Causal Inference:
prediction, explanation, and intervention

Lecture 10: Mechanisms, Interventions, and Randomized Controlled Trials

Samantha Kleinberg
samantha.kleinberg@stevens.edu

Final projects

- If you were asked to update your proposal and haven’t done so, please do it ASAP.

Next week: journal club

- Goal: evaluate and discuss work other than your own that may be outside your field, learn about new work
- **For all papers**: read in depth, and prepare to discuss
- **For your assigned paper**:
  - Read the article (+ other references if needed for context)
  - Prepare to give a brief summary
  - Prepare questions and lead discussion

Format

- Summary of paper
  - What's the main argument/hypothesis?
  - How is this supported?
    - Overview experiments, figures

- Discussion
  - Bring comments, criticism, questions

- Timing
  - 30 min/paper

Paper assignments

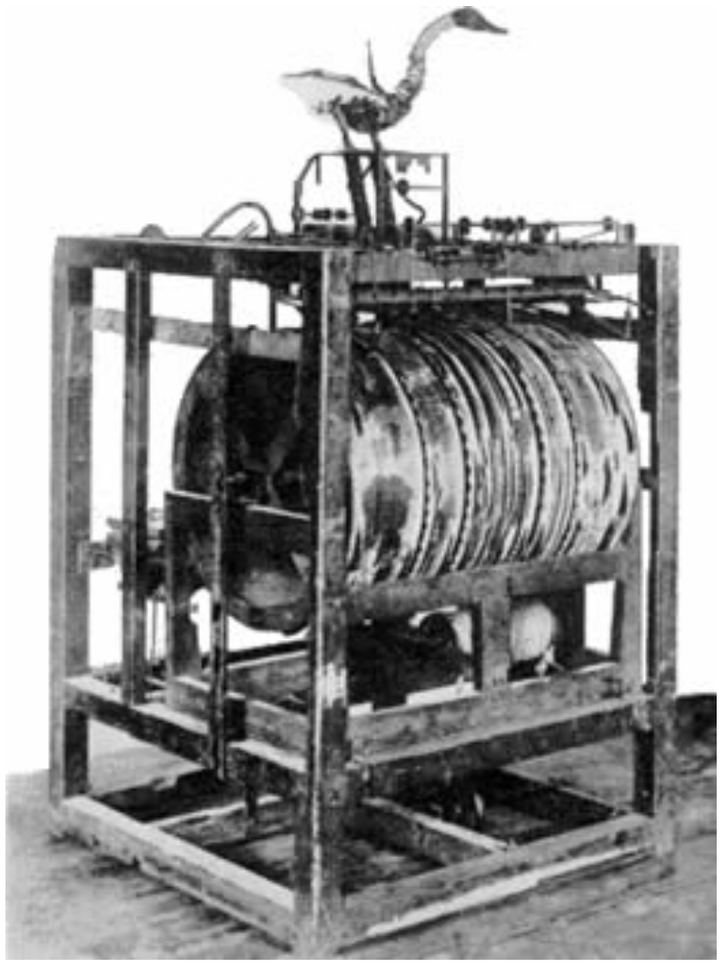
- Traditional experiment: poverty and cognitive function
- Natural experiment: Cancer twin study
- Field study: canvassing can change opinion longterm
- Observational: TV and teen pregnancy
- Honorable mention papers: unintended consequences of voter persuasion; presence of smartphone reduces cognitive capacity; News + public expression; Donations and access to congress; scarcity frames value

