Databasing molecular neuroimaging studies

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Databasing molecular neuroimaging studies

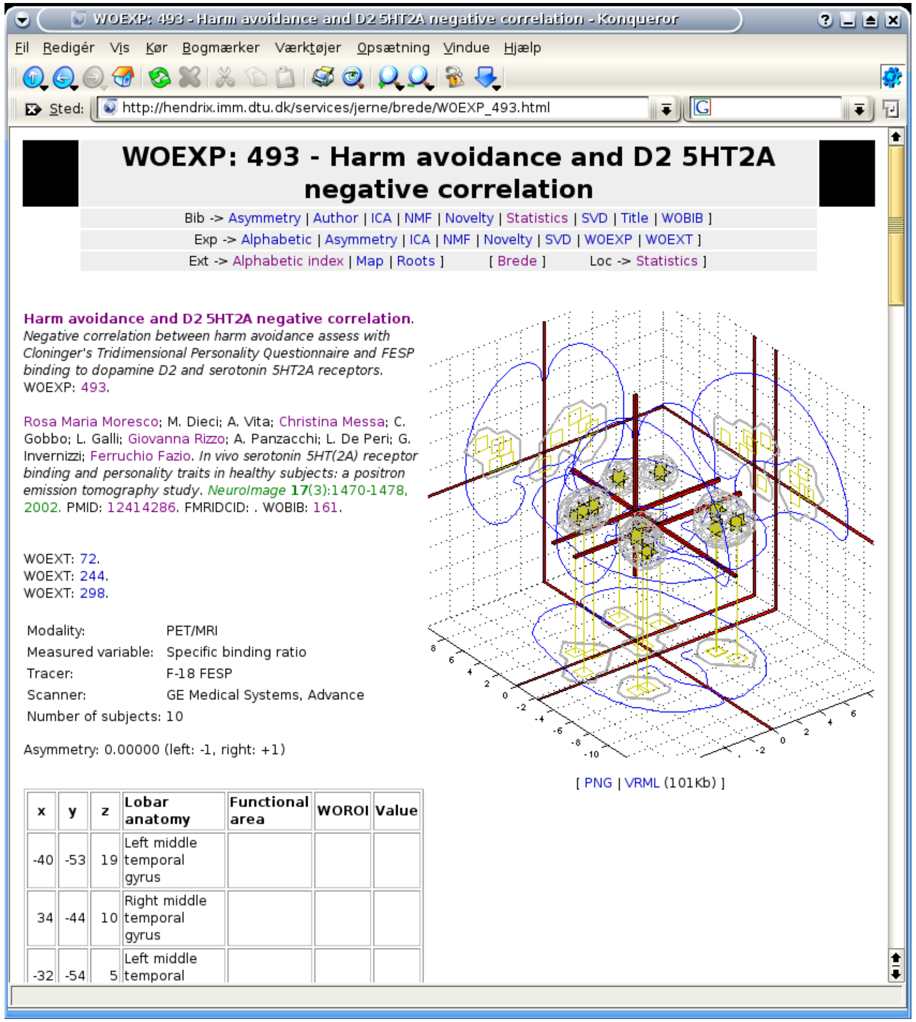
Issues in databasing information from the human molecular neuroimaging literature are:

1. Find a suitable representation for the data: How should the results from a typical molecular neuroimaging study be represented?

2. Construct information retrieval tools: Is it possible, e.g., to find "Related Articles" based on the quantitative neuroimaging results presented in papers?

3. Construct analysis tools: Is it possible to develop methods to extract information across studies?

Brede Database



Contains stereotaxic Talairach coordinates, cf. BrainMap (Fox and Lancaster, 1994).

Search on “Related Articles” based on stereotaxic coordinates possible (Nielsen and Hansen, 2004).

Multivariate analysis of abtract text and voxelized stereotaxic coordinates (Nielsen et al., 2004; Nielsen et al., 2005)

Available on the Internet in HTML and XML (Nielsen, 2003).

Handling molecular neuroimaging

Most molecular imaging studies relies on analysis of values from brain regions and report descriptive statistics for these values. There are not many voxel-based studies reporting in stereotaxic space, thus the standard Brede Database framework cannot be used.

There are two significant difficulties when comparing molecular neuroimaging studies:

1. Regions differ between studies: E.g., some include values for "temporal cortex" others do not. Solution: Build a taxonomy for brain regions and use imputation.

2. Measured and reported values differ between studies and they are not comparable: Tracers and receptors; transport rates (e.g., K_1), distribution volume, binding potentials; different methods to compute the values. Solution: Use some kind of normalization.

Entry of data

Information from molecular neuroimaging studies are entered in much the same way as for stereotaxic coordinate-based studies using the Brede Toolbox (Nielsen and Hansen, 2000).

Instead of stereotaxic coordinate the reported regional value is entered as well as an identifier for the associated item in a brain region taxonomy.

Extra information include bibliographic information and description of the experiment, such as tracer and scanner. Furthermore the experiment is linked to items in a taxonomy for so-called "external components", which, e.g., relate the individual neuroreceptors in a directed acyclic graph (Nielsen, 2005).

