Is there phenotypic and neurobiological differentiation between schizotypal disorder and ASD in children? (Autism: past, present and future)

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Diagnosis of Neurodevelopmental disorders

The Past:
A categorical approach based on phenomenology (careful clinical observation of behaviours, description of symptoms, and mental state)
A diagnosis is an hypothesis based on clinical judgement which has treatment, prognostic and research implications

• Leo Kanner 1943 “infantile autism” → “autistic disorder”– delayed and deviant language, socially aloof, repetitive ritualistic behaviour. ID common
• Hans Asperger 1945 “autistic psychopathy” → “Asperger Disorder”- normal intellectual and language development, social impairment, repetitive ritualistic behaviour
Evolution of Diagnostic categories- DSM and ICD

• DSM/ICD have been periodically reviewed and significantly revised since the first publication e.g. DSM-I 1952.

• There has been a wealth of new information in neurology, genetics and the behavioural sciences that dramatically expands our understanding of mental illness.

• Researchers have generated knowledge about the prevalence of mental disorders, biologic, psychological and ecological treatments, brain function, and physiology and the lifelong influences of genes and environment on a person’s health and behaviour.

• The introduction of scientific technologies, ranging from brain imaging techniques, animal and cell models, sophisticated data analytic techniques, and population health methodology, give us new tools to better understand these illnesses.
Categorical approach
Autistic Disorder – knowledge gains

- Early brain overgrowth disrupts connections
- Functional under-connectivity of brain systems
- Local over-connectivity
Neuropathology of Autism

• Abnormal development
  • Cerebellum
  • Limbic structures (hippocampus and amygdala)
  • Brain stem (olivary nuclei)
  • Cerebral cortex (megalencephaly and increased neuronal density)

“straddle the neurology-psychiatry boundary”
# Neuropsychiatric Symptoms

Taken from Amaral, 2008

<table>
<thead>
<tr>
<th>Social Impairment</th>
<th>Communication deficits</th>
<th>Reared traits behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>OFC – Orbitofrontal cortex</td>
<td>IFG – Inferior frontal gyrus</td>
<td>OFC – Orbitofrontal cortex</td>
</tr>
<tr>
<td>ACC – Anterior cingulate cortex</td>
<td>(Broca’s area)</td>
<td>ACC – Anterior cingulate cortex</td>
</tr>
<tr>
<td>FG – Fusiform gyrus</td>
<td>STS – Superior temporal sulcus</td>
<td>BG – Basal ganglia</td>
</tr>
<tr>
<td>STS – Superior temporal sulcus</td>
<td>SMA – Supplementary motor area</td>
<td>Th – Thalamus</td>
</tr>
<tr>
<td>A – Amygdala mirror neuron regions</td>
<td>BG – Basal ganglia</td>
<td></td>
</tr>
<tr>
<td>IFG – Inferior frontal gyrus</td>
<td>SN – Substantia nigra</td>
<td></td>
</tr>
<tr>
<td>PPC – Posterior parietal cortex</td>
<td>Th – Thalamus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PN – Pontine nuclei cerebellum</td>
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TRENDS in Neurosciences
Individuals with autism showed sig. less activation in the anterior cingulate, DLPFC, and caudate nucleus than controls. - disruption of the network underlying key aspects of executive function and working memory.

Figure 1. Mental Rotation Task

Figure 2. Between-group statistical map showing regions of activations significantly greater in controls than autism overlaid on subjects mean T1 image.

Neuromotor Investigations
3D Gait Studies
Neuropsychological Tests
Developing neuropsychological tests for autism screening?

• Executive Functioning

• Weak Central Coherence

• Theory-of-Mind

• Visual Search Theories
Male ArKO mouse  Boon, Simpson, Tonge, Rinehart, Mahindan, Hill
Animal Models ? Aromatase (CYP19)

ANDROGENS

androstenedione \(\rightarrow\) estrone

testosterone \(\rightarrow\) 17\(\beta\)-estradiol

ESTROGENS

Aromatase (CYP19)

estrone

17\(\beta\)-estradiol
Male ArKO mouse Symptoms/Characteristics

- impairment in social interaction
- qualitative impairment in communication
- repetitive behaviour
- abnormal gait – clumsy, awkward
- bigger brain
- high androgen serum levels
- metabolic disturbances
- abnormal purkinje cells
- Male and reduced sexual behaviour / aggression / increased sleep
The Present:
Dimensional assessment approach of DSM-5

• Justification for change

• The categorical syndromes do not always fit with the reality of the range of symptoms that individuals experience – e.g. individuals with Schizophrenia often have other symptoms such as insomnia, depression and anxiety.

