Pulling it all Together: Resting State Pharmacologic Calibrated FMRI Study of Alcohol and Nicotine

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Overview

- Background & Motivation for the Study
- Hypotheses
- Study Design
- Experience to Date
Biswal (Magn Reson Med 1995) reported first resting state FMRI study of functional connectivity (RSFC)

Beckmann (Phil Trans Roy Soc B, 2005) first to report “characteristic” set of RSNs using group ICA:
- Healthy subjects (Damoiseaux, PNAS, 2006)
- Sessions (Chen, Brain Res, 2008)
- Method (Zuo, Neuroimage, 2010)
Acute Effects of Zolpidem

The hypnotic zolpidem increases the synchrony of BOLD signal fluctuations in widespread brain networks during a resting paradigm.

Stephanie C. Licata a,*, Lisa D. Nickerson b, Steven B. Lowen a, b, George H. Trksak a, c, Robert R. MacLean a, Scott E. Lukas a,b,c

Licata et al. (2011) Prog Neuropsychopharmacol Biol Psychiatry 35: 1645-1652
Alcohol and nicotine co-use

- 20 million Americans are alcohol dependent or regularly drink alcohol in harmful quantities and nearly 50 million Americans smoke cigarettes.
- As many as 88% to 96% of alcoholics are also smokers.
- Approximately 60% of smokers binge drink or consume significant amounts of alcohol.
- Individuals who co-use alcohol and nicotine demonstrate greater alcohol consumption than non-smoking alcoholics and have more severe nicotine dependence and greater difficulties quitting than nonalcoholic smokers.
Why are nicotine and alcohol frequently co-used?

- Mesocorticolimbic Reward System

Hypotheses

I. The effects of alcohol on brain reward-related circuits will be “enhanced” by nicotine

II. Impairing effects of alcohol in primary visual, motor, & sensory networks will be counteracted by nicotine
A more complicated picture…

Stimulation

Neural Response

Signalling

Vascular Response

Hemodynamics and Metabolism

Alcohol

GABA_A

5-HT

opiate

DA

nAChR

Nicotine

ph

Synaptic signalling

glia

Metabolic signalling

Vascular reactivity

arteriole
capillary bed

capillary bed

venule

Metabolism (CMRO_2)

Cerebral Blood Flow (CBF)

Cerebral Blood Volume (CBV)

BOLD fMRI signal
## Study Design: Reference

### Drug Effects: multiple sessions, pre/post

<table>
<thead>
<tr>
<th>BOLD FMRI</th>
<th>QFMRI</th>
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<tr>
<td><strong>Task</strong></td>
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<tr>
<td>- Control behavior</td>
<td>- Multi-modal measurements of BOLD-, CBF-, and CMRO$_2$-signal changes and ~vascular reactivity</td>
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<td>- Built in compliance checks (button press, etc)</td>
<td>- Calibrated FMRI approach well established</td>
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<td>- Can provide a “control” for global effects</td>
<td>- Control behavior, compliance, global “control”</td>
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<tr>
<td>- Analysis methods/tools well established</td>
<td>- Difficult</td>
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<td>- Drug effects on neurovascular factors</td>
<td>- Spatial/temporal resolution &amp; brain coverage trade-offs</td>
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<td>- Drug effects on task performance</td>
<td>- Gas delivery (not with breathhold)</td>
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<td>- Assessing subjective effects requires careful design</td>
<td>- Analysis more complicated with multi-modal data</td>
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<td>- Analysis tools for CBF, not CMRO$_2$</td>
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<td>- Gas delivery (not with breathhold)</td>
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<td>- Multi-modal measurements of BOLD-, CBF- and CMRO$_2$-weighted resting state, ~vascular reactivity, quantitative CBF &amp; CMRO$_2$ (hyperoxia/capnia)</td>
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<td>- Analysis methods more complicated with multi-modal data plus modality-specific noise confounds</td>
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<td>- Analysis tools for CBF, not CMRO$_2$</td>
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<td>- Spatial/temporal resolution &amp; brain coverage trade-offs</td>
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<td><strong>Rest</strong></td>
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<td>- Easy for participants and investigator</td>
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<td>- Investigate all brain networks simultaneously in relatively short scan time</td>
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<tr>
<td>- Analysis methods/tools reasonably well-developed</td>
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<tr>
<td>- No confounds due to differences in task performance…but FC differences between awake/asleep/eyes open/eyes closed</td>
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<tr>
<td>- Drug effects on neurovascular factors</td>
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<td>- Assessing subjective effects may be more intuitive in RSFC framework?</td>
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Methods

