Mining Posterior Cingulate

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Abstract in Danish

Functional brain imaging studier kortlgger funktion til hjerneomrder. Vi har anvendt automatisk usuperviseret textanalyse p PubMed databasen med henblik p at finde hvilke funktioner bliver associeret med et hjerneomrde - posterior cingulate cortex (PCC). PCC er specielt interessant for neurovidenskablig data mining da dens funktion ikke er klarlagt. En sgning i Pubmed begrnset til artikler som havde bde PCC and functional brain imaging som keywords returnerede 271 abstracts. Non-negative matrix factorization blev brugt til at identificere hovedkontekster i form af clusters af ord som hyppigt forekommer sammen i disse abstracts. Vi fandt at hukommelse, Alzheimer's disease og smerte er hovedkonteksterne i de artikler som nvner PCC. De frste to hovedkontekster er i overenstemmelse med resultater fra manuelle reviews som forbinder PCC med episodisk genkaldelse og tidlige metabolismndringer i Alzheimer's disease. Yderligere finder vi at smerte- og hukommelsesrelaterede aktiveringer er rumligt adskilte. Hukommelsesrelaterede aktiveringer befinder sig oftest inferiort og posteriort i PCC mens smerte-relaterede aktiveringer er oftest fundet anteriort i PCC.

Manual review

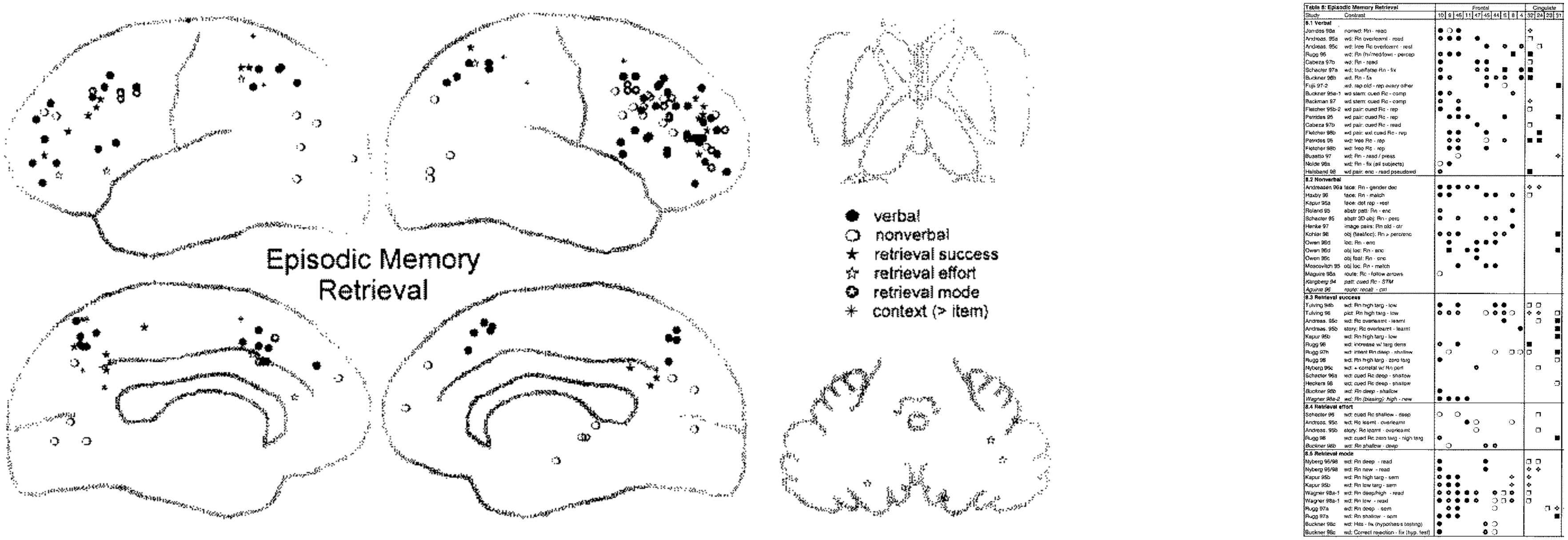
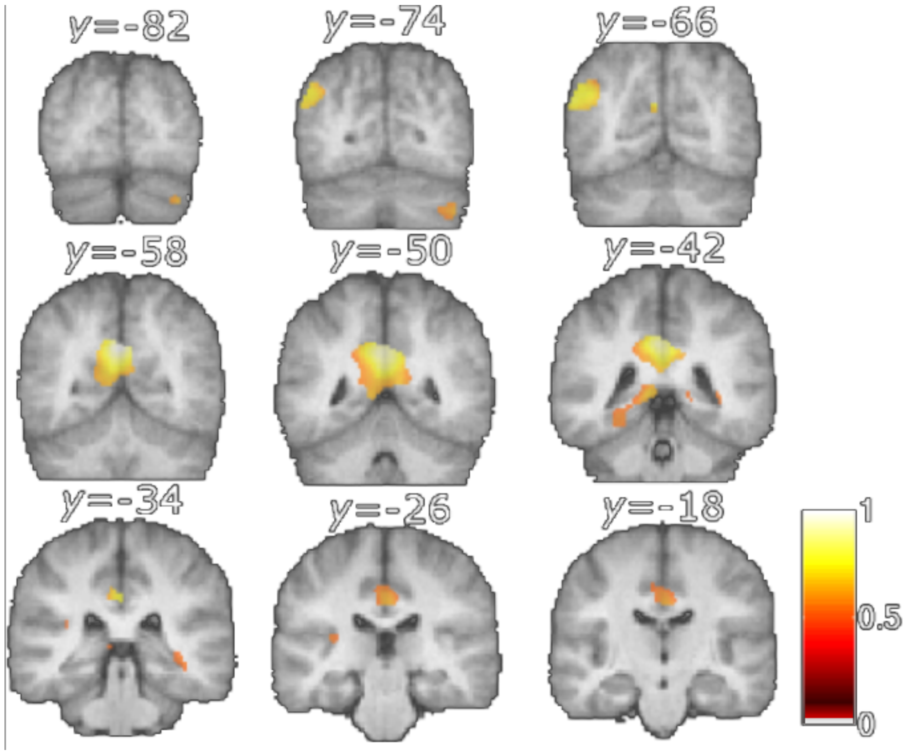


Figure 1: Example: Episodic memeory retrieval (Cabeza and Nyberg, 2000, figure 10 and table 8).

"Manual review": Manual reading and classification of articles. Report activation in tables and figures. Relate brain regions to psychological functions.

