

# Meta-analytic methods for neuroimaging data

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# Meta-analyses: why?

- Exponential increase of neuroimaging research:
  - Findings cannot be straightforwardly summarized and often may seem contradictory.
  - Some neuroimaging research could be thus useless.
- We need methods able to summarize:
  - Showing which findings are robust, and thus,
  - Making research useful for the patients.

# Index

- Classic meta-analyses: summarizing a single measure.
- Challenges in neuroimaging data – i.e. summarizing many measures (ROIs, voxels...).
- Main methods for neuroimaging data.

# Classic meta-analyses

- Combination of findings from previous studies about a subject. Usually only one variable of interest.
- Example: volume of a rare neuroradiological abnormality.

Study	N	Mean	SD
A	15	50.4 ml	6.2 mm
B	97	82.3 ml	9.4 mm
C	6	76.0 ml	8.3 mm
D	19	74.8 ml	20.4 mm

# Classic meta-analyses

- We could calculate the simple mean:

$$\sum_i \frac{1}{4} \times mean_i = \frac{50.4 + 82.3 + 76.0 + 74.8}{4} = 70.9$$

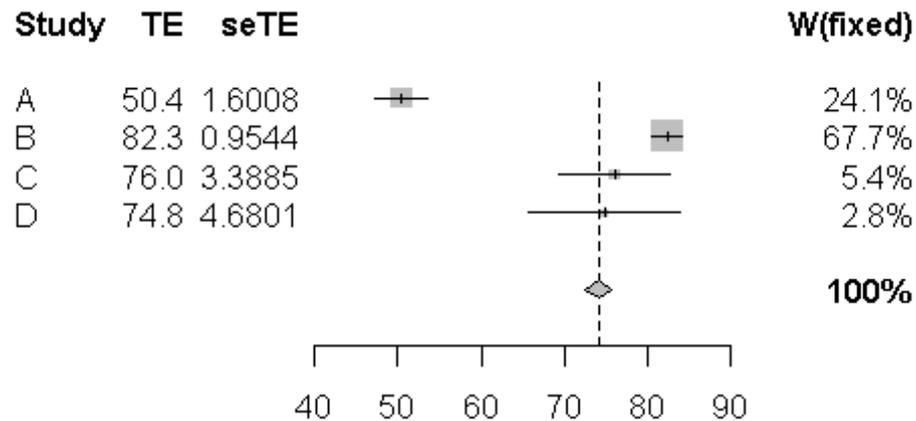
But... studies with large **sample size**, as well as studies with lower **within-study variance** (i.e. more precision) should have more weight than small imprecise studies !

- We could weight each study by  $\frac{N}{SD^2} = \frac{1}{SE^2}$  :

$$\sum_i \frac{\left(\frac{1}{SE_i^2}\right)}{\sum_i \left(\frac{1}{SE_i^2}\right)} \times mean_i = 0.24 \times 50.4 + 0.68 \times 82.3 + 0.05 \times 76.0 + 0.03 \times 74.8 = 74.1$$

# Classic meta-analyses

- Means and weights may be represented in a “forest plot”:



But... studies are **too** different accounting for their relatively low within-study variance: there's **between-study heterogeneity** !

- Let's do subgroups / meta-regressions and random-effects.

# Classic meta-analyses

- Subgroups / meta-regressions: analyze subgroups separately, fit (weighted) general linear models... in order to explain the between-study heterogeneity:

$$\beta = (X^T \times W \times X)^{-1} \times X^T \times W \times Y$$

Example: let's imagine study A was in patients with a special subtype of the disorder.

And sometimes these analyses yield new insights!

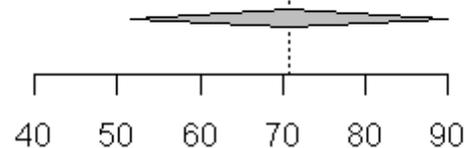
# Classic meta-analyses

- Random-effects: we should assume that effect-sizes vary

randomly between samples: 
$$\sum_i \frac{\left( \frac{1}{SE_i^2 + Var_{between}} \right)}{\sum_i \left( \frac{1}{SE_i^2 + Var_{between}} \right)} \times mean_i$$

Study	TE	seTE		W(random)
A	50.4	1.6008		25.4%
B	82.3	0.9544		25.5%
C	76.0	3.3885		24.8%
D	74.8	4.6801		24.2%

*tau-squared=373.5*



**100%**

# Classic meta-analyses

- **Are findings reliable?**

→ Jackknife and other sensitivity tests.

- Repeat many times the meta-analysis, each time including all studies but one...
- Repeat the meta-analysis separately for different subtypes of studies...

... are findings similar?

# Classic meta-analyses

- **Is there residual between-study heterogeneity?**

→ Statistical significance (chi-square).

