Neurocognitive Functioning in Opiate and Stimulant Users

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Phase I: R21DA18086
Neuro-Cognitive Sequelae of Opiate Use and Antisocial Behavior

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Why in Bulgaria?
“Pure” monosubstance drug users

Chart 6: Drug smuggling channels crossing Southeast Europe

Goals

1. Assist Bulgarian scientists in developing research capacity for the study of neurocognitive functioning in relation to drug addiction and antisocial behavior

2. Take advantage of the unique patterns of heroin addiction in Bulgaria to address research questions that cannot be adequately addressed with data collected in USA
Initial Findings

Vassileva et al., 2007
Impaired decision-making in psychopathic heroin addicts

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Psychopathic heroin addicts are not uniformly impaired across neurocognitive domains of impulsivity

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Phase II: Varieties of Impulsivity in Opiate and Stimulant Users

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Drug Addiction – Major Public Health Problem in Bulgaria

- Heroin – Balkan Drug Trafficking Route
- Amphetamines – major European producer
- HIV risk behaviors
Objectives

• To understand the role of impulsivity in drug addiction

• Impulsivity is implicated both as antecedent risk factor and as a consequence of drug addiction

• Impulsivity is multidimensional and has different personality, psychiatric, and neurocognitive dimensions
Aims

1. **Aim 1** - To determine whether individual differences in trait-like personality and psychiatric dimensions of impulsivity increase vulnerability to neurocognitive deficits in impulsivity

2. **Aim 2** - To determine whether some dimensions of impulsivity are common across addictions, whereas others are unique to specific classes of drugs
## Participants

<table>
<thead>
<tr>
<th></th>
<th>Heroin</th>
<th>Amphetamine</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>96</td>
<td>87</td>
<td>105</td>
</tr>
<tr>
<td>Age</td>
<td>29.0</td>
<td>23.3</td>
<td>24.5</td>
</tr>
<tr>
<td>Estimated IQ</td>
<td>103.4</td>
<td>108.4</td>
<td>109.3</td>
</tr>
<tr>
<td>Years of Education</td>
<td>12.8</td>
<td>12.8</td>
<td>13.6</td>
</tr>
<tr>
<td>% Female</td>
<td>20</td>
<td>23</td>
<td>25</td>
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</table>
# Assessment Battery

<table>
<thead>
<tr>
<th>Neurocognitive Measures of Impulsivity</th>
<th>Personality Measures of Impulsivity</th>
<th>Psychiatric Measures of Impulsivity</th>
<th>Other Relevant Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impulsive Choice</td>
<td>Impulsive Action</td>
<td>Addictions</td>
<td>Alcohol/Drug toxicology screen</td>
</tr>
<tr>
<td>- Iowa Gambling Task (ABCD &amp; EFGH versions)</td>
<td>- Immediate Memory Task</td>
<td>- Substance Abuse / Dependence (SCID; Addiction Severity Index)</td>
<td>- Opiate/Stimulant Withdrawal</td>
</tr>
<tr>
<td>- Cambridge Gambling Task</td>
<td>- Stop Signal Task</td>
<td>- Pathological Gambling</td>
<td>- Fagerstrom Test for Nicotine Dependence</td>
</tr>
<tr>
<td>- Delayed Reward Discounting Task</td>
<td>- Go/No-go Task</td>
<td>(Addiction Severity Index)</td>
<td>- Pedigree (Family History of Substance Use Disorders)</td>
</tr>
<tr>
<td>- Balloon Analog Risk Task</td>
<td></td>
<td>Externalizing Psychopathology</td>
<td>- IQ Estimation (Raven’s)</td>
</tr>
<tr>
<td>Impulsive Action</td>
<td></td>
<td>- ADHD (Wender Utah Rating Scale)</td>
<td>- Handedness</td>
</tr>
<tr>
<td>- Immediate Memory Task</td>
<td></td>
<td>- Conduct Disorder (SCID)</td>
<td>- Beck Depression Inventory-II</td>
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<tr>
<td>- Stop Signal Task</td>
<td></td>
<td>- Antisocial Personality Disorder (SCID)</td>
<td>- State-Trait Anxiety Inventory</td>
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<tr>
<td>- Go/No-go Task</td>
<td></td>
<td>- Psychopathy (Psychopathy Checklist-Screening Version)</td>
<td>- Anxiety Sensitivity Index</td>
</tr>
<tr>
<td></td>
<td>Barratt Impulsiveness Scale</td>
<td></td>
<td>- Risk Assessment Battery</td>
</tr>
<tr>
<td></td>
<td>(BIS-11)</td>
<td></td>
<td>- HIV Risk Behavior Scale</td>
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<tr>
<td></td>
<td>Sensation Seeking Scale</td>
<td></td>
<td>- Social Adjustment Scale</td>
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<td></td>
<td>UPPS Impulsive Behavior Scale</td>
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<td></td>
<td>Buss-Durkee Hostility Inventory</td>
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<td></td>
<td>Levenson’s Self-Report Psychopathy Scale</td>
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</tbody>
</table>
Results
Effects of Trait Impulsivity on Neurocognitive Impulsivity

