The Interaction of Placebos and Treatment Implications for Power and Trial Design

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Placebo Effects may Add Value

- "Behavior" is often described as a "placebo", and discounted from treatment
- Behavior can interact with treatment—part of the efficacy of treatment!

Example

- Anti-depressant treatment: making new friends
- New treatment (drug): helps to reduce social anxiety
- In a trial:
  - Those who believe they are treated go to parties;
  - Those who don't, don't.
- Effect of drug is all through the interaction of a treatment (drug) with a behavior (going to parties)

Conflicts of Interest

Overview

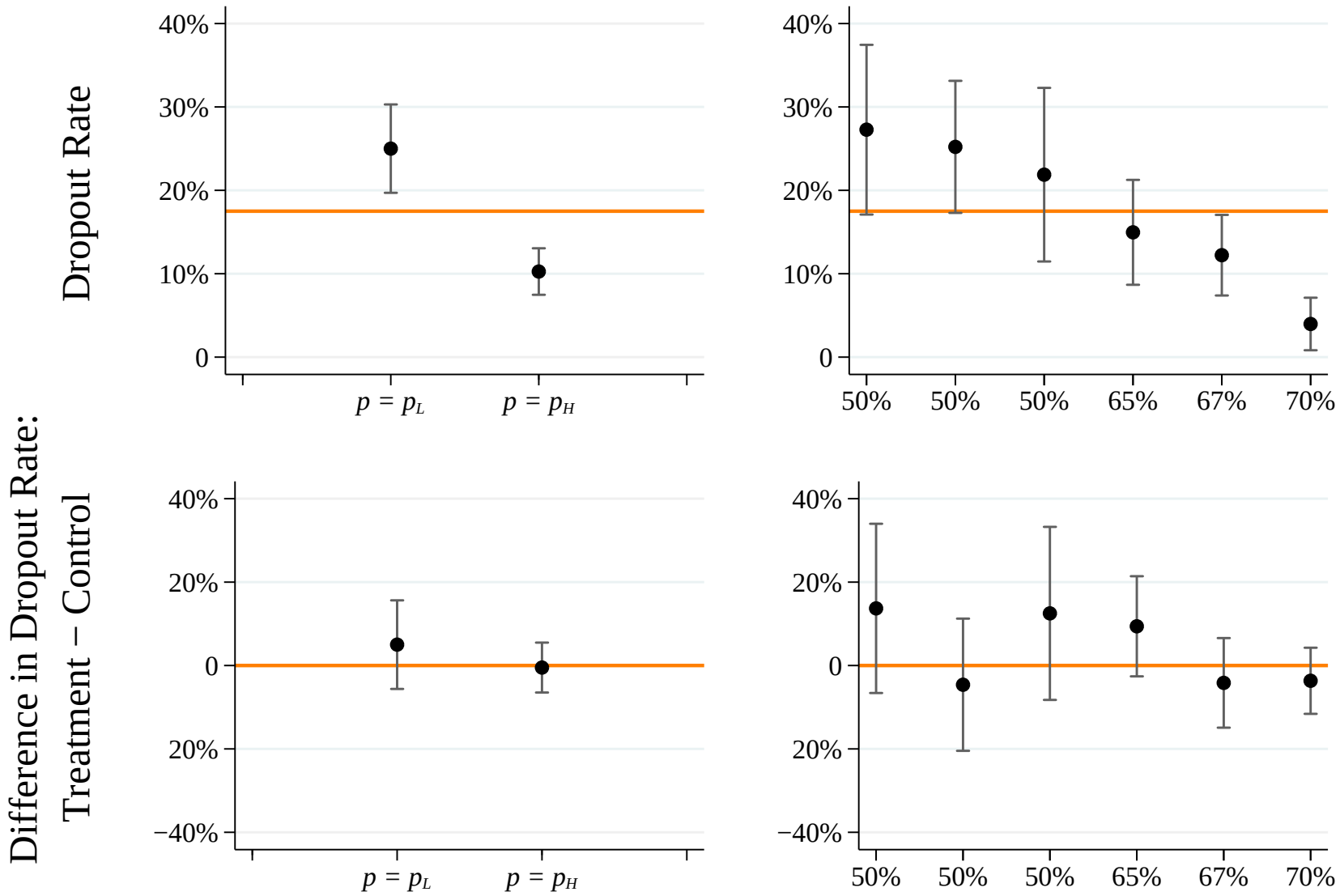
- Most clinical trials with 50/50 treatment/control are underpowered
  - $\sim$70% of two-armed trials on ClinicalTrials.gov use this protocol
- Two causes, likely to vary across treatment and participant population. Higher probability of treatment $\Rightarrow$
  - lower dropout rate
  - stronger interaction of behavior and treatment

