When Feeling Meets Thinking: How cognitive impairment and emotional regulation drive (mis)behavior

Tony J. Simon Ph.D.
MIND Institute
University of California, Davis
tjsimon@ucdavis.edu
Twitter: @22qUCDMIND
Outline of Talk

- Introduce several neurodevelopmental disorders (NDDs)
- Present the Coper/Struggler challenge notion
- Show patterns of impairment across syndromes
- Explore the cognition/emotion relationship
- Ask if explains behaviors that can lead to diagnostic labels
- Some responses to reduce challenges & unwanted behavior

**TAKE AWAY**: In challenged children, cognitive impairment and emotional dysregulation influence each other bi-directionally. This account might help explain the problem and guide responses.
Chr. 22q11.2 Deletion Syndrome

Deletion on chromosome 22 at q11.2 (22q11.2DS)
❖ aka Velocardo[facial (VCFS), DiGeorge & other names
❖ prevalence of 1:1000 - 2000 live births (> fragile X syndrome)

Major manifestations include: heart defects, cleft palate, facial dysmorphisms, autoimmune disorders (thymus), anomalous brain development - many MIDLINE anomalies

❖ ADHD (child - 20-50%), Anxiety (50-60% child/adult),
❖ Schizophrenia (adult ~30% vs. 1% general population)
❖ Autism Spectrum Disorders 20-50% (Antshel ’07; Vorstman ‘06)
❖ based on parental interview (ADI-R) alone
❖ Based ADOS & SCQ (& clinical impression) 0% Angkustsiri et al ‘13
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
❖ Reading/Spelling (low avg.) relative strengths
❖ Comprehension poor (learning to read - OK; reading to learn - very hard)
❖ Rote memory strong, complex memory verbal and all spatial memory is poor. Working memory is poor
❖ Attention (volitional selection) is impaired
❖ Executive function (Cognitive Control, WM, Inhibition) is impaired
22q11.2 Deletion Neural Cascade

Figure 4 | A framework for the pathogenesis and pathophysiology of 22q11.2 deletion syndrome. Reduced gene-dosage of more than one gene affects brain function at multiple levels in 22q11.2 deletion syndrome (22q11.2DS).
Other Syndromes

**fragile X (Full Mutation)**
- Source - Xq27.3 mutation, > 200 CGG repeats
- Verbal Domains (VCI) > Nonverbal (PRI/WMI)
- Impaired space, time, numbers & “executive” cognition
- Anxiety: “significant”, ADHD: majority of boys, ~30% girls

**Turner**
- Source - X monosomy (45,X)
- Verbal Domains (VCI) > Nonverbal (PRI/WMI)
- Impaired space, time, numbers & “executive” cognition
- Anxiety & ADHD: common/significant (rates unclear)
Other Syndromes

Trisomy X (XXX)/Klinefelter (XXY)

Standardized tests show a unclear pattern for XXY / XXX

Full Scale IQ: reduced in most affected individuals

❖ Nonverbal (PRI/WMI) > Verbal Domains (VCI)
  ❖ in most individuals studied, but considerable variability
  ❖ Reading/Spelling/Expressive Language & comprehension problems
  ❖ Math impairments present & appear to persist into adulthood
  ❖ Attention (selective and “executive”) is impaired

Increased ADHD (child ~35-45% XXY, 25-25% XXX), anxiety have been reported but incidence remains unclear
Overall Intellectual Functioning

WISC-IV IQ Data

Average Score

Diagnostic Group

- 22q11.2 Deletion Syndrome
  - N = 150
- Fragile X Syndrome
  - N = 20
- Turner Syndrome (X)
  - N = 15
- Klinefelter's Syndrome (XXY)
  - N = 25
- Trisomy X Syndrome (XXX)
  - N = 18
- Typically Developing
  - N = 73

Subscale

- FSIQ
- VCI
- PRI
- WMI
- PSI
Core Working Hypothesis

Cognitive impairments limit competence in numerous domains
❖ but vary widely among children and across ages
Despite cognitive limitations some children outperform predictions from testing while others fall very short
❖ “copers” show lower anxiety, higher real world functioning and often achieve in academics far beyond what cognitive testing would predict
❖ “strugglers” show the reverse pattern - more anxiety poorer adaptive functioning and worse academics
Q: does coper/struggler status affect psychiatric diagnoses?
Matching Abilities to Requirements

Fear, Hyperarousal, Fight or Flight

Emotional Dysregulation, Allostatic Load?
Anxiety, Not IQ Predicts Adaptive Function

Angkustsiri et al., J. Dev. Beh. Peds., 2012

Unlike TD children, FSIQ is NOT related to adaptive function in children with 22q11.2DS aged 7-14 years.

