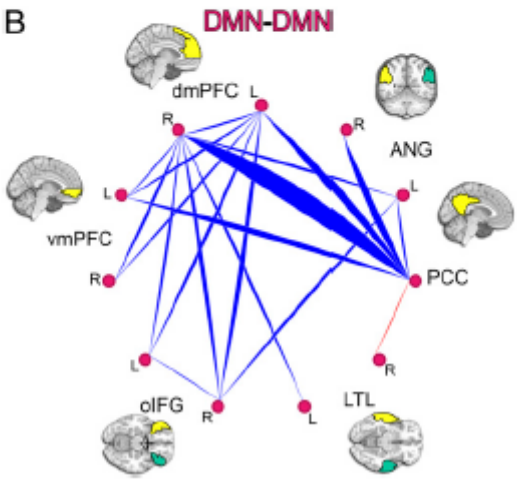
Lag in maturation of the brain's intrinsic functional architecture in attention-deficit/hyperactivity disorder

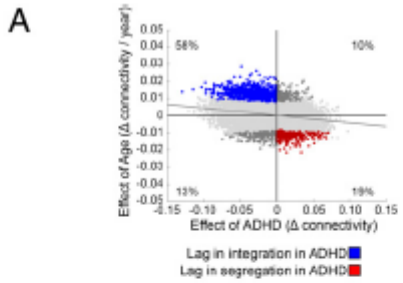
Chandra S. Sripada[1], Daniel Kessler, and Mike Angstadt

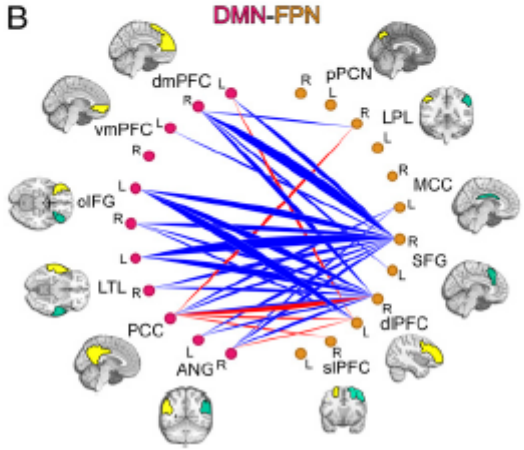
Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109

