Brede Database

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Information increase

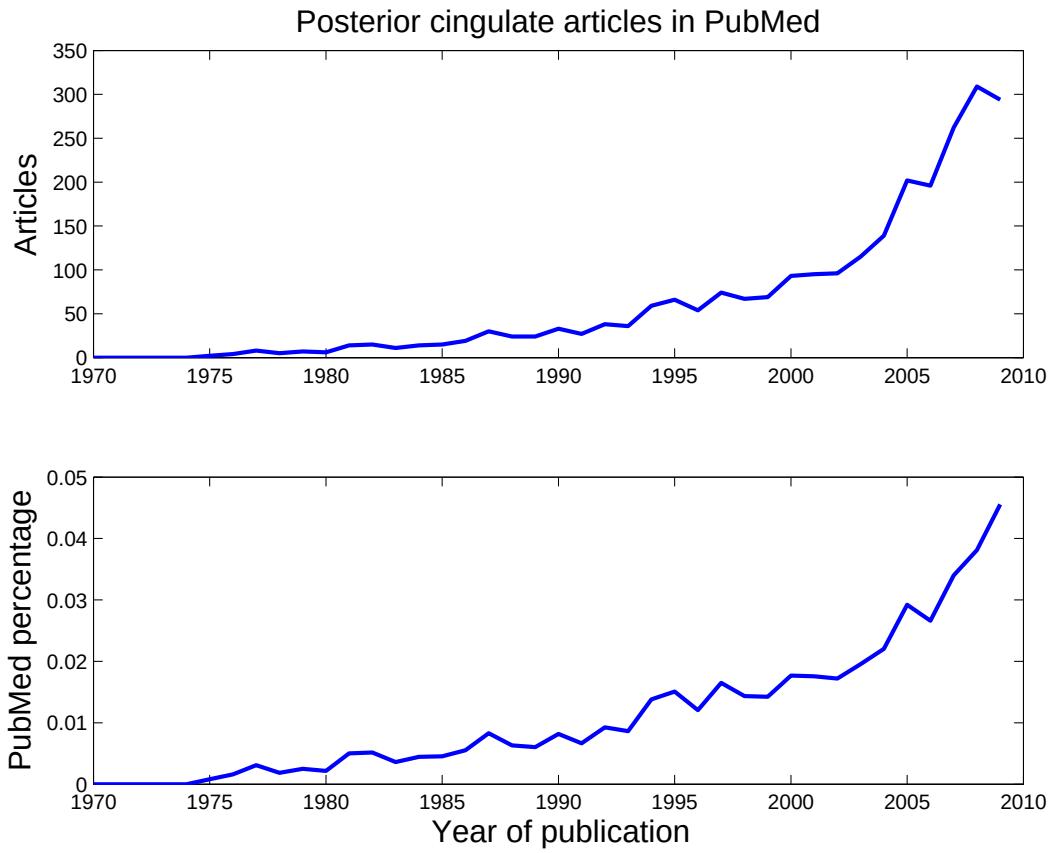


Figure 1: Increase in the number of articles in PubMed which are returned after searching on posterior cingulate and related brain areas.

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, . . .

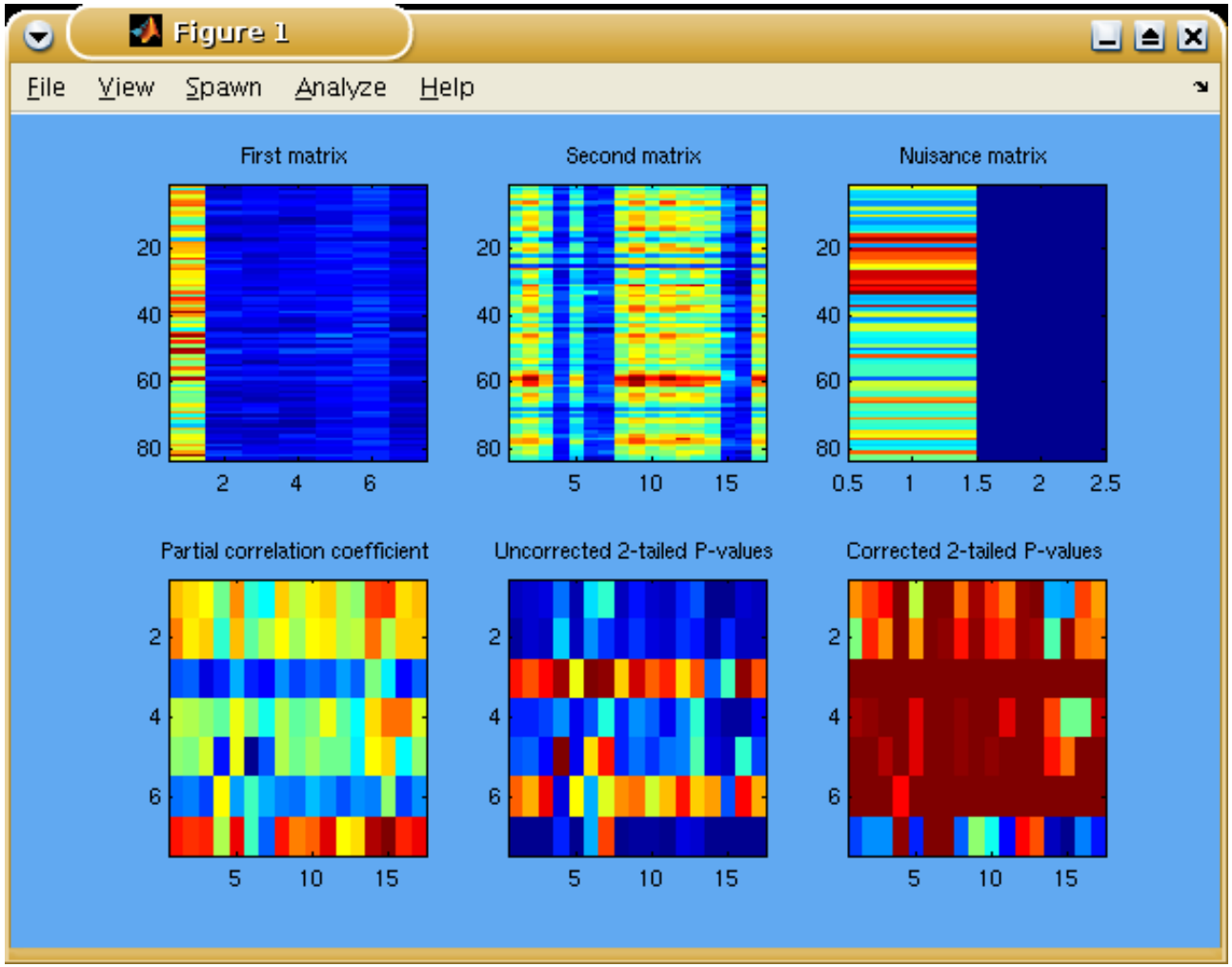
Neuroinformatics: Brede tools

Brede Toolbox: A program package primarily written in Matlab. Handles visualization, linear modeling, multivariate analysis, locations (Talairach coordinates), volumes, papers, texts.

Brede Database: Basically a collection of XML files with data from neuroimaging papers as well as ontologies. Distributed with the Brede Toolbox. "Output" and query services to the Brede Database (generated with the Brede Toolbox) is available on the Internet: http://neuro.imm.dtu.dk

Brede Wiki: A wiki with data from neuroimaging papers as well as ontologies. Both freeform text and "semantically" organized within MediaWiki templates.

Brede Toolbox: partial correlation analysis



Command line or graphical user interface (GUI) can be used flexibly and interchangeably

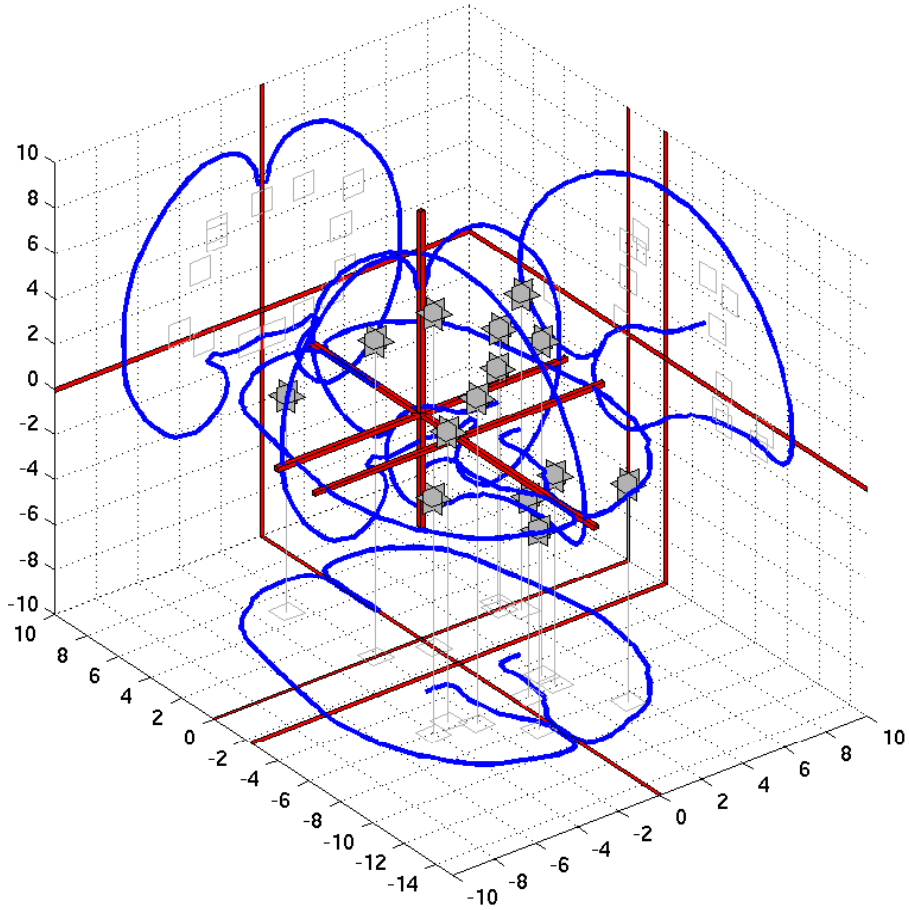
Here window for partial correlation analysis to analyze data across brain regions and multiple personality traits with permutation test for multiple comparisons across the two sets of variables.

