CINGULUM

Virtual Neuroanatomy

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I. Overview

II. Afferents and Efferents

III. Neurophysiology

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VI. Behavioral Correlates

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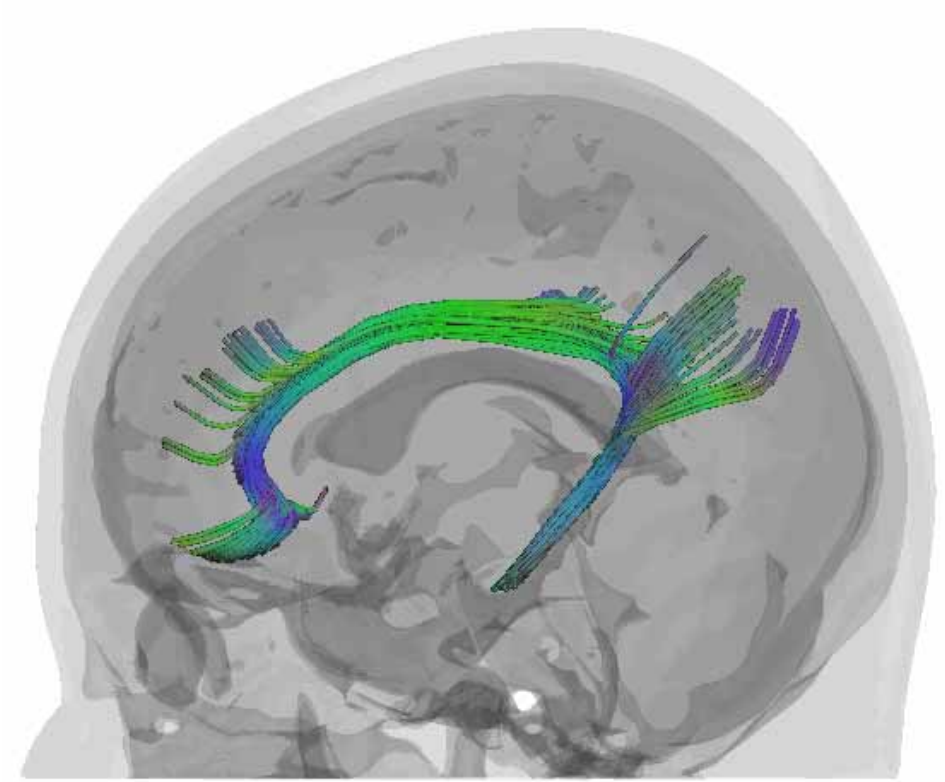
Overview

-Association Pathway of the limbic system.

-Communicates cortical, subcortical and all the sections of the cingulate cortex via long and short fibers.

-Can be divided in subcomponents along its length with different anatomical features.

-Communicate areas involved in
--Autonomic function
--Skelomotor function
--Emotion processing
--Memory
--Attention
--Pain processing
--Spatial orientation



Cingulum, different representations

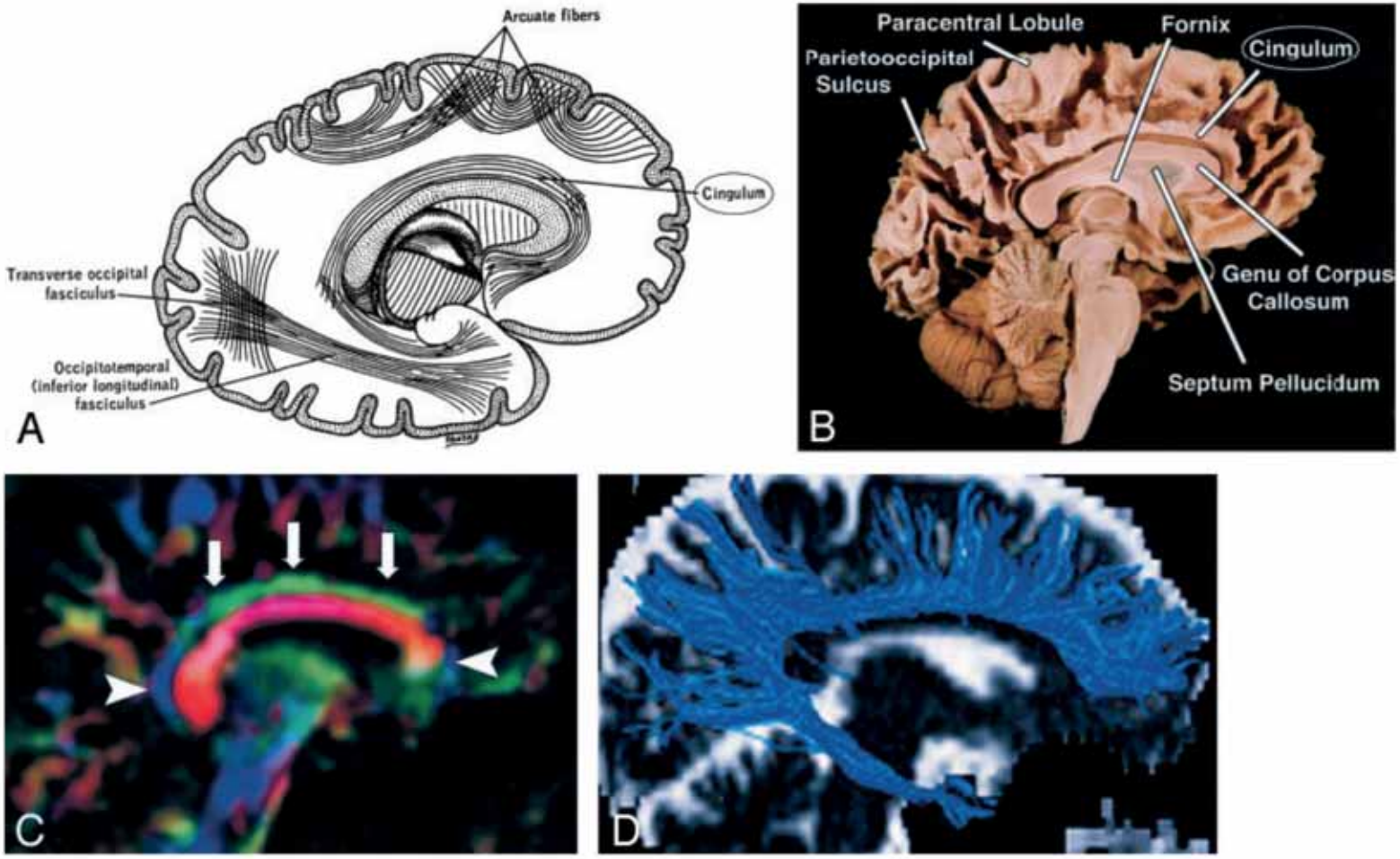


FIG 4. Cingulum, sagittal view.

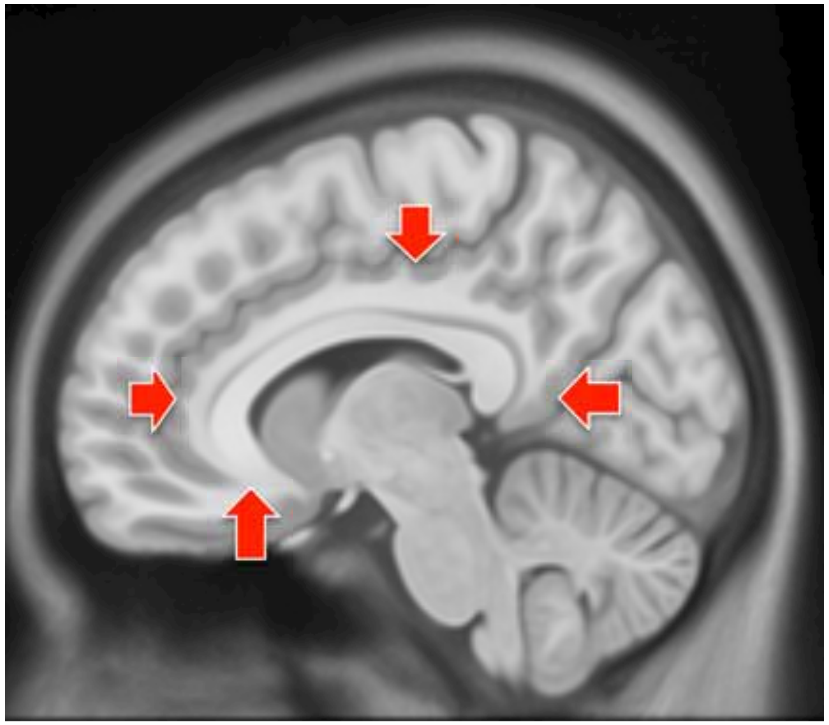
A, Illustration shows the cingulum arching over the corpus callosum.

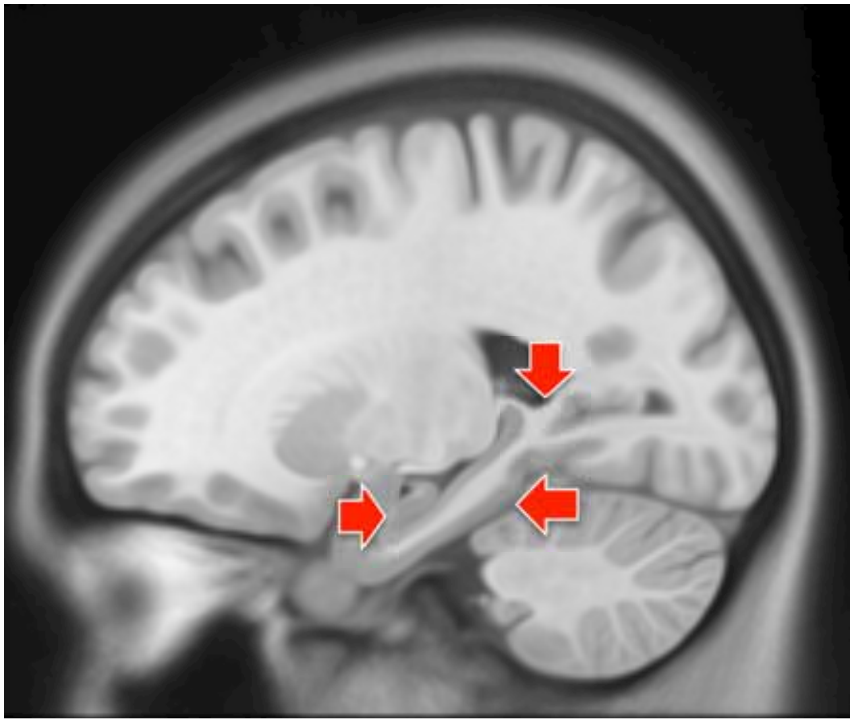
B, Gross dissection, median view.