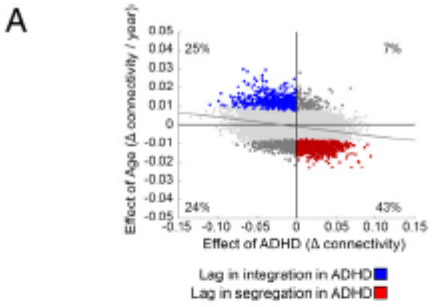
PNAS 2014

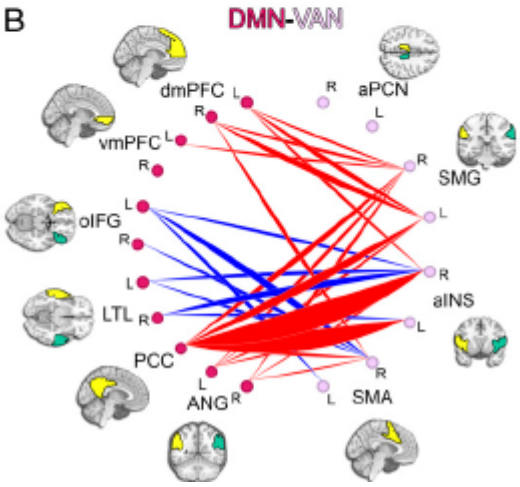










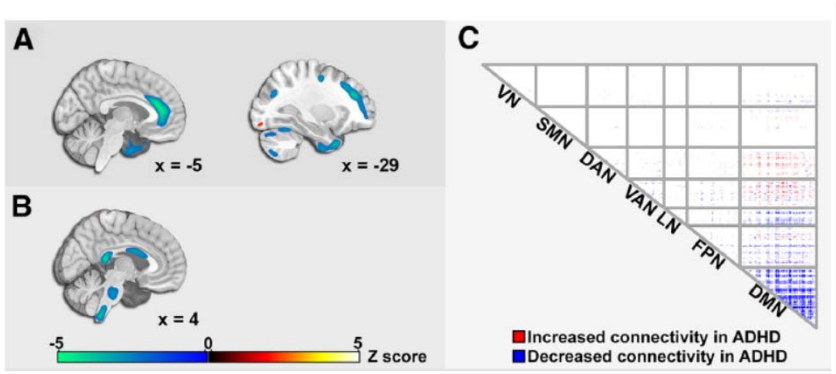


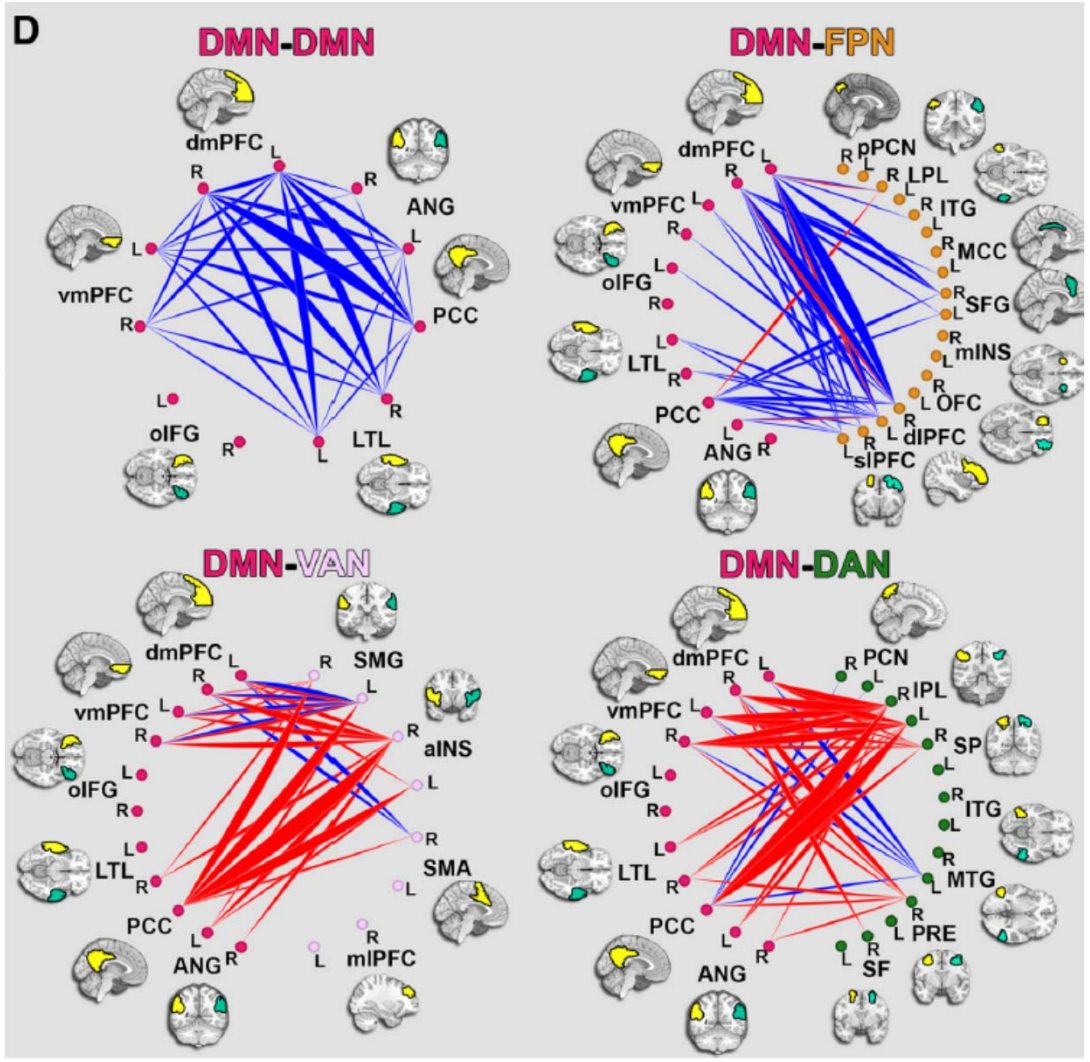
Modality-Spanning Deficits in Attention-Deficit/ Hyperactivity Disorder in Functional Networks, Gray Matter, and White Matter

The Journal of Neuroscience, December 10, 2014

Daniel Kessler,[1] Michael Angstadt,[1] Robert C. Welsh,[1,2] and Chandra Sripada[1]

