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Meta-analysis of neuroimaging data

Martin Jáni

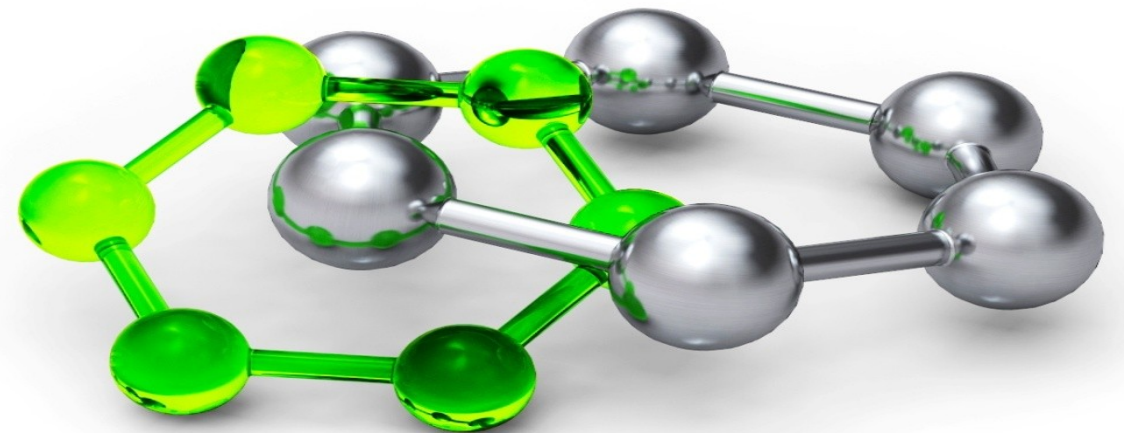
Selected Topics in Contemporary Neuroscience

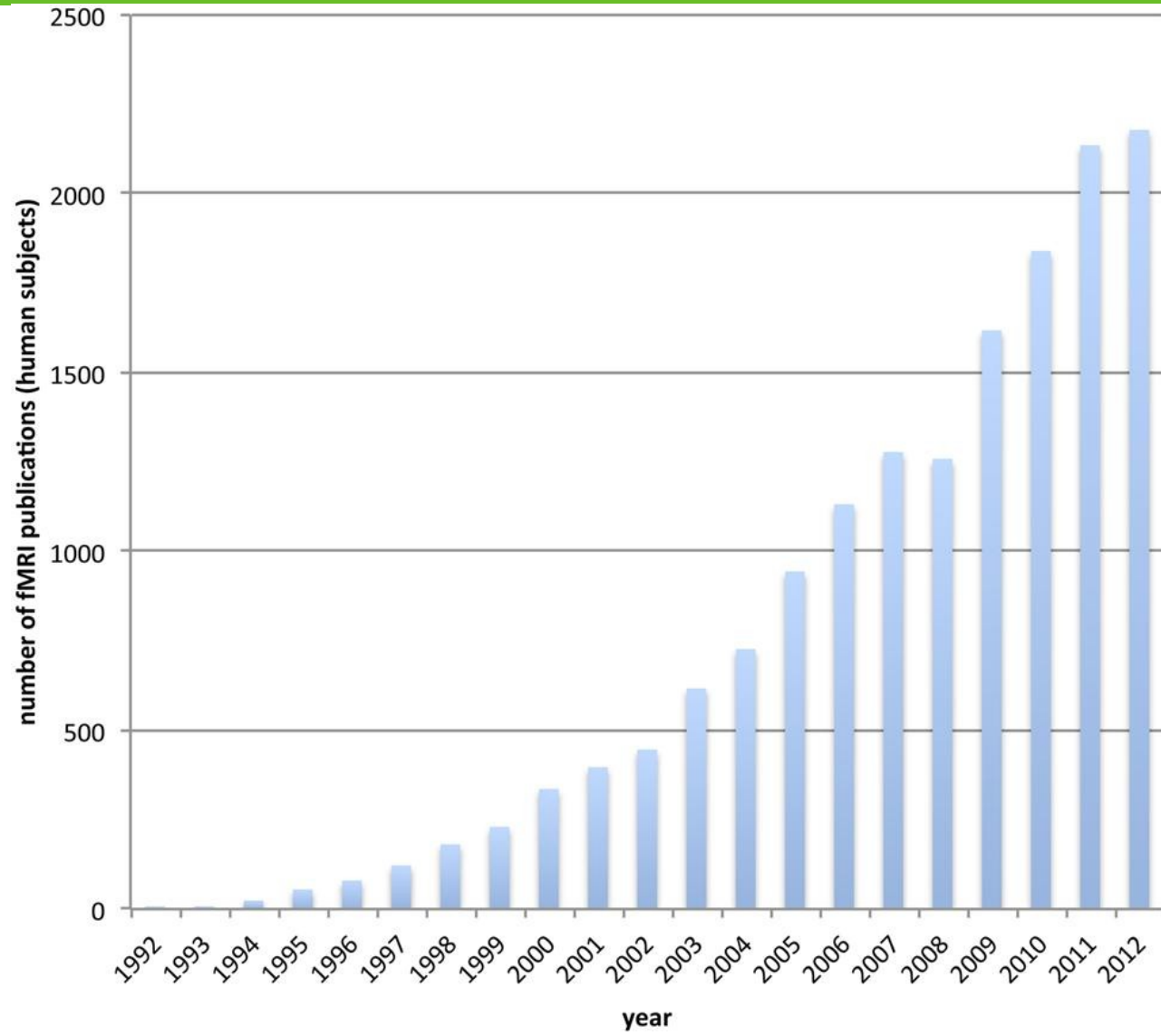


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**OP Research and
Development for Innovation**





[Stelzer et al., 2014]

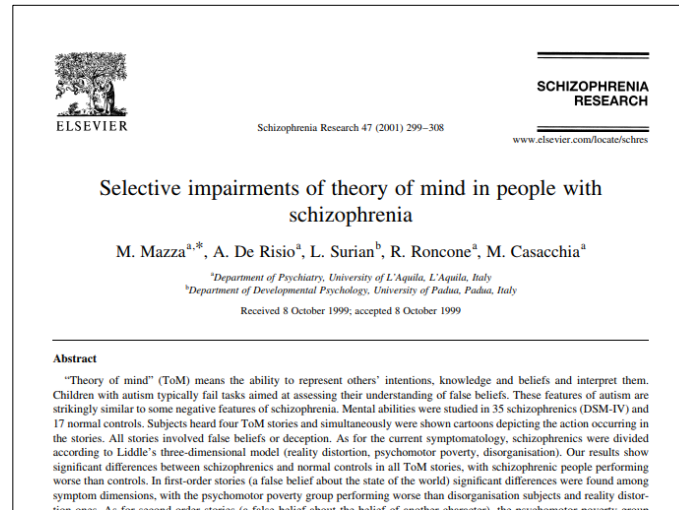
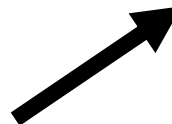
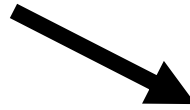


why and what?



need for comprehensive summary

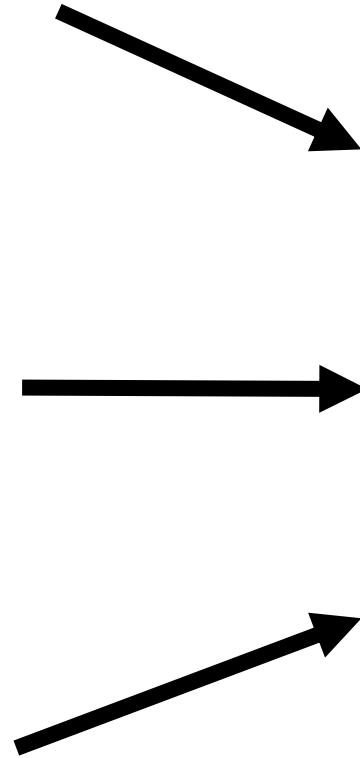
- meta-analysis = quantitative review
- 1 study represents 1 subject
- units of measurement = summary statistics (effect sizes)
- standard IMRaD structure



$$\bar{x} = \frac{\sum x}{N}$$

$\sum x$ = the sum of x
 N = number of data

t-statistic
p value



BRITISH JOURNAL OF PSYCHIATRY (2007), 191, 5–13. REVIEW ARTICLE

Theory of mind in schizophrenia

Meta-analysis

MIRJAM SPRONG, PATRICIA SCHOTHORST, ELLEN VOS, JOOP HOX
and HERMAN VAN ENGELAND

Background Mentalising impairment (an impaired ability to think about people in terms of their mental states) has frequently been associated with schizophrenia.

Aims To assess the magnitude of the deficit and analyse associated factors.

Method Twenty-nine studies of mentalising in schizophrenia (combined $n=1518$), published between January 1993 and May 2006, were included to estimate overall effect size. Study descriptors predicted to influence effect size were analysed using weighted regression-analysis techniques. Separate analyses were performed for symptom subgroups and task types.

Results The estimated overall effect size was large and statistically significant

and *Psychological Medicine*. Studies considered eligible for this meta-analysis were empirical research studies written in the English language and published in peer-reviewed journals. Research samples had to be composed of adults diagnosed with schizophrenia or schizoaffective disorder according to the established diagnostic systems (DSM or ICD). Their sample group's mentalising performance had to be compared with that of healthy controls. Measures of mentalising included in this meta-analysis are described below. Finally, sufficient data had to be reported for the computation of the standardised mean difference (Lipsey & Wilson, 2001).

