Meta-analysis and databasing of neuroimaging studies

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October 13, 2009



When you have published a study you haven't published the study!



Writing a 'paper' in a text processing environment, submitting it to a journal and let the journal publish the paper.



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The paper is not published for computers to read its specialized data.



Information increase

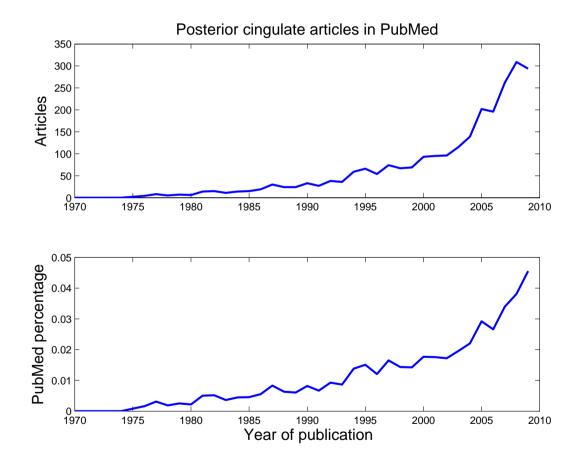


Figure 1: Increase in the number of articles in PubMed which are returned after searching on posterior cingulate and related brain areas.

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-analytic databases**

Classical: PubMed, OMIM, Google Scholar, The Cochrane Collaboration, ...



When you have published your study you need to publish you data in neuroinformatics databases.



Content

Neuroinformatics databases for MRI & Co. results

Searching in databases.

Meta-analysis of coordinates: Supervized with one set of coordinates. Supervized with two sets of coordinates. Unsupervized.

Text mining

Combining text mining and coordinate-based meta-analysis.



BrainMap

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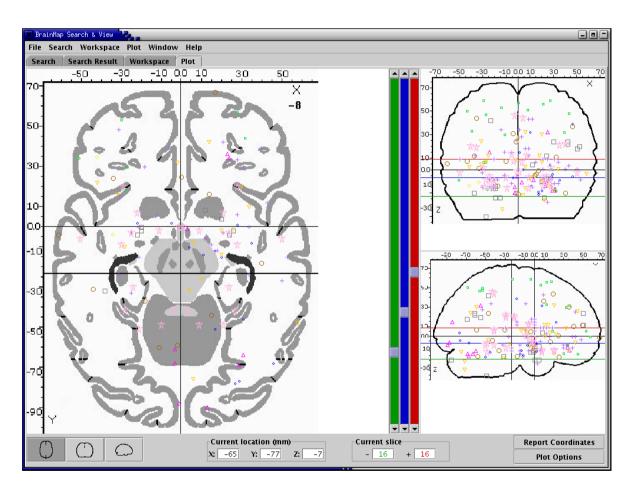
One of the first and most comprehensive databases (Fox et al., 1994; Fox and Lancaster, 2002)

Presently 69210 locations from 1831 papers (2009 October)

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

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BrainMap



The Java program, *sleuth*, is able to show retrieved coordinates in 2D interactive plots.

Possible to enter data with the *Scribe* Java program.

http://brainmap.org

Figure 2: Screen shot of a graphical user interface to the Brain-Map database with Talairach coordinates plotted after a search for experiments on olfaction.



SumsDB

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		76278	Luhmann_JN08	48	-45	13	STG: LOBE.TEMPORAL: SUL STS	: Brodmann.39:	right	.1118	19118180	Luhmann CC, Chun NM, Yi DJ, Lee D, V			
		79533	Gagnepain_JN08	52	-32	8	middlelposterior superior temporal sulcus: LOBE TEMPORAL; SUL STS	; Brodmann.22;	right	1036	18480284	Gagnepain P. Chételat G. Landeau B. D			
ount		75147	Besle_JN08	43	-39	3	Posterior STS; LOBE.TEMPORAL; SUL STS	; Brodmann.22;	right	1039	19109511	Besle J, Fischer C, Bidet Caulet A, Leca			
gn .		74935	Bedry_JN08	50	-40	14	Superior Temporal G.Insula; LOBE.TEMPORAL; SUL STS	13/41/42; ; Brodmann.22;	right	1033	18971476	Bedny M, Caramazza A, Grossman E, P			
19		74910	Beaver_JN08	54	-36	3	Superior Temporal Sulcus (STS); LOBE.TEMPORAL; SUL.STS	; Brodmann.22;	right	1031	18337401	Beaver JD, Lawrence AD, Passamoni L			
		70327	lacoboni_NID4	52	-34	4	Mid STS; LOBE TEMPORAL; SUL STS	; Brodmann.22;	right	.1211	15006683	lacoboni M, Lieberman MD, Knowlton B.			
		70223	Hooker_BrainResCogBrainRes03	45	-44	11	Right Superior Temporal Sulcus; LOBE.TEMPORAL; SUL.STS	; Brodmann.39;	right	1215	12880911	Hooker CI, Paller KA, Gitelman DR, Par			
		70016	Grossman_Neuron02	50	-33	4.3	STSa; LOBE.TEMPORAL; SUL.STS	STBa; ; Brodmann.22;	right	1224	12354405	Grossman ED, Blake R			
		70014	Grossman_Neuron02	46.1	-48.5	12.4	STSp; LOBE.TEMPORAL; SUL.STS	STBp; ; Brodmann.39;	right	1224	12354405	Grossman ED, Blake R			
		69733	Ishai_JCogNeurosci00	54	-47	9	Right superior temporal gyri; LOBE.TEMPORAL; SUL.STS	; Brodmann.39;	right	1245	11306646	Ishai A, Ungerleider LB, Nartin A, Haxby			
		68592	Bor_EurJNeurosci04	50	-49	11	R. lateral temporal cortex; LOBE.TEMPORAL; SUL STS	; Brodmann.39;	right	1148	15217392	Bor D, Cumming N, Scott CE, Owen AM			
			Baron-Cohen EurJNeurosci99	43	-33	4	Middle temporal gyrus; LOBE TEMPORAL; SUL STS	; Brodmann.22;	right	1199	10336637	Baron-Cohen S, Ring HA, Wheelwright S			
		68501 68423	Baron-Cohen_EuGNeuroscise	+3	- 22	-				1152	15006041				

