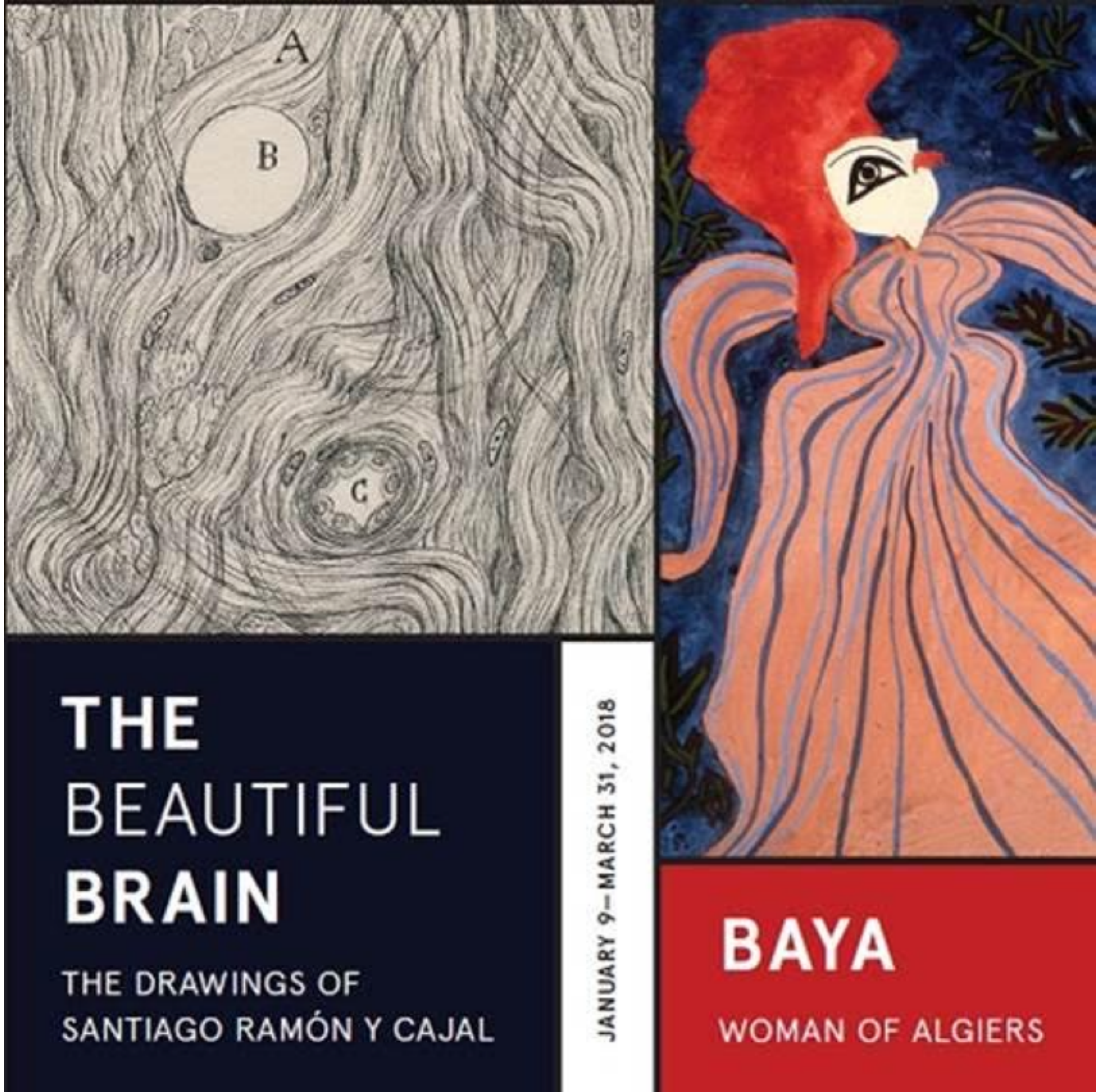
Applied Neuroscience

Computational Neuromodulation

Diseases of the Will

- Contemplators
- Bibliophiles and Polyglots
- Megalomaniacs
- Instrument Addicts
- Misfits

