Drugs are bad...for pathogens

Testing an alternative to the reward model of recreational drug use and its implications for smoking cessation.

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Most recreational drugs are plant neurotoxins

Relationships between plant neurotoxins commonly used as drugs and CNS receptors.

Drug	Plant	Toxin	Neurotransmitter	Receptor
Tobacco, Pituri	*Nicotiana, Duboisia*	Nicotine[a]	Acetylcholine	Nicotinic receptor
Betel nut	*Areca catechu*	Arecoline[a]	Acetylcholine	Muscarinic receptor
Coca	*Erythroxylum*	Cocaine[c]	Norepinephrine, epinephrine	Adrenergic receptors
Khat	*Catha edulis*	Ephedrine[c], cathinone[a,c]	Norepinephrine, epinephrine	Adrenergic receptors
Cactus	*Lophophora*	Mescaline	Serotonin	Serotonin receptor
Coca	*Erythroxylum*	Cocaine[c]	Dopamine	Dopamine receptor
Khat	*Catha edulis*	Cathinone[a,c]	Dopamine	Dopamine receptor
Coffee, Cola nut	*Coffea, Cola nitida*	Caffeine[b]	Adenosine	Adenosine receptor
Tea	*Camellia sinensis*	Caffeine[b], theophylline[b], theobromine[b]	Adenosine	Adenosine receptor
Chocolate	*Theobromine cacao*	Theobromine[b]	Adenosine	Adenosine receptor
Opium	*Papaver somniferum*	Codeine[a], morphine[a]	Endorphins	Opioid receptor
Cannabis	*Cannabis sativa*	Δ9-THC[a]	Anandamide	Cannabinoid receptor

[a]receptor agonist, [b]receptor antagonist, [c]reuptake inhibitor

The reward model

Drugs of abuse stimulate reward circuitry in the brain

Drugs

dopamine

=

The paradox of drug reward

Nicotine, caffeine, and other drugs only exist because they deterred herbivores, not rewarded them.

Herbivores, in turn, have evolved to avoid, expel, and neutralize toxins – reactions to toxins should generally be aversive, not be rewarding.

Sullivan et al. 2008 *Proc R Soc*.
Hagen et al. 2009 *Neuroscience*.

Tobacco Hornworm *Manduca sexta*

Nicotine is extremely toxic to humans

Toxin	Recreational dose	Lethal dose
Hydrogen cyanide		50 mg
Nicotine	1-4 mg	30-60 mg

But, this acute toxicity plays almost no role in mainstream drug use theory

(Nicotine is not a carcinogen)

Why no nicotine overdoses?

~ 1 billion tobacco users

~15 billion cigarettes smoked every day

Acute mortality from recreational tobacco use is essentially non-existent

Why?

Nicotine activates many toxin defense mechanisms

- Bitter taste receptors
- Gastrointestinal “taste” receptors
- Xenobiotic-sensing nuclear receptors
- Xenobiotic metabolizing enzymes
- Aversion circuitry in the CNS

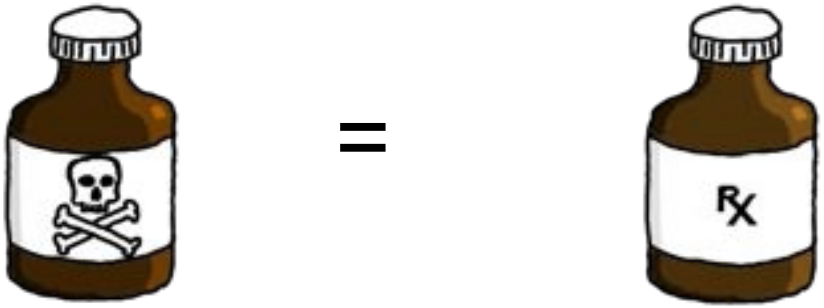
Is the brain regulating exposure to plant neurotoxins?

