Cognitive Function is Related to Anxiety and Adaptive Function in Children with 22q11.2DS

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Core Working Hypothesis

Attentional/Cognitive Control impairments limit competence
- mental representation impairments limit development in domains like space, time, number
- cognitive control impairments limit behavioral/cognitive regulation

Impaired cognition (borderline IQ) creates/interacts with increased stress/anxiety to further modulate/challenge development
- stress/anxiety increase inattention and decrease cognitive control

Family/School/Community supports further modulate above interaction & influence “coper/struggler” trajectory
- strugglers might experience higher “allostatic load” & psychosis risk

If so, we can help target cognitive, emotional and environmental factors for intervention to improve academics, mental health, family dynamics
Clinical Evaluations in our 22q Healthy Minds Clinic

Information for families with children affected by chromosome 22q11.2 deletion syndrome

An important part of your visit to the MIND Institute is the opportunity for your child to have a detailed clinical evaluation completed by a developmental and behavioral pediatrician, licensed psychologist with expertise in developmental clinical neuropsychology and, where appropriate, child and adolescent psychiatrist. Each of these clinical experts in 22q11.2DS (VCFS/D/George) will complete a best practices evaluation, consult together as an interdisciplinary team, talk with you about the results, provide individualized recommendations for support and intervention, and prepare a written report that will be delivered to you. They also may be available for some limited supportive follow-up.

Recently, grants from the Dempster Foundation and numerous private donations have enabled us to establish the “22q Healthy Minds Clinic” for clinical assessments on a case-by-case basis. We have had some success seeking authorization and payment from health insurance and associated mental health carve-outs, and are now inviting families to contact us to see if their child is an appropriate candidate.

The first step towards a possible assessment appointment is to contact our Coordinator at cabil@ucdmc.ucdavis.edu for information. Please put “22q Clinical Assessment” in the Subject Line. We will then assist you in the process of securing a referral (if appropriate) by providing information to help you follow the steps outlined here. To further assist you, we have provided a sheet with answers to Frequently Asked Questions about the Clinic appointments.
Spatial Resolution & Comparison

Tests ability to mentally represent & compare quantitative info
Tests specificity/generality impairment using adaptive algorithm
- spatial magnitudes & auditory pitch to test "crowding"
- first or second blue bar longer? (first or second pitch higher?)
Almost all of our data comes from 7-15 year old children

Adaptive magnitude comparison:

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<tr>
<th>Target/Standard Ratio</th>
<th>TD (n=32)</th>
<th>22q (n=35)</th>
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Adaptive pitch comparison:

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<th>Target/Standard Ratio</th>
<th>TD (n=31)</th>
<th>22q (n=36)</th>
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Cognitive Control

Go/No-Go Response Inhibition Task:

- “Go” trials (75%): press a button as quickly as possible to “whack” the mole
- “No-Go” trials (25%): do NOT press button to avoid “squashing” the vegetable
  - Preceded by 1, 3, or 5 “Go” trials
Cognitive Control - Overall Results

Do These Problems Cause Stress?

Some quotes from an adult posting on Facebook:

- "it seems like I really only have a few things that stress me out. One of my big stressers is dealing with change and coins. ... I have no clue why change makes me panic, but I am trying to learn it....They don't understand that its difficult for me even if it shows the amount or not, I am not able to process it in my head. That is the most frustrating thing ever. For some reason when I am not in a rush, or when I am not feeling stressed, I can do it just fine. Math is the other big stresser; Its always going to be hard for me no matter how many classes I take, I just like to stay away from it as much as possible”.

- "I feel like this direction stuff is driving me nuts. No matter how many times we practice driving to the new spot, I still don't get it. I am completely lost. I am not making it up, it's frustrating cause I dont know why it's so confusing for me. I have to practice knowing where I'm going, and then people eventually notice, and then I get embarrassed :(("
Core Working Hypothesis

- Attentional/Cognitive Control impairments limit competence
  - Spatiotemporal capacity/acuity limits from reduced resolution impair development in domains like space, time, number
  - Cognitive control limits reduce effective resource deployment

- Impaired cognition (borderline IQ) creates/interacts with increased stress/anxiety to further modulate/challenge development
  - Anxiety increases inattention/decreases cognitive control

- Family/School/Community supports further modulate above interaction & influence “coper/struggler” trajectory
  - Strugglers experience higher allostatic load & schizophrenia risk

Integrative stress-diathesis model indicates tractable early intervention targets in child, family and environment

Biological Indicators of Stress

- Mock MRI scanner and daily saliva collection tubes with event recorder (inset).

- Mean salivary CORTISOL levels (ug/dL) before mock-MRI practice session, 25 mins post Time 1 and total CORT output.