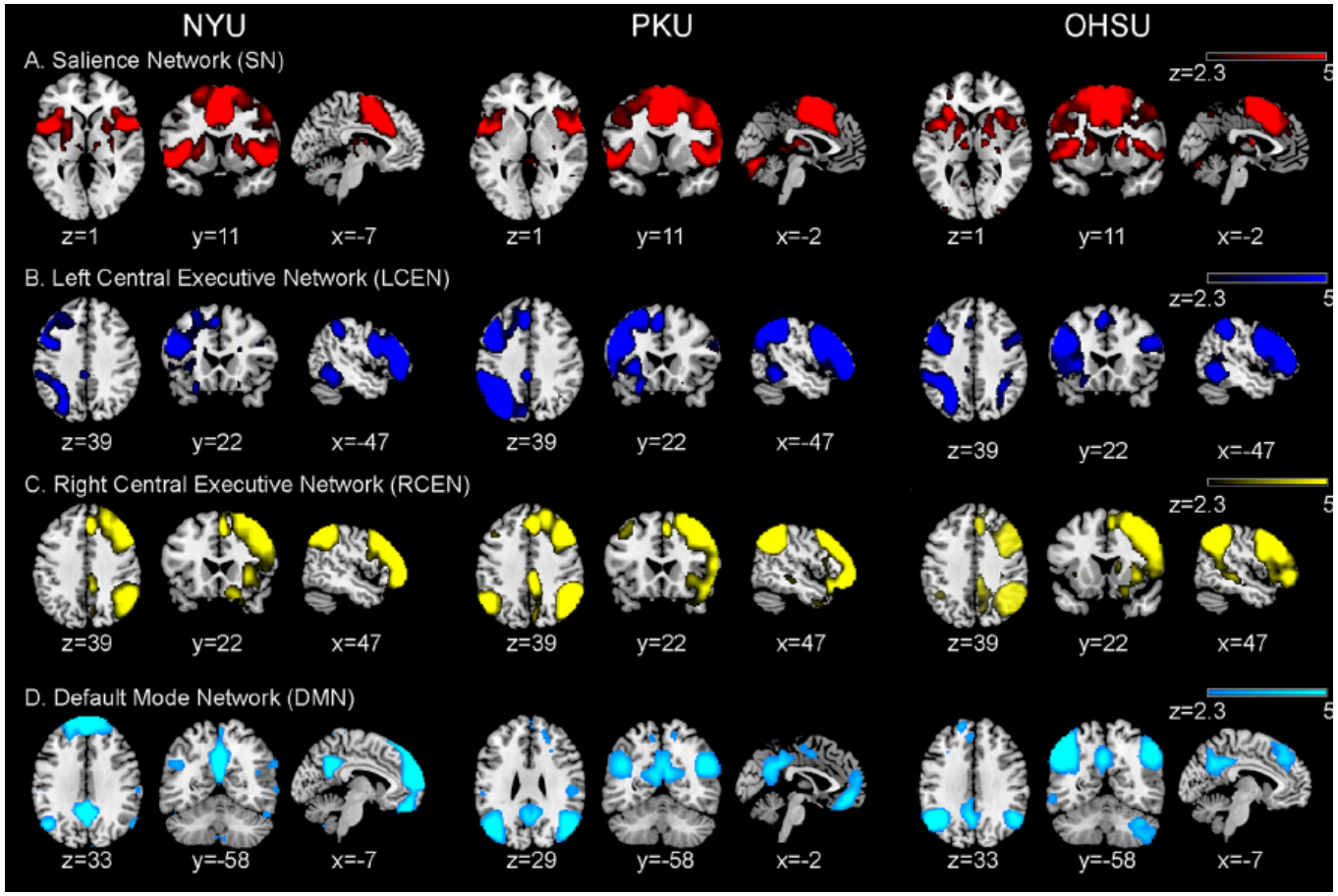
[1]Department of Psychiatry and [2]Department of Radiology, University of Michigan, Ann Arbor, Michigan 48109





Aberrant Cross-Brain Network Interaction in Children With Attention-Deficit/Hyperactivity Disorder and Its Relation to Attention Deficits: A Multisite and Cross-Site Replication Study

