UPSOM Neurobiology of Disease Course
Lecture on Autism
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Part 1. The Clinical Syndrome

"If you know one person with autism, you know one person with autism."

Heterogeneity is the rule.

Hallmarks of ASD

- Perceived as odd or strange
- Often expressionless face or one expression
- Poor use of eye contact for communication
- Focus on details or facts but poor concepts
- Poor common sense, poor abstraction
- Obsessions/special interests with focus on details or facts/don’t get big picture
- To them, we are illogical, erratic and scary

Autism Spectrum Disorder (DSM-5)

- Autism Spectrum Disorder is defined by underdevelopment (child-like state) of social, communication, emotion regulation, and conceptual/problem solving skills
- And a major impairment in functioning in a dynamic world, e.g., impaired adaptive function
- Syndrome is also defined by relative sparing or even enhanced basic skills in same domains as impairments

DSM-5 Criteria for ASD

A. Persistent deficits in social communication and social interaction across multiple contexts
    1. Deficits in social-**emotional** reciprocity
    2. Deficits in nonverbal communicative behaviors used for social interaction
    3. Deficits in developing, maintaining, and understanding relationships

DSM-5 Criteria for ASD

B. Restricted, repetitive patterns of behavior, interests, or activities (at least two of the following)

1. Stereotyped or **repetitive** motor movements, use of objects, or speech
2. **Insistence on sameness**, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior
3. Highly restricted, **fixated interests** that are abnormal in intensity or focus
4. Hyper- or hypo-reactivity to **sensory** input or unusual interest in sensory aspects of the environment

Co-Morbidity

70% of those with ASD have one psychiatric disorder and 40% have two or more:

- ADHD
- Developmental coordination disorder
- Anxiety disorder
- Depressive disorder
- Specific learning disabilities (literacy, numeracy)
- Epilepsy, sleep problems, and GI problems

Infant Sibs Research Confirms A Broad Range of Biologically Related Impairments in ASD

- Earliest differences are subtle- involve sensory & motor behaviors (information integration delays)
- Socially normal at 6 months
- "Associated symptoms" are integral-irritability, sensory responsivity, activity level, poor gross motor development
- "These findings do not support the view that autism is primarily a social-communicative disorder and instead suggest that autism disrupts multiple aspects of development rather simultaneously."

Sally Rogers, 2009

The Severity Spectrum

- **50%** have **IQ scores >85**
- **Another 23%** have **IQ scores of 71-85**
- Many of these cases are not diagnosed until adolescence or adulthood- these cases account for rise in prevalence.
- Chances are you will miss their diagnosis- everyone else does.

Autism Is Really About Skills Everyone Needs to Survive and Do Well

- Social
- Communication
- Problem solving
- Emotion regulation
- Real world function

Interventions designed for ASD will be broadly applicable in society.

ASD Prevalence: 1.5%- 2.9%

Source	Year	Prevalence
National Survey of Children's Health[1]	2007	1/86
CDC 14-site ADDM network[2]	2008	1/88
CDC 14-site ADDM network[3]	2010	1/68
National Survey of Children's Health[4]	2011-2012	1/50
South Korea[5]	2011	1/35
National Survey of Children's Health[6]	2014	1/45

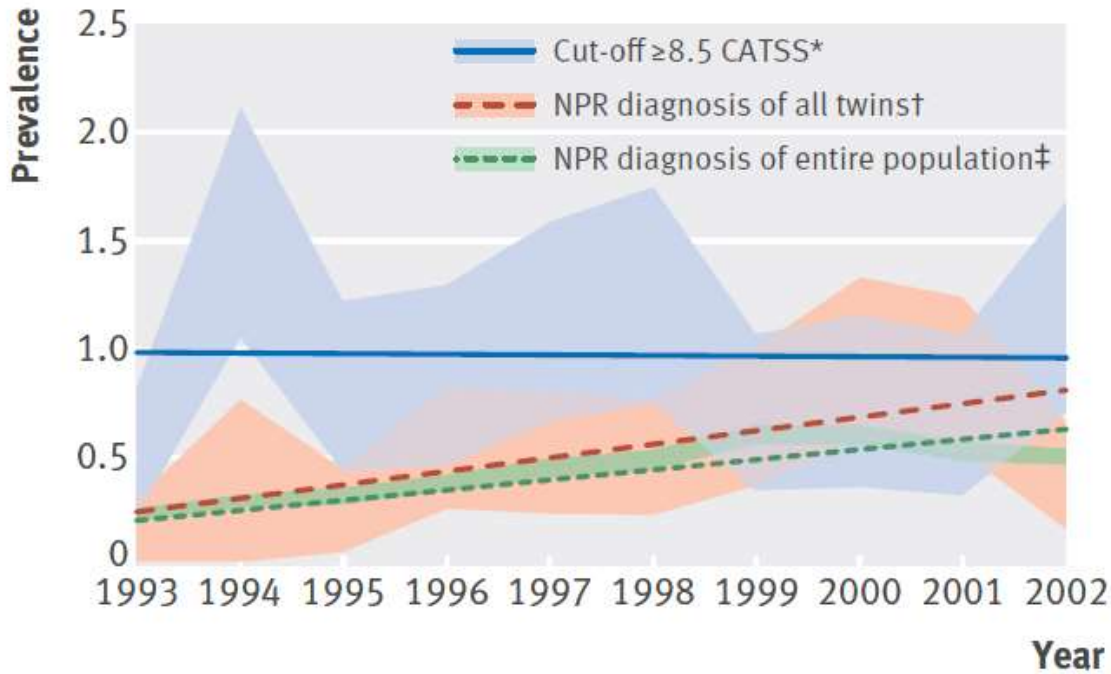
- [1] Centers for Disease Control and Prevention, National Center for Health Statistics, State and Local Area Integrated Telephone Survey. 2007 National Survey of Children's Health Frequently Asked Questions.
- [2]Prevalence of Autism Spectrum Disorders – Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008
- [3]Centers for Disease Control and Prevention, Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years – Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2010
- [4]Centers for Disease Control and Prevention, National Center for Health Statistics, State and Local Area Integrated Telephone Survey. 2011-2012 National Survey of Children's Health Frequently Asked Questions. April 2013. Available from URL: http://www.cdc.gov/nchs/slaits/nsch.htm
- [5]Kim et. al. "Prevalence of Autism Spectrum Disorders in a Total Population Sample" Am. J. Psychiatry 2011:168:904-912
- [6]Centers for Disease Control and Prevention, National Center for Health Statistics, 2014 National Health Interview Survey. Nov 13, 2015 Available from URL: http://www.cdc.gov/nchs/data/nhsr/nhsr087.pdf

Prevalence Estimates Do Not Include:

- Those with a fragment of ASD
- Those with functional social, communication and reasoning impairments due to abuse, violence, poor models, poverty, etc
- Those with social cognitive and non-social cognitive deficits but intact basic abilities- they are missed on usual autism measures and there is no real diagnostic category for them now.

Autism phenotype versus registered diagnosis in Swedish children: prevalence trends over 10 years in general population samples

Sebastian Lundström,[1 2] Abraham Reichenberg,[3] Henrik Anckarsäter,[2] Paul Lichtenstein,[4] Christopher Gillberg[1]



Cite this as: *BMJ* 2015;350:h1961
doi: 10.1136/bmj.h1961

Changes in Prevalence of Autism Spectrum Disorders in 2001–2011: Findings from the Stockholm Youth Cohort

Selma Idring · Michael Lundberg · Harald Sturm · Christina Dalman · Clara Gumpert · Dheeraj Rai · Brian K. Lee · Cecilia Magnusson

J Autism Dev Disord (2015) 45:1766–1773
DOI 10.1007/s10803-014-2336-y

Abstract In a record-linkage study in Stockholm, Sweden, the year 2011 prevalence of diagnosed autism spectrum disorders (ASD) was found to be 0.40%, 1.74%, 2.46% and 1.76% among 0-5, 6-12, 13-17 and 18-27 year old.

Theoretical/Methodological/Review Article

Clinical Psychological Science
1–23
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DOI: 10.1177/2167702614540646
cpx.sagepub.com

A Two-Hit Model of Autism: Adolescence as the Second Hit

Giorgia Picci and K. Suzanne Scherf
Department of Psychology, Pennsylvania State University

DOI: 10.1177/2167702614540646
cpx.sagepub.com

The “Second Hit” is Adaptive Behavior

The circuitry that connects information into an integrated meaningful schema, relates it to one’s self and to function in a dynamic world accelerates in adolescence.

Externally imposed structure helps children to function without these skills but is inadequate in adolescence and adulthood.

Applying This To Behavior & Care

Children are simpler than adolescents and life for them is simpler

- Clear rules and authority structure that they respect, value and conform to or try to
- Children value these rules and the opinion of their teachers
- They are child-like in their hearts and spirits
- They have yet to develop the cognitive capacity or desire for deception, manipulation, or retaliation, or they usually choose not to
- **In the ideal world, these things are true.**

Life gets much more complicated and real world-like in adolescence

- Adolescence is a time of greatly increasing social, emotional and cognitive demands
- Students with ASD do not have the typical growth in advanced social, emotional and thinking skills that other students do
- But you will see impaired social, emotional, communication and problem solving skills for different reasons in many non-ASD students

Autism is Really

- A disorder of those abilities most unique to humans
- It is ultimately therefore a disorder of adaptive function

Wide recognition of the ASD severity spectrum has led to recognition of the tremendous phenotypic variability that is independent of severity

Large impact of background genetics, common variants and additive genetics are shedding light on this.