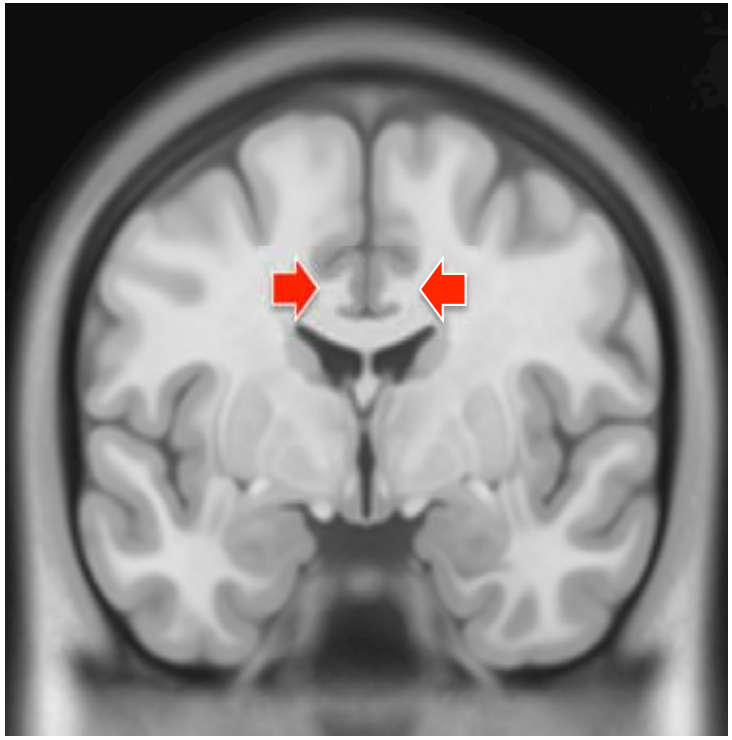
C, Directional map. Because DTI reflects tract orientation voxel by voxel, the color changes from green to blue as the cingulum (arrows) arches around the genu and splenium (arrowheads). Green indicates anteroposterior; red, left-right; blue, superior-inferior.

D, Tractogram. (See also Fig 5A, axial directional map.)

Jellison et al., (2004)



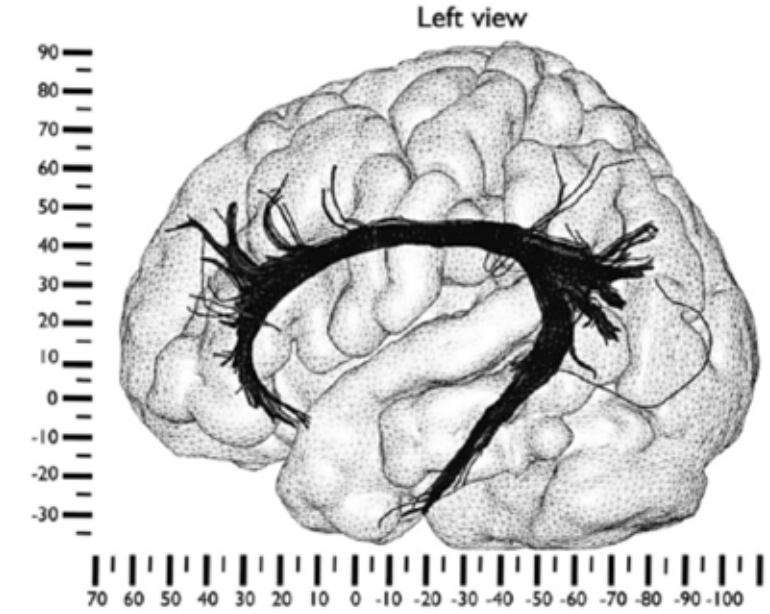


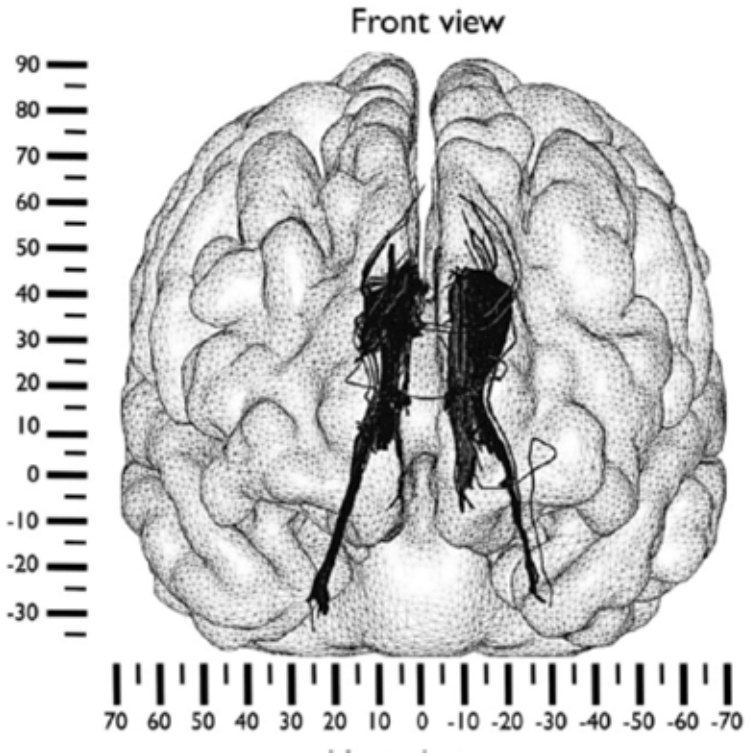


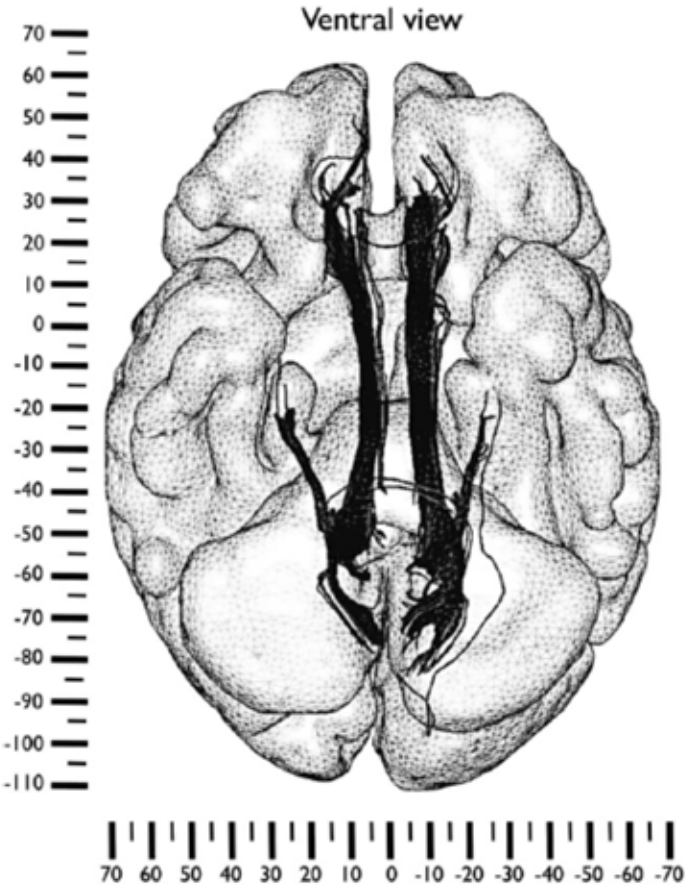
MR imaging of the human cingulum

MNI152

DTI tractography of the human cingulum







Catani, M., & Thiebaut de Schotten, M., (2008).

In relation to other association tracts

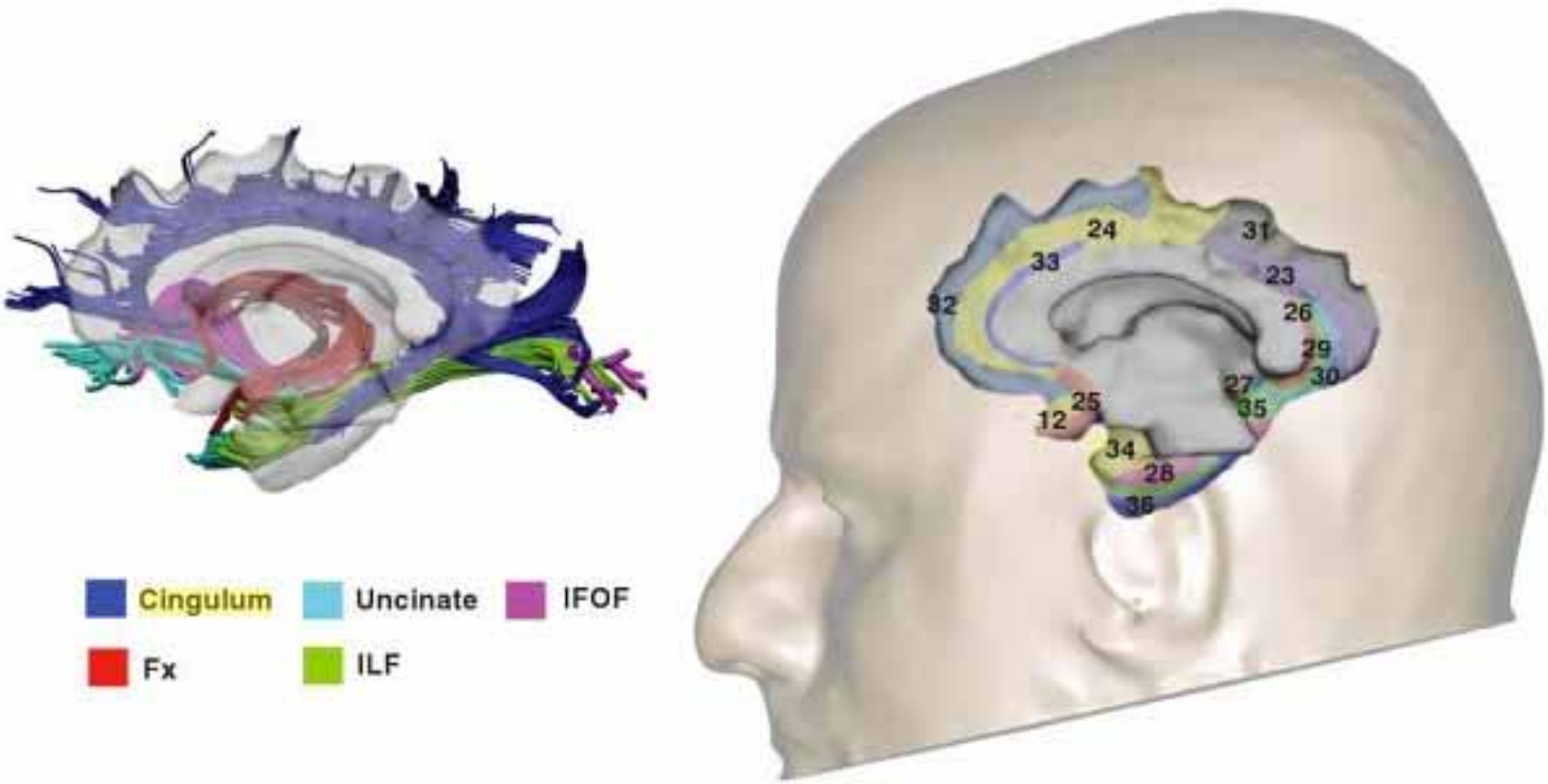
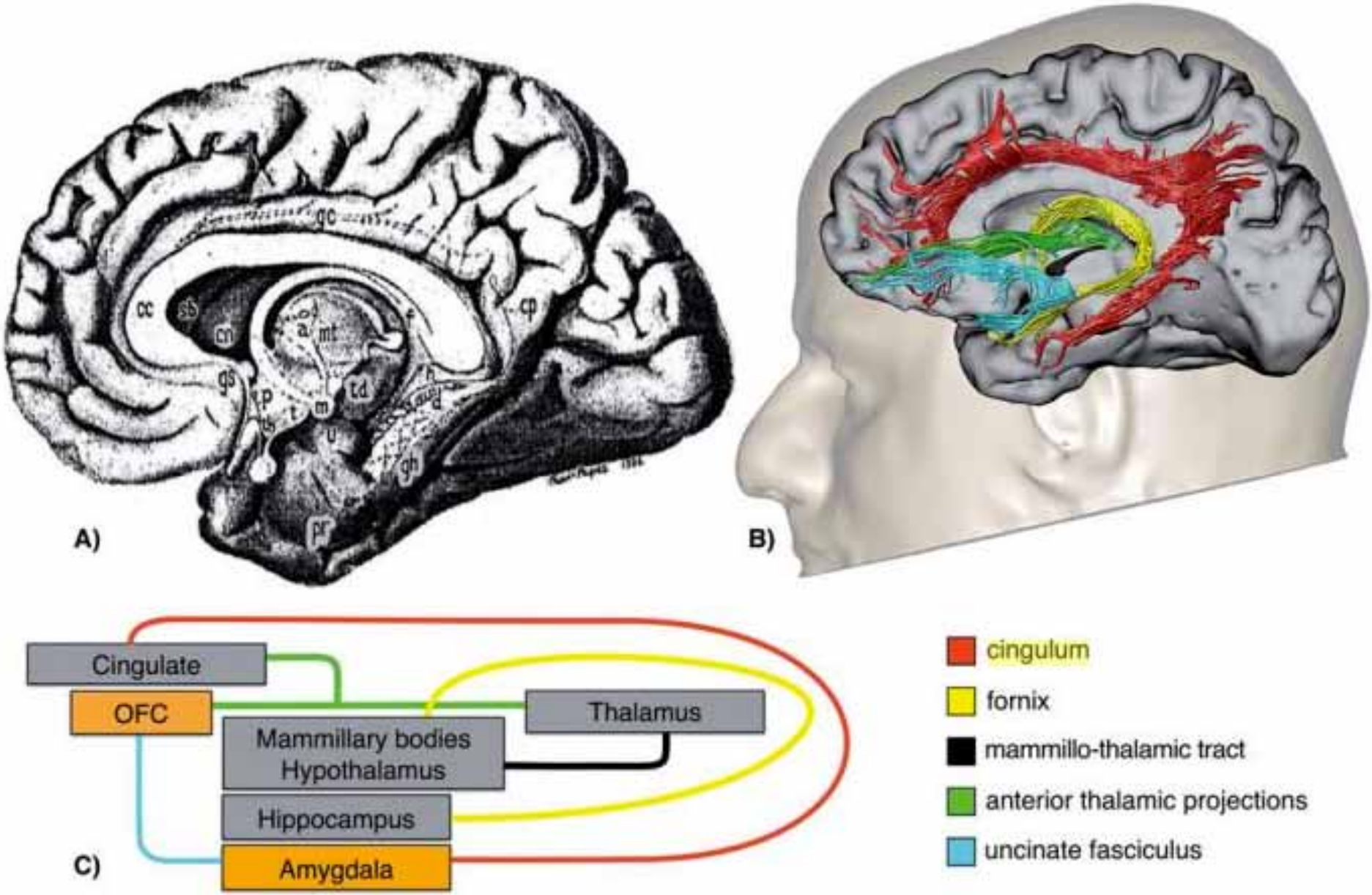


