“Information Processing & Brain Connectivity in ASD”

“12th Annual Autism Conference
Innovative Advancements in Autism Spectrum Disorders”

Center for Autism and Related Disorders (CARD)
At Kennedy Krieger Institute
October 28, 2012

Nancy Minshew, MD
Director, Center for Autism Research
Professor Psychiatry & Neurology
University of Pittsburgh
Part 1. Research Advances in ASD

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All of the advances I will describe were only possible because of the individuals and their families who participated in our research studies, again and again and again and again. We all need to thank the few for the benefits that will come to the many.
Become One of the Few Who Participate

To make the future better for all.
Where Are We Coming From

Autistic Disorder: DSM IV
  3 Core Symptoms
  Associated symptoms: sensory, motor
  Co-morbid Conditions: intellectual disability, ADHD, seizures, mood problems, long list of behavior issues (Pg. 71-72 TR version)

Not a biologically or clinically valid conceptualization and no longer functional. Do we wonder why families & clinicians are confused?
DSM-5 Coming 2014
Studies Comparing DSM-IV & DSM 5 Criteria for ASD

- Two studies show that diagnosis is unchanged by changes in criteria as long as history and observation are adequate.
- Where the new “social communication disorder” category will end up is unknown e.g. with developmental language disorders vs ASD.
Brief Report: Comparability of DSM-IV and DSM-5 ASD Research Samples

C. A. Mazefsky · J. C. McPartland · H. Z. Gastgeb · N. J. Minshew
Abstract  Diagnostic and Statistical Manual (DSM-5) criteria for ASD have been criticized for being too restrictive, especially for more cognitively-able individuals. It is unclear, however, if high-functioning individuals deemed eligible for research via standardized diagnostic assessments would meet DSM-5 criteria. This study investigated the impact of DSM-5 on the diagnostic status of 498 high-functioning participants with ASD research diagnoses. The percent of participants satisfying all DSM-5-requirements varied significantly with reliance on data from the Autism Diagnostic Observation Schedule (ADOS; 33 %) versus Autism Diagnostic Interview-Revised (ADI-R; 83 %), highlighting the impact of diagnostic methodology on ability to document DSM-5 symptoms. Utilizing combined ADOS/ADI-R data, 93 % of participants met DSM-5 criteria, which suggests likely continuity between DSM-IV and DSM-5 research samples characterized with these instruments in combination.
Application of DSM-5 Criteria for Autism Spectrum Disorder to Three Samples of Children With DSM-IV Diagnoses of Pervasive Developmental Disorders
Objective: Substantial revisions to the DSM-IV criteria for autism spectrum disorders (ASDs) have been proposed in efforts to increase diagnostic sensitivity and specificity. This study evaluated the proposed DSM-5 criteria for the single diagnostic category of autism spectrum disorder in children with DSM-IV diagnoses of pervasive developmental disorders (PDDs) and non-PDD diagnoses.

Method: Three data sets included 4,453 children with DSM-IV clinical PDD diagnoses and 690 with non-PDD diagnoses (e.g., language disorder). Items from a parent report measure of ASD symptoms (Autism Diagnostic Interview–Revised) and clinical observation instrument (Autism Diagnostic Observation Schedule) were matched to DSM-5 criteria and used to evaluate the sensitivity and specificity of the proposed DSM-5 criteria and current DSM-IV criteria when compared with clinical diagnoses.

Results: Based on just parent data, the proposed DSM-5 criteria identified 91% of children with clinical DSM-IV PDD diagnoses. Sensitivity remained high in specific subgroups, including girls and children under 4. The specificity of DSM-5 ASD was 0.53 overall, while the specificity of DSM-IV ranged from 0.24, for clinically diagnosed PDD not otherwise specified (PDD-NOS), to 0.53, for autistic disorder. When data were required from both parent and clinical observation, the specificity of the DSM-5 criteria increased to 0.63.

Conclusions: These results suggest that most children with DSM-IV PDD diagnoses would remain eligible for an ASD diagnosis under the proposed DSM-5 criteria. Compared with the DSM-IV criteria for Asperger's disorder and PDD-NOS, the DSM-5 ASD criteria have greater specificity, particularly when abnormalities are evident from both parents and clinical observation.

(Am J Psychiatry 2012; 169:1056–1064)
DSM-5 Coming 2014

Started 2005
World-wide work of many
A $20 Million investment by APA
On the Road to DSM-5

David J. Kupfer, M.D.
Professor of Psychiatry, University of Pittsburgh
Chair, DSM-5 Task Force

Psych/Epidemiology & Alcohol Research Training Seminar
March 23, 2012
Pittsburgh, PA
Revision Principles

- DSM is, above all, a manual to be used by clinicians, and changes made for DSM-5 must be implementable in routine specialty practices.

- Make revisions that will lead to better clinical diagnostic practice.

- Recommendations should be guided by research evidence.
Why do DSM-5’s Revisions Matter?

- Revisions are designed to produce more accurate and more valid diagnostic criteria and nosology
  - Earlier diagnosis
  - Earlier treatment
  - More accurate treatment
  - Prevention of later complications
Revision Principles

- Add dimensional concepts & measurements of distress, disability, and severity
- Add developmental dimension - life span view of disorders
- “Living document”
Initial List of Tasks and Activities

• Consider **severity** as a separate dimension

• Consider **disability/ impairment/ functioning** as a separate dimension

• Identify **broad/super-ordinate** categories of diagnosis
DSM-5 Work Groups- 18

- ADHD & Disruptive Behavior Disorders
- Anxiety, Obsessive-Compulsive Spectrum, Post-traumatic, and Dissociative Disorders
- Disorders in Childhood and Adolescence
- Eating Disorders Mood Disorders
- Neurocognitive Disorders
- Neurodevelopmental Disorders
DSM-5 Work Groups, Cont’d

- Personality and Personality Disorders
- Psychotic Disorders
- Sexual and Gender-Identity Disorders
- Sleep-Wake Disorders
- Somatic Distress Disorders
- Substance-Related Disorders
Cross-Cutting Study Groups

- Diagnostic Spectra Study Group
- Life Span Developmental Approach Study Group
- Gender and Cross-Cultural Study Group
- Psychiatric/General Medical Interface Study Group
- Impairment Assessment and Instruments Study Group
- Diagnostic Assessment Instruments Study Group
Country Representation of Approved Nominees

- United States, 123
- Europe, 22
  - Denmark, 1
  - France, 1
  - Germany, 3
  - Italy, 1
  - Netherlands, 6
  - Sweden, 1
  - Switzerland, 1
  - UK, 8
- South Africa, 1
- Latin America, 3
  - Brazil, 1
  - Mexico, 1
  - Puerto Rico, 1
- Western Pacific, 4
  - Australia, 2
  - China, 2
- Canada, 8

Race and Ethnicity of Approved Nominees

- White (non-Hispanic), 131
- Hispanic, 12
- African American, 7
- Native American, 1

Gender Representation of Approved Nominees

- Male, 112
- Female, 49
Proposed Major Changes to DSM-5
Revised DSM Chapter Structure

