Illustrating the need for biomarkers by reference to Conduct Disorder and showing what might be done

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Talk plan

- Two concerns for child and adolescent psychiatry
  - Reliability of diagnosis
  - Predicting treatment response
- Using work with patients with Conduct Disorder to illustrate some of the issues.
- The beginnings of the development of a biomarker
- Conclusions

The difficulties for DSM/ICD: Reliability

kappa:
0.8+: Outstanding
0.6-0.8: Substantial
0.4-0.6: Moderate
<0.4: Pretty awful

TABLE 4. Test-Retest Reliability of Target DSM-5 Diagnoses at the Child/Pediatric Field Trial Sites[a]

Target DSM-5 Diagnosis and Field Trial Site	Intraclass Kappa	95% CI	Interpretation	DSM-IV Prevalence	DSM-5 Prevalence (95% CI)
Autism spectrum disorder[b]					
Baystate	0.66	0.51–0.79	Very good	0.23	0.24 (0.20–0.30)
Stanford	0.72	0.54–0.86	Very good	0.26	0.19 (0.15–0.24)
Pooled	0.69	0.58–0.79	Very good		
ADHD					
Baystate	0.71	0.56–0.82	Very good	0.59	0.69 (0.62–0.74)
Columbia	0.45	0.29–0.62	Good	0.55	0.58 (0.51–0.65)
Pooled	0.61	0.51–0.71	Very good		
Disruptive mood dysregulation disorder					
Baystate	0.06	−0.07 to 0.29	Unacceptable	n/a[c]	0.05 (0.03–0.08)
Colorado	0.49	0.33–0.66	Good	n/a[c]	0.15 (0.11–0.19)
Columbia	0.11	−0.09 to 0.37	Unacceptable	n/a[c]	0.08 (0.04–0.12)
Pooled[d]	0.25	0.15–0.36	Questionable		
Mixed anxiety-depressive disorder					
Colorado	0.02	−0.09 to 0.20	Unacceptable	n/a[c]	0.07 (0.04–0.09)
Stanford	0.13	−0.04 to 0.45	Unacceptable	n/a[c]	0.04 (0.02–0.06)
Pooled	0.05	−0.08 to 0.17	Unacceptable		
Major depressive disorder					
Colorado	0.33	0.14–0.52	Questionable	0.21	0.12 (0.09–0.15)
Stanford	0.23	0.03–0.41	Questionable	0.21	0.12 (0.08–0.15)
Pooled	0.28	0.15–0.41	Questionable		
Avoidant/restrictive food intake disorder (Stanford)	0.48	0.25–0.68	Good	n/a[c]	0.11 (0.07–0.15)
Oppositional defiant disorder (Columbia)	0.40	0.18–0.61	Good	0.22	0.17 (0.12–0.22)
Nonsuicidal self-injury (Baystate)	−0.03	−0.05 to −0.01	Unacceptable	n/a[c]	0.03 (0.01–0.04)

[a] Kappa estimates shown are those with standard errors ≤0.1 and 95% CI sizes ≤0.5.
[b] For autism spectrum disorder, the estimated DSM-IV prevalence represents the DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified.
[c] Not applicable because the diagnosis is new to DSM.
[d] Since the individual intraclass kappas for the stratified samples and their 95% CIs do not overlap, the pooled intraclass kappa needs to be interpreted with caution.

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We need biomarkers!!!

Not as diagnosis markers

But:

To identify treatment targets

To understand the difficulties the patient faces

Illustrating some of the issues with Conduct Disorder**(s)**
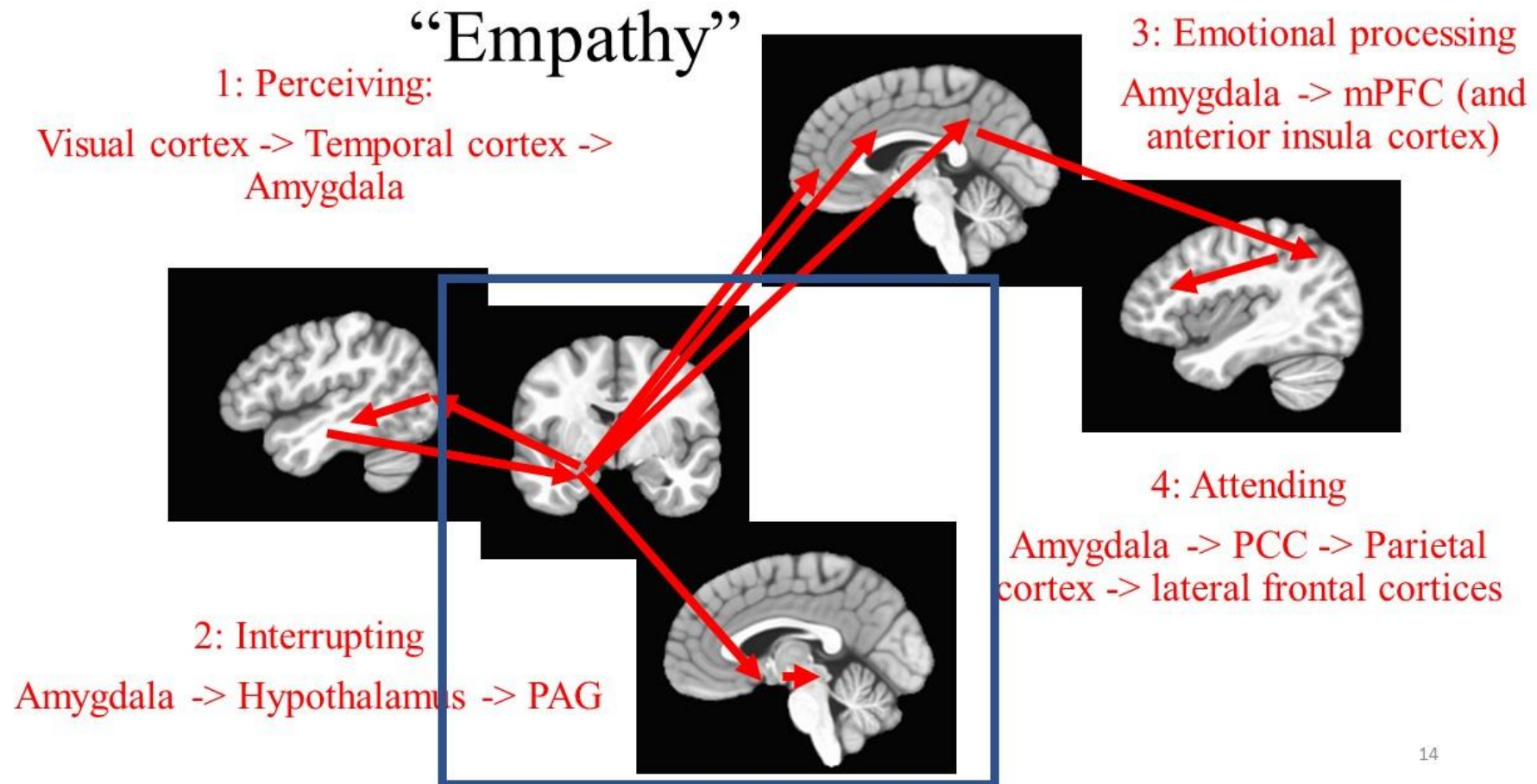
Conduct Disorder

- Conduct disorder refers to a group of repetitive and persistent behavioral and emotional problems in youngsters.