The posterior cingulate: Hic sunt dracones



Surprising activation in the posterior cingulate cortex (PCC) in an experiment on visuoproprioceptive integration and motor learning (Balslev and Nielsen, 2003; Balslev et al., 2003)

How is the activation to be explained?

No textbook consensus has emerged for the PCC.

- Electrophysiology: PCC = sensory
  - Visual stimulation (Vogt et al., 1992)
  - Eye/hand/head position and movement (Vogt et al., 1992; Cho and Sharp, 2001)
  - Electrical stimulation elicits proprioceptive illusions (Richer et al., 1993)

- Functional imaging: PCC = cognition/emotion
  - Memory (Cabeza and Nyberg, 1997; Cabeza and Nyberg, 2000): Episodic retrieval (275 different studies)
  - Emotion (Maddock, 1999) (25 studies)
  - Spatial navigation (Maguire, 2001) (14 studies)
  - Semantic versus sensory (Binder et al., 1999)
  - Resting/deactivation (Shulman et al., 1997) (9 studies)

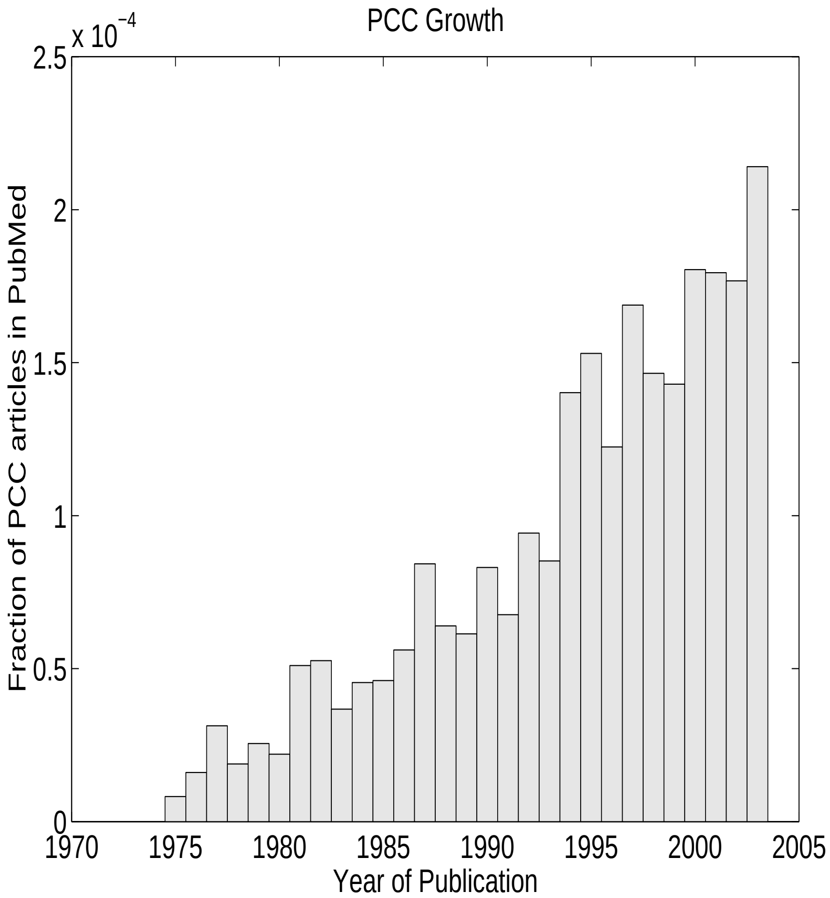


Figure 2: Growth in articles in PubMed responding to "Posterior cingulate" query: a popular area

Can we mine with automatic computerized methods for information about PCC, specifically:

Can we find alignment between reviews and automatic text analysis? (Lars Kai)

Evidence for PCC activation related to sensorimotor processing ? (Daniela)

Are there functional segregation in PCC? (Finn)

Method

- Include all published studies that mention PCC downloaded from PubMed with the query: `("posterior cingulate" OR "posterior cingulum" OR "retrosplenial" OR "retrosplenium") AND ("magnetic resonance imaging" OR ("positron emission tomography")`

- Represent abstracts of articles on vectorial form ("vector space model"/"bag-of-words") (Salton, 1971).

- Elimination of stop-words ("the", "of", "results", "anterior", ...) and only maintaining words associated with brain function.

- Cluster articles and words (latent class analysis) with non-negative matrix factorization (Lee and Seung, 1999) varying the number of clusters/latent classes. SVD/PCA, ICA and K-means were also tried.

Non-negative matrix factorization

Non-negative matrix factorization (NMF) (Lee and Seung, 1999)

$$\mathbf{X} = \mathbf{W}\mathbf{H} + \mathbf{E} \tag{1}$$

Data matrix with vectorized abstracts: $\mathbf{X}$(abstracts $\times$ words).

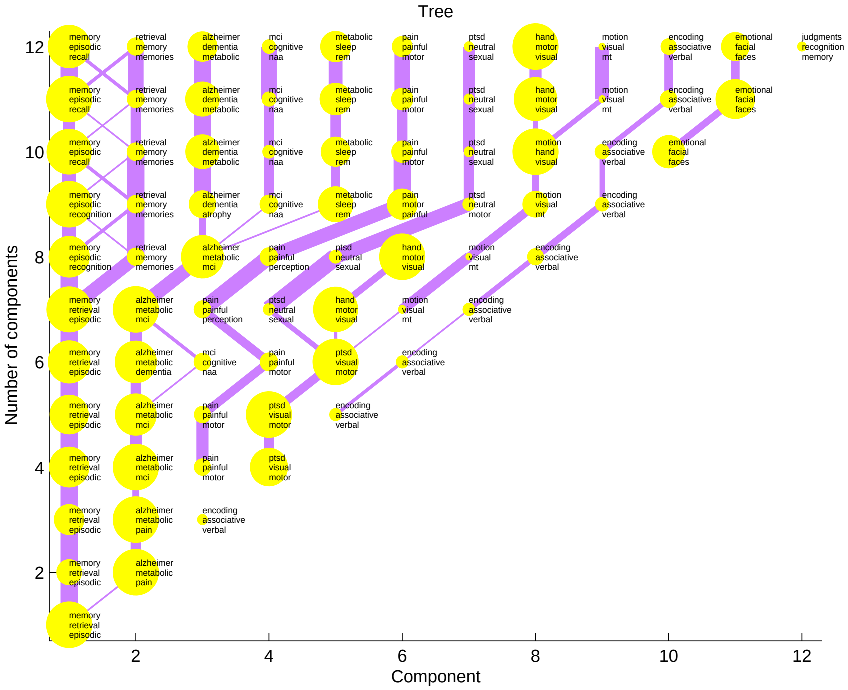
Factorized matrices: $\mathbf{W}$(abstracts $\times$ K) and $\mathbf{H}$(K $\times$ words) are sparse and greater than or equal to zero.