- Put disorders that share genes and dimensions next to each other
- Create alignment with NIMH Research Domain Criteria (RDoC) Project
- Alignment with ICD-11
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<th>L. Elimination Disorders</th>
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<td>M. Sleep-Wake Disorders</td>
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<tr>
<td>Other Psychotic Disorders</td>
<td>N. Sexual Dysfunctions</td>
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<td>C. Bipolar and Related Disorders</td>
<td>P. Gender Dysphoria</td>
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<td>D. Depressive Disorders</td>
<td>Q. Disruptive, Impulse</td>
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<td>R. Substance Use and</td>
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<td>Addictive Disorders</td>
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<td>G. Trauma and Stressor-Related</td>
<td>S. Neurocognitive</td>
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<td>H. Dissociative Disorders</td>
<td>T. Personality Disorders</td>
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<tr>
<td>J. Somatic Symptom Disorders</td>
<td>U. Paraphilias</td>
</tr>
<tr>
<td>K. Feeding and Eating Disorders</td>
<td>V. Other Disorders</td>
</tr>
</tbody>
</table>
Proposed Major Revisions to DSM-5:

♦ DSM-5 could benefit from offering explicit criteria for both categories and dimensions (not or)

♦ For any psychiatric disorder, a number of aspects could be conceptualized and assessed dimensionally

♦ Behavioral dimensions can capture co-occurring disorders & subthreshold symptoms

DSM-5 Field Trials
DSM-5 Field Trials

Field trials were designed to...

- examine whether proposed revisions to existing disorders and new disorders are reliable over time
- assess whether proposed revisions are useful to clinicians
- determine how proposed changes impact diagnosis as well as treatment planning
DSM-5 Field Trials

- **Clinical utility and feasibility**
  - Patient-completed questionnaires as to whether dimensional assessments seemed useful
  - Clinician-completed questionnaires as to whether dimensional assessments and diagnostic checklists were helpful in diagnosis, treatment planning
  - Standardized assessment of disability (WHO-DAS II) in lieu of GAF rating
  - RCP Field Trials specifically designed to assess performance of DSM-5 changes in small or solo offices
DSM-5 Field Trials

- Large, academic-medical settings
  - Examining proposed changes to DSM-5 in large, diverse samples
  - Includes 11 sites (7 adult, 4 pediatric)
  - Data collection ended in 2011

- Routine clinical practice settings
  - Do “real world” clinicians find DSM-5 diagnoses useful?
  - Psychiatrists plus psychologists, licensed clinical social workers, marriage and family counselors, and advanced-practice mental health nurses
  - Data collection ended in 2012
Clinicians found the DSM-5 diagnostic criteria “moderately to extremely useful” compared to DSM-IV.

Fig 1: Usefulness of DSM-5 diagnostic criteria, compared to DSM-IV, for the primary diagnosis of Mood, Trauma, SUD, and Other. For Dallas VA, Study Visit 1, N=236. The legend is as follows: 1 = Not at all, 2 = Slightly, 3 = Moderately, 4 = Very, 5 = Extremely.
Clinicians found it “moderately to extremely easy” to perform the patient evaluation with the diagnosis-specific dimensional measures.
Patients reported that the questionnaires described their symptoms “moderately to extremely well”.

**Fig 6: Usefulness of the questionnaires in describing symptoms the patients have been experiencing**

**Patient’s perspective - Dallas VA, Study Visit 1, N=236**

**LEGEND:**
1 = Not at all
2 = Slightly
3 = Moderately
4 = Very
5 = Extremely
Patients believed the questionnaires helped clinicians better understand their symptoms.

**Fig 7: Usefulness of the questionnaires in helping clinicians understand the patient's symptoms**

**Patient's perspective - Dallas VA, Study Visit 1, N=236**

- **LEGEND:**
  - 1 = Yes
  - 2 = No
  - 3 = Maybe
  - 4 = I don’t know

**Categories:**
- Mood
- Trauma
- SUD
- Other
Current Activities of DSM-5

- Analyze all field trial data and identify needed revisions
- Independent review of criteria by experts not involved in creation
- Review of all public comments
Future DSM-5 Developments

DSM-5 go electronic:
- **adding links** to key supporting documents/evidence/descriptions and
- **electronic communications** between patients and clinicians
Dimensional Approaches: Translational Research & Blending DSM-5 and RDoC

David J. Kupfer, M.D.
Professor of Psychiatry, University of Pittsburgh

WPIC Summer Series - 2012
Pittsburgh, PA
July 12, 2012
Two Ongoing Endeavors

- DSM-5
- RDoC- Research Domain Criteria
Strategic goal 1.4 of the NIMH Strategic Plan calls for the development, for research purposes, of new ways of classifying psychopathology based on dimensions of observable behavior and neurobiological measures.

The Research Domain Criteria project (RDoC) has been launched by NIMH to implement this strategy. RDoC defines dimensions that cut across disorders and consist of functions that can be studied across levels of expression from gene to neural circuits.

The intent is to translate rapid progress in basic neurobiological and behavioral research to an improved integrative understanding of psychopathology and the development of new and/or optimally matched treatments for mental disorders.
Once the mechanisms underlying heterogeneity in each domain or dimension are defined, the door is open to individualized treatment.
Important Caveats About RDoC

♦ Five constructs or dimensions have been articulated so far in an attempt to identify dimensions that cut across disorders.

♦ RDoC does not yet cover the symptoms represented by all current disorders.

♦ Emphasis is on neural circuits; it is the targeted unit of treatment.

♦ RDoC is a WIP - work in progress.
Two criteria for a Construct: Empirical support for (1) a functional dimension of behavior and (2) an implementing brain circuit.
# Negative Valence Systems Matrix Specifications

## Construct: Acute Threat ("Fear")

<table>
<thead>
<tr>
<th>Genes</th>
<th>Molecules</th>
<th>Cells</th>
<th>Circuits</th>
<th>Physiology</th>
<th>Behavior</th>
<th>Self-Reports</th>
<th>Paradigms</th>
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<td>BDNF, 5HT/5HTRs, CRF, FKBP5, GABAARs, Glutamate system, NMDARs, Opioid system, COMT, Cannabinoid system, Dopamine, DAT, Cam kinase, MAP kinase, PI-3 kinase, PKA, PKC, Acetylcholine, Norepinephrine, Stratum, Pkap, TRBC5</td>
<td>NMDAR, Glutamate, Dopamine, Serotonin, BDNF, GABA, Cortisol/Corticosterone, Endogenous cannabinoids, orexin, NPY, CRF family, FGF2, Oxytocin, Vasopressin, CCK, Neuropeptide S, Neurosteroids</td>
<td>Neurons, Glia, Pyramidal cells, GABAergic cells</td>
<td>Central Nucleus, BasAmyg, LatAmyg, vPAG, dPAG, v-hippocampus (post), d-hippocampus (ant), latPFC/insula, vmPFC (dl), dmPFC (pl), OFC, Hypothalamus, dorsal ACC, rostral/vent ACC, ICMe, Medial Amyg, PAG, RPVM, Pons, autonomic nervous system, insular cortex, LC</td>
<td>Fear Potentiating Startle, Context Startle, Skin Conductance, Heart Rate, EMG, BP, Eye Tracking, Response accuracy, facial EMG, Respiration, pupillometry</td>
<td>Freezing, Response time, Avoidance, Response inhibition, Open field, Social approach, Analgesia, approach (early development), Risk assessment, Facial expressions</td>
<td>Fear survey schedule, BAL, STAI, SUDS, Fear Questionnaire, Trait Fear Inventory, Eilam Ethogram, Structured Diagnostic and Assessment scales, Albany Panic &amp; Phobia</td>
<td>Fear conditioning, viewing aversive pictures or films, emotional imagery</td>
</tr>
</tbody>
</table>

