Meta-analysis techniques

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Why meta-analysis?

"Why Most Published Research Findings Are False" (Ioannidis, 2005):

> "There is increasing concern that in modern research, false findings may be the majority or even the vast majority of published research claims."

> "The greater the flexibility in designs, definitions, outcomes, and analytical modes in a scientific field, the less likely the research findings are true."

Is the last quote especially true for neuroimaging?

Why meta-analysis?

"The Difference Between 'Significant' and 'Not Significant' is not Itself Statistically Significant" (Gelman and Stern, 2006)

Two apparently conflicting studies—one significant, another not significant—may not necessarily be conflicting. One may simply not have enough power.

Information increase

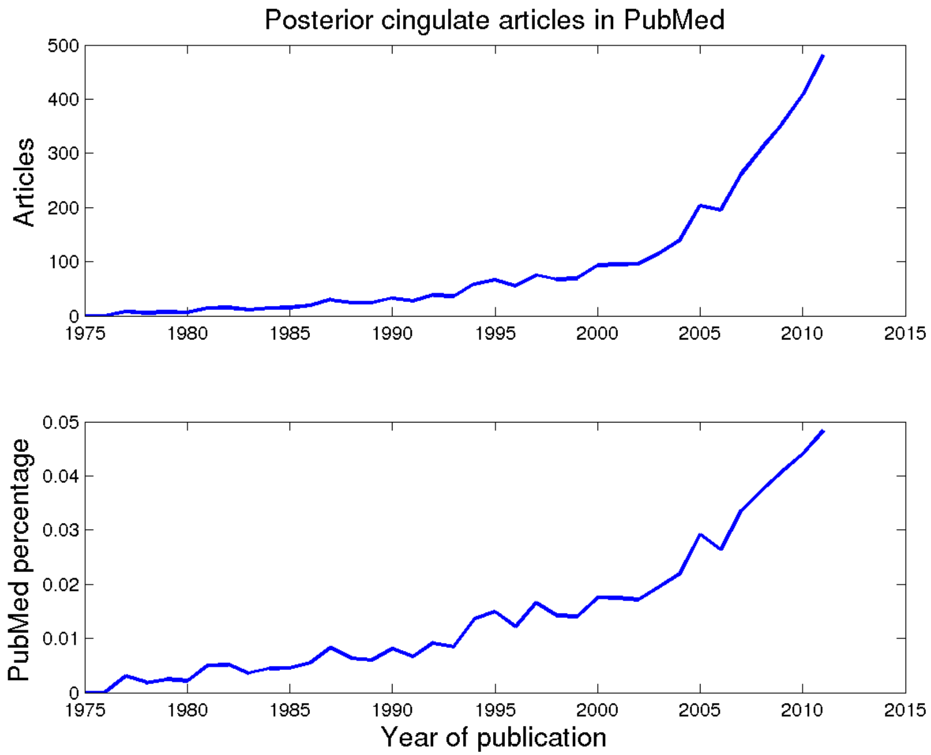


Figure 1: Increase in the number of articles in PubMed which are returned after searching on posterior cingulate and related brain areas.

There are too much data for one person to grasp

The results across experiments are too conflicting

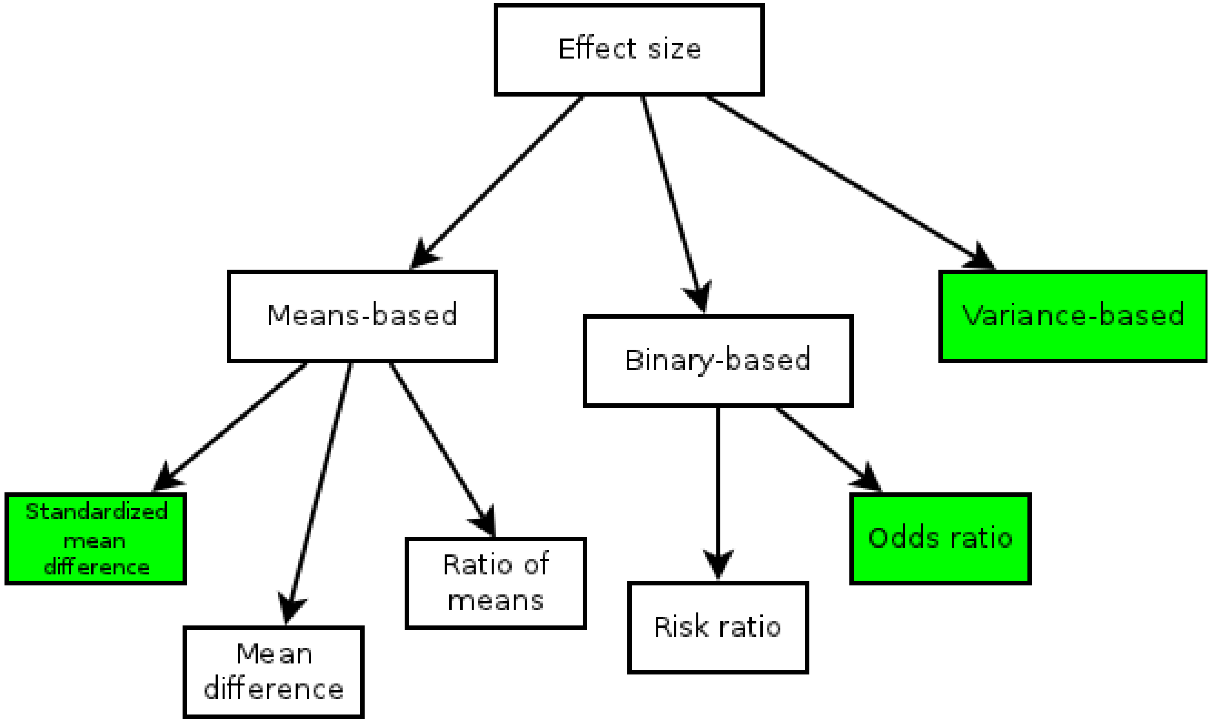
Need for tools that collect data across studies, bring order to data, make search easy and automate analyses to bring out consensus results: **meta-analysis and meta-analytic databases**

Meta-analysis

The page-one definition (Hartung et al., 2008):

> The statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings.

Effect sizes



The *effect size* is the central measure in ordinary meta-analysis.

The mean effect size is (usually) independent of the number of subjects.

Effect sizes can be formed from other variables than those shown in the figure: correlation, proportions.

Standardized mean difference (SMD)

For continuous data with (approximately) normal distribution. Example:

Study	Bipolars			Controls		
	N	Mean	SD	N	Mean	SD
Strakowski SM, 1999	24	7.1	1.1	22	6.3	0.8
Altshuler LL, 2000	24	3825.9	695	18	3375	639
...						

Table 1: Data for meta-analysis with SMD. Amygdala volume from bipolar patients and controls.