The pharmacophagy model

Psychoactivity is a reliably cue of neurotoxicity, and although neurotoxins are bad for us they might be worse for pathogens with nervous systems.

The brain is regulating exposure to psychoactive substances as a form of:

- Chemoprophylaxis: recreational drug use deters infection by pathogens with nervous systems
- Chemotherapy: recreational drug use treats infection by pathogens with nervous systems



Psychoactive drugs

Hypothesis

Recreational tobacco use is an (unconscious) form of self-medication against helminths

Efficacy of nicotine against helminths

- Many commercial anthelmintics (e.g., levamisole, pyrantel) attack same neuroreceptor system as nicotine (nAChRs).
- Nicotine sulfate was widely used to de-worm livestock.
- Aqueous tobacco extracts still used in developing world to de-worm livestock.
- Tobacco widely reported as an anthelmintic in the ethnomedical literature.

Testing the chemotherapy hypothesis with a randomized control trial

Predictions

Infection with helminths should increase smoking

Elimination of helminths should decrease smoking

Study population: Aka foragers of the Central African Republic

Aka camp

Study site rationale

- High levels of intestinal parasites
- Heavy tobacco use
- Almost no access to commercial anthelmintics.

Study population

- Three neighboring populations of Aka
- 191 males (most Aka women do not smoke)

Worm burden

Measure worm burden

- Appreciable levels of 3 (4) species
  - Hookworm *Ancylostoma duodenale, Necator americanus* (99%)
  - *Ascaris lumbricoides* (57%)
  - Whipworm *Trichuris trichiura* (56%)

- Semi-quantified total egg count of all species

Stool collection kit
Formalin/PVA

Randomize into treatment and placebo control groups (double-blind)

400 mg albendazole

Placebo

Outcome variable

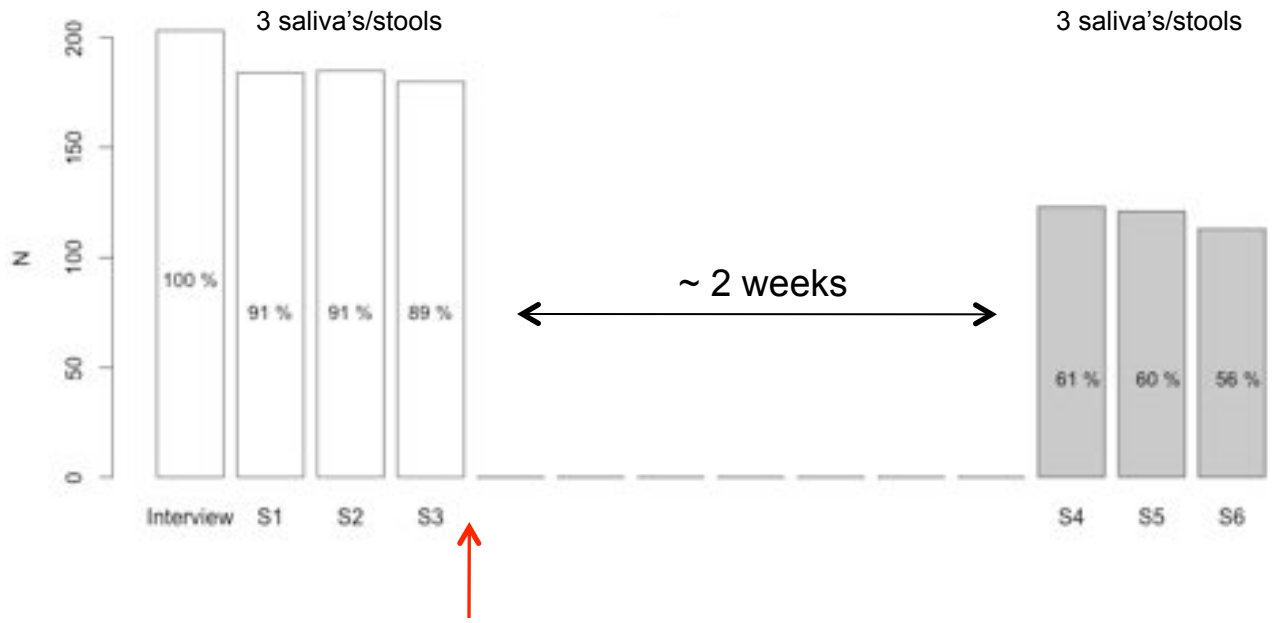
Barry Hewlett and Casey Roulette interviewing
Aka about tobacco use