## Construct: Potential Harm ("Anxiety")

<table>
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<tr>
<th>CRF</th>
<th>CRF family, cortisol</th>
<th>Pituitary cells</th>
<th>Bed nucleus of stria terminalis</th>
<th>Average cortisol levels, ACTH, potentiating startle</th>
<th>Contextual threat, darkness (in humans), light (in rodents)</th>
</tr>
</thead>
</table>
Other Dimensions Impacting Expression

- Developmental Aspects (orthogonal)
- Environmental Aspects (orthogonal)
- Gender – “Two Species”
- Psychiatric and Medical Comorbidity
1. Spontaneous Mutations: Increased rate of "de novo" copy number variations: submicroscopic deletions or duplications of DNA sequences. More common in simplex than multiplex families. Opened door to two genetic mechanisms: inherited gene mutations and spontaneous copy number mutations - instability in replication of DNA.

2. Potential reversal of Neurodevelopmental Disorders (in Fragile X, Rett & Angelman Syndromes) in adult mice.

From DNA to Behavior: A Complex Sequence of Mechanisms

- Abnormalities in Genetic Code for Brain Development
  - Abnormal Mechanisms of Brain Development
    - Structural and Functional Abnormalities of Brain
      - Cognitive & Neurological Abnormalities
        - Behavioral Syndrome
The Link Between New Treatments & Discovery of Genetic, Molecular & Circuitry Mechanisms

- Explain/predict variability in syndrome & in response to treatments.
- The closer a treatment is to the originating mechanism, the more specific it is to the manifestations and the more efficacious it is. With fewer undesired side effects.
An Example of an RDoC Dimension Highly Relevant to ASD and to Many
AMY-ACC-DLPFC are core regions of neural network of identification and regulation of emotion

Role in mood/affect regulation:

- **Amygdala** (AMY). Critical to sensing and assessing emotionally-salient stimuli.

- **Anterior cingulate cortex** (subgenual ACC; BA 25): integrates information about emotional salience (bottom-up) with cognitive control and motivational states (top-down).

- **Dorsolateral prefrontal cortex**: cognitive assessment of emotional salience (cortical top-down regulation)

*Phillips et al, Mol Psy, 2008*

**AMY**, amygdala; **ACC**, anterior cingulate cortex; **DLPFC**, dorsolateral prefrontal cortex
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Advances in Imaging Technology That Are Enhancing Discoveries

- Improved specification of alterations in brain circuitry/connections
- Capacity to link brain changes to early alterations in brain developmental processes
- Enables detection of change with treatment
- Forerunner of individualized medicine
Scientists have discovered that the brain is even more beautifully organized than they had imagined.

Neurons in the brain zip messages to one another along long white fibers called axons. Previously scientists traced axon pathways in dissected animal brains, but now they can see the structure of this amazing information superhighway in a living human organ. Using new software with a technique called “diffusion tensor MRI” that tracks water molecules as they move along the axons, Van Wedeen of Massachusetts General Hospital and colleagues found that the fibers are arranged in a surprisingly regular 3-D grid.

“Biology gives you a brain. Life turns it into a mind.” Jeffrey Eugenides

By Laura Helmuth
Neurons in the brain zip messages to one another along long white fibers called axons. Previously scientists traced axon pathways in dissected animal brains, but now they can see the structure of this amazing information superhighway in a living human organ. Using new software with a technique called “diffusion tensor MRI” that tracks water molecules as they move along the axons, Van Wedeen of Massachusetts General Hospital and colleagues found that the fibers are arranged in a surprisingly regular 3-D grid. For instance, the red axons in the image converge on the purple pathway at a 90-degree angle. Axons are interwoven like "the warp and weft of a fabric," the researchers say, with the pattern bent along the brain's convolutions. “It's really pretty, all the little loops and folds,” Wedeen says.
The technique Wedeen and colleagues use is called "diffusion spectrum MRI," a variation on an existing technique. By monitoring how water moves along axons and at what angle these brain fibers cross one another, the researchers found a surprisingly geometric pattern. The three-dimensional grid is visible in this detail from a rhesus monkey brain.
This image from a rhesus monkey shows the larger-scale structure of the grid of axons as they swoop and swirl through the convolutions of the primate's brain.
Images used from:
- Animal Brains, More Beautiful Than You Could Ever Imagine
  More than just eye candy, these images are teaching scientists new insights into how the brain is organized
  By Laura Helmuth
  Smithsonian magazine, July-August 2012

Schematic drawing of white matter tracts from 25 years ago

Contemporary image of a single participant’s white matter tracts
More than 1,000 genes identified in ASD
A window into heterogeneity and into altered mechanisms of brain development
Forerunner of individualized medicine
Gene expression “omics” are helping to define the function of the implicated genes
Complex is an under-statement for “omes” but then so is brain & its development
Infant DNA Tests Speed Diagnosis of Rare Diseases

By GINA KOLATA

From the day she was born, the girl had seizure after seizure. Doctors at Children’s Mercy Hospital in Kansas City, Mo., frantically tried to keep her alive. Weeks passed and every medication failed. Finally, her family decided to let their baby go, and the medical devices were withdrawn. She was 5 weeks old.

Her doctors suspected a genetic disorder, and as it happened the hospital had just begun a study of a new technique for quickly analyzing the DNA of newborns, zeroing in on mutations that can cause disease.

This new method, published on Wednesday in the magazine Science Translational Medicine, is a proof of concept — a demonstration in four babies that it is possible to quickly scan a baby’s entire DNA and pinpoint a disease-causing mutation in a couple of days instead of the more typical weeks or months. The study’s investigators said the test could be one of the first practical fruits of the revolution in sequencing an individual’s entire DNA.