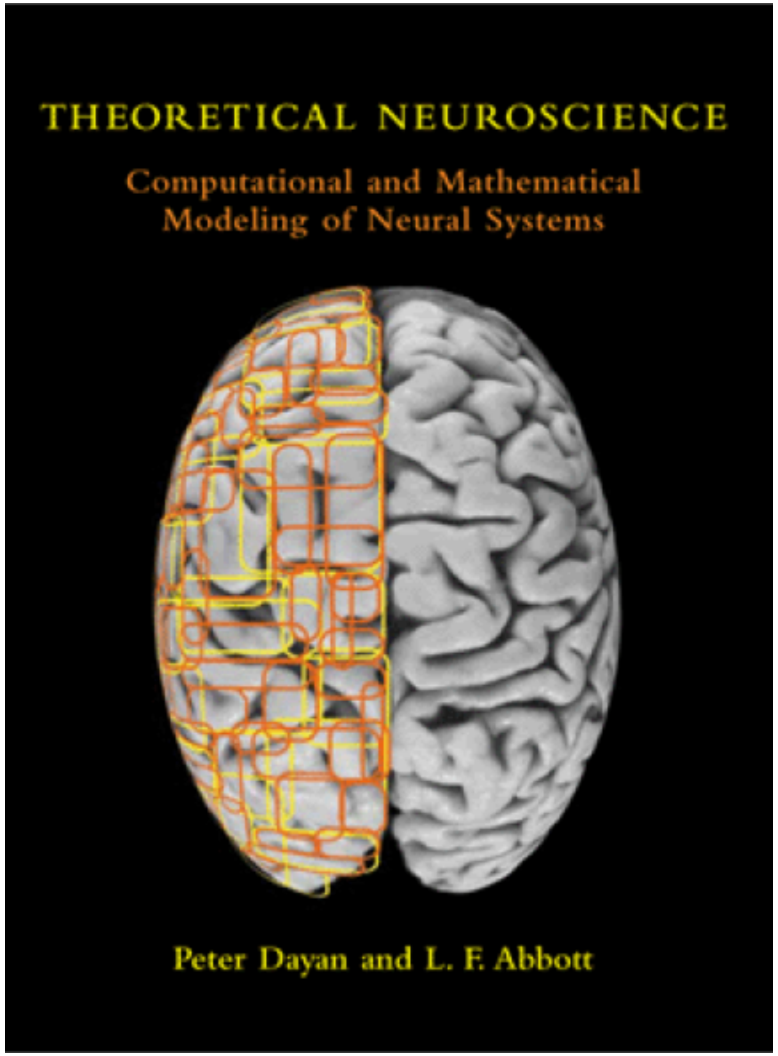
  According to Cajal



Theorists

"There are highly cultivated, wonderfully endowed minds whose wills suffer from a particular form of lethargy. Its undeniable symptoms include a facility for exposition, a creative and restless imagination, an aversion to the laboratory, and an indomitable dislike for concrete science and seemingly unimportant data… When faced with a difficult problem, they feel an irresistible urge to formulate a theory rather than question nature."

