Cognitive Neuroscience Approaches to Nicotine Dependence Treatment

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Nicotine Addiction is a Chronic, Relapsing Brain Disease

Quitting Smoking is Difficult

6-MONTH SUCCESS RATES

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Success Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline</td>
<td>High</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Medium</td>
</tr>
<tr>
<td>NRT</td>
<td>Medium</td>
</tr>
<tr>
<td>Placebo</td>
<td>Low</td>
</tr>
</tbody>
</table>

Merging Biology and Behavior

Screening of novel compounds and repurposed meds

Cognitive and neural biomarkers of treatment effects

Preclinical and genomic studies to identify potential targets

Behavioral endpoint: smoking cessation
Treatment (Development) Research
Cognition as a Therapeutic Target
Cognition as a Therapeutic Target

Rationale: Following chronic exposure, nicotine deprivation produces in cognitive deficits that promote relapse.

Research Objectives:
1) To clarify the neural substrates underlying abstinence-induced cognitive deficits
2) To establish the profile of a “best in class” medication (varenicline) to use as a benchmark against with novel therapeutics can be compared and selected for future development
3) To screen novel (or repurposed) compounds and behavioral treatments (e.g., cognitive exercises) to identify promising new treatments
Smoking vs. Abstinence Profile and Relapse Prediction

**PRE-QUIT**

COUNTERBALANCED ORDER

- **fMRI SCAN #1** (QUIT 24 HRS)
- **fMRI SCAN #2** (SMOKING)

**WEEK**

-2  1-2  3-4

**Neuroimaging Protocol**
- Resting state (BOLD)
- Cognitive Tasks (BOLD)
- Diffusion Tensor Imaging

**POST-QUIT**

60-day period

- Target Quit Date

**MONITORING VISITS**
- Self-report smoking
- Carbon monoxide (CO)
- Cotinine
- Withdrawal, urges

**COUNSEL**
- (pre-quit counseling session)
Fractal N-back (Working Memory Task)

Participant responds to stimuli based on 3 rules:

0 - back  Press the button when you see the target picture

1 - back  Press the button when the picture is the same as the one immediately before

2 - back  Press the button when the picture is the same as the one two before

3 - back  Press the button when the picture is the same as the one three before
Abstinence Effects on Working Memory

Study:
N = 63 treatment-seeking smokers performed N-back task: smoking as usual and after 24 abstinence (within-subject)

Regression Results:
Abstinence led to reduced accuracy (p = 0.008), slower median correct response time (p = 0.001), and reduced BOLD signal change (ps < 0.001)

BOLD signal in a priori ROIs accounted for ~35% of the effect of abstinence on performance.

Falcone et al., *Addict Biol*, in press
“Best in Class” Varenicline Effects

Gonzales et al., JAMA, 2006

[Graph showing continuous abstinence rates for Varenicline (n=352), Bupropion SR (n=329), and Placebo (n=344) at Weeks 9-12*, Weeks 9-24†, and Weeks 9-52†.]

[Diagram illustrating Varenicline (L) blocks nicotine receptors and partial agonist effects stimulate moderate dopamine release.]
Neurocognitive Mechanisms of Varenicline Efficacy

Patterson et al., *Biological Psychiatry*, 2009; Loughead et al., *Biological Psychiatry*, 2010
Subtle Differences in Working Memory Performance Predict Relapse

Correct RT after 72hrs abstinence predicts short-term (7-day) quit success

Accounts for 15% of variance beyond baseline performance

Patterson et al., *Drug Alc Depend*, 2010
Neural Signature for Varenicline Effects

Varenicline (vs. Placebo)

N=25 within-subject, drug x load interaction p=0.005; drug x FTND on WM performance p<0.05

Varenicline Improves Performance in Highly Dependent Group

Correct Response Time (ms)

- Dependence by treatment interaction (p=0.03), significant in high dependence group only (p=0.014)

- In high dependence group, DLPFC BOLD signal shows inverse correlation with performance (p=0.03)

Loughead et al., *Biological Psychiatry*, 2010
Resting State Functional Connectivity Analysis

ICA of the resting-state data. Spatial maps converted to z-score images via a normalized mixture-model fit and then thresholded at $Z = 3.5$.