Measure salivary cotinine

- Nicotine metabolite
- Half life ~ 18 hrs (nicotine half life ~ 2 hrs)
- Indexes intensity of recent nicotine exposure

Saliva collection tube

Randomized control trial

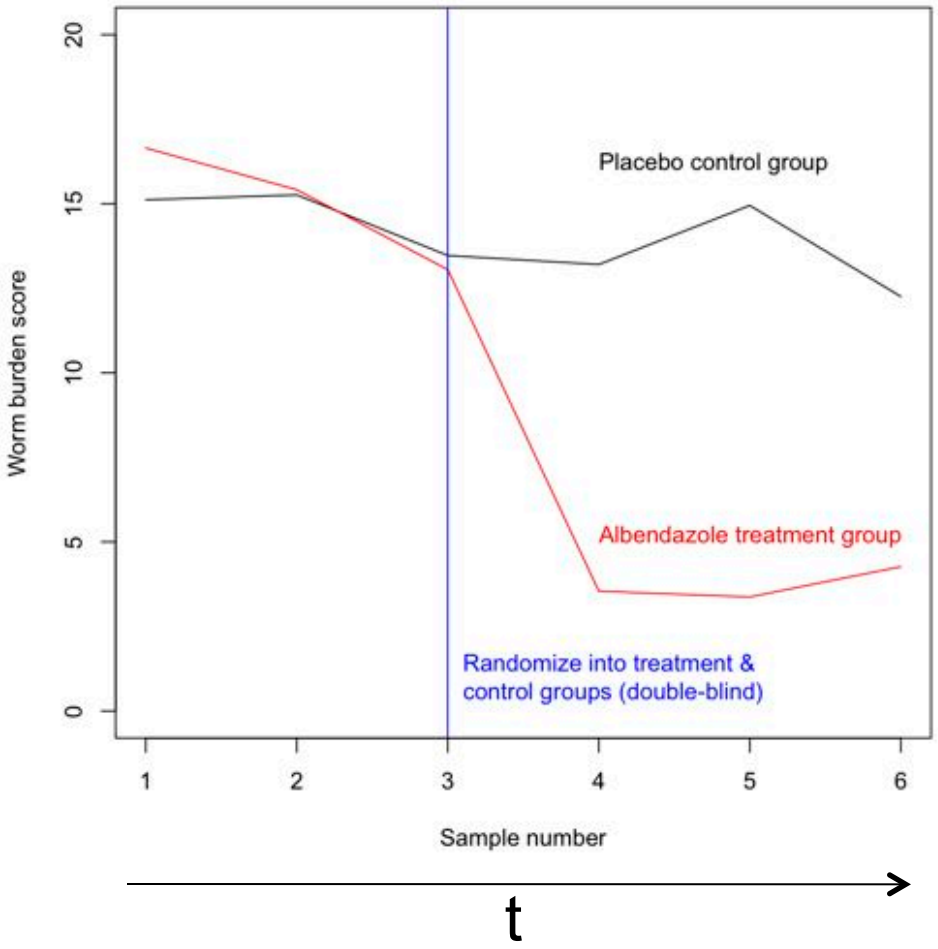


Administer 400 mg albendazole or placebo
(double-blind)