Peter Dayan, University College London

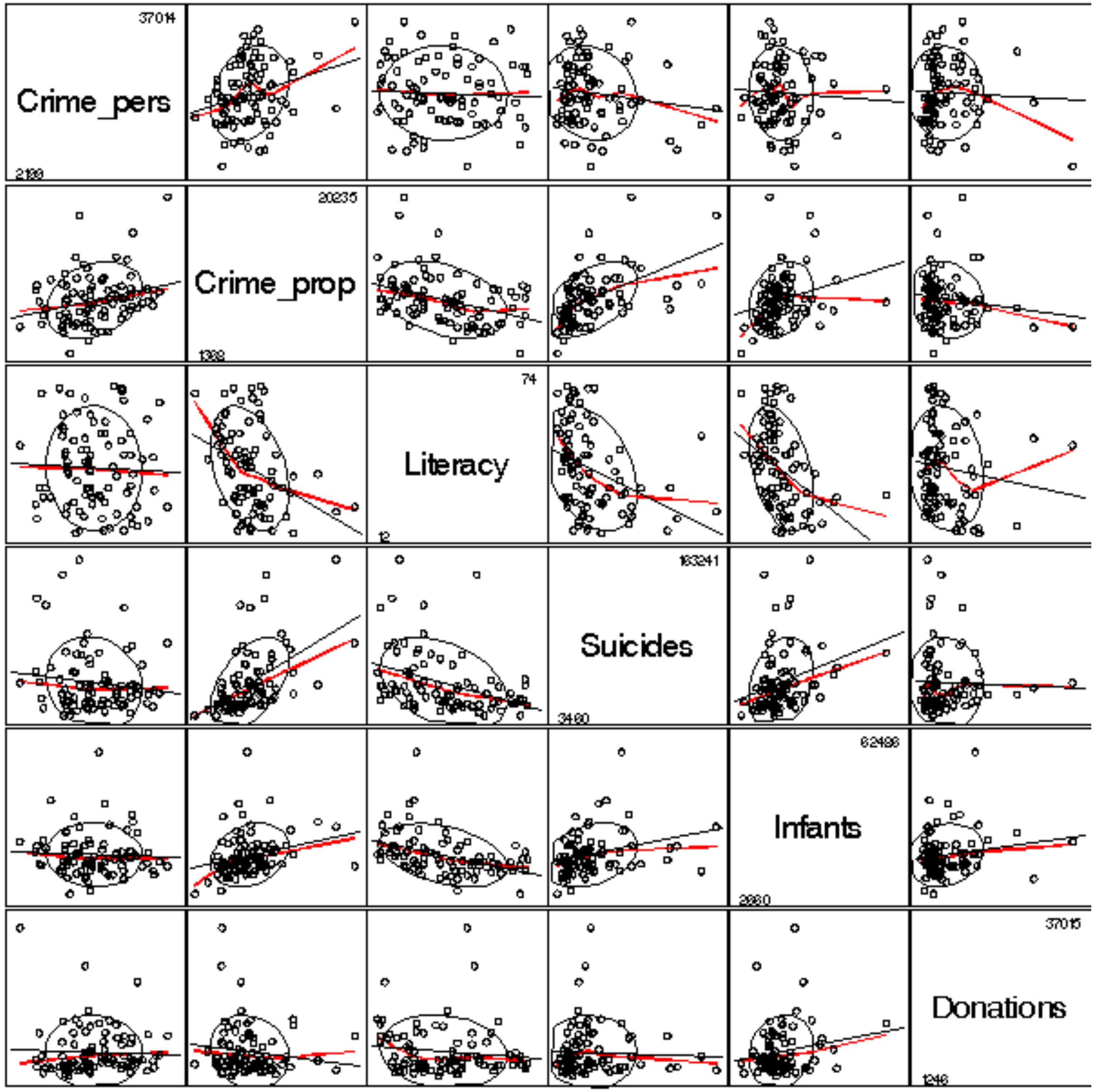


Types of data analysis

- Exploratory analysis
  - Graphical
  - Interactive
  - Aimed at formulating hypotheses
  - No rules – whatever helps you find a hypothesis
- Confirmatory analysis
  - For testing hypotheses once they have been formulated
  - Several frameworks for testing hypotheses
  - Rules need to be followed
  - In principle, you should collect a new data set for confirmatory analysis
    - Critical for drug trials
    - Not as important for basic research

Exploratory analysis

- In low dimensions:
  - Histograms
  - Scatterplots
  - Bar charts
- In high dimensions:
  - Scatterplot matrix
  - Dimensionality reduction (PCA)
  - Cluster analysis
- Does NOT confirm a hypothesis
- Requires confirmatory analysis



Confirmatory analysis

- Three types of confirmatory analysis
  - Classical hypothesis test (p-value)
  - Model selection with cross-validation
  - Bayesian inference
- Most analyses have a natural "summary plot" to go with them
  - For correlation, a scatter plot
  - For ANOVA, a bar chart
- Ideally, the summary plot makes the hypothesis test obvious

Statistics

- Statistics involves collecting, organizing, and interpreting data
- Descriptive statistics:
  - Describe what is there in our data
- Inferential statistics:
  - Make inferences from our data to more general conditions
  - Data taken from a sample is used to estimate a population parameter
  - Explain the relationship between the observed state of affairs to a hypothetical true state of affairs

  - Hypothetical testing (P-values)
  - Point estimation (confidence intervals)

Introduction to T-test

- The t-test is a basic test that is limited to two groups. For multiple groups, you have to compare each pair of groups.
  - How many tests for three groups?
  - How about seven groups?

- The basic principle is to test the ***null hypothesis*** that the means of the two groups are equal

Classical hypothesis testing

- Null hypothesis
  - What you are trying to disprove
- Test statistic
  - A number you compute from the data
- Null distribution
  - The distribution of the test statistic if the null hypothesis is true
- p-value
  - Probability of getting at least the test statistic you saw, if the null hypothesis is true

T-test

- The t-test assumes:
  - A normal distribution ***(parametric data)***
  - Underlying variances are equal
- It is used when there is random assignment and only two sets of measurements to compare
- There are two main types of t-test:
  - ***Independent-measures t-test:*** when samples are not matched
  - ***Matched-pair t-test:*** when samples appear in pairs (i.e. before and after)
- A single sample t-test compares a sample against a known figure, for example when measures of a manufactured item are compared against a required standard

Applications of T-test

- To compare the mean of a sample with population mean
- To compare the mean of one sample with the mean of another sample
- To compare between the values of one sample but in two different occasions