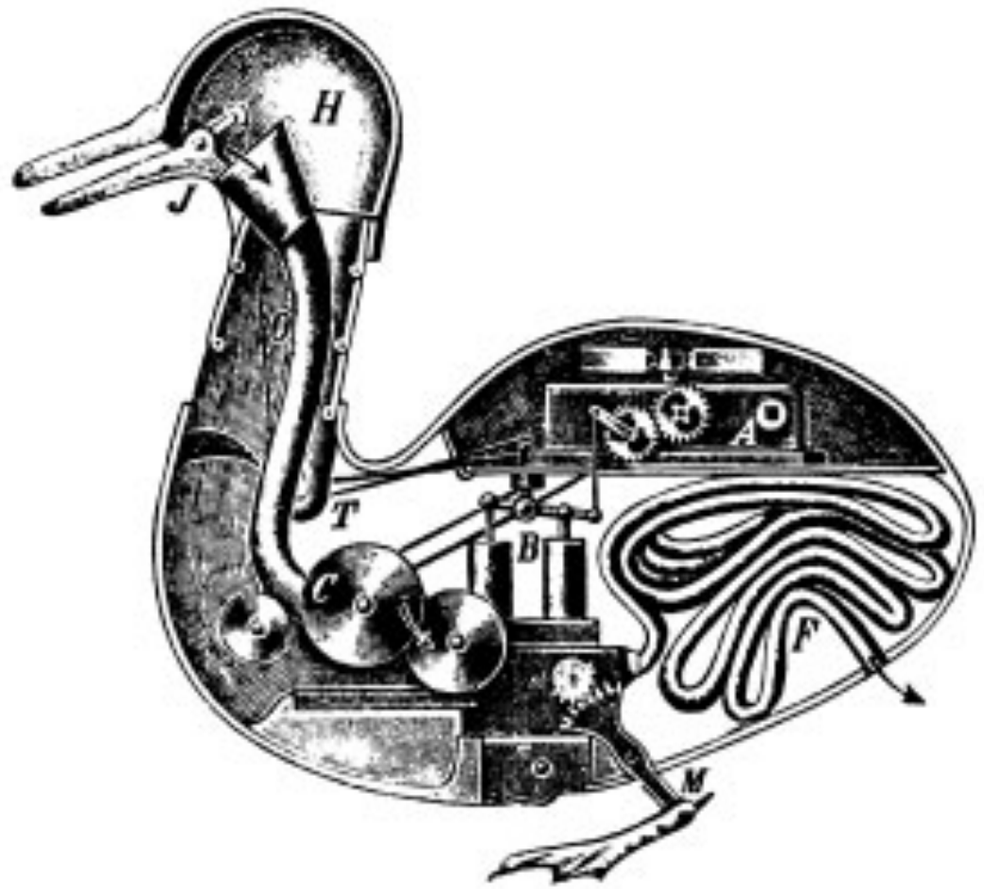
Paper assignments

- Traditional experiment: poverty and cognitive function (Last name G-K)
- Natural experiment: Cancer twin study (Last name L-S)
- Field study: canvassing can change opinion longterm (Last name T - W)
- Observational: TV and teen pregnancy (Y - Z)

Coffee

- Study of 402,260 AARP members
- Men who had 2-3 cups/day 10% less likely to die than non-coffee drinkers, Women 13%
- Women drinking 4-5 cups 16% less likely to die of stroke, accidents, diabetes, among others




H
J
A
T
B
C
F
M

Mechanisms

"Causal processes, causal interactions, and causal laws provide the mechanisms by which the world works; to understand ***why*** certain things happen, we need to see ***how*** they are produced by these mechanisms"

Salmon, W. C. (1984). *Scientific explanation and the causal structure of the world.* Princeton University Press, Princeton, NJ.

Example

Smoking causes yellowed fingers

The tar in cigarette smoke stains fingers

- Regularities/Probabilistic causality
  - People usually develop a fever after contracting the flu

- Mechanisms
  - An infection sends signals to the brain, which regulates body temperature, which in turn raises this in response to the infection.

Mechanisms and intervention

Smoking →LC

-If we don’t know how smoking causes LC, can only intervene to reduce smoking rates

-If we know how it causes LC, can intervene in later parts of the process

What is a mechanism?

- Like causality, no agreement/single definition

- General idea
  - A system of interacting parts that regularly produce some change

Definitions of mechanisms

- Glennan: A mechanism underlying a behavior is a complex system which produces that behavior by the interaction of a number of parts according to direct causal laws. [Glennan, 52]
- Machamer, Darden, Craver (MDC): Mechanisms are entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions [MDC, 3]
- Bechtel and Abramson: A mechanism is a structure performing a function in virtue of its component parts, component operations, and their organization. The orchestrated functioning of the mechanism is responsible for one or more phenomena. (BA, 423).

Key points

- Phenomenon produced
- Invariance, predictability
- Set of organized interactions/activities
- Component parts
- Not just “a mechanism”, a mechanism **for a behavior**

Granularity

Carl Sagan (343): Some ancient Asian cosmological views are close to the idea of an infinite regression of causes, as exemplified in the following apocryphal story: A Western traveler encountering an Oriental philosopher asks him to describe the nature of the world:

``It is a great ball resting on the flat back of the world turtle.''

``Ah yes, but what does the world turtle stand on?''

``On the back of a larger turtle.''

``Yes, but what does he stand on?''

``A very perceptive question. But it's no use, mister; it's turtles all the way down.''

Sagan, C. (1979). Broca's brain: Reflections on the romance of science. Ballantine Books

