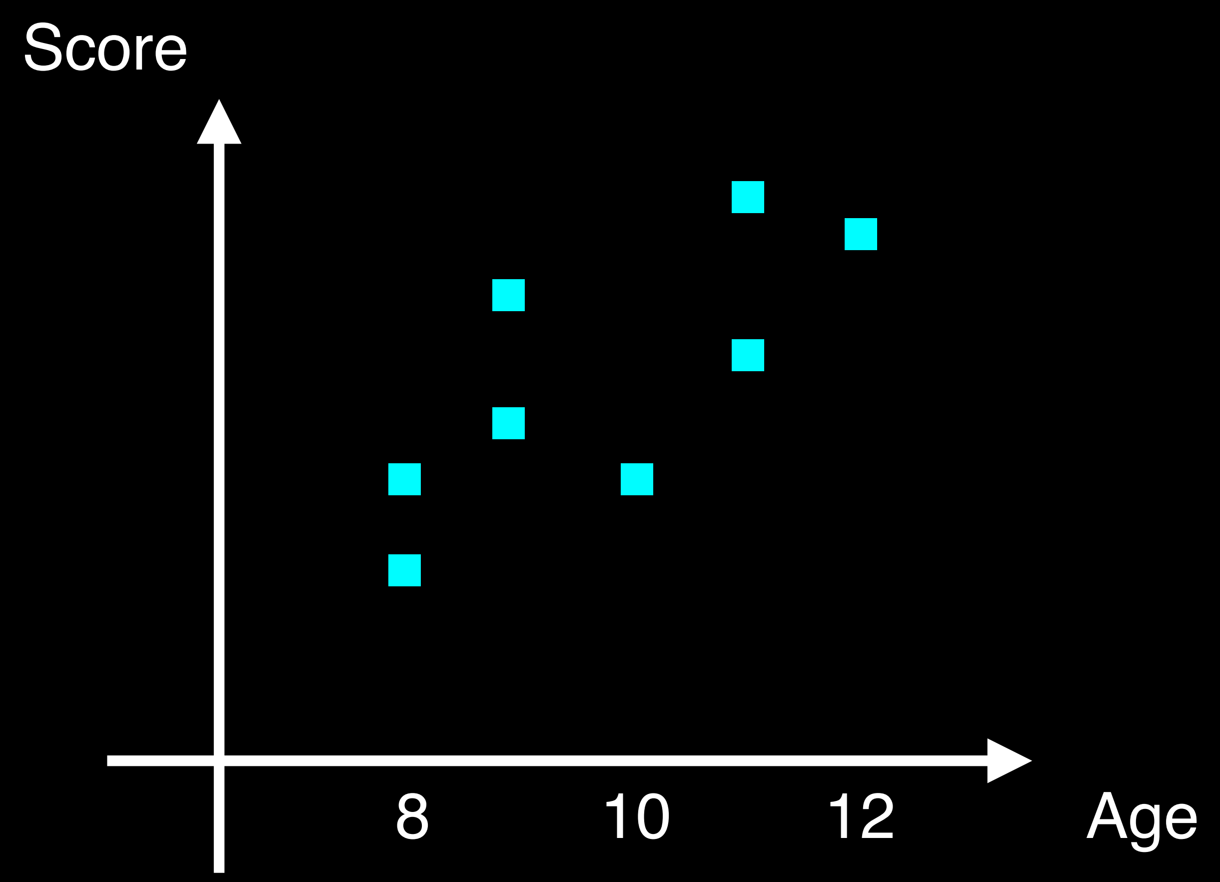
Mixed Model

Scenario

- Neuropsychological test score among children (8-12yrs old)
- Want to understand the trajectory of score improvement over time

