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

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Overview

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- Background & Motivation for the Study
- Hypotheses
- Study Design
- Experience to Date

Resting State FMRI

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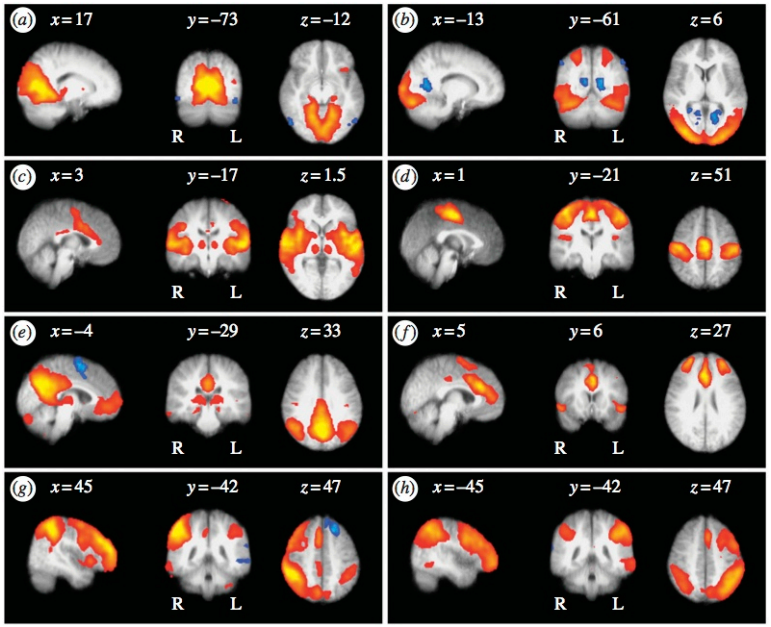
- Biswal (Magn Reson Med 1995) reported first resting state FMRI study of functional connectivity (**RSFC**)

- 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)
  - Long-term (Chou, Amer J Neurorad, 2012; Blautzik, J Alzh Dis, 2013)



Beckmann, PTRSB, 2005

Acute Effects of Zolpidem

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

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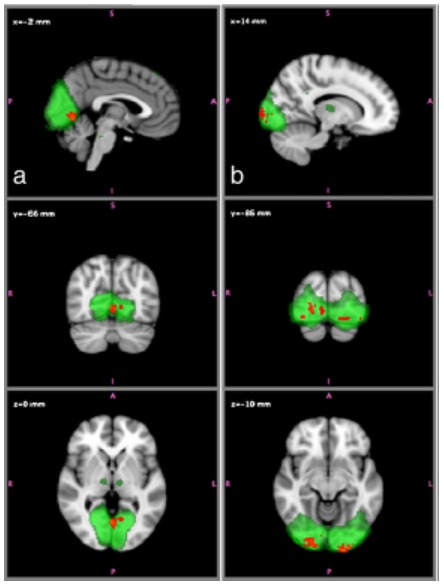
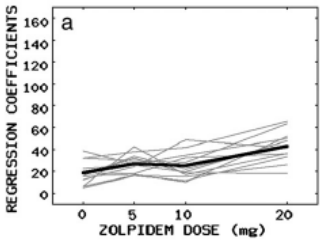
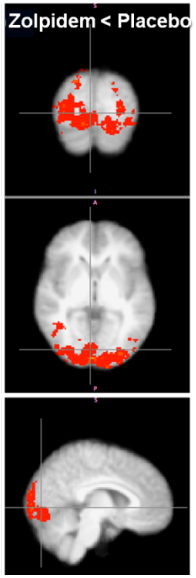
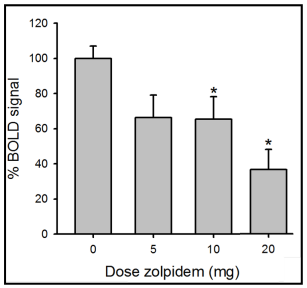
Resting State





Visual Stimulation





Licata et al. (2011) Prog Neuropsychopharmacol Biol Psychiatry 35: 1645-1652

Alcohol and nicotine co-use

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- 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?