Prediction

Albendazole treatment group will have reduced salivary cotinine relative to placebo control group

Manipulation check



Worm burden

```
t = 7.0537, df = 86.781, p-value = 2.001e-10
95 percent confidence interval:
 7.78      Inf
sample estimates:
  mean in group control mean in group treatment
                 13.66                      3.47
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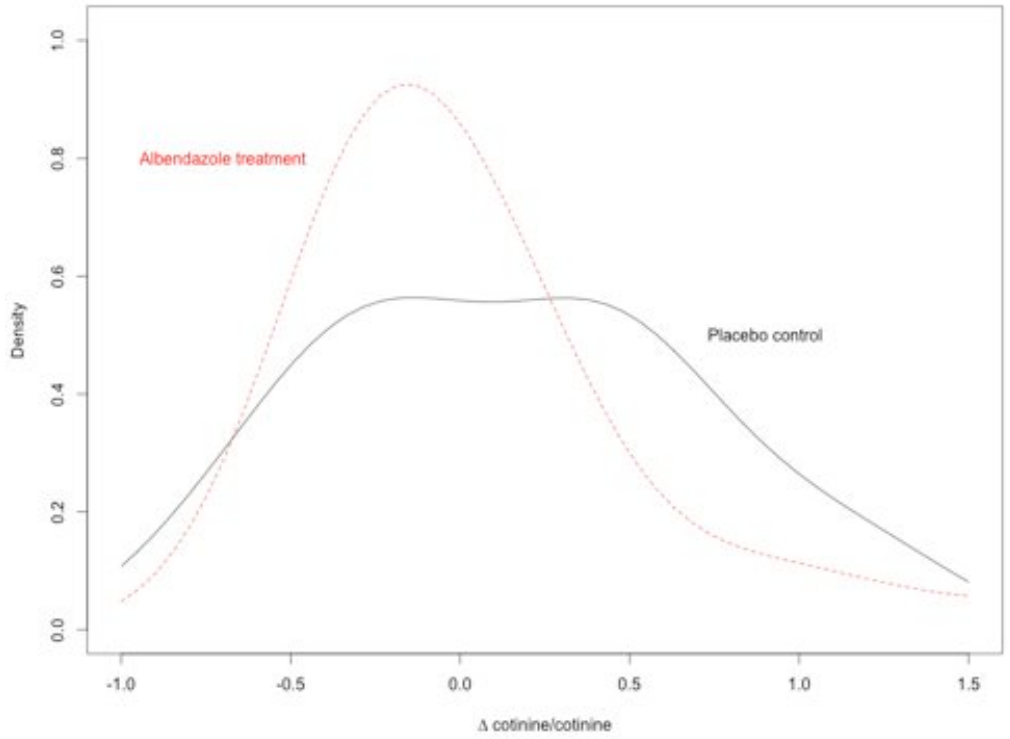
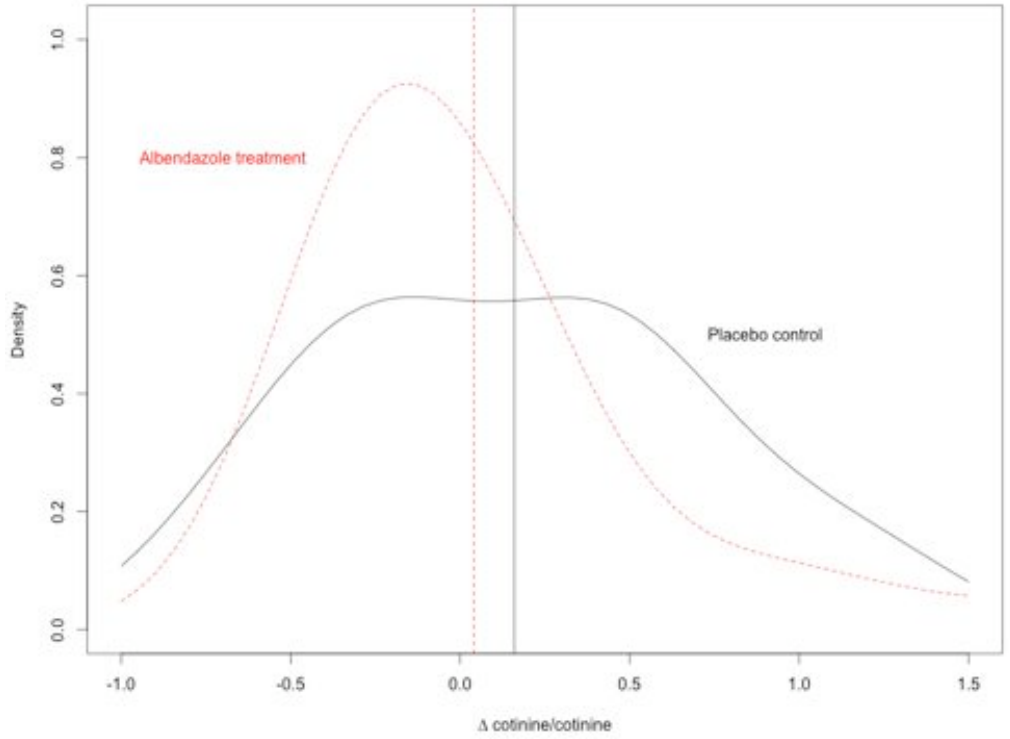