Figure 5.14 Medial view of the cortical anatomy of the limbic lobe and its main associative connections. Numbers indicate cytoarchitectonic areas according to Brodmann's nomenclature. The major association pathways of the limbic lobes are the cingulum, the uncinate, the inferior longitudinal fasciculus (ILF), and the fornix.

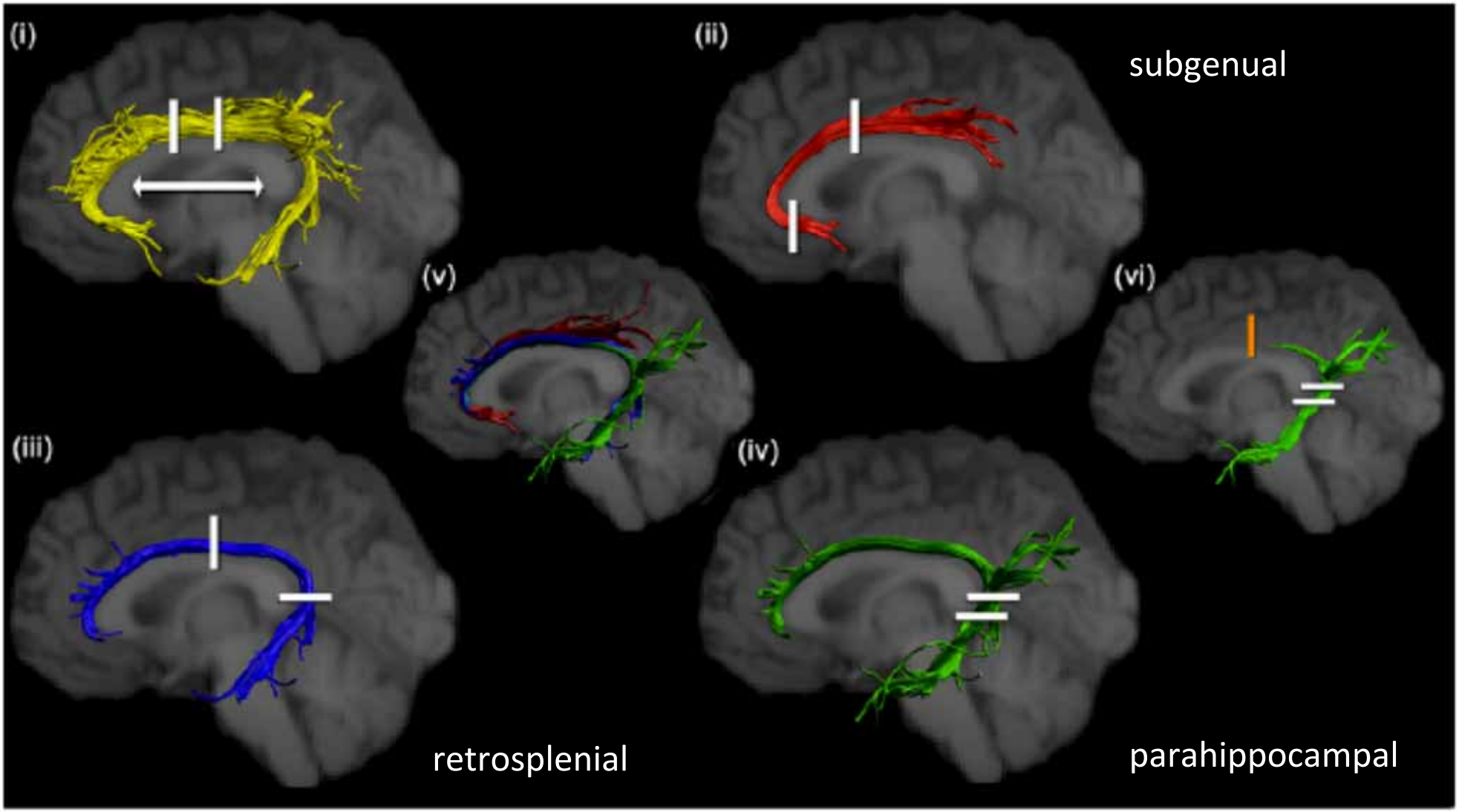
Catani, M., & Thiebaut de Schotten, M., (2012)

Representation of the limbic system



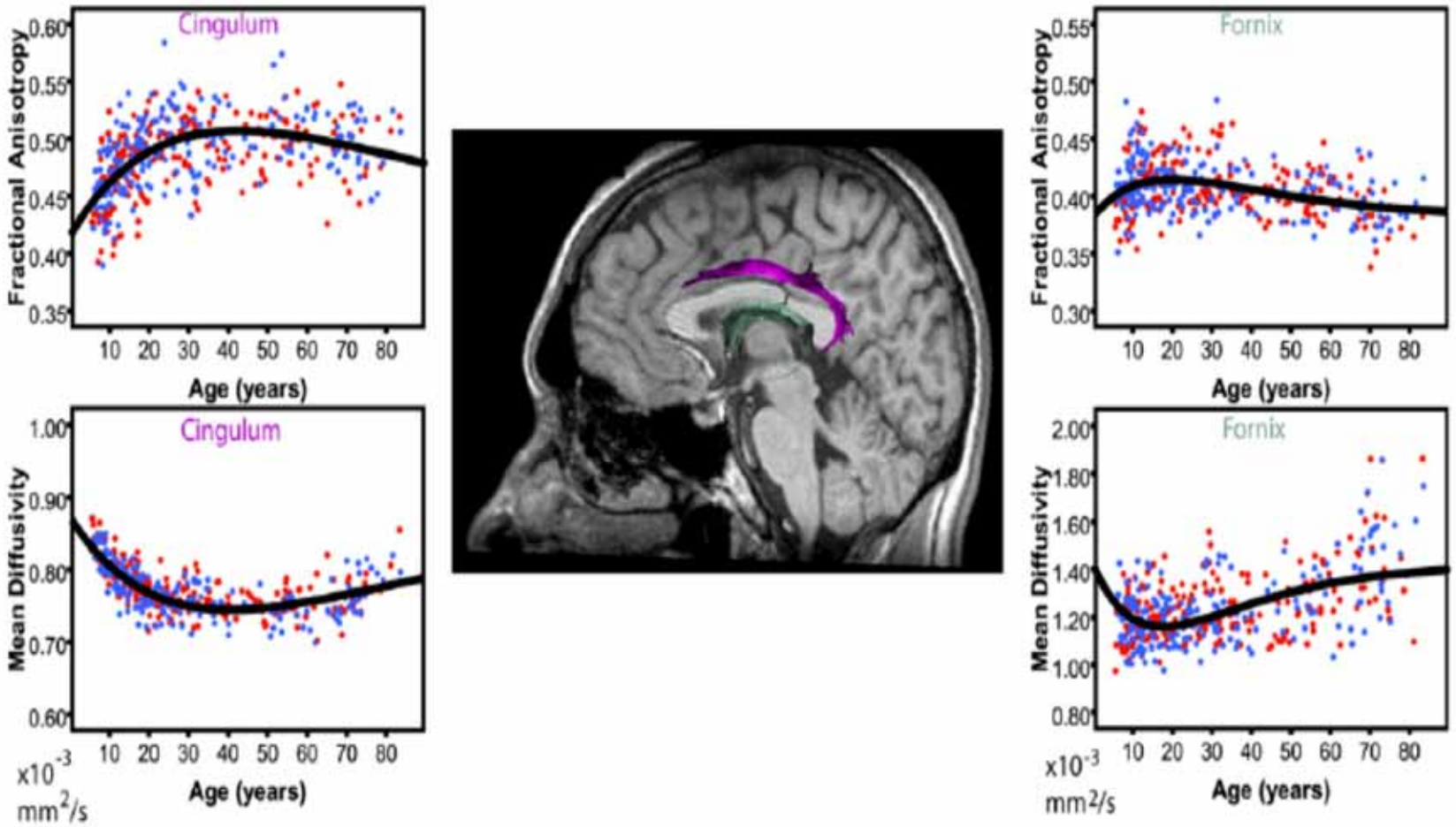
Catani, M., & Thiebaut de Schotten, M., (2012)

Proposed sub-division of the cingulum



Jones et al., (2013)

