The problem of reproducibility for Imaging genetics

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Reproducibility - preliminary remarks

- Reminding ourselves : Reproducibility is the backbone of scientific activity
- Reproducibility versus replicability
- Is there a problem ?
  - Not everybody is convinced that there is a problem
  - Do we have hard evidence ?
- Plan:
  - Evidence for the problem
  - Causes: especially power issues
  - What should we do

Reproducibility - evidence of the problem

- In general: Nature, "Reducing our irreproducibility", 2013.
  - A new mechanism for independently replicating findings needed: Nature Biotech. (2012)
  - Easy to misinterpret artefacts as biologically important results: Nature (2012)
  - Too many sloppy mistakes: Nature (2012)
  - Revised standard for statistical evidence (PNAS 2013)
- In epidemiology
  - Ioannidis 2011: "The FP/FN Ratio in Epidemiologic Studies:"
- In social sciences and in psychology
  - Reproducibility Project: Psychology (open science foundation)
  - Simmons, et al. "... Undisclosed Flexibility ... Allows Presenting Anything as Significant." 2011.
- In cognitive neuroscience
  - Barch, Deanna M., and Tal Yarkoni. "Special Issue on Reliability and Replication in Cognitive and Affective Neuroscience Research." 2013.

Reproducibility - evidence of the problem

- Oncology Research:
  - Begley C.G. & Ellis L. Nature, (2012): "6 out of 53 key findings could not be replicated"
- In brain imaging
  - Functional and Structural Neuroimaging: Reproducibility Issues in Multicentre MRI Studies, Jorge Jovicich, Univ. of Trento
- In genetics
  - Ionannidis 2007: 16 SNPs hypothesized, check on 12-32k cancer/control: "... results are largely null."
  - Many references and warning: eg:"Drinking from the fire hose ..." by Hunter and Kraft, 2007.
- And in imaging genetics ?

Why do we have a problem?

- Things are getting complex
- Publication pressure is high
- Mistakes are done
- **Power issues**

Why do we have a problem?

Things are getting complex

- Data complexity (eg: chip idiosynchrasis, format, preprocessings, etc)
- Data need to be linked appropriately (remember the Duke scandal)
- Data size: number of variables - files you cannot check visually
- Methods: we have to trust external software
- Methods: complexity higher

Why do we have a problem?

Publication pressure is high

- There's no way there isnt a paper out of this data set.
- You will not get your Phd if you don't publish this study
- You won't get tenure
- You won't get funding and peers recognition
- Ratio Benefice / Risk in favor of risky and quick publication
- Conclusion: the pressure is *very* high

Why do we have a problem?

Mistakes are done

The "Mistakes" argument : an unpopular topic.

- Anatomy of an Error: in praise for transparency
- The Left/Right issue
- The Siemens slice ordering
- The ADHD 1000 connectome scripts

The power issue

- Ioannidis 2005
- Remember what is power
- What exactly are the issues of low powered studies
- Tools to compute power
- What is our effect size?

The power issue

What exactly is power ?

