A Brief History of Imaging Genetics

A reproducibility perspective

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A short history of imaging genetics - the reproducibility view

- Motivations
- Quick background on genetic variations
- An historical perspective
- Some practical examples : How do I compute . . . ?
- What will we need in the future

Motivations

- Geneticists: understand the genes
- Neuroscientists: understand the brain
- Psychologists: understand the behaviour
- Clinicians:
  - Personalized medicine
  - Predictive medicine
- No great model system for human brain!

Motivations: illustration

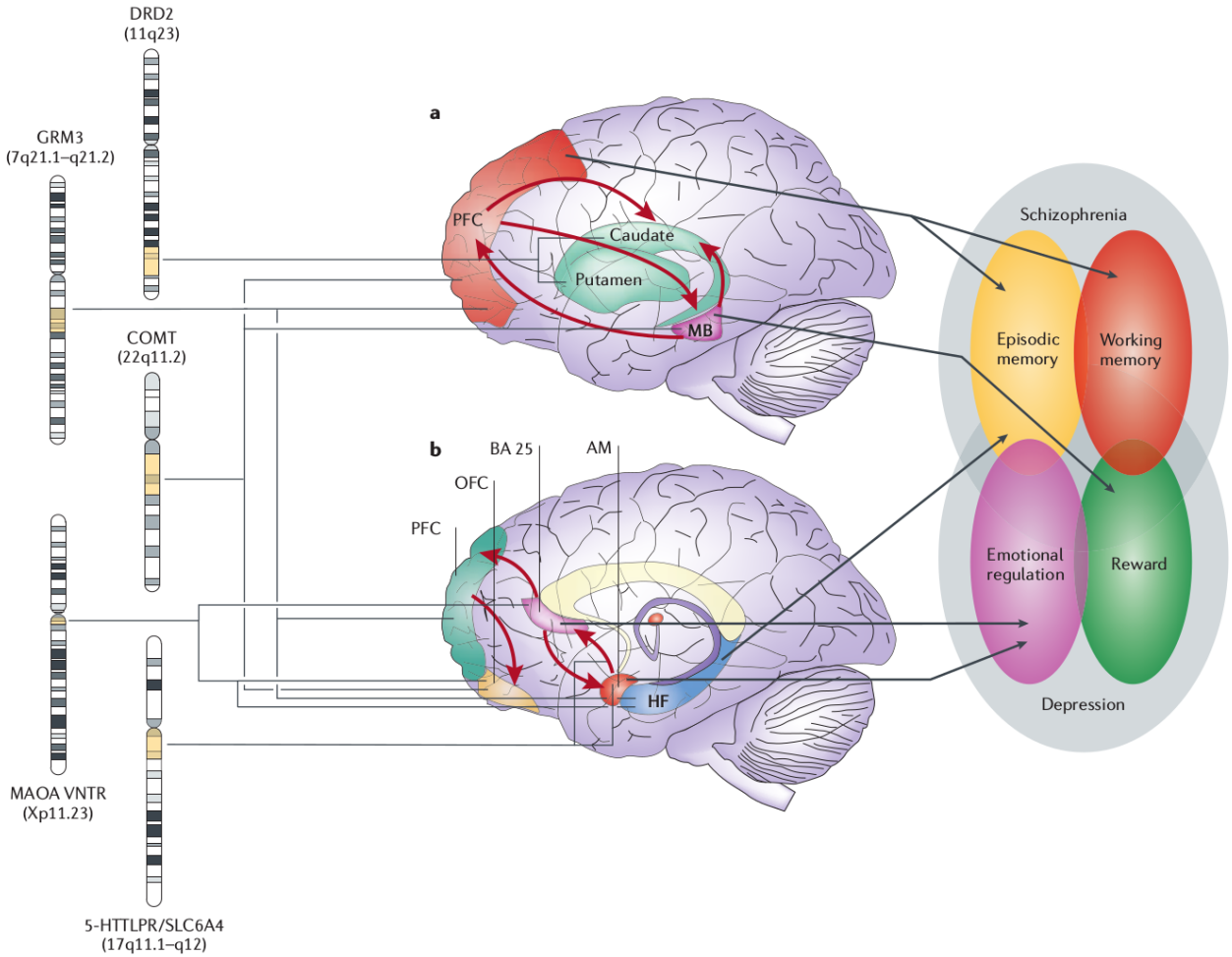


Figure 1: Meyer-Lindenberg, 2006

Genetic variations:

