Finding related functional neuroimaging volumes

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September 13, 2002

Running title: Finding related volumes
Keywords: Functional neuroimaging, information retrieval, content-based image retrieval, multivariate analysis.

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Abstract

We describe a content-based image retrieval technique for finding related functional neuroimaging experiments by voxelization of sets of stereotactic coordinates in Talairach space, comparing the volumes and reporting related volumes in a sorted list. Voxelization is accomplished by convolving each coordinate with a Gaussian kernel. The scheme allows us to compare experiments represented as either lists of coordinates or volumes, and we introduce alternative entrances to databases by image-based indices constructed via novelty measures and singular value decomposition.

1 Introduction

Identification of related research in functional neuroimaging can be carried out, e.g., by searching in bibliographic databases such as PubMed, browsing "table of contents" of scientific journals or searching BrainMap [Fox and Lancaster, 1994] with, e.g., behavioral or location criteria. Here we describe a content-based image retrieval method based on activation information in 3-dimensional (3D) Talairach space [Talairach and Tournoux, 1988]. The information might either come in the form of a list of points representing activation hot spots or it might come as a statistical parametric map, e.g., a volume of t-statistics from a statistical analysis of a functional neuroimaging data set. Our first goal is to establish a service comparable to "Related Articles" of PubMed.

Retrieval systems for digital text have existed for several decades and are often based on the vector space model [Salton, 1971], where a document is represented in a vector with each element associated with a word or phrase. Retrieval systems for other digital objects than text have also been proposed, e.g, on images and sounds [Feiten and Günzel, 1994]. Some image retrieval systems are based on text description of images, but others have included features, e.g., color, texture, shape and keywords. This allows for image query by example, i.e., "Show me images similar to this image" as in the IBM QBIC (Query by Image Content) system [Flickner et al., 1995, Faloutsos et al., 1994, Niblack et al., 1993]. A number of other systems exists, see [Eakin, 2000] for a list. Web-based image retrieval systems have also been suggested [Sclaroff, 1995] and implemented in, e.g., WebSEEk [Smith and Chang, 1996] and ImageRover [Sclaroff et al., 1997] as well as AltaVista (http://www.altavista.com).

Neuroimaging retrieval systems have also been constructed, e.g., [Liu and Dellaert, 1998] describe image retrieval for 3D medical images specifically CT brain scans containing normal, stroke and "blood cases". The basic "object" is a half 2D slice where features are extracted from, such as mean, standard deviation and asymmetry measures. Other medical image retrieval systems and methods have been described, e.g., [Petrakis and Faloutsos, 1997], [Chu et al., 1998], I^2net [Orphanoudakis et al., 1996], MIMS [Chbeir et al., 1999] and a system for decision support in clinical pathology [Comaniciu et al., 1999].

In research-oriented functional neuroimaging retrieval systems the BrainMap stands out: BrainMap is a database holding functional neuroimaging studies [Fox and Lancaster, 1994] both accessible through a web-interface and a stand-alone program [Lancaster et al., 1997]. It allows for search via "reference", "behavioral", "location" and "protocol" criteria. A location criterion can consist of a bounding box in Talairach space.

Finding related volumes was also considered in [Van Horn et al., 2001] in connection with the Functional Magnetic Resonance Data Center, though this database at the time of writing implements search via the bibliographic information only, and [Ford et al., 2001] describe briefly an "inter- and intra-study data mining" tool for functional magnetic resonance imaging (fMRI) activation maps based on "activation signatures" such as size, shape, number of foci, location and orientation.

A related method identifies global patterns and "cluster" experiments [Lloyd, 2000]: Multidimensional scaling was used to map 35 positron emission tomography (PET) studies to a 3D space based on their activations represented in an 87-dimensional space redundantly comprising Brodmann areas, gyri, sulci and lobes.

Earlier, brief descriptions of our work are available in [Nielsen, 2001, Nielsen and Hansen, 2002a].