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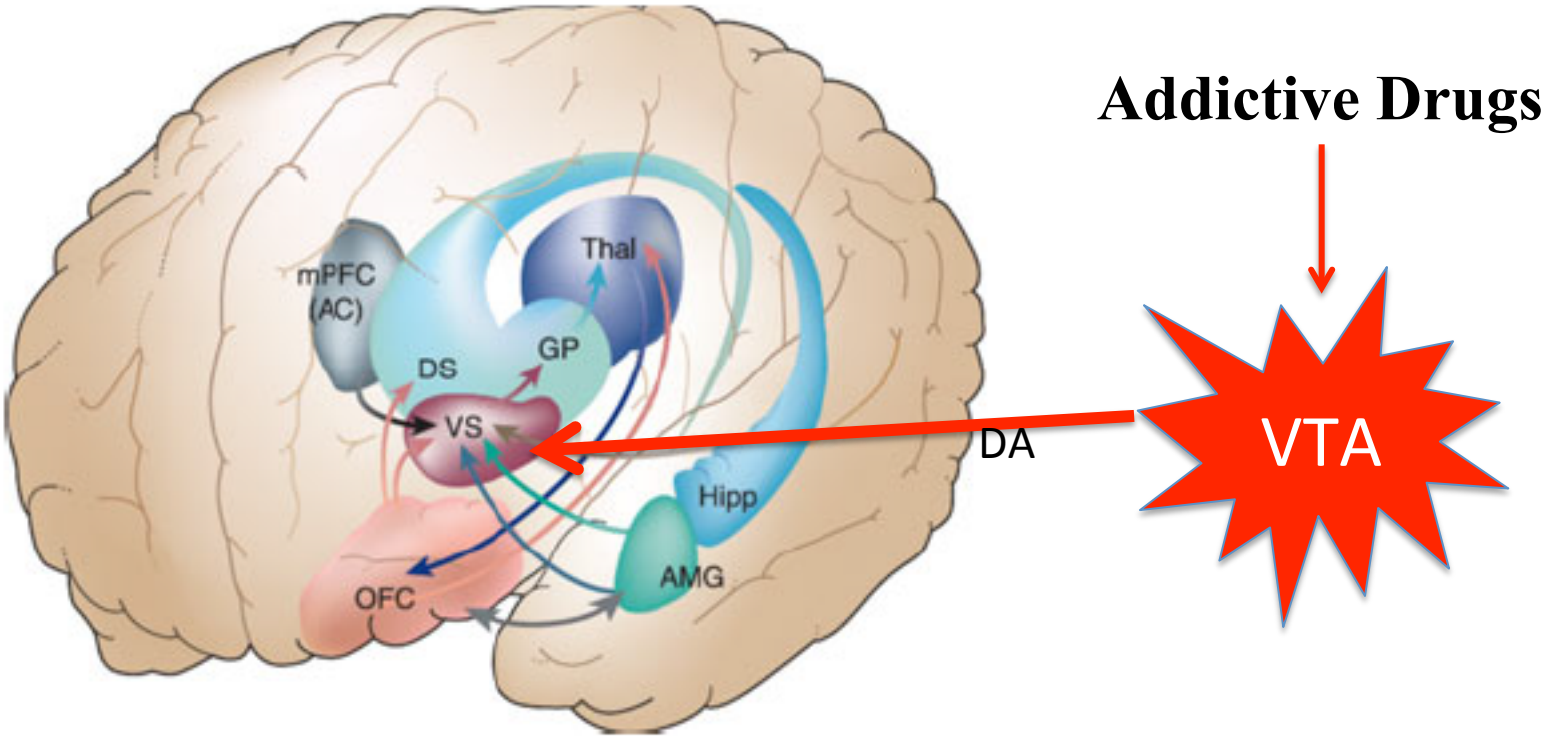
- Mesocorticolimbic Reward System



Buhler and Mann, 2010. Alc: Clin Exp Res, 35: 1771,
adapted from Everitt & Robbins, 2005. Nat Neurosci 8:1481

