MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

The Neuroscience Revolution:
How will it Affect Patient Care?

THURSDAY, OCTOBER 22, 2020

44TH ANNUAL PSYCHOPHARMACOLOGY CONFERENCE

LIVE STREAM CONFERENCE

THURSDAY – SUNDAY, OCTOBER 22-25, 2020

PRESENTED BY

MASSACHUSETTS GENERAL HOSPITAL

A FOUNDING MEMBER OF PARTNERS HEALTHCARE

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

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The Neuroscience Revolution: How will it Affect Patient Care?

PROGRAM AGENDA

THURSDAY, OCTOBER 22, 2020

4:00-4:10 PM	**Welcome & Introduction** Joshua Roffman, MD
4:10-4:45PM	**Psychiatric Genetics in the Direct-To-Consumer Era** Joshua Roffman, MD
4:45-5:00 PM	**Q&A 1**
5:00-5:35 PM	**The Human Connectome Project: Mapping brain networks with MRI** Randy Buckner, PhD
5:35-5:50 PM	**Q&A 2**
5:50-6:10	**Break**
6:10-6:45 PM	**The NIMH RDoC Initiative – What Does it Mean for Psychiatric Nosology?** Thomas McCoy, MD
6:45-7:00 PM	**Q&A 3**
7:00-7:35 PM	**Targeting brain circuits with non-invasive brain stimulation** Tracy Barbour, MD
7:35-7:50 PM	**Q&A 4**
7:50-8:00 PM	**Conclusion & Wrap-up**

FACULTY

Tracy A. Barbour, MD
Medical Director
Transcranial Magnetic Stimulation, Clinical Service
Massachusetts General Hospital

Randy L. Buckner, PhD
Sosland Family Professor of Psychology and of Neuroscience
Harvard University and *Harvard Medical School*
Director, Psychiatric Neuroimaging Research, *Massachusetts General Hospital*

Joshua L. Roffman, MD
Co-Director, Mass General Neuroscience
Co-Director, Division of Psychiatric Neuroimaging, MGH
Director of Research, MGH Schizophrenia Clinical and Research Program
Associate Professor of Psychiatry, *Harvard Medical School*

Thomas McCoy, MD
Assistant Professor, Psychiatry & Medicine
Harvard Medical School

WELCOME AND INTRODUCTION

Joshua Roffman, MD

NOTES

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Psychiatric Genetics in the Direct-To-Consumer Era

Joshua Roffman, MD

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MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Psychiatric Genetics in the Direct-to-Consumer Era

Joshua L. Roffman MD, MMSc
Co-Director, Mass General Neuroscience
Associate Professor of Psychiatry,
Harvard Medical School

Learning objectives

- To review genetic measures that have been introduced into clinical psychiatry, or may be in the near-term
- To understand implications of direct-to-consumer genetic testing on routine care
- To anticipate patient questions on genetic testing, and be able to answer them based on the latest scientific evidence

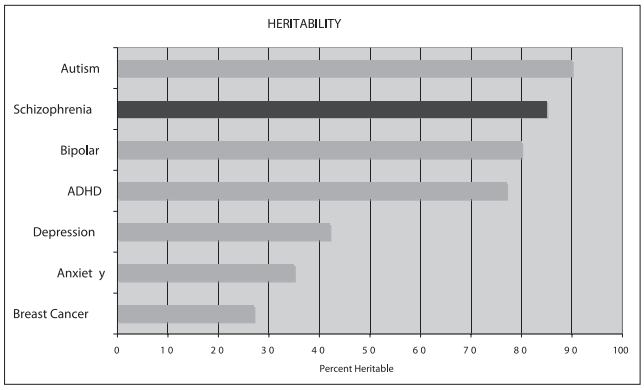
Case study

Your new patient is a 23 year old man with a diagnosis of schizophrenia, and who has persistent negative symptoms. He is accompanied by his parents, who have brought with them a report on their son's genetic profile from 23andMe®.

His parents are concerned that he is an "MTHFR double heterozygote" and want to know what this means for his long-term prognosis and treatment options.

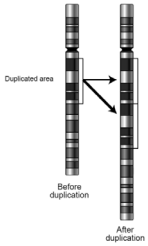
They have gone online and found several "MTHFR support groups," and based on what they have found are wondering if he should take a special form of folic acid called methylfolate.

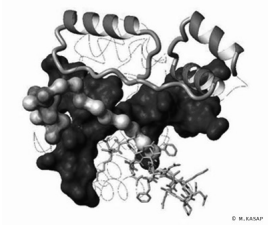
Why are genetics important?



Some basic terminology…

Copy Number Variant (CNV)





Possible consequences of CNV change:

- Genes duplicated, deleted, or disrupted
- Amount and/or function of protein changes

Some basic terminology…

Single Nucleotide Polymorphism (SNP)

…A G C G T A A G A T C G T G A A C G T A G A C C…

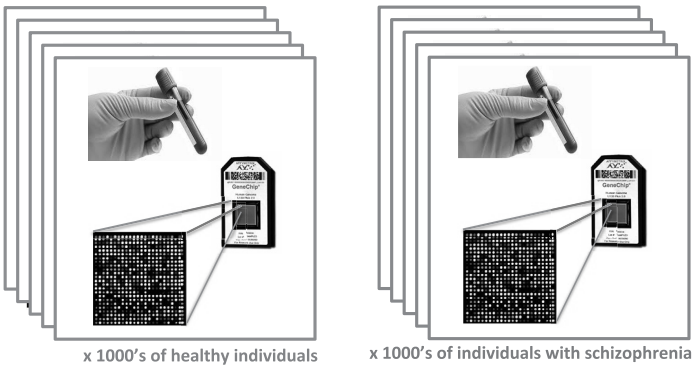
…A G C G T A A C A T C G T G A A C G T A G A C C…

Possible consequences of G to C change:

- Silent or unknown
- Change in protein structure
- Change in amount of protein that is made

Some basic terminology…

Genome Wide Association Study (GWAS)

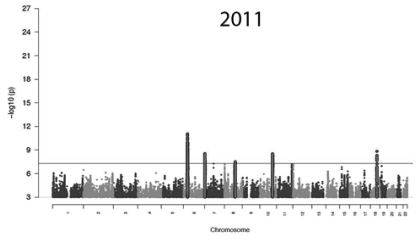


x 1000's of healthy individuals

x 1000's of individuals with schizophrenia

Schizophrenia GWAS

Psychiatric Genomics Consortium (PGC)
Nat Genet 2011, Nature 2014

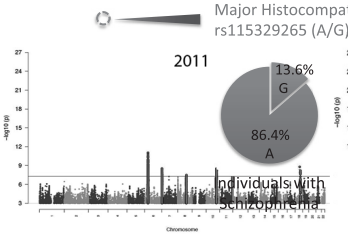


21,856 participants
5 loci

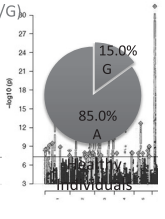
Schizophrenia GWAS

Psychiatric Genomics Consortium (PGC)
Nat Genet 2011, Nature 2014

Major Histocompatibility Complex (MHC)
rs115329265 (A/G)



Individuals with Schizophrenia



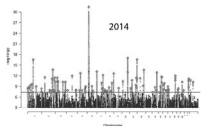
Healthy Individuals

21,856 participants
5 loci

150

Schizophrenia GWAS

Psychiatric Genomics Consortium (PGC)
Nat Genet 2011, Nature 2014

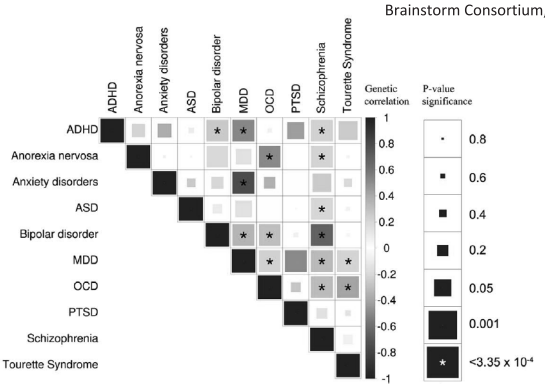


Σ

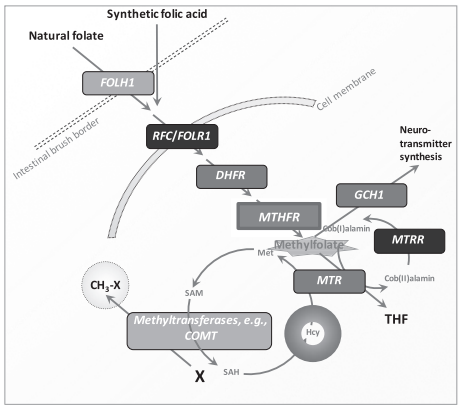
>18% of genetic risk explained by common genetic variants

Polygenic risk

Brainstorm Consortium, Science 2018



MTHFR

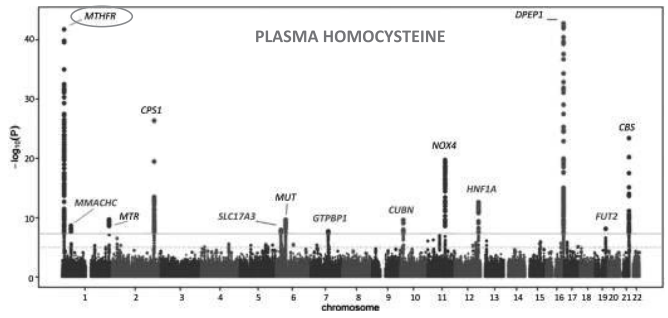


Common variants:

rs1801133
677C>T
222Ala>Val

rs1801131
1298A>C
429Glu>Ala

MTHFR



van Meurs et al., Am J Med Nutr 2013

MTHFR "double heterozygote"

rs1801133
Copy 1: 677C
Copy 2: 677T

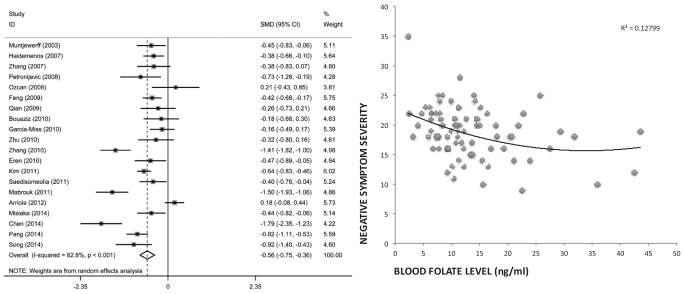
rs1801131
Copy 1: 1298A
Copy 2: 1298C

…~40% of the U.S. population are double heterozygotes

MTHFR genotype: clinical value

- Does being a double heterozygote increase risk for schizophrenia?
  …No
- Does being a double heterozygote increase risk for negative symptoms of schizophrenia?
  …Maybe

