AUTISM SPECTRUM DISORDER (ASD): Neural Basis

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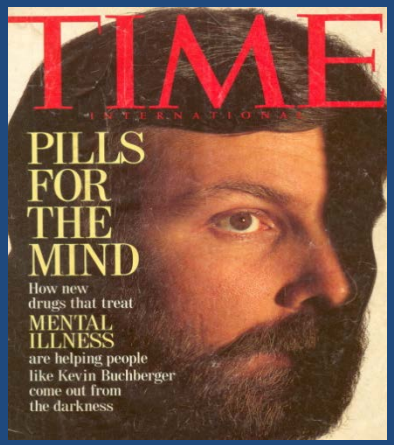
NEW SCIENCE OF MIND

Mind is generated by the **Brain**.

Psychiatry is the Application of **Basic Neurosciences** to man's day-to-day problems.



Psychiatry is a Branch of Medicine.

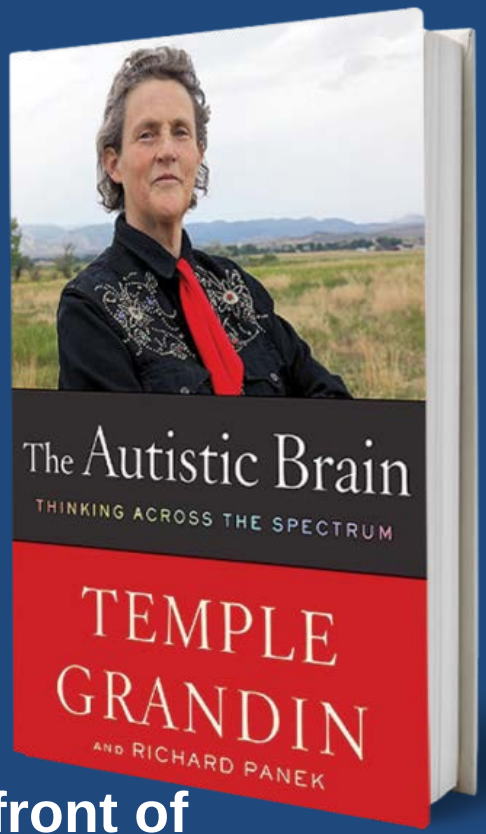
Psychiatric Disorders are Physical Disorders.

Psychiatrists are primarily Physicians.

Application of Basic Neurosciences

‘The Autistic Brain’
Ms Temple Grandin
Adult with Autism

Professor of Animal Science
University of Colorado, USA



She reports from the forefront of
Autism Science from her own experience:
as a Brain Disorder.

DEVELOPMENTAL DISORDERS IN CHILDREN

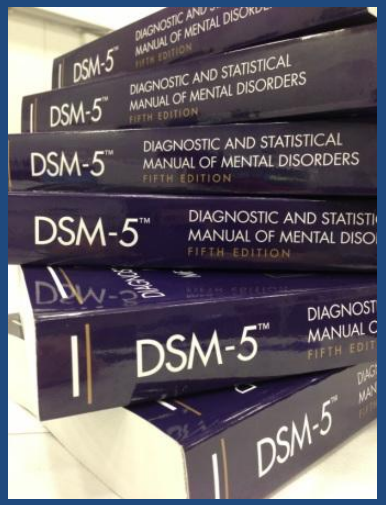
Classification : ICD-10

DEVELOPMENTAL DISORDERS BLOCK : F 80 - 89

'DELAY' & 'DEVIANCE'

- **SPECIFIC DEVELOPMENTAL DISORDERS (SDD)**
  (F80, 81, 82) - DELAY
- **PERVASIVE DEVELOPMENTAL DISORDERS (PDD)**
  (F84 - Autism, Rett, Asperger's etc) - DEVIANCE