Hypotheses

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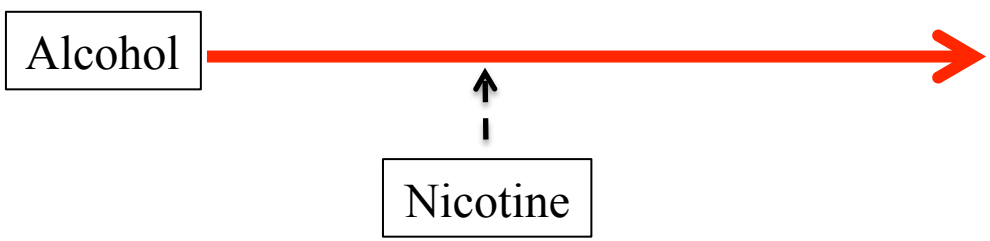
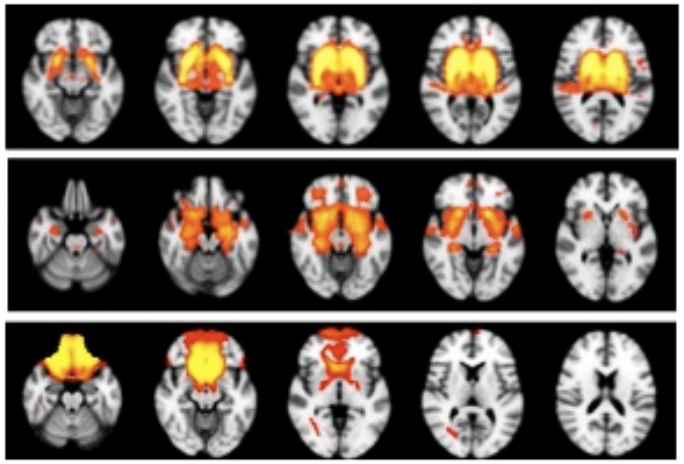
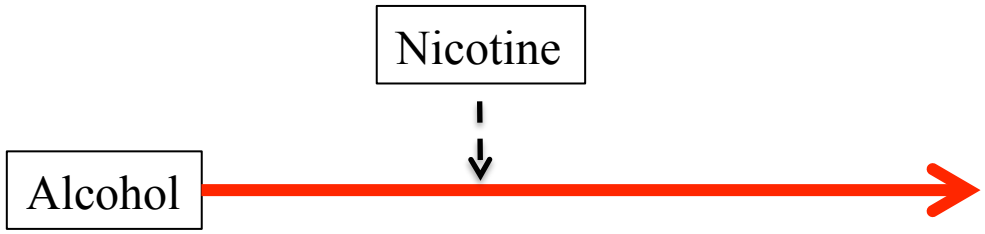
I. The effects of alcohol on brain reward-related circuits will be "enhanced" by nicotine