2 Method

We downloaded the BrainMap database through its web-site and extracted fields that were relevant for our purpose. Since its activation data is in an "experiment" structure containing a variable length list of activation foci ("locations") we convert the 3D locations to a voxel-volume representation by a *voxelization* step where each location $\mathbf{z}_j$ in an "experiment" is convolved with a Gaussian kernel in the same manner as a Parzen window/Specht kernel estimation [Nielsen and Hansen, 2002b, Turkeltaub et al., 2002]. Some of the locations carry a sign and in the present application we maintain this sign and negate the kernel for the negative locations. For those voxels where the sign is not explicit we assume that it is positive. We normalize with the number of locations in each experiment, thus if there are no negative locations the voxelized

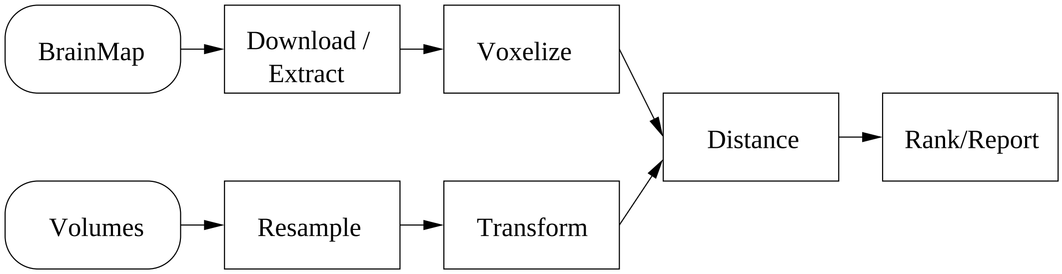


Figure 1: Pipeline for finding related volumes for data from the BrainMap database.

volume is a probability density volume. The full voxelization equation determining the value v at the voxel $\mathbf{z}$ is from J locations

$$v(\mathbf{z}) = \frac{1}{J}\left(2\pi\sigma^2\right)^{-3/2}\sum_{j}^{J}\operatorname{sgn}(z_j)\exp\left(-\frac{1}{2\sigma^2}(\mathbf{z}-\mathbf{z}_j)^{\mathsf{T}}(\mathbf{z}-\mathbf{z}_j)\right). \tag{1}$$

We fix the kernel width at $\sigma = 10$ mm corresponding to approximately 24 mm full width half maximum. This width should incorporate both the uncertainty of the location as well as the spatial extent of the original activation [Brett et al., 2002]. Due to memory constraints we use a coarse sampling with $8 \times 8 \times 8$ mm^3 voxel-sizes. Voxelization can be regarded as the inverse operation of finding a local maxima or the identification of the center of gravity/mass of a connected region in a thresholded volume.

Once all N volumes are constructed we vectorize each volume into a P-length vector $\mathbf{x}_n = [v(\mathbf{z}_1^n), \ldots, v(\mathbf{z}_P^n)]$ and collect all vectors in a matrix $\mathbf{X}(N \times P) = [\mathbf{x}_1, \ldots, \mathbf{x}_N]^{\mathsf{T}}$. A similarity matrix $\mathbf{S}$ is computed as a normalized inner product between the N vectors

$$\mathbf{S} = \mathbf{D}^{-1}\mathbf{X}\mathbf{X}^{\mathsf{T}}\mathbf{D}^{-1}, \qquad \text{where } \mathbf{D} = \operatorname{diag}\left(\left[\sqrt{\mathbf{x}_1^{\mathsf{T}}\mathbf{x}_1}, \ldots, \sqrt{\mathbf{x}_N^{\mathsf{T}}\mathbf{x}_N}\right]\right). \tag{2}$$

This measure is related to the reproducibility index in the NPAIRS framework [Strother et al., 2002]. The similarities are sorted and for each volume the most similar and most dissimilar volumes are reported in two lists. Static HTML web-pages are generated containing both lists as well as summaries of the experiment, a simple Corner Cube visualization [Rehm et al., 1998] and links to BrainMap and Pubmed. We further included six volumes from a motor learning positron emission tomography (PET) study [Balslev et al., 2002]. These volumes represent the cluster centers of a K-means clustering [MacQueen, 1967, Goutte et al., 1999]. They were resampled and converted from MNI to Talairach space with Brett's transformation [Brett, 1999]. The complete pipeline for both the volume data and the BrainMap data is displayed in figure 1.