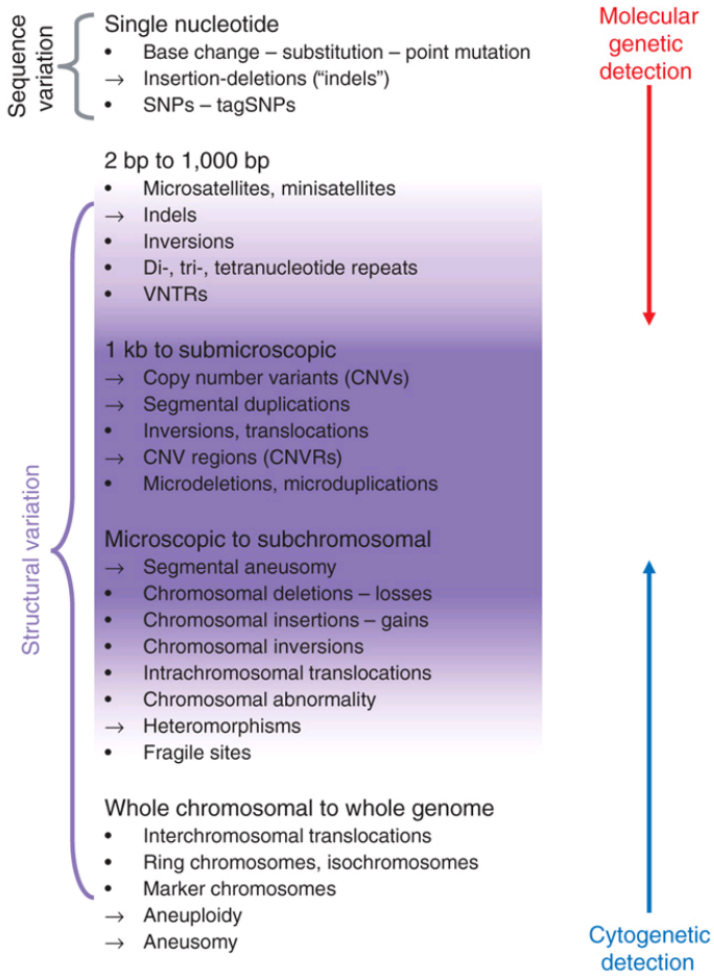
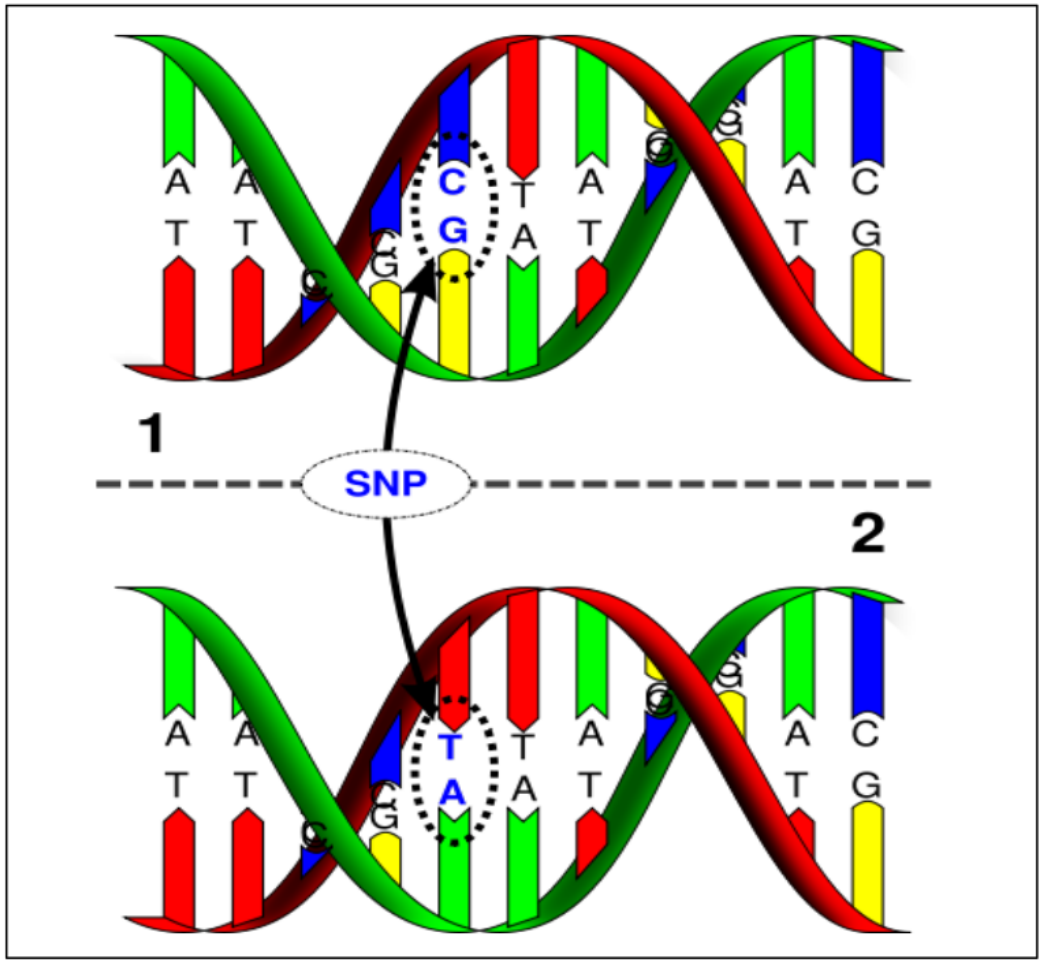