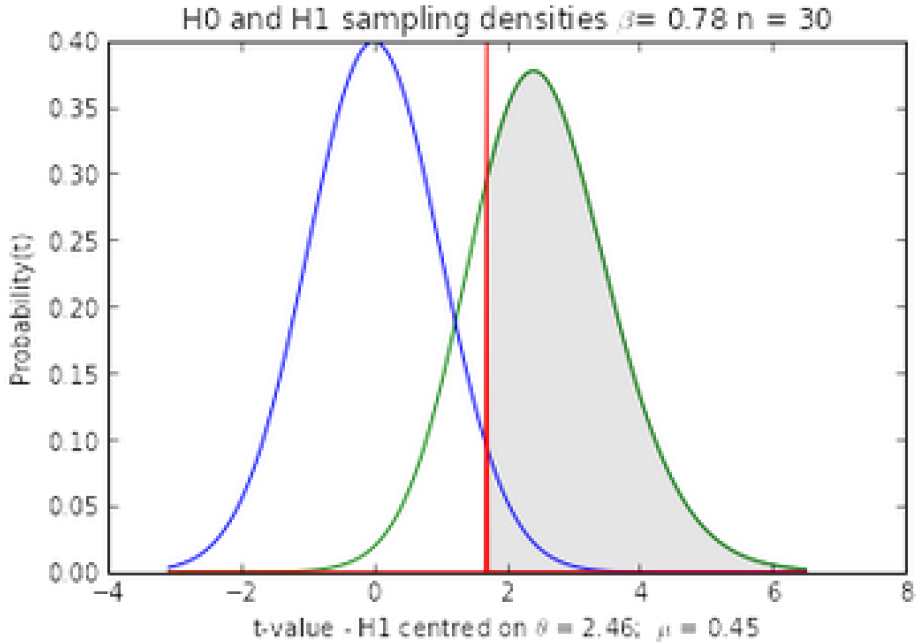


Figure: Power: $W = 1 - \beta$ Here W=77%

Relation with n :

$$\theta = \frac{\mu\sqrt{n}}{\sigma}$$

The power issue

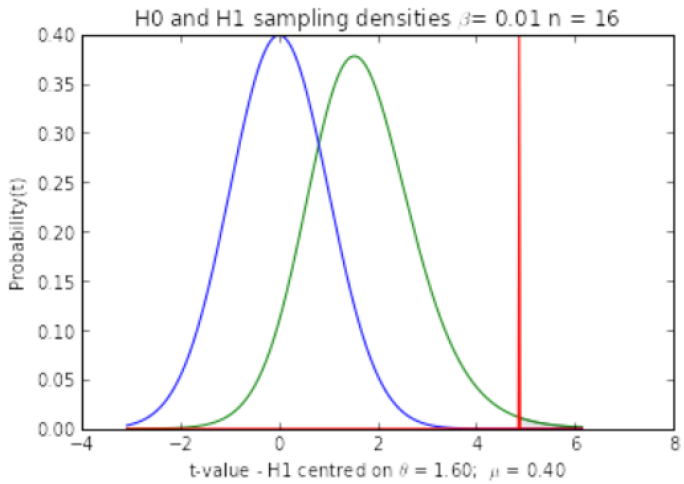
- Studies of low power have low probability of detecting an effect (indeed!)
- Studies of low power have low positive predictive value. If we have 4 chances over 5 that H0 is true (odd ratio = 1/4), and 1/5 that H1 true, with 30% power we have PPV = 60%.

$$PPV = P(H1\,True|Detection) = \frac{W\,P_1}{\alpha\,P_0 + W\,P_1}$$

odd ratio=0.25	power=0.10,	alpha=0.05	PPV=0.33
odd ratio=0.25	power=0.30,	alpha=0.05	PPV=0.60
odd ratio=0.25	power=0.50,	alpha=0.05	PPV=0.71
odd ratio=0.25	power=0.70,	alpha=0.05	PPV=0.78
odd ratio=0.25	power=0.90,	alpha=0.05	PPV=0.82

The power issue

What happens if the risk of error is increased ?



- effect on power: gets down
- effect on PPV: gets down
- effect on estimated effect size bias: gets up

The power issue

What is the estimated power in common meta analyses?

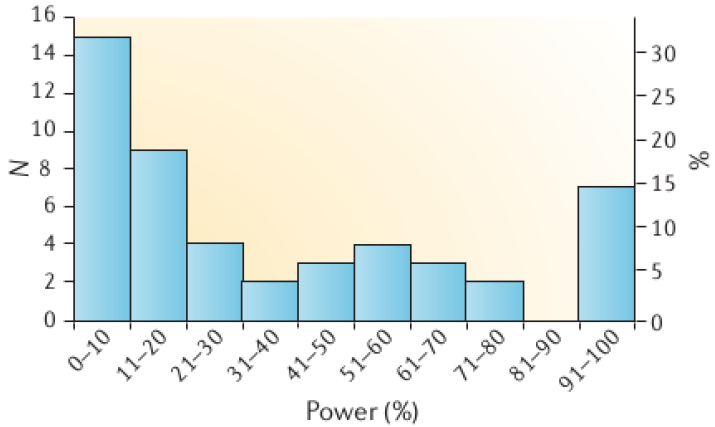


Figure: Button et al. NRN, 2013

The power issue

Studies of low power inflate the detected effect (1)