Problem similar to normality tests:

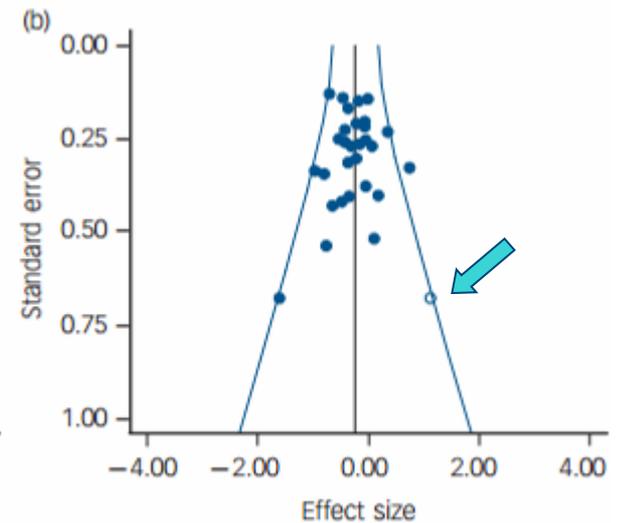
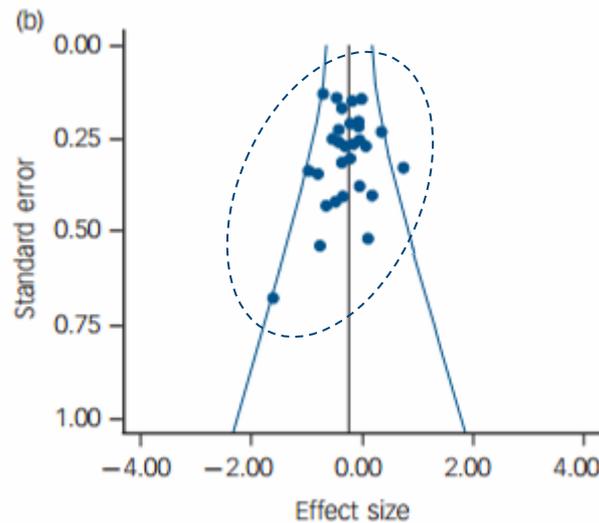
- Only large levels of heterogeneity reach statistical significance in small meta-analyses.
- Negligible levels of heterogeneity may reach statistical significance in large meta-analyses.

→  $I^2$ : percentage of variation due to heterogeneity.

# Classic meta-analyses

- Are small studies only published if they find something sexy?

- Funnel plot
- Trim and fill
- ...



## ***Cognitive-behavioural therapy for the symptoms of schizophrenia.***

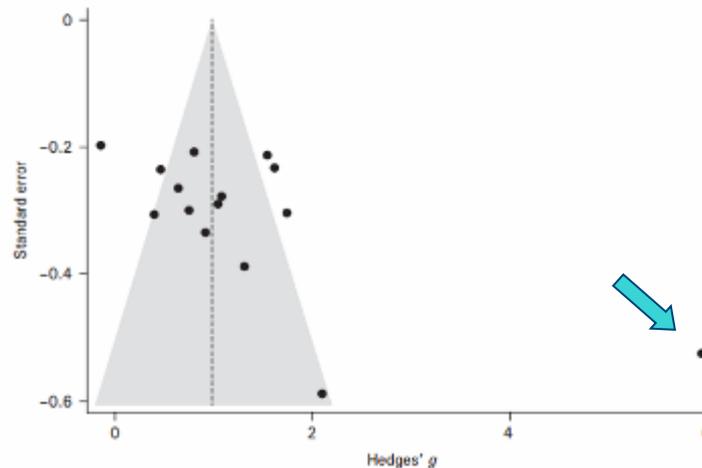
Jauhar S, McKenna PJ, Radua J, Fung E, Salvador R, Laws KR.

*British Journal of Psychiatry* 2014; 204:20-29.

# Classic meta-analyses

- Are small studies only published if they find something sexy?

- Egger test
- Outliers
- ...



## ***Neurological soft signs in Obsessive-Compulsive Disorder: Two empirical studies and meta-analysis.***

Jaafari N, Fernandez de la Cruz L, Grau M, Knowles E, Radua J, Wooderson S, Segalas C, Alonso P, Phillips ML, Menchon JM, Mataix-Cols D.  
*Psychological Medicine* 2013, 43:1069-1079.