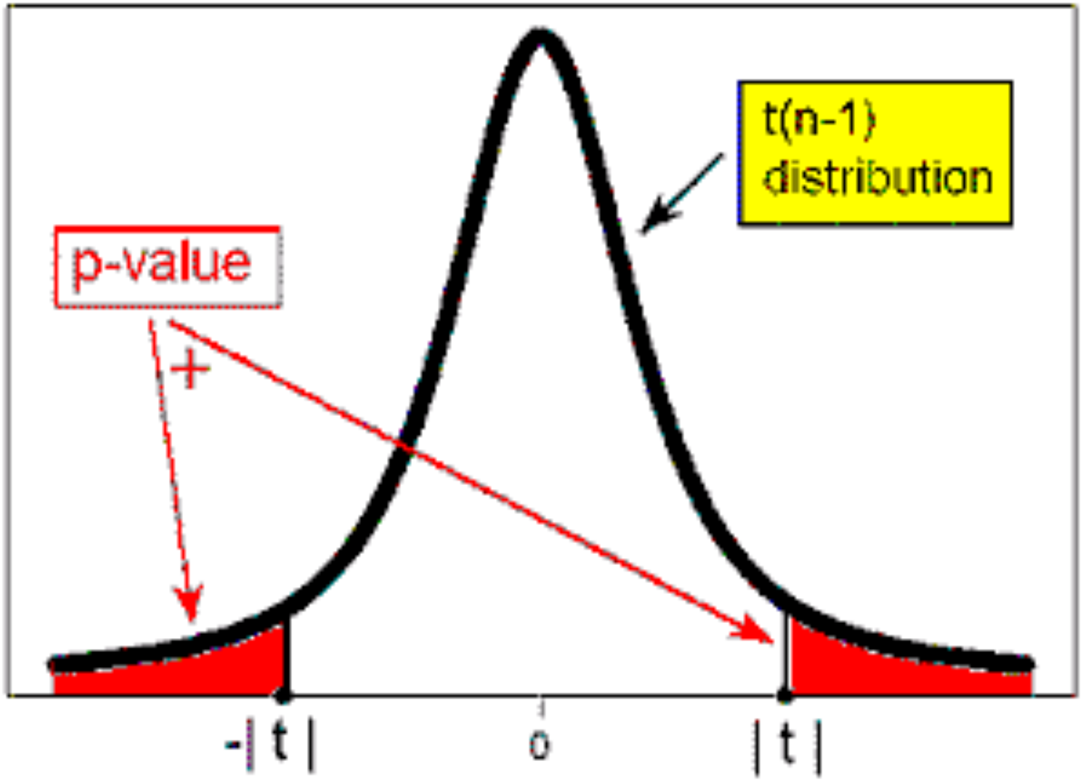
  - Degrees of Freedom = $n-1$

T-test

two sources of variation

$$t = \frac{\bar{X} - \mu}{\underbrace{s/\sqrt{n}}_{\text{Standard Error of } \bar{X} \text{ (SE of } \bar{X})}}$$

$$Ha: \mu \neq \mu_0 \Rightarrow p-value = 2P(t(n-1) \geq |t|):$$



What a p-value is

- P-value is defined as the probability of obtaining a result equal to or more extreme than what was previously observed
- The smaller the p-value, the larger the significance because it tells the researcher that the hypothesis under consideration may not adequately explain the observation

Cut-off for p-value

- Arbitrary cut-off is 0.05 (5% chance of a false positive conclusion)
- If $p < 0.05$, then result is statistically significant
  - Reject H0
  - Accept H1
- If $p > 0.05$, then result is not statistically significant
  - Accept H0
  - Reject H1

Significant Testing

- **Statistical significance** does not necessarily mean **real significance.**
  - If sample size is large, even very small differences can have a low p-value.
- Lack of significance does not necessarily mean that the null hypothesis is true
  - If sample size is small, there could be a real difference. We may lack the sensitivity to detect it.

What a hypothesis test is **NOT**

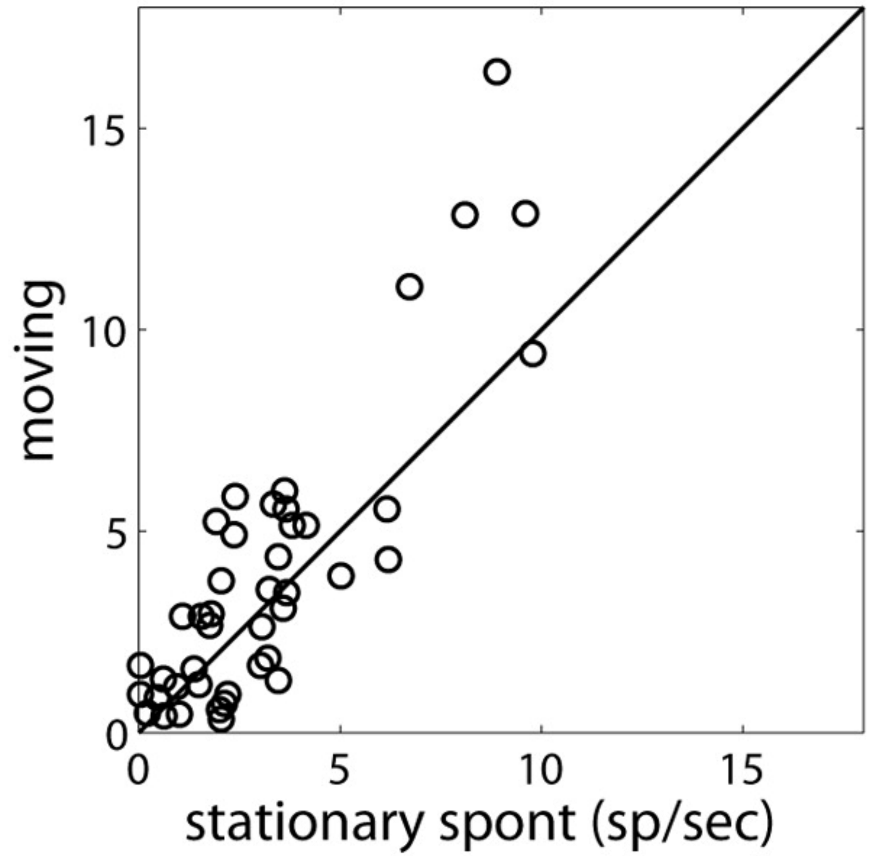
- Failure to disprove a null hypothesis tells you **nothing at all.** It does not tell you the null hypothesis is true.