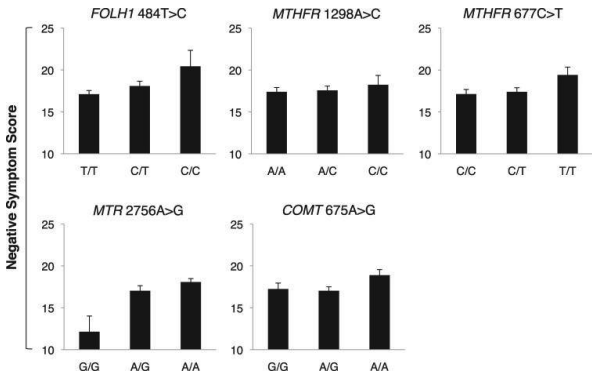
Folate and negative symptoms



Cao et al., Psychiatry Res 2016

Goff et al, Am J Psychiatry 2004

MTHFR and negative symptoms



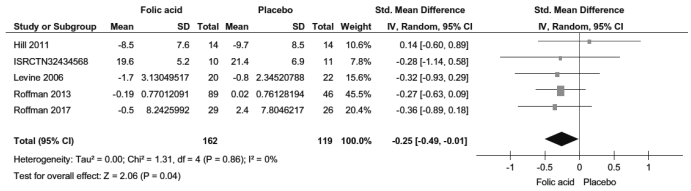
Roffman et al., Schiz Bull 2013

MTHFR genotype: clinical value

- Does being a double heterozygote increase risk for schizophrenia?
  …No
- Does being a double heterozygote increase risk for negative symptoms of schizophrenia?
  …Maybe
- Does taking folic acid help?
  …Maybe

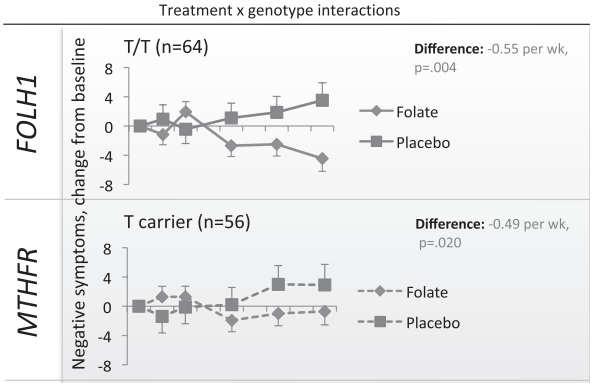
Folic acid for negative symptoms

	N	*n*	I^2 (%)	SMD	WMD	95% CI	*p* value
Total symptoms[a]	7	340	0	−0.20		−0.41 to 0.02	0.08
Negative symptoms	5	281	0	−0.25		−0.49 to −0.01	0.04
PANSS positive subscale score	4	260	21		−0.07	−0.69 to 0.55	0.83
PANSS general subscale score	2	97	0		−1.57	−3.62 to 0.48	0.13
CDSS score	5	281	28		0.18	−0.45 to 0.81	0.58



Sakuma et al., Psychopharmacology, 2018

Folic acid for negative symptoms

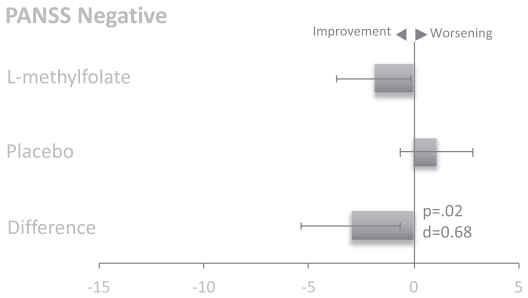


Roffman et al., JAMA Psychiatry, 2013

MTHFR genotype: clinical value

- Does being a double heterozygote increase risk for schizophrenia?
  …No
- Does being a double heterozygote increase risk for negative symptoms of schizophrenia?
  …Maybe
- Does taking folic acid help?
  …Maybe
- Should methylfolate be taken instead of folic acid?
  …Maybe

Methylfolate for negative symptoms



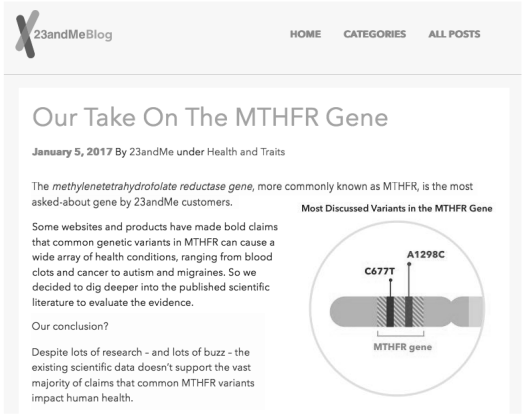
Results not dependent on genotype

Roffman et al., Mol Psychiatry, 2017

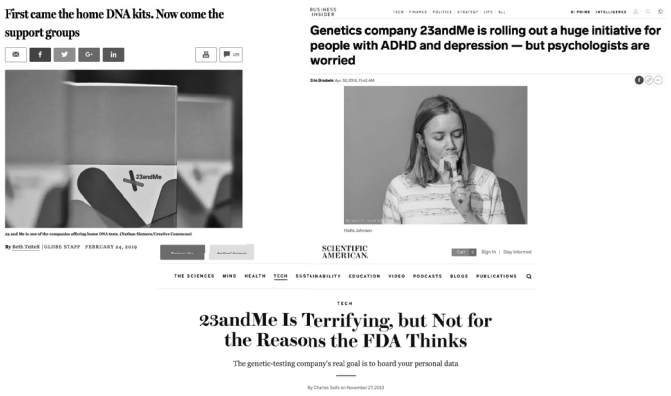
Does MTHFR genotype add value?

- Worried about low serum folate?
  …Check it. No need to genotype, at 10x the cost, and questionable utility.
- Does your patient have negative symptoms?
  …No good reason not to treat empirically with folic acid first.
- But could MTHFR genotype help get to methylfolate more quickly?
  …Insufficient evidence to say, either from cost effectiveness or efficacy perspective.

Even 23andMe® agrees…



…but the genie is out of the bottle



When *is* genetic testing indicated?

- **FDA guidance:**

HLA-B*1502 prior to carbamazepine in patients of Asian descent (boxed warning)
Other pharmacogenomic panels (PGx):

CYP2D6	Clomipramine	Imipramine	Thioridazine
	Clozapine	Modafinil	Trimipramine
Amitriptyline	Desipramine	Nefazodone	Venlafaxine
Amoxapine	Desvenlafaxine	Nortriptyline	Vortioxetine
Amphetamine	Doxepin	Paliperidone	
Arapiprazole	Duloxetine	Paroxetine	CYP2C19
Atomoxetine	Escitalopram	Perphenazine	
Brexpiprazole	Fluoxetine	Pimozide	Citalopram
Carprazine	Fluvoxamine	Protriptyline	Doxepin
Citalopram	Iloperidone	Risperidone	Escitalopram

Consensus is that they are of limited value in routine clinical use – e.g., among Caucasians, 7-10% are poor metabolizers and <1% are ultrarapid metabolizers

- **Autism spectrum disorder with intellectual disability** (Copy number variants)

Conclusions and recommendations

- At present, there is no high-quality evidence to support use of direct-to-consumer genetic testing to guide clinical decision-making
- More broadly, despite significant research advances on genetic origins of psychiatric illness, genetic testing is unlikely to be of benefit in the clinic in the near term
- Watch this space though…

Proof-of-concept…

RISK STRATIFICATION

Table 4. Coronary Artery Calcification Burden, by Polygenic Risk Score Quintile in CARDIA (Coronary Artery Risk Development in Young Adults)

Polygenic Risk Score Quintile	CAC>1%, %	CAC >0*	
		OR (95% CI)	*P* Value
1	8.7	1	
2	12.1	2.08 (0.89–4.83)	0.09
3	10.9	2.08 (0.87–4.98)	0.10
4	14.3	3.02 (1.31–7.00)	0.01
5 (High)	15.6	2.51 (1.08–5.85)	0.04

Natarajan et al., Circulation 2017

Thank you!

PREVENTION

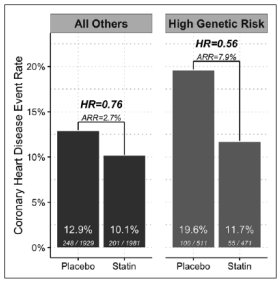


Figure 1. **Incident coronary heart disease events by statin therapy and genetic risk group in WOSCOPS (West of Scotland Coronary Prevention Study).**

NOTES

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Q&A 1

NOTES

The Human Connectome Project: Mapping Brain Networks with MRI

Randy Buckner, PhD

The Human Connectome Project
Mapping Brain Networks With MRI

Randy L. Buckner, PhD
Sosland Family Professor of Psychology and of Neuroscience,
Harvard University
Director of Psychiatric Neuroimaging, Massachusets General Hospital

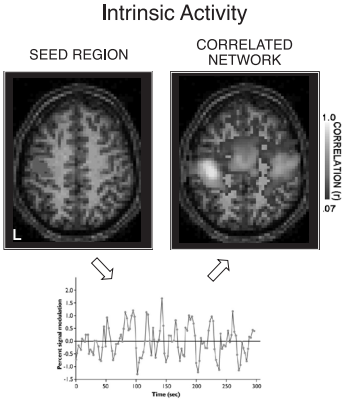
Learning objectives

- To understand how MRI methods can map organization of brain networks.
- To understand limits of available techniques.
- To review recent discoveries that map the organization of brain networks important to higher-level brain function.