Cost function for NMF

$$E = \text{trace}(\mathbf{E}\mathbf{E}^{\mathsf{T}}) = \text{trace}(\mathbf{E}^{\mathsf{T}}\mathbf{E}) = ||\mathbf{E}||_F^2, \tag{2}$$

NMF performed with varying number of clusters: $K = 1, \ldots, 12$

Non-negative matrix factorization tree



Yellow dots are the kth cluster (x-axis) in an NMF with K number of clusters (y-axis)

The words associated with high value in $\mathbf{h}_k$ are shown for each cluster.

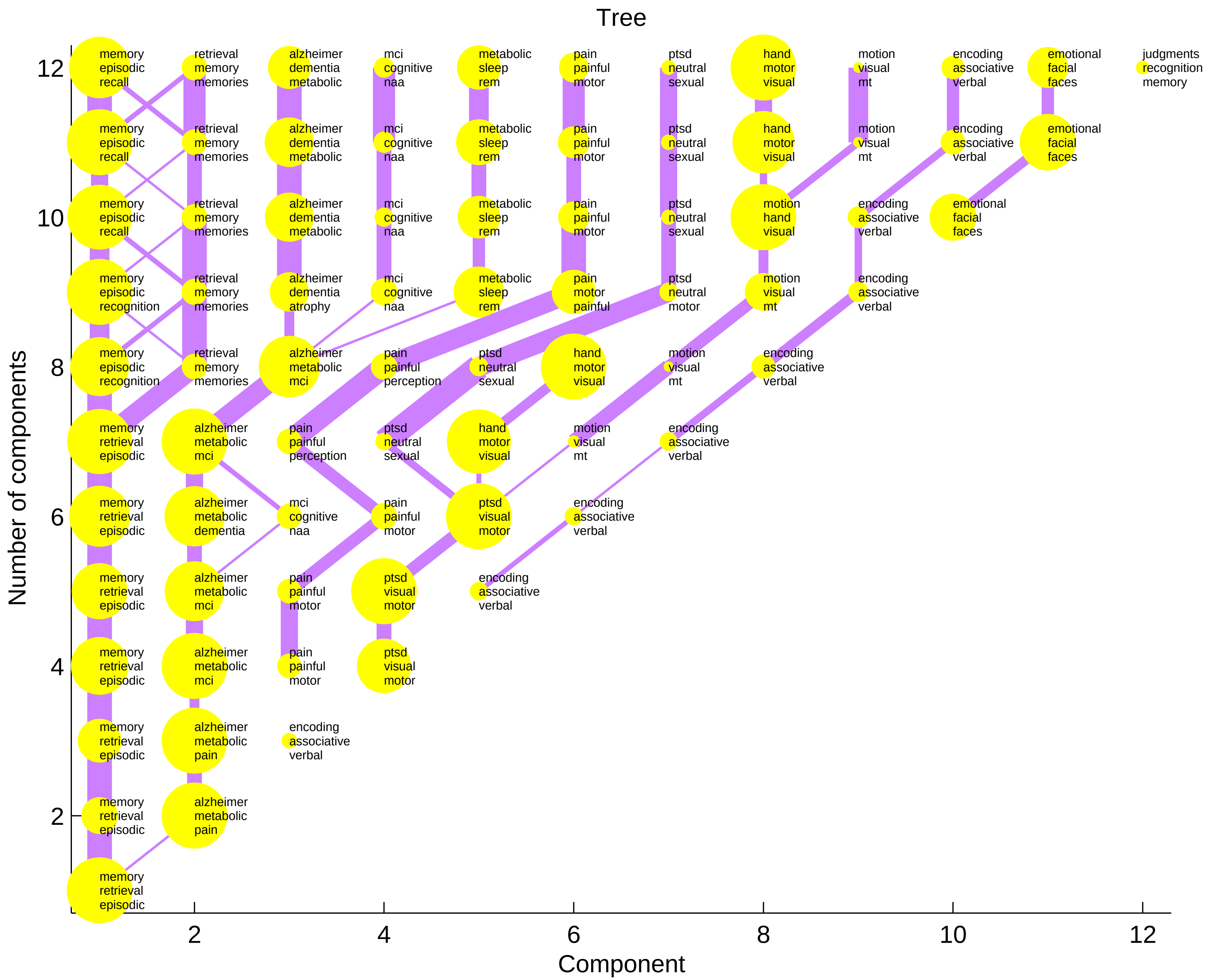
Lines between dots are shown if the similarity is high

$$s_{k,k'} = \left(\mathbf{w}_k^K\right)^\mathsf{T} \mathbf{w}_{k'}^{K+1}. \qquad (3)$$

Thickness correspond to similarity

Documents clustered with winner-take all

$$\tilde{w}_{nk} = \begin{cases} w_{nk} & \text{if } \forall_{k'} : w_{nk} \geq w_{nk'}, \\ 0 & \text{otherwise.} \end{cases} \qquad (4)$$


Tree
Number of components
Component
2
4
6
8
10
12
memory episodic recall
retrieval memory memories
alzheimer dementia metabolic
mci cognitive naa
metabolic sleep rem
pain painful motor
ptsd neutral sexual
hand motor visual
motion visual mt
encoding associative verbal
emotional facial faces
judgments recognition memory
memory episodic recall
retrieval memory memories
alzheimer dementia metabolic
mci cognitive naa
metabolic sleep rem
pain painful motor
ptsd neutral sexual
hand motor visual
motion visual mt
encoding associative verbal
emotional facial faces
memory episodic recall
retrieval memory memories
alzheimer dementia metabolic
mci cognitive naa
metabolic sleep rem
pain painful motor
ptsd neutral sexual
motion hand visual
encoding associative verbal
emotional facial faces
memory episodic recognition
retrieval memory memories
alzheimer dementia atrophy
mci cognitive naa
metabolic sleep rem
pain motor painful
ptsd neutral motor
motion visual mt
encoding associative verbal
memory episodic recognition
retrieval memory memories
alzheimer metabolic mci
pain painful perception
ptsd neutral sexual
hand motor visual
motion visual mt
encoding associative verbal
memory retrieval episodic
alzheimer metabolic mci
pain painful perception
ptsd neutral sexual
hand motor visual
motion visual mt
encoding associative verbal
memory retrieval episodic
alzheimer metabolic dementia
mci cognitive naa
pain painful motor
ptsd visual motor
encoding associative verbal
memory retrieval episodic
alzheimer metabolic mci
pain painful motor
ptsd visual motor
encoding associative verbal
memory retrieval episodic
alzheimer metabolic mci
pain painful motor
ptsd visual motor
memory retrieval episodic
alzheimer metabolic pain
encoding associative verbal
memory retrieval episodic
alzheimer metabolic pain
memory retrieval episodic