SumsDB (Van Essen, 2009)

http://sumsdb.wustl.edu/sums/

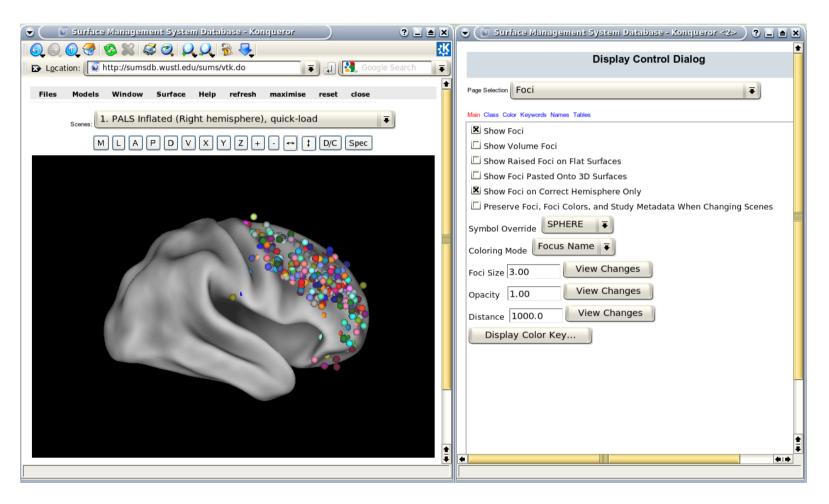
93919 foci(?)

Less annotated, younger and more(?) coordinates than BrainMap.

Possible to upload other data, e.g., surfaces.



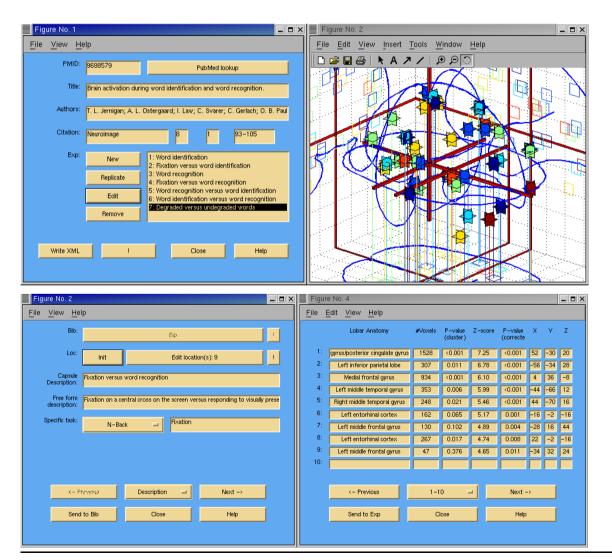
SumsDB



WebCaret server-side display of returned coordinates from the Surface Management System Database (SumsDB) with a query on 'middle frontal gyrus'



The Brede Database



A database with results from published neuroimaging studies as well as ontologies for, e.g., brain regions and brain function (Nielsen, 2003).

Data stored in XML available on the Web

Data entered in graphical user interface programmed in Matlab: The "Brede Toolbox".