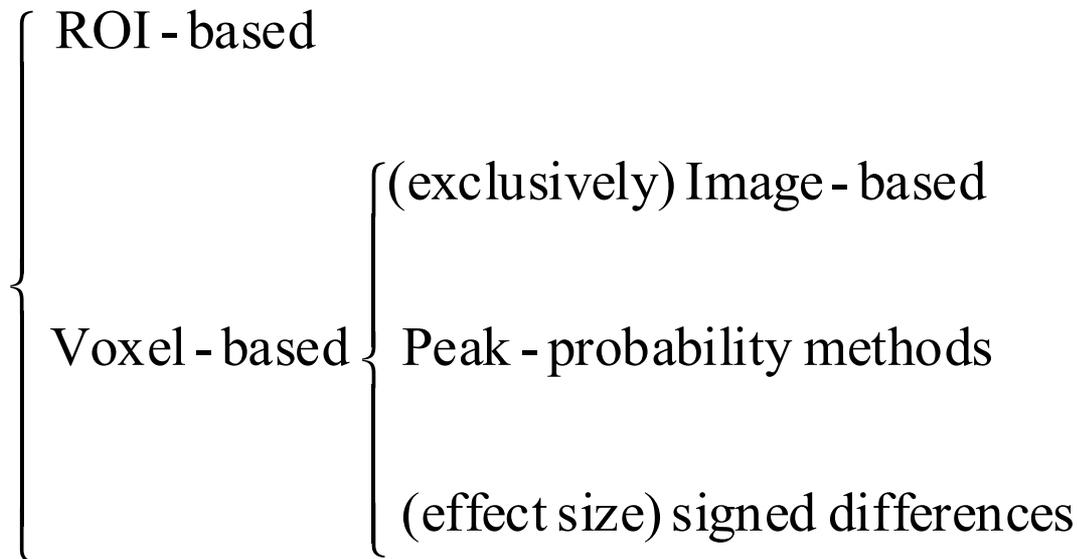
# Classic meta-analyses

- Garbage in, garbage out  
→ Appropriate inclusion criteria, funnel plots...
- One number cannot summarize a research field  
→ Heterogeneity, reliability, subgroups, meta-regressions...
- Mixing apples and oranges  
→ Subgroup analyses, meta-regressions...
- The file drawer problem  
→ Funnel plots...

# Challenges in neuroimaging

- No single variable, but as many as voxels.
- Voxel values (e.g. mean and SD) not reported.
- Possible answers:
  - Ignore voxels (use ROIs).
  - Obtain SPMs (i.e. voxel values).
  - Use peak coordinates.
  - Estimate SPMs.

# Main methods



***Meta-analytic methods for neuroimaging data explained.***  
Radua J and Mataix-Cols D.  
*Biology of Mood and Anxiety Disorders* 2012; 2:6.

# Main methods

## ROI-based meta-analyses:

- A classic meta-analysis for each ROI.
- Main advantages: complete information (SE) and optimal statistics.
- Main issue: each included study only studies few ROIs:
  - Each ROI has been studied for few / no studies.
  - Potential publication bias in studies using automated methods for extracting ROIs.
  - Control for multiple comparisons?

# Main methods

## (exclusively) Image-based meta-analyses:

- A classic meta-analysis for each voxel (using the SPM maps).
- Main advantage: complete information (SE) and good statistics.
- Main issue:
  - SPM maps are seldom available making these meta-analyses unfeasible.
  - Common statistical problems of VBA: no human check, multiple comparisons...

# Main methods

## Peak probability methods (ALE):

- Based on the regional likelihood or frequency of the peaks reported in the studies.
- Main advantage: they only need the coordinates of the peaks, allowing exhaustive meta-analyses.
- Main issues:
  - Based on much summarized information.
  - Statistics may be suboptimal.
  - Cannot account for increases / decreases at the same time.

# Main methods

## Effect-Size Signed Differential Mapping (ES-SDM):

- Recreate SPM maps from peak information (coordinates and effect-sizes), and then conduct an image-based meta-analysis.
- Main advantages:
  - It only *requires* coordinates → exhaustive meta-analyses.
  - It *may* incorporate effect-sizes (broadly available) and raw SPM maps (highly increasing power), as well as SE.
- Main issue:
  - Recreation of SPM maps and statistics may be suboptimal.