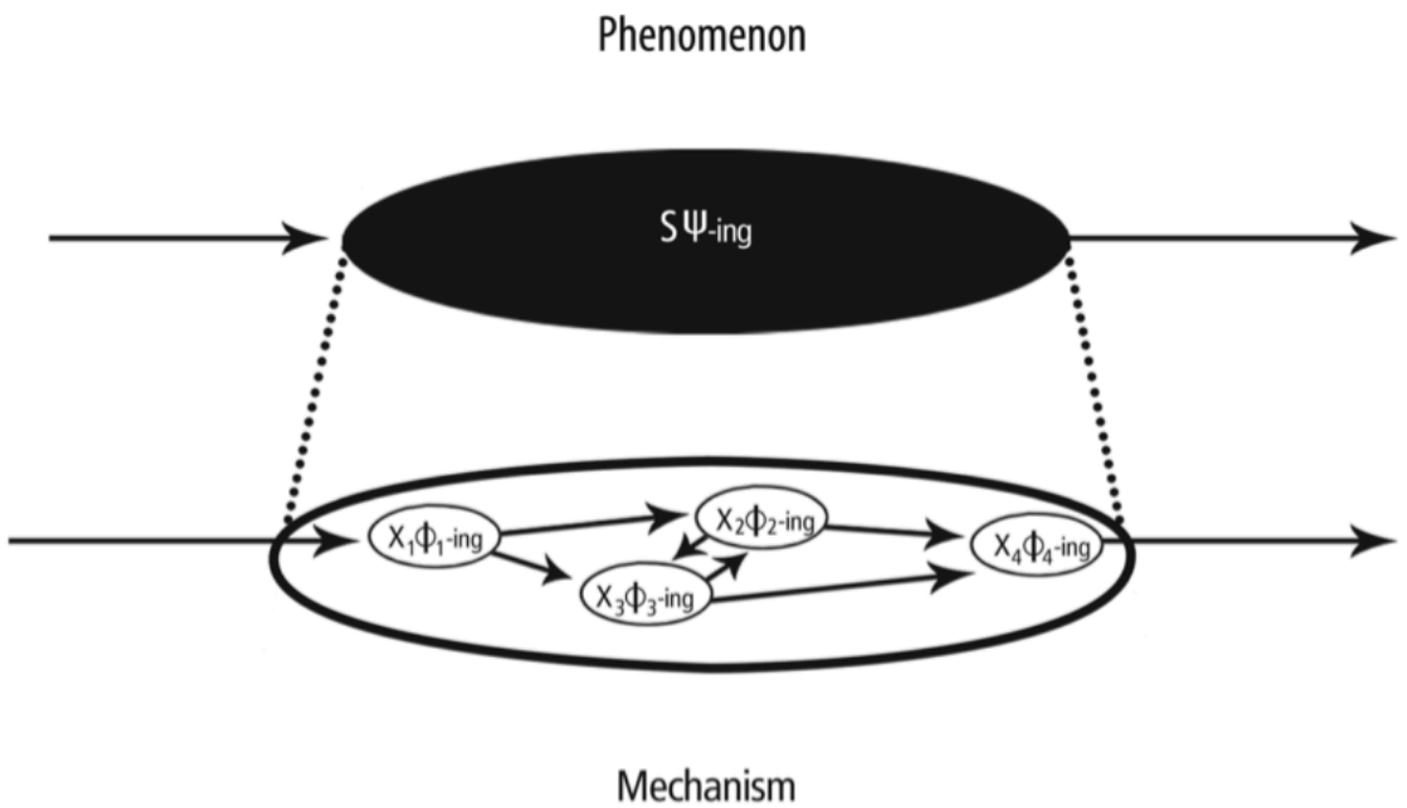


Figure 1. A visual representation of a mechanism (adapted from Craver 2007).

Hierarchy

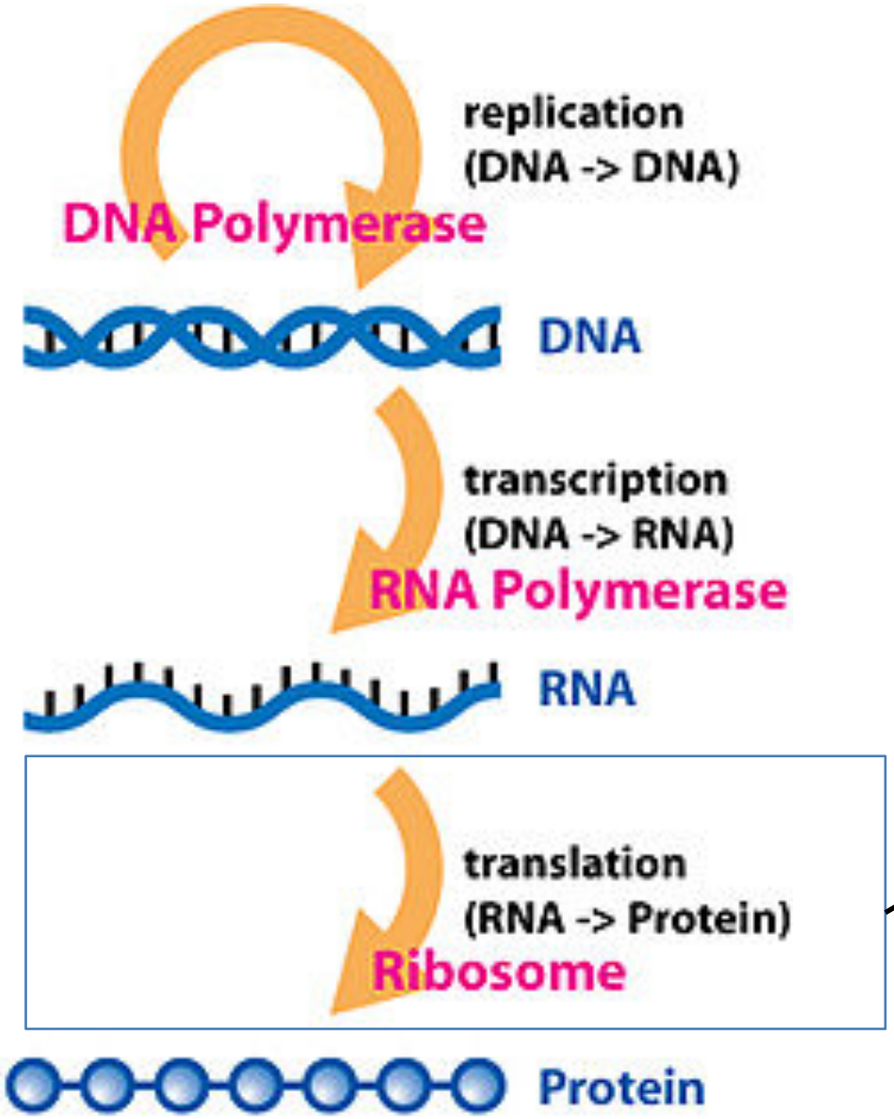
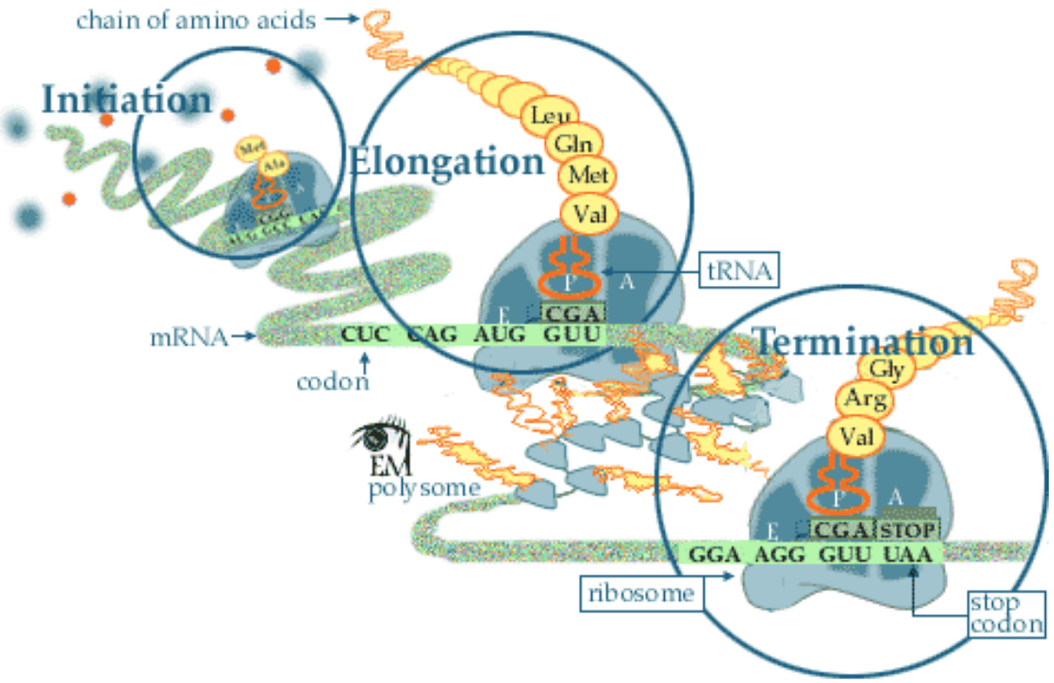