- Extremely high comorbidity with ADHD (up to 78% in cases with CD at BT).

- Associated with abuse/neglect and substance use.

- Gold standard techniques only effective with 50% of cases

- Significant comorbidity with internalizing conditions.

- Two important considerations:
  - Forms of aggression
  - Callous unemotional traits

Consideration 1

Former for aggression

Instrumentel/proaktiv aggression
(stadig fra gudfaderen)

Reaktiv aggression
(mand slår snemand)

Consideration 2: Callous-Unemotional Traits

- Callous-Unemotional (CU) traits **reflect reduced guilt, uncaring behavior, and reduced empathy.**
- **Core feature here is that elevated CU traits are associated with behavioral indications of a relative indifference to the suffering of other individuals.**
- DSM-5 introduced a specifier to conduct disorder (CD) - "with limited prosocial emotions." This is an analog of CU traits.
- Maybe 10–32% of the individuals with CD will qualify for the limited prosocial emotions (CU) specifier (Kahn, Frick, Youngstrom, & Kogos Youngstrom, 2012).
- **Elevated CU traits are particularly associated with an increased risk for instrumental aggression**

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Empathy (response to distress cues)
(Blair, *Nature Neuroscience Reviews*, 2014; cf. 2004)

"Empathy"

1: Perceiving:
Visual cortex -> Temporal cortex -> Amygdala

3: Emotional processing
Amygdala -> mPFC (and anterior insula cortex)

2: Interrupting
Amygdala -> Hypothalamus -> PAG

4: Attending
Amygdala -> PCC -> Parietal cortex -> lateral frontal cortices

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Reduced Amygdala Response to Fearful Expressions in Children and Adolescents With Callous-Unemotional Traits and Disruptive Behavior Disorders

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Elizabeth C. Finger, M.D.

Derek G.V. Mitchell, Ph.D.

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Courtney Sims

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Kenneth E. Towbin, M.D.

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Daniel S. Pine, M.D.

R.J.R. Blair, Ph.D.

Objective: Extensive work implicates abnormal amygdala activation in emotional facial expression processing in adults with callous-unemotional traits. However, no research has examined amygdala response to emotional facial expressions in adolescents with disruptive behavior and callous-unemotional traits. Moreover, despite high comorbidity of callous-unemotional traits and attention deficit hyperactivity disorder (ADHD), no research has attempted to distinguish neural correlates of pediatric callous-unemotional traits and ADHD.

Method: Participants were 36 children and adolescents (ages 10–17 years); 12 had callous-unemotional traits and either conduct disorder or oppositional defiant disorder, 12 had ADHD, and 12 were healthy comparison subjects. Functional MRI was used to assess amygdala activation patterns during processing of fearful facial expressions. Patterns in the callous-unemotional traits group were compared with those in the ADHD and comparison groups.

Results: In youths with callous-unemotional traits, amygdala activation was reduced relative to healthy comparison subjects and youths with ADHD while processing fearful expressions, but not neutral or angry expressions. Functional connectivity analyses demonstrated greater correlations between the amygdala and the ventromedial prefrontal cortex in comparison subjects and youths with ADHD relative to those with callous-unemotional traits. Symptom severity in the callous-unemotional traits groups was negatively correlated with connectivity between amygdala and ventromedial prefrontal cortex.

Conclusions: This is the first study to demonstrate reduced amygdala responsiveness in youths with callous-unemotional traits. These findings support the contention that callous and unemotional personality traits are associated with reduced amygdala response to distress-based social cues.
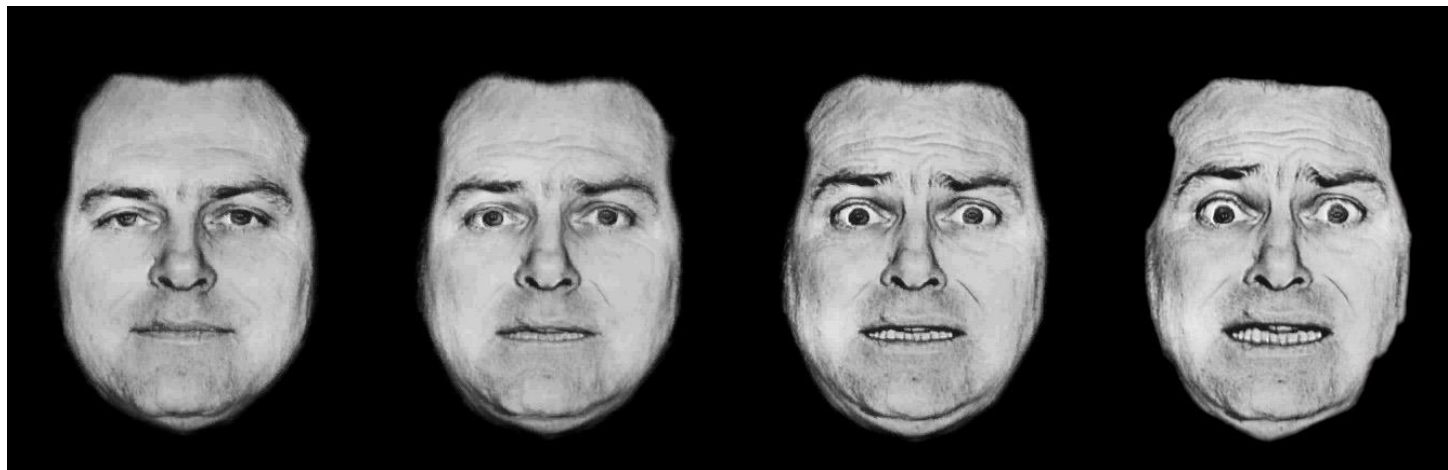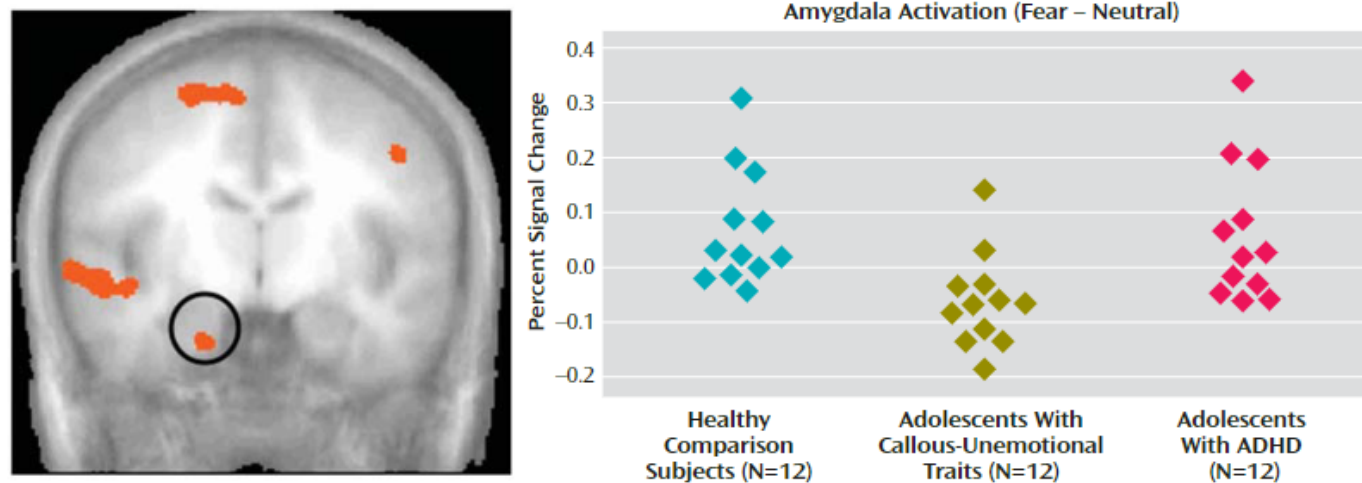
FIGURE 1. Results of a Group-by-Emotional Expression Analysis of Variance of Amygdala Activity in Response to Fearful and Neutral Expressions[a]

[a] The image on the left shows the region of the right amygdala in which an interaction effect was observed. The graph on the right summarizes amygdala activation in each group.

