### Meta-analysis techniques

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September 19, 2012



## 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

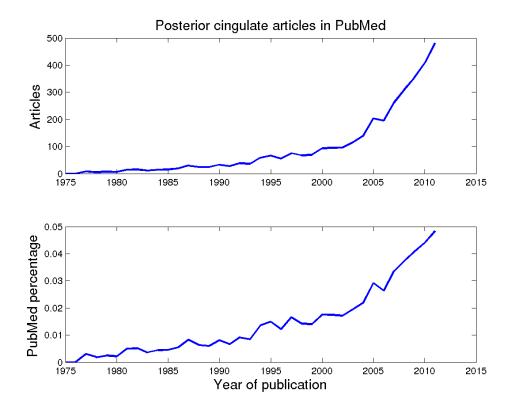


Figure 1: Increase in the number of articles in PubMed which are returned after searching on posterior cingulate and related brain areas.

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** 



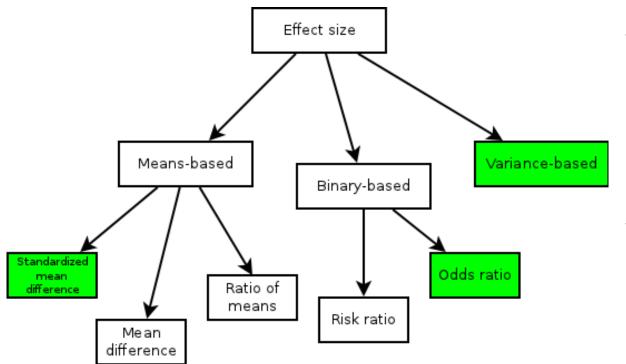
# Meta-analysis

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	5		Contro	S
	N	Mean	SD	N	Mean	SD
Strakowski SM, 1999						•••
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

$$g_{\rm smd} = rac{ar{x}_e - ar{x}_c}{s_{
m pooled}}$$

 $g_{smd}$  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:

$$s_{\text{pooled}} = \sqrt{\frac{(n_e - 1)s_e^2 + (n_c - 1)s_c^2}{n_e + n_c - 2}}$$
(1)  
$$d_{\text{smd}} = \mathsf{E}[g_{\text{smd}}] \approx \left(1 - \frac{3}{4(n_e + n_c) - 9}\right)g_{\text{smd}}$$
(2)  
$$\widehat{\mathsf{Var}}[g_{\text{smd}}] \approx \frac{1}{\tilde{n}} + \frac{g_{\text{smd}}}{2(n_e + n_c - 3.94)}$$
where  $\tilde{n} = \frac{n_e n_c}{n_e + n_c}$ . (3)

If the effect size is small  $(g_{smd} \rightarrow 0)$  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

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

$$d_{\rm Or} = \ln \left[ \frac{c(n_{es})/c(n_e - n_{es})}{c(n_{cs})/c(n_c - n_{cs})} \right], \qquad \text{where e.g., } c(x) = x + 0.$$

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

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

5



## Variance ratio

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

We should test this

 $\sigma_{\rm men}^2 > \sigma_{\rm women}^2$ 

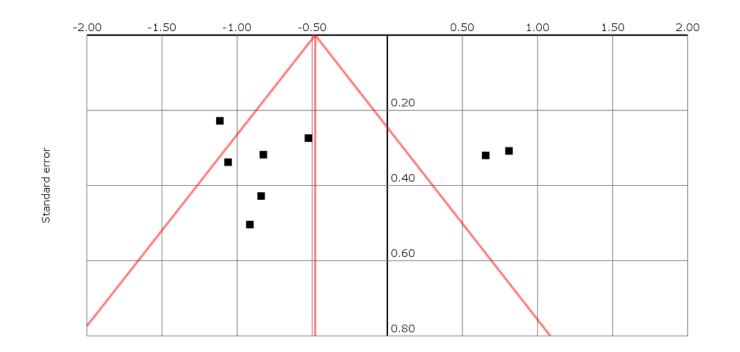
The logarithm of the ratio between the two variations (Invr) results in a good statistics (Shaffer, 1992)