Figure 2: Scherer 2007, Credit S. Cichon

Genetic variation: SNP



C-allele: 70% frequency

C = major allele

T-allele: 30% frequency

T = minor allele

Figure 3: Credit S. Cichon

Genetic variation: CNV

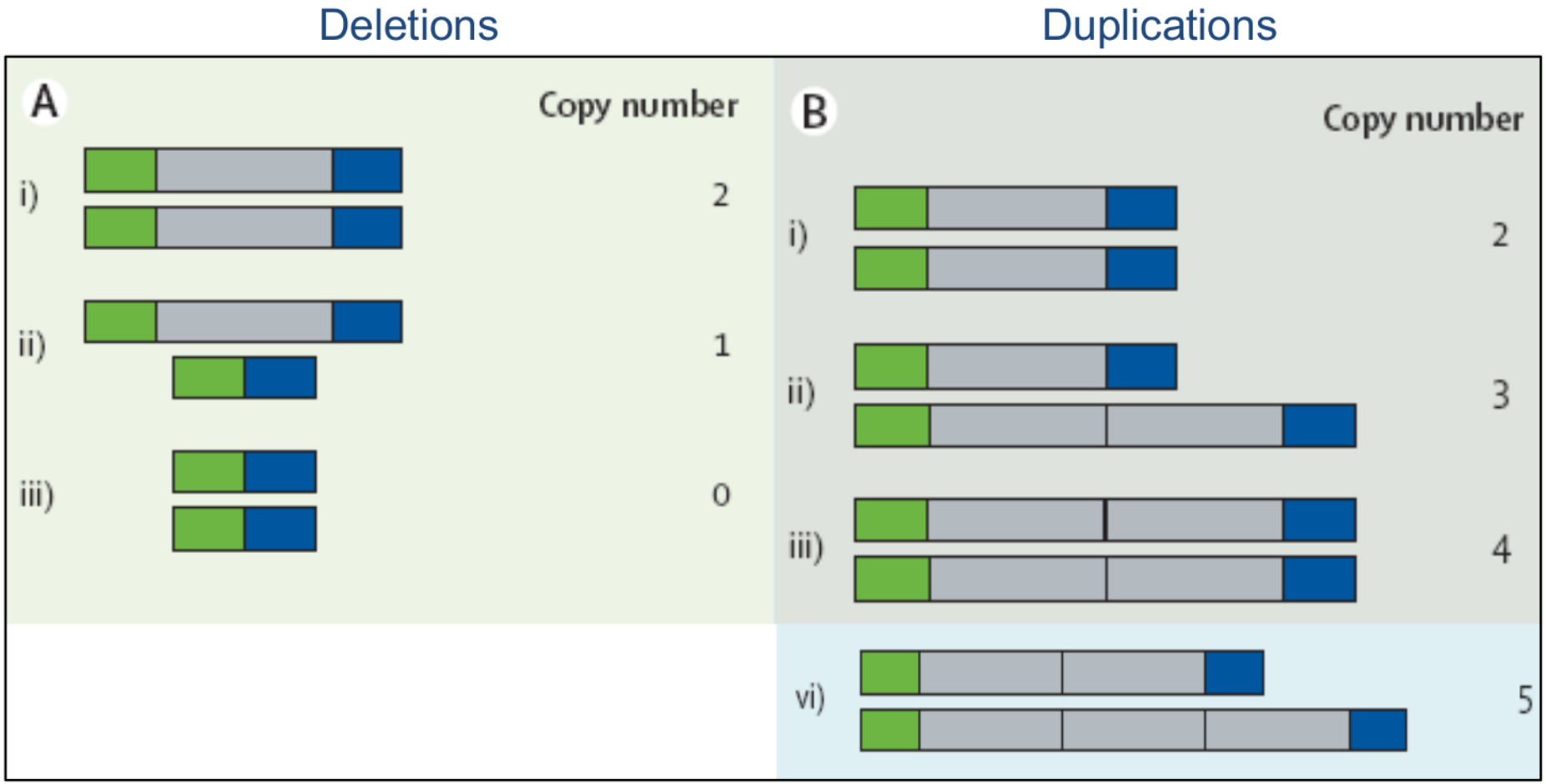


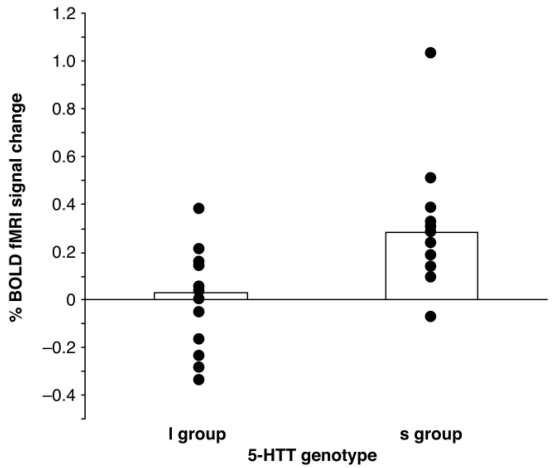
Figure 4: Credit S. Cichon

The imaging genetic studies

- One variant, small Ns
- GWAS, small then large Ns
- Genome-wide-Brain-wide
- Multivariate analyses
- [Heritability]
- Networks
- Interpretation

Some first studies: small Ns

- Example of Hariri 2002: In Fig 3, Authors report
  $m_1 = .28, m_2 = .03, \mathrm{SDM}_1 = 0.08, \mathrm{SDM}_2 = 0.05, N_1 = N_2 = 14$



- How do we compute the effect size ?
  - we know: the means, the standard deviations, and the Ns.

Computing effect size

What is the effect ?

$$\mu = \bar{x_1} - \bar{x_2}$$

What is the standardized effect ? (eg Cohen's d)

$$d = \frac{\bar{x_1} - \bar{x_2}}{\sigma} = \frac{\mu}{\sigma}$$

"Z" : Effect accounting for the sample size

$$Z = \frac{\mu}{\sigma/\sqrt{n}}$$

Computing Effect size: practice

- First, compute the standard deviation of the data from the SDM
  - get σ from SDM : $\sigma = \sqrt{14-1}\mathrm{SDM}$
  - Combine the σ to have one estimation across the groups
    - formula easy to recompute or find
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  - $V_e = \frac{(n_1+n_2)(m_1-m_2)^2}{n_1 s_1^2 + n_2 s_2^2 + (n_1+n_2)(m_1-m_2)^2} > 40\%$

Multiple hypothesis: the curse of GWAS–wise. . .

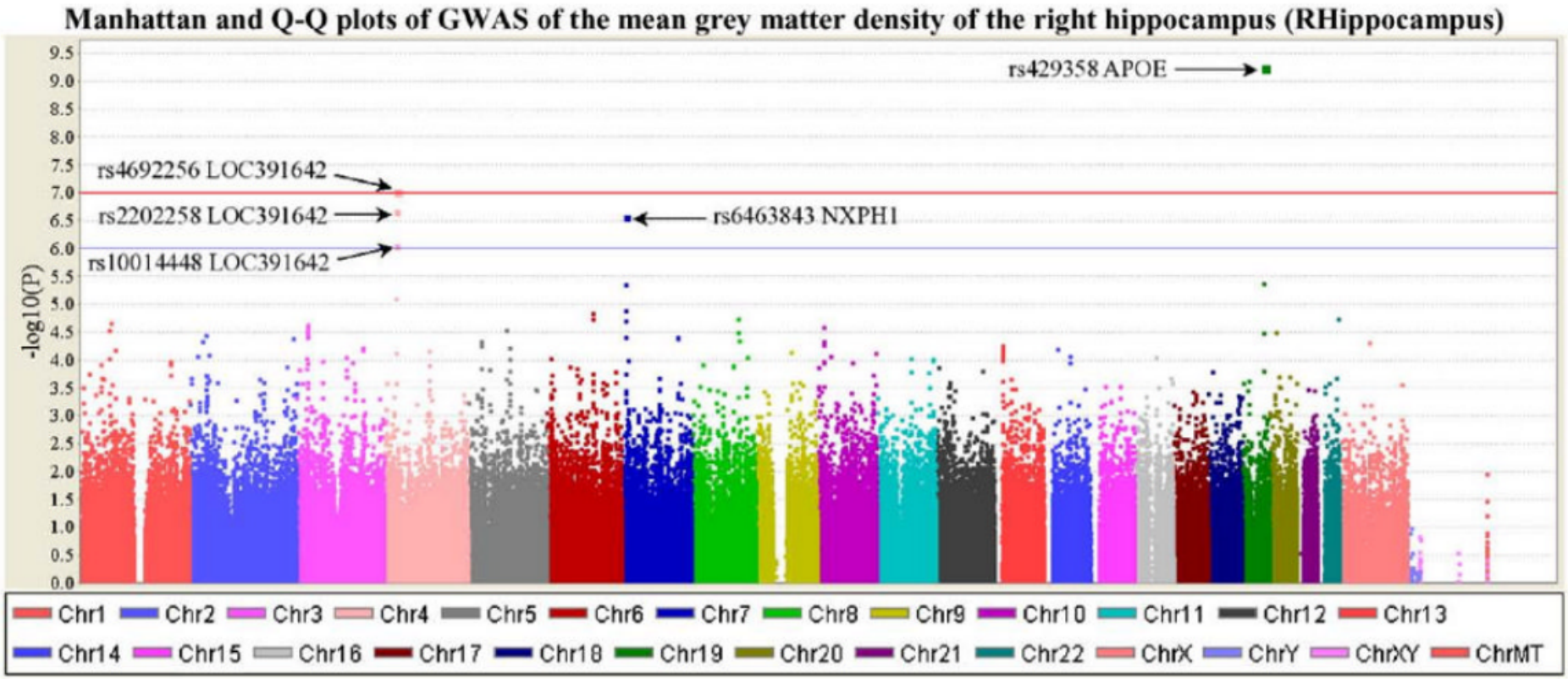

Figure 5: Shen et al., 2010

- See also Stein et al., 2010 (SNP X Voxel), Hibar et al., 2011, (Gene X Voxel)

Computing effect size in imaging genetics (2)

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  - From Z score to Cohen's d ? 6.064/sqrt(733) = 0.224
- Question: what is the power for p=5.e-8 and d=0.22, N=733?