Take the difference between the means of the two groups (experimentals e and controls c) and divide by the pooled standard deviation

$$g_{\text{smd}} = \frac{\bar{x}_e - \bar{x}_c}{s_{\text{pooled}}}$$

g_{smd} independent of unit of the original study, e.g., whether a brain volume was reported in qubic millimeters or qubic centimeters. it is also independent of the number of subjects (n_e in experimental group)

SDM — details & inference

With, e.g., s_e as the standard deviation for the experimental group:

$$s_{\text{pooled}} = \sqrt{\frac{(n_e - 1)s_e^2 + (n_c - 1)s_c^2}{n_e + n_c - 2}} \quad (1)$$

$$d_{\text{smd}} = \text{E}[g_{\text{smd}}] \approx \left(1 - \frac{3}{4(n_e + n_c) - 9}\right) g_{\text{smd}} \quad (2)$$

$$\widehat{\text{Var}}[g_{\text{smd}}] \approx \frac{1}{\tilde{n}} + \frac{g_{\text{smd}}}{2(n_e + n_c - 3.94)} \qquad \text{where } \tilde{n} = \frac{n_e n_c}{n_e + n_c}. \quad (3)$$

If the effect size is small ($g_{\text{smd}} \to 0$) and the two groups are of the same size ($n_e = n_c$) then the variance becomes proportional to the number of subjects in the groups

$$\widehat{\text{Var}}[g_{\text{smd}}] \approx 2/n_e = 2/n_c, \quad (4)$$

i.e., the more subjects the better the effect size is determined.

Odds ratio

For binary data we can construct a contingency table for the results:

	"Success"	"Failure"	total
"Experimentals"	n_{es}	n_{ef}	n_e
"Controls"	n_{cs}	n_{cf}	n_c
Total	n_s	n_f	n

One effect size for binary data is the (natural) logarithm of the odds ratio (Hartung et al., 2008, p. 20)

$$d_{\mathrm{or}} = \ln \left[\frac{c(n_{es})/c(n_e - n_{es})}{c(n_{cs})/c(n_c - n_{cs})} \right], \qquad \text{where e.g., } c(x) = x + 0.5$$

Addition of 0.5 to get around a problem if there is zero count in any of the cells (Hartung et al., 2008, p. 117)

An estimate of its variance as an estimator is

$$\widehat{\mathrm{Var}}[d_{\mathrm{or}}] = \frac{1}{c(n_{es})} + \frac{1}{c(n_e - n_{es})} + \frac{1}{c(n_{cs})} + \frac{1}{c(n_c - n_{cs})}.$$

Variance ratio

Example claim: Men have higher variation in intelligence than women.

We should test this

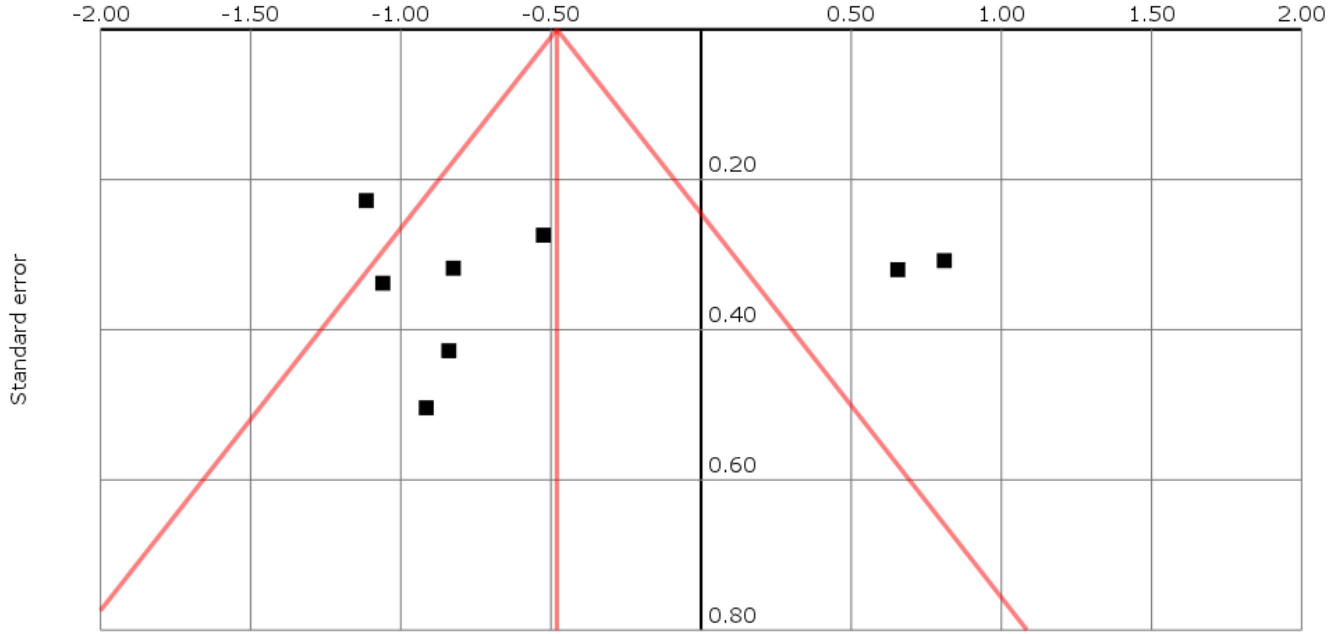
$$\sigma^2_{\text{men}} > \sigma^2_{\text{women}}$$

The logarithm of the ratio between the two variations (lnvr) results in a good statistics (Shaffer, 1992)

$$d_{vr} = \ln \left(\frac{s_e^2}{s_c^2} \right) \tag{5}$$

This is better than the variance ratio s_e^2/s_c^2 (or standard deviation difference $s_e - s_c$)

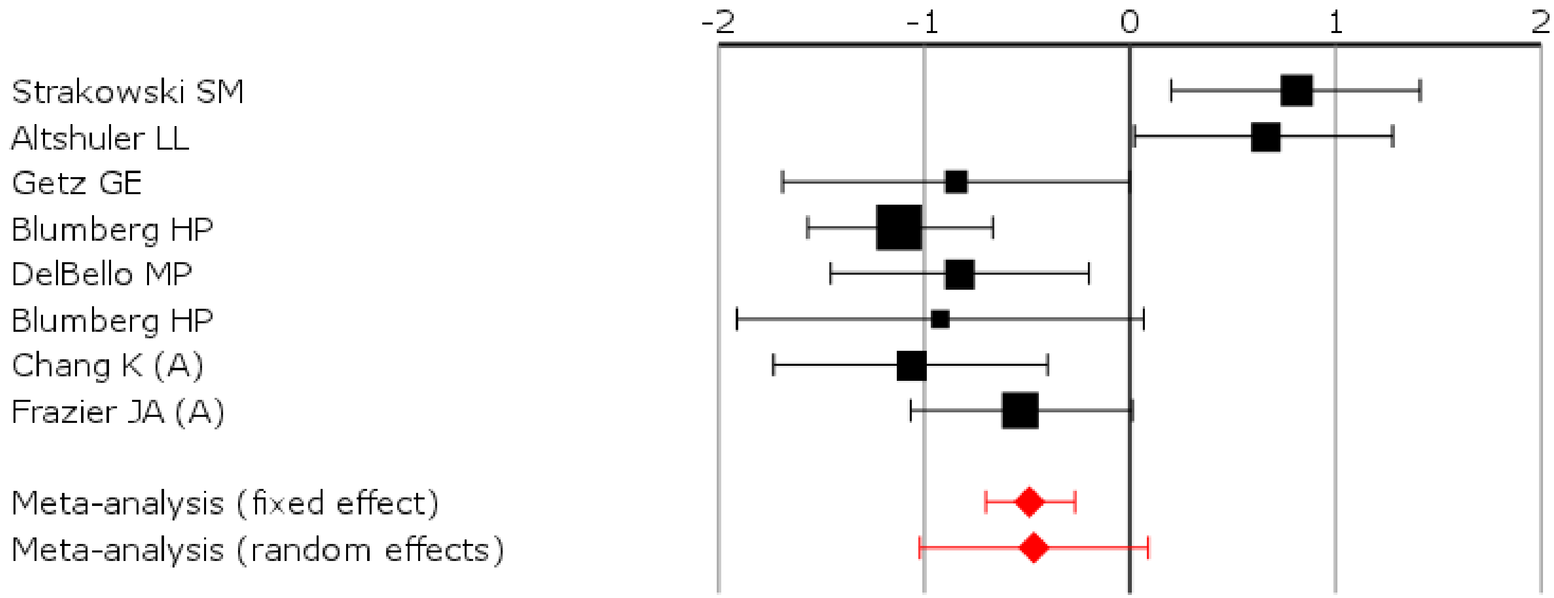
Funnel plot with multiple studies



Scatter plot of the effect sizes and their standard errors (related to variance and sample size) for multiple studies.