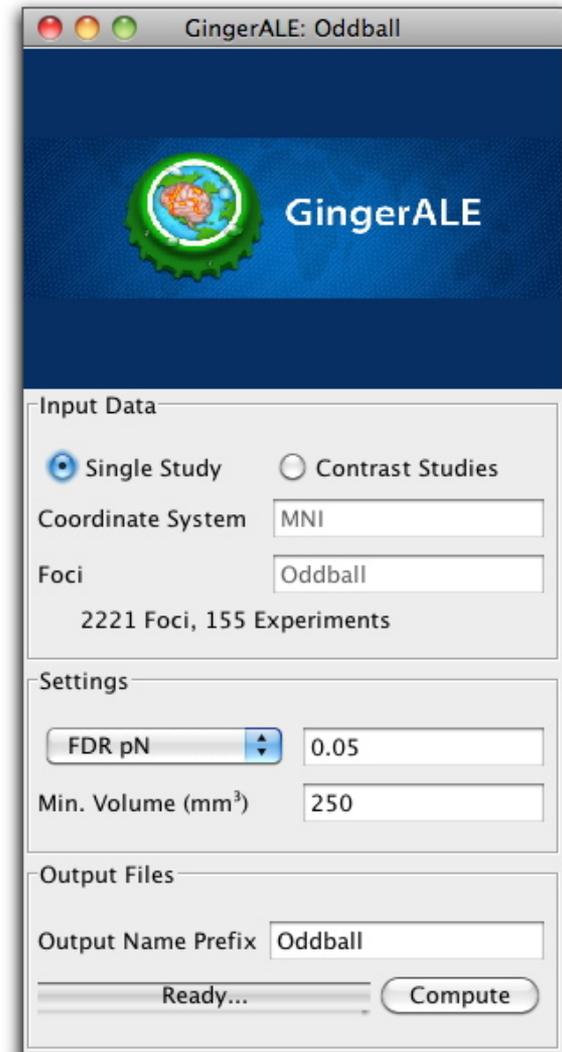
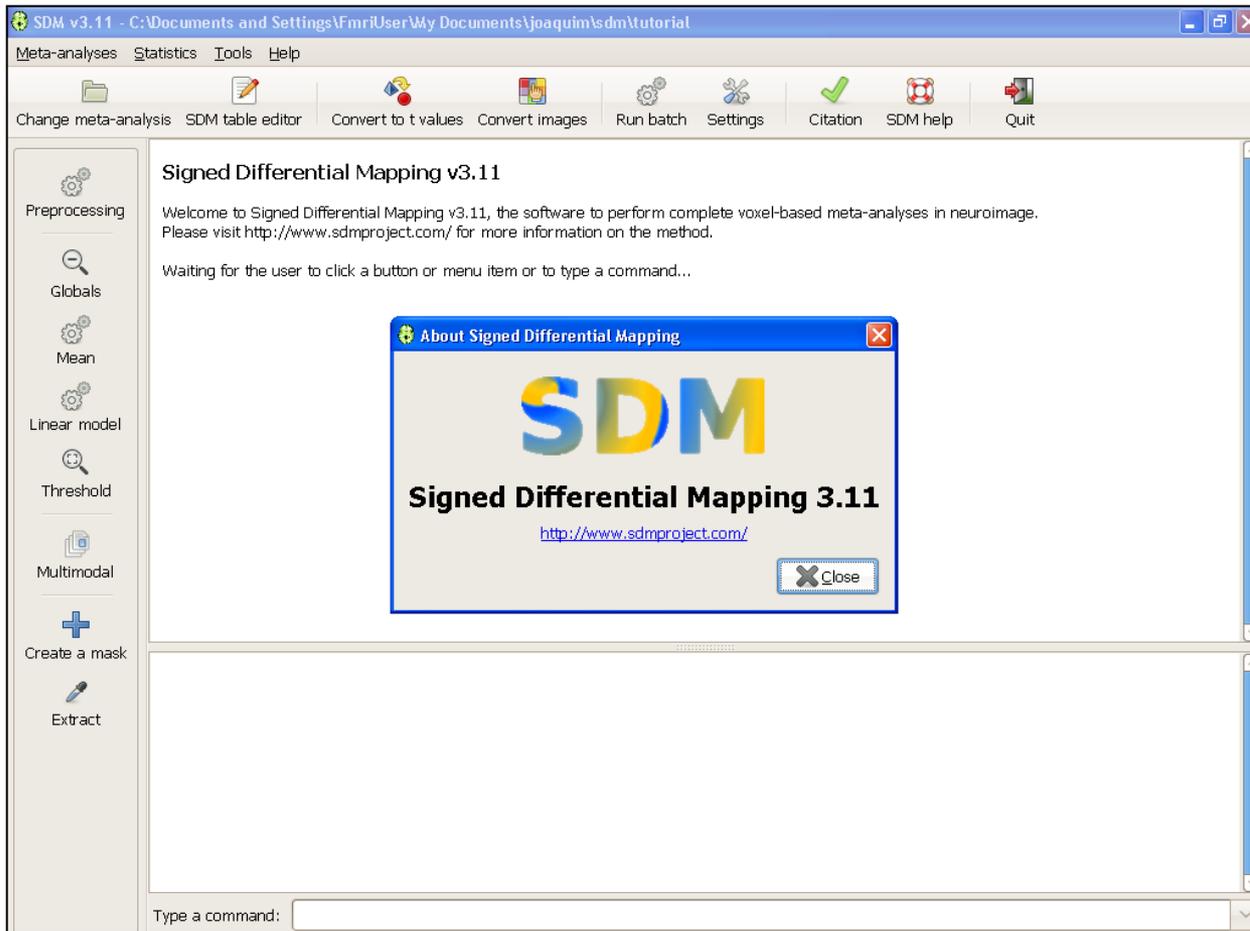
# Steps (simplified)

- A cluster is “recreated” for each peak.  
Positive peak (e.g. patients > controls) → ↑  
Negative peak (e.g. patients < controls) → ↓  
Effect size → intensity of the cluster
- Clusters are “combined” to “recreate” the ES map.
- ES map and sample size are used to create the variance map.

