

第十屆認知神經科學暑期學校

Experimental Designs

實驗設計之基本概念及實際應用

講師: 吳仕煒 助理教授
陽明大學神經科學研究所

Aims of the Lecture

- As a reminder of the fundamental ideas in conducting scientific research before you dive deep into the fancy techniques.
- As a review of basic knowledge of experimentation

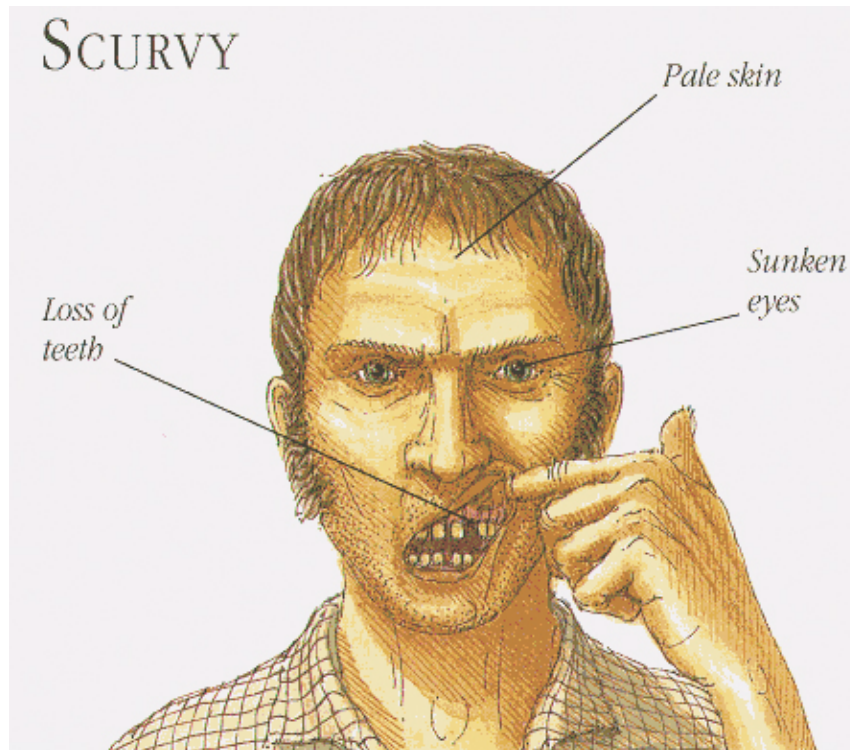
What is an **experiment**? Why do we need it?
Why bother to **design** it carefully?

壞血病（scurvy）曾經是長期航海的水手容易發生的疾病



(1932 才有第一次證據顯示和缺少 Vitamin C 有關)

What is an **experiment**? Why do we need it?
Why bother to **design** it carefully?



症狀：

皮膚蒼白、有血紅色斑點、
牙齦紅腫、無精打采

掉牙、傷口潰爛、黃疸、發
燒、精神異常、死亡

What is an **experiment**? Why do we need it?
Why bother to **design** it carefully?

George Anson 的遠洋航海旅程 (1740) :
1700 人，1400 死於壞血病



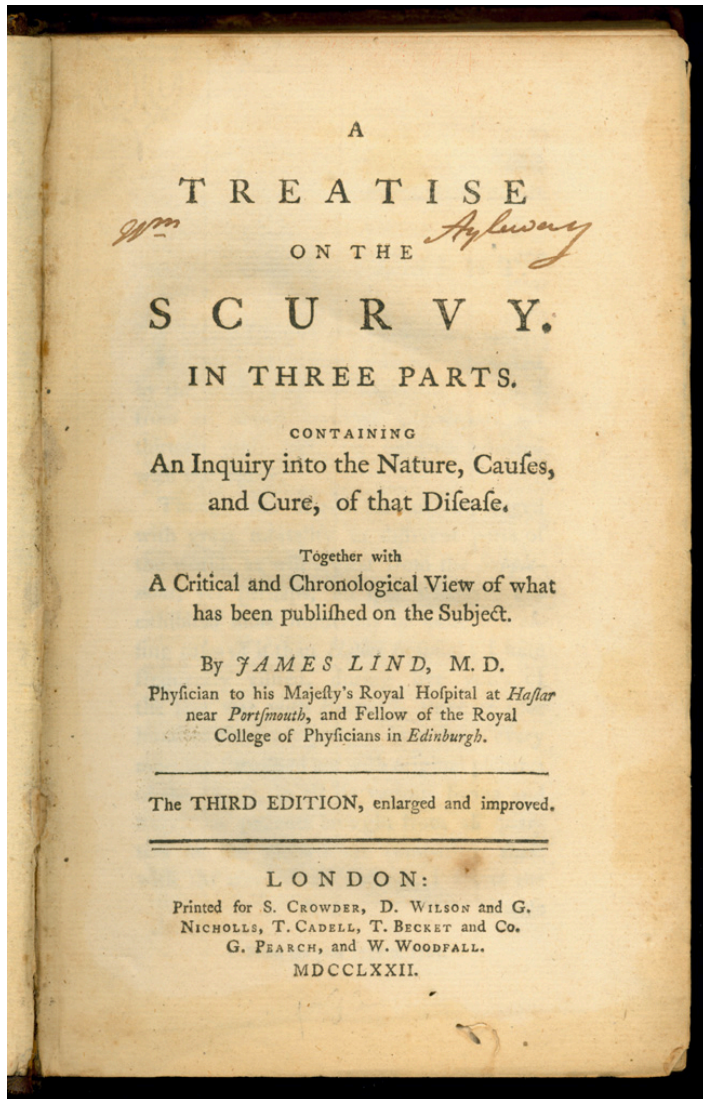
The first preclinical testing experiment (1747)



James Lind (1716-1794)

- 英國皇家艦隊的醫生
- 航海衛生研究先驅
- 進行第一個臨床前試驗 (preclinical trial): 研究壞血病的食療

The first preclinical testing experiment (1747)



將12個水手分派到六個治療組
(treatment group):

- (1) A quarter of cider (蘋果酒)
- (2) 25 drops of elixir of vitriol (硫酸藥劑)
- (3) 3 spoonfuls of vinegar (醋)
- (4) Half a pint of seawater
- (5) 2 oranges + 1 lemon
- (6) A spicy paste + a drink of barley water (薏米水, a British herbal tea)

The first preclinical testing experiment (1747)



將12個水手分派到六個治療組 (treatment group):

- (1) A quarter of cider (蘋果酒)
- (2) 25 drops of elixir of vitriol (硫酸藥劑)
- (3) 3 spoonfuls of vinegar (醋)
- (4) Half a pint of seawater
- (5) 2 oranges + 1 lemon**
- (6) A spicy paste + a drink of barley water (薏米水, a British herbal tea)

Treatment 5 六天後症狀明顯改善，水手可正常值勤

James Lind's experimental design

- 設計不同的治療組 (treatment) (實驗獨變項)
- 平均分派水手到各組 (每組人數相同)
(balanced assignment, though not random)
- 控制可能影響結果的變因 (control for possible confounding variables) :

“On the 20th of May 1747, I selected twelve patients in the scurvy, on board the Salisbury at sea. **Their cases were as similar as I could have them.** They all in general had putrid gums, the spots and lassitude, with weakness of the knees. They lay together in one place, being a proper apartment for the sick in the fore-hold; and **had one diet common to all**, viz. water gruel sweetened with sugar in the morning; fresh mutton-broth often times for dinner; at other times light puddings, boiled biscuit with sugar, etc., and for supper, barley and raisins, rice and currants, sago and wine or the like.”

實驗設計為其中一環

研究問題：What might be the effective treatment(s) for scurvy?

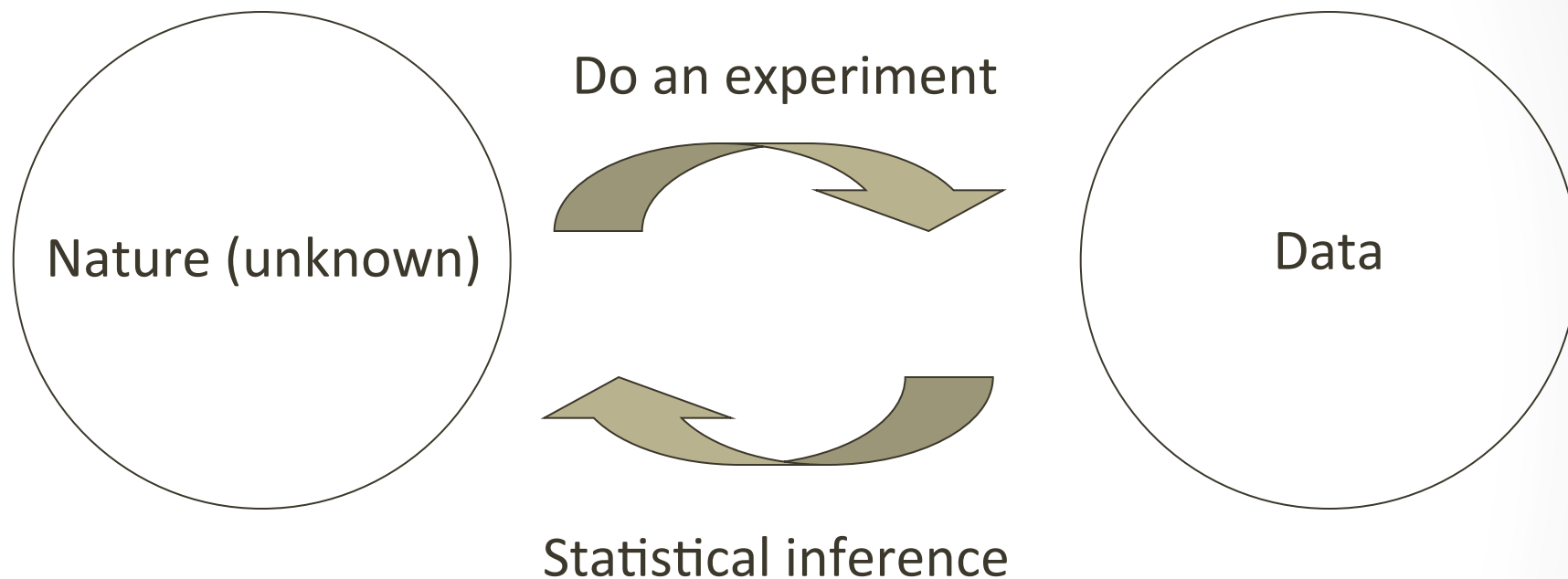
研究假設：If a treatment is effective, it would XXXX

實驗設計：6 treatments, each 2 subjects. Other confounding factors, e.g. daily diet, are controlled

資料收集、分析、解釋：Observing symptoms and providing descriptions on changes of symptoms

Every step in conducting a research project is important!