Resource Allocation Index (RAI)

Composite index reflecting strength of coupling of SN-ECN (SE) and SN-DMN (SD)

Lerman et al., (under review); Collaboration with Elliot Stein Lab (NIDA IRP)
**Decreased Network Coupling in Abstinence vs. Smoking**

3D rendering map of the composition of RAI and change in abstinence vs. smoking

Anti-correlation between SN and DMN was significantly reduced during abstinence vs. smoking; suggests weaker inhibition of DMN responsible for RAI reduction

Lerman et al., (under review); Collaboration with Elliot Stein Lab
Greater decreases in RAI ($m_R$) in abstinence (vs. smoking) predict increase in abstinence-induced withdrawal and craving.

Greater decreases in RAI ($m_L$) in abstinence (vs. smoking) predict increased DMN activity (less suppression) during working memory task in abstinence; trends for worse performance.
Cognition as a Target

• Abstinence from smoking produces mild deficits in working memory that predict relapse.

• Abstinence-induced deficits are associated with decreased activation in ECN regions, less suppression of DMN regions, and decreased connectivity between SN-DMN.

• Effective medications, such as varenicline, reverse these effects, comparable to smoking satiety.

• Other potential pro-cognitive treatments can be compared and selected for further development based on reversal of this signature.
Identifying Novel Targets and Pro-Cognitive Medications: Repurposing ACHEIs
**Cholinergic System Genetic Analysis of Smoking Cessation**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Name</th>
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<tbody>
<tr>
<td>ACHE</td>
<td>Acetylcholinesterase</td>
</tr>
<tr>
<td>ChAT</td>
<td>Choline Acetyltransferase</td>
</tr>
<tr>
<td>CHRNA2</td>
<td>Cholinergic Nicotinic Receptor Alpha 2</td>
</tr>
<tr>
<td>CHRNA3</td>
<td>Cholinergic Nicotinic Receptor Alpha 3</td>
</tr>
<tr>
<td>CHRNA4</td>
<td>Cholinergic Nicotinic Receptor Alpha 4</td>
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<td>CHRNA5</td>
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</tr>
<tr>
<td>CHRNB2</td>
<td>Cholinergic Nicotinic Receptor Beta 2</td>
</tr>
<tr>
<td>CHRNB3</td>
<td>Cholinergic Nicotinic Receptor Beta 3</td>
</tr>
<tr>
<td>CHRNB4</td>
<td>Cholinergic Nicotinic Receptor Beta 4</td>
</tr>
<tr>
<td>SLC18A3</td>
<td>Vesicular Acetylcholine transporter -3</td>
</tr>
<tr>
<td>SLC5A7</td>
<td>Choline transporter member 7</td>
</tr>
</tbody>
</table>

- 170 SNPs selected on 11 genes & 329 Ancestry informative markers
- *GoldenGate® 768-plex genotyping assays*
Choline Acetyltransferase (ChAT) gene is associated with nicotine dependence

- Association of ChAT SNPs and haplotypes with prospective smoking cessation (n=472 EA); no association of nAChR SNPs
- ChAT SNPs associated w/ multiple measures of nicotine dependence in EA and AA smokers (n=2037) - Ming Li

Targeting endogenous levels of acetylcholine may be an effective therapeutic strategy

Ray et al., Neuropsychopharm, 2010
Replication: Wei et al., Human Gen, 2010
Repurposing AChE Inhibitors as Therapeutics for Smoking Cessation

- No available ChAT enzyme modulator.
- Acetylcholinesterase inhibitors increase duration of ACh in synaptic cleft.
- AChE inhibitors improve working memory in Alzheimer’s disease and healthy volunteers; working memory predicts smoking relapse
- ACHEI inhibitors may be effective for smoking cessation treatment

**Galantamine**: inhibits acetylcholinesterase, and acts as a positive allosteric modulator nAChRs - binding sites at α5 highly sensitive
Acute Administration

**Acquisition of SA (FR5, 0.03mg.kg per infusion then PR)**

ACHEI i.p. dosing 20 min prior operant session.