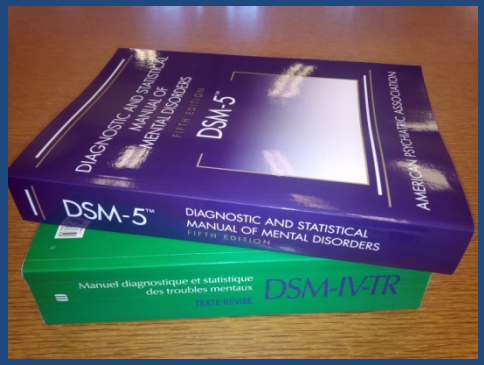
DSM-5 : Paradigm Shifts



***Structured information to diagnose disorder*.**

- **DIAGNOSTIC MANUAL**
- **Developmental issues represented: 'Life-span Approach'.**
- **Genetic & Neuro-imaging linkages across diagnostic groups.**
- **ID to ADHD as Neuro-developmental Disorders: (ICD F70 to F90).**
- **Consolidation of Autistic Disorder (AD), Asperger's, Rett and PDD into ASD.**

DSM-5 : Neuro-developmental Disorders



1. Intellectual Disability (ID)
2. Communication Disorder (CD) : Language and Speech
3. **Autism Spectrum Disorder (ASD).**
4. Attention Deficit Hyperactive Disorder (ADHD).
5. Specific Learning Disorder (SLD).
6. Developmental Coordination Disorder (DCD).

ASD: Neural Basis

PRESENTATION FORMAT

- On Neural Basis of ASD,
  Behavior Disorder to Brain Disorder,
  From Frustration to Focus,
  ASD as Neurological Disorder.

- Linking cardinal clinical features to their Neuro-biology, Neural Circuits.

- Strategy of stratifying ASD to target Neural Circuits for symptom-management – Cochin Experience.

Autism Spectrum Disorder (ASD) : Features

- **Behaviorally defined Disorder. Leo Kanner, 1943: 11 Children.**
- **Now, ASD: Consolidation of Autistic Disorder, Asperger's, Rett and PDD into ASD: DSM-5.**

- **Impaired reciprocal Social Interaction, Poor Eye Contact.**
- **Delayed and Disordered Language.**
- **Abnormal response to Sensory stimuli – touch, sound..**
- **Insistence on sameness. Repetitive stereotyped behavior.**
- **Unusual capacity for rote memory and visuals. Splinter skills.**
- **Normal physical appearance.**
- **Now, Brain Disorder.**

Autism Spectrum Disorder: Clinical Features (Refreshed)

Diagnostic Criteria (DSM-5) : A,B,C,D & E

A. Persistent deficits in Social Communication and Social Interaction in multiple contexts. Verbal and non-verbal.
(No Social or Emotional Reciprocity, No Sharing of Interests, No Language.)

B. Restricted, Repetitive, Stereotyped patterns of behavior, interests, activities – *currently or by history*.
(Stereotyped movements, use of same objects, lining up toys, echolalia..
Insistence on sameness, inflexible routines, distress with any change…
Abnormal response to sensory stimuli: indifference to pain,temperature, smell…)

Severity Specifier : Level 3 : 'Requires very substantial support'
Level 2 : 'Requires substantial support'
Level 1 : 'Requires support'

A & B : 'BIAD' instead of 'TRIAD'
"Solitude and Sameness": T. Grandin

Autism Spectrum Disorder: Clinical Features Cont'd…

Diagnostic Criteria (DSM-5)

C. Symptoms present in Early Developmental Period, but may manifest in later times when social demands exceed his limited capacities. (cf. ICD: 3 years).

D. Symptoms cause clinically significant impairment in social, occupational or other areas of current functioning.

E. These disturbances are not better explained by Intellectual Disability (ID/MR). Make co-morbid diagnoses of ASD & ID.

Specifiers:

ASD with, or without ID,
With, or Without Language Impairment (eg. Aspergers),
Associated with medical/ genetic condition, or
another Neuro-developmental Disorder.

ASD: NONDESCRIPT CLINICAL FEATURES

- Islets of skills. Splinter or savant skills.
- ID (MR) – 50%, Seizure in 1/3. Low Functioning ASD.
  Reason for the lack of clarity about the notion of Autism.
- Sensory abnormalities: increased or decreased-
  to sounds (hyperacusis), light, touch, pain.
  inability to tolerate touch- a hug or handshake.
- Erratic sleep, food fads and allergies, GI ('diets').
- Self-injurious behaviour (SIB) (head, hair, skin). ? ID.
- Poorly regulated immune responses- Allergies, URI.