Example visualization

Load the Brede Database with Talairach coordinate information in `B`

Display the coordinates from the first 'paper' (Law et al., 1997)

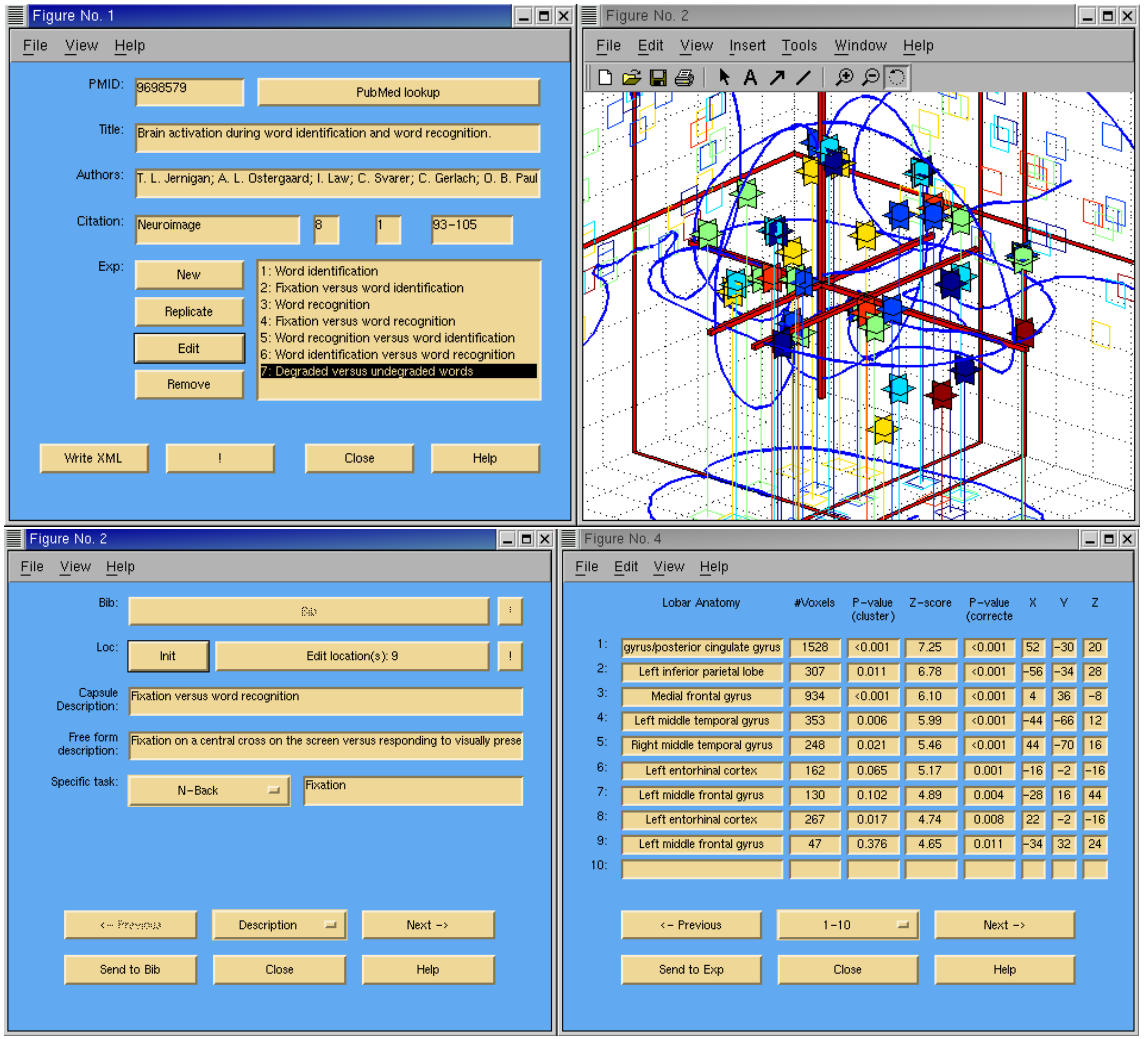
Construct a initial frame with `brede_ta3_frame`



Add component (locations) with a `brede_ta3_` function

```
% Download http://neuro.imm.dtu.dk/services/brededatabase/wobibs.mat
>> B = brede_bdb; % Load from wobibs.mat if available, else wobibs.xml
>> brede_ta3_frame, brede_ta3_bib(B{1}, 'color', [0.7 0.7 0.7])
```

Brede Toolbox with the Brede Database

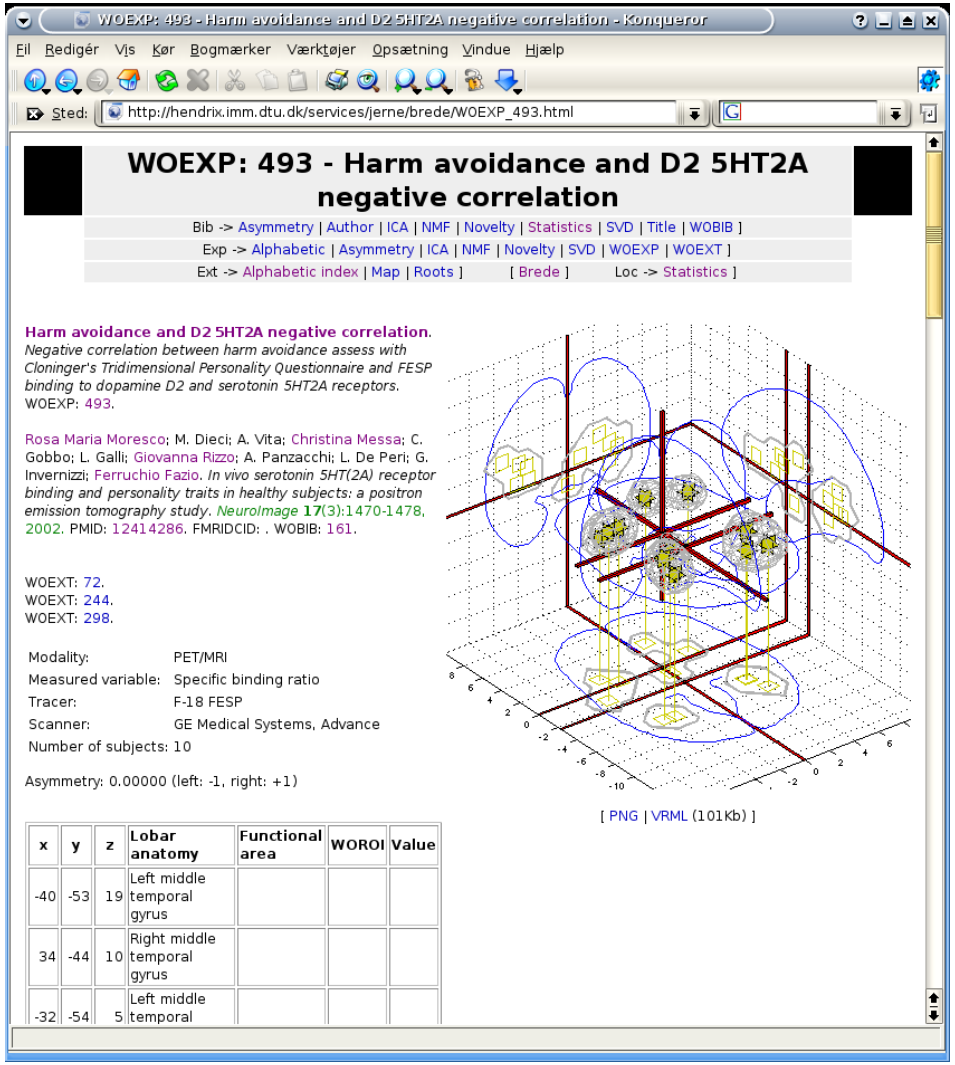


Graphical user interface of Brede Toolbox used to enter data into the Brede Database.

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

Data stored in XML available on the Web

The Brede Database on the Web

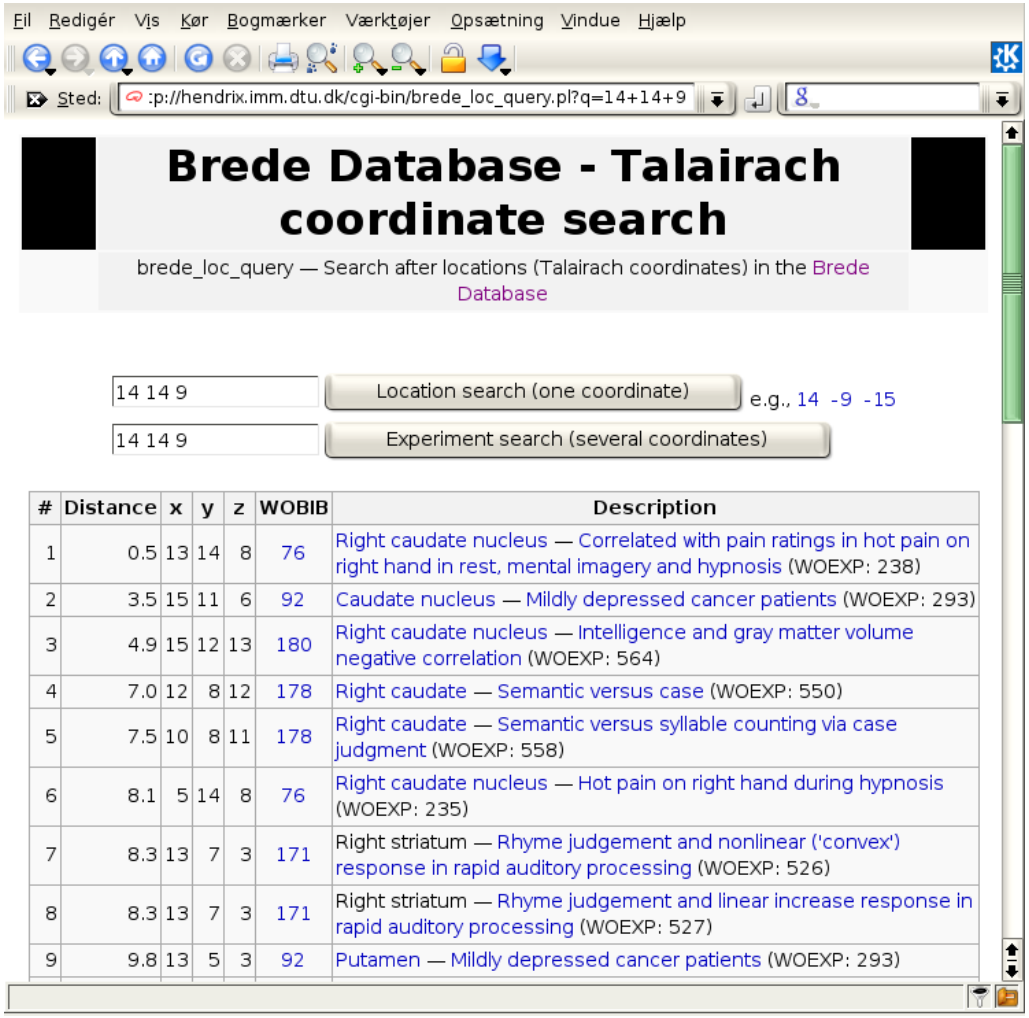


Presentation on the Web

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).

Searching on Talairach coordinate



#	Distance	x	y	z	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)
3	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	Right striatum — Rhyme judgement and nonlinear ('convex') response in rapid auditory processing (WOEXP: 526)
8	8.3	13	7	3	171	Right striatum — Rhyme judgement and linear increase response in rapid auditory processing (WOEXP: 527)
9	9.8	13	5	3	92	Putamen — Mildly depressed cancer patients (WOEXP: 293)

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.