In children with 22q11.2DS aged 7-14 years, adaptive function is strongly and negatively related to anxiety levels.

22q11.2, N=62; r=-0.34,
Anxiety, Not IQ Predicts Adaptive Function

- Parent-reported symptoms in child of Panic/Agoraphobia, Obsessive Compulsive, Separation Anxiety symptoms are related to Adaptive Function in 22q11.2DS

- But NO relationship between Social Phobia/Generalized Anxiety Disorder and General Adaptive Score in 22q11.2DS

Angkustsiri et al. submitted
Atypical Anxiety Pattern With Age

The less well you feel you can/expect to be able to cope, the more fear/worry you have, the less confident you feel.

So you are more anxious about coping in the world by yourself?
Check-In #1

The Story So Far

❖ Overall ability (e.g. IQ) may not predict functioning well
❖ How well abilities match requirements may predict better
❖ Being “out of your depth” provokes anxiety / stress
❖ Anxiety = anticipation of (repeated challenge)
❖ Anxiety and ability to function affect each other
One Critical Cognitive Impairment

❖ Fix your eyes on the cross on left. Count the bars on the right without moving eyes

![Image of cross and bars](image)

This is the phenomenon of spatial “crowding"
❖ you can “see” and mentally represent each of the 5 bars, BUT
❖ even though you can count, you cannot count EACH of these
❖ your brain cannot represent each one as a unique item
Spatial Resolution & Comparison

Tests ability to mentally represent & compare quantitative info
Find “threshold” for impairment using adaptive algorithm
❖ spatial/temporal magnitudes & auditory pitch to test “crowding"
❖ first or second blue bar longer? (1st/2nd duration/pitch greater?)
Temporal/Pitch Resolution

Temporal Duration Judgment – Auditory (TDJ – A)
❖ 2 rockets in a race to space. Rocket 1 emits tone, then Rocket 2
❖ Determine which rocket had a longer sound (or trip to space)

Temporal Duration Judgment – Visual (TDJ – V)
❖ Which panda was on the screen longer?

Auditory Pitch Comparison (APC) - which tone higher?
Reduced Spatiotemporal Resolution

Children with 22q have much worse spatial/temporal resolution. Similar pitch performance suggests ability to compare unimpaired. Impairment comes from nature of information being processed.

❖ SCA group combines XXY & XXX groups
Searching For/Counting Things

Task: Say out loud, as fast as possible, how many green boxes you see

Mental pictures of 3 or fewer usually created “all at once”
But for larger sets must find and count one object at a time
• then treat all the collected parts as a whole = 7
Enumeration Performance

Enumeration Verbal Response: MEDIAN Reaction Time Values
22q (N=36), TD (N=48), TS (N=30), FXS (N=21)
Primary outcome measures were response time and error rate.

Data analysis

Data processing and statistical analyses were conducted using R, version 2.11.1 (R Core Team, 2012). Response times (RTs) less than 150 ms were defined as anticipatory responses, and these trials were removed from the analysis. For girls with 22q11.2DS on average 1.5 trials were removed, girls with TS had 2.0 trials removed, girls with FXS had 3.7 trials removed, while TD girls only had 0.1 trials removed. Of the remaining trials, the median RT and percentage of incorrect trials were calculated and used for further analysis. The mean percentage of incorrect trials for each group is listed in Table 1. No participants performed below chance level.

Within each condition, we calculated an adjusted RT by using the formula RT/(1 - error rate) to reflect both speed and accuracy for each child. The use of an adjusted RT was done, as before [26], to assess the full performance range of children with NDDs who are known to produce higher error rates. Using this adjustment, error-free RT remains unchanged at 100% accuracy, and increases in proportion to the number of errors. Such a RT adjustment has been previously used to account for speed-accuracy trade-off and reflects the efficiency of a system to perform its calculation successfully [61-63]. Therefore, the main dependent variables for each experimental condition were the median unadjusted RT and median adjusted RT. A participant was defined as an outlier if their median adjusted RT was greater than 2.5 times the interquartile range in a number of conditions. One girl with 22q11.2DS qualified as an outlier for three of the six conditions and on this basis was removed from all further analysis. To assess the contribution of motor reaction time, the average simple motor reaction time (SRT) was measured as part of the larger study in a separate task. Eleven girls did not complete the SRT task: four girls with 22q11.2DS, six girls with TS and one TD girl.