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

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

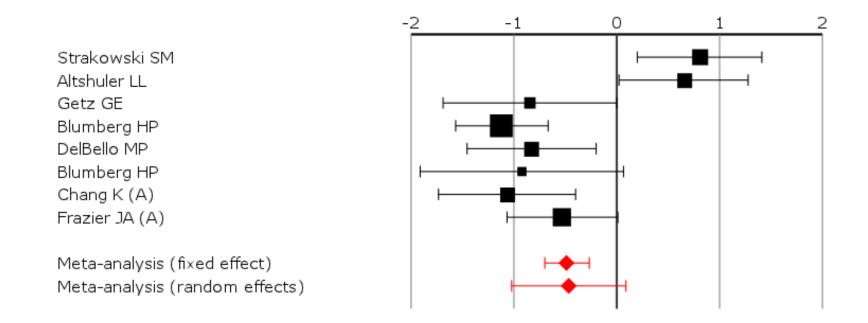


Scatter plot of the effect sizes and their standard errors (related to variance and sample size) for multiple studies.

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:  $d_i \pm 1.96\sqrt{Var[d_i]}$ 

# 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)

$$d_{\text{meta}} = \frac{\sum_{i} w_{i} d_{i}}{\sum_{i} w_{i}}$$
(6)

where  $d_i$  is the effect size for the *i*th study and the weight for the *i*th study is determined as the inverse variance

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

Variance:

$$\operatorname{Var}[d_{\mathrm{meta}}] \approx \frac{1}{\sum_{i} w_{i}}$$
 (8)

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





# 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

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ortal She	eline YI	1998		20	20	3374	582.4946352	3534	560.6719183	54	100.0	-	5	70.0				MRI	1.5	1.25
s Bre	emner JD	2000		16	16	1676	474	1341	449	43	37.5			100.0	0.0	0.0	0.0	MRI	1.5	3
Fro	odl 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
Fro	ul T	2003	multiple	27	27	3542	458.2534233	3556	530.3728877	49.1	48.1	37.4	21.3				12.3	MRI	1.5	1.5
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	ietano SC	2004		31	31	3.87		4.2	0.73054774	39.2					0.0	2053	100.0	MRI	1.5	1.5
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	nge C	2004		17	17	2.55	0.49	2.26	0.33	34				100.0			0.0	MRI	1.5	1.3
e Xia	isso IM	2004		22	13	4477.23		4629.23	84.87261137	39.5	45.5		21.45 16.55		0.0	0.0		MRI	1.5	1.2
es	lakoulis D	2005		20	87	4.62 3508	0.76 593.4409827		0.735 461.1333863			21.5	16.55	0.0	0.0	0.0	100.0	MRI	1.5	1.5
	niger G	2006		21	23	2.6		2.3	0.379473319	22.6			23	100.0			0.0	MRI	1.5	1.5
L		2006		19	23	3.02	0.426919196			13		10.3		47.4			52.6	MRI	1.5	1
	tkie IB (A)	2007		45	16	3.02	0.6	3.4	0.5	52				64.4			52.0	MRI	15	1.5
	ann MA	2007		26	18	28943.6	3425.699339	0.1	0.0	20.54		15.58	20.0	04.4				MBI	1.5	1
	dreescu C	2008		71	32	0.22	0.04	0.26	0.04	72.2			18.3	16.9		1.4		MRI	1.5	1.5
Kel		2008		23	11	4.85	0.939627586		0.854025761	36.5					17.4		17.4	MRI	3	1.5
Kel	ller 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
Ma	acMaster (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
Tan	mburo RJ	2008		14	11	2728	692.0411837	3100	590.1908166	69.8	35.7		13.8					MRI	1.5	1.5
Kro	onenberg	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
Lor (B)	renzetti V )	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
Lor (B)	renzetti∨ )	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
var Eijr	n ndhoven 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
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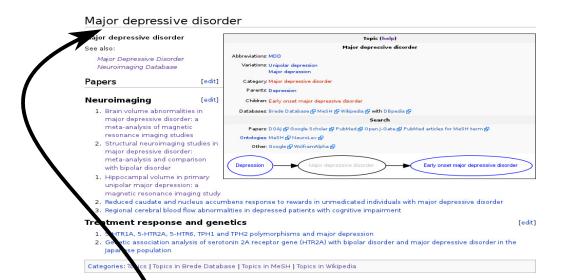
Store numerical data on a spreadsheetlike page in a MediaWiki. Describe the data in structured format on the wiki.