Types of mentalising tasks

There is a fair amount of agreement on the definition of theory of mind among researchers. However, this definition is broad, perhaps reflecting the fact that it is probably not a unitary function. This has led to a wide variation in the operationalisation of the concept. One of the most frequently used types of mentalising tasks is the false belief or deception task (e.g. Frith & Corcoran, 1996; Corcoran *et al.*, 1997; Doody *et al.*, 1998; Mazza *et al.*, 2001). In a first-order false belief/deception task, the ability to understand that someone can hold a belief that is different from the actual state of affairs is assessed. In a second-order false belief/deception task, participants have to infer the (false) beliefs of one character about the (false) beliefs

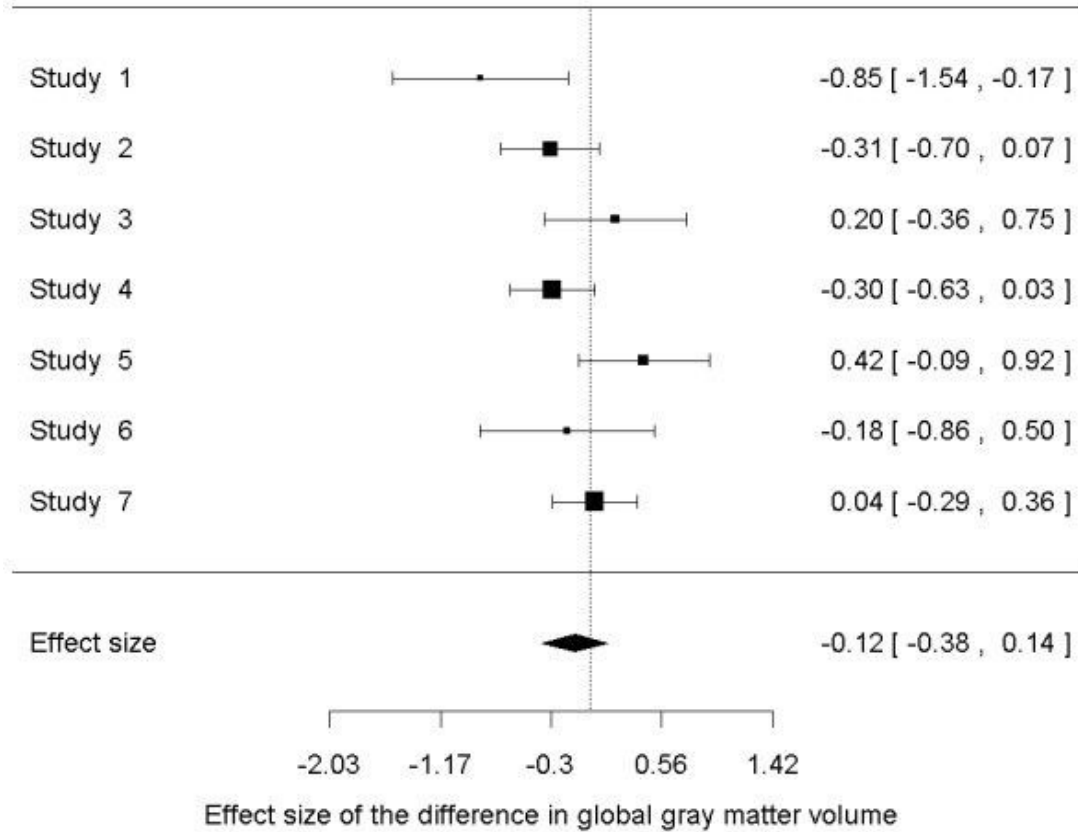
- difference in means / pooled standard deviation

- *Cohen's d*
- *Glass' Δ*
- *Hedges' g*

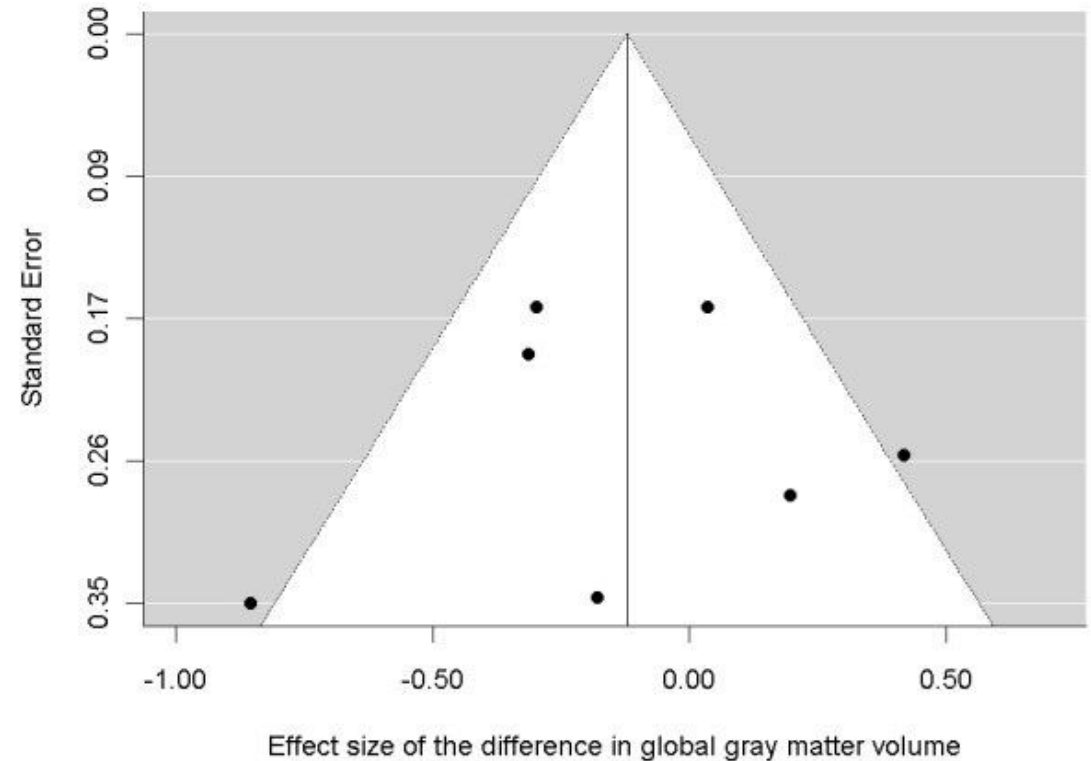
$$\text{Hedges' } g = \frac{M_1 - M_2}{SD_{pooled}^*}$$

