Bayesian statistical inference in neuroimaging

Turku PET Centre Neuroimaging Course, September 2022

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Turku PET CENTRE

HOSPITAL DISTRICT OF SOUTHWEST FINLAND

Åbo Akademi University

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Mission

- Statistical inference
- Bayesian statistical inference
- Bayesian inference in neuroimaging
  - Example analysis with PET data

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Statistical inference

Statistical inference

?

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Ref. Thomas D. Gauthier, Mark E. Hawley (2015). Introduction to Environmental Forensics (Third Edition).

Statistical inference

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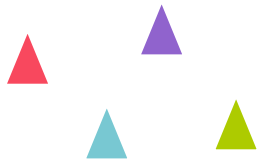
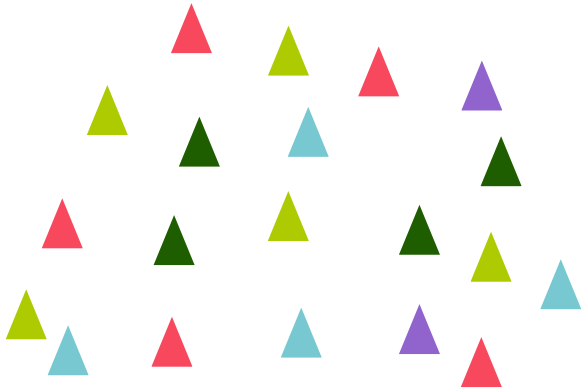
Ref. Thomas D. Gauthier, Mark E. Hawley (2015). Introduction to Environmental Forensics (Third Edition).

Statistical inference



Sample

Conclusions →



Population

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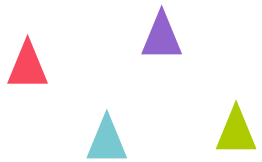
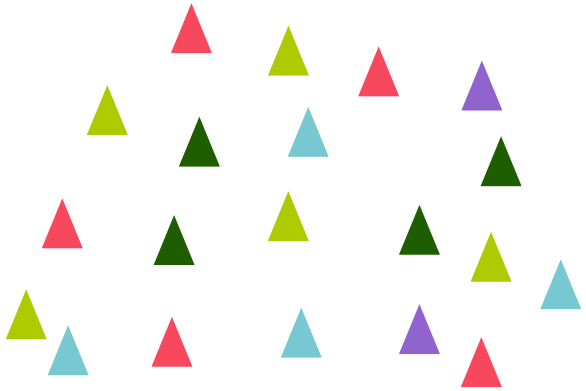
Statistical inference



Sample

Conclusions



Population

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Statistical inference: frameworks

Frequentist

- Null hypothesis testing
- t-test
- p-value
- multiple comparison correction
- confidence interval

Bayesian

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Ref. Gelman, A., Carlin, J. B., Stern, H. S., & Rubin, D. B. (1995-2020). Bayesian data analysis. Chapman and Hall/CRC.

Bayesian statistical inference

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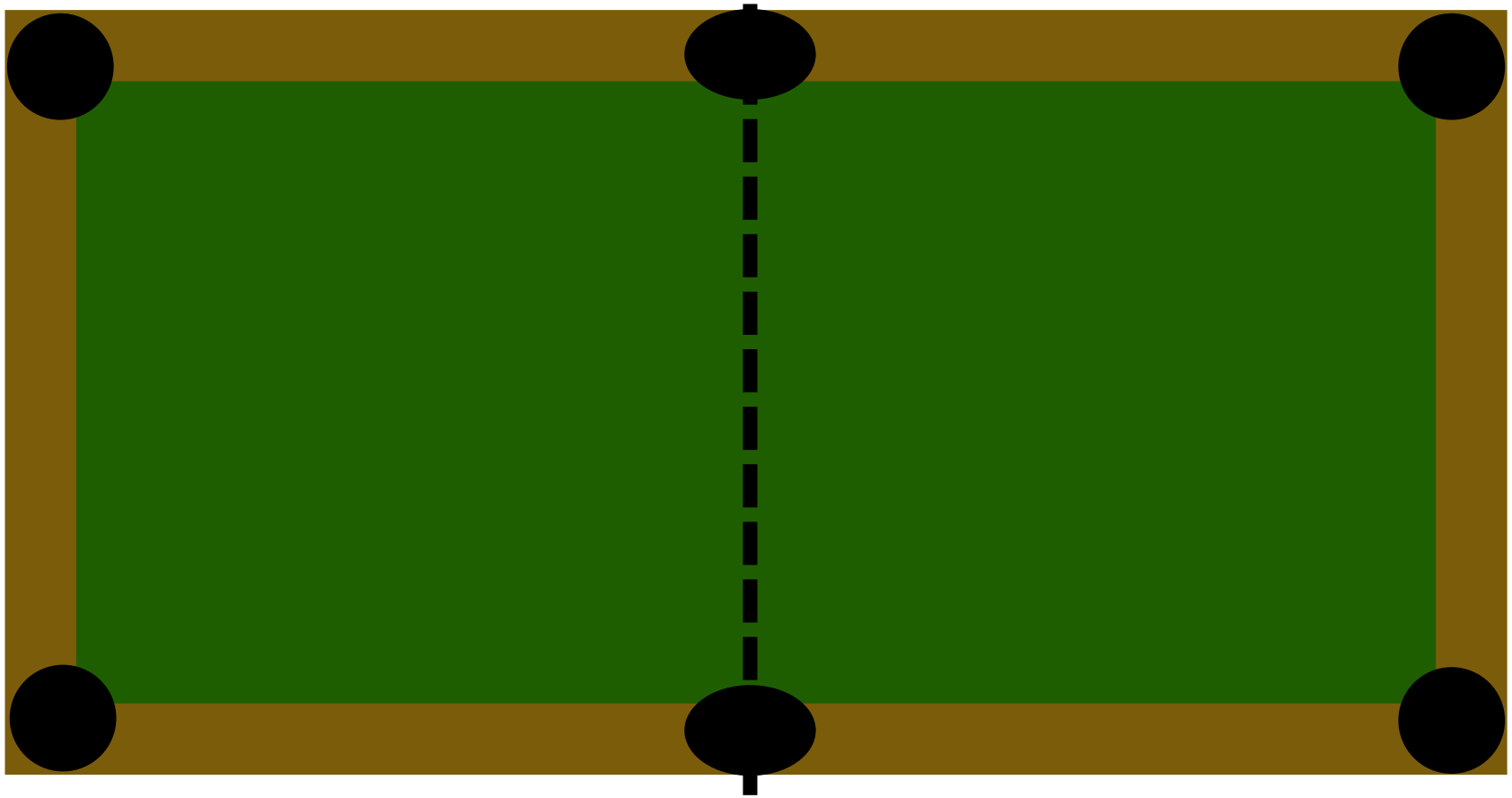
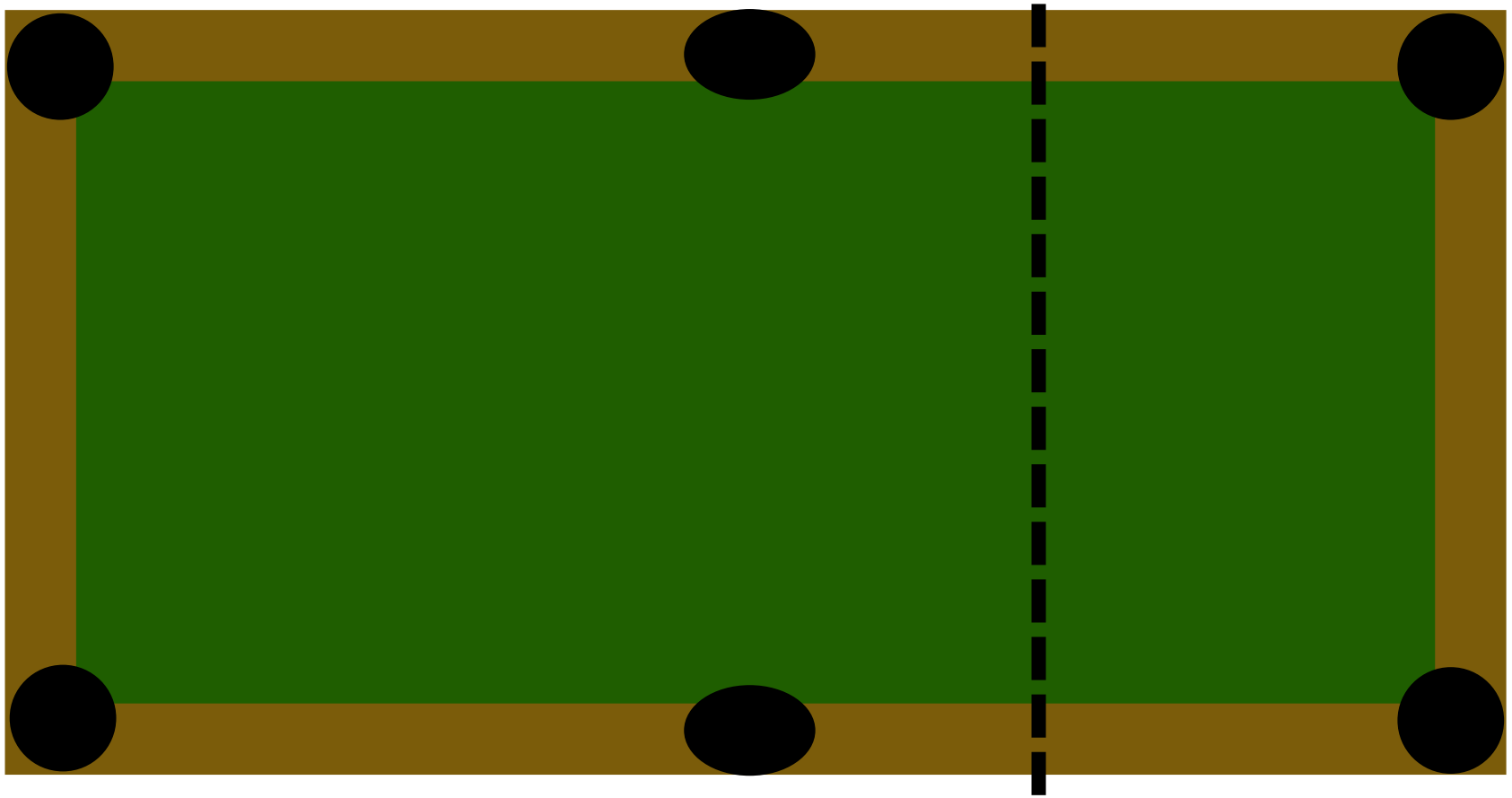
Take a mindset of a philosopher…

Thomas Bayes



Ref. Gower, B. (1997). Scientific method. Routledge.