Reward-Related "Enhancement": DA

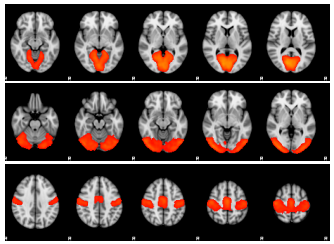


II. Impairing effects of alcohol in primary visual, motor, & sensory networks will be counteracted by nicotine

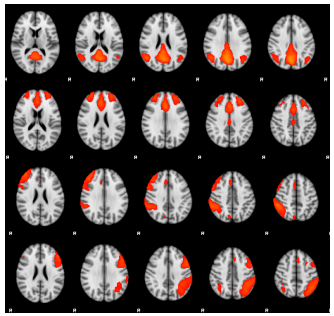


Impairing Effects

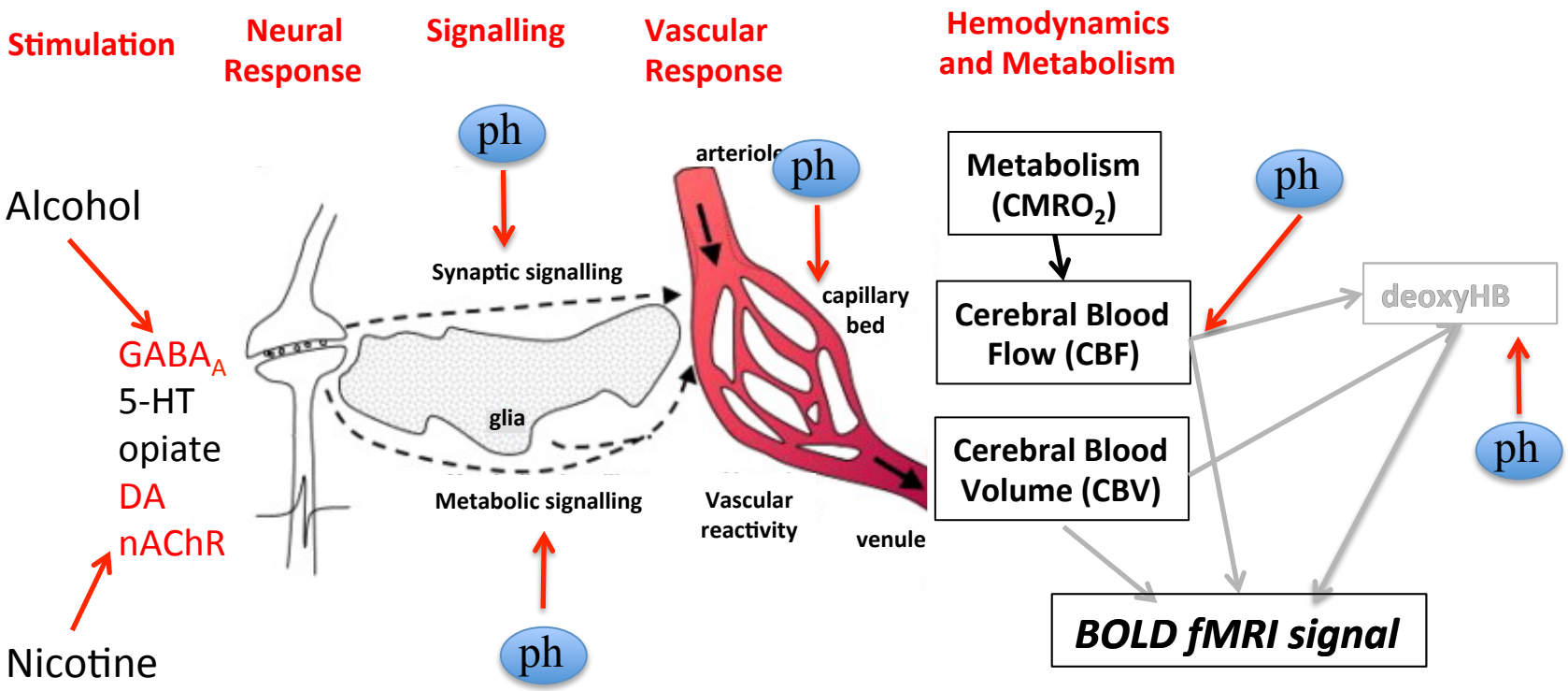
GABA?



nAChR?



A more complicated picture…



Study Design: Reference

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Drug Effects: multiple sessions, pre/post

	BOLD FMRI	QFMRI
Task	• Control behavior • Built in compliance checks (button press, etc) • Can provide a "control" for global effects • Analysis methods/tools well established • *Drug effects on neurovascular factors* • Drug effects on task performance • Assessing subjective effects requires careful design	• Multi-modal measurements of BOLD-, CBF-, and $CMRO_2$-signal changes and ~vascular reactivity • Calibrated FMRI approach well established • Control behavior, compliance, global "control" • Difficult • Spatial/temporal resolution & brain coverage trade-offs • Gas delivery (not with breathhold) • Analysis more complicated with multi-modal data • Analysis tools for CBF, not $CMRO_2$
Rest	• Easy for participants and investigator • Investigate all brain networks simultaneously in relatively short scan time • Analysis methods/tools reasonably well-developed • No confounds due to differences in task performance…but FC differences between awake/asleep/eyes open/eyes closed • *Drug effects on neurovascular factors* • Assessing subjective effects may be more intuitive in RSFC framework?	• Multi-modal measurements of BOLD-, CBF- and $CMRO_2$-weighted resting state, ~vascular reactivity, *quantitative CBF & $CMRO_2$* (hyperoxia/capnia) • Easy, investigate all brain networks in short time • Calibrated FMRI for RSFC not well validated • Analysis methods more complicated with multi-modal data plus modality-specific noise confounds • Analysis tools for CBF, not $CMRO_2$ • Gas delivery (not with breathhold) • Spatial/temporal resolution & brain coverage trade-offs

Methods

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- 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
  - phyically 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

