Neuro-cognitive systems underpinning antisocial behavior and the impact of maltreatment and substance abuse on their development

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Talk plan

• Boys Town and the mission of the Center for Neurobehavioral Research.
• Neuro-cognitive systems underpinning antisocial behavior
  • “Empathy”
  • Acute threat response
  • Response control
  • Reinforcement-based decision-making
Boys Town

• Large residential treatment center in Omaha Nebraska.
• The residential center itself caters for approximately 400+ youth each year (40% female). Psychosocial focus to the intervention though considerable psychiatric input.
• In addition, there are a number of Boys Town centers around the USA, most of which see adolescents as outpatients (35,000+ patients per year)
• BT and local donor community invested in the Center for Neurobehavioral Research (CNR). The CNR launched properly in 2016. I moved from NIMH to run the CNR in late August 2016.
Boys Town sample (as of March 2017)
(40% female)

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>%</th>
<th>N</th>
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<tbody>
<tr>
<td>ADHD</td>
<td>42.6</td>
<td>52</td>
</tr>
<tr>
<td>ODD</td>
<td>37.7</td>
<td>46</td>
</tr>
<tr>
<td>CD</td>
<td>34.4</td>
<td>42</td>
</tr>
<tr>
<td>MDD</td>
<td>11.5</td>
<td>14</td>
</tr>
<tr>
<td>GAD</td>
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<td>19</td>
</tr>
<tr>
<td>SAD</td>
<td>10.7</td>
<td>13</td>
</tr>
<tr>
<td>PTSD</td>
<td>9.02</td>
<td>11</td>
</tr>
</tbody>
</table>
The current situation

• Currently, all mental health diagnoses are driven by child and care-giver reports of the child’s behavior.
• There is no other branch of medicine like this.

• Problems
  • How do we know what a person has?
  • How do we know when/if the intervention has been successful?

• Brain level differences have significant implications for treatment
Problem space

Acute threat response/
Response control/
Reinforcement-based decision-making

Aggression

Conduct problems

Trauma

Substance abuse
The goals of the CNR

• Identify neural signatures of healthy development

• Identify neural signatures related to atypical development
  • The impact of substance abuse
  • The impact of maltreatment
  • Neural signatures related to particular forms of psychopathology.

• Determine the extent to which the Boys Town intervention “normalizes” atypical brain signatures.

• Determine which brain level problems the Boys Town intervention works best for.

• Determine whether the identified neural signatures can be used diagnostically.
“Empathy”

The fearful expression: A signal of distress.

A healthy response to this distress cue involves an interruption in current behavior and learning the negative value of actions associated with this distress.
Callous Unemotional Traits

DSM-5 (low prosocial emotions)
Lack of remorse or guilt
Callous-lack of empathy
Unconcerned about performance
Shallow or deficient affect
Empathy: The response to the distress of others. It is significantly reduced in those with conduct disorder and callous-unemotional traits (Marsh et al 2008).
The framework

Genetic level

Neural Dysfunction

Cognitive impairment

Symptom sets

- CU traits/Instrumental aggression
- Reactive aggression, irritability and anxiety
- Conduct problems

Environment
The framework

Genetic level

Pathological environment
Amygdala/Insula responding
Decreased empathy

Cognitive impairment
CU traits/Instrumental aggression
Reactive aggression, irritability and anxiety
Conduct problems

Symptom sets

Environment

Environment

12
Acute Threat Response  
Affective Stroop (Blair KS et al 2007)

a

+ 400 ms 400 ms 400 ms 400 ms 1000 ms

b

+ 400 ms 400 ms 400 ms 400 ms 1000 ms

5 5 5 5 5

5 5 5 5 5

c

+ 400 ms 400 ms 400 ms 400 ms 1000 ms

5 5 5 5 5
The case of Conduct Disorder

Why be concerned? Implications for treatment!
BUT!