Thomas Bayes



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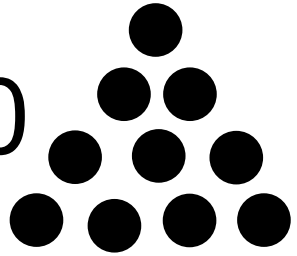

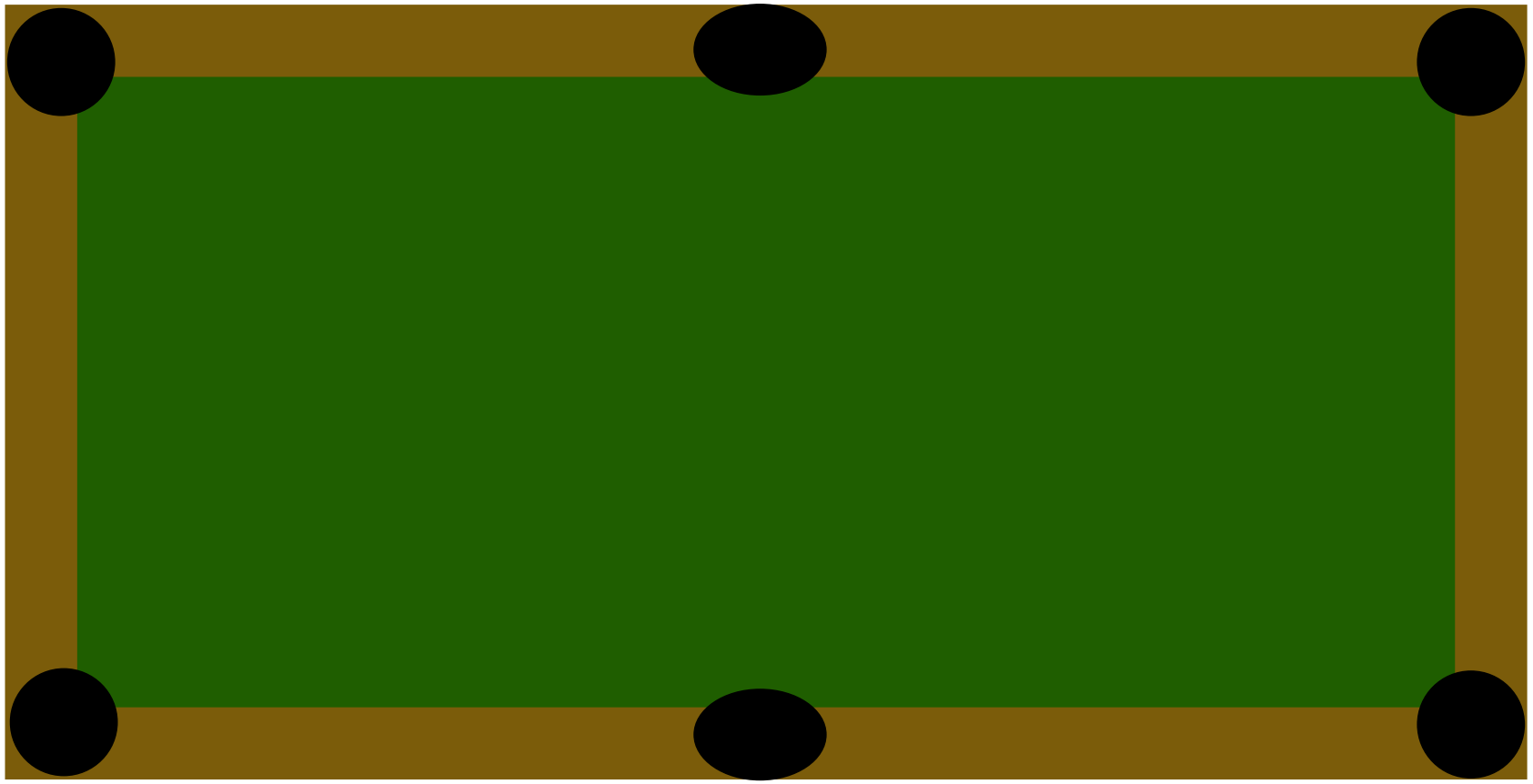

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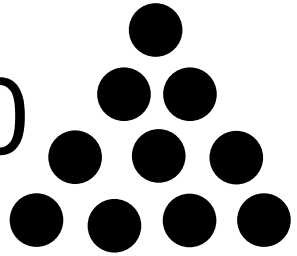

What do we know at this stage?

Random toss →
random location= probability of each location equal

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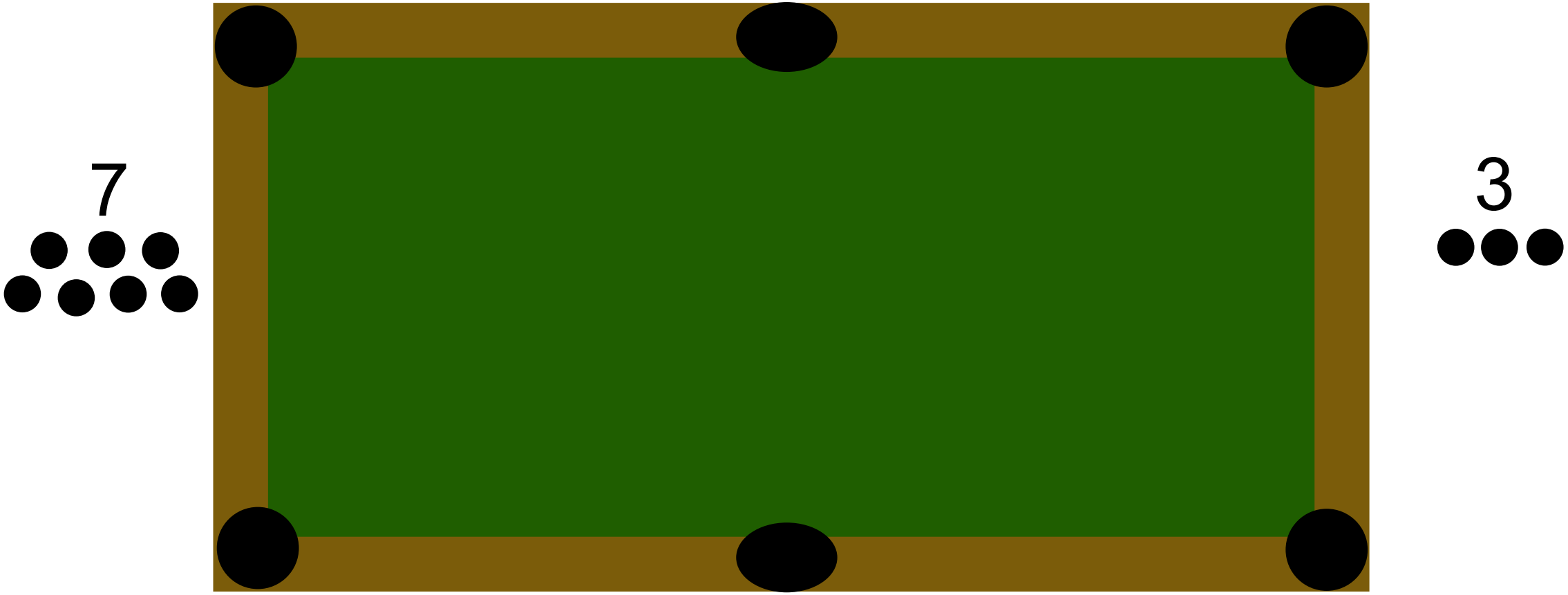
Ref. Gower, B. (1997). Scientific method. Routledge.



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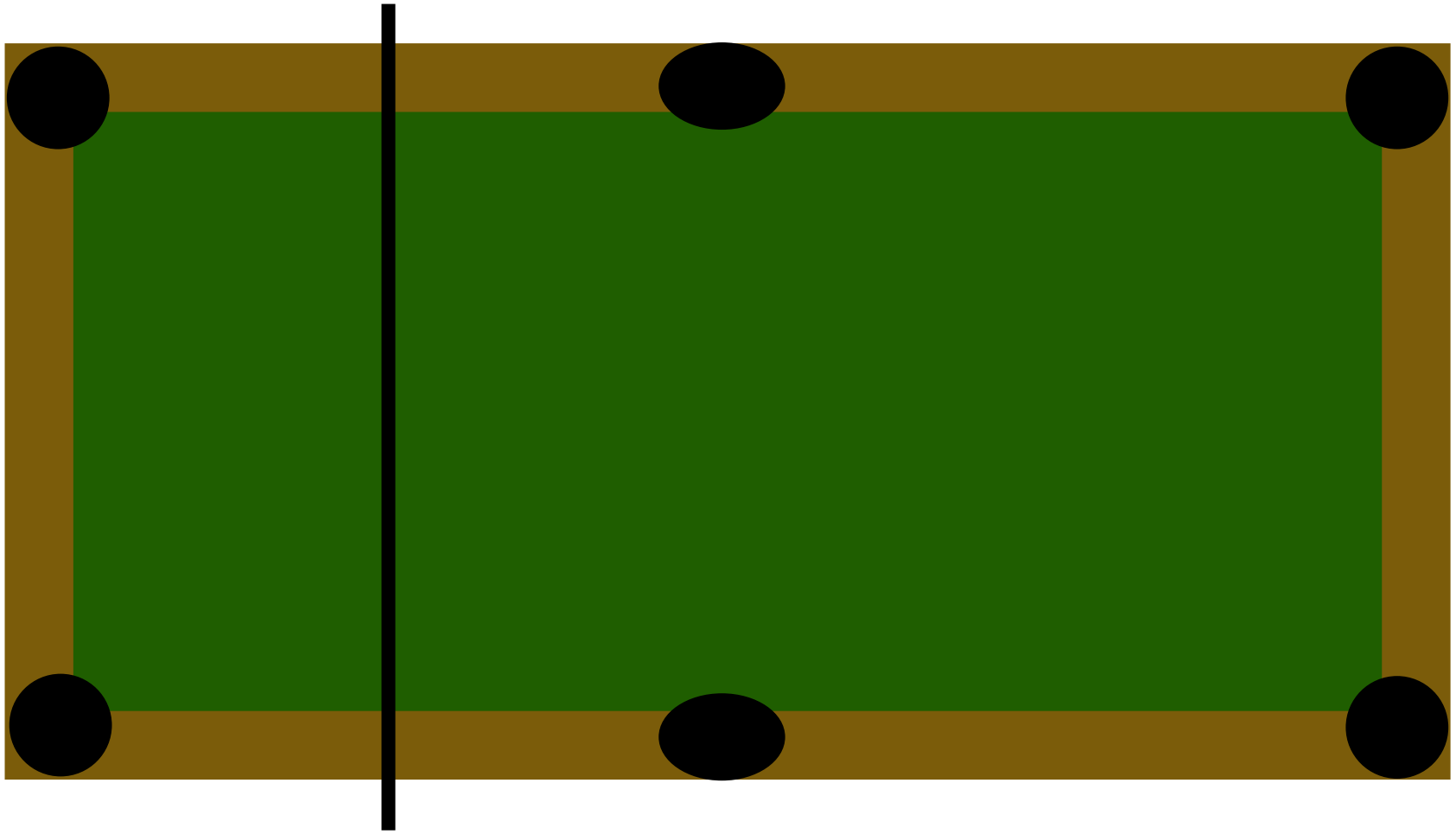

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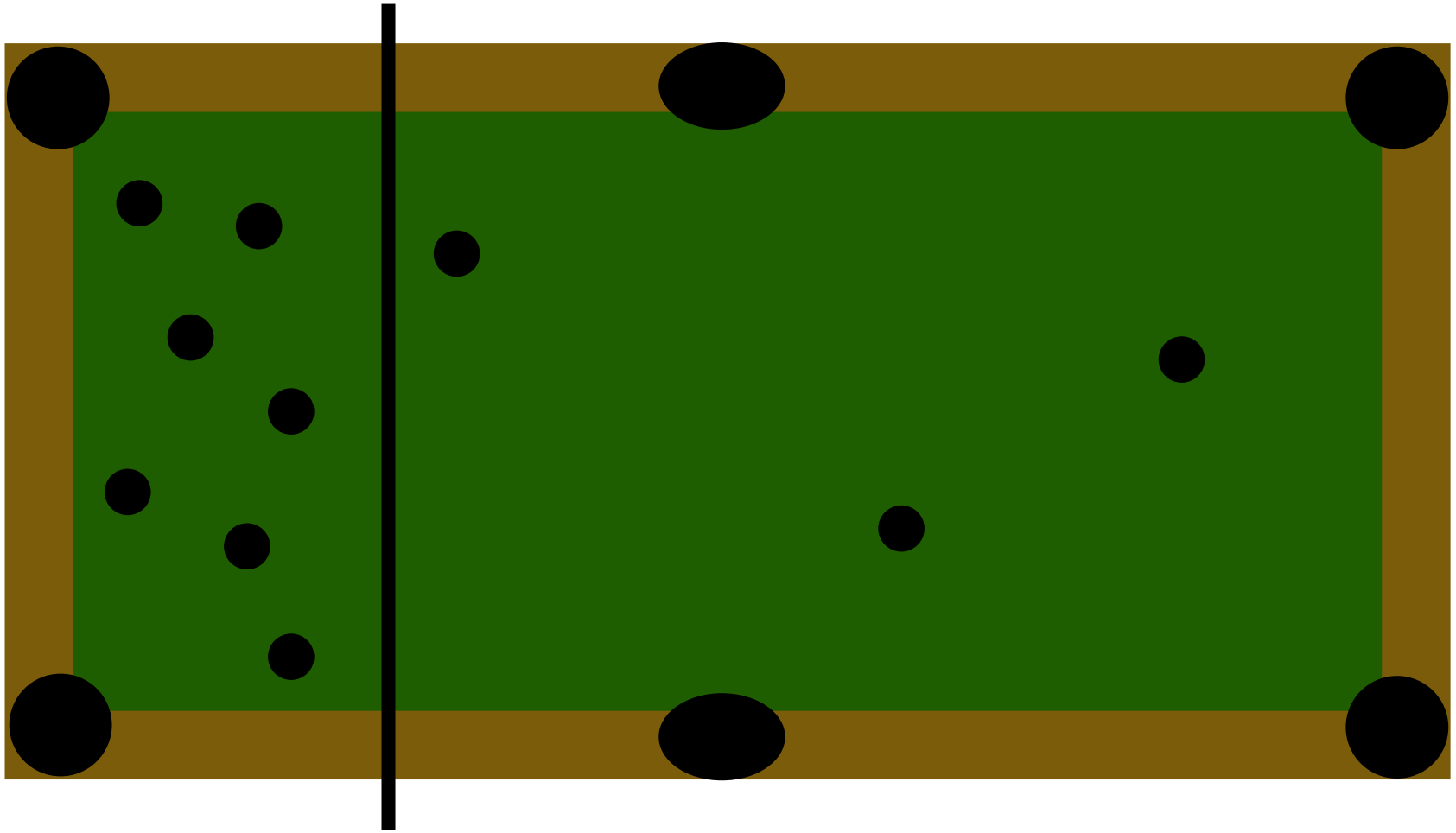