***A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps.***

Radua J, Mataix-Cols D, Phillips ML, El-Hage W, Kronhaus DM, Cardoner N and Surguladze S.

*European Psychiatry* 2012; 27:605-11.



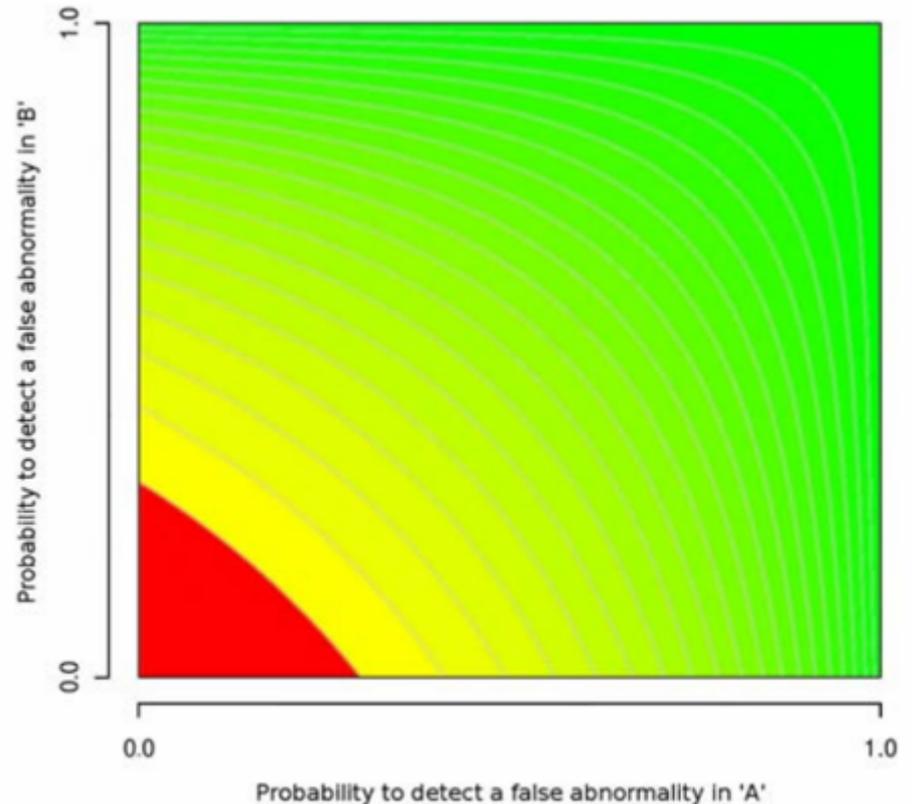
# Multimodality

- Conduct the meta-analyses separately, and then “overlap” accounting for error in the p-values.

***A general approach for combining voxel-based meta-analyses conducted in different neuroimaging modalities.***

Radua J, Romeo M, Mataix-Cols D, Fusar-Poli P.

*Current Medicinal Chemistry*  
2013; 20:462-466.



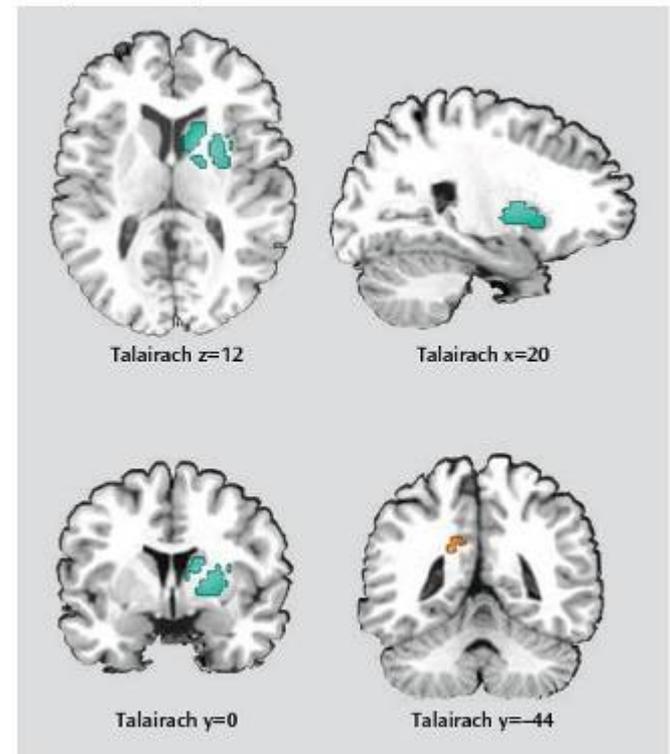
# Examples: ADHD – VBM

- 14 VBM studies (at that moment), 378 patients, but confusing findings when reading the papers.
- Main finding: decrease of GM in right basal ganglia.