Image from Dhorspool at en.wikipedia



http://www.nobelprize.org/educational/medicine/dna/a/translation/

Mechanistic causality

- Glennan: a relation between two events (other than fundamental physical events) is causal when and only when these events are connected in the appropriate way by a mechanism [Glennan, 56]

- MDC: An entity acts as a cause when it engages in a productive activity… It is not the penicillin that causes the pneumonia to disappear, but what the penicillin does. [MDC, 6]

Probabilistic causality

Recall:

Umbrella vendors and rain

Pirates and global warming

Combining probability and mechanisms

- No plausible way…
  - Pirates can lower the earth's temperature
  - Umbrella vendors can produce rain

- Two sources of evidence
  - Neither necessary, but together can corroborate relationship

Russo, F. and Williamson, J. 2007. Interpreting Causality in the Health Sciences. International Studies in the Philosophy of Science. 21(2): 157—170.

Evidence for causality

- Neither difference making nor mechanisms are sufficient to establish causality
- Each provides different supporting information
  - Plausible connection between cause and effect (the how)
  - Cause actually has impact on effect

- Distinguish between causal relationship itself and evidence supporting its existence

Example: genetic variations and voting behavior

Fowler and Dawes (2008): people with certain variants of MAOA are more likely to vote than those with others

Charney and English (2012, commentary): Same variants also linked to IBS, schizophrenia, and other traits. Implausible that single variant explains all of these.

Example: mechanism w/o causality

It is not known what causes most cases of autism in humans.

But, know that problems w/signaling in brain may be a cause and have drugs for this.

If drugs work in cases where cause not known, can postulate it was a signaling problem.

Structural equations, counterfactuals and mechanisms

Pearl/Woodward

- For intervention [do] need to know alteration doesn’t affect mechanisms
  - The structural eq. aren’t affected by the intervention
- When eq. invariant in this way, said to correspond to mechanisms

Further Reading

- Bechtel, W. and A. Abrahamsen, 2005, “Explanation: A Mechanistic Alternative”, Studies in History and Philosophy of the Biological and Biomedical Sciences, 36: 421–441.
- Dowe, P. (2000). Physical causation. Cambridge University Press.
- Glennan, S. S. (1996). Mechanisms and the nature of causation. Erkenntnis (1975-), 44(1), 49-71.
- Machamer, P., Darden, L., & Craver, C. F. (2000). Thinking about mechanisms. Philosophy of Science, 67(1), 1-25.
- Woodward, J. (2005). Making things happen: A theory of causal explanation. Oxford University Press, USA.

We want to know whether a heartburn medication works, so we compare incidence of heartburn in users/non-users of the drug.