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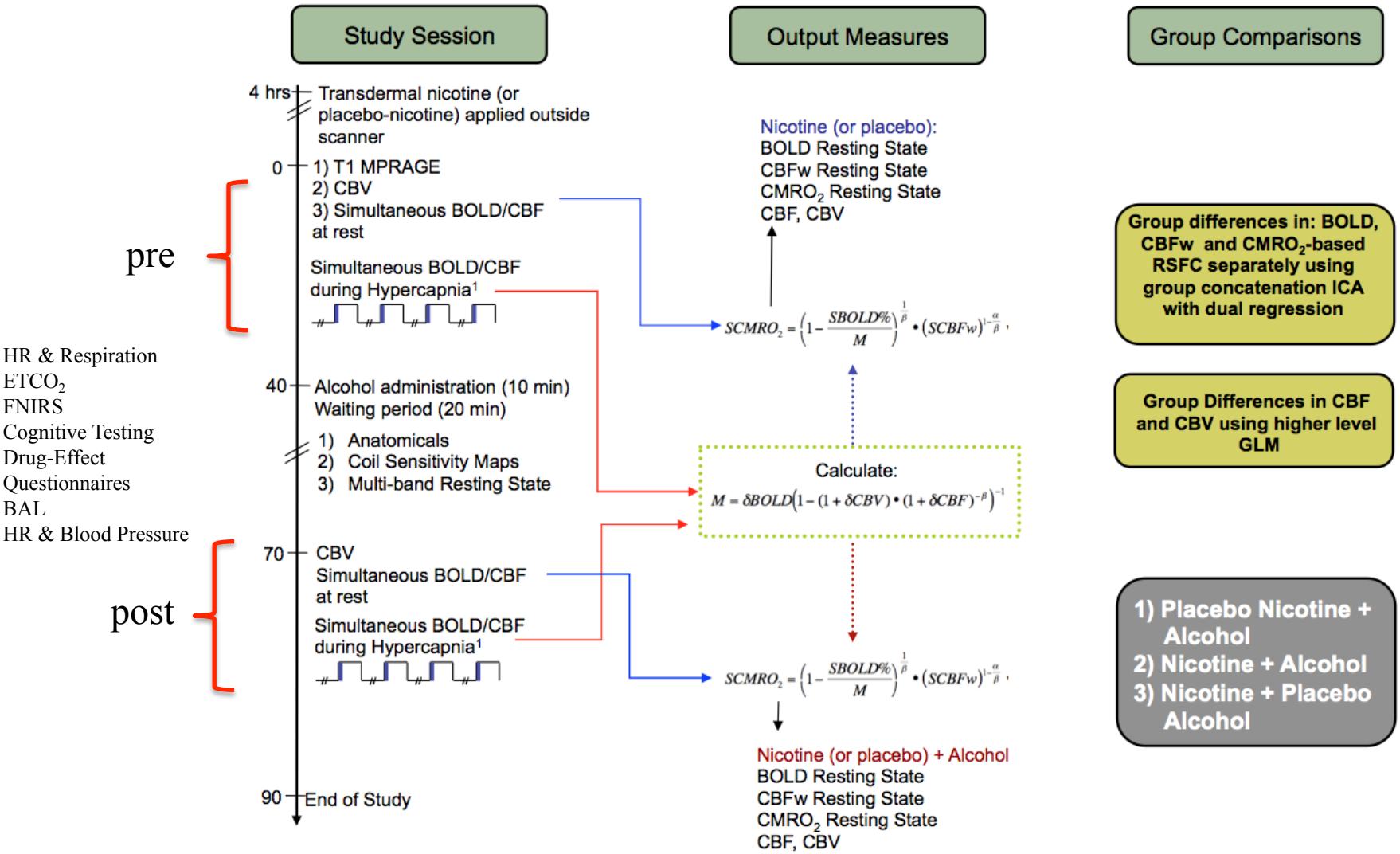

Methods

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- Dual-Echo PCASL: TE_1/TE_2 = 10 ms/25 ms, TR = 3.5 sec, whole brain, 3.44 x 3.44 x 7 mm^3, 19 slices, other params according to J.J. Wang recommendations
  - Rest: fixation, 144 timepoints, 72 control-tag pairs, ~8.5 min
  - Breathhold using visual cues: ~46 sec fixation + 4 sec "Exhale" + 16 sec "Breathold", repeated 5 times, ~7.33 min
  - M0 calibration scan: same acquisition params but TR = 20 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, ~4.5 min
- Multi-band BOLD FMRI: 2 x 2 x 2 mm^3 whole-brain, 64 slices, 1.5 sec TR, 345 shots, rest, ~7.75 min

Results

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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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