May indicate publication bias, if researchers of small studies only publish if they see an effect then the funnel plot becomes asymmetric.

Forrest plot with multiple studies



Forest plot shows the effect size for 8 different studies (Amygdala volume in bipolar disorder).

The squares are the 8 effect sizes (d_i) and the lines indicate 0.05-confidence interval: $d_i \pm 1.96\sqrt{\mathrm{Var}[d_i]}$

Combining effect sizes across studies

Meta-analytic effect size: Inverse variance-weighting (in so-called fixed effect) for weighted averging of studies (Hartung et al., 2008, p. 36)

$$d_{\text{meta}} = \frac{\sum_i w_i \, d_i}{\sum_i w_i} \tag{6}$$

where d_i is the effect size for the ith study and the weight for the ith study is determined as the inverse variance

$$w_i = 1/\operatorname{Var}[d_i] \tag{7}$$

Variance:

$$\operatorname{Var}[d_{\text{meta}}] \approx \frac{1}{\sum_i w_i} \tag{8}$$

when the number of subject for study i increases ($n_i \to \infty$), then the variance decreases ($\operatorname{Var}[d_i] \to 0$), the weight increases ($w_i \to \infty$) and the meta-analytic variance decreases ($\operatorname{Var}[d_{\text{meta}}] \to 0$)

Random effects analysis

"Random effects" in meta-analysis adds an extra parameter that models the variation between studies.

One approach is the so-called DerSimonian-Laird (Hartung et al., 2008, p. 108)

Free tools for meta-analysis

R with `meta` package by Guido Schwarzer

RevMan and Archie of the Cochrane Library (Elamin et al., 2009)

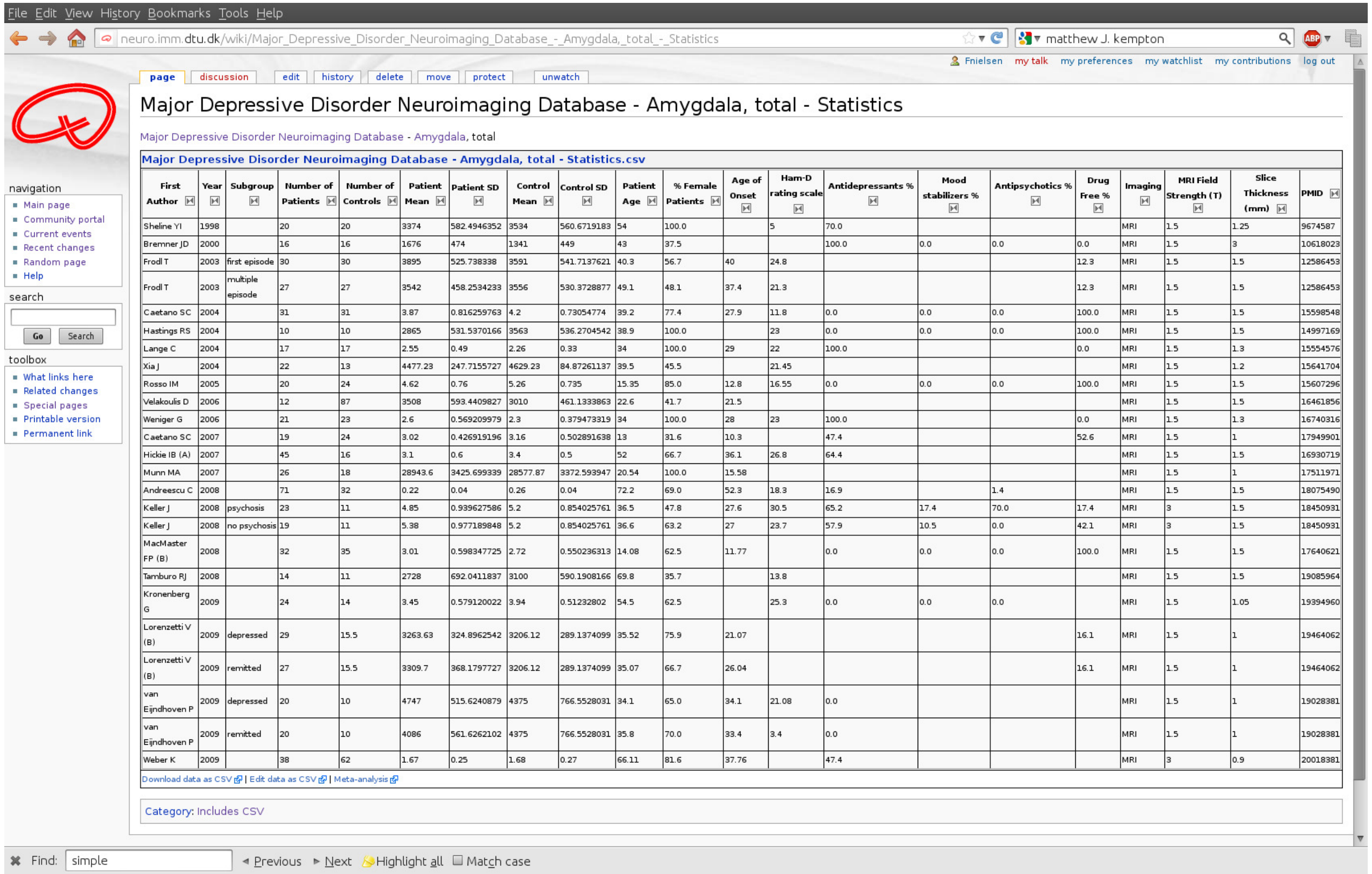
Open science meta-analysis

Brede Wiki & its meta-analysis service

Brede Wiki for personality genetics

Online data and meta-analyses

Brede Wiki with data



Major Depressive Disorder Neuroimaging Database - Amygdala, total - Statistics

Major Depressive Disorder Neuroimaging Database - Amygdala, total

Major Depressive Disorder Neuroimaging Database - Amygdala, total - Statistics.csv