Scientific inquiry



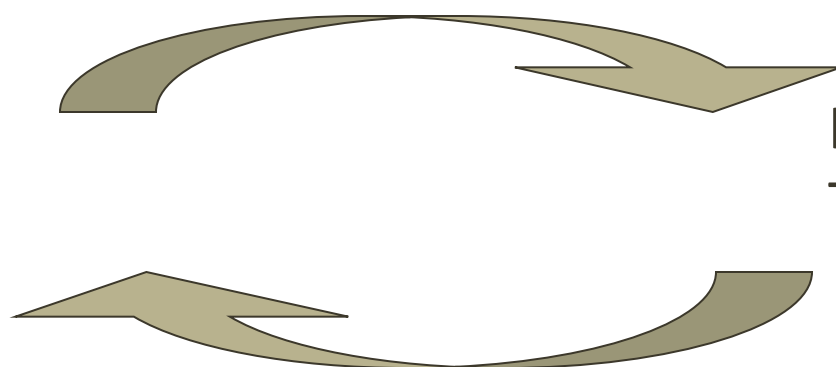
You wish to say something about the unknown nature based on the data you collected from an experiment

Example

Experiment: Flip the coin 10 times



$P(\text{Head})=?$



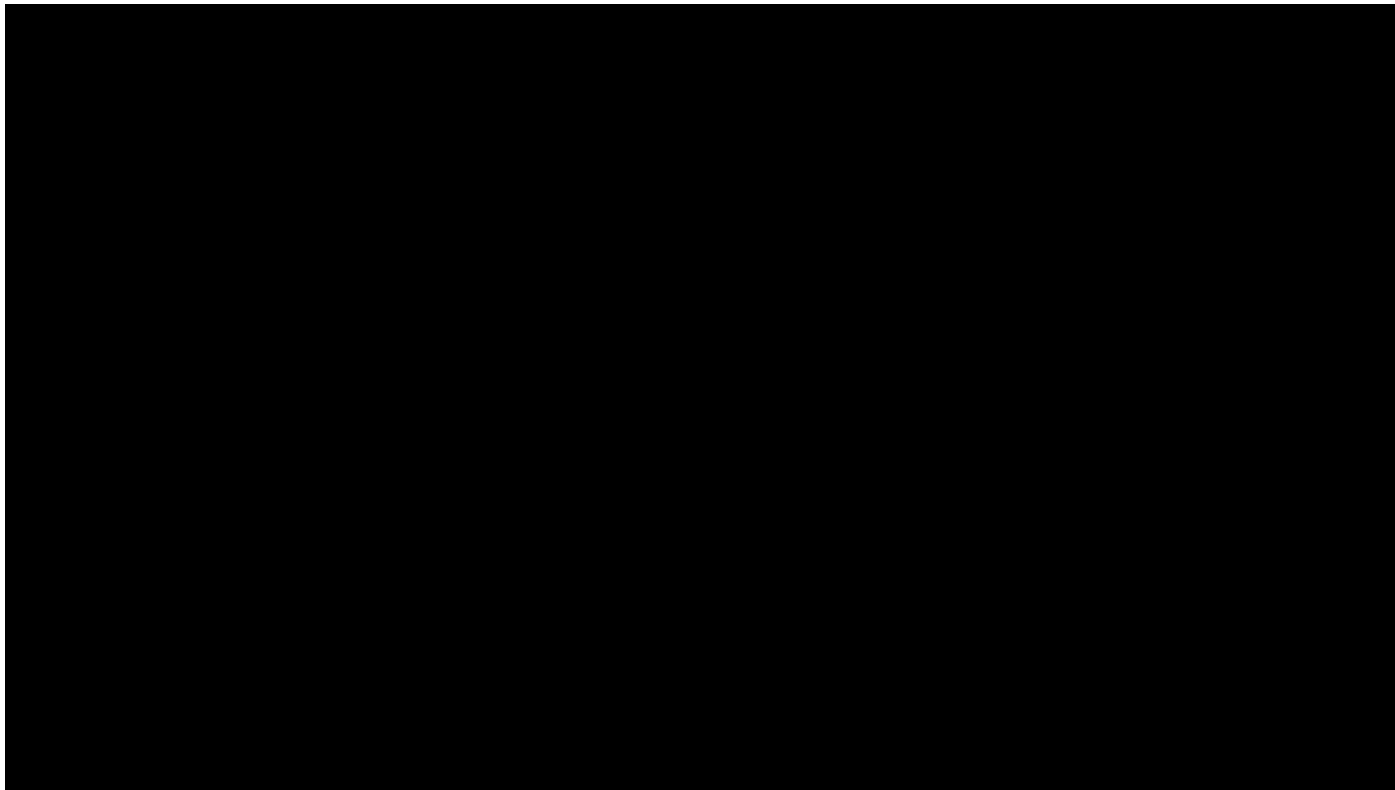
H,H,H,H,H,H,H,T,
T,H

Statistical inference

What can you say about the coin?

Example 2 (real story)

The lady testing tea experiment



Example 2 (real story)

The lady testing tea experiment

- How would you determine the order in which the cups are presented? **Randomization**
- How would you conclude that the lady is not making her judgment by chance?

Fisher's exact test

From behavior to the brain

Understanding behavior itself is complicated enough. Now we are trying to understand the brain and their linkage?



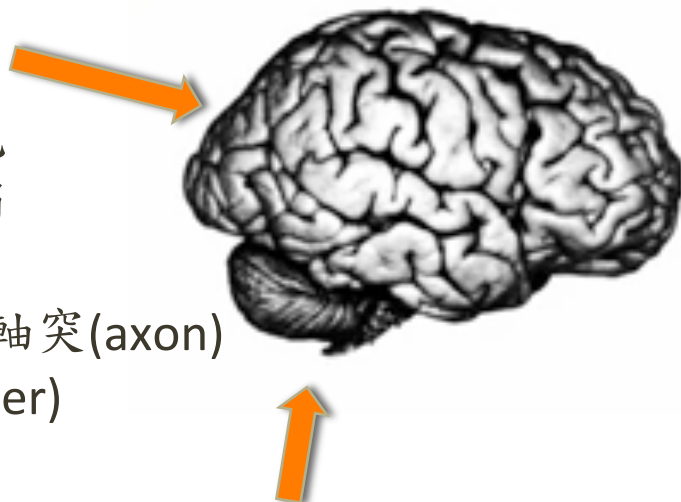
From behavior to the brain

Some facts about the brain

1.5 KG, ~900億神經原細胞

大腦皮質：

- 160億個神經元
- 150兆神經突觸 (synapse)
- 16萬公里長的軸突(axon) 於白質(white matter)



皮層下結構

- (subcortical structure)：
- 7 億個神經元

小腦：

- 690 億個神經元

Watch David Van Essen's talk: <https://www.youtube.com/watch?v=i2W570VgV6I>

The BRAIN initiative

- Brain Research through Advancing Innovative Neurotechnologies (透過新神經科學技術進行大腦研究)
- 為何需要？了解正常和疾病的腦，需要更完整的工具 (tools) 和訊息 (information)
- 為何在此時間點？過去十年中，了解大腦的功能和技術有重大進展：基因模組的序列、神經聯結地圖的技術、神經造影技術的演進、奈米科學的發展
- 我們仍需要發展新世代的工具，結合奈米科學、神經造影、工程科學、資訊學等，讓神經科學家能紀錄更多數量的神經元活動

The BRAIN initiative

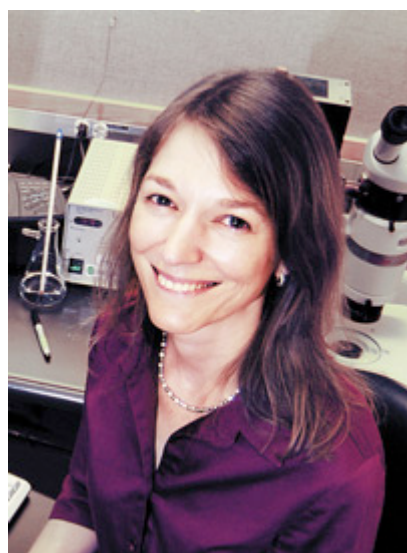
Goals

- 了解大腦活動如何型塑知覺 (perception)、決策 (decision making) 和行動 (action)
- 發展新造影技術、了解訊息如何在神經網路中被儲存及處理
- 對退化性疾病提供新知
- 從基因、神經迴路、到行為的層次，對大腦進行深入的研究及了解

The BRAIN initiative

➤ How will it work?