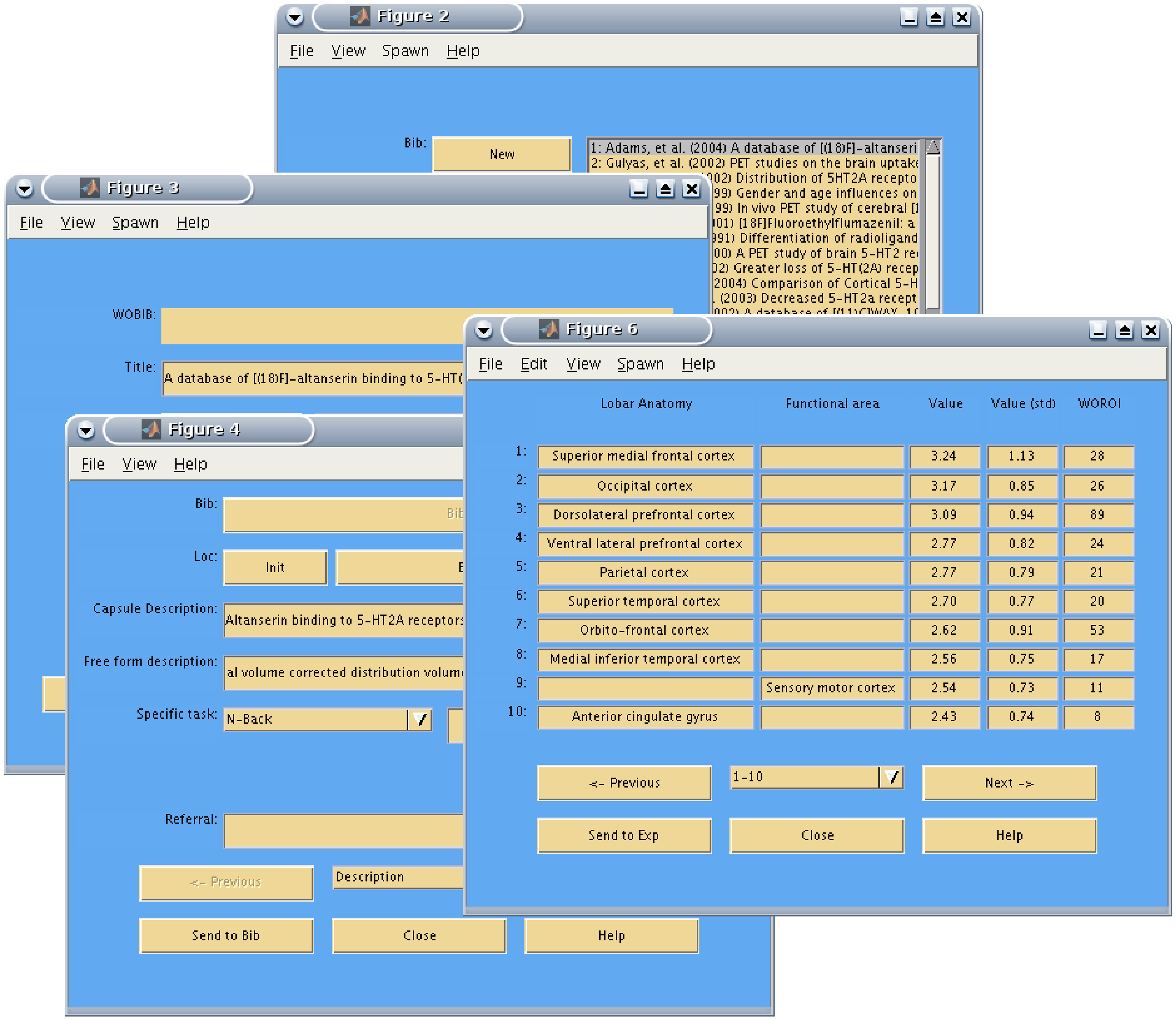


Figure 2
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1: Adams, et al. (2004) A database of [(18)F]-altanseri
2: Gulyas, et al. (2002) PET studies on the brain uptake
Figure 3
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Figure 6
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3: Dorsolateral prefrontal cortex 3.09 0.94 89
4: Ventral lateral prefrontal cortex 2.77 0.82 24
5: Parietal cortex 2.77 0.79 21
6: Superior temporal cortex 2.70 0.77 20
7: Orbito-frontal cortex 2.62 0.91 53
8: Medial inferior temporal cortex 2.56 0.75 17
9: Sensory motor cortex 2.54 0.73 11
10: Anterior cingulate gyrus 2.43 0.74 8
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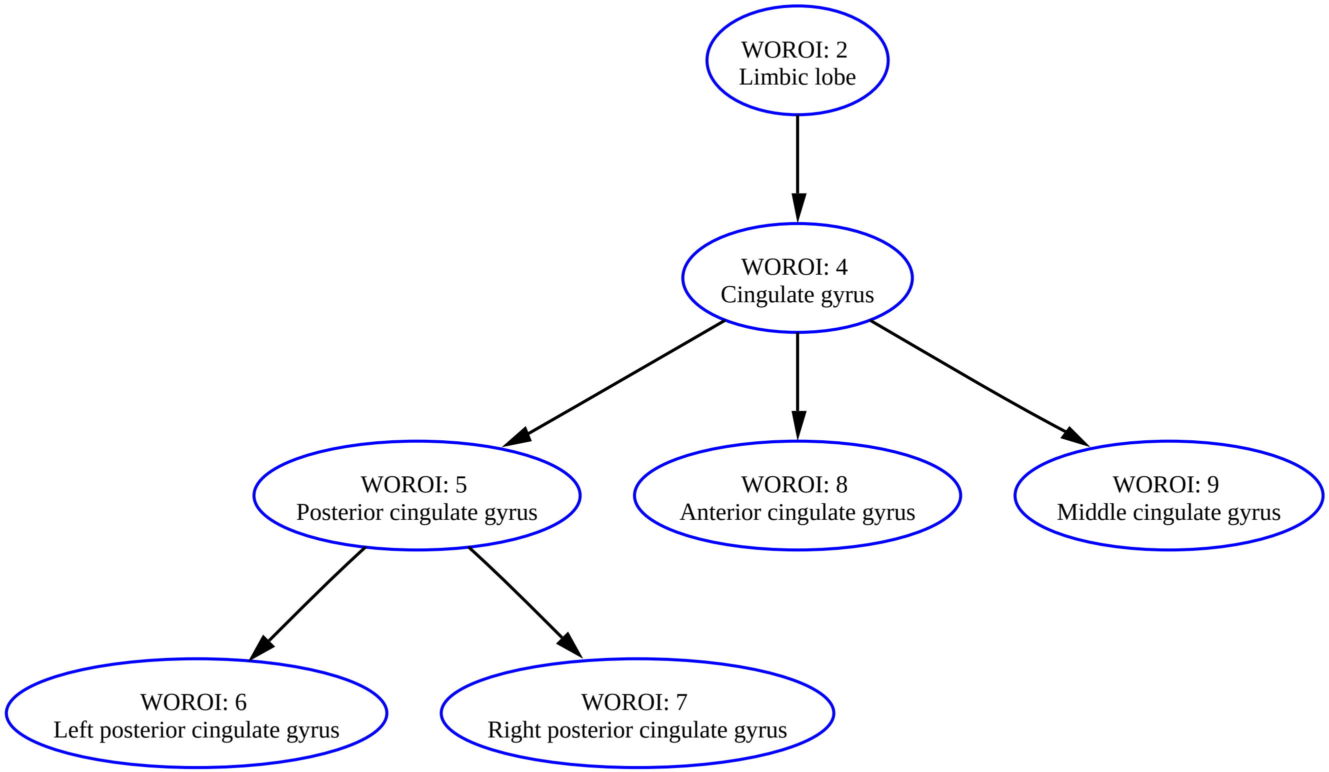
Brain region taxonomy