- comparable with other studies
- unit of measure is lost
- less straightforward

Publication bias

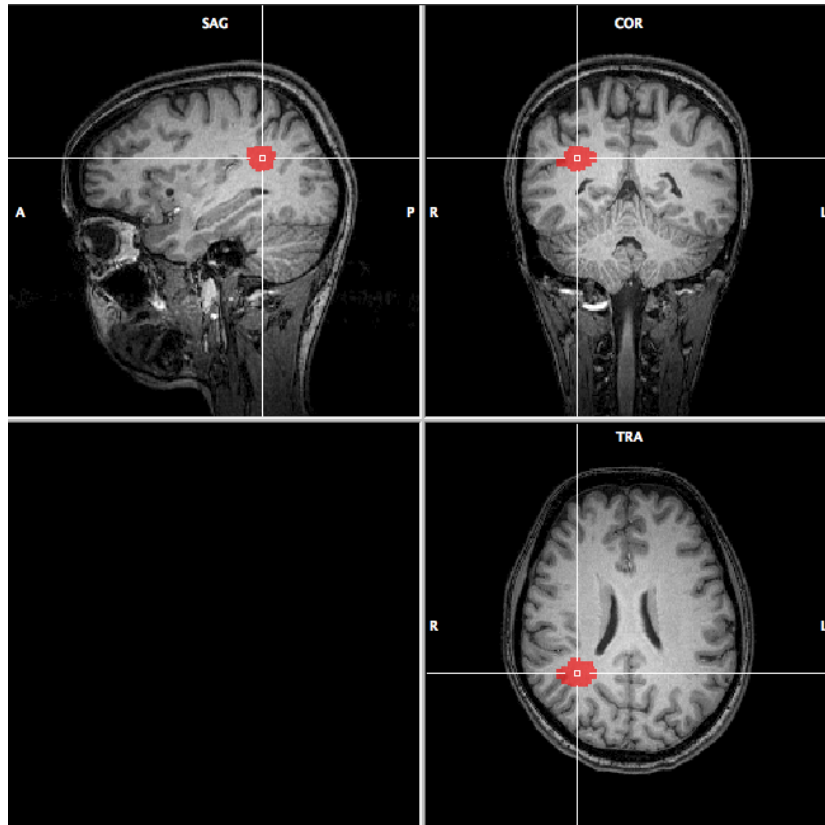


Forest plot

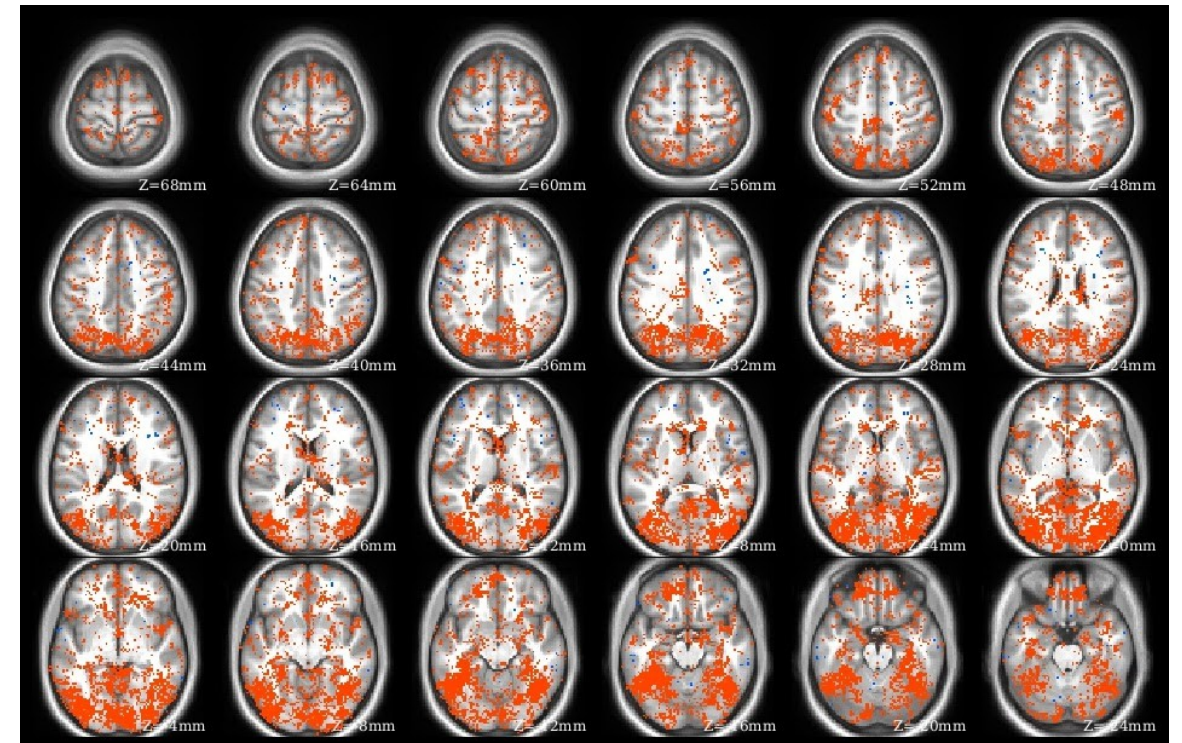


Funnel plot

Region of interest-based meta-analyses



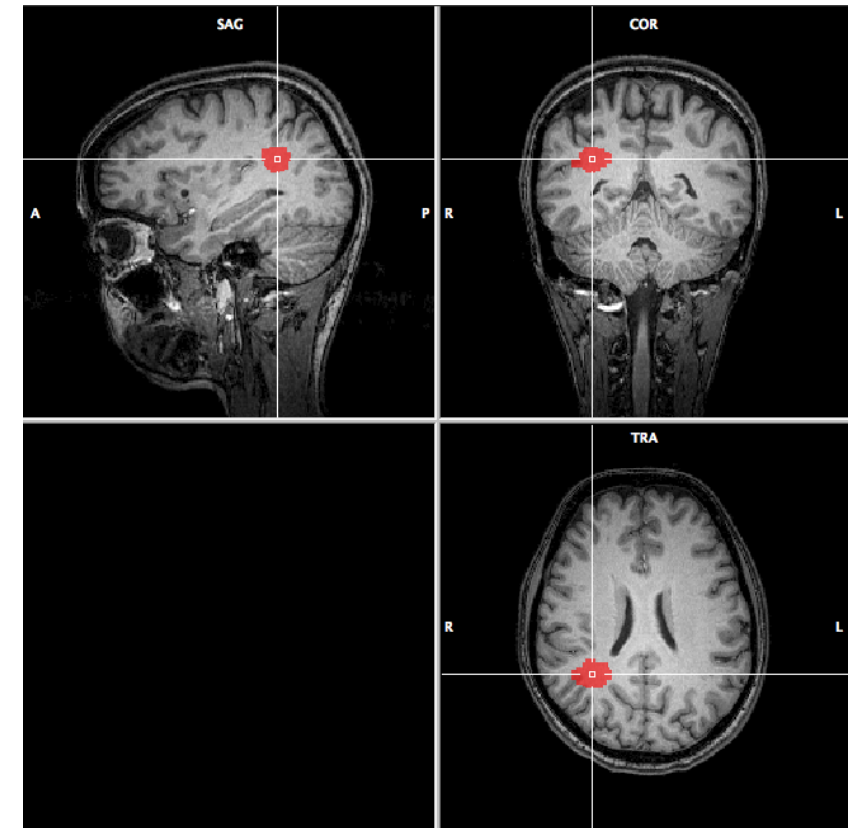
Voxel-based meta-analyses

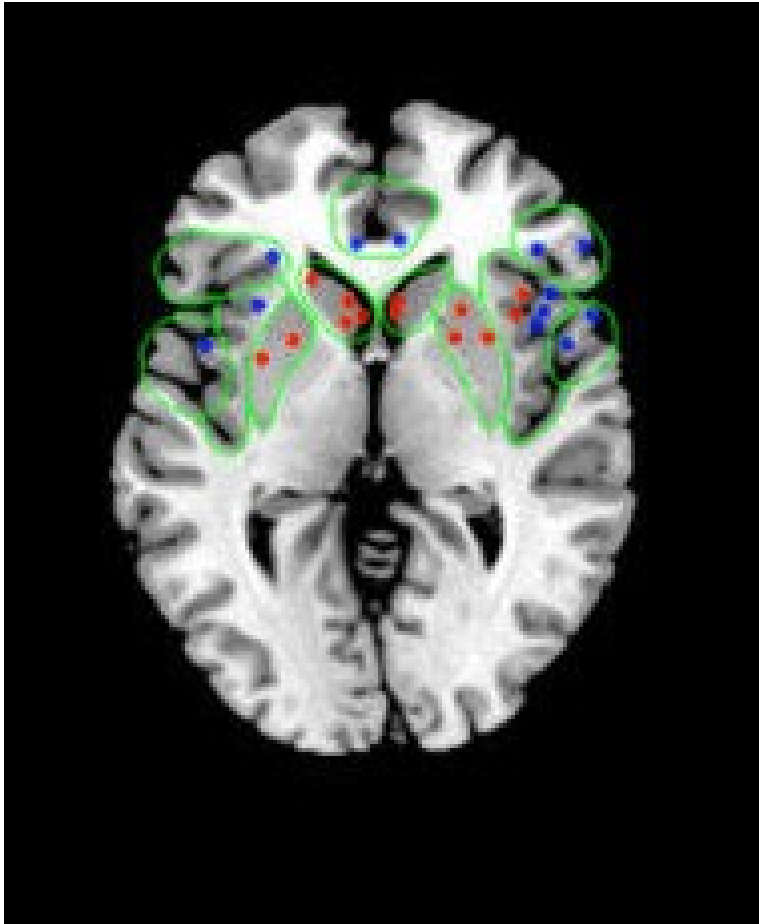


Region of interest-based meta-analyses



- set of different meta-analyses for every ROI
- selective = some regions more studied than others
- a priori hypotheses influence selection of ROI
- strong publication bias





[Radua and Mataix-Cols, 2012]

peak of a cluster plotted as a dot

number of dots count in each region

- **increase**
- **decrease**
- **borders of conventional regions**

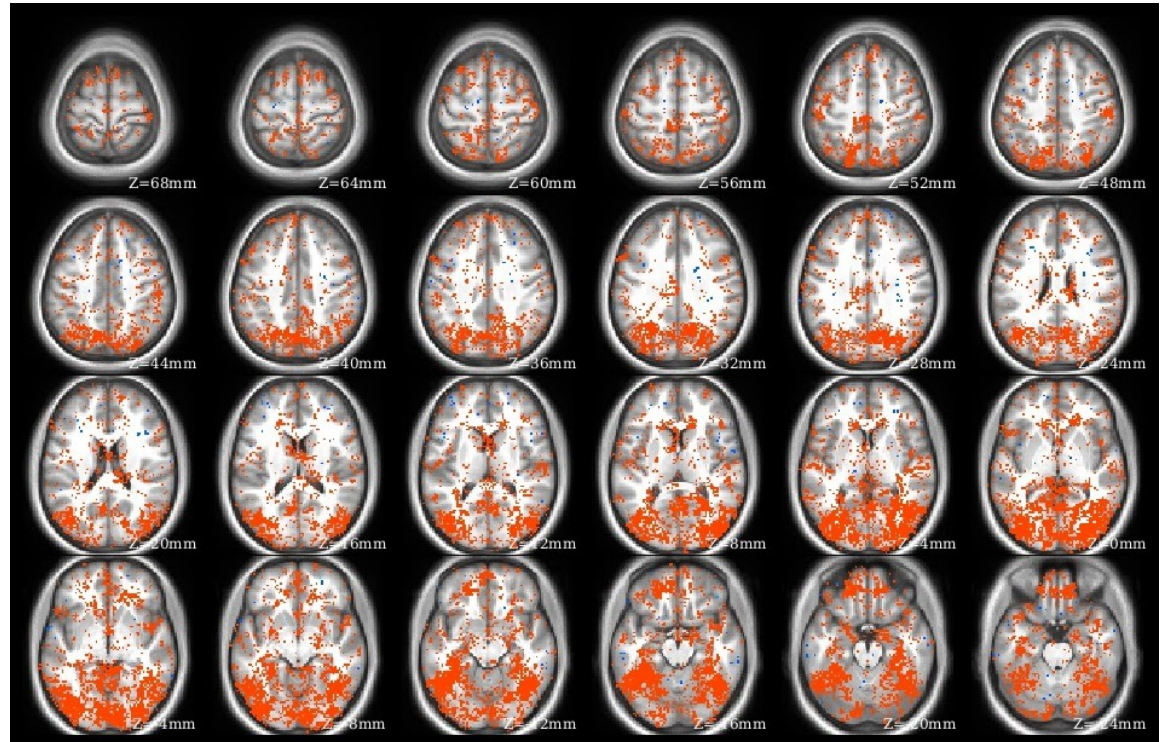
drawbacks: no weighting, loss of information,
selective

- Image-based meta-analyses
- Coordinate-based meta-analyses
- Mixed image- and coordinate-based meta-analyses

- **Image-based meta-analyses**
- Coordinate-based meta-analyses
- Mixed image- and coordinate-based meta-analyses

Image-based meta-analyses

- use of parametric maps
- meta-analysis for each voxel
- multiple-comparisons problem
- hard to find (contacting authors)



- Image-based meta-analyses
- **Coordinate-based meta-analyses**
- Mixed image- and coordinate-based meta-analyses

