Comparative analysis of spatial and temporal cognition in children with XXY or XXX. Is this the root of learning difficulties?

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2011 Mile High Families’ Conference for X & Y Chromosome Variations
Outline of Talk

- Focus on XXX/XXY in context of studies of 22q11.2DS
- Cognitive and neural characteristics in childhood
- Implications of cognitive/emotional challenge interactions
- Next steps
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XXX/XXY Syndromes

Fewer behavioral studies of extra X chromosome in boys & girls, though several longitudinal studies of each syndrome exist

- many more to date on 47/XXY(KS) than 47/XXX
- primarily using standardized neuropsychological instruments
- KS: many reports of verbal/language impairments & reading delay
- XXX: similar pattern but more global cognitive impairments?

Some reports of anomalous brain development; atypical lateralization of brain hemispheres (in XXY)

Increased ADHD (child), Schizophrenia (adult), anxiety have been reported but incidence remains unclear
Neuropsych/Cognitive Profile

Standardized tests show a unclear pattern for XXY/XXX

- Reviews: XXY (Geschwind et al 2000), XXX (Tartaglia et al 2010)

Full Scale IQ: reduced to superior (less discrepant in adulthood?)

- Verbal Domains (VCI) < Nonverbal (PRI/WMI)
  - in most individuals studied, but considerable variability is reported

- Reading/Spelling/Expressive Language & comprehension problems

- Math impairments present & appear to persist into adulthood

- Visuospatial impairments described but not systematically studied

- Attention (selective and “executive”) is impaired & ADHD rates are increased
  - i.e. inattention, planning, problem solving and inhibition are challenged

Experimental cognitive studies have not been carried out to date.
Chromosome 22q11.2 Deletion Syndrome

Deletion on chromosome 22 at q11.2 (22q11.2DS)

- aka Velocardiofacial (VCFS), DiGeorge & other names
- prevalence of \( \geq 1:4000 \) live births (~ fragile X syndrome)

Major manifestations include: heart defects, cleft palate, facial dysmorphisms, autoimmune disorders, anomalous brain development

ADHD (child), Schizophrenia (adult), anxiety/specific phobias, (both) elevated
Neuropsych/Cognitive Profile

Standardized tests show a stable pattern for 22q11.2DS

Full Scale IQ: 70-85 (±15)

- Verbal Domains (VCI) > Nonverbal (PRI/WMI) (in most children)
- Receptive > Expressive language < 5yrs, then pattern reverses
- Reading/Spelling (low avg) relative strengths, but comprehension poor
- Rote memory strong, complex memory verbal and all spatial memory is poor (Woodin). Working memory is poor
- Attention (selective and “executive”) is impaired

Experimental cognitive studies show: visuospatial, temporal, numerical & executive cognitive domain impairments

Simon, 2008 spatiotemporal limitations key to some impairments

- provides possible target for intervention (more later)
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Overall Intellectual Functioning

WISC IV IQ Data

\( N = 90, N = 21, N = 92, N = 20, N = 15 \)
Reaction Time Task

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

Measures simple psychomotor speed
- a key part of many of our measures.
Simple Reaction Time Task

Average Reaction Time (median adjusted)

TD=58

22q11.2DS=31

SCA=19
Objects, Space & Numbers

Space/Time play some role in language but critical for reading/math.

Space and Time are very 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.
- “Digital camera” analogy of mental representation -> Crowding.

Reading requires spatial/temporal integration. Impaired by crowding.
“Crowding” & Attentional Resolution

From Cavanagh, 2004
Crowding makes it hard to see one of the children in the street. Whitney & Levi, 2011
Spatial Vision “Sanity Check”

Keep your eyes fixed on the blue “pirate ball”
Judge if the middle line is to the left, right or aligned with those above & below it

The 22q11.2DS group has the same spatial visual acuity as TD kids and those with XXY/XXX
Spatial Resolution & Comparison

Tests representational basis & specificity of quantitative comparison impairment
- spatial magnitudes & auditory pitch

Task uses limited *adaptive* algorithm
“Target” initially 50% of length of “standard”
- if 3/4 trials correct reduce difference 50%
- else increase difference by 50%
- all stimuli followed by mask

Q: First or second blue bar longer?

Auditory pitch task tests specificity
Adaptive task indicates reduced resolution of analog spatial but not auditory pitch representations.

Graph shows % of each group that "pass" each level & proceed to next most difficult.
Spatial Resolution

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.
Reduced resolution in 22q11.2DS only lowers spatial accuracy when location in space is unclear (i.e. not center or ends)
Temporal Resolution

Tests resolution of temporal attention.

“Oddball” alien flickers out of phase with other 3. Pick the oddball at different flickering speeds. At what speed, i.e. temporal resolution does detection performance drop?

All groups well above 25% chance.
All best at 2-4 cycles/sec.
22q11.2DS group 25% worse
In “real life” we use attention to integrate information over space and time:
- to track where we and other things are
- to estimate distance and duration
- to read, to navigate ..... 

We can measure amount resolution reduction:
- is 3 a “crowd”, or 2?
Spatiotemporal Resolution

All kids in study accurately track fewer than 3 targets

*Dynamic crowding* reduces capacity in 22q11.2DS group only

- less spatiotemporal information available for mental processes
Spatial/Temporal Processing Summary

So far boys with XXY, girls with XXX show no cognitive impairment

- BUT, small samples to date & hard to assess variability
- basic spatial/temporal processing appears totally typical
- unlike to be underlying “dysfunction” behind reading/math issues

Experiments don’t address issues of language/comprehension

- need new studies for that

Q: Any clues from brain imaging concerning basis of impairments?
Brain Structure, Function & Circuitry

Well-defined brain circuits typically process different information.