For each individual, we calculated an index of the efficiency of the subsystem's functioning [42] (Figure 1D). In this study, we will refer to the efficiency of performance (i.e. response time/accuracy within a condition) as "Attentional Index." Figure 1 Outline of experimental task. (A) Each trial in this children’s version of the attention networks test is made up of the following: an intertrial interval jittered between 400 to 1,600 ms (pseudorandomly distributed at 200 ms intervals), followed by the presentation of a cue stimulus, then after a 400 ms fixation period, the target alien spaceship appears and remains on screen till the child responds or 3,000 ms has passed. (B) One of four cue types were presented in each trial. (C) The target alien spaceship was centrally presented and could be flanked by other alien spaceships. (D) Attentional indices are calculated from the difference score between pairs of conditions. RT, response time.
Not much help from a cue that object is coming

All but FXS worse when incorrect location cued

FXS & TS more impaired than TD with "bad" flankers

**Attentional Networks Test**

**Figure 1 Outline of experimental task.** (A) Attention received varied between 400 to 1 than after a 400 ms fixation period, the target alien spaceship appears and remains on screen until the child responds or 3,000 ms has passed. (B) Congruent, (C) Neutral, (D) Incongruent, (E) Valid, (F) Invalid.

**Figure 2 Analyses of ANT performance for TD girls and girls with 22q11.2DS, FXS, or TS. (A) Group analyses of response times for the neutral condition. (B) Group analysis of alerting index score, covaried for age, showed that girls with a NDD responded similarly to TD girls. (C) Group analysis of orienting index score, covaried for age, showed that girls with a NDD responded similarly to TD girls. (D) Executive index score, covaried for age, showed that girls with a NDD responded similarly to TD girls.
Check-In #2

The Story So Far

❖ IQ not good predictor of cognitive functioning
❖ Different profiles of similarities/differences for each NDD
❖ Makes predicting your own abilities difficult/confusing
❖ Lack of competence leads to lack of confidence?
Selecting what the brain processes can be driven:

- **internally** - controlled by goals or plans (volitional/endogenous)
- **externally** - driven by objects/events in the world (reactive/exogenous)

A big question is: “What is the most salient thing to attend to?”
- usually defined in “cold”, objective terms to simplify experiments
- but, what captures a child’s attention when cognition gets “hot”?
“Hot” Cognition: Attention

Does manipulating emotional content change attentional control?
❖ we use a “Dot Probe Threat Bias” (exogenous) task
❖ anxious children orient attention to “threat”, losing some control
Anxious State & Affect and Attention

Clustering used ONLY anxiety/adaptive function scores, not 22q/TD Dx

- C2=Strugglers (ALL w/22q): low adaptive scores, high anxious scores
- C1=Copers (Mostly TD): high adaptive scores, low anxiety score
Anxious State, Affect and Attention

Eye tracking data show different looking patterns to different emotions:

- Angry: copers and strugglers look more overall at Angry vs. Neutral
- Happy: copers and strugglers look more overall at Happy vs. Neutral
- Averaged over entire experiment, all show bias toward emotional faces
Eye Gaze, Emotion and Adaptation

What about adaptation to emotion with repeated exposure?
>0 (up) = more gaze over time, <0 (down) = less gaze over time

❖ Angry: Copers look less @ no face with some angry bias (wary vigilance?)
❖ Angry: Strugglers ongoing no face gaze and angry bias (mild avoidance)?
❖ Happy: Copers look less @ no face area (evaluating emotions?)
❖ Happy: Strugglers no change gaze over time (unclear pattern?)
How “attracting” is negative affect?

#1 TD child with low anxiety, #2 a child with 22q with high fear anxiety

Red dot shows where the child is looking, size of dot shows for how long
Emotion Dysregulation in Attention Deficit Hyperactivity Disorder

Philip Shaw, M.B.B.Ch., Ph.D.
Argyris Stringaris, M.D., Ph.D.
Joel Nigg, Ph.D.
Ellen Leibenluft, M.D.