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The Brede Database on the Web

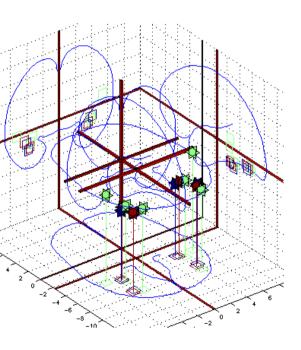


Parents	Siblings	Children
Visual object recognition		

WOEXT: 23. Face recognition. Processing of face images.

Experiments:

- Face visual object. Visual objects: Faces versus building. WOEXP: <u>11</u>.
 I Levy; U Hasson; G Avidan; T Hendler; R Malach. Center-periphery organization of human object areas.. Nat Neurosci 4(5):533-9, 2001.
 PMID: <u>11319563</u>. WOBIB: <u>5</u>.
- Photographs of faces versus houses and chairs. Conjunction between passive viewing and delayed match-to sample of gray-scale photographs versus scrambled pictures and faces versus houses and chairs, with matching choice indicated by pressing a button with the right of left thumb. WOEXP: <u>91</u>.
 A. Ishai; L. G. Ungerleider; A. Martin; J. V. Haxby. The representation of objects in the human occipital and temporal cortex... J Cogn Neurosci <u>12</u> Suppl <u>2</u>:35-51, 2000.
 PMID: <u>11506646</u>, FMRIDCID: <u>2-2000-1113D</u>.
 WOBIB: <u>28</u>.
- Front-face. Line drawings of front face versus line drawings of tumblers. WOEXP: <u>123</u>.
 U. Hasson; T. Hendler; D. Ben Bashat; R. Malach. Vase or face? A neural correlate of shape-selective grouping processes in the human brain. J Cogn Neurosci 13(6):744-53, 2001.
 PMID: <u>11564319</u>. FMRIDCID: <u>2-2001-111P8</u>. WOBIB: <u>36</u>.



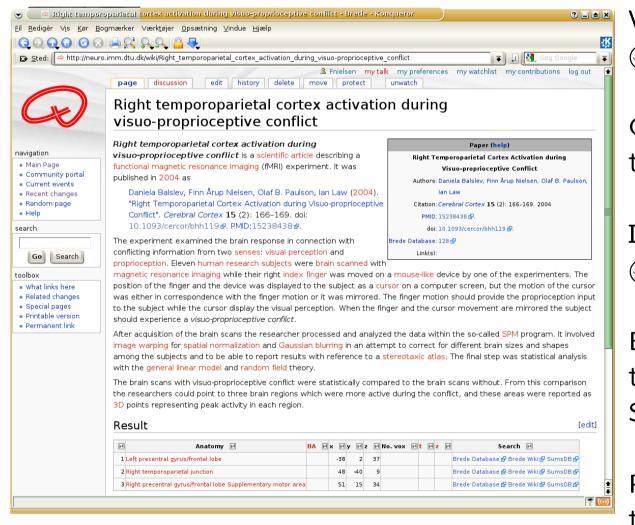
Presentation on the Web via Matlab batch scripts from the Brede Toolbox.

Off-line meta-analysis and generation of indices and visualization in static HTML.

Interactive search on coordinates from Web page or within a image analysis program (Wilkowski et al., 2009).



Brede Wiki



Wiki with structured data

Quick to add new information

Incremental edit possible \odot

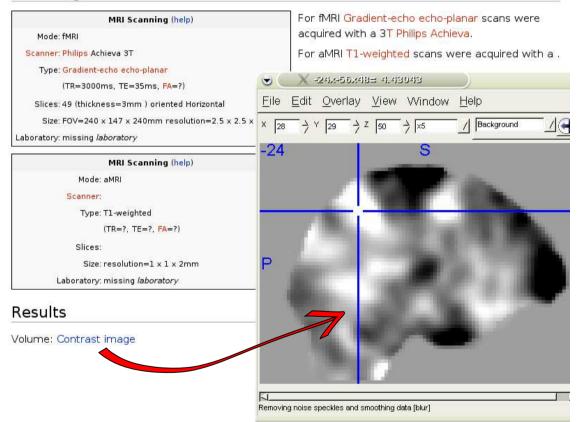
Brede Wiki = MediaWiki templates + Extraction + SQL

Possible to search outside the wiki



Brede Wiki

Scanning



Possible to add volume to the database.