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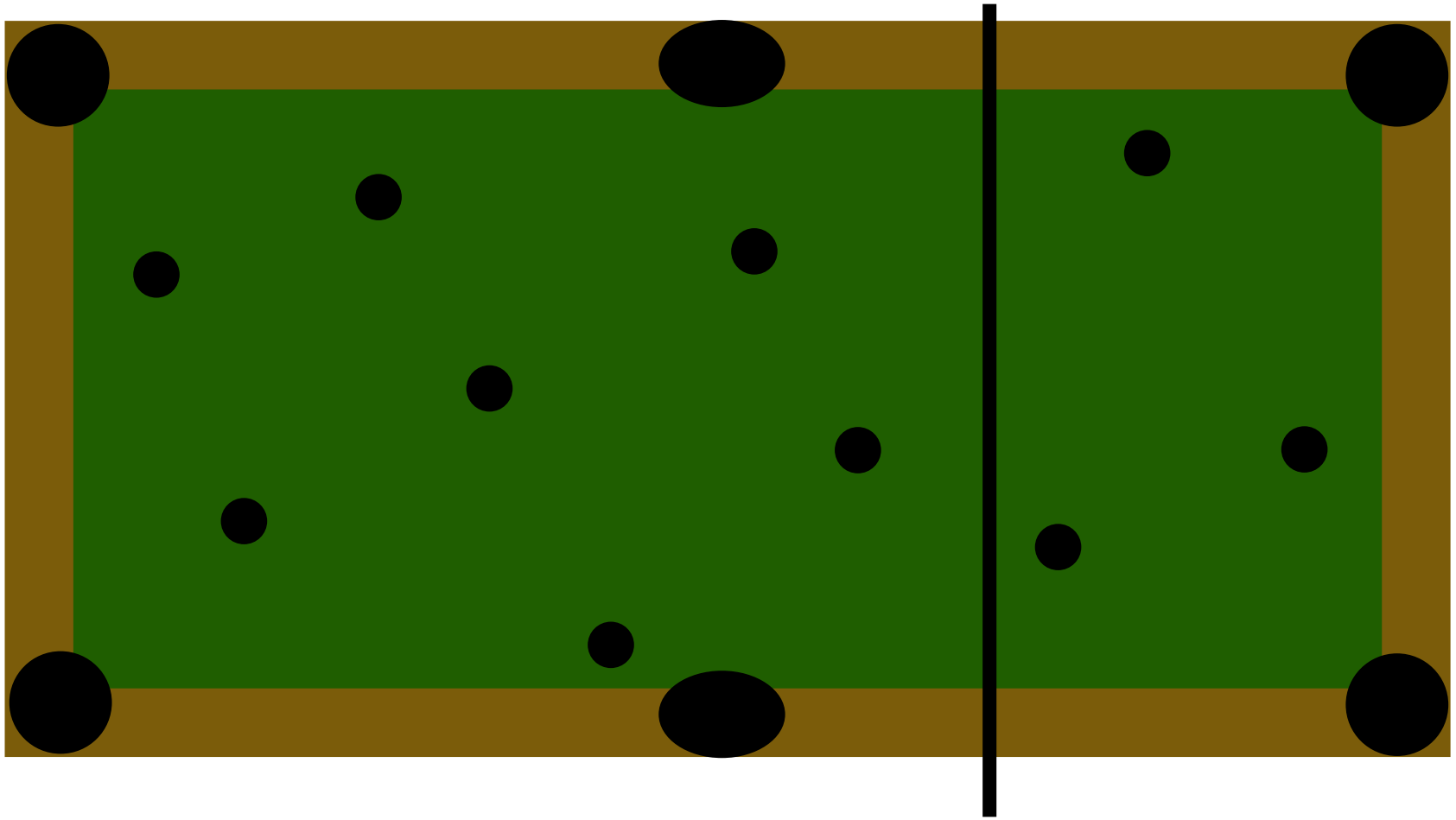

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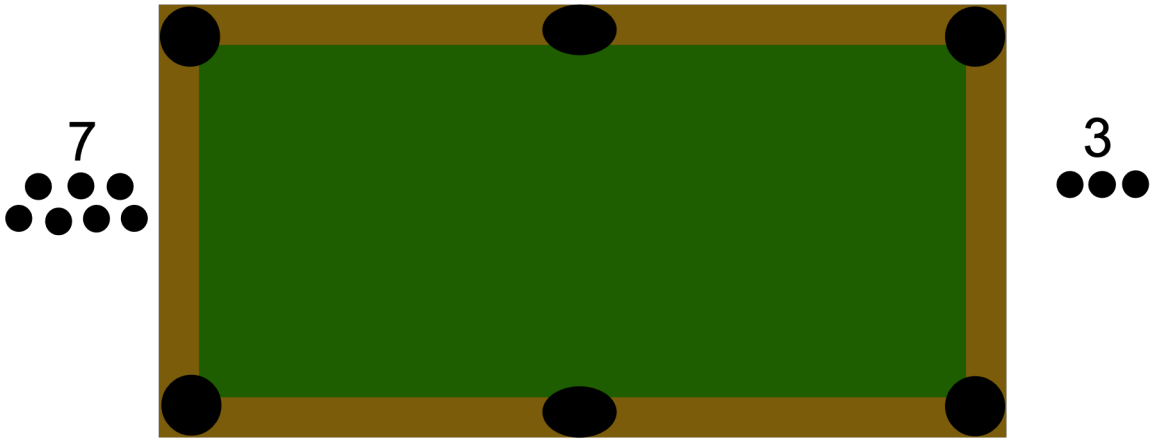
Ref. Gower, B. (1997). Scientific method. Routledge.

Where the line?



1) What do we know **prior** to data?

- Each ball gets a random position
- All positions equally probable

2) What is our **data**?

- 7 on the left
- 3 on the right

Both the **prior** knowledge and the **data** affect our **posterior** understanding

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Ref. Gelman, A., Carlin, J. B., Stern, H. S., & Rubin, D. B. (1995-2020). Bayesian data analysis. Chapman and Hall/CRC.

Key

Prior & data → Conclusions of the parameter

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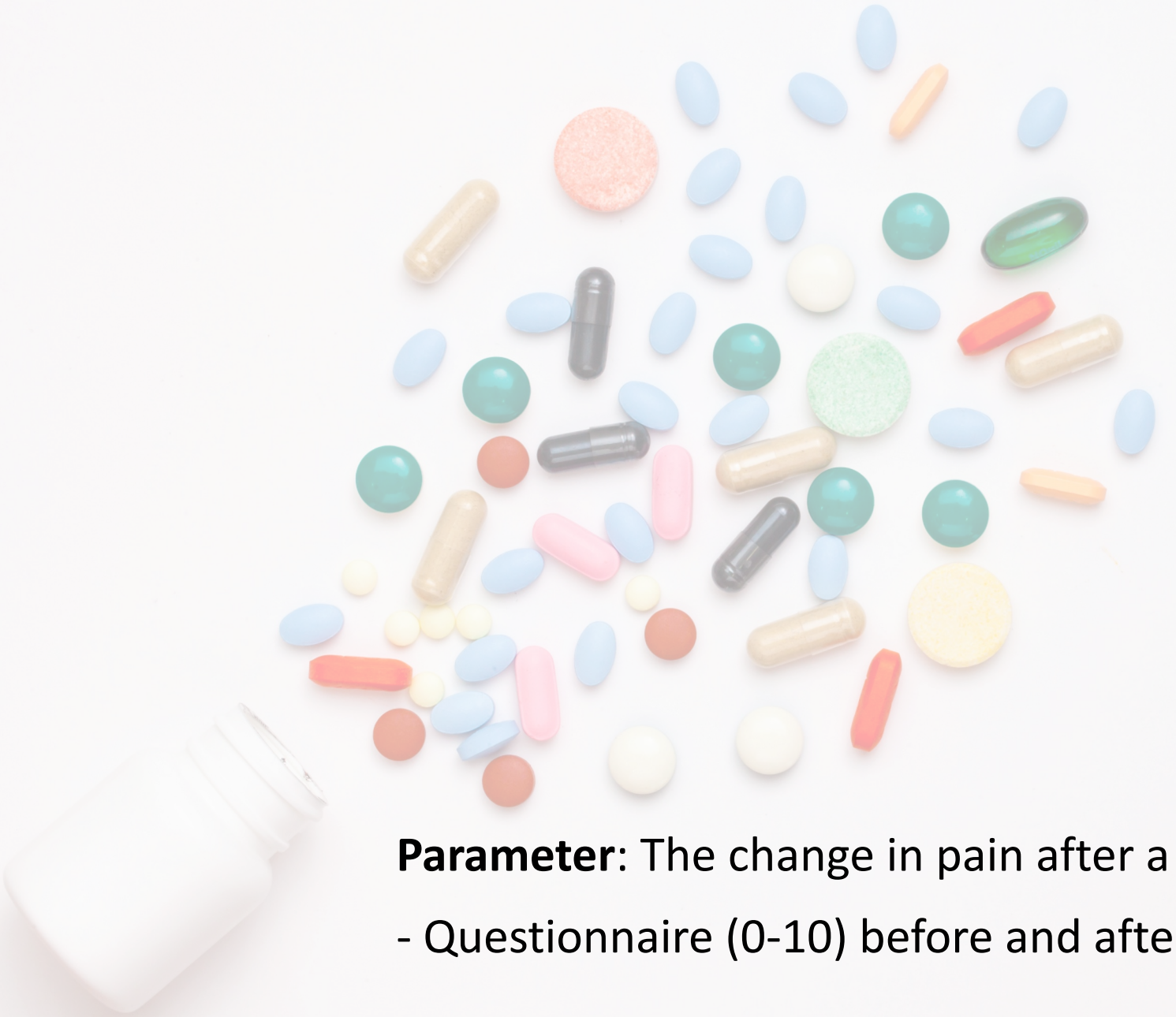

Parameter: The change in pain after a drug

- Questionnaire (0-10) before and after taking the drug

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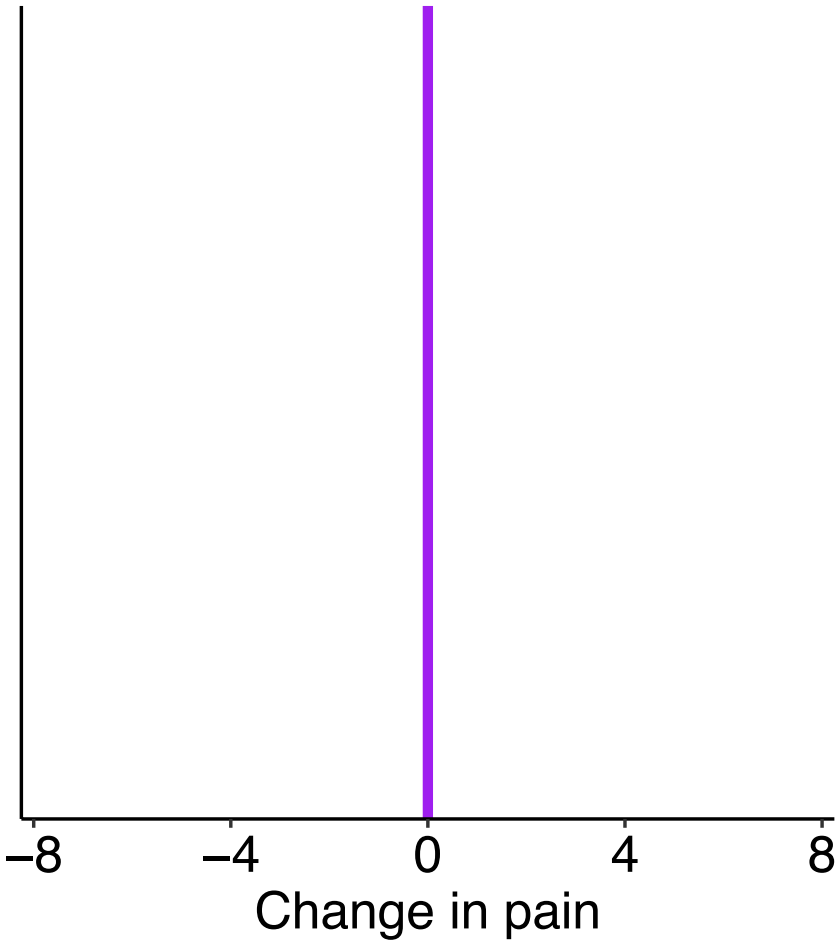
Image: PowerPoint image bank.