Hierarchical taxonomy of brain regions records which brain areas are a part of other brain areas.

Imputation: If "left posterior cingulate" and "right posterior cingulate" values are available in a specific study these are used to define a value for "limbic lobe" — if this is not available.

Brain region taxonomy in the Brede database

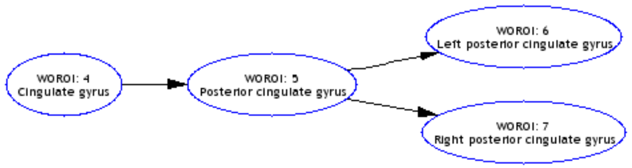
WOROI: 5 - Posterior cingulate gyrus

Bib -> Asymmetry | Author | ICA | NMF | Novelty | Statistics | SVD | Title | WOBIB]
Roi -> Alphabetic | Hammers | Tzourio-Mazoyer]
[Brede]

WOROI: 5 - Posterior cingulate gyrus

Abbreviation: **PCgG**

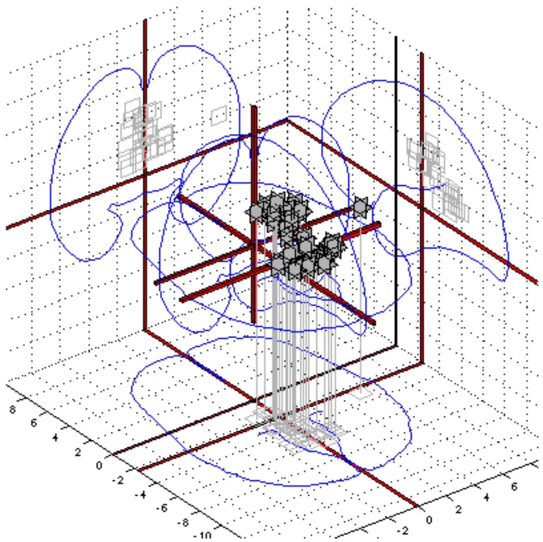
Variation: *posterior cingulate*
Variation: *posterior cingulate area*
Variation: *posterior gyrus cinguli*
BrainInfo: 144



Parents	Siblings	Children
Cingulate gyrus		Left posterior cingulate gyrus Right posterior cingulate gyrus

Talairach coordinates

x	y	z	Lobar anatomy	WOBIB	WOEXP
6	-29	38	Right posterior cingulate gyrus and precuneus	21	66
9	-53	14	Right posterior cingulate gyrus	32	109
4	-53	14	Right posterior cingulate gyrus	32	110
2	-40	40	Posterior cingulate gyrus	35	117
52	-30	20	Right postcentral gyrus/posterior cingulate gyrus	35	119
-4	-36	24	Left posterior cingulate gyrus	41	135
-4	-35	29	Left posterior cingulate gyrus	41	137
-4	-35	40	Left posterior cingulate gyrus	41	138
0	-26	29	Posterior cingulate gyrus	41	140
-2	-48	20	Left posterior cingulate gyrus	49	164
-9	-33	46	Posterior cingulate gyrus	57	183
0	-17	28	Right posterior cingulate gyrus	60	186
3	-53	15	Right posterior cingulate gyrus	71	223



Brain region taxonomy included in the Brede Database.

Talairach coordinates extracted where their anatomical label corresponds to the item in the taxonomy.

Links to NIH MeSH, BrainInfo (NeuroNames) (Bowden and Martin, 1995), segmented volumes, IBVD, Wikipedia.