Interventions to causes

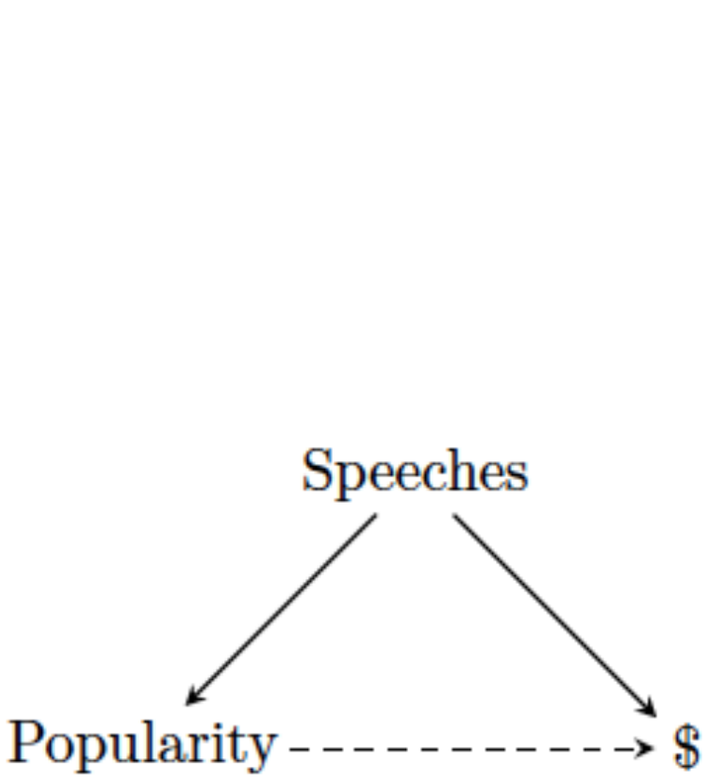
- Running shoes A -> 5K race
- Running shoes B -> 5K race

If pace different, what can we conclude?

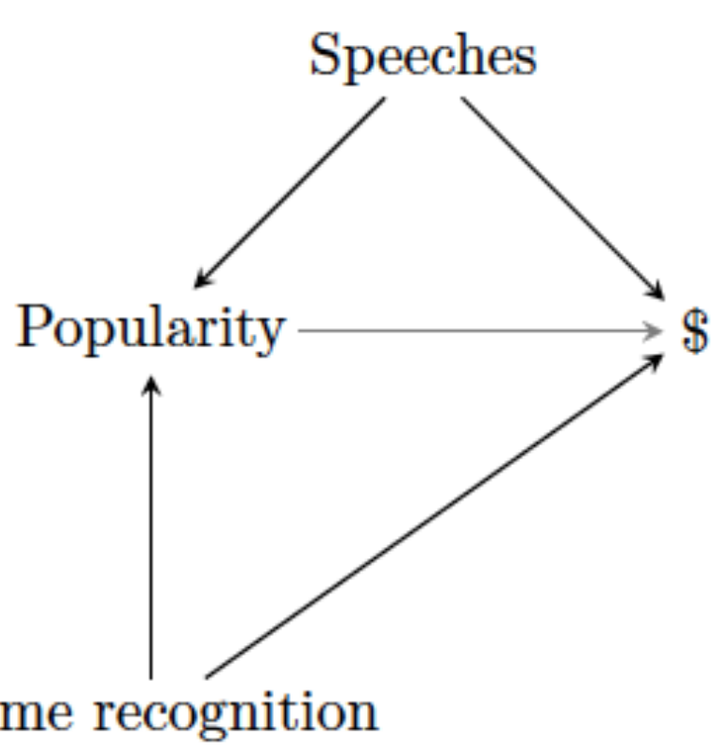
- Could have improved in ability over time (or gotten injured in between)
- Weather may have changed (external effect of different time periods)
- Delayed effect of training during first time period

Ideal intervention

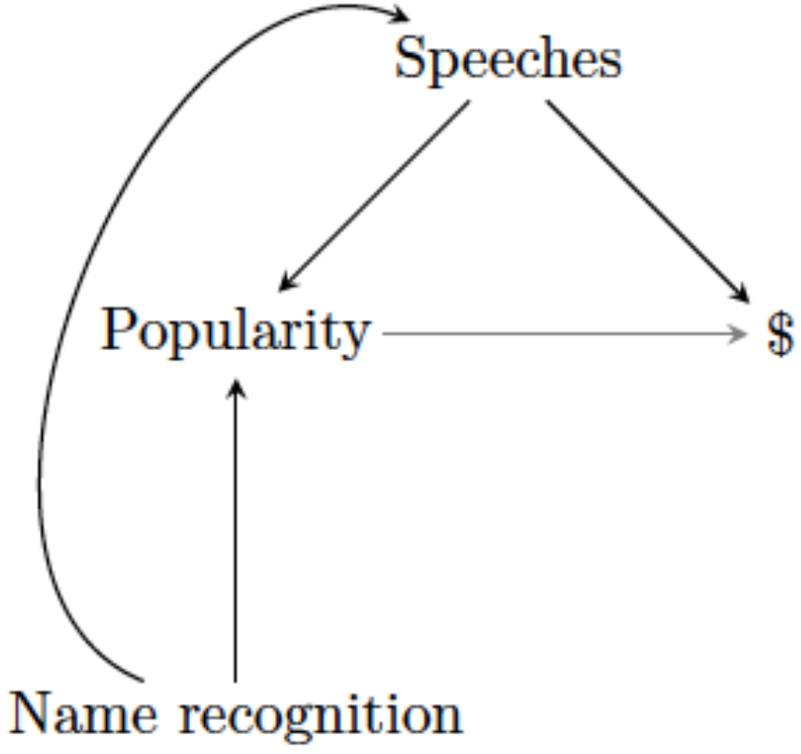
Change only the cause – not any causes of it, or other causes of the effect – and see if effect still happens



(a) Hypothesized structure



(b) Intervention directly causing effect



(c) Intervention indirectly causing effect

Intervention and RCTs

Ideal: two groups that are identical in every way except one assigned to possible cause. Any differences between the groups then must be a result of the cause.

RCT

- Two groups: control and intervention
- Assignment to group is random
  - Various methods for randomizing: e.g. by patient, by site
- Only difference is the policy/treatment

Limits (more later)

Tradeoff between control of study…

And generalizability of results

Not just for medicine!