- Randomized double-blind (me & the subject) within subjects repeated measures design
- Placebo-controlled three-arm study design
  - 14 mg nicotine patch + alcohol
  - placebo nicotine patch + alcohol
  - 14 mg nicotine patch + placebo alcohol
- 12 males aged 21-40
  - physically healthy
  - light/moderate smokers
  - alcohol drinkers
  - Exclusion Criteria: female, past/current alcohol dependence, Axis I psychiatric illness, other drug dependence, daily medication use, heavy caffeine use
Methods

Study Session

4 hrs
- Transdermal nicotine (or placebo-nicotine) applied outside scanner

0
1) T1 MPRAGE
2) CBV
3) Simultaneous BOLD/CBF at rest

Simultaneous BOLD/CBF during Hypercapnia

40
- Alcohol administration (10 min)
- Waiting period (20 min)
1) Anatomicals
2) Coil Sensitivity Maps
3) Multi-band Resting State

70
- CBV
- Simultaneous BOLD/CBF at rest
- Simultaneous BOLD/CBF during Hypercapnia

90
End of Study

Output Measures

- Nicotine (or placebo): BOLD Resting State
- CBFW Resting State
- CMRO2 Resting State
- CBF, CBV

Calculate:

\[ M = \delta\text{BOLD} \left(1 - (1 + \delta \text{CBV}) \cdot (1 + \delta \text{CBF})^{-\frac{1}{3}}\right) \]

\[ SC\text{MO}2 = \left(1 - \frac{\text{SBOLD}^n}{M}\right)^{\frac{1}{n}} \cdot (\text{SCBFw})^{-\frac{1}{n}} \]

Group Comparisons

Group differences in: BOLD, CBFW and CMRO2-based RSFC separately using group concatenation ICA with dual regression

Group Differences in CBF and CBV using higher level GLM

1) Placebo Nicotine + Alcohol
2) Nicotine + Alcohol
3) Nicotine + Placebo Alcohol

HR & Respiration
ETCO2
FNIRS
Cognitive Testing
Drug-Effect
Questionnaires
BAL
HR & Blood Pressure
Methods

• Dual-Echo PCASL: $TE_1/TE_2 = 10 \text{ ms}/25 \text{ ms}$, $TR = 3.5 \text{ sec}$, whole brain, $3.44 \times 3.44 \times 7 \text{ mm}^3$, 19 slices, other params according to J.J. Wang recommendations
  • Rest: fixation, 144 timepoints, 72 control-tag pairs, $\sim 8.5 \text{ min}$
  • Breathhold using visual cues: $\sim 46 \text{ sec}$ fixation + 4 sec “Exhale” + 16 sec “Breathhold”, repeated 5 times, $\sim 7.33 \text{ min}$
  • M0 calibration scan: same acquisition params but $TR = 20 \text{ sec}$, 1 rep, 1.33 min
• iVASO: single slice (axial slice at bottom of anterior corpus callosum), see Donahue et al. (JCBFM 2010, 30: 1329-1342), rest, $\sim 4.5 \text{ min}$
• Multi-band BOLD FMRI: $2 \times 2 \times 2 \text{ mm}^3$ whole-brain, 64 slices, 1.5 sec TR, 345 shots, rest, $\sim 7.75 \text{ min}$
Results

Data acquisition is ongoing with only a small number of subjects to date, so preliminary results will be presented in the talk but are not available for downloading.
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