For the baby with seizures, her doctors provided a sample of her blood. The analysis took only 50 hours and provided an answer. The baby had a mortal gene mutation so rare that it had been reported just once before.
ORIGINAL ARTICLE
Predicting the diagnosis of autism spectrum disorder using gene pathway analysis

E Skafidas¹, R Testa²,³, D Zantomio⁴, G Chana⁵, IP Everall⁵ and C Pantelis²,⁵
Autism spectrum disorder (ASD) depends on a clinical interview with no biomarkers to aid diagnosis. The current investigation interrogated single-nucleotide polymorphisms (SNPs) of individuals with ASD from the Autism Genetic Resource Exchange (AGRE) database. SNPs were mapped to Kyoto Encyclopedia of Genes and Genomes (KEGG)-derived pathways to identify affected cellular processes and develop a diagnostic test. This test was then applied to two independent samples from the Simons Foundation Autism Research Initiative (SFARI) and Wellcome Trust 1958 normal birth cohort (WTBC) for validation. Using AGRE SNP data from a Central European (CEU) cohort, we created a genetic diagnostic classifier consisting of 237 SNPs in 146 genes that correctly predicted ASD diagnosis in 85.6% of CEU cases. This classifier also predicted 84.3% of cases in an ethnically related Tuscan cohort; however, prediction was less accurate (56.4%) in a genetically dissimilar Han Chinese cohort (HAN). Eight SNPs in three genes (KCNMB4, GNAO1, GRM5) had the largest effect in the classifier with some acting as vulnerability SNPs, whereas others were protective. Prediction accuracy diminished as the number of SNPs analyzed in the model was decreased. Our diagnostic classifier correctly predicted ASD diagnosis with an accuracy of 71.7% in CEU individuals from the SFARI (ASD) and WTBC (controls) validation data sets. In conclusion, we have developed an accurate diagnostic test for a genetically homogeneous group to aid in early detection of ASD. While SNPs differ across ethnic groups, our pathway approach identified cellular processes common to ASD across ethnicities. Our results have wide implications for detection, intervention and prevention of ASD.
Common and rare genetic variants in the etiology of ASD: where are we heading?

Bernie Devlin
University of Pittsburgh SOM
Psychiatry & Human Genetics
Exciting times for genetics of Autism Spectrum Disorders

Adapted from Betancur (2011, Brain Res. 1380:42-77)
Can exciting times continue?
Prediction: rapid progress

• Technologies:
  – Array-based technologies for genotypes and Copy Number Variants
  – High Throughput Sequencing
• Designs & analytic methods
• Samples + Collaboration
• Funding!
Projection

Total Number of Autism Genes Identified

Year

[Graph showing the increase in the total number of autism genes identified from 1995 to 2015]
Copy Number Variations (CNVs)
The Awakening to Small DNA Alterations

Small (micro-) deletions or duplications of DNA distributed across chromosomes, inherited and spontaneous, occur constantly.
Functional impact of global rare copy number variation in autism spectrum disorders
The autism spectrum disorders (ASDs) are a group of conditions characterized by impairments in reciprocal social interaction and communication, and the presence of restricted and repetitive behaviours\(^1\). Individuals with an ASD vary greatly in cognitive development, which can range from above average to intellectual disability\(^2\). Although ASDs are known to be highly heritable (\(\sim 90\%\))\(^3\), the underlying genetic determinants are still largely unknown. Here we analysed the genome-wide characteristics of rare (<1% frequency) copy number variation in ASD using dense genotyping arrays. When comparing 996 ASD individuals of European ancestry to 1,287 matched controls, cases were found to carry a higher global burden of rare, genetic copy number variants (CNVs) (1.19 fold, \(P = 0.012\)), especially so for loci previously implicated in either ASD and/or intellectual disability (1.69 fold, \(P = 3.4 \times 10^{-4}\)). Among the CNVs there were numerous \textit{de novo} and inherited events, sometimes in combination in a given family, implicating many novel ASD genes such as \textit{SHANK2}, \textit{SYNGAP1}, \textit{DLGAP2} and the X-linked \textit{DDX53–PTCHD1} locus. We also discovered an enrichment of CNVs disrupting functional gene sets involved in cellular proliferation, projection and motility, and GTPase/Ras signalling. Our results reveal many new genetic and functional targets in ASD that may lead to final connected pathways.
**Figure 3 | A functional map of ASD.** Enrichment results were mapped as a network of gene sets (nodes) related by mutual overlap (edges), where the colour (red, blue or yellow) indicates the class of gene set. Node size is proportional to the total number of genes in each set and edge thickness represents the number of overlapping genes between sets. a, Gene sets enriched for deletions are shown (red) with enrichment significance (FDR q-value) represented as a node colour gradient. Groups of functionally related gene sets are circled and labelled (groups, filled green circles; subgroups, dashed line). b, An expanded enrichment map shows the relationship between gene sets enriched in deletions (a) and sets of known ASD/intellectual disability genes. Node colour hue represents the class of gene set (that is, enriched in deletions, red; known disease genes (ASD and/or intellectual disability (ID) genes), blue; enriched only in disease genes, yellow). Edge colour represents the overlap between gene sets enriched in deletions (green), from disease genes to enriched sets (blue), and between sets enriched in deletions and in disease genes or between disease gene-sets only (orange). The major functional groups are highlighted by filled circles (enriched in deletions, green; enriched in ASD/intellectual disability, blue).
Identifying fragmentation of chromosomes during replication and recombination - a new cause of microscopic duplications and deletions
Sequencing Chromosomal Abnormalities Reveals Neurodevelopmental Loci that Confer Risk across Diagnostic Boundaries

Michael E. Talkowski,1,5,7 Jill A. Rosenfeld,8 Ian Blumenthal,1 Vamsee Pillalamarri,1 Colby Chiang,1 Adrian Heilbut,1 Carl Ernst,1 Carrie Hanscom,1 Elizabeth Rossin,1,2,7 Amelia M. Lindgren,9 Shahrin Pereira,9 Douglas Ruderfer,1,7 Andrew Kirby,1,2,7 Stephan Ripke,1,2,7 David J. Harris,10 Ji-Hyun Lee,1 Kyungsoo Ha,12 Hyung-Goo Kim,13 Benjamin D. Solomon,14 Andrea L. Gropman,15,16 Diane Lucente,1 Katherine Sims,1 Toshiro K. Ohsumi,3 Mark L. Borowsky,3 Stephanie Loranger,17 Bradley Quade,4 Kasper Lage,2,7,18,19,20 Judith Miles,21 Bai-Lin Wu,4,11,22 Yiping Shen,1,4,11,23 Benjamin Neale,1,2,7 Lisa G. Shaffer,8 Mark J. Daly,1,2,7,17 Cynthia C. Morton,7,4,9 and James F. Gusella1,6,7,17,*