- Hypothesis tests should not falsely reject the null hypothesis very often (1 time in 20)

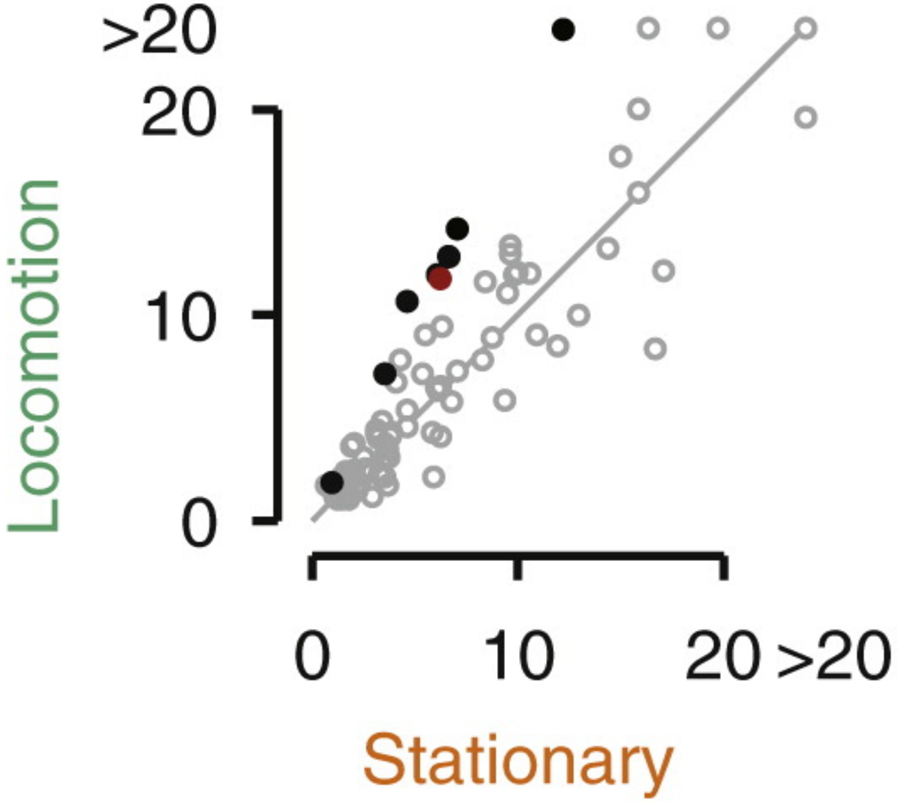
- They never falsely confirm the null hypothesis, because they **never confirm the null hypothesis.**

- There is nothing magic about the number .05, it is a convention.

Does running modulate LGN firing rates?