Elimination of the PDDNOS category has revealed individuals with the social and non social cognitive deficits of ASD & low adaptive behavior scores

- Don’t meet ASD criteria on diagnostic measures which are loaded for early developmental features and impairments in the elementary mechanics of social interactions and language
- This group used to be captured clinically under the PDDNOS category (DSM-IV) but not well
- Social Communication Disorder is not a fit

Requires Instrument Development, Much Work, and Future Revisions to Diagnostic Classification System

Deficits Underlying Symptoms

- Social (reciprocity, ToM, perspective-taking, social cognition)
- Formal language, semantic pragmatic language, nonverbal language
- **Emotion regulation** (perception in others and self, names, regulation, cognition)
- Executive function
- Abstraction (rule-learning, concept formation)
- **Prototype learning/generalization**
- **Learning from experience**
- **Automatic versus conscious processing**
- **Processing speed**
- Motor learning, motor praxis, motor coordination, motor speed
- Postural control (multi-sensory integration)
- Sensory processing disturbances
- **Adaptive function** (deficit in its own right)

Overall characteristic of all these impairments: lack of integration of elementary features or input to form higher order schema that support comprehension, learning/wisdom and adaptive function AND dependence on cortical systems

Long List of Deficits Categorized by Clinical Domain- Problem List Approach

- I find it more useful to think in terms of altered information processing that is present across all domains- from motor and sensory to memory and learning to reasoning and social
- This construct of altered information processing makes it easier to think about what the person does not know but needs to know in order to function well and appropriately

Another dimension: Understanding what information means about and to themselves

- Brain imaging studies show that people with ASD lack a brain representation of “self”
- Social interactions, like hugging others or being hugged, are facts about the external world but not ones they experience in relation to themselves and to others.

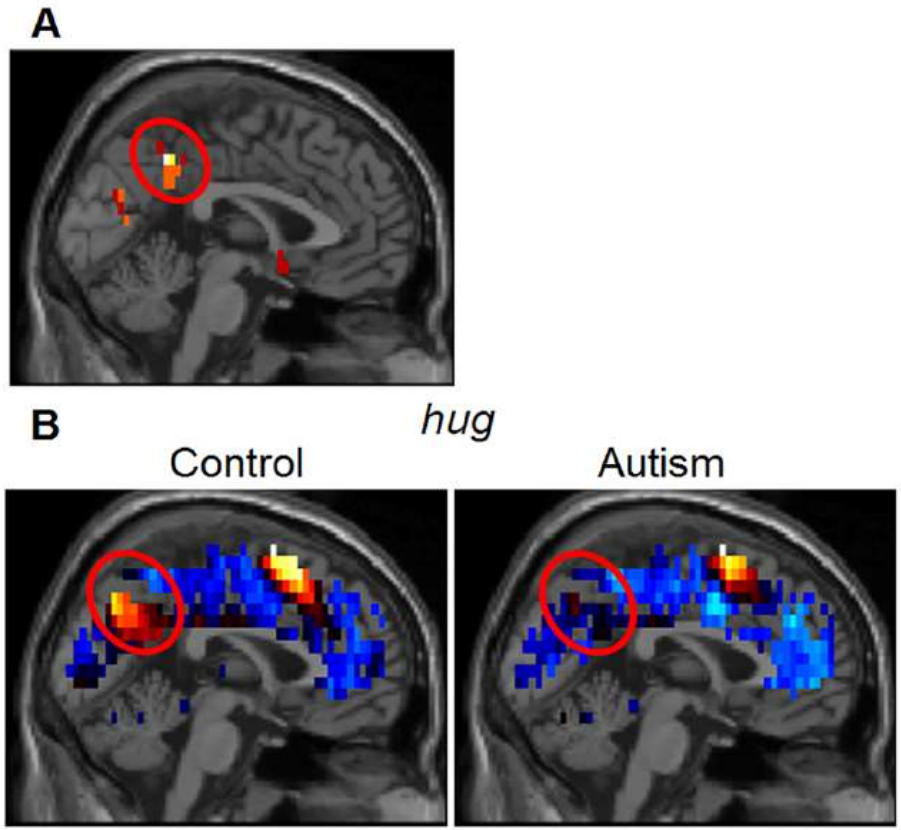


Figure 2. Posterior midline *self* factor location. A. Location of the voxels (circled) derived from the factor analysis of the Control Group that defined the posterior cingulate/precuneus sphere of this group's *self* factor. Voxels in this cluster (with MNI x-coordinates extending from 0 to −9) are shown projected on the mid-sagittal plane. (The coordinates and radii of all 6 spheres associated with this factor are shown in Table S1 in File S1). B. Mean activation in midline brain structures for the verb *hug* (averaged over agent and recipient roles) for the two groups, differing in posterior cingulate/precuneus. The verb *hug* was chosen for illustration here because of the salience of hugging as a social interaction in autism, where enveloping pressure is sometimes desired but without physical contact between oneself with another person, as in Temple Grandin's squeeze machine [40]. The depiction of the activation in this slice for all of the other verbs was very similar to *hug*, for both groups.

PLoS ONE 9(12): e113879.
doi:10.1371/journal.pone.0113879

Identifying Autism from Neural Representations of Social Interactions: Neurocognitive Markers of Autism

PLoS One. 2014; 9(12)
Published online 2014 Dec 2

Marcel Adam Just[1*], Vladimir L. Cherkassky[1], Augusto Buchweitz[1,3], Timothy A. Keller[1], Tom M. Mitchell[2]

Autism is a psychiatric/neurological condition in which alterations in social interaction (among other symptoms) are diagnosed by behavioral psychiatric methods. The main goal of this study was to determine how the neural representations and meanings of social concepts (such as *to insult*) are altered in autism. A second goal was to determine whether these alterations can serve as neurocognitive markers of autism. The approach is based on previous advances in fMRI analysis methods that permit (a) the identification of a concept, such as the thought of a physical object, from its fMRI pattern, and (b) the ability to assess the semantic content of a concept from its fMRI pattern. These factor analysis and machine learning methods were applied to the fMRI activation patterns of 17 adults with high-functioning autism and matched controls, scanned while thinking about 16 social interactions. One prominent neural representation factor that emerged (manifested mainly in posterior midline regions) was related to *self*-representation, but this factor was present only for the control participants, and was near-absent in the autism group. Moreover, machine learning algorithms classified individuals as autistic or control with 97% accuracy from their fMRI neurocognitive markers. The findings suggest that psychiatric alterations of thought can begin to be biologically understood by assessing the form and content of the altered thought's underlying brain activation patterns.

Recurring Patterns in their Behavior Resulting From Their Choices

- Often do not recognize the connection between their choices of words and actions and outcomes
- Often do not appreciate that there are consistent patterns across situations that lead to undesirable/desirable outcomes
- Short journal entries as a way to insight
- Pictures (visual format) may help

Motivation To Change

- For a child, rules or authority may work; for adolescents, it is up to them to choose change.
- Life can go better for them.
- If they continue to think and do things in the same way, the outcome will continue to be the same.
- If they would like life to have better outcomes for them, they will need to learn to think and act in new ways.
- They can do this. It is a process not an event.
- Challenge: it is hard to see patterns in a complex society where the behavior of others can obscure relationships between behavior and outcome.

Empowerment

- As long as people with ASD see themselves as victims, they see themselves as powerless.
- If they can come to see and experience that they can do things to take care of themselves and determine their outcomes, they are empowered and powerful. This is a life changer.

Adult Outcomes in ASD

Howlin et al 2004; Mazefsky & White, 2014

- Limited data- that's a problem!
- Poor for majority with low IQ in terms of living independently, jobs, and significant social relationships
- 10 participants with IQ >70: did better than low IQ people with ASD but outcome highly variable and not predictable by IQ score. Lack of a job and low paying jobs very limiting.

For Severely Impaired

- Interventions not changing severity
- Treat complications or challenging behavior
- Always consider alternate form of communication periodically; never know what they understand.
- Hope is ultimately on biologically based treatments that can change structural and functional connectivity of the brain.

Spectrum Has Major Implications For Treatment

- Behaviorally based treatments for infants, toddlers, and preschoolers, and those with low IQ
- Cognitive rehabilitation treatments for those with language and IQ scores in normal range- in trial
- Neural based approaches for all- “emerging”
- Neurobiologically driven drug approaches- greatly needed for those with intellectual disability and little to no language- on the horizon
- Combinations of the above, individualized, likely to be most effective- pending phenotyping advances and development of interventions

Brain Systems in ASD Are Plastic, But Not in All and Not Enough

- Several interventions have shown cortical systems repair in toddlers, preschoolers, and adults.
- Behavioral and cognitive rehabilitation interventions have biological effects.
- Is plasticity measureable to predict intervention outcome and can plasticity be amplified?