First NMF component: Memory

#	Load	Title	Reference
1	7.81	Remembering the past: two facets of episodic memory explored with positron emission tomography.	(Andreasen et al., 1995)
2	7.56	Differential remoteness and emotional tone modulate the neural correlates of autobiographical memory.	(Piefke et al., 2003)
3	5.74	Differential modulation of a common memory retrieval network revealed by positron emission tomography.	(Maguire and Mummery, 1999)
4	5.11	Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval.	(Maddock et al., 2001)
5	5.06	Neuroanatomical correlates of episodic encoding and retrieval in young and elderly subjects.	(Daselaar et al., 2003)
6	4.89	Verbal encoding deficits in a patient with a left retrosplenial lesion.	(McDonald et al., 2001)
7	4.73	The functional neuroanatomy of episodic memory: the role of the frontal lobes, the hippocampal formation, and other areas.	(Desgranges et al., 1998)
8	4.57	Parietal and hippocampal contribution to topokinetic and topographic memory.	(Berthoz, 1997)
9	4.43	The effects of bilateral hippocampal damage on fMRI regional activations and interactions during memory retrieval.	(Maguire et al., 2001)
10	4.33	Network analysis in episodic encoding and retrieval of word-pair associates: a PET study.	(Krause et al., 1999)

Table 1: Memory: Values in $\tilde{\mathbf{w}}_{k=\text{memory}}$. For this specific list the $(1,4)$-node from figure was selected.

Second NMF component: Alzheimer's disease

#	Load	Title	Reference
1	8.37	Longitudinal PET Evaluation of Cerebral Metabolic Decline in Dementia: A Potential Outcome Measure in Alzheimer's Disease Treatment Studies.	(Alexander et al., 2002)
2	6.64	Neocortical and hippocampal glucose hypometabolism following neurotoxic lesions of the entorhinal and perirhinal cortices in the non-human primate as shown by PET. Implications for Alzheimer's disease.	(Meguro et al., 1999)
3	5.96	Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease.	(Minoshima et al., 1997)
4	5.46	Detection of grey matter loss in mild Alzheimer's disease with voxel based morphometry.	(Frisoni et al., 2002)
5	5.36	Cerebral metabolic changes accompanying conversion of mild cognitive impairment into Alzheimer's disease: a PET follow-up study.	(Drzezga et al., 2003)
6	5.22	Mild cognitive impairment and Alzheimer disease: regional diffusivity of water.	(Kantarci et al., 2001)
7	5.08	Voxel-based analysis of confounding effects of age and dementia severity on cerebral metabolism in Alzheimer's disease.	(Salmon et al., 2000)
8	4.99	Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E.	(Reiman et al., 1996)
9	4.38	Three-dimensional stereotactic surface projection analysis of macaque brain PET: development and initial applications.	(Cross et al., 2000)
10	4.31	Declining brain activity in cognitively normal apolipoprotein E epsilon 4 heterozygotes: A foundation for using positron emission tomography to efficiently test treatments to prevent Alzheimer's disease.	(Reiman et al., 2001)

Table 2: Alzheimer: Values in $\tilde{\mathbf{w}}_{k=\mathrm{Alzheimer}}$. For this specific list the $(2,4)$-node from figure was selected.

Third NMF component: Pain

#	Load	Title	Reference
1	9.87	Central representation of chronic ongoing neuropathic pain studied by positron emission tomography.	(Hsieh et al., 1995)
2	8.14	Regional brain activity changes associated with fentanyl analgesia elucidated by positron emission tomography.	(Adler et al., 1996)
3	7.97	Region-specific encoding of sensory and affective components of pain in the human brain: a positron emission tomography correlation analysis.	(Tölle et al., 1999)
4	7.66	Central processing of rectal pain: a functional MR imaging study.	(Baciu et al., 1999)
5	6.60	Phantom limb pain in the human brain: unraveling neural circuitries of phantom limb sensations using positron emission tomography.	(Willoch et al., 2000)
6	5.70	A PET activation study of dynamic mechanical allodynia in patients with mononeuropathy.	(Petrovic et al., 1999)
7	5.38	A comparative fMRI study of cortical representations for thermal painful, vibrotactile, and motor performance tasks.	(Gelnar et al., 1999)
8	4.71	Spatial summation of pain processing in the human brain as assessed by cerebral event related potentials.	(Chen et al., 2002)
9	4.56	Pain processing in four regions of human cingulate cortex localized with co-registered PET and MR imaging.	(Vogt et al., 1996)
10	4.45	Functional MR imaging analysis of pain-related brain activation after acute mechanical stimulation.	(Creac'h et al., 2000)

Table 3: Pain class: Values in $\tilde{\mathbf{w}}_{k=\text{pain}}$. For this specific list the $(3, 4)$-node from figure was selected.

NMF Component: Emotion

#	Load	Title	Reference
1	14.15	Investigation of facial recognition memory and happy and sad facial expression perception: an fMRI study.	(Phillips et al., 1998)
2	11.60	Ketamine alters neural processing of facial emotion recognition in healthy men: an fMRI study.	(Abel et al., 2003)
3	7.60	Posterior cingulate cortex activation by emotional words: fMRI evidence from a valence decision task.	(Maddock et al., 2003)
4	4.79	The neural correlates of person familiarity. A functional magnetic resonance imaging study with clinical implications.	(Shah et al., 2001)
5	4.76	Dissociable prefrontal brain systems for attention and emotion.	(Yamasaki et al., 2002)
6	2.66	Cerebral blood flow in subjects with social phobia during stressful speaking tasks: a PET study.	(Tillfors et al., 2001)
7	2.56	Functional neuroanatomy of visually elicited simple phobic fear: additional data and theoretical analysis.	(Fredrikson et al., 1995)
8	2.39	Activation of left posterior cingulate gyrus by the auditory presentation of threat-related words: an fMRI study.	(Maddock and Buonocore, 1997)
9	2.20	Cerebral blood flow during anxiety provocation.	(Fredrikson et al., 1997)
10	1.82	A functional cerebral response to frightening visual stimulation.	(Wik et al., 1993)

Table 4: Emotion class: Abstracts associated with the Emotion class sorted according to loading, i.e., values in $\tilde{\mathrm{w}}_{k=\text{emotion}}$. For this specific list the $(11, 12)$-node from figure was selected.