Frequentist

Null-hypothesis (H0): fixed parameter value



Refs. Holopainen, M. & Pulkkinen P. (2012). *Tilastolliset menetelmät*. Sanoma Pro Oy.; Cumming, G. (2013). Intro Statistics 9 Dance of the p Values. Video. Retrieved from: https://www.youtube.com/watch?v=5OL1RqHrZQ8. Cited: 13.8.2021.; McElreath, R. (2020). Statistical rethinking: A Bayesian course with examples in R and Stan. Chapman and Hall/CRC.

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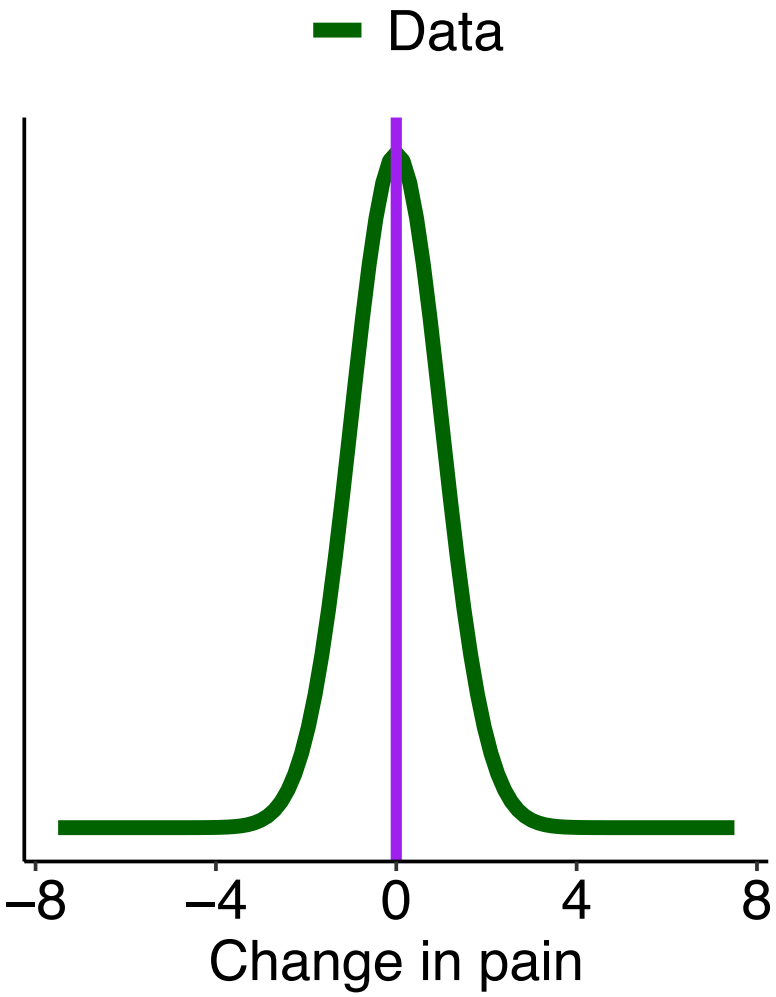
Frequentist

Null-hypothesis (H0): fixed parameter value

Data: observations from 100 subjects



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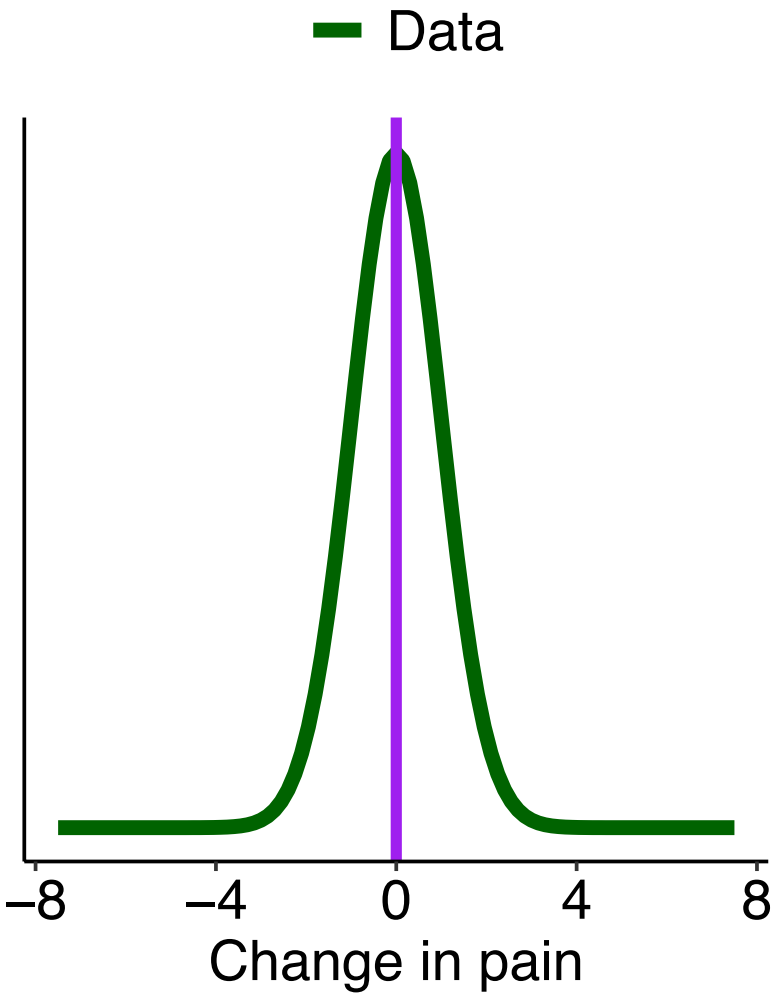
Frequentist

Hypothesis testing:

p-value close to 1= data well aligned with H0

→ Support for H0 (no change in the pain)



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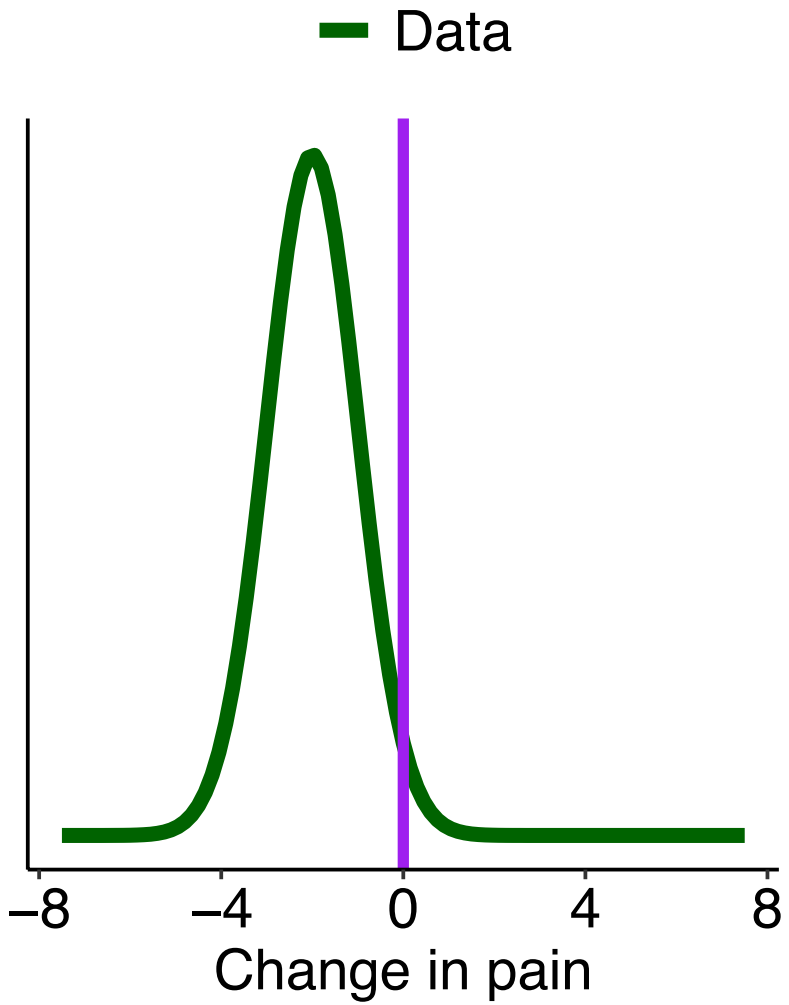
Frequentist

Hypothesis testing:

p-value small, close to 0= data deviating from H0

→ If H0 is true, data rare*

*Sometimes the data is rare just by chance



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Frequentist

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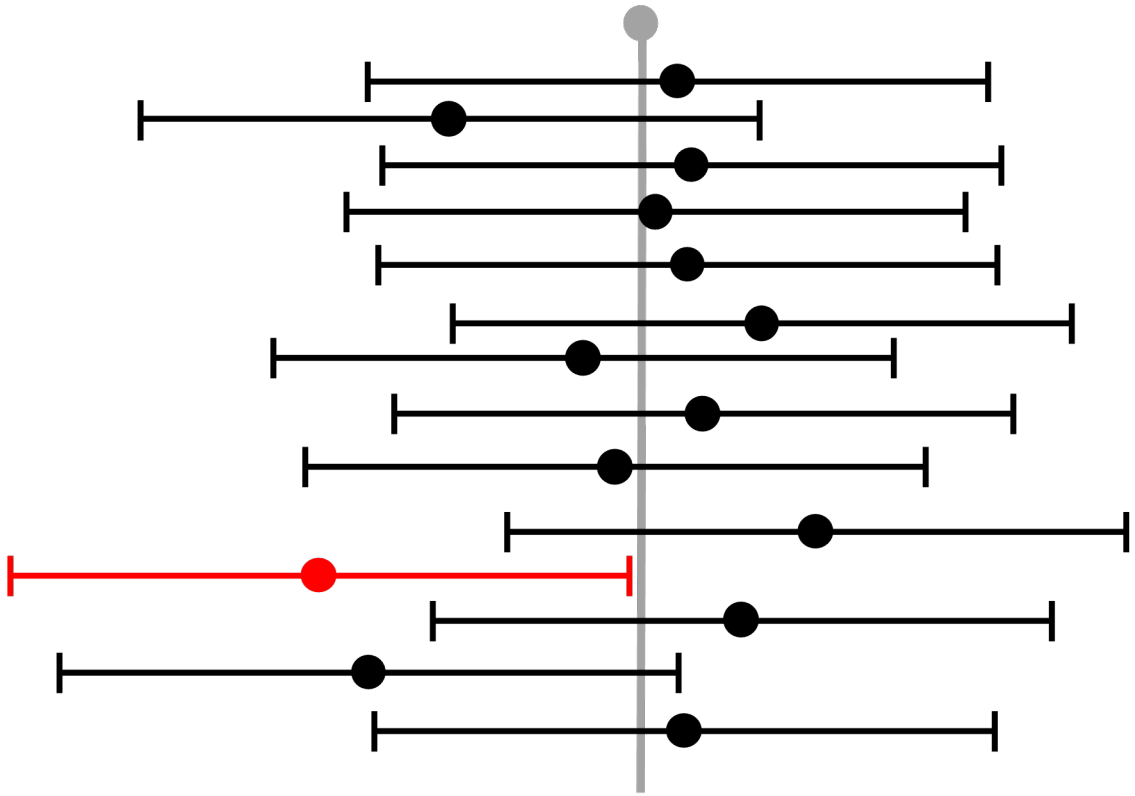

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Frequentist

How does our *data* look like?