Part 2. The Science

Understanding Autism: The Basic Architecture of Its Cause, Emerging New Treatments & Challenges

Finding New Treatments That Target Different Levels of the Pathophysiology

Conflict of Interest Disclosure

- No financial conflicts
- I am a member of the Autism Sequencing Consortium (ASC) as a contributor of samples
- My genetic colleagues in Pittsburgh are Dr. Bernie Devlin and Dr. Kathryn Roeder

Other Major Collaborations

- Marcel Just
- Tim Keller
- Rob Masson
- Rajesh Kana
- Marlene Behrmann
- John Sweeney
- Beatrix Luna
- Joseph Furman
- Diane Williams
- Gerald Goldstein
- Mark Strauss

Shaun Eack*
Jana Iverson*
Suzanne Scherf*

* intervention development

Topics

- Large phenotypic variability
- Genetic underpinings
- Altered cortical systems connectivity
- How altered connectivity relates to symptoms
- How cortical systems might be targets for treatment
- Development of new interventions
- The way forward

SUMMARY

- Clinical syndrome marked by much phenotypic variability now understandable based on genetics & on variability inherent to humans
- 300-1,000 unidentified common variants at play
- 71 rare variants so far implicate synaptic function and transcription/chromatin remodeling
- Genetic background plays a strong role in ASD risk gene expression
- Selective impact on higher order abilities across domains, AND poor adaptive function
- Equally broad cortical systems underconnectivity
- Cortical-cortical and cortical-subcortical connections

SUMMARY

- Cognitive and neural profiles are consistent with disturbances in neuronal organizational events etc
- Brain in ASD is plastic across the age span
- Effective behavioral and cognitive rehabilitation interventions exist but NOT enough data and not disseminated
- These interventions change neural systems
- rTMS and tDCS likely to have significant role, in combination with cognitive rehabilitation methods
- Biologically based pharmacological strategies-WIPs

Genetic Contributions to Understanding the Clinical Syndrome

Finding the missing heritability of complex diseases

Teri A. Manolio[1], Francis S. Collins[2], Nancy J. Cox[3], David B. Goldstein[4], Lucia A. Hindorff[5], David J. Hunter[6], Mark I. McCarthy[7], Erin M. Ramos[5], Lon R. Cardon[8], Aravinda Chakravarti[9], Judy H. Cho[10], Alan E. Guttmacher[1], Augustine Kong[11], Leonid Kruglyak[12], Elaine Mardis[13], Charles N. Rotimi[14], Montgomery Slatkin[15], David Valle[9], Alice S. Whittemore[16], Michael Boehnke[17], Andrew G. Clark[18], Evan E. Eichler[19], Greg Gibson[20], Jonathan L. Haines[21], Trudy F. C. Mackay[22], Steven A. McCarroll[23], and Peter M. Visscher[24]

Nature. 2009 October 8; 461(7265): 747–753.

Find ASD Risk Genes Here:

Rare alleles with large effect size on risk for ASD

Common variants with small effect size on risk

Not Here:

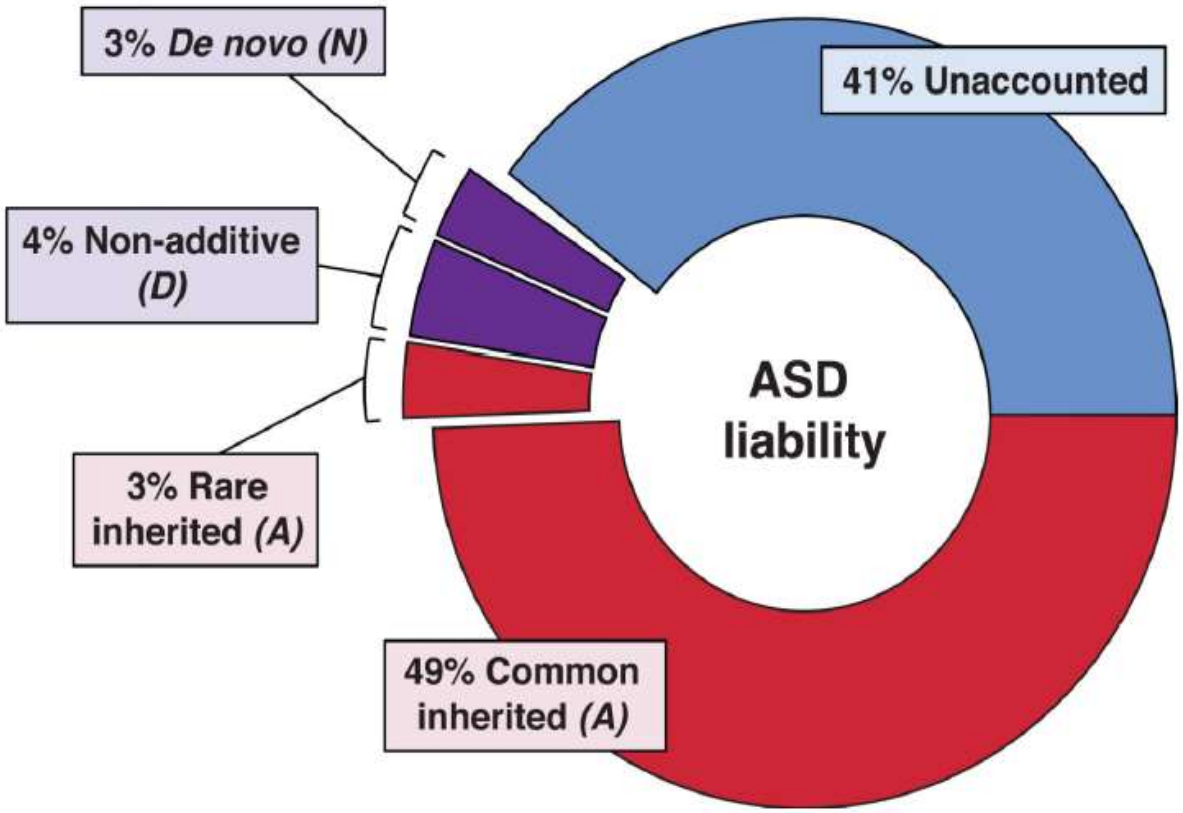
Rare variants with small effect- hard to detect

Common variants with large effect size- eliminated from gene pool in severe early life disorders

Most genetic risk for autism resides with common variation

Trent Gaugler[1], Lambertus Klei[2], Stephan J. Sanders[3,4], Corneliu A. Bodea[1], Arthur P. Goldberg[5,6,7], Ann B. Lee[1], Milind Mahajan[8], Dina Manaa[8], Yudi Pawitan[9], Jennifer Reichert[5,6], Stephan Ripke[10], Sven Sandin[9], Pamela Sklar[6,7,8,11,12], Oscar Svantesson[9], Abraham Reichenberg[5,6,13], Christina M. Hultman[9], Bernie Devlin[2], Kathryn Roeder[1,14], and Joseph D. Buxbaum[5,6,8,11,15,16]

Nature Genetics Vol. 46 No. 8 August 2014



Discovery of Common Risk Variants: 49% of ASD Risk

- Consortiums and sharing
- GWAS
- 1 identified so far

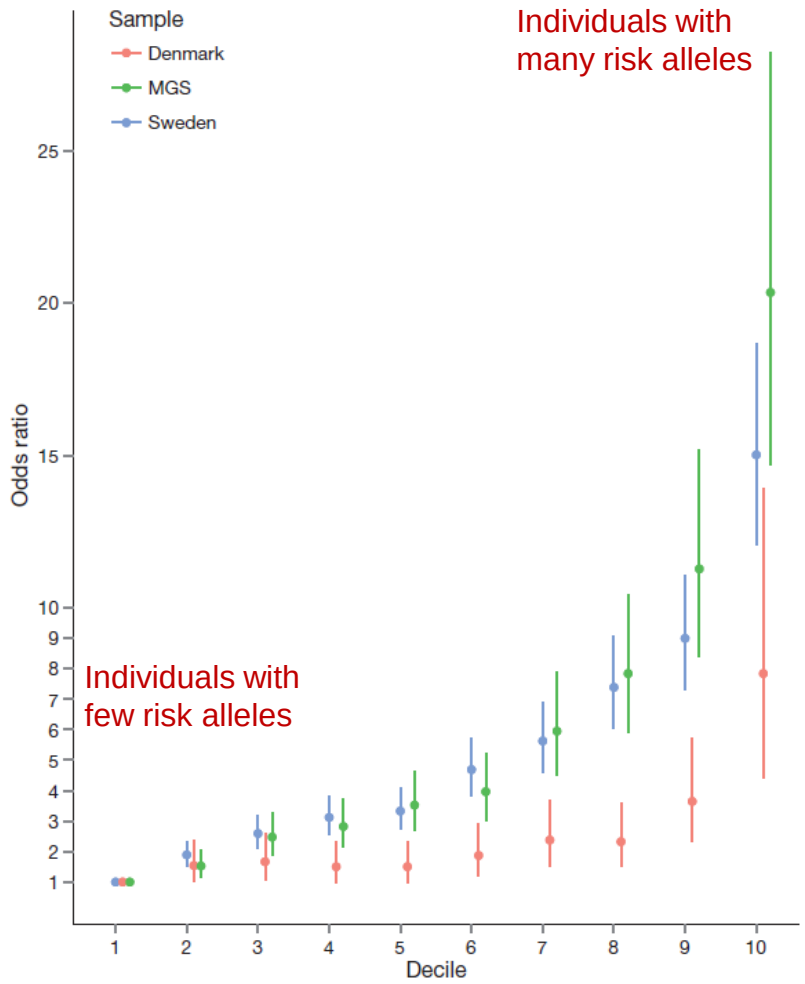
Common Variants Associated With ASD Risk Identified So Far By GWAS

- 1 based on sample of 7,000 with ASD
- Estimated # in ASD: 300 or 1,000
- In schizophrenia, 108 common variants; sample of 25,000 affected and 25,000 controls
- Effect of common variants on risk is additive.

Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium*

24 JULY 2014 | VOL 511 | NATURE



Discovery of Rare Variants: 3-6% of ASD Risk

- Genetic diagnosis by microarray is uncommon
- Consortiums and sharing
- Exome sequencing
- Identify autism risk genes
- Identify associated biological processes

Rare Variants: Contributing to ASD Risk

- Three large exome sequencing studies: ASC, SSC, ASC + SSC
- 71 risk alleles in two clusters:
  - Synaptic genes- long suspected (neurexin, neuroligin, contactin…)
  - Transcriptional and Chromatin Remodeling genes- relative surprise: these genes are involved in early brain development during which areas of DNA are opened or closed for transcription

ARTICLE

doi:10.1038/nature13772

Synaptic, transcriptional and chromatin genes disrupted in autism

A list of authors and their affiliations appears at the end of the paper

ARTICLE

doi:10.1038/nature13908

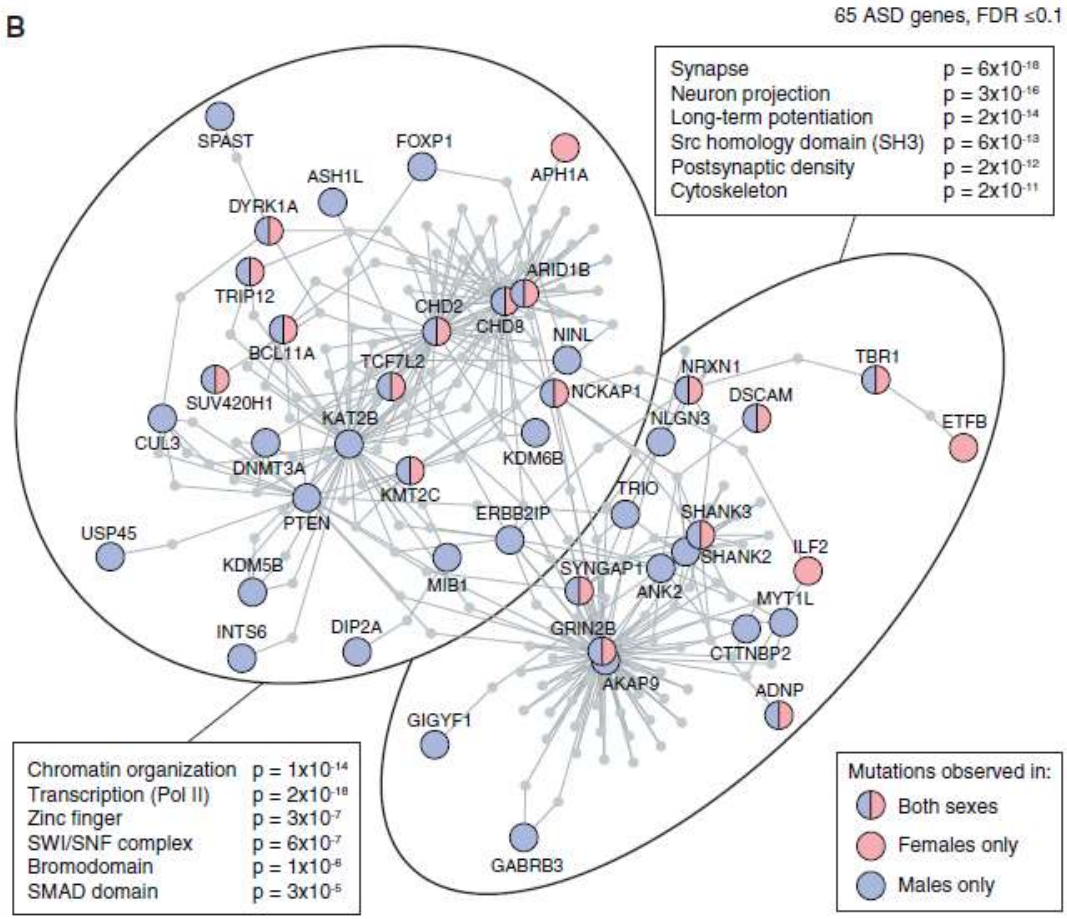
The contribution of *de novo* coding mutations to autism spectrum disorder

Ivan Iossifov[1]*, Brian J. O'Roak[2,3]*, Stephan J. Sanders[4,5]*, Michael Ronemus[1]*, Niklas Krumm[2], Dan Levy[1], Holly A. Stessman[2], Kali T. Witherspoon[2], Laura Vives[2], Karynne E. Patterson[2], Joshua D. Smith[2], Bryan Paeper[2], Deborah A. Nickerson[2], Jeanselle Dea[4], Shan Dong[5,6], Luis E. Gonzalez[7], Jeffrey D. Mandell[4], Shrikant M. Mane[8], Michael T. Murtha[7], Catherine A. Sullivan[7], Michael F. Walker[4], Zainulabedin Waqar[7], Liping Wei[6,9], A. Jeremy Willsey[4,5], Boris Yamrom[1], Yoon-ha Lee[1], Ewa Grabowska[1,10], Ertugrul Dalkic[1,11], Zihua Wang[1], Steven Marks[1], Peter Andrews[1], Anthony Leotta[1], Jude Kendall[1], Inessa Hakker[1], Julie Rosenbaum[1], Beicong Ma[1], Linda Rodgers[1], Jennifer Troge[1], Giuseppe Narzisi[1,10], Seungtai Yoon[1], Michael C. Schatz[1], Kenny Ye[12], W. Richard McCombie[1], Jay Shendure[2], Evan E. Eichler[2,13], Matthew W. State[4,5,7,14] & Michael Wigler[1]

Insights into Autism Spectrum Disorder Genomic Architecture and Biology from 71 Risk Loci

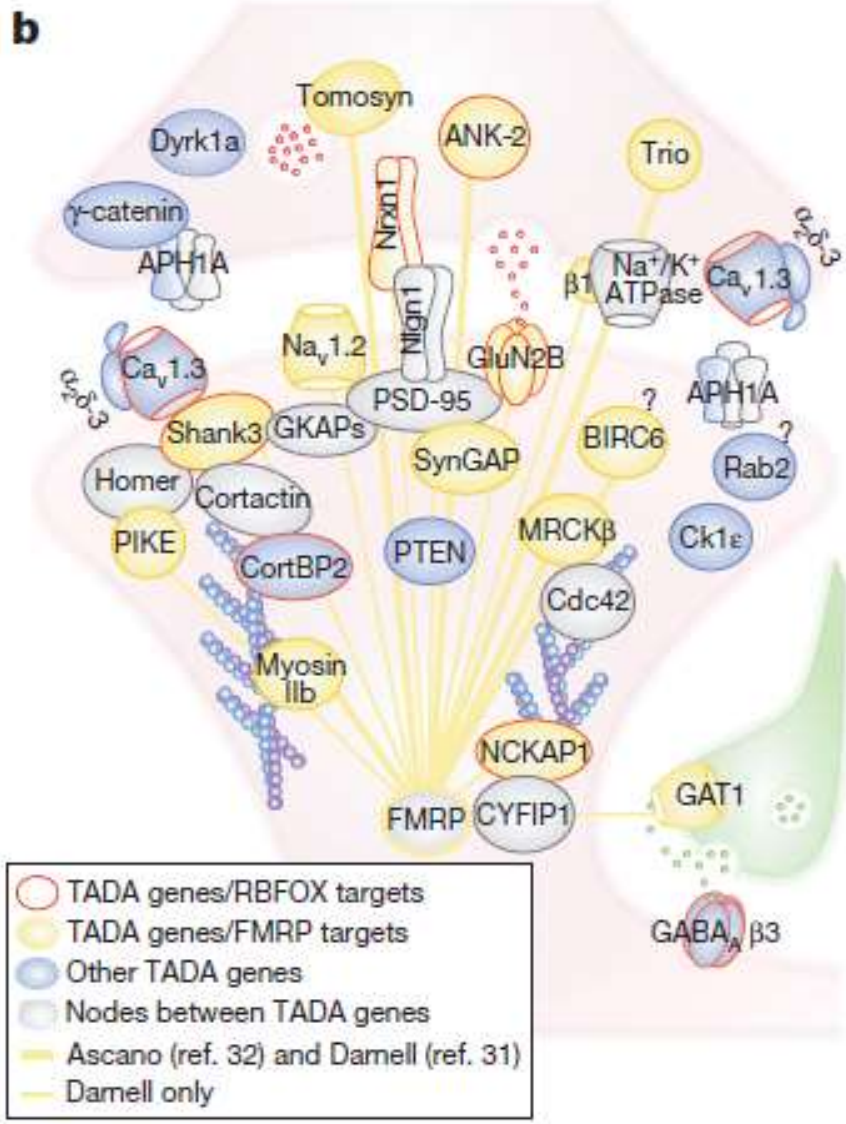
Stephan J. Sanders,[1,*] Xin He,[2] A. Jeremy Willsey,[1] A. Gulhan Ercan-Sencicek,[3] Kaitlin E. Samocha,[4,5,6] A. Ercument Cicek,[7,8] Michael T. Murtha,[3] Vanessa H. Bal,[1] Somer L. Bishop,[1] Shan Dong,[9] Arthur P. Goldberg,[10,11] Cai Jinlu,[10,11] John F. Keaney III,[12] Lambertus Klei,[13] Jeffrey D. Mandell,[1] Daniel Moreno-De-Luca,[14] Christopher S. Poultney,[10,11] Elise B. Robinson,[4,5] Louw Smith,[1] Tor Solli-Nowlan,[15] Mack Y. Su,[16] Nicole A. Teran,[17] Michael F. Walker,[1] Donna M. Werling,[1] Arthur L. Beaudet,[18] Rita M. Cantor,[19] Eric Fombonne,[20] Daniel H. Geschwind,[21] Dorothy E. Grice,[11] Catherine Lord,[22] Jennifer K. Lowe,[21] Shrikant M. Mane,[23] Donna M. Martin,[24] Eric M. Morrow,[25] Michael E. Talkowski,[26] James S. Sutcliffe,[27] Christopher A. Walsh,[28] Timothy W. Yu,[28] Autism Sequencing Consortium, David H. Ledbetter,[29] Christa Lese Martin,[29] Edwin H. Cook,[30] Joseph D. Buxbaum,[10,11] Mark J. Daly,[4,5] Bernie Devlin,[13] Kathryn Roeder,[7,31] and Matthew W. State[1,*]