Data matrix

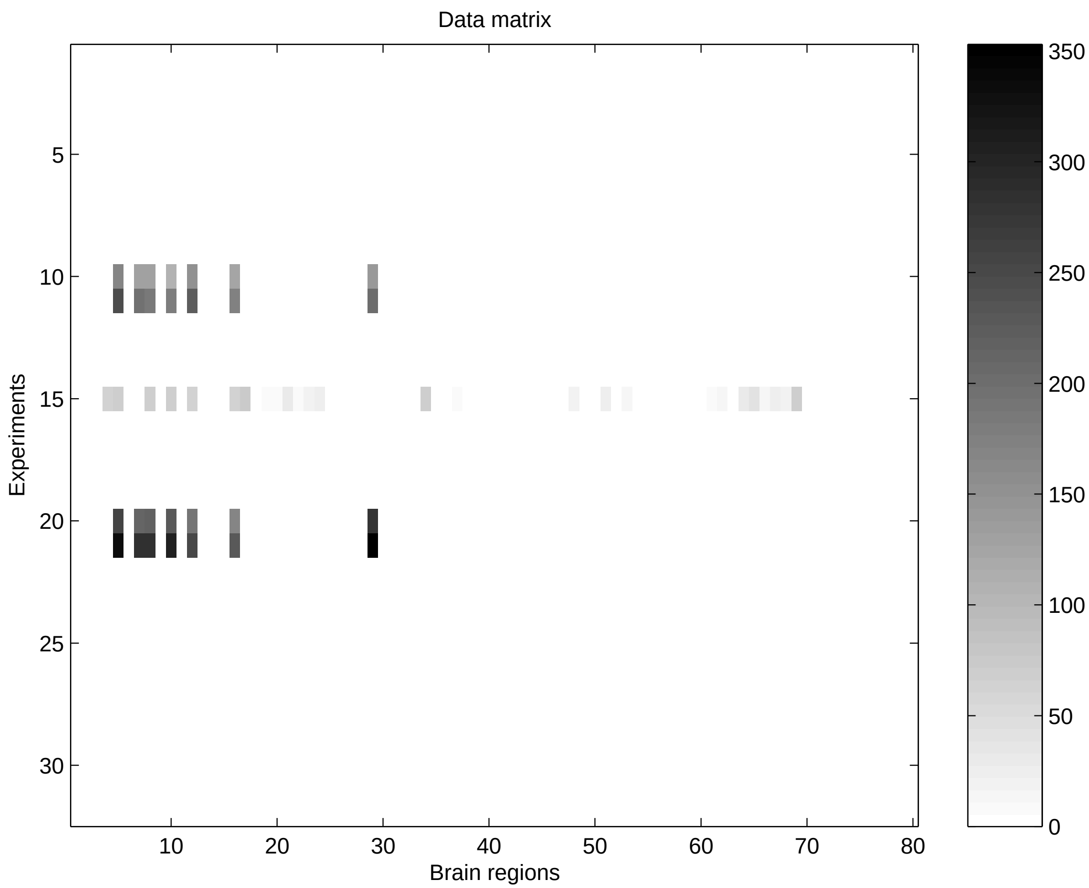


Figure 1: For serotonin-2A part of the datamatrix $\mathbf{X}(32\times80)$: Original matrix: $\approx$ 13% defined. "One-back" imputation: $\approx$ 17% defined. Full forward/backward imputation: $\approx$ 64% defined

When data from a number of experiments are entered a data matrix can be constructed:

$\mathbf{X}$(experiments $\times$ regions),

where each row corresponds to an "experiment" (e.g., computed values of binding across brain regions) and where each column represents a specific item in the brain region taxonomy.

Data matrix

Further processing works on the data matrix

- By normalizing the values in a row, i.e., within an experiment.
- By imputation of the missing value in the matrix setting an element based on the values of its taxonomic children, e.g., setting the value of "cingulate gyrus" to the value of "posterior cingulate gyrus" if that is defined.
- By excluding columns of the matrix (i.e. brain regions) so only key brain regions, such as the lobes, remain.

Normalization

Studentize values across $P_n = |\mathcal{P}_n|$ regions with the n'th experiment: $\tilde{x} = (x - \bar{x}_n)/s_n$ with missing values

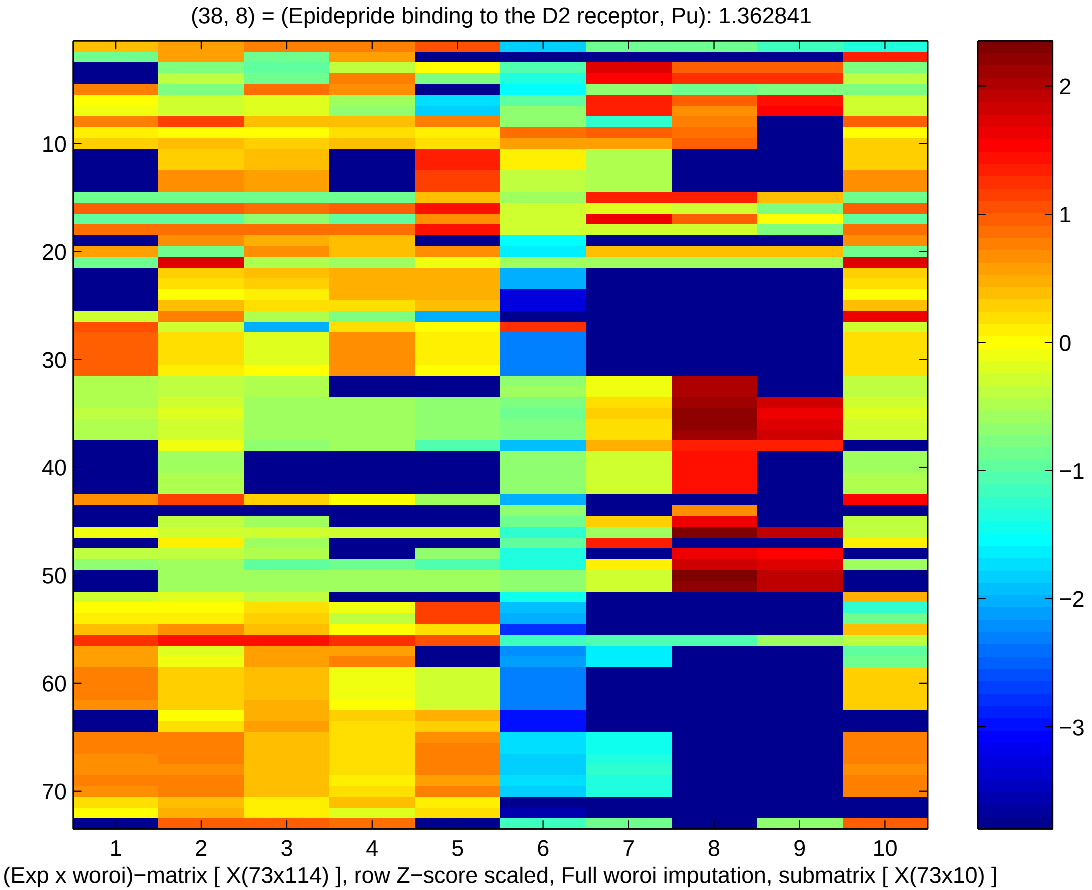
$$\bar{x}_n = \frac{1}{|\mathcal{P}_n|} \sum_{p \in \mathcal{P}_n} x_{np}, \qquad s_n = \sqrt{\frac{1}{|\mathcal{P}_n| - 1} \sum_{p \in \mathcal{P}_n} (x_{np} - \bar{x}_n)^2}. \tag{1}$$