First Author	Year	Subgroup	Number of Patients	Number of Controls	Patient Mean	Patient SD	Control Mean	Control SD	Patient Age	% Female Patients	Age of Onset	Ham-D rating scale	Antidepressants %	Mood stabilizers %	Antipsychotics %	Drug Free %	Imaging	MRI Field Strength (T)	Slice Thickness (mm)	PMID
Sheline YI	1998		20	20	3374	582.4946352	3534	560.6719183	54	100.0		5	70.0				MRI	1.5	1.25	9674587
Bremner JD	2000		16	16	1676	474	1341	449	43	37.5			100.0	0.0	0.0	0.0	MRI	1.5	3	10618023
Frodl T	2003	first episode	30	30	3895	525.738338	3591	541.7137621	40.3	56.7	40	24.8				12.3	MRI	1.5	1.5	12586453
Frodl T	2003	multiple episode	27	27	3542	458.2534233	3556	530.3728877	49.1	48.1	37.4	21.3				12.3	MRI	1.5	1.5	12586453
Caetano SC	2004		31	31	3.87	0.816259763	4.2	0.73054774	39.2	77.4	27.9	11.8	0.0	0.0	0.0	100.0	MRI	1.5	1.5	15598548
Hastings RS	2004		10	10	2865	531.5370166	3563	536.2704542	38.9	100.0		23	0.0	0.0	0.0	100.0	MRI	1.5	1.5	14997169
Lange C	2004		17	17	2.55	0.49	2.26	0.33	34	100.0	29	22	100.0			0.0	MRI	1.5	1.3	15554576
Xia J	2004		22	13	4477.23	247.7155727	4629.23	84.87261137	39.5	45.5		21.45					MRI	1.5	1.2	15641704
Rosso IM	2005		20	24	4.62	0.76	5.26	0.735	15.35	85.0	12.8	16.55	0.0	0.0	0.0	100.0	MRI	1.5	1.5	15607296
Velakoulis D	2006		12	87	3508	593.4409827	3010	461.1333863	22.6	41.7	21.5						MRI	1.5	1.5	16461856
Weniger G	2006		21	23	2.6	0.569209979	2.3	0.379473319	34	100.0	28	23	100.0			0.0	MRI	1.5	1.3	16740316
Caetano SC	2007		19	24	3.02	0.426919196	3.16	0.502891638	13	31.6	10.3		47.4			52.6	MRI	1.5	1	17949901
Hickie IB (A)	2007		45	16	3.1	0.6	3.4	0.5	52	66.7	36.1	26.8	64.4				MRI	1.5	1.5	16930719
Munn MA	2007		26	18	28943.6	3425.699339	28577.87	3372.593947	20.54	100.0	15.58						MRI	1.5	1	17511971
Andreescu C	2008		71	32	0.22	0.04	0.26	0.04	72.2	69.0	52.3	18.3	16.9		1.4		MRI	1.5	1.5	18075490
Keller J	2008	psychosis	23	11	4.85	0.939627586	5.2	0.854025761	36.5	47.8	27.6	30.5	65.2	17.4	70.0	17.4	MRI	3	1.5	18450931
Keller J	2008	no psychosis	19	11	5.38	0.977189848	5.2	0.854025761	36.6	63.2	27	23.7	57.9	10.5	0.0	42.1	MRI	3	1.5	18450931
MacMaster FP (B)	2008		32	35	3.01	0.598347725	2.72	0.550236313	14.08	62.5	11.77		0.0	0.0	0.0	100.0	MRI	1.5	1.5	17640621
Tamburo RJ	2008		14	11	2728	692.0411837	3100	590.1908166	69.8	35.7		13.8					MRI	1.5	1.5	19085964
Kronenberg G	2009		24	14	3.45	0.579120022	3.94	0.51232802	54.5	62.5		25.3	0.0	0.0	0.0		MRI	1.5	1.05	19394960
Lorenzetti V (B)	2009	depressed	29	15.5	3263.63	324.8962542	3206.12	289.1374099	35.52	75.9	21.07					16.1	MRI	1.5	1	19464062
Lorenzetti V (B)	2009	remitted	27	15.5	3309.7	368.1797727	3206.12	289.1374099	35.07	66.7	26.04					16.1	MRI	1.5	1	19464062
van Eijndhoven P	2009	depressed	20	10	4747	515.6240879	4375	766.5528031	34.1	65.0	34.1	21.08	0.0				MRI	1.5	1	19028381
van Eijndhoven P	2009	remitted	20	10	4086	561.6262102	4375	766.5528031	35.8	70.0	33.4	3.4	0.0				MRI	1.5	1	19028381
Weber K	2009		38	62	1.67	0.25	1.68	0.27	66.11	81.6	37.76		47.4				MRI	3	0.9	20018381

Download data as CSV | Edit data as CSV | Meta-analysis

Category: Includes CSV

Store numerical data on a spreadsheet-like page in a MediaWiki. Describe the data in structured format on the wiki.

Data in the Brede Wiki primarily from large meta-analyses by Matthew Kempton, Institute of Psychiatry, and his coworkers (Kempton et al., 2008; Kempton et al., 2010; Kempton et al., 2011)

Meta-analysis with the Brede Wiki

Major depressive disorder

Major depressive disorder

See also:

Major Depressive Disorder Neuroimaging Database

Topic (help)	
Major depressive disorder	
Abbreviations:	MDD
Variations:	Unipolar depression Major depression
Category:	Major depressive disorder
Parents:	Depression
Children:	Early onset major depressive disorder
Databases:	Brede Database MeSH Wikipedia with DBpedia
Search	
Papers:	DOAJ Google Scholar PubMed Open J-Gate PubMed articles for MeSH term
Ontologies:	MeSH NeuroLex
Other:	Google WolframAlpha

Depression → Major depressive disorder → Early onset major depressive disorder

Papers [edit]

Neuroimaging [edit]

1. Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies
2. Structural neuroimaging studies in major depressive disorder: meta-analysis and comparison with bipolar disorder

1. Hippocampal volume in primary unipolar major depression: a magnetic resonance imaging study
2. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder
3. Regional cerebral blood flow abnormalities in depressed patients with cognitive impairment

Treatment response and genetics [edit]

1. 5-HTR1A, 5-HTR6, TPH1 and TPH2 polymorphisms and major depression
2. Genetic association analysis of serotonin 2A receptor gene (HTR2A) with bipolar disorder and major depressive disorder in the Japanese population

Categories: Topics | Topics in Brede Database | Topics in MeSH | Topics in Wikipedia

Meta-analyses [edit]

Topic	Data	Raw data	Meta-analysis
Amygdala — Major depressive disorder — MaND	Data	CSV	Meta-analysis
Amygdala — Bipolar disorder — BiND	Data	CSV	Meta-analysis
Amygdala — Obsessive-compulsive disorder — ObND	Data	CSV	Meta-analysis

Obsessive-compulsive disorder Neuroimaging Database - Amygdala

ObND for amygdala

Obsessive-compulsive disorder Neuroimaging Database - Amygdala.csv

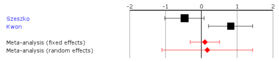
Author	Year		Region	Patient mean	Patient SD	Number of patients	Controls mean	Controls SD	Number of controls	Patient Y-BOCS mean	Patient Y-BOCS SD	Controls Y-BOCS-mean	Controls Y-BOCS SD	Patient mean age	Patient SD age	Controls mean age	Controls SD age	Notes	PMID	Title
Szeszko	1999		Amygdala	3865	576	26	4215	877	26	22.4	6.9			32.2	8	29.8	6.3		10530633	Orbital frontal and amygdala volume reductions in obsessive-compulsive disorder
Kwon	2003		Amygdala	1.50	0.3115	22	1.25	0.2831	22					26.7	7.2	26.2	6.1	Values computed from left/right	12810792	Similarity and disparity of obsessive-compulsive disorder and schizophrenia in MR volumetric abnormalities of the hippocampus-amygdala complex