Neuron *87*, 1215–1233, September 23, 2015



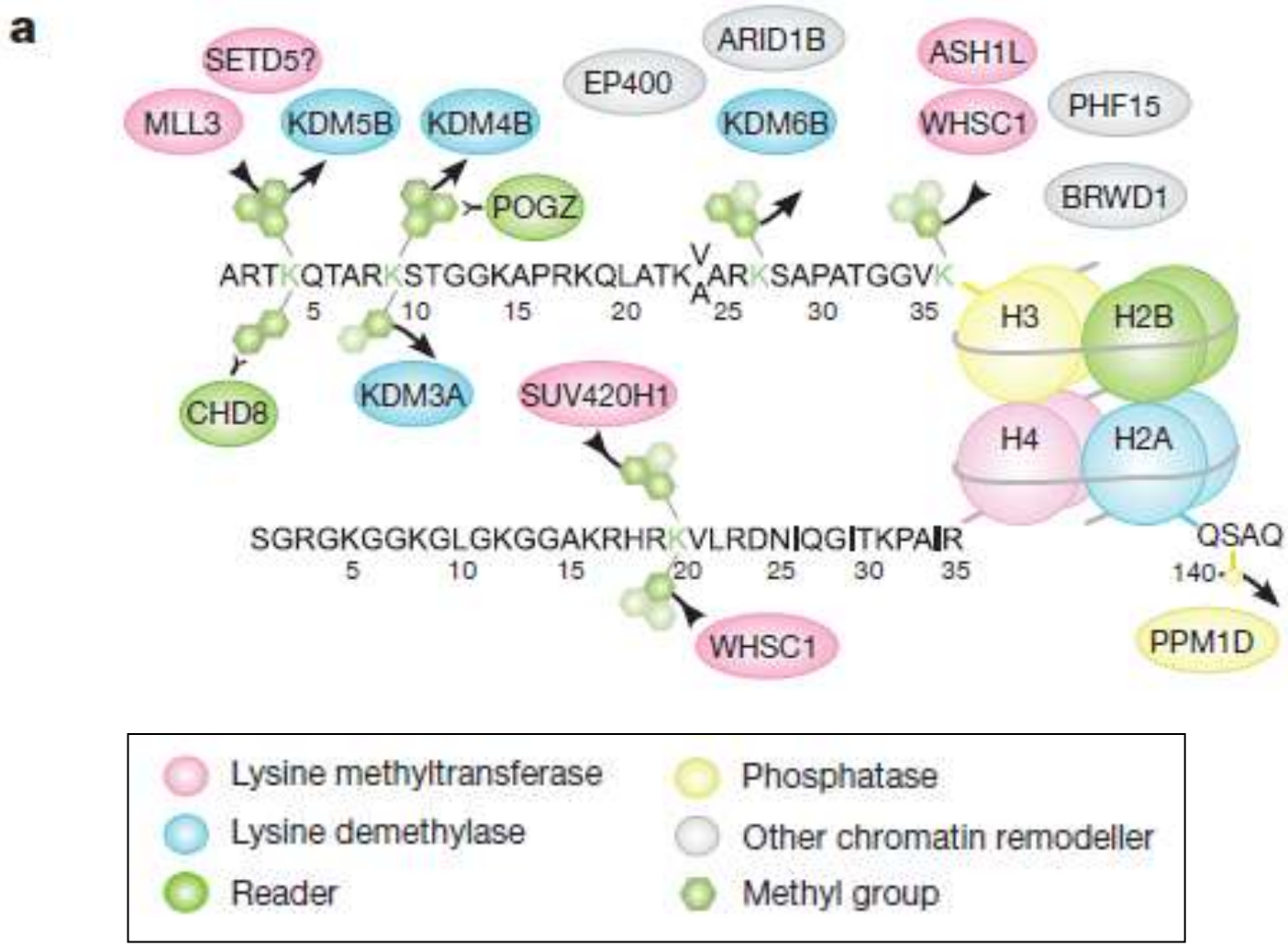
Many of the genes are synaptic

Autism Sequencing Consortium study



Chromatin remodeling genes

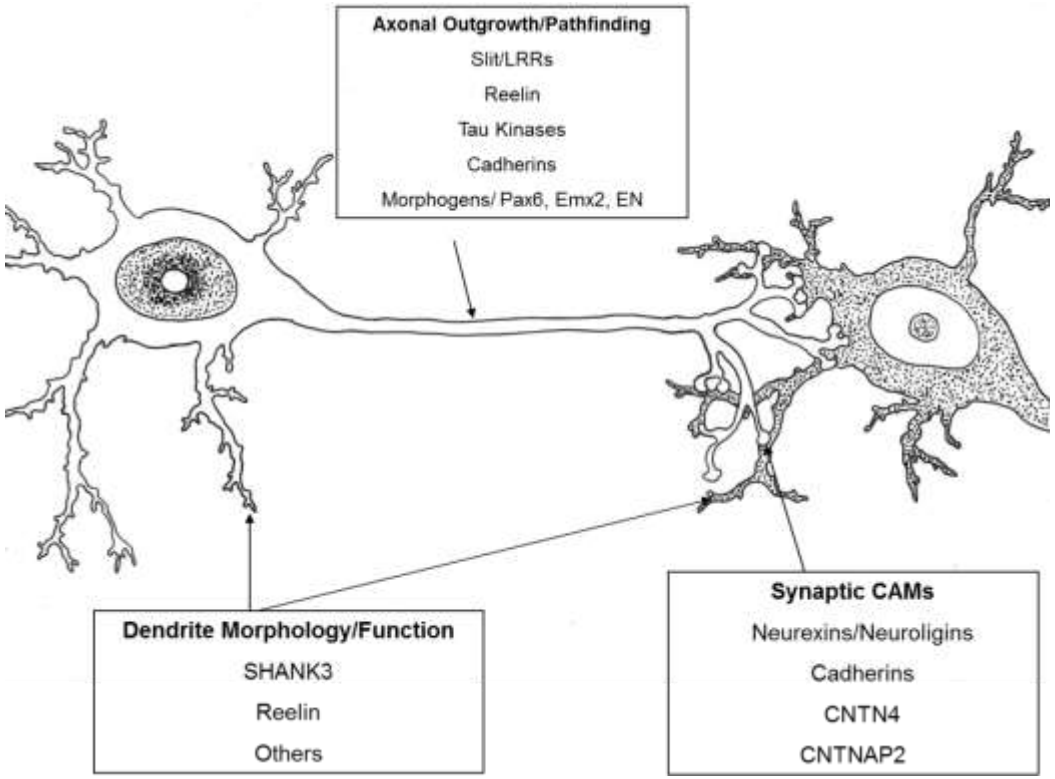
Autism Sequencing Consortium study



Axonal Model of ASD Neurobiology

Kate McFadden & Nancy Minshew

- Preliminary reading of AGP GWAS analyses showed CNVs and association of SNP alleles with autism that are proximate to genes of interest more than would be expected by chance in:
  - synaptic CAMS
  - Leucine rich repeat (LRR) protein genes
  - various mediators of axonal microtubule stabilization
- These are all known to mediate axonal outgrowth, stability, and targeting.



Background Effects Are A Major Factor Influencing Risk Allele Expression

Modifying Behavioral Phenotypes in *Fmr1*KO Mice: Genetic Background Differences Reveal Autistic-Like Responses

Corinne M. Spencer, Olga Alekseyenko, Shannon M. Hamilton, Alexia M. Thomas, Ekaterina Serysheva, Lisa A. Yuva-Paylor, and Richard Paylor

Fragile X syndrome (FXS) is the most common inherited form of intellectual disability in humans. In addition to cognitive impairment, patients may exhibit hyperactivity, attention deficits, social difficulties and anxiety, and autistic-like behaviors. The degree to which patients display these behaviors varies considerably and is influenced by family history, suggesting that genetic modifiers play a role in the expression of behaviors in FXS. Several studies have examined behavior in a mouse model of FXS in which the *Fmr1* gene has been ablated. Most of those studies were done in *Fmr1* knockout mice on a pure C57BL/6 or FVB strain background. To gain a better understanding of the effects of genetic background on behaviors resulting from the loss of *Fmr1* gene expression, we generated F1 hybrid lines from female *Fmr1* heterozygous mice on a pure C57BL/6J background bred with male *Fmr1* wild-type (WT) mice of various background strains (A/J, DBA/2J, FVB/NJ, 129S1/SvImJ and CD-1). Male *Fmr1* knockout and WT littermates from each line were examined in an extensive behavioral test battery. Results clearly indicate that multiple behavioral responses are dependent on genetic background, including autistic-like traits that are present on limited genetic backgrounds. This approach has allowed us to identify improved models for different behavioral symptoms present in FXS including autistic-like traits.