由 Cori Bargmann (Rockefeller University) 和 Bill Newsome (Stanford University) 等組成的 15 人諮詢小組，負責研擬科學目標和規劃多年期計畫



Cori Bargmann



Bill Newsome

<http://www.nih.gov/science/brain/>

If neuroimaging is the answer, what is the question?

S. M. Kosslyn

832 William James Hall, Harvard University, 33 Kirkland Street, Cambridge, MA 02138, USA (smk@wjh.harvard.edu)

“Attending a poster session at a recent meeting, I was reminded of the old adage ‘**To the man who has only a hammer, the whole world looks like a nail.**’ In this case, however, instead of a hammer we had a magnetic resonance imaging (MRI) machine and instead of nails we had a study. Many of the studies summarized in the posters did not seem to be designed to answer questions about the functioning of the brain; neither did they seem to bear on specific questions about the roles of particular brain regions. Rather, they could best be described as ‘exploratory’. People were asked to engage in some task while the activity in their brains was monitored, and this activity was then interpreted post hoc.”

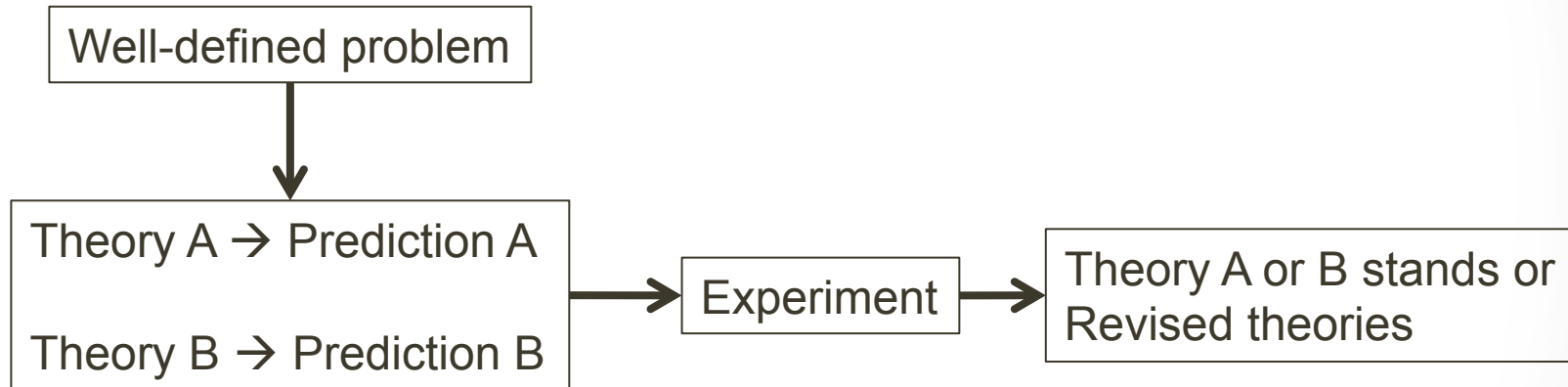
-- Stephen M. Kosslyn (1999). If neuroimaging is the answer, what is the question? *Phil Trans R Soc Lond B*, 354, 1283-1294.

Brains Needed (researcher's ...)

- "...the single most critical piece of equipment is still the researcher's own brain. All the equipment in the world will not help us if we do not know how to use it properly, which requires more than just knowing how to operate it. Aristotle would not necessarily have been more profound had he owned a laptop and known how to program. What is badly needed now, with all these scanners whirring away, is an understanding of exactly what we are observing, and seeing, and measuring, and wondering about."
- -- Endel Tulving, interview in *Cognitive Neuroscience* (2002, Gazzaniga , Ivry & Mangun, Eds., NY: Norton, p. 323)

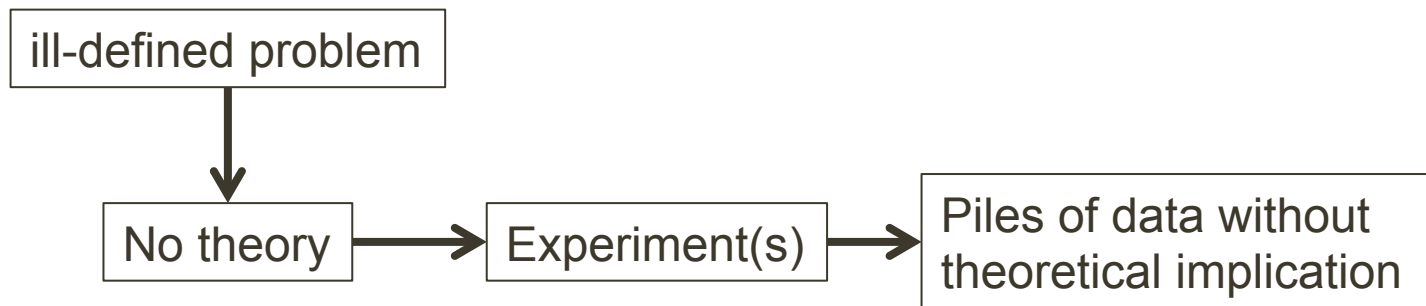
Ideally...

- An experiment should help the researcher determine the more appropriate theory for explaining the world:



In Reality...

- Let's try this and see what happens...



Outlines of this Lecture

- Fundamental concepts in scientific research
- Essential components of an experiment

- Design Issues
 - Between-subject
 - Within-subject

First Part

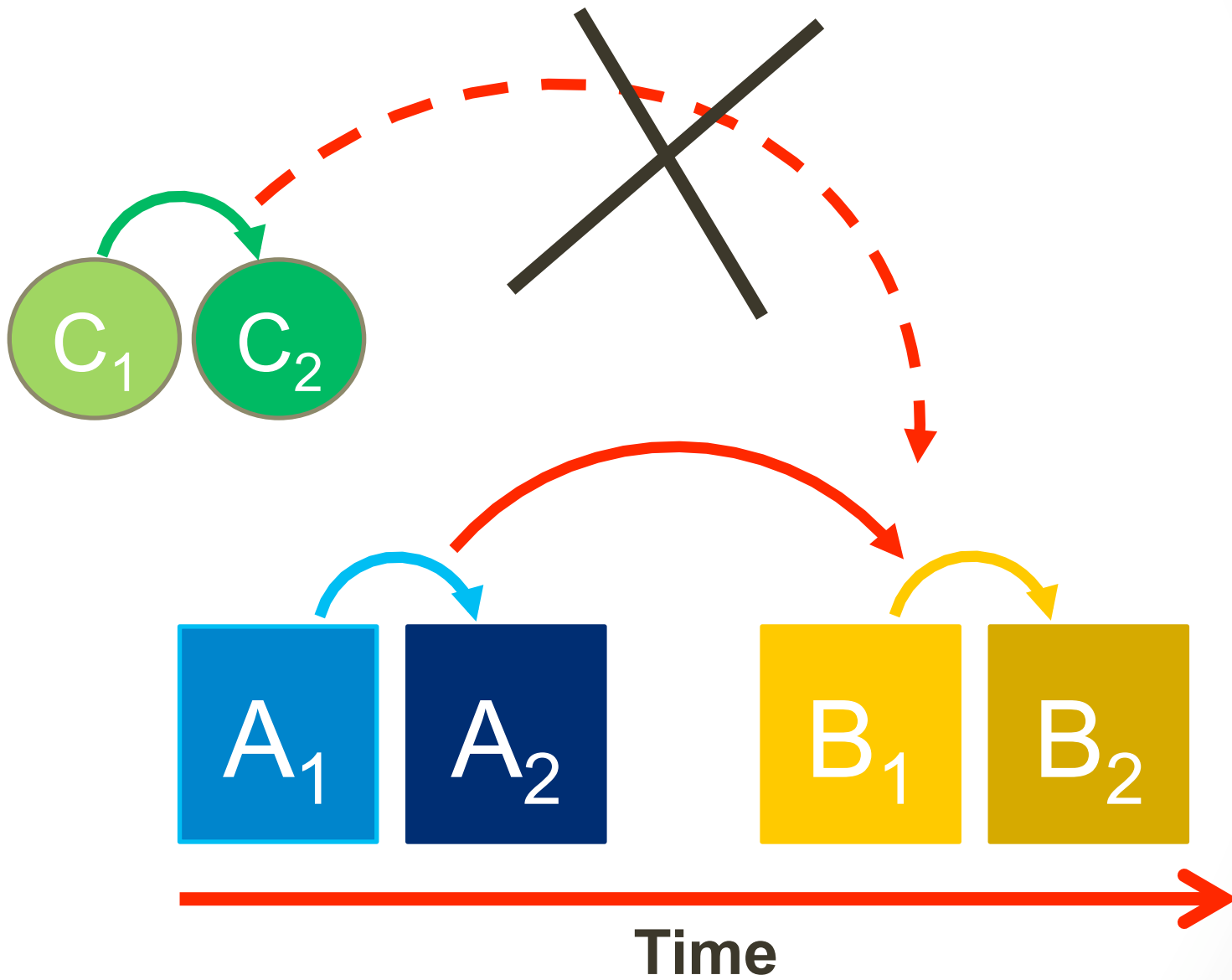
Second Part

Fundamental Concepts

- Causal (因果) vs. correlational (相關) relationships
- Validity (效度) and threats to it
 - Internal (內部)
 - External (外部)