Refs. Holopainen, M. & Pulkkinen P. (2012). *Tilastolliset menetelmät*. Sanoma Pro Oy.; Cumming, G. (2013). Intro Statistics 9 Dance of the p Values. Video. Retrieved from: https://www.youtube.com/watch?v=5OL1RqHrZQ8. Cited: 13.8.2021.; McElreath, R. (2020). Statistical rethinking: A Bayesian course with examples in R and Stan. Chapman and Hall/CRC.

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What if…

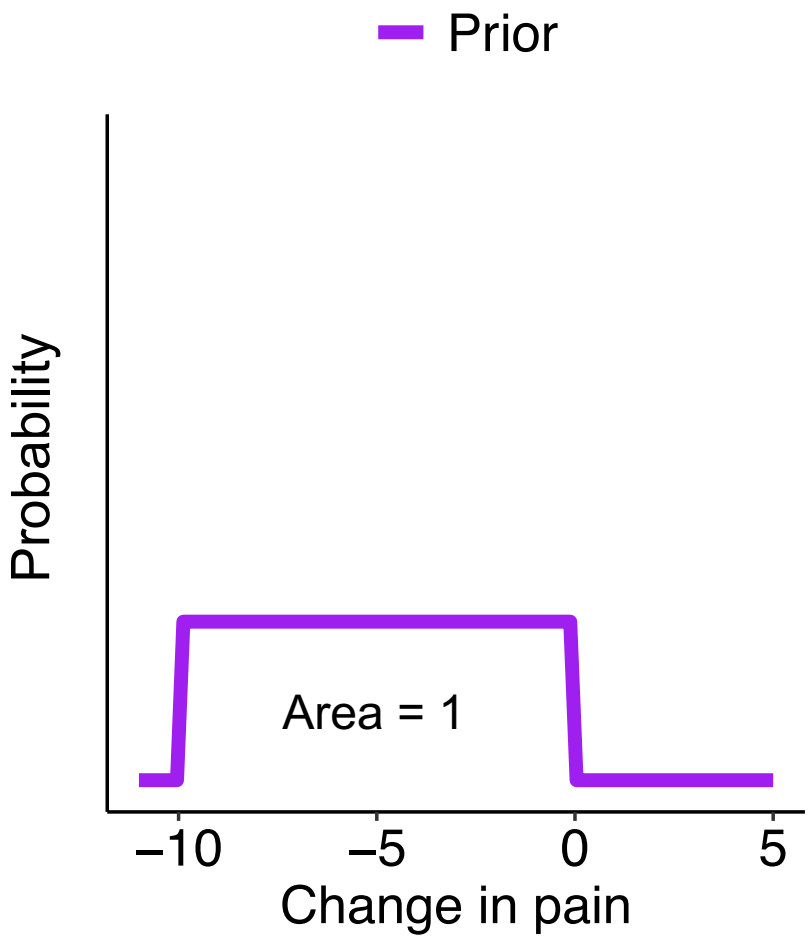
… we did not have to fix the hypothesis (parameter, the change)?

<u>Bayesian:</u>

Consider multiple parameter values at once

This is the prior knowledge (in a form of a probability distribution)!

Prior is always given to each parameter in the model



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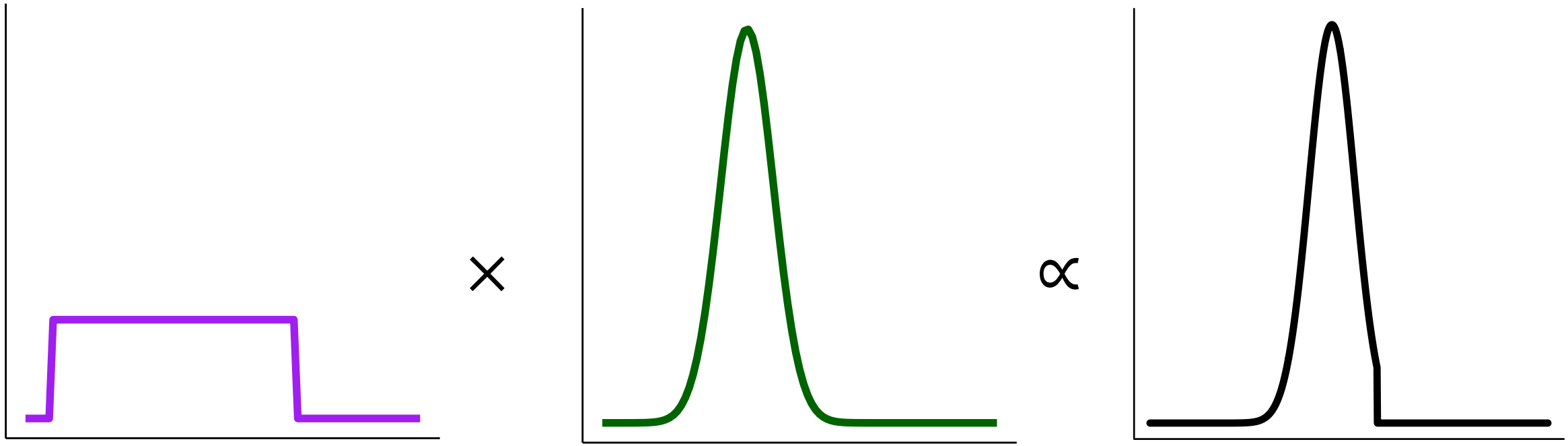
Prior & data form posterior



Posterior= prior probability distribution updated with the data, combines information of prior and data

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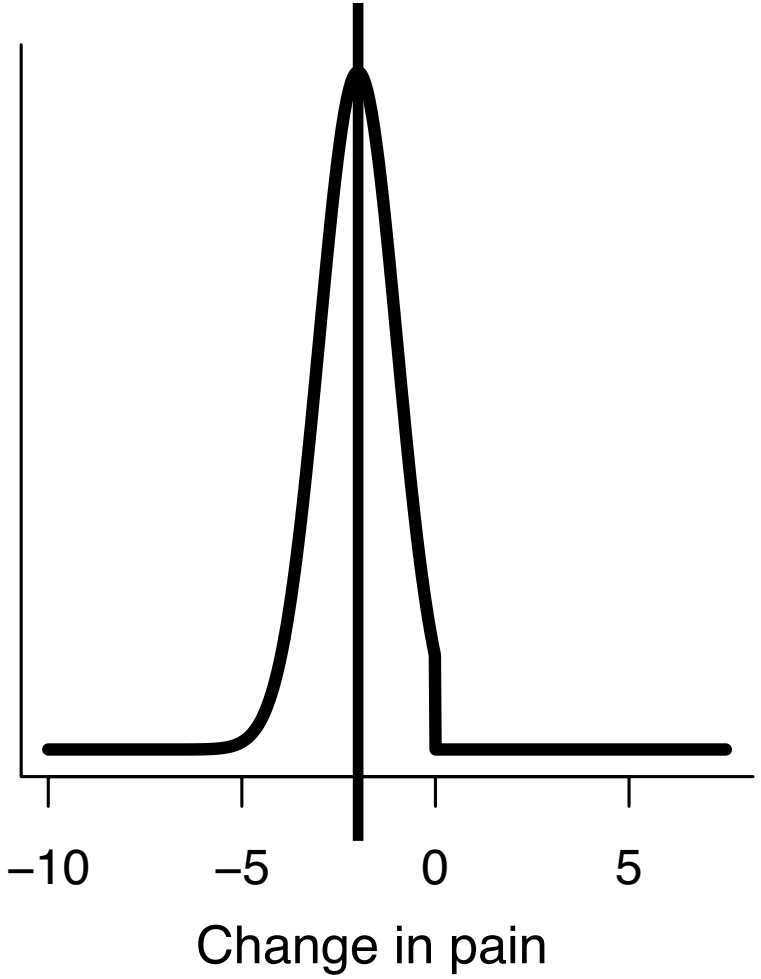
Ref. McElreath, R. (2020). Statistical rethinking: A Bayesian course with examples in R and Stan. Chapman and Hall/CRC.

Posterior probabilities



Bayes: Probability for each parameter value

The strongest probability that the pill decreases the pain by 2

Most of the probability mass supports the decrease from 0-5

Frequentist: Assuming the drug does not change the pain, our data is aligned/ rare… (p-value)

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Ref. McElreath, R. (2020). Statistical rethinking: A Bayesian course with examples in R and Stan. Chapman and Hall/CRC.

The frameworks answer a ’different question’

Frequentist

The probability of our **data**, assuming a fixed parameter value

- *Probability* only in the data, cannot apply to the parameter that is something for sure (we just don’t know it)

Bayesian

The probability of different **parameter** values

- *Probability* in the data but also in the parameter
- Prior knowledge
- *Subjective* probability

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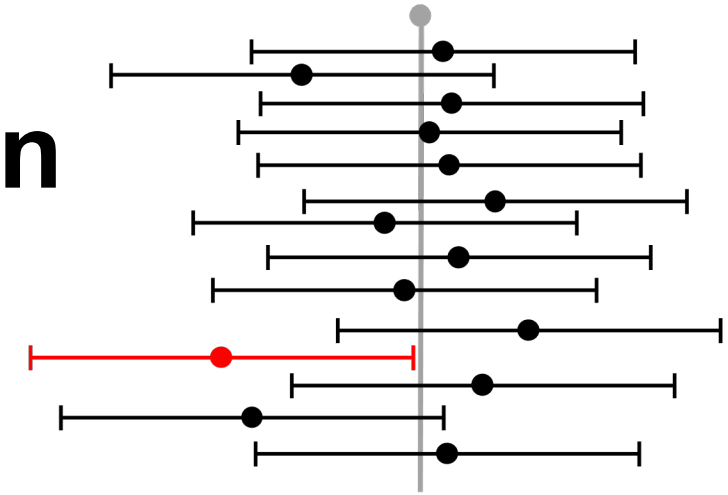
Refs. McElreath, R. (2020). Statistical rethinking: A Bayesian course with examples in R and Stan. Chapman and Hall/CRC; Holopainen, M. & Pulkkinen P. (2012). *Tilastolliset menetelmät*. Sanoma Pro Oy.

Multiple comparison correction



Multiple comparison= hypothesis testing multiple times

→ increased risk for false null-hypothesis rejection

→ correct the p-value (e.g. Bonferroni p-value*number of comparisons/ tests)

No (p-value based) hypothesis testing in Bayesian modeling, no corrections needed

Refs. Hollestein, L. M., Lo, S. N., Leonardi-Bee, J., Rosset, S., Shomron, N., Couturier, D. L., & Gran, S. (2021). MULTIPLE ways to correct for MULTIPLE comparisons in MULTIPLE types of studies. *British Journal of Dermatology*, *185*(6), 1081-1083.; Gelman, A., Hill, J., & Yajima, M. (2012). Why we (usually) don't have to worry about multiple comparisons. *Journal of research on educational effectiveness*, *5*(2), 189-211.