Effect size in imaging genetics

- BDNF and hippocampal volume: genuine effect or winners curse? d=0.12, p=0.02, Molendijk (2012)

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- Stein et al, 2012: marker is associated with 0.58% of intracranial volume per risk allele
- Flint 2014: Effect size of intermediate phenotype not much greater than others
- For psychiatric diseases: mean OR is 1.15, QT: variance explained by 1 locus « 0.5%, 0.1-0.3% for protein or serum concentration

Some example of SNP effect size

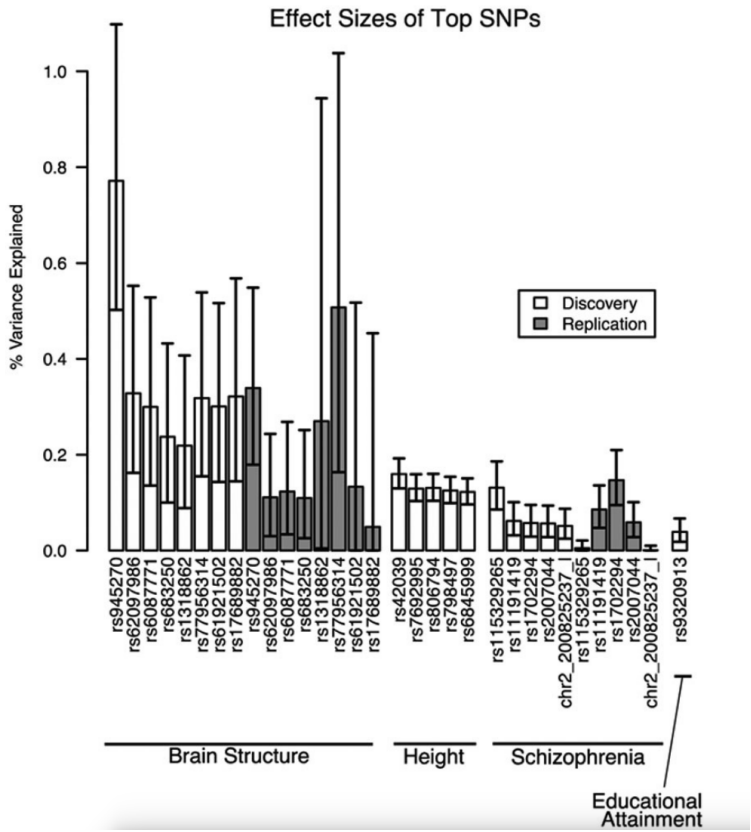


Figure 6: Franke et al., 2015

Effect size and reproducibility?

- HTTLPR and amygdala: Hariri 2002: p-value implies that locus explain $>$ 40% of phenotypic variance. d=1.05
- COMT and DLPFC: meta analysis : d = 0.55, most studies N $<$ 62 subjects (Meir, 2010)
- KCTD8 / cortical area: Paus 2012: 21% of phenotypic variance (250 subjects), d=1.03.

Multivariate approaches 1

- Why ? Effect of several genes - Effect on several regions

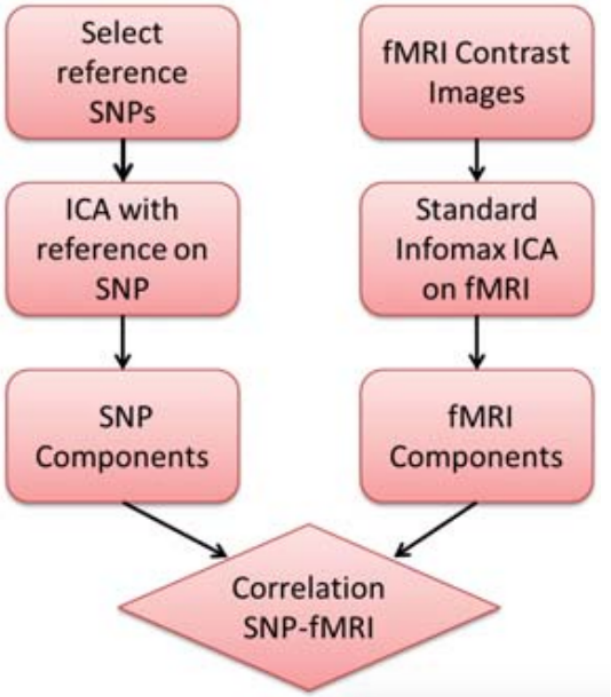


Figure 7: J. Liu et al, 2009

- Review: Calhoun et al., 2009. Application to Schizophrenia.