Autism Research 4: 40–56, 2011

Influence of Genetic Background on Genetically Engineered Mouse Phenotypes

Thomas Doetschman

Ralf Kuhn, Wolfgang Wurst (eds.), *Gene Knockout Protocols: Second Edition, vol. 350*; 423-33

The history of mouse genetics, which involves the study of strain-dependent phenotype variability, makes it clear that the genetic background onto which a gene-targeted allele is placed can cause considerable variation in genetically engineered mouse (GEM) phenotype. This variation can present itself as completely different phenotypes, as variations in penetrance of phenotype, or as variable expressivity of phenotype. In this chapter we provide examples from gene-targeting literature showing each of these types of phenotype variation. We discuss ways in which modifier genes can affect the phenotype of a mouse with a mutant gene, and we give examples of modifier locus identification. We also review approaches to minimize gene polymorphism and flanking gene differences between experimental animals, and between them and their controls. In addition, we discuss the advantages and disadvantages of performing the first analysis of a knockout mouse on a mixed genetic background. We conclude that a mixed background provides the quickest preview of possible strain-dependent phenotypes *(1, 2)*. Finally, we review recent approaches to improving genetic diversity by generating new inbred strains that encompass a broader range of alleles within the mouse species.

Commentary

Biological Psychiatry

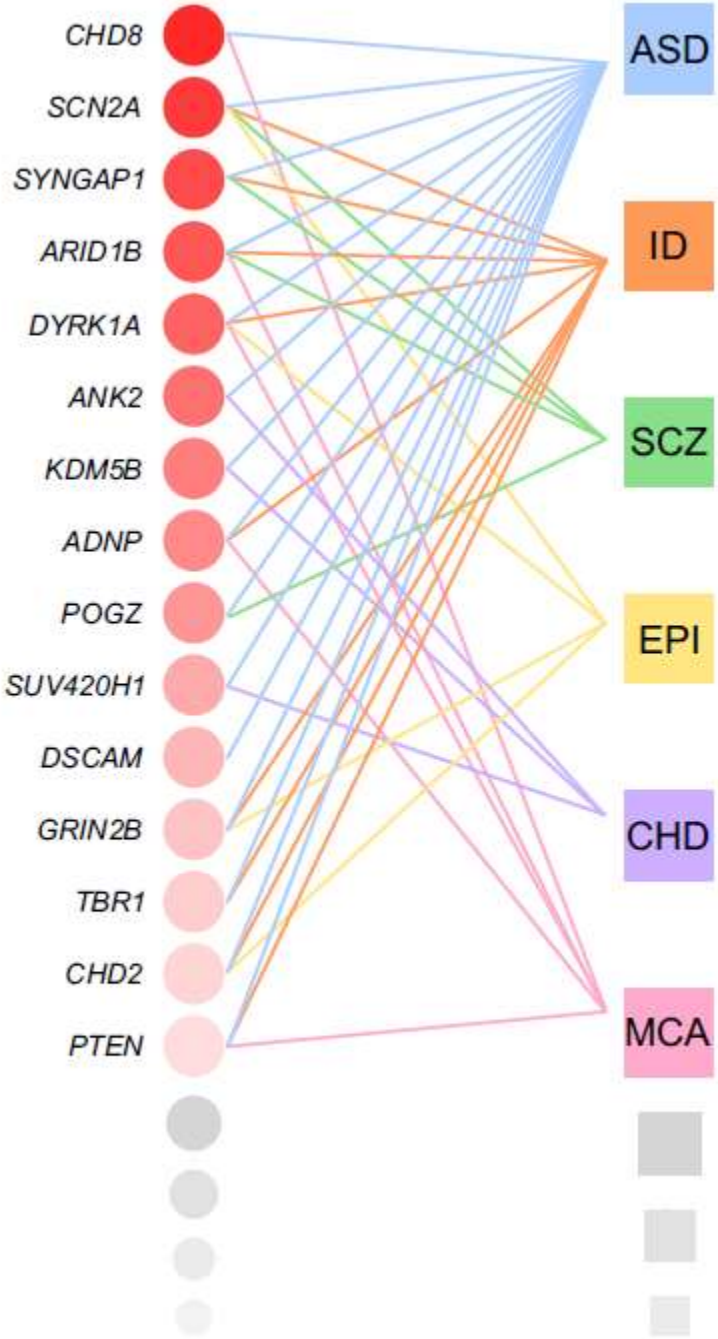
DSM-5 and Psychiatric Genetics — Round Hole, Meet Square Peg

Joseph D. Buxbaum

Biological Psychiatry May 1, 2015; 77:766–768

Combining data sets reveals more genes. Interestingly, some autism genes are not ID genes, some impact both, and some just ID.

Will treatments developed for one disorder work for other disorders that share genes? Will treatment effect relate broadly to gene category, eg synaptic versus chromatin remodeling genes? Will treatments for synaptic genes be very different from treatments for chromatin remodeling genes? Is the brain biology different in a fundamental way or is there a common downstream pathway?



Other News

- Excess of de novo loss of function genes
- Highest prevalence LoF mutations are: CHD5 (chromatin gene) and SCN2A (ion channel gene)- both have large downstream effects on expression of hundreds to thousands of genes
- Two of latest findings: mutations disrupting projection neurons between cortical and subcortical structures and -some genes found only in ID and some only in ASD and some in both.

Rare Variants, Mouse Models, and the Hunt For Neurobiologically Based Drugs

- Identify an altered cellular mechanism for a relevant behavior/function in animal genetic model of ASD
- Identify an agent that corrects that defect and behavior
- Clinical trials in humans with same genetic basis for ASD.

Rare variant models:

- *FMR1*/Xq27.3/Fragile X Syndrome/synaptic plasticity & maturation/
- *Shank3*/22q13/Phelan-McDermid Syndrome/synaptic transmission/ insulin-like growth factor-1 (IGF-1)
- *TSC1/9q34, TSC2/16p13.3*/Tuberous Sclerosis Associated Neuropsychiatric Disorders (TANDs)/mTORopathies/mTOR signaling pathway/rapamycin

Induced Pluripotent Stem Cell Model

KCC2 rescues functional deficits in human neurons derived from patients with Rett syndrome

Xin Tang[a], Julie Kim[a], Li Zhou[a], Eric Wengert[b], Lei Zhang[a], Zheng Wu[a], Cassiano Carromeu[c], Alysson R. Muotri[c], Maria C. N. Marchetto[d], Fred H. Gage[d,1], and Gong Chen[a,1]

www.pnas.org/cgi/doi/10.1073/pnas.1524013113

Rett syndrome is a severe form of autism spectrum disorder, mainly caused by mutations of a single gene methyl CpG binding protein 2 (*MeCP2*) on the X chromosome. Patients with Rett syndrome exhibit a period of normal development followed by regression of brain function and the emergence of autistic behaviors. However, the mechanism behind the delayed onset of symptoms is largely unknown. Here we demonstrate that neuron-specific K^+-Cl^- cotransporter2 (*KCC2*) is a critical downstream gene target of *MeCP2*. We found that human neurons differentiated from induced pluripotent stem cells from patients with Rett syndrome showed a significant deficit in KCC2 expression and consequently a delayed GABA functional switch from excitation to inhibition. Interestingly, overexpression of KCC2 in MeCP2-deficient neurons rescued GABA functional deficits, suggesting an important role of KCC2 in Rett syndrome. We further identified that RE1-silencing transcriptional factor, *REST*, a neuronal gene repressor, mediates the *MeCP2* regulation of *KCC2*. Because KCC2 is a slow onset molecule with expression level reaching maximum later in development, the functional deficit of KCC2 may offer an explanation for the delayed onset of Rett symptoms. Our studies suggest that restoring KCC2 function in Rett neurons may lead to a potential treatment for Rett syndrome.

ASD Is A Behaviorally Defined Syndrome: Defining the Cognitive Basis of Behavior

- Defining a profile of deficits in higher order abilities across domains that included sensory, motor, & memory aspects
- Recognizing the implications of intact abilities for local cortical connections
- This profile conforms to the underlying cause
- Arrive at a distributed cortical systems localization that accounts neurologically for the co-occurrence of all manifestations as a syndrome

Neuropsychologic functioning in autism: Profile of a complex information processing disorder

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Journal of the International Neuropsychological Society (1997), **3**, 303–316.

