“A Different Sense of Reality: Helping Professionals Understand the Brain & Mind in ASD”

Prairie Saint John’s Fall Workshop
Fargo, North Dakota

December 4, 2012

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Director, Center for Autism Research
Professor of Psychiatry & Neurology
University of Pittsburgh
Advances Through Participation

The advances I will talk about were only possible because of the individuals and their families who participated in research studies, again and again and again and again.

We thank the few for the benefits to the many.
Become One of the Few Who Participate

Or be the helper families need.
DSM-IV Diagnostic Criteria for PDDs: What is wrong with them?

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. No accurate distinctions in the community between autism, Asperger’s or PDDNOS. Individuals often receive all of these and families think that no one knows what they have.
Modified from Kooy 2010

ASD

All the rest

Schizophrenia

Non-Syndromic Intellectual Disability

CNTNAP2
Neurexin1
SHANK2
NRG3
22q11
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.
Part 1. Information Processing & Brain Connectivity in ASD

The mind, the brain and “the heart”
Showed that the human mind, when encountering the unfamiliar, could absorb roughly 7 new things at a time. This is the statistical average for short term storage. Long-term memory is virtually unlimited.

“Whatever else the brain might be, it was an information processor with systems that obeyed mathematical rules that could be studied.”
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.
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? What is the shared characteristic of all behavioral manifestations and of brain alterations?

Courtesy of Michael Rutter, 2007 “Autism: Clinical features and research challenges”
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
Abnormalities in complex behavior, cognition, language, intellectual disability, seizures
No primary sensory deficit
No long tract signs (cerebral palsy)
No focal findings (dyslexia, visuospatial deficits)
De novo developmental disorder
Association cortices
Distributed neural network disorder
Disorder of neuronal organization
Differential Diagnosis For De Novo Neurodevelopmental Disorders

Sequence of Events in Brain Development:

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

*Implicated in ASD
Neurologists characterize all impaired AND all intact abilities to identify common characteristics that reflect their shared dependence on a common underlying cause.

This approach was particularly beneficial in autism because both were part of the abnormal profile that defines behavior.
## Discriminant Function Analysis\(^1\): Domains With Deficits

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests Passing Tolerance</th>
<th>Percent Correct</th>
<th>Kappa</th>
</tr>
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<tbody>
<tr>
<td>Motor</td>
<td>Grooved Pegboard; Trail Making A</td>
<td>75.80</td>
<td>0.52</td>
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<tr>
<td>Complex Language</td>
<td>K-TEA Reading Comprehension; Verbal Absurdities; Token Test</td>
<td>72.70</td>
<td>0.45</td>
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<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>
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</tbody>
</table>

\(^1\)Based 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)
Kappa below .40 indicates poor agreement beyond chance

Significant Kappa reflects superior performance by autistic subjects

Based on 33 individually age, IQ, gender matched pairs of subjects

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests Passing Tolerance</th>
<th>Percent Correct</th>
<th>Kappa</th>
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</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>
</tr>
<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>0.42²</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>

¹Kappa below .40 indicates poor agreement beyond chance
²Significant Kappa reflects superior performance by autistic subjects
³Based on 33 individually age, IQ, gender matched pairs of subjects
## The Profile of Intact & Impaired Abilities in High Functioning Autistic Individuals

<table>
<thead>
<tr>
<th>Intact or Enhanced</th>
<th>Cognitive Weaknesses</th>
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<tbody>
<tr>
<td>• Attention</td>
<td>• Complex Sensory</td>
</tr>
<tr>
<td>• Sensory Perception</td>
<td>• Complex Motor</td>
</tr>
<tr>
<td>• Elementary Motor</td>
<td>• Complex Memory</td>
</tr>
<tr>
<td>• Simple Memory</td>
<td>• Complex Language</td>
</tr>
<tr>
<td>• Formal Language</td>
<td>• Concept-formation</td>
</tr>
<tr>
<td>• Rule-learning</td>
<td>• Face Recognition</td>
</tr>
<tr>
<td>• Visuospatial processing</td>
<td></td>
</tr>
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</table>
fMRI Activation During a Spatial Working Memory Task (Courtesy John Sweeney)
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 underdeveloped- they are reliant on more elementary circuitry particularly visual circuitry to function.
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></th>
<th>Tracking performance</th>
<th></th>
<th>Mu score</th>
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<tbody>
<tr>
<td></td>
<td>single</td>
<td>dual</td>
<td>single</td>
<td>dual</td>
<td></td>
</tr>
<tr>
<td>People with autism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>86.19</td>
<td>&gt; 48.13</td>
<td>52.75</td>
<td>&gt; 37.81</td>
<td>66.87</td>
</tr>
<tr>
<td>SD</td>
<td>7.55</td>
<td>16.77</td>
<td>10.47</td>
<td>8.22</td>
<td>10.74</td>
</tr>
<tr>
<td>Controls (n = 16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>87.25</td>
<td>= 86.88</td>
<td>54.06</td>
<td>= 55.25</td>
<td>84.75</td>
</tr>
<tr>
<td>SD</td>
<td>4.81</td>
<td>7.58</td>
<td>14.61</td>
<td>7.39</td>
<td>11.52</td>
</tr>
</tbody>
</table>

Digit recall is expressed as a percentage of correct sequences.