- Statistically higher CORT output in 22q11.2 DS. Beaton et al. submitted
Anxiety & Functional Abilities

Adaptive function NOT related to overall IQ. Unlike TD/most other NDDs

Adaptive function IS related to anxiety levels

Anxiety levels related to stress hormone level, maybe psychosis risk

Parent-reported symptoms in child of Panic/Agoraphobia, Obsessive Compulsive, Separation Anxiety symptoms are related to Adaptive Function. But NO relationship between Social Phobia/Generalized Anxiety Disorder and General Adaptive Score

Angkustsiri et al, submitted

Beaton et al, submitted; Beaton & Simon, 2011
Anxiety and Attention

Very new tasks gently manipulate emotional content with different faces to see if “threat” changes functioning:
- anxious children switch attention to “threat” losing some control

Dot probe RTs suggest 22q group drawn to angry faces (threat bias):
- positive scores indicate “vigilance” for angry faces
- some evidence of relation to the one fear anxiety index checked so far
Anxiety and Attention

What does this actually look like? How “distracting” is threat?
- Movie #1 a typical child with no emotion bias
- Movie #2 a child with 22q11 with a strong threat (i.e. angry face bias)

Anxiety and Executive Function

Does any relationship exist between anxiety, adaptive function and the cognitive precursors of schizophrenia?
- more anxiety might related to weaker Executive Function
- better adaptive function might relate to stronger cognitive control
- Bishop, ’09; Krug & Carter ’10: anxiety impacts PFC function
Atypical Anxiety Development

Unlike TD children, separation anxiety increases with age in 22q11.2DS
- likely complex interaction of developmental delay, “sheltering” ...
- notice diverging trajectories after 9yrs - copers vs strugglers?

IQ of 75 means operating as a 9-year-old in a 12-year-old’s world
- 35-50% % Children with 22q11.2DS get a diagnosis of ADD mainly Inattentive or combined type) and take medications
  - Does “ADD” = hyperarousal/hypervigilance from anxiety?
- Many children get diagnosed with OCD (part of anxiety)
  - most likely anxiety-driven “coping” behaviors (control)
- Mismatches between capabilities and demands induce stress, which can lead to anxiety, avoidance and reduced motivation and self esteem
  - reducing “allostatic load” might protect against psychosis
- Mismatched cognitive and social demands & resulting anxiety and avoidance might explain frequent “Autism” diagnoses
Children with 22q11.2DS have social and communication impairments, sometimes along with repetitive behaviors, but is it really autism?

Many (20-50%) children screen positive for ASD symptoms or meet criteria based on the ADI-R, which is only one part of the gold-standard assessment for ASD diagnosis (Antshel et al., 2007; Kates et al., 2007; Vorstman et al. 2006) as is the case for CABIL cohort (N=90)

No one has published ASD diagnoses using gold-standard assessments. This requires BOTH

- Autism Diagnostic Interview-Revised (ADI-R) or (Social Communication Questionnaire-SCQ based on ADI-R)
- Autism Diagnostic Observation Schedule (ADOS)
Autism? Or Anxiety & Cognitive Delay?

- 29 children with 22q11.2DS ages 7-14, 16 boys; 13 girls
- using only one assessment, 7-18% demonstrated concerns for ASD, but no child met strict diagnostic criteria for ASD using both SCQ and ADOS

<table>
<thead>
<tr>
<th>Test</th>
<th>positive</th>
<th>total</th>
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<tr>
<td>SCQ</td>
<td>2 (7%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>ADOS</td>
<td>4 (15%) ASD</td>
<td>1 (3%) Autism</td>
</tr>
<tr>
<td>SCQ+ADOS</td>
<td>0</td>
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29 children with 22q11.2DS ages 7-14, 16 boys; 13 girls using only one assessment, 7-18% demonstrated concerns for ASD, but no child met strict diagnostic criteria for ASD using both SCQ and ADOS.

Depression Measures (CDI)

Beaton et al. submitted
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Conclusions

Cognitive impairments/Developmental Delay induce stress
- Chronic stress induces anxiety, depression, reduces self-esteem
- Avoidance of challenge slows development further, increasing challenge

Family/School/Community supports further modulate this interaction & influence “coper/struggler” trajectory
- strugglers might experience higher “allostatic load” & psychosis risk

Strugglers can be converted to copers with child, school, family change
- not with stem cells or brain surgery but commonly available therapy
  Child: cognitive behavioral/behavioral therapy, SSRI, cognitive training
  School: effective IEP, careful calibration of challenge based on testing
  Family: coping strategies for parents, matching parent/child expectations
Thanks

MOST important: Kids who participated & their families!!

Majority of the work presented here was done by:

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