Neurobiology of Impulsivity: Dopamine and Beyond

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Overview

- Impulsivity and its intermediate phenotype: behavioral inhibition
- Right-lateralized frontostriatal network
- Modulatory role of dopamine system-related genes
  - DAT/SLC4A3
  - COMT
- DA genetic imaging of the behavioral inhibition neural network
- Dopamine-glutamate interaction in impulsivity
Impulsivity

• Predisposition to respond to internal or external events without regard to the consequences: tendency to act prematurely without foresight

• **Two dimensions**: response disinhibition and temporal discounting of reward

• Elevated in multiple forms of psychopathology and antisocial behavior

• Prototypical disorders expressing impulsive behavior include ADHD, substance abuse/dependence, ASD and bipolar disorder

• **Genetic basis** of impulsivity: heritability 0.45

• Behavioral inhibition: right-lateralized frontostriatal network
Control of impulsive behavior

Executive inhibition → Motivational inhibition

Interference control → Cognitive inhibition → Behavioral inhibition

Response to punishment cues

Oculomotor inhibition

Response to novelty

Behavioral inhibition: “the ability to suppress a prepotent response”; top-down
Two Major Modulatory Systems of Impulsive Behavior

Gonadal steroids?

Serotonin

Impulsive-reactive-hostile-affective

Dopamine

Controlled-proactive-instrumental-predatory

AGGRESSION

Impulsive and reflective neurocircuits

Prefrontal cortex

DLPC

AC

Striatum

Insula

VMPC

Ventral striatum

Amygdala

ADHD CRU
# Impulsivity and Imaging Genetics

<table>
<thead>
<tr>
<th>Diagnostic categories</th>
<th>ADHD</th>
<th>SA/SD</th>
<th>ASD</th>
<th>BPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trait dimensions</td>
<td>Non-planning</td>
<td>Disinhibition</td>
<td>Sensation seeking</td>
<td></td>
</tr>
<tr>
<td>Behavioral dimensions</td>
<td><strong>Impulsivity: Behavioral inhibition</strong></td>
<td><strong>Motivational impulsivity: reward response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuro-biological systems</td>
<td>Right frontal cortex</td>
<td>Basal ganglia (Subthalamic nucl., STN)</td>
<td>Reward circuitry</td>
<td></td>
</tr>
<tr>
<td>Genetics &amp; epigenetics</td>
<td>DRD4</td>
<td>DAT/SLC4A3</td>
<td>COMT</td>
<td>Environ</td>
</tr>
</tbody>
</table>
Aims and predictions

Examine pattern of activation during inhibition and test for individual differences

- Greater activation in right IFC, pre-SMA, STN and GP for successful inhibition vs. response
- Correlation between activation in right IFC and STN during inhibition
- Individual differences in activation: negative correlation between activation during inhibition and performance (SSRT)

Test influence of DA system-related polymorphisms on brain activation during a behavioral inhibition task

- Difference in activation in regions of interest during inhibition between DAT/SLC4A3 genotype groups
- Difference in activation in COMT genotype groups

Test additive effect of both DA gene polymorphisms on brain activation during inhibition

- Difference in activation in regions of interest during inhibition between DAT/SLC4A3 + COMT groups

In collaboration with: E. Congdon and T. Canli, Stony Brook University, New York
Stop-signal task: race model of stopping

- Measures race between go and stop processes
- Two trial types: Go and Stop-signal trials
- **Tracking**: Onset of stop-signal (SSD) varies according to performance on previous stop-signal trial (+/- 50 ms)
- **Ensures 50% inhibition**
  - Comparable performance + difficulty level
  - Equal number of trials across subjects
  - Prevents floor and ceiling effects
  - Estimate measure of participant’s inhibitory function

Band et al., 2003; Logan, 1994
Stop-signal task and neural activation:
StopInhibit — fixation

Congdon et al. 2008
Tonic-Phasic Dopamine Model

Optimal range of DA needed for successful inhibition

Dopamine availability

Hypo-impulsive

Signal-to-noise ratio

HYPER-Perseverative

DAT/SLC4A3: 10/10 vs. 9+

Subcortical phasic DA

10/10 vs. 9+

10/10 vs. 9+

COMT: m/m vs. v/m vs. v/v

Cortical phasic and tonic DA

m/m vs. v/m vs. v/v

m/m vs. v/m vs. v/v

v/v vs. m/m vs. v/v

v/v vs. m/m vs. v/v
StopInhibit — Go: DAT 9+ > 10/10

ROI analyses, uncorrected, \( p = .01 \)

Congdon et al. 2008
StopInhibit — Fixation: COMT v/v < v/m < m/m

Congdon et al. 2008
Additive effect of both DA gene polymorphisms on brain activation during inhibition

Dopamine availability

<table>
<thead>
<tr>
<th>DAT/SLC4A3 + COMT groups</th>
<th>10/10 - v/v</th>
<th>10/10 - v/m; 9+ - v/v</th>
<th>10/10 - m/m; 9+ - v/m</th>
<th>9+ - m/m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/females</td>
<td>5/3</td>
<td>7/13</td>
<td>5/10</td>
<td>2/0</td>
</tr>
</tbody>
</table>
StopInhibit — Fixation: DAT + COMT