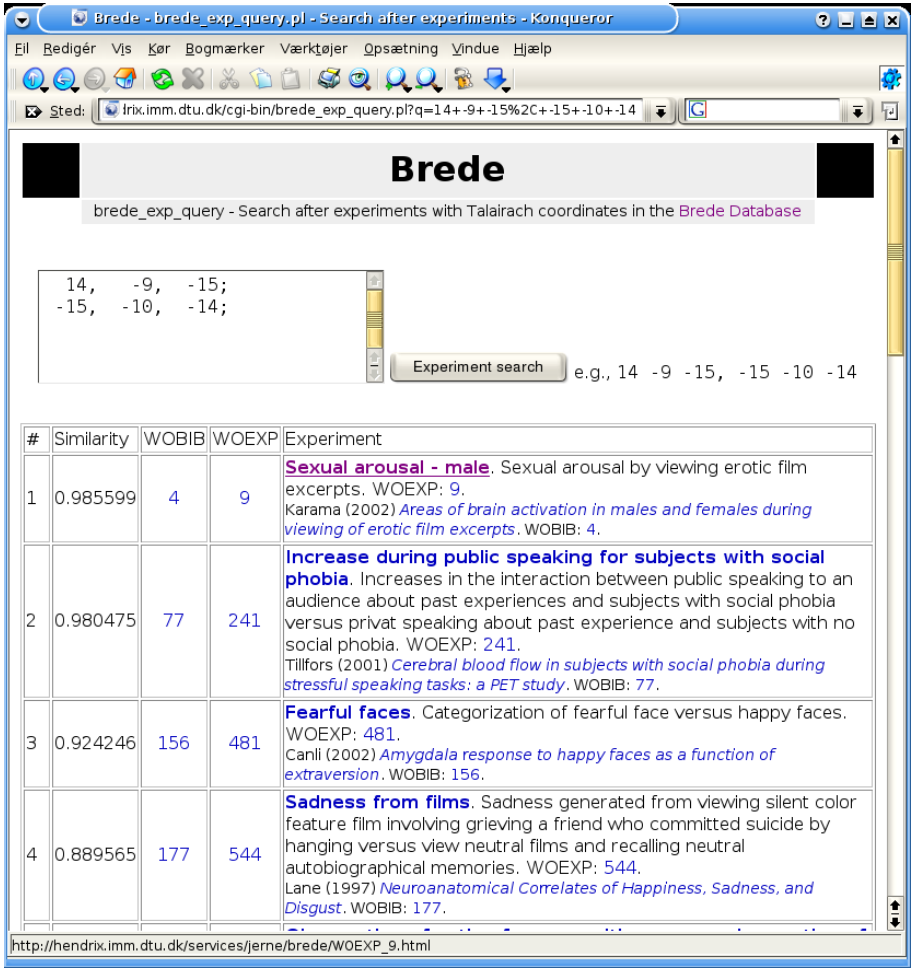
Online experiment search (multiple coordinates)

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

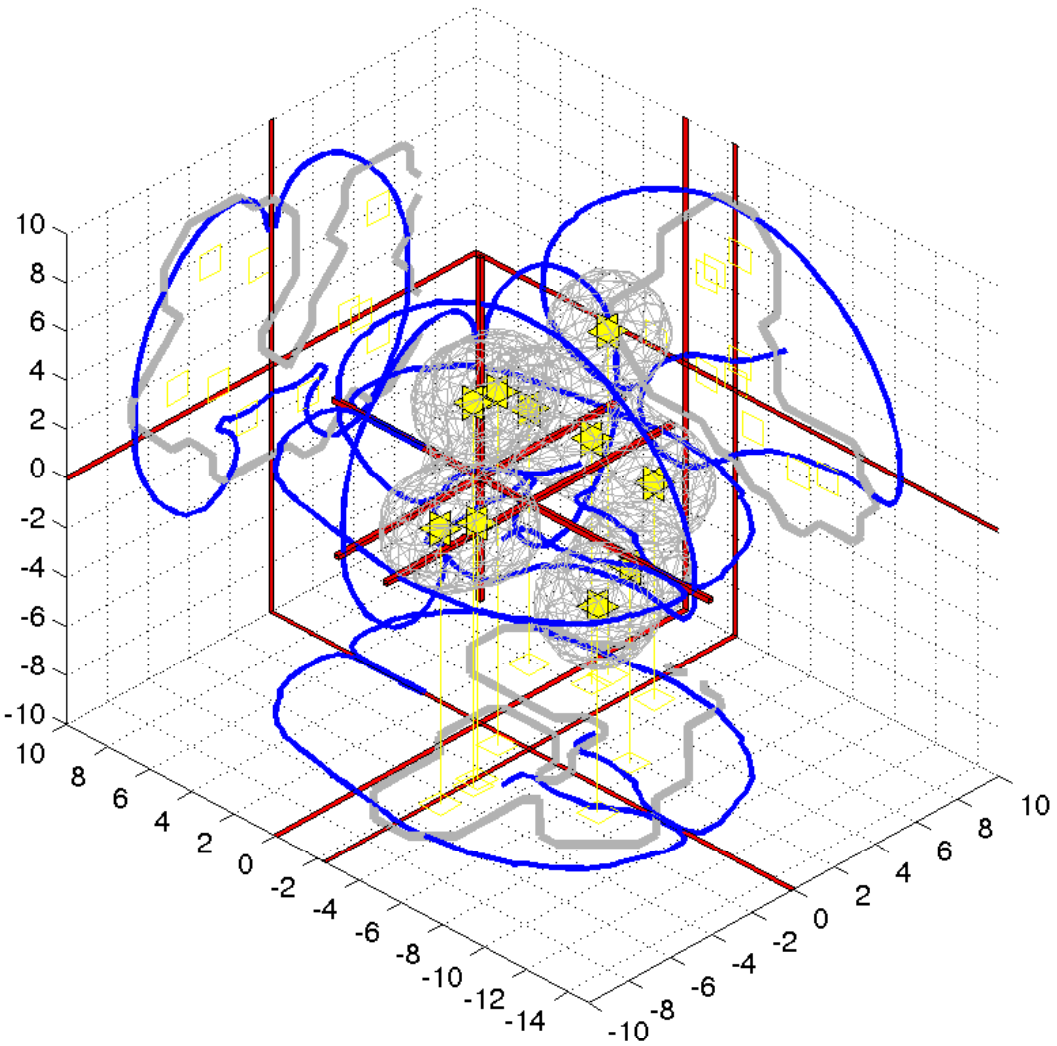
"Related volume" also available from the "original" BrainMap database (Nielsen and Hansen, 2004):

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

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



Coordinates-to-volume transformation



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

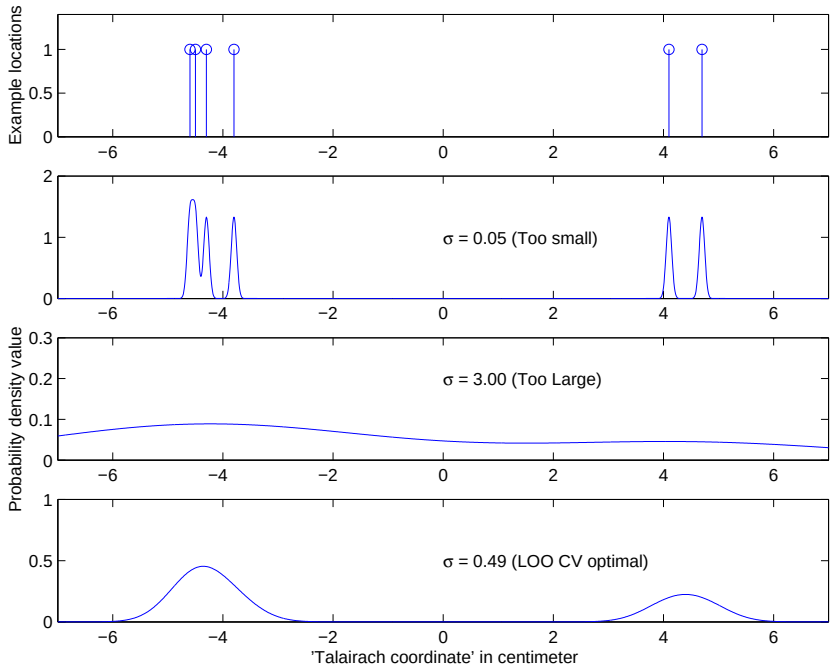


Figure 2: Example in one dimension with six coordinates and their kernel density estimate.

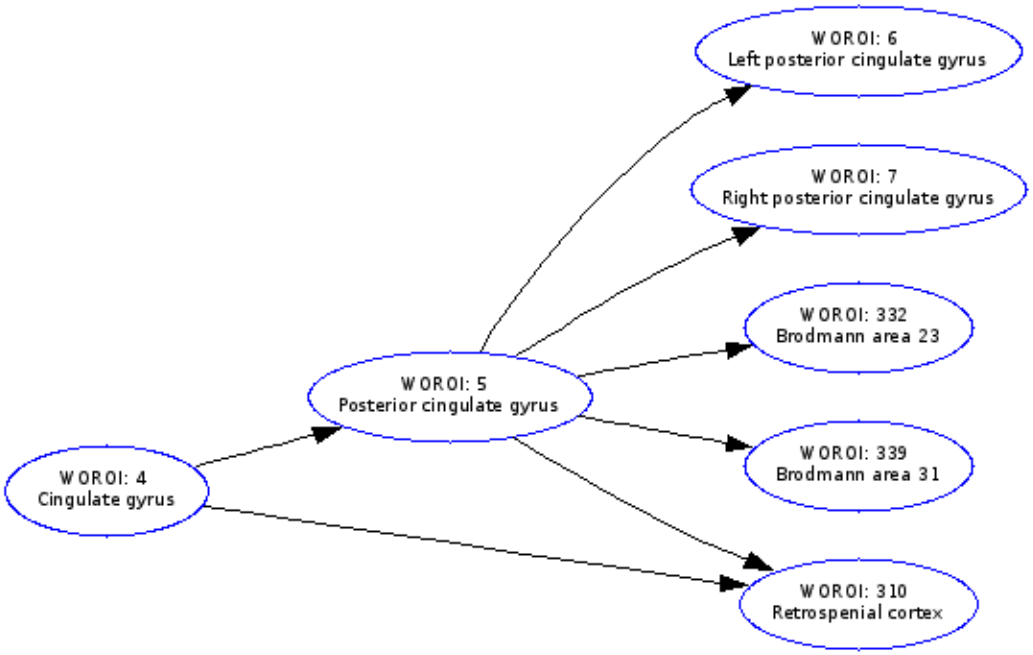
Regard the coordinates as being generated from a distribution $p(\mathbf{x})$, where $\mathbf{x}$ is in 3D Talairach space (Fox et al., 1997).