Multivariate approaches 2

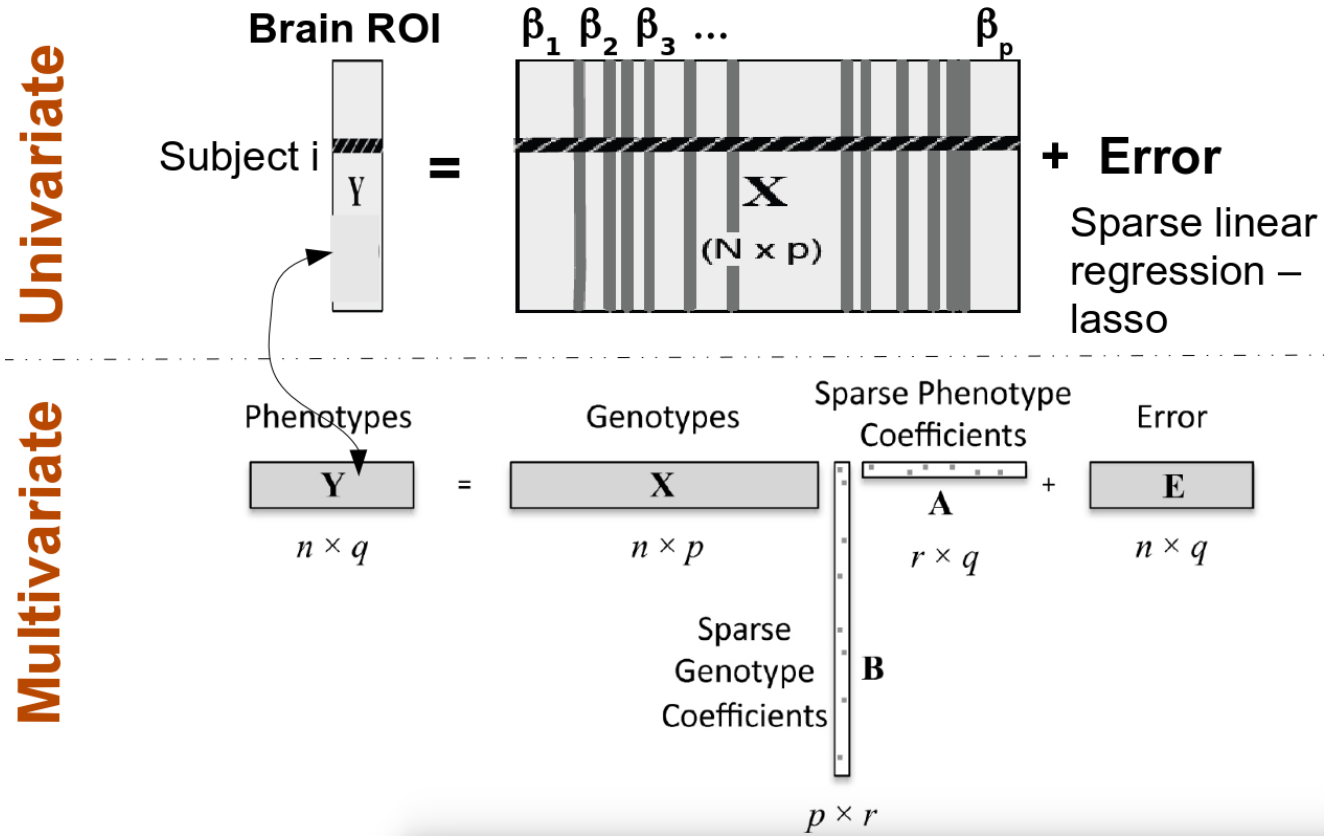


Figure 8: Vounou et al, 2010, LeFloch et al., 2012

Multivariate analyses: what do you get

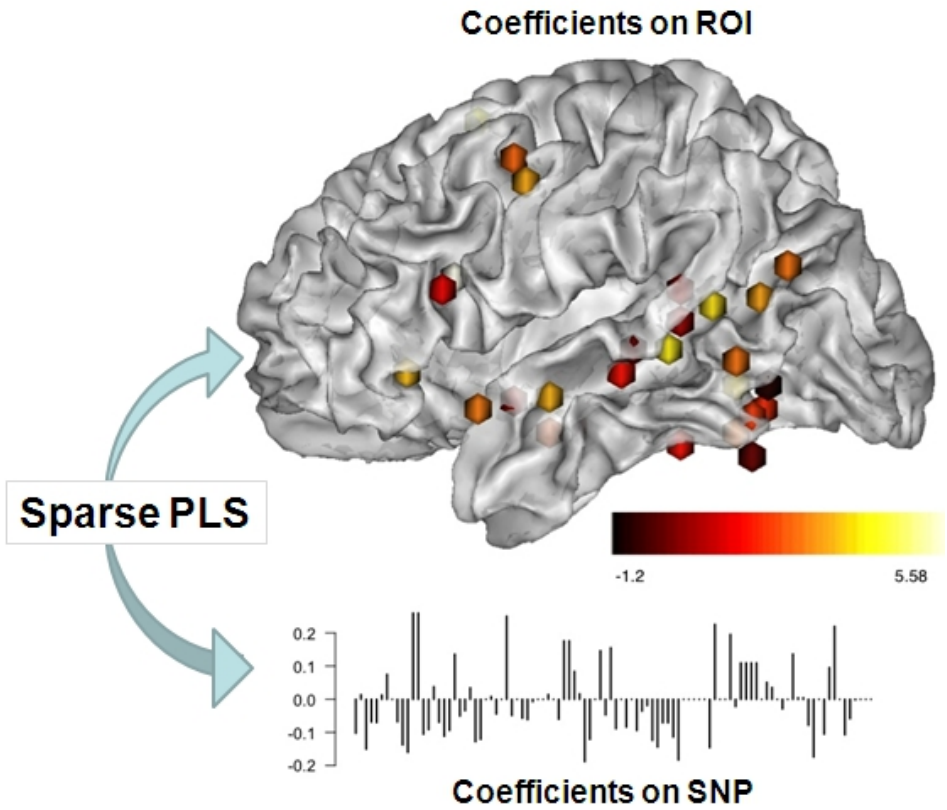


Figure 9: Vounou et al, 2010, LeFloch et al., 2012

- Then: issues of interpretation - and statistics needed to determine which region/voxel and which SNP/gene can be reported

Heritability : more constraints - more interpretable

- Definition (simple): percentage of variance due to genetic

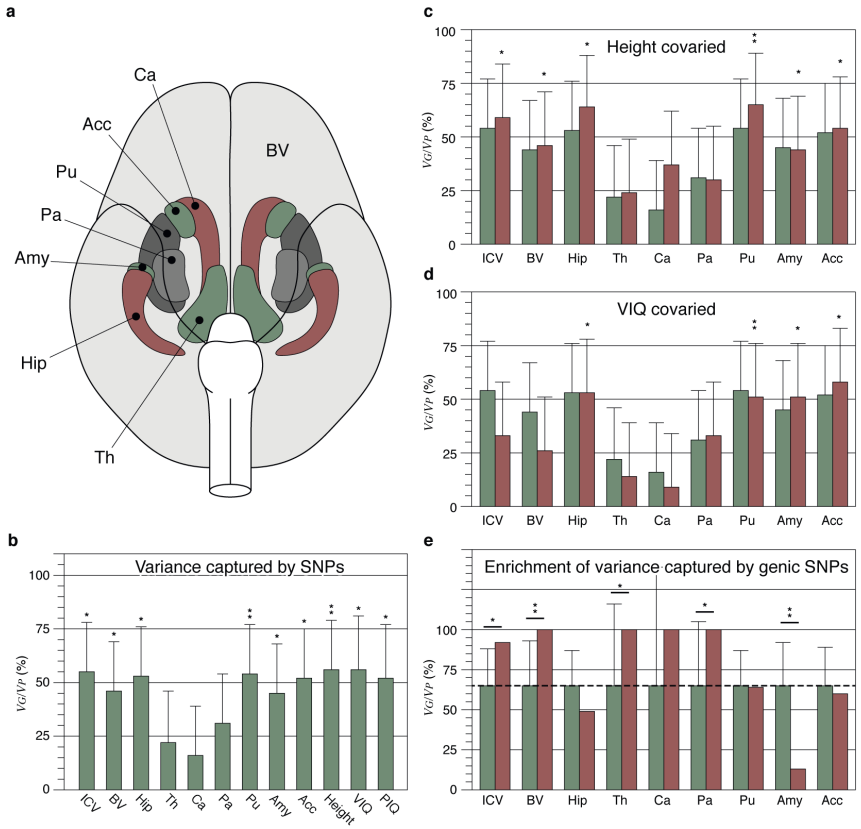
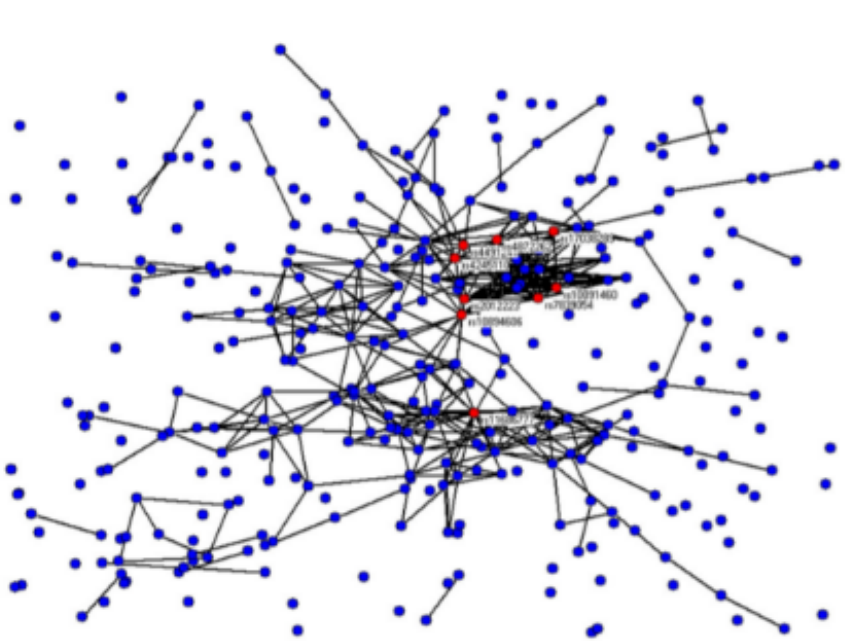