Searching on Talairach coordinate

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brede_loc_query — Search after locations (Talairach coordinates) in the Brede Database									
14 14 9 14 14 9						Location search (one coordinate) e.g., 14 -9 -15 Experiment search (several coordinates)			
# Distance x y z WOBIE					WOBIB	Description			
1	0.5	13	14	8	76	Right caudate nucleus — Correlated with pain ratings in hot pain on right hand in rest, mental imagery and hypnosis (WOEXP: 238)			
2	3.5	15	11	6	92	Caudate nucleus — Mildly depressed cancer patients (WOEXP: 293)			
з	4.9	15	12	13	180	Right caudate nucleus — Intelligence and gray matter volume negative correlation (WOEXP: 564)			
4	7.0	12	8	12	178	Right caudate — Semantic versus case (WOEXP: 550)			
5	7.5	10	8	11	178	Right caudate — Semantic versus syllable counting via case judgment (WOEXP: 558)			
6	8.1	5	14	8	76	Right caudate nucleus — Hot pain on right hand during hypnosis (WOEXP: 235)			
7 8.3 13 7 3 171			3	171	Right striatum — Rhyme judgement and nonlinear ('convex') response in rapid auditory processing (WOEXP: 526)				
8 83 13 7 3 171 Right striatum — Rhyme judgement and						Right striatum — Rhyme judgement and linear increase response in			
8	8.3	13	/	3	1/1	rapid auditory processing (WOEXP: 527)			

Result after search for nearest coordinates to (14, 14, 9) with the Brede Database.

Translation of the data from XML to SQL (Szewczyk, 2008)

Perl + SQLite web-script

Similar searches possible in Antonia Hamilton's AMAT programs, BrainMap, SumsDB and Brede Wiki.



Online experiment search (multiple coordinates)

Online search on two coordinates in left and right amygdala in the experiments recorded in the Brede Database.

"Related volume" also available from the "original" BrainMap database (Nielsen and Hansen, 2004):

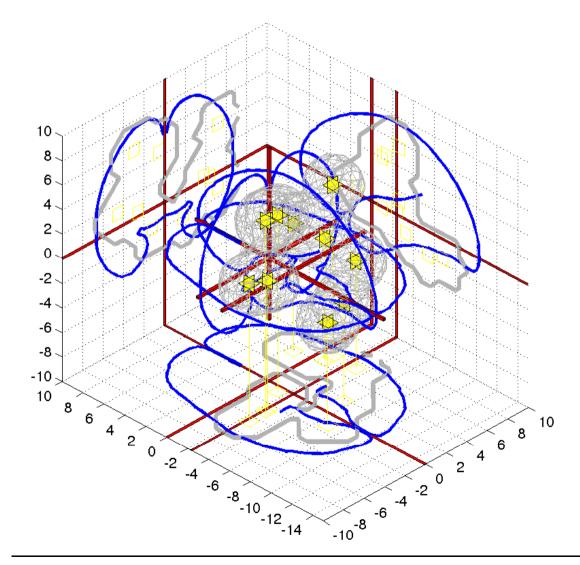
http://neuro.imm.dtu.dk/services/jerne/ninf/

Search available to the Brede Database from SPM plugin (Wilkowski et al., 2009).

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	brede	_exp_que	ery - Searc	Brede thafter experiments with Talairach coordinates in the Brede Database
	14, - -15, -1	9, -1 0, -1	5; 4;	Experiment search e.g., 14 - 9 - 15, - 15 - 10 - 14
#	Similarity	WOBIB	WOEXP	Experiment
1	0.985599	4	9	Sexual arousal - male. Sexual arousal by viewing erotic film excerpts. WOEXP: 9. Karama (2002) Areas of brain activation in males and females during viewing of erotic film excerpts. WOBIB: 4.
2	0.980475	77	241	Increase during public speaking for subjects with social phobia. Increases in the interaction between public speaking to an audience about past experiences and subjects with social phobia versus privat speaking about past experience and subjects with no social phobia. WOEXP: 241. Tillfors (2001) Cerebral blood flow in subjects with social phobia during stressful speaking tasks: a PET study. WOBIB: 77.
				Fearful faces. Categorization of fearful face versus happy faces. WOEXP: 481.
3	0.924246	156	481	Canli (2002) Amygdala response to happy faces as a function of extraversion. WOBIB: 156.



Coordinates-to-volume transformation



Coordinates in an article converted to volume-data by filtering each point (kernel density estimation) (Nielsen and Hansen, 2002; Turkeltaub et al., 2002)

One volume for each article or one volume for a set of coordinates in multiple articles.

Yellow coordinates from a study by (Blinkenberg et al., 1996), with grey wireframe indicating the isosurface in the generated volume



Kernel density estimators for coordinates

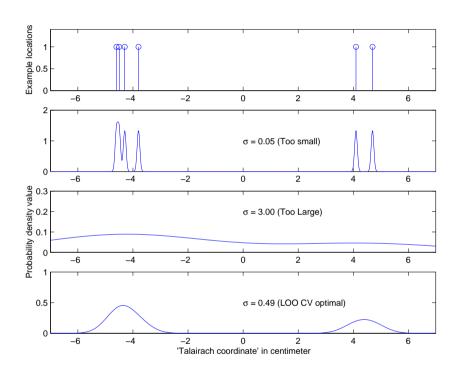


Figure 3: Example in one dimension with six coordinates and their kernel density estimate. Regard the coordinates as being generated from a distribution $p(\mathbf{x})$, where \mathbf{x} is in 3D Talairach space (Fox et al., 1997).