The impact of maltreatment
An interaction between CU-traits prior trauma on fear intensity modulated BOLD response in the right amygdala

Meffert et al. under revision
The framework

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Pathological environment

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Symptom sets

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Genes

Amygdala/Insula responding

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CU traits/Instrumental aggression

Reactive aggression, irritability and anxiety

Conduct problems
The framework

Genetic level

Pathological environment

Neural Dysfunction

Amygdala/Insula responding

Decreased empathy

Genes

Genes

Amygdala/Hypothalamus/PAG responding

Hostile attribution biases?

Environment

Cognitive impairment

CU traits/Instrumental aggression

Conduct problems

Reactive aggression, irritability and anxiety

“CU traits”/hostility

Symptom sets

Maltreatment

Environment
The framework

Genetic level

- Amygdala/Insula responding
- Decreased empathy
- Conduct problems

Neural Dysfunction

- Amygdala/Hypothalamus/PAG responding
- Increased acute threat response

Cognitive impairment

- CU traits/Instrumental aggression
- Reactive aggression, irritability and anxiety

Symptom sets

- Pathological environment
- Environment

Genes

Maltreatment

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Symptom sets

- Pathological environment
- Environment

Genes

Maltreatment

- Hostile attribution biases?
- "CU traits"/hostility
Response control Dysfunction
The brain network for reactive stopping. (A) Regions that are critical for stopping in the standard stop signal paradigm. Two regions of the ventral cortex (IFC) are the inferior frontal junction (IFJ) and the posterior (p)IFG. The presupplementary motor area (preSMA) is in the medial part tractography using diffusion tensor imaging reveals a three-way network in the right hemisphere between nodes that are action. Reprinted with permission from (31).
Affective Stroop Task (Blair et al., 2007)

a

\[
\begin{array}{cccc}
+ & + & + & \text{400ms} \\
\text{400ms} & \text{400ms} & \text{400ms} & \text{1300ms}
\end{array}
\]

b

\[
\begin{array}{cccc}
+ & 3 & 3 & 3 \\
\text{400ms} & \text{400ms} & \text{400ms} & \text{1300ms}
\end{array}
\]

c

\[
\begin{array}{cccc}
+ & 5 & 5 & 5 \\
\text{400ms} & \text{400ms} & \text{400ms} & \text{1300ms}
\end{array}
\]
Decrease activation in insula in children/adolescents with DBD (N=35, HC=18) in presence of increased cognitive demand and its correlation with ADHD symptom severity (Hwang et al., 2015)
Increasing alcohol abuse related problems are associated with increasingly compromised brain functioning.
Figure 2: A & B: Task specifier from the Affective Stroop task (healthy participants: N = 100); C & D: Signatures distinguishing healthy youth (N=100) from youth with SU (N=50).
Response Control:
Increasing maltreatment – particularly sexual and emotional abuse - are associated with increasingly compromised brain functioning
The framework

Genetic level

Substance abuse

Neural Dysfunction

vmPFC & PCC?

Decreased Subjective value

Cognitive impairment

Decreased Response control

Impulsivity/SU

Decreased Response control

Impulsivity/SU

Reactive aggression, irritability and anxiety

Motor cortex

Superior frontal cortex

Conduct problems

Environment

Maltreatment

Environment

Symptom sets

Impulsivity/SU
Talk plan

- The problem space and basic framework

- Neural systems involved in approach and avoidance reinforcement-based decision-making.

- Ventromedial frontal cortex and expected value based choices

- Anterior insula cortex and expected value based avoidances

- Striatal involvement in prediction error signaling

- Throughout consideration of impairments present in individuals with a diagnosis vs. impairments related to a specific symptom set.
Systems engaged in reward value: Clithero & Rangel (SCAN: 2014)

Striatum
Prediction error (PE) = The difference between the expected and received reinforcement:

\[ PE(t) = F(t) - EV(t) \]

vmPFC
Expected value (EV) = The expected reinforcement if the action is undertaken:

\[ EV(t) = EV(t-1) + (\alpha \times PE(t-1)) \]
Systems engaged in avoidance (Lin et al, 2015)
The framework

Trauma

Neural Dysfunction

Environment

Choice: EV
Response selection

Feedback: PE
Value learning

Avoidance: EV avoidance

Genes

vmPFC ←→ striatum

dmFC/ aIC

Genes

Cognitive impairment

Symptom sets

Reactive aggression

Substance abuse Problems (Impulsivity)

Conduct problems
Talk plan

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“Instrumental-reactive” Aggression
A. Pam takes $10 and offers you $10.