Kernel methods (N kernels centered on each location: $\boldsymbol{\mu}_n$) with homogeneous Gaussian kernel in 3D Talairach space $\mathbf{x}$

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

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

Brede brain region taxonomy/ontology



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

Records parent region, child region, naming variations,

Links to other brain region ontologies

Links to digital brain atlases (AAL, Claus Svarer, Alexander Hammers)

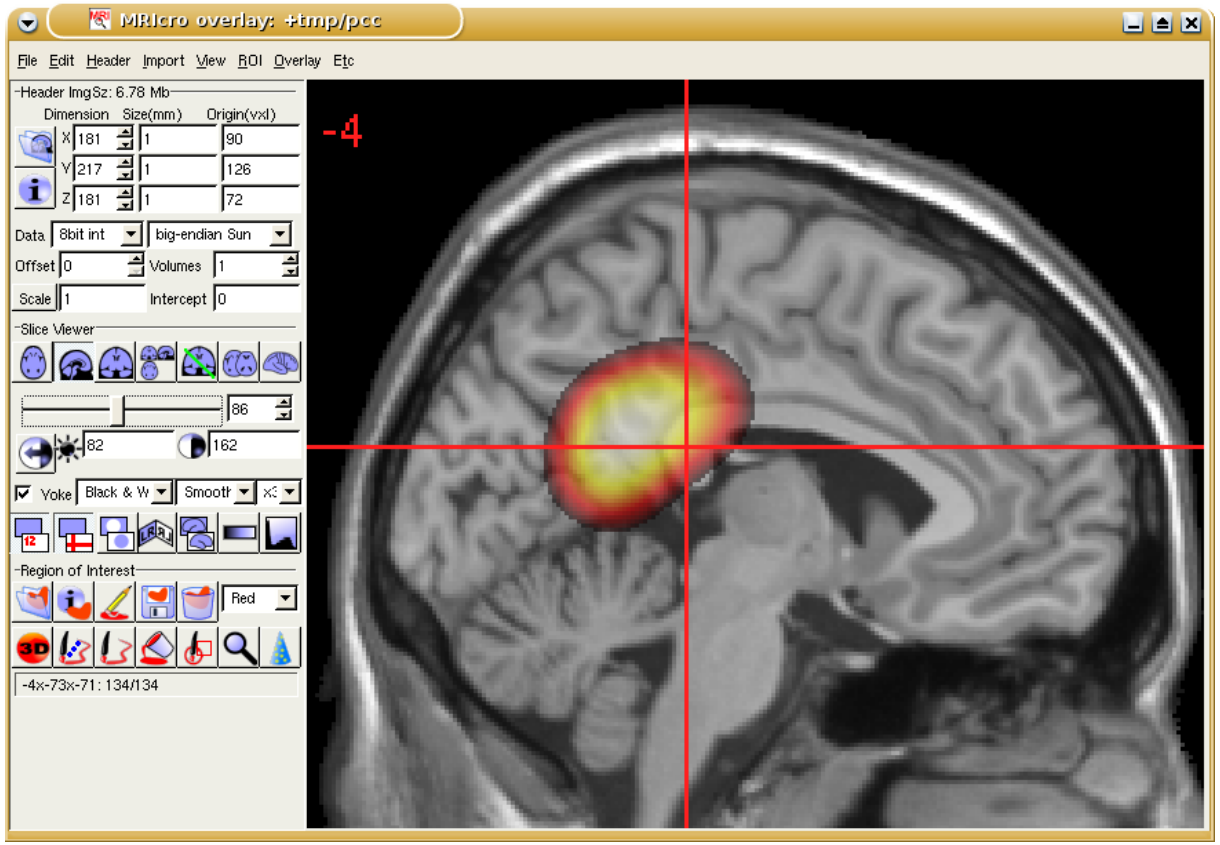
Example with Brain region ontology

The ontology enables one to get all names for PCC and its subregions. Output is (24 names in total):

```
'Posterior cingulate gyrus'
'Posterior cingulate'
'Posterior cingulate area'
'Posterior gyrus cinguli'
'Posterior cingulate cortex'
'Left posterior cingulate gyrus'
'Left posterior cingulate'
'Posterior cingulate gyrus, left'
...  e.g., BA23, retrosplenial, ...
```

Suitable for text mining where you identify as many occurrences in a corpus that is not using a controlled vocabulary, such as ordinary scientific articles.

Example: Get PCC locations



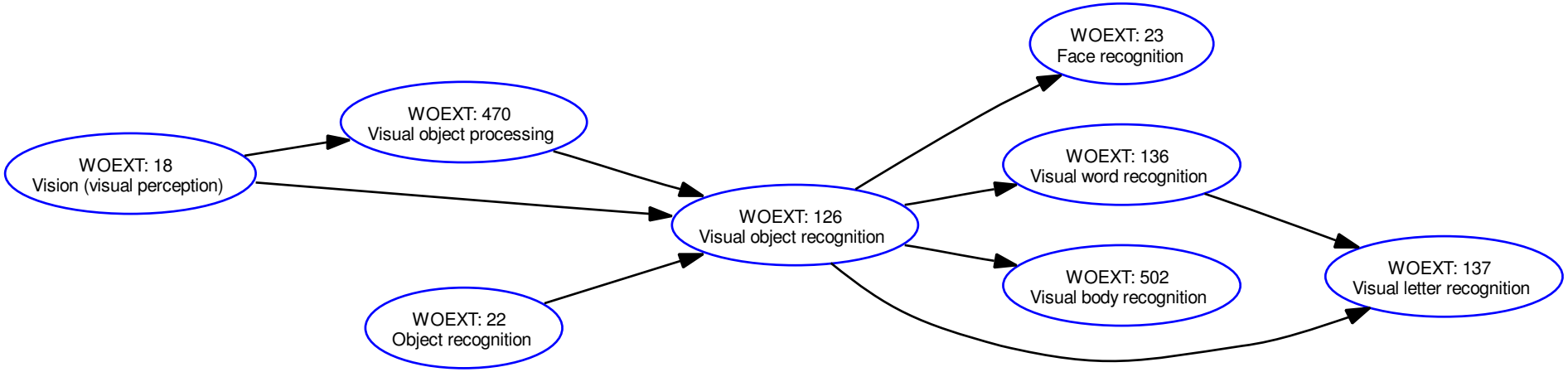
Get all posterior cingulate locations that match on of the naming variation for the regions and its subregion.

Model the locations with kernel density estimation, and convert the density to a probability.

Volume written to an Analyze file

Viewed in the external MRIcro program

Topics ontology



Topics, such as brain functions and mental disorders, organized in a hierarchy. Example: episodic memory retrieval, OCD, 5-HT2A receptor.

Used to label each neuroimaging experiment

Other efforts: MeSH (too coarse), BrainMap, Cognitive Atlas (Poldrack), Cognitive Paradigm Ontology (Laird, Turner).

Cognitive components are "open to interpretation"

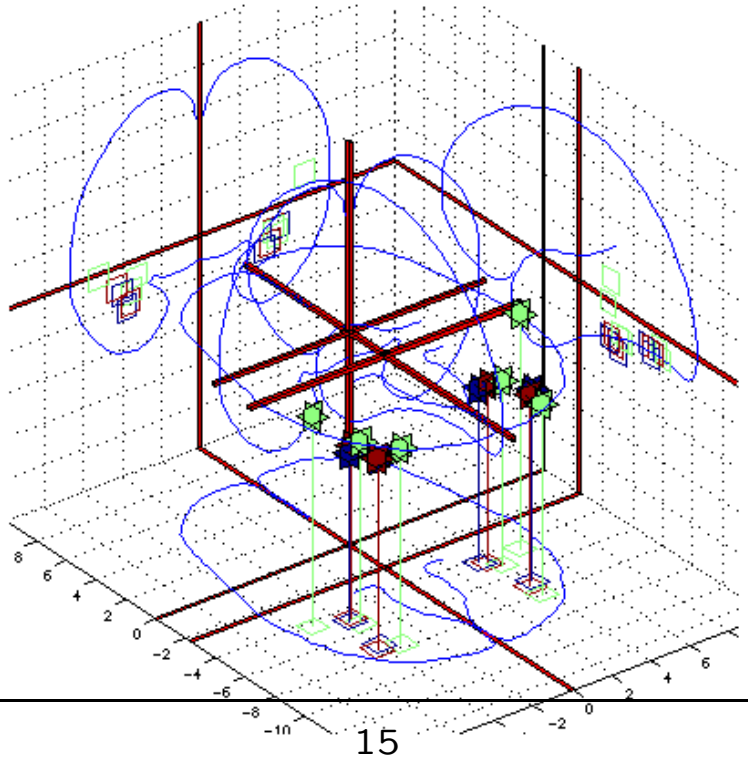
Supervised labeling

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

Parents	Siblings	Children
Visual object recognition		

Experiments:

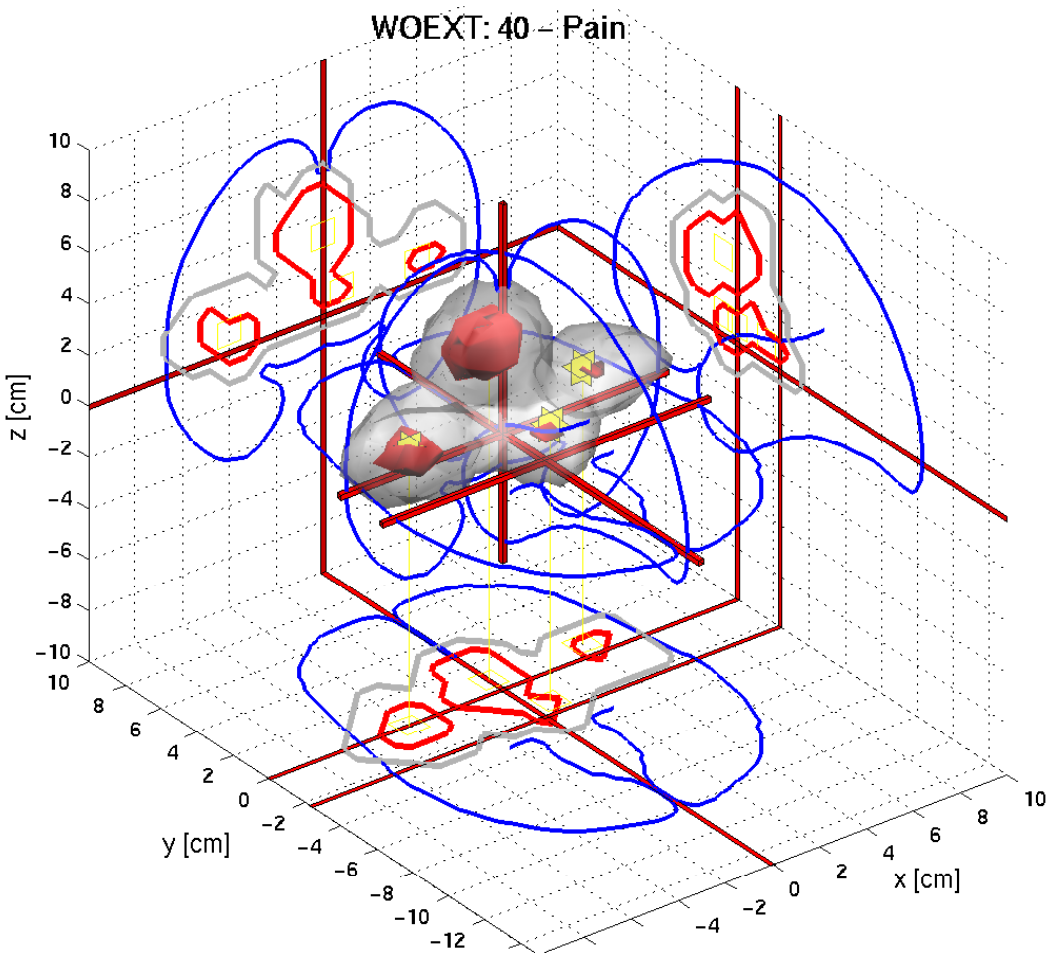
1. **Face visual object**. *Visual objects: Faces versus building*. WOEXP: 11.
   I Levy; U Hasson; G Avidan; T Hendler; R Malach. *Center–periphery organization of human object areas.*. *Nat Neurosci* **4**(5):533–9, 2001.
   PMID: 11319563. WOBIB: 5.
2. **Photographs of faces versus houses and chairs**. *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.
   A. Ishai; L. G. Ungerleider; A. Martin; J. V. Haxby. *The representation of objects in the human occipital and temporal cortex.*. *J Cogn Neurosci* **12 Suppl 2**:35–51, 2000.
   PMID: 11506646. FMRIDCID: 2–2000–1113D.
   WOBIB: 28.
3. **Front–face**. *Line drawings of front face versus line drawings of tumblers*. WOEXP: 123.
   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: 11564319. FMRIDCID: 2–2001–111P8.
   WOBIB: 36.