Download data as CSV | Edit data as CSV | Meta-analysis

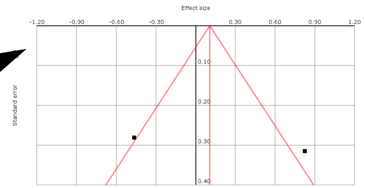
Study	Experimentals				Controls				Effects							
	Mean	SD	Events	N	Mean	SD	Events	N	SD_{pooled}	Effect	SE	CI	Weight		$Weight_{DSL}$	
Szeszko 1999	3865.000000	576.000000	nan	26	4215.000000	877.000000	nan	26	741.924861	-0.465	0.281	-1.016 0.087	12.631195	55.665%	1.217619	50.608%
Kwon 2003	1.500000	0.311500	nan	22	1.250000	0.283100	nan	22	0.297639	0.825	0.315	0.207 1.443	10.060243	44.335%	1.188344	49.392%
Meta-analysis (fixed effect)				48				48		0.107	0.210	-0.304 0.519		100%		
Meta-analysis (random effects, DSL)										0.172	0.645	-1.091 1.436				100%

σ_a:	0.861456	Q:	9.311643	dof:	1.0	P-value:	0.002

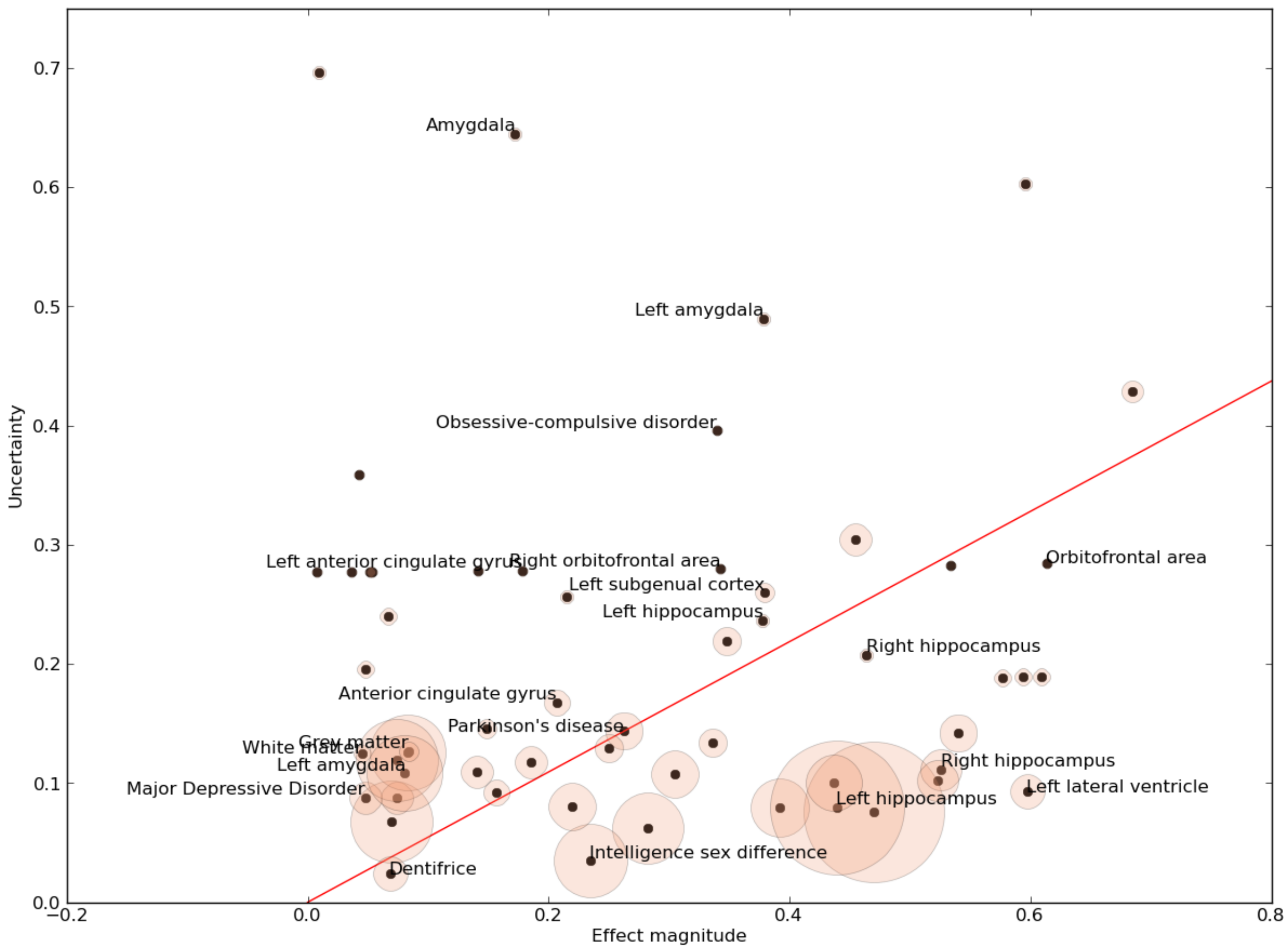
Forest plot



Funnel plot



Mass meta-analysis



With numerical data and information about it in the wiki it is possible to download and analyze all meta-analysis together.

Here a L'Abbé-like plot of many of the meta-analyses in the Brede Wiki with effect magnitude on the x-axis and its uncertainty on the y-axis.

Brede Wiki for personality genetics

	Effect	Std	P	Studies	Subjects	Gene	Polymorphism	Trait
1	0.854	0.223	0.00013	2	107	ESR1	TA repeat	Harm avoidance
2	-1.102	0.289	0.00014	2	245	HTR3A	C178T	Harm avoidance
3	-0.779	0.220	0.00039	1	90	ESR1	TA repeat	Anxiety
4	-0.445	0.135	0.00098	1	247	TH	TCAT repeat	Extraversion
5	-0.401	0.123	0.00108	1	315	DRD4	Exon 3 VNTR	Positive emotions
6	0.165	0.051	0.00118	13	1747	MAOA	uVNTR	Reward dependence
7	-0.393	0.123	0.00135	1	315	DRD4	Exon 3 VNTR	Extraversion
8	-1.355	0.427	0.00152	1	125	HTR3A	C178T	Nonconformity
9	-0.758	0.240	0.00161	1	122	SLC6A4	5-HTTLPR	Activity
10	-0.174	0.055	0.00163	16	1791	SLC6A4	5-HTTLPR	Agreeableness

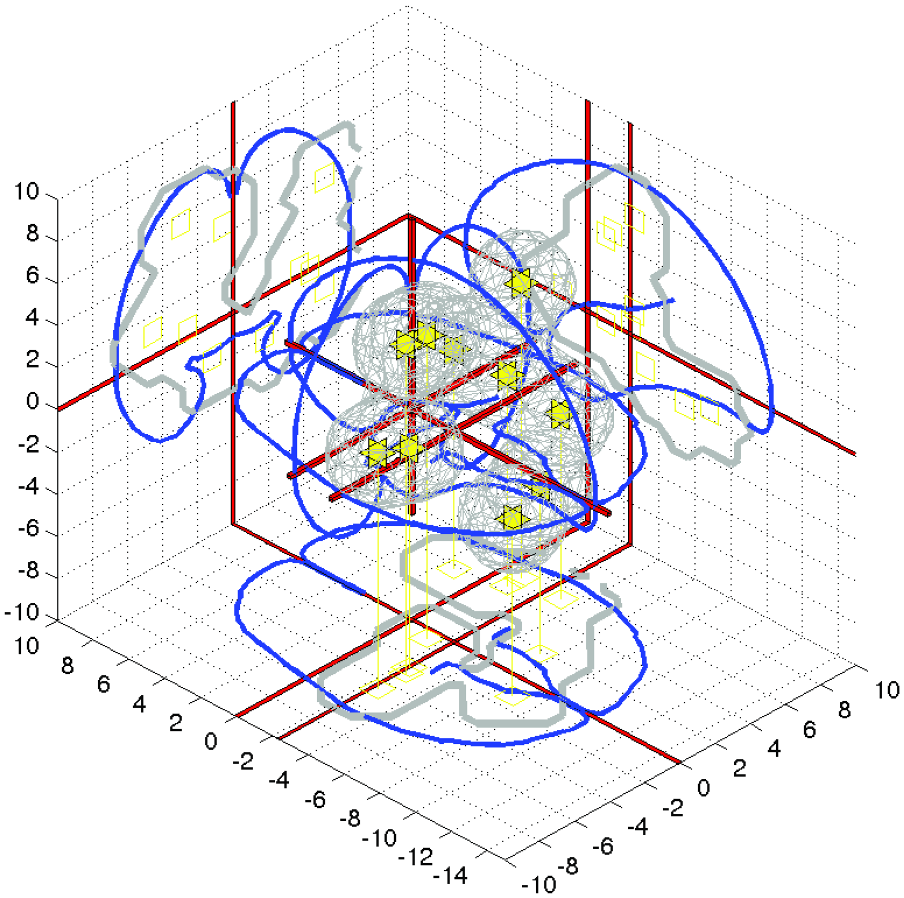
Meta-analysis across traits and polymorphisms