Weidong Cai, Tianwen Chen, Luca Szegletes, Kaustubh Supekar, and Vinod Menon



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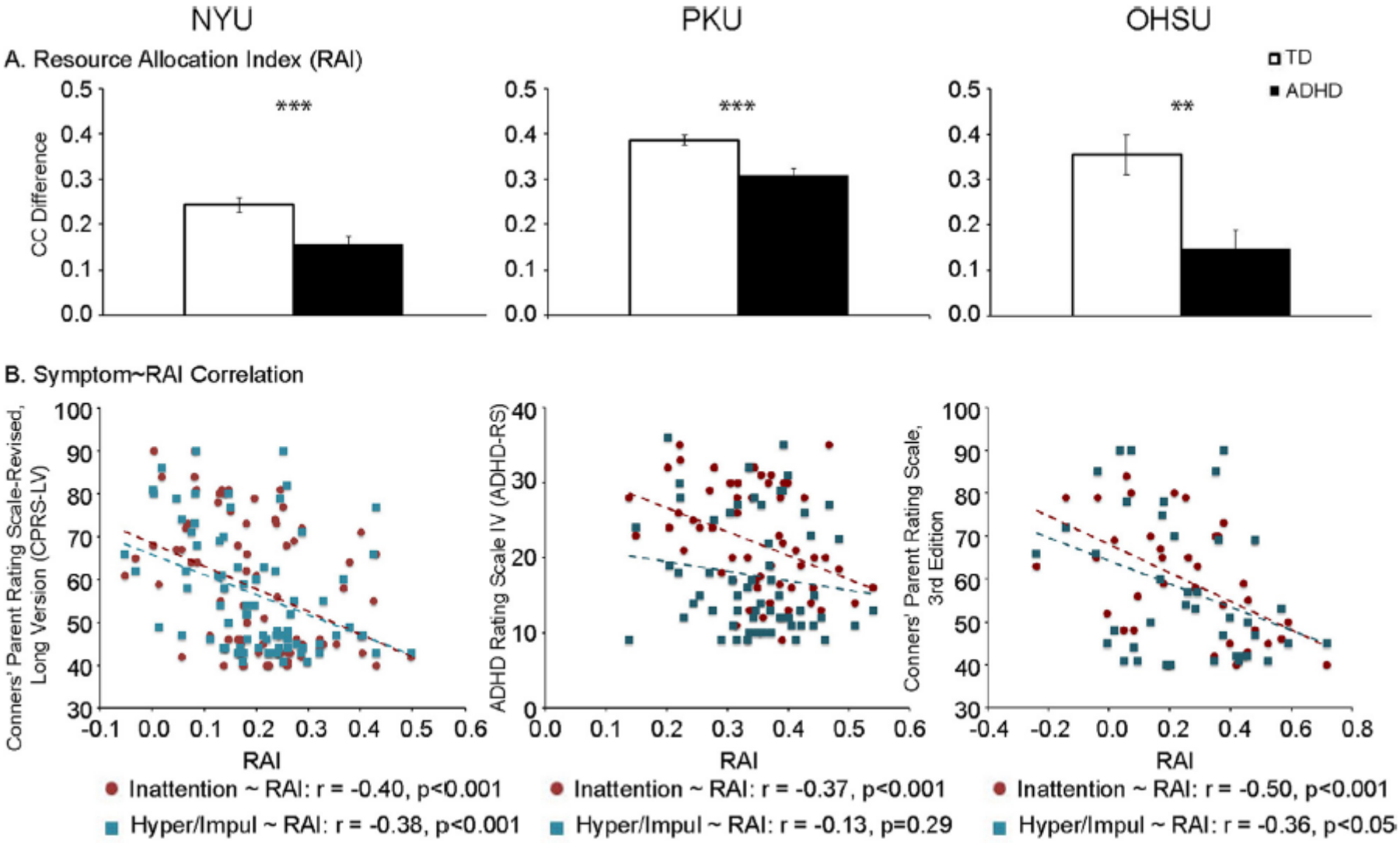