Cell, 149, 525-537, April 27, 2012
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<td>DGAP155</td>
<td>ASD 11p11.2</td>
<td>EHMT1</td>
<td>3.3 × 10⁻⁷</td>
<td>histone methyltransferase</td>
<td></td>
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<tr>
<td>2</td>
<td>DGAP142</td>
<td>ASD 2q23.1</td>
<td>MBD5</td>
<td>3.1 × 10⁻⁵</td>
<td>methylation binding</td>
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<tr>
<td>2</td>
<td>DGAP211</td>
<td>ASD 2q33.1</td>
<td>SATB2</td>
<td>1.1 × 10⁻³</td>
<td>transcriptional regulation and chromatin remodeling</td>
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<tr>
<td>3</td>
<td>DGAP148</td>
<td>NDD 1q11.2</td>
<td>KIRREL3</td>
<td>1.6 × 10⁻⁴</td>
<td>cell adhesion</td>
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<tr>
<td>3</td>
<td>DGAP154</td>
<td>NDD 1q11.2</td>
<td>SMG6</td>
<td>5.9 × 10⁻⁴</td>
<td>nonsense-mediated decay</td>
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<td>3</td>
<td>NDR26867</td>
<td>ASD 14q11.2</td>
<td>CHD8</td>
<td>2.4 × 10⁻²</td>
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<tr>
<td>3</td>
<td>DGAP125</td>
<td>NDD 1q13.1</td>
<td>ZNF507</td>
<td>8.0 × 10⁻²</td>
<td>zinc finger</td>
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<tr>
<td>3</td>
<td>DGAP132c</td>
<td>ASD 2q21.2</td>
<td>PON3</td>
<td>1.5 × 10⁻¹</td>
<td>lactonase</td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td>AC02-0053</td>
<td>ASD 1q21.3</td>
<td>GNA14</td>
<td>2.7 × 10⁻¹</td>
<td>g-protein signaling</td>
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<tr>
<td>3</td>
<td>DGAP131</td>
<td>NDD 3p33</td>
<td>ZNHIT6</td>
<td>2.7 × 10⁻¹</td>
<td>zinc finger protein</td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td>DGAP193</td>
<td>ASD 2p22.3</td>
<td>SPAST</td>
<td>2.7 × 10⁻¹</td>
<td>membrane trafficking</td>
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<tr>
<td>3 and 4</td>
<td>DGAP143</td>
<td>NDD 6q21.2</td>
<td>PDE10A</td>
<td>5.2 × 10⁻³</td>
<td>phosphodiesterase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 and 4</td>
<td>DGAP171</td>
<td>NDD 1p13.2</td>
<td>C18orf1</td>
<td>3.2 × 10⁻²</td>
<td>unknown</td>
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</tr>
<tr>
<td>3 and 4</td>
<td>DGAP180c</td>
<td>NDD 2q32</td>
<td>ZNF804A</td>
<td>4.7 × 10⁻²</td>
<td>zinc finger protein</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The following abbreviations are used: Cat, disruption category; Dx, diagnosis; ASD, autism spectrum disorder; NDD, other neurodevelopmental disorders; ChrA and ChrB = sequenced chromosomal sub-band containing the BCA. For the entire data set used to generate this table, see also Tables S1, S2, and S3.

*BCA-disrupted genes individually implicated by case-control CNV burden at uncorrected p < 0.10 or by a minimum of 3 CNVs in cases with none in controls are provided. See Table S1 and Supplemental Information for all subjects and phenotypes and Table S2 for CNV counts on all subjects.

Fisher's exact test p value from comparison of CNV burden between NDD cases and controls.

BCA inherited from similarly affected parents.
Figure 5. Network Analysis of Genes Implicated in Autism or Neurodevelopment in This Study

A large network of genes disrupted by BCAs in this study are connected by first-, second-, or higher-order interactions. No networks were significantly enriched for genes disrupted by BCAs after correction for multiple comparisons, though a number of loci have limited functional annotation available or remain of unknown function. See also Figure S4.
Figure 2. Genes Disrupted by Chromosomal Abnormalities Confer Risk across Diagnostic Groups

All genes disrupted by a BCA and analyzed in the CNV analyses are shown. Although all genes are implicated in ASD or NDD by BCA disruption in this study, some loci also represented single-gene contributors to previously recognized genomic disorder (GD) regions (three microdeletion syndromes, two terminal deletion syndromes, and one duplication syndrome). There were also genes discovered in ASD or NDD in this study that had been previously linked to adolescent- or adult-onset neuropsychiatric disorders (NPD) by common variation association studies. The asterisk (*) denotes a gene not previously implicated in ASD or NDD (category 3). See also Table 1 and Table S2 for CNV and GWAS support for each locus.
This study compared the behavioral expression or phenotype associated with the fragile-x gene loss in different strains of mice.

The phenotype or behavioral expression varied widely from strain to strain.
Modifying Behavioral Phenotypes in Fmr1KO Mice: Genetic Background Differences Reveal Autistic-Like Responses

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.
Genetic Studies Provide Insight into Brain Development Mechanisms in ASD

Synapse formation/maintenance
Axonal outgrowth/pathfinding
Development of cortical organization
Some early and recent identified genes converge on synapse

- **TSC1/TSC2** (Gillberg et al., 1994, Fombonne et al. 1997)
- **PTEN** (Goffin et al., 2001, Butler et al. 2005)
- **FMR1** (Kielinen et al., 2004, Clifford et al. 2007)
- **NLGN4/NLGN3** (Jamain et al 2003; Thomas et al 1999)
- **CNTN4** (Fernandez et al 2004 and 2008; Roohi et al 2009, Wang et al 2009)
- **SHANK3/SHANK2** (Durand et al 2007; Berkel et al 2010, Pinto 2010)
- **NRXN1** (Szatmari et al. 2007; Kim et al 2008)

Cartoon of
Excitatory synapse

State, Neuron 2010
Axonal Model

- 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.
Axonal Model

• Plausible substrate for functional manifestations
• Maybe a more plausible substrate for anatomic findings in ASD
  – white matter compartment size and diffusion differences in ASD
  – higher proportion of small, highly branching myelinated axons directly under anterior cingulate gyrus
<table>
<thead>
<tr>
<th>Gene</th>
<th>Study Type</th>
<th>Reference</th>
</tr>
</thead>
</table>
ASD

Schizophrenia

Non-Syndromic Intellectual Disability

CNTNAP2
Neurexin1
SHANK2
NRG3
22q11

All the rest

Modified from Kooy 2010
Select features of genetic architecture

- 100s
- # of genes
- Effect sizes
- Mode of action

Dominant, Recessive, Additive

Genetic variation accounts for large fraction of risk, but ...
Conclusions

• Understand much about the genetic architecture of autism; will understand much more very soon.
• More genes and more potential drug targets
• Momentum for discovery is huge and due to
  – Pooling data
  – Funding
• 5 years from now gene discovery in ASD will become passé: translation will be the key for ASD in the near future!
Genes + Environment

- Antiquated notion: G or E, nature or nurture
- e.g., human height: 90% heritable
- Increased immensely over last century
- It’s G + E!
But What Are These Genes Doing?

And how do we figure this out?
The “omics” are elucidating mechanisms of action of genes implicated in autism, and creating order out of what looked like clutter and chaos. This helps identify shared mechanisms and distinguish between primary and remote effects of genes.
Conclusions

• Understand much about the genetic architecture of autism; will understand much more very soon.
• More genes and more potential drug targets
• Momentum for discovery is huge and due to
  – Pooling data
  – Funding
• 5 years from now gene discovery in ASD will become passé: translation will be the key for ASD in the near future!
Prepare for Warp Jumps

To Be Followed By…
Translational Medicine - New Treatments

Coming Soon
Individualized or Designer Medicine
“Information Processing & Brain Connectivity in ASD”

“12th Annual Autism Conference
Innovative Advancements in Autism Spectrum Disorders ”

Center for Autism and Related Disorders (CARD)
At Kennedy Krieger Institute
October 28, 2012

Nancy Minshew, MD
Director, Center for Autism Research
Professor Psychiatry & Neurology
University of Pittsburgh
How the Mind & Brain in Autism Thinks & Feels
Why is that important to you?