NMF Component: Visuomotor

#	Load	Title	Reference
1	10.11	[Compulsive manipulation of tools in the left hand following damage to the right medial frontal lobe]	(Hashimoto et al., 1998)
2	10.03	The role of posterior parietal cortex in visually guided reaching movements in humans.	(Kertzman et al., 1997)
3	6.11	Functional reorganization of the brain in recovery from striatocapsular infarction in man.	(Weiller et al., 1992)
4	5.08	Mapping of human and macaque sensorimotor areas by integrating architectonic, transmitter receptor, MRI and PET data.	(Zilles et al., 1995)
5	4.75	PET study of pointing with visual feedback of moving hands.	(Inoue et al., 1998)
6	4.26	Cortical function in amyotrophic lateral sclerosis. A positron emission tomography study.	(Kew et al., 1993)
7	3.31	Functional neuroanatomical correlates of electrodermal activity: a positron emission tomographic study.	(Fredrikson et al., 1998)
8	2.60	Overactive prefrontal and underactive motor cortical areas in idiopathic dystonia.	(Ceballos-Baumann et al., 1995)
9	2.50	Relation between cerebral activity and force in the motor areas of the human brain.	(Dettmers et al., 1995)
10	2.04	Cortical networks for working memory and executive functions sustain the conscious resting state in man.	(Mazoyer et al., 2001)

Table 5: Visuo-motor class: Abstracts associated with the visuomotor class sorted according to loading, i.e., values in $\tilde{\mathbf{w}}_{k=\text{visuomotor}}$. For this specific list the $(5,7)$-node from figure was selected.

Memory

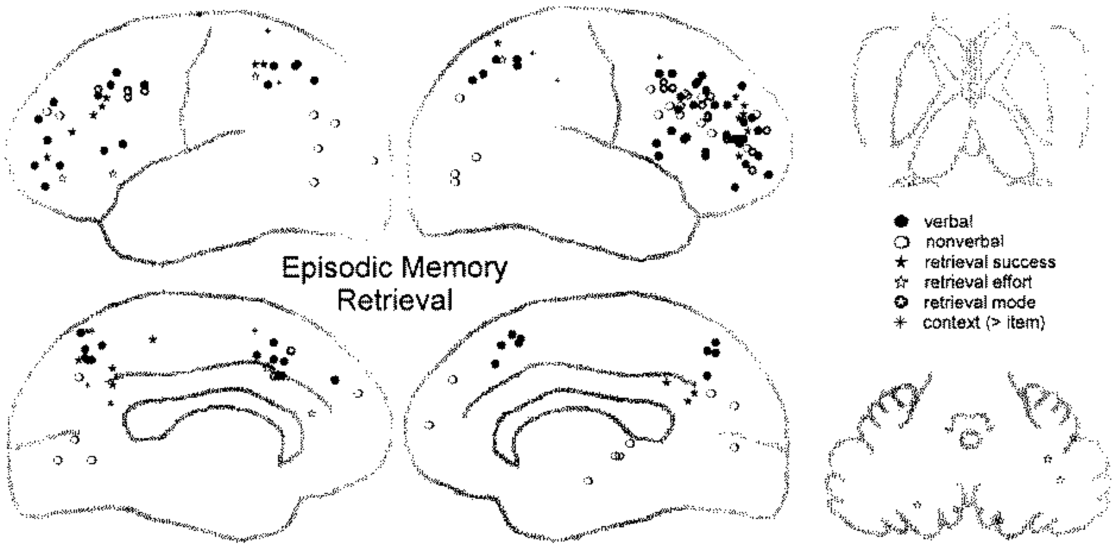


Figure 3: (Cabeza and Nyberg, 2000, figure 10).

Memory is the main component in our analysis

Successful episodic memory retrieval found as the most important cognitive function for PCC in a large review (Cabeza and Nyberg, 2000).

Alzheimer's disease

A manual review: "In very early AD flow or metabolism reduces first in the posterior cingulate gyrus and precuneus" (Matsuda, 2001).

Healthy APOE $\epsilon 4$ allele carriers show hypometabolism in PCC (Reiman et al., 1996).

Pain

Major pain areas: Anterior cingulate cortex (ACC), thalamus, S1 and S2, anterior insular (Ingvar, 1999) .

PCC is not among the major pain areas.

Reviews: Anterior cingulate cortex “activated in almost every study” (Ingvar, 1999), and seldomly more posterior than $y = -2.35$cm, i.e., confined to the regions with Brodmann area 24/32 (Peyron et al., 2000, figure 3).

Spatial navigation

Spatial navigation (Maguire, 2001), spatial orientation (Vogt et al., 1992) attributed to PCC.

11 PET and fMRI navigation studies (Maguire, 2001)

Nine studies not contained in our analysis because they are not indexed with the query words.

Two studies assigned to the memory component

How to find the 9 remaining: Full text search, databases, such as BrainMap DBJ and Brede.