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



Meta-analyses

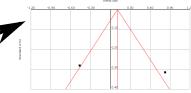
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Amygdala — Major depressive disorder — MaND	Data	CSV	Meta-analysis 🗗
Amygdala — Bipolar disorder — BiND	Data	CSV	Meta-analysis 🗗
Amygdala — Obsessive-compulsive disorder — ObND	Data	CSV	Meta-analysis 🗗



Szeszko Kiesn

[edit]





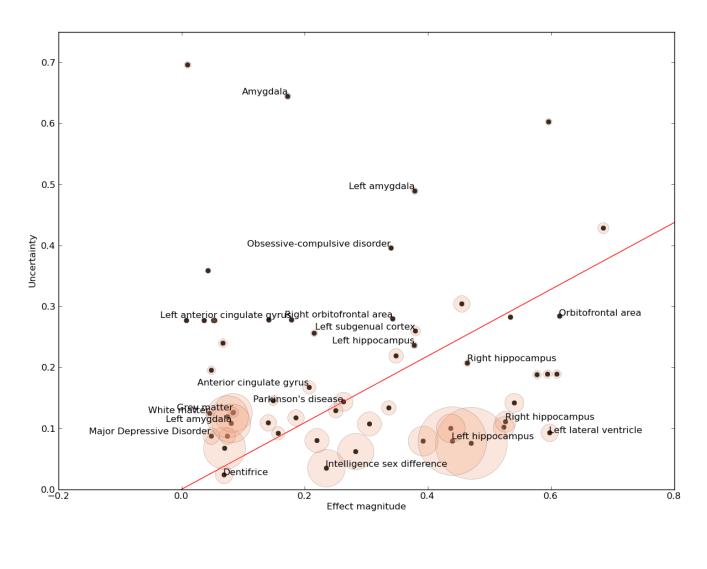
Obsessive-compulsive disorder Neuroimaging Database - Amygdala

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Szeszko	1999	Amygdala	3865	576	26	4215	877	26	22.4	6.9			32.2	8	29.8	6.3			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	it data as CI	5V 🗗   Met	a-analysis 🗗														

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### Mass meta-analysis



With numerical data and information about it in the wiki it is possible to download and analyze all metaanalysis 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 yaxis.



## Brede Wiki for personality genetics

Effect	Std	P	Studies	Subjects	Gene	Polymorphism	Trait
0.854	0.223	0.00013	2	107	ESR1	TA repeat	Harm avoidance
-1.102	0.289	0.00014	2	245	HTR3A	C178T	Harm avoidance
-0.779	0.220	0.00039	1	90	ESR1	TA repeat	Anxiety
-0.445	0.135	0.00098	1	247	тн	TCAT repeat	Extraversion
-0.401	0.123	0.00108	1	315	DRD4	Exon 3 VNTR	Positive emotions
0.165	0.051	0.00118	13	1747	MAOA	uVNTR	Reward dependence
-0.393	0.123	0.00135	1	315	DRD4	Exon 3 VNTR	Extraversion
-1.355	0.427	0.00152	1	125	HTR3A	C178T	Nonconformity
-0.758	0.240	0.00161	1	122	SLC6A4	5-HTTLPR	Activity
-0.174	0.055	0.00163	16	1791	SLC6A4	5-HTTLPR	Agreeableness
	0.854 -1.102 -0.779 -0.445 -0.401 0.165 -0.393 -1.355 -0.758	0.854       0.223         -1.102       0.289         -0.779       0.220         -0.445       0.135         -0.401       0.123         -0.165       0.051         -0.393       0.123         -1.355       0.427         -0.758       0.240	0.854         0.223         0.00013           -1.102         0.289         0.00014           -0.779         0.220         0.00039           -0.445         0.135         0.00098           -0.401         0.123         0.00118           -0.165         0.051         0.00118           -0.393         0.123         0.00135           -1.355         0.427         0.00152           -0.758         0.240         0.00161	0.854         0.223         0.00013         2           -1.102         0.289         0.00014         2           -0.779         0.220         0.00039         1           -0.445         0.135         0.00098         1           -0.445         0.123         0.00108         1           -0.401         0.123         0.00118         13           -0.165         0.051         0.00135         1           -0.393         0.123         0.00135         1           -1.355         0.427         0.00152         1           -0.758         0.240         0.00161         1	0.854         0.223         0.00013         2         107           -1.102         0.289         0.00014         2         245           -0.779         0.220         0.00039         1         90           -0.445         0.135         0.00098         1         247           -0.401         0.123         0.00108         1         315           0.165         0.051         0.00118         13         1747           -0.393         0.123         0.00135         1         315           -1.355         0.427         0.00152         1         315           -0.778         0.220         0.00135         1         247	0.854         0.223         0.00013         2         107         ESR1           -1.102         0.289         0.00014         2         245         HTR3A           -0.779         0.220         0.00039         1         90         ESR1           -0.445         0.135         0.00098         1         247         TH           -0.445         0.123         0.00108         1         315         DRD4           -0.401         0.123         0.00118         13         1747         MAOA           -0.393         0.123         0.00135         1         315         DRD4           -1.355         0.427         0.00152         1         315         DRD4           -0.758         0.240         0.00152         1         315         DRD4	0.854         0.223         0.00013         2         107         E SR1         TA repeat           -1.102         0.289         0.00014         2         245         HTR3A         C178T           -0.779         0.220         0.00039         1         90         E SR1         TA repeat           -0.779         0.220         0.00039         1         90         E SR1         TA repeat           -0.445         0.135         0.00098         1         247         TH         TCAT repeat           -0.445         0.132         0.00108         1         315         DRD4         Exon 3 VNTR           -0.401         0.123         0.00118         13         1747         MAOA         uVNTR           -0.393         0.123         0.00135         1         315         DRD4         Exon 3 VNTR           -1.355         0.427         0.00152         1         315         DRD4         Exon 3 VNTR           -1.355         0.427         0.00152         1         125         HTR3A         C178T           -0.758         0.240         0.00161         1         122         SLC6A4         5-HTTLPR