Cingulum FA and MD over the lifespan

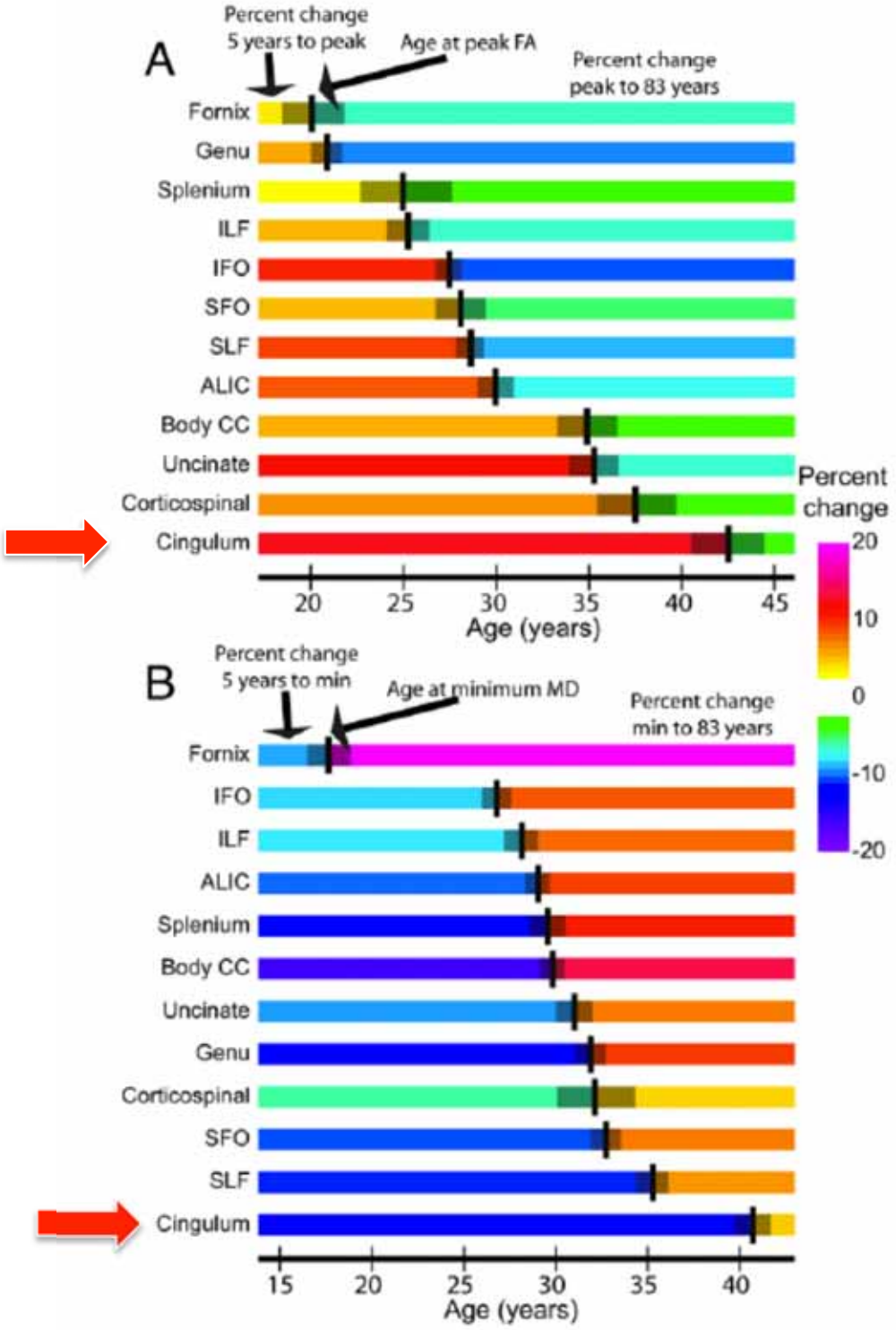


Lebel et al., (2011)

Comparative development

FA

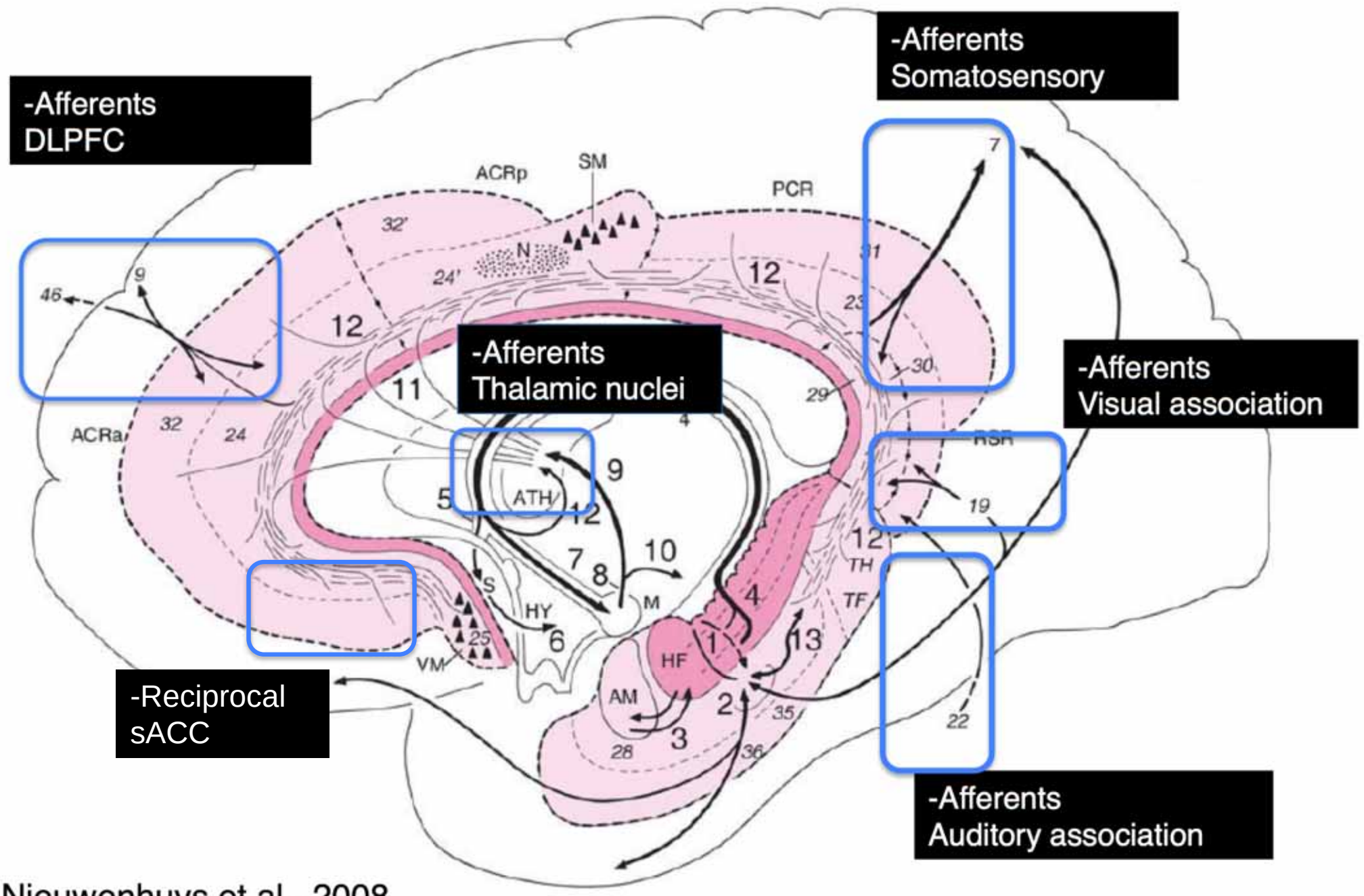
MD



Lebel et al., (2011)