Figure 10: Toro et al, 2014

Networks



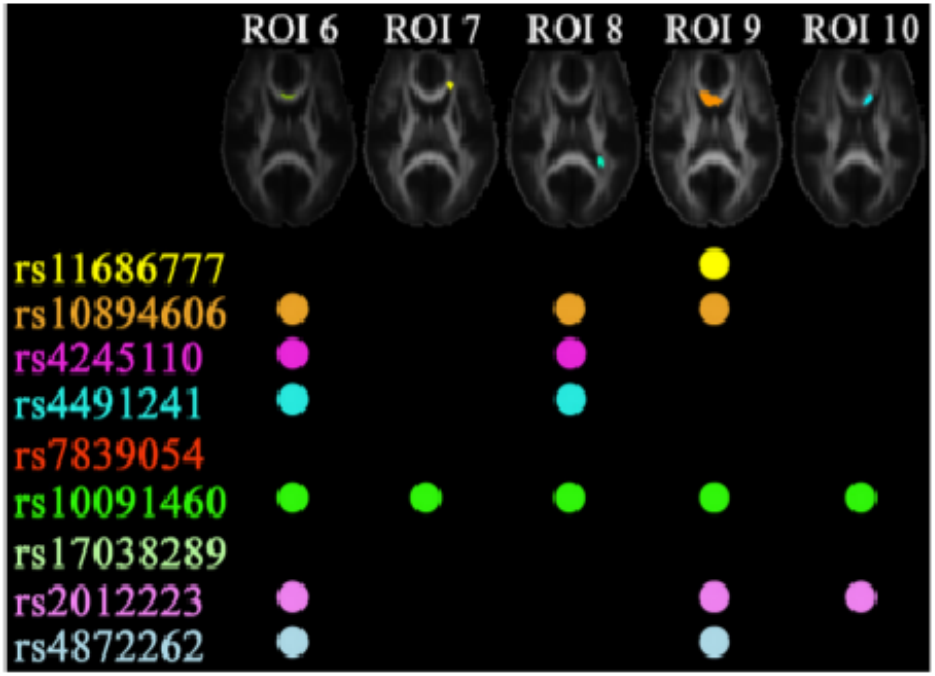


Figure 11: Network SNP/Diffusion Chiang et al 2012

- See also Silver et al., 2012, Richiardi 2015

A few specificities of Imaging Genetics

- Combinaison of imaging and of genetics issues (the "AND" problem)
- Large number of subjects is necessary for GWAS and but too costly to scan
- The multiple comparison issues
- The flexibility of analyses / exploration
- The "trendiness" of the field
- The capacity to "rationalize findings"
  - noise in brain images is always interpretable
  - genes are always interpretable

Conclusion 1: Ioannidis again

- Young fields tend to have less stringent criteria
- Ioannidis 2005: When are results more likely to be false?
  - The smaller the studies ...
  - The smaller the effect size ...
  - The larger the number of tests ...
  - The more flexibility in the analyses
  - The more trendy ...
  - The more financial interest ...

Conclusion 2: Effect-size = f(years, sample, . . .)

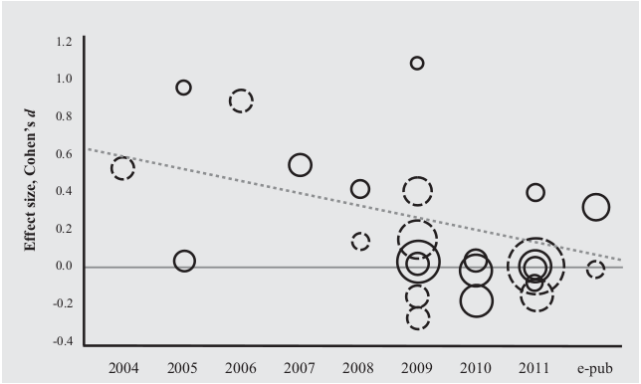


Figure 12: Molendijk, 2012, BDNF and hippocampal volume

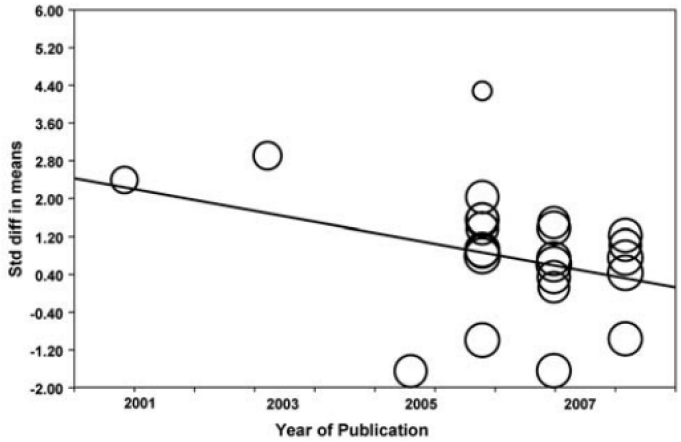


Figure 13: Mier, 2009, COMT & DLPFC

Conclusion 3: What's next

- Greater interpretability
  - include pathways / biological information
  - heritable phenotypes
  - analyzing other existing databases / datasets (eg ABI)
  - more complex methods (multivariate)
- More documented data needed for
  - power
  - interpretability
- Move from p-values to prediction ?

Acknowledgements

- Berkeley: M. D'Esposito, M. Brett, S. Van der Walt, J.Millman
- Pasteur: R. Toro, G. Dumas, T. Bourgeron, A. Beggiato
- Neurospin: B. Thirion, G. Varauquaux, V. Frouin, others

Thank you for your attention - Questions ?