Large-scale data mining across all recorded personality traits and genetic polymorphisms and present the result on the wiki.

Order meta-analytic results, e.g., with respect to P-value

Neuroimaging meta-analysis

Image-based meta-analysis if you got the summary images (Salimi-Khorshidi et al., 2009).

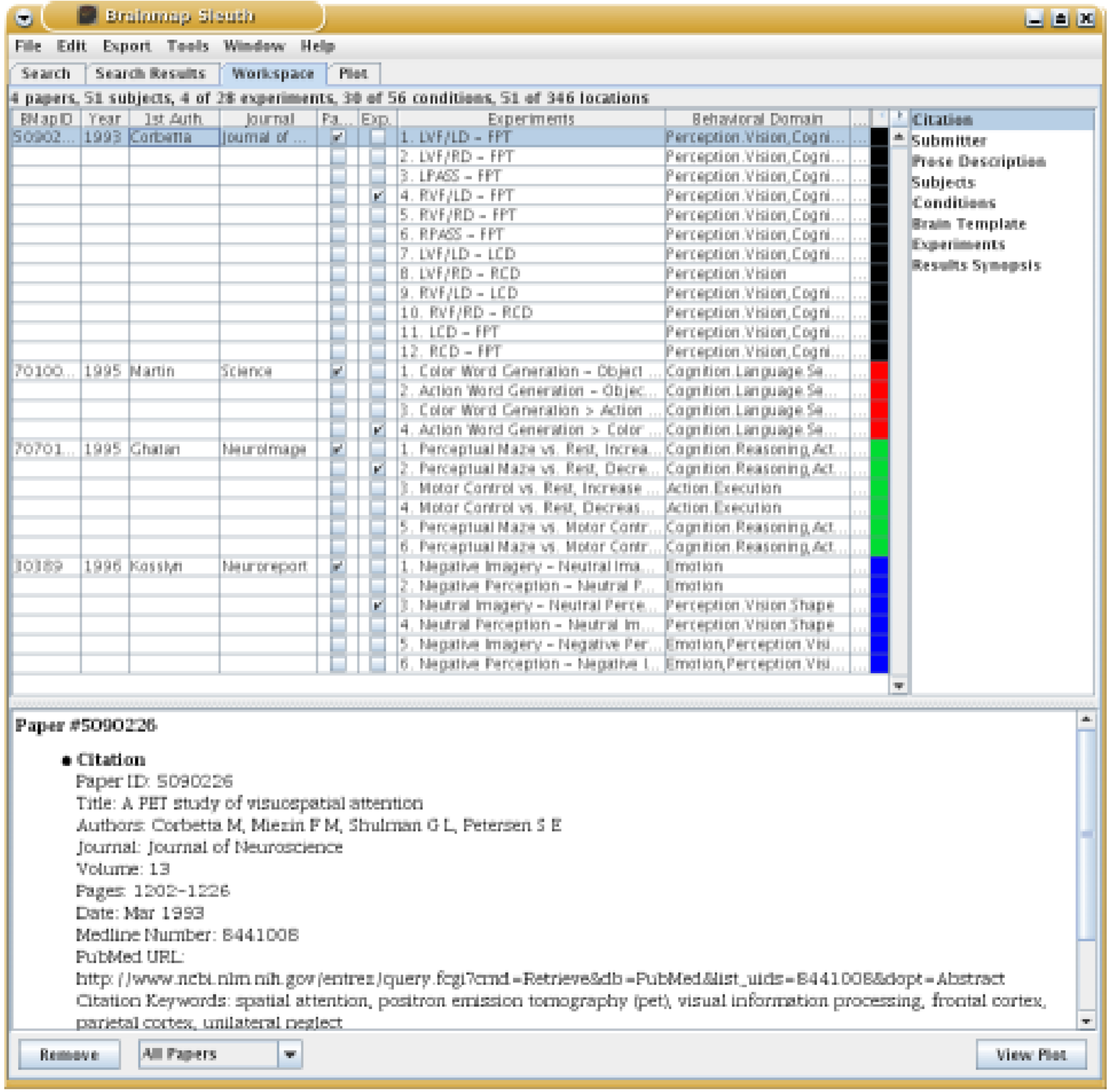


Coordinate-based meta-analysis if you got the stereotaxic coordinates (Fox et al., 1997; Nielsen and Hansen, 2002; Turkeltaub et al., 2001).