Causal Relationship

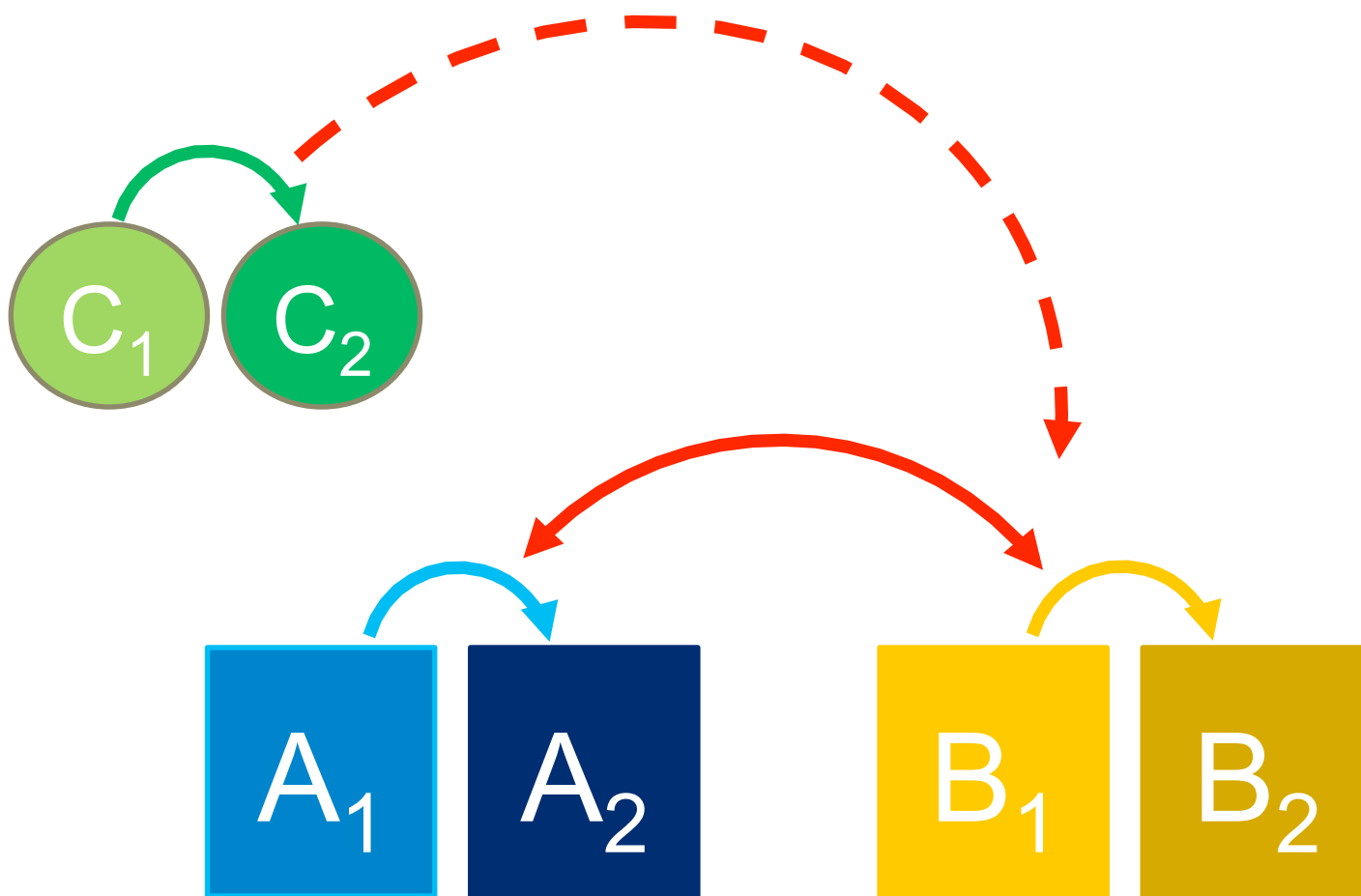
- Causality; causation
- When we say A causes B, basically we are saying that:
 - A and B co-vary
 - Changes in A precedes changes in B
 - There is no other explanation for changes in B except for changes in A



Examples of Causal Relationship

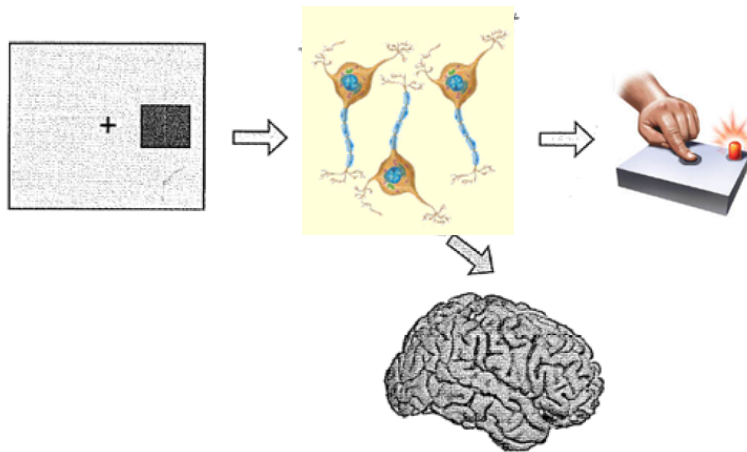
- 開冷氣 → 室內溫度降低
- 學會運用記憶術 → 提取長期記憶內容更有效率、更準確
- 臉的影像顛倒呈現 → 辨認身份的時間變長、正確率下降

Correlational Relationship

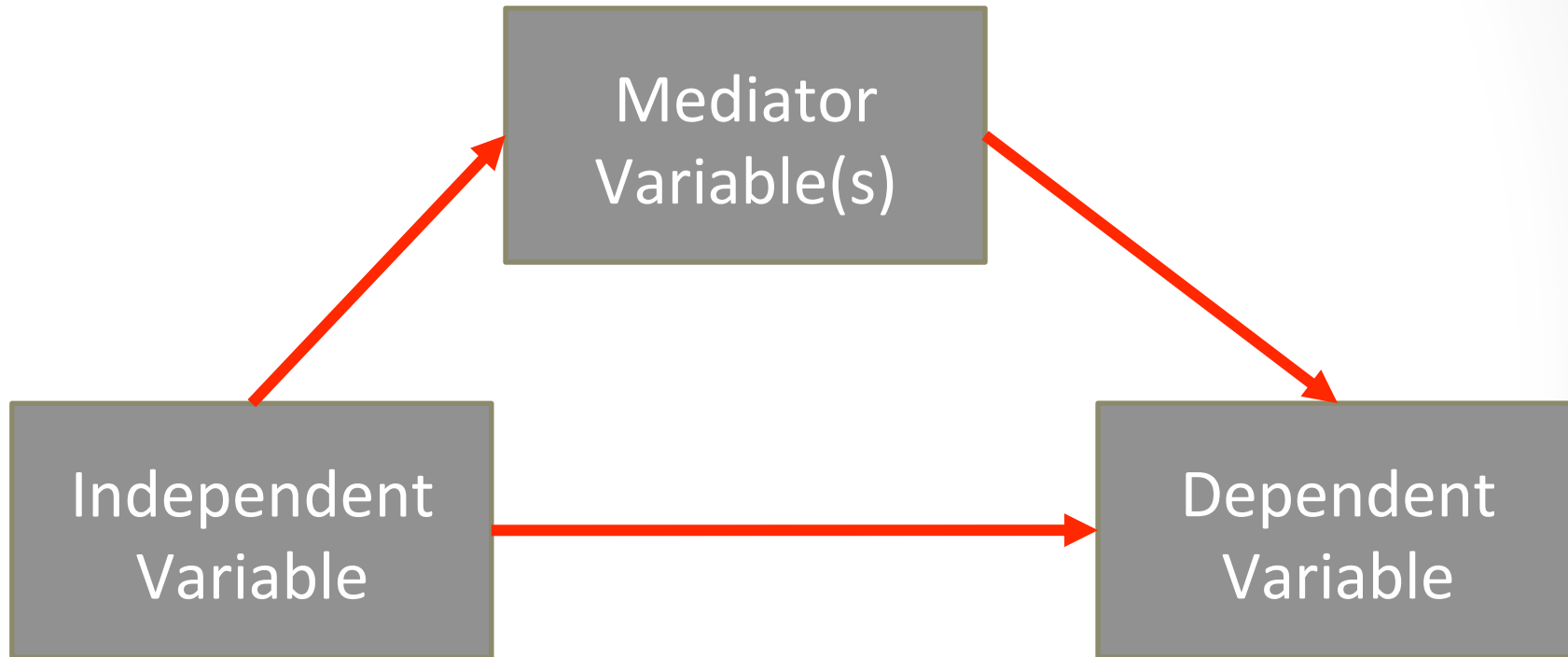


Examples of Correlational Relationship

- 月暈而風，礎潤而雨
(月亮周圍出現暈圈就要颶風，柱子下面的基石潮濕就要下雨)
- Brain activity in region XX is correlated with stimulus XX