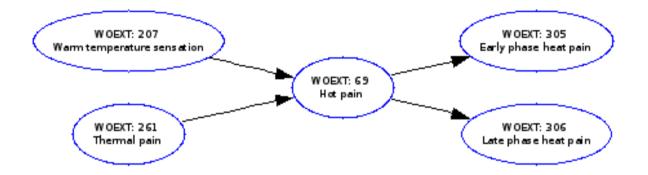
Kernel methods (N kernels centered on each location: μ_n) with homogeneous Gaussian kernel in 3D Talairach space x

$$\hat{p}(\mathbf{x}) = \frac{(2\pi\sigma^2)^{-3/2}}{N} \sum_{n=1}^{N} e^{-\frac{1}{2\sigma^2}(\mathbf{x} - \boldsymbol{\mu}_n)^2}$$

 σ^2 fixed ($\sigma = 1$ cm) or optimized with leave-one-out cross-validation (Nielsen and Hansen, 2002).



Taxonomy for cognitive components, ...



Brede Database: Memory, episodic memory, episodic memory retrieval, empathy, disgust, 5-HT2A receptor, ...

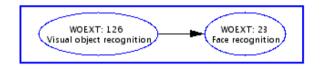
Organized in a hierarchy — a directed acyclic graph.

Mass meta-analysis possible with the graph (Nielsen, 2005)

Others: BrainMap taxonomy. Brede Wiki "Topics", MeSH. Under development: Cognitive Atlas (Poldrack), Cognitive Paradigm Ontology (Laird, Turner)

Supervised labeling

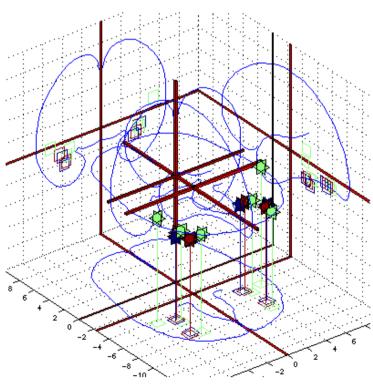
WOEXT: 23. Face recognition. Processing of face images.



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- Photographs of faces versus houses and chairs. Conjunction between passive viewing and delayed match-to sample of gray-scale photographs versus scrambled pictures and faces versus houses and chairs, with matching choice indicated by pressing a button with the right of left thumb. WOEXP: 91.
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 WOBIB: 28.
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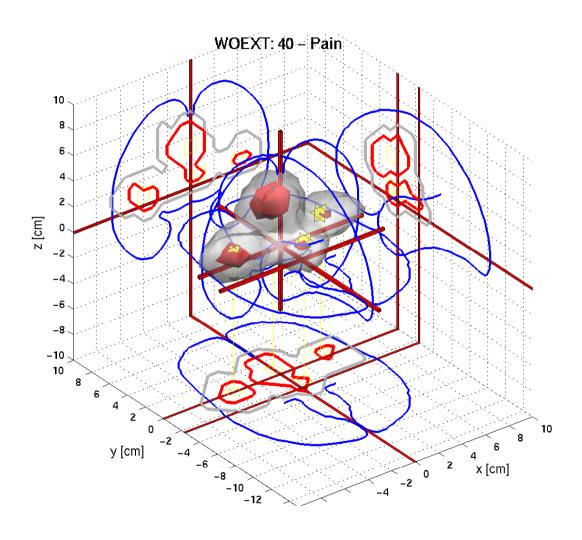
Example with "Face recognition" studies in a "corner cube" visualization.

The "expert" label added during database entry can provide the grouping structure.

Statistical tests can be constructed to measure whether the spatial distribution is "clustered" (Turkeltaub et al., 2002; Nielsen, 2005).



Supervised data mining



Volume for a specific taxonomic component: "Pain" 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).

Implementations of supervized datamining in the Brede Toolbox and in GingerALE.



Two sets of coordinates: Compare these!