Mediation of the Relationship Between Callous-Unemotional Traits and Proactive Aggression by Amygdala Response to Fear Among Children With Conduct Problems

Leah M. Lozier, BS; Elise M. Cardinale, BA; John W. VanMeter, PhD; Abigail A. Marsh, PhD

IMPORTANCE Among youths with conduct problems, callous-unemotional (CU) traits are known to be an important determinant of symptom severity, prognosis, and treatment
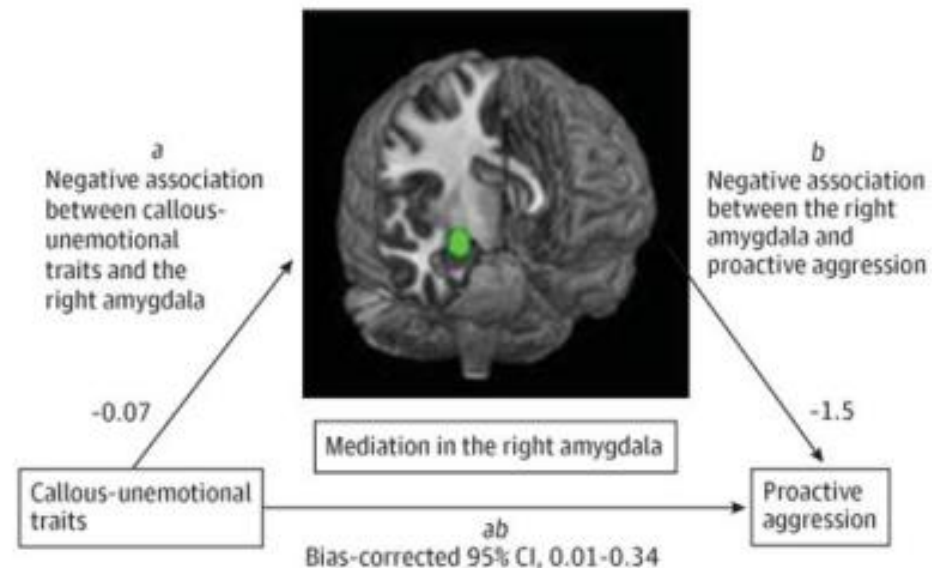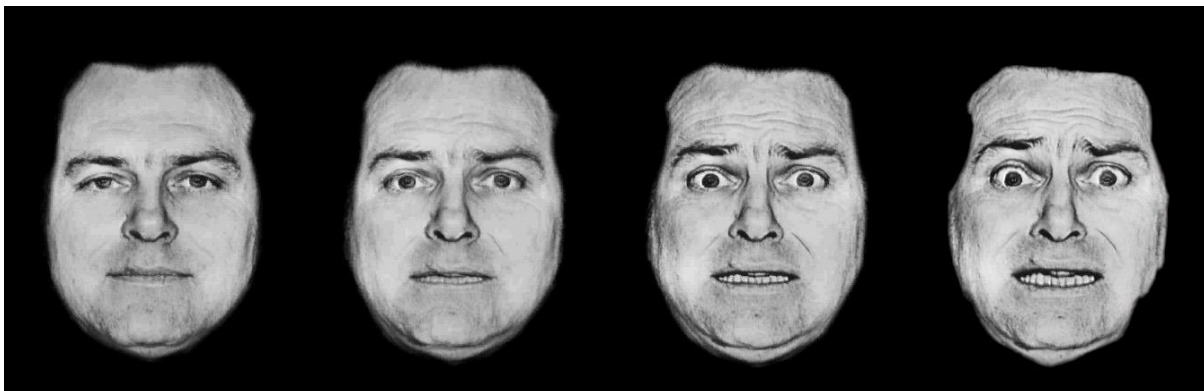
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Figure 2. Amygdala Response Mediates the Relationship Between Callous-Unemotional Traits and Proactive Aggression

Unstandardized regression coefficients and bias-corrected 95% CI for the indirect effect from a bootstrap-mediation analysis that found that right amygdala responses to fearful expressions mediated the relationship between callous-unemotional traits and proactive aggression among 30 youths with conduct problems.

Basic Threat (Emotion Response) System
(Blair, *Nature Neuroscience Reviews*, 2014; cf. 2004)
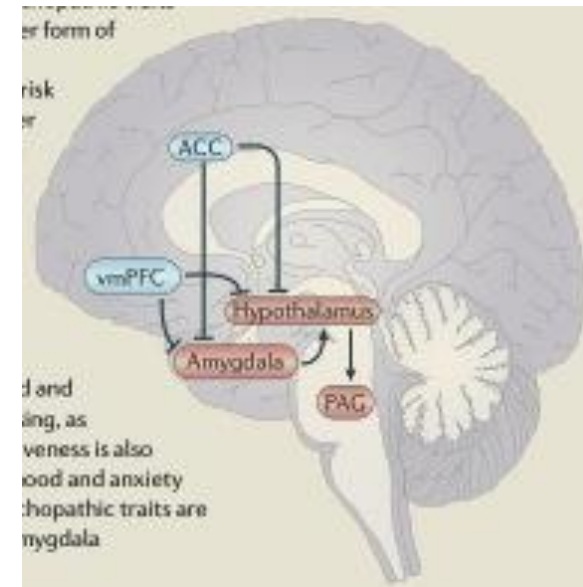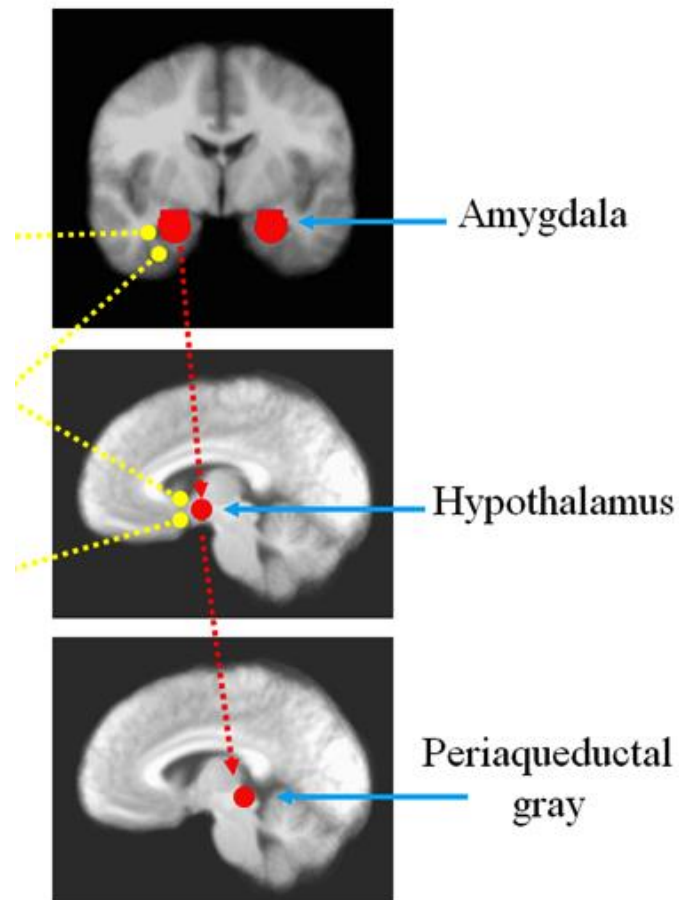
Dual Neuro-circuitry Dysfunctions in Disruptive Behavior Disorders: Emotional Responding and Response Inhibition

