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How high is psychosis risk, & how to explain some mental health-related cognitive challenges?

Tony J. Simon, Ph.D.

Director, 22q11.2 Research Center and Clinic

Disclosure

cognivive

A Digital Neurotherapeutics Company

Co-Founder, CEO & Chief Science Officer

Outline of Talk

- Is schizophrenia really so common in 22q?
- What really are “psychosis proneness” symptoms & how are they measured?
- What do we find in our study, using those measures?
- Might cognition/emotion interactions explain (some of the) risk/protection?
- Some initial indicators possible predictors of risk/protection?

TAKE AWAY: In challenged individuals, cognitive difficulties and ability to control emotions interact with each other to affect the ability to function well

This account might help explain some of the problems and guide responses

Is schizophrenia really so common in 22q?

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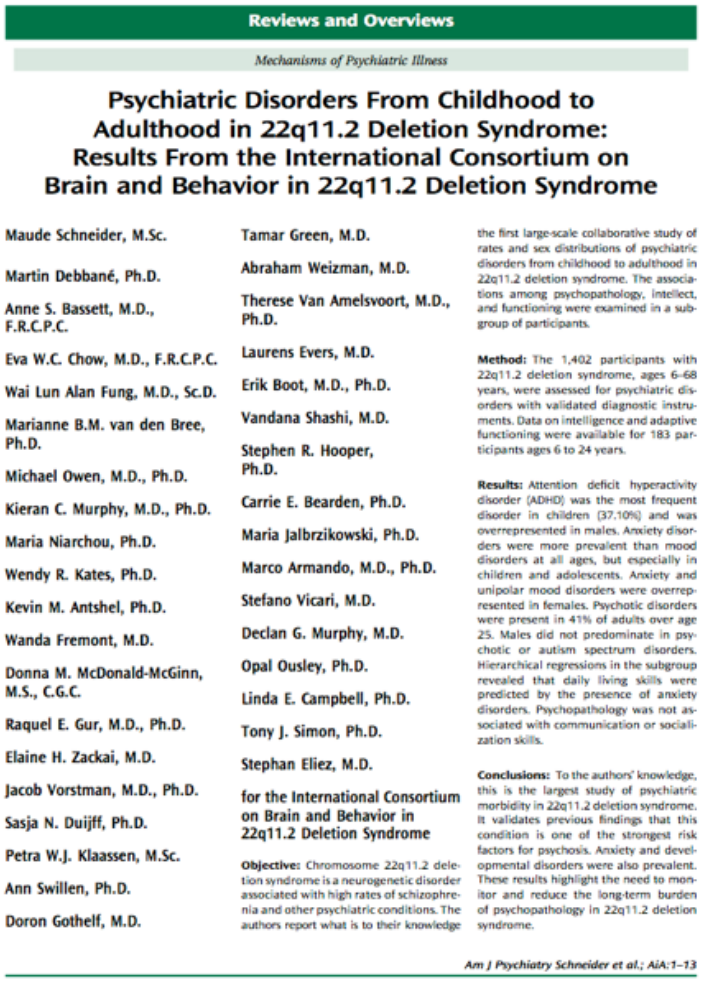
Psychosis Proneness in 22q11.2



Reviews and Overviews

Mechanisms of Psychiatric Illness

Psychiatric Disorders From Childhood to Adulthood in 22q11.2 Deletion Syndrome: Results From the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome

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Donna M. McDonald-McGinn, M.S., C.G.C.
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Therese Van Amelsvoort, M.D., Ph.D.
Laurens Evers, M.D.
Erik Boot, M.D., Ph.D.
Vandana Shashi, M.D.
Stephen R. Hooper, Ph.D.
Carrie E. Bearden, Ph.D.
Maria Jalbrzikowski, Ph.D.
Marco Armando, M.D., Ph.D.
Stefano Vicari, M.D.
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Opal Ousley, Ph.D.
Linda E. Campbell, Ph.D.
Tony J. Simon, Ph.D.
Stephan Eliez, M.D.
for the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome

Objective: Chromosome 22q11.2 deletion syndrome is a neurogenetic disorder associated with high rates of schizophrenia and other psychiatric conditions. The authors report what is to their knowledge the first large-scale collaborative study of rates and sex distributions of psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome. The associations among psychopathology, intellect, and functioning were examined in a subgroup of participants.

Method: The 1,402 participants with 22q11.2 deletion syndrome, ages 6–68 years, were assessed for psychiatric disorders with validated diagnostic instruments. Data on intelligence and adaptive functioning were available for 183 participants ages 6 to 24 years.

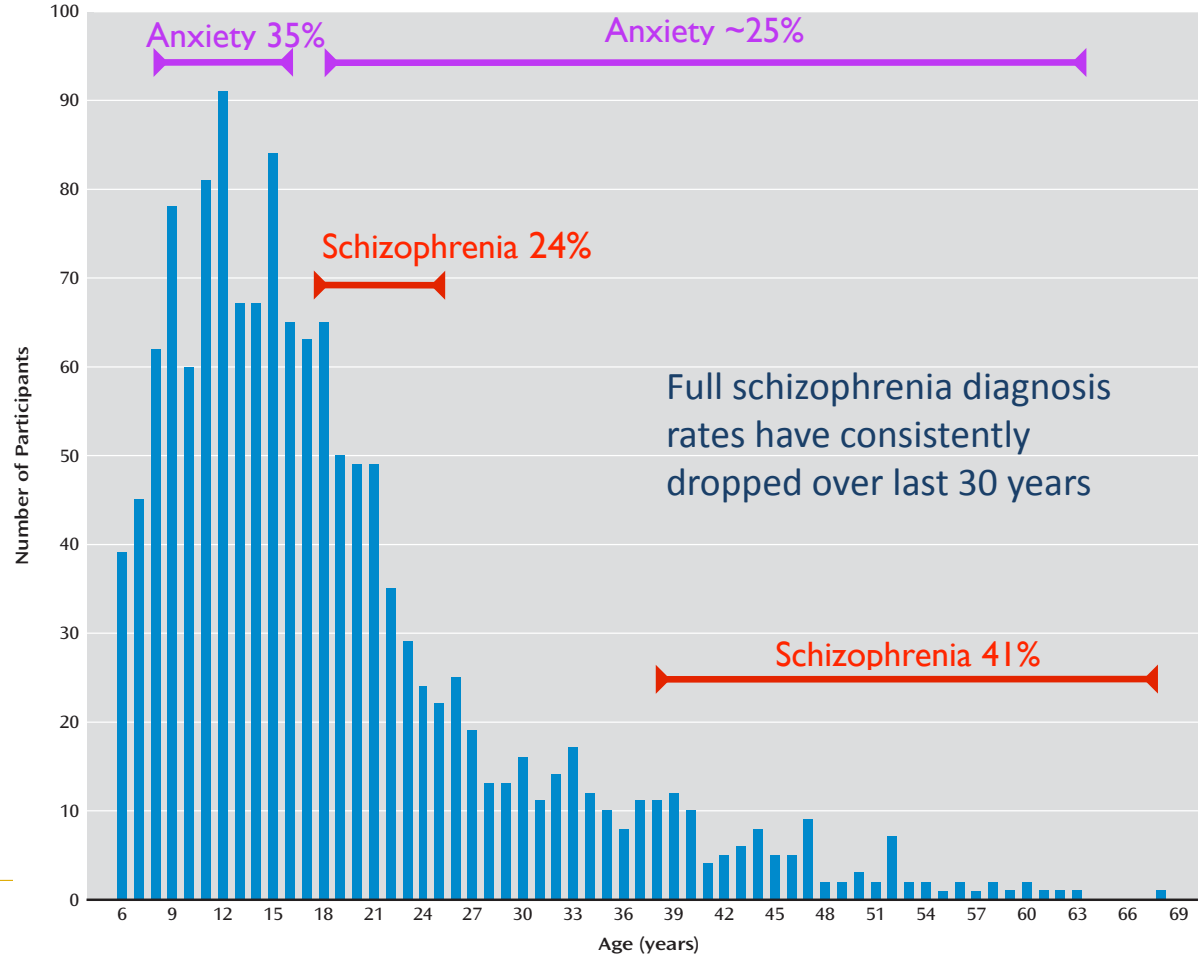
Results: Attention deficit hyperactivity disorder (ADHD) was the most frequent disorder in children (37.10%) and was overrepresented in males. Anxiety disorders were more prevalent than mood disorders at all ages, but especially in children and adolescents. Anxiety and unipolar mood disorders were overrepresented in females. Psychotic disorders were present in 41% of adults over age 25. Males did not predominate in psychotic or autism spectrum disorders. Hierarchical regressions in the subgroup revealed that daily living skills were predicted by the presence of anxiety disorders. Psychopathology was not associated with communication or socialization skills.

Conclusions: To the authors' knowledge, this is the largest study of psychiatric morbidity in 22q11.2 deletion syndrome. It validates previous findings that this condition is one of the strongest risk factors for psychosis. Anxiety and developmental disorders were also prevalent. These results highlight the need to monitor and reduce the long-term burden of psychopathology in 22q11.2 deletion syndrome.

Am J Psychiatry Schneider et al.; AiA:1–13

Psychosis Proneness in 22q11.2

FIGURE 1. Age Distribution of 1,402 Participants With 22q11.2 Deletion Syndrome Assessed for Psychiatric Disorders



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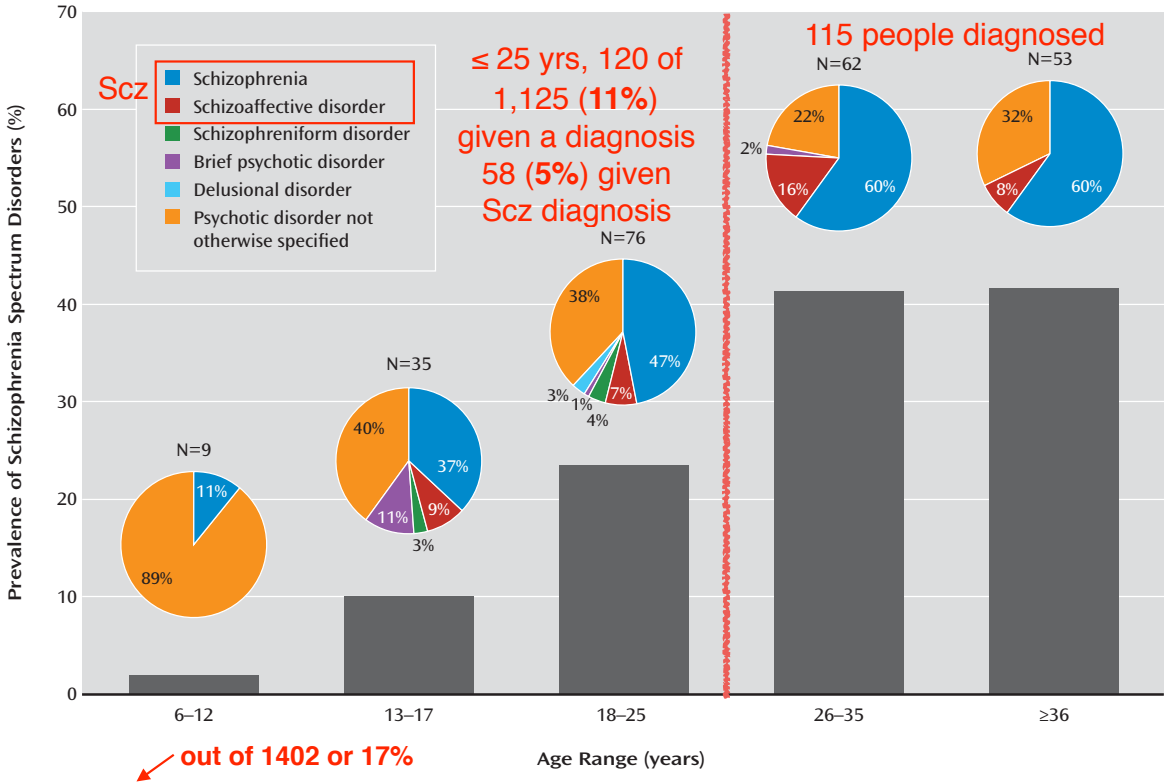
Psychosis Proneness in 22q11.2

FIGURE 2. Prevalence of Schizophrenia Spectrum Disorders and Distribution of Specific Disorders by Age in Participants With 22q11.2 Deletion Syndrome[a]



[a] Among the 235 subjects with schizophrenia spectrum disorders, the prevalence of a schizophrenia diagnosis increased significantly over the age groups (χ^2=12.54, df=4, p=0.01), whereas the diagnosis of psychotic disorder not otherwise specified decreased (χ^2=17.17, df=4, p=0.002).