More material

What are the solutions:

- Pre-register hypotheses
  - More hypotheses
  - Candidate versus GWAS: cf Flint & Mufano, 2012
- Statistics:

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- Meta analysis - cf Enigma / Replication whenever possible

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- Take robust statistical tools
- Meta analysis - cf Enigma / Replication whenever possible
- Effect size variation estimation (bootstrapping)

The power issue

What exactly is power ?

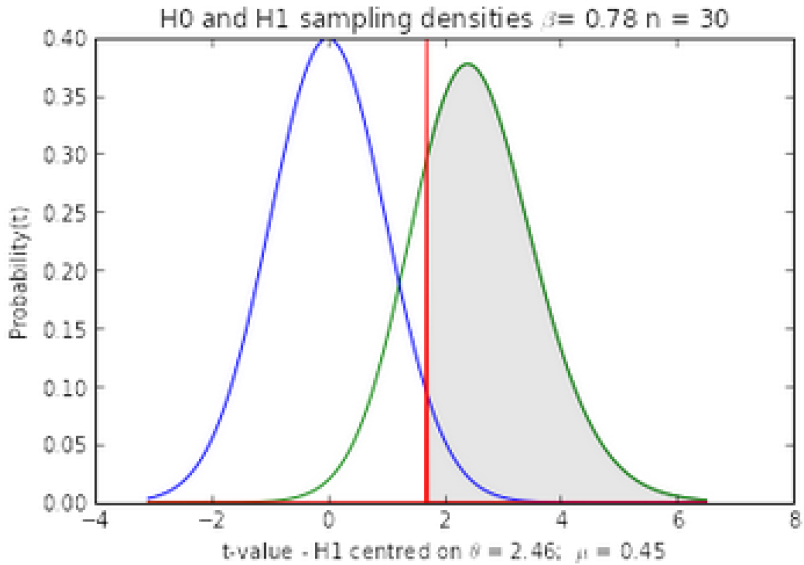

Figure 14: Power: $W = 1 - \beta$ Here W=77%

Cohen's d and relation with n :

$$d = \frac{\bar{x_1} - \bar{x_2}}{\sigma} = \frac{\mu}{\sigma} \qquad Z = \frac{\mu\sqrt{n}}{\sigma} = d\sqrt{n}$$

The power issue

- Studies of low power have low probability of detecting an effect (indeed!)
- Studies of low power have low positive predictive value: $PPV = P(H1\,True|Detection)$
- Studies of low power are likely to show inflated effect size

The power issue

- $PPV = P(H1\,True|Detection) = \frac{W\,P_1}{\alpha\,P_0 + W\,P_1}$
- If we have 4/5 that H0 is true, and 1/5 that H1 true, with 30% power: PPV = 60%.

P1/P0 =0.25	power=0.10,	alpha=0.05	PPV=0.33
P1/P0 =0.25	power=0.30,	alpha=0.05	PPV=0.60
P1/P0 =0.25	power=0.50,	alpha=0.05	PPV=0.71
P1/P0 =0.25	power=0.70,	alpha=0.05	PPV=0.78

The power issue

What happens with more stringent α?

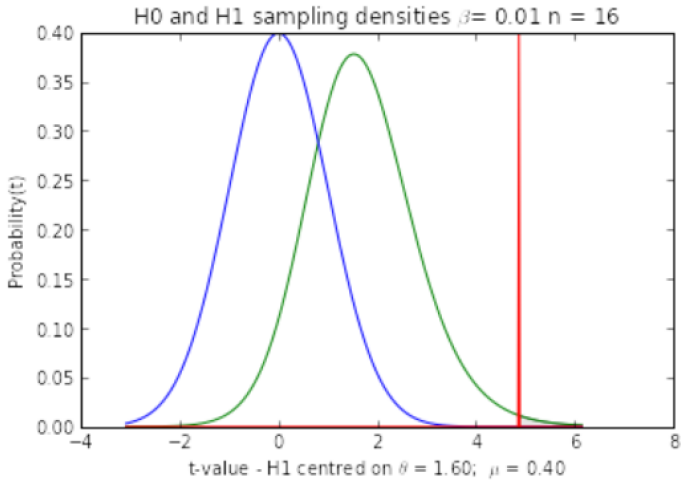

Figure 15: higher type I error threshold to account for MC

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

The power issue

Studies of low power inflate the detected effect (2)

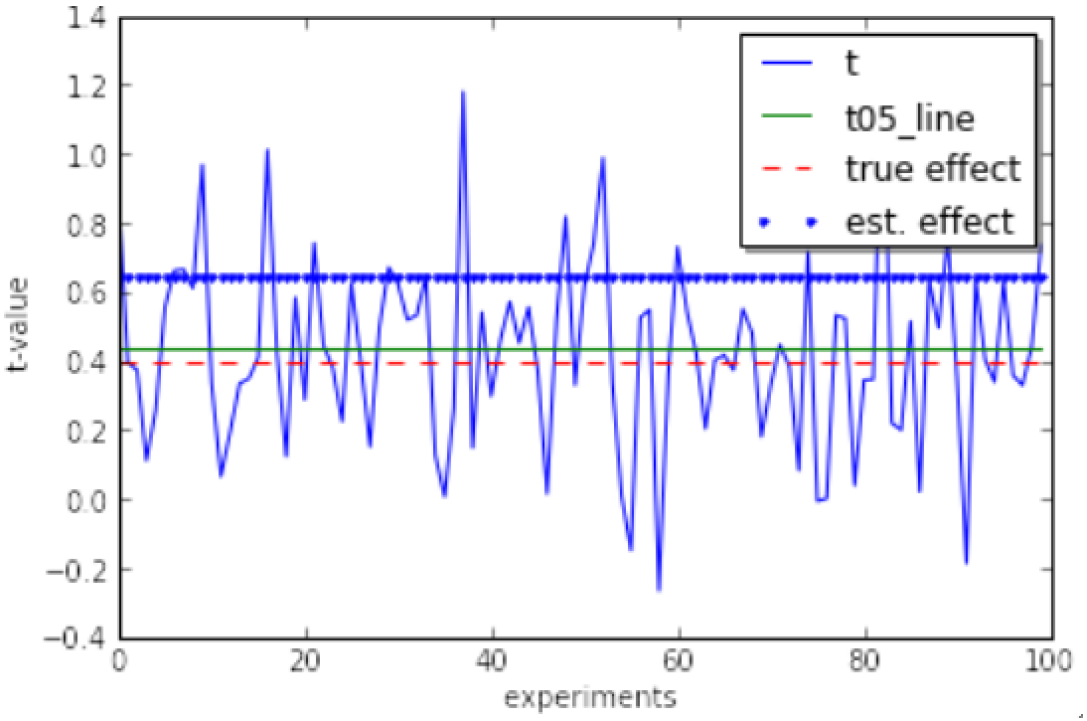

Figure 16: Repeating experiments: estimated effects are above t05 line, leading to a biased estimation compared to true simulated effect.