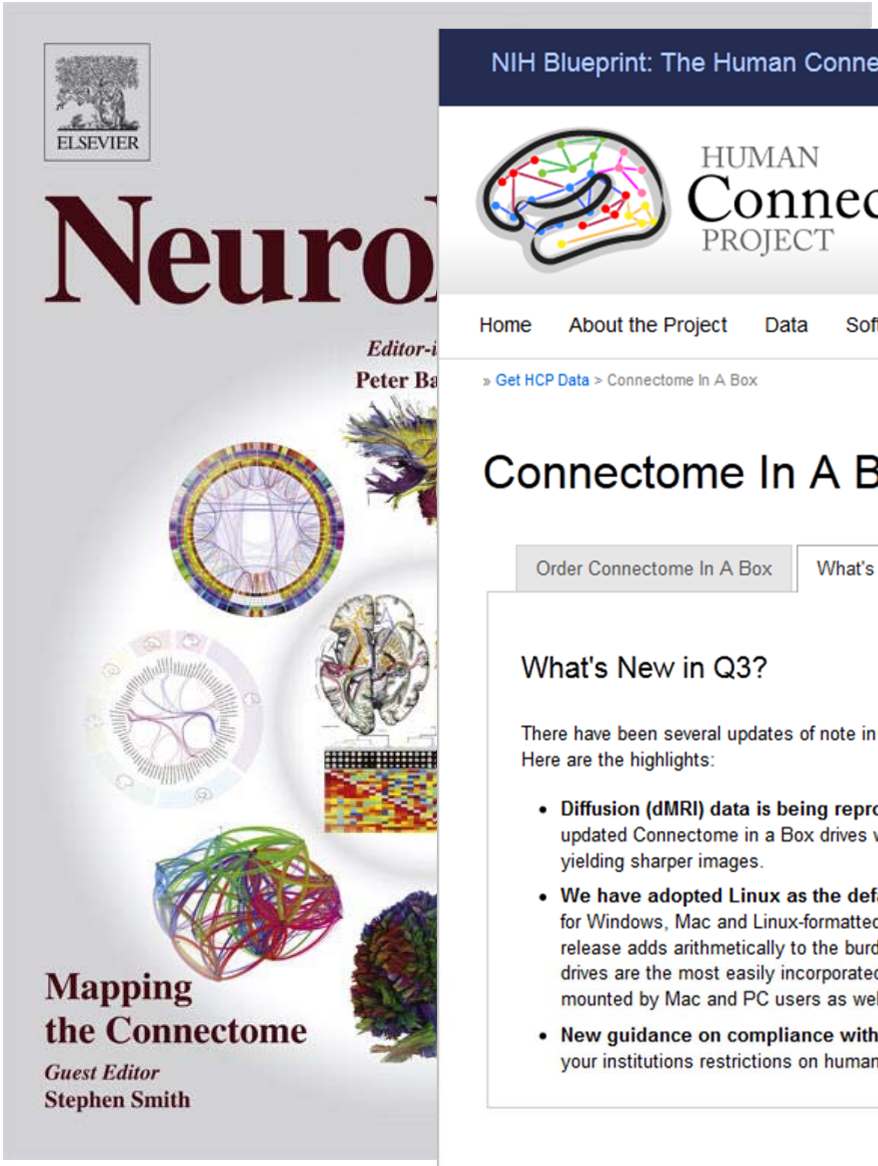

NIH Blueprint: The Human Connectome Project

NIH Blueprint for Neuroscience Research

HUMAN Connectome PROJECT

Mapping structural and functional connections in the human brain

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Connectome In A Box

Order Connectome In A Box | What's New in Q3? | What about MEG data? | Save Money with the HCP Drive Recycling Program

What's New in Q3?

There have been several updates of note in Q3 for current users of Connectome In A Box. Here are the highlights:

- **Diffusion (dMRI) data is being reprocessed and re-released.** The release of updated Connectome in a Box drives will include all updated diffusion sessions, yielding sharper images.
- **We have adopted Linux as the default drive format.** In Q1, we supported orders for Windows, Mac and Linux-formatted hard drives equally. However, each new release adds arithmetically to the burden on our fulfillment process. Linux-formatted drives are the most easily incorporated into network storage, but they can also be mounted by Mac and PC users as well.
- **New guidance on compliance with your IRB.** All Connectome data administrators should read this notice on data usage and compliance with your institutions restrictions on human subject research.

IMPORTANT:
Before you begin to use HCP Data, please review the set of available HCP Data Use Terms, and follow the steps to accept the terms that apply to your research.

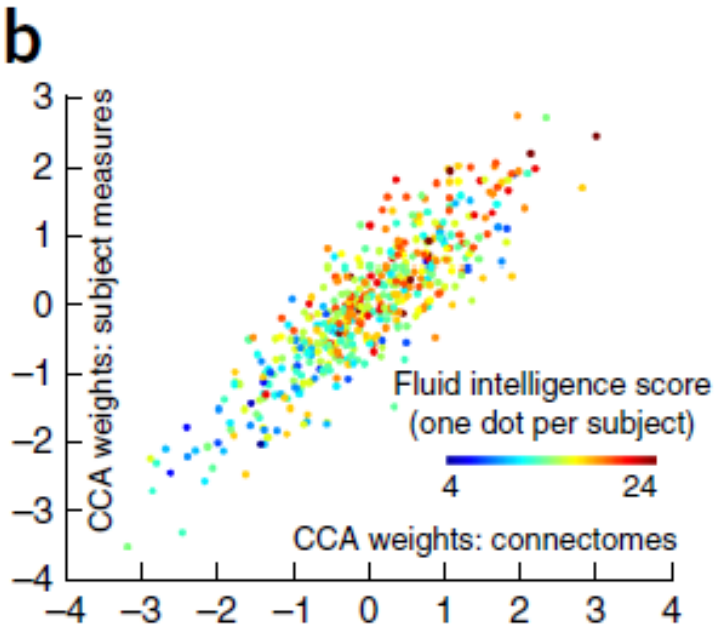
Before You Order:
Explore Data on ConnectomeDB