Convolve a smooth kernel on its stereotaxic coordinate

Tools: BrainMap's GingerALE, Brede Toolbox

BrainMap

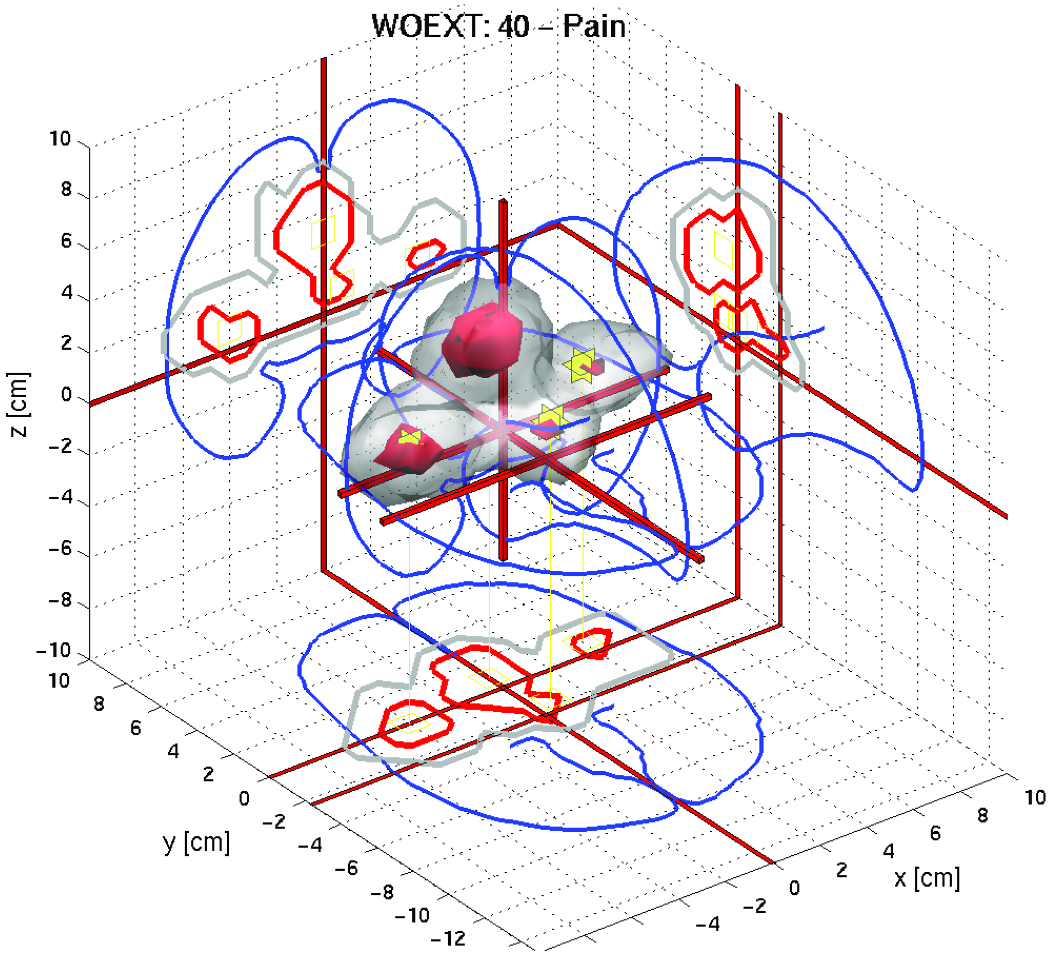


One of the first and most comprehensive databases (Fox et al., 1994; Fox and Lancaster, 2002)

Presently 85007 locations from 2238 papers (2012 September)

Graphical Internet-based interface in Java, *sleuth*, with search facilities, e.g., on author, 3D coordinate, an others and *GingerALE* meta-analysis

Example on meta-analysis

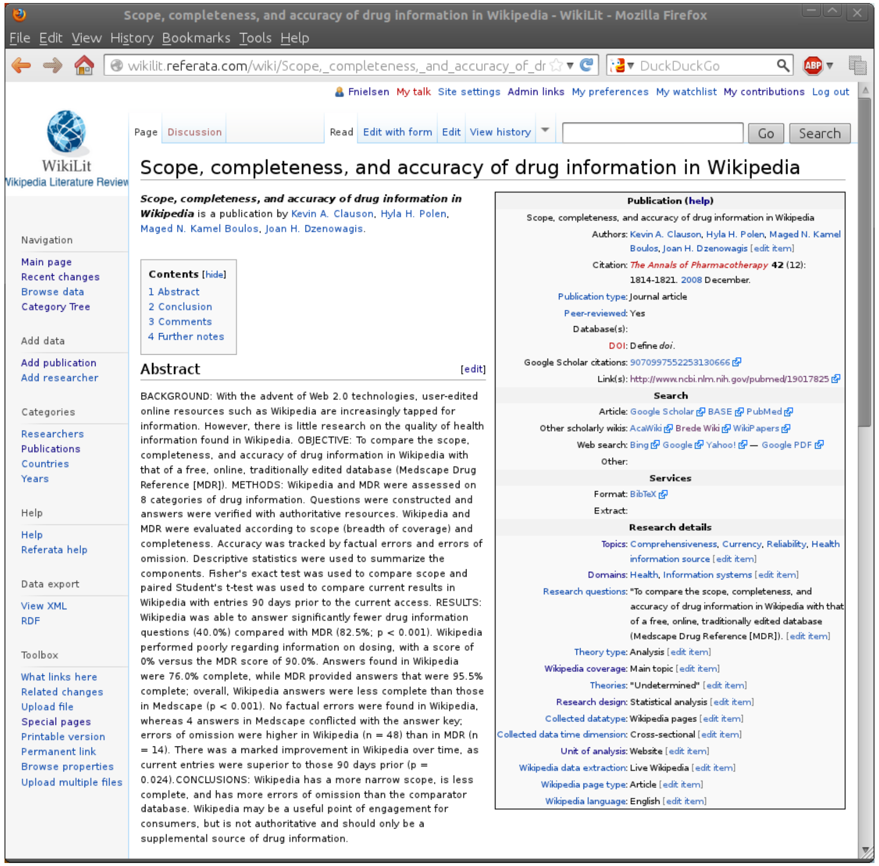


Coordinate-based meta-analysis with the Brede Toolbox on pain studies

Volume threshold at statistical values determined by resampling statistics (Nielsen, 2005).

Red areas are the most significant areas: Anterior cingulate, anterior insula, thalamus. In agreement with "human" reviewer (Ingvar, 1999).

Semantic MediaWiki for databasing papers

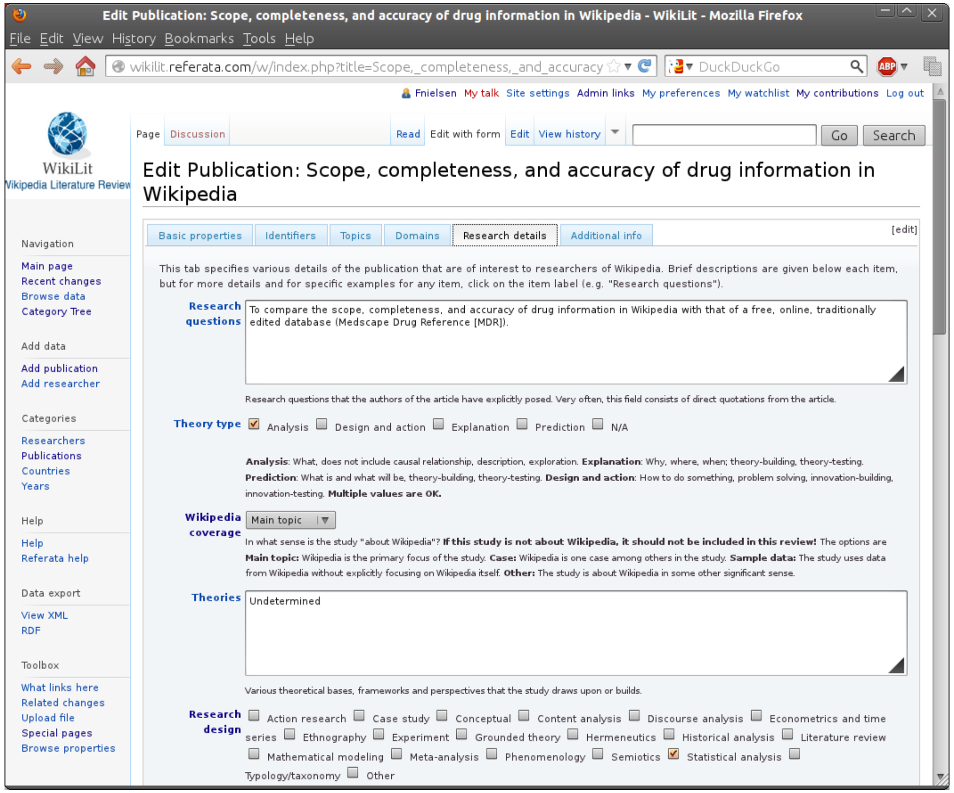


The Semantic MediaWiki allows you to construct a database on the Web without having to setup a standard database management system :-)

Semantic MediaWiki has a flexible schema: You can add fields after you have setup "table", e.g., add a "is peer reviewed" field or "imaging modality" field. :-)

A full setup of a Semantic MediaWiki with forms and templates requires mastering of the somewhat obscure MediaWiki template language :-(

Semantic MediaWiki



Our Semantic MediaWiki instance http://wikilit.referata.com/ setup for a systematic review

Semantic MediaWiki allows you to define forms for input: text and categorical.