Measuring Brain Networks in the Human

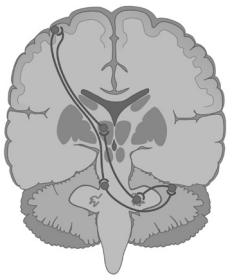
Diffusion

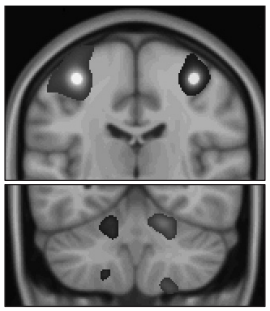
Intrinsic Activity



Example Validation

Cerebro-Cerebellar Circuit

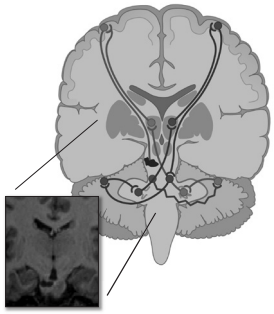


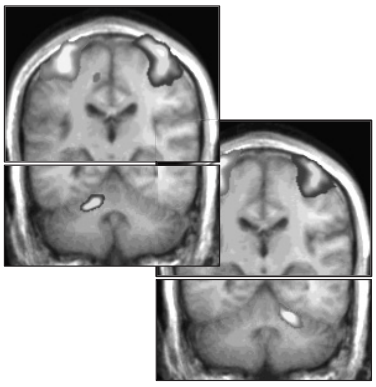


Krienen and Buckner, 2009, *Cerebral Cortex*

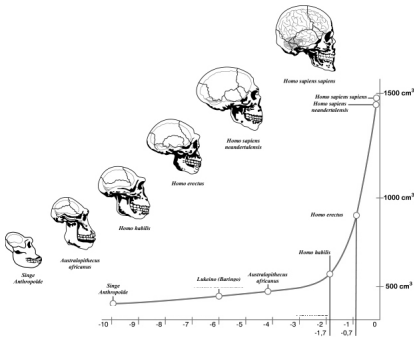
Example Validation

Cerebro-Cerebellar Circuit



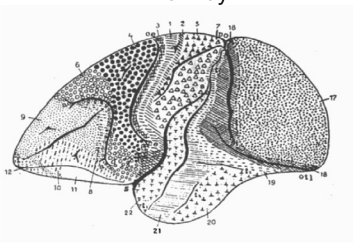


Lu, Liu et al., 2011, *J. Neurosci.*

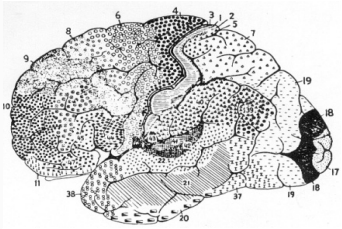


Human Association Cortex is Dramatically Expanded

Monkey



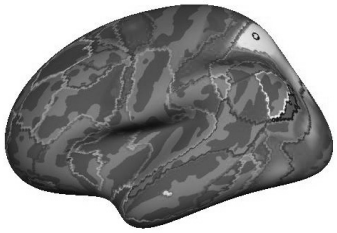
Human

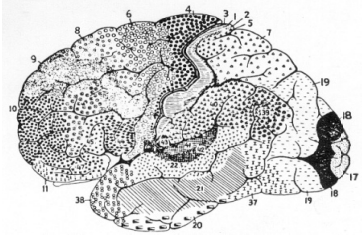


Korbinian Brodmann

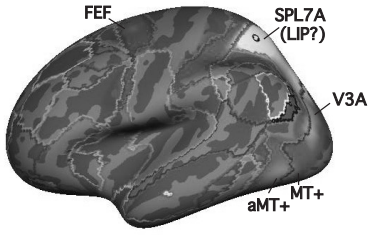
Canonical Hierarchical Sensory-Motor Network

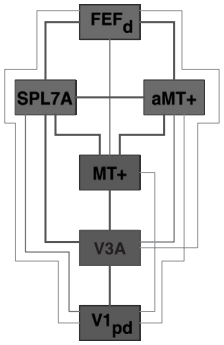
Human





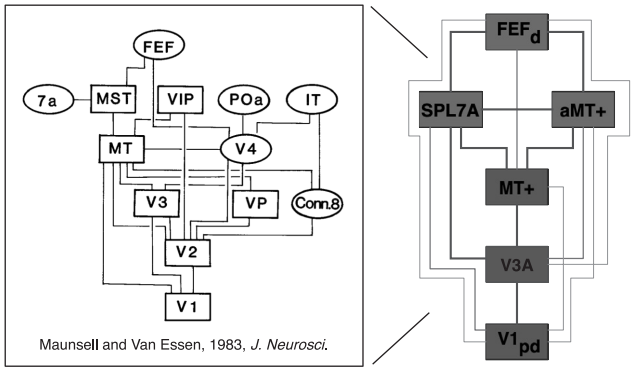
Canonical Hierarchical Sensory-Motor Network





Yeo, Krienen et al., 2011, *J. Neurophysiol.*

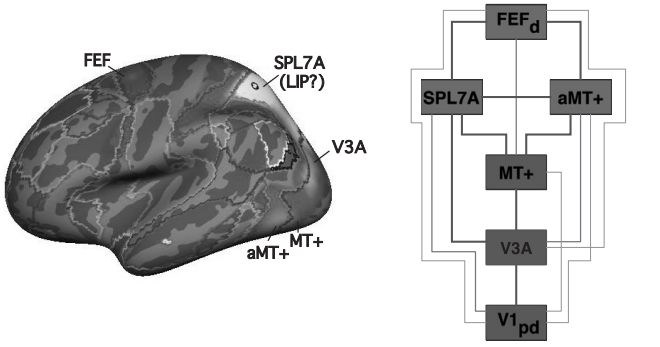
Canonical Hierarchical Sensory-Motor Network



Maunsell and Van Essen, 1983, *J. Neurosci.*

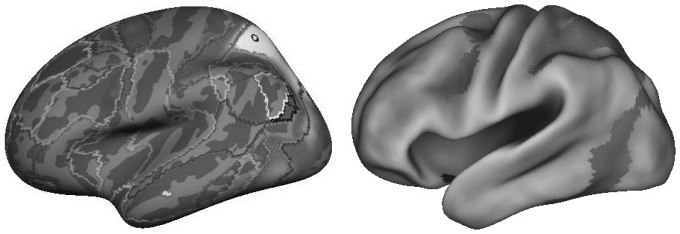
Yeo, Krienen et al., 2011, *J. Neurophysiol.*

Canonical Hierarchical Sensory-Motor Network



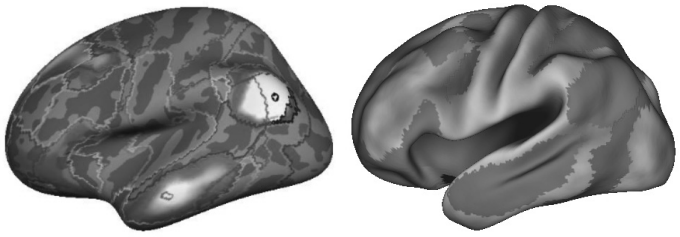
Yeo, Krienen et al., 2011, *J. Neurophysiol.*

Distributed Association Networks



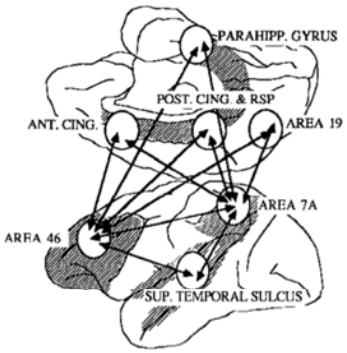
Yeo, Krienen et al., 2011, *J. Neurophysiol.*

Distributed Association Networks

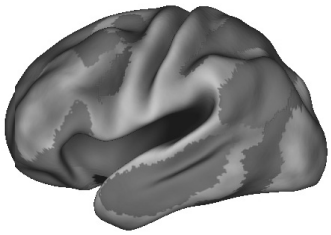


Yeo, Krienen et al., 2011, *J. Neurophysiol.*

Distributed Association Networks

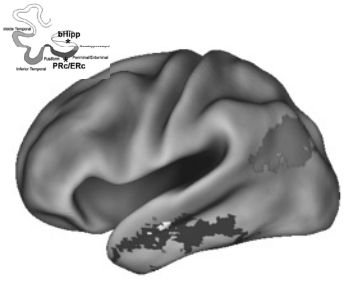


Goldman-Rakic (1988) *Ann. Rev. Neurosci.*



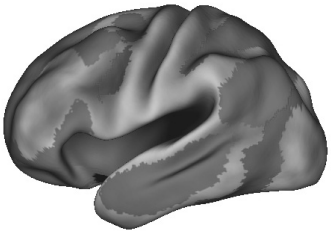
Yeo, Krienen et al., 2011, *J. Neurophysiol.*

Distributed Association Networks



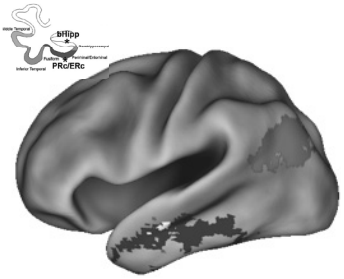
Coupled to Hippocampal Memory System

Vincent et al., 2007, *J. Neurophysiol.*
Kahn et al., 2008, *J. Neurophysiol.*



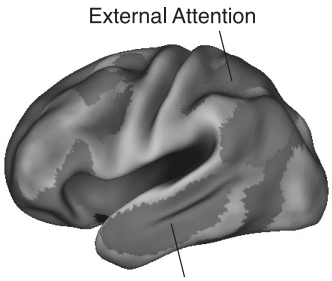
Yeo, Krienen et al., 2011, *J. Neurophysiol.*

Distributed Association Networks



Coupled to Hippocampal Memory System

Vincent et al., 2007, *J. Neurophysiol.*
Kahn et al., 2008, *J. Neurophysiol.*



Yeo, Krienen et al., 2011, *J. Neurophysiol.*
(Andreasen et al., 1995, *Am. J. Psychiatry*)