Conversion of data matrix to a "rank order data matrix": $\mathbf{X}(N \times P) \rightarrow \tilde{\mathbf{X}}\left(N \times \frac{P!}{2(P-2)!}\right)$ (Jajuga et al., 2003)

$$\tilde{x}_{n\tilde{p}} = \begin{cases} 1 & \text{if } x_{np} > x_{np'} \\ -1 & \text{if } x_{np} < x_{np'} \\ 0 & \text{otherwise,} \end{cases} \tag{2}$$

where "otherwise" is with $x_{np} = x_{np'}$ or if any of the values for the two regions p or p' is not defined.

The transformed data matrix



Restriction to key regions: The 5 lobes, cerebellum, caudate, putamen, thalamus and hippocampus: $\mathbf{X}(73 \times 10)$

After full imputation and restriction to key regions: $\approx$ 74% defined values

Outlying brain regions (columns in the data matrix) are: Cerebellum (blue), Caudate and Putamen (red).

Measuring difference between experiments

Comparison of two experiments represented in vectors $\mathbf{x}_n$ and $\mathbf{x}_m$ with the cross-correlation for missing values (pairwise complete version)

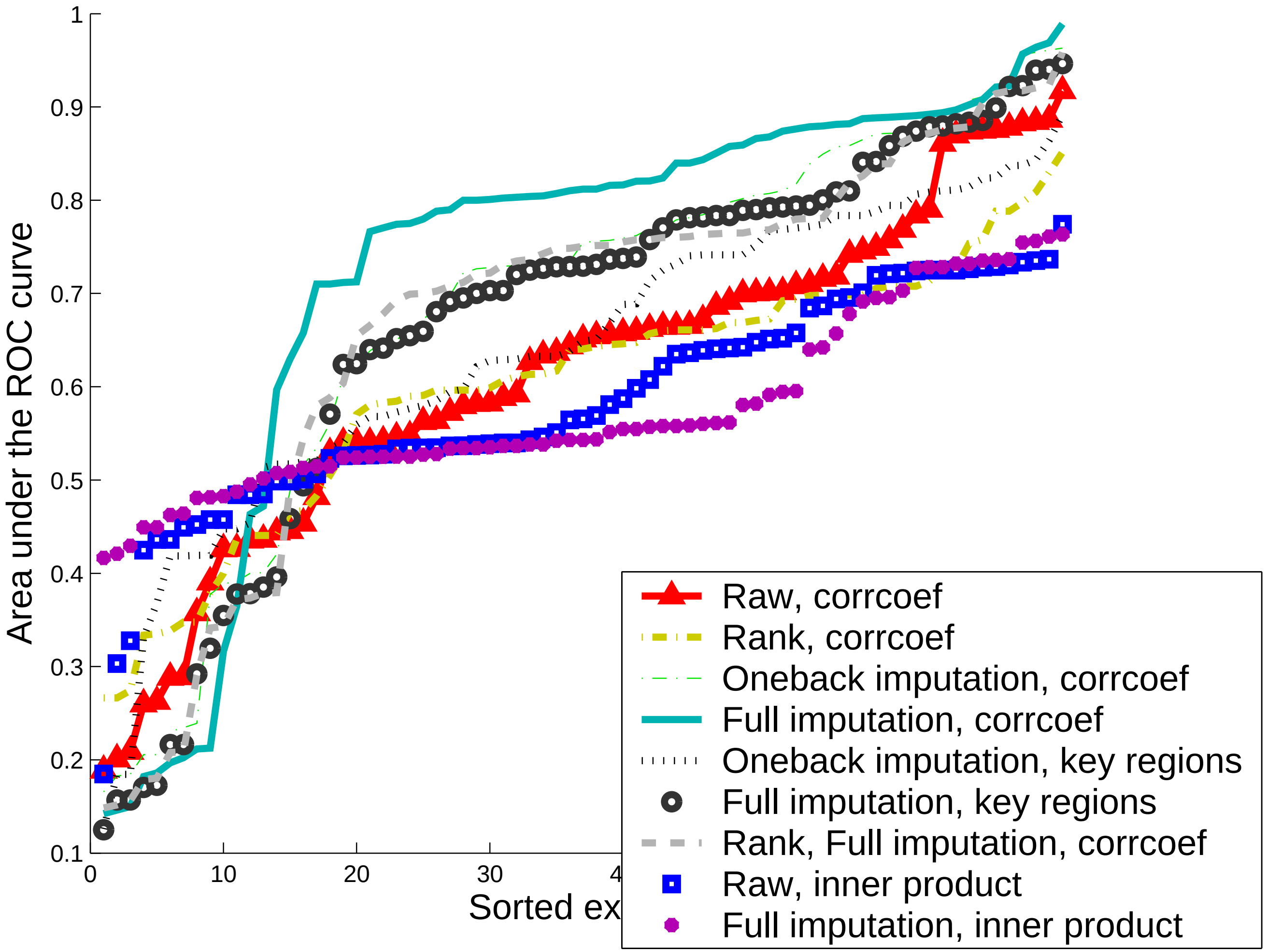
$$\tilde{r}_{nm} = \frac{\sum_{p \in \mathcal{P}_{nm}} \tilde{x}_{np} \tilde{x}_{mp}}{\sqrt{\sum_{p \in \mathcal{P}_{nm}} \tilde{x}_{np}^2} \sqrt{\sum_{p \in \mathcal{P}_{nm}} \tilde{x}_{mp}^2}}, \qquad (3)$$

where $\mathcal{P}_{nm} = \mathcal{P}_n \cap \mathcal{P}_m$ with centered data.