Distribution of Δcotinine/cotinine in treatment vs control groups



Δcotinine = post-treatment cotinine conc. - pretreatment cotinine conc.

Means not significantly different



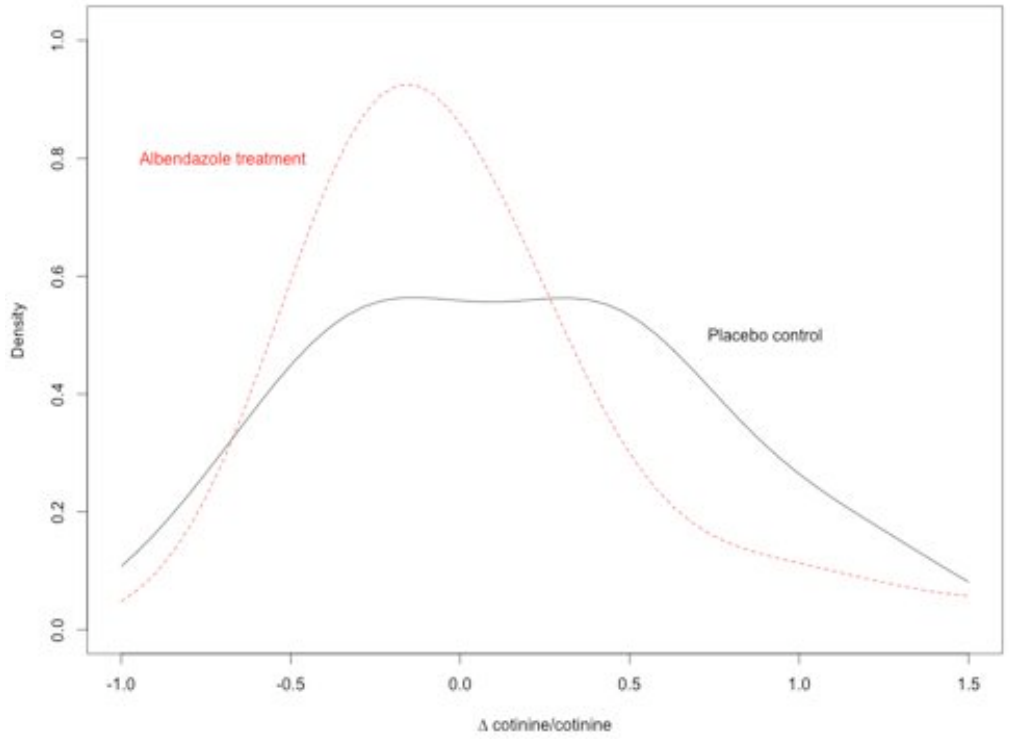
Δcotinine/cotinine

mean in group control 0.16

mean in group treatment 0.04

p-value = 0.17

Distributions are significantly different



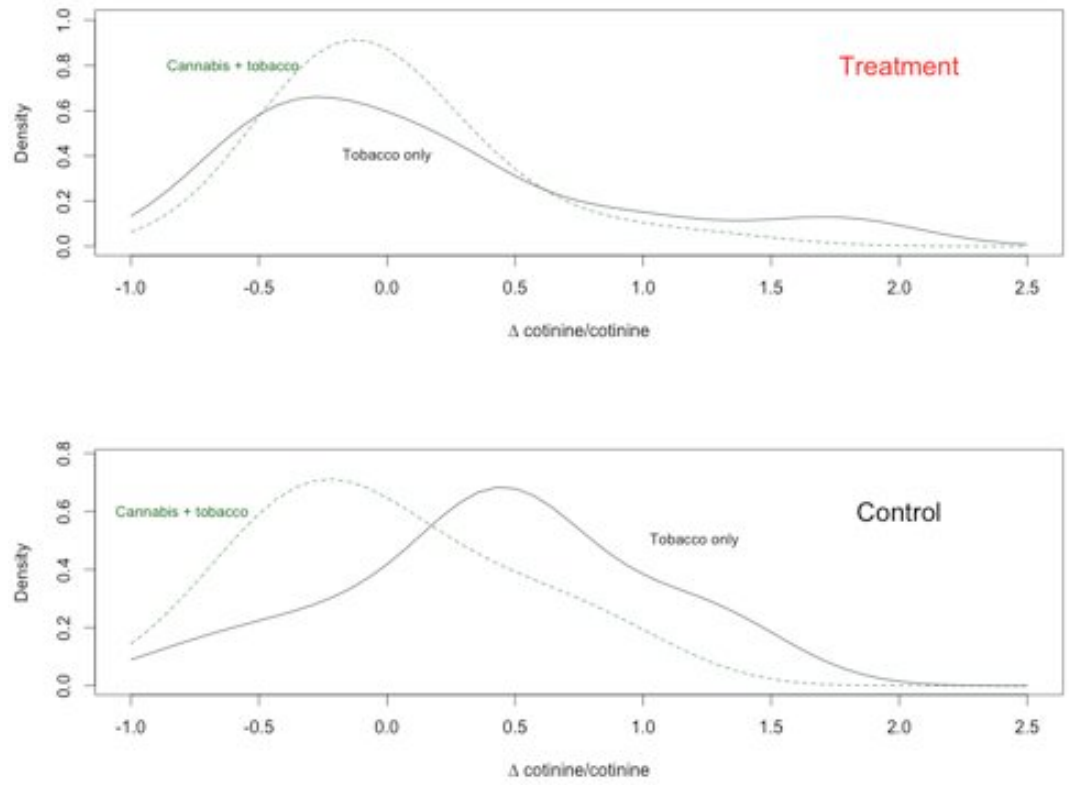
Two-sample Kolmogorov-Smirnov test

D^- = 0.32, p-value = 0.019

Treatment group is significantly more

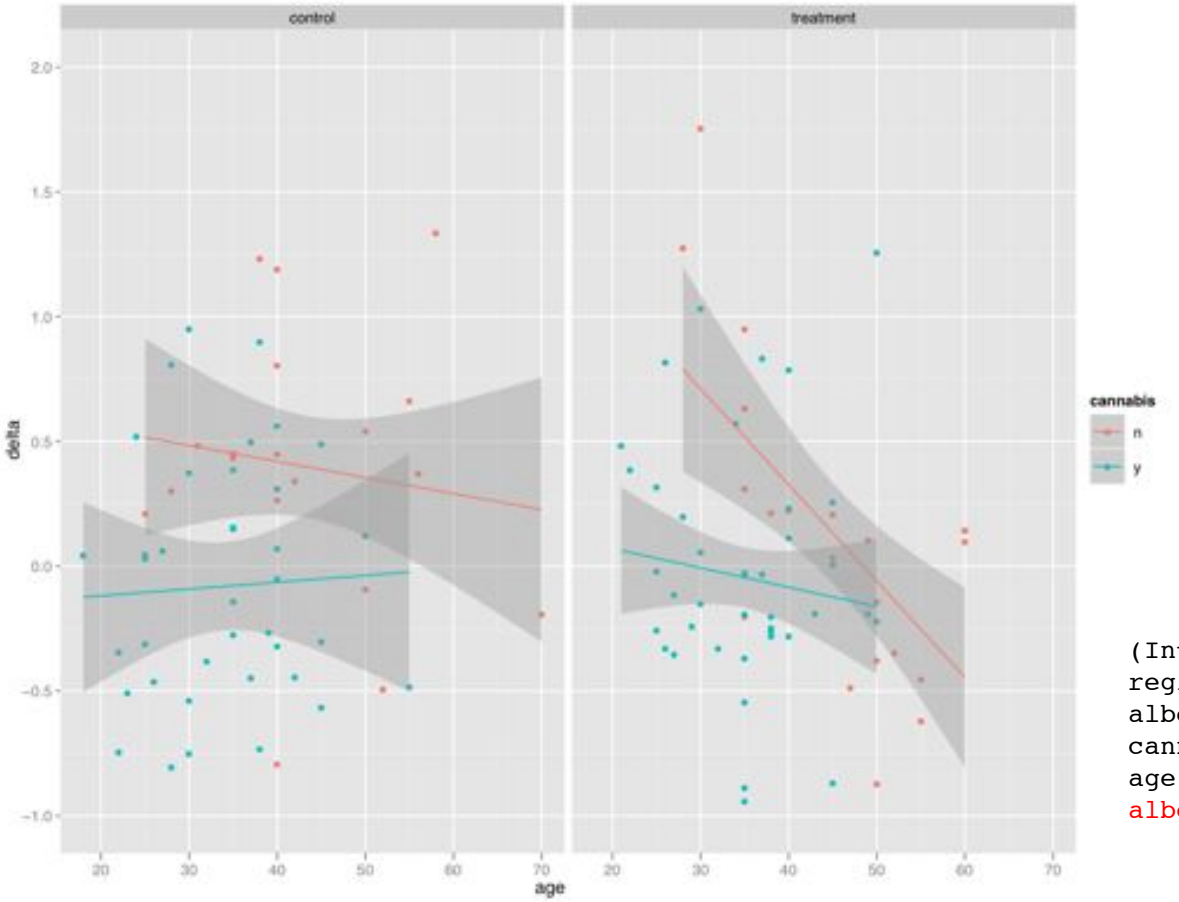