Soonjo Hwang, M.D.[1,*], Zachary T. Nolan, B.A.[2], Stuart F. White, Ph.D.[3], W. Craig Williams, B.A.[4], Stephen Sinclair, Ph.D.[5], and R. J. R. Blair, Ph.D.[5]
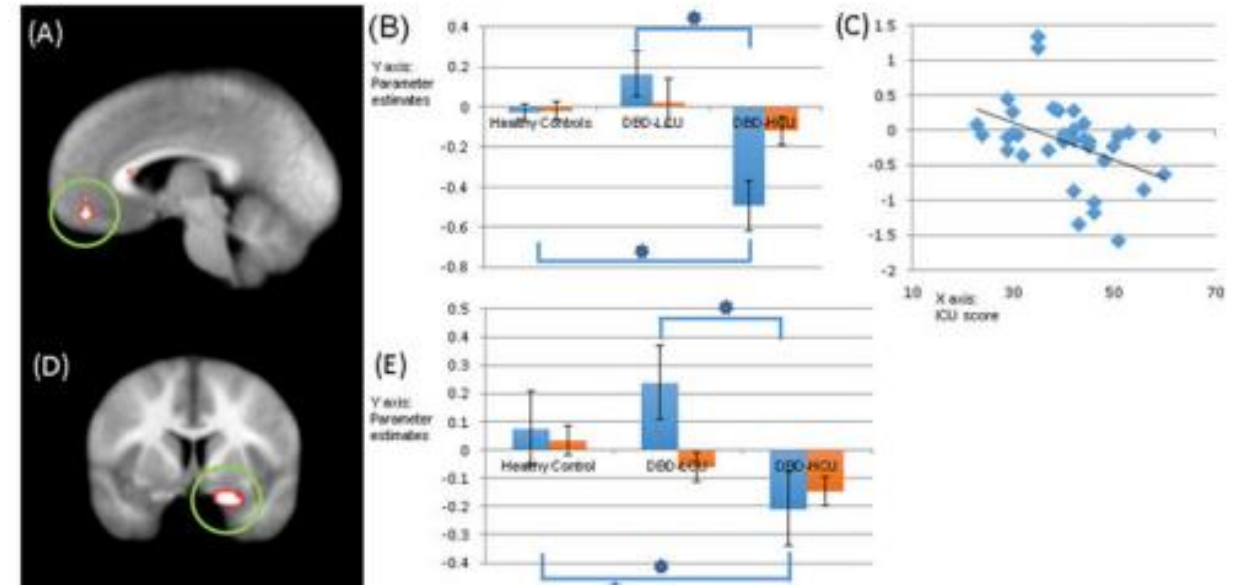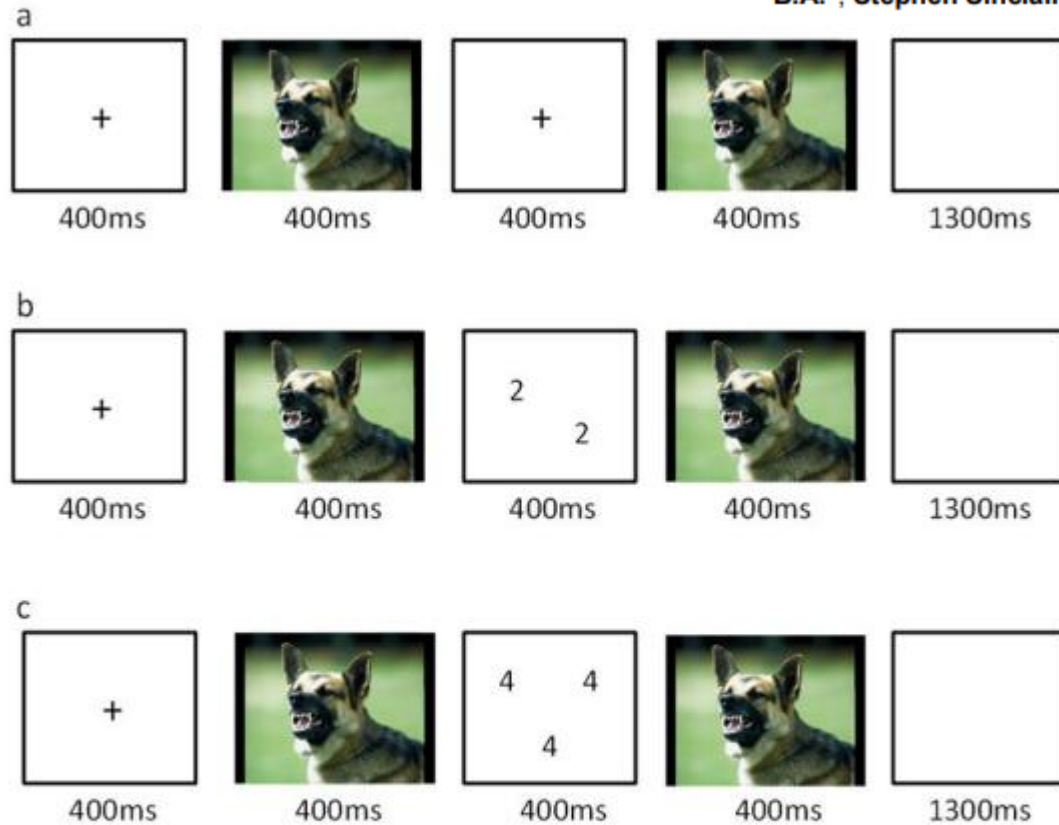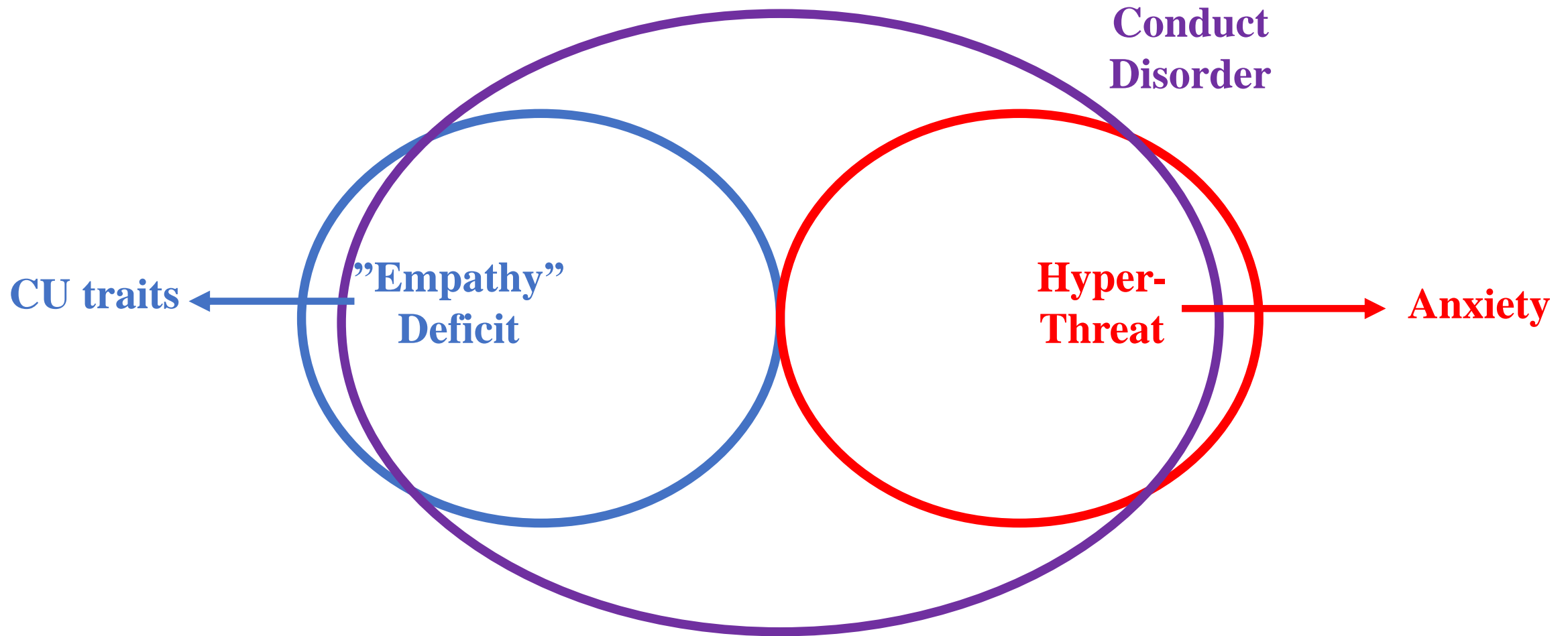
Figure 1.
Example trial sequences. (a) negative view trial; (b) negative congruent trial; (c) negative incongruent trial.