Analysis of the spatial distribution

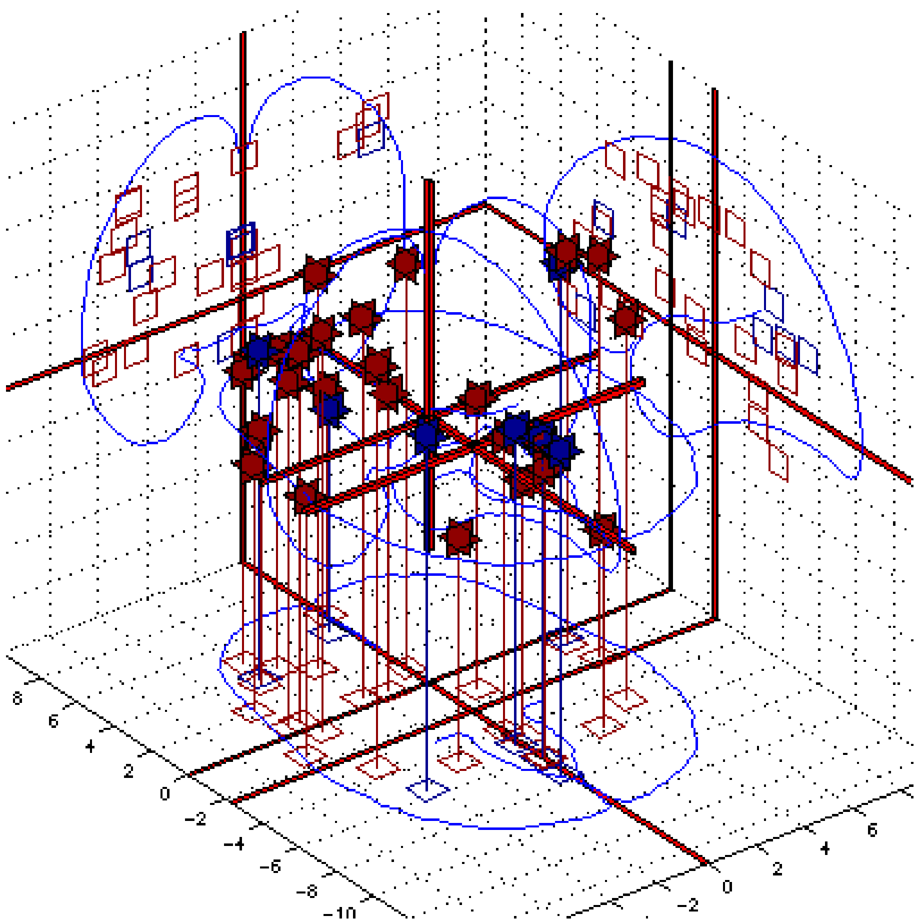
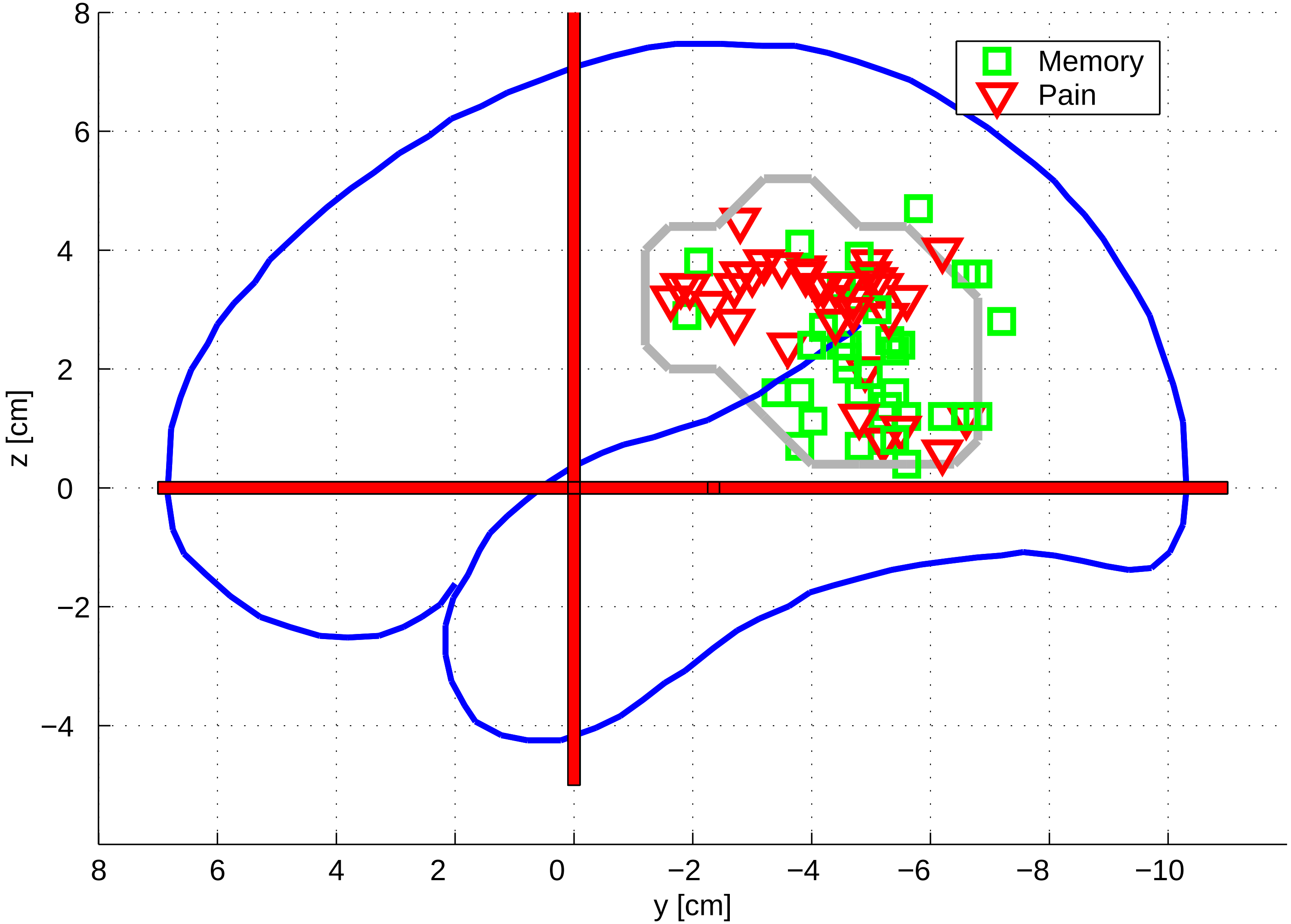


Figure 4: Coordinates from (Maddock et al., 2001).

Extract PCC Talairach coordinates from the top-twenty article in each cluster.

Extracted coordinates from the Brede database or by manual entering.

For example: $\mathbf{Z}(38 \times 3)$ for memory, $\mathbf{Z}(23 \times 3)$ for Alzheimer.


Memory
Pain
8
6
4
2
0
−2
−4
z [cm]
8
6
4
2
0
−2
−4
−6
−8
−10
y [cm]

Tests on segregation

Two-sample Hotelling T^2 test follows an F-distribution if multivariate Gaussian distributions are assumed (Mardia et al., 1979, p. 77)

$$\frac{M_1 M_2 (M - P - 1)}{M(M-2)P} D^2 \sim F_{P, M-P-1}. \tag{5}$$

The Mahalanobis distance is computed as

$$D^2 = (\bar{\mathbf{z}}_1 - \bar{\mathbf{z}}_2)^{\mathsf{T}} \mathbf{S}_u^{-1} (\bar{\mathbf{z}}_1 - \bar{\mathbf{z}}_2), \tag{6}$$

with the covariance $\mathbf{S}_u$ found as

$$\mathbf{S}_u = (M_1 \mathbf{S}_1 + M_2 \mathbf{S}_2)/(M-2), \tag{7}$$

$\bar{\mathbf{z}}_1$ and $\mathbf{S}_1$ are the mean and covariance for one set of Talairach coordinates

Permutation test also possible.