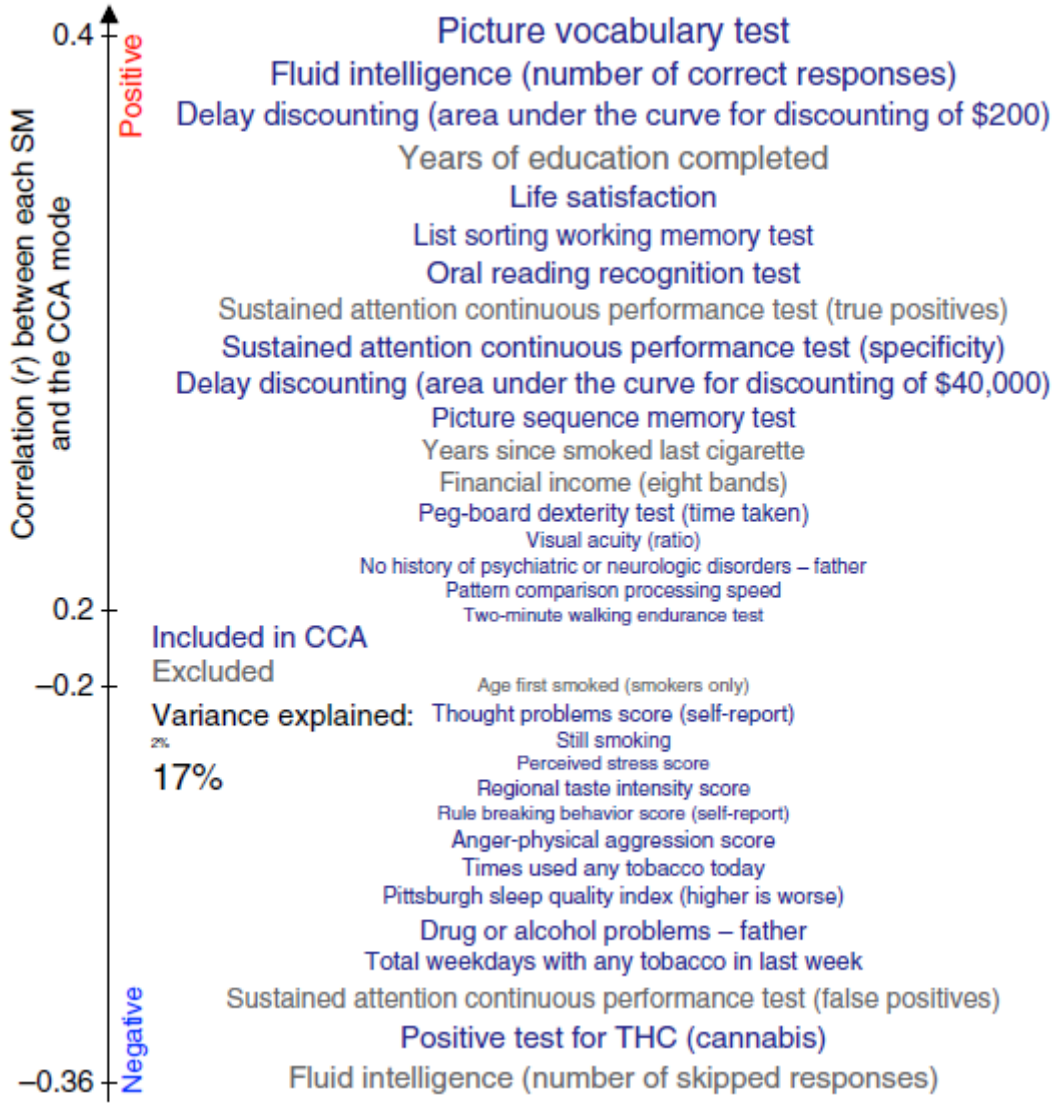
What is Connectome in a Box?