So, YES. More common in 22q than general population. But probably ~5 times, not 30 times, more common

How are “psychosis proneness” symptoms measured in research, & what really are they?

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Structured Interview for Prodromal Syndromes (SIPS)

- Purpose: Identify individuals who are showing ***sub-threshold symptoms*** of psychosis and may be at higher risk for psychosis (NOT developed for 22q!)
- Research based, structured interview with teen/young adult and caregivers
- Collateral information gathered from treatment providers and significant others

- Interview goals:

1. Rule out past and/or current psychosis
2. Rule in one or more of the 3 types of *clinical high risk syndromes (not 22q)*
3. Rate the current severity of the high risk symptoms

Symptoms measured by the SIPS

Nonspecific Symptoms!

Positive Symptoms

1. Unusual thoughts/ Delusions
2. Perceptual Abnormalities/ Hallucinations
3. Disorganized communication

Can Predict PSYCHOSIS

Negative Symptoms

1. Social Anhedonia
2. Avolition
3. Flat Affect
4. Poverty of Speech
5. Ideational Richness
6. Occupational Functioning

Disorganization Symptoms

1. Odd behavior or appearance
2. Bizarre Thinking
3. Trouble with Focus & Attention
4. Poor Personal Hygiene

General Symptoms

1. Sleep Disturbance
2. Dysphoric Mood
3. Motor Disturbances
4. Poor tolerance to normal stress

Focus is on "degeneration" or progressive worsening

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Thanks to Dr. Tara Niendam

Structured Interview for Prodromal Syndromes (SIPS)

Positive Symptoms Scale:
Positive Symptoms are rated on a SOPS scale that ranges from 0 (Absent) to 6 (Severe and Psychotic):

Positive Symptom SOPS

0	1	2	3	4	5	6
Absent	Questionably Present	Mild	Moderate	Moderately Severe	Severe but Not Psychotic	Severe and Psychotic

Negative/Disorganized/General Symptoms Scale:
Negative/Disorganized/General Symptom Symptoms are rated on a SOPS scale that ranges from 0 (Absent) to 6 (Extreme):

Negative/Disorganized/General Symptom SOPS

0	1	2	3	4	5	6
Absent	Questionably Present	Mild	Moderate	Moderately Severe	Severe	Extreme

Score ≥3 is threshold for level of concern

SIPS Negative Symptoms (Selected)

N.1. **Social Anhedonia** "*a. **Lack of close friends or confidants other than first degree relatives.** b. **Prefers to spend time alone, although participates in social functions when required.** Does not initiate contact. c. Passively goes along with most social activities but in a disinterested or mechanical way. Tends to recede into the background.*"

- Q's: Do you usually prefer to be alone or with others? Would you be more social if you had the opportunity? Who tends to initiate social contact, you or others?

N.2. **Avolition** "*a. **Impairment in the initiation, persistence, and control of goal-directed activities.** b. Low drive, energy or productivity.*"

- Q's: Do you find that you have trouble getting motivated to do things? Do you find that people have to push you to get things done?

SIPS Negative Symptoms (Selected)

N.5. **Ideational Richness** "*a. **Unable to make sense of familiar phrases or to grasp the "gist" of a conversation or to follow everyday discourse**. b. … Some rigidity in attitudes or beliefs. Does not consider alternative positions or has difficulty shifting from one idea to another. c. **Simple words and sentence structure**; paucity of dependent clauses or modifications (adjectives/adverbs). d. **Difficulty in abstract thinking. Impairment in the use of the abstract-symbolic mode of thinking, as evidenced by difficulty in classification, forming generalizations, and proceeding beyond concrete or egocentric thinking in problem- solving tasks; often utilizes a concrete mode**."*

- Q's: Do you sometimes find it hard to understand what people are trying to tell you because you don't understand what they mean? Do people more and more use words you don't understand?

SIPS Disorganized & General Symptoms (Selected)

D.3. **Focus & Attention** *"a. Failure in focused alertness, manifested by poor concentration, distractibility from internal and external stimuli. b. Difficulty in harnessing, sustaining, or shifting focus to new stimuli. c. Trouble with short-term memory including holding conversation in memory."*

- Q's: Have you had difficulty concentrating or being able to focus on at ask? Reading? Listening? Is this getting worse than it was before?

G.2. **Dysphoric Mood** "*Sleeping problems. Difficulty concentrating.* Feelings of worthlessness and/or guilt. *Anxiety, panic, multiple fears and phobias*. Irritability, hostility, rage. *Unstable mood*"

- Q's: Do you ever generally just feel unhappy for any length of time? Have you ever been depressed? Do you find yourself feeling irritable a lot of the time? Have you felt more nervous, anxious lately? Has it been hard for you to relax?

SIPS Disorganized & General Symptoms (Selected)

G.4. **Impaired Tolerance to Normal Stress** "*a. Avoids or exhausted by stressful situations that were previously dealt with easily. b.* ***Marked symptoms of anxiety or avoidance in response to everyday stressors****."*

- Q's: Are you feeling more tired or stressed than the average person at the end of a usual day? Do you get thrown off by unexpected things that happen to you during the day? Are you finding that you are feeling challenged or overwhelmed by some of your daily activities? Are you avoiding any of your daily activities? Are you finding yourself too stressed, disorganized, or drained of energy and motivation to cope with daily activities?

What do we find in our study using these measures?

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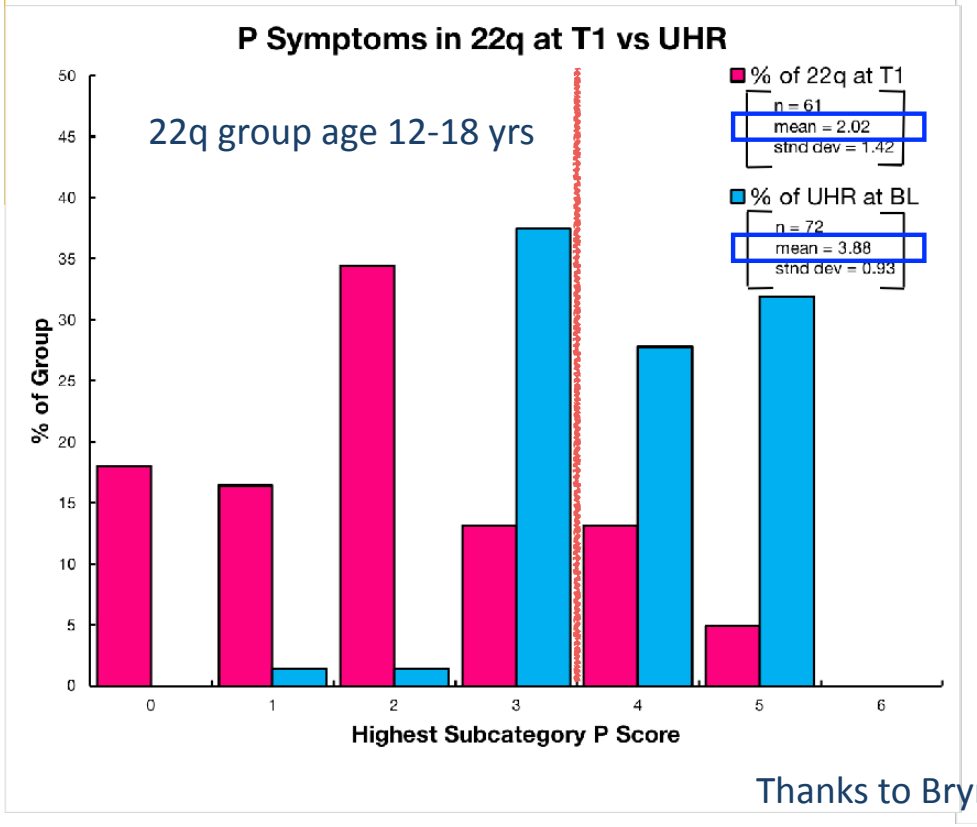
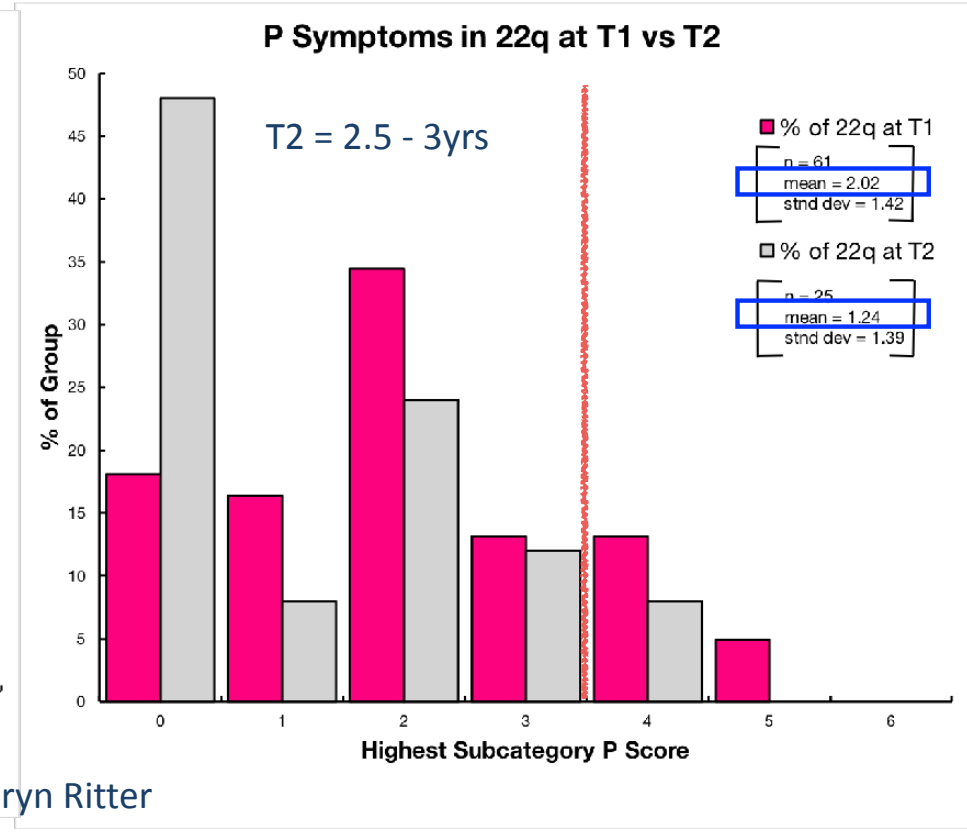
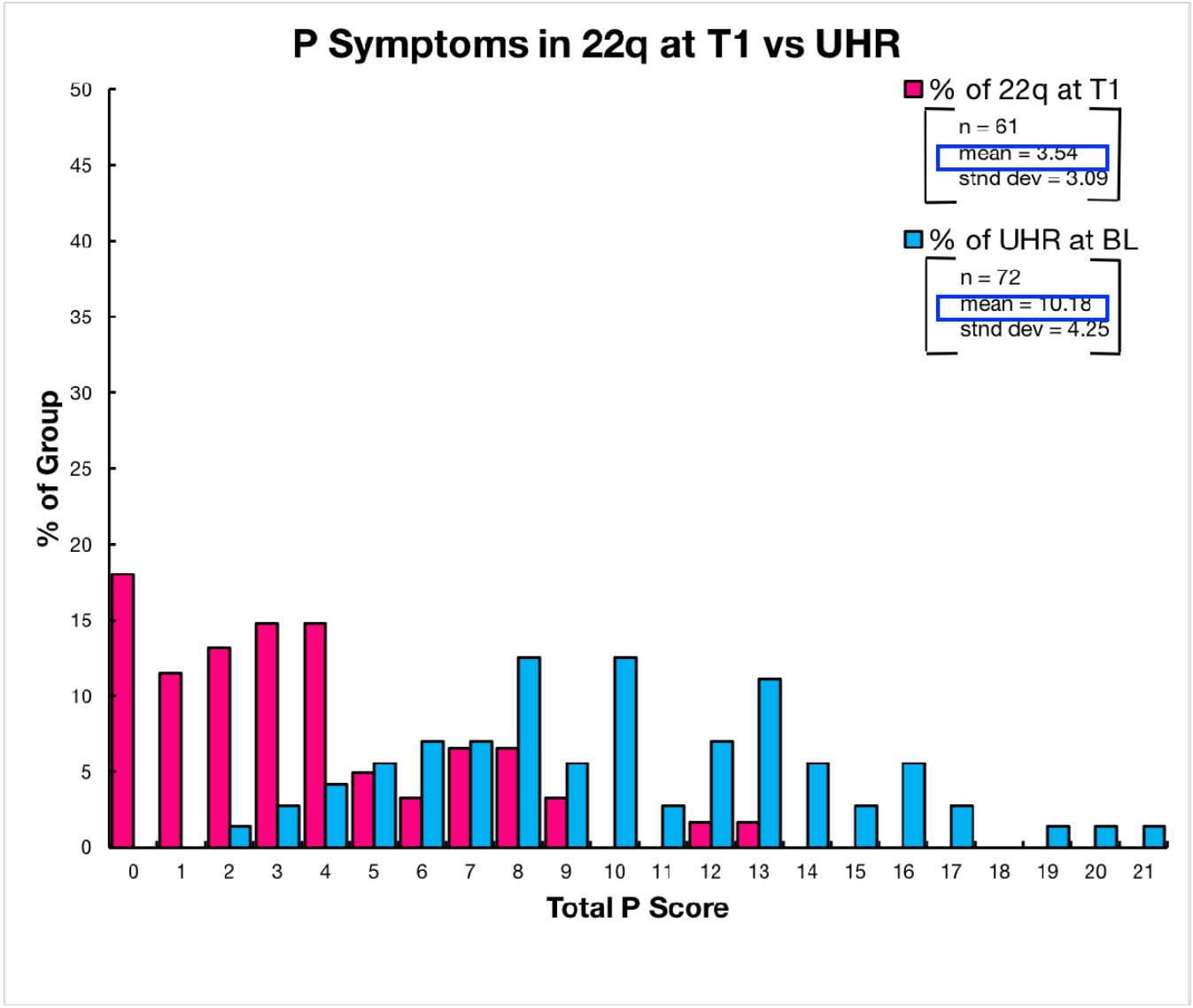
What Symptom Profiles Have We Found?