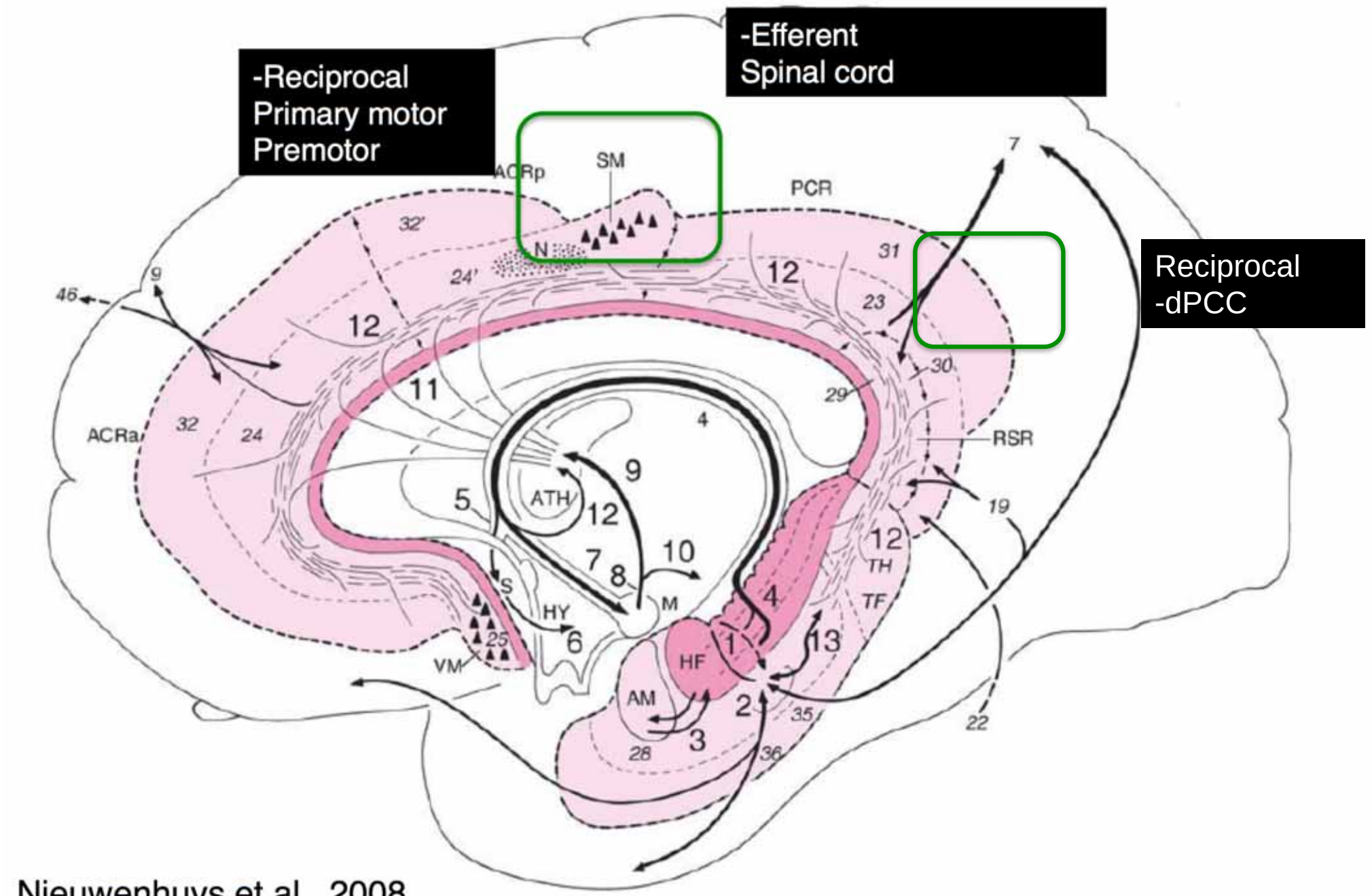
Afferent and Efferents

Posterior Cingulate Cortex



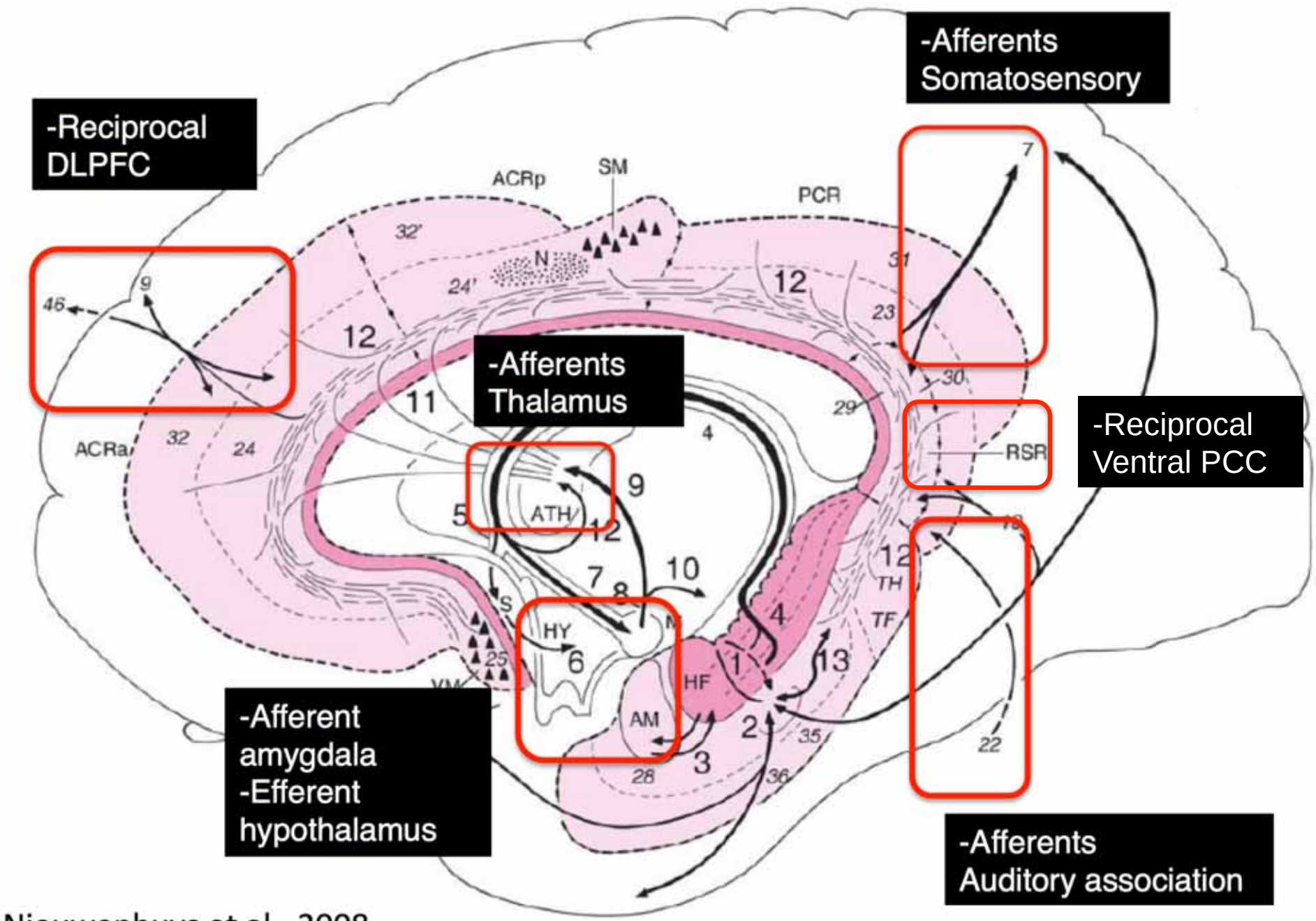
Nieuwenhuys et al., 2008

Anterior Cingulate Cortex-Posterior part
(Medial Cingulate Cortex)



Nieuwenhuys et al., 2008

Anterior Cingulate Cortex



Nieuwenhuys et al., 2008

Regions co-activated with ACC in task imaging studies

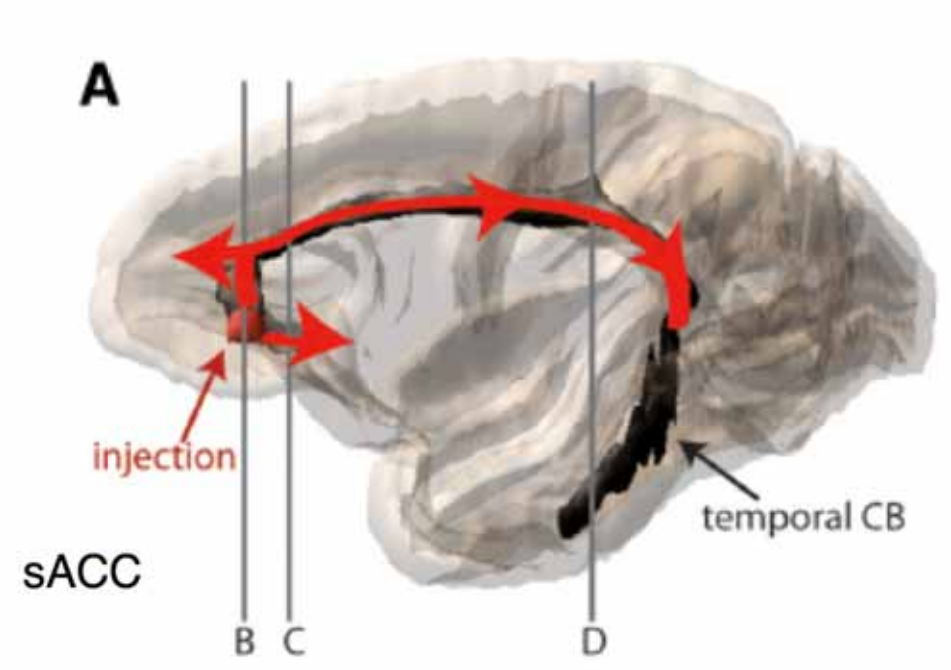
Table 4
Cortical regions showing increased coactivated neuroimaged activity with ACC in studies using healthy participants.

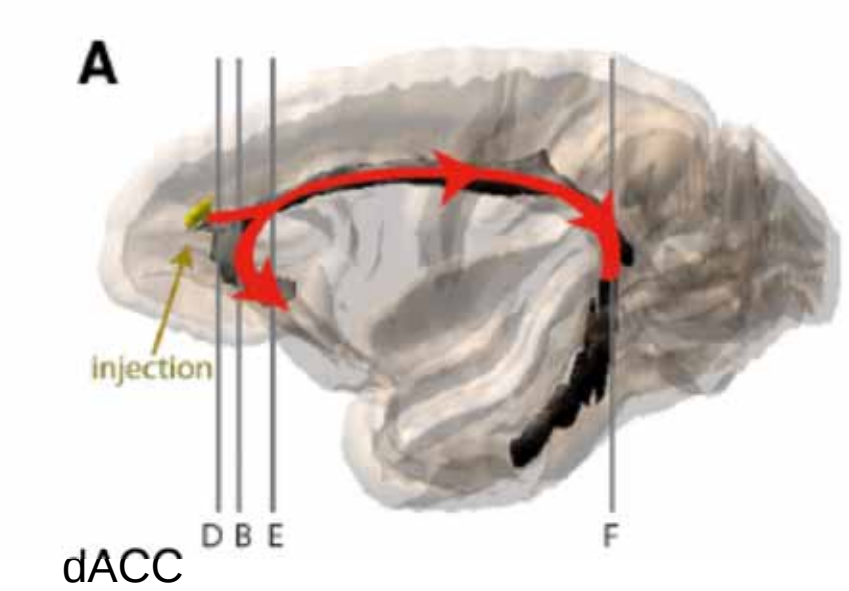
Study	Stimulus/task	Cortical regions
Bie-Olsen et al. (2009)	Hypoglycemia during reaction time tasks	Bilateral frontal gyrus, right parahippocampal gyrus, right lingual gyrus, left superior temporal gyrus
Carlson et al. (2012)	Masked fearful faces	Basal forebrain
Critchley et al. (2003)	*n*-back	Dorsolateral, medial frontal, orbitofrontal, parietal
Dosenbach et al. (2007)	Resting state connectivity	Medial superior frontal, insular, anterior prefrontal
Eisenberger et al. (2003)	Exclusion from a virtual game	Right ventral prefrontal
Farrell et al. (2008)	Thirst	Premotor, superior temporal gyrus, primary sensory and primary motor
Freedman et al. (2006)	Thermal regulation	Insular
Grabenhorst et al. (2010)	Rating the pleasantness of dairy drinks	Orbitofrontal varying in fat content
Guo et al. (2011)	Word production in bilinguals	Supplemental motor area
Haxby et al. (2000)	Working memory	Inferior frontal, anterior and posterior middle frontal gyrus, superior frontal sulcus, medial superior frontal
Karama et al. (2002)	Visual sexual stimuli	medial prefrontal, orbitofrontal, insular, occipitotemporal
Killgore and Yurgelun-Todd (2004)	Masked sad and happy faces	None
Lindgren et al. (2012)	Moving human touch	Insular, contralateral primary somatosensory
Lorberbaum et al. (1999)	Crying babies (mothers' response)	Right medial prefrontal
MacDonald et al. (2000)	Stroop-like	Dorsolateral prefrontal
Mies et al. (2011)	Feedback valence in time estimation	Right superior frontal gyrus
Milham et al. (2003)	Stroop-like	Dorsolateral prefrontal
Mohanty et al. (2007)	Stroop-like	Dorsolateral prefrontal
Nee et al. (2011)	Animal vs. human body part identification	Analysis limited to ACC
Pardo et al. (1990)	Stroop	Left premotor, left postcentral, right superior temporal, bilateral peristriate
Redoute et al. (2000)	Visual sexual stimuli	Orbitofrontal
Roberts and Hall (2008)	Stroop-like	Lateral prefrontal, anterior insular, parietal
Schulz et al. (2011)	Cued go/no-go	Dorsolateral prefrontal, frontal operculum, sensory association, extra-pyramidal motor
Seeley et al. (2007)	Resting state connectivity	Insular
Tataranni et al. (1999)	Hunger	Insular, orbitofrontal, parahippocampal
van Veen et al. (2001)	Letter identification with congruent/conflicting cues	Dorsolateral prefrontal, right parietal, posterior cingulate gyrus left inferior frontal, left precuneus, left polar frontal
von Leupoldt et al. (2009)	Breathlessness and thermal pain	Insular
Weissman et al. (2005)	Reaction time for global/local letters	Dorsolateral prefrontal
Zang et al. (2003)	Sternberg working memory	Middle frontal gyrus, left inferior frontal