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Dual task performance deficit in autism;
*(but matched performance in single task conditions)*

Garcia-Villamisar & Della Sala, 2002 Cognitive Neuropsychiatry
Resources for Teachers, Parents, & Therapists

The Incredible 5 Point Scale, Kari Dunn Baron
Autism Speaks website
Tony Attwood website
Books by Dr. Temple Grandin, by John Robison
The movie “Temple Grandin”
SFARI website (research findings)
Validation of Altered Information Processing-Brain Connectivity As Core Characteristics of ASD

**Studies of Infants At Risk For ASD**

A syndrome with many affected domains and all domains reflect information processing/brain connectivity disturbances.

All manifestations are connected through common mechanisms at the cognitive and brain levels.
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
How altered is information processing in autism? What is the neural basis of this?

Lots of Details:
- elementary perception at its most elementary

Lots of Facts:
- meaning associated with details

Little True Knowledge:
- connecting related details; understanding

Very Little Wisdom:
- capacity to use knowledge to negotiate life
Rapid Automatic Processing: Implicit learning

A new mechanism that is hindering learning and understanding in ASD.
Impairments in all of these:
- 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?
Your brain automatically formed a prototype based on 14 examples without your awareness.

Categorization or prototyping are automatic, nonconscious & fast.
The way individuals with autism learn/think 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”

Gastgeb, Strauss, & Minshew. Child Dev 2006; 77: 1717-1729
Typically developing infants can form prototypes. They recognize gender, attractiveness, expressions, animal categories etc.

Infants who are later diagnosed with 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 & incompletely develops.
Biggest discovery:
Altered connections between brain regions; these are neural systems. Autism is now considered a disorder of altered brain connections in multiple brain systems.
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
Forceps Major (LH)
Imaging Language Differences in ASD: What have we learned?
In autism, language areas of the brain process language;

BUT

Key players in the language processing network do not work together like they should. Compensatory connections use atypical circuits with inherent limits.
The brain of individuals with autism processes words and sentences differently; probably means they learned them differently.

It also means they have a different understanding and meaning for words and sentences. It is vital to understand what they understand and what they mean by words and sentences. Do not assume!
Unlike individuals with typical development, individuals with autism may not automatically recode visual information into verbal information, or vice versa. Visual format limits processing demands and is therefore very helpful.
- ASD group lacked 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.
What is happening in the BRAIN in infant sibs?

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 linearmodel centered at 12 months).
Sequence of Events in Brain Development:

- Organogenesis
- Neuronal proliferation*
- Glial proliferation, migration
- Neuronal migration** \textit{CNTNP2}
- Neuronal organization***
- Myelination

*Implicated in ASD
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.
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

A One month old

B Six month old

C 24 month old
Part 3. New Interventions
Can Cognitive Treatments Change The Brain? In infants? In adults?

Yes; see Early Start Denver Model

Yes; for less severe ASD.
  Intervention is lifelong.
  Progress can be lifelong.
For severe cases of ASD: we await biological interventions which tell signaling pathways in brain cells to stop over-growing. The first ones exist. Others are entering trials.
Big Question For New Interventions

• Can we induce plasticity in developing (and even mature) neural systems (brain) to modify the profile of aberrant connectivity?
Evidence-Based Cognitive Rehabilitation to Improve Functional Outcomes for Adults with Autism Spectrum Disorders

Shaun M. Eack, Ph.D.
Nancy J. Minshew, M.D.
University of Pittsburgh
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?
Cognitive Rehabilitation Strategies

- Based on secondary learning
- Learning while doing
- Makes automatic processes explicit with hope that they shift to being automatic
- Target core deficits
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 of Trial

- *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 ASD (ADI + ADOS)
  - Autism
  - Asperger’s Syndrome
  - PPD-NOS
- Age – 17-45
- “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 (pairs)
  - **Social-Cognitive Groups** – Training in perspective-taking, gistfulness, non-verbal communication, emotion perception, and more (small group)

- 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)

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

aPercentile Scores, N = 41
Early Results

- CET is as effective for ASD as for schizophrenia and more effective than EST
- Active ingredients of CET: increased speed of processing and perspective taking
Recommendations/Implications

- Likely to reduce a significant amount of disability in this population
- Will contribute to increased work and improved relationships.
- Efficacy in two major neuropsychiatric disorders is a first.
- Implies that a domain approach across disorders will be effective.
Part 4. Changing Diagnostic Criteria

- DSM-5 Clinical Criteria for Disorders
- RDoC - Research Domain Criteria - Organizing scientific advances and facilitating translation of advances into clinical practice
What do changes in the criteria mean for clinical diagnosis of ASD? Will some individuals no longer “have autism”? 
Three studies show that diagnosis for 93+% of PDD cases is unchanged by changes in DSM criteria, when history & observations were thorough (ADI + ADOS).