Coordinate-based meta-analyses



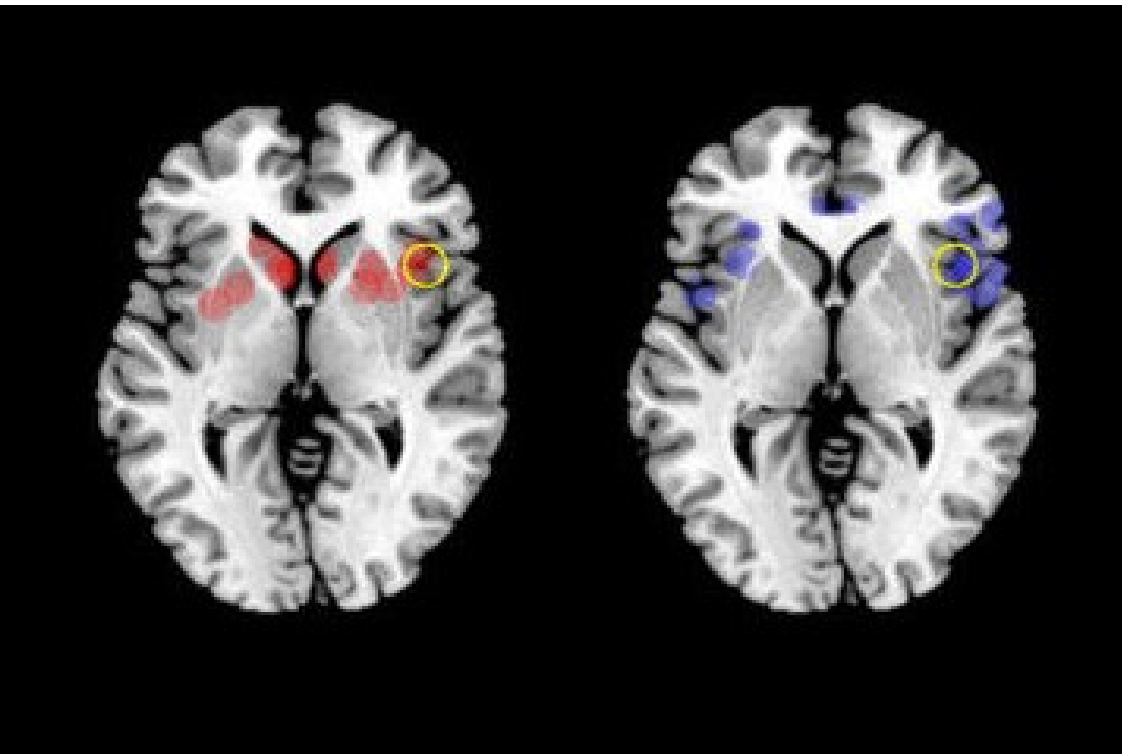
Table 2. Activation differences between BD patients, relatives and their respective controls and PPI results

	H	BA	MNI coordinates			Cs	Z-value	T-value
			x	y	z			
<i>Rel > Con: reappraisal-view emotional</i>								
Amygdala	L		-21	-7	-14	20	3.06	3.32
	R		33	5	-20	26	2.87	3.09
Ventral ACC	L	10	-12	50	-2	108	4.20	4.90
Insula	L	48	-39	2	-11	69	3.36	3.71
	R	48	36	-16	1	161	3.84	4.37
<i>BD > Con: reappraisal-view emotional</i>								
Amygdala	L		-15	-4	-17	18	2.99	3.18
Amygdala/parahippocampal	R		21	5	-26	60	4.31	4.87
<i>BD > Con: PPI L-amygdala seed</i>								
Orbitofrontal	L	47	-42	35	-8	53	4.94	5.79
<i>BD > Con: PPI R-amygdala seed</i>								
Orbitofrontal	L	47	-12	50	-5	23	4.41	5.01
<i>Rel > Con: PPI L-amygdala seed</i>								
Orbitofrontal	L	47	-39	29	-14	60	4.45	5.29
	R	47	36	56	-8	15	4.59	5.52
<i>Rel > Con: PPI R-amygdala seed</i>								
Orbitofrontal	R	47	39	56	-5	49	5.06	6.33

Abbreviations: BA, Brodmann area of the peak activation; Con, control; CS, cluster size in number of activated voxels; H, hemisphere; L, left; MNI, Montreal Neurological Institute; PPI, psychophysiological interaction analysis; R, right; Rel, relative.

Kanske et al.
2015

Kernel density analysis (KDA)

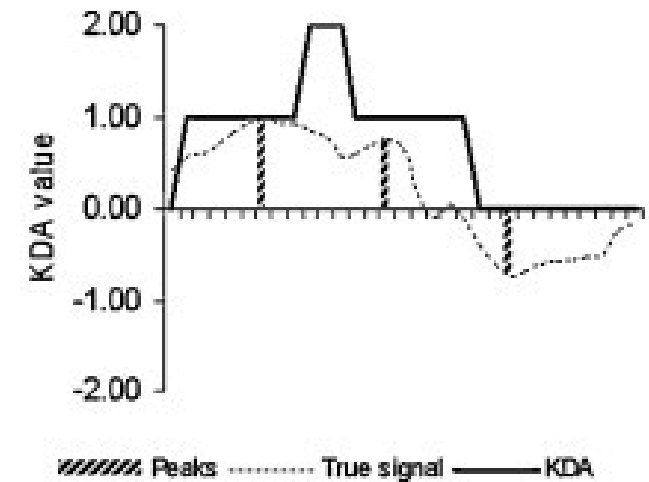


peak as a sphere

number of spheres surrounding

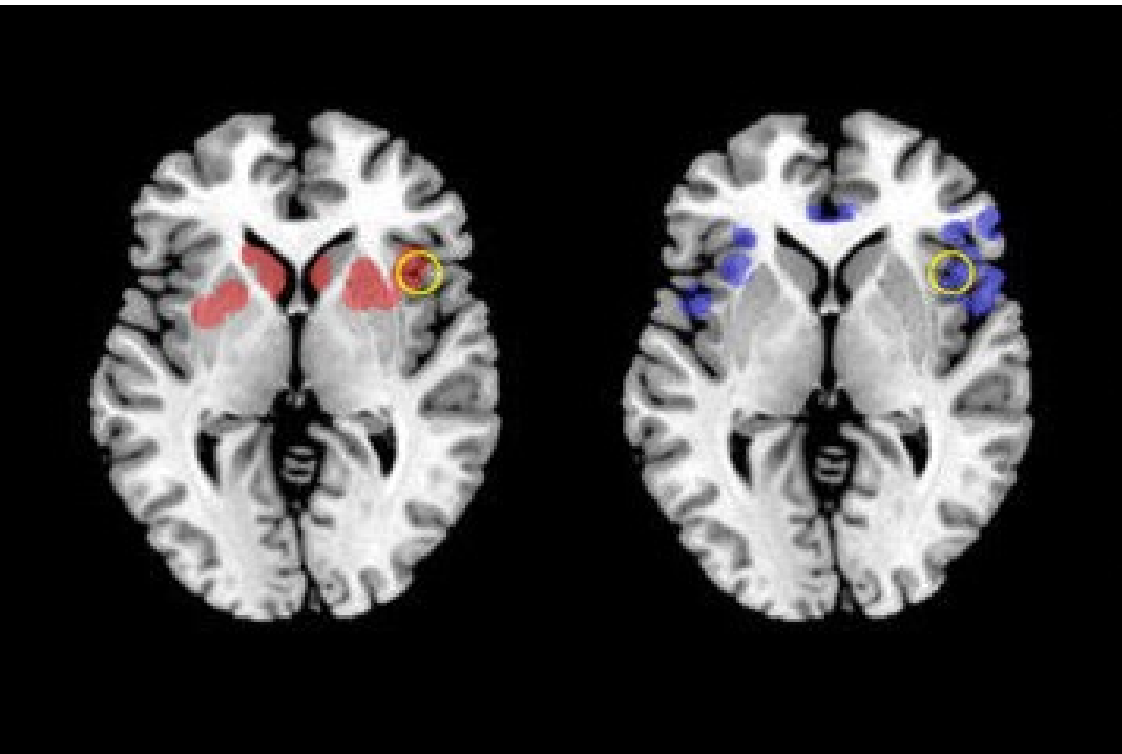
each voxel are counted

- **increase**
- **decrease**



[Radua and Mataix-Cols, 2012]

Multilevel kernel density (MKDA)