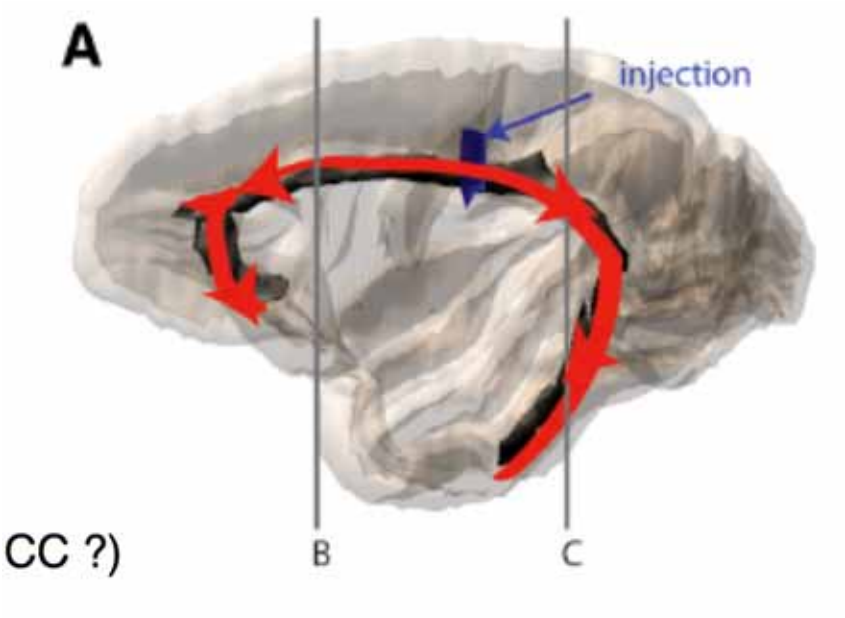
Gasquoine, (2013)

Trace studies in macaque monkeys

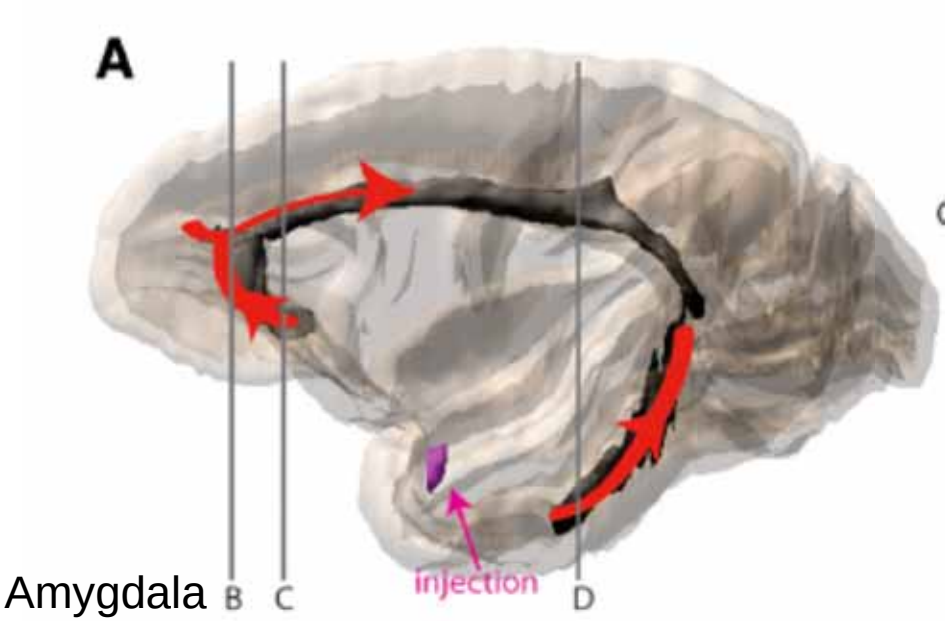
Heilbronner and Haber, (2014).







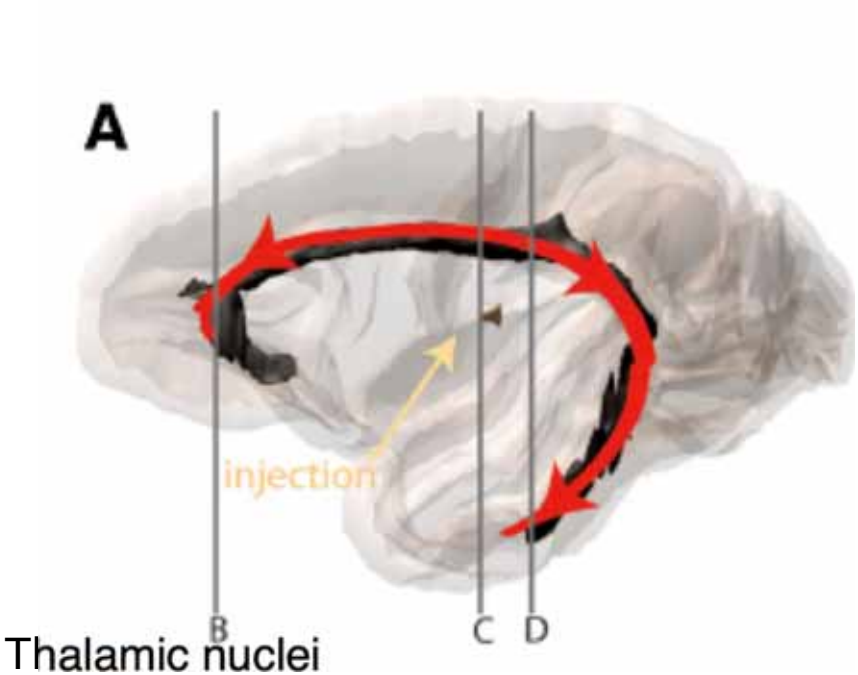
PCC (MCC ?)



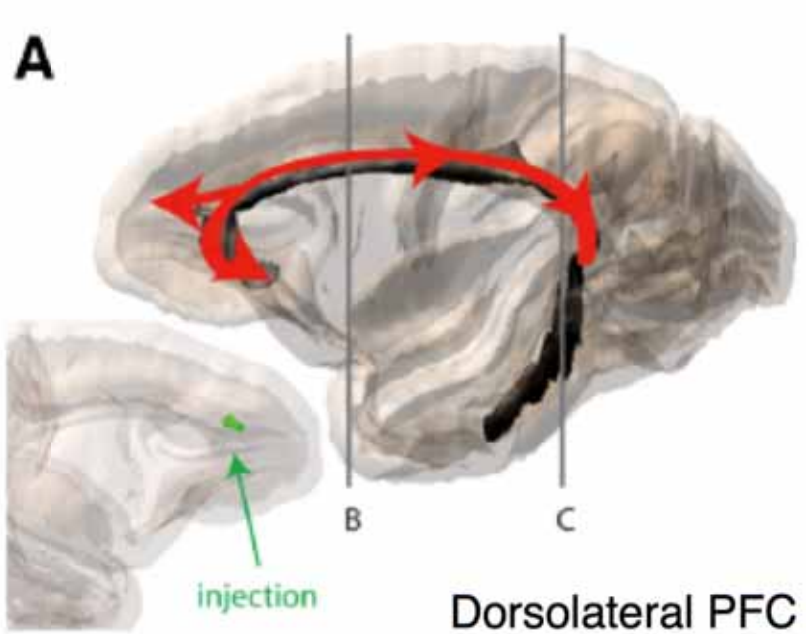
Amygdala

Trace studies in macaque monkeys

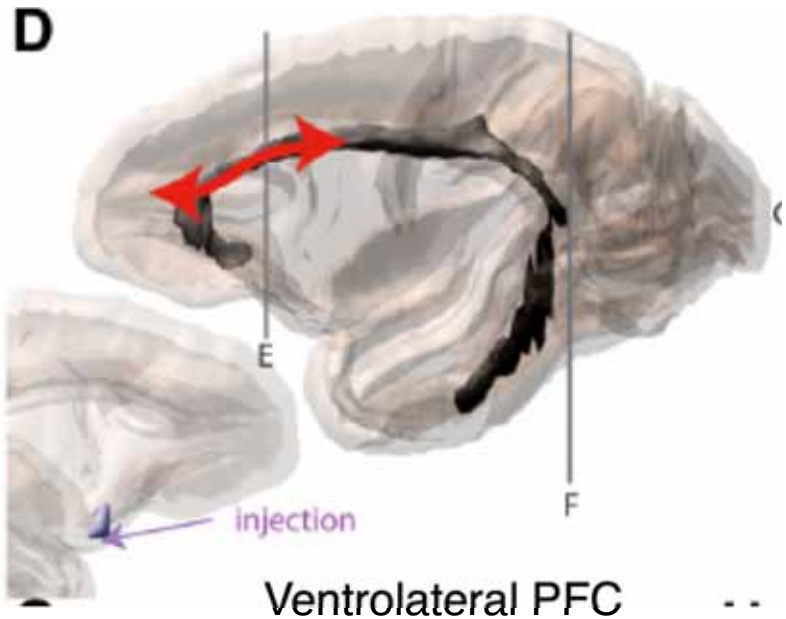
Heilbronner and Haber, (2014).