Chain of Causal Inference



Internal Validity

- The confidence in the causal relationship
- Threats to internal validity
 - Confounding (混淆變項)
 - Selection bias (選取偏誤)
 - History (與實驗無關的事件)
 - Maturation (受試者在實驗過程中成熟度改變)
 - Repeated testing (重複施測)
 - Instrument change (測量工具改變)
 - Regression toward the mean (回歸到平均值)
 - Mortality/differential attrition (死亡)
 - Experimenter bias (實驗者偏誤) (double-blind design can correct)

Example of Confounding: “Clever” Hans

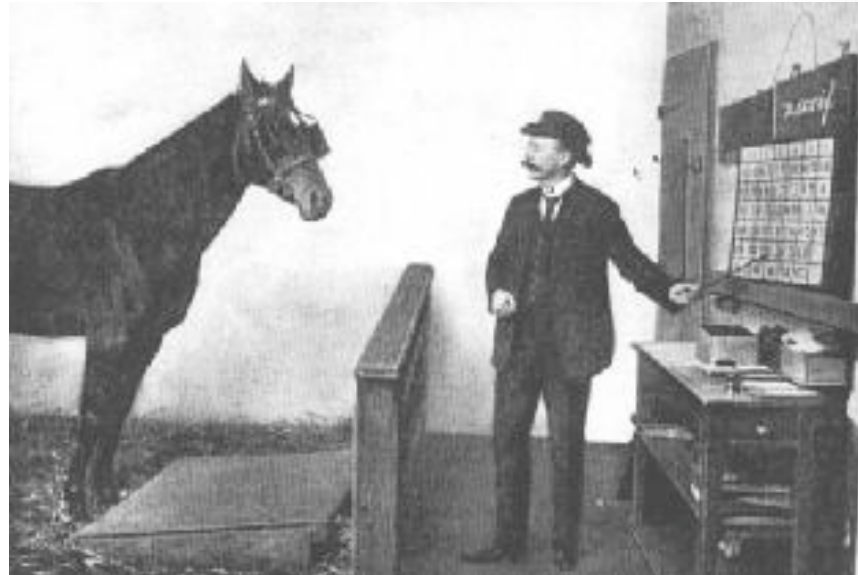
“CLEVER HANS” AGAIN.

Expert Commission Decides That the Horse Actually Reasons.

From The London Standard.

BERLIN, Sept. 13.—The remarkable horse called “Clever Hans” has just been examined by a special commission of experts, in order that a decision might be arrived at whether it is a horse possessed of extraordinary brain power or merely, like many others of its tribe, peculiarly adapted to learning tricks from patient trainers. The commission consisted of the well-known circus proprietor, Herr Paul Busch; Count Otto zu Castell Ruedenhausen, a retired army-Captain; Dr. Grabow, a retired schoolmaster; Dr. Ludwig Heck, Director of the Berlin Zoological Gardens; Major von Keller, Major-Gen. Koering, Dr. Miessner, a veterinary surgeon; Prof. Nagel of the Physiological Institute of the University of Berlin, and several other prominent men.

The commission has issued a statement declaring that it is of opinion that there is no trickery whatever in the performances of the horse, and that the methods employed by the owner, Herr von Osten, in teaching Hans differ essentially from those used by trainers, and correspond with those used in teaching children in elementary schools. They hold that the methods employed have in principle nothing whatever to do with “training” in the accepted sense of the word, and are worthy of scientific examination. The report of these gentlemen is interesting, for Herr von Osten had tried in vain to persuade scientific men to take the case of “Clever Hans” seriously. Herr Busch, of circus fame, who was one of the commission, had openly admitted beforehand that he was extremely skeptical about the matter, and believed that



- Can perform simple arithmetic with close to 90% accuracy

Clever Hans Effect: Observer Expectancy

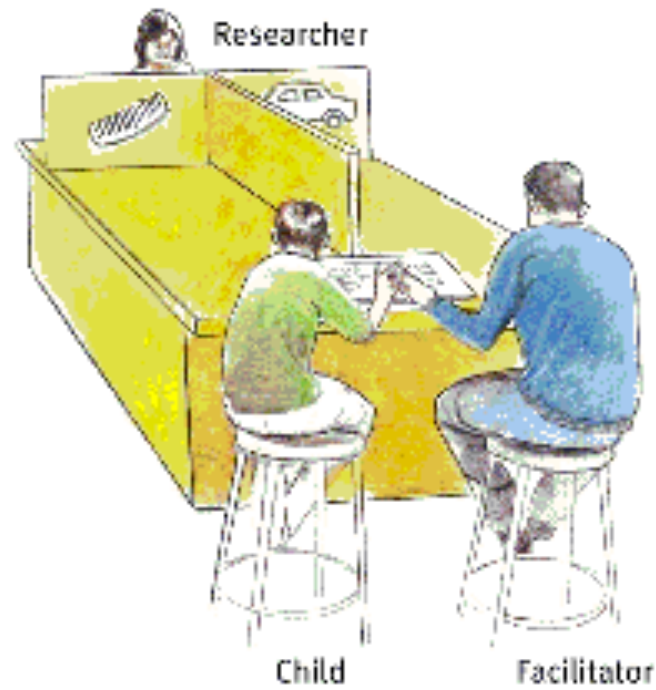
When Hans is clever



When Hans is not clever



Modern Hans: Facilitated Communication



Source: <http://home.vicnet.net.au/~dealcc/TcpBnet.htm>

Source: <http://www.psychologymatters.org/facilitated.html>

Essential Components in An Experiment

- 實驗是科學方法中仲裁相互競爭之模型或假設的關鍵步驟
(Experiment is the step in the scientific method that arbitrates between competing models or hypotheses)
- Components of an experiment
 - 依變項 (Dependent variable)
 - 獨變項 (Independent variable)
 - 操弄、隨機化、選擇 (Manipulation/randomization/
selection)

Dependent Variables

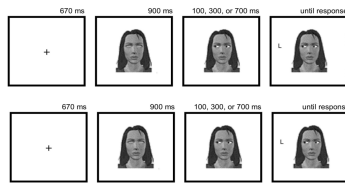
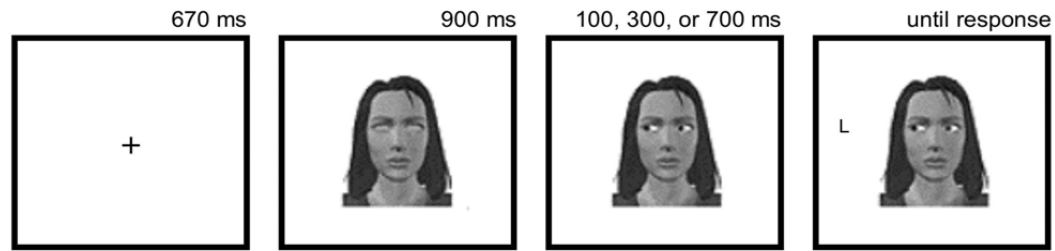
- 行為量測 (Behavioral measures)
 - Reaction time, error rate, d' , spatial errors
- 生理量測 (Physiological measures)
 - Heart rate, blood pressure, respiration rate, cortisol level
 - BOLD signal, EEG, EPR, MEG

Jargons in An Experiment

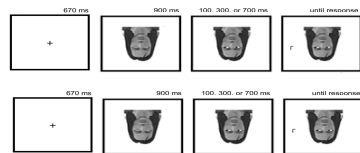
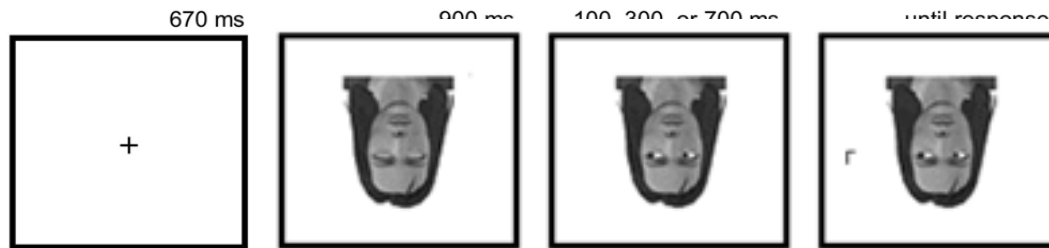
- 事件 (Event)
- 嘗試次 (Trial)
- Block
- Condition
- Session

A Trial

Event



Condition 1



Condition 2

<u>Block #1</u>	<u>Block #2</u>		<u>Block #5</u>
Trial #1	Trial #21		Trial #91
Trial #2	Trial #22		Trial #92
Trial #3	Trial #23	Trial #93
Trial #4	Trial #24		Trial #94
Trial #5	Trial #25		Trial #95
.....
Trial #20	Trial #40		Trial #100



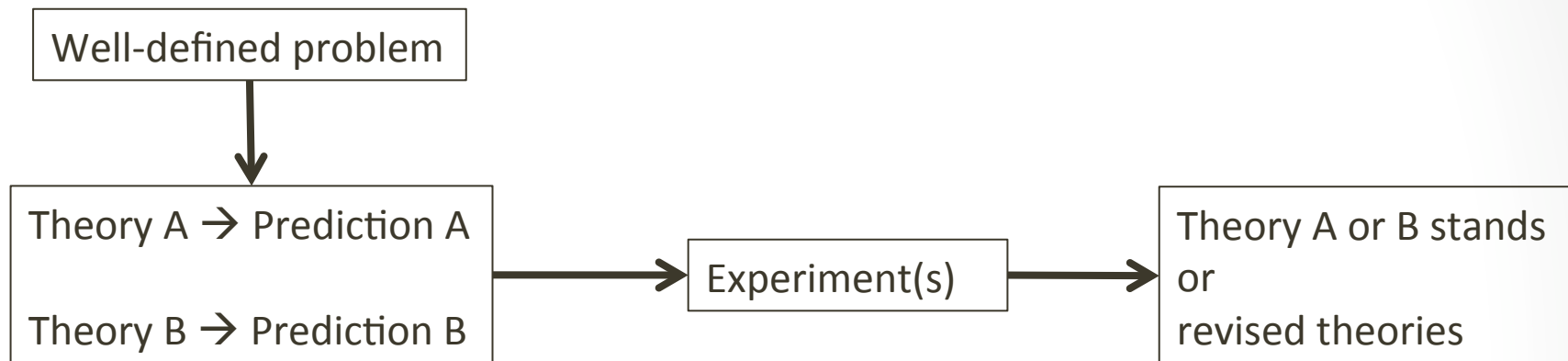
Session



Why Conducting an Experiment?