Meta-analysis across traits and polymorphisms

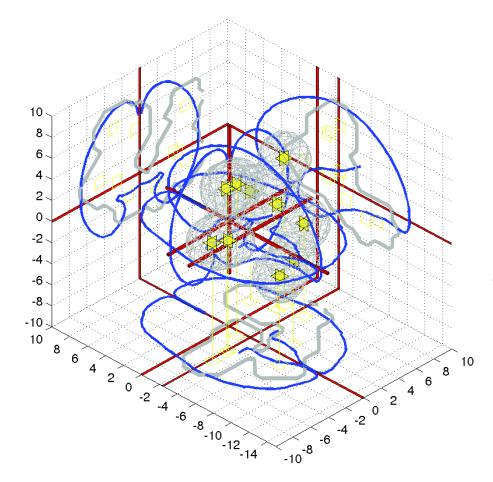
Large-scale data mining across all recorded personality traits and genetic polymorphisms and present the result on the wiki.

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

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						<ol><li>LVF/RD – FPT</li></ol>	Perception Vision, Cogni	Prose Description
						3. LPASS - FPT	Perception Vision, Cogni	Subjects
					P.	4. RVF/LD - FPT	Perception Vision, Cogni	Conditions
						5. RVF/RD - FPT	Perception Vision, Cogni	Brain Template
						6. RPASS - FPT	Perception Vision, Cogni	Experiments
						7. DVF/LD - LCD	Perception Vision, Cogni	Results Synopsis
						8. LVF/RD - RCD	Perception Vision	
						9. RVF/LD - LCD	Perception Vision, Cogni	
						10. RVF/RD - RCD	Perception.Vision,Cogni	
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	pariet	al cortex, u	nilateral neg	tiect				
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One of the first and most comprehensive databases (Fox et al., 1994; Fox and Lancaster, 2002)

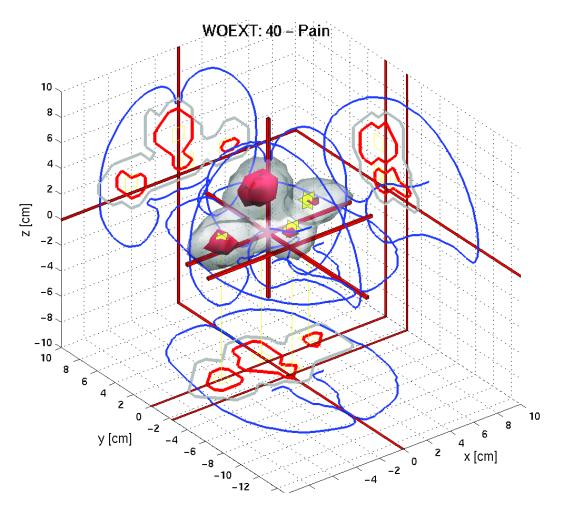
Presently 85007 locations from 2238 papers (2012 September)