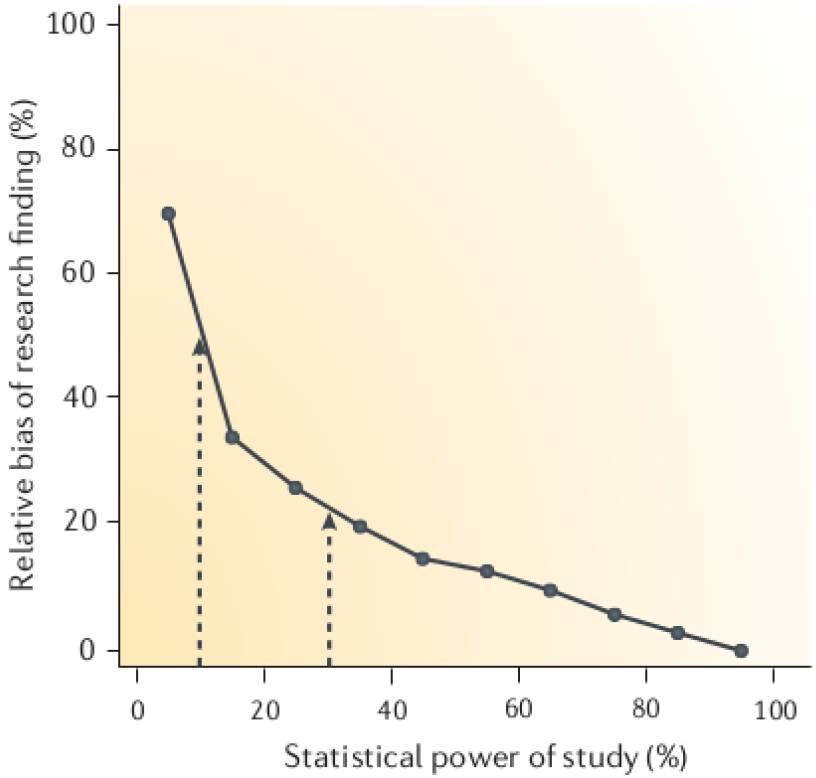


Figure: Button et al. NRN, 2013

The power issue

Studies of low power inflate the detected effect (2)