PART 1

TRANSLATIONAL APPROACH TO ASD NEUROBIOLOGY

ASD: Genetics & Clinical Symptoms

- Neurons : Signal Transduction &
  Synapses : Signal Transmission.
- Candidate *genes* in ASD *code* for important *proteins in Synaptic* structure, for their function & maintenance.
- Hence, our emphasis is on '**Connectivity of Circuits**' and '**Central Coherence**' in the pathophysiology of ASD.

- Pure Autism is thus re-defined: distinct from ASD with ID. ASD without comorbidity **R**esponds **T**o **I**ntervention (RTI).
- Dramatic paradigm shift for more successful clinical and psychopharmacological management.

ASD: BROADER PHENOTYPES

HIGH vs LOW FUNCTIONING ASD : Cochin Perspective

- In ID (MR), global lag in development at cellular level. Inadequate Signal Transduction. Minimal RTI possible.

- Whereas in ASD, level of development in a brain area determines final function. ***'High vs Low'.*** Greater the level of development, greater the RTI.

- In pure ASD, individual brain areas develop as 'islands.' Lack of 'bridges' between 'islands'. DTI studies show Neural Transmission Delays. Hence, no output of function.

"Pure ASD"- (without co-morbidities of ID / Epilepsy etc) : 'High-functioning'. DSM 5 Perspective, ID co-morbid.

ASD: OUR COCHIN PERSPECTIVE:

LOW vs HIGH FUNCTIONING : CO-MORBID vs PURE ASD

- Paradigm shift in management. Based on outcome. RTI.
- ASD co-morbid with ID/ Epilepsy: Low functioning.
- "Pure ASD": High functioning. RTI possible.

- Pure ASD: deficits in connectivity among brain areas.
  More about Neural Transmission and
  Less about Signal Transduction.

High functioning ASD more amenable to strategies of intervention, including pharmacotherapy.

ASD: NEUROBIOLOGY IN PURE AUTISM

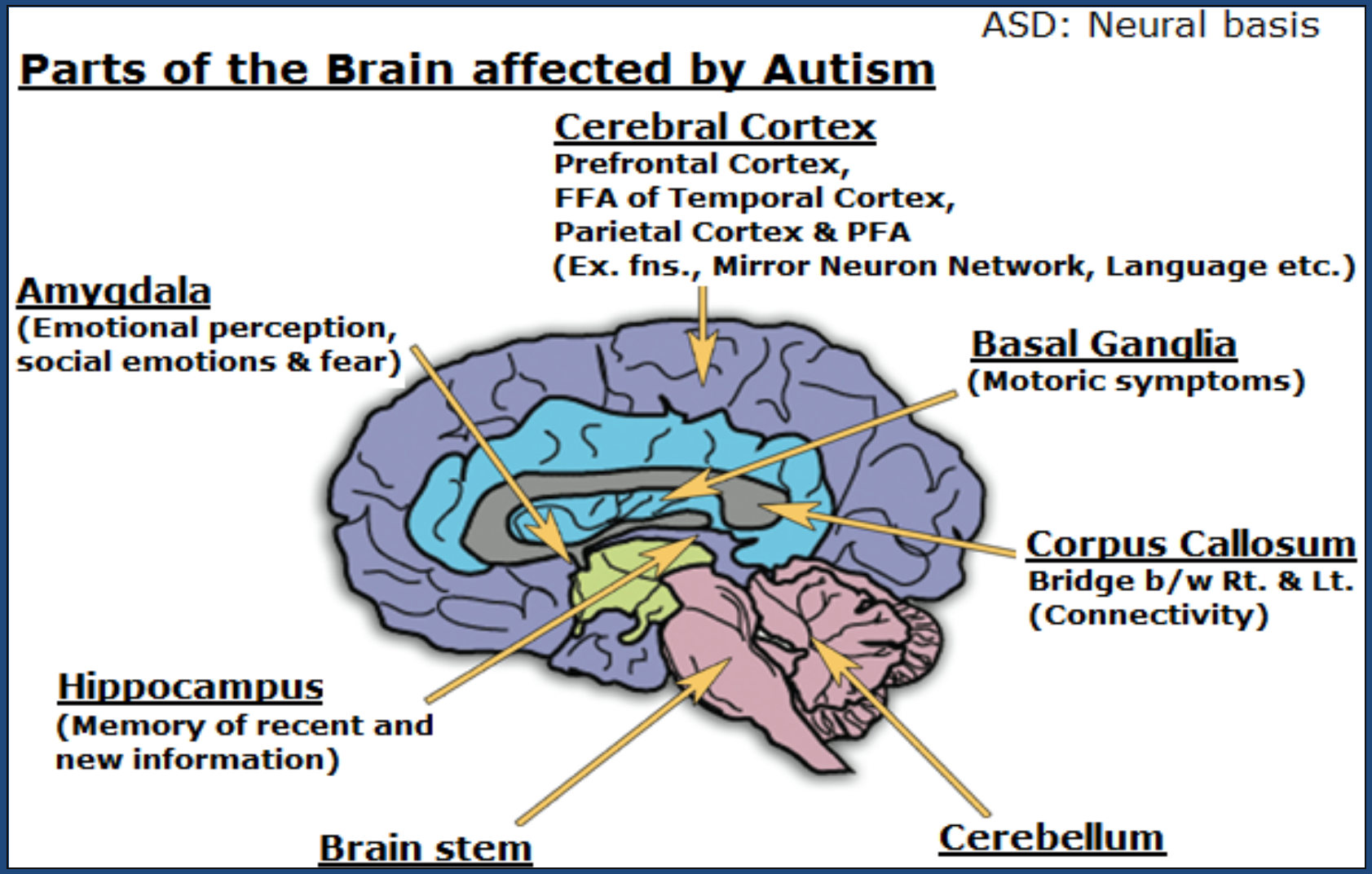
Often, in ASD without co-morbidity, milestones 'dropped'.