- High trait impulsivity is associated with worse performance on neurocognitive tasks of motor impulsivity / impulsive action in amphetamine users.
- High trait impulsivity is associated with better performance on these tasks in heroin users.

Paxton et al., under review
Effects of Psychopathy on Neurocognitive Impulsivity

Cambridge Gambling Task
Overall Proportion Bet

Cambridge Gambling Task
Risk Taking

Wilson et al., in preparation
Common Effects across Addictions

Go/No-Go Task (Motor Imp.):
- Heroin: 12
- Amphetamines: 14
- Controls: 16

Immediate Memory Task (Attentional Imp.):
- Heroin: 0.90
- Amphetamines: 0.95
- Controls: 1.00

Discriminability (d')
Unique Effects of Opiates and Stimulants

Cambridge Gambling Task (Cognitive Imp.)

Heroin Amphetamines Controls

Delay Aversion

0.25 0.30 0.35 0.40 0.45

Heroin Amphetamines Controls

Delayed Rewards Discounting Task (Cognitive Imp.)

Magnitude Large Medium Small

Discount Parameter k

0.04 0.06 0.08 0.10 0.12 0.14 0.16 0.18 0.20

Controls Amphetamines Heroin

Heroin Amphetamines
New Directions for Future Research
Computational Modeling of Decision-Making

Decay-reinforcement learning:

\[ E_j(t) = \alpha \cdot E_j(t-1) + \beta_j(t) \cdot u(t) \]

Valuation of expectancies of 4 decks

Updating expectancies

Probabilistic Action Selection

Subjective Outcome Evaluation

Prospect Valence Learning (PVL) is the best fitting model (Ahn et al., 2008).

Luce choice rule:

\[ Pr[D(t+1) = j] = \frac{e^{\theta_j(t)} \cdot E_j(t)}{\sum_{k=1}^{4} e^{\theta_k(t)} \cdot E_k(t)} \]

Prospect utility function:

\[ u(t) = \begin{cases} 
    x(t)^\alpha & \text{if } x(t) \geq 0 \\
    -\lambda |x(t)|^\alpha & \text{if } x(t) < 0 
\end{cases} \]

Four parameters that reflect distinct psychological processes:

- \( \alpha \): utility shape parameter (High \( \alpha \): high reward sensitivity, low \( \alpha \): low reward sensitivity)
- \( \lambda \): loss aversion (High \( \lambda \): high loss aversion, low \( \lambda \): low loss aversion)
- \( c \): exploration/exploitation parameter (High \( c \): high adherence to their expectancies, low \( c \): random choice)
- \( A \): learning rate (High \( A \): good learning/memory, low \( A \): rapid memory decay)

Ahn et al., in preparation
Distinct mechanisms underlying the performance deficits of the amphetamine and heroin users.