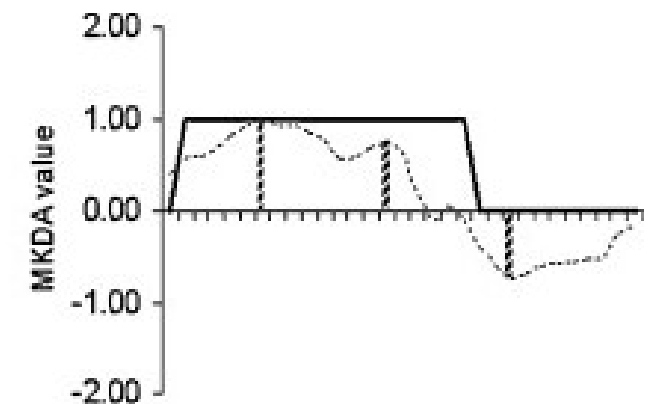
similar to KDA

voxel close to two
spheres from one
study counts as one

avoids false high
values at intersections

weighted by sample
size

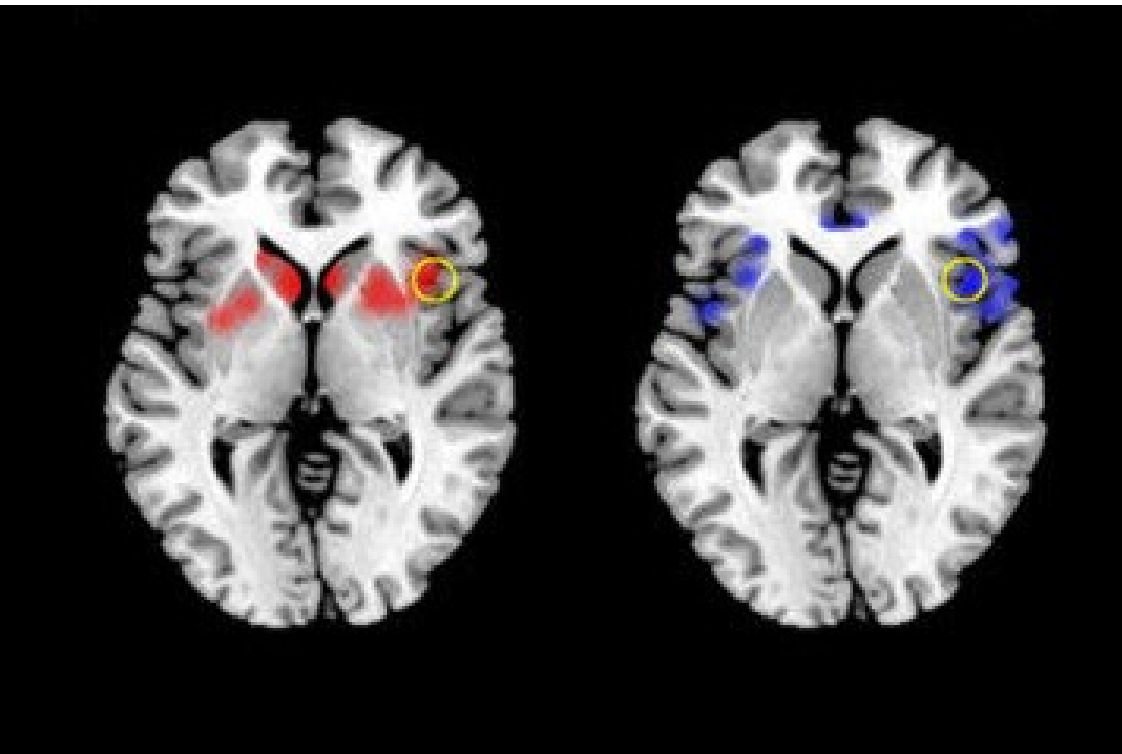
robustness analysis



[Radua and Mataix-Cols, 2012]

//// Peaks True signal — MKDA

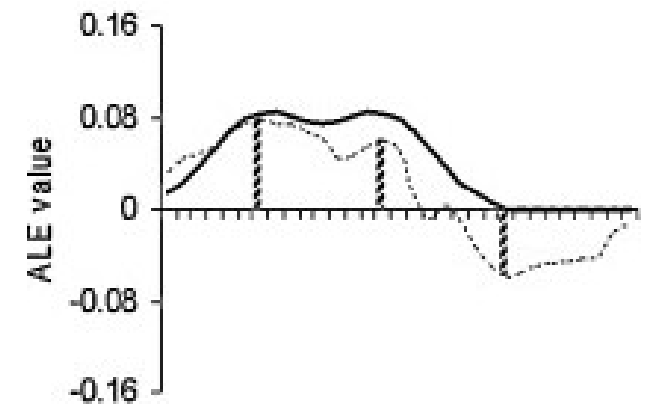
Activation likelihood estimation (ALE)



peak as a smoothed sphere
(Gaussian Kernel at FWHM)

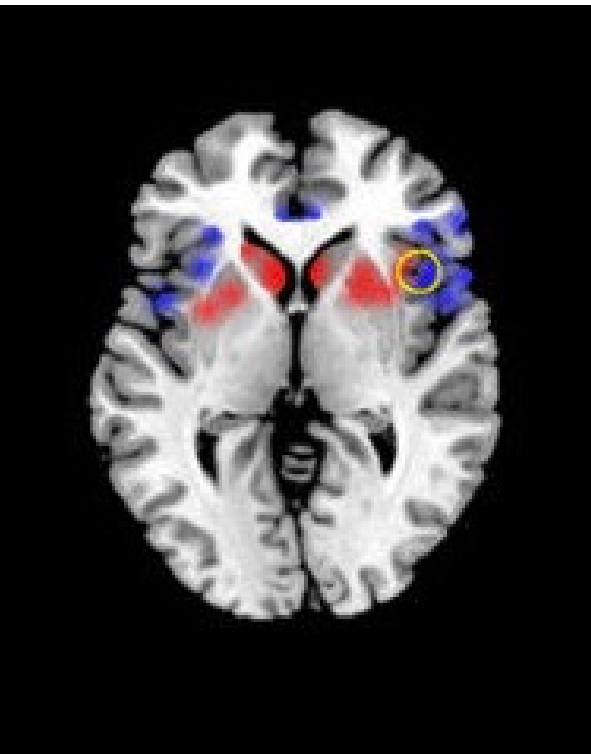
higher value for voxels closer to
the center of the sphere (peak)

- **increase**
- **decrease**



[Radua and Mataix-Cols, 2012]

Signed differential mapping (SDM)



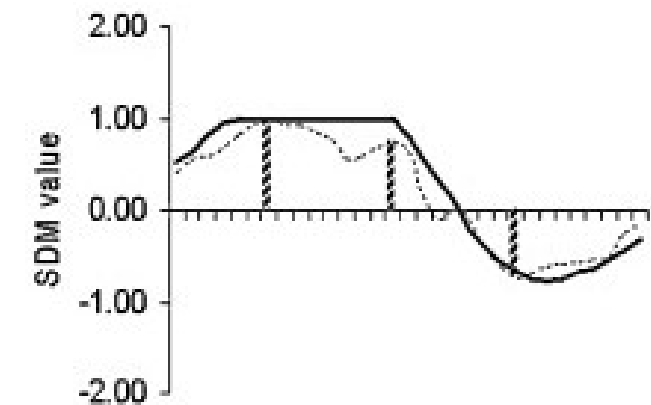
smoothed spheres like in ALE

weighted by sample size, robustness analysis like MKDA

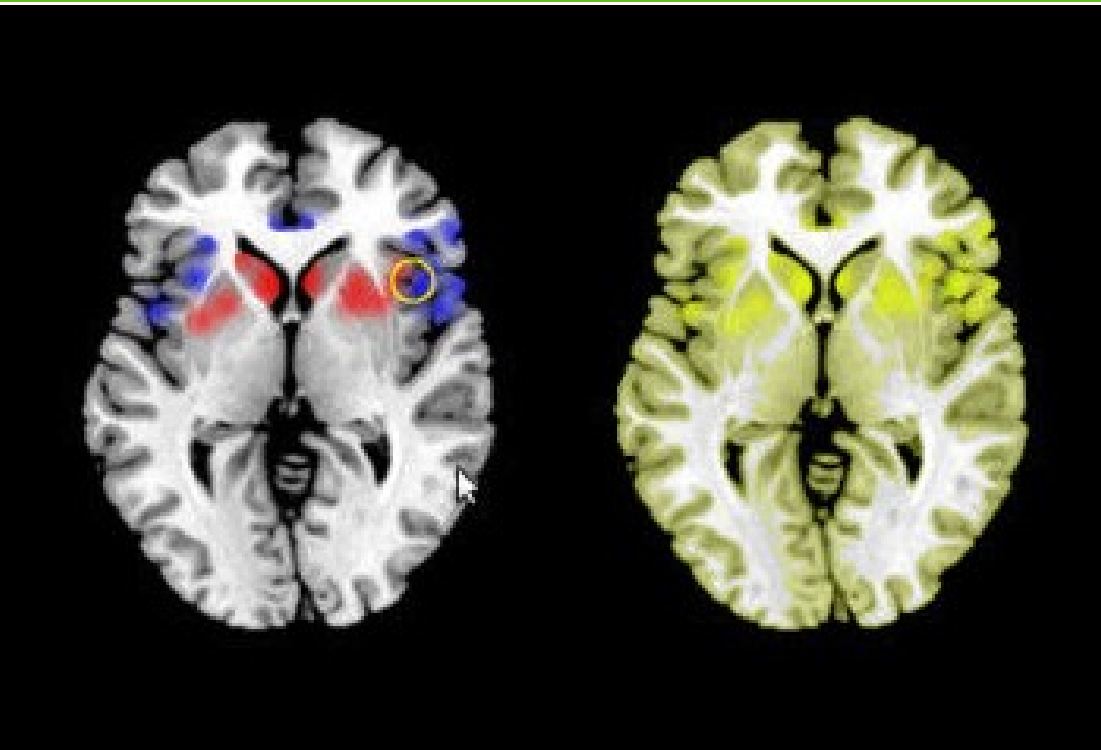
combines positive and negative values

adds heterogeneity analysis

[Radua and Mataix-Cols, 2012]



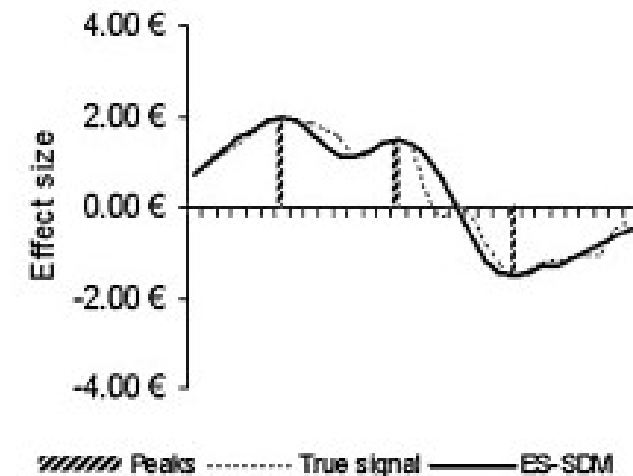
Effect size-Signed differential mapping (ES-SDM)



similar to SDM, but values are effect sizes weighted by variance (right)