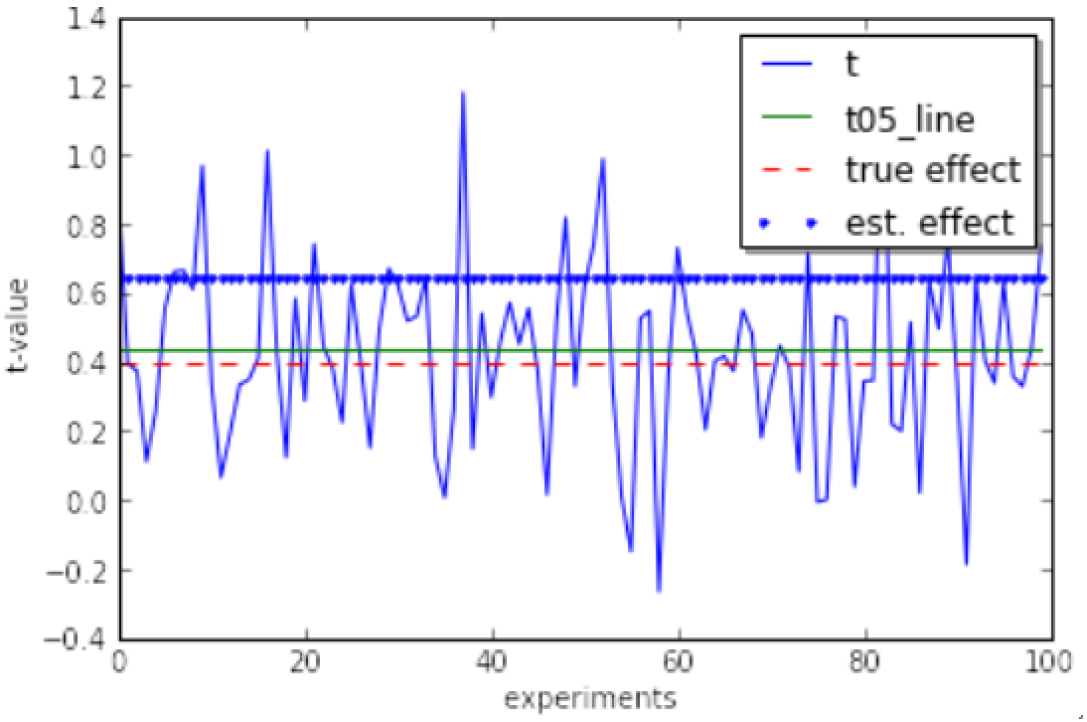


Figure: A quick simulation

What is specific to Imaging Genetics

- Combinaison of imaging and of genetics issues: "AND" (if independent: prob. of getting it right would multiply: .7 * .7 = .5)
- The combination of having to get very large number of subjects for GWAS and not being able to get them in imaging
- The multiple comparison issues
- The "trendiness" of the field
- The flexibility of analyses / exploration
- The capacity to "rationalize findings" (eg: noise in brain images is always interpretable)

Are imaging genetics studies reproducible?

- Effect size in imaging genetics:
  - HTTLPR and amygdala: Hariri 2002: p-value implies that locus explain about 28% of phenotypic variance.
  - BDNF and hippocampal volume :
  - COMT and DLPFC:
  - Stein et al, 2012: rs10784502 marker is associated with 0.58% of intracranial volume per risk allele
- reproducibility / error rate
  - Silver, Montanna, Nichols (beware of low threshold forming clusters)
  - Meyer-Lindenberg et al., 2008: Not a problem ? False positives in imaging genetics. However . . .
  - Flint and Mufano: First 2002 5-HTT result is unlikely

What are the solutions: technical

- Pre-register hypotheses
- Statistics:
  - Always try to get a sense of the power
  - Take robust statistical tools
  - Meta analysis if you can
  - Replication if you can
  - Power analyses with the smallest effect size (cost does not enter in this calculation)
  - Effect size variation estimation (bootstrapping)

Power Calculator with

- Purcell, et al. "Genetic Power Calculator [. . .]" Bioinformatics 19, no. 1 (2003): 149–50.

Modules

Case-control for discrete traits	Notes
Case-control for threshold-selected quantitative traits	Notes
QTL association for sibships and singletons	Notes
TDT for discrete traits	Notes
TDT and parenTDT with ascertainment	Notes
TDT for threshold-selected quantitative traits	Notes
Epistasis power calculator	Notes
QTL linkage for sibships	Notes
Probability Function Calculator	Notes

Figure: http://pngu.mgh.harvard.edu/~purcell/gpc/

What are the solutions: learning

- Learn the right computing tools:
  - How can I check my code ? How can I go back to a certain state ? (learn git/mercurial, learn git Annex or others)
  - How can others check my analyses? Learn the emerging social open science frameworks
- Learn "one layer below" (A. Martelli)

Train the new generation

- Statistics: in depth
- Computing: in depth
- A more collaborative (eg Enigma) and a more open science model
- Work such that the next post-doc will need weeks to start progress - not months
- Work such that others in the community can reproduce **and** build upon

What are the solutions: social

- Put some pressure on editors to
  - Accept replication studies
  - Accept preregistration
  - Increase the verifiability of analyses (code and data available)
- Share data / share intermediate results
  - Increase the capacity of the community to verify
  - Increase capacity to do meta/mega analyses
  - Because we are interested in reproducibility and replication
- Change evaluation criteria - Decrease publication pressure

Acknowledgement & Conclusion

- My colleagues in Saclay
- My colleagues in UCB
- Jason (who reviewed all talks and had quite some work with mine :) and Tom

> An article about computational science in a scientific publication is not the scholarship itself, it is merely advertising of the scholarship. The actual scholarship is the complete software development environment and the complete set of instructions which generated the figures.
>
> —D. Donoho

Figure: Donoho on publication