Example with "Face recognition" studies in a "corner cube" visualization.

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.

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

Grouping of words from articles

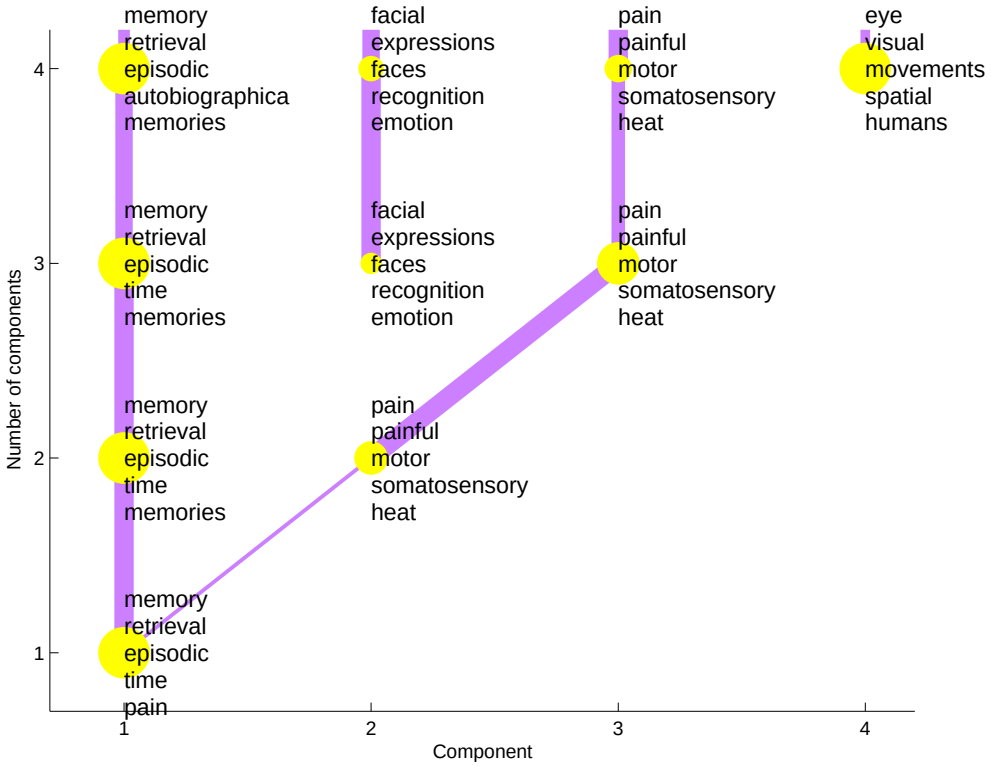


Figure 3: Grouped words.

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).

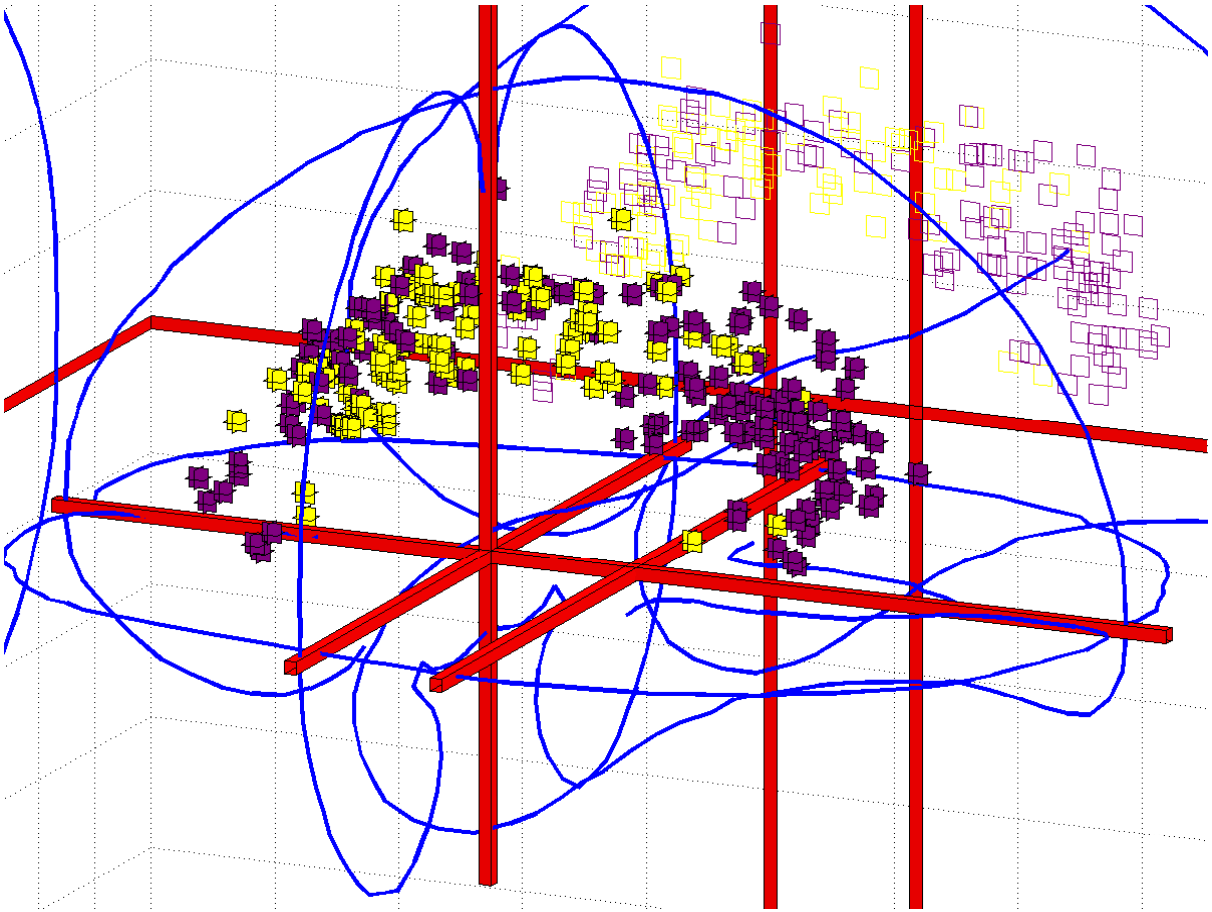
Most dominating words: memory, retrieval, episodic

pain, painful, motor, somatosensory

facial, expressions, faces,

eye, visual, movements

Combining text analysis and coordinates



Is there a difference in 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).

Text and volume: Functional atlas

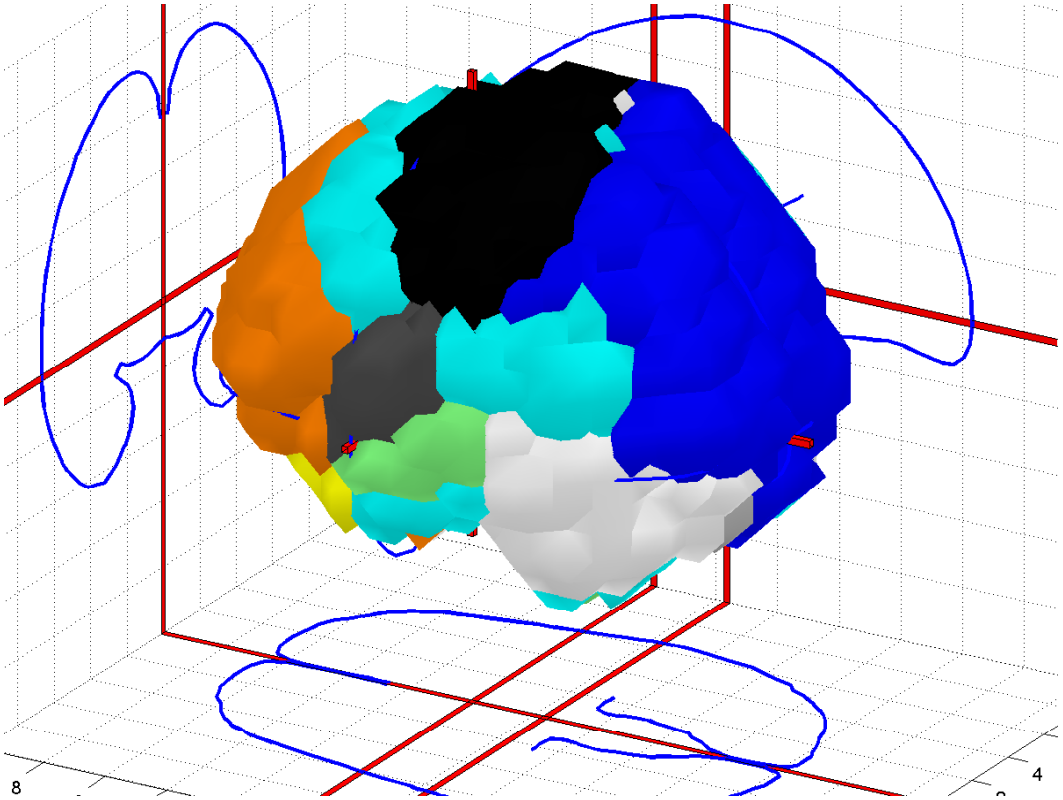


Figure 4: Functional atlas in 3D visualization.

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

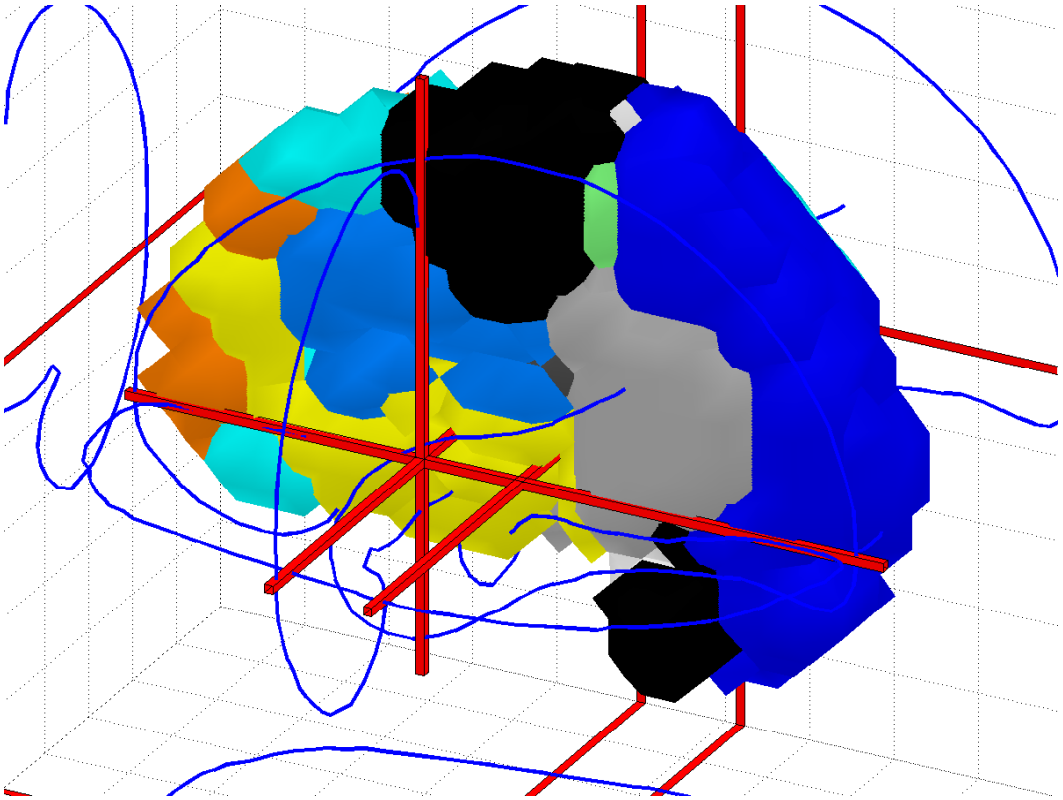


Figure 5: Visualization of the medial area.