B. Pam takes $14 and offers you $6.

C. Pam takes $16 and offers you $4.

D. Pam takes $18 and offers you $2.

Press:
1 to ACCEPT.
2 to spend $1 and make Pam lose $7
3 to spend $2 and make Pam lose $14
4 to spend $3 and make Pam lose $21

Offer-phase 3 seconds
Jittered Interval .5-3.5 seconds
Decision-phase 4 seconds
Outcome-phase 3 seconds
Jittered Interval .5-3.5 seconds

Pam takes $10. You get $10.

Pam gets $13. You get $2.

Pam gets $6. You get $1.

Pam gets -$1. You get $0.
FIGURE 3. Group Differences in the Ventromedial Prefrontal Cortex Between Healthy Youths (N=28) and Youths With Disruptive Behavior Disorders and Low (N=15) or High (N=15) Levels of Callous-Unemotional Traits.

A. Main Effect of Diagnosis in vmPFC

B. Diagnosis-by-Provocation Level Interaction in Functional Connectivity Between Right Amygdala and vmPFC

C. Attenuated vmPFC response

D. vmPFC-amygdala connectivity
The framework

Environment

Genes

vmPFC \(\leftrightarrow\) striatum

Choice: EV
Response selection

Feedback: PE
Value learning

Avoidance: EV avoidance

Genes

dmFC/aIC

Genes

Cognitive impairment

Trauma

Neural Dysfunction

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Substance abuse Problems (Impulsivity)

Conduct problems

Symptom sets

Conduct problems

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The framework

Trauma → Genes → vmPFC → striatum → Genes → dmFC/aIC → Environment

Neural Dysfunction

Choice: EV
Response selection

Feedback: PE
Value learning

Avoidance: EV avoidance

Cognitive impairment

Symptom sets

- Reactive aggression
- Substance abuse Problems (Impulsivity)
- Conduct problems

Environment
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Passive avoidance learning (White et al, AJP)

Critical though to distinguish BOLD responses to cue from those to feedback.

1000ms 0 - 3000ms Lose $5 (OR -$1/+1$/$+$5) 1000ms 0 - 3000ms

Regressors for Chosen, Non-Chosen and Reward, Punishment were weighted according to learning theory: Rescorla-Wagner:
Prediction error for the current trial, \( PE(t) \) equaled the feedback value for the current trial minus the expected value for the current trial.

\[
PE_{(t)} = F_{(t)} - EV_{(t)}
\]

EV was calculated via the following formula:

\[
EV_{(t)} = EV_{(t-1)} + (\alpha*PE_{(t-1)})
\]
PA details; Impairment in CD

• Impairment in learning to avoid “bad” responses.
White et al (AJP: 2013)

- Youth with DBD (N=20; 85% CD) and TD youth (N=18)

- Matched for age (DBD: 15.2, TD: 14.9) & gender (majority male)
Left AIC/iFG (White et al., 2016)

- Object Chosen
- Object Not Chosen

**Conduct Problems**
- BOLD response modulated by EV
  - \( r = -0.264; p = 0.025 \)
  - \( r_{\text{chosen}} = 0.265 \)
  - \( r_{\text{not chosen}} = -0.415 \)
  - \( r = -0.244; p = 0.039 \)
  - \( r_{\text{partial}} = -0.164; p = 0.172 \)

**Task Performance**
- BOLD response modulated by EV
  - \( r = 0.364; p = 0.002 \)

**Conduct Problems**
- BOLD response modulated by EV
  - \( r = -0.264; p = 0.025 \)
  - \( r = -0.244; p = 0.039 \)

**Task Performance**
- BOLD response modulated by EV
  - \( r = 0.364; p = 0.002 \)
  - \( r_{\text{partial}} = 0.321; p = 0.006 \)
The framework