Whether the new default category of “social communication disorder” will end up with developmental language disorders or with ASD is undecided.
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)
Bottom Line For Clinicians

Will need more documentation about history of development and about current behavior across more domains to establish an ASD diagnosis under the new criteria.
DSM-5
A Monumental Effort With Auspicious Goals

Work started 2005
World-wide effort 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.

- Revisions should be guided by research evidence.
Why Are Revisions Needed & Important?

Many scientific advances need to be incorporated.

- Revisions are designed to lead to:
  - Earlier diagnosis
  - Earlier treatment
  - More accurate treatment
  - Prevention of later complications
Revision Principles

- Add dimensional concepts
- Add measurements of distress, disability, and severity
- Add developmental dimension - life span view of disorders
- “Living document” that will change
12 DSM-5 Work Groups

- 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
6 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

- Europe, 22
- South Africa, 1
- United States, 123
- Canada, 8
- Latin America, 3
- Western Pacific, 4

Race and Ethnicity of Approved Nominees

- White (non-Hispanic), 131
- Hispanic, 12
- African American, 7
- Native American, 1
- Asian, 10

Gender Representation of Approved Nominees

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

Put Disorders That Have Common Biology and Genes Together To Inform Clinicians of Related Disorders and Key Differential Diagnoses
Revised Chapter Organization

A. Neurodevelopmental Disorders
B. Schizophrenia Spectrum and Other Psychotic Disorders
C. Bipolar and Related Disorders
D. Depressive Disorders
E. Anxiety Disorder
F. Obsessive-Compulsive and Related Disorders
G. Trauma and Stressor-Related Disorders
H. Dissociative Disorders
J. Somatic Symptom Disorders
K. Feeding and Eating Disorders
L. Elimination Disorders
M. Sleep-Wake Disorders
N. Sexual Dysfunctions
P. Gender Dysphoria
Q. Disruptive, Impulse Control, and Conduct Disorders
R. Substance Use and Addictive Disorders
S. Neurocognitive Disorders
T. Personality Disorders
U. Paraphilias
V. Other Disorders


Proposed Major Revisions to Criteria Format:

♦ 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 & sub-threshold symptoms

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 and treatment planning
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
- Utility & feasibility of new standardized assessment of disability (WHO-DAS II) in lieu of GAF rating
- Designed to assess performance of DSM-5 changes in small or solo offices & academic centers
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.
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”
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*

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<th>Mood</th>
<th>Trauma</th>
<th>SUD</th>
<th>Other</th>
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<tr>
<td>3</td>
<td>Maybe</td>
<td>Maybe</td>
<td>Maybe</td>
<td>Maybe</td>
</tr>
<tr>
<td>4</td>
<td>I don’t know</td>
<td>I don’t know</td>
<td>I don’t know</td>
<td>I don’t know</td>
</tr>
</tbody>
</table>

**LEGEND:**
1 = Yes
2 = No
3 = Maybe
4 = I don’t know
Con-Current Task Force Projects

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

DSM-5 will 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, the beginning of individualized treatment and a new tool box
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 behavioral 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 to identify behavioral 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 new target 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.
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.

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

From DNA to Behavior: A Complex Sequence of Mechanisms Centered on Neural Systems

Abnormalities in Genetic Code for Brain Development

Abnormal Mechanisms of Brain Development

Structural and Functional Abnormalities of Brain

Cognitive & Neurological Abnormalities

Behavioral Syndrome
An Example of an RDoC Dimension Highly Relevant to ASD and to Many People
AMY-ACC-DLPFC are core regions of neural network for 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
Part 5. Technology Advances That Are Changing the Future of Treatment
Advances in Brain Imaging Technology

- Improved visualization of micro-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
“Biology gives you a brain. Life turns it into a mind.” *Jeffrey Eugenides*

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.

**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

More than 1,000 genes identified in ASD
A window into heterogeneity and into altered mechanisms of brain development
Gene expression studies or “omics” are helping to define the function of the implicated genes
Complex is an under-statement for “omes”, the brain & brain development
Exciting times for genetics of Autism Spectrum Disorders

Adapted from Betancur (2011, Brain Res. 1380:42-77)
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.
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.
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.
Modified from Kooy 2010
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.
Genetic Studies Provide Insight into Altered Brain Development Mechanisms

Synapse formation/maintenance
Axonal outgrowth/pathfinding
Development of cortical organization
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!
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.
Prepare for Warp Jumps

To Be Followed By…
Translational Medicine - New Treatments

On the horizon: Individualized or Designer Medicine