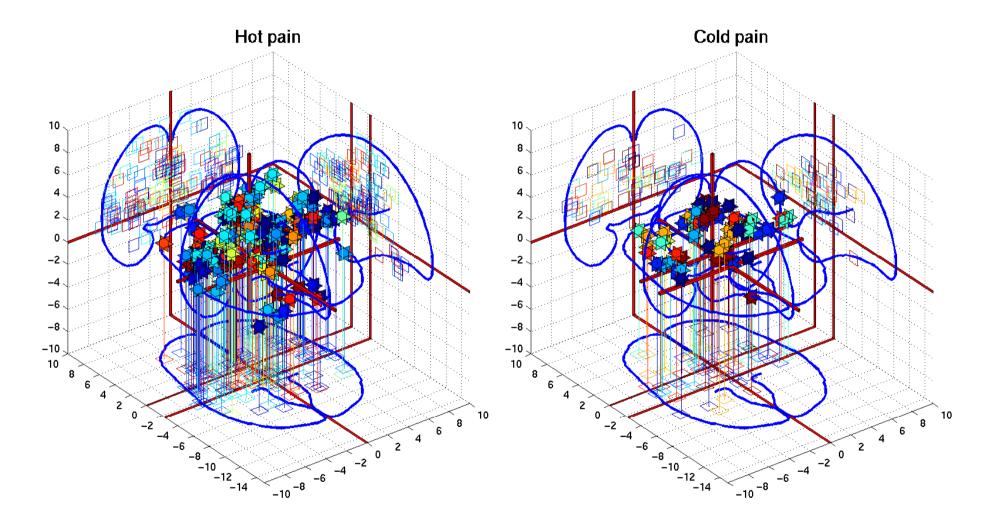
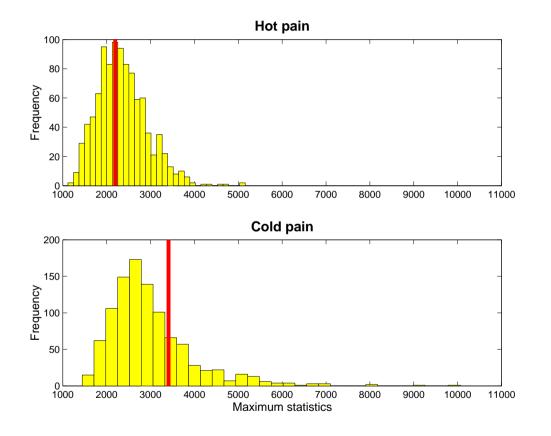


Figure 4: Visualization of the Talairach coordinates from hot pain and cold pain studies



Testing with resampling distribution



Two groups are compared by looking at the subtraction volume image

$$\mathbf{t}=\mathbf{v}_1-\mathbf{v}_2.$$

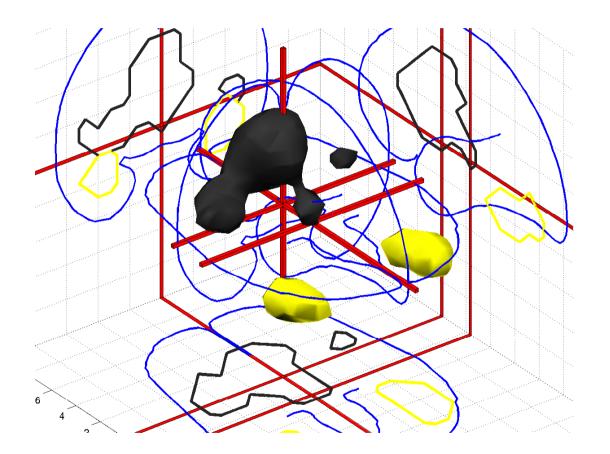
Histogram of resampled maximum statistics with 1000 resamplings:

$$t_{hot} = \max(\mathbf{v}_{hot} - \mathbf{v}_{cold})$$

$$t_{cold} = \max(\mathbf{v}_{cold} - \mathbf{v}_{hot}).$$

Figure 5: Empirical histograms of the maximum statistics t^* after 1000 permutations. The thick red lines indicate the maxima for the hot and cold pain statistics t_{hot} and (Nielsen et al., 2004a) t_{cold} .

Testing between pain and object vision



Isosurfaces at thresholds in t_{pain} and $t_{\text{object}}.$

 $\cdot \geq$

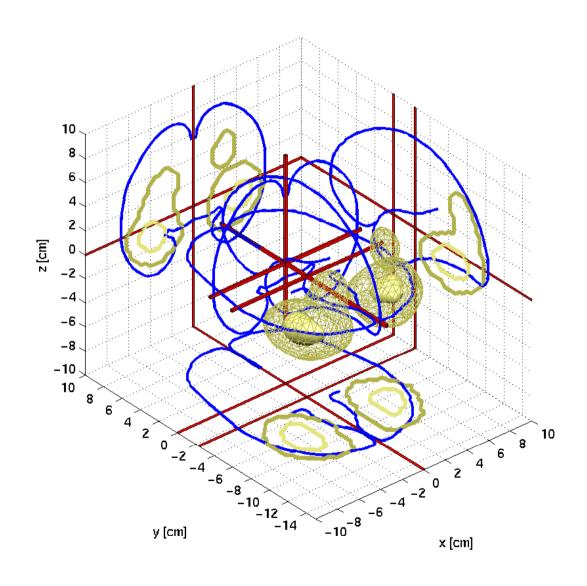
Thresholds are at the usual 0.05-level.

Expected areas appear above threshold. For pain: Anterior cingulate, insula, thalamus. For visual object recognition: fusiform gyrus.