Apart from indices based on the bibliographic information associated with an experiment we can produce image-based indices. A simple *ad hoc* novelty/outlier measure I is generated by finding the mean volume $\bar{\mathbf{x}}$ as the average across all volumes and comparing this through the inner product with all the volumes. The novelty for the n'th experiment is returned as the absolute value of the inverse normalized inner product

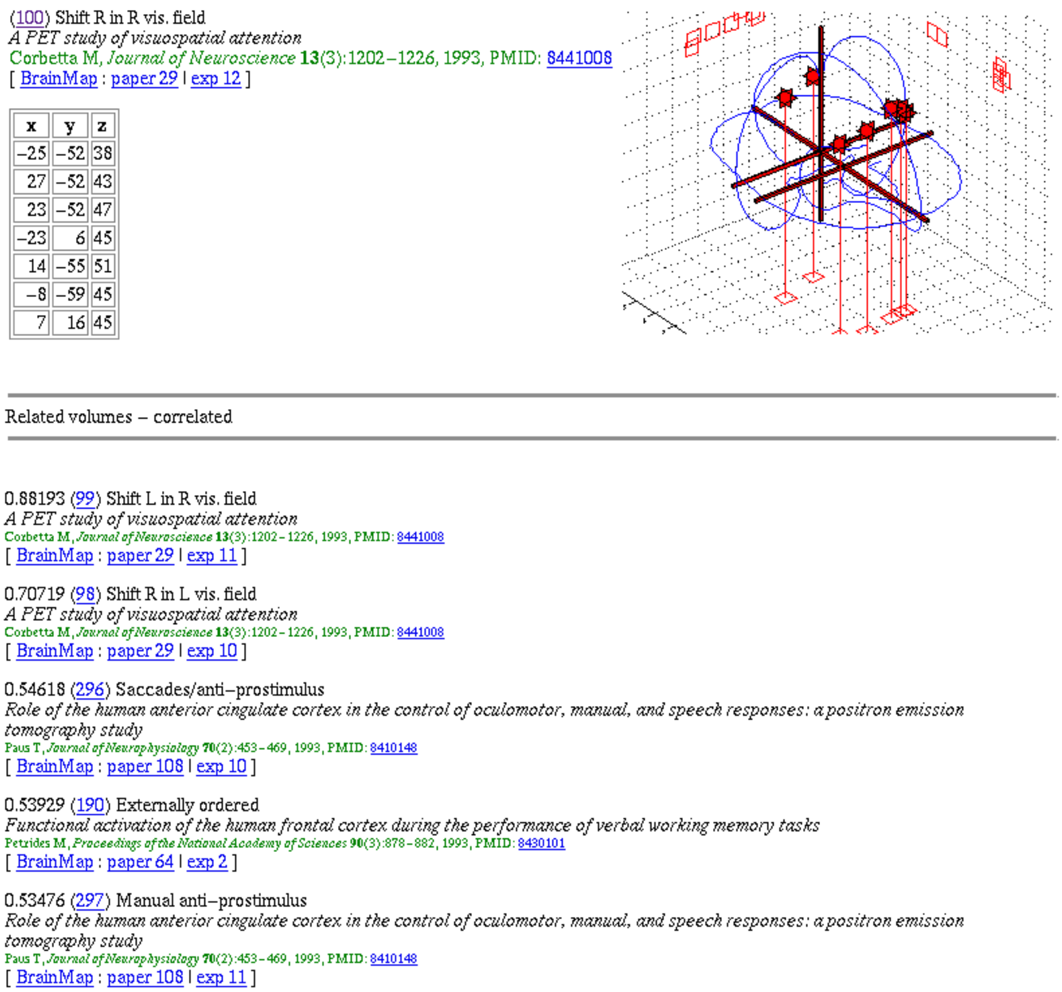
$$I_{\text{novel},n} = \operatorname{abs}\left(\frac{\bar{\mathbf{x}}^{\mathsf{T}}\bar{\mathbf{x}}}{\mathbf{x}_n^{\mathsf{T}}\bar{\mathbf{x}}}\right). \tag{3}$$

See [Nielsen and Hansen, 2002b] for more advanced outlier detection in neuroinformatics.