- Trauma
  - Neural Dysfunction
    - Cognitive impairment
      - Symptom sets
        - Reactive aggression
        - Substance abuse Problems (Impulsivity)
        - Conduct problems
      - Choice: EV
        - Response selection
      - Feedback: PE
        - Value learning
    - Avoidance: EV avoidance
  - Environment

- Environment
  - Genes
    - vmPFC
    - striatum
    - dmFC/aIC
The framework

Trauma

Genes

Neural Dysfunction

Choice: EV
Response selection

Feedback: PE
Value learning

Avoidance: EV avoidance

Cognitive impairment

Genes

Environment

vmPFC

striatum

dmFC/aIC

Environment

Genes

Genes

Symptom sets

Reactive aggression

Substance abuse Problems (Impulsivity)

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Value learning

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Conduct problems
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\]

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\]
Reward prediction error response (White et al., AJP 2013)
Monetary incentive delay task
Decreased striatal responses to reward associated with increased substance abuse (particularly alcohol abuse)
Gerin et al (2017)

- Well characterized sample of youth with maltreatment and comparison individuals.

- Profound impairment in PE signaling within striatum and vmPFC.
Reward processing: Increasing maltreatment is associated with reduced reward responsiveness.

Figure 2. Peak activation in each ROI modulated by EV during avoidance responses. Error bars represent 95% CI. * = p<.05 FWE. Initial threshold p<.005 uncorrected.
The framework

Trauma

Genes → vmPFC ← striatum → Genes → dmFC/aIC

Neural Dysfunction

Choice: EV → Feedback: PE ↔ Avoidance: EV avoidance
Response selection → Value learning

Cognitive impairment

Genes → Reactive aggression
Genes → Substance abuse Problems (Impulsivity)
Genes → Conduct problems

Environment

Symptom sets

Value learning
Avoidance: EV avoidance
Conduct problems
The framework

Trauma

Neural Dysfunction

vmPFC ← ⟷ striatum

Choice: EV

Response selection

Feedback: PE

Value learning

Avoidance: EV avoidance

Symptom sets

Cognitive impairment

Genes

Genes

Genes

Environment

Substance abuse

Environement

Ev avoidance

Reactive aggression

Substance abuse Problems (Impulsivity)

Conduct problems

Avoidance: EV avoidance

Value learning

Response selection

Choice: EV

vmPFC ← ⟷ striatum

Gene

Genes

Genes

Ev avoidance

vmPFC ← ⟷ striatum
Conclusions

• The extent to which vmPFC fails to represent the value of choices relates to level of reactive aggression.

• The individual fails to represent the potential reward loss of retaliation.

• The extent to which aIC fails to represent the value of avoidances relates to level of conduct problems generally.

• The individual fails to avoid bad choices.

• A problem in PE signaling within striatum is also seen in youth with DBD but is not related to symptom severity.

• The individual is compromised in learning the value of actions.

• Failure in appropriate PE signaling is seen as a consequence of substance abuse and maltreatment.
The framework: Emotional responding
The framework: Response control

- Genetic level
  - Substante abuse
  - Neural Dysfunction
    - dmFC
    - vmPFC & PCC?
    - Superior frontal cortex
    - Motor cortex
  - Cognitive impairment
    - Decreased Response control
    - Decreased Subjective value
    - Reactive aggression, irritability and anxiety
    - Impulsivity/SU
  - Conduct problems
    - Impulsivity/SU

- Environment
  - Maltreatment

- Symptom sets
  - Cognitive impairment
  - Conduct problems
The framework: Reinforcement-based decision-making

- **Trauma**
- **Genes**
- **Neural Dysfunction**
  - **Environmental** influence
  - **Cognitive Impairment**
  - **Symptom sets**

- **Choice: EV**
- **Response selection**
- **Feedback: PE**
  - **Value learning**
  - **Avoidance: EV avoidance**

- **Reactive aggression**
- **Substance abuse Problems (Impulsivity)**
- **Conduct problems**

- **vmPFC**
- **striatum**
- **dmFC/aIC**
PRELIMINARY data regarding the impact of the Boys Town program on adolescent brain development

BT program increases striatal responsiveness to reward

BT program increases emotional regulation (vmPFC) activity in response to threats