Test results

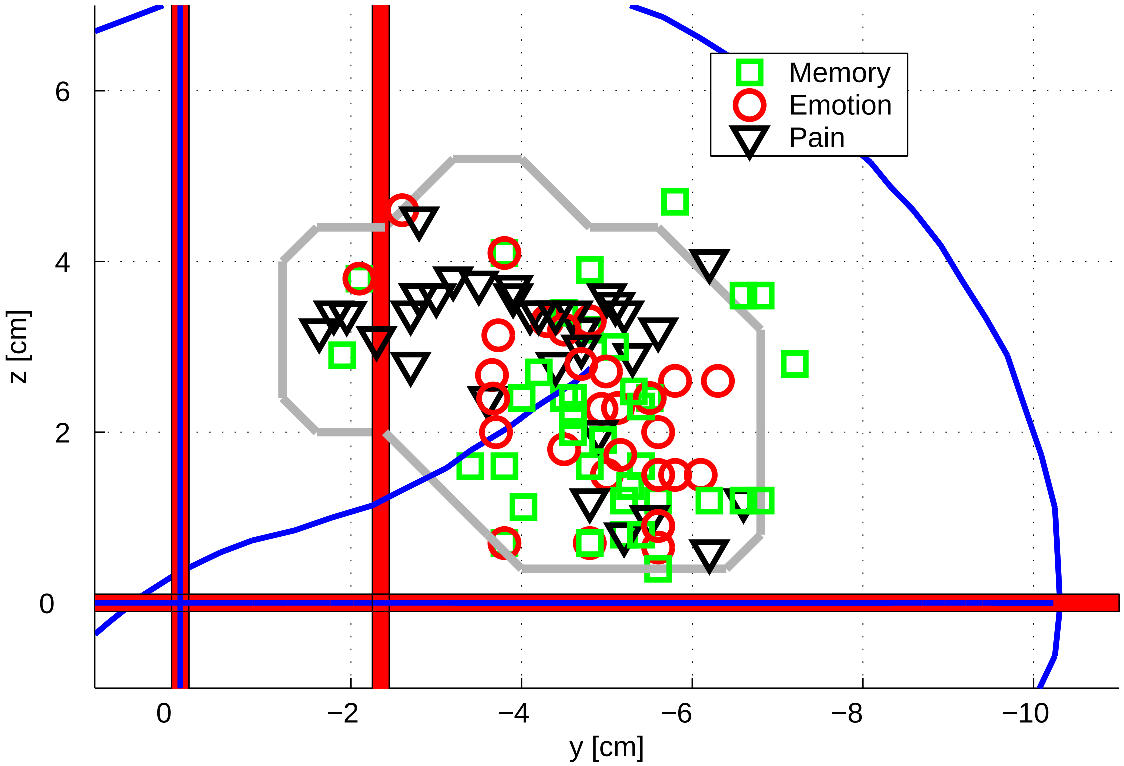
With three dimensions - Memory/pain	(Hotelling)	0.009494
With three dimensions - Memory/pain	(Maha. perm.)	0.008500
With three dimensions - Memory/pain	(Mean perm.)	0.002100
Sagittal test - Memory/pain	(Hotelling	0.003741
Sagittal test - Memory/pain	(Maha. perm.)	0.003400
Sagittal test - Memory/pain	(Mean perm.)	0.002600
x-coordinate - memory/pain	(Hotelling)	0.193429
x-coordinate - Memory/pain	(Mean Perm.)	0.191200

Major segregation in the sagittal (y and z) dimensions

No left/right segregation

Only minor difference between parametric and permutation based tests.

Emotion spatial distribution



No Memory/emotion separation ($P > 0.5$)

Pain/emotion separation ($P \approx 0.02$, Sagittal Hotelling T^2)

Successful autobiographical memory retrieval has previously been associated with caudal PCC (Maddock et al., 2001)

Cytoarchitecnics of PCC

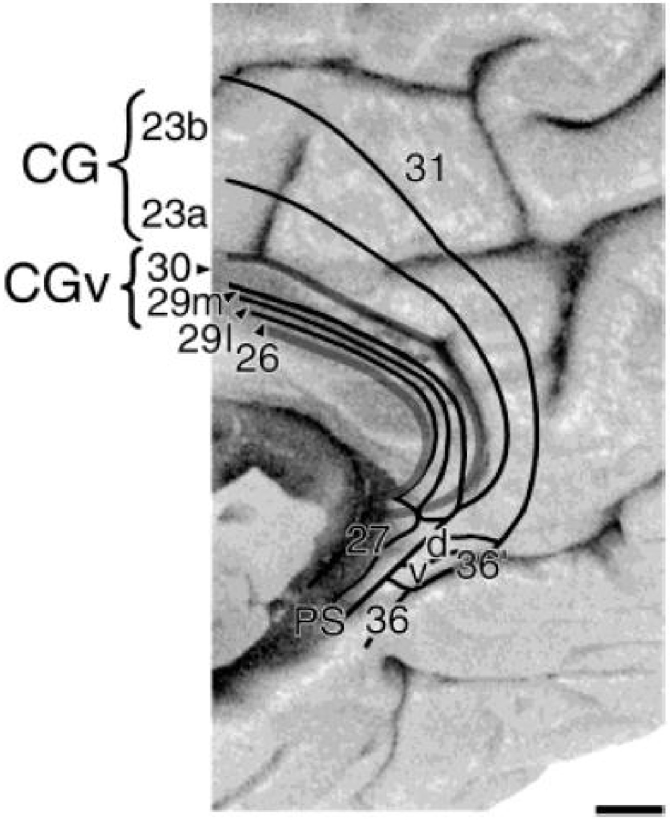


Figure 5: Cytoarchitectonics of PCC (Vogt et al., 2001, figure 14).

Cytoarchitectonic major divisions (ventral/-dorsal, Brodmann number 23/31) are orthogonal to our division (anterior/posterior).