Not all adolescents receiving the diagnosis of CD have the same clinical condition!

Not all adolescents receiving the diagnosis of CD have the same clinical condition! What are the implications for treatment?

Archival Report

Biological Psychiatry
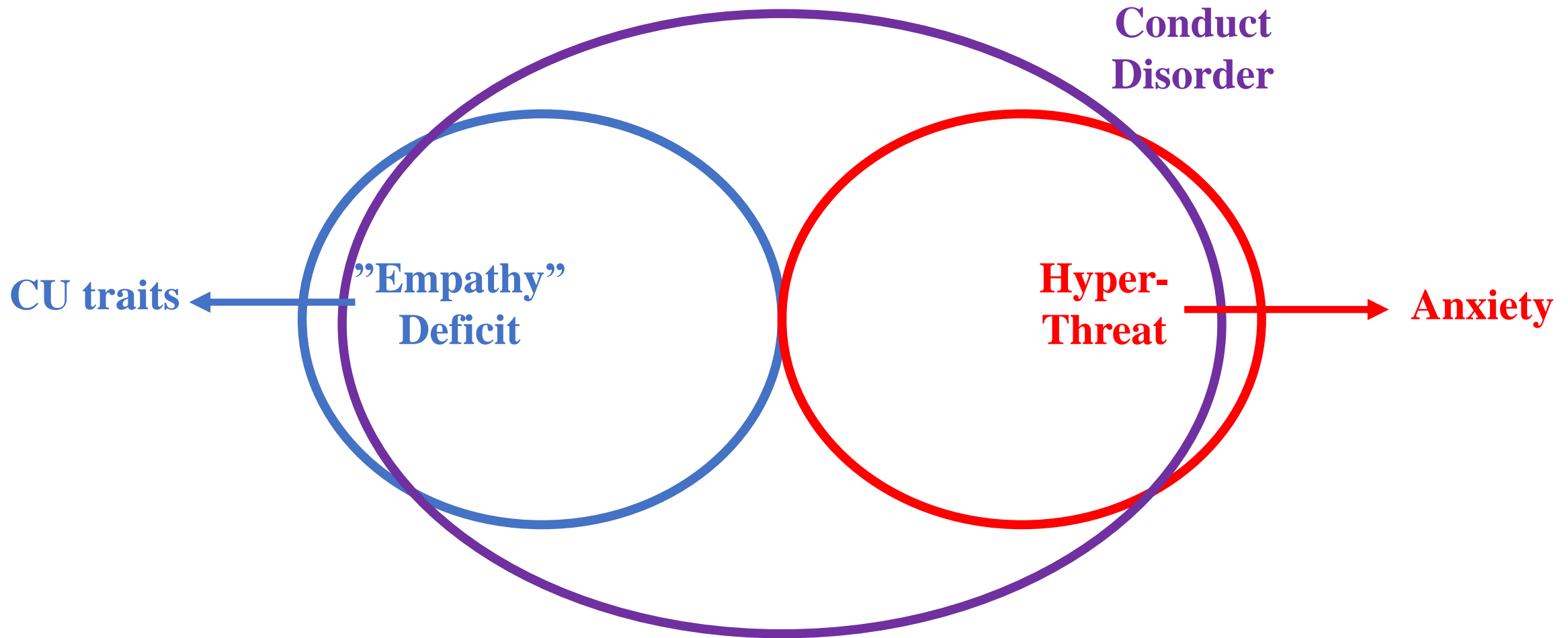
Selective Amygdala Hypoactivity to Fear in Boys With Persistent Conduct Problems After Parent Training

Arjun Sethi, Suzanne O'Brien, James Blair, Essi Viding, Mitul Mehta, Christine Ecker, Nigel Blackwood, Moira Doolan, Marco Catani, Stephen Scott, Declan G.M. Murphy, and Michael C. Craig
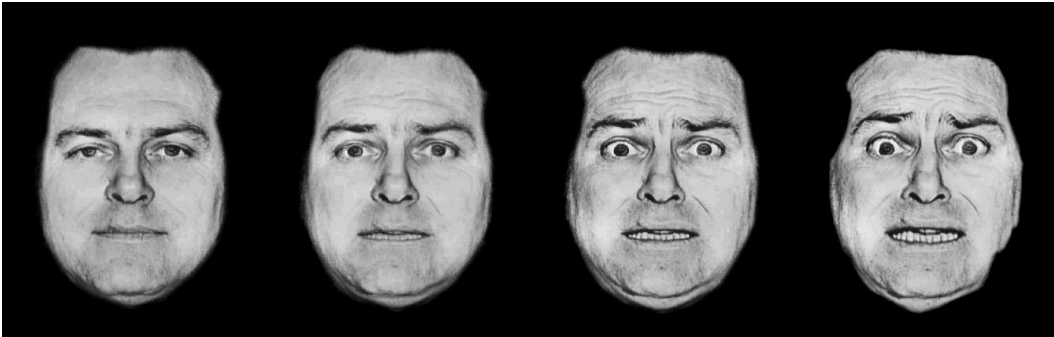
A

The study involved 57 CP and 36 TD boys.