• Also, because the criteria for diagnosis are “yes/no” there is no method in DSM-IV to account for the severity of the disorder, thus no specified way to determine if the patient is improving with treatment.

APA 2011
Dimensional assessments

• Dimensional assessments would allow clinicians to:
  1. rate both the presence and the severity of the symptoms, such as “very severe,” “severe,” “moderate” or “mild”
  2. track a patient’s progress on treatment,
  3. document all of a patient’s symptoms and not just those that were tied to their primary diagnosis.
Controversies

1. Where to set the threshold? (Disorder VS Health). Spectrum is not defined in the new criteria. In research, reliance on arbitrary scales e.g. ADOS, SRS.

2. Introduces a neurodevelopmental cluster of disorders – no dimensional description – no differentiation of distress and impairment (disability) from disorder. Suggestion to also code with ICF to describe disability.

3. High level of co-morbidity will persist

4. Onset specific to childhood but need to allow for life course descriptions

5. ? Evidence for changes (removal of language/left brain deficits criteria for which there is evidence, addition of sensory sensitivities criteria which lacks research evidence)
Controversies

1. Loss of multi-axial diagnoses. May be covered by the vaguely defined “descriptors”: 2 Severity levels 1,2,3; Cognition, Medical; Comorbid disorders; Psychosocial.

2. Research dilemmas: prevalence, subtypes, specifiers, differential diagnoses vs co-morbid disorders, genetic/physiological risk factors (causes), gender differences, family environment (e.g. abuse/neglect), cultural factors, life span changes, validation and meta-analytic studies.

3. “Diagnosis” driven by service funding imperative (NDIS ASD Level 2).

4. Clinical utility. Current evidenced based treatments are mainly for specifiers not core symptoms (language delay, cognition, disruptive behaviour, parenting).
Challenge for clinicians

• Key challenge for clinicians will be to not lose a biopsychosocial formulation which provides the focus and rationale for interventions
Challenges for Research

1. How to create dimensional descriptions which can be applied to genetic/pathophysiological data to define endo and behavioural phenotypes

2. How to move to classification based on “neuroscience framework” (grouped by underlying pathophysiology, e.g. fronto-striatal disorders) an aspiration for the future
SCHIZOTYPAL DISORDER
(ICD-10, DSM-5)

• Pervasive social and interpersonal difficulties
• Reduced capacity for close relationships
• Cognitive and behavioural distortions
  • ideas of reference
  • odd beliefs
• unusual perceptions
• odd thinking / speech
• suspicious / paranoid ideas
• inappropriate or constricted affect
• eccentric/odd behaviour / appearance
• social anxiety associated with paranoid fears
• May be present from early childhood
Melbourne Assessment of Schizotypy in Kids (MASK)


Designed to measure CSD

• Draws on:
  – Schizotypy diagnostic symptoms and measures.
  – Other mental health scales for children.
  – Fantasy proneness and imaginary companions.

Format

• Semi-structured interviews for parent and child.
• Checklist of 57 schizotypal symptoms (rated on a 4-point Likert scale)
  – Reflect DSM- criteria for SPD.
  – Additional characteristics including fantasies, motor delays and attention deficits.
• Appropriate for use with young children.
• Takes approximately 1 hour and 30 minutes to administer.
Results – Group Differences