. . . Or just with an inner product

$$t_{nm} = \sum_{p \in \mathcal{P}_{nm}} x_{np} x_{mp} \qquad (4)$$

Information retrieval performance



Area under the ROC curve as performance measure

Task: Segregate between serotonin-2A and non-serotonin-2A studies.

Full imputation with cross-correlation coefficient is the best method.

Example on "Related Experiments"

Related - positive correlated volumes

+1: 29.90915 **Altanserin binding in normal women**. *Altanserin binding to the 5-HT2A receptor in normal women.*
W. H. Kaye; G. K. Frank; C. C. Meltzer; J. C. Price; C. W. McConaha; P. J. Crossan; K. L. Klump; L. Rhodes. *Altered serotonin 2A receptor activity in women who have recovered from bulimia nervosa.*. *Am J Psychiatry* **158**(7):1152-1155, 2001. PMID: 11431241. FMRIDCID: .

+2: 29.51611 **Altanserin binding in former bulimic women**. *Altanserin binding to the 5-HT2A receptor in women recovered from bulimia nervosa.*
W. H. Kaye; G. K. Frank; C. C. Meltzer; J. C. Price; C. W. McConaha; P. J. Crossan; K. L. Klump; L. Rhodes. *Altered serotonin 2A receptor activity in women who have recovered from bulimia nervosa.*. *Am J Psychiatry* **158**(7):1152-1155, 2001. PMID: 11431241. FMRIDCID: .

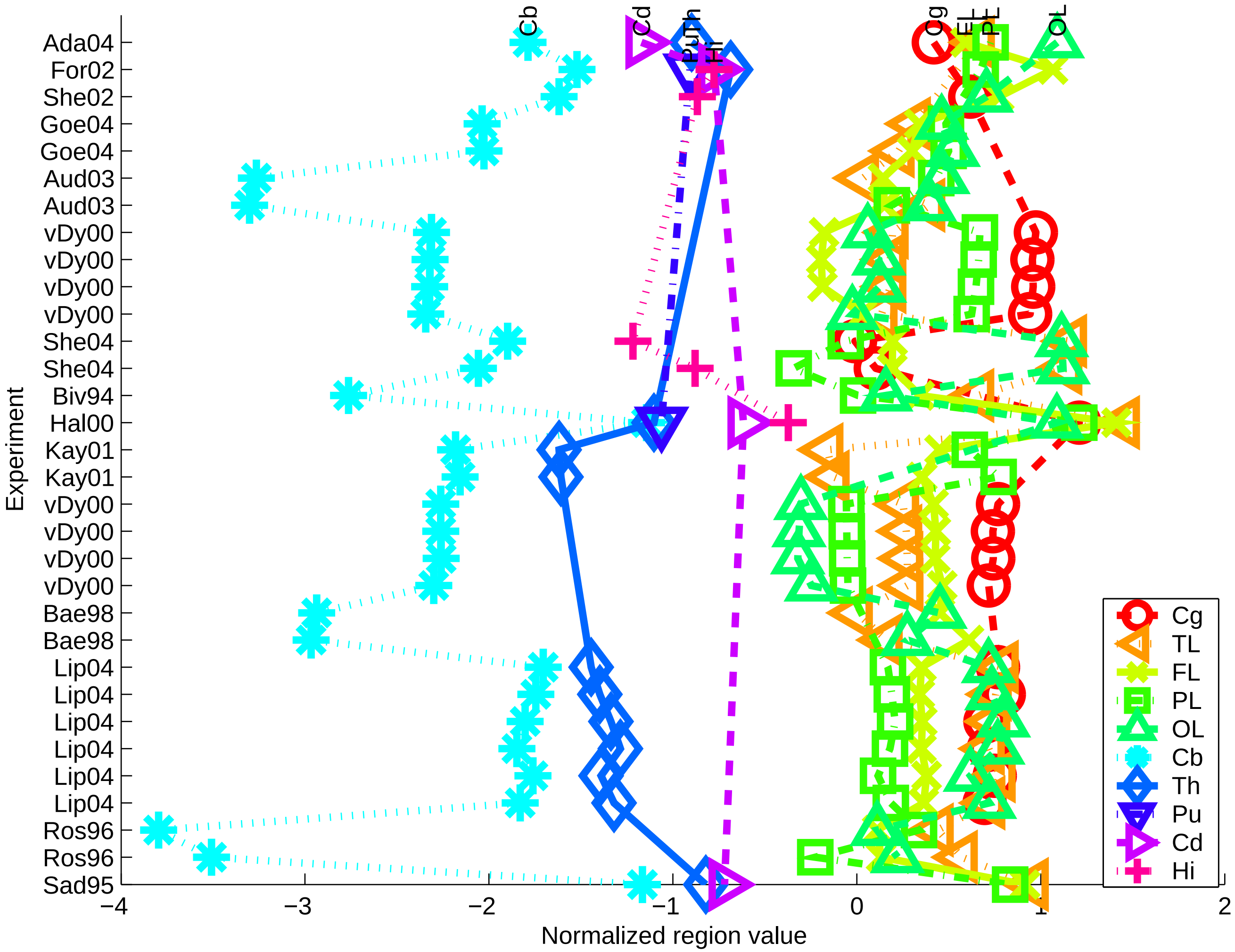
+3: 12.58705 **Altanserin binding in depressed patients**. *Altanserin binding to the serotonin-2A receptor in older major depression disorder patients.*
Yvette I. Sheline; Mark A. Mintun; Deanna M. Barch; Consuelo Wilkins; Abraham Z. Snyder; Stephen M. Moerlein. *Decreased hippocampal 5-HT(2A) receptor binding in older depressed patients using [18F]altanserin positron emission tomography.*. *Neuropsychopharmacology* **29**(12):2235-2241, 2004. PMID: 15367923. DOI: 10.1038/sj.npp.1300555. FMRIDCID: .