***Gray matter volume abnormalities in ADHD: Voxel-based meta-analysis exploring the effects of age and stimulant medication.***

Nakao T, Radua J, Rubia K, Mataix-Cols D.  
*American Journal of Psychiatry* 2011,  
168:1154-1163

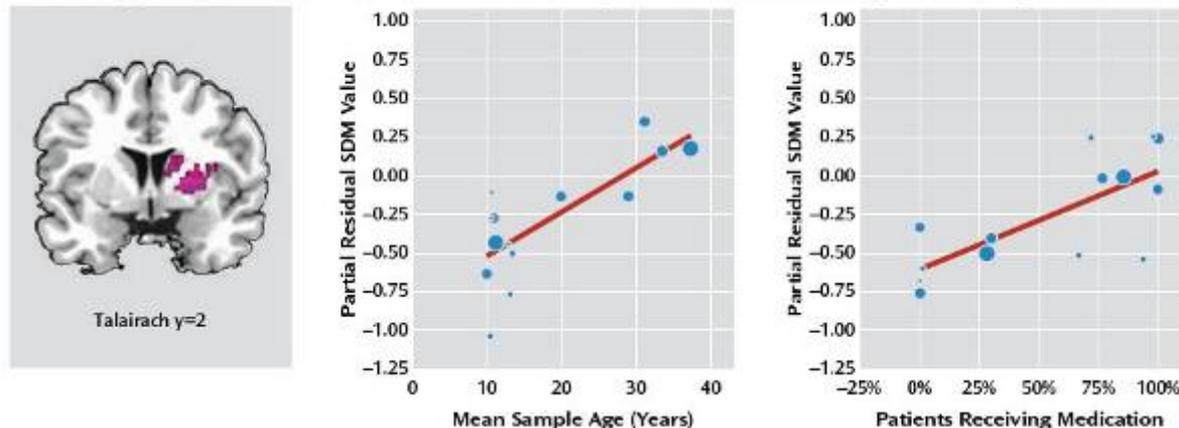
FIGURE 1. Regions of Smaller and Larger Gray Matter Volumes in Individuals With ADHD Compared With Healthy Comparison Subjects<sup>a</sup>