- Many components of space/time/attention atypical in 22q11.2DS.
- Much less is known about XXX/XXY.

Genetic influence might create suboptimal processing circuits.

- Their “dysfunction” could impair typical development.
- Weaker cortical circuits for cognitive function might result.

However, much brain circuitry sculpted in experience-dependent (both good and bad) fashion into young adulthood.

- Thus, enhancing optimal behavior will enhance brain development.

Q: What are optimal behaviors for each population’s impairments?
Studying Multiple Object Tracking in the MRI scanner allows us to see:

- if similar circuits are used by those with/without impairments
- if degree and pattern of activation relates to performance

... and maybe

- if intervention can change activation and performance
2 targets vs. passive MOT

TD (n = 16)

22q11.2DS (n = 14; c2)

XXX (n = 4)

XXY (n = 7)
Diffusion Tensor Imaging

DTI images connective tracts

Can measure three major diffusion directions
• $\lambda_1$, $\lambda_2$ & $\lambda_3$

In brain $\lambda_1$ represents diffusion parallel to main fiber pathways ... referred to as axial diffusivity

Diffusivities perpendicular to main fiber pathways, $\lambda_2$ & $\lambda_3$, 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
Superior Longitudinal Fasciculus (SLF)
- connects frontal, parietal, temporal and occipital lobes
- “association fiber pathway” - linked to many cognitive functions
  - esp. visuospatial, numerical

Arcuate Fasciculus (AF)
- component of SLF
- connects frontal & temporal lobes
  - Broca’s/Wernicke’s areas
- strongly linked to language functions
  - comprehension
  - lexical function
  - disconnection hypothesis
SLF & AF in XXY/XX vs 22q & TD

TD

posterior SLF towards parietal cortex

22q

pSLF: fewer parietal fibers than TD

XXX/XXY

AF towards STG

pSLF: similar to TD

AF: fewer STG fibers

Michelle Deng
Brains Change Over A Long Time

Time-lapse "movie" compresses 15 years of normal brain development (ages 5-20) into just a few seconds. Red indicates more gray matter, blue less gray matter. Gray matter wanes in a back-to-front wave as the brain matures and neural connections are pruned. Areas performing more basic functions mature earlier; areas for higher order functions mature later. The prefrontal cortex, which handles reasoning and other "executive" functions, emerged late in evolution and is among the last to mature.

Gogtay et al., 2004 PNAS

Some of the last regions to mature
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Attention, Arousal & Behavior

Attention functions to select among competing, salient inputs
- salience changes dynamically and is driven internally & externally
  - External:
    - what teacher is writing on the board
    - what the kid next to me is doing
  - Internal:
    - how much do I want/need to learn to read?
    - how much does reading make make head/tummy hurt?
    - how much yummier does that cookie look when dieting?

Stress & Anxiety alter arousal & arousal alters salience
- threshold for what enters consciousness drops (survival)
- suddenly more things are competing for (impaired) attention
- “spotlight of attention” is pulled in multiple directions
- nothing is attended long/deeply enough for reading & learning

Explains significant proportion of ADHD Dx?
Anxiety & Functional Abilities

Adaptive function NOT related to IQ in 22q but IS related in TD kids

Adaptive function IS related to anxiety levels

N=78, r=0.03; p=0.74

N=78, r=-0.27; p=0.017

Angkustsiri et al., in preparation
Anxiety & Functional Abilities

Adaptive function NOT related to IQ in XXY/XXX

Adaptive function IS related to anxiety levels.
In TD also, but few in ≥60 range of significant anxiety.
Stress/Anxiety Intervention

Evidence Based Behavioral Approaches

- Cognitive Behavioral Therapy (CBT)
  - high linguistic/conceptual demands
- Biofeedback, Meditation, Exercise ...

Work with (any) good clinician

Pharmacological Approaches

- SSRI - Selective Serotonin Reuptake Inhibitors
  - reasonable concerns but safe & effective
- Stimulants - ADHD medications

Work with pediatrician/psychiatrist
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Next Steps

- Study continues for 2.5 - 3 more years
  - need to recruit more participants - 20 to 30 per XXX/XXY group
  - ESPECIALLY girls with XXX!

- Larger groups will enable examination of variability

- Similarities/Differences will likely lead to hypotheses about what IS the source of main learning challenges

- Hopefully that is focus of new grants and explorations of targeted, evidence-based interactions
Our research approach integrates several areas for translation:

- Representational changes underlying cognitive impairments
- What is and is not the source across several disorders
  - Spatial/temporal processing likely not key cause in XXX/XXY
- Resulting explanations inspire designs for targeted intervention
- Allostatic load of challenges & neurobiological stress responses likely modulate coping success (+/- family & community supports)
- Cognitive control/executive function changes that might result and impair further cognitive & behavioral development

Interaction of cognition, social-emotional & biological factors to identify risk and protective factors for cognitive & behavioral outcomes
The Genetic Disorders Puzzle

- **Genetics**: heart, immune, brain
- **Trauma**: surgery, illness, loss
- **Cognition**: academic, social, practical
- **Community**: family, school, friends
- **Affect**: stress, fear, anxiety
- **Biology**: regulation, expression
- **OUTCOMES**: behavioral, psychiatric, educational, vocational, interpersonal, romantic, parenting

The Gene’c Disorders Puzzle
Thanks

MOST important: Kids who participated & their families!!

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