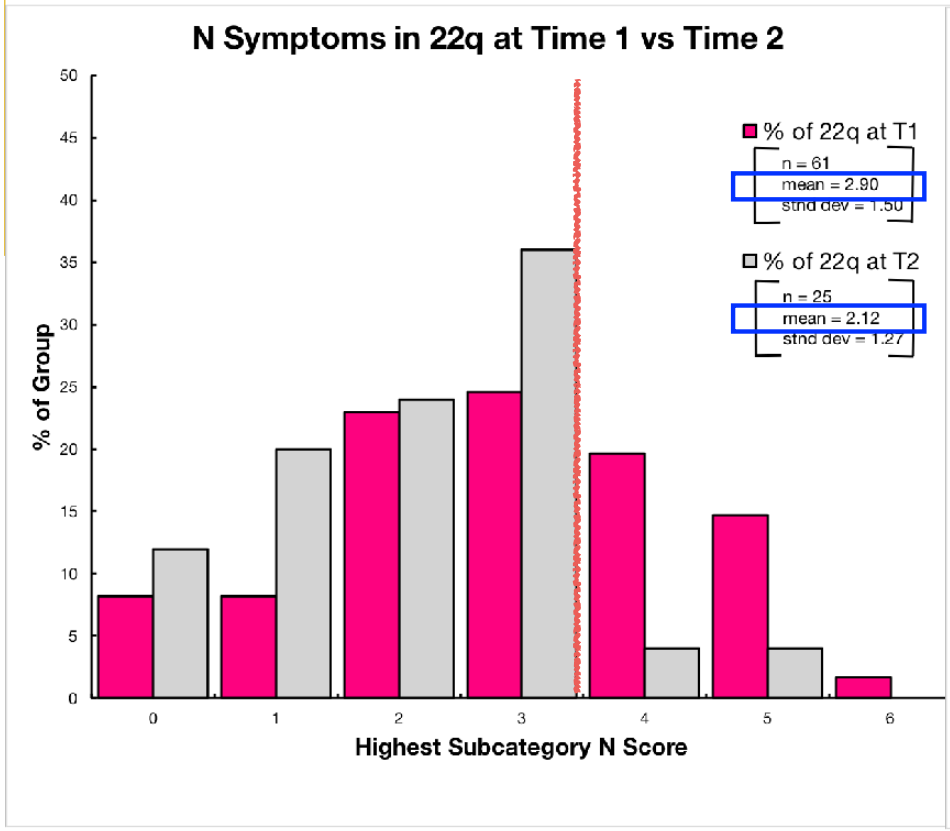


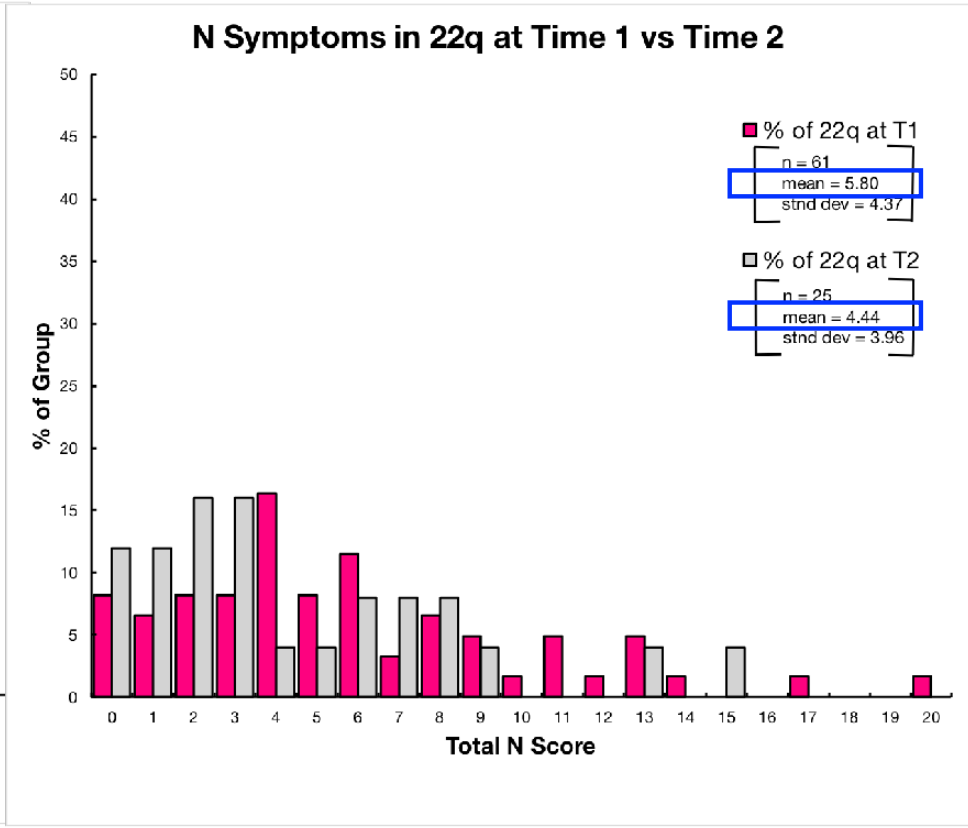


Thanks to Bryn Ritter


P Symptoms in 22q at T1 vs UHR
% of 22q at T1
n = 61
mean = 3.54
stnd dev = 3.09
% of UHR at BL
n = 72
mean = 10.18
stnd dev = 4.25
% of Group
Total P Score
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
0 5 10 15 20 25 30 35 40 45 50

What Symptom Profiles Have We Found?





More of group had lower scores when aging into the greatest risk age window

CHECK IN

- Schizophrenia rates have dropped over time (22q or not), partly from Dx changes
- Biggest 22q study found very low schizophrenia rates
- SIPS helps detect psychosis-specific risk signs + loss of more general abilities
- In 22q those general abilities not lost, just developmentally delayed.
- Should be wary of calling them psychosis-proneness “symptoms”
- Our study finds ALL scores lower than high-risk group & getting lower still with age

What led us to carry out our current study?

- History of statements of much increased risk for schizophrenia in 22q11.2
- Almost unaddressed question of **protective** as well as risk factors
  - ~90% with same/similar genetic change, ≤30% developing psychosis

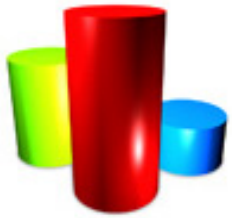
- Our focus on behavioral outcomes not diagnostic categories
  - Our Main Goal - find out how to increase mental health with focus on common behavioral disturbances
- Our coper/struggler ideas led to novel question

How might cognition/emotion interactions impact risk/protection?