+4: 12.27997 **Altanserin binding in normals**. *Altanserin binding to the serotonin-2A receptor in normal elders.*
Yvette I. Sheline; Mark A. Mintun; Deanna M. Barch; Consuelo Wilkins; Abraham Z. Snyder; Stephen M. Moerlein. *Decreased hippocampal 5-HT(2A) receptor binding in older depressed patients using [18F]altanserin positron emission tomography.*. *Neuropsychopharmacology* **29**(12):2235-2241, 2004. PMID: 15367923. DOI: 10.1038/sj.npp.1300555. FMRIDCID: .

+5: 5.31778 **Altanserin binding to 5-HT2A receptors**. *Altanserin binding to 5-HT2A receptors as partial volume corrected distribution volume (DV'3) with cerebellum as reference region.*
Karen H. Adams; Lars H. Pinborg; Claus Svarer; Steen G. Hasselbalch; Soren Holm; Steven Haugbol; Karine Madsen; Vibe Frokjaer; Lars Martiny; Olaf B. Paulson; Gitte M. Knudsen. *A database of [(18)F]-altanserin binding to 5-HT(2A) receptors in normal volunteers: normative data and relationship to physiological and demographic variables.*. *Neuroimage* **21**(3):1105-13, 2004. PMID: 15006678. DOI: 10.1016/j.neuroimage.2003.10.046.

+6: 4.96921 **Altanserin specific binding to non-specific binding ratio**. *Ratio between specific binding and non-specific binding with cerebellum as the reference region for altanserin to the 5-HT2A receptor.*
Annemie Rosier; Patrick Dupont; Jozef Peuskens; Guy Bormans; Rik Vandenberghe; Michael Maes; Tjibbe de Groot; Christian Schiepers; Alfons Verbruggen; Luc Mortelmans. *Visualisation of loss of 5-HT2A receptors with age in healthy volunteers using [18F]altanserin and positron emission tomographic imaging*. *Psychiatry Research* **68**(1):11-22, 1996. PMID: 9027929. FMRIDCID: .

Comparisons on serotonin-2A studies



3 "clusters": Cerebellum (reference), Low binding (caudate, putamen, thalamus, hippocampus), high binding (cerebral cortex).

Little coherence among serotonin studies in the cerebral cortex, i.e., the ordering change between regions change.

Clustering

K-means clustering capable of handling missing values in the data matrix $\mathbf{X}$(experiments $\times$ regions) (Wishart, 2003).

Clustering experiments

$$\mathbf{X} = \mathbf{AC} + \mathbf{U}, \tag{5}$$

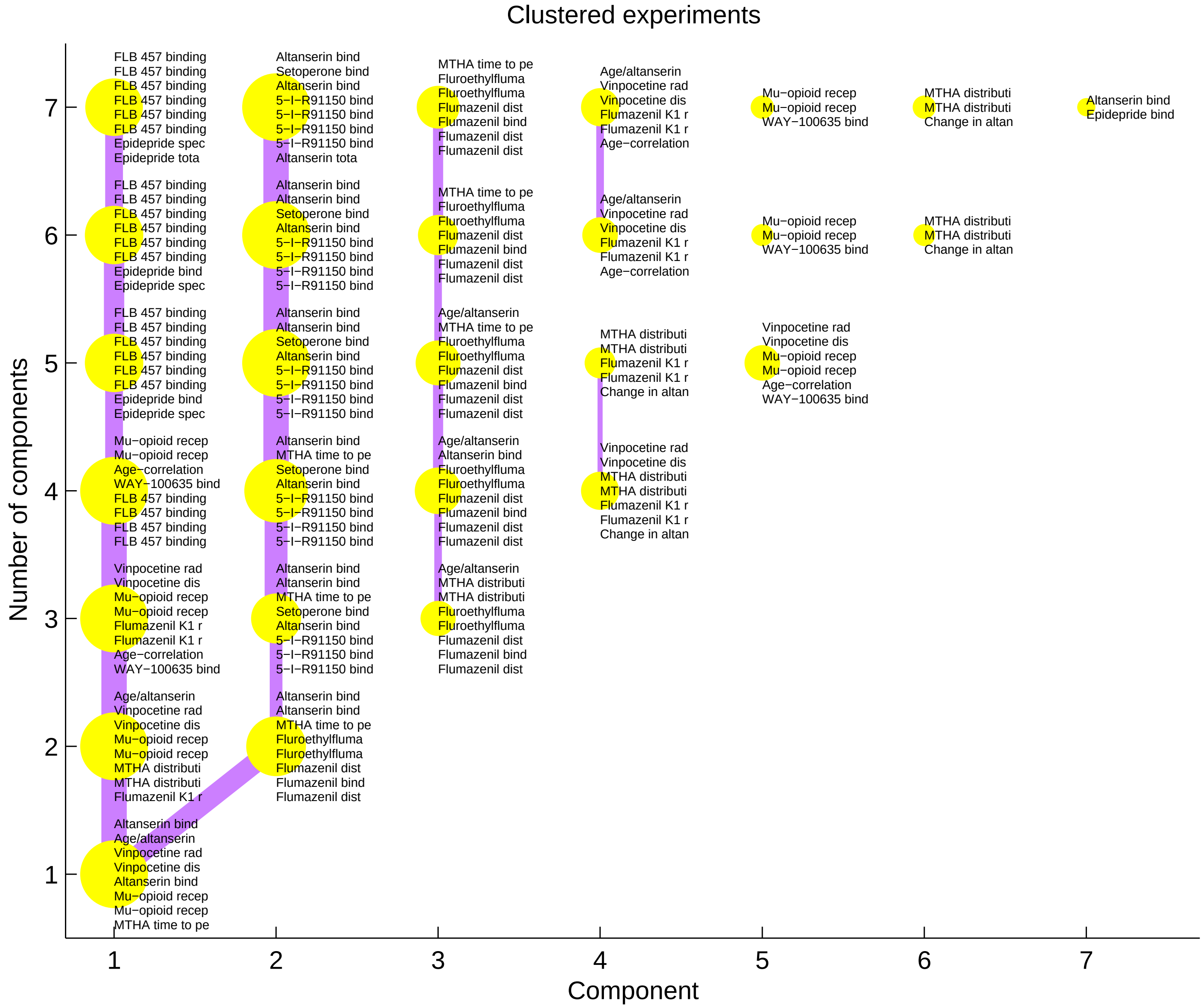
where $\mathbf{A}$ contains assignments for experiments, $\mathbf{C}$ the pattern across brain regions for prototypical tracers and $\mathbf{U}$ residuals.