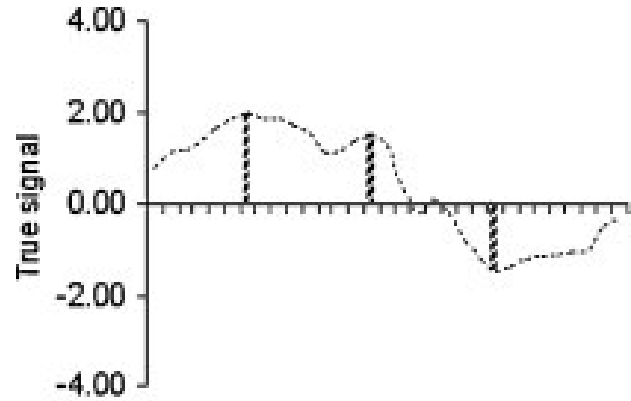
random effects model

combination of peaks and statistical parametric maps

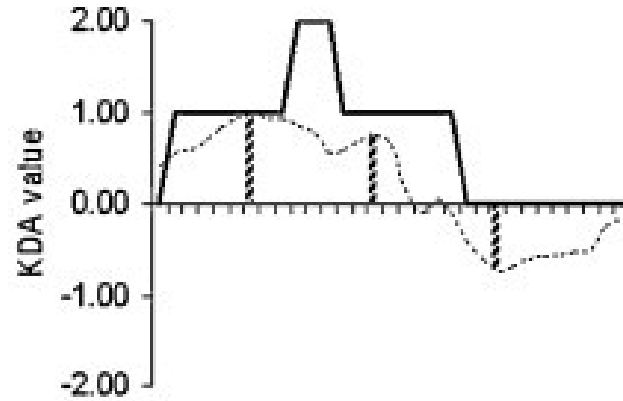


[Radua and Mataix-Cols, 2012]

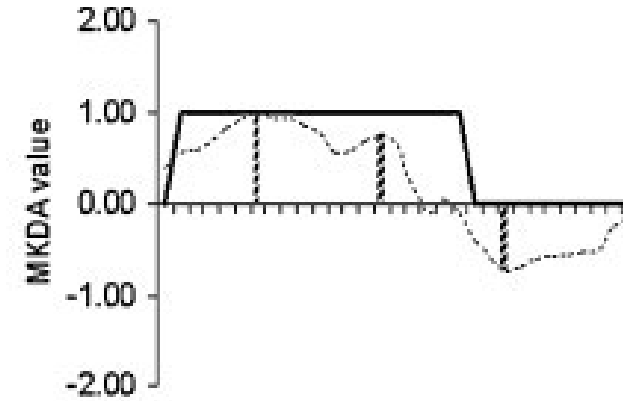
Voxel-based meta-analyses



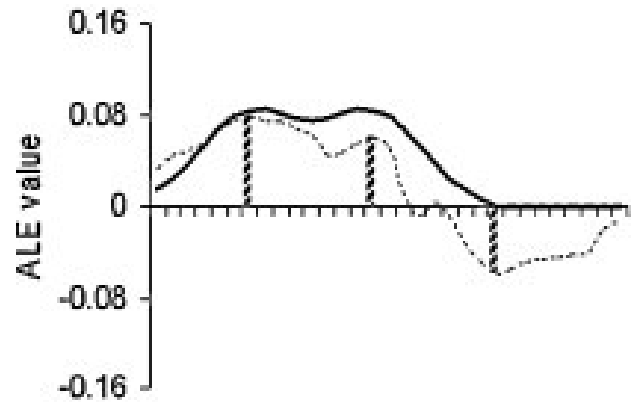
//// Peaks True signal



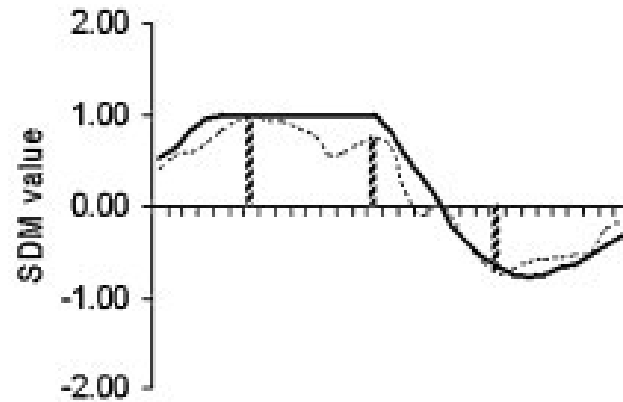
//// Peaks True signal — KDA



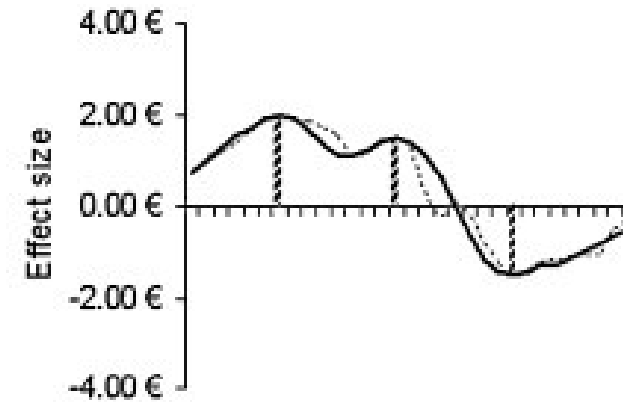
//// Peaks True signal — MKDA



//// Peaks True signal — ALE



//// Peaks True signal — Original SDM



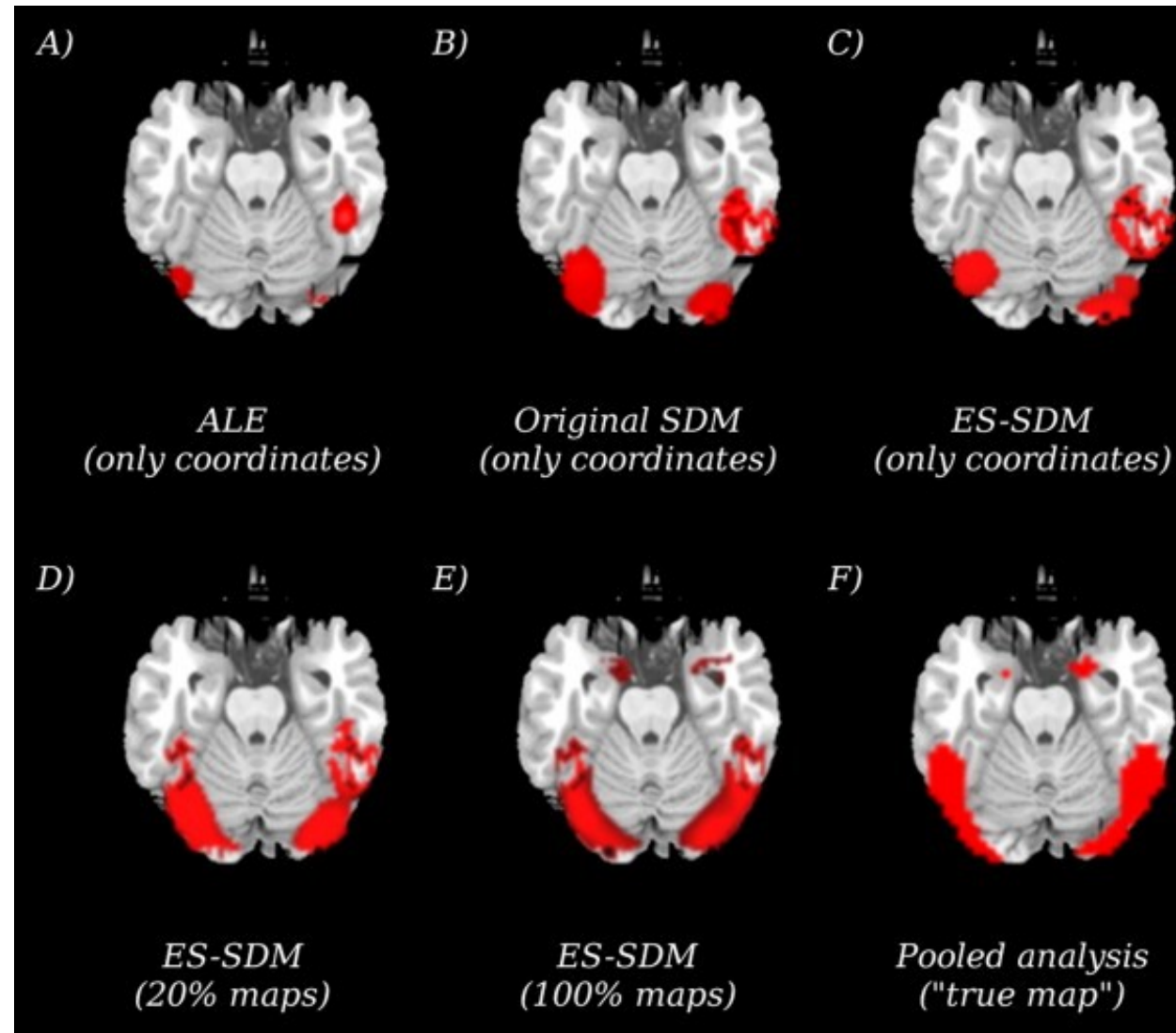
//// Peaks True signal — ES-SDM

Voxel-based meta-analyses



- Image-based meta-analyses
- Coordinate-based meta-analyses
- **Mixed image- and coordinate-based meta-analyses**

Mixed image- and coordinate-based meta-analyses



[Radua et al., 2012]

- Meta-analysis is a quantitative systematic review
- Pretty accessible and valuable research to do
- Different approaches and methods
- ROI based and Voxel based