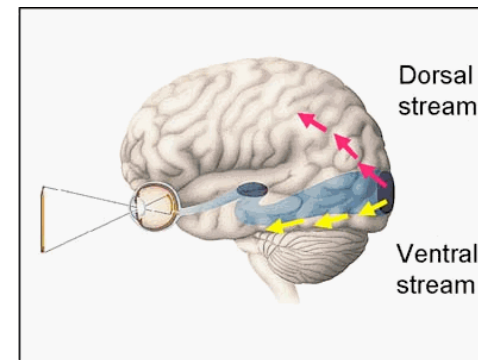
- Theoretically oriented
 - To test competing hypotheses
- Data-driven
 - To explore effect of a treatment

Theoretically Driven



- Division of labor in the visual system

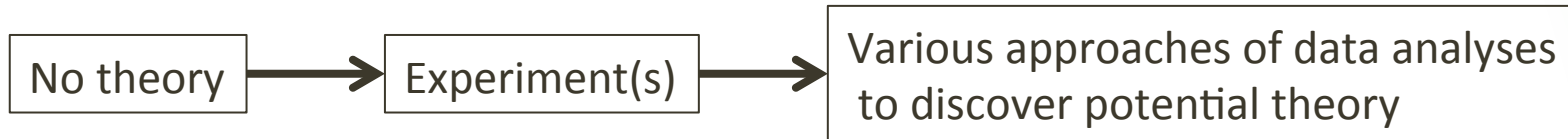
- Dorsal stream for action
- Ventral stream for perception



- Predictions

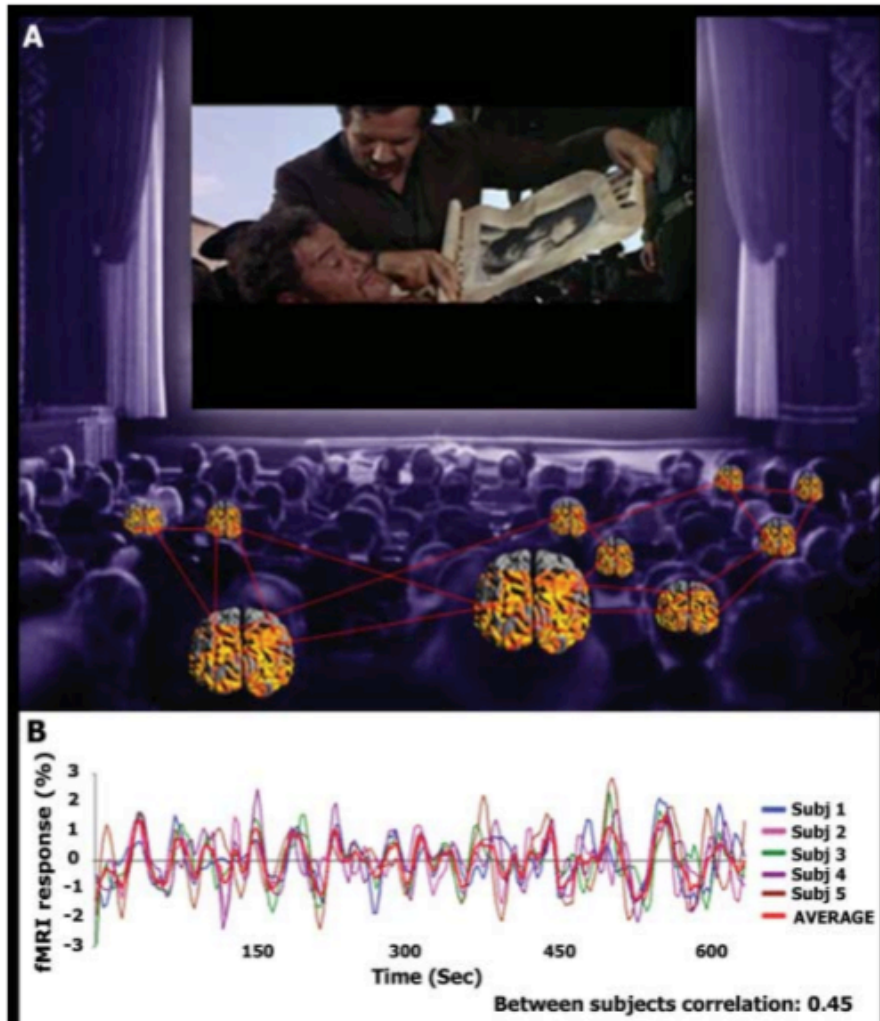
- Motor tasks lead to activation in the dorsal stream
- Perceptual tasks lead to activation in the ventral stream

Data-driven



- 禪修提升注意力表現
- 注意力相關作業
 - 空間注意力移動速度
 - 視覺搜尋
 - 抑制迴轉效應
 - 持續注意力

Data-driven approach: Neurocinematics



- Intersubject correlation (ISC) in brain activity can serve as a measure of the level of a control a film exerts to its audience
- Hitchcock's movie showed highest ISC (compared with some other films)

Questions to Ponder **BEFORE** You Start ...

- What do you hope to find?
- What would that tell you about the cognitive process involved?
- Would it add anything to what is already known from other techniques?
- Could the same question be asked more easily & cheaply with other techniques?

[Source: http://psychology.uwo.ca/fmri4newbies/Tutorials.html](http://psychology.uwo.ca/fmri4newbies/Tutorials.html)

Questions to Ponder **BEFORE** You Start...

- What would be the alternative outcomes (and/or null hypothesis)?
- Or is there not really any plausible alternative?
- If the alternative outcome occurred, would the study still be interesting?
- If the alternative outcome is not interesting, is the hoped-for outcome likely enough to justify the attempt?

Questions to Ponder **BEFORE** You Start... III

- What would the “headline” be if it worked? Is it sexy enough to warrant the time, funding and effort?
- What are the possible confounds? Can you control for those confounds?
- **Has the experiment already been done? “An hour on PubMed can save you a year of research!”**

Source: <http://psychology.uwo.ca/fmri4newbies/Tutorials.html>

Experimental Designs

- Between-subject designs
 - Independent group
 - Matched group
 - Natural group
- Within-subject designs

Between-subject Designs



Independent Groups Designs

- Subject assignment
 - Different group of subjects are assigned to different conditions as defined by the independent variable.
(實驗中每一組均是由不同受試者組成)
- Balancing confounding factors 平衡組間混淆因素
 - Intelligence
 - Motivation
 - Conscientiousness
 - Gender
 - Major in school

Independent-groups Design

Group 1: 60



Group 2: 90



One Group Study

服藥前

發燒、
咳嗽、
流鼻水

服藥



服藥後

症狀消失

Experimental vs. Control

服藥前

服藥

服藥後

實驗組

發燒、
咳嗽、
流鼻水



症狀
消失

對照組
(控制組)

發燒、
咳嗽、
流鼻水

多休息喝水

症狀
消失

Independent Groups Designs

- Random groups design

- Matched groups design

受試者依某變項（此變項與依變項關聯性甚高）的表現被分組。表現相似的受試者會隨機被分派到不同組（所以確定這個可能影響結果的變項被控制）

- Natural groups design

Random Groups Design

- All respect being comparable among groups but only the treatment received differs
- Comparable group formed by random assignment

Random Assignment

- Achieved by any procedure that assigns units to conditions based only chance
 - Ex. Tossing coins or dices
- Has different purpose from random sampling



Block Randomization

- All conditions are randomized within a block, and there are as many blocks as the sample size of each condition.

Block Randomization

10 Blocks	Participants	Condition	
1. CAEBD	Cara	C	} 1 st Block
2. ECDAB	Andy	A	
3. DBEAC	Jacob	E	
4. BACED	Molly	B	
5. ACEDB	Emily	D	
6. ADEBC	Erik	E	} 2 nd Block
7. BCADE	Anna	C	
8. DCAEB	Laura	D	
9. EDBCA	Sarah	A	
10. CEBDA	Lisa	B	
	Tom	D	

Threats to Internal Validity

- **Intact groups** are used
- **Extraneous variables** are not controlled
- **Selective subject loss** occurs
- **Demand characteristics and experimenter effects** are not controlled.

Intact Groups

- Noncomparable groups formed beyond the experimenter's control.
- Solution
 - Don't test them.
 - Divide testing time into several blocks.
 - Assign participants in the same group to different conditions (when viable).