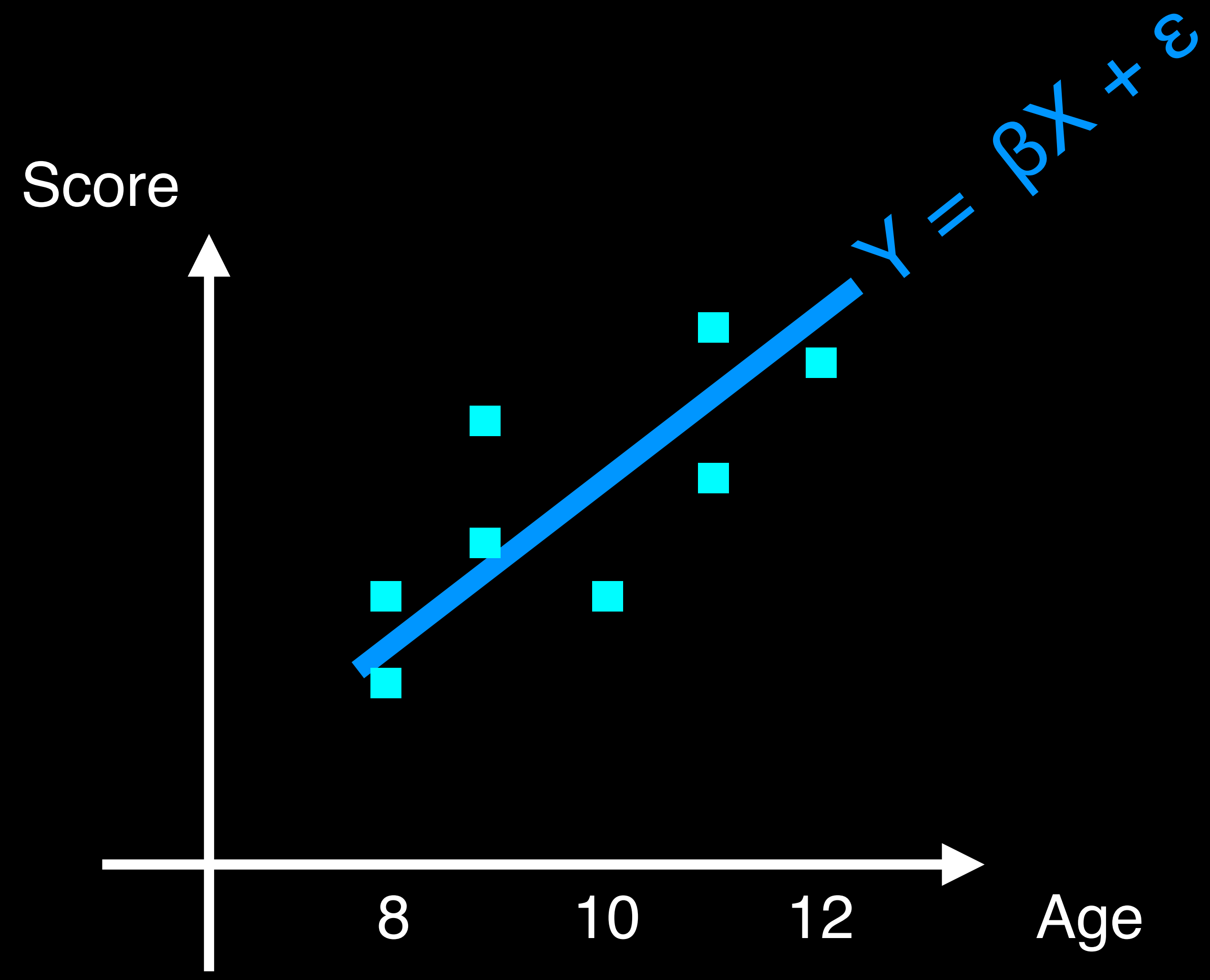
Cross-Sectional Study

- One observation per subject



Cross-Sectional Study

- One observation per subject



* No intercept for simplicity

Cross-Sectional Study

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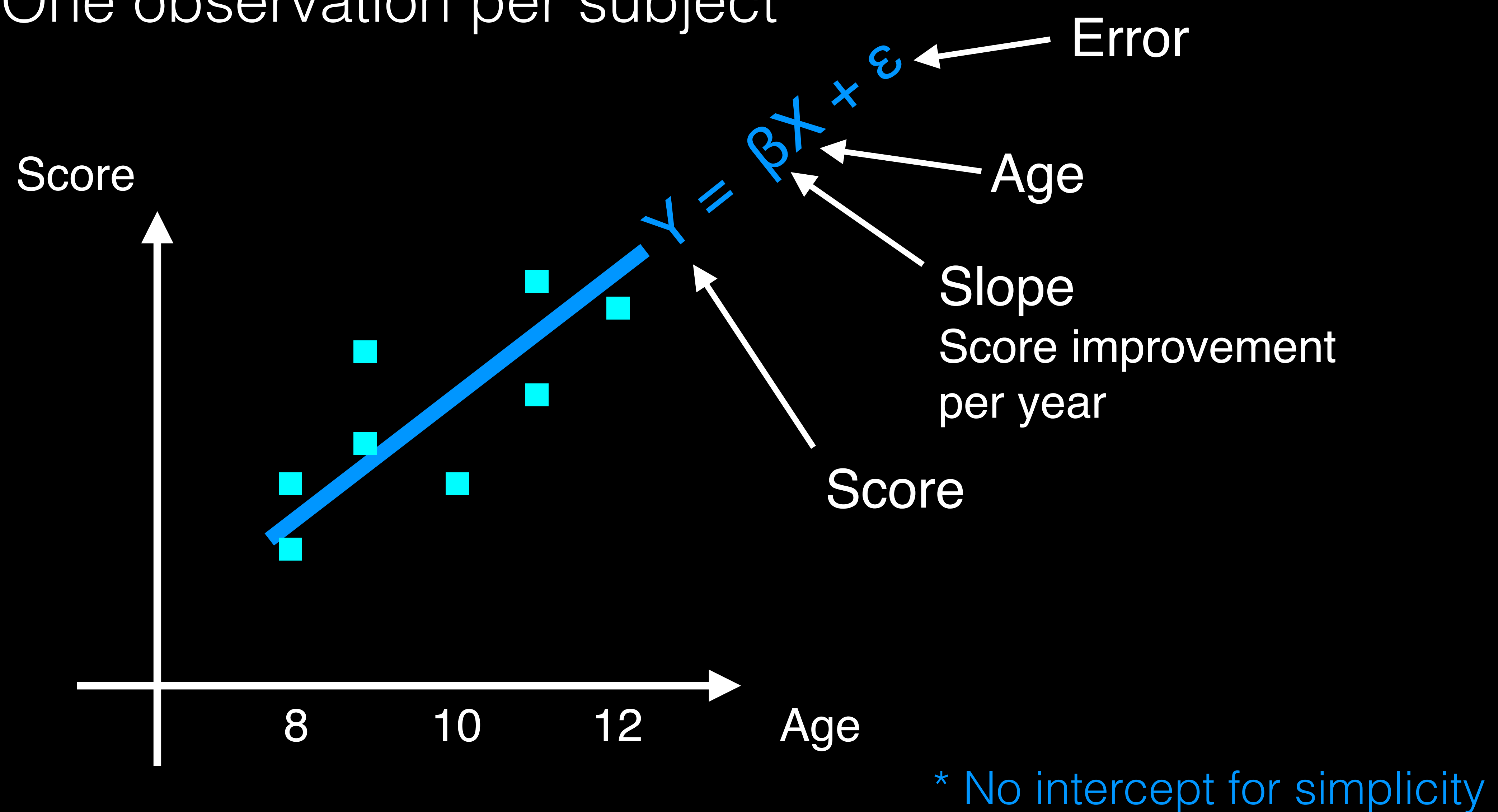
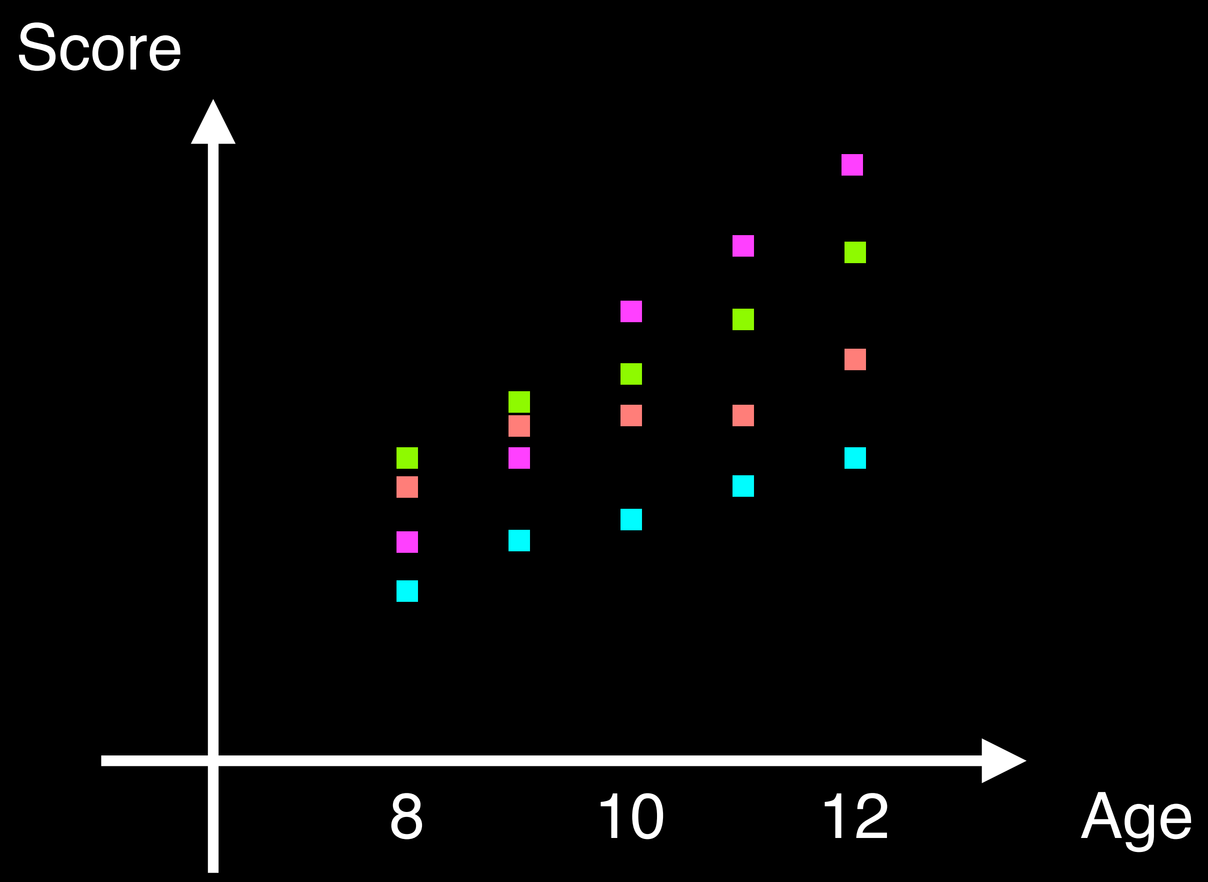