- **Early brain overgrowth and excess of neurons, lack of pruning and over-connectivity – result in *deviant functioning*. eg. Language.**
- **Disrupted Neuronal Migration in early gestation, results in *loss of function*.**
- **Disrupted development of Synapses, causing *disruption of functional brain* circuits: ASD.**
- **Maturational deficits within neurons themselves, causing *under-functioning*: ID, Epilepsy etc.**

Pure Autism: mostly about 'Underconnectivity'.

BRAIN REGIONS IN AUTISM

LOW INTERCONNECTIVITY



ASD: NEUROBIOLOGY

MIRROR NEURONS & THEORY OF MIND (TOM) DEFICITS

- A 'Mirror Neuron' fires when the person acts, and when he observes the same action performed by another.

- Important recent discovery- *VS Ramachandran* (Phantoms in the Brain): Learning by imitation.

- Mirror Neuron System integral to learning Language, Imitation Learning, Empathy and to understand others' Actions & Intentions.

- Mirror Neuron System in Inferior Frontal Gyrus Superior Temporal Sulcus, Superior Parietal Lobe..

THEORY OF MIND (TOM)

- Denotes ability to infer ‘what goes on in the other person’s head’. Social Cognition. ‘Mind-reading’ or ‘Mentalising’.

- Mirror neurons account for TOM - to infer feelings, desires, intentions, dreams and beliefs of others as well as of self. Critical for social cognition.

- ‘Mind Blindness’ in Autism (‘word blindness’ in LD).

- Empathy and language are involved in this TOM.

- Components of this ‘Social Brain’ are Amygdala, Sub-region of both OFC, MFC, Superior Temporal Gyrus.

PART 2

ASD: BIOLOGY OF CLINICAL FEATURES :ICD 10

Linking Clinical Features to Specific Biology

1. Age *at* onset.
2. Impaired SOCIAL INTERACTIONS.
3. Impaired Verbal/ Non-verbal COMMUNICATION.
4. Restricted Repertoire of ACTIVITIES/ INTERESTS.
5. Co-morbid ADHD, ID (MR), Seizure, SIB etc.

ASD: BIOLOGY OF CLINICAL FEATURES : ICD 10

1. Age *at* Onset

Before 3 years: Language fails to develop.
(12-18 months)

- **Normal brain size at birth. Swells 10% – too many synapses without meaningful connections, causing marked disruption of cortical-subcortical connectivity.**

- **Hyperconnectivity, Aberrant connectivity, Hypoconnectivity – all lead to core Developmental Deficits of ASD, esp. social communication, language..**

ASD: BIOLOGY OF CLINICAL FEATURES

2. Impaired Social Interaction

As infant, no attachment, no joint attention, no imitation, no experiential learning.