. . . clustering brain regions

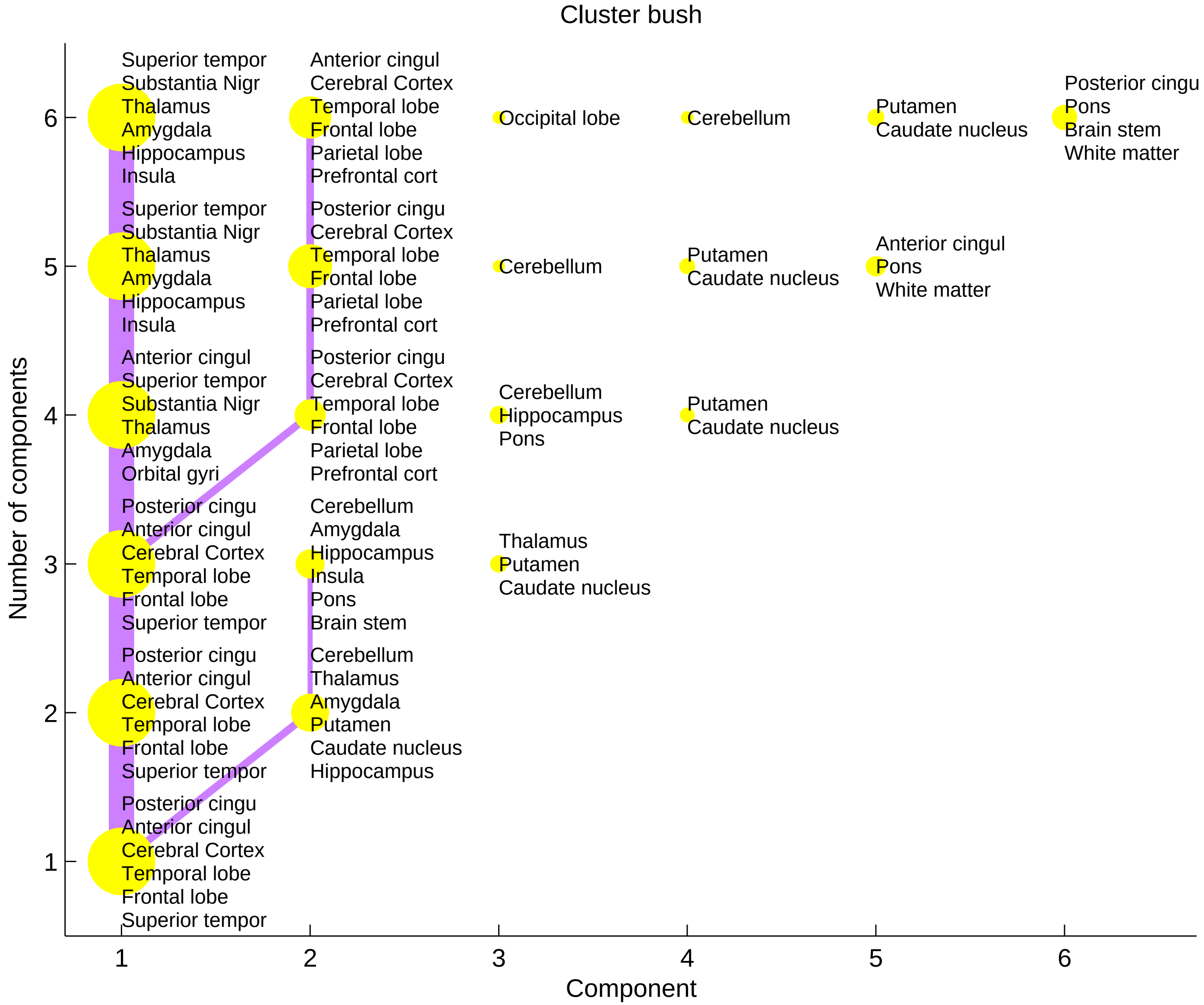
$$\mathbf{X} = \mathbf{CA} + \mathbf{U} \tag{6}$$

These kind of analyses have been made in humans and macaque with autoradiography, e.g., (Kötter et al., 2001).

Clustering of experiments



Clustering of brain regions



Summary

Framework established for databasing molecular neuroimaging studies.

Possible to make information retrieval methods that work on the quantitative region-based neuroimaging results.

Possible to make meta-analysis, e.g., by K-means clustering where experiments or brain regions are clustered.

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