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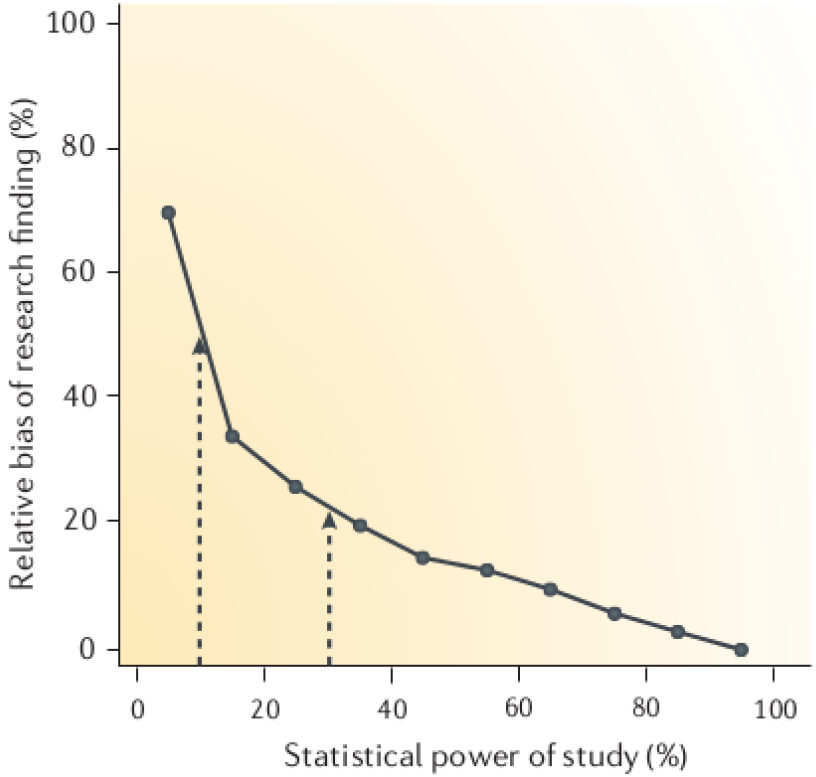


Figure 17: Button et al. NRN, 2013

The power issue

What is the estimated power in common meta analyses?

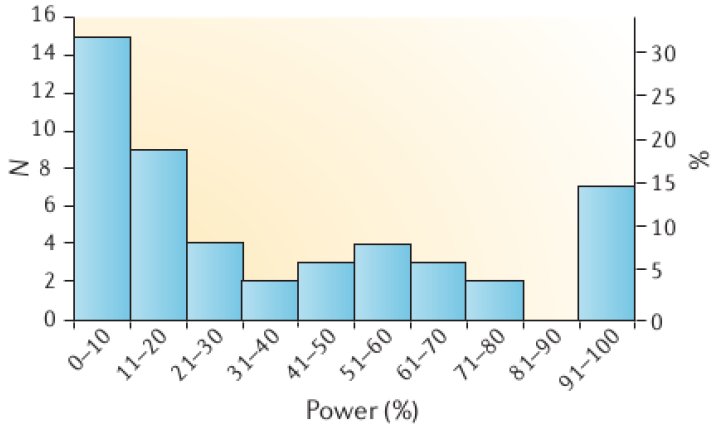
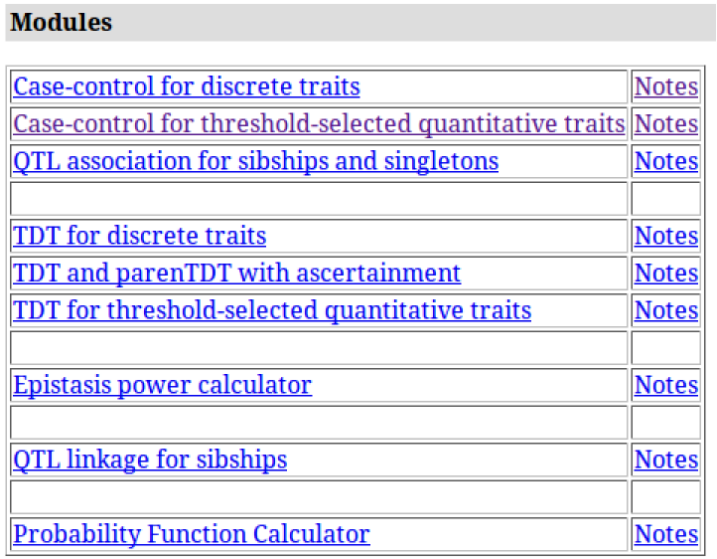


Figure 18: Button et al. NRN, 2013

Power Calculator with

- Purcell et al. "Genetic Power Calculator" Bioinformatics (2003).



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

- http://www.sph.umich.edu/csg/abecasis/cats/

CaTS-text –additive –risk 1.3 –pisample .95 –pimarkers 1. –frequency .3 –case 1067 –control 1067 –alpha 0.00000001 : yields For a one-stage study 0.314.

Recall-by-Genotype and intermediate phenotype

- Flint et al., Assessing the utility of intermediate phenotype, Trends in Neurosciences, 2014.

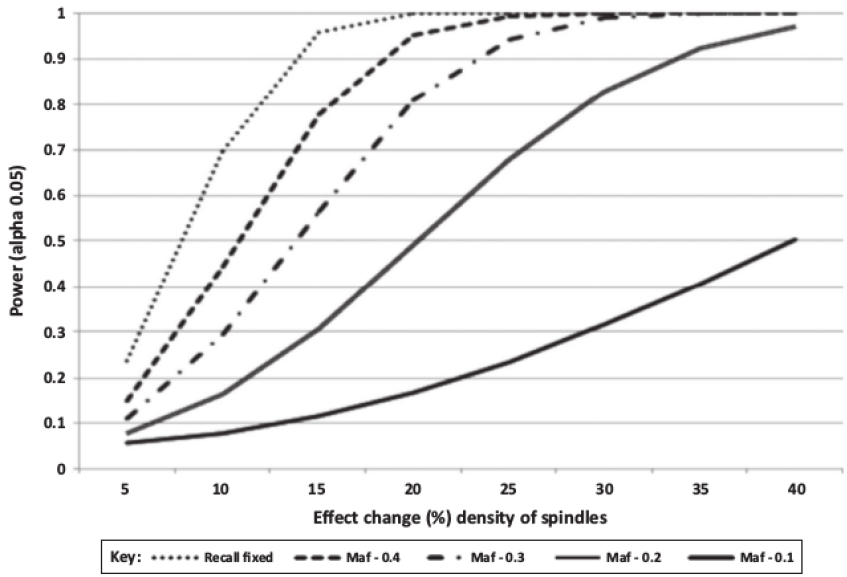


Figure 20: Recall by Genotype: Genotypic assignment vs randomisation assignment