Longitudinal Study

- One observation per year for each subject



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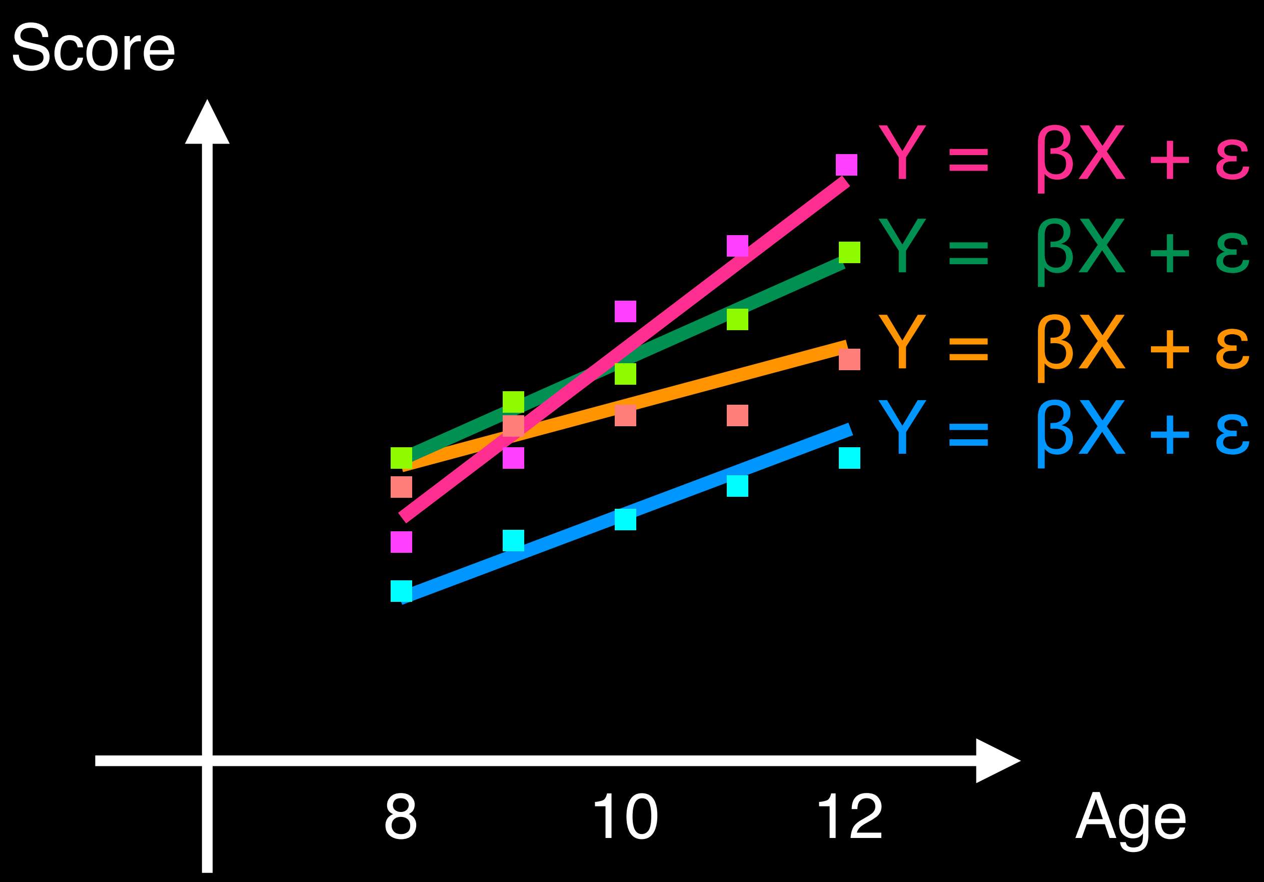
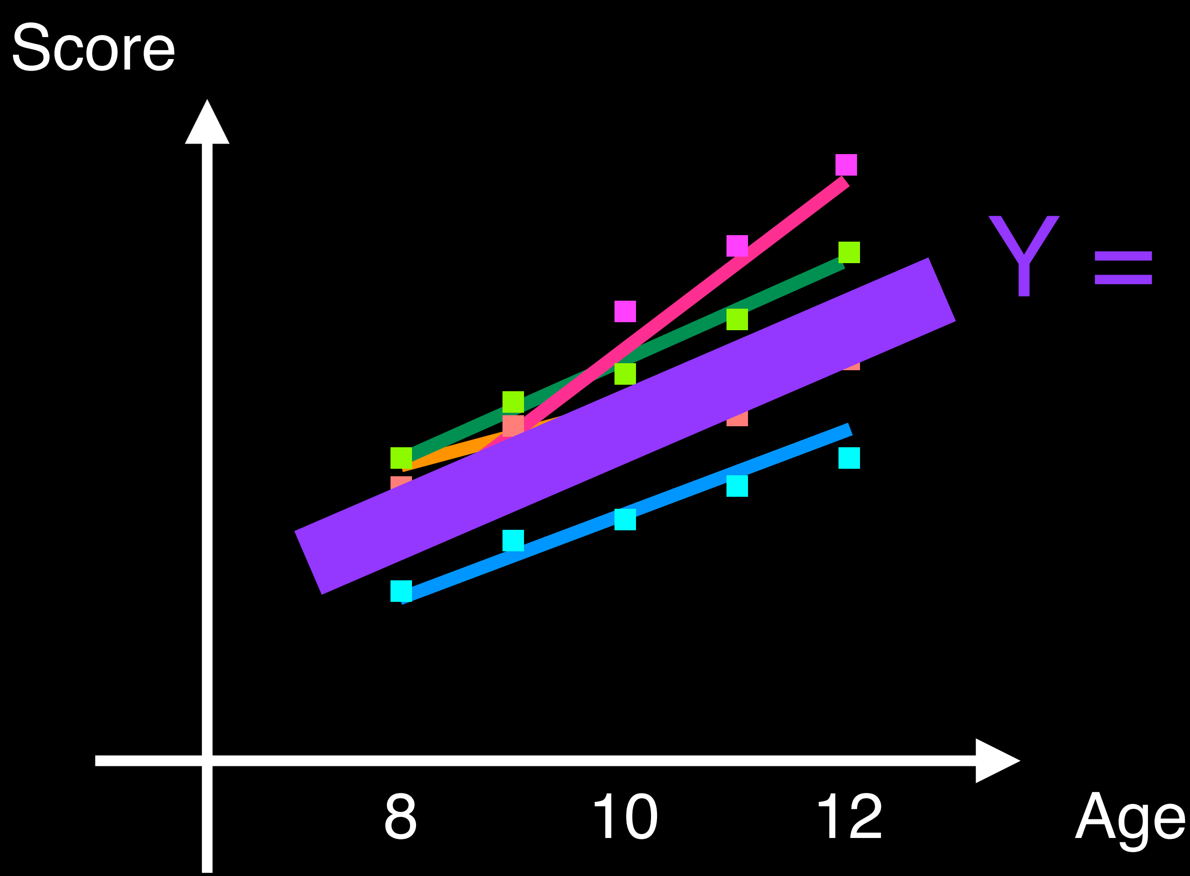


You can fit a regression line individually

* No intercept for simplicity

Longitudinal Study

- One observation per year for each subject



$$Y = \beta X + \varepsilon$$

What you want:

A regression line that summarizes all individual regression lines

* No intercept for simplicity

Mixed Model

$$Y = b_i X + \beta X + \varepsilon$$

* No intercept for simplicity

Mixed Model

$$\underbrace{Y}_{\text{Score}} = b_i \underbrace{X}_{\text{Age}} + \beta \underbrace{X}_{\text{Age}} + \varepsilon$$