Example: SDM



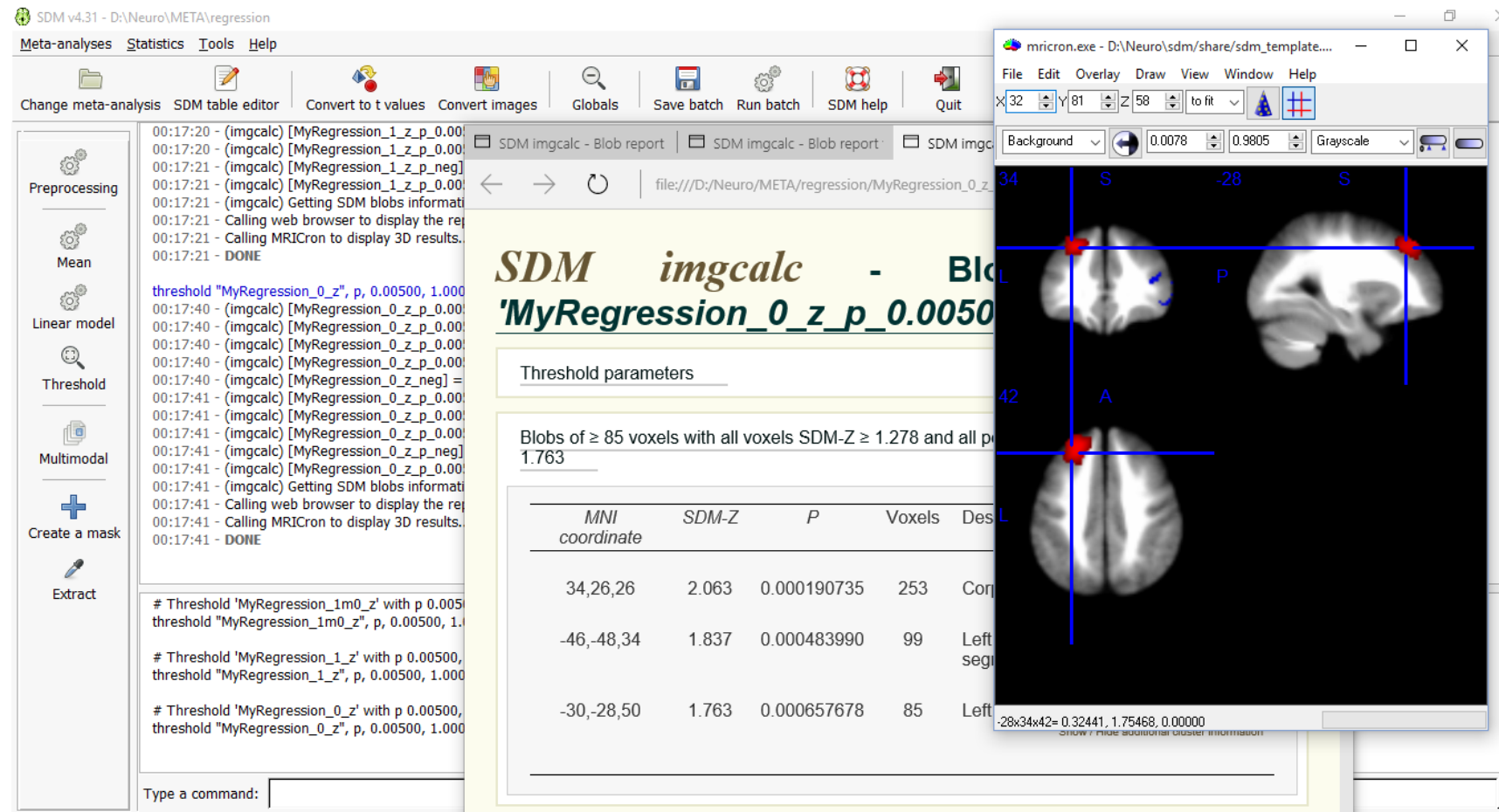
www.sdmproject.com

The screenshot shows a web browser displaying the SDM Project website. The browser's address bar shows the URL <https://www.sdmproject.com>. The page title is "Seed-based d Mapping" with a subtext "formerly 'Signed Differential Mapping'". A search bar is visible in the top right. The main content area features the "SDM" logo and a description: "Neuroimaging software library including meta-analytic methods for fMRI, VBM, DTI and PET and other tools". Below this, there are links for "Download software", "Meta-analysis Tutorial", "Meta-analysis Manual", and "SDM tools manual". A prominent yellow box contains a "New Anisotropic ES-SDM version 5.141 (Dec 2016) available" announcement, listing features like a new GUI, support for repeated measures, and funnel plots. A left sidebar provides navigation for "SDM Project web" with links to Home, Download software (Linux, Mac OSX, Windows, SPM), Meta-analysis tutorial, Meta-analysis manual (Introduction, Preparation, Globals, Calculations, Results, Batch processing, Settings, SPM extension, How to cite), and SDM Tools manual. At the bottom, a cookie consent banner is partially visible.

Example: SDM

1. research question
2. data collection
3. formatting
4. preprocessing
5. model estimation
6. results

www.sdmproject.com



The screenshot displays the SDM v4.31 software interface. The main window shows a report titled "SDM imgcalc - Blob report" for the regression analysis "MyRegression_0_z_p_0.0050". The report includes a table of significant blobs and a visualization of these blobs on a brain slice.

SDM imgcalc - Blob report
'MyRegression_0_z_p_0.0050'

Threshold parameters

Blobs of ≥ 85 voxels with all voxels SDM-Z ≥ 1.278 and all p ≥ 1.763

MNI coordinate	SDM-Z	P	Voxels	Description
34,26,26	2.063	0.000190735	253	Cor...
-46,-48,34	1.837	0.000483990	99	Left seg...
-30,-28,50	1.763	0.000657678	85	Left

The MRICron window shows a brain slice with three red dots indicating the locations of the significant blobs. The coordinates are 34, 26, 26; -46, -48, 34; and -30, -28, 50. The MRICron window also shows the threshold parameters: 0.0078, 0.9805, and Grayscale.

Example: SDM



1. **research question**

- consistent task/process

2. data collection

- choose contrasts

3. formatting

4. preprocessing

5. model estimation

6. results

Example: SDM



1. research question
 - similar to systematic review
- 2. data collection**
 - search in databases
3. formatting
 - selection of papers
4. preprocessing
 - 1 study as 1 subject
5. model estimation
 - contact authors for missing data
6. results

Example: SDM



1. research question
2. data collection
3. **formatting**
4. preprocessing
5. model estimation
6. results

A screenshot of the SDMGUI software interface. The window title is "SDMGUI - D:/Neuro/AES-meta/meanER". The menu bar includes "Meta-analyses", "Statistics", "Tools", and "Help". The toolbar contains icons for "Change meta-analysis", "SDM table editor", "Convert peaks", "Convert images", "Combine images", "Globals", "Save batch", "Run batch", "SDM help", and "Quit". On the left, a vertical sidebar lists processing steps: "Preprocessing", "Mean" (with \bar{y} symbol), "Linear model" (with βX symbol), "Threshold", "Multimodal", "Create mask", "Extract", and "Funnel Plot". The main area is titled "Processing status" with a progress indicator. To the right, there is a "Batch listing" section with a "Recording off" toggle and a large empty box. Below this is a "Type a command:" input field with a search icon and a blue arrow button. At the bottom, a "Log:" section contains an empty text area. The status bar at the very bottom shows "Current working directory: D:/Neuro/AES-meta/meanER".

Example: SDM



1. research question
2. data collection
3. **formatting**
4. preprocessing
5. model estimation
6. results

The screenshot shows the SDMGUI software interface. The window title is "SDMGUI - D:/Neuro/AES-meta/meanER". The interface includes a sidebar with various processing options: "Change meta-analysis", "Preprocessing", "Mean", "Linear model", "Threshold", "Multimodal", "Create mask", "Extract", and "Funnel Plot". The main area displays a table of studies with columns for study name, n1, n2, threshold, template, illness, PANSS_p, PANSS_n, and CPZ. The table contains 12 rows of data. Below the table, there is a "Log:" section and a "Current working directory:" field showing "D:/Neuro/AES-meta/meanER".

study	n1	n2	threshold	template	illness	PANSS_p	PANSS_n	CPZ
DerntlER	15	15	corr	MNI	07.3	12.3	14.6	329.9
Fakra	14	14	corr	MNI	NA	24	71	13.14
Gur_2007	16	17	uncorr	Tal	09.6	11.55078	7.55666	NA
Gur_2002	14	14	uncorr	Tal	NA	11.31795	7.65752	NA
Habel	17	17	uncorr	MNI	09.9	18	19.9	NA
Choudhary	21	20	uncorr	MNI	0.39	19.8	16.3	0
Johnston	10	10	corr	Tal	NA	NA	NA	NA
Mier_2010ER	16	16	uncorr	MNI	NA	11.57665	9.789028	901.59
Mier_2014	11	16	corr	MNI	10.18	11.566302	9.335158	472.56
Pinkham	35	37	corr	Tal	15.21	11.457648	7.597004	378.19
Reske	18	18	uncorr	MNI	NA	8	13.61	NA
Satterthwaite	12	21	uncorr	Tal	NA	NA	NA	290

Example: SDM



1. research question
2. data collection
3. formatting
4. preprocessing
5. model estimation
6. results

The screenshot displays the SDMGUI software interface. The main window shows a table of meta-analysis data with columns for study, n1, n2, threshold, template, illness, PANSS_p, PANSS_n, and CPZ. A window titled 'Fakra.spm_mni - Poznámkový blok' is open over the table, showing a list of coordinates for the 'Fakra' study. The current working directory is D:/Neuro/AES-meta/meanER.

study	n1	n2	threshold	template	illness	PANSS_p	PANSS_n	CPZ
DerntER	15					12.3	14.6	329.9
Fakra	14					24	71	13.14
Gur_2007	16	20, -4, -16, -5.40				11.55078	7.55666	NA
Gur_2002	14	-16, -2, -16, -4.76				11.31795	7.65752	NA
Habel	17	-26, 6, 26, -3.86				18	19.9	NA
Choudhary	21	25, -2, 14, -3.73				19.8	16.3	0
Johnston	10	52, -42, 10, -4.32				NA	NA	NA
Mier_2010ER	16	-30, 2, 30, -5.02				11.57665	9.789028	901.59
Mier_2014	11	-40, 2, 32, -3.49				11.566302	9.335158	472.56
Pinkham	35	48, 20, 18, -3.74				11.457648	7.597004	378.19
Reske	18	38, 40, -12, -3.36				8	13.61	NA
Satterthwaite	12	-4, -3, -3, -3.67				NA	NA	290
		-42, -40, -16, -3.39						
		-36, -44, 56, 4.40						
		-54, -31, 46, 4.34						
		-26, -44, 61, 4.16						
		42, -36, 52, 4.05						
		25, -440, 56, 3.57						