Although it has long been recognized that many individuals with attention deficit hyperactivity disorder (ADHD) also have difficulties with emotion regulation, no consensus has been reached on how to conceptualize this clinically challenging domain. The authors examine the current literature using both quantitative and qualitative methods. Three key findings emerge. First, emotion dysregulation is prevalent in ADHD throughout the lifespan and is a major contributor to impairment. Second, emotion dysregulation in ADHD may arise from deficits in orienting toward, recognizing, and/or allocating attention to emotional stimuli; these deficits implicate dysfunction within a striato-amygdalo-medial prefrontal cortical network. Third, while current treatments for ADHD often also ameliorate emotion dysregulation, a focus on this combination of symptoms reframes clinical questions and could stimulate novel therapeutic approaches. The authors then consider three models to explain the overlap between emotion dysregulation and ADHD: emotion dysregulation and ADHD are correlated but distinct dimensions; emotion dysregulation is a core diagnostic feature of ADHD; and the combination constitutes a nosological entity distinct from both ADHD and emotion dysregulation alone. The differing predictions from each model can guide research on the much-neglected population of patients with ADHD and emotion dysregulation.

(Am J Psychiatry 2014; 171:276–293)
Affect, Anxiety and Attention

Re-clustered Dot Probe using Spence, SNAP-IV scores, not 22q/TD Dx

❖ C1 = 4 22q, 17 TD: lower anxiety, lower ADHD scores (the copers)
❖ C2 =17 22q, 3 TD: higher anxiety, higher ADHD scores (the strugglers)
❖ supports anxiety-arousal-inattention-disinhibition hypothesis
ADHD and Anxiety

22q = 74

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Michelle Y Deng, Ph.D.
Check-In #3

The Story So Far

❖ Cognitive challenge related to emotional dysregulation
❖ More anxious kids have less control of cognition (& V/V)
❖ Challenge <—> Anxiety
❖ Anxiety may drive inattention (& ADHD diagnosis?)
"Cold" Cognition: Inhibition

Go/NoGo Task adapted from Casey et al. 2007

❖ “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
“Cold” Cognition: Inhibition

Shapiro et al.

Atypical response inhibition in 22q11.2DS

FIGURE 2 | Proactive response inhibition was typical in children with 22q11.2DS. (A) Accuracy and (B) response time on Go trials did not differ between groups.

FIGURE 3 | Reactive response inhibition was atypical in children with 22q11.2DS. (A) TD children demonstrated better No-Go accuracy as a function of more preceding Go trials, while children with 22q11.2DS did not demonstrate this pattern. (B) There were no group differences in response time on incorrect No-Go trials (false alarms).
“Hot” Cognition: Inhibition

Whacking moles & protecting vegetables is all very well but ..... What happens when what you want to do really COUNTS?

Whoa, that was stressful! And that was for something that feels good! What happens if you have to control yourself when things feel bad?
“Hot” Cognition: Inhibition

Do emotionally salient stimuli affect the ability to withhold responses?

- Go trials (75%): press a button as quickly as possible in response to Happy (50%) or Angry (50%) face
- No-Go trials (25%): do NOT press button in response to Neutral face
- Preceded by 1, 3, or 5 “Go” trials
“Hot” Cognition: Inhibition

TD: Accuracy for Happy 65-80% close to “cold” cognition variant
TD: Accuracy for Angry 65-90% -threat seems to enhance inhibition
22q: Similar but improved pattern -threat seems to enhance inhibition ... for some but not for all!

Emotive Go / Neutral No-Go

angry Go / neutral No-Go:

happy Go / neutral No-Go:
“Hot” Cognition: Inhibition

TD: Accuracy for Happy 65-80% close to “cold” cognition variant
TD: Accuracy for Angry 65-90% - threat seems to enhance inhibition
22q: Similar but improved pattern - threat seems to enhance inhibition ... for some but not for all!