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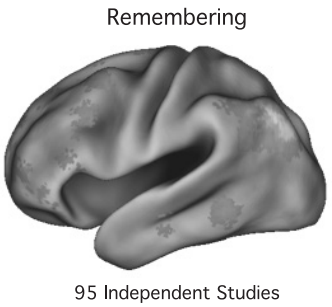
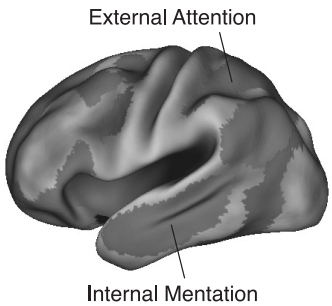


95 Independent Studies

Andrews-Hanna, Saxe, & Yarkoni, 2014, *NeuroImage*



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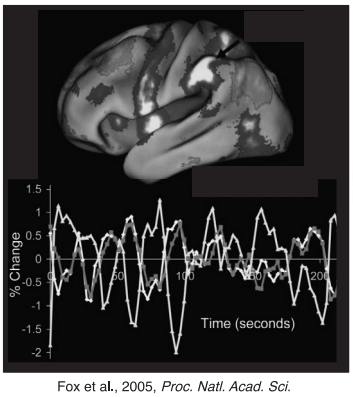
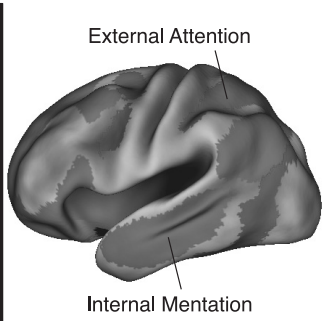


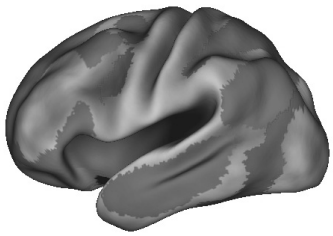
Fox et al., 2005, *Proc. Natl. Acad. Sci.*



Yeo, Krienen et al., 2011, *J. Neurophysiol.*

Distributed Association Networks

Control Network?



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Distributed Association Networks

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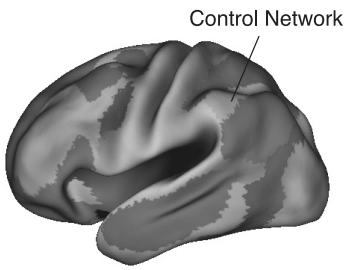
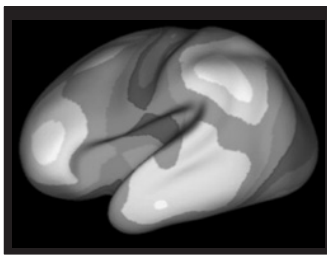
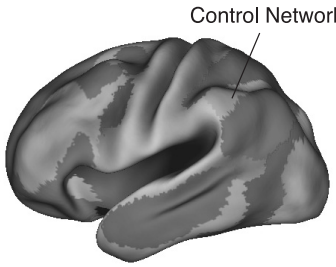


Vincent et al., 2006, *J. Neurophysiol.*

Expansion in Human Evolution

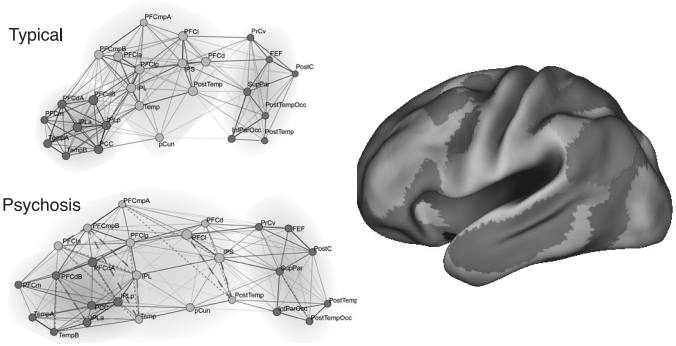


Hill et al., 2010 *Proc Natl Acad Sci*



Vincent et al., 2006, *J. Neurophysiol.*

Relevance to Mental Illness

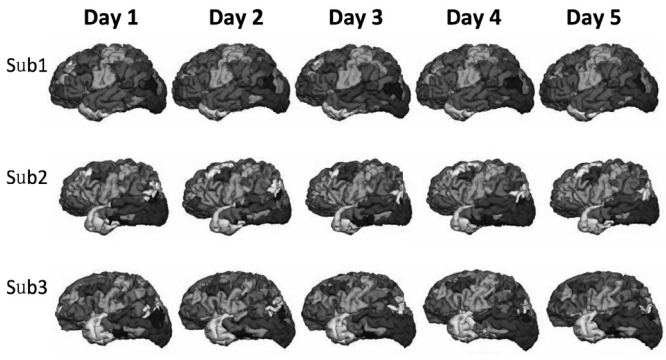


Baker et al., 2013, *JAMA Psychiatry*

Vincent et al., 2006, *J. Neurophysiol.*

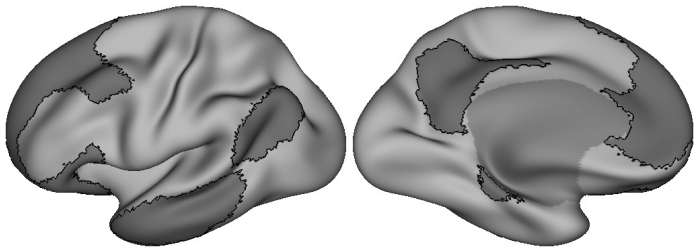
(See also Whitfield-Gabrieli et al., 2009, *PNAS;* Anticivic et al., 2013 *Cereb Ctx*; Yang et al., 2016 *PNAS*)

Variability Across Individuals



Mueller…Liu, 2013 *Neuron*; Wang…Liu, 2015, *Nat Neurosci;*

Group Association Network (n=1000)



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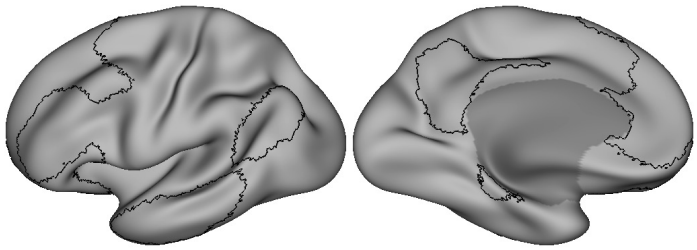
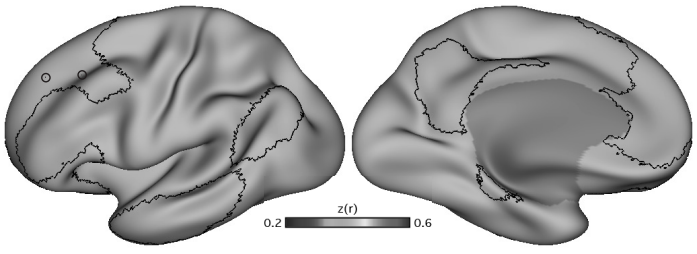


Braga and Buckner, 2017, *Neuron*

Single Subject (24 MRI Sessions)



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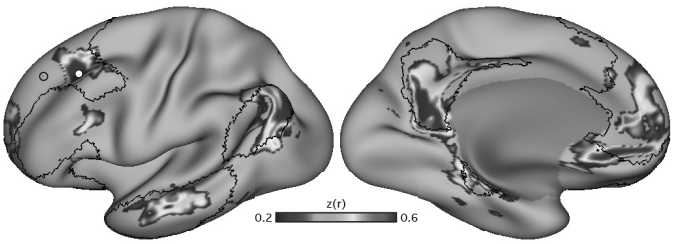

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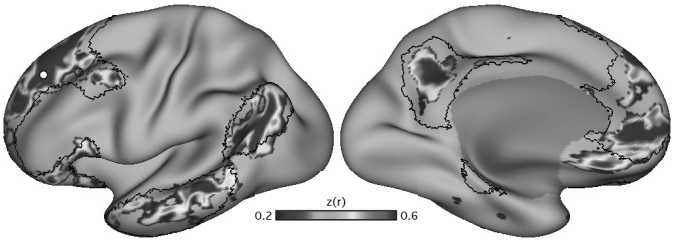

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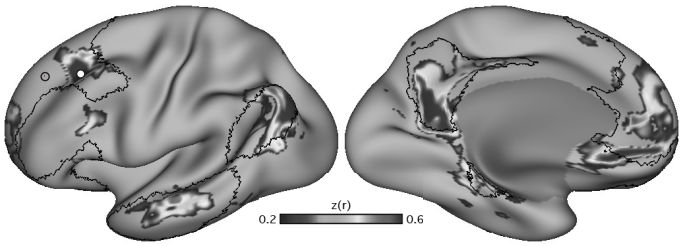

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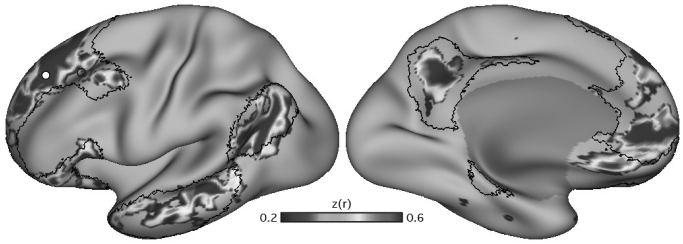

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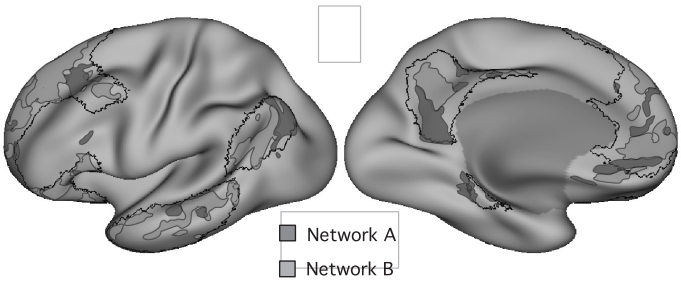

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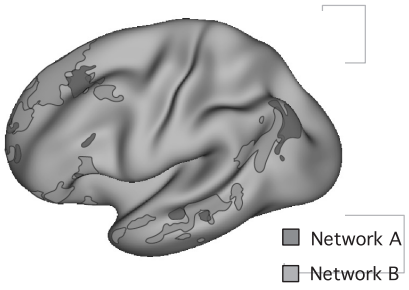
Human Specialization for Higher Brain Function?