An other image-based index is generated through singular value decomposition (SVD) of the experiment $\times$ voxel matrix $\mathbf{X}$, — related to principal component analysis (PCA) as used for PET and fMRI [Friston et al., 1993, Hansen et al., 1999]

$$\mathbf{U}\mathbf{S}\mathbf{V}^{\mathsf{T}} = \mathsf{svd}(\mathbf{X}). \tag{4}$$

For this operation we only include entries from the BrainMap database that have "Peer Reviewed" as publication type, excluding reviews and unpublished studies that would otherwise contribute



(100) Shift R in R vis. field
A PET study of visuospatial attention
Corbetta M, *Journal of Neuroscience* **13**(3):1202–1226, 1993, PMID: 8441008
[BrainMap : paper 29 | exp 12]

x	y	z
−25	−52	38
27	−52	43
23	−52	47
−23	6	45
14	−55	51
−8	−59	45
7	16	45

Related volumes – correlated

0.88193 (99) Shift L in R vis. field
A PET study of visuospatial attention
Corbetta M, *Journal of Neuroscience* **13**(3):1202–1226, 1993, PMID: 8441008
[BrainMap : paper 29 | exp 11]

0.70719 (98) Shift R in L vis. field
A PET study of visuospatial attention
Corbetta M, *Journal of Neuroscience* **13**(3):1202–1226, 1993, PMID: 8441008
[BrainMap : paper 29 | exp 10]

0.54618 (296) Saccades/anti–prostimulus
Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: a positron emission tomography study
Paus T, *Journal of Neurophysiology* **70**(2):453–469, 1993, PMID: 8410148
[BrainMap : paper 108 | exp 10]

0.53929 (190) Externally ordered
Functional activation of the human frontal cortex during the performance of verbal working memory tasks
Petrides M, *Proceedings of the National Academy of Sciences* **90**(3):878–882, 1993, PMID: 8430101
[BrainMap : paper 64 | exp 2]

0.53476 (297) Manual anti–prostimulus
Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: a positron emission tomography study
Paus T, *Journal of Neurophysiology* **70**(2):453–469, 1993, PMID: 8410148
[BrainMap : paper 108 | exp 11]

Figure 2: Example view of the related volumes for an experiment reported in [Corbetta et al., 1993] and available in the BrainMap database.

with a considerable part of the variance in $\mathbf{X}$. We compare the 20 first eigenimages in $\mathbf{V}$ with each individual volume in $\mathbf{X}$ by a simple inner product and construct two lists for each eigenimage: One with the volumes that are most similar with the eigenimage and a second with volumes that are most dissimilar (or similar to the eigenimage with all signs reversed). Both lists are equally important since the sign on an eigenimage $\mathbf{v}_k$ can be reversed if the sign of $\mathbf{u}_k$ is also changed. We expect that the eigenimages will correspond to global patterns within the entire set of studies.

As a small test we compared two extra studies [Hyder et al., 1997, Phelps et al., 1997] to the data set from the BrainMap database. These two studies are fMRI reproductions of PET studies investigating a "willed action" component with a sensorimotor and a verbal task [Frith et al., 1991]. We should expect the corresponding volumes to appear high in the list of related volumes. [Hyder et al., 1997, Phelps et al., 1997] have restricted field of view only covering the frontal part of the brain.

The tools for this analysis are implemented in the Brede toolbox [Nielsen and Hansen, 2000] available from http://hendrix.imm.dtu.dk/software/brede/ and the resulting web-pages with volumes are presently available from http://hendrix.imm.dtu.dk/services/jerne/.