Extraneous Variables

- Inconstant factors that are not interesting but confound the effect of IVs.
- Examples
 - Multiple experimenters
 - Time in a semester (Evans & Donnerstein, 1974)
 - Don't test participants in the experimental condition early in the term, and don't test participants in the control condition late in the term. WHY?
- Solution
 - Block randomization

Demand Characteristics and Experimenter Effects

- Demand characteristics
 - Cues and other information that participants use to guide their behavior
 - Novelty effects
 - Innovations elicit excitement and motivation
 - Hawthorne effect: changes in behavior because of the awareness of being observed
- Experimenters effects
 - Different treatments
 - Biased observations

Placebo Control and Double-blind Procedure

- Placebo ("I shall please")
 - Inactive substance “thought” to be therapeutic
- Double-blind
 - Both the participant and the observer are blind to which treatment is given

Matched Group Design

- Special populations



- Typically, comparable groups are formed according to a pretest task (matching task).

Matching Participants: *Example*

TABLE 1. Mean (\pm SD) demographic and neuropsychological characteristics of the young and older adult samples

	Young adults ($N = 20$)	Older adults ($N = 20$)
Age	23.1 (2.8)	71.0 (6.9)
Years of Education	15.6 (1.6)	15.7 (2.0)
Laterality [‡]	81.4 (21.4)	88.4 (19.4)
mMMS [§]	55.5 (1.2)	54.2 (1.7)*
Digits Forward	7.3 (0.8)	6.9 (1.4)
Digits Backward	5.1 (0.9)	5.5 (1.1)
VIQ	117.2 (10.8)	125.3 (11.9)*
PIQ	118.8 (12.8)	115.9 (22.9)
Dementia ¹	NA	0.0 (0.0)
Depression ¹	NA	1.88 (1.8)
ADL ¹	NA	0.53 (1.2)

* $p < .03$ or less.

Friedman et al. (2008). Aging, Neuropsychology, and Cognition.

Matching Task

- Best matching task
 - The experimental task itself. That is, matching the significant dimensions.
 - But you might not want to spoil the participants
 - Alternatively, use tasks highly correlated with experimental task as the pretest.

Natural Group Design

- Individual-difference variables are selected rather than manipulated
 - Religion, gender, personality, race, age
- Correlational
 - One can use the results for description and prediction, but not for causal inference
- Which essential component in causal relationship is lacking?

Example

- Divorced people are more likely than married people to receive psychiatric care.
- Problem of temporal order
 - Which precedes which?
- Problem of eliminating alternative accounts
 - Two groups may differ in many other aspects, such as religion practices or financial status.

Example

- Females and males differ in throwing accuracy → Gender difference in motor control
 - Is it a real gender difference, or do social-cultural factors shape the motor ability?



Within-subject Designs



Within-Subject Design

- Subjects participate in both the experimental and control conditions, and thus serve as their own control

Within-subjects Design

Test 1: 60



Test 2: 90



Advantages

- Fewer participants
- More efficient
- Higher sensitivity
- Suitable for studying changes in behavior over time
- No worry of confounding by individual differences variables

When you have no choice

- If trials are very short (e.g., reaction time)
 - Collecting huge amount of data in a short period of time
- Participants are difficult to recruit (e.g., brain surgeons, serial murderers)
- Subjective comparison of different levels along a physical dimension
- **When one adopts neuroimaging or neurophysiological measures, and the aim is not to study subject variables**

Practice Effects or Progressive Errors

- Participants can change due to repeated performance of the task
 - Improvement → Practice effects
 - Fatigue or boredom → Progressive errors

Subject Loss

- Mechanical subject loss
 - Computer crashes
 - Wrong instruction
 - Interruption
- Selective subject loss
 - Differential loss across different conditions
 - Due to some subject's characteristics
 - This characteristic is related to the DV

Procedure to Overcome Practice Effects

- Practice effects must be *balanced*, or averaged, across the conditions of the experiment.
- Counterbalancing the order of the conditions makes sure that the practice effects are distributed equally across the conditions of the experiment.

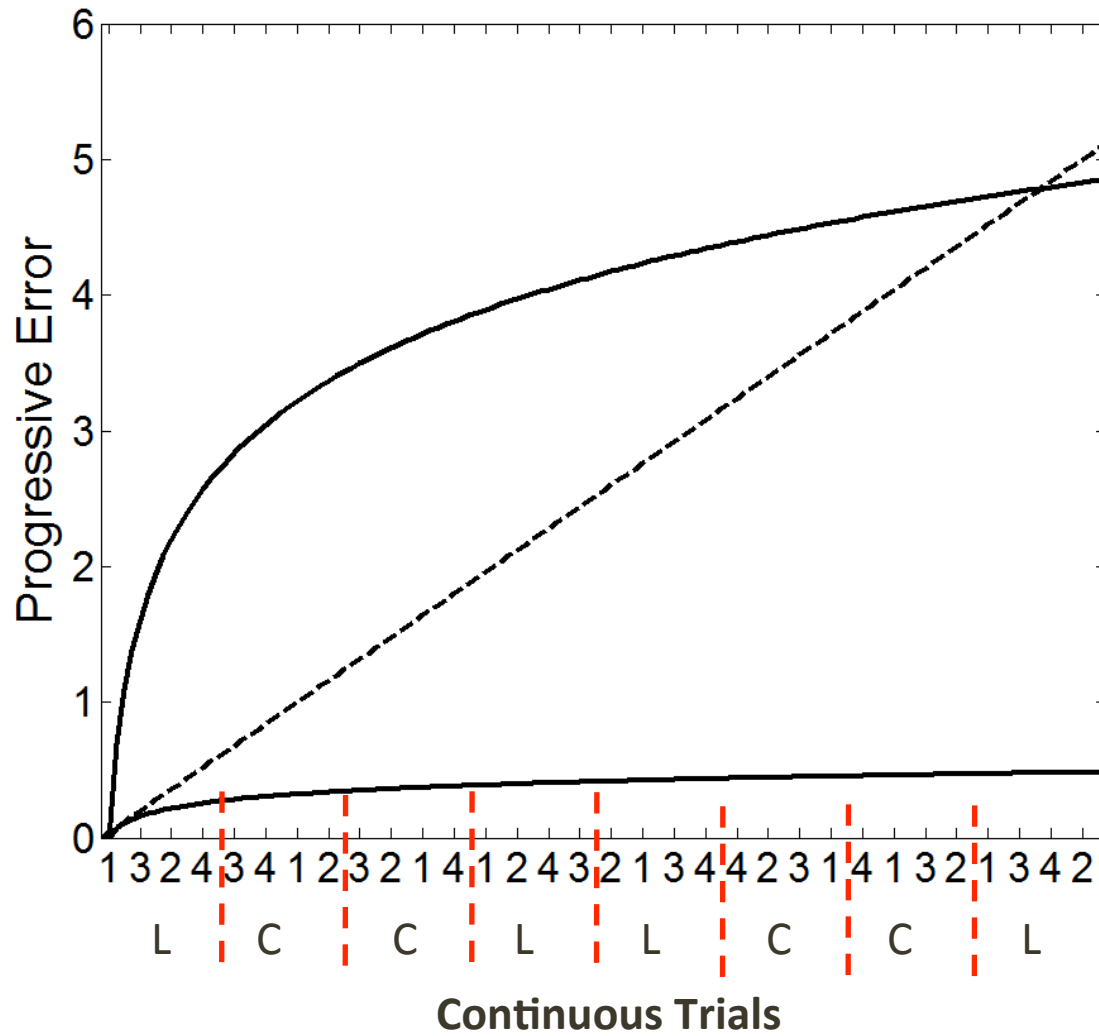
Procedures for Balancing Practice/Ordinal Effects

- Complete
 - Block randomization
 - ABBA counter balancing
- Incomplete
 - All possible order
 - Selected order
 - Latin square
 - Random starting order with rotation

Complete Design: ABBA Counter Balancing

- Presenting conditions in one sequence followed by the opposite of that sequence
 - Advantage: ease of usage → don't have to switch instructions or equipments very often
- Only appropriate when the practice effect is linear
- Also problematic when there is possibility of anticipation.

Example: Combining All Possible Order and ABBA



Incomplete Design: All Possible Orders

- Use all possible orders of the conditions
- ABC, ACB, BAC, BCA, CAB, CBA (N!)
 - 4 conditions: 24
 - 5 conditions: 120
 - 6 conditions: 720

Incomplete Design: Latin Square

- An $n \times n$ table filled with n different symbols in such a way that each symbol occurs exactly once in each row and exactly once in each column



Leonhard Paul Euler
1707-1783

1 2 4 3
2 3 1 4
3 4 2 1
4 1 3 2

A B D C
B C A D
C D B A
D A C B

Rules for Generating Latin Square

- Randomly order the conditions of the experiment (e.g., ABCD).
- Number the conditions in your random order (e.g., A = 1, B = 2, C = 3, D = 4).
- To generate the first order of conditions, use the rule:
 - 1, 2, N, 3, N - 1, 4, N - 2, 5, N - 3, 6, etc.

Generating Latin Square: Four Conditions

- 1, 2, N, 3, N - 1, 4, N - 2, 5, N - 3, 6, etc.
- For the four conditions in the example, the order would be

1 2 4 3	A B D C
2 3 1 4	B C A D
3 4 2 1	C D B A
4 1 3 2	D A C B

Incomplete Design: Random Starting Order with Rotation

- Generate a random order of the conditions (e.g., ABCD), and then rotate the sequence by moving each condition one position to the left each time.