Chronic administration

**Sucrose Administration**

*Hopkins et al. 2012; Kimmey et al. 2012*
Nicotine Reinstatement:

AChEI Effects on Nicotine Reinstatement

Pilot Study of Donepazil in Non-Abstaining Smokers

Ashare et al., *Drug and Alcohol Dependence*, 2012

**Working hypothesis:** Galantamine will have a neurocognitive signature similar to varenicline, and will reduce relapse risk.
Cognitive Training Clinical Trial

Pre-treatment fMRI scan (-2)

Study Weeks

Begin Training

Begin Patch

End Patch & Training

Follow-Up Assessments

Post-treatment fMRI (12)

Cognitive Remediation Training (CRT)

Nicotine Patch Therapy

Target Quit Date (TQD)

Nicotine Patch Therapy

Cognitive Stimulation Control (CSC)

Primary Quit Endpoint (6M post-TQD)

NIDA R01 2010-2015
Retraining Cognitive Function for Behavior Change

Neurocognitive Training → Cognitive control processes → Improved attention, working memory, response inhibition

Cognitive control processes → Neural processes → Decreased DLPFC activity → Altered activity in reward sensitive regions (VS, VMPFC)

Neural processes → Decision-making processes → Choose larger delayed reward over immediate reward; Choose safe option over risky option

Reduction in Health Risk Behaviors that Lead to Cancer

DLPFC = dorsolateral prefrontal cortex; VS = ventral striatum, VMPFC = ventromedial prefrontal cortex

Multi-PI R01 with Joe Kable, Penn Psychology (2012-2017)
Opioid mechanisms in nicotine reward and relapse
Opioid Mechanisms in Nicotine Reward

**Rationale:** Nicotine increases release of endogenous opioids that bind to mu opioid receptors (MORs), resulting in dopamine release.

**Research Objectives:**
1) To understand the role of MOR genetic variation (OPRM1) in nicotine reward and relapse
2) To identify neurobehavioral mechanisms that mediate MOR-nicotine interactions
3) To screen MOR modulators as potential therapeutics
Mouse Model of Nicotine Reward

Pairing Days 2-8

Day 1

Test Day

Work by Julie Blendy
Naloxone on Test Day Blocks Conditioned Rewarding Effects of Nicotine in 129/C57 B16 Mice

Walters et al, Neuron, 2005
OPRM1 Asn40Asp Variant is Associated with Response to Nicotine Replacement Therapy

**OR** = 1.9, *p* = .01

<table>
<thead>
<tr>
<th></th>
<th>Treatment Phase</th>
<th>Follow-up Phase</th>
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<tbody>
<tr>
<td>% quit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spray</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mu opioid receptor gene**

**OPRM1 Asn40Asp**

**A118G**

Lerman et al., *Pharmacogenomics J*, 2004
Human Model of Nicotine Reward

Subjective Ratings (nicotine minus denic cig)

- Satisfaction
  - p=0.05

- Strength
  - p=0.03

Number of Nicotine Puffs out of 24

- p(genotype by gender)=0.036

- 2 hour deprivation period
- Initial (blinded) exposure to 4 puffs of Quest cigarettes: denic. (.05 mg) vs nic. (.6 mg)
- Assess subjective effects
- Self-administer 4 puffs at 30 minute intervals in 6 trials over a 3-hour period

Using Targeted Genetic Mutations in the Mouse to Understand Human OPRM1 SNP

Julie Blendy Lab

- Molecular
- Cellular
- Imaging
- Behavioral
MOPR expression is decreased in A112G knock-in mice

Female G/G mice failed to show a conditioned place preference to morphine-paired environments (10 mg/kg)

Mague, Isiegas, Huang, Liu-Chen, Lerman, Blendy 2009
Translational Characterization of Genetic Variation in the Mu Opioid Receptor

**OPRM1 A112G Knock-In Mice Exhibit Reduced MOR mRNA, Protein, Binding**

**OPRM1 A118G Carriers Exhibit Decreased MOR Binding Availability**

Mague..Lerman, Blendy, *PNAS*, 2010

Ray..Blendy, Lerman, *PNAS*, 2011
Future Directions:
Opioid Mechanisms in Nicotine Reward

• Parallel rodent and human studies nicotine effects on receptor binding by *OPRM1* with Julie Blendy

• Screening of MOR partial agonists or modulators for nicotine addiction treatment

• Translate genetic and imaging paradigms to targeted therapy for cancer pain management
Collaborators

Penn CIRNA Collaborators
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DS Wilkinson
David Gulick
J Davis
C Sullivan
Tom Gould

NIDA IRP
Elliot Stein
Hong Gu
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Funding
P50 CA143187
U01 DA020830
R01 DA026849
R21 DA027066
R01 DA030819
Pfizer, AstraZeneca