3 Results

797 HTML pages were generated and the voxelized volumes consisted of 7752 voxels. An example of one of the generated web-pages is displayed in figure 2 based on one of the 12 experiments/volumes reported in [Corbetta et al., 1993]. It shows two clusters of activations: one in the parietal lobe

Novelty	Entry
14278.361	265 Allison T, McCarthy G,Nobre A,Puce A,Belger A. *Human extrastriate visual cortex and the perception of faces, words, numbers, and colors* . Cerebral Cortex **5**:544–554, 1994.
2795.242	469 McGinnis S, –. *ROI Template II*.
1775.454	470 McGinnis S, –. *ROI Template II*.
1649.295	681 McGinnis S, –. *Anxiety Metanalysis*. , 1998.
1518.474	19 Reiman E M, Fusselman M J,Fox P T,Raichle M E. *Neuroanatomical correlates of anticipatory anxiety*. Science **243**(4894 Pt 1):1071–1074, 1989. PMID: 2784226.
1345.256	797 Daniela Balslev; Finn Årup Nielsen; Sally A. Frutiger; John J. Sidtis; Torben B. Christiansen; Claus Svarer; Stephen C. Strother; David A. Rottenberg; Lars K. Hansen; Olaf B. Paulson; I. Law. *Cluster analysis of activity–time series in motor learning*. Human Brain Mapping **15**(3), 2002. PMID: 11835604.
1206.135	555 Kawashima R, O'Sullivan B T,Roland P E. *Positron–emission tomography studies of cross–modality inhibition in selective attentional tasks: closing the "mind's eye"*. Proceedings of the National Academy of Sciences **92**:5969–5972, 1995.
1192.062	456 McGinnis S, –. *ROI template I*.
1022.440	279 Davis W, –. *Testing*. Unpublished, 1995.

Figure 3: Novelty index showing a list of the most novel experiments.

and an other in the frontal lobe. This pattern is repeated for the five most related experiments.

The top of the novelty index is shown in figure 3: The highest novelty is recorded in one of the three experiments of [Allison et al., 1994]. The paper is the only one recorded with the "electrophysiological" modality (through implanted electrodes and combined with MRI). Only x and y Talairach coordinates are shown in the article, and the z-coordinate in the database have been estimated during entry. Its high novelty might be due to this estimation and the rare modality. The second largest novelty for a "Peer Reviewed" experiment appears for the 5th entry in the table: [Reiman et al., 1989] finds activation in the temporal pole in connection with anticipatory anxiety. A correction to this article later appeared where it was found that the activation might not be a brain activation but an extracranial muscle "activation" from teeth-clenching [Drevets et al., 1992]. The third highest novelty for a peer reviewed experiment is our cluster volume described in [Balslev et al., 2002] and it is confined to the rim of the brain, and which we attributed to a possible motion artifact.

Since the mean of the images is not extracted our first eigenimage from the SVD separates experiments with positive and negative activations. The top of the positive end contains among others two experiments by [Parsons et al., 1995] each which contain 59 locations distributed across large parts of the brain. At the other end is an experiment [Silbersweig et al., 1993] with 12 negative activations. The subsequent eigenimages show high loadings on specific regions, e.g., the positive part of the second eigenimage covers the central sulcus and nearby areas with a large weight on the left hemisphere, see figure 4. This implies that motion studies score high. The other end of the eigenimage shows a loading in the occipital lobe with the top experiments all involving visual stimulation, e.g., a passive movement observation versus imaging grasping objects contrast from [Decety et al., 1994] scores highest. The next principal component distinguishes between cognitive and sensorimotor experiments. Higher components relates, e.g., to auditory presentation of words or (visuo-)spatial processing. Yet higher eigenimages show increasing spatial frequency and are harder to interpret.

When the sensorimotor experiments of [Hyder et al., 1997] and [Frith et al., 1991] are compared then [Hyder et al., 1997] is found as the 4th most related of published studies in the list of [Frith et al., 1991], and [Frith et al., 1991] as the 9th most related to [Hyder et al., 1997] (The list order is not necessarily symmetric). A total of 11 experiments from 9 different papers appear in the interval between the two [Buckner et al., 1995, Petrides et al., 1993b, Jahanshahi et al., 1995, Deiber et al., 1991, Petrides et al., 1993a, George et al., 1993, Ceballos-Baumann et al., 1995, Grasby et al., 1993, Kapur et al., 1994] where the two latter are PET studies with apomorphine which both "activate" the anterior cingulate cortex.