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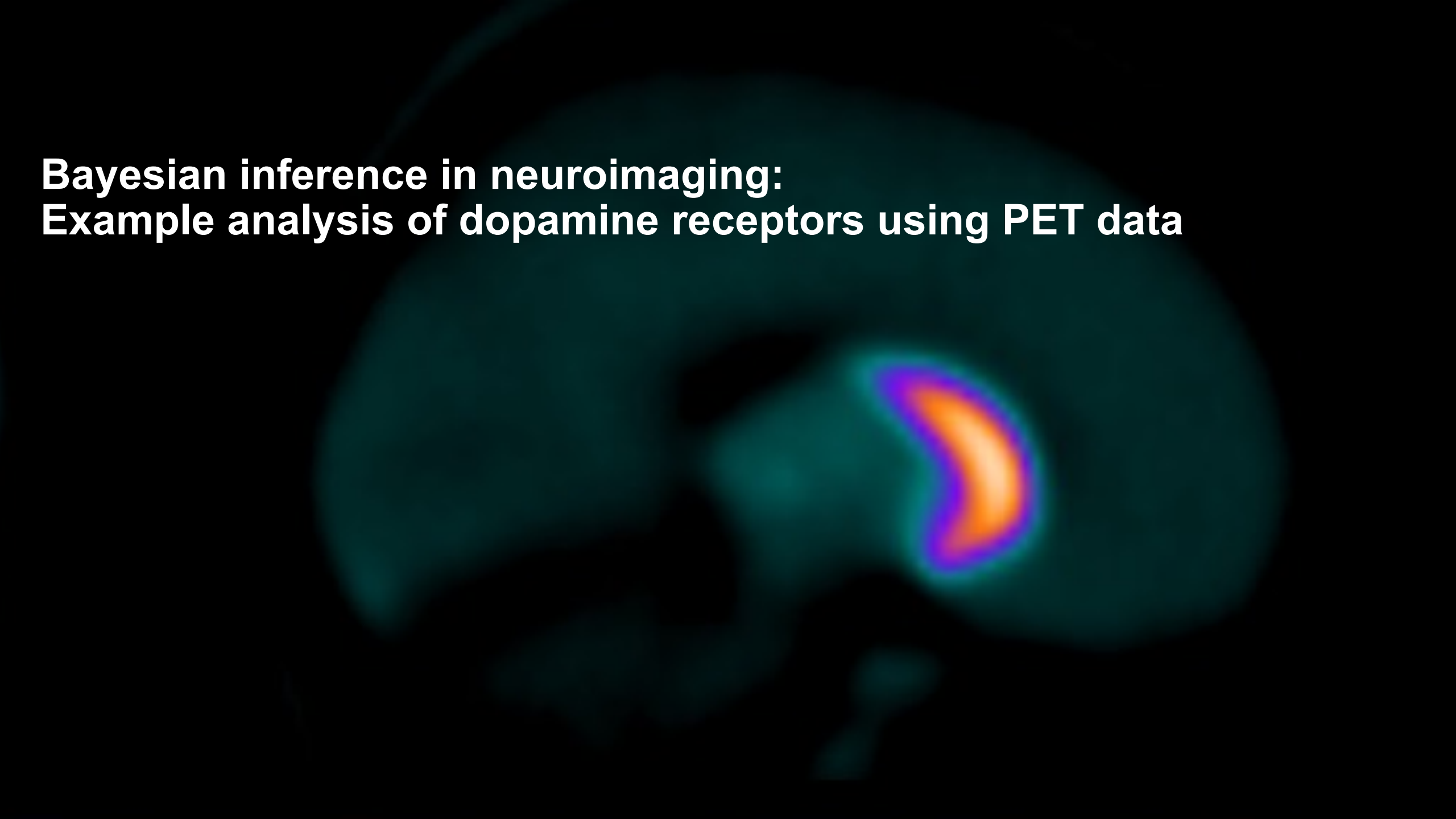
Bayesian inference in neuroimaging:
Example analysis of dopamine receptors using PET data



Dopamine

the molecule of more…and much more!

Emotions (excitement, reward)

Cognition (attention, learning)

Behavior, motor function (voluntary movement)

Goal-directed behavior

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Refs. Beaulieu, J. M., Espinoza, S., & Gainetdinov, R. R. (2015). Dopamine receptors–IUPHAR R eview 13. *British journal of pharmacology*, *172*(1), 1-23.; Bonci, A., & Hopf, F. W. (2005). The dopamine D2 receptor: new surprises from an old friend. *Neuron*, *47*(3), 335-338., Lieberman, D. Z., & Long, M. E. (2018). *The Molecule of More: How a Single Chemical in Your Brain Drives Love, Sex, and Creativity--and Will Determine the Fate of the Human Race*. BenBella Books.

Dopamine

the molecule of more…and much more!

Emotions (excitement, reward)

Cognition (attention, learning)

Behavior, motor function (voluntary movement)

→ Neuropsychiatric symptoms

Goal-directed behavior

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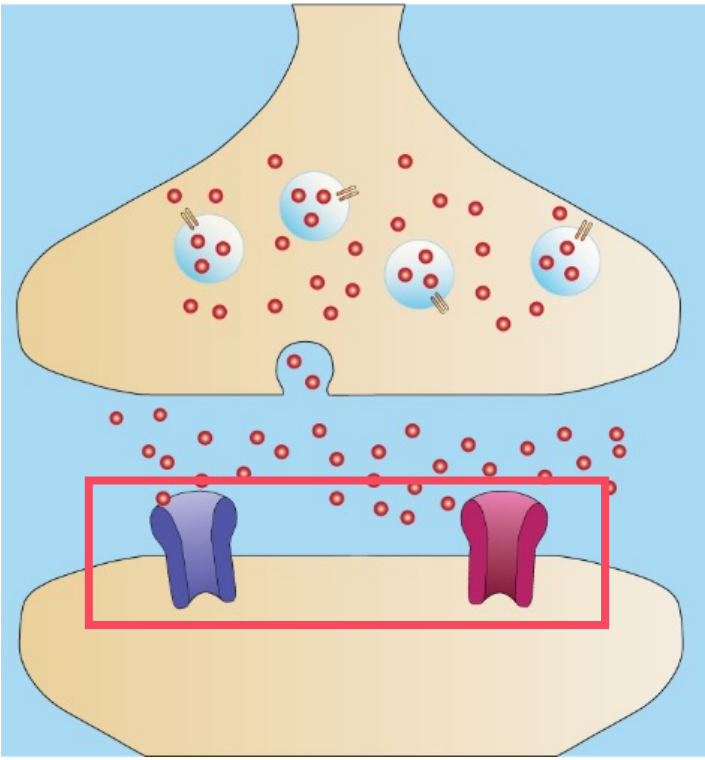
Refs. Beaulieu, J. M., Espinoza, S., & Gainetdinov, R. R. (2015). Dopamine receptors–IUPHAR R eview 13. *British journal of pharmacology*, *172*(1), 1-23.; Bonci, A., & Hopf, F. W. (2005). The dopamine D2 receptor: new surprises from an old friend. *Neuron*, *47*(3), 335-338., Lieberman, D. Z., & Long, M. E. (2018). *The Molecule of More: How a Single Chemical in Your Brain Drives Love, Sex, and Creativity--and Will Determine the Fate of the Human Race*. BenBella Books.

Dopamine receptors

Synapse

Synaptic cleft



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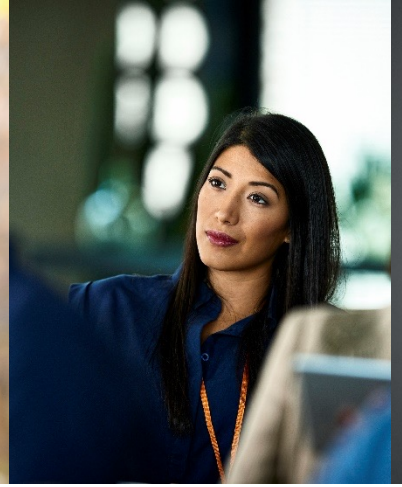
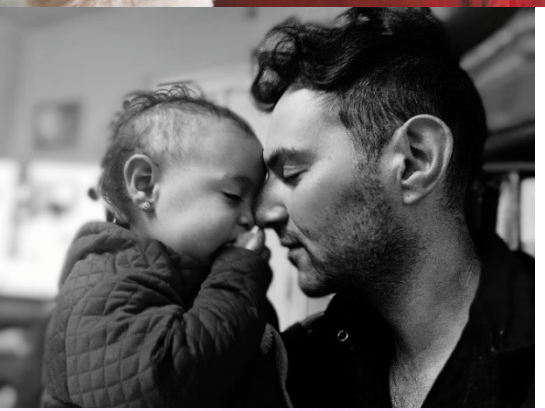
Ref. Purves, Augustine, Fitzpatrick, Hall, Lamantia, Mooney, Platt & White, 2018. Neuroscience. *Oxford University Press*.; Image: Wikimedia Commons, 21.3.2022



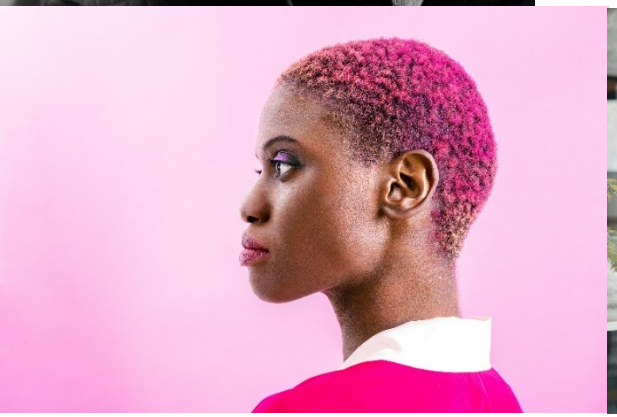


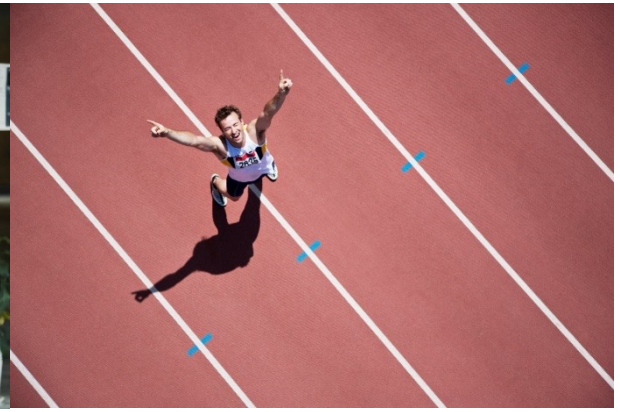


Are we different in our dopamine receptors?

→ Vulnerability to neurological and psychiatric conditions?

- *Age*
- *Sex*
- *Body mass index*





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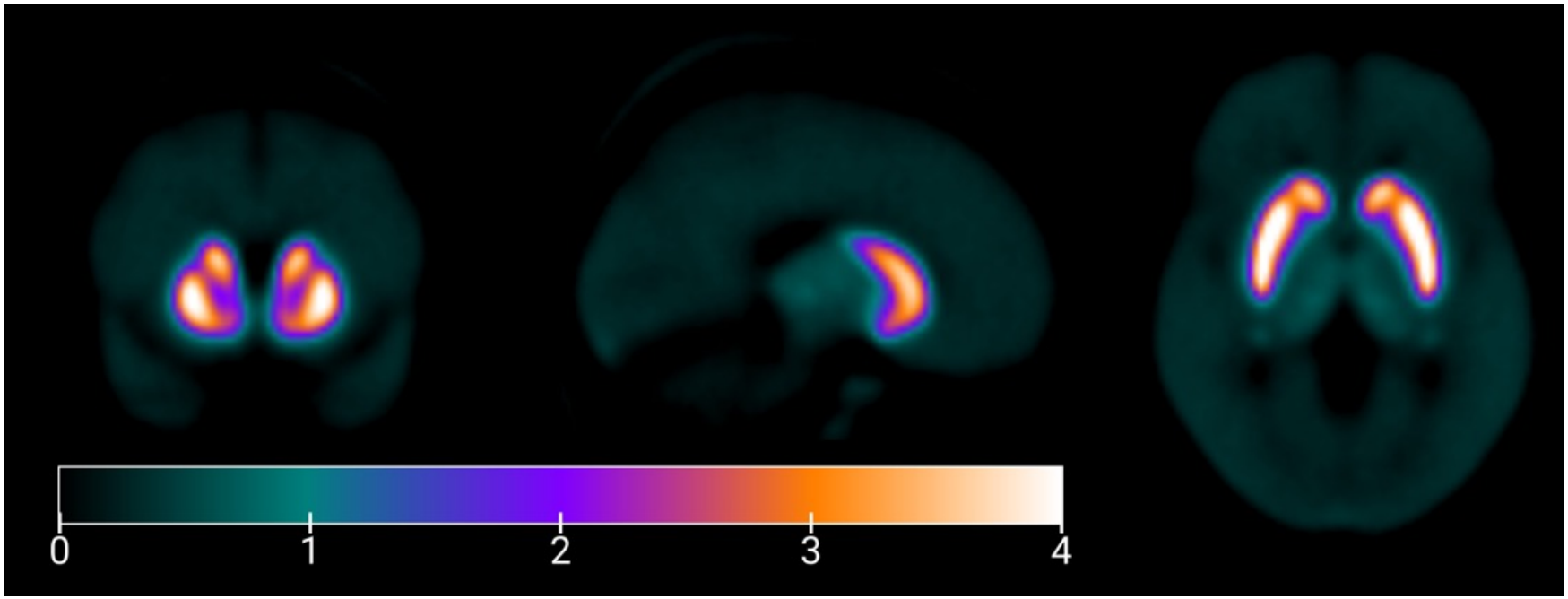
Example: Analysis based on Malén, T., Karjalainen, T., Isojärvi, J., Vehtari, A., Bürkner, P. C., Putkinen, V., ... & Nummenmaa, L. (2022). Atlas of type 2 dopamine receptors in the human brain: Age and sex dependent variability in a large PET cohort. NeuroImage, 255, 119149. (QR code).; Images. Power Point image bank

Dopamine receptors with positron emission tomography (PET)

Striatum:
Caudate nucleus



BP_{ND}= binding potential, density and affinity of unoccupied receptors, receptor availability

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Ref. Innis et al. (2007). Consensus nomenclature for in vivo imaging of reversibly binding radioligands. Journal of Cerebral Blood Flow & Metabolism, 27(9), 1533-1539.; fig. Mean [11C]raclopride BP_{ND} of 235 healthy subjects imaged at the Turku PET Centre.