* No intercept for simplicity

Mixed Model

$$Y = b_i X + \underbrace{\beta X}_{\text{Fixed effect}} + \varepsilon$$

* No intercept for simplicity

Mixed Model

$$Y = b_i X + \beta X + \varepsilon$$

Overall regression slope
for the population

* No intercept for simplicity

Mixed Model

$$Y = \underbrace{b_i X}_{\text{Random effect}} + \beta X + \varepsilon$$

* No intercept for simplicity

Mixed Model

$$Y = b_i X + \beta X + \varepsilon$$

Individual slope

($i = 1, 2, \ldots, N$)

Deviation from the overall slope in the fixed effect

* No intercept for simplicity

Mixed Model

$$Y = b_i X + \beta X + \varepsilon$$

b_i follows a normal distribution $N(0, \underline{\sigma_b^2})$

Individual slope

(i = 1, 2, …, N)

Deviation from the overall slope in the fixed effect

Between-subject variance

* No intercept for simplicity

Mixed Model

$$Y = b_i X + \beta X + \varepsilon$$

Error

* No intercept for simplicity

Mixed Model

$$Y = b_i X + \beta X + \varepsilon$$

Follows a normal distribution $N(0, \underline{\sigma_w^2})$

Error

Within-subject variance

can be identical for all subjects

or

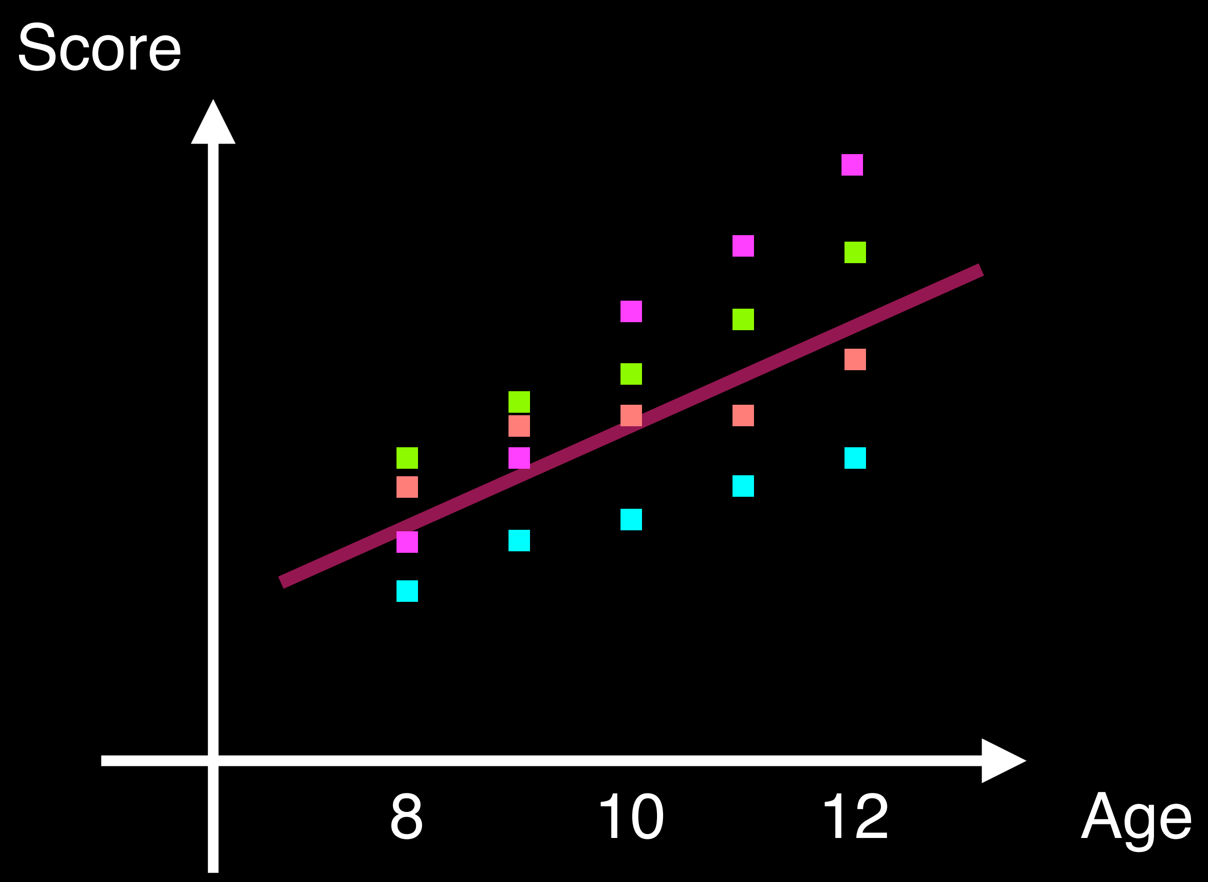
varies from subject to subject

$\sigma_{w1}^2, \sigma_{w2}^2, \ldots, \sigma_{wN}^2$

* No intercept for simplicity

Why Mixed Model?

- Can we just fit a regular regression line?
    - Forget random effects. Ignore repeated observations



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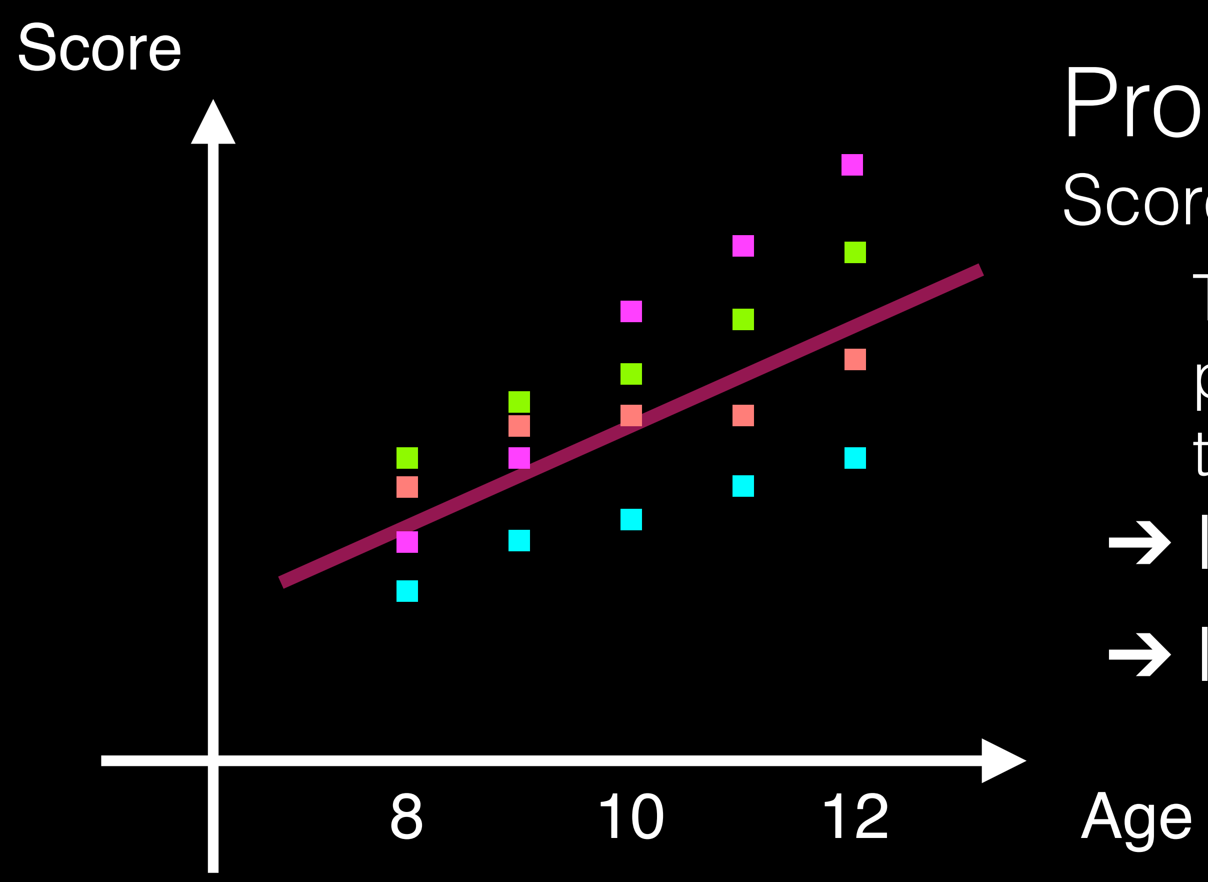


Problem

Scores likely correlated within subject

Those scoring high at earlier time points likely to score high on later time points

➔ Incorrect within-subject variance

➔ Incorrect p-values

Mixed Model or Fixed Effect Model?