- 'Mirror-Neuron' deficits, no imitative actions. No reciprocity.
- Theory of Mind (TOM) deficits. No response to, say, stretching hands to pick up the child.
- Amygdala: a major component in the foundation of social cognition. Eye contact.
- Fusiform Face Area (FFA) deficit.
  This area on Rt. Ventral Temporal Lobe specifically perceives FACES.. Mother's face excites the child. In ASD, robust findings of FFA deficits.

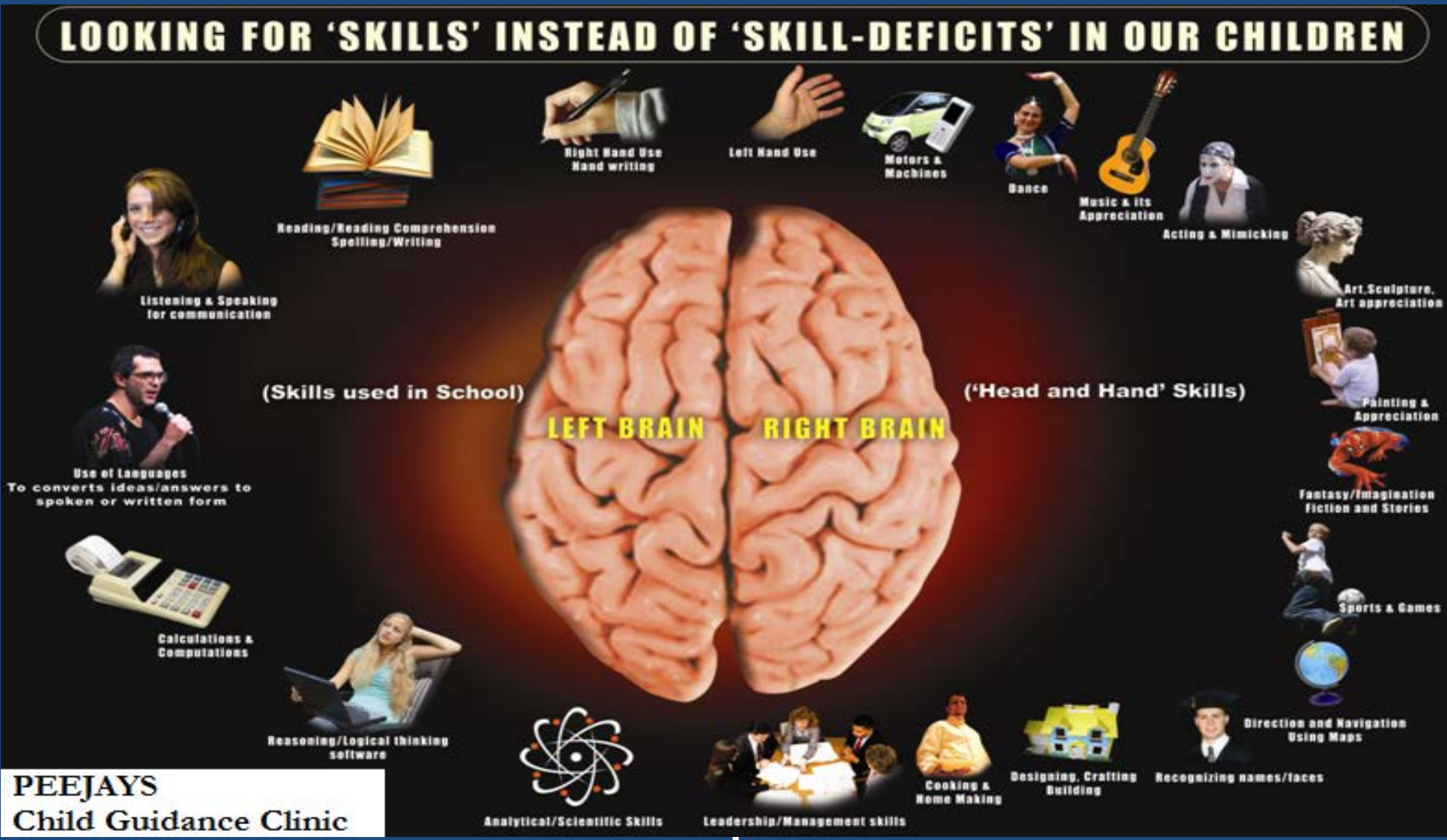
ASD: BIOLOGY OF CLINICAL FEATURES

3. Verbal and Non-verbal Communication : Language

Bottlenecks in Information Processing (in simple terms)
(40% ASD 'never speak' (Volkmar))