The verbal experiments [Phelps et al., 1997, Frith et al., 1991] show little similarity, and neither are listed among the top 25 most related volumes of the other.

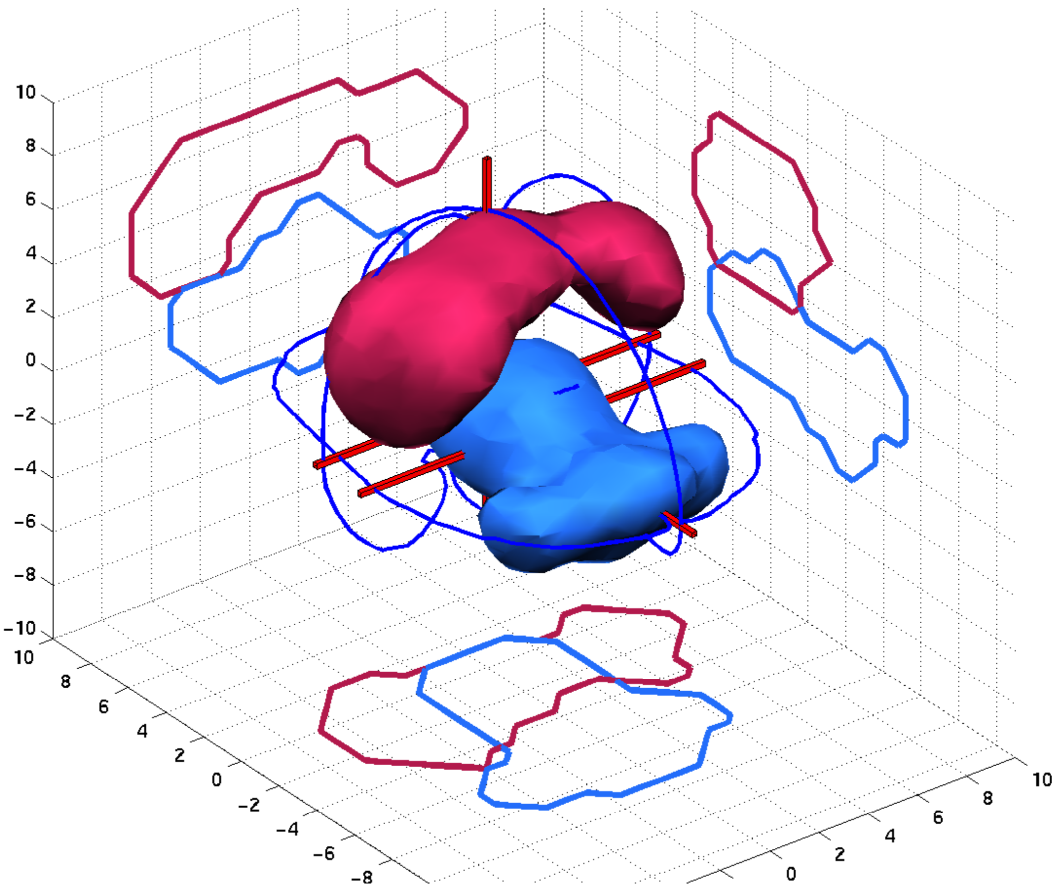


Figure 4: The isosurfaces from the positive and the negative end of the second eigenimage.

4 Discussion

The experiments of [Frith et al., 1991, Hyder et al., 1997] show relatively good agreement. Many of the related volumes for the two experiments resemble the task: self-initiated/"willed action" motor response where the subjects have to choose direction, time of response or which finger to move [Jahanshahi et al., 1995, Deiber et al., 1991, Ceballos-Baumann et al., 1995, Petrides et al., 1993b]. However, the discrimination between other tasks is not complete since other related experiments have remotely related tasks: Recall word from stem [Buckner et al., 1995], emotional recognition [George et al., 1993] and the apomorphine studies [Grasby et al., 1993, Kapur et al., 1994].