It is the cornerstone of treatment.
It is the footprint of the cause.
Autism is the result of alterations in how the brain processes information that alters how the mind sees the world.
What Does ‘cause’ Mean?

Etiology
Pathophysiology
Functional analysis of behavior
Disconnection between behavior & brain
Why Is Cause Important?

Defining Mechanisms
Leads to more efficacious treatments
That specifically target mechanisms
Leads to nindividualization of treatment
1. Spontaneous Mutations: Increased rate of "de novo" copy number variations: submicroscopic deletions or duplications of DNA sequences. More common in simplex than multiplex families. Opened door to two genetic mechanisms: inherited gene mutations and spontaneous copy number mutations - instability in replication of DNA.

2. Potential reversal of Neurodevelopmental Disorders (in Fragile X, Rett & Angelman Syndromes)

Abnormalities in Genetic Code for Brain Development

Abnormal Mechanisms of Brain Development

Structural and Functional Abnormalities of Brain

Cognitive & Neurological Abnormalities

Behavioral Syndrome

From DNA to Behavior: A Complex Sequence of Mechanisms
Where Are We Coming From

Autistic Disorder: DSM IV

3 Core Symptoms
Associated symptoms: sensory, motor
Co-morbid Conditions: intellectual disability, ADHD, seizures, mood problems, long list of behavior issues (Pg. 71-72 TR version)

Not a biologically or clinically valid conceptualization and no longer functional. Do we wonder why families & clinicians are confused?
Q: Is the constellation inherent in a cohesive syndrome or is it an artifact of diagnostic practice?

What causes these signs and symptoms to co-occur?
Brain disturbances produce a constellation of neurologic signs & symptoms: symptoms/signs equally important.

The constellation & mode of presentation reflect the underlying brain mechanism and its location.

Impairments present when the time in brain development comes for that skill to appear.
Child Neurologists Differential Diagnosis For De Novo Neurodevelopmental Disorders

- Organogenesis
- Neuronal proliferation*
- Glial proliferation, migration
- Neuronal migration** *CNTNP2*
- Neuronal organization***
- Myelination

*Implicated in ASD
Abnormalities in complex behavior, cognition, language, intellectual disability, seizures

- No primary sensory deficit
- No long tract signs
- No focal findings (dyslexia, visuospatial deficits)
- De novo developmental disorder

Association cortices

Distributed neural network disorder

Disorder of neuronal organization
Neurologists characterize all impaired AND all intact abilities to identify common characteristics (information processing) that reflect their shared dependence on a common underlying cause (altered brain connectivity).

This approach was particularly beneficial in autism because both were part of the abnormal profile that defines behavior.
### Discriminant Function Analysis¹:
**Domains With Deficits**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests Passing Tolerance</th>
<th>Percent Correct</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor</td>
<td>Grooved Pegboard; Trail Making A</td>
<td>75.80</td>
<td>0.52</td>
</tr>
<tr>
<td>Complex Language</td>
<td>K-TEA Reading Comprehension; Verbal Absurdities; Token Test</td>
<td>72.70</td>
<td>0.45</td>
</tr>
<tr>
<td>Complex Memory</td>
<td>Nonverbal Selective Reminding-Consistent Long Term Retrieval; WMS-R Story Recall-Delayed Recall; Rey-Osterrieth Figure-Delayed Recall</td>
<td>77.30</td>
<td>0.55</td>
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<tr>
<td>Reasoning</td>
<td>20 Questions; Picture Absurdities; Trail Making B</td>
<td>75.8</td>
<td>0.52</td>
</tr>
</tbody>
</table>

¹Based on 33 individually matched pairs of autistic & control subjects (Neuropsychologic Functioning in Autism: Profile of a Complex Information Processing Disorder, *JINS*, 3:303-316, 1997)
## Discriminant Function Analysis: Domains Without Deficits

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests Passing Tolerance</th>
<th>Percent Correct</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Letter Cancellation; Number Cancellation</td>
<td>66.70</td>
<td>0.33</td>
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<tr>
<td>Sensory Perception</td>
<td>Finger Tip Writing; Luria-Nebraska Sharp/Dull Tactile Scale item</td>
<td>64.40</td>
<td>0.29</td>
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<tr>
<td>Simple Language</td>
<td>K-TEA Reading; K-TEA Spelling WRMT-R Attack; Controlled Oral Word Association</td>
<td>71.20</td>
<td>0.42</td>
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<tr>
<td>Simple Memory</td>
<td>CVLT Trial 1</td>
<td>65.20</td>
<td>0.30</td>
</tr>
<tr>
<td>Visuo-Spatial</td>
<td>WAIS-R Block Design</td>
<td>56.10</td>
<td>0.12</td>
</tr>
</tbody>
</table>

1. Kappa below .40 indicates poor agreement beyond chance
2. Significant Kappa reflects superior performance by autistic subjects
3. Based on 33 individually age, IQ, gender matched pairs of subjects
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)

Healthy Group  Autism Group
What Are the Shared Underlying Features: Information Processing, Brain Connectivity

- Simpler abilities are intact or enhanced
- Information processing capacity is limited & integrative processing (& higher order cognitive abilities) is disproportionately impaired
- Inference: higher order brain circuitry is under developed- they are reliant on more elementary circuitry particularly visual circuitry to function.
Neuroimaging of the functional and structural networks underlying visuospatial vs. linguistic reasoning in high-functioning autism.

Sahyoun CP, Belliveau JW, Soulières I, Schwartz S, Mody M.

MGH/MIT/HMS Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA 02129-2060, USA. cherif@mit.edu

High-functioning individuals with autism have been found to favor visuospatial processing in the face of typically poor language abilities. We aimed to examine the neurobiological basis of this difference using functional magnetic resonance imaging and diffusion tensor imaging. We compared 12 children with high functioning autism (HFA) to 12 age- and IQ-matched typically developing controls (CTRL) on a pictorial reasoning paradigm under three conditions: V, requiring visuospatial processing; S, requiring language (i.e., semantic) processing; and V+S, a hybrid condition in which language use could facilitate visuospatial transformations. Activated areas in the brain were chosen as endpoints for probabilistic diffusion tractography to examine tract integrity (FA) within the structural network underlying the activation patterns. The two groups showed similar networks, with linguistic processing activating inferior frontal, superior and middle temporal, ventral visual, and temporoparietal areas, whereas visuospatial processing activated occipital and inferior parietal cortices. However, HFA appeared to activate occipito-parietal and ventral temporal areas, whereas CTRL relied more on frontal and temporal language regions. The increased reliance on visuospatial abilities in HFA was supported by intact connections between the inferior parietal and the ventral temporal ROIs. In contrast, the inferior frontal region showed reduced connectivity to ventral temporal and middle temporal areas in this group, reflecting impaired activation of frontal language areas in autism. The HFA group’s engagement of posterior brain regions along with its weak connections to frontal language areas suggest support for a reliance on visual mediation in autism, even in tasks of higher cognition.

PMID: 19698726 [PubMed - in process]  
PMCID: PMC2795068 [Available on 2011/1/1]
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
What is happening in the brain in infant sibs?