**Total MASK Score**

- **TD**
- **ASD**
- **CSPD**

***p < .001
<table>
<thead>
<tr>
<th>MASK Item</th>
<th>Factor 1 (Social/Pragmatic) Symptoms</th>
<th>Factor 2 (Positive Schizotypal Symptoms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has/displays difficulties completing fine motor tasks (e.g. has trouble writing neatly)</td>
<td>1.015</td>
<td></td>
</tr>
<tr>
<td>Has/displays difficulties when fine motor skills are required (e.g. manipulating, buttons, tools, utensils etc.)</td>
<td>0.950</td>
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<tr>
<td>Avoids eye contact during first session with clinician</td>
<td>0.945</td>
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<tr>
<td>Bases conversation topics on own interests</td>
<td>0.928</td>
<td></td>
</tr>
<tr>
<td>Has difficulty switching from own interests to other topics or activities</td>
<td>0.925</td>
<td></td>
</tr>
<tr>
<td>Fails to demonstrate the reciprocal nature of conversation (e.g. does not take turns)</td>
<td>0.900</td>
<td></td>
</tr>
<tr>
<td>Bases play themes on own interests</td>
<td>0.896</td>
<td></td>
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<tr>
<td>Is clumsy while completing tasks</td>
<td>0.851</td>
<td></td>
</tr>
<tr>
<td>Finds it difficult to communicate and socialise with other kids</td>
<td>0.838</td>
<td></td>
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<tr>
<td>Has/displays difficulties learning new motor skills after repeated attempts</td>
<td>0.817</td>
<td></td>
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<tr>
<td>Is fidgety or restless</td>
<td>0.810</td>
<td></td>
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<tr>
<td>Is pre-occupied with these fantasies to the point where behaviour is influenced</td>
<td>0.962</td>
<td></td>
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<tr>
<td>Describes a make-believe world or place as if it were real</td>
<td>0.961</td>
<td></td>
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<tr>
<td>Interprets innocuous or irrelevant events as being personally salient</td>
<td>0.927</td>
<td></td>
</tr>
<tr>
<td>Is paranoid or suspicious about innocuous or irrelevant events</td>
<td>0.901</td>
<td></td>
</tr>
<tr>
<td>Reports hearing voices/sounds that are not based on reality</td>
<td>0.877</td>
<td></td>
</tr>
<tr>
<td>Refers to a make-believe world or place</td>
<td>0.869</td>
<td></td>
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<tr>
<td>Imaginary characters, creatures or events appear important to the child, more so than actual friends or events</td>
<td>0.847</td>
<td></td>
</tr>
<tr>
<td>Has paranoid or suspicious ideas about the behaviour and motives of others</td>
<td>0.835</td>
<td></td>
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<tr>
<td>Expresses odd or bizarre ideas in speech</td>
<td>0.822</td>
<td></td>
</tr>
<tr>
<td>Refers to imaginary characters, creatures or events</td>
<td>0.821</td>
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The 2 Factor solution explains 54% of the variance with $SD_C$ scoring significantly higher than ASD or on Schizotypal Symptoms ($p<0.001$). Validity ROC analysis area under the curve 0.98 with 90.5% sensitivity and 93.3% specificity for $SD_C$ at cut-off score of 132
Differences between ASD and CSD

- The first empirical demonstration of this difference in childhood.

Does the phenotypical overlap between ASD and SDC reflect different cognitive styles and mechanisms at either end of a spectrum of attention and information processing?

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  3. School of Psychological Sciences, Monash University, Clayton, Victoria Australia
  4. The Child and Adolescent Neuropsychology Group, East Melbourne, Victoria, Australia
  5. Centre for Neural Engineering, University of Melbourne, Parkville, Victoria, Australia
  6. Centre for Developmental Psychiatry and Psychology, School of Clinical Sciences, Monash University, Victoria, Australia
  7. University of Warwick, UK.
Neurocognitive (CANTAB intra/extra dimensional attentional set shifting task) differentiation. $S_{DC}$ (8) and ASD (15) $S_{DC}$/ASD (12) and TD (32) (FSIQ <70 male 39/67). TD significantly higher FSIQ than ASD/$S_{DC}$. No other group difference (age, gender).

RESULTS: Both $S_{DC}$ and ASD perform worse than TD and co-morbid $S_{DC}$/ASD (0.001). In comparison with TD –  
- SDC had difficulty with intra dimensional shifts (<0.05)  
- ASD had difficulty with extra dimensional shifts (<0.00)  
- $S_{DC}$/ASD not significantly different from TD  
Controlling for gender, FSIQ, TD perform better than others ($p<0.001$) but co-morbid group perform better than SDC and ASD ($p<0.02$).