Matching Abilities to Requirements

Everyday Demands

Cognition/ Behavior

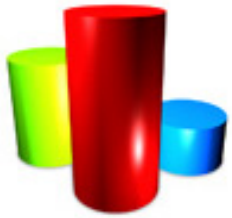


Coping Resources

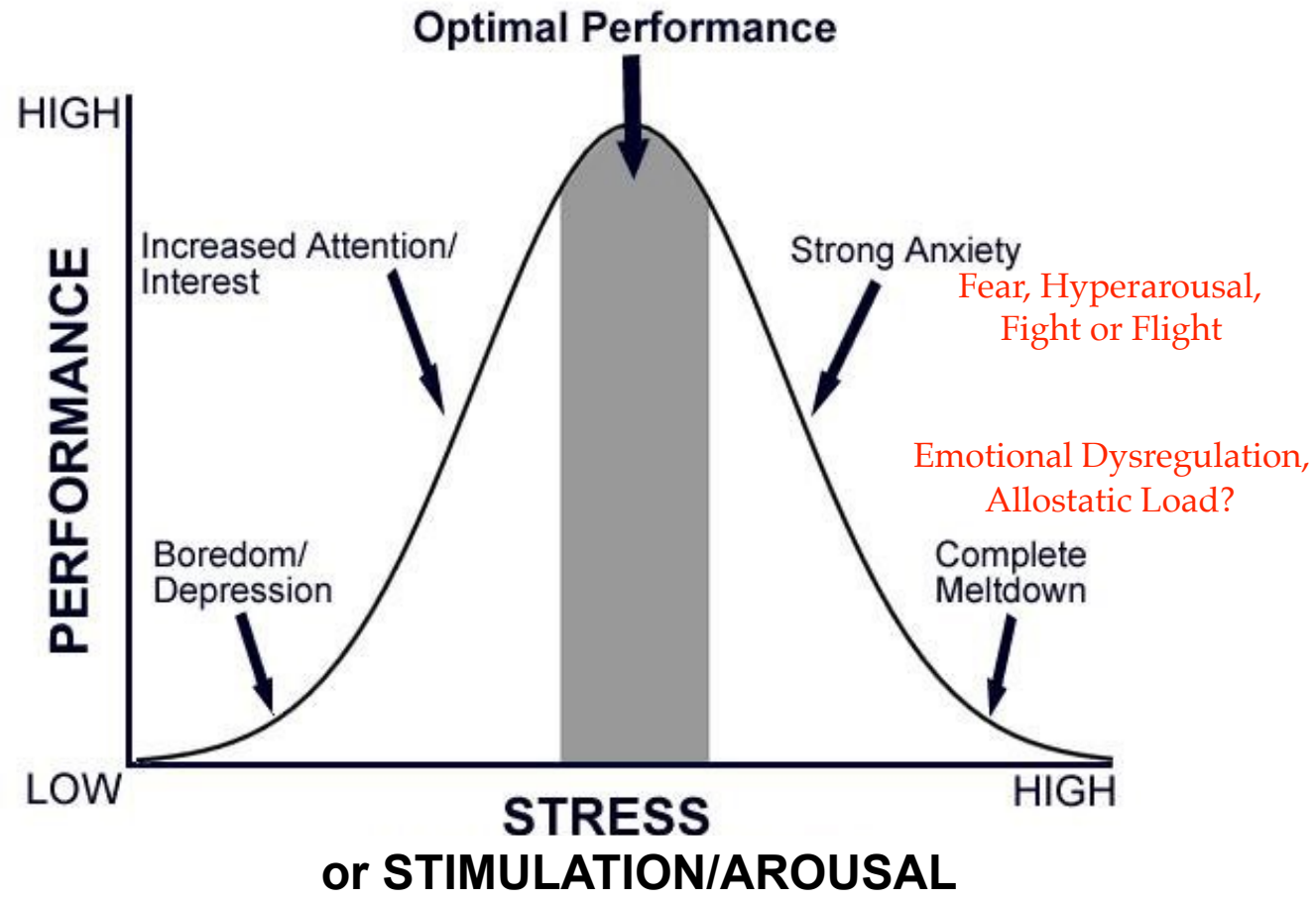
Matching Abilities to Requirements

Everyday Demands

Cognition/ Behavior

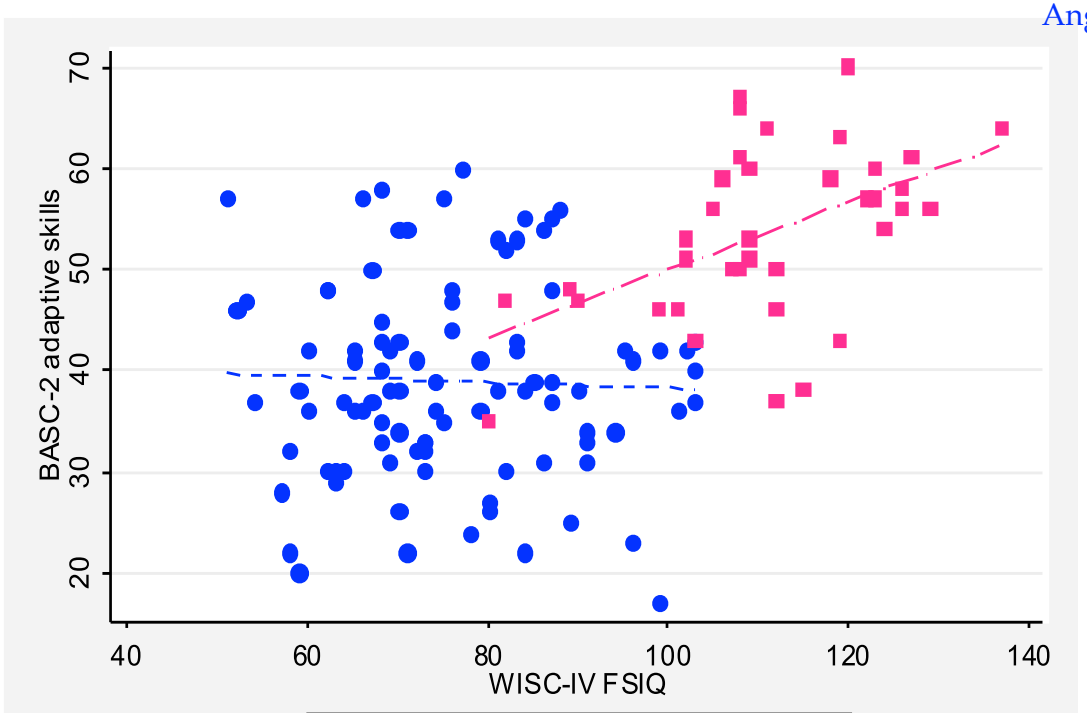


Coping Resources


Optimal Performance
HIGH
PERFORMANCE
LOW
Increased Attention/
Interest
Strong Anxiety
Fear, Hyperarousal,
Fight or Flight
Emotional Dysregulation,
Allostatic Load?
Boredom/
Depression
Complete
Meltdown
HIGH
STRESS
or STIMULATION/AROUSAL

Anxiety, Not IQ, Predicts Adaptive Function

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



22q: N=99; r=-0.04;

TD: N=45; r=0.5;

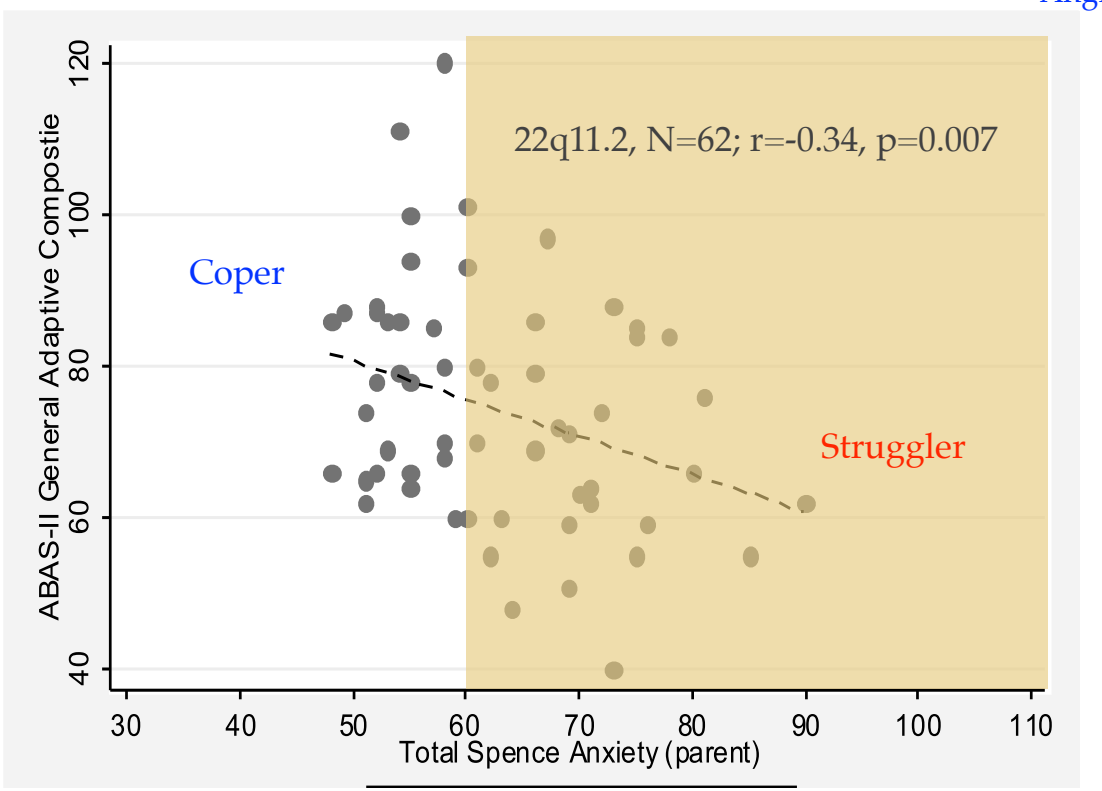
Unlike TD children, FSIQ is NOT related to adaptive function in children with 22q11.2DS aged 7-14 years

Anxiety, Not IQ, Predicts Adaptive Function

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

Anxiety, Not IQ, Predicts Adaptive Function

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



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

Does this happen in real life?

"The problem is not the learning difference,
its the anxiety provoked by the learning difference."

"Its the hole I've been climbing out of all my life"

Max Brooks, Author & Dyslexia Advocate
EdRev, 2016 Keynote

Does the way we balance “thinking” and “feeling” explain some of this?

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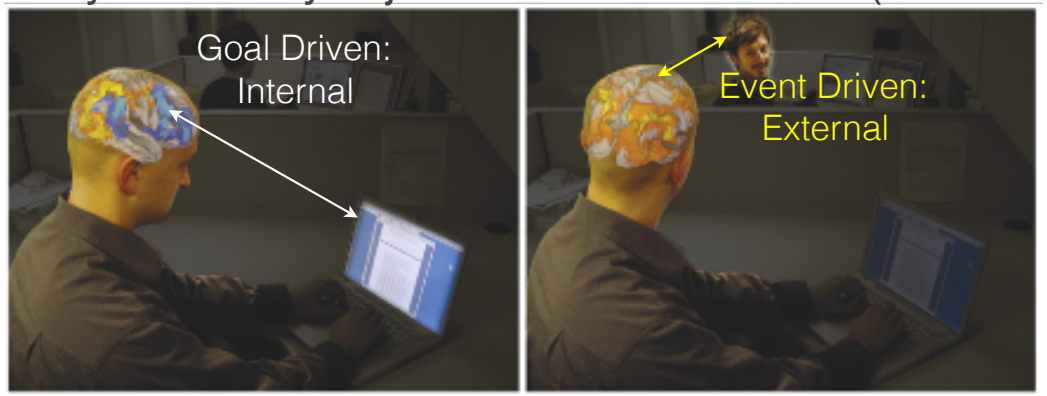
Attention: Selection and Filtering

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)



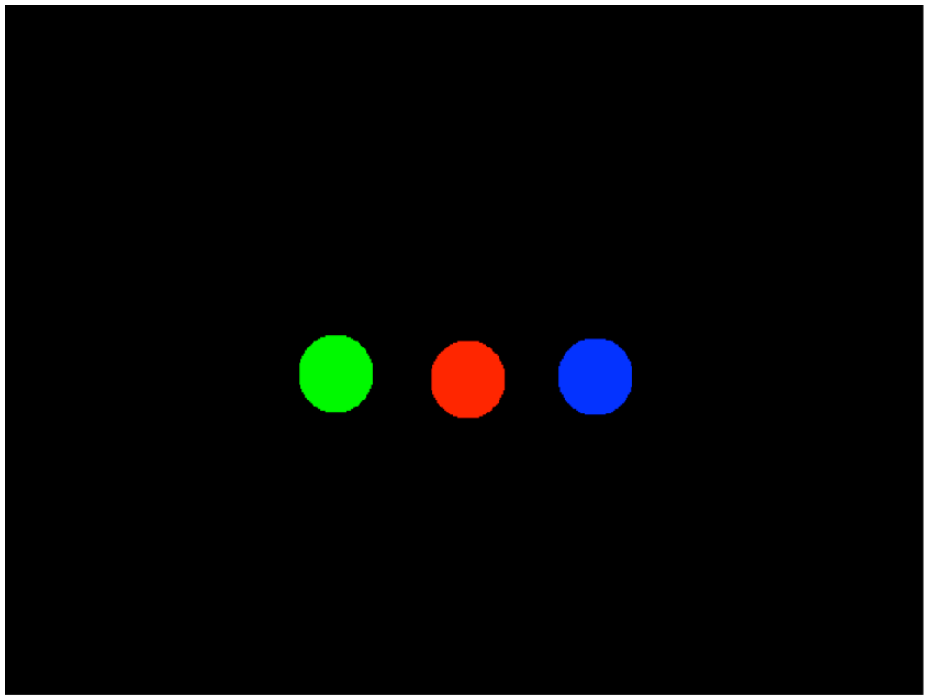
Corbetta, Patel & Shulman, Neuron, 2008

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"?