ROI analyses, uncorrected, $p = .01$

Congdon et al. 2008
Impulsivity and imaging genetics

**Diagnostic categories**
- ADHD
- SA/SD
- ASD
- BPD

**Trait dimensions**
- Non-planning
- Disinhibition
- Sensation seeking

**Behavioral dimensions**
- Impulsivity: Behavioral inhibition
- Motivational impulsivity: reward response

**Neuro-biological systems**
- Right frontal cortex
- Basal ganglia (Subthalamic nucl., STN)
- Reward circuitry

**Genetics & epigenetics**
- DRD4
- DAT/SLC4A3
- COMT
- Environ
- G x E
Delay Discounting in ADHD

**Hypoactivation of ventral striatum**
(All rewards)

A

\[ r = 0.34 \text{ (ns)} \]

B

\[ r = 0.49^* \]

\[ r = 0.52^* \]

\[ r = 0.58^* \]

Hyperactivation of dorsal striatum
(Delayed rewards)

Hyperactivation of amygdala
(Delayed rewards)

Hyperactivation of dS and Amy correlate with hyperactivity / impulsivity

A

B

Plichta et al., 2008
Frontostriatal dysfunction in ADHD
Overview of Lphn3 studies in zebrafish

**Morpholino injection**

Exon 1  Exon 2  Exon 3  Exon 4  Exon 17

**Locomotor behaviour**

Zebrabox set-up

**Neuroanatomy**

Focus on dopaminergic system

Posterior tuberculum homologous of mammalian SN and VTA (ISH of *dat, th*)

In collaboration with: M. Lange, W. Norton, L. Bally-Cuif, CNRS, Gif-sur-Yvette, France
DA neurons in the posterior tuberculum

Dopamine-positive neurons

Distribution of DA neurons in posterior tuberculum groups 1, 2 and 4/5 is altered in morphants

Control

Iphn3 knockdown

Lange et al. 2012
Lphn3 morphants and locomotor activity

Lphn3 “knock-down” results in **hyperactivity** and **increased impulsivity** in zebrafish larvae

Lange et al. 2012
*Lphn3* morphants are hyperactive

Lphn3 knock-down triggers **hyperactivity** and **increased impulsivity** in the zebrafish juvenile

Locomotor activity measured as the total distance swum in 5 min (P≤0.001)

Lange et al. 2012
Conclusions

• Successful inhibition of motor responses relies on a right-lateralized frontostriatal circuit: right IFC, STN, pre-SMA and GP activation

• Greater engagement of key brain regions and neural circuits associated with better inhibitory control

• There are significant individual differences in activation patterns during behavioral inhibition, even when the task controls for difficulty level

• Dopaminergic variation mediates the relationship between neural activation and behavioral inhibition (and responding)

• Dopamine – glutamate system interaction impacts impulsivity and locomotor activity: zebrafish model of ADHD?
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Aggressotype
LOOPACT
Participants

• 68 healthy, right-handed adults (mean age 23.22 (SEM = 0.51), range 18-44; 42 females)
  – 55 participants scanned
  – **46** final participants (mean age 22.85 (SEM = 0.49), range 18-30; 26 females)
• Recruited from Yale/New Haven Area
• Screened for mental health and counter-indications to scanning
Stop-signal Task

500 ms

Delay 1500 ms

Variable ITI

250 ms

250 ms
fMRI Scanning

- 3T Siemens Trio Scanner, Yale MRRC
- Data acquisition:
  - Initial Localizer scans
  - Functional images—T2*-weighted EPI scans
    - Axial-oblique
    - Flip angle = 80 degrees
    - TR = 1.5s
    - TE = 35 ms
    - 24 slices, 5 mm thick
    - FOV = 22 x 22 cm
  - Final high-resolution anatomical scans
  - Dummy scans collected at beginning will be discarded
- Stop-signal task:
  - Stimulus presentation = 500 ms; Variable ITIs = 500-4000 ms
  - Go trials: N = 108 (75%); Stop-signal trials: N = 36 (25%)
  - 3 sessions (each 9 min, 21 s)
- fMRI data preprocessed individually in Matlab/SPM2
**DAT**

**Functional Significance**
- Affects mRNA transcription, stability, translational efficiency
- Increased expression in 10-repeat variant

**Association Studies**
- 10-allele and ADHD; symptom severity; neuropsychological impairment; response to methylphenidate
- DAT + DRD4 interaction
- DAT + COMT interaction

*(Bannon et al., 2001)*
Catechol-O-Methyltransferase (COMT)

- Enzyme degrades catecholamines
- Widely distributed throughout brain; frontal cortex
- COMT: Mutation at codon 108/158 (val^{108/158}met)