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 Database in outlier detection

#	Value	x	y	z	term	Lobar anatomy	WOBIB	WOEXP
1	-111.6671	-11	-76	-53	parietal	Left superior parietal lobe	176	539
2	-86.8558	-50	-52	17	right	Right occipitotemporal cortex	4	9
3	-71.9572	57	-22	13	left	Left Heschl's gyrus	164	499
4	-59.8896	-46	-25	13	right	Right superior temporal gyrus	164	499
5	-56.9524	46	40	-4	left	Left middle frontal gyrus	88	283
6	-56.4492	-11	-76	-53	superior	Left superior parietal lobe	176	539
7	-56.1964	-30	59	3	lobule	Left middle frontal lobule	88	283
8	-55.4707	-39	-33	46	right	Right intraparietal sulcus	24	77
9	-53.914	-44	-62	4	anterior	Left anterior middle temporal gyrus	104	324
10	-53.3065	40	10	0	left	Left frontal insula	17	50
11	-52.9443	-8	-32	-4	frontal	Mesolimbic, right inferior frontal gyrus	111	343
12	-51.4662	52	-30	20	cingulate	Right postcentral gyrus/posterior cingulate gyrus	35	119
13	-44.1041	-34	-48	-18	right	Right fusiform gyrus	145	443
14	-42.5693	8	-68	-35	precuneus	Right precuneus	23	73
15	-40.5044	-37	35	36	right	Right middle frontal gyrus	178	561
16	-39.5277	-44	32	9	lobule	Left inferior frontal lobule	88	283
17	-37.978	-15	-53	-2	anterior	Left lingual gyrus/anterior calcarine sulcus	3	7
18	-36.8332	-34	3	15	right	Right inferior frontal cortex	161	493
19	-34.993	-30	-40	-25	anterior	Left anterior cerebellum	180	563
20	-33.018	38	18	-26	fusiform	Fusiform gyrus	31	104

What about data entry errors and other peculiarities?

Data mining for outliers using an automated algorithm that looks at the redundancy between the anatomical label and the 3D coordinate (Nielsen and Hansen, 2002a).

Here "parietal" in "left superior parietal lobe" does not "fit" with $z = -53$ and "right" in "Right occipitotemporal cortex" does not fit with $x = -50$.

Problems

Difficult to add new information to the Brede Database

Difficult to do incremental additions.

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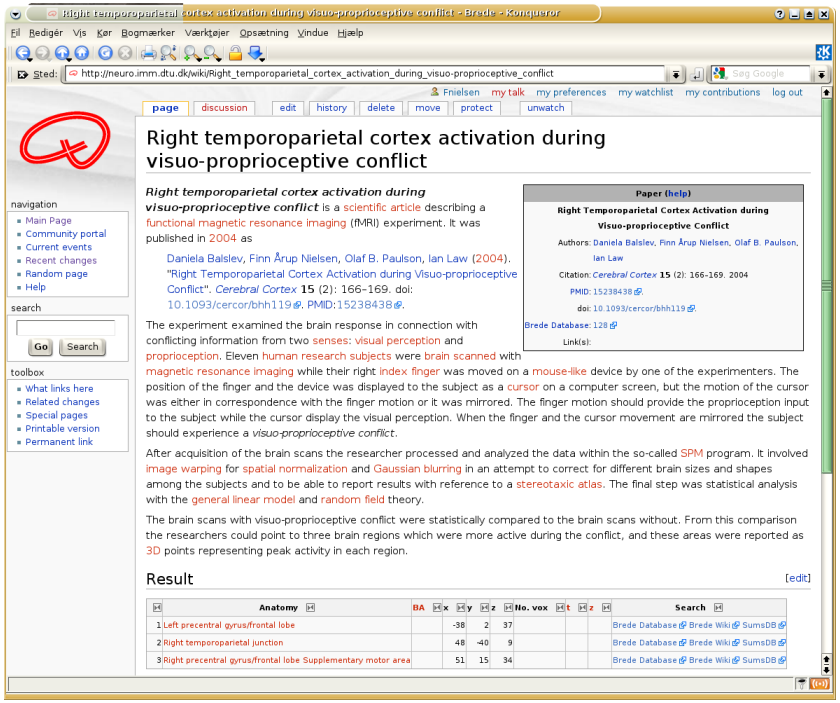
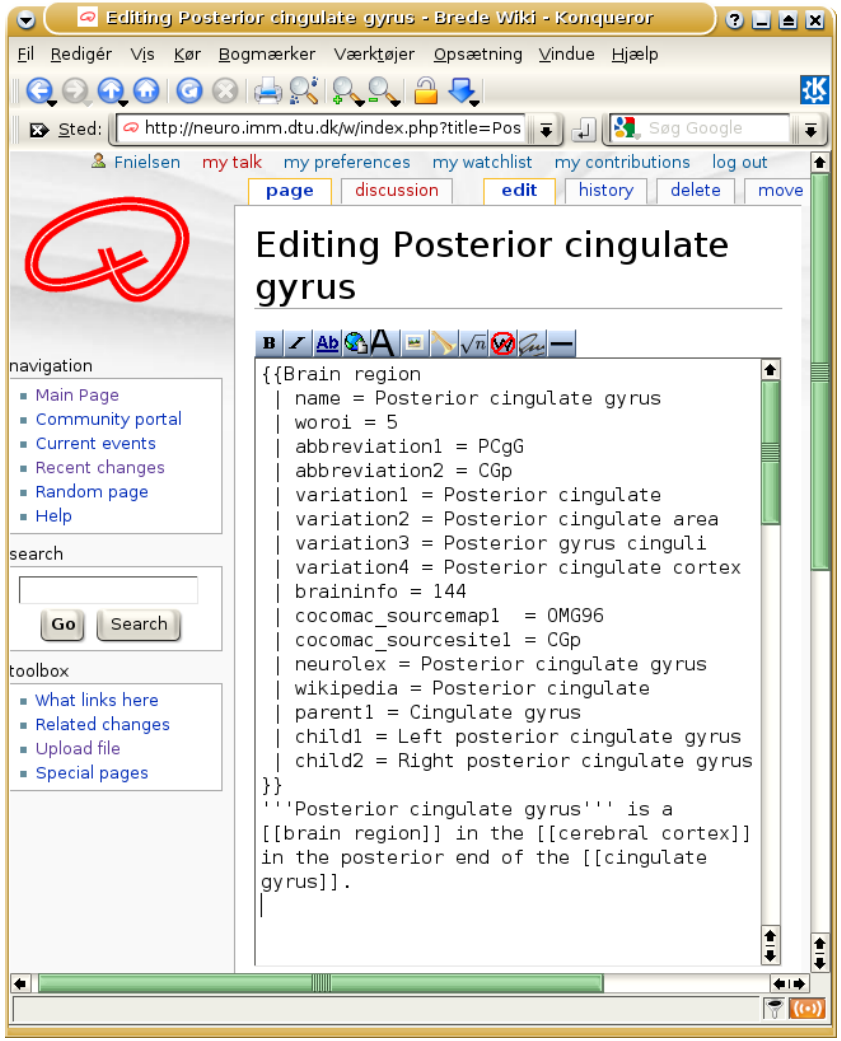
Solution?

Wiki with structured data

Brede Wiki = MediaWiki templates + Extraction + SQL + Neuroscience



Principles of the Brede Wiki



Structured information is stored in the so-called "templates" of Mediawiki.

Template use simple so it is easy to convert data all template instantiations to an SQL representation: No wiki formating in field values, non-nested templates, lower case field names (a one-to-one mapping of MediaWiki templates and ontology classes). (Nielsen, 2009)

Link as much as possible in the template values.

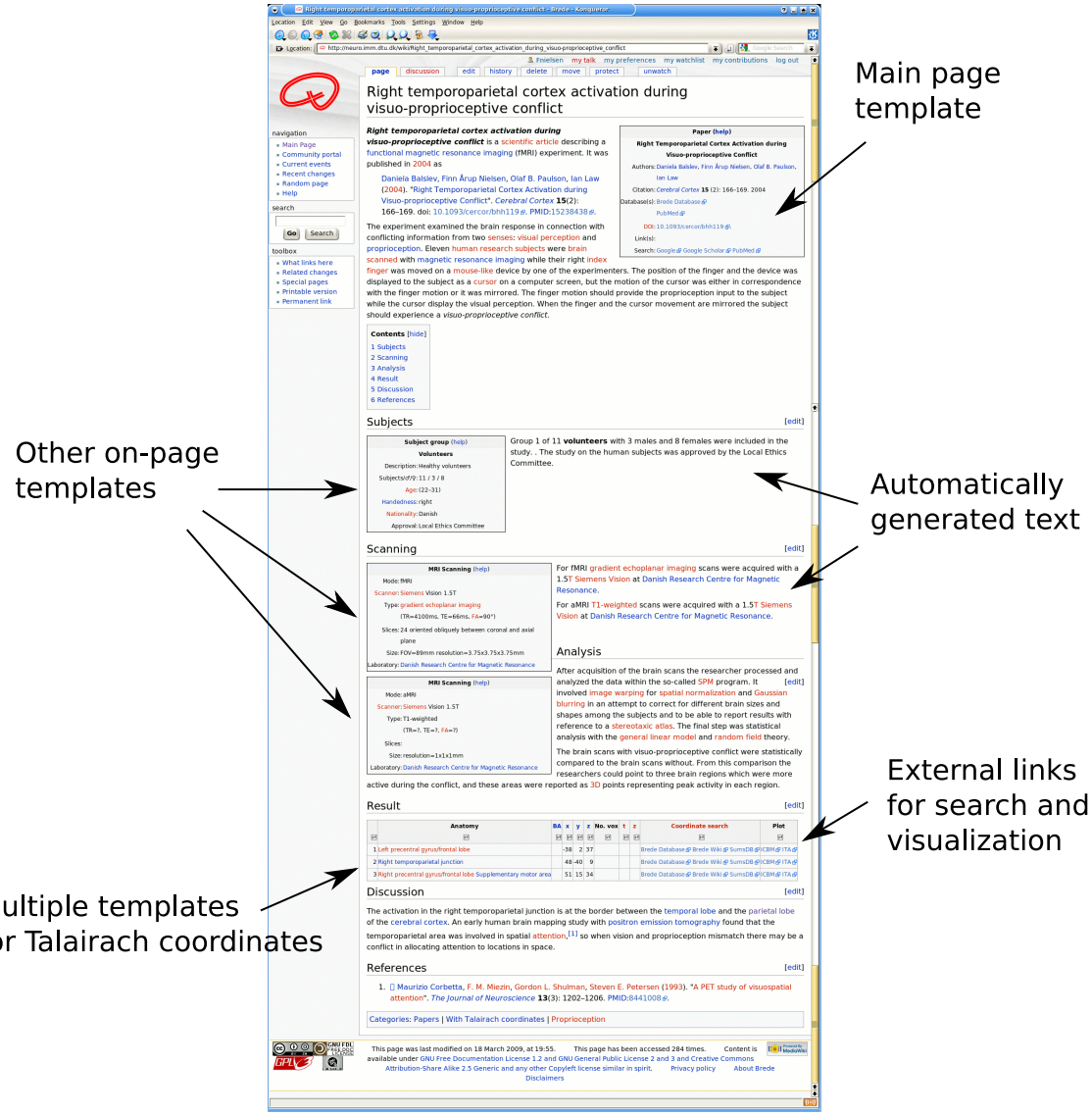
Link to external sites whenever possible.

