Nonverbal Cognitive Impairments in Fragile X Syndrome: A Neurocognitive Basis Shared With Other Developmental Disorders?

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Overview of Syndromes

**fragile X** (Full Mutation)
- Source - Xq27.3 mutation, > 200 CGG repeats
- Prevalent VIQ>PIQ pattern
- Impaired space, time, numbers & “executive” cognition

**Turner**
- Source - X monosomy (45,X)
- Prevalent VIQ>PIQ pattern
- Impaired space, time, numbers & “executive” cognition
Overview of Syndromes

Chromosome 22q11.2 Deletion (22q11.2DS/VCFS)
- Source - 1.5 - 3Mb chromosome 22q11.2 deletion
- Prevalent VIQ>PIQ pattern
- Impaired space, time, numbers & “executive” cognition

Williams

- Source - 7q11.23 deletion
- Prevalent VIQ>PIQ pattern
- Impaired space, time, numbers & “executive” cognition
What is the Research Question?

Children from several different developmental disorder populations have similar impairments in “non verbal functioning”

- visual-spatial, visual-motor, time, numbers, math, attention

Often called “Nonverbal Learning Disorders” (NLD)

Reasonable(-ish) description, but what is explanation?

- is there an underlying brain/mind account?

What follows is a possible explanation & supporting data
Collapsed WASI, WISC III, WISC IV IQ DATA
22q (N=57), TD (N=45), Turners (N=15), Fragile X (N=15)

Population IQ Profiles

<table>
<thead>
<tr>
<th>Indices</th>
<th>TD</th>
<th>DS22q11.2</th>
<th>Turner Syndrome</th>
<th>Fragile X</th>
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<tbody>
<tr>
<td>FSIQ</td>
<td>114</td>
<td>116</td>
<td>111</td>
<td>112</td>
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<td>VIQ/VCI</td>
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<tr>
<td>PIQ/PRI</td>
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<td>PSI</td>
<td>72</td>
<td>84</td>
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<td>74</td>
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</tbody>
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Reaction Time Task

Task: Press the button as quickly as you can when you see the alien

Measures simple psychomotor speed
Reaction Time Task

Average Median Manual RT

- Control: 368.6 milliseconds
- DS22q11.2: 362.7 milliseconds
- FXS: 428.3 milliseconds
- TS: 410.0 milliseconds
Objects, Space & Numbers

Space and Time are abstract concepts that have “scale” but no actual values attached to them. We use mental “units” to break them up meaningfully. We have to learn “how” much is a(n): inch/second, foot, hour. Numbers were invented to describe “how many” units.

What if your “mental units” don’t match parts of the real world accurately?

- Space/time estimates will be wrong, numbers won’t make sense.
- This is what I now think explains most of the overlapping cognitive impairments.

If so, we’ll know what to fix and how. We’re about ready to try!
Methods

Experimental Cognitive performance tasks
- Attention, Enumeration, Magnitude Judgment

MRI analysis
- Structure, Connectivity, Function

Standardized neuropsychological testing
- WISC IV, WIAT, Key Math, DKEFS, JLO ….
Prefrontal/Parietal Areas

Figure 2.24  Four lobes of the cerebral cortex, in lateral view of the left hemisphere. See text for details.

- Prefrontal Cortex (PFC)
- Central sulcus
- Parietal lobe
- Parieto-occipital sulcus
- Temporal lobe
- Pre-occipital notch
- Occipital lobe
Hypotheses

Spatiotemporal/Numerical/Executive impairments all derive from impairments in “building block” functions that typically depend on a “frontoparietal” brain network

- Posterior parietal lobe (PPL): objects, space, number
- PreFrontal Cortex (PFC): working memory, control

H$_1$: lower resolution “mental pictures” increase error
e.g. compare detail in image from 8mP vs. 1mP digital camera

H$_2$: neural network connection differences affect speed
e.g. Drive St. Louis - Chicago on I55 vs. via Indianapolis

All following experiments are designed to test these
If you fix your eyes (attention) on the cross, you cannot accurately count the bars to the right.
“Crowding” & Attentional Resolution
Reduced Space & Time Resolution

[Diagram of reduced space and time resolution]
Measuring Parts of Space

Task: Press button to choose who Kermit the Frog is closer to (Miss Piggy or Fozzie Bear?)