- Fixed effect model
  - One observation per subject
  - No within-subject variance
- Mixed model
  - Multiple observations per subject
  - Need to separate within- and between-subject variance

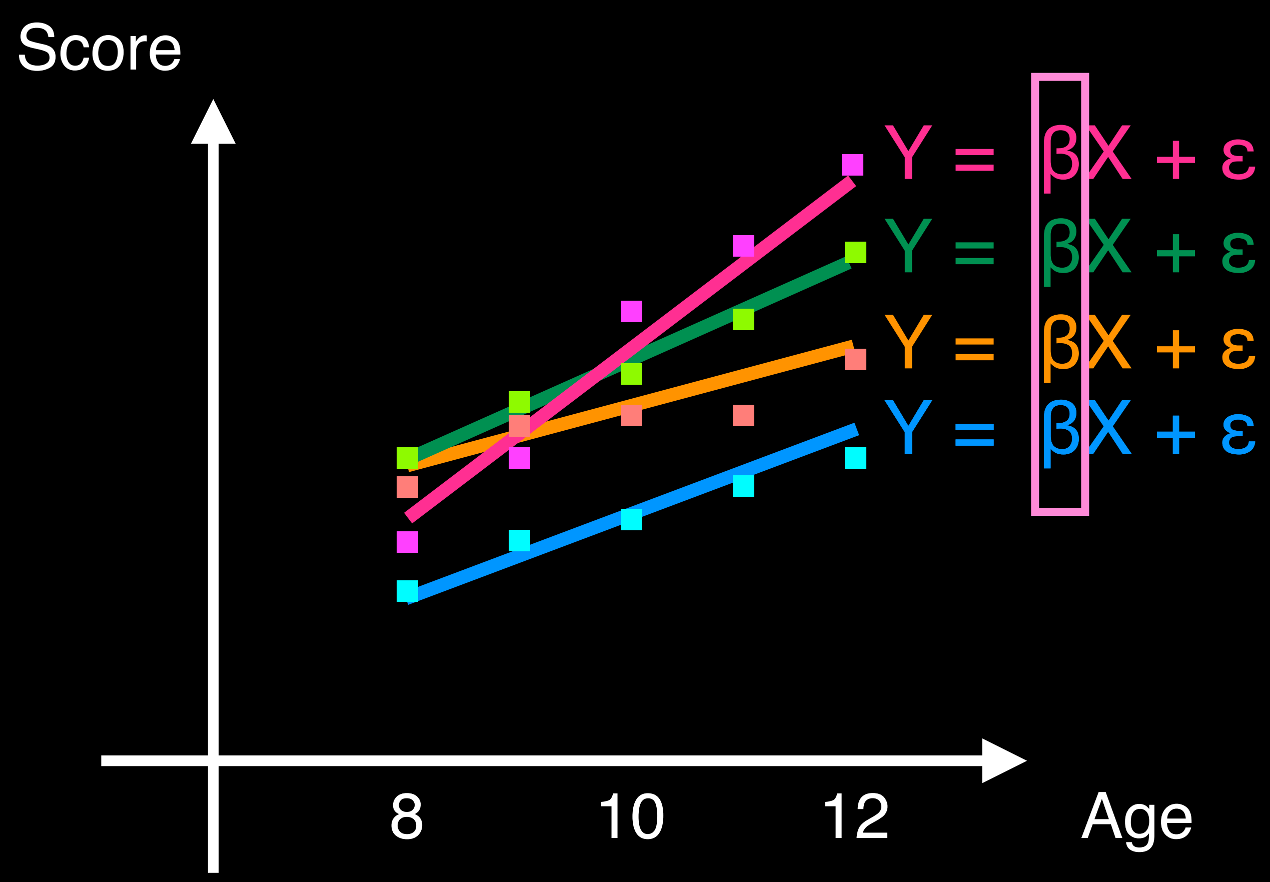
Notes on Mixed Model

$$Y = b_i X + \beta X + \varepsilon$$

- Fitting a mixed model ➔ estimating many parameters
    - Fixed effect regression parameters
    - Random effect regression parameters
    - Within-subject variance
    - Between-subject variance
- Parameters can be estimated at once — computationally intensive