It examined the current gold standard for CP – early intervention with parent-training programmes (Institute of Psychiatry variant).

These successful though up to 50% of children may only gain limited benefit.
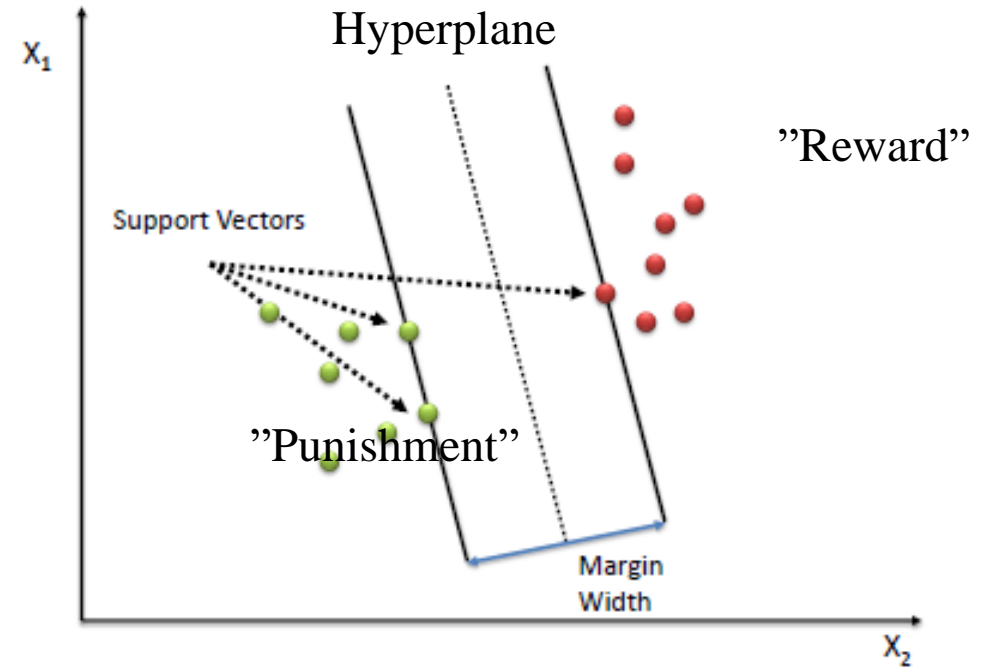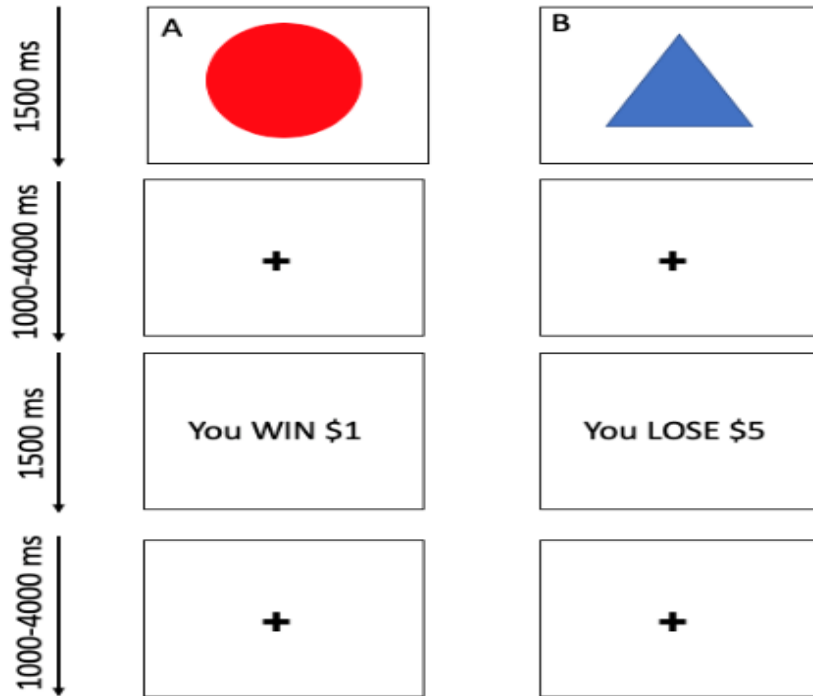
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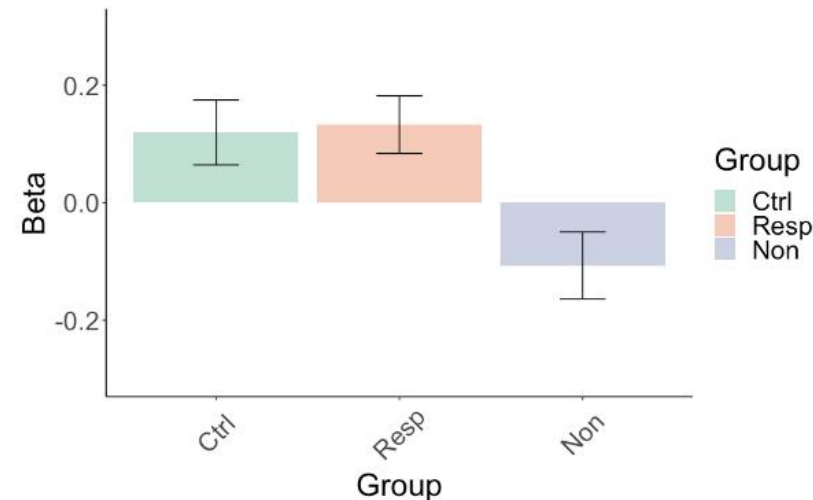
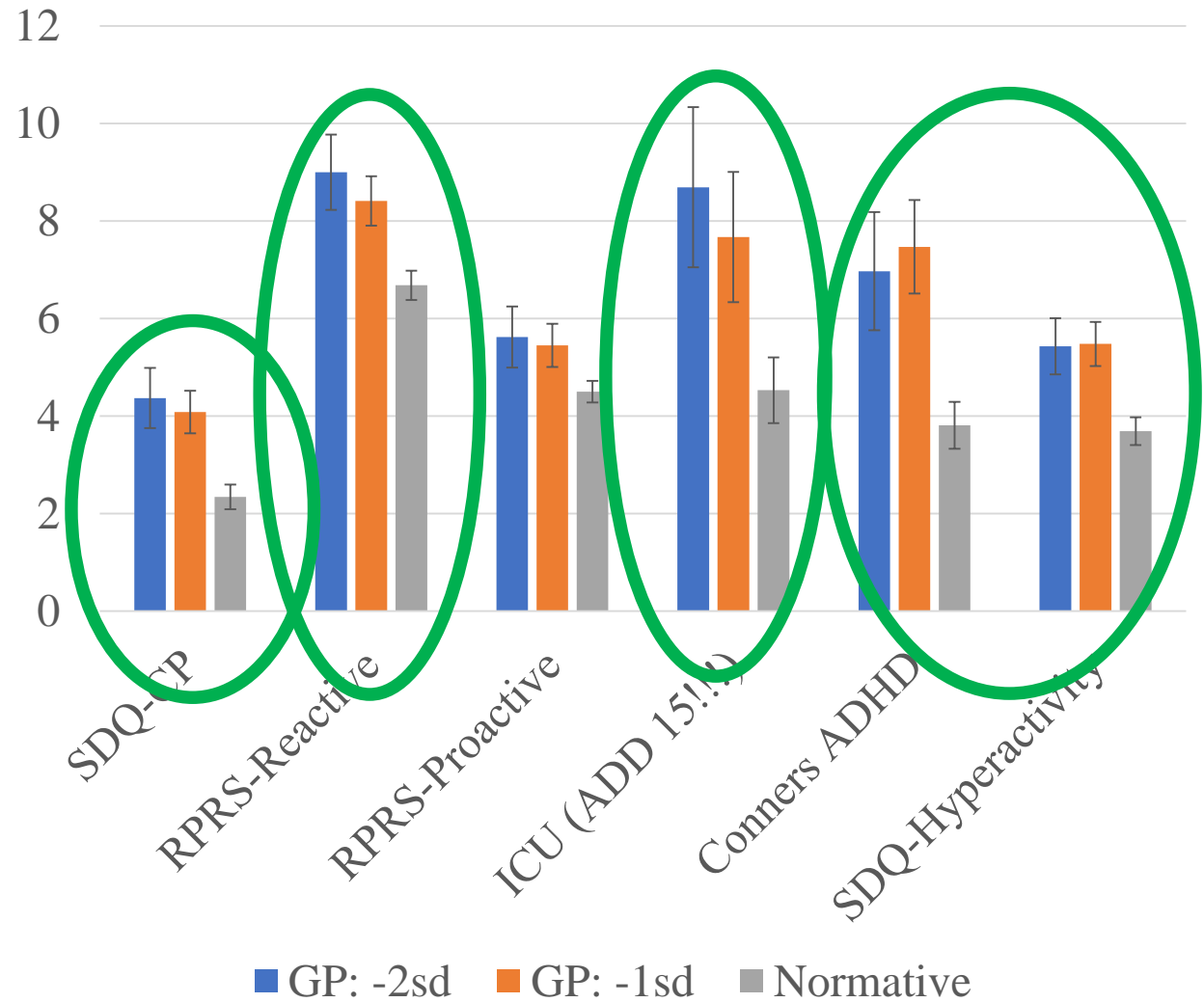# Neurobiology of conduct problems in the classroom and clinic