Semantic queries can be made so you can get the inputted data in comma-separated values suitable for further numerical processing

. . . and you can filter with the queries, e.g., peer-reviewed publications if that category is setup

Automated literature reviews with text mining

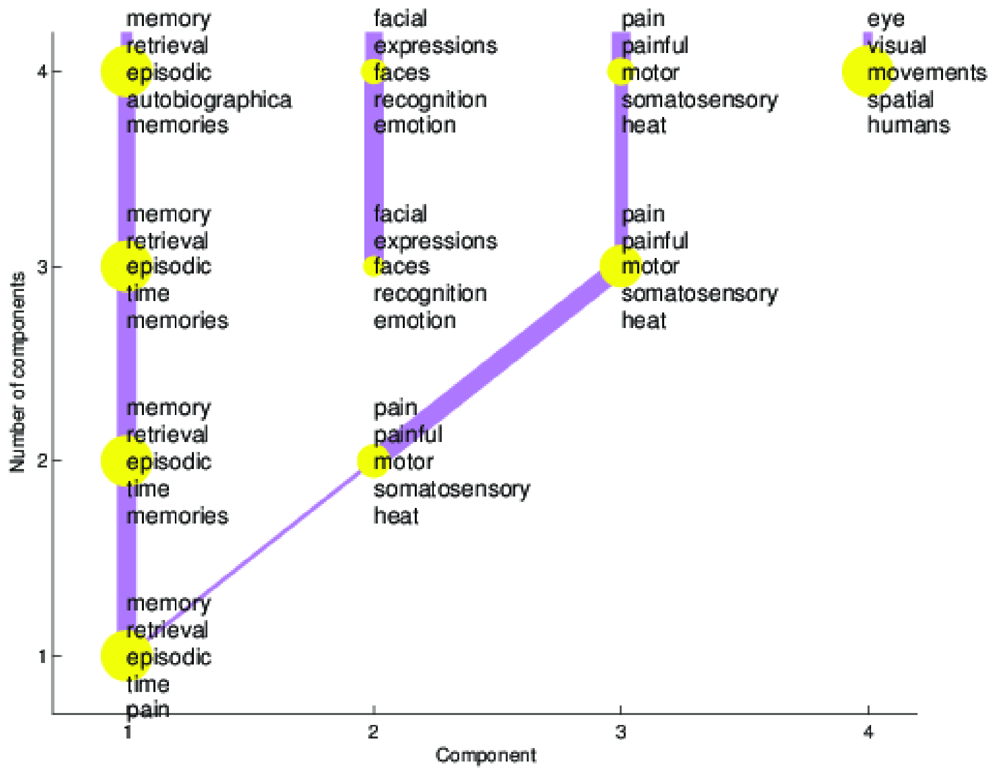
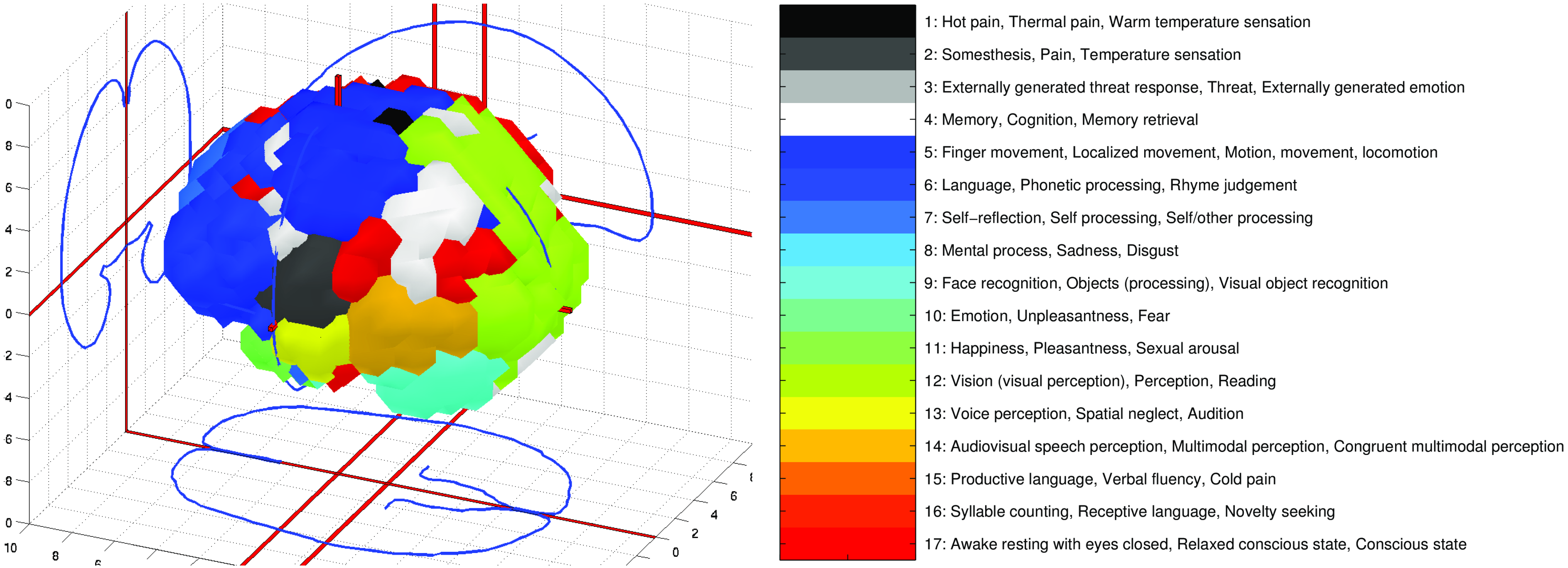


Figure 2: Some of the topics found in a corpus on posterior cingulate neuroimaging.

Download papers, extract words and represent them in a bag-of-words matrix, perform topic mining with an unsupervized multivariate analysis method, e.g., non-negative matrix factorization, to find themes (Nielsen et al., 2005).

For a recent example with NeuroSynth see (Poldrack et al., 2012)

Combining ontologies and coordinates



Combining the cognitive ontology in Brede with the coordinate-based meta-analysis to constructed a functional atlas

What can you do?

Report the summary statistics: mean, standard deviation and number of subjects.

Report summary statistics for all groups

Open Science

References

Elamin, M. B., Flynn, D. N., Bassler, D., Briel, M., Alonso-Coello, P., Karanicolas, P. J., Guyatt, G. H., Malaga, G., Furukawa, T. A., Kunz, R., Schunemann, H., Murad, M. H., Barbui, C., Cipriani, A., and Montori, V. M. (2009). Choice of data extraction tools for systematic reviews depends on resources and review complexity. *Journal of Clinical Epidemiology*, 62(5):506–510. PMID: 19348977. DOI: 10.1016/j.jclinepi.2008.10.016.

Fox, P. T. and Lancaster, J. L. (2002). Mapping context and content: the BrainMap model. *Nature Reviews Neuroscience*, 3(4):319–321. Link. *Describes the philosophy behind the (new) BrainMap functional brain imaging database with "BrainMap Experiment Coding Scheme" and tables of activation foci. Furthermore discusses financial issues and quality control of data.*

Fox, P. T., Lancaster, J. L., Parsons, L. M., Xiong, J.-H., and Zamarripa, F. (1997). Functional volumes modeling: Theory and preliminary assessment. *Human Brain Mapping*, 5(4):306–311. Link.

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