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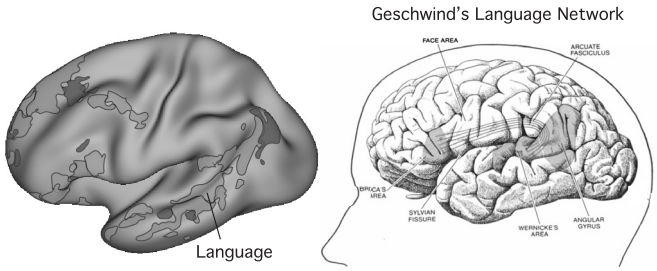

Courtesy of Rodrigo Braga

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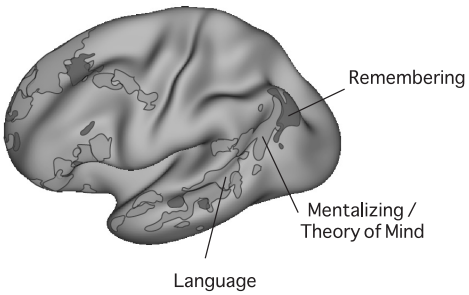

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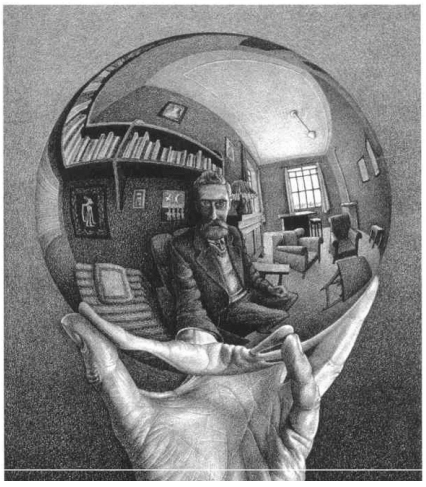
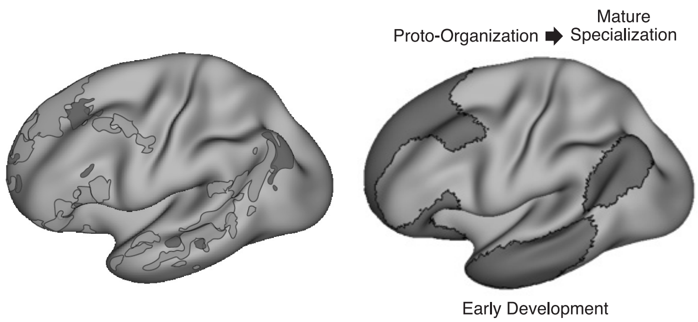


Developmental Specialization



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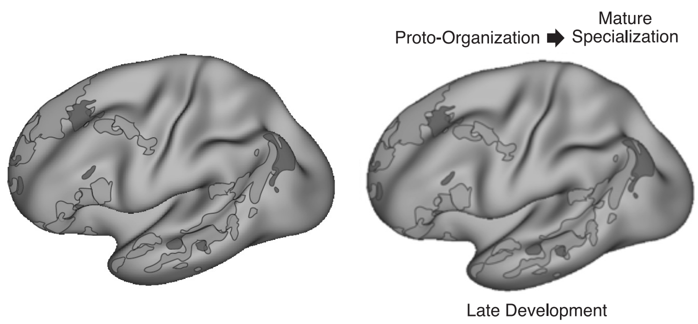


Courtesy of Rodrigo Braga

Human Neuromodulation

Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases

Michael D. Fox[a,b,c,1], Randy L. Buckner[c,d,e], Hesheng Liu[c], M. Mallar Chakravarty[f,g], Andres M. Lozano[h,i], and Alvaro Pascual-Leone[a]

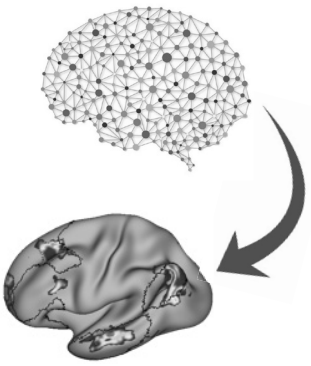
Table 1. Diseases with evidence of efficacy for both invasive and noninvasive brain stimulation

Disease	Target for invasive stimulation (DBS)	Target for noninvasive stimulation (TMS, tDCS)
Addiction	NA	DLPFC (laterality unclear)
Alzheimer's disease	Fornix	Bilateral DLPFC (± parietal, temporal)
Anorexia	NA, subgenual	Left DLPFC
Depression	Subgenual, VC/VS, NA, MFB, habenula	Left DLPFC, *right DLPFC*
Dystonia	GPi	*SMA/ACC, premotor*
Epilepsy	Thalamus (AN, CM), MTL	*Active EEG focus*, cerebellum
Essential tremor	VIM	*Midline cerebellum, lateral cerebellum, M1*
Gait dysfunction	PPN	M1 (leg area)
Huntington's disease	GPi	*SMA*
Minimally conscious	Thalamus (intralaminar/CL, CM/Pf)	Right DLPFC, M1
Obsessive compulsive disorder	VC/VS, NA, ALIC, STN	*Left orbitofrontal, pre-SMA*
Pain	PAG, thalamus (VPL/VPM)	M1
Parkinson's disease	STN, GPi	M1, *SMA*
Tourette's syndrome	Thalamus (CM/Pf), GPi, NA, ALIC	*SMA*

Artificial Intelligence


Neuron
Review

Neuroscience-Inspired Artificial Intelligence



Conclusions

1) Human brain imaging methods are able to detect network organization in individual people.

2) Distinct networks that are distributed across the brain are specialized for language, social, and mnemonic functions.

3) The identification of the networks provide targets for neuromodulation but have not yet provided translatable clinical tests or interventions.

NOTES

NOTES

Q&A 2

NOTES

The NIMH RDoC Initiative – What Does it Mean for Psychiatric Nosology?

Thomas McCoy, MD

The NIMH RDoC Initiative:
What Does it Mean for Psychiatric Nosology?

Thomas McCoy, MD

April 29, 2013

In a few weeks, the APA will release its new edition of the DSM. ...

Symptom-based diagnosis, once common in other areas of medicine, has been largely replaced in the past half century as we have understood that symptoms alone rarely indicate the best choice of treatment. ...

Patients with mental disorders deserve better. ... **Going forward, we will be supporting research projects that look across current categories – or sub-divide current categories – to begin to develop a better system.**

https://www.nimh.nih.gov/about/directors/thomas-insel/blog/2013/transforming-diagnosis.shtml

April 29, 2013

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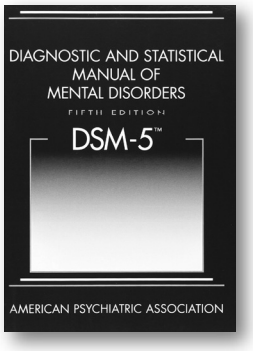
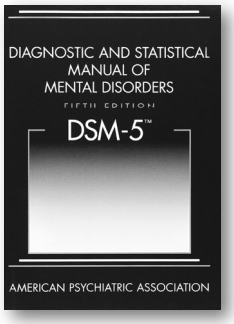
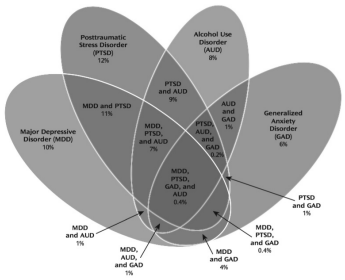
Categorical Nosology



(Useful) Syndrome Soup





Regier, D. A. *et al* (2013). DSM-5 field trials in the United States and Canada, Part II: test-retest reliability of selected categorical diagnoses. *AJP*, 170(1), 59-70.

What is RDoC?

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  - Rooted in neurobiology (gene -> behavior)

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What RDoC is **Not**

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- Threshold setting
  - Hopes to move to threshold model but not inherent

Cuthbert and Insel *BMC Medicine* 2013, **11**:126
http://www.biomedcentral.com/1741-7015/11/126

BMC Medicine

DEBATE Open Access

Toward the future of psychiatric diagnosis: the seven pillars of RDoC

Bruce N Cuthbert[1,3*] and Thomas R Insel[2,3]

" Develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures"

Research Domain Criteria

ORIGIN STORY

RDoC Origin

2008: NIMH Strategic Plan – Strategy 1.4

- Initiate a process for bringing together experts in clinical and basic sciences to jointly identify the fundamental behavioral components that may span multiple disorders (e.g., executive functioning, affect regulation, person perception) and that are more amenable to neuroscience approaches.
- Determine the full range of variation, from normal to abnormal, among the fundamental components to improve understanding of what is typical versus pathological.
- Develop reliable and valid measures of these fundamental components of mental disorders for use in basic studies and in more clinical settings.
- Integrate the fundamental genetic, neurobiological, behavioral, environmental, and experiential components that comprise these mental disorders.

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Commentar y

Research Domain Criteria (RDoC): To wa rd a Ne w Classification Frame wo rk for Resear ch on Mental Disorder s

Insel T, Cuthbert B, Garvey M, et al. *AJP*. 2010;167:748-751.

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2010: Named RDoC

2010-2012: Committee process

Journal of Abnormal Psychology
2010, Vol. 119, No. 4, 631–639

0021-843X/10/$12.00 DOI: 10.1037/a0020909

Developing Constructs for Psychopathology Research:
Research Domain Criteria

Charles A. Sanislow
Wesleyan University

Daniel S. Pine, Kevin J. Quinn, Michael J. Kozak,
Marjorie A. Garvey, Robert K. Heinssen,
Philip Sung-En Wang, and Bruce N. Cuthbert
National Institute of Mental Health, Bethesda, Maryland

RDoC Origin

2008: NIMH Strategic Plan – Strategy 1.4

2010: Named RDoC

2010-2012: Committee process

1. Clinical ***and*** basic evidence of valid behavioral function
2. Evidence that a neural circuit implements the function

RDoC Origin

2008: NIMH Strategic Plan – Strategy 1.4

2010: Named RDoC

2010-2012: Committee process

2012: Release concept matrix (v1)

State of the art

Research Domain Criteria: cognitive systems, neural circuits, and dimensions of behavior

Sarah E. Morris, PhD; Bruce N. Cuthbert, PhD

Dialogues Clin Neurosci. 2012 March; 14(1): 29–37.