LGN spontaneous activity. Niell, Stryker, Neuron 2010. P>0.05



Erisken et al, Curr Biol 2014. P<.05

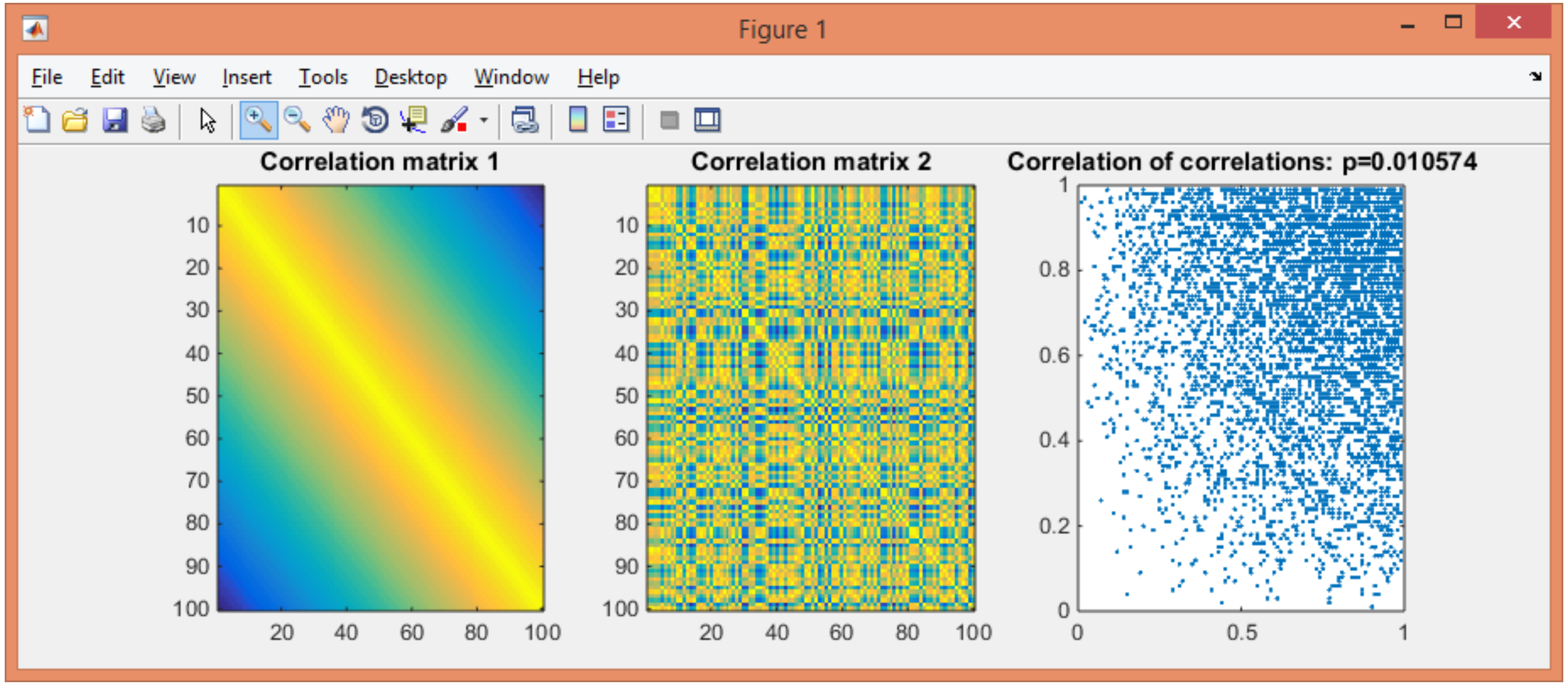
Assumptions made by hypothesis tests

- Many tests have specific assumptions e.g.
  - Large sample
  - Gaussian distribution
  - Check these on a case-by-case basis
  - This matters most when your p-value is marginal

- Nearly all tests make one additional, major assumption
  - Independent, Identically Distributed samples (**IID**)
  - Think carefully whether this holds

Example: correlation of correlations

- IID assumption violated (even excluding diagonal elements)
- False positive result for Pearson and Spearman correlation much more than 1 time in 20 (39.4%, 26.2% for chosen parameters).



Computation and the Brain

Statistical Computations

- Learning
- Sensory and memory inference
- Combining uncertain information over space and time
  - Decision-Making
    - Reward and Error