  $\Rightarrow$ more power
- 2×2 trials can uncover superior treatment probabilities
  - Can be used in Phase II
  - Produce a deeper understanding of the true value added of a treatment

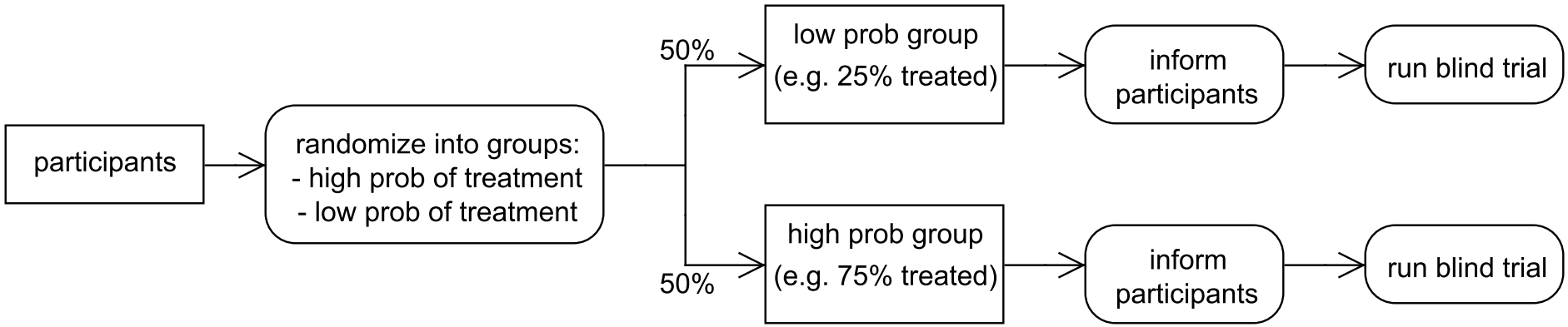
Meta-Analysis

- Chassang et al. (2015 PLOS ONE) analyzes every placebo controlled anti-depressant trial where patient-level data is available
  - Data from Fournier et. al. (2010)
- These trials have different probabilities of randomization:
  - Three for SSRI paroxetine: $p = 0.5,\ 0.65,\ 0.67$
  - There for TC imipramine: $p = 0.5,\ 0.5,\ 0.7$

Dropout Rates



2x2 Blind Trial



Accounting for Behavior in Value Added

- Problem: Behavior is not randomly assigned
- But, behavior responds the probability of treatment p: $b(p)$