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

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### 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

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WikiLit dia Literature Review	Scope, completeness, and accuracy	of drug information in Wikipedia
	Scope, completeness, and accuracy of drug information in	Publication (help)
vigation	<b>Wikipedia</b> is a publication by Kevin A. Clauson, Hyla H. Polen, Maged N. Kamel Boulos, Joan H. Dzenowagis.	Scope, completeness, and accuracy of drug information in Wikipedia Authors: Kevin A. Clauson, Hyla H. Polen, Maged N. Kamel Boulos, Joan H. Dzenowagis (edit item)
in page cent changes	Contents [hide]	Citation: The Annals of Pharmacotherapy 42 (12): 1814-1821. 2008 December.
owse data tegory Tree	1 Abstract 2 Conclusion 3 Comments	Publication type: Journal article Peer-reviewed: Yes
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tegories	BACKGROUND: With the advent of Web 2.0 technologies, user-edited online resources such as Wikipedia are increasingly tapped for	Search Article: Google Scholar 댨 BASE 중 PubMed 중
searchers blications	information. However, there is little research on the quality of health information found in Wikipedia. OBJECTIVE: To compare the scope, completeness, and accuracy of drug information in Wikipedia with	Other scholarly wikis: AcaWki ৫ Brede Wki ৫ Wiki Papers 윤 Web search: Bing 윤 Google 윤 Yahoo! 윤 — Google PDF 윤 Other
untries ars	that of a free, online, traditionally edited database (Medscape Drug	Other: Services
ai 5	Reference [MDR]). METHODS: Wikipedia and MDR were assessed on	Format: BibTeX r
lp	8 categories of drug information. Questions were constructed and answers were verified with authoritative resources. Wikipedia and	Extract
	MDR were evaluated according to scope (breadth of coverage) and	Research details
lp ferata help	completeness. Accuracy was tracked by factual errors and errors of omission. Descriptive statistics were used to summarize the	Topics: Comprehensiveness, Currency, Reliability, Health information source [edit item]
ta export	components. Fisher's exact test was used to compare scope and	Domains: Health, Information systems [edit item]
	paired Student's t-test was used to compare current results in Wikipedia with entries 90 days prior to the current access. RESULTS:	Research questions: "To compare the scope, completeness, and
F XML	Wikipedia was able to answer significantly fewer drug information	accuracy of drug information in Wikipedia with that of a free, online, traditionally edited database
F	questions (40.0%) compared with MDR (82.5%; p < 0.001). Wikipedia	(Medscape Drug Reference [MDR]). [edit item]
lbox	performed poorly regarding information on dosing, with a score of	Theory type: Analysis [edit item]
	0% versus the MDR score of 90.0%. Answers found in Wikipedia	Wikipedia coverage: Main topic [edit item]
at links here	were 76.0% complete, while MDR provided answers that were 95.5%	Theories: "Undetermined" [edit item]
lated changes load file	complete; overall, Wikipedia answers were less complete than those in Medscape (p < 0.001). No factual errors were found in Wikipedia,	Research design: Statistical analysis [edit item]
ecial pages	whereas 4 answers in Medscape conflicted with the answer key;	Collected datatype: Wikipedia pages (edit item)
ntable version	errors of omission were higher in Wikipedia (n = 48) than in MDR (n	Collected data time dimension: Cross-sectional [edit item]
rmanent link	= 14). There was a marked improvement in Wikipedia over time, as	Unit of analysis: Website [edit item]
owse properties	current entries were superior to those 90 days prior (p =	Wikipedia data extraction: Live Wikipedia [edit item]
load multiple files	0.024).CONCLUSIONS: Wikipedia has a more narrow scope, is less	Wikipedia page type: Article (edit item)
	complete, and has more errors of omission than the comparator database. Wikipedia may be a useful point of engagement for	Wikipedia language: English [edit.item]

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 Media-Wiki with forms and templates requires mastering of the somewhat obscure MediaWiki template language :-(