Cold Cognition: Attention

Adapted from Sawaki, Geng & Luck,2012 by Abbie Popa & Steve Luck

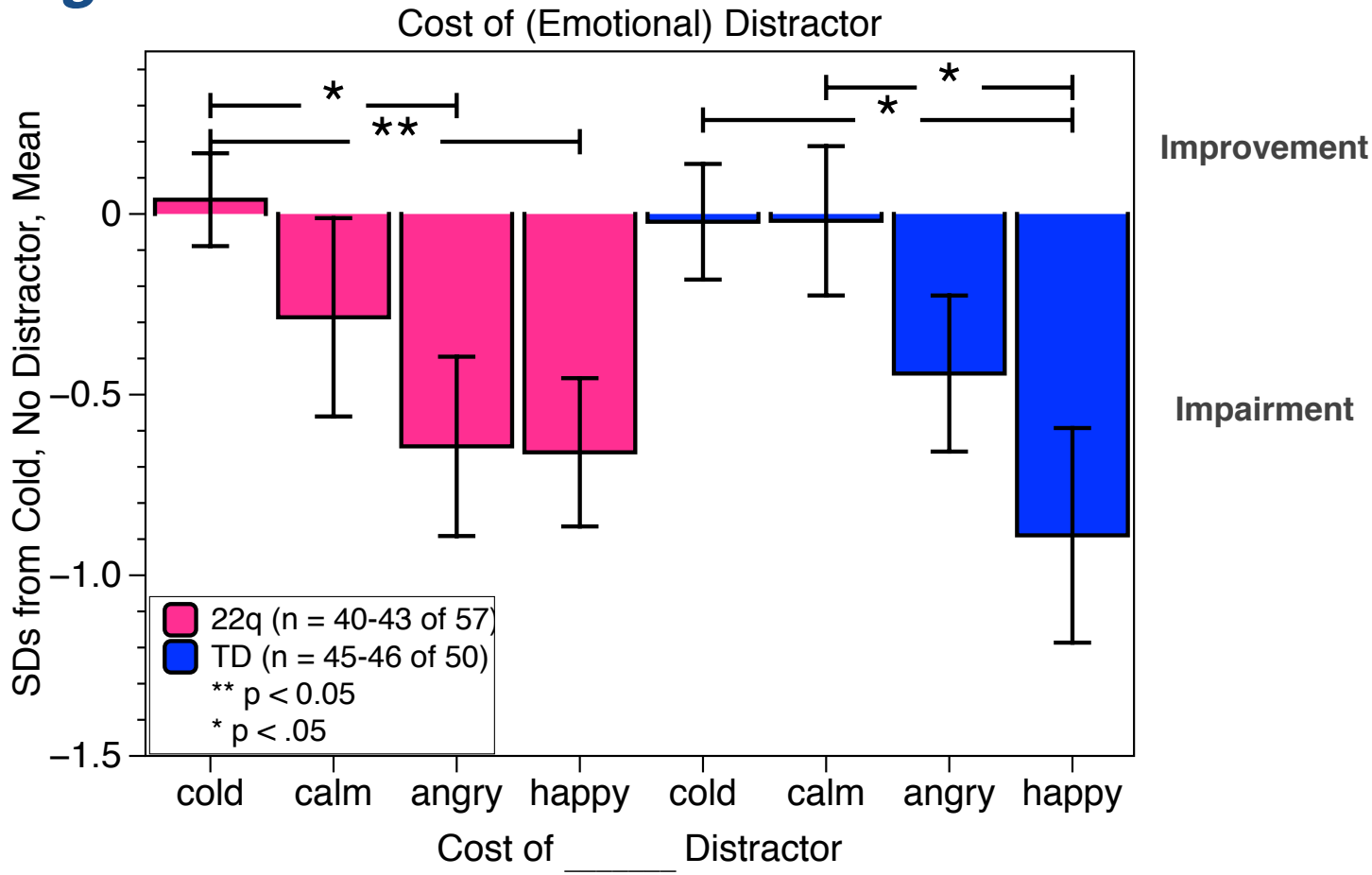


Data from 12-18 Yr-Olds

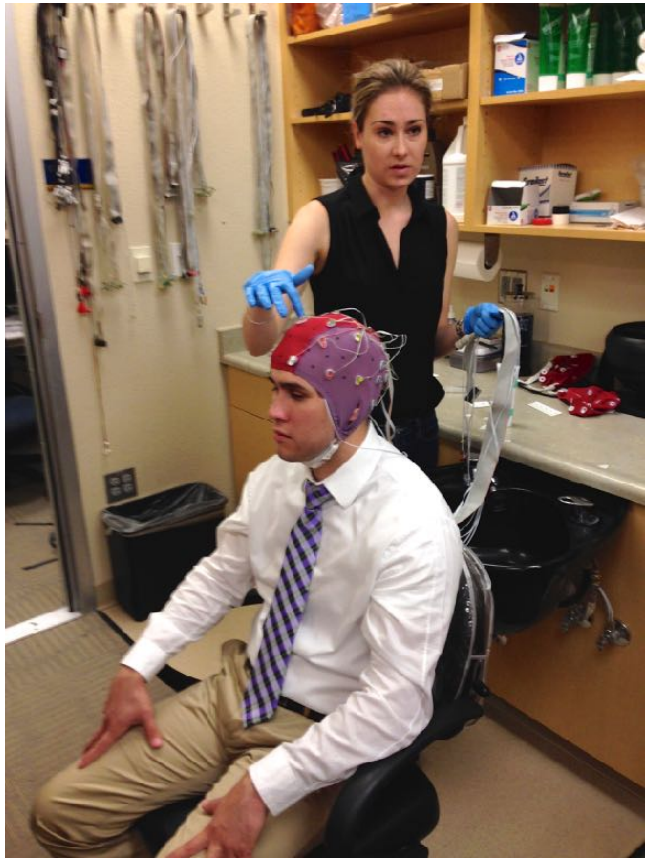
Task: Respond to specific color (red, green, blue) ONLY in center position

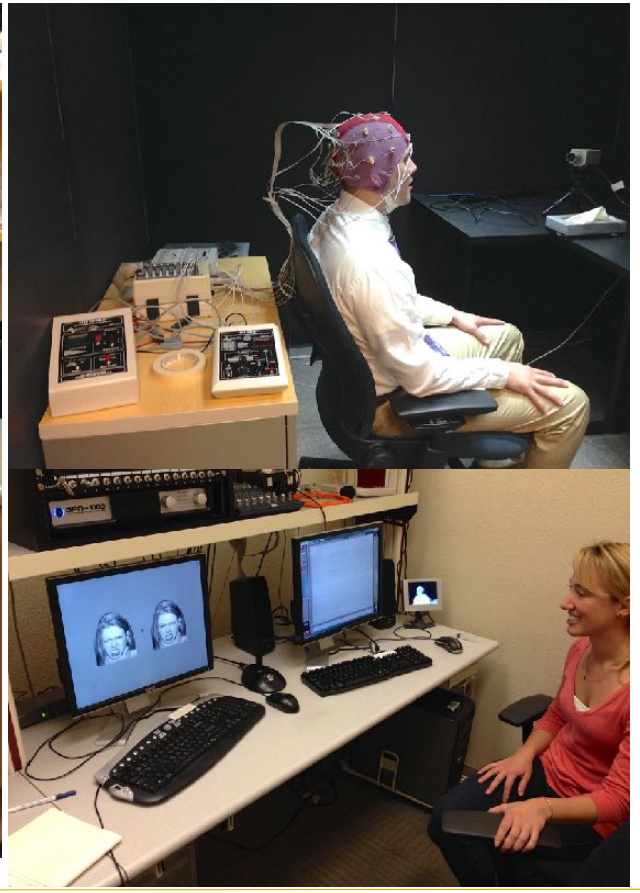
- BUT, that Target rarely appears in center
  - 70% gray, 10 % red, 10% green, 10% blue
- AND, colors appear often on one side or other (called a "Flanker")
  - 33% red, 33% green, 33% blue

Cold Cognition: Attention Emotional Distractor "Cost"

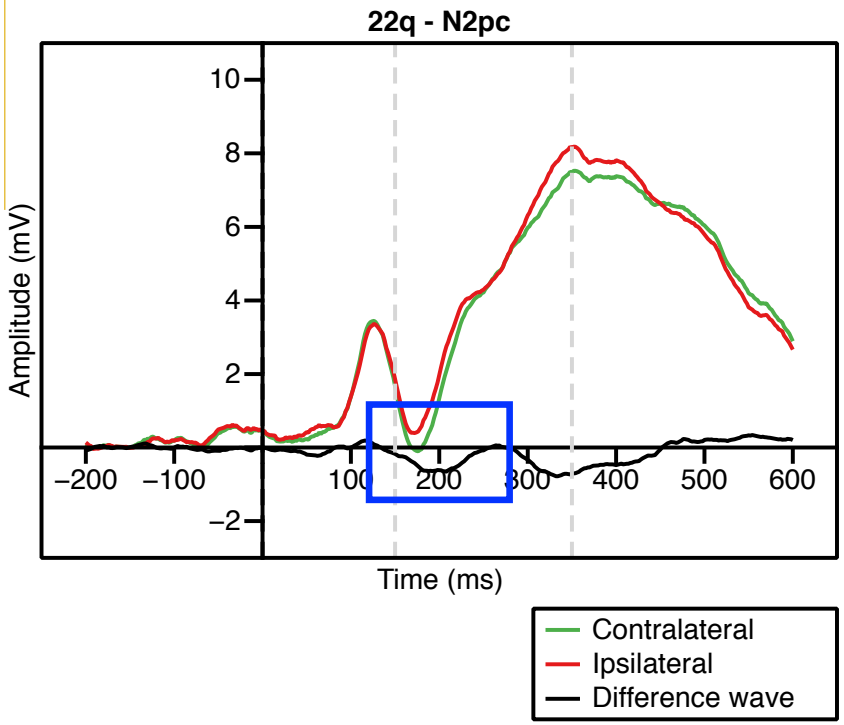


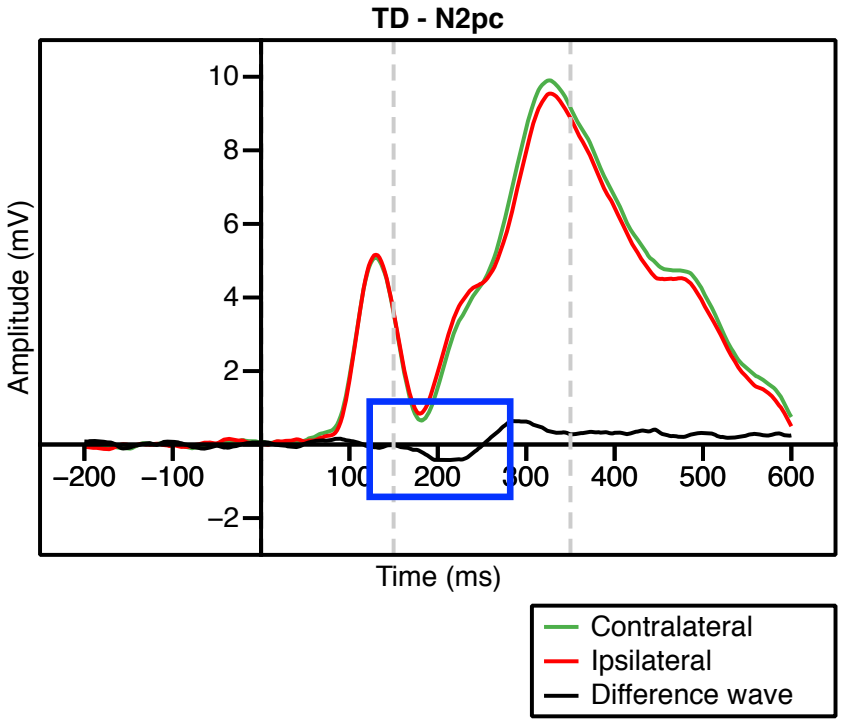
Watching the Brain Process Information (ERPs)





