Fragile X Syndrome & Recent Advances in Behavioural Phenotype Research

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Fragile X Syndrome (Turk, 2011)

- The most common identifiable inherited cause of intellectual disability & autism spectrum conditions

- Intellectual functioning
  - Usually mild to moderate intellectual disability range
  - Language skills superior to non-verbal abilities
  - Slowing of skill acquisition towards adolescence because of sequential information processing challenges
Fragile X Syndrome: Speech & Language (Cornish, Sudhalter & Turk, 2004)

- jocular litanic phraseology
- perseveration
- repetitiveness
- echolalia
- cluttering
- sounds more rapid “but isn’t”
Fragile X Syndrome: Social impairments (Turk & Graham, 1997)

- social anxiety
- aversion to eye contact
- self-injury, usually hand biting in response to anxiety or excitement
- delayed imitative and symbolic play
- Insistence on sameness & routines
- stereotyped & repetitive behaviours, especially hand flapping
Fragile X Syndrome & Autism: 
(Cornish, Turk & Levitas: 2007)

- 4-6% of people with autism have fragile X syndrome
- A substantial minority of people with fragile X syndrome have autism (29%)
- Many more have a characteristic friendly, sociable (shy & socially anxious) personality with communicatory and stereotypic “autistic-like” behaviours
Distinguishing Behaviours:

- delayed echolalia
- repetitive speech
- hand flapping
- gaze aversion
- good understanding of facial expression (Turk & Cornish, 1998)

- Theory of mind as expected for general levels of ability (Garner, Callias & Turk 1999)
- friendly and sociable but may be shy
Fragile X Syndrome: Attentional deficits *(Turk, 1998)*

- poor concentration
- restlessness
- fidgetiness
- impulsivity
- distractibility
- +/- overactivity
When you control for age and intellectual ability:

- Boys with fragile X syndrome show similar rates of Hyperkinetic Disorder to those with intellectual disability of unknown cause.
- And the same levels of overactivity.
- But they show greater inattentiveness, restlessness & fidgetiness.
- And these features don’t diminish with increasing developmental ability.
## Follow-up Study of Boys & Young Men: Social Aspects (Das & Turk, 2002; Turk et al., 2003)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>1992</th>
<th>2002</th>
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<tbody>
<tr>
<td>AUTISM</td>
<td>28.6%</td>
<td>58.8%</td>
</tr>
<tr>
<td>ATYPICAL AUTISM (PDD-NOS)</td>
<td>30.6%</td>
<td>26.5%</td>
</tr>
<tr>
<td>AUTISTIC SPECTRUM DISORDER</td>
<td>59.2%</td>
<td>85.3%</td>
</tr>
<tr>
<td>NO AUTISTIC DISORDER</td>
<td>40.8%</td>
<td>14.3%</td>
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Premutation Effects

- Developmental & behavioural phenotypes
- Premature ovarian insufficiency
- Tremor-ataxia syndrome
Boys with Fragile X Premutations:
(Aziz et al., 2003)

↑ rates of:
• Uneven cognitive profile
• Delayed development of adaptive behaviours
• Autistic spectrum disorders
• Attention deficit disorders
• Speech & language problems
  • Social use of language
  • Speech intelligibility
  • Expressive language
Fragile X Tremor-Ataxia Syndrome
(Kogan et al., 2007; Cornish et al., 2008)

- Progressive cognitive decline from middle age onwards with development of atypical Parkinsonism
- Molecular: CGG repeat 55 – 200
- Clinical
  - Major: intention tremor, gait ataxia
  - Minor: Parkinsonism, short-term memory problems, executive function deficits
- Radiological:
  - Major: MRI white matter lesions involving middle cerebellar peduncles
  - Minor: MRI white matter lesions involving cerebral white matter, generalised brain atrophy
- Histological: intracellular inclusions
Fragile X Syndrome: Sleep Disorders
(Gould et al., 2000)

- ↑ variability in total sleep time
- Difficulties with sleep maintenance
- ↑ nocturnal & daytime melatonin levels
Fragile X Syndrome: Longitudinal Developmental Trajectories (5-35 yrs)

- Intellectual functioning levels stable over time
  - But impact of difficulties with *sequential information processing* & *working memory* difficulties increases
- Verbal/performance discrepancy stable over time
- Adaptive behaviours & social independence improve over time, but small minority do badly? why
- Gross motor overactivity diminishes over time, but inattentiveness, impulsiveness and distractibility persist
- Language tendencies and anomalies persist
Targeted Medications

- mGlu5R
- GABAergics
- Glutamate antagonists: e.g. mavoglurant
- Lithium
- Minocycline
- Baclofen & Arbaclofen
- Suramin – purinergic antagonist
- Cannabinoids
• mGlu5R antagonist AFQ056 ("mavoglurant")
• 30 males with fragile X syndrome aged 18-35
• Aberrant Behavior Checklist scores significantly ↓
• Side Effects:
  • Fatigue
  • Headache

• But recent studies less positive
Leigh et al., 2013

- Randomised, double-blind, placebo-controlled cross-over trial; **minocycline**
- 66 humans with fragile X syndrome aged 3.5 – 16 years
- Clinical Global Impression Scale significantly improved
- Anxiety ↓
- Mood-related behaviours ↓
- N.B. Short-term study – long terms follow-up needed
- N.B. risks of permanent dentition staining & opportunistic fungal infections
Berry-Kravis et al., 2012

- Arbaclofen
- Randomised double-blind placebo-controlled cross-over study
- 63 human males, full mutation, 6-39 years
- Significant improvements in parent-rated problem behaviours
- Social avoidance ↓
- Irritability unchanged
Naviaux et al., 2015

- Suramin – purinergic antagonist
- Initially used medically for treatment of trypanosomiasis
- Behavioural analysis, mass spectrometry, metabolomics, electron microscopy, Western Blot analysis
- Earlier work: antipurinergic therapy reverses behavioural & metabolic abnormalities in maternal immune activation (MIA) mouse model of ASD in juveniles & adults
- Antipurinergic therapy with suramin restores normal FMRP & normal behaviours in MIA mouse model
- But potentially toxic long-term side-effects
  - Nausea, vomiting, urticaria, adrenocortical damage, tingling/crawling sensations
  - More rarely kidney damage, exfoliative dermatitis
Cannabinoids
Endocannabinoid System = key modulator of
Synaptic plasticity
Cognitive performance
Anxiety
Nociception
Seizure susceptibility
CB1R blockade in male FMR1 knockout mice
  o Normalisation of cognitive impairment
  o Normalisation of nociceptive desentisation
  o ↓ susceptibility to audiogenic seizures
  o Normalisation of altered spine morphology

CB2R blockade in male FMR1 knockout mice
  o Normalised anxiolytic-like behaviour
Rational Prescribing

- Psychostimulants: ADHD
- Clonidine: ADHD, anxiety, sleep
- SSRIs: ↓ mood, anxiety (including social), OCD
- Traditional anticonvulsants: mood & behaviour stability
- Melatonin: sleep induction