Example: SDM



1. research question
 2. data collection
 3. formatting
 4. **preprocessing**
 5. model estimation
 6. results
- convert **coordinate peaks** to estimate parametric maps
 - optionally include **original** parametric maps

 - creates
 - a) parametric maps of **effect sizes**
 - b) heterogeneity maps

Example: SDM



1. research question
2. data collection
3. formatting
- 4. preprocessing**
5. model estimation
6. results

The screenshot shows a dialog box titled "Preprocessing parameters" with a close button (X) and a help button (?). The main text reads: "A new meta-analysis will be created. Note that any **previous meta-analysis in this folder will be removed.**" There are two buttons: "OK" and "Cancel". Below the text are several settings:

- Modality: Functional MRI or PET (dropdown menu)
- Number of randomizations: 50 (spin box)
- Correlation template: gray matter (dropdown menu)
- Anisotropy: 1,00 (spin box)
- Isotropic FWHM (mm): 20 (spin box)
- Mask: gray matter (dropdown menu)

At the bottom, a note states: "Note that these parameters are automatically set according to the modality you select. However, you can still change them for special purposes. The effects of isotropic FWHM are negligible with full anisotropy."

- modality: VBM, fMRI, PET, DTI
- template: GM, WM, FA, CSF

Example: SDM



1. research question
2. data collection
3. formatting
4. preprocessing
- 5. model estimation**
 - estimate mean
 - linear model
 - a) compare groups
 - b) meta-regression
 - multimodal meta-analysis
6. results

Example: SDM



1. research question
 - threshold results
2. data collection
 - extract peaks (seed)
3. formatting
 - funnel plot
4. preprocessing
5. model estimation
6. **results**

Example: SDM



1. *SDM imgcalc* - Blob report for 'MyMean_z_p_0.00500_1.000_10'

Threshold parameters

Show / Hide

2. Blobs of ≥ 14 voxels with all voxels SDM-Z ≥ 1.048 and all peaks SDM-Z ≥ 1.112

Show / Hide

<i>MNI coordinate</i>	<i>SDM-Z</i>	<i>P</i>	Voxels	Description	
-46,-32,48	1.702	0.000060380	1280	Left postcentral gyrus, BA 2	Show / Hide additional cluster information
44,-4,56	1.289	0.001252234	75	Right middle frontal gyrus, BA 6	Show / Hide additional cluster information
-28,-88,22	1.121	0.003381133	15	Left middle occipital gyrus, BA 19	Show / Hide additional cluster information
-10,-58,40	1.112	0.003565371	14	Left median network, cingulum	Show / Hide additional cluster information

5. Blobs of ≥ 580 voxels with all voxels SDM-Z ≤ -1.634 and all peaks SDM-Z ≤ -1.976

Show / Hide

<i>MNI coordinate</i>	<i>SDM-Z</i>	<i>P</i>	Voxels	Description	
48,34,-6	-3.336	~0	5651	Right inferior frontal gyrus, orbital part, BA 47	Show / Hide additional cluster information
2,26,30	-1.976	0.000938237	580	Right median cingulate / paracingulate gyri, BA 24	Show / Hide additional cluster information

6.

Example: SDM

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.

SDM imgcalc - Blob r

Threshold parameters

Blobs of ≥ 14 voxels with all voxels SDM-Z ≥ 1

MNI coordinate

-46,-32,48

44,-4,56

-28,-88,22

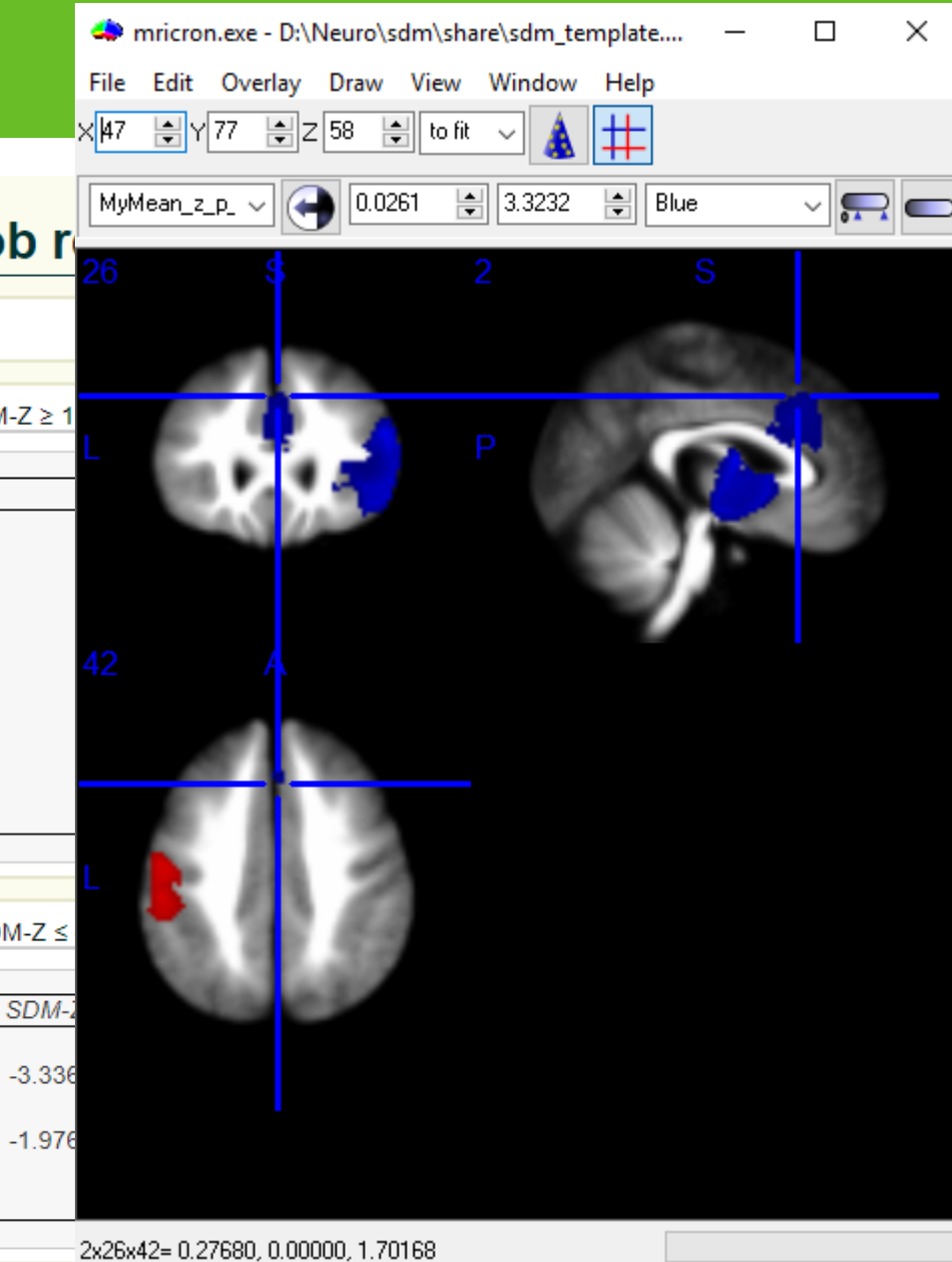
-10,-58,40

Blobs of ≥ 580 voxels with all voxels SDM-Z \leq

MNI coordinate

48,34,-6

2,26,30



0_10'

Show / Hide

Show / Hide

option

stcentral gyrus, BA 2

Show / Hide additional cluster information

middle frontal gyrus, BA 6

Show / Hide additional cluster information

iddle occipital gyrus, BA 19

Show / Hide additional cluster information

edian network, cingulum

Show / Hide additional cluster information

Show / Hide

s, orbital part, BA 47

Show / Hide additional cluster information

paracingulate gyri, BA 24

Show / Hide additional cluster information

- **sets of original data (eg raw scanned images)**
 - BRAINNet (<http://www.brainnet.net>)
 - fMRI Data Center (<http://www.fmridc.org>)
 - OpenfMRI (<http://www.openfmri.org>)
- **summary statistics from the studies included in one meta-analysis (mean and SD of ROI volumes)**
 - Bipolar Disorder Neuroimaging Database (<http://www.bipolardatabase.org>)
 - Major Depressive Disorder Neuroimaging Database (<http://www.depressiondatabase.org>)
 - Peak-coordinate databases from SDM meta-analyses (<http://www.sdmproject.com/database>)
- **sets of summary statistics of virtually all published studies**
 - BrainMap (<http://www.brainmap.org>)
 - NeuroSynth (<http://www.neurosynth.org>)

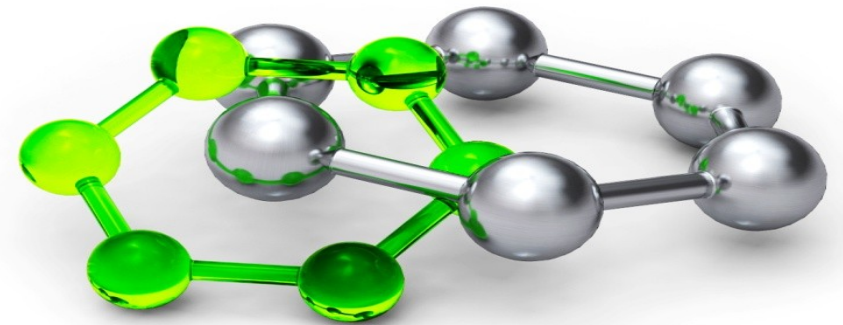
Thank you for your attention



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