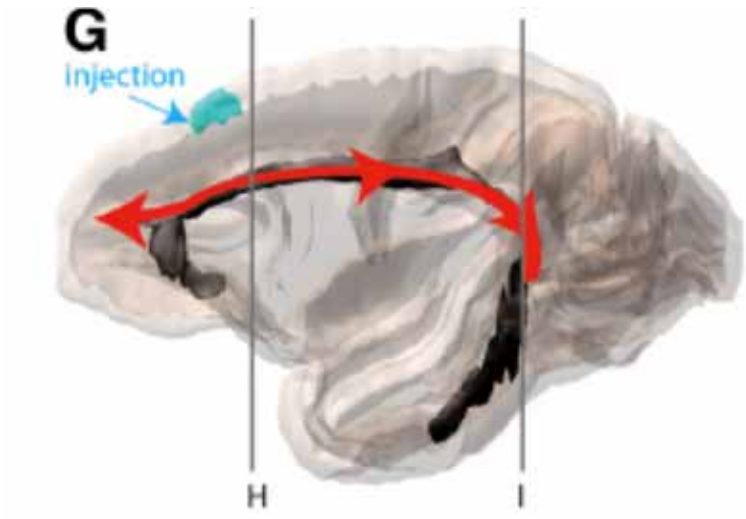
Thalamic nuclei



Dorsolateral PFC



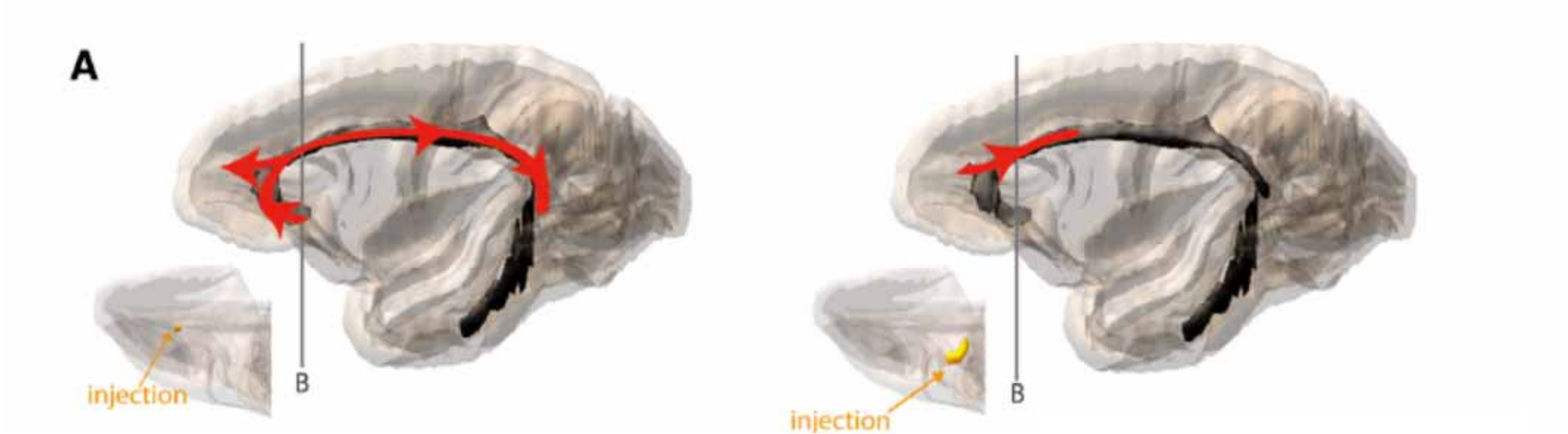
Ventrolateral PFC



Dorsomedial PFC

Trace studies in macaque monkeys

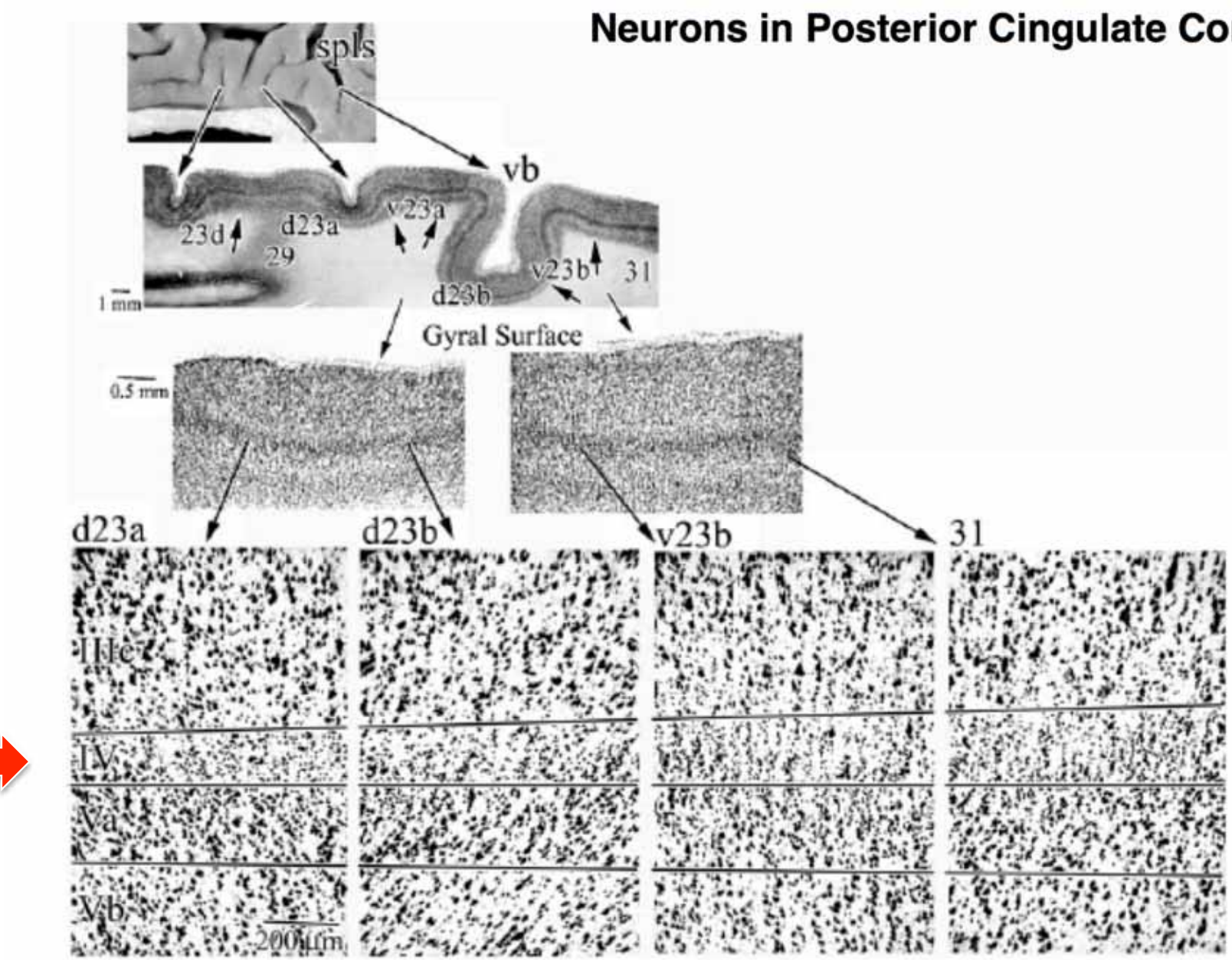
Heilbronner and Haber, (2014).



Central OFC

Lateral OFC

Neurophysiology



IV

Vogt et al., (2006)

Neurons in Middle Cingulate Cortex

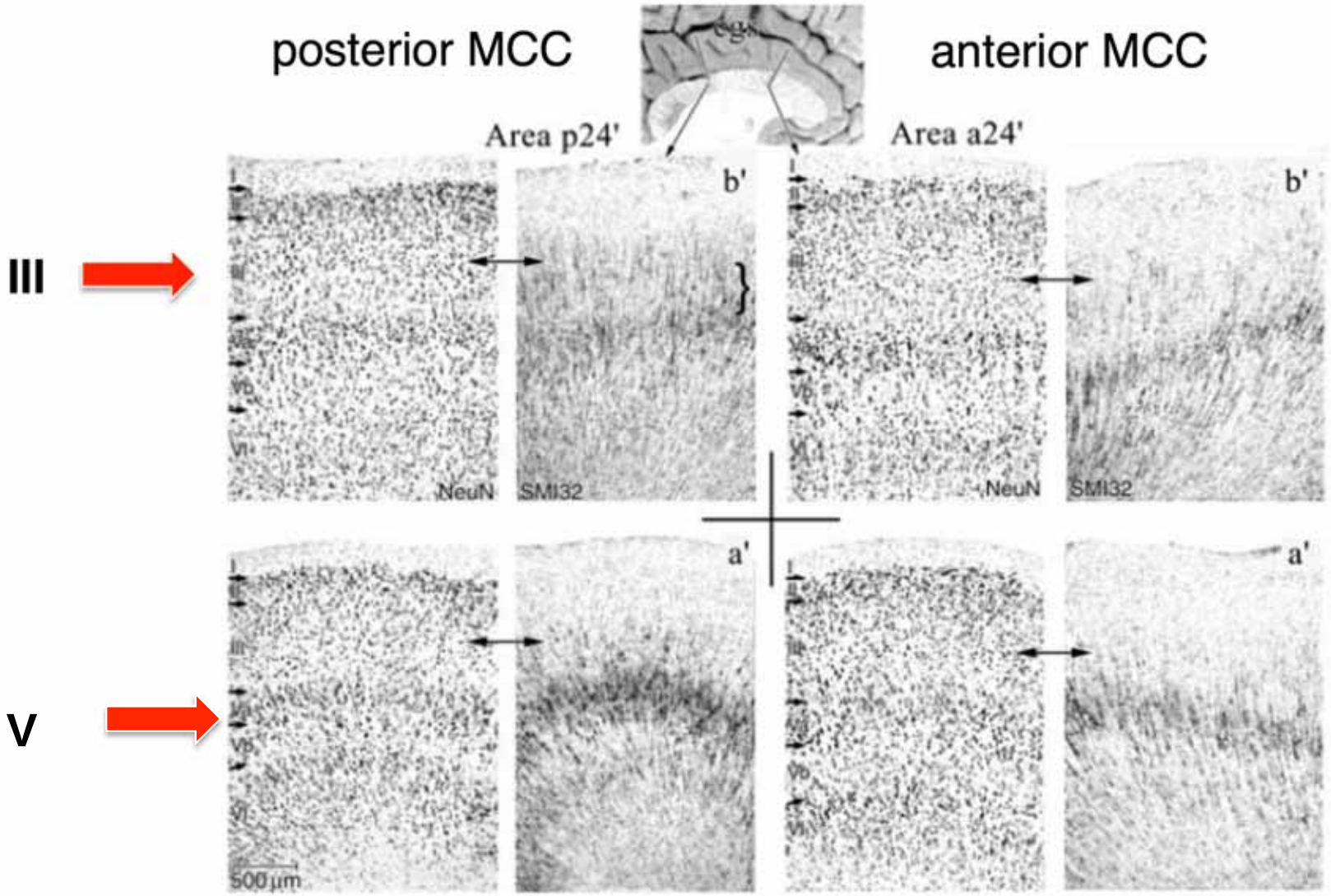
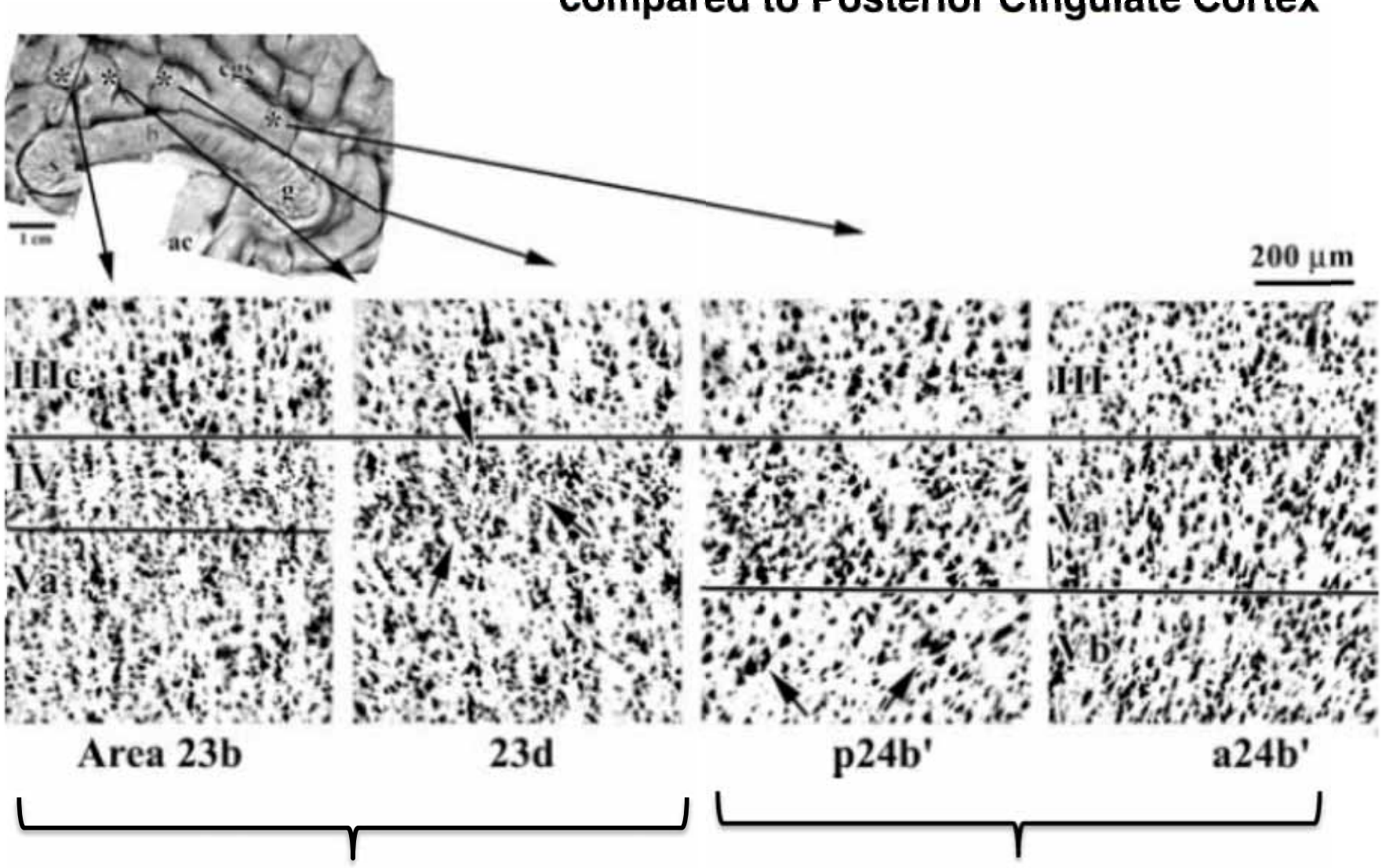


FIG. 3. Features of MCC areas a24′ and p24′ for both 'a' and 'b' subdivisions in NeuN and SMI32 of Case 2. Of particular note are the higher densities of NFP-expressing neurons in deep layer III (SMI32; below double arrows) and the greater density of neurons in layer Va and their expression of NFP in area p24′. Because the layers in NeuN and SMI32 sections were exactly co-registered, they are not re-labelled in SMI32.