The Matrix

DOMAINS/CONSTRUCTS	UNITS OF ANALYSIS: Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Reports	Paradigms
Negative Valence Systems								
Acute threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrative nonreward								
Positive Valence Systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Reward learning								
Habit								
Cognitive Systems								
Attention								
Perception								
Working memory								
Declarative memory								
Language behavior								
Cognitive (effortful) control								
Systems for Social Processes								
Affiliation/attachment								
Social communication								
Perception/understanding of self								
Perception/understanding of others								
Arousal/Modulatory Systems								
Arousal								
Biological rhythms								
Sleep-wake								

~~Five~~ **Six** Domains
- Negative Valence
- Positive Valence
- Cognitive Systems
- Social Processes
- Arousal/Modulation
- *Sensorimotor (Jan '19*)*

*https://www.nimh.nih.gov/news/science-news/2019/sensorimotor-domain-added-to-the-rdoc-framework.shtml

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Multiple constructs per domain

*https://www.nimh.nih.gov/news/science-news/2019/sensorimotor-domain-added-to-the-rdoc-framework.shtml

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Units of Analysis
- *Genes (May '17*)*
- Molecules
- Cells
- Circuits
- Physiology
- Behavior
- Self-reports
- Paradigms

*https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/update-on-genes-in-the-rdoc-matrix.shtml

The Matrix -- Today

Negative Valence Systems

Construct/Subconstruct	Genes Notice	Molecules	Cells	Circuits	Physiology	Behavior	Self-Report	Paradigms
Acute Threat ("Fear")		Elements	Elements	Elements	Elements	Elements	Elements	Elements
Potential Threat ("Anxiety")		Elements	Elements	Elements	Elements		Elements	Elements
Sustained Threat		Elements	Elements	Elements	Elements	Elements	Elements	
Loss		Elements		Elements	Elements	Elements	Elements	Elements
Frustrative Nonreward		Elements		Elements		Elements	Elements	Elements

Positive Valence Systems

Construct/Subconstruct		Genes Notice	Molecules	Cells	Circuits	Physiology	Behavior	Self-Report	Paradigms
Reward Responsiveness	Reward Anticipation								Elements
	Initial Response to Reward		Elements		Elements		Elements	Elements	Elements
	Reward Satiation								Elements
Reward Learning	Probabilistic and Reinforcement Learning								Elements
	Reward Prediction Error		Elements		Elements	Elements	Elements	Elements	Elements
	Habit - PVS		Elements	Elements	Elements		Elements	Elements	Elements
Reward Valuation	Reward (probability)								Elements
	Delay								Elements
			Elements		Elements			Elements	Elements

https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/rdoc-matrix.shtml

RDoC Domains and Constructs

http://tiny.cc/rdocdef

https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/definitions-of-the-rdoc-domains-and-constructs.shtml

RDoC Origin

2008: NIMH Strategic Plan
2010: Named RDoC
2010-2012: Committee process
2012: Release concept matrix (v1)
2013: Funding shift

RDoC Origin

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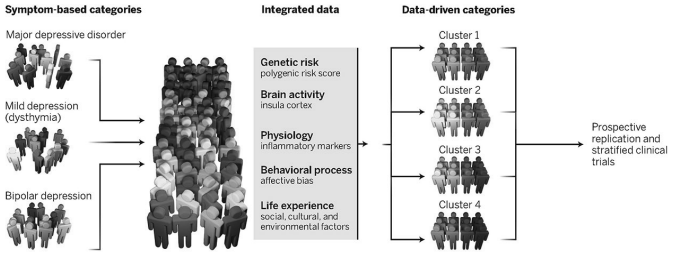
2015: RDoC for more precise medicine

Brain disorders? Precisely

Thomas R. Insel, Bruce N. Cuthbert

Science 01 May 2015:
Vol. 348, Issue 6234, pp. 499-500
DOI: 10.1126/science.aab2358

Building a Valid Nosology



Brain disorders? Precisely

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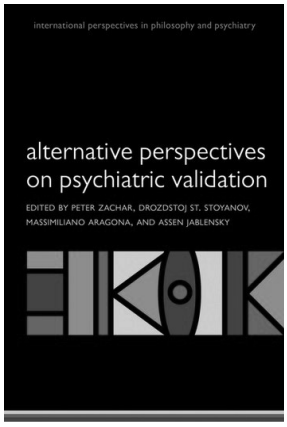
"Valid" Nosology



RDoC for a ICD/DSM World

F32.2 + F10.221 ← ???

" 22 y/o male with intentional GSW in ctx of breakup and new unemployment now s/p 3wk SICU stay admitted to ILOC reporting 6 mo decline in mood and self worth, increased irritability, social isolation (left soccer team and lost job), and marked increase in EtOH use w/ family Hx of suicide and BPAD… "

Deploying RDoC

Techniques and Methods

Biological Psychiatry

High Throughput Phenotyping for Dimensional Psychopathology in Electronic Health Records

Thomas H. McCoy Jr., Sheng Yu, Kamber L. Hart, Victor M. Castro, Hannah E. Brown, James N. Rosenquist, Alysa E. Doyle, Pieter J. Vuijk, Tianxi Cai, and Roy H. Perlis

ABSTRACT

BACKGROUND: Relying on diagnostic categories of neuropsychiatric illness obscures the complexity of these disorders. Capturing multiple dimensional measures of neuropathology could facilitate the clinica and neurobiological investigation of cognitive and behavioral phenotypes.

METHODS: We developed a natural language processing–based approach to extract five symptom dimensions, based on the National Institute of Mental Health Research Domain Criteria definitions, from narrative clinical notes. Estimates of Research Domain Criteria loading were derived from a cohort of 3619 individuals with 4623 hospital admissions. We applied this tool to a large corpus of psychiatric inpatient admission and discharge notes (2010-2015), and using the same cohort we examined face validity, predictive validity, and convergent validity with gold standard annotations.

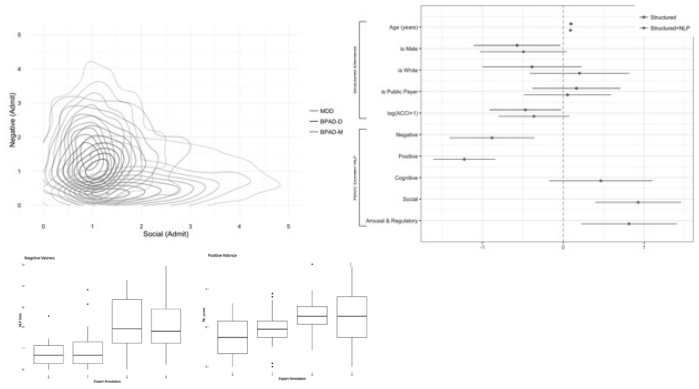
RESULTS: In mixed-effect models adjusted for sociodemographic and clinical features, greater negative and positive symptom domains were associated with a shorter length of stay ($\beta = -.88$, $p = .001$ and $\beta = -1.22$, $p < .001$, respectively), while greater social and arousal domain scores were associated with a longer length of stay ($\beta = .93$, $p < .001$ and $\beta = .81$, $p = .007$, respectively). In fully adjusted Cox regression models, a greater positive domain score at discharge was also associated with a significant increase in readmission risk (hazard ratio = 1.22, $p < .001$). Positive and negative valence domains were correlated with expert annotation (by analysis of variance [$df = 3$], $R^2 = .13$ and .19, respectively). Likewise, in a subset of patients, neurocognitive testing was correlated with cognitive performance scores ($p < .008$ for three of six measures).

CONCLUSIONS: This shows that natural language processing can be used to efficiently and transparently score clinical notes in terms of cognitive and psychopathologic domains.

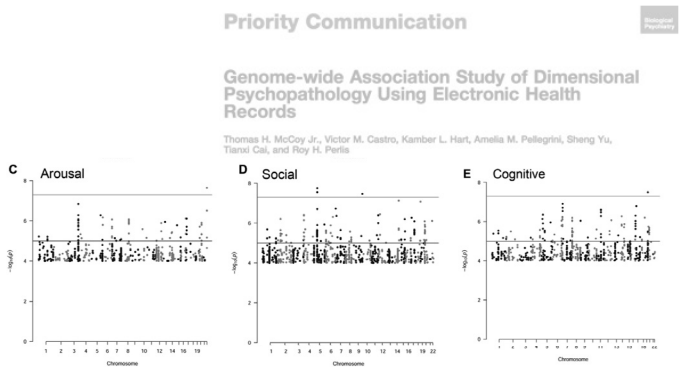
Keywords: Computed phenotype, Electronic health record, Natural language processing, Research Domain Criteria, Topic modeling, Transdiagnostic

https://doi.org/10.1016/j.biopsych.2018.01.011

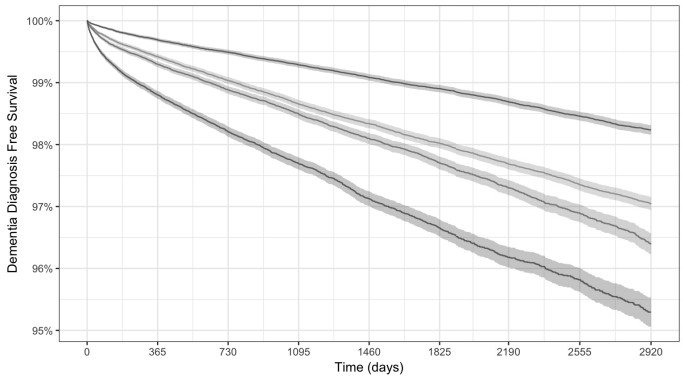
RDoC Validation



RDoC Biology

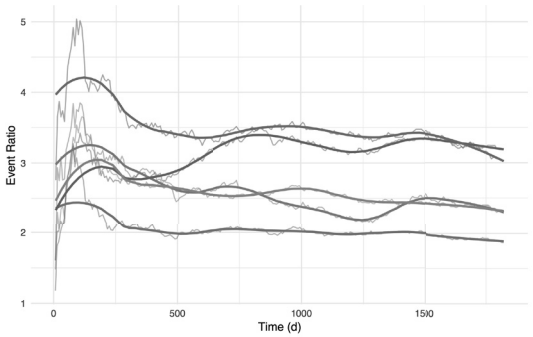


RDoC Stratification of Cognition



Dementia | X^2=378.8; p <.000001

RDoC Stratification of Suicide

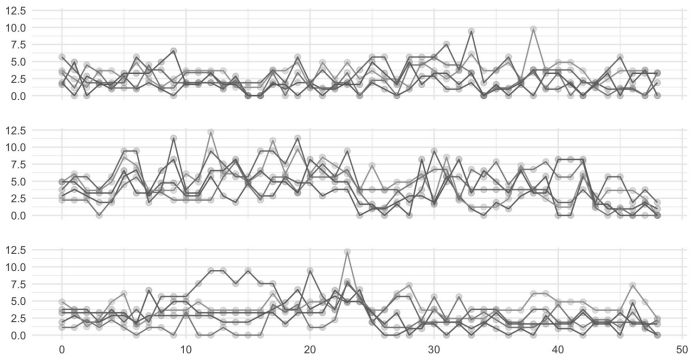


RESEARCH ARTICLE

WILEY

Research Domain Criteria scores estimated through natural language processing are associated with risk for suicide and accidental death