Brede Wiki templates

Templates may describe a paper with bibliographic information or a researcher or journal.

Hierarchical templates: Brain regions, Topics, Organizations, Software.

Multiple templates on each page, e.g., to describe subject group, brain scan, experimental condition, Talairach coordinate, brain volume, gene personality association.



Storing of volumes

Scanning

MRI Scanning (help)

Mode: fMRI

Scanner: Philips Achieva 3T

Type: Gradient-echo echo-planar

(TR=3000ms, TE=35ms, FA=?)

Slices: 49 (thickness=3mm) oriented Horizontal

Size: FOV=240 x 147 x 240mm resolution=2.5 x 2.5 x

Laboratory: missing *laboratory*

For fMRI Gradient-echo echo-planar scans were acquired with a 3T Philips Achieva.

For aMRI T1-weighted scans were acquired with a .

MRI Scanning (help)

Mode: aMRI

Scanner:

Type: T1-weighted

(TR=?, TE=?, FA=?)

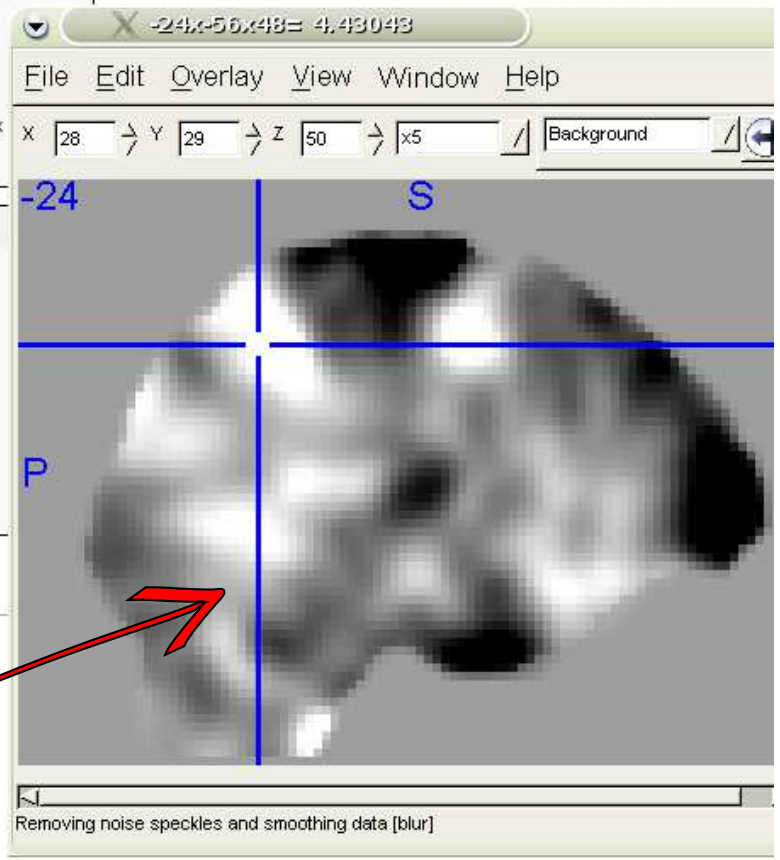
Slices:

Size: resolution=1 x 1 x 2mm

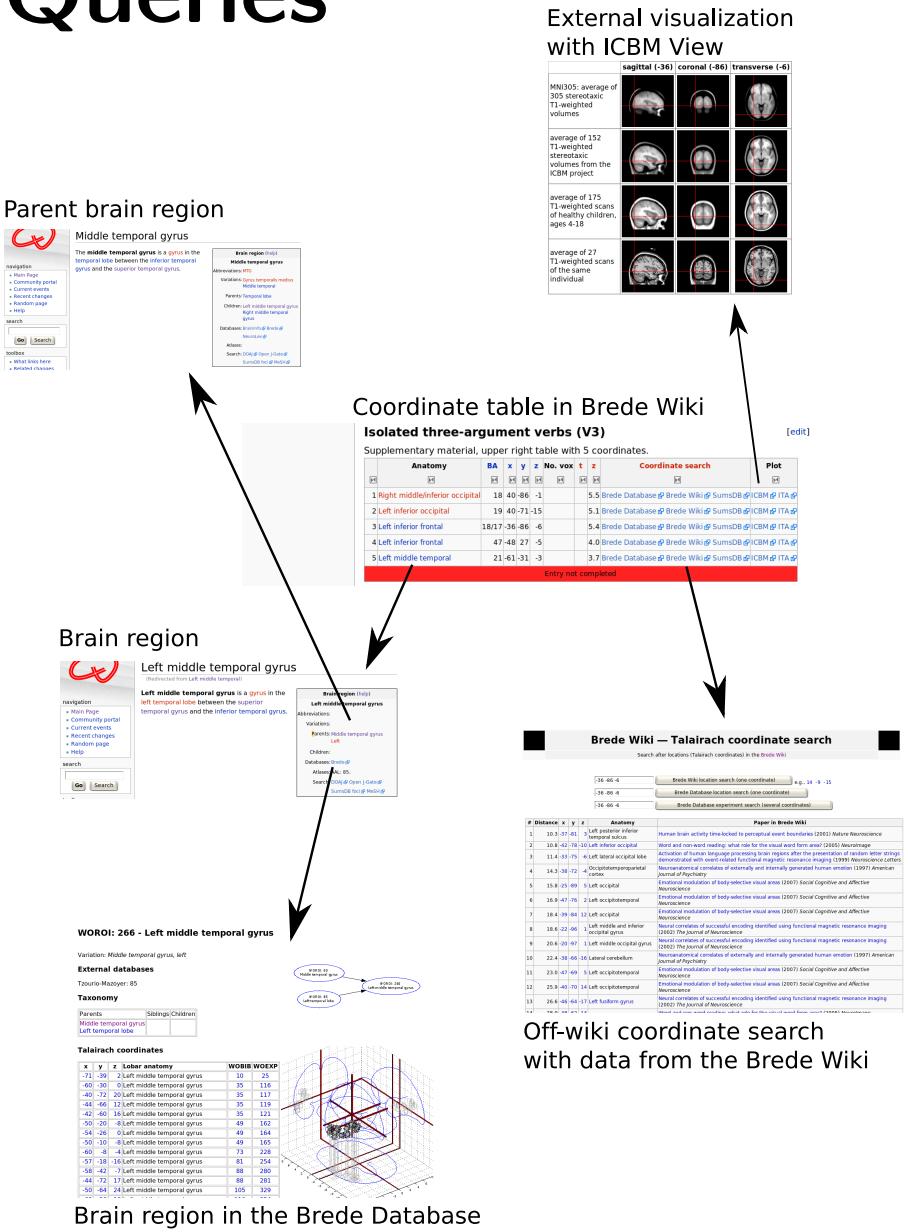
Laboratory: missing *laboratory*

Results

Volume: Contrast image



Queries



Structured content can be extracted (like DBpedia on Wikipedia)

Queries are possible, but not within the wiki

Query on nearby coordinates with an off-wiki script.

So-called "SKOS file" (Miles and Bechhofer, 2009) generated for brain region and topic hierarchies from the structured content.

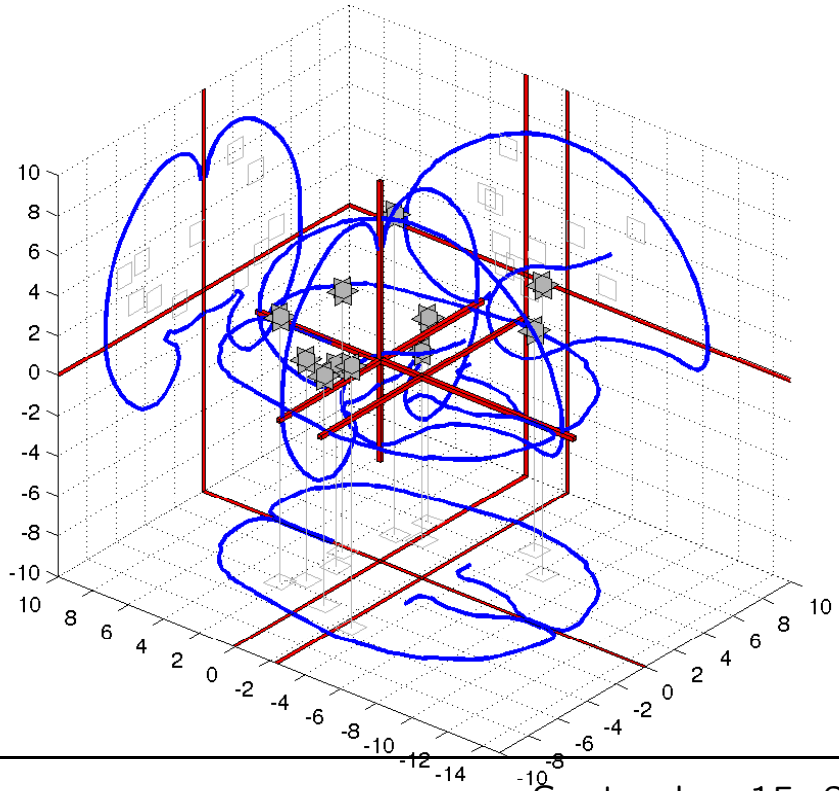
Brede Wiki and Toolbox integration

Paper in the Brede Wiki (Lin et al., 2008):

```
>> title = 'Brain maps of Iowa gambling task';
>> Ls = brede_web_bw2loc(title);
>> figure, brede_ta3_frame, brede_ta3_loc(Ls)
```

Get the page from the Web site and extract the information within the templates and convert to a structure that fits the Brede Toolbox and Database.

Finally, plot the locations.