Conditioning

Prediction: of important events

Control: in light of those predictions

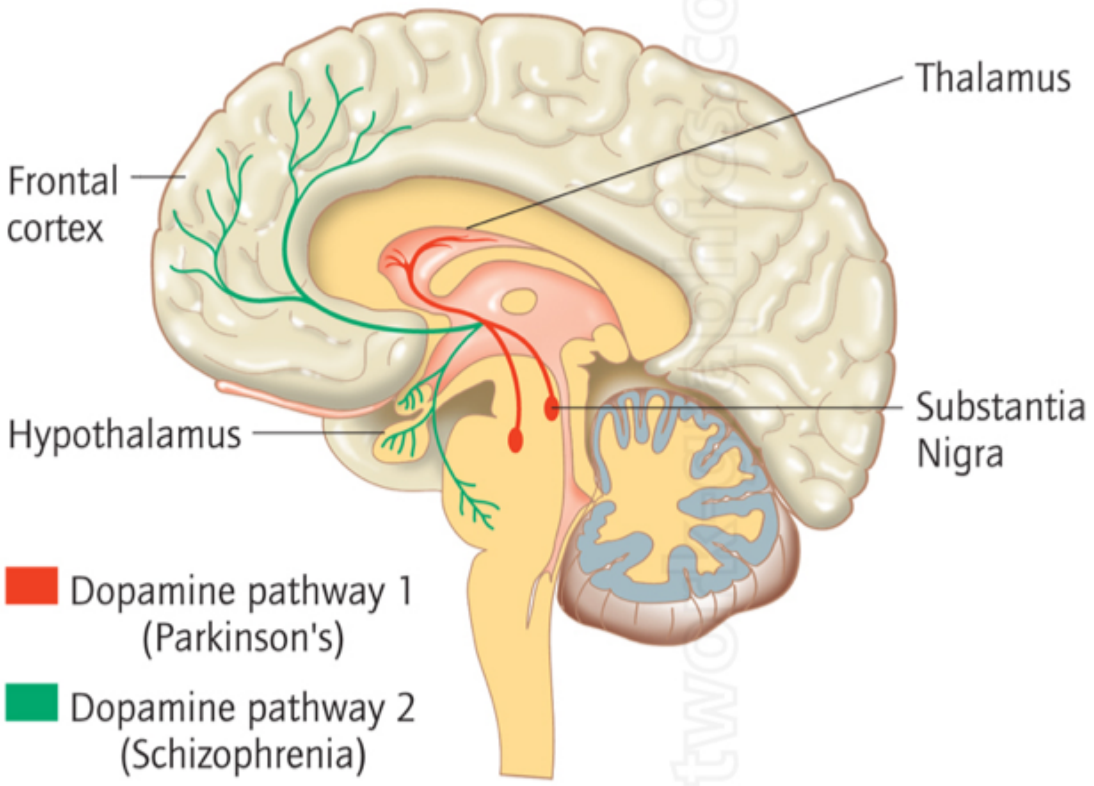
Uncertainty

Computational **functions** of uncertainty:

- Weaken **top-down** influence over sensory processing
- Promote **learning** about the relevant representations

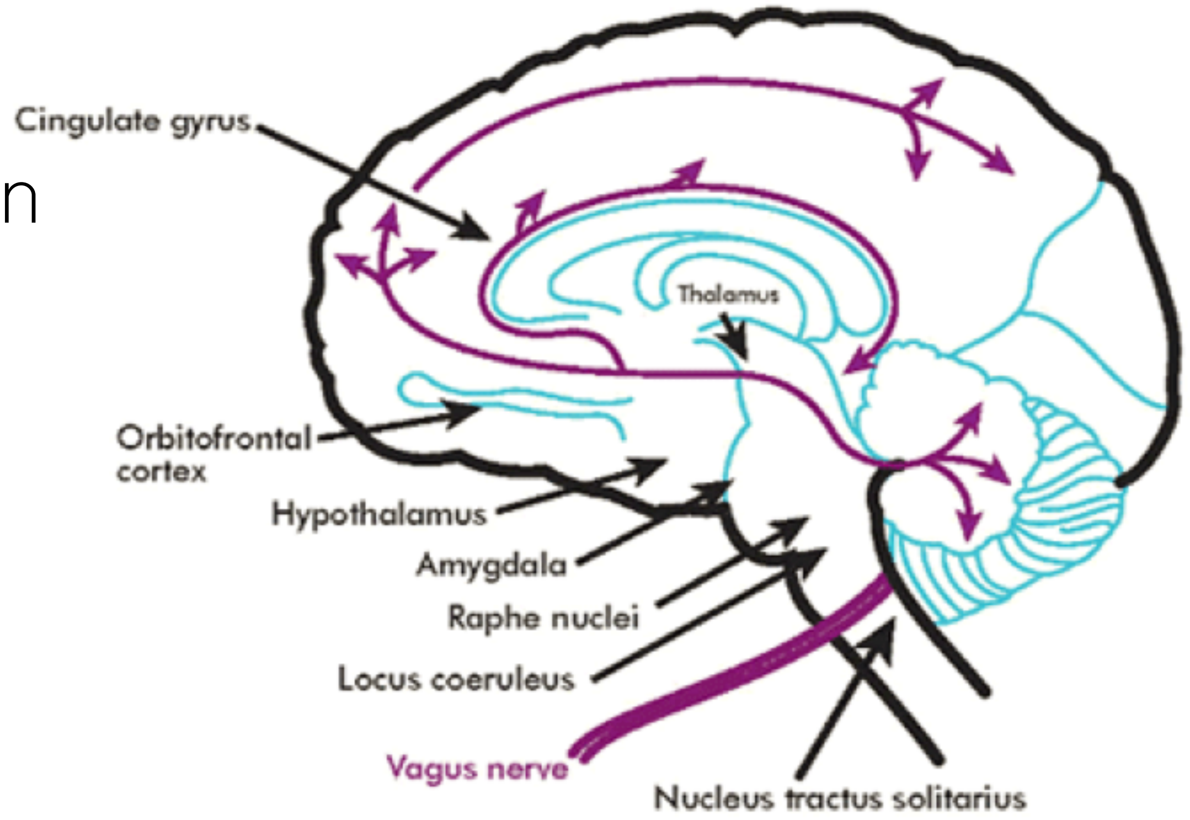
Dopamine

- Drug addiction, self-stimulation
- Effect of antagonists
- Effect on vigor
- Link to action
- *“Scalar” signal*