- **Individual functional areas may develop: "Pure ASD".**
- **Cortical Under-connectivity, Aberrant connectivity for inter-hemispheric communication. Impacts Language.**
- **Intra-cortical aberrant connectivity, hypo-connectivity in Left Frontal Cortex leads to non-development of grammar and pragmatics for Language.**
- **Absence of Inter-hemispheric Coherence…..**

ASD: BOTTLENECKS IN VERBAL COMMUNICATION



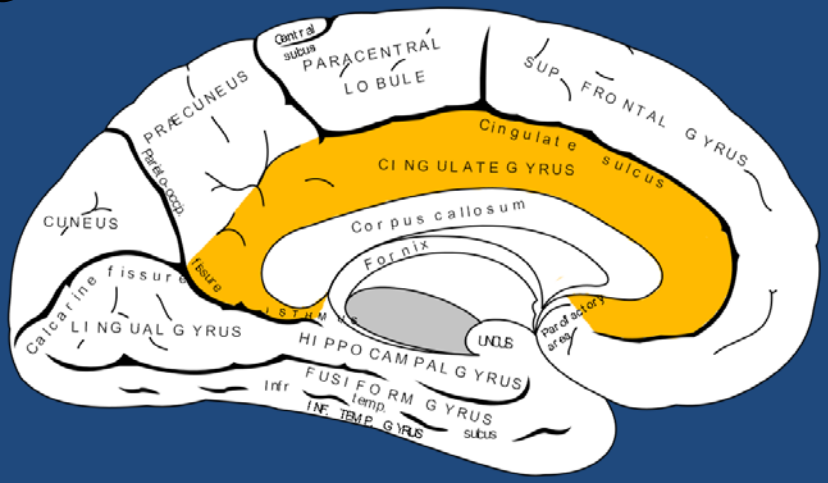
Lexicons,Semantics,Pragmatics (no verbal communication)

Mirror Neuron Deficits (no gestural communication)

ASD: BIOLOGY OF CLINICAL FEATURES

4. Restricted Repertoire of Interests/ Activities

- **Resistance to Change**
- **Obsessive insistence on Sameness**
- **Stereotyped Behaviour**



Culprit*: Cingulate gyrus*
Prefrontal Cortex
Basal Ganglia

Serotonin (5HT) is implicated, as in OCD.

ASD: BIOLOGY OF CLINICAL FEATURES

Neurotransmitters & Neural Circuits

- Event-related **electrical potentials** in the neurons are altered in ASD in language, face processing, impulse control etc. Hypo-connectivity/ Seizure etc.
- **DA** implicated in executive skills, mind-reading, anticipation etc.
- **5HT** (Serotonin) in resistance to change, stereotyped behaviour, anxiety etc.
- **Glutamate**, **GABA** implicated in signal transmission, seizure propensity etc.

Pharmacotherapy by targetting these circuits.