CONCLUSION: That a cognitive point of differentiation is that $S_{DC}$ are internally focussed and ASD are externally focussed, but when comorbid the attention impairments are attenuated in a compensatory manner.

Brain Function (fMRI) : Assessing Internal vs. External Cognition

**Active Task: Forced Choice**

Self-Referential (Internal) Condition: "Which do you like more?"

Veridical (External reality) Condition: "Which is bigger?"

Design: Alternating blocks of 5 item-pairs from each condition

**Passive Task: Attention**

Internal Condition: *Think about...* (individually meaningful event/activity)

External Condition: "Watch for the Arrow to appear"

Design: Alternating 30-second blocks of each
fMRI: Main Effects (All Participants)

Active Task: Forced Choice  
Passive Task: Attention

The tasks successfully tap into:

• “Internalizing” brain regions of the Default Mode Network, including: ventromedial PFC and posterior cingulate

• “Externalizing” brain regions comprising the “Central Executive Network”: dorsolateral PFC and posterior parietal cortices
fMRI: Between-Group Effects, SPD (n=8) vs. ASD (n=4)

- Active Task: Forced Choice
- Passive Task: Attention

• Preliminary data points to greater activity in BOTH the Default Mode and Central Executive Networks in SPD relative to ASD under both active and passive conditions.

• Definitive interpretations require further study, but early results suggest that the interplay between “internal” and “external” cognitive systems may reflect a point of distinction between these disorders.
Dean: age 6 yrs.

- Cognition difficult to assess with poor concentration and non-compliance, low average range
- Grade prep, often excluded due to aggression but at times ‘delightful, sociable but feared by children’.
- “Probably on the spectrum”
- Caring but anxious mother at ‘wits end’, reports a caring and lovely son who ‘switches into a real world of angry characters. Then you can’t reason with him.’
- Step–father bewildered and unable to cope.
Dean: Family history

• Father. No contact. Alcohol and substance abuse. Violence during the pregnancy ended the relationship.


• Dean has securely known his stepfather from the age of 18 months
School observation

• Period of constructive play ‘cooking’ with 2 children. Suddenly rushes to a group of children making rapid punching movements yelling to them to stop talking about him because he was a super hero.
• Aloof, muttering, aggressive play with blocks and scribbling on paper. Suddenly runs across room to “stab” teacher in the back with play scissors yelling “stop talking.. Not me.. Evil Dean will kill you”.
• On a group garden walk acts as if and indicates that he can see, hear and is being directed by “Mario”
Mental State

• Constructive interactive play with train set. Sees red crayon mark on wooden tracks. Jumps up, startled, punching movements, shouting, “that’s evil blood.. Evil Dean.. Punch you in the face”.. Incoherent and distressed.

• Visual mood scales: unable to focus and complete. (sad/happy) points , ‘more bad, fighting him ..I’ll punch him real fast, I need red and he’s getting.. ??
Draw a Dream1a. ‘Another evil Dean .. that’s me in red clothes. . Punch him real fast (roars). (can you hear someone?) talking, growling (?). Saying Yoshi you’ll die (his soft toy),(? Your imagination). No a real ‘ Traff Tragon ‘ (?)}
Draw a Dream 1(b) (rapid agitated drawing, muttering) ‘a mortal combat fight... shoots lasers... (rapidly does drawings 3, & 4 with disjointed incoherent comments e.g ‘a little Helf’... evil school things (?) scorpions.. Yoshi died’.
Management

• Uncontrollable at school with aide and in psychological treatment.
• Remove access to violent pc games and media.
• Daily key behaviours score (0,1,2) to track change.
• Risperidone 0.25mg nocte.
• Implement behaviour & communication skills strategies.
• Dramatic shift: cooperative, friendly, amenable to receive assistance to play cooperatively with children who had been fearful of him.
• Loving towards Mother Step father and step sister.
• Progressive return to full time school.
• Rejected for NDIS funding, “not ASD level 2 severity, SD not recognised as a chronic mental health disability”.