- Webpage design
- Political campaigns
- Education
- Social interventions

Randomization

1747: Lind discovers treatment for scurvy

But assigned men on boat to dietary additions (sea water, citrus, etc). Could have led to bias

Why randomize?

- Sever link between causes of intervention and effects (selection bias)
  - E.g. birth control pills and pregnancy
- Isolate cause
  - Single difference between groups, removes confounding

- Observational study shows women taking HRT after menopause have decreased risk of heart attacks (37% lower death rate, 53% lower risk of CV death)

- HERS trial: RCT showing no effect

- WHI: RCT where heart attacks increase 29% (from 30 to 37 per 10,000 person-years)

- Latest: HRT may be beneficial if it's started early

Example

Testing text messages to promote physical activity

Randomize 13-year-olds in a school to either text messages promoting 30 minutes of activity, or just giving weather report

Problem: contamination between groups

Solution: cluster randomization

Who to randomize?

Back to heartburn medication…

Should population be…?

-Everyone

-People with history of heartburn

-People w/heartburn and not taking drugs that may interact w/proposed one

-People in a certain age group

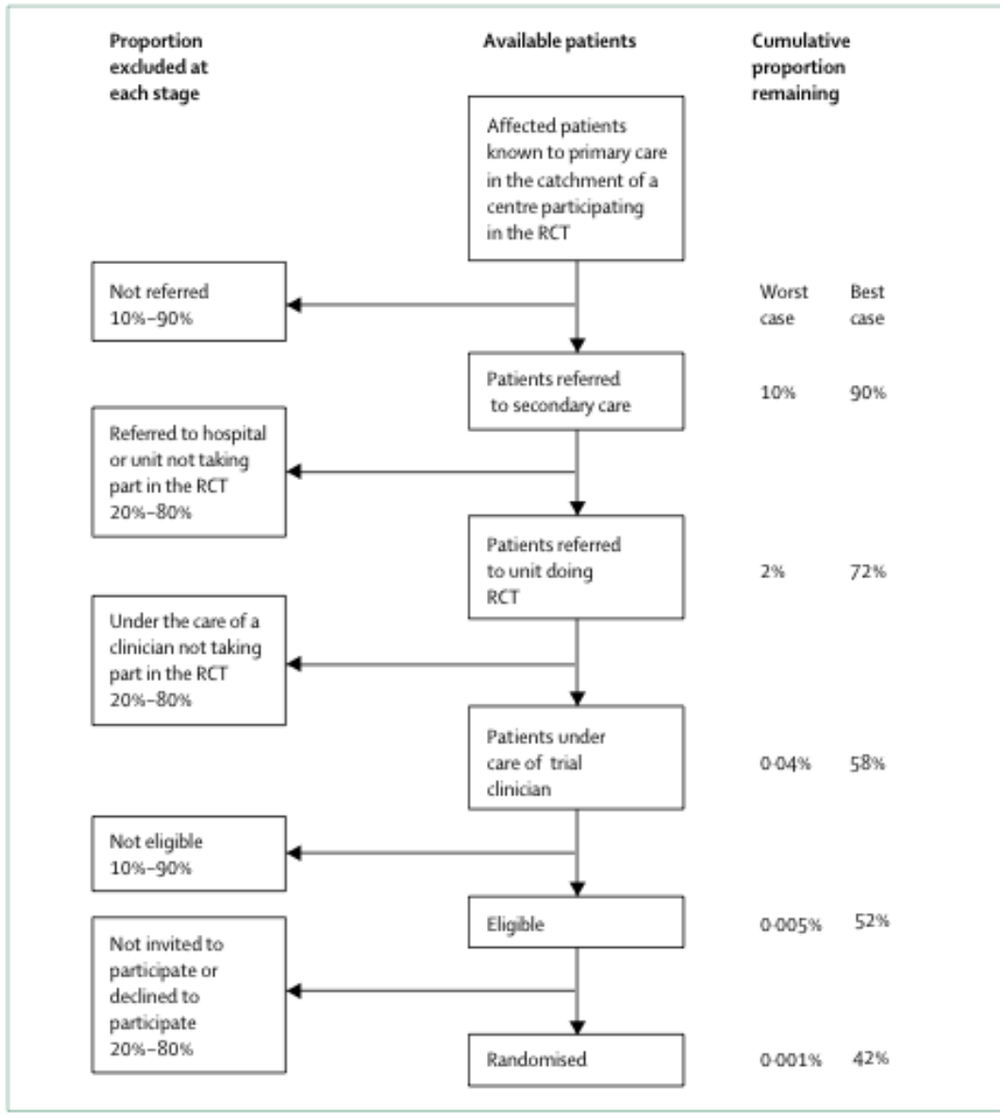


Figure 4: **Schematic diagram illustrating effect of multiple stages of selection inherent in clinical practice on proportion of patients in catchment of participating centre entered into an RCT done in secondary care**
Worst case assumes proportion of patients excluded at each stage is at top of range and best case is based on lowest proportion of patients excluded.

Rothwell, P. M. (2005). Treating individuals 1 external validity of randomised controlled trials:To whom do the results of this trial apply?. Lancet, 365(9453), 82-9

Population/patients not truly random

- Hospital/clinic - who participates?
- Clinician - who refers patients?
- Patient - who chooses to enroll?

Who to analyze?