<u>1st</u>	<u>2nd</u>	<u>3rd</u>	<u>4th</u>
A	B	C	D
B	C	D	A
C	D	A	B
D	A	B	C

- Note that each condition appears in each ordinal position to counterbalance practice effects across the conditions of the experiment. Unlike the Latin Square, however, the order of the conditions is not balanced.

When Within-Subject Design Is Not Appropriate

- Instructional variable
 - Response strategies in one condition might influence another
- Irreversible manipulation
 - Learning (unless you are interested in studying dynamics)
- Subject variables
 - Age, gender, ...

Differential Transfer (Carry-over Effect)

- The effects of one condition persist and affect participants' experiences during subsequent conditions.
- When this is possible, use an independent groups design.
 - Unless the differential transfer itself is the focus of investigation
- How to discover differential transfer?

Differential Transfer

- Three conditions: A, B, C
 - Complete Balance
 - $A \rightarrow B \rightarrow C \rightarrow B \rightarrow A$
 - 1 2
 - Incomplete Balance
 - Sequence 1. $A \rightarrow B \rightarrow C$
 - Sequence 2. $C \rightarrow B \rightarrow A$
- Performance of B differs between Sequence 1 & 2

Examining Differential Transfer

- Average across lists with different order but at the same practice stage
- In an incomplete counterbalance design, compare conditions from the first serial position
 - Virtually independent groups design here

A B D C
B C A D
C D B A
D A C B

Franciscus Cornelis Donders (1818~1889)

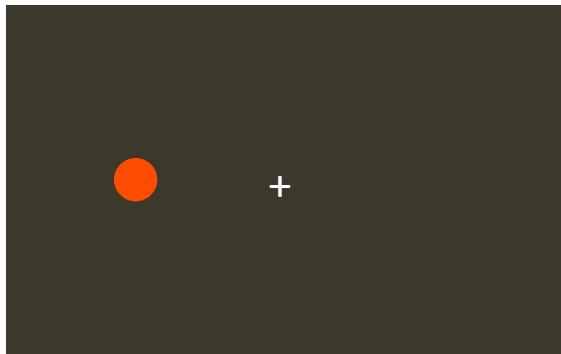


- Mental chronometry (Reaction time)
- Subtraction method (1868)

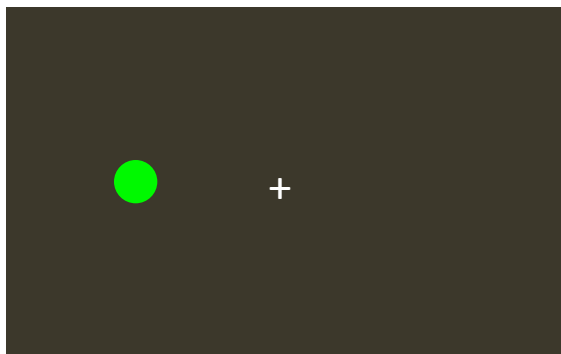
Source: <http://en.wikipedia.org/wiki/Donders>

Tasks with Different Number of Processing Stages

Stimulus



OR



A. Simple RT

Respond to ANY target



B. Discrimination RT

Respond to the **RED** target



C. Choice RT

Response A to the **RED** target, B to the **GREEN** target

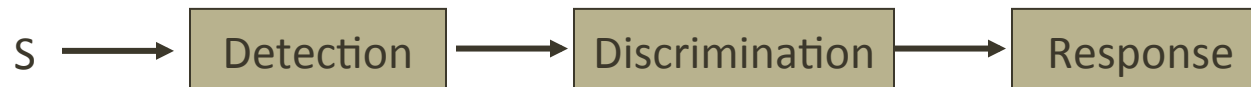


Processing Stages

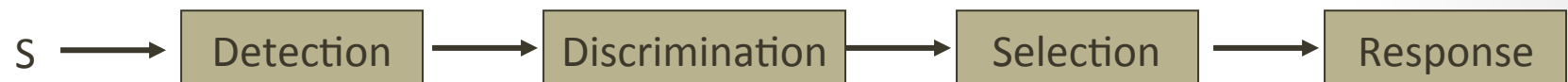
- Simple RT (Detection RT)



- Discrimination RT (Go/No Go RT)

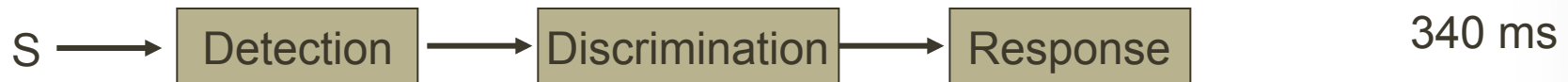


- Choice RT



Processing Duration of Each Stage

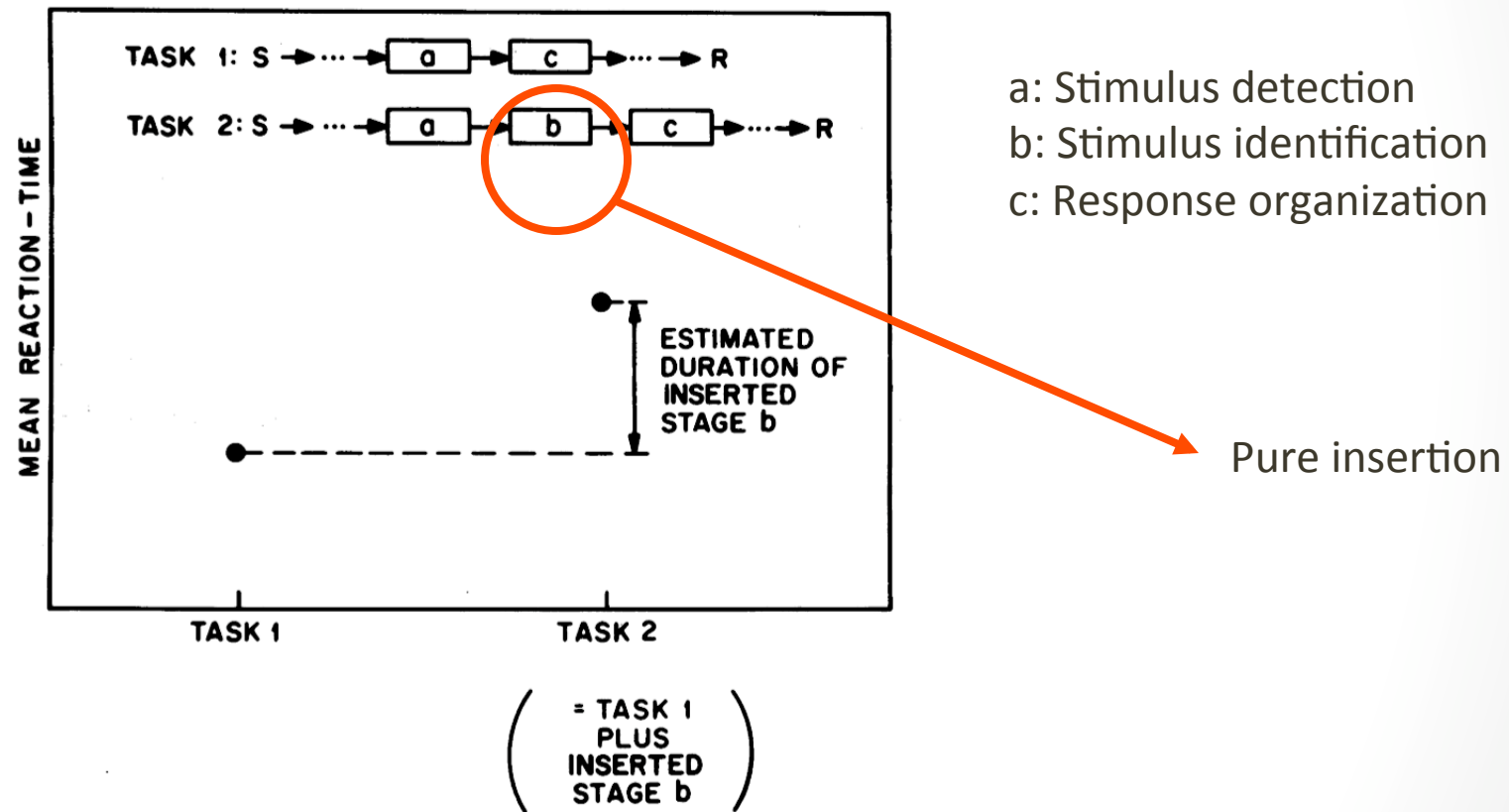
- Discrimination Time = 120 ms



- Response Selection = 70 ms



The Logic of Donders' Subtraction Method



Source: Sternberg, S. (1969). Memory-scanning: Mental processes revealed by reaction-time experiments. American Scientist, 57, 421-457.

Comparison of Experimental Designs

- Advantages/Disadvantages
- Possible ways to overcome disadvantages

Advantages

- Between-subjects design
 - Participants in each condition are naïve as to purpose of the study
 - No order effects
- Within-subject design
 - Fewer participants
 - Equivalent sample in each condition

Possible Ways to Overcome Disadvantage

- Between-subjects design
 - Increase sample size
 - Random assignment to groups
- Within-subject design
 - Counterbalance or randomize order of conditions