The Profile of Intact & Impaired Abilities in High Functioning Autistic Individuals

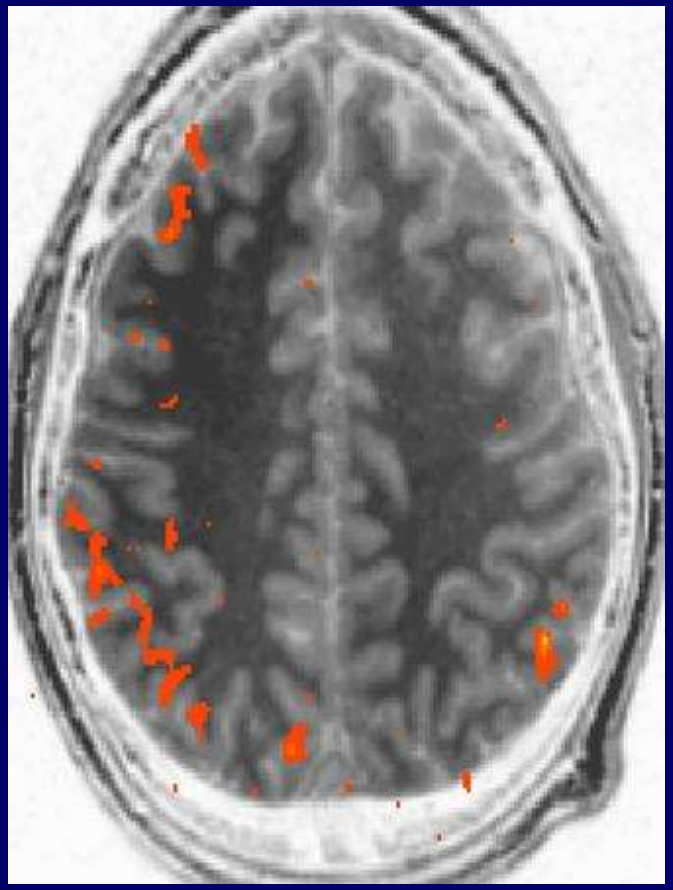
Intact or Enhanced

- Attention
- Sensory Perception
- Elementary Motor
- Simple Memory
- Formal Language
- Rule-learning
- Visuospatial processing

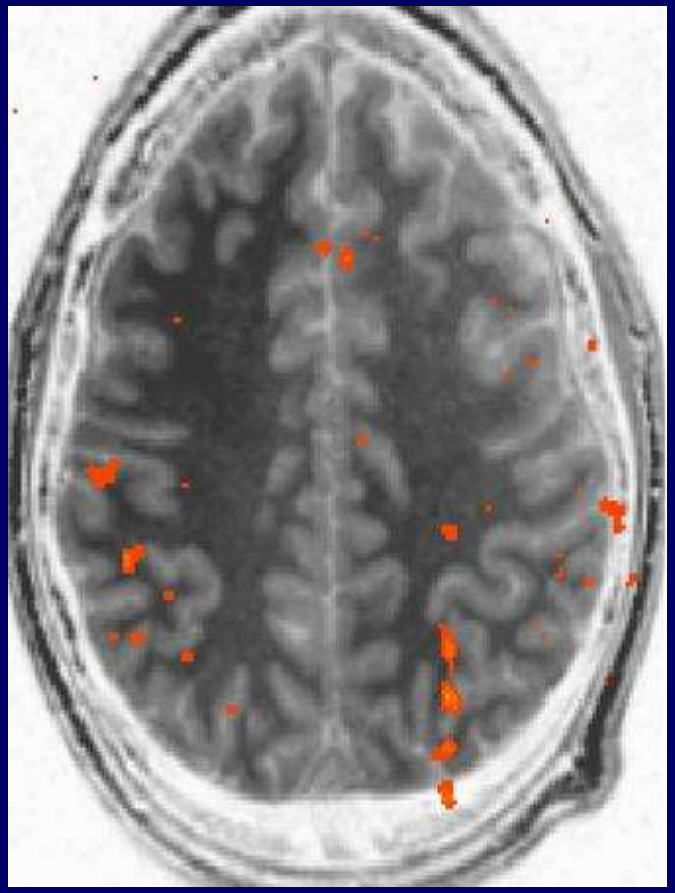
Cognitive Weaknesses

- Complex Sensory
- Complex Motor
- Complex Memory
- Complex Language
- Concept-formation
- Face Recognition

fMRI Activation During a Spatial Working Memory Task (Courtesy John Sweeney)



Typical Group



Autism Group

Dual task performance deficit in autism;

(but matched performance in single task conditions)

Garcia-Villamisar & Della Sala, 2002 Cognitive Neuropsychiatry

Effect of dual task on memory span and tracking performance

	Digit recall			*Tracking performance*			*Mu score*
People with autism (n = 16)	*single*		*dual*	*single*		*dual*	
Mean	86.19	>	48.13	52.75	>	37.81	66.87
SD	7.55		16.77	10.47		8.22	10.74
Controls (n = 16)							
Mean	87.25	=	86.88	54.06	=	55.25	84.75
SD	4.81		7.58	14.61		7.39	11.52

Digit recall is expressed as a percentage of correct sequences.

Fundamental Impairments in Thinking

Have facts and details but:

- Slow processors in a fast world- impaired rapid, nonconscious automatic processes
- Don’t understand what facts mean about themselves, and have poor sense of self.
- Don’t understand what facts mean about function in the world.
- Their minds do not form an integrated schema of what they mean, and they do not learn from experience.

Cognitive Enhancement Therapy (CET) for Adults With ASD, Schizophrenia, Public School Children

- Cognitive rehabilitation program
- Active ingredients: improved processing speed, acquisition of perspective taking
- Targets core deficits
- Outcome is improved adaptive behavior across life roles
- Imaging paradigms capture circuitry changes

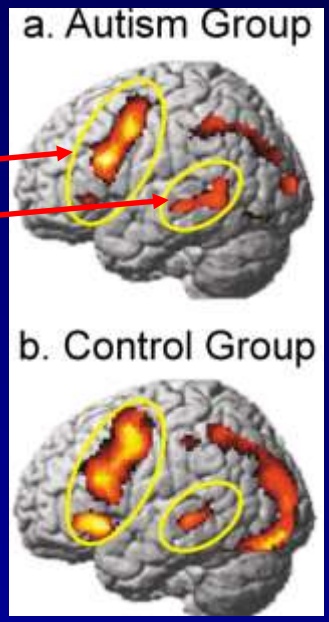
Next Steps in This Intervention Development

- Define subgroups with specific challenges that interfere with response to treatment
- Target these specific individual challenges
- Combine with CET
- Explore direct brain stimulation in combination with CET or other clinical intervention

Understanding the Neural Basis of Behavior in ASD

- Altered pattern of cortical activation
- Altered cortical-cortical connectivity
- Altered cortical-subcortical connectivity

Evidence for atypical "processing style" in autism driven by reduced frontal-posterior connectivity



- Increased reliance in language on word level processing and decreased reliance on integrative processing, manifested as
  - Decreased frontal (Broca's) and increased posterior (Wernicke's) activation (Just et al., 2004)
- Increased visual coding and decreased verbal coding of verbal symbols
  - Manifested as less frontal and more occipito-parietal activation in verbal working memory tasks (e.g., Koshino et al., 2005)
- Increased reliance on visual imagery in language comprehension
  - Manifested as increased activation in imagery-related parietal areas (Kana et al., 2006)
- Increased visual and decreased social processing of faces
  - Manifested as less frontal and right superior temporal

Review

Autism as a neural systems disorder: A theory of frontal-posterior underconnectivity

Marcel Adam Just[a,*], Timothy A. Keller[a], Vicente L. Malave[a], Rajesh K. Kana[b], Sashank Varma[c]

Neuroscience and Biobehavioral Reviews 36 (2012) 1292–1313

A B S T R A C T

The underconnectivity theory of autism attributes the disorder to lower anatomical and functional systems connectivity between frontal and more posterior cortical processing. Here we review evidence for the theory and present a computational model of an executive functioning task (Tower of London) implementing the assumptions of underconnectivity. We make two modifications to a previous computational account of performance and brain activity in typical individuals in the Tower of London task (Newman et al., 2003): (1) the communication bandwidth between frontal and parietal areas was decreased and (2) the posterior centers were endowed with more executive capability (i.e., more autonomy, an adaptation is proposed to arise in response to the lowered frontal-posterior bandwidth). The autism model succeeds in matching the lower frontal-posterior functional connectivity (lower synchronization of activation) seen in fMRI data, as well as providing insight into behavioral response time results. The theory provides a unified account of how a neural dysfunction can produce a neural systems disorder and a psychological disorder with the widespread and diverse symptoms of autism.

Lower Functional Connectivity in Many Domains

- Reduced frontal-parietal functional connectivity in autism occurs in a number of higher cognitive functions, such as
  - Sentence comprehension (Just et al., 2004)
  - problem solving (Just et al., 2007)
  - language comprehension (Kana et al., 2006)
  - response inhibition (Kana et al., 2007)
  - working memory (Koshino et al., 2005)
  - Theory of Mind (Mason et al., 2008; Kana et al., 2015)

- Reduced functional connectivity in autism between frontal and posterior areas even during resting-state (Cherkassky et al., 2006)

For complete list, go to Marcel Just's website at Carnegie Mellon U.

frontiers in
SYSTEMS NEUROSCIENCE

REVIEW ARTICLE
published: 22 February 2011
doi: 10.3389/fnsys.2011.00010

Inter-regional brain communication and its disturbance in autism

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In this review article, we summarize recent progress toward understanding disturbances in functional and anatomical brain connectivity in autism. Autism is a neurodevelopmental disorder affecting language, social interaction, and repetitive behaviors. Recent studies have suggested that limitations of frontal–posterior brain connectivity in autism underlie the varied set of deficits associated with this disorder. Specifically, the underconnectivity theory of autism postulates that individuals with autism have a reduced communication bandwidth between frontal and posterior cortical areas, which constrains the psychological processes that rely on the integrated functioning of frontal and posterior brain networks. This review summarizes the recent findings of reduced frontal–posterior functional connectivity (synchronization) in autism in a wide variety of high-level tasks, focusing on data from functional magnetic resonance imaging studies. It also summarizes the findings of disordered anatomical connectivity in autism, as measured by a variety of techniques, including distribution of white matter volumes and diffusion tensor imaging. We conclude with a discussion of the implications of these findings for autism and future directions for this line of research.

Altered Cortical-Subcortical Connectivity

Aberrant Striatal Functional Connectivity in Children with Autism

Biol Psychiatry. 2011 May 1; 69(9): 847–856. doi:10.1016/j.biopsych.2010.10.029.