- Not everyone who starts a study finishes..
  - May be removed by investigator
  - May withdraw
  - May be lost to follow-up

- Survival bias

Controlling

1950: Hill and others use RCT to study treatment for tuberculosis

Compared streptomycin to standard of care (bed rest)

Assigned treatment with numbered & sealed envelopes

- Instead of does effect happen or not after treatment, how does result compare to standard or no treatment

- Why is this needed?

Blinding

- Single: Patient unaware of what treatment being received
- Double: Patient + clinician unaware of what treatment being administered/received
- Triple: Double + person analyzing results not aware of which group is which

Example

RCT of two treatments + placebo for multiple sclerosis

Examination by blinded and unblinded neurologists

Unblinded Neurologists showed one treatment beneficial at 6, 12, 24 months, p-value<0.05

Noseworthy, J. H., Ebers, G. C., Vandervoort, M. K., Farquhar, R. E., Yetisir, E., & Roberts, R. (1994). The impact of blinding on the results of a randomized, placebo-controlled multiple sclerosis clinical trial. Neurology, 44(1), 16-16.

Sidenote on placebos

- Treatment that is known to have no impact on the effect (e.g. sugar pills, fake surgery)

- Why can’t we use no treatment?
  - The act of treatment can induce effects

Placebo effect

- Dosage
- Injection vs pill
- Color of pills
- Packaging/branding
- Surgeries

Placebos without Deception: A Randomized Controlled Trial in Irritable Bowel Syndrome

Ted J. Kaptchuk[1,2]*, Elizabeth Friedlander[1], John M. Kelley[3,4], M. Norma Sanchez[1], Efi Kokkotou[1], Joyce P. Singer[2], Magda Kowalczykowski[1], Franklin G. Miller[5], Irving Kirsch[6], Anthony J. Lembo[1]

1 Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, United States of America, **2** Osher Research Center, Harvard Medical School, Boston, Massachusetts, United States of America, **3** Psychology Department, Endicott College, Beverly, Massachusetts, United States of America, **4** Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, United States of America, **5** Department of Bioethics, National Institutes of Health, Bethesda, Maryland, United States of America, **6** Department of Psychology, University of Hull, Hull, United Kingdom

Abstract

Background: Placebo treatment can significantly influence subjective symptoms. However, it is widely believed that response to placebo requires concealment or deception. We tested whether open-label placebo (non-deceptive and non-concealed administration) is superior to a no-treatment control with matched patient-provider interactions in the treatment of irritable bowel syndrome (IBS).

Methods: Two-group, randomized, controlled three week trial (August 2009-April 2010) conducted at a single academic center, involving 80 primarily female (70%) patients, mean age 47±18 with IBS diagnosed by Rome III criteria and with a score ≥150 on the IBS Symptom Severity Scale (IBS-SSS). Patients were randomized to either open-label placebo pills presented as "placebo pills made of an inert substance, like sugar pills, that have been shown in clinical studies to produce significant improvement in IBS symptoms through mind-body self-healing processes" or no-treatment controls with the same quality of interaction with providers. The primary outcome was IBS Global Improvement Scale (IBS-GIS). Secondary measures were IBS Symptom Severity Scale (IBS-SSS), IBS Adequate Relief (IBS-AR) and IBS Quality of Life (IBS-QoL).

Findings: Open-label placebo produced significantly higher mean (±SD) global improvement scores (IBS-GIS) at both 11-day midpoint (5.2±1.0 vs. 4.0±1.1, $p<.001$) and at 21-day endpoint (5.0±1.5 vs. 3.9±1.3, $p=.002$). Significant results were also observed at both time points for reduced symptom severity (IBS-SSS, $p=.008$ and $p=.03$) and adequate relief (IBS-AR, $p=.02$ and $p=.03$); and a trend favoring open-label placebo was observed for quality of life (IBS-QoL) at the 21-day endpoint ($p=.08$).

Why blind?

- Confirmation bias

- Placebo effect

n=1

How can we figure out which of two interventions is best for one individual?

Instead of randomizing people, randomize order of treatment

Considerations

- How many treatment periods?
- How to randomize order?
- Washout period?

Journal club

Using RCT results

- Heartburn study was a success! Reduced frequency and severity
- Now: new 80 y.o. patient on 10 meds. Should this new one be prescribed?

Why Olanzapine Beats Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine: An Exploratory Analysis of Head-to-Head Comparison Studies of Second-Generation Antipsychotics

Stephan Heres, M.D.

John Davis, M.D.

Katja Maino, M.D.

Elisabeth Jetzinger, M.D.

Werner Kissling, M.D.

Stefan Leucht, M.D.

Objective: In many parts of the world, second-generation antipsychotics have largely replaced typical antipsychotics as the treatment of choice for schizophrenia. Consequently, trials comparing two drugs of this class—so-called head-to-head studies—are gaining in relevance. The authors reviewed results of head-to-head studies of second-generation antipsychotics funded by pharmaceutical companies to determine if a relationship existed between the sponsor of the trial and the drug favored in the study's overall outcome.

Method: The authors identified head-to-head comparison studies of second-generation antipsychotics through a MEDLINE

sources of bias that could have affected the results in favor of the sponsor's drug.

Results: Of the 42 reports identified by the authors, 33 were sponsored by a pharmaceutical company. In 90.0% of the studies, the reported overall outcome was in favor of the sponsor's drug. This pattern resulted in contradictory conclusions across studies when the findings of studies of the same drugs but with different sponsors were compared. Potential sources of bias occurred in the areas of doses and dose escalation, study entry criteria and study populations, statistics and methods, and reporting of results and wording of findings.