## Semantic MediaWiki

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	Page Discussion Read Edit with form Edit View history T Go Search
WikiLit ipedia Literature Reviev	Edit Publication: Scope, completeness, and accuracy of drug information in Wikipedia
Navigation	Basic properties         Identifiers         Topics         Domains         Research details         Additional info         [edit]
Main page Recent changes Browse data	This tab specifies various details of the publication that are of interest to researchers of Wikipedia. Brief descriptions are given below each item, but for more details and for specific examples for any item, click on the item label (e.g. "Research questions").
Category Tree	Research To compare the scope, completeness, and accuracy of drug information in Wikipedia with that of a free, online, traditionally questions edited database (Medscape Drug Reference (MDR)).
Add data	
Add publication Add researcher	Research questions that the authors of the article have explicitly posed. Very often, this field consists of direct quotations from the article.
Categories	Theory type 🗹 Analysis 🔲 Design and action 💭 Explanation 💭 Prediction 💭 N/A
Researchers Publications Countries Years	Analysis: — obsign and action — Exploration — resection — NA Analysis: What, does not include causal relationship, description, exploration: Explanation: Why, where, when theory-building, theory-testing. Prediction: What is and what will be, theory-building, theory-testing. Design and action: How to do something, problem solving, innovation-building, innovation-testing. Multiple values are OK.
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Help Referata help	coverage in what serse is the study "about Wkipedia"? If this study is not about Wikipedia, it should not be included in this review! The options are Main topic! Wkipedia is the primary focus of the study. Case: Wkipedia is one case among others in the study. Same data: The study uses data from Wkipedia wikhout explicitly focusing on Wkipedia is affort the study is about Wikipedia is none other significant sense.
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What links here Related changes Upload file Special pages	Various theoretical bases, frameworks and perspectives that the study draws upon or builds.         Research       Action research       Case study       Conceptual       Content analysis       Discourse analysis       Econometrics and time         design       series       Ethnography       Experiment       Grounded theory       Hermeneutics       Historical analysis       Literature review
Browse properties	ante antical modeling in Meta-analysis in Phenomenology in Semiotics in Society analysis in Txpoloxytaxonomy in Other

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

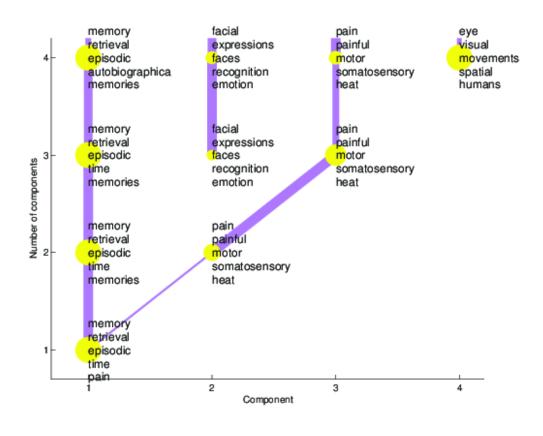
Semantic MediaWiki allows you to define forms for input: text and categorical.

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



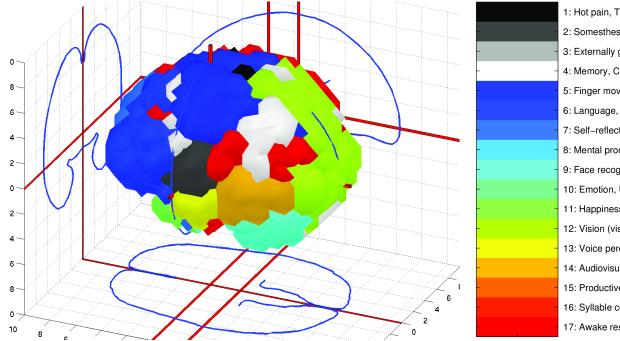
Download papers, extract words and represent them in a bag-of-words matrix, perform topic mining with an unsupervized multivariate analysis method, e.g., non-negative matrix factorization, to find themes (Nielsen et al., 2005).

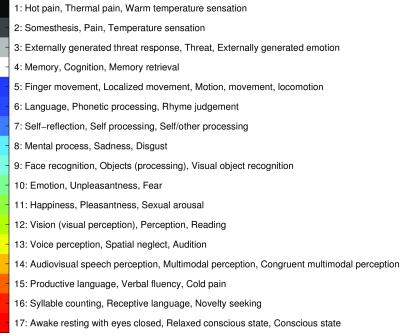
For a recent example with NeuroSynth see (Poldrack et al., 2012)

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



### **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



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