RDoC in Time



RDoC is …

- Explicitly dynamic
  - Addition of motor domain
  - Removal of specific genes
- Structure for future research
  - Multidimensional & continuous
  - Rooted in neurobiology (gene -> behavior)
- Anticipates precision medicine

Thank You

MGH CQH
Roy Perlis
Victor Castro
Kamber Hart
Amelia Pellegrini
Funders
Stanley Center
NIA / NIMH / NHGRI
NARSAD
MIP

NOTES

Q&A 3

NOTES

Targeting Brain Circuits With Non-Invasive Brain Stimulation

Tracy Barbour, MD

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

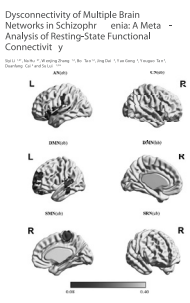
Targeting brain circuits with non-invasive brain stimulation

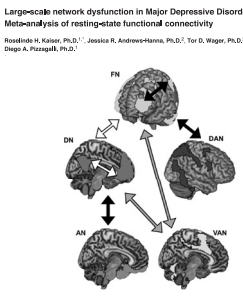
Tracy Barbour MD
Medical Director, Transcranial Magnetic Stimulation Clinical Service
Instructor, Harvard Medical School

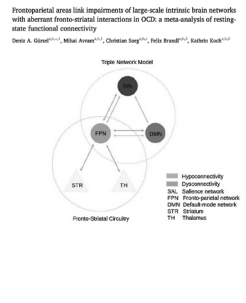
Outline

- rTMS for Depression
- rTMS for OCD
- Combining Therapies to Improve Outcomes
- Theta Burst Stimulation
- Accelerated Protocols
- Transcranial Direct Current Stimulation

Psychiatric disorders are disorders of neural circuits

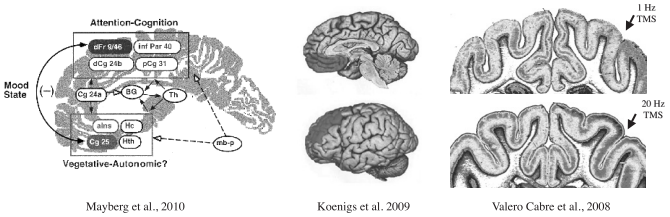






Circuit-based Interventions: need to know…

The circuit(s) | The target(s) | Direction of modulation



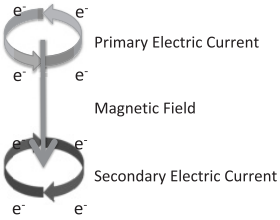
Mayberg et al., 2010

Koenigs et al. 2009

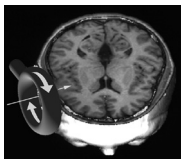
Valero Cabre et al., 2008

Transcranial Magnetic Stimulation

1831 Faraday's Electromagnetic Induction

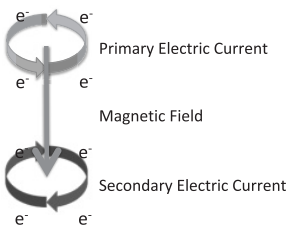


Anthony Barker 1984



Transcranial Magnetic Stimulation

1831 Faraday's Electromagnetic Induction



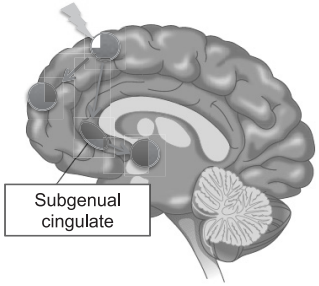
Anthony Barker 1984

What is Transcranial Magnetic Stimulation (TMS)?

- Safe
- Noninvasive
- Nonconvulsive
- Neuromodulation therapy
  - Changes neural excitability and activity

TMS Theory

- Target treatment to a specific, affected region
- Changes spread to other regions
- Effects are network wide
- Repeated treatments lead to lasting effects



Liston 2014

TMS Parameters

1) Location (low tech vs. neuronavigation)
2) Focality & Depth (coil selection)
3) Frequency (up- or downregulate)
4) Intensity (relative to stimulator or subject)
5) Duration (number of pulses / sessions)

Current Therapeutic Uses

FDA Approved

- Unipolar Depression
- Obsessive Compulsive Disorder
- Migraine with Aura

Investigative

- Auditory Hallucinations
- Post Traumatic Stress Disorder
- Generalized Anxiety Disorder
- Tourette Syndrome
- Bipolar Depression
- Autism
- Neurorehabilitation
- Parkinson Disease
- Alzheimer Disease
- Epilepsy
- Focal Dystonia
- Chronic Pain

TMS – Basic Equipment

MagVenture © System

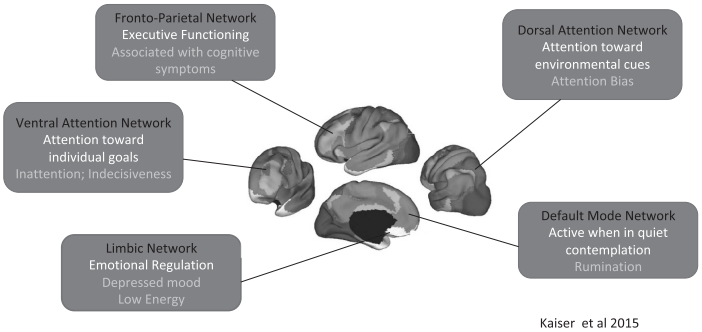
Brainsway © System

Treatment Logistics

- Remain **awake** during treatment
- No restrictions on activity
- Initial treatment course: five daily treatment per week (M-F) for 4-6 weeks
- Taper period: 1-3 treatments per week
- Daily treatment duration: 3 - 30 minutes
- A tapping sensation is experienced
- A clicking noise accompanies each electromagnetic pulse

Magventure ©

Neural Networks Associated with Depression



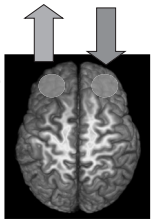
Kaiser et al 2015

Therapeutic applications: MDD

- Early PET data argued for an overall hypofrontality and metabolic asymmetry in the two frontal areas

Depression Rx Strategy:

Left DLPFC: High Frequency (5-20 Hz)



Right DLPFC: Low Frequency (1 Hz)

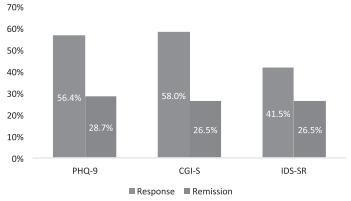
TMS Clinical Trials in MDD

- Multiple small single center trials since 1996
- Large multicenter trials in US leading to FDA approval in 2008 (O'Reardon et al., 2007)
- Follow up large NIMH trial confirms (George et al. 2010).
- Deep TMS (dTMS) system was granted FDA approval in 2013, after showing response rate of 38.4 % and remission rate of 32.6 % after 20 sessions.
- 7 companies have FDA-cleared devices for the treatment of MDD (6 Conventional rTMS systems and 1 dTMS system)

TMS in the Treatment of Depression

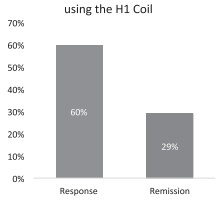
- Conventional rTMS was FDA approved for the treatment of unipolar depression in 2008
- The H1 coil (deep TMS) was FDA approved for treatment of depression in 2013

Open label study of 10 Hz rTMS using conventional TMS device



Carpenter et al. 2012

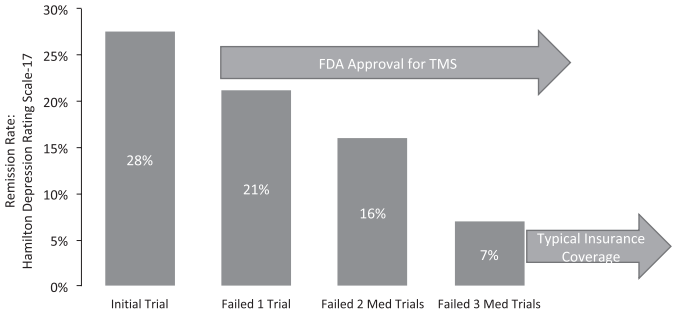
Meta-Analysis of 18 Hz rTMS using the H1 Coil



Kedzior et al, 2015

Why Consider TMS treatment for Depression?