What’s the cause here?

- Intervention: office chairs
- Outcome: weight loss

Weight loss in first test!

Failure in new population. How?

If an RCT shows a measurable effect of a variable, does that mean it's causal?

If an RCT doesn't show an effect, does that mean the variable is not causal?

- Inappropriate surrogate outcome measures, so that what is said to have been measured is in fact not (see Gøtzsche et al. 1996; Jaeschke and Sackett 1989);
- Incomplete intenti statistical analysis (Feinstein a ne Working Group 20
- Problems with blin n inade- quate controls on t 8);
- Inability to generalize from the trial's results, due to ambiguous objectives or failure to report inclusion/exclusion criteria (Jaeschke and Sackett 1989);
- False negatives, resulting from small numbers or insensitive outcome measures (Jaeschke and Sackett 1989).

JASON GROSSMAN AND FIONA J. MACKENZIE

To argue from the fact that RCTs have certain advantages, other things being equal, to the claim that the RCT is a gold standard, is like arguing that since being tall makes for a good high-jumper, it follows that a 6′ elderly drunkard with a spinal injury is bound to be a better high-jumper than a 5′11″ Olympic athlete.

Problems with RCTs

- Can be
  - Infeasible
  - Unethical
- External validity
- True randomization difficult
- Cost (+ duration, sample size)
- Power

Infeasible/unethical

There will never be an RCT to determine:

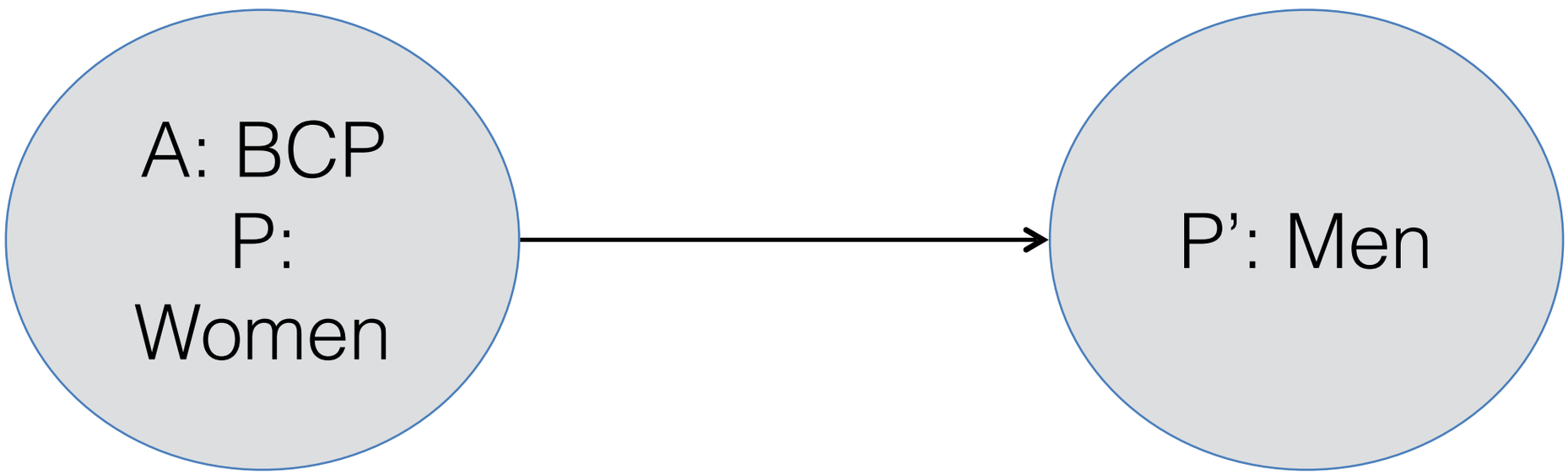
-whether parachutes prevent death from sky diving

-if smoking causes lung cancer

-whether socioeconomic status causes health

External validity

Goal of an RCT: test whether A works in population P, use A in some other population P’



Cost

- Sample size (each additional person costs money and also increases recruitment time)

- Data length

What do we need to know before we can use the results of an RCT?

- Study is internally valid
  - i.e. it can answer the question it aims to answer

- Factors affecting external validity
  - Characteristics of setting
  - Selection of patients
  - Characteristics of patients
  - Follow-up

- Control?

- Blinding – single, double, triple

See also: Rothwell, P. M. (2006). Factors that can affect the external validity of randomised controlled trials. PLoS Clin Trials, 1(1), e9.

Going from here to there

- Works somewhere: X caused Y in P
- Works in general: X causes Y
- Will work here: X causes Y in P’

Cartwright, N., & Hardie, J. (2012). Evidence-Based policy: A practical guide to doing it better. OUP US

Recall INUS

- Remember: cause is insufficient but necessary part of some unnecessary but sufficient condition
  - Full set contains all factors such that effect will be produced
  - Includes what we may think of as background conditions

- For external validity, need to know the background conditions
  - If oxygen necessary for cause to be effective, but oxygen is absent from the target case, then won't be effective

Cartwright's main point

- Cause doesn't happen in a vacuum – there are always necessary conditions for it to be effective (at a minimum, things that prevent it from being effective must be absent)

- To know that an intervention will work, we need to know a) what these conditions are and b) that they're present

Next few weeks

- 11/5: class cancelled
- 11/12: Journal club all day
- 11/19 Class
- 11/26 Papers due, round 1 presentations
- 12/3 Round 2 of presentations