How do neurologists analyze this presentation and this broad profile of impairments and enhanced abilities?
Brain disturbances produce a constellation of neurologic signs & symptoms: symptoms/signs equally important.

The constellation & mode of presentation reflect the underlying brain mechanism and its location.

Impairments present when the time in brain development comes for that skill to appear.
Organogenesis
Neuronal proliferation*
Glial proliferation, migration
Neuronal migration** \textit{CNTNP2}
Neuronal organization***
Myelination

*Implicated in ASD
Jim was admitted for possible mania. He was agitated and had been sending money to television evangelists and became preoccupied with sin and being good, which he talked about constantly. The psychiatrists attempted daily to PERSUADE him to try lithium but he refused. His reason was that he took lithium on June 4, 1978 and he got a stomachache. He went to the clinic and a scene ensued. Staff yelled at him. No amount of REASONING worked to change his mind, until he was told and SHOWN there were now two forms of lithium - one was pink and one was blue. He took the bad blue before, but this time he would take the good pink. He immediately agreed to the medication. The deterioration in his behavior was the result of losing his job for asking a woman a question about her clothing, which was interpreted as sexual harassment. All structure was gone from his life. Socially-emotionally he was three years old. He was not reciprocal in conversation. He talked, the doctors talked.
Bill is a young adult with autism who decided to take figure skating lessons. His mother drove to the rink several times a week. After a while, she decided to skate while he had his lesson. Bill performed his routine, but people learned to stay out of his way. He went where his program required him to go regardless of others. One day his mother forgot to note where Bill was and he ran her over, knocking her unconscious. The emergency team was called and she was given first aide and taken to the hospital. The next day she asked Bill why he did not come to her assistance since he was an Eagle Scout with a first aide badge. He replied “It expired.”
## Effect of dual task on memory span and tracking performance

<table>
<thead>
<tr>
<th></th>
<th>Digit recall</th>
<th>Tracking performance</th>
<th>Mu score</th>
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<tr>
<td></td>
<td></td>
<td>single</td>
<td>dual</td>
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<tr>
<td><strong>People with autism</strong> <em>(n = 16)</em></td>
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<tr>
<td>Mean</td>
<td>86.19</td>
<td>48.13</td>
<td>52.75</td>
</tr>
<tr>
<td>SD</td>
<td>7.55</td>
<td>16.77</td>
<td>10.47</td>
</tr>
<tr>
<td><strong>Controls</strong> <em>(n = 16)</em></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>87.25</td>
<td>86.88</td>
<td>54.06</td>
</tr>
<tr>
<td>SD</td>
<td>4.81</td>
<td>7.58</td>
<td>14.61</td>
</tr>
</tbody>
</table>

Digit recall is expressed as a percentage of correct sequences.

---

**Dual task performance deficit in autism;**

*(but matched performance in single task conditions)*

Garcia-Villamisar & Della Sala, 2002 Cognitive Neuropsychiatry
How altered is information processing in autism? What is the neural basis of this?

Details:
elementary perception at its most elementary

Facts:
meaning associated with details

Knowledge:
connecting related details; understanding

Wisdom:
capacity to use knowledge to negotiate life
What do we not know?

What does the pattern look like in severest cases? What does that imply about the brain disturbance?

How are the severest and mildest cases integrated into a single neurobiological model? What accounts for the heterogeneity in all findings in ASD?
Overall Characteristics of Thinking

- Reduced capacity for processing information
- Reduced integration of information
- Slower speed of processing
- Impaired implicit learning

- Details-Facts-Knowledge-Wisdom
- Learning from experience
- Learn by seeing or doing, not by thinking about it
Rapid Automatic Processing: Implicit learning or processing

A new mechanism that is hindering learning and comprehension in ASD.
Concept Formation Deficits: Search for More Fundamental Cognitive Mechanisms

- Motor concept learning
- Memory dependent on strategies
- Story creation or theme identification
- Face recognition
- Face affect recognition
- Strategy formation, problem solving
Rapid Automatic Processing: Implicit learning or processing

- Non-conscious
- Not verbally mediated
- Flexible
Infants are born with automatic mechanisms that allow them to form Prototypical Representations of Information.
Abilities that adults take for granted that normally develop in infancy and toddlerhood:

For example:

- Our abilities to recognize faces and emotional expressions
- Our abilities to understand the difference between basic categories in the world—cats, dogs, lions...
Which of the following two faces looks more familiar to you?
The way individuals with autism come to learn about both the world and people is different from individuals who do not have autism.

There are core differences in the way they learn categorical information and acquire “expertise”

Gasgeb, Strauss, & Minshew. Child Dev 2006; 77: 1717-1729
Infants Later Diagnosed With ASD Cannot Form Prototypes During First Year of Life

- Typically developing infants can form prototypes. They recognize gender, attractiveness, expressions, animal categories etc
- Infants who later develop autism cannot.
- Furthermore, infants later diagnosed with autism do not exhibit the left visual field preference/right brain specialization for face recognition. This means that the development of cortical specialization is delayed & develops incompletely
Overall Characteristics of Thinking

- Reduced capacity for processing information
- Reduced integration of information
- Slower speed of processing
- **Impaired implicit learning**

- Details-Facts-Knowledge-Wisdom
- Learning from experience
- Learn by seeing or doing, not by thinking about it
Defining Alterations in Brain Connectivity in ASD
Cortical activation & synchronization during sentence comprehension in HFA subjects

Marcel Just
Vlad Cherkassky
Tim Keller
Nancy Minshew

Just et al. 2004, Brain 127: 1811-1821
Sentence reading task and comprehension probe

The player was followed by the parent

Who was following?

player  parent
Autism group has less activation in Broca’s area than the control group and more in Wernicke’s area.

Results are consistent with poorer comprehension of complex sentences, coupled with good word reading.

(Just et al., 2004)
Pairs of key areas are less synchronized in autism
Reliable differences in functional connectivity: autism group has lower functional connectivity but same rank order
In autism, language areas of the brain process language;

BUT

Key players in the language processing network do not work together like they should.
Irony:
Tommy was raking leaves into large mounds. His brother ran through the piles.
Tommy said, “You are a big help.”
Does Tommy think his brother helped him?

(Williams et al., 2012)
Both children & adults with autism had lower functional connectivity than controls when comprehending irony.
The brains of individuals with autism do not automatically process semantic information in the same way that controls do.

Individuals with autism recruit more right hemisphere language areas which indicates that semantic processing is more challenging for them.
Unlike individuals with typical development, individuals with autism may not automatically recode visual information into verbal information.
Individuals with autism process words and sentences differently, which probably means they learned them differently.
**ASD group had a lack of differential activation to the artificial language condition with the frequency & stress cues and to the condition with the frequency cues alone.**

- 8-month old children with typical development are sensitive to frequency and stress cues.
The brains of individuals with autism do not automatically process semantic information in the same way that controls do.

Individuals with autism may recruit more right hemisphere language areas which indicates that semantic processing is more challenging for them.
What is happening during brain development?
Onset of acceleration in brain growth at 9-12 months coincident with onset of symptoms.