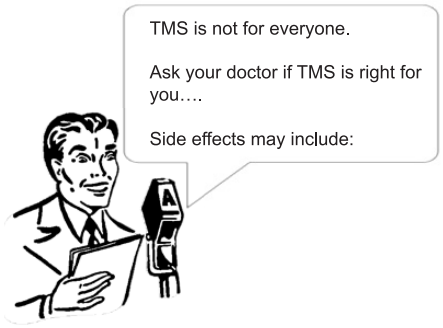
STAR*D Study: Depression Treatment Outcomes



Likelihood of achieving remission drops with each subsequent medication trial

Rush AJ et al. Am J Psych 163:1905-1917, 2006

Potential Side Effects of TMS



- Headache
- Pain/Discomfort
- Nausea
- Syncope
- Psychiatric Symptoms
- Fatigue
- Hearing Loss
- Seizure

Rossi et al, 2009

TMS Safety

CONTRAINDCATION	EXERCISE CAUTION	CONSIDER RISK
• Cochlear Implant	• Pacing device • Aneurysm clips • History of Seizure • Intracranial lesions	• Medications • Age • Hearing impairment • Pregnancy

Current Therapeutic Uses

FDA Approved

- Unipolar Depression
- Obsessive Compulsive Disorder
- Migraine with Aura

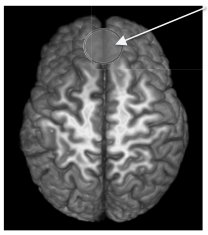
Investigative

- Auditory Hallucinations
- Post Traumatic Stress Disorder
- Generalized Anxiety Disorder
- Tourette Syndrome
- Bipolar Depression
- Autism
- Neurorehabilitation
- Parkinson Disease
- Alzheimer Disease
- Epilepsy
- Focal Dystonia
- Chronic Pain

OCD Targets

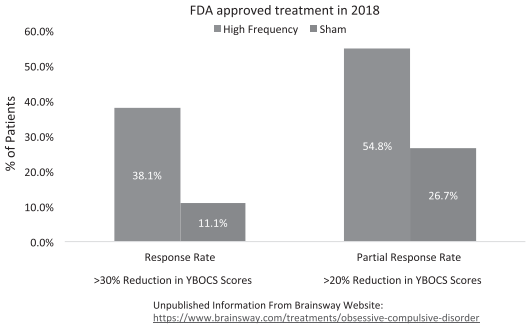
OCD has a well-defined neurologic basis:

- The Cortical – Striatal – Thalamic – Cortical pathway is a brain circuit that controls movement execution, habit formation, and reward.
- OCD is associated with hyperactivity of this pathway
- Poor thalamic gating may increase anterior cingulate cortex activity
- Medial prefrontal stimulation decreases anterior cingulate cortex activity



Medial prefrontal cortex/Anterior Cingulate Cortex

dTMS outcomes for OCD after 6 weeks of treatment



Unpublished Information From Brainsway Website:
https://www.brainsway.com/treatments/obsessive-compulsive-disorder

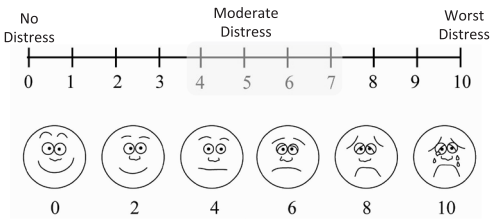
Parameters	
Coil	H7
Frequency	20 Hz
Train Duration	2 sec
Inter-Train Interval	20 sec
Total Pulses	2000
Intensity	100 % Ant. Tib RMT
Total Duration	18.3 minutes

Adapted from Carmi et al. 2019, AJP

OCD Symptoms Must Be Provoked!

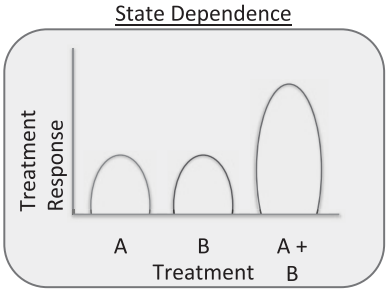
- Provocation consists of internal or external stimuli which will provoke or induce typical OCD symptoms and distress the subject – lasts up to 5 minutes
- The goal is to induce a moderate-to-major distress immediately before initiating TMS

How much does the script/photo cause you distress right now?



Enhancing the effect of TMS?

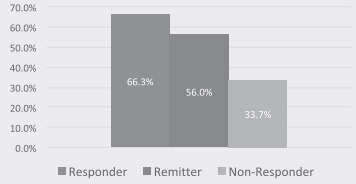
State Dependence



Idea: TMS + Second Therapy = Synergistic Effects

Activating a network with a task → Increases susceptibility of network to the changes introduced by TMS

State Effects: Simultaneous TMS + Therapy

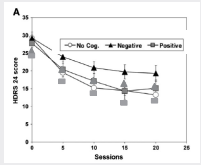


Donse et al. 2018

State Effects: Mood Alteration + TMS

Prior to dTMS for depression subjects randomized to:

- –Positive cognitive emotional reactivation
- –Negative cognitive emotional reactivation
- –None



Isserles et al, 2011

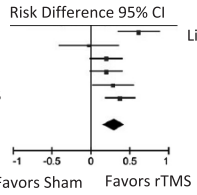
Medications

- Alter physiology:
  - – Excitability → Affects Motor Threshold!
  - – Plasticity → Affect Treatment Efficacy

Might continuing medication help the efficacy of treatment?

Antidepressant + Active or Shame rTMS

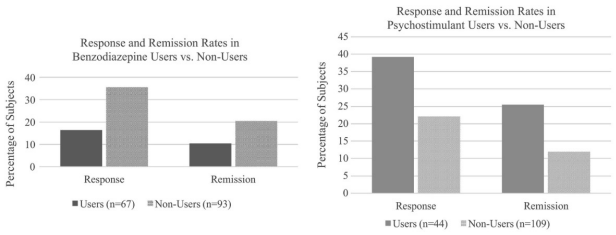
- –Augmentation with rTMS in treatment resistant depression is significantly superior to sham rTMS
- –OR: 5.12



Liu et al, 2014

Augmentation of medication management with rTMS in treatment-resistant depression leads to significant symptom improvement

Medications Effects on Treatment Outcomes



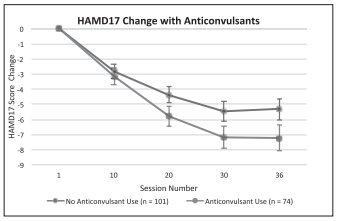
Medications May Impact Response

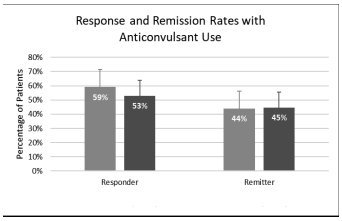
Hunter et al (2019) Brain and Behavior

Medication Effects on Treatment Outcome

Patients taking anticonvulsants had a *faster* rate of response than those not taking anticonvulsants.

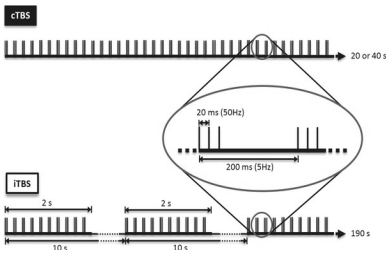
There was not significant difference between response and remission rates between those taking anticonvulsants and those not taking anticonvulsants.





Unpublished data from our clinic

Theta Burst Stimulation



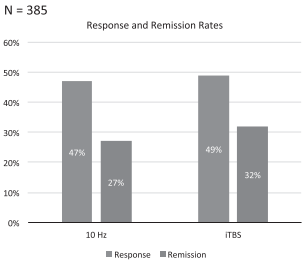
- Shorter duration
- May allow more sessions per day
- Longer-lasting physiological and cognitive effects are established in mechanistic studies

Standard 10 Hz vs iTBS

TBS is an FDA approved treatment protocol that takes ~3 minutes to administer!

Parameters	10 Hz	iTBS
Train Duration	4 seconds	2 seconds
Inter-Train Interval	26 seconds	8 seconds
Total Pulses	3000	600
Total Treatment Duration	**27 min 30 sec**	**3 min 9 sec**
Frequency	120% resting MT	120% resting MT

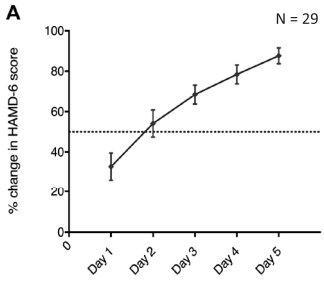
N = 385



Adapted from Blumberger et al. 2018; *The Lancet*

Accelerated Protocols

Accelerated iTBS treatment of depression in an inpatient setting



- Each patient received 10 iTBS treatments per day
- Number of pulses delivered to in 1 day of treatment = standard treatment course.

HAMD-6
- Response Rate = 87.1%
- Remission Rate = 83.9%

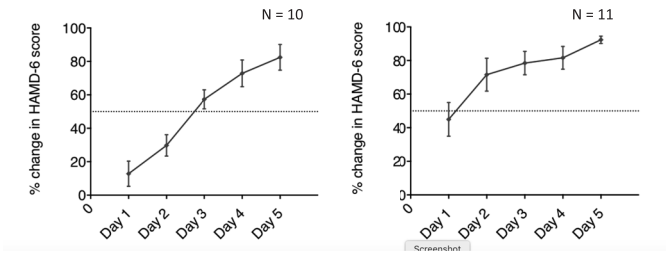
MADRS
- Response Rate = 90.3%
- Remission Rate = 90.3%

Are safe and can shorten the duration of treatment!

Cole et al, 2019

MDD participants with previous TMS non-response

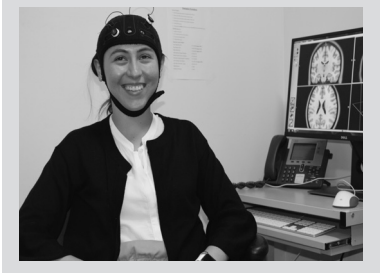
All Other TMS Participants



Patients with more treatment resistant depression may need more time to achieve response

Cole et al, 2019
(unpublished)

Transcranial Direct Current Stimulation



- Continuous low amplitude electrical current is delivered to a specified cortical regions using scalp electrodes
- Anodal Stimulation: Increases cortical excitability via depolarization of neuronal membrane potential
- Cathodal Stimulation: Decreases cortical excitability via hyperpolarization of neuronal membrane potential
- Repeated use may lead to neural plasticity
- Voltage: 2 mA over 30 minutes
- NOT FDA APROVED

Transcranial Direct Current Stimulation

Advantages:
- Easy to use
- Inexpensive
- Safe
- Potential for Home Use

Recent meta-analysis of 7 studies in Bipolar Depression
- Standardized Mean Difference after acute phase: 0.71
- Standardized Mean Difference after furthest endpoint from treatment: 1.97

May be good option for bipolar depression

Donde et al. 2017

Thank you for your attention!

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Q&A 4

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Conclusion & Wrap-up

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