- Positively skewed (1.2 vs. 0.24)
- Leptokurtotic (1.8 vs. -1.0)

Self-reported cannabis use



	Chisq	Df	RobustF	Pr(F)	
(Intercept)		1			
region		2	5.96	0.013	*
albendazole		1	0.50	0.472	
cannabis		1	2.14	0.136	
albendazole:cannabis		1	4.17	0.038	*

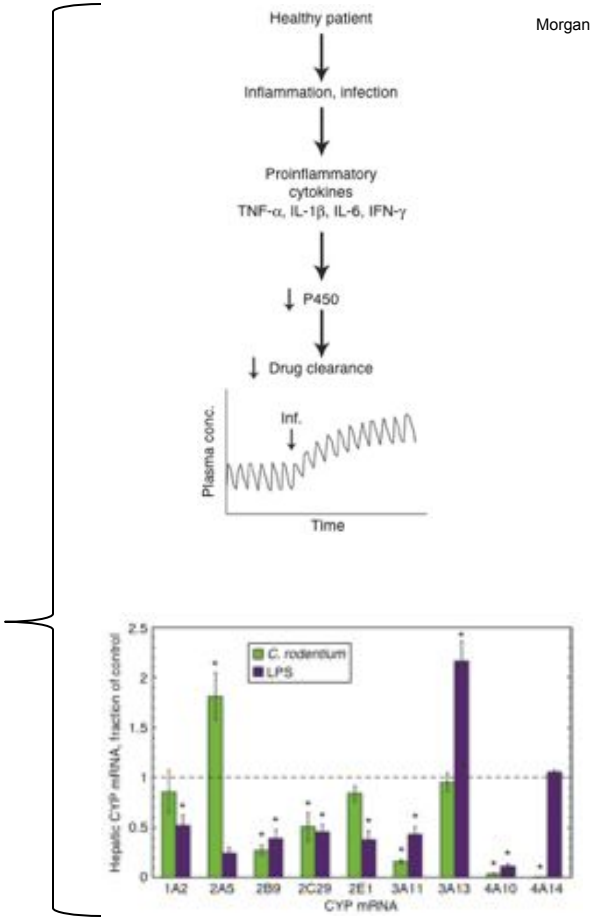
Adding age to the model



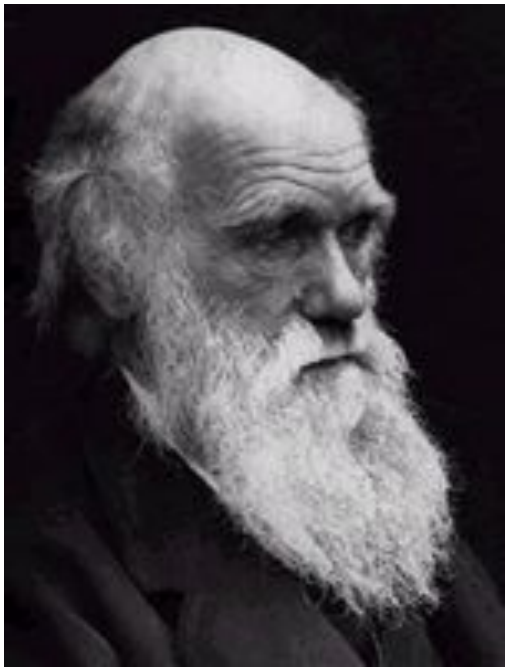
	Chisq	Df	RobustF	Pr(F)	
(Intercept)		1			
region		2	5.34	0.019	*
albendazole		1	0.59	0.43	
cannabis		1	9.50	0.002	**
age		1	0.07	0.79	
albendazole:age		1	4.85	0.025	*

Limitations: Altered behavior or altered metabolism?

- Cotinine biomarker conflates smoking behavior and nicotine metabolism
- Drugs, including albendazole, induce & inhibit metabolic enzymes
  - Nicotine largely metabolized by CYP2A6
  - No evidence that albendazole induces or inhibits CYP2A6 (?)
  - Post-treatment saliva collected ~ 2 weeks after treatment
- Infections & inflammation alter xenobiotic metabolism (usually down-regulate)



Morgan 2009



Conclusions

- Hypothesis
  - Humans might have an evolved (but unconscious) propensity to consume plant neurotoxins to kill pathogens: plant neurotoxins are bad for us but worse for our pathogens.
  - If so, treating helminths might decrease smoking behavior
- In support, we found
  - Albendazole treatment skewed Δcotinine to lower values relative to placebo.
  - Significant mean effect of treatment depended on self-reported cannabis use and/or age
- Limitation
  - Study design cannot disentangle behavioral changes from metabolic changes

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