**Reward sensitivity (Amphetamine > HC)**

**Loss Aversion (Heroin < HC, Amphetamine)**

Similar learning/memory and exploration/exploitation across groups.
Heroin Drought in Europe 2010-2012

- Current Methadone Abusers n=26
- Compared with stable MMT patients (target n=30)
- In collaboration with “Initiative for Health Foundation” in Sofia
Neurogenetics

• DNA from 199 consenting participants (61 heroin, 61 amphetamines, 77 controls) collected, extracted and stored at the Molecular Medicine Center, Medical University, Sofia.
• 45 SNPs genotyped on 88 participants
• R01DA018823 “Neurogenetic Mechanisms of Opioid Dependence in a Bulgarian Roma Isolate” (under review)
• Co-PI with Alexandre Todorov (Washington University, St. Louis)
Focus on the Roma Population

- Genetic isolate with high specific vulnerability to heroin addiction
- Heroin – 1st drug used in 60% of cases, 53% report never having used another illicit drug other than heroin more than 5 times
- Particularly high risk group: 4.8% HIV+ (vs. 0.4% of non-Roma)
- In collaboration with Foundation Roma in Plovdiv and Diverse and Equal Foundation in Sofia
- Preparing targeted school-based drug and alcohol abuse prevention interventions for adolescents
Research Capacity-Building

• Translation and piloting of psychiatric instruments, self-report questionnaires, experimental neurocognitive paradigms, and clinical neuropsychological measures

• Cross-cultural adaptations of assessment instruments:
  • Psychopathy Checklist: Screening Version (Wilson et al., Submitted)
  • Barratt Impulsiveness Scale – 11 (Turan et al., in preparation)

• Student training and involvement in research
  • New Bulgarian University (2 graduate students)
  • Medical University Sofia (1 MD/PhD student, 2 graduate students)
  • Sofia University (1 graduate student)
Research Capacity-Building

• Publications in Bulgarian journals:
  – Bozgunov et al. (2011), *Clinical and Consulting Psychology*
  – Vassileva et al. (in press), *Bulgarian Journal of Psychology*

• 3 additional publications, 4 under review

• Conference presentations in Bulgaria:
  – 6th National Congress of the Bulgarian Psychological Association Sofia, (2011)
    • Keynote Address “Addiction as a brain disease” (Vassileva)
    • Symposium “The role of impulsivity in drug addiction and comorbid disorders” (Vasilev, Bozgunov, Naslednikova, Raynov, Vassileva)
    • Poster “Validation of the Bulgarian version of the Barratt Impulsiveness Scale -11” (Turan, Milanova, Vasilev, Vassileva)
  – Summer Research Forum at Varna Free University “Czernorisetz Hrabar” (Bozgunov, 2012; Vasilev, 2012)
  – Research conference at St. Cyril and Methodius University, Veliko Tarnovo (Bozgunov, 2012)
  – New Bulgarian University, Dept. of Cognitive Science (Naslednikova, 2012)

• 8 presentations in USA and 2 in Europe
Research Capacity-Building

- Development of additional international research collaborations
  - Molecular Medicine Center, Medical University, Sofia (Dr. Radka Kaneva)
  - Dept. of Psychiatry, Alexandrovska University Hospital, Sofia (Prof. Vihra Milanova)
  - Washington University, St. Louis, MO (Dr. Alexandre Todorov)
  - Indiana University, Bloomington, IN (Dr. Jerome Busemeyer)
  - King’s College London (Dr. Patricia Conrod)
Challenges

• Post-communist / authoritarian style of leadership
• Unreasonably high financial expectations
• No traditions in local collaboration
• Stigma against drug addiction
• Brain drain
• Financial crisis
• Currency exchange rates
Collaborators

USA
Eileen Martin, PhD
Raul Gonzalez, PhD
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F. G. Moeller, MD, PhD
Woo-Young Ahn, MS
Laura Segala, MS
Michael Wilson, MS
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Jerome Busemeyer, PhD
Alexandre Todorov, PhD
Joseph Newman, PhD
John Kruschke, PhD

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Stefan Georgiev, PhD
Nikolai Tomov, MD
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Turhan Turan, MD
Margarita Raycheva, PhD
Pavlina Petkova, PhD
Peter Marinov, MD, PhD
Vladimir Velinov, MD
Dorita Krasteva, MD
Thank You!