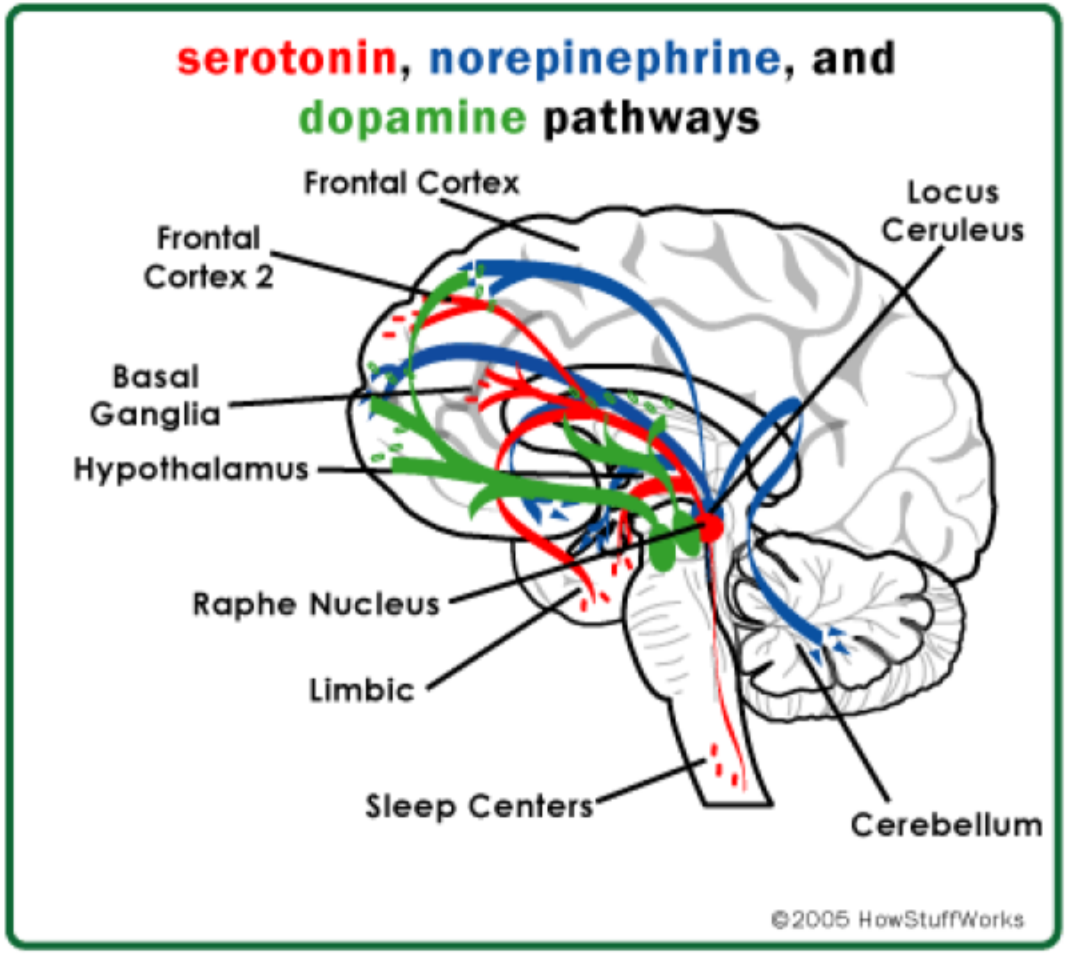
Norepinephrine

- Vigilance
- Reversals
- Modules plasticity and exploration
- Scalar quantity



Computational Neuromodulation

1. Dopamine
2. Serotonin (5-HT)
3. Norepinephrine
4. Acetylcholine



General signal:

- Excitability
- Signal to noise ratios

Specific signal:

- Prediction errors
- Uncertainty signals

Experimental Modulation

Acetylcholine (Ach) and Norepinephrine (NE) have similar **physiological** effects

- Suppress recurrent and feedback processing
- Enhance thalamo-cortical transmission
- Boost experience-dependent plasticity

Acetylcholine (Ach) and Norepinephrine (NE) have distinct **behavioural** effects

- Ach boosts learning to stimuli with uncertain consequences
- NE boosts learning upon encountering global changes in the environment

Model Scheme