Adriana Di Martino, MD[1], **Clare Kelly, PhD**[1], **Rebecca Grzadzinski, BA**[1], **Xi-Nian Zuo, PhD**[1], **Maarten Mennes, PhD**[1], **Maria Angeles Mairena, MA**[2], **Catherine Lord, PhD**[3], **F. Xavier Castellanos, MD**[1,4], and **Michael P Milham, MD PhD**[1,4]

Abstract

Background—Models of Autism Spectrum Disorders (ASD) as neural dysconnection syndromes have been predominantly supported by examinations of abnormalities in cortico-cortical networks in adults with autism. A broader body of research implicates subcortical structures, particularly the striatum, in the physiopathology of autism. Resting state fMRI has revealed detailed maps of striatal circuitry in healthy and psychiatric populations, and vividly captured maturational changes in striatal circuitry during typical development.

Results—Children with ASD mostly exhibited prominent patterns of ectopic striatal functional connectivity (i.e., functional connectivity present in ASD but not in TDC), with increased functional connectivity between nearly all striatal subregions and heteromodal associative and limbic cortex previously implicated in the physiopathology of ASD (e.g., insular and right superior temporal gyrus). Additionally, we found striatal functional hyperconnectivity with the pons, thus expanding the scope of functional alterations implicated in ASD. Secondary analyses revealed ASD-related hyperconnectivity between the pons and insular cortex.

Conclusions—Examination of functional connectivity of striatal networks in children with ASD revealed abnormalities in circuits involving early developing areas such as the brainstem and insula, with a pattern of increased functional connectivity in ectopic circuits that likely reflects developmental derangement rather than immaturity of functional circuits.

Decomposing Deficits Into Component Systems

- Help account for individual variability- the same behavior may have different bases in different individuals and in the same individual in different contexts

Underconnectivity between voice-selective cortex and reward circuitry in children with autism

Daniel A. Abrams[a,1], Charles J. Lynch[a], Katherine M. Cheng[a], Jennifer Phillips[a], Kaustubh Supekar[a], Srikanth Ryali[a], Lucina Q. Uddin[a], and Vinod Menon[a,b,c,d,1]

Published online before print June 17, 2013, doi: 10.1073/pnas.1302982110
PNAS June 17, 2013

Individuals with autism spectrum disorders (ASDs) often show insensitivity to the human voice, a deficit that is thought to play a key role in communication deficits in this population. The social motivation theory of ASD predicts that impaired function of reward and emotional systems impedes children with ASD from actively engaging with speech. Here we explore this theory by investigating distributed brain systems underlying human voice perception in children with ASD. Using resting-state functional MRI data acquired from 20 children with ASD and 19 age- and intelligence quotient-matched typically developing children, we examined intrinsic functional connectivity of voice-selective bilateral posterior superior temporal sulcus (pSTS). Children with ASD showed a striking pattern of underconnectivity between left-hemisphere pSTS and distributed nodes of the dopaminergic reward pathway, including bilateral ventral tegmental areas and nucleus accumbens, left-hemisphere insula, orbitofrontal cortex, and ventromedial prefrontal cortex. Children with ASD also showed underconnectivity between right-hemisphere pSTS, a region known for processing speech prosody, and the orbitofrontal cortex and amygdala, brain regions critical for emotion-related associative learning. The degree of underconnectivity between voice-selective cortex and reward pathways predicted symptom severity for communication deficits in children with ASD. Our results suggest that weak connectivity of voice-selective cortex and brain structures involved in reward and emotion may impair the ability of children with ASD to experience speech as a pleasurable stimulus, thereby impacting language and social skill development in this population. Our study provides support for the social motivation theory of ASD.

Resting-state functional connectivity predicts longitudinal change in autistic traits and adaptive functioning in autism

Mark Plitt[a,1], Kelly Anne Barnes[a], Gregory L. Wallace[a,b], Lauren Kenworthy[a,c], and Alex Martin[a,1]

PNAS | Published online November 16, 2015 | E6699–E6706

(mean follow-up latency = 2 y, 10 mo). We found that connectivity involving the so-called salience network (SN), default-mode network (DMN), and frontoparietal task control network (FPTCN) was highly predictive of future autistic traits and the change in autistic traits and adaptive behavior over the same time period. Furthermore, functional connectivity involving the SN, which is predominantly composed of the anterior insula and the dorsal anterior cingulate, predicted reliable improvement in adaptive behaviors with 100% sensitivity and 70.59% precision. From rs-fcMRI data, our study successfully predicted heterogeneity in outcomes for individuals with ASD that was unaccounted for by simple behavioral metrics and provides unique evidence for networks underlying long-term symptom abatement.

Direct Brain Stimulation

- tDCS
- rTMS

Synchronizing theta oscillations with direct-current stimulation strengthens adaptive control in the human brain

Robert M. G. Reinhart, Julia Zhu, Sohee Park[1], and Geoffrey F. Woodman[1]

Department of Psychology, Center for Integrative and Cognitive Neuroscience, Vanderbilt Vision Research Center, Vanderbilt University, Nashville, TN 37240

9448–9453 | PNAS | July 28, 2015 | vol. 112 | no. 30

Executive control and flexible adjustment of behavior following errors are essential to adaptive functioning. Loss of adaptive control may be a biomarker of a wide range of neuropsychiatric disorders, particularly in the schizophrenia spectrum. Here, we provide support for the view that oscillatory activity in the frontal cortex underlies adaptive adjustments in cognitive processing following errors. Compared with healthy subjects, patients with schizophrenia exhibited low frequency oscillations with abnormal temporal structure and an absence of synchrony over medial-frontal and lateral-prefrontal cortex following errors. To demonstrate that these abnormal oscillations were the origin of the impaired adaptive control in patients with schizophrenia, we applied noninvasive dc electrical stimulation over the medial-frontal cortex. This noninvasive stimulation descrambled the phase of the low-frequency neural oscillations that synchronize activity across cortical regions. Following stimulation, the behavioral index of adaptive control was improved such that patients were indistinguishable from healthy control subjects. These results provide unique causal evidence for theories of executive control and cortical dysconnectivity in schizophrenia.

REVIEW ARTICLE

Transcranial Magnetic Stimulation in Autism Spectrum Disorder: Challenges, Promise, and Roadmap for Future Research

Lindsay M. Oberman, Peter G. Enticott, Manuel F. Casanova, Alexander Rotenberg, Alvaro Pascual-Leone, James T. McCracken, and the TMS in ASD Consensus Group†

Autism Spectrum Disorder (ASD) is a behaviorally defined complex neurodevelopmental syndrome characterized by impairments in social communication, by the presence of restricted and repetitive behaviors, interests and activities, and by abnormalities in sensory reactivity. Transcranial magnetic stimulation (TMS) is a promising, emerging tool for the study and potential treatment of ASD. Recent studies suggest that TMS measures provide rapid and noninvasive pathophysiological ASD biomarkers. Furthermore, repetitive TMS (rTMS) may represent a novel treatment strategy for reducing some of the core and associated ASD symptoms. However, the available literature on the TMS use in ASD is preliminary, composed of studies with methodological limitations. Thus, off-label clinical rTMS use for therapeutic interventions in ASD without an investigational device exemption and outside of an IRB approved research trial is premature pending further, adequately powered and controlled trials. Leaders in this field have gathered annually for a two-day conference (prior to the 2014 and 2015 International Meeting for Autism Research, IMFAR) to share recent progress, promote collaboration across laboratories, and establish consensus on protocols. Here we review the literature in the use of TMS in ASD in the context of the unique challenges required for the study and exploration of treatment strategies in this population. We also suggest future directions for this field of investigations. While its true potential in ASD has yet to be delineated, TMS represents an innovative research tool and a novel, possibly transformative approach to the treatment of neurodevelopmental disorders. ***Autism Res*** *2015, 00: 000–000.* © 2015 International Society for Autism Research, Wiley Periodicals, Inc.

An integrated framework for targeting functional networks via transcranial magnetic stimulation

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NeuroImage 127 (2016) 86–96

A B S T R A C T

Transcranial magnetic stimulation (TMS) is a powerful investigational tool for in vivo manipulation of regional or network activity, with a growing number of potential clinical applications. Unfortunately, the vast majority of targeting strategies remain limited by their reliance on non-realistic brain models and assumptions that anatomo-functional relationships are 1:1. Here, we present an integrated framework that combines anatomically realistic finite element models of the human head with resting functional MRI to predict functional networks targeted via TMS at a given coil location and orientation. Using data from the Human Connectome Project, we provide an example implementation focused on dorsolateral prefrontal cortex (DLPFC). Three distinct DLPFC stimulation zones were identified, differing with respect to the network to be affected (default, frontoparietal) and sensitivity to coil orientation. Network profiles generated for DLPFC targets previously published for treating depression revealed substantial variability across studies, highlighting a potentially critical technical issue.

SUMMARY

- Clinical syndrome marked by much phenotypic variability understandable based on genetics & on variability inherent in humans
- 300-1,000 unidentified common variants at play
- 71 rare variants implicate synaptic function and transcription/chromatin remodeling
- Genetic background plays strong role in ASD risk gene expression
- Selective impact on higher order abilities across domains, and poor adaptive function
- Equally broad cortical systems underconnectivity
- Cortical-cortical and cortical-subcortical connections

SUMMARY

- Cognitive and neural profiles are consistent with disturbances in neuronal organizational events etc
- Brain in ASD is plastic across the age span
- Effective behavioral and cognitive rehabilitation interventions exist but not disseminated
- These interventions change neural systems
- rTMS and tDCS likely to have significant role in combination with cognitive rehabilitation methods
- Biologically based pharmacological strategies-WIPs