Issues

Contribution is difficult: Presently "raw" data entry ☹

Online interactive meta-analysis is not immediately available ☹

Personality genetics

Table 1. TCI Scores grouped by genotype

Genotype (No./%)	TCI factor scores			
	Harm avoidance	Novelty seeking	Reward dependence	Persistence
"ss" (95/60.1)	17.14±7.11	20.36±6.15	15.40±3.48	4.81±2.13
"ls" (54/34.2)	16.59±7.71	20.28±6.13	15.72±4.31	4.69±2.36
"ll" (9/5.7)	18.78±4.02	20.67±7.58	15.22±1.99	5.22±2.05
F	0.71	0.93	0.23	0.55
p	0.62	0.46	0.95	0.74
"ss" (95/60.1)	17.14±7.11	20.36±6.15	15.40±3.48	4.81±2.13
"ls+ll" (63/39.9)	16.90±7.31	20.33±6.23	15.65±4.05	4.76±2.31
F	1.03	0.01	0.35	0.07
p	0.38	0.99	0.79	0.97

teered the study. They were from Hong-Ik University, located in Seoul, Korea. There were 69 males and 89 females, average age of 23.8±3.1 (mean±S.D.) yr. All subjects were Korean ancestry. All subjects participated in the study after giving informed consent. The study protocol was approved by the Institutional Review Board of Asan Medical Center. A K-TCI (16) was administered to the participants.

A 10 mL venous blood sample was obtained, and genomic DNA was isolated from peripheral blood leukocytes according to standard procedures. DNA fragments were amplified by polymerase chain reaction using 5′-GGCGTTGCCGCTCTGAATTGC (-1,416 ->-1,397) and 5′-GAGGGACTGAGCTGGACAACCCAC (-910 ->-889) primers (3). The PCR reaction mixture contained a total volume of 20 μL with the following composition: 12 ng genomic DNA, 4 pmoles of the each primers, 2.5 mM dNTPs, 5 mM of deaza dGTP, and 1 U Ampli *Taq* with the appropriate buffer. After an initial 5 min denaturation step at 95°C, 5 cycles were performed consisting of 40 sec at 95°C, 40 sec at 58°C, and 60 sec at 72°C, followed by an additional 35 cycles of 40 sec at 95°C, 40 sec at 61°C, and 60 sec at 72°C. The reaction was ended by incubation at 72°C for 7 min. PCR products were separated by the long (524 bp) and short (484 bp) variants on

Ninety-five subjects (60.1%) were "ss" genotype, and subjects with "sl" and "ll" were 54 (34.2%) and 9 (5.7%), respectively. Neither allele nor genotype frequencies differed according to sex. There were no significant differences in the scores of harm avoidance ($F=0.38$, $p=0.69$), novelty seeking ($F=0.07$, $p=0.93$), reward dependence ($F=0.16$, $p=0.86$) and persistence ($F=0.24$, $p=0.79$) using genotype and sex as independent variables (Table 1). When dividing the subjects into 2 groups of "ss" (60.1%) and "sl"+"ll" (39.9%), we could not find associations between the two genotype group and personality traits, either (Table 1).

While the 5-HTTLPR genotypes frequencies ($\chi^2=111.04$, $p<0.001$) and the allele frequencies ($\chi^2=110.21$, $p<0.001$) in our sample were significantly different from those of Lesch et al. (2), those frequencies are quite similar to other studies of Korean (20, 21), Japanese (6, 12, 13), and Chinese (22).

DISCUSSION

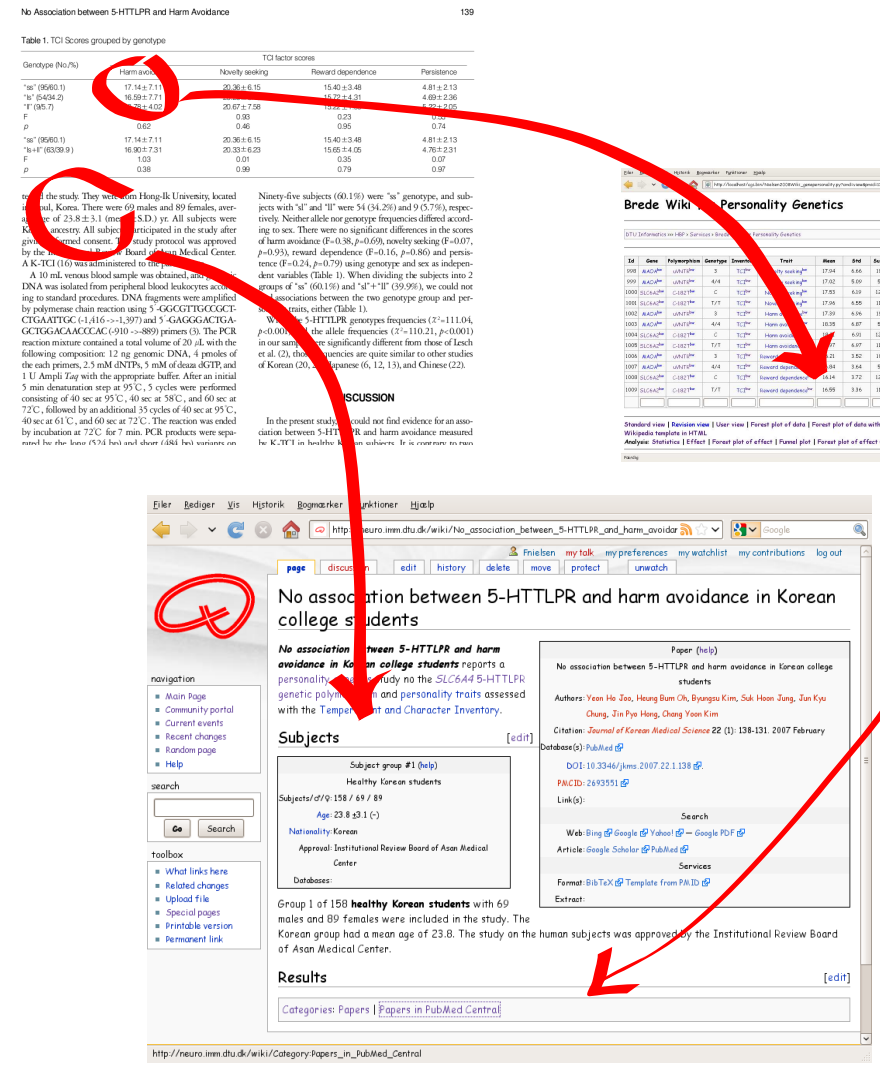
In the present study, we could not find evidence for an association between 5-HTTLPR and harm avoidance measured by K-TCI in healthy Korean subjects. It is contrary to two

Association between genetic variant and personality traits assessed with personality inventories such as NEO PI-R.

There are several hundreds of these kind of studies.

Typical candidate gene studies report all results (personality scores), — not just significant personality scores.

Brede Wiki for personality genetics



Data entry in the wiki in a table-like interface: Gene, polymophism, genotype, inventory, trait, personality scores, subject group, PMID.

"Normal" Brede Wiki keeps track of data entry.

Data can also be exported to the Brede Wiki.

So far typed in data from 87 studies with 2815 personality scores.

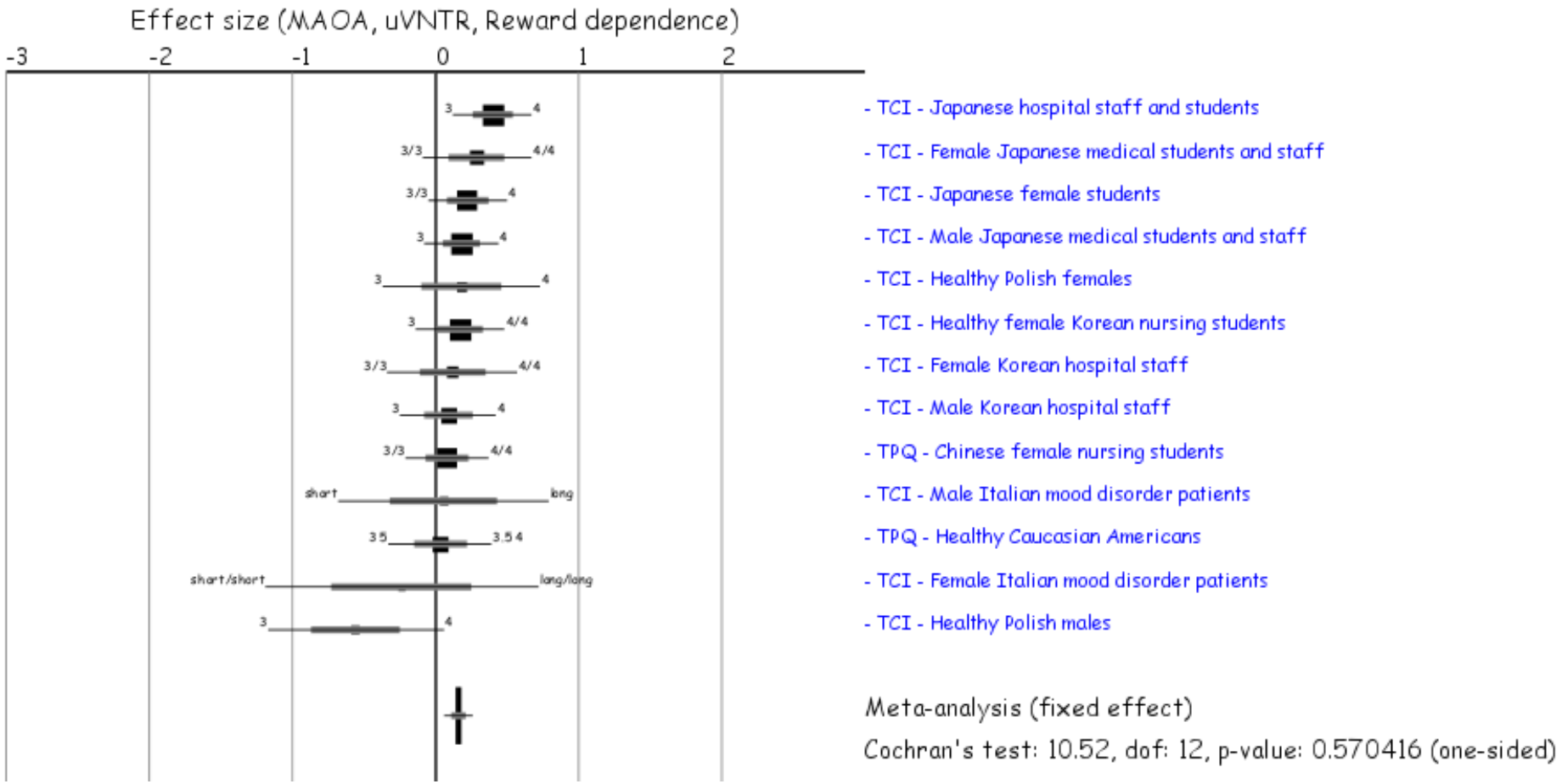
Meta-analysis across traits and polymorphisms

	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

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

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

MAOA uVNTR/reward dependence



Forest plot generated by the wiki for the "warrior gene" and Cloninger's reward dependence with meta-analysis and Cochrane's test.

Open Science

Open Science = Open Methods + Open Data

Open Methods: Available through Brede Toolbox

Open Data: Data downloadable as Brede Database XML. Aggregated into SumsDB and AMAT coordinate databases as well as the NIF neuroinformatics federated database.

The Brede Wiki available from

http://neuro.imm.dtu.dk/wiki/

Brede Database

http://neuro.imm.dtu.dk/services/bredeatabase

Brede Toolbox

http://neuro.imm.dtu.dk/software/brede

Thanks!

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