AUTISM: TREATMENT GOALS

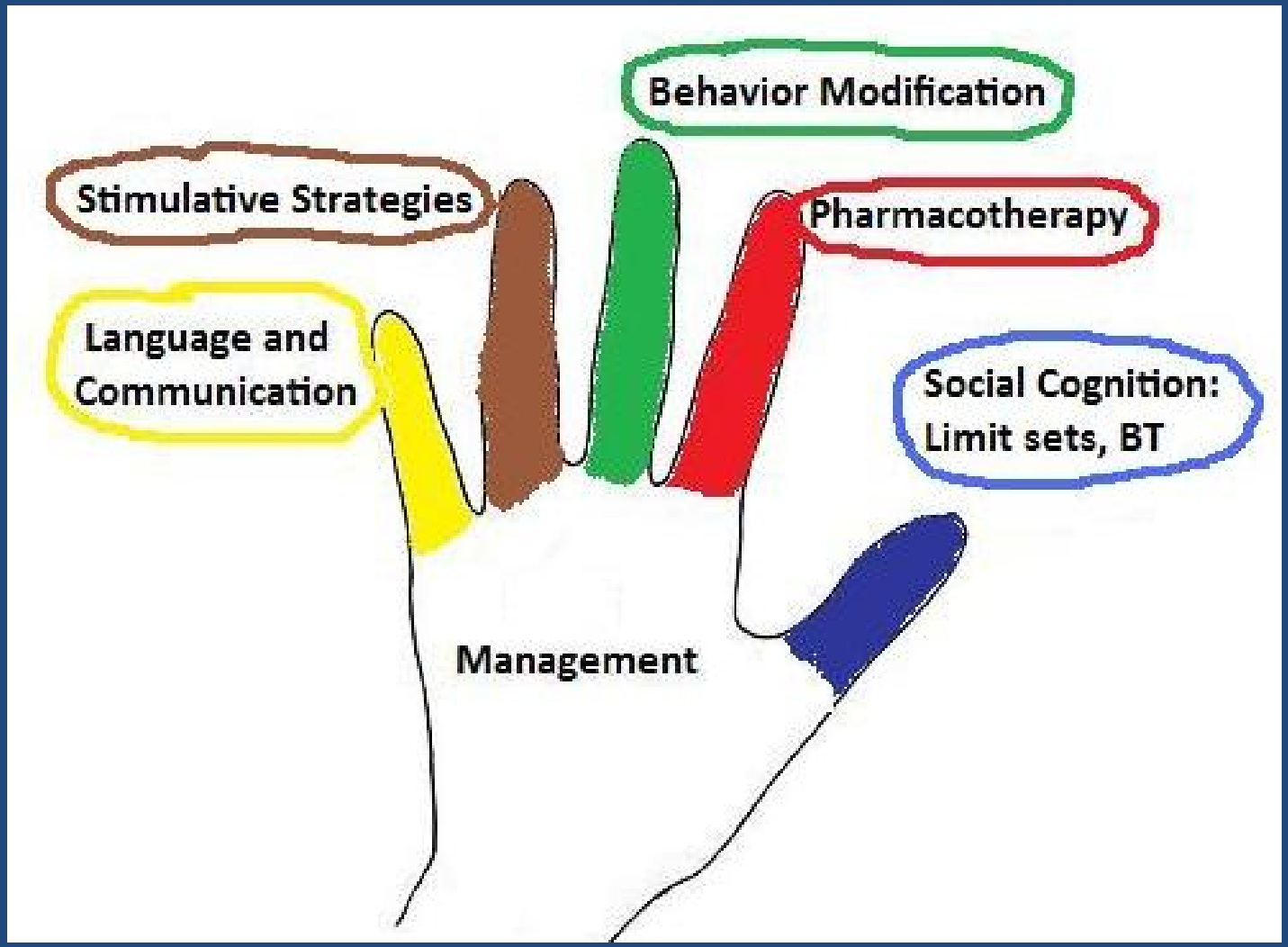
Both medical and non-medical together

- STIMULATE DEVELOPMENT (MULTI-PRONGED STRATEGIES, IEP)
- REMOVE DISRUPTIONS (PHARMACOTHERAPY..)

"Brain Circuitry Determines the Destiny in Dysfunctions"
- *Stephen Stahl*

J Clin Psychiatry. 2003;64 Suppl 14:6-17.

5 finger approach



Five-finger Approach: Prompts for Counseling

AUTISM: THE 'NGO INDUSTRY'

EXPLOITING HOPE AGAINST SCIENCE

- "Late Talkers": undiagnosed, just speech therapy.
- Pure CDs- misdiagnosed, lifelong label as AD!
- Multidisciplinary- minus Medical!
- "NO TREATMENT" for ASD- except NGO inputs!
- Agonising misinformation: MMR, Vaccinations!
- GLUTEN-CASEIN-FREE DIETs. Claiming cure!
- 'CHO-Drive'- to modulate.
- 'Diets' are nuisance, nutrition imbalance.
- 'Diets' delay appropriate treatment.

Pediatrics 2012;129;330

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THANK YOU FOR YOUR ATTENTION