Figure 6: Statistical image. Black is thermal pain and yellow is visual object recognition.



Unsupervised data mining



Decomposition of this matrix by multivariate analysis PCA, ICA, NMF, clustering (Nielsen and Hansen, 2004; Nielsen et al., 2004b).

Other technique: Replicator dynamics (Neumann et al., 2005).

Comparison of components with resting-state (Smith et al., 2009)



Issues with meta-analysis

Variable number of subjects between studies.

Varying brain structures examined and reported: Field of view for the scanner, scanner sequence regional sensitivities.

Varying statistical levels used.

Small volume correction is bad for whole brain meta-analysis.

Varying strength between individual coordinates. 🔅

In summary: Be careful in interpreting the result of a neuroimaging metaanalysis.

Image-based meta-analysis is coming ☺ Neurogenerator, Brede Wiki upload, SumsDB, (Salimi-Khorshidi et al., 2009b; Salimi-Khorshidi et al., 2009a) 1

Text representation: a "bag-of-words"

	'memory'	'visual'	'motor'	'time'	'retrieval'	
Fujii	6	0	1	0	4	
Maddock	5	0	0	0	0	
Tsukiura	0	0	4	0	0	
Belin	0	0	0	0	0	
Ellerman	0	0	0	5	0	
:	÷	:	:	:	:	· · .

Representation of the abstract of the articles in "bag-of-word". Table counts how often a word occurs

Exclusion of "stop words": common words (the, a, of, ...), words for brain anatomy, and a large number of common words that appear in abstracts. Mostly words for brain function are left. More advanced extraction: Match to ontologies

Cimbi 🍙 🚆



Grouping of words from articles

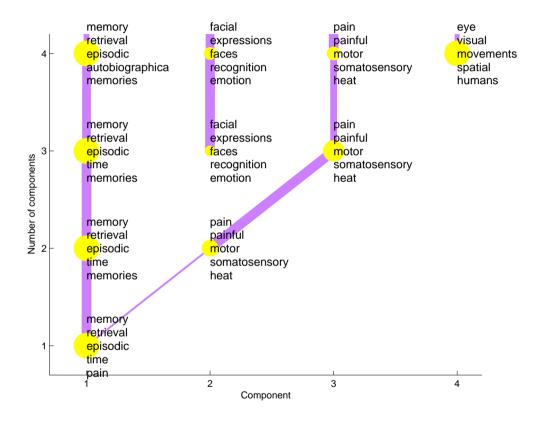


Figure 7: Grouped words.

Multivariate analysis (NMF) of the text in *posterior cingulate* articles to find "themes", which can be represented with weights over words and articles (Nielsen et al., 2005).

Most dominating words: memory, retrieval, episodic

pain, painful, motor, somatosensory

facial, expressions, faces,

eye, visual, movements

Text and volume: Functional atlas

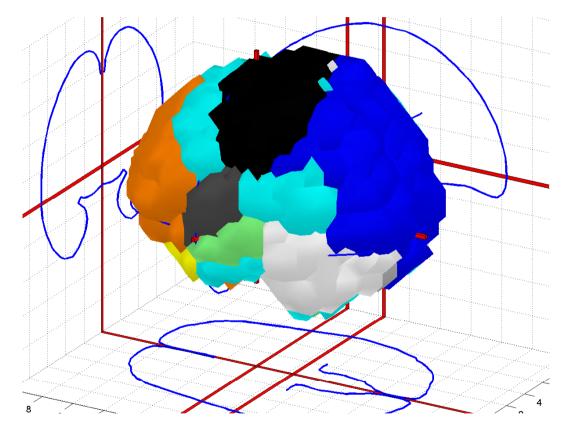


Figure 8: Functional atlas in 3D visualization.

Automatic construction of functional atlas, where words for function become associated with brain areas

Two matrices: Bag-of-words matrix, matrix from voxelization of coordinates. NMF on the product matrix.

Example components: Blue area: visual, eye, time. Black: motor, movements, hand. White: faces, perceptual, face.

Functional atlas — medial view

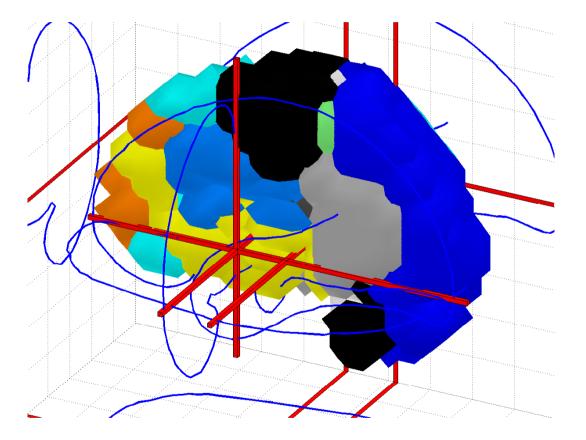


Figure 9: Visualization of the medial area.