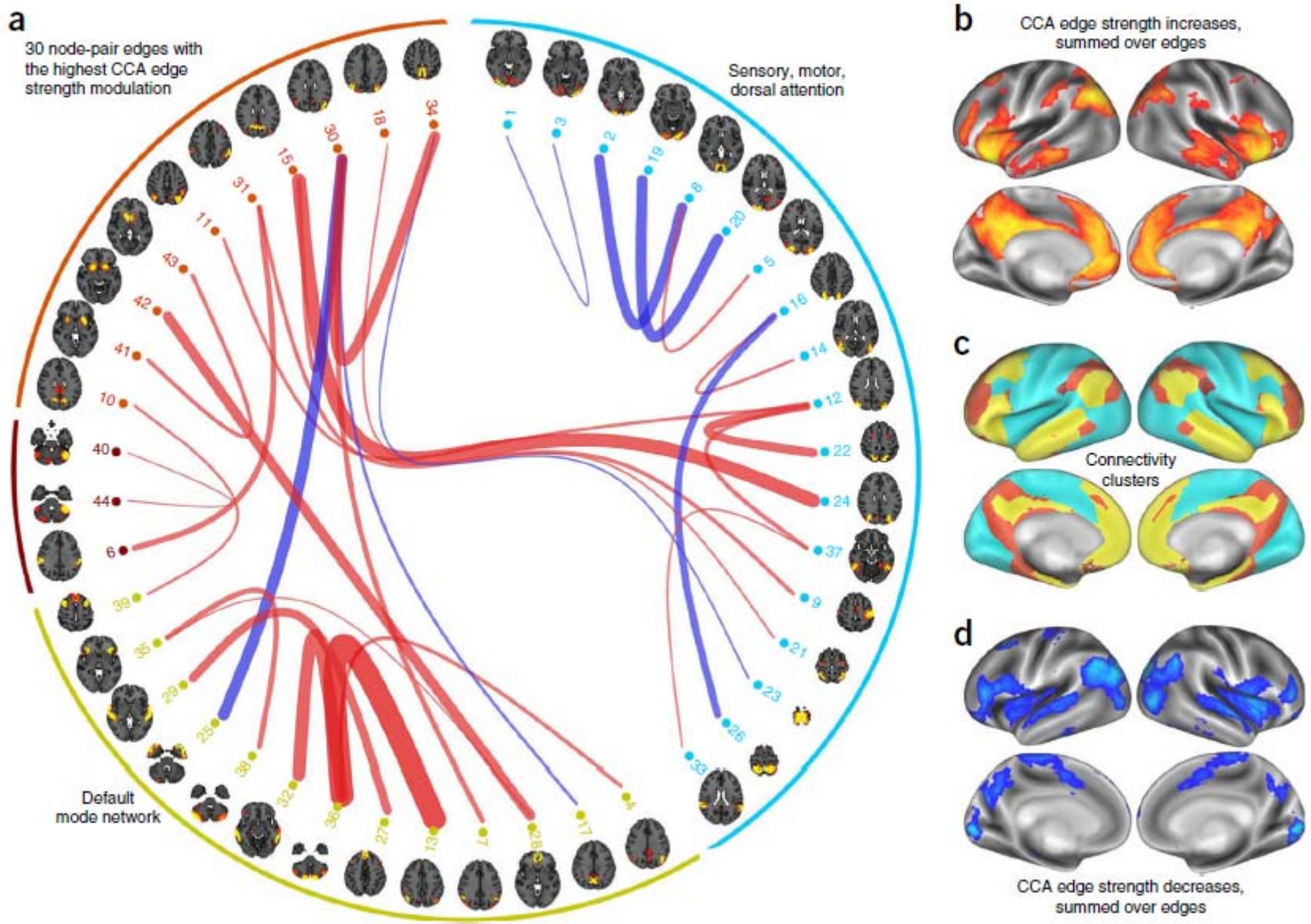
A positive-negative mode of population covariation links brain connectivity, demographics and behavior

Stephen M Smith[1], Thomas E Nichols[2], Diego Vidaurre[3], Anderson M Winkler[1], Timothy E J Behrens[1], Matthew F Glasser[4], Kamil Ugurbil[5], Deanna M Barch[4], David C Van Essen[4] & Karla L Miller[1]

nature neuroscience







S M Smith et al. 2016, Nat NS

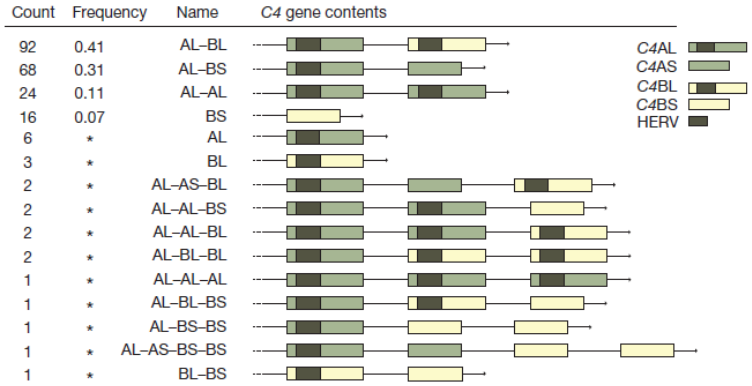
NIH ABCD Study

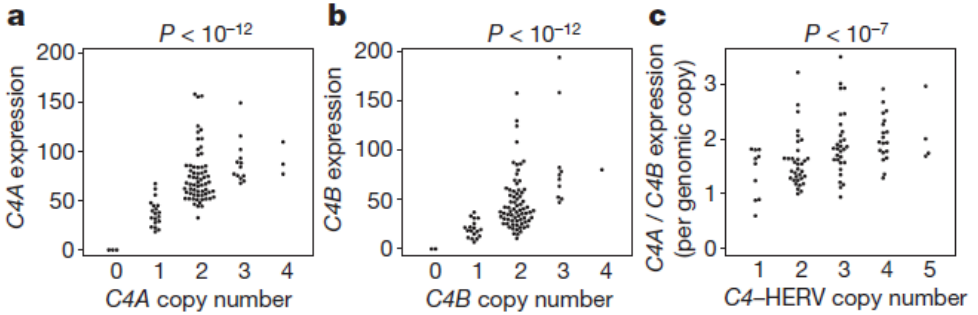
- Adolescent Brain Cognition Development
- +10.000 children will be studied starting at ages 9-10 for 10 years
- Developmental trajectories of behavior, brain, psychopathology, substance use will be measured
- All data will be shared