Notes on Mixed Model

- Quick and easy (i.e., less computationally intensive) way



Fit individual regression lines first

Then calculate the average of slopes

➔ slope for the population

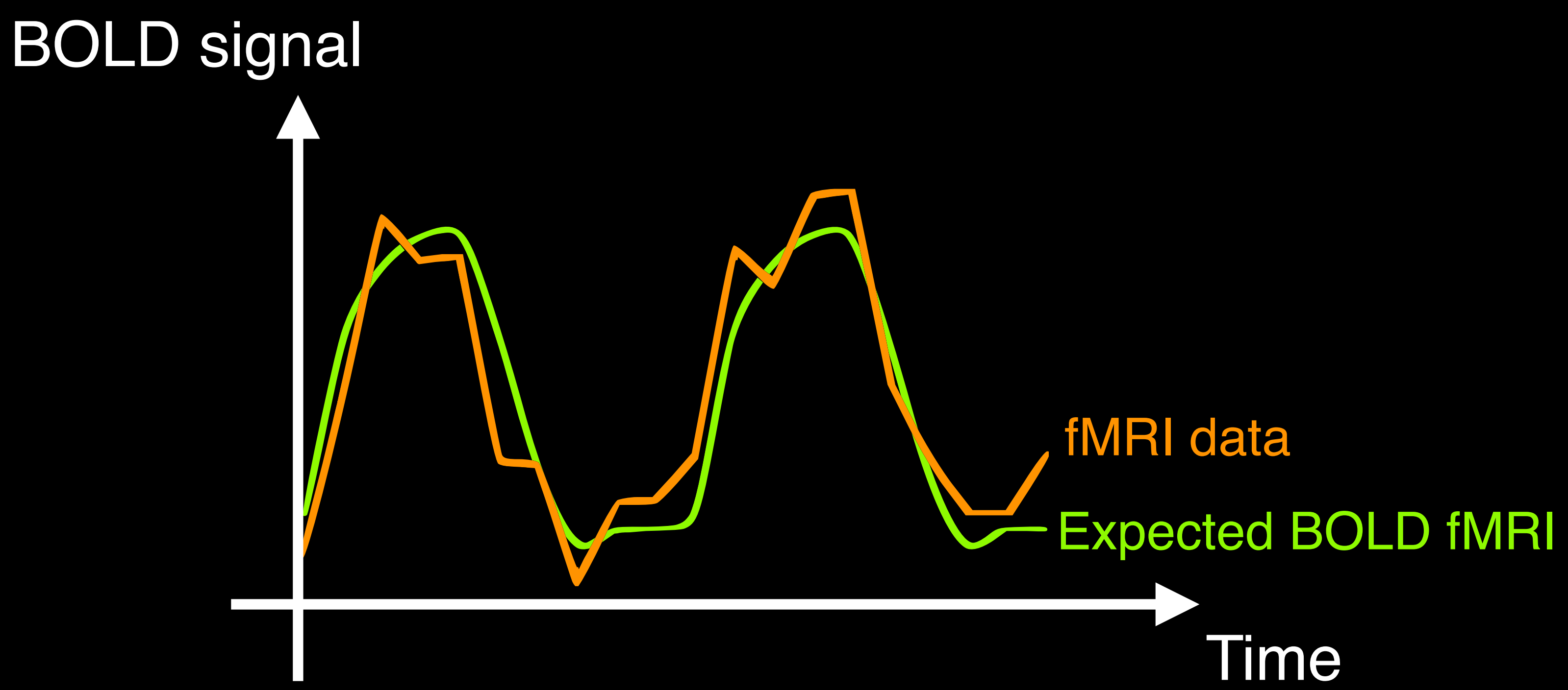
Very common in fMRI

* No intercept for simplicity

Second-Level Analysis

First-Level Analysis

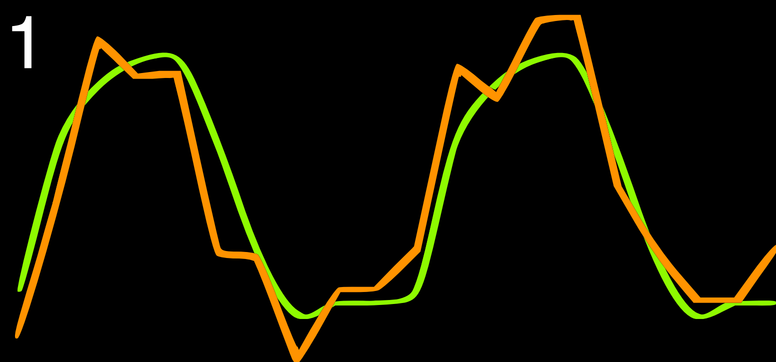
- Fitting expected BOLD fMRI signal to observed fMRI time series — in a single subject



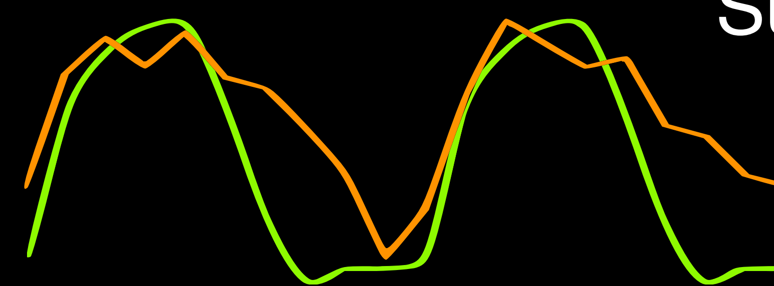
Multi-Subject Analysis

- What if there are multiple subjects?

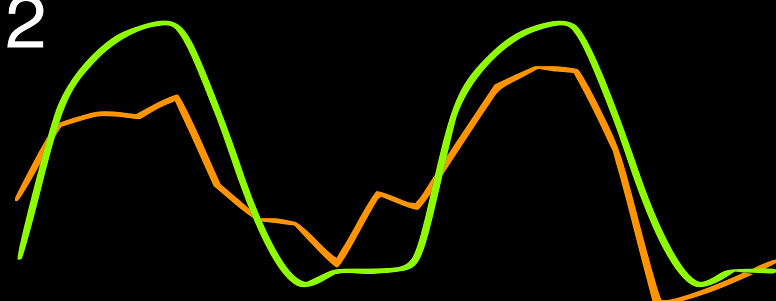
Subject 1



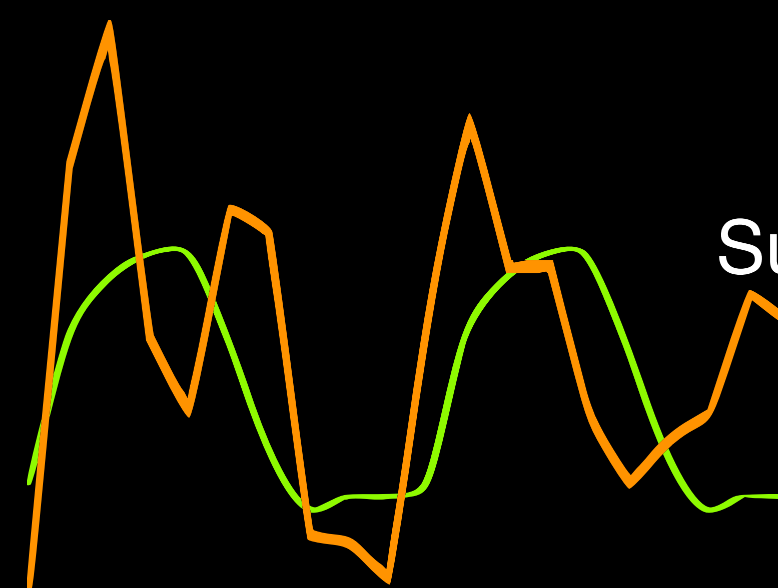
Subject 3



Subject 2

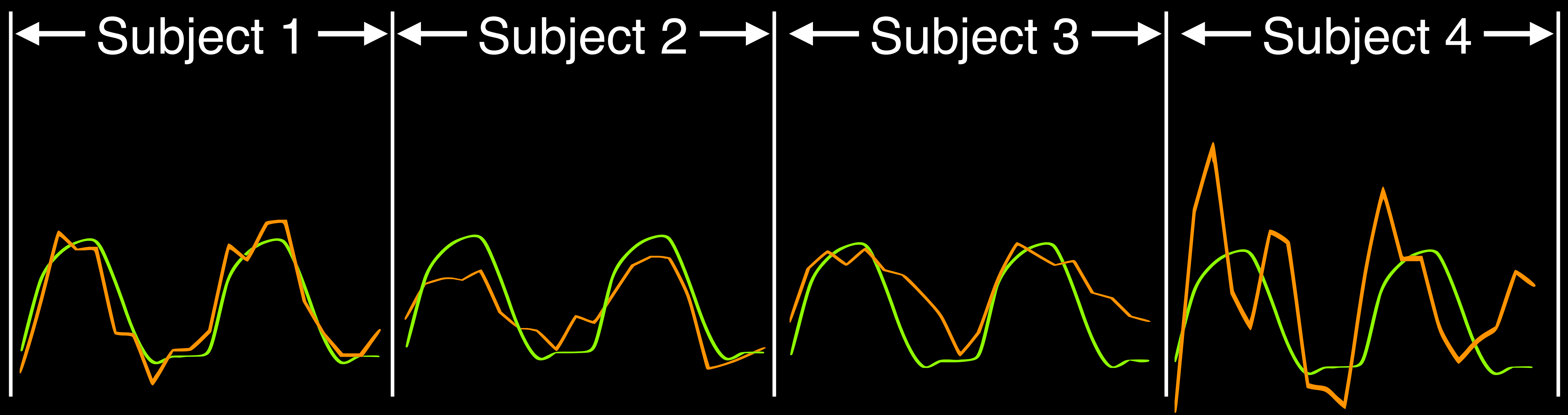


Subject 4



Multi-Subject Analysis

- Can we concatenate fMRI data across subjects?