(Goldberg & Weinberger, 2004)
**COMT**

**Functional Significance**
- met enzyme has 4-fold reduction in activity vs. the val enzyme

**Association Studies**
- Prefrontal cognitive function:  
  \[
  m/m > v/m > v/v
  \]
- Neural activation during cognitive and emotional tasks
- Inhibition and conflict central

<table>
<thead>
<tr>
<th>G / val / High</th>
<th>A / met / Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>= Less DA available</td>
<td>= More DA available</td>
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</table>
Stop-signal task and neural activation: StopInhibit — fixation

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>Region</th>
<th>Coordinates (x, y, z)</th>
<th>t</th>
<th>Voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral</td>
<td>Occipital cortex/cerebellum/temporal-parietal gyri</td>
<td>-46 -72 4</td>
<td>15.81</td>
<td>24350</td>
</tr>
<tr>
<td>Bilateral</td>
<td>Thalamus</td>
<td>12 -20 12</td>
<td>11.35</td>
<td>3885</td>
</tr>
<tr>
<td>Left</td>
<td>Insula/putamen/globus pallidus</td>
<td>12 6 46</td>
<td>12.25</td>
<td>2203</td>
</tr>
<tr>
<td>Bilateral</td>
<td>Supplementary motor area (SMA)/mid-cingulate/ACC</td>
<td>32 16 8</td>
<td>10.43</td>
<td>2075</td>
</tr>
<tr>
<td>Right</td>
<td>Insula/inferior frontal cortex (IFC)/putamen/precentral gyrus</td>
<td>-52 -28 20</td>
<td>8.26</td>
<td>615</td>
</tr>
<tr>
<td>Left</td>
<td>Temporal/intraparietal</td>
<td>-42 -18 58</td>
<td>8.64</td>
<td>406</td>
</tr>
<tr>
<td>Right</td>
<td>Inferior/middle/superior frontal gyri</td>
<td>32 38 32</td>
<td>8.54</td>
<td>312</td>
</tr>
</tbody>
</table>

Congdon et al. 2008
Results (N = 46)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean</th>
<th>SEM</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIS-11 Total Score</td>
<td>56.07</td>
<td>1.30</td>
<td>38</td>
<td>77</td>
</tr>
<tr>
<td>RT–Correct Go Trials</td>
<td>484.48</td>
<td>13.74</td>
<td>368.36</td>
<td>760.04</td>
</tr>
<tr>
<td>% Correct—Go Trials</td>
<td>96.39</td>
<td>1.13</td>
<td>51.86</td>
<td>100.00</td>
</tr>
<tr>
<td>RT–Stop Respond Trials</td>
<td>433.95</td>
<td>11.24</td>
<td>313.46</td>
<td>653.88</td>
</tr>
<tr>
<td>% Inhibition—Stop Trials</td>
<td>52.11</td>
<td>1.55</td>
<td>4.63</td>
<td>80.56</td>
</tr>
<tr>
<td>SSRT</td>
<td>214.55</td>
<td>6.78</td>
<td>140.05</td>
<td>366.84</td>
</tr>
</tbody>
</table>

- Approximately 50% commission errors on Stop trials
- No differences in performance by demographic variables
- No correlation between SSRT and BIS-11 scores
Go — Fixation: COMT v/v < v/m < m/m

ROI Analyses, uncorrected, $p = .01$
ADHD risk haplotype of the Latrophilin-3 gene (LPHN3)

ADHD = 2627
Relatives = 2161
Controls = 2531

LPHN3: \( P < 3.01 \times 10^{-8} \), RR 1.3
Risk allele frequency: 22%

Arcos-Burgos et al., 2010
Latrophilin 3 is an adhesion GPCR
Syndromal dimensions of ADHD

Attention deficit

Hyperactivity

Increased impulsivity

AGGRESSION

Emotional dysregulation

Oppositional-defiant behaviour

Risk seeking behaviour – Substance use, behavioural addictions

Impaired social behaviour
Gene-by-environment Interaction and Epigenetic Mechanisms in Aggression

Outline

- Impulsivity, aggression and social impairment in ADHD: a role for serotonin?
- Neural circuits of emotion regulation and social cognition: modulation by genes of the serotonin signaling pathway
- Nonhuman primates as a model of gene x environment interaction (G x E) in human aggression and antisocial behavior
- Knockout mice as a tool to investigate serotonin system dysregulation during brain development and molecular substrates of epigenetic programing
Various genes of the serotonin signaling pathway are involved in (defensive) aggression and social impairment.

Increasing evidence that G x E is related to specific phenotypes, including aggression and antisocial behavior.

Non-human primates are useful in the study of psychosocial consequences of G x E.

Genetically modified mice are helpful models to investigate the neural correlates of G x E and molecular mechanisms of epigenetic programing.

Behavioral genes are NOT destiny - they are just permissive for the positive and negative environmental effects.
Methylphenidate blocks hyperactivity and impulsivity in \textit{Lphn3} morphants.

Similar effects also observed for the norepinephrine reuptake inhibitor atomoxetine.

Lange et al. 2012