When Kermit is not close to one end or at the center, error occurs
Measuring Space

Spatial resolution reduced by ~30% on this task
Measuring Time

Duration comparison:
Judge longer of two durations: 400ms vs +/- 10ms diff.
(staircase method)
Auditory & visual

From Debbané et al., 2005

Temporal resolution reduced by ~35% on this task
Much evidence of spatial representations of magnitude
- adults create analog repns of approximate quantity
  - activations show large network w/PPL focus
- “near” quantities hard to distinguish than “far”
- infants discriminate large sets w.r.t. Weber law

**Predict:** Hypergranularity effects largest with small $\partial$, Dysconnectivity impairs speed
Distance Effect

Diffs = 1 to 7 (excl. 4), attempted balance for large/small $n$
Distance Effect Results: Blocks

Distance Effect Task: BLOCKS
22q (N=58), Controls (N=60), TS (N=28), FXS (N=14)
Distance Effect Results: Digits

Distance Effect Task: NUMBERS
22q (N=58), Controls (N=60), TS (N=28), FXS (N=14)
Comparing Quantities

Median Pitch Values

- Target Size
- Pitch

- Median 22q
- Median TD
- STANDARD

Sound (pitch) resolution appears to be identical!
So children with 22q are not just worse overall at comparing values...
Quantifying small sets (subitizing) does not require spatial “search” (shifts of attention) in adults
• PPL not involved (Sathian et al., 1999)
**Predict:** Hypergranularity effects minimal, Dysconnectivity effects not expected

Quantifying larger sets requires spatial attention shifts
• PPL (& other areas) are involved
**Predict:** Hypergranularity effects large, predict undercounts
Dysconnectivity impairs speed also
Enumerating & Attention

Enumeration task requires subitizing/counting of objects (or aliens)

within 2 degrees visual angle
Enumerating & Attention

**Enumeration Verbal Response: MEDIAN Reaction Time Values**

22q (N=36), Control (N=43), TS (N=25), FXS (N=14)
Attentional Networks Test - ANT

Single

Congruent

Incongruent

Predict: Hypergranularity effects varying by network tested. Dysconnectivity impairs speed.
ANT Orienting Results

Attention Networks Task (ANT) Gratton Version: Overall ORIENTING
22q (N=48), ALL Con (N=52), FXS (N=12), TS (N=23)
ANT Gratton ALERTING INDEX: NEUTRAL - NONE
22q (N=48), ALL Controls (N=52), TS (N=23), FXS (N=12)
ANT Executive Results

Attention Networks Task (ANT) Gratton Version: Overall EXECUTIVE MEDIAN Adjusted Reaction Time

22q (N=48), ALL Con (N=52), TS (N=23), FXS (N=12)
Diffusion Tensor Imaging

Tensor Matrix has three primary diffusivities
• $\lambda_1, \lambda_2 & \lambda_3$

In brain $\lambda_1$ represents diffusion parallel to axonal fibers ... referred to as axial diffusivity

Diffusivities perpendicular to axonal fibers, $\lambda_2 & \lambda_3$, are averaged & referred to as radial diffusivity

Fractional Anisotropy (FA) is the fraction of the magnitude of [the tensor] we can ascribe to anisotropic diffusion
22q11.2DS Dysonnectivity

4 common clusters
- parietal L&R SLF
- frontal L&R FOF

FA: 22q11.2DS > TD
RD: TD > 22q11.2DS

Reduced cortical connectivity in fronto-parietal network?

FA/cognition correlation
(spatial attention task)
22q +ve in R. SLF
TD -ve in R. FOF

Axial = x (primary)
Radial = average(y+z)
FA = Axial/Total

In all clusters:
FA: 22q>TD, p<.0001
RD: TD>FA, p<.0001
Common Dysconnectivity Locus

FA: 22q>TD
FA: FXS>TD
FA: TD>TS

R. Inferior Parietal Lobe
Common Dysconnectivity Locus!

FA: 22q>TD
FA: FXS>TD
FA: TD>TS
Object Tracking Task

Ready?
Brain Activation Differences

22q: 1 > passive
TS: 1 > passive
TD: 1 > passive

Activations
1 target > passive view
FDR p < .01 corrected
t > 3.5
k = 100 voxels

22q N = 8  90% correct
TS   N = 7 90% correct
TD   N = 7 90% correct
FXS  N = 0 (high error)
NeuroTherapeutics

Now studying entire range of repeats and their “outcomes”

“dosage effect” is evident even in early findings

Suggests that interventions could reduce negative impact

- bring cognitive profile back closer to unaffected range?
- combination of planned video games & pharmacology?
Summary

Strikingly similar cognitive “endophenotype”
- despite differences on standardized measures

Preliminary evidence of similar neural dysconnectivity
- fiber tract integrity & “functional network”

Early evidence of common neurogenetic pathway?
- developmental convergence on similar “end state” from several different “start states”
Implications & Interventions

Advances in our research provide better understanding of:

- “software” running in minds of those with several disorders
- “data” that makes software less effective (hypergranularity)
- “hardware” that changes typical software & data

If we can explain it, maybe we should be able to “fix” it.

Evidence shows that typical spatiotemporal system is “plastic”

- i.e. gets better, faster, “sharper” with practice/stimulation

We need to do 2 things (together) to test our explanation:

1) carry out new studies to see if we are right
2) build and test intervention video games based on it
Collaborators

- Jim Gee, Brian Avants, Gary Zhang - Penn
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