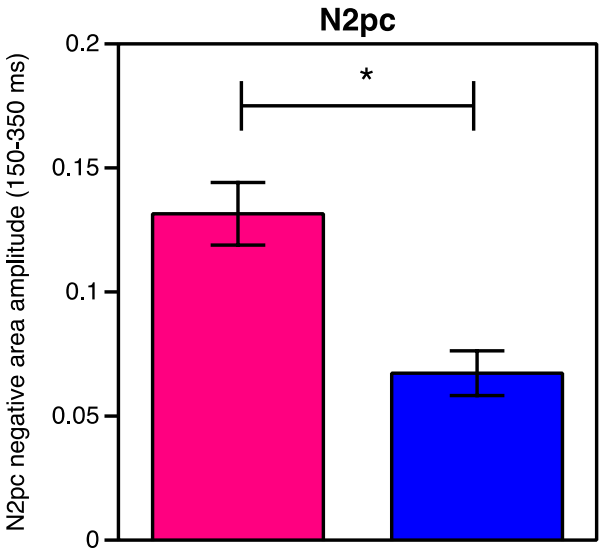
Attention Brain Responses to Distractors

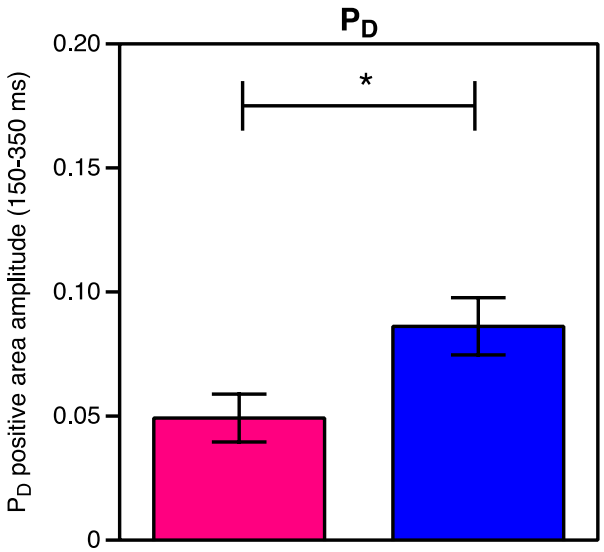


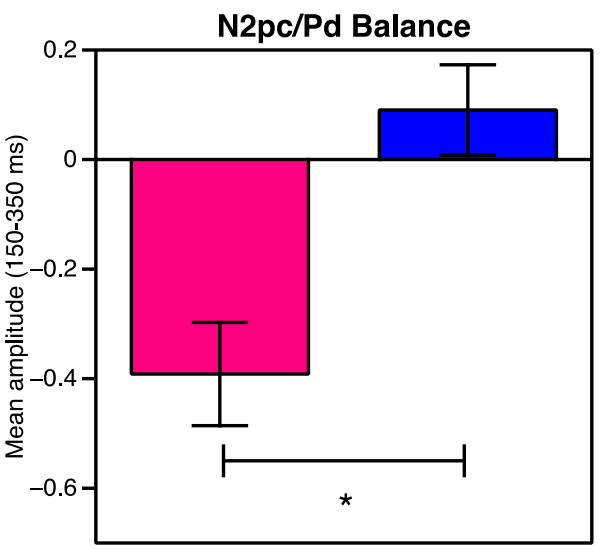


Attention Brain Responses to Distractors

Attention Brain Responses to Distractors







Youth with 22q are MUCH LESS able to avoid & then suppress “attention grabbers”

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.

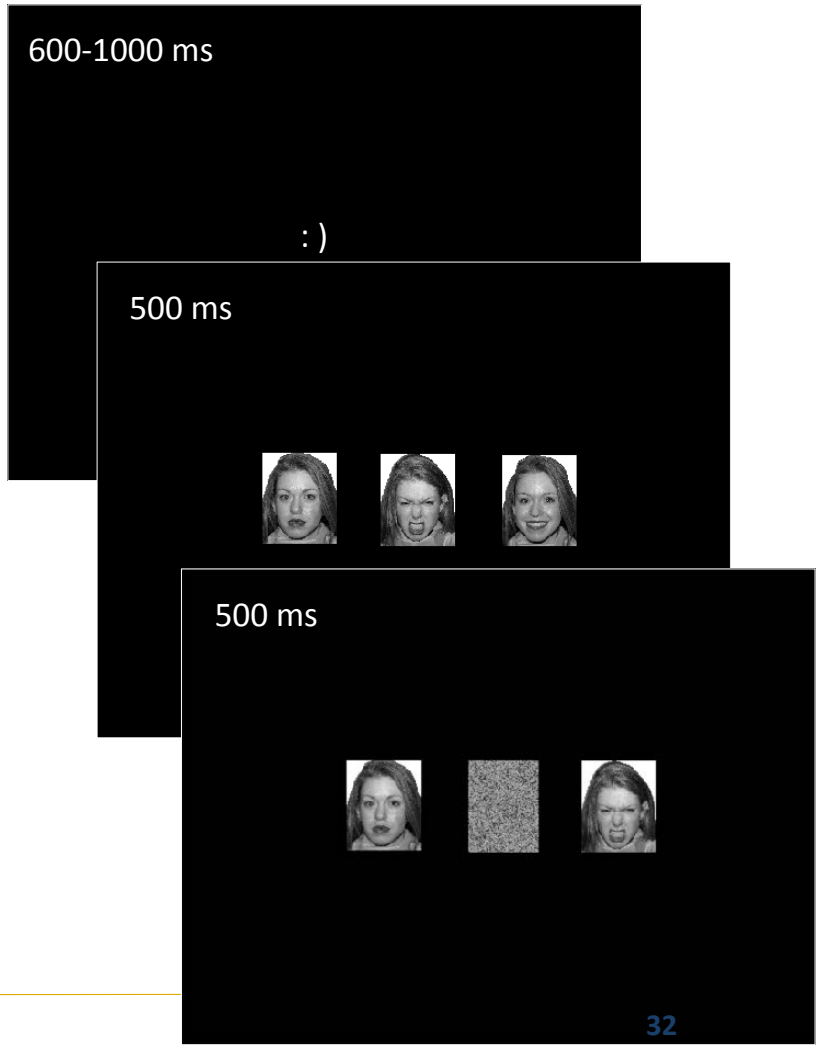
Although it has long been recognized that many individuals with attention deficit hyperactivity disorder (ADHD) also have difficulties with emotion regulation, no consensus has been reached on how to conceptualize this clinically challenging domain. The authors examine the current literature using both 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)

Hot Cognition: Attention

Task: Respond to specific emotion (happy, calm, angry) ONLY in center position

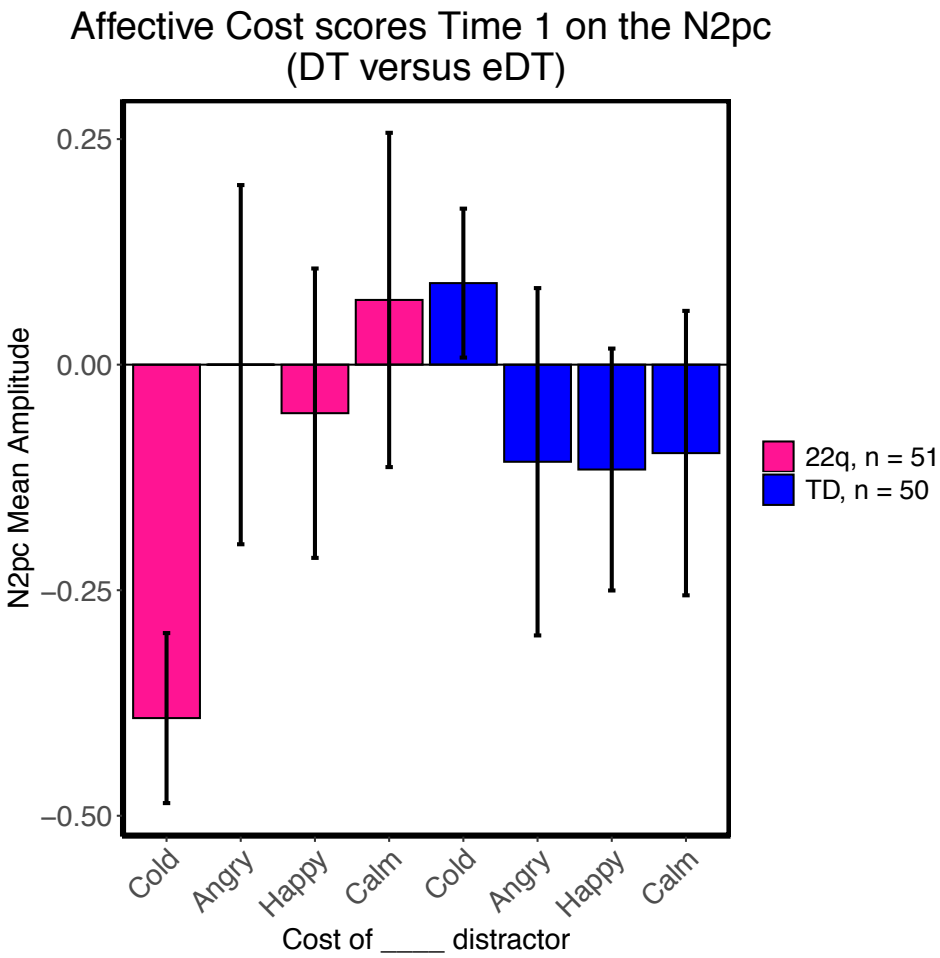
- BUT, that Target rarely appears in center
  - 70% scrambled, 10 % happy, 10% calm, 10% angry
- AND, emotional faces appear often on one side or other (called a "Flanker")
  - 33% happy, 33% calm, 33% angry



Hot Cognition: Attention

Negative Value = More attention to Non-Target "flanker"

- In TD group, attention captured by ALL emotional faces
- In 22q group, essentially opposite pattern.
  - More (for us) evidence of suppressing attention to emotional faces

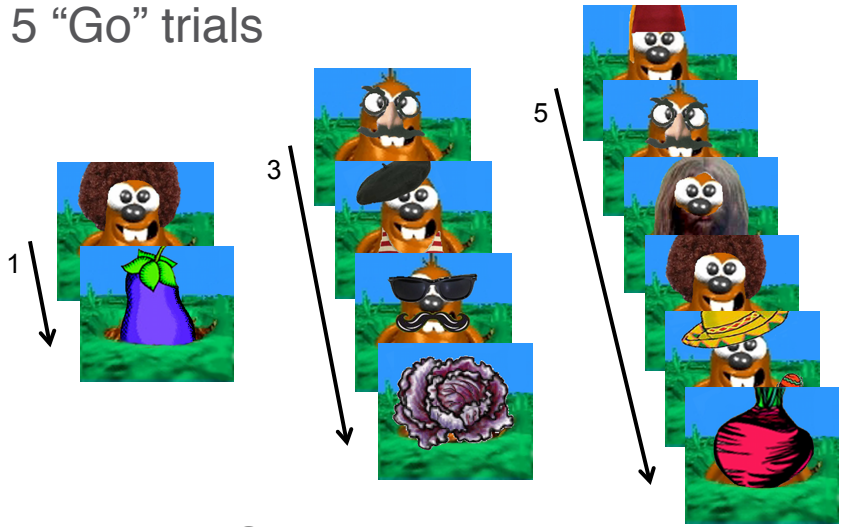


Cold Cognition: Inhibition

"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



Go/NoGo Task adapted from Casey et al. 2007

Cold Cognition: Inhibition

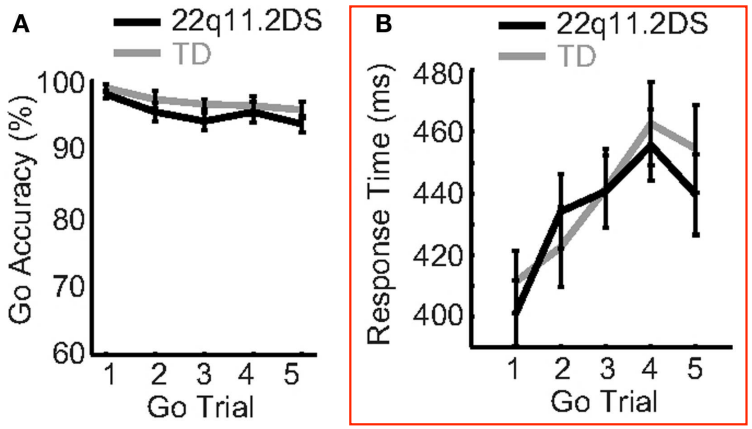


FIGURE 2 | Proactive response inhibition was typical in children with 22q11.2DS. **(A)** Accuracy and **(B)** response time on Go trials did not differ between groups.