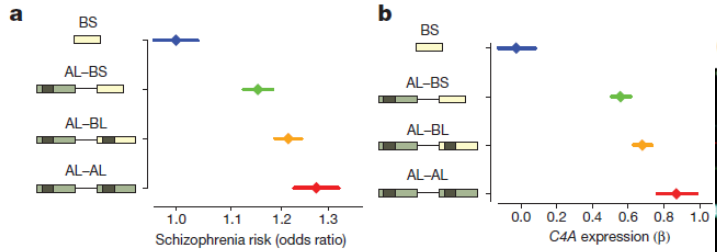
doi:10.1038/nature16549

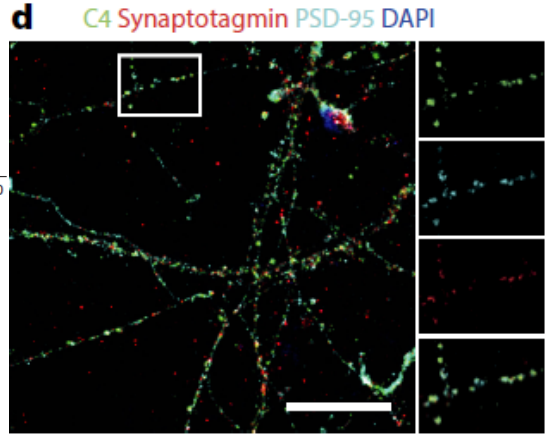
Schizophrenia risk from complex variation of complement component 4

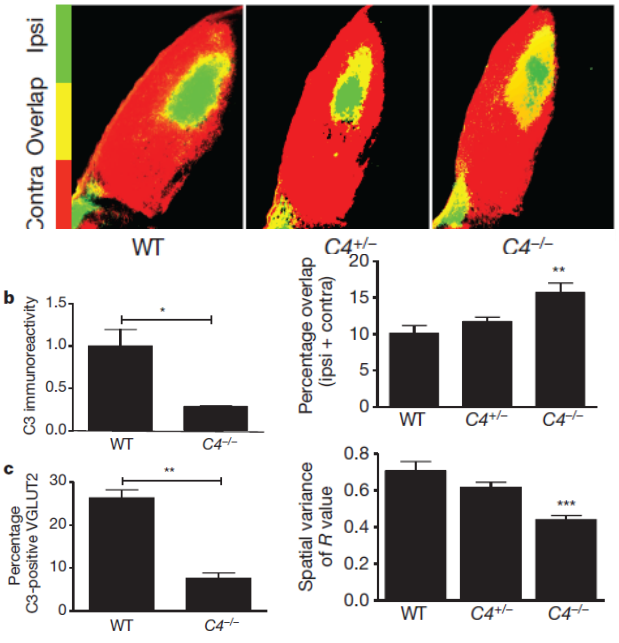
Aswin Sekar[1,2,3], Allison R. Bialas[4,5], Heather de Rivera[1,2], Avery Davis[1,2], Timothy R. Hammond[4], Nolan Kamitaki[1,2], Katherine Tooley[1,2], Jessy Presumey[5], Matthew Baum[1,2,3,4], Vanessa Van Doren[1], Giulio Genovese[1,2], Samuel A. Rose[2], Robert E. Handsaker[1,2], Schizophrenia Working Group of the Psychiatric Genomics Consortium*, Mark J. Daly[2,6], Michael C. Carroll[5], Beth Stevens[2,4] & Steven A. McCarroll[1,2]











Conclusions

- Future diagnoses must be based on pathophysiology
- Foundational work has been ongoing for decades; beginning to bear fruit
- Need to seek simplicity within complexity
- The brain's DMN is "implicated" in neuropsychiatric disorders
  - But that's just the beginning…
  - Inter-network interactions… DMN with attention or cognitive control networks
- Data sharing is reshaping the scientific enterprise

Share that Brain!

Mike Milham
Clare Kelly
Adriana Di Martino

Samuele Cortese
Daniel Margulies
Maarten Mennes
Chao-Gan Yan
Juan Zhou
Xi-Nian Zuo

NYU Langone MEDICAL CENTER

nki

Thank you for your attention

http://www.humanconnectome.org/data/connectome-in-a-box.html

http://fcon_1000.projects.nitrc.org/indi/adhd200/

http://fcon_1000.projects.nitrc.org/indi/abide/

http://www.nitrc.org/projects/cpac/

http://rfmri.org/