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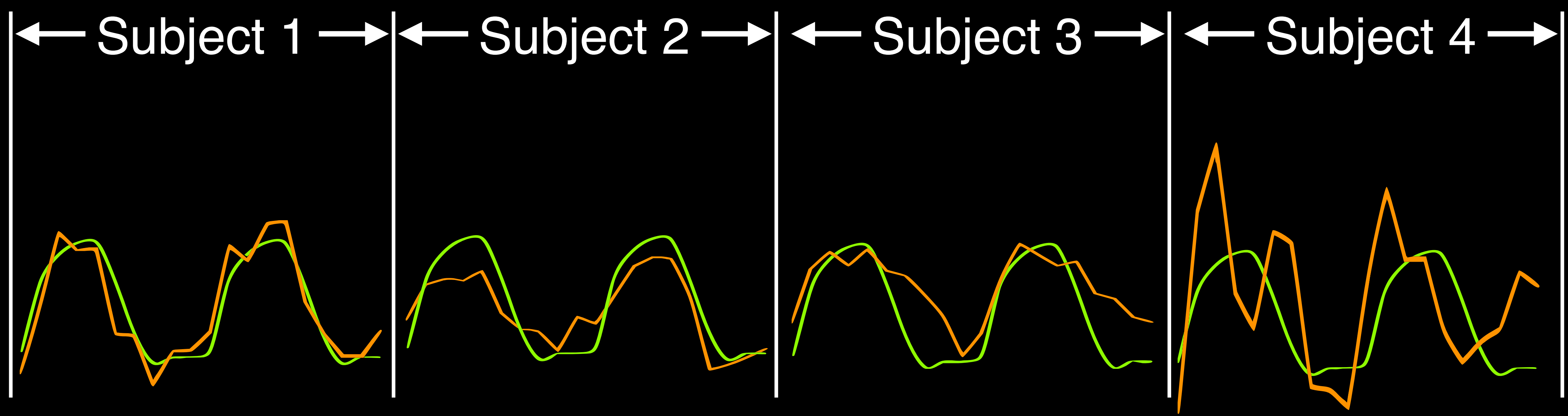
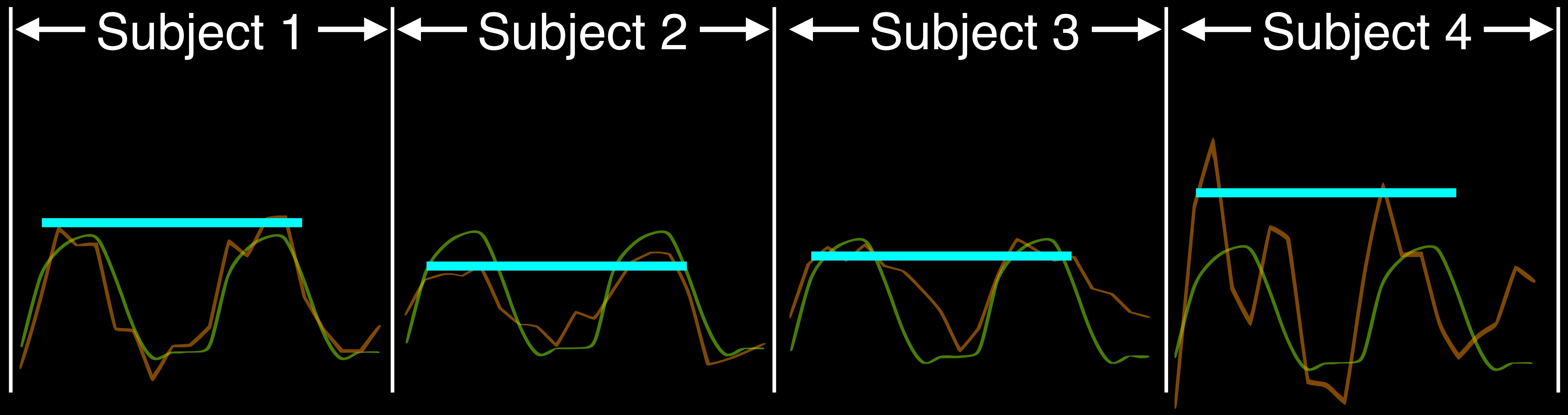


No!