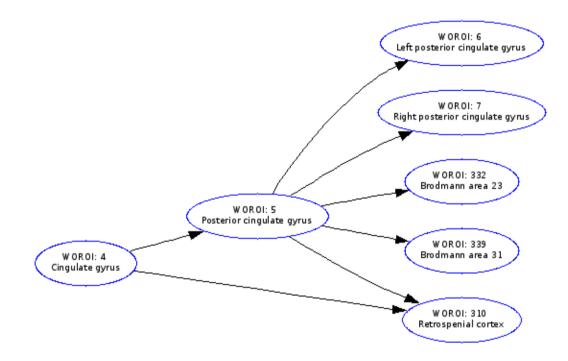
Grey area: retrieval, neutral, words, encoding.

Yellow: emotion, emotions, disgust, sadness, happiness

Light blue: pain, noxious, verbal, unpleasantness, hot

See also *PubBrain* Web service which queries the PubMed database and count occurences of brain regions in abstracts.

Brede brain region taxonomy

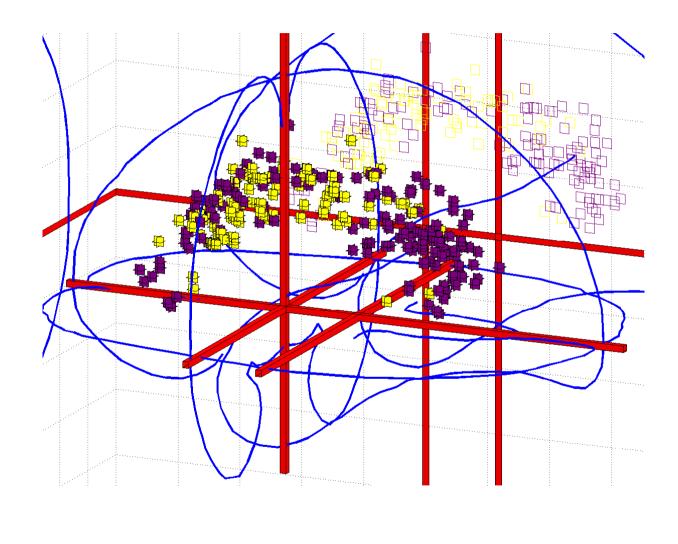


Taxonomy of neuroanatomical areas with items linked in a hierarchy with "Brain" in the top root and smaller areas in the leafs.

Based on another neuroanatomical database "BrainInfo/Neuro-Names" (Bowden and Martin, 1995; Bowden and Dubach, 2003) and atlases, e.g. "Mai atlas" (Mai et al., 1997).

Searching for all "cingulate" coordinates

Combining text analysis and coordinates

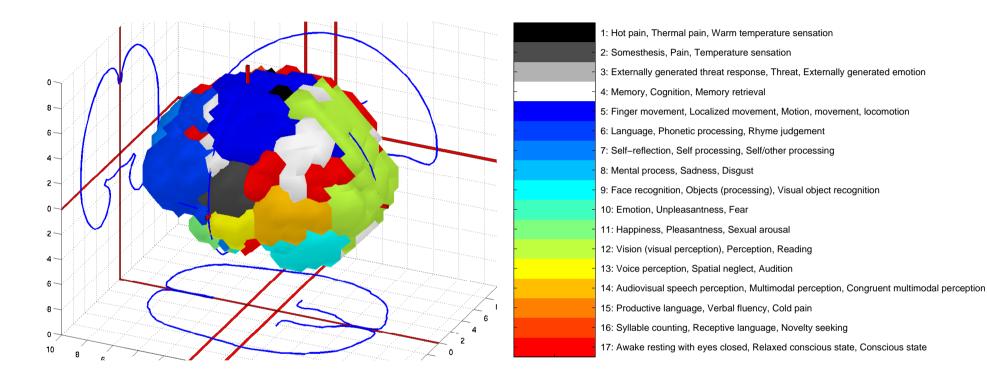


Is there a different between how brain functions distribute in the cingulate gyrus?

Possible to find the corresponding articles for the coordinates — and text mine these articles for clustering and label the coordinate according to cluster.

Sagittal plot of memory (magenta) and pain (yellow).

Combining ontologies and coordinates



Conversion of the Brede Database function taxonomy to a matrix and using that together with matrix from voxelization of the coordinates in the experiments and non-negative matrix factorization.



More information

Articles about neuroinformatics (Nielsen et al., 2006; Nielsen, 2009)

Brede Database Brede Wiki Brede Toolbox

Bibliography on Neuroinformatics:

http://www.imm.dtu.dk/~fn/bib/Nielsen2001Bib/



You should submit you data to a neuroinformatics database to get published.



The End



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