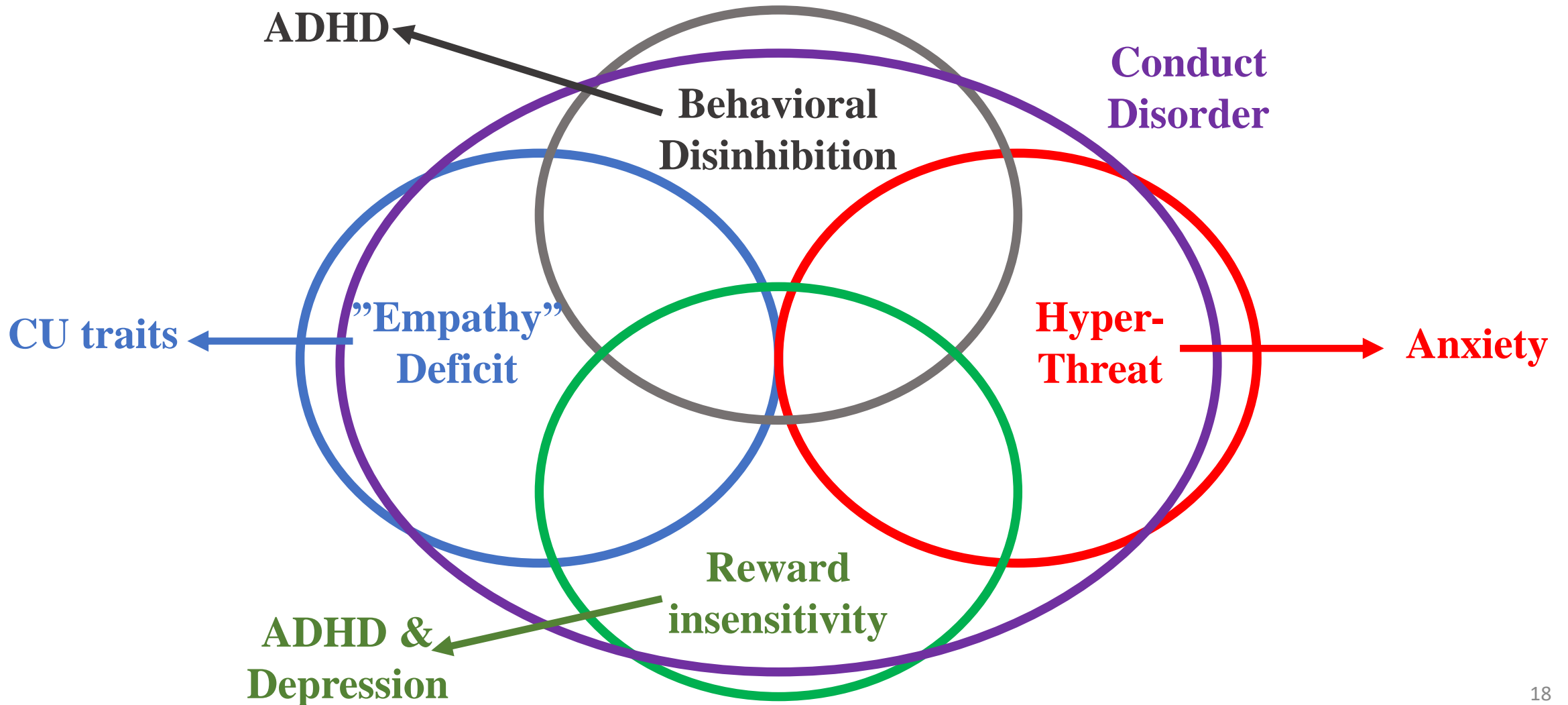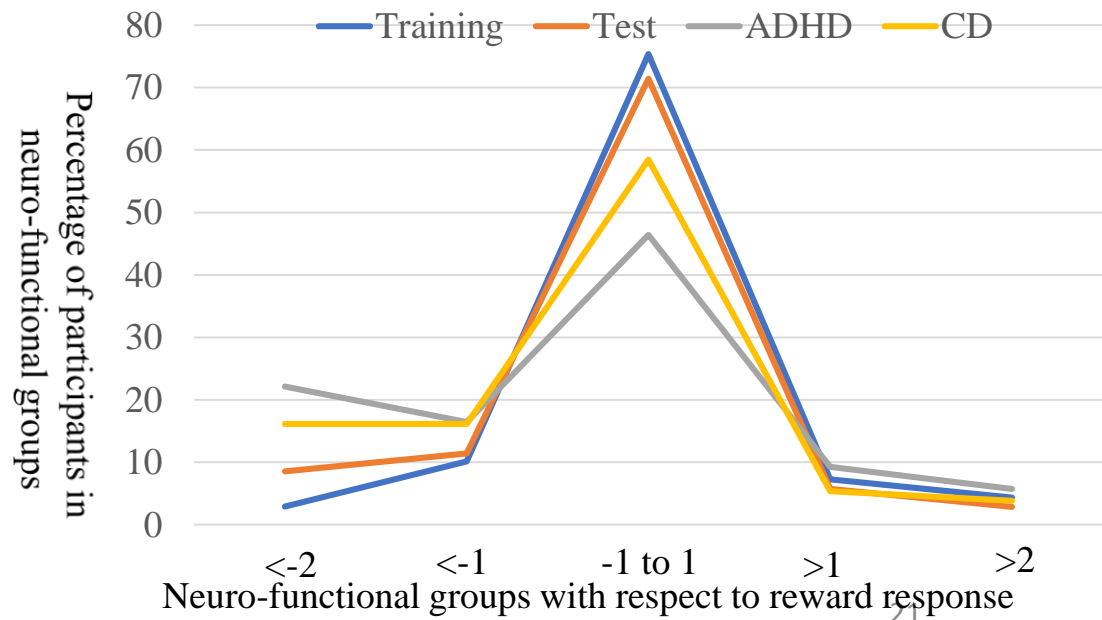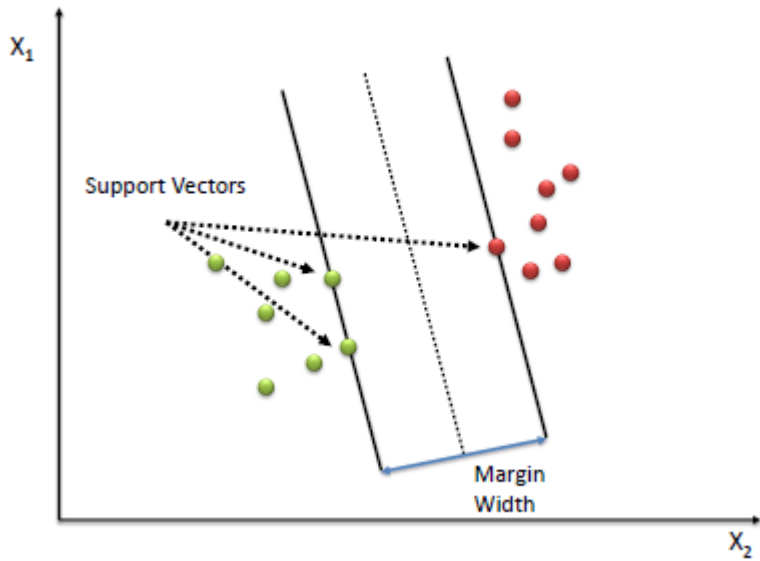
Neurobiology of conduct problems in the classroom and clinic
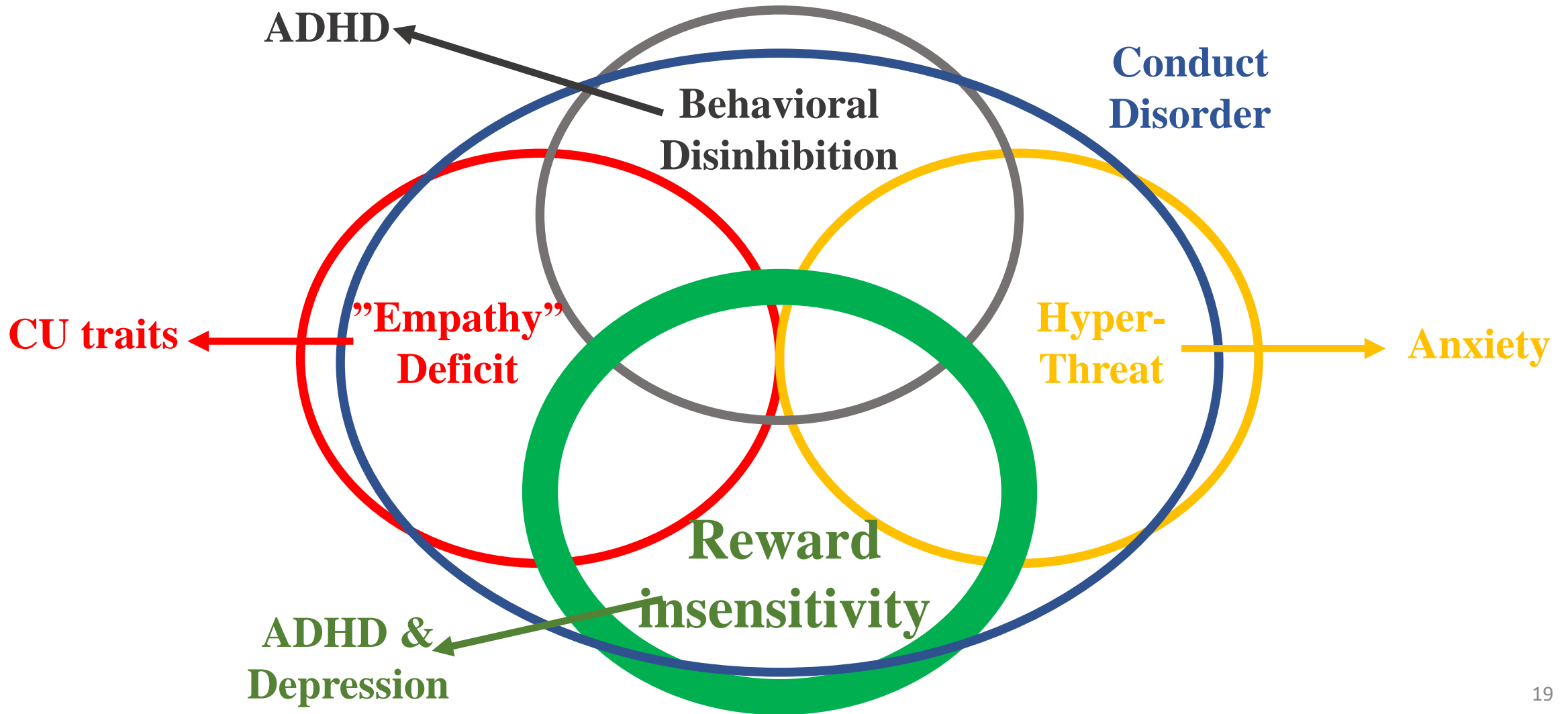
The decision-making machine learning project (Blair … Bajaj, under revision)

Results

Conclusions

- We face concerns: Reliability of assessment and prediction of treatment response.

- The development of biomarkers would mitigate (not remove!!!) these concerns.

- The diagnosis of CD embodies some of these problems.

- At least three main forms:
  - Empathy disrupted
  - Threat hyper-sensitive
  - No significant neurobiology?

- Additional difficulties too: Reinforcement processing.

- Functional markers may be possible via machine learning (probably not fMRI though….)
  - Provide treatment targets
  - Provide information for clinicians – An adolescent with empathy disrupted CD may not be the first choice for parent training interventions.