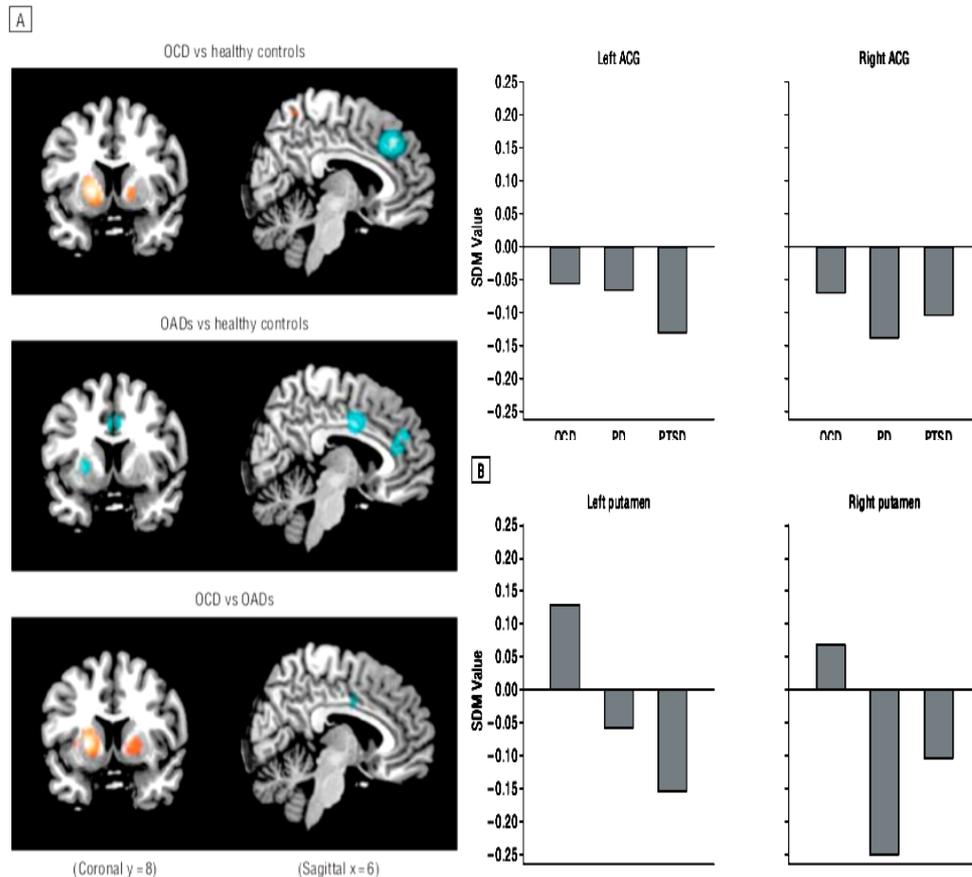
# Examples: ADHD – VBM

- Jackknife: the finding reached statistical significance in all 14 combinations of 13 studies.
- Subgroups (pediatric, modulated): the finding was statistically significant. Not enough studies for adult and unmodulated subgroups.
- Multiple meta-regression by age and treatment:

FIGURE 2. Results of the Metaregression Analysis Showing Independent Associations of Mean Age and Percentage of Patients Receiving Stimulant Medication With More Normal Gray Matter Volumes in the Right Basal Ganglia\*



# Examples: OCD vs. other AD



‘ANOVA’ between AD

→ dACC: ↓ in all

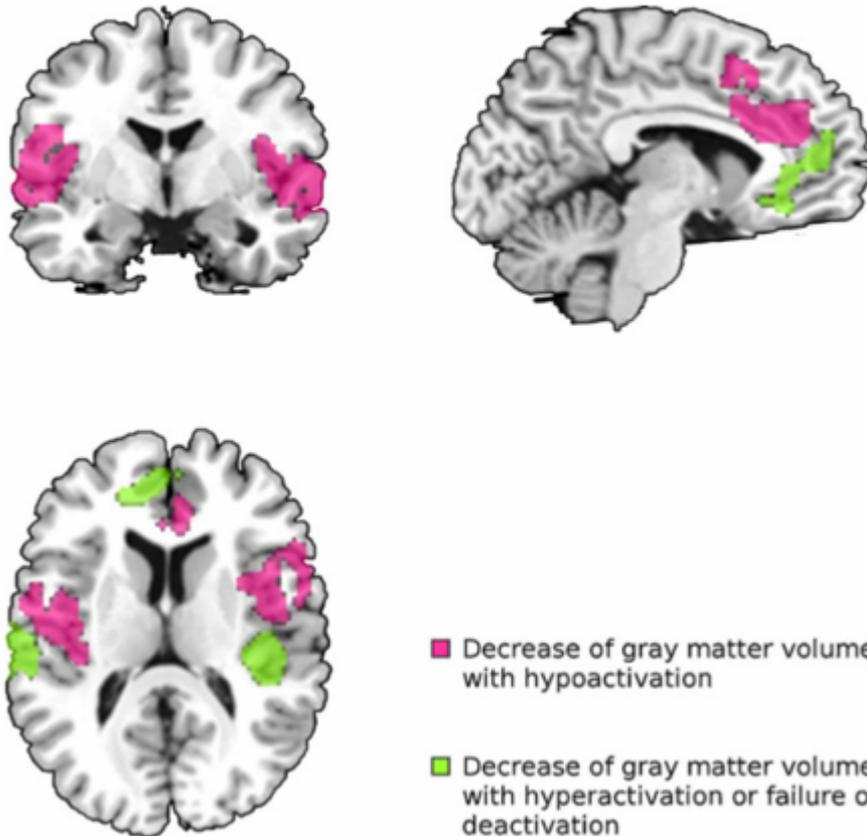
→ BG: ↑ in OCD  
↓ in other

**Meta-analytical comparison of voxel-based morphometry studies in OCD vs. other anxiety disorders.**

Radua J, Van den Heuvel OA, Surguladze SA and Mataix-Cols D.

*Archives of General Psychiatry* 2010; 67:701-711.

# Examples: FEP – Multimodal

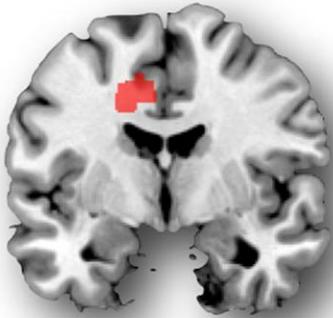
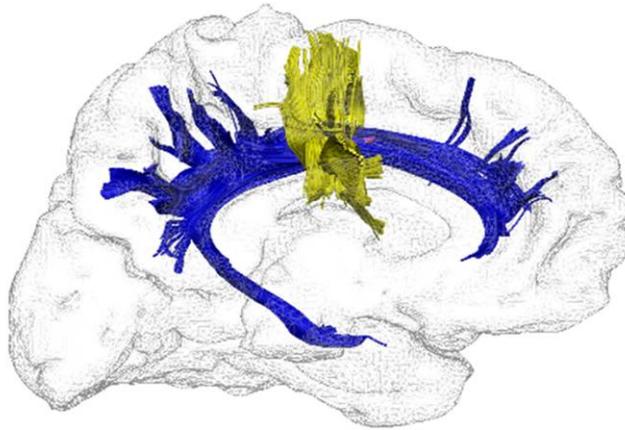


***Multimodal meta-analysis of structural and functional brain changes in first episode psychosis and the effects of antipsychotic medication.***

Radua J, Borgwardt S, Crescini A, Mataix-Cols D, Meyer-Lindenberg A, McGuire PK, Fusar-Poli P.