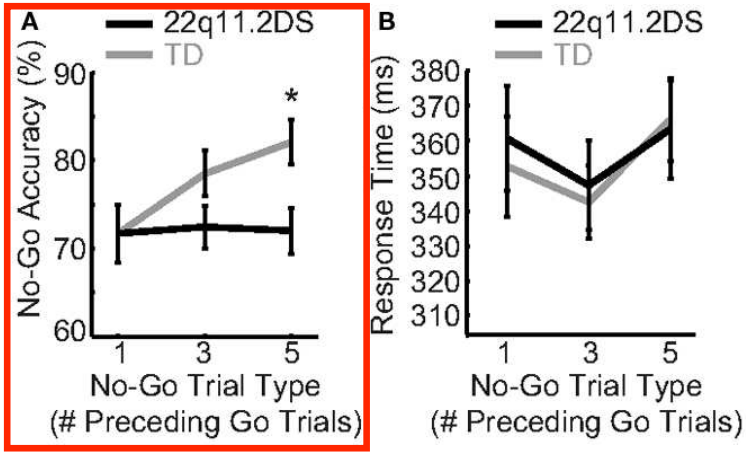


FIGURE 3 | Reactive response inhibition was atypical in children with 22q11.2DS. **(A)** TD children demonstrated better No-Go accuracy as a function of more preceding Go trials, while children with 22q11.2DS did not demonstrate this pattern. **(B)** There were no group differences in response time on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

Go trials, respectively). Diagnostic group, No-Go trial type, and

Hot Cognition: Inhibition

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

Did YOU feel stressed? And that was for something that feels good!
What happens if you have to control yourself when things feel bad?

Hot Cognition: Inhibition

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

Did YOU feel stressed? And that was for something that feels good!
What happens if you have to control yourself when things feel bad?

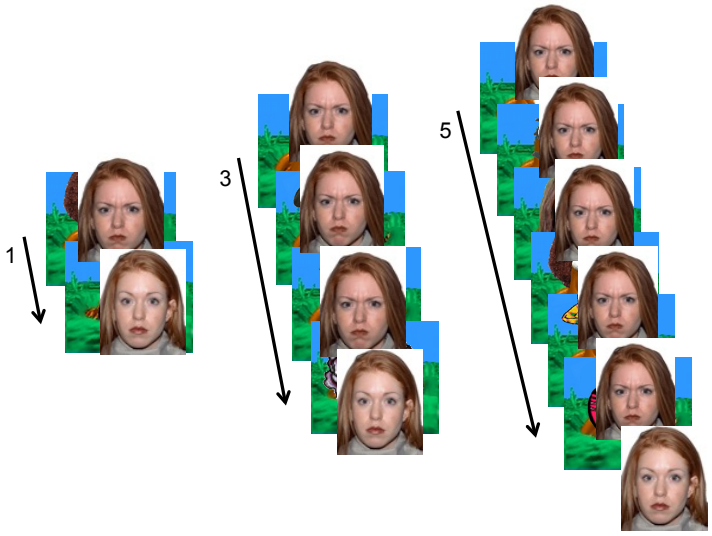
Hot Cognition: Inhibition

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

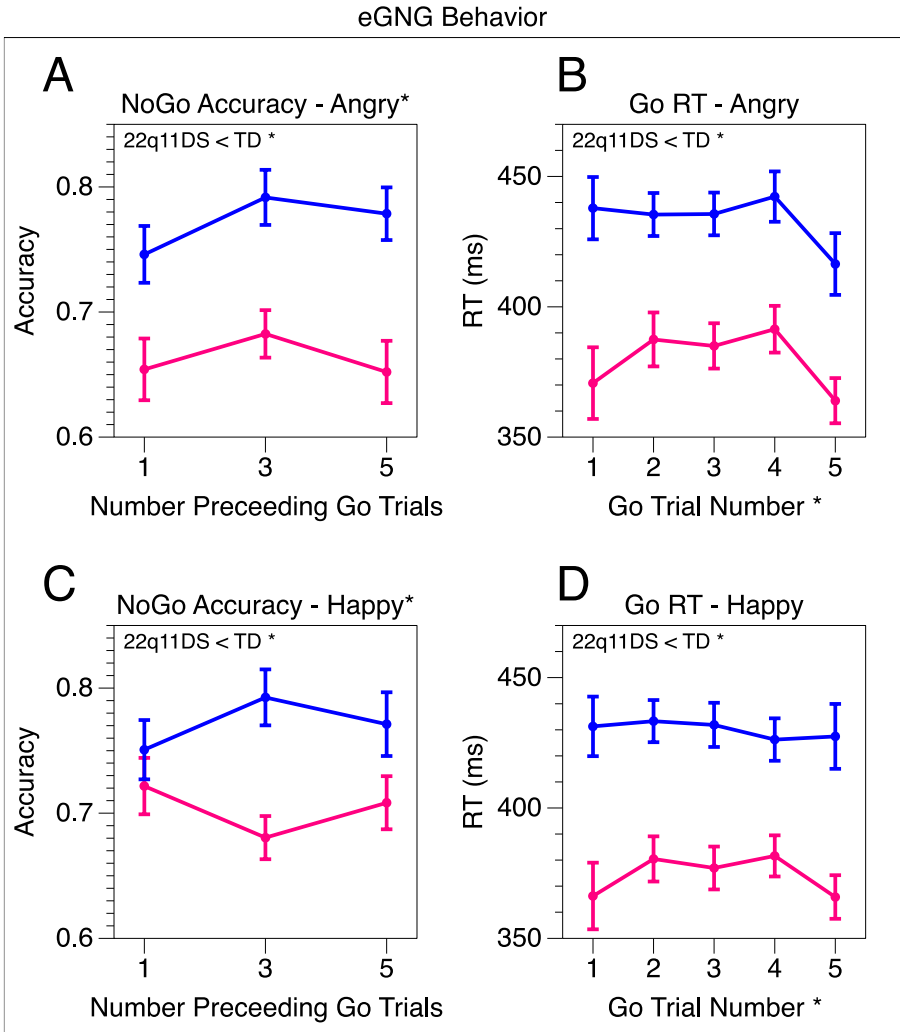
  - Preceded by 1, 3, or 5 “Go” trials



Hot Cognition: Inhibition

These data are from current study with 12-18 year-olds

- as a group, youth with 22q respond more quickly (impulsively)
- as a group, youth with 22q are much less able to inhibit a response than TD youth when emotion is negative (Angry)

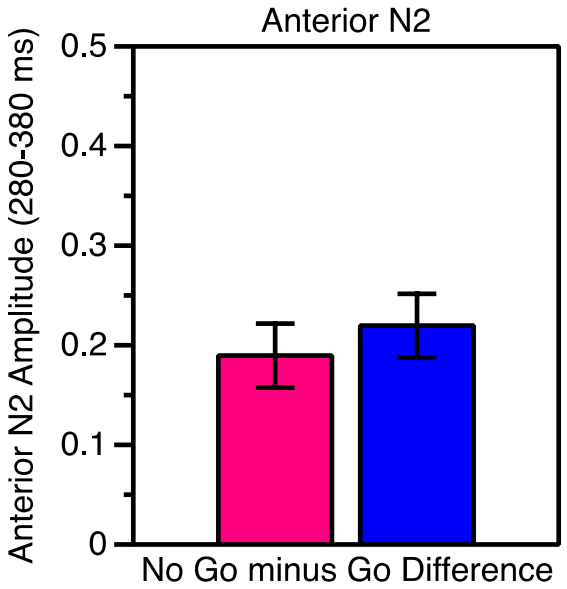


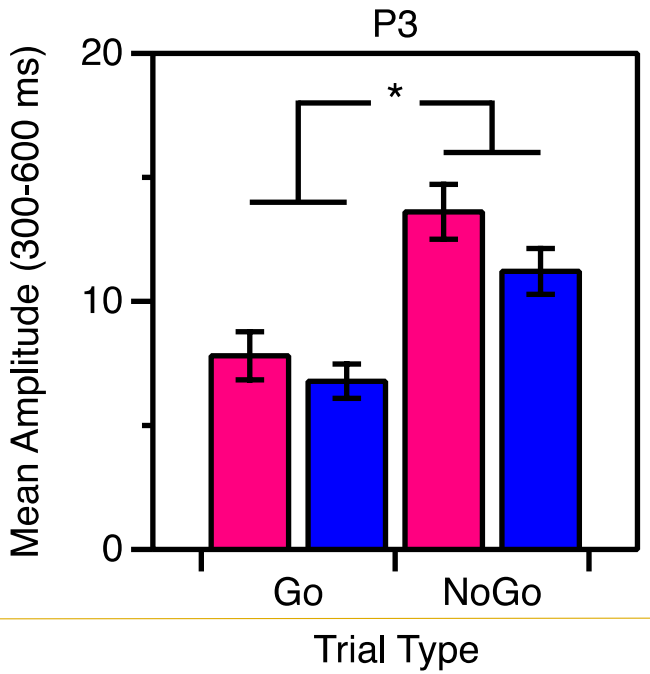
Cognitive Control Brain Responses to Conflict

The “Anterior N2” signal indicates the brain’s detection of conflicting information

- sudden shift from GO indicator to NOGO indicator in COLD task variant

The “P3” signal indicates detection of a rare event (“oddball”)