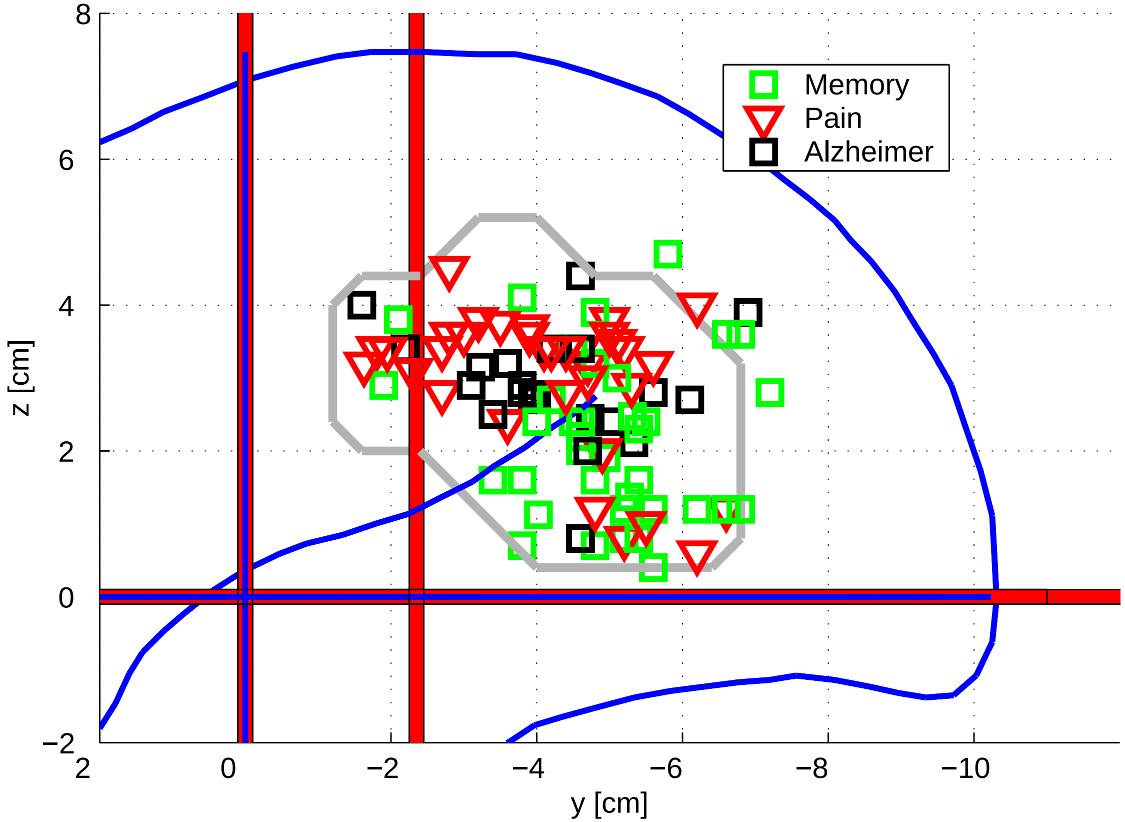
Anterior/posterior division also made for ACC orthogonal to its cytoarchitectonic (Bush et al., 2000).

Limited resolution in functional neuroimaging and differences in brain templates might make it difficult to see a ventral/dorsal division.

Conclusion

- Demonstrates the feasibility of text-mining techniques for automatic review.
- Methodology not limited to posterior cingulate
- Confirms the role of the PCC in memory.
- Functional heterogeneity in PCC: Pain/memory
- Some evidence for visuomotor processing in PCC. However, this is not the main function of PCC.

Alzheimer spatial distribution



Alzheimer coordinate in between memory and pain coordinates

Alzheimer separated from memory ($P = 0.03$, sagittal Hotelling T^2)

Alzheimer not separated from pain ($P = 0.7$, sagittal Hotelling T^2). Though a permutation test on the median of the z-coordinate is significant ($P \approx 0.003$)

Post-traumatic Stress Disorder (PTSD)

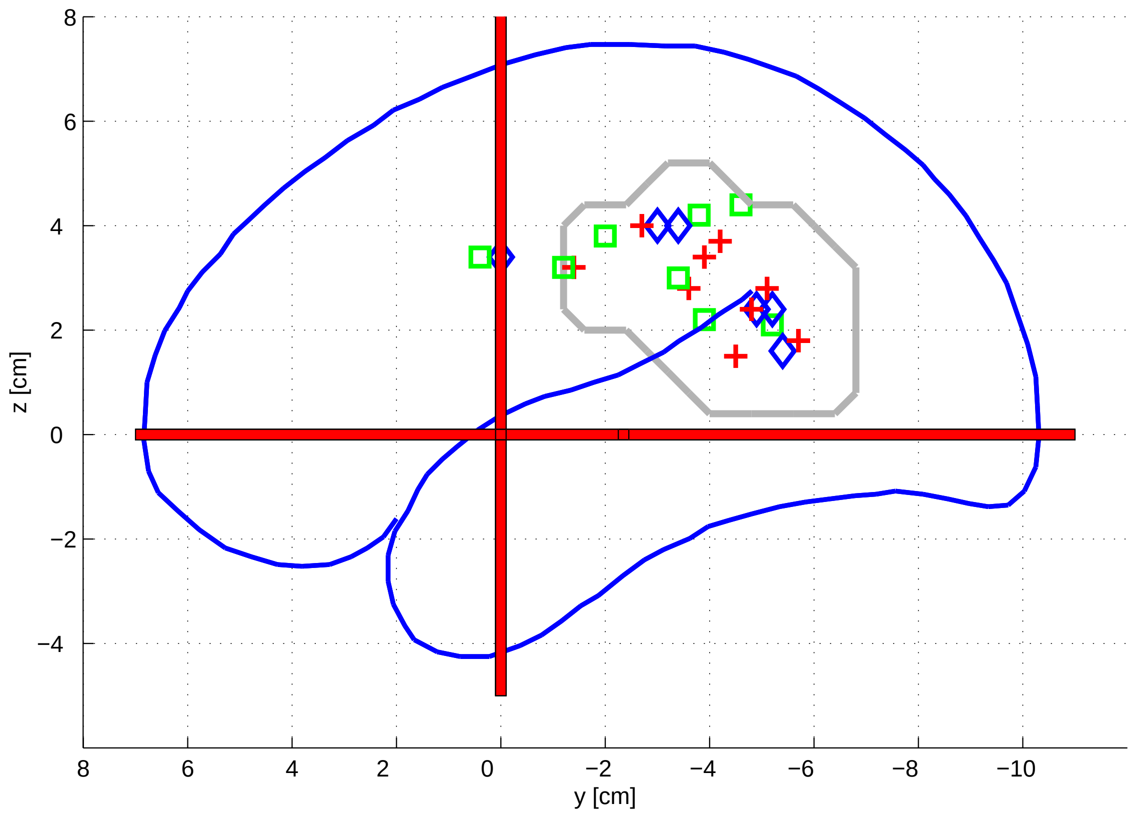


Figure 6: Green diamonds: Initial studies, red pluses: PTSD activation, blue minus: PTSD deactivations

Combination of memory and negative emotion?

Cluster dominated by a single author (J. D. Bremner).

Initial eight location confined to the rostral part of PCC.

Augmented with other studies: Distributed over the entire PCC.

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