[Phelps et al., 1997] write "there is excellent agreement between the present fMRI study and the PET study" in comparing their study with [Frith et al., 1991]. This statement is based on the small distance (6.2 mm) between two corresponding locations in each study. Our method, that is globally oriented, finds little relatedness between the two partly due to field of view (FOV): Brain scanners have restricted FOV and some of them do not scan the entire brain. Furthermore, some researchers may choose to focus attention to a few slices, e.g., in fMRI for gaining faster acquisition time. Potentially (and probably), there is activation outside the FOV. In the present method we assume these potential activations to be zero, while a more elaborate scheme would treat them as unknown. This would require a more precise specification of the stereotactic location of the FOV than is found in the typical article. The comparison between [Frith et al., 1991, Hyder et al., 1997, Phelps et al., 1997] is influenced by the fact the fMRI studies had restricted FOV compared to the PET study. However, the method is not insensitive to detect similar patterns across experiments with different FOV, e.g., the experiment by [Phelps et al., 1997] and the "generate use from auditory presented nouns" experiment by [Petersen et al., 1988] show high similarity even though 2 out of 5 locations in the experiment by [Petersen et al., 1988] appear outside the FOV of [Phelps et al., 1997].

Space	Dimension	Description
Voxel	≈10000	The distance between voxel values in a (voxelized) volume
Experiment	≈1000	The distance computed in a subspace
Location	3	The distance in 3D Talairach space between points

Table 1: Spaces for calculation of distance/similarity.

The BrainMap database records not only original "Peer Reviewed" research articles but also meta-analyses and unpublished studies, where some carry little information and are irrelevant, see, e.g., the 2–4 and 8–9 entries in the novelty list in figure 3. In the present application we let it up to the user to ignore these studies. A more flexible interactive search would allow the user to determine which data to include.

There are several ways in which we can compute a similarity S or distance D measure between two experiments. Table 1 shows some of the spaces we can work in: For the present application we have relied on a conceptual simple voxel representation which has the advantage that voxelized point data directly can be compared to other voxel-volume data provided they are resampled and in the same stereotactic space. However, it requires large data structures and a large number of computations for every comparison where vectors with several thousand elements has to be constructed and compared. Since the number of experiment $N \approx 1000$ is lower than the number of voxels $P \approx 10000$ (in the present data set) the experiments can be represented in the lower N-dimensional space with an orthogonal transformation. Using PCA for the transformation we might even further restrict the space regarding the highest principal components as noise. It is also possible to compare the volumes using only the sets of locations computing the distance measure in the 3D Talairach space. The voxelization is avoided but it is not possible to produce an SVD-based index. Contrary to the voxelization based methods this procedure has no sampling errors. A further reduction in the computational complexity can be obtained by using more advanced data structures than simple lists of points [Samet, 1990], such that not all $I \times J$ terms need to be computed. Regardless of the space of distance computation the optimal distance metric is still an open issue: kernel type, kernel width, normalization and how the sign and magnitude of locations should be treated. If we had labeled data, e.g., from manual scoring, we could optimize for best performance.

5 Conclusion

We have shown the possibility in performing volume searches where related experiments are found. Experiments that report activation as points can be compared to volumes by voxelization, and compared with normal search our method incorporates an incertitude aspect with fuzzy queries. We showed that image-based indices can be generated and these produce meaningful novel entrances to a database.

Extensions to the scheme can include combination with text-based queries and ad hoc retrieval, where users supply a volume and related volumes are returned. The method opens up for a quantitative comparison of activation volumes where the reproducibility of tasks and the cognitive components under study is assessed.

6 Acknowledgments

Daniela Balslev for help and discussion. Research Imaging Center in San Antonio for access to the BrainMap database. Funding where provided by European Union (MAPAWAMO), American Human Brain Project (International Neuroimaging Consortium) and the Danish Research Councils (THOR Center for Neuroinformatics).

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