Some suggestion in 22q group of better inhibition with higher trait anxiety
“Hot” Cognition: Inhibition

Larger N2 for “Angry” NoGo P300 for uncommon No Go “oddballs”
“Hot” Cognition: Inhibition

P300 for uncommon No Go “oddballs”

Larger N2 for “Angry” NoGo
Check-In #4

The Story So Far

❖ Executive impairment, too many unwanted behaviors
❖ Tends to get you in trouble, maybe increases anxiety
❖ Anxiety may affect No-Go ability (& ADHD diagnosis?)
❖ A little anxiety may help, too much might = failure
Cognition, Emotion & Psychiatric Diagnoses

IQ = 75 can be like operating like 9-year-old in 12-year-old’s world (in SOME situations)

Creates constant, variable (i.e. unpredictable) mismatch

Which psychopathologies get diagnosed?

❖ Many children with NDDs/challenge have significant anxiety
  ❖ low levels of diagnosis or treatment
❖ Many children with NDDs/challenge get a diagnosis of ADHD (often Inattentive or Combined type) and take medications
❖ Many children with NDDs/challenge get ASD diagnoses
  ❖ helps get services, but usually not (inappropriate) ABA

Can cognition/affect interactions explain & target treatment?
Attention: Selection & Filtering

Attention: select among competing items/events in mind & environment
Selecting what the brain processes can be driven:
- internally - controlled by goals or plans (volitional/endogenous)
- externally - driven by objects/events in the world (reactive/exogenous)

Figure 1. Focusing Attention and Reorienting Attention Recruit Interacting Networks
(Left panel) Focusing attention on an object produces sustained activations in dorsal frontoparietal regions in the intraparietal sulcus, superior parietal lobule, and frontal eye fields, as well as visual regions in occipital cortex (yellow and orange colors) but sustained deactivations in more ventral regions in supramarginal gyrus and superior temporal gyrus (TPJ) and middle and inferior prefrontal cortex (blue and green colors). (Right panel) When an unexpected but important event evokes a reorienting of attention, both the dorsal regions and the formerly deactivated ventral regions are now transiently activated.

A big question is: “What is the most salient thing to attend to?”
- usually defined in “cold”, objective terms to simplify experiments
- but, what captures a child’s attention when cognition gets “hot”?
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 understand this math?
  ❖ how much does math 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 learning e.g. math
Mismatch-driven hyper-arousal & hyper-vigilance increases salience of otherwise mundane objects/events
❖ increased competition for limited attentional resources
   ❖ attention drawn to more distracting stimuli
❖ reduced inhibitory ability in emotionally activated states
   ❖ less able to “not attend” to inappropriate stimuli
   ❖ more responding to objects/events that should be ignored

Cognition selects too little “desired” information and too much “undesired” information
❖ “inattention” to (e.g. teacher-defined) salient info may really be adaptive attending to own (emotionally-defined) salient targets
Explains some proportion of ADHD Diagnoses?
Mismatches between cognitive capabilities and social demands induce avoidance and/or anxiety and disinhibited responding
❖ socially motivated kids unable to match peer’s abilities?
❖ lower language/conceptual abilities obscure meaning of speech?
❖ lower emotion recognition/“Theory of Mind” abilities obscure intent of speech?
❖ impairs turn-taking & reading of other’s interest in content
❖ leads to out of context “downloads” of own favorite topic

All of this makes peer social interaction unpleasant, unrewarding
❖ anxiety creates repetitive responses, gaze avoidance or opt out
❖ but, successful & rewarding with ability-matched/flexible others
Brains Change Over A Long Time

There is a LONG period for potentially effective interventions

Gogtay et al., 2004 PNAS
Treatment Implications

NB: I am NOT a clinician/physician - work directly with yours!

Reducing mismatches enhances functioning & coping
“Adjust child towards demands & adjust demands toward child”
❖ but only with “evidence-based” methods

Anxiety:
❖ enhanced child cognition to reduce challenge
❖ enhance child coping via behavioral, biological therapy
❖ adjust environmental demands via IEP, parent/family/social expectations, coping & protection vs. enhancing independence
Treatment Implications

ADHD:
❖ enhanced child cognition to reduce challenge, enhance control via executive function training & biological therapy
❖ optimize environmental demands e.g. IEP, other accommodations

Autism Spectrum Disorders
❖ enhanced child cognition to support linguistic/emotional skills via tutoring, social skills groups etc
❖ optimized social demands via ability-matched friends
❖ reduced anxiety via behavioral and biological therapies
Conclusions

Cognitive impairments/mismatch to demands induce challenge
Chronic challenge likely 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” & more psychiatric diagnoses
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

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