Implies disturbances in axonal outgrowth & pathfinding.

Brain growth in ASD is inverse of Retts syndrome.
Figure 2. Occipital–frontal (OFC) Z score measurements (N 195) with mean estimated growth trajectory for 28 children with autism spectrum disorder (hierarchical linear model two-piece linear model centered at 12 months).
Developmental Processes


- Organogenesis
- Neuronal proliferation
- Glial proliferation, migration
- Neuronal migration
- Neuronal organization
- Myelination
Neuronal organization refers to the events in brain development that result in the abilities that are most unique to humans.

Neuronal organizational events include the development of neuronal processes, dendritic arborizations, synaptogenesis, and the rich interconnections between neurons.
<table>
<thead>
<tr>
<th><strong>Peak Time Period</strong></th>
<th>5 months’ gestation-years postnatal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Events</strong></td>
<td></td>
</tr>
<tr>
<td>Subplate neurons: establishment and differentiation</td>
<td></td>
</tr>
<tr>
<td>Lamination: alignment, orientation, and layering of cortical plate neurons</td>
<td></td>
</tr>
<tr>
<td>Neurite outgrowth: dendritic and axonal ramifications</td>
<td></td>
</tr>
<tr>
<td>Synaptogenesis</td>
<td></td>
</tr>
<tr>
<td>Cell death and selective elimination of neuronal processes and of synapses</td>
<td></td>
</tr>
<tr>
<td>Glial proliferation and differentiation</td>
<td></td>
</tr>
</tbody>
</table>
How the Brain Develops

15-1/2 wks  22 wks  23 wks  ~25 wks

27 weeks  Full term brain  Adult
Camera Lucida composite drawings of neurons in the visual (calcarine) cortex of human infants indicated gestational ages. Note the appearance and elaboration of basilar dendrites and the tangential spread of apical dendrites, as well as the accompanying maturation of the visual evoked response (top). (Courtesy of Dr. Dominick Purpura).
How the Brain Develops
How the Brain Develops

A One month old

B Six month old

C 24 month old
Minicolumnar pathology in autism
MF Casanova, MD; DP Buxhoeveden, PHD; AE Switala; & E Roy, PhD
Can Treatment Change The Brain?
In adults?
Deciphering Altered Brain Connectivity in ASD to Improve Intervention

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A Neurological Disorder: Searching for Underlying Brain Mechanisms

Convergence Among Genetic, Neuroimaging, and Behavioral findings
Disruption of Connectivity within Neural Systems

Neuronal Level

Structural Connections

Functional Connections

Multiple Levels of Analysis
Big Questions

• How does aberrant neuronal connectivity arise?

• Can we induce plasticity in developing (and even mature) neural system to modify profile of aberrant connectivity?
Aberrant Connectivity: Neuronal Level

- Dysregulated axonal growth and pathfinding

- Process linking implicated genes to clinical manifestation of ASD

- Genome-wide association studies implicate Leucine Rich Repeats (LRR) genes
LRR Candidate Genes - Expression

- Expressed in frontal cortical neurons of mouse embryos in neuronal processes (dendrites and axons)

- Expressed prenatally in human cortical neurons (neuronal processes)

- Higher expression rates in frontal compared to posterior regions for most part
LRR Candidate Genes - Modulation

- Growing neural stem cells
- Modulate expression and observe effects on neural maturation and behavior

Differentiated Neurons – Day 1
Process staining

Differentiated Neurons – Day 4
Synaptic staining pattern

- Looking at axonal behavior in neurons derived from a mouse model of syndromic ASD (Tuberous Sclerosis)
Disruption of Connectivity within Neural Systems

Neuronal Level

Structural Connections

Functional Connections

Inducing Plasticity
Evidence-Based Cognitive Rehabilitation to Improve Functional Outcomes for Adults with Autism Spectrum Disorders

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Autism spectrum disorders are characterized by core brain-based impairments in information processing.

Cognitive impairments make the transition to adulthood particularly challenging.

Few interventions exist that successfully target core information processing deficits, and even fewer in adults.

Cognitive rehabilitation has repeatedly shown success at addressing brain-based cognitive impairments:

- Stroke
- TBI
- Alzheimer’s
- Schizophrenia
- Autism Spectrum Disorder?
Objectives

- Examine the impact of Cognitive Enhancement Therapy on functional outcome
- Examine the impact of Enriched Supportive Therapy on functional outcome
- Compare the effectiveness of Cognitive Enhancement Therapy vs. Enriched Supportive Therapy
- Examine the neural underpinnings of response
Design

- Randomized controlled trial
- 1:1 random assignment to CET or EST
- Treated for 18 months
- Followed post-treatment for 12 months
- Quality of life, functioning, cognitive, and behavioral outcome assessment every 9 months
- Neuroimaging assessments at study baseline and 18 months
- 30 month durability assessment
Design

- 54 adults with autism spectrum disorder
  - Autism
  - Asperger’s Syndrome
  - PPD-NOS
- Age – 16-45
- “High Functioning” – verbal, IQ > 80
- Significant social and cognitive disability
- Inclusive of those with “comorbid” disorders
Cognitive Enhancement Therapy

- **Aim:** To help improve thinking and social wisdom (social cognition)

- **Two parts:**
  - **Neurocognitive Training** – Computer-based training in attention, memory, and problem-solving
  - **Social-Cognitive Groups** – Training in perspective-taking, gistfulness, non-verbal communication, emotion perception, and more

- Conducted in a small group (6-8) individuals with a skilled CET therapist/coach
Enriched Supportive Therapy

- **Aim:** To help prevent the meltdown
- **Teaches individuals:**
  - About autism spectrum disorders
  - How to manage emotions and stress
  - How to improve social skills
  - Cope with everyday problems and changes
- **Individual therapy approach with a skilled EST therapist**
Best Practices

- **Cognitive Enhancement Therapy**
  - Targeted to the cognitive and neural deficits observed in the disorder
  - Uses evidence-based cognitive rehabilitation established in schizophrenia

- **Enriched Supportive Therapy**
  - Targeted to remediating the emotional disturbances of autism
  - Uses evidence-based cognitive-behavioral therapy methods established in many conditions
CET Effects in Schizophrenia

Effect Size (Cohen's $d$)

- Neurocognition
- Processing Speed
- Cognitive Style
- Social Cognition
- Social Adjustment
- Symptoms

Hogarty et al., 2004. Arch Gen Psychiatry. 61:866-876.
CET Effects in Schizophrenia

Eack et al., 2010. *Arch Gen Psychiatry* 67:674-682.
Cognition vs. IQ in Adult ASD

Eack et al., under review

\(^a\)Percentile Scores, \(N = 41\)
Recommendations/Implications

- Provide targeted interventions to improve quality of life and adaptive function in adults with ASD
- Likely to reduce a significant amount of disability in this population
- Will contribute to increased work, and reduced reliance on social insurance
Advances Through Participation

All of the advances I described were only possible because of the individuals and their families who participated in our research studies, again and again and again and again. We all need to thank the few for the benefits that will come to the many.
Become One of the Few Who Participate

To make the future better for all.