Data

	Dependent variable	Predictor	Predictor	Predictor
Subject	**BP_{ND} (caudate)**	**Age**	**Sex**	**Body mass index**
1	2.8	20	f	18
2	2.5	23	m	30
3	1.7	35	f	25
4	2.2	50	m	20
…	…	…	…	…

BP_{ND}= binding potential, density and affinity of unoccupied receptors, receptor availability

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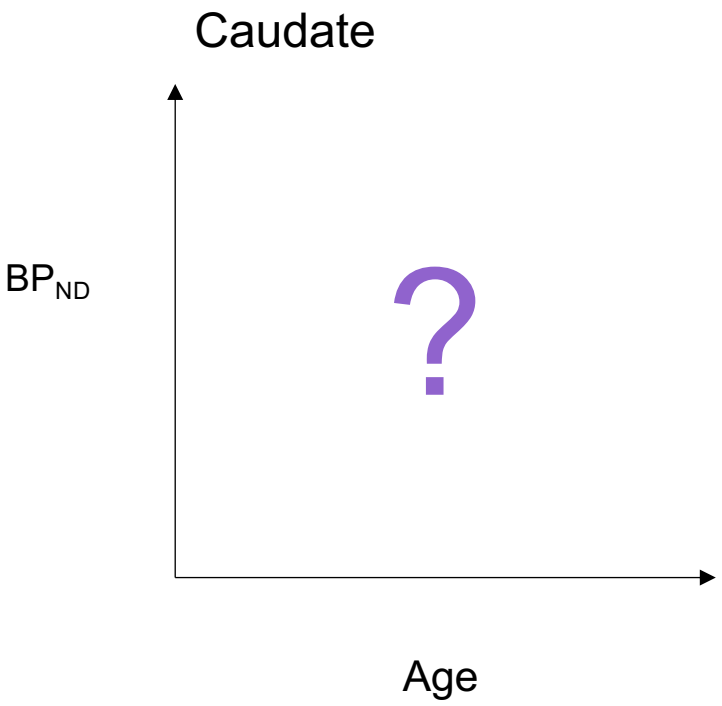
Ref. Innis et al. (2007). Consensus nomenclature for in vivo imaging of reversibly binding radioligands. Journal of Cerebral Blood Flow & Metabolism, 27(9), 1533-1539.; Data: mock-up

Regression: association

Age → BP_{ND} in caudate



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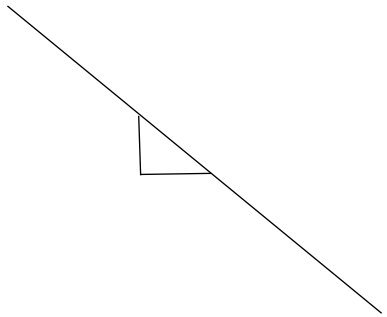
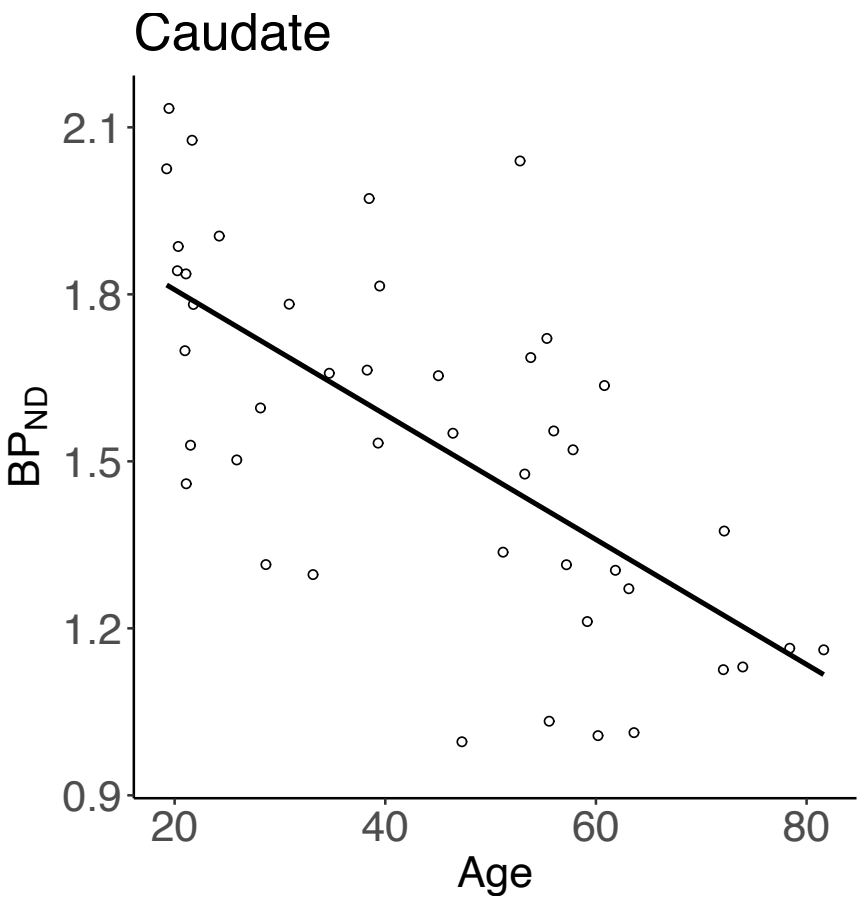
Parameter of interest

β



Regression coefficient
Ageing one unit, the change in BP_{ND}



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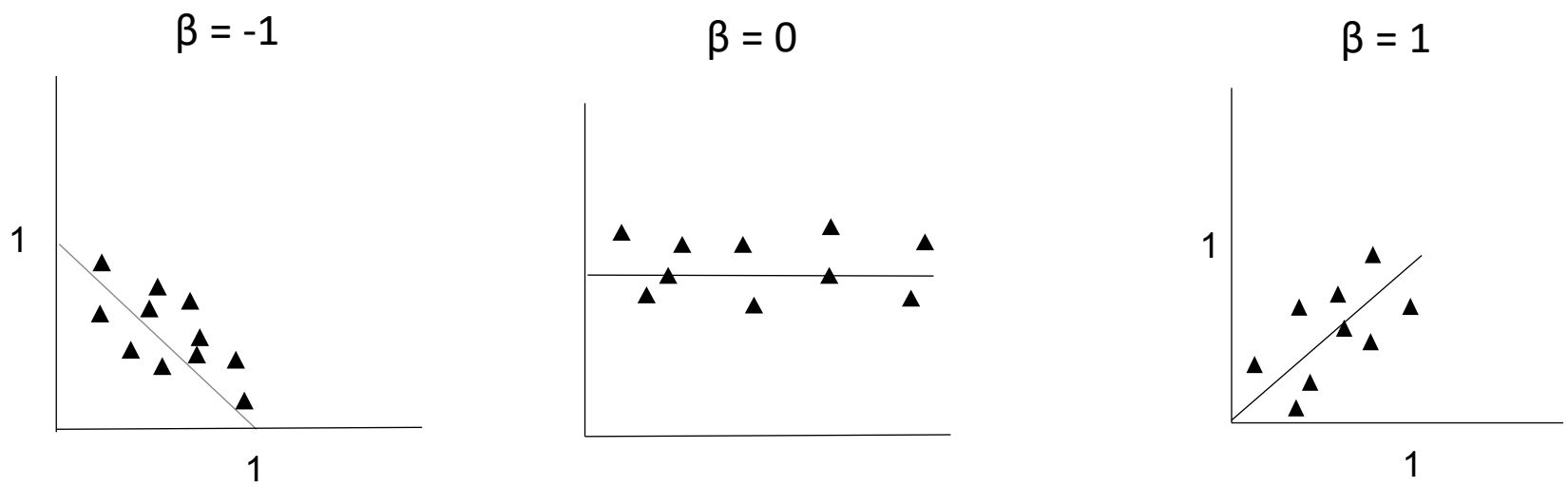
Ref. McElreath, R. (2020). Statistical rethinking: A Bayesian course with examples in R and Stan. Chapman and Hall/CRC.; Data: [11C]raclopride PET scans imaged at the Turku PET Centre



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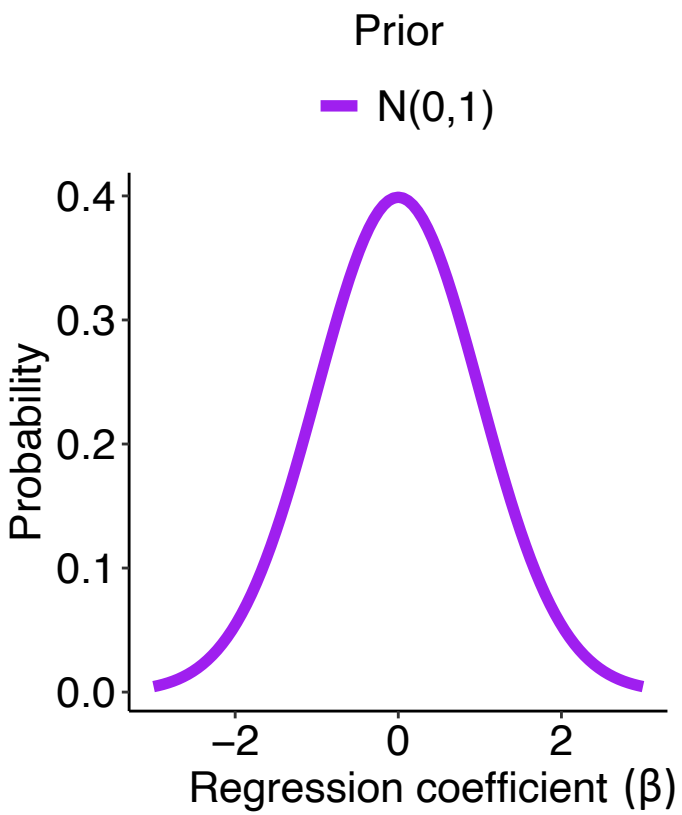
Prior for β

Prior knowledge as a probability distribution

Normal distribution with mean 0 and standard deviation of 1

- Range not limited
- Symmetrical (not weighted on either side)
- Weakly-informative: mean at zero, standard deviation wide



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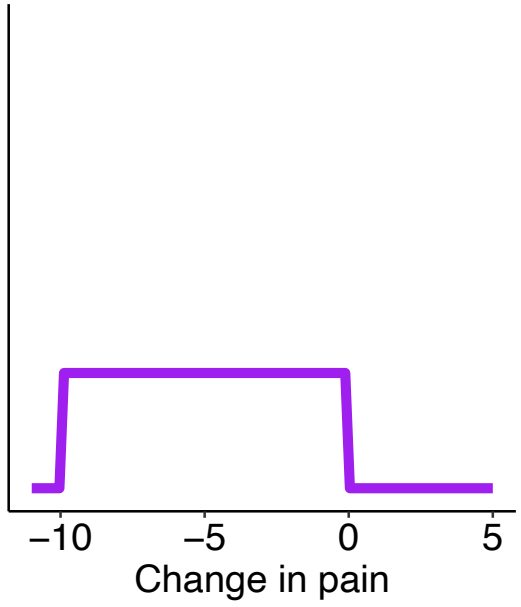
Ref. McElreath, R. (2020). Statistical rethinking: A Bayesian course with examples in R and Stan. Chapman and Hall/CRC

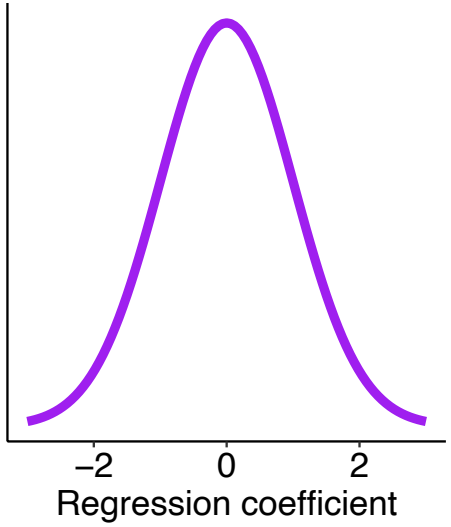
What’s great about priors?