*Neuroscience and Biobehavioral Reviews* 2012; 36:2325-33.

# Examples: OCD – Multimodal



Increase of white matter volume (WMV) *but* decrease of fractional anisotropy (FA)

(B) Crossing between the anterior body of the corpus callosum (yellow) and cingulum bundle (dark blue)

Peak at -8,-4,-38. Slice:  $y = -4$

***Multimodal Voxel-Based Meta-Analysis of White Matter Abnormalities in Obsessive-Compulsive Disorder.***

Radua J, Grau M, van den Heuvel OA, de Schotten MT, Stein DJ, Canales-Rodríguez EJ, Catani M, Mataix-Cols D.

*Neuropsychopharmacology* 2014.

# A “compulsory” inclusion criterion

- Some studies apply liberal statistical thresholds to some regions (e.g. amygdala) → biased effect-sizes...

**A STUDY CAN ONLY BE INCLUDED  
IF IT APPLIES  
THE SAME THRESHOLD  
THROUGHOUT THE BRAIN**

***Voxel-wise meta-analysis of gray matter changes in obsessive-compulsive disorder.***

Radua J and Mataix-Cols D.

*British Journal of Psychiatry.* 2009; 195:391-400.

# Specific templates

- White matter VBM / FA.
- TBSS – special procedure for SPM maps.

***Voxel-based meta-analysis of regional white-matter volume differences in autism spectrum disorder versus healthy controls.***

Radua J, Via E, Catani M and Mataix-Cols D.

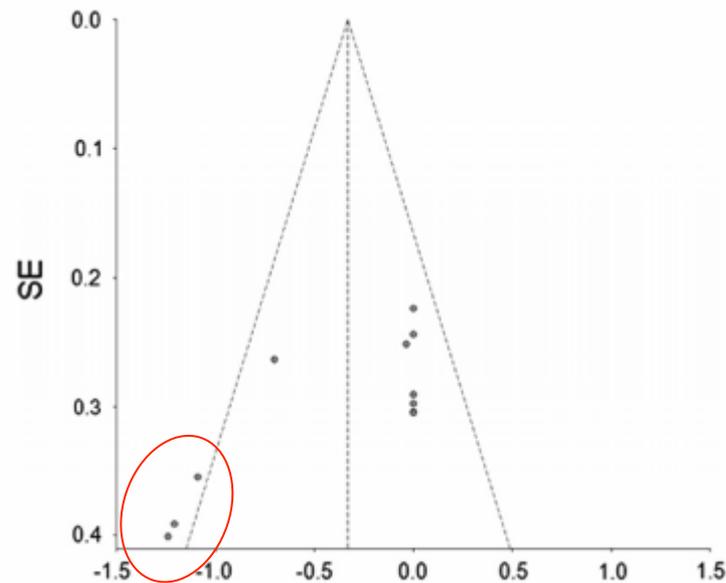
*Psychological Medicine* 2011; 41:1539-1550.

***White matter development in adolescence: diffusion tensor imaging and meta-analytic results.***

Peters BD, Szeszko PR, Radua J, Ikuta T, Gruner P, Derosse P, Zhang JP, Giorgio A, Qiu D, Tapert SF, Brauer J, Asato MR, Khong PL, James AC, Gallego JA and Malhotra AK.

*Schizophrenia Bulletin* 2012; 38:1308-17.

# Publication bias



***Systematic review and voxel-based meta-analysis of diffusion tensor imaging studies in bipolar disorder.***

Nortje G, Stein DJ, Radua J, Mataix-Cols D, Horn N.  
*Journal of Affective Disorders* 2013; 150:192-200.

# Publication bias

- In the absence of reporting bias, there would be strong correlations” between sample size and number of findings.
- There were not.

## ***Potential reporting bias in small fMRI studies of the brain.***

David SP, Ware JJ, Chu IM, Loftus PD, Fusar-Poli P, Radua J, Munafo MR, Ioannidis JPA.

*PLoS One* 2013; 8:e70104.

## ***Evidence of reporting biases in voxel based morphometry (VBM) studies of neuropsychiatric disorders.***

Fusar-Poli P, Radua J, Frascarelli M, Mechelli A, Borgwardt S, Di Fabio F, Biondi M, Ioannidis J, David S.

*Human Brain Mapping* 2013; in Press.

**Thank you!**