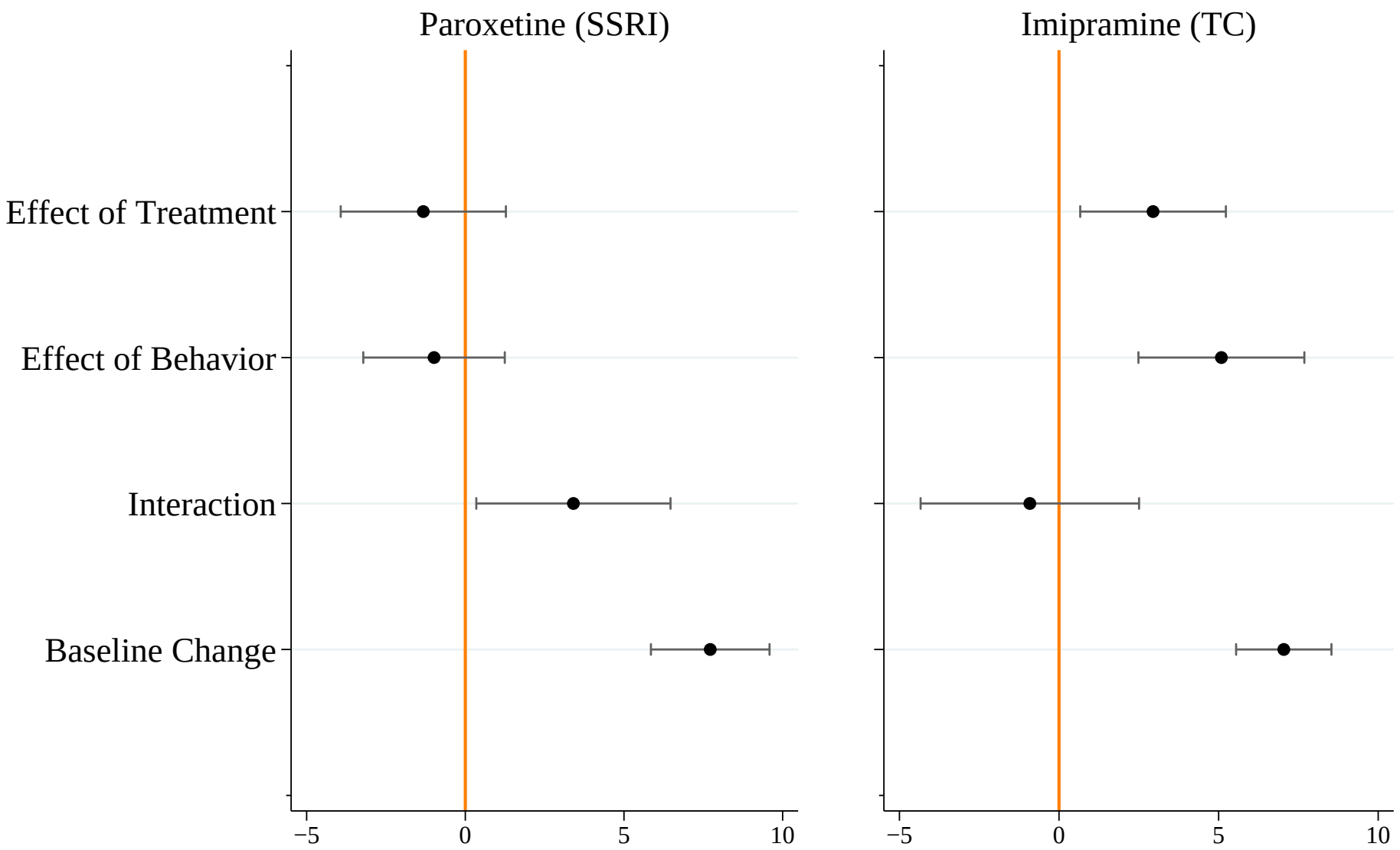
$$\begin{aligned} Y_i &= \tau_i Y_{i1} + (1-\tau_i) Y_{i0} \\ &= \tau_i (E_T + b(p) E_B + b(p) E_I) \\ &\quad + (1-\tau_i)(b(p) E_B) + \widetilde{U_{Y_i}} \\ &= \alpha + b(p) \times E_B + \tau_i \times E_T + \tau_i \times b(p) \times E_I + U_{Y_i} \end{aligned}$$

  - E_T pure effect of treatment
  - E_B pure effect of behavior change
  - E_I interaction of treatment and behavior

- Value added of drug is $E_T + E_I$
- 50/50 blind trial identifies: $E_T + E_I \times b(50\%)$
- Two-by-two blind trial identifies: E_T, E_I, and even E_B

$\Rightarrow$ provides a full accounting of value added

Effects of Behavior, Treatment, and Interaction



Conclusion

- Effect of a new treatment might be enhanced by interactions with behavior (placebo)
- Higher probability of treatment may lead to lower dropout, stronger placebo effects
- Thus, 50/50 trials may be sub-optimally powered
- Two-by-two blind trial can identify when this is the case,
  - Can be run in Phase II, or in research

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- Two-by-two blind trial can identify when this is the case,
  - Can be run in Phase II, or in research
- We are always looking for partners

Analysis of Dropout Rates

Dependent Variable:	Dropout	
	SSRI	TC
Treatment	0.041	-0.0073
	(.039)	(.041)
High Probability of Treatment	-0.15***	-0.20***
	(.055)	(.037)
High Probability × Treatment		
Constant	0.25***	0.24***
	(.051)	(.037)
N	384	334

Analysis of Outcomes

Dependent Variable:	HDRS reduction	
	SSRI	TC
Treatment	-1.32	2.94***
	(1.32)	(1.16)
High Probability of Treatment	-0.98	5.09***
	(1.13)	(1.32)
High Probability × Treatment	3.41**	-0.91
	(1.56)	(1.74)
Constant	7.72***	7.04***
	(0.95)	(0.76)
N	384	334

What Next?

- New approach to designing trials
- Analysis of data available to us suggests techniques may actually be useful

What Next?

- NSF grant for more theory work: dynamic experiments, experiments with spill-overs
  - Some other funding for more lab studies
- Some additional funding for studies of technology adoption in developing countries
- Looking for collaborators: especially people involved in evaluating new drugs / weight loss / smoking cessation / etc.