- Between-subject variance
- Within-subject variance

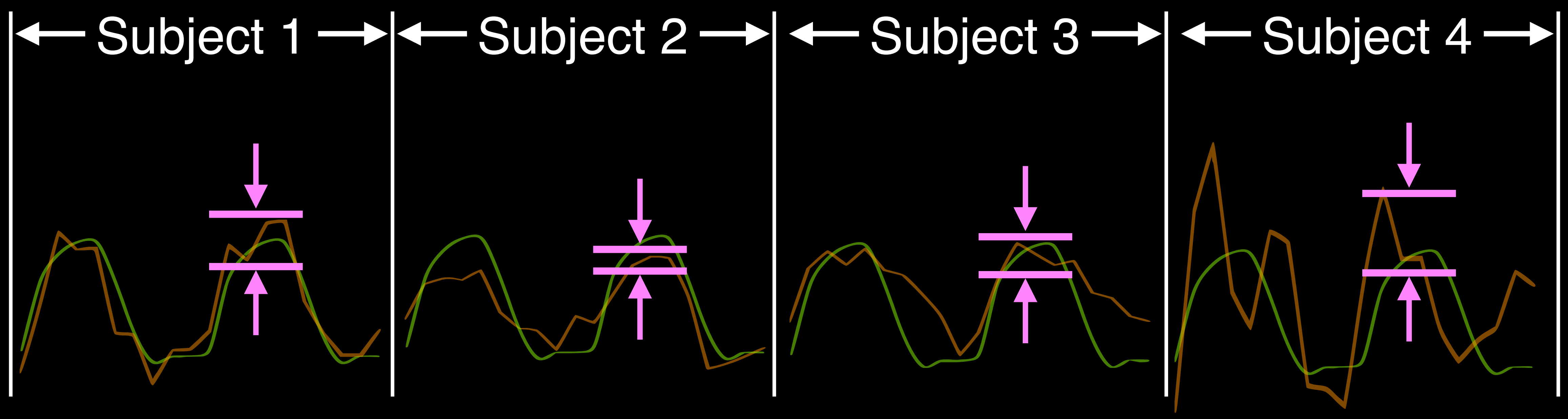
Multi-Subject Analysis

- Between-subject variability in activation magnitude



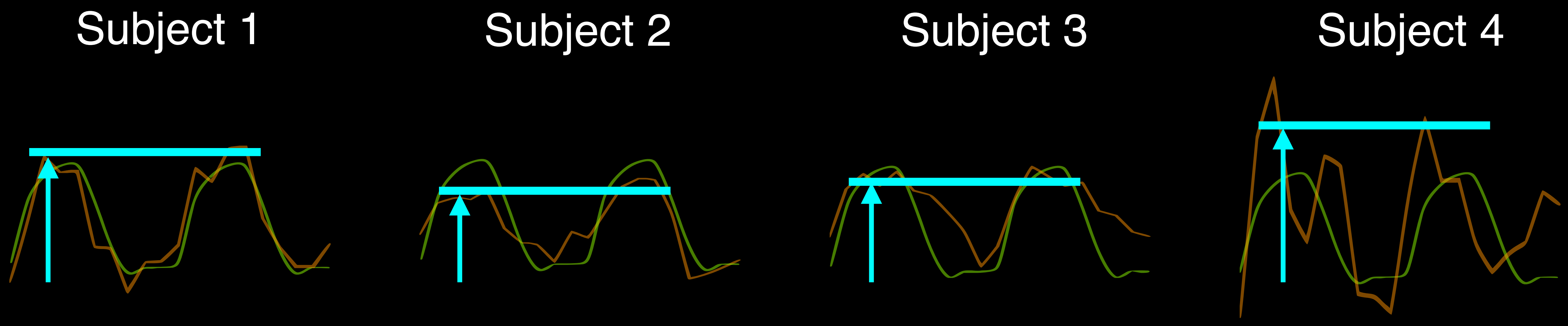
Multi-Subject Analysis

- Within-subject variance



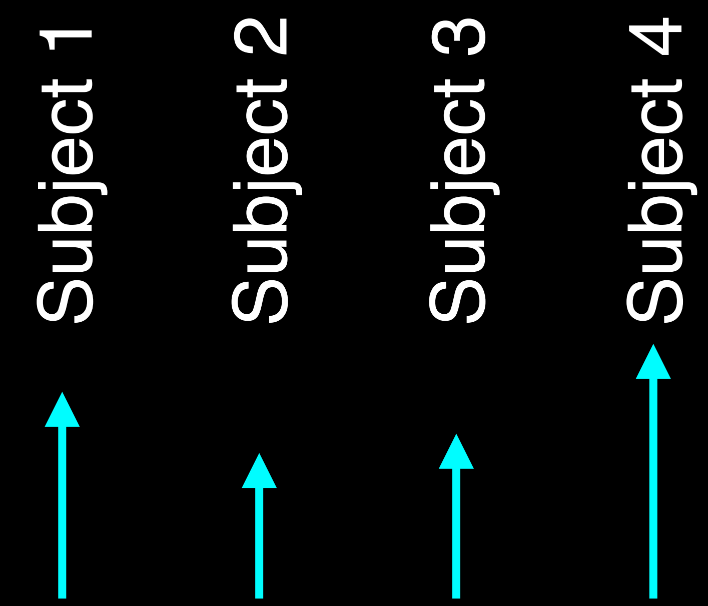
Second-Level Analysis

- First-level analysis individually
  - Estimate activation magnitude (i.e., contrast)



Second-Level Analysis

- Fixed-effect model on contrast
  - One observation per subject
  - Focus on between-subject variance



- Quick and easy way to fit a mixed model

Second-Level Analysis

- Often a simple statistical model is adequate
  - One-sample T-test (to assess significant activation)
  - Two-sample T-test
    - Independent groups (to compare activation magnitudes)
    - Paired (to examine changes within same subjects)

Contrasts
in
2nd-Level Analyses

Contrasts in 2nd Level

- Each Beta corresponds to a group

One-sample setting

		Beta1 (Group 1)
Group 1	Subject 1	1
	Subject 2	1
	Subject 3	1
	Subject 4	1
	Subject 5	1
	Subject 6	1
	Subject 7	1
	Subject 8	1

Contrasts in 2nd Level

- Each Beta corresponds to a group

Two-sample setting

		Beta1 (Group 1)	Beta2 (Group 2)
Group 1	Subject 1	1	0
	Subject 2	1	0
	Subject 3	1	0
	Subject 4	1	0
Group 2	Subject 5	0	1
	Subject 6	0	1
	Subject 7	0	1
	Subject 8	0	1

Contrasts in 2nd Level

- Contrasts of interests

One-sample setting

	Beta1 (Group 1)
Activation:	[1]
Deactivation:	[-1]

Contrasts in 2nd Level

- Contrasts of interests

Two-sample setting

	Beta1 (Group 1)	Beta2 (Group 2)
Activation, Group 1	[1	0]
Activation, Group 2	[0	1]
Group 1 > Group 2	[1	-1]
Group 2 > Group 1	[-1	1]

Higher-Level Analyses
(Higher than 2)

Paired Two-Sample T-Test

- Two conditions to be compared
- Each subject scanned under 2 conditions — serving as own control

Subject 1	Condition 1	Condition 2	→	Difference
Subject 2	Condition 1	Condition 2	→	Difference
Subject 3	Condition 1	Condition 2	→	Difference
Subject 4	Condition 1	Condition 2	→	Difference
Subject 5	Condition 1	Condition 2	→	Difference

Paired Two-Sample T-Test

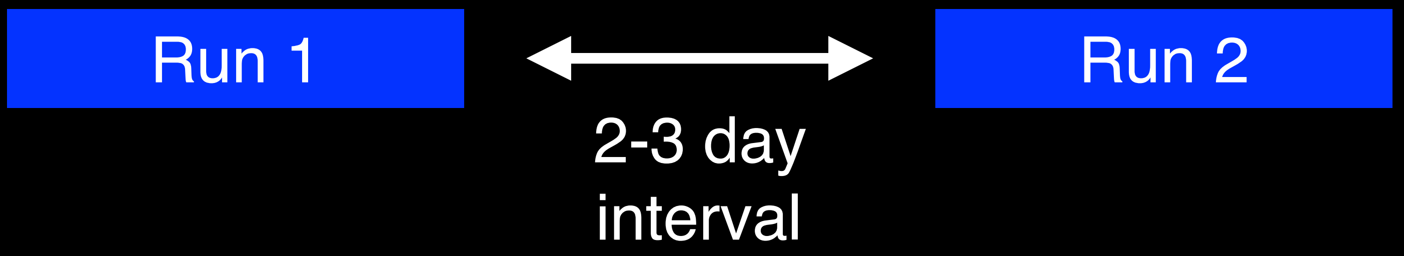
- Special case of higher-level analysis
  - First-level: individual scanning session
  - Second-level: calculating difference within individual
    - E.g., pre- vs. post-, condition 1 vs. condition 2
  - Third-level: calculating significant paired difference across subjects

Multi-Session Experiment

- Possible scenarios:
  - Same experiment was repeated multiple times on the same subject
    - Within the same session or separate sessions

E.g., within the same session

E.g., separate sessions



Multi-Session Experiment

- Multiple 4D fMRI time series on the same experiment
  - Distinct runs — cannot be concatenated
  - Need to be treated as 2nd level analysis
    - Within-run variance
    - Between-run variance
- Results from individual 2nd level analyses combined as the 3rd level analysis

Multi-Session Experiment

1st-level Analysis on each run on each subject

Subject 1	Run 1	Run 2	Run 3
Subject 2	Run 1	Run 2	Run 3
Subject 3	Run 1	Run 2	Run 3
Subject 4	Run 1	Run 2	Run 3
Subject 5	Run 1	Run 2	Run 3

Note: very time consuming!

Multi-Session Experiment

2nd-level Analysis on contrast images from multiple runs within each subject

Subject 1	Contrast: Run 1	Contrast: Run 2	Contrast: Run 3	→	Contrast: Subject 1
Subject 2	Contrast: Run 1	Contrast: Run 2	Contrast: Run 3	→	Contrast: Subject 2
Subject 3	Contrast: Run 1	Contrast: Run 2	Contrast: Run 3	→	Contrast: Subject 3
Subject 4	Contrast: Run 1	Contrast: Run 2	Contrast: Run 3	→	Contrast: Subject 4
Subject 5	Contrast: Run 1	Contrast: Run 2	Contrast: Run 3	→	Contrast: Subject 5

Multi-Session Experiment

3rd-level Analysis on contrast images from 2nd-level analysis

Subject 1 Contrast: Subject 1

Subject 2 Contrast: Subject 2

Subject 3 Contrast: Subject 3 → Overall contrast

Subject 4 Contrast: Subject 4

Subject 5 Contrast: Subject 5