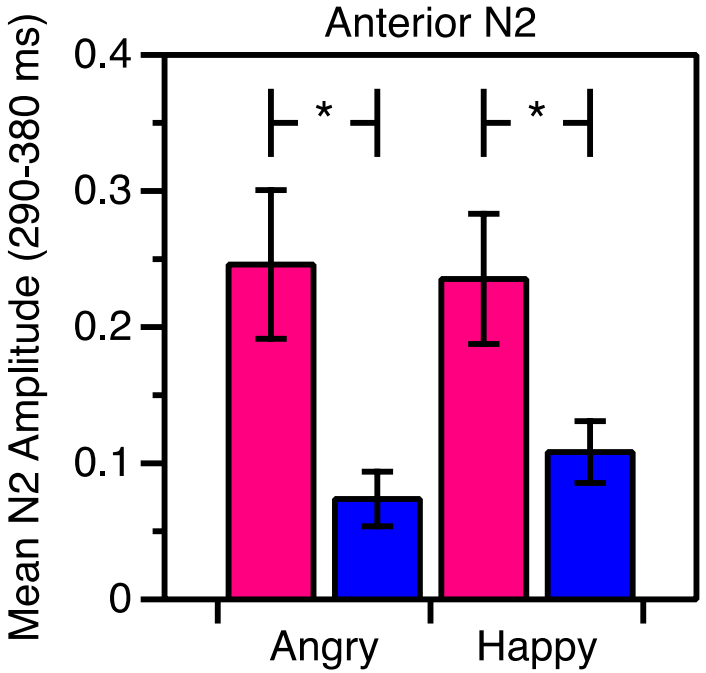


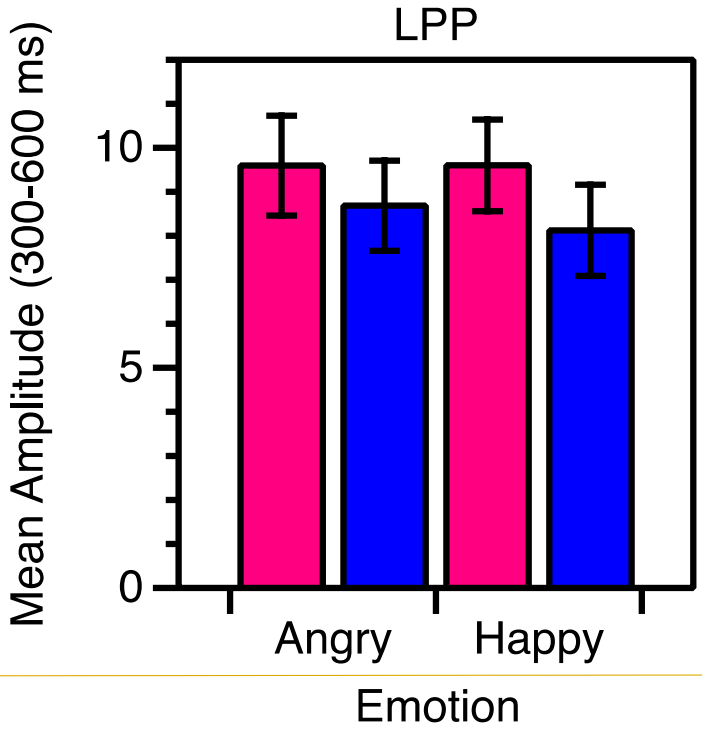
Cognitive Control Brain Responses to Conflict

When emotional faces replace moles & vegetables the conflict response in youth with 22q goes from the same as to MUCH bigger than the typical youth

- shows again that emotional stimuli alter brain responses in the 22q group

LPP is brain signal for extended processing of emotional information



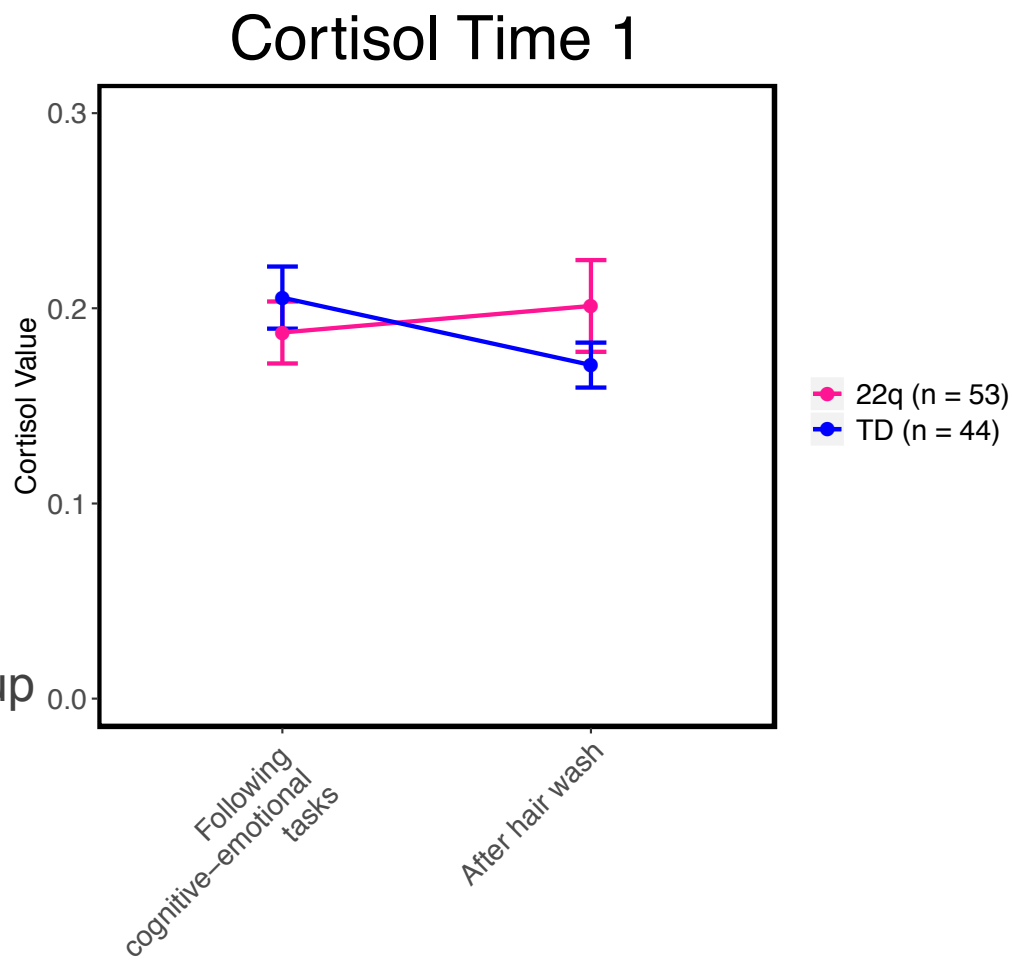


Stress Biology Differences

Cortisol is a hormone released in response to stress & found in saliva

Measured before, during & after ERP tasks

- Cortisol "Shut-Off" is the typical response <u>after</u> challenge
- ***As a group***, youth with 22q show significantly less shut off than TD group
  - so still producing stress response long after stressor is removed



Do our findings so far suggest any potential risk/protection predictors?

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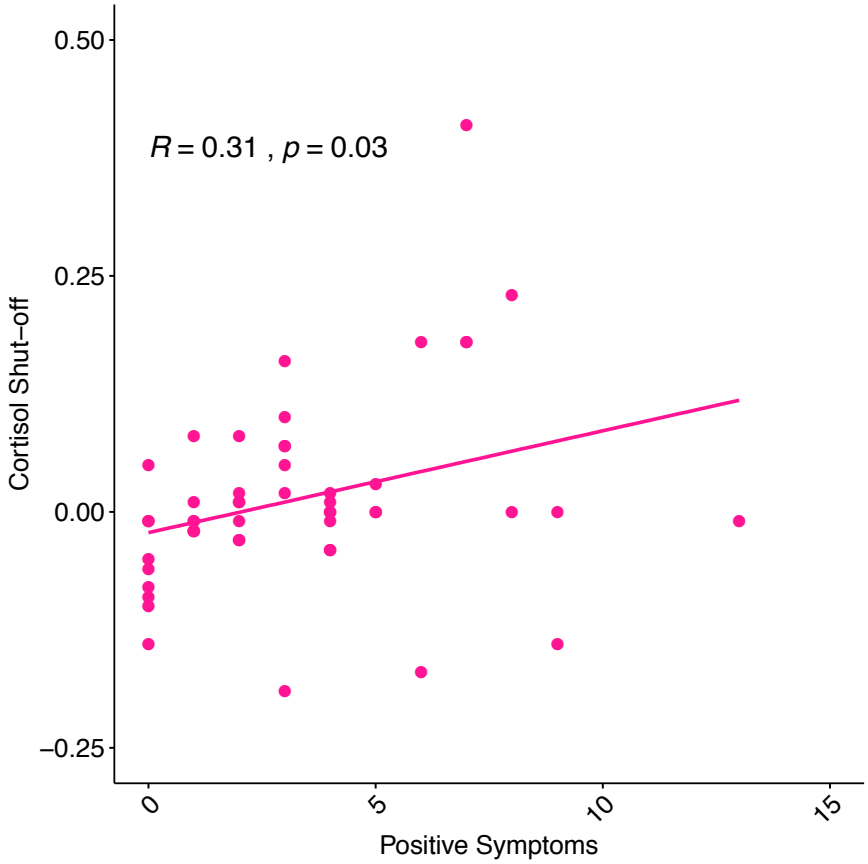
Cortisol Shut-Off and P symptoms

- Reduced cortisol shut-off IS related to significantly more positive SIPS symptoms in young people with 22q (at T1)
- Many studies have found relationships between stress and psychosis-proneness in people without 22q
- ***Coping Strategies Mediate the Effect of Stressful Life Events on Schizotypal Traits and Psychotic Symptoms in 22q11.2 Deletion Syndrome*** - Armando et al 2018

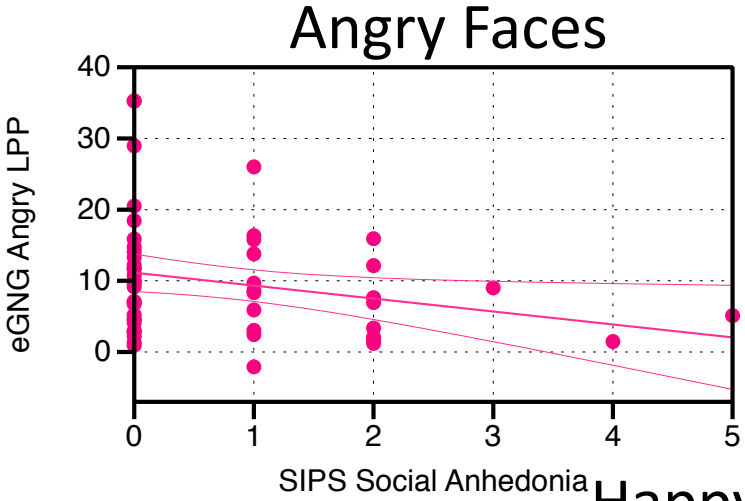


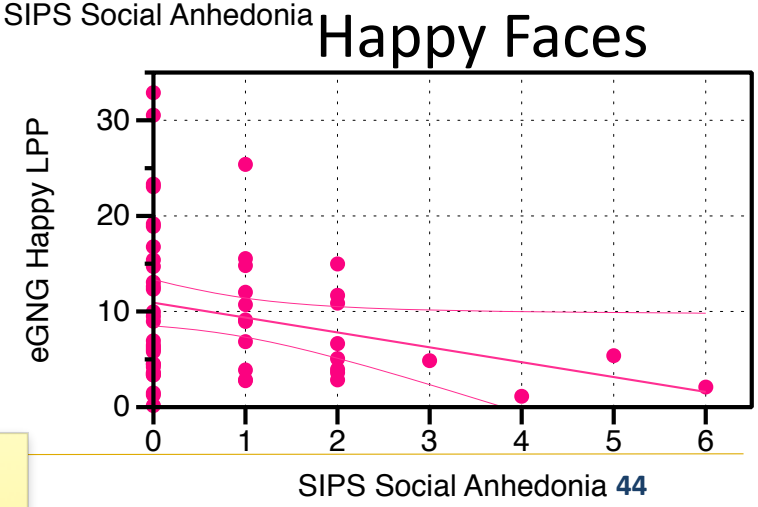
Emotion Processing and Social Reward

Social Anhedonia is lack of reward from social interaction

In youth with 22q, MORE emotion processing (larger LPP) was associated with greater ability to find social interaction rewarding

- So less emotional processing and more Social Anhedonia, likely indicates withdrawal and avoidance of emotional inputs are related





NAPLS etc have found Social Anhedonia predicts psychosis risk

Conclusions

Schizophrenia does occur more commonly in 22q & sometimes seriously

- but likely at nowhere near the rate once believed

Our informal *coper/struggler* concept likely extends beyond childhood

- excessive challenge increases anxiety and reduces ability to function

Adding emotionally challenging content increases cognitive challenge

- youth with 22q seem less able to control cognition in more emotional states
- reduced cognitive control is what many negative "symptoms" describe

Youth with who handle stress less well and avoid social situations are the ones likely to show more of the "psychosis-proneness" characteristics

- consistent with psychosis-proneness is at-risk youth without 22q

Emotional coping & social skills likely increase protection, independence & QoL

Huge Thanks To:

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