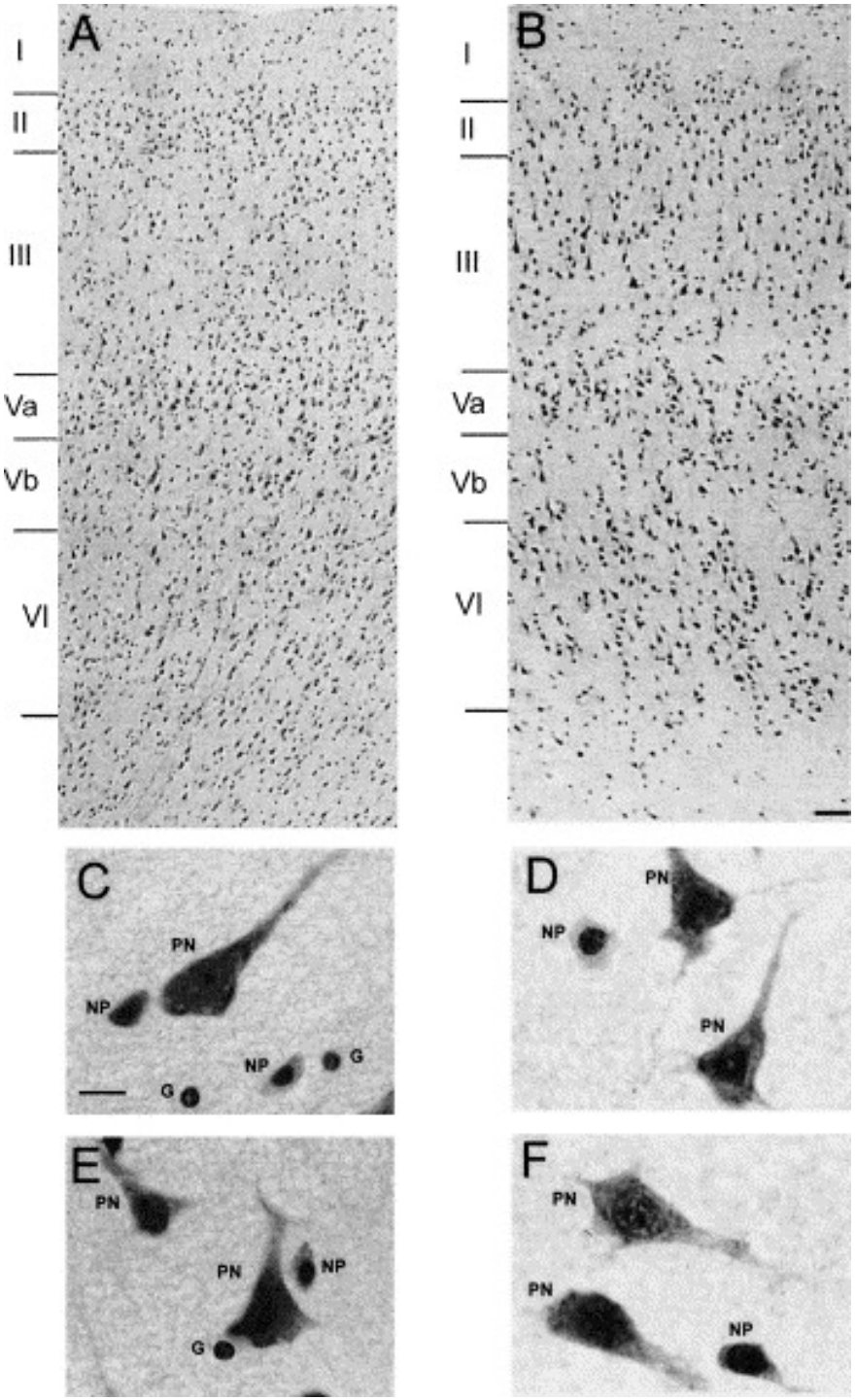
Neurons in Middle Cingulate Cortex compared to Posterior Cingulate Cortex



Posterior cingulate cortex

Posterior and anterior MCC

Vogt et al., (2003)



Neurons in Anterior Cingulate Cortex

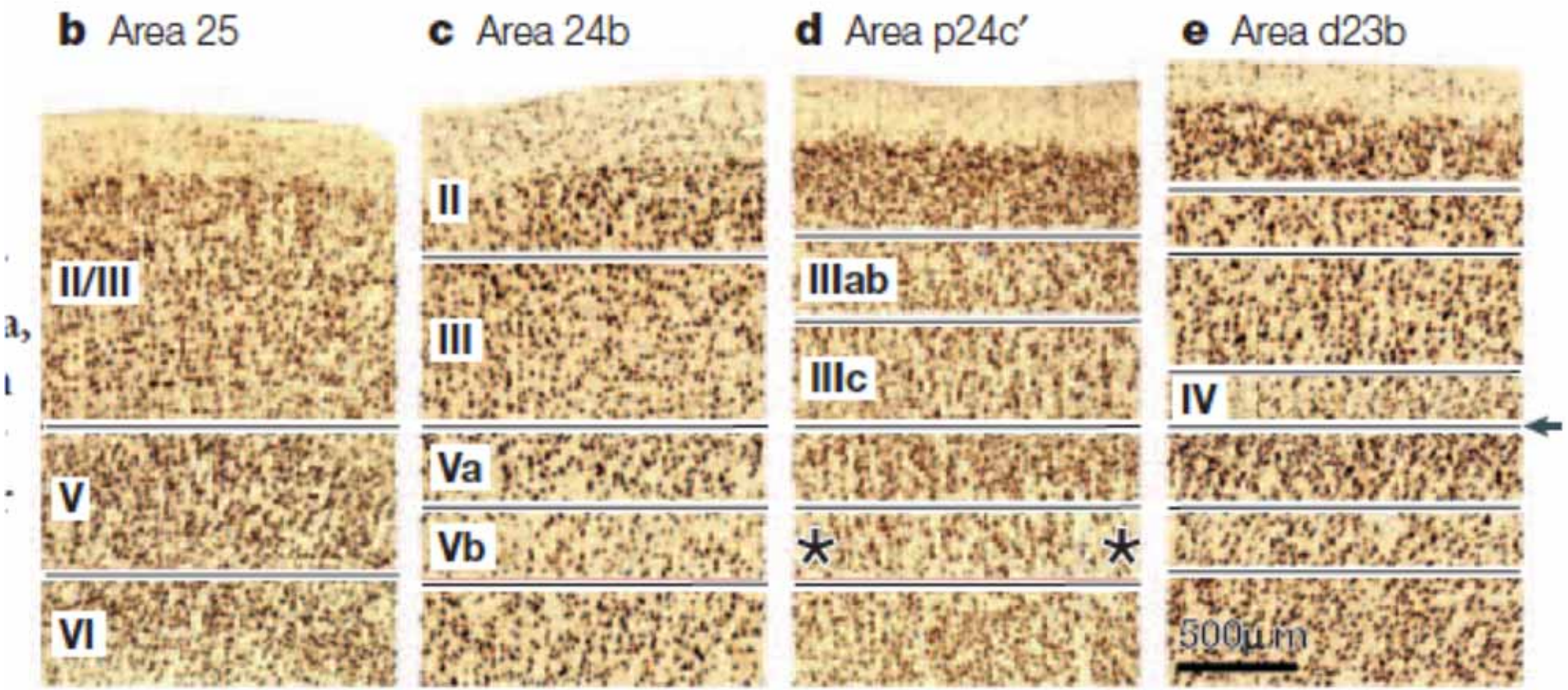
Pyramidal > Non-pyramidal

	Nissl	NeuN	Nissl	NeuN
II	89	102	67	69
III	49	55	25	29
Va	72	86	41	45
Vb	45	49	22	25
VI	64	76	11	16

Gittins and Harrison, (2004)

Rostro-caudal progressive laminar differentiation

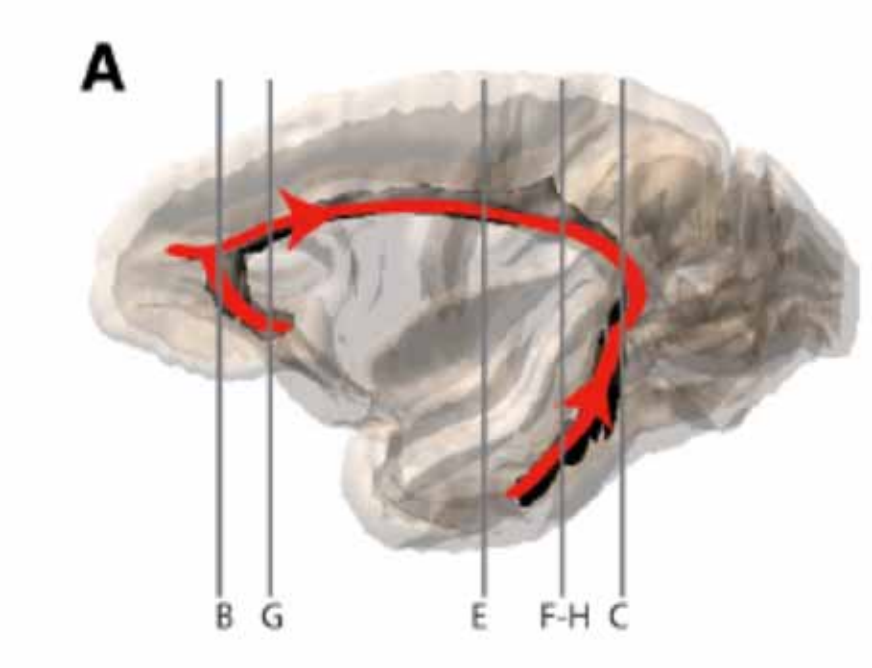
Subgenual ACC **Dorsal ACC** **Middle CC** **Posterior CC**



Vogt, (2005)

Neurochemical Systems

Neuromodulator pathways in macaque monkeys