Regularize and exclude impossible parameter values

Previous findings to priors

Direct interpretation of the parameter probabilities
(interpretation of the data in frequentist inference)



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Ref. McElreath, R. (2020). Statistical rethinking: A Bayesian course with examples in R and Stan. Chapman and Hall/CRC.

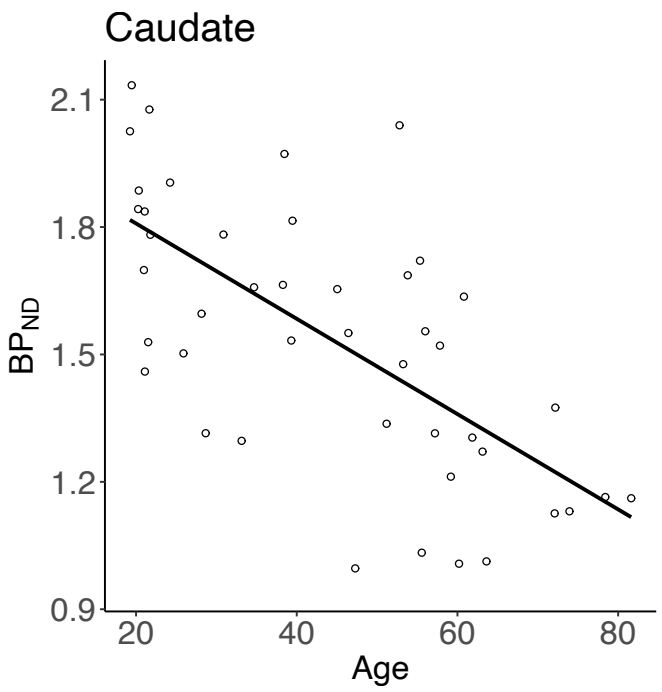
*Nothing Bayesian of frequentist about them

Model: linear regression*

BP_{ND} = Intercept + β*age + error

Intercept= BP_{ND} when age is 0

β= regression coefficient for age



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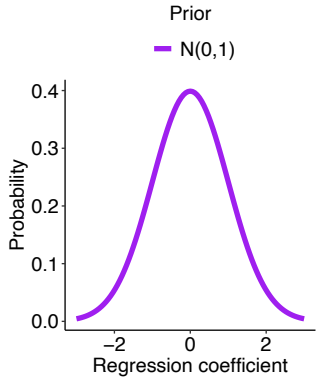
Refs. McElreath, R. (2020). Statistical rethinking: A Bayesian course with examples in R and Stan

*Nothing Bayesian of frequentist about that

Model: linear regression*



brms-package in R

```
model <- brm(formula = bf(BPND ~ 1 + age_z),
             data = data,
             prior = set_prior('normal(0,1)', class = 'b', coef = 'age_z'),
             chains = 4,
             iter = 4000,
             warmup = 1000)
```

BP_{ND} = Intercept + β*age + error

Intercept= BP_{ND} when age is 0

β= regression coefficient for age

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Refs. R Core Team (2020). R: A language and environment for statistical computing; Paul-Christian Bürkner (2017). brms: An R Package for Bayesian Multilevel Models Using Stan. Journal of Statistical Software, 80(1), 1-28. doi:10.18637/jss.v080.i01; Paul-Christian Bürkner (2018). Advanced Bayesian Multilevel Modeling with the R Package brms. The R Journal, 10(1), 395-411. doi:10.32614/RJ-2018-017; McElreath, R. (2020). Statistical rethinking: A Bayesian course with examples in R and Stan

(R is doing the tricks)

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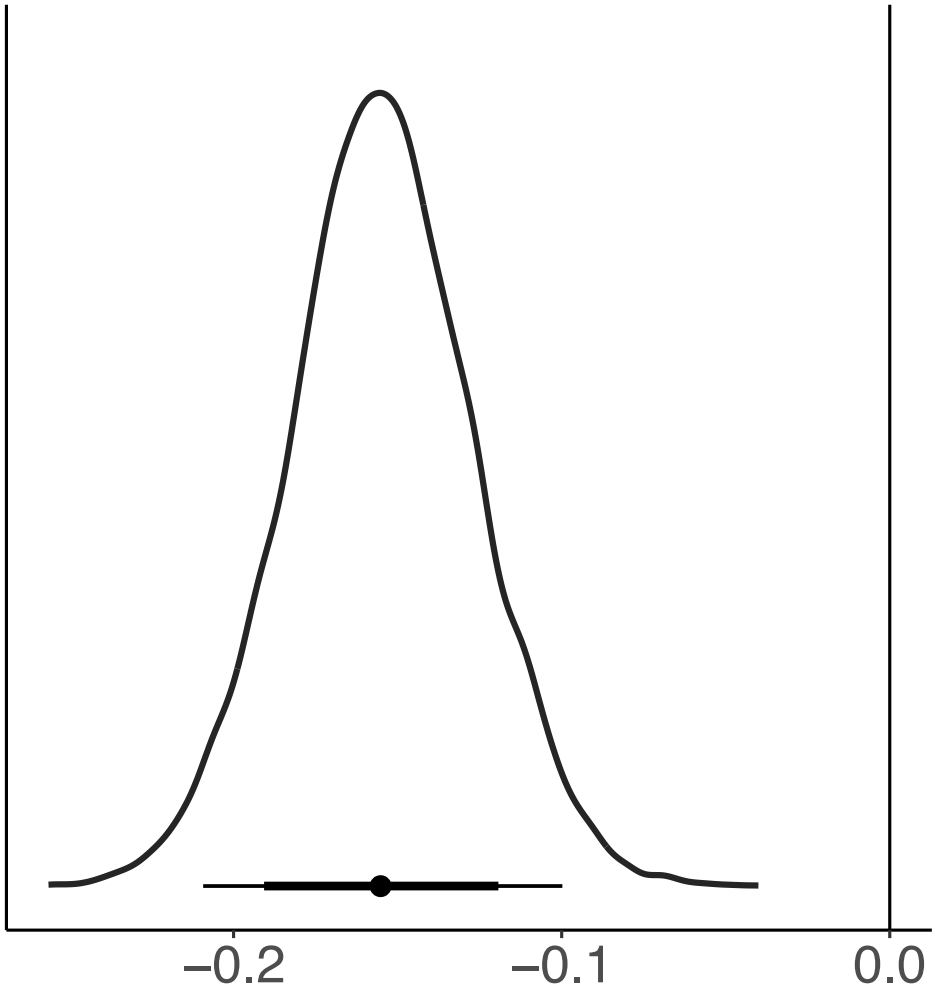
Ref. R Core Team (2020). R: A language and environment for statistical computing

Posterior age effect (beta)



	Estimate	Est.Error	Q2.5	Q97.5
Intercept	1.6723457	0.04432914	1.5853905	1.75987669
age_z	-0.1549403	0.02783491	-0.2092666	-0.09979254

Ageing 1 unit (~20 years), BP_{ND} decreases 0.1 - 0.2

→ Dopamine recepetor availability (density and/ or affinity) decreases through age in caudate

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Inspiration to the fig: Maeyer (2021, March 24). Reproducible Stats in Education Sciences: Time to switch?. Retrieved from https://svendemaeyer.netlify.app/posts/2021-03-24_Time-to-Switch/

To take home

Bayesian statistical inference allows

- Direct inference on the parameter (how probable each parameter value is)
- Regularization with priors: Exclude impossible parameter values, while letting the data talk (objectivity, assumptions also in frequentist)
    - Population of Finland versus world
- Modeling without multiple comparison corrections
- Multiple ways to do inference: know your options and what question they answer to

Refs. McElreath, R. (2020). Statistical rethinking: A Bayesian course with examples in R and Stan. Chapman and Hall/CRC.; Harrison, X. A., Donaldson, L., Correa-Cano, M. E., Evans, J., Fisher, D. N., Goodwin, C. E., ... & Inger, R. (2018). A brief introduction to mixed effects modelling and multi-model inference in ecology. *PeerJ*, *6*, e4794.; Gelman, A., Hill, J., & Yajima, M. (2012). Why we (usually) don't have to worry about multiple comparisons. *Journal of research on educational effectiveness*, *5*(2), 189-211.

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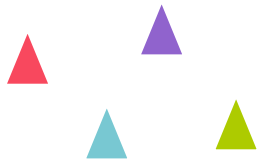
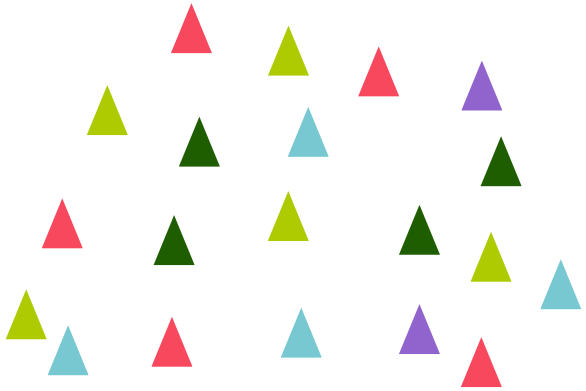
Statistical inference



Sample



Population

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Ref. Thomas D. Gauthier, Mark E. Hawley (2015). Introduction to Environmental Forensics (Third Edition).; Images: PowerPoint image bank.

Learning Material

- Bayesian Data Analysis, by Andrew Gelman, John Carlin, Hal Stern, David Dunson, Aki Vehtari, and Donald Rubin
  - http://www.stat.columbia.edu/~gelman/book/

- McElreath, R. (2018). *Statistical rethinking: A Bayesian course with examples in R and Stan*. Chapman and Hall/CRC.
  - https://www.youtube.com/watch?v=4WVelCswXo4
  - Scripts and datasets

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Thank you!

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emotion.utu.fi

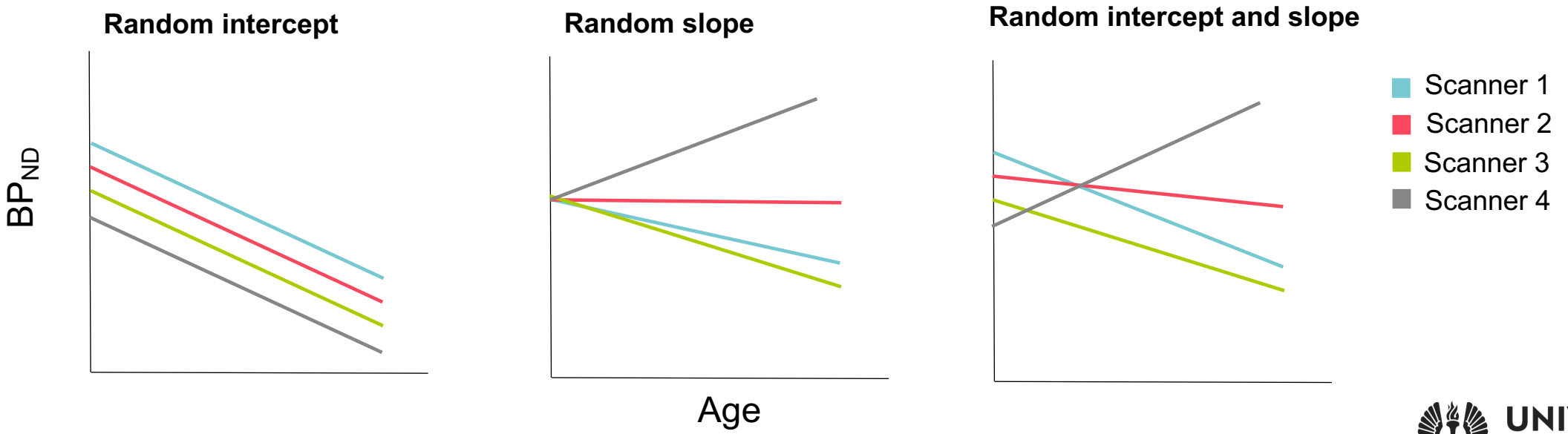
Bonus slide / Fun to know

*Nothing Bayesian of frequentist about them

Mixed effects models*

Fixed, interest in these particular levels of the variable (age), comparison between the levels

Random, random sample of the variable that groups the data (scanner) but we are not interested in the comparison of these particular levels, instead their average difference



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Ref. Harrison, X. A., Donaldson, L., Correa-Cano, M. E., Evans, J., Fisher, D. N., Goodwin, C. E., ... & Inger, R. (2018). A brief introduction to mixed effects modelling and multi-model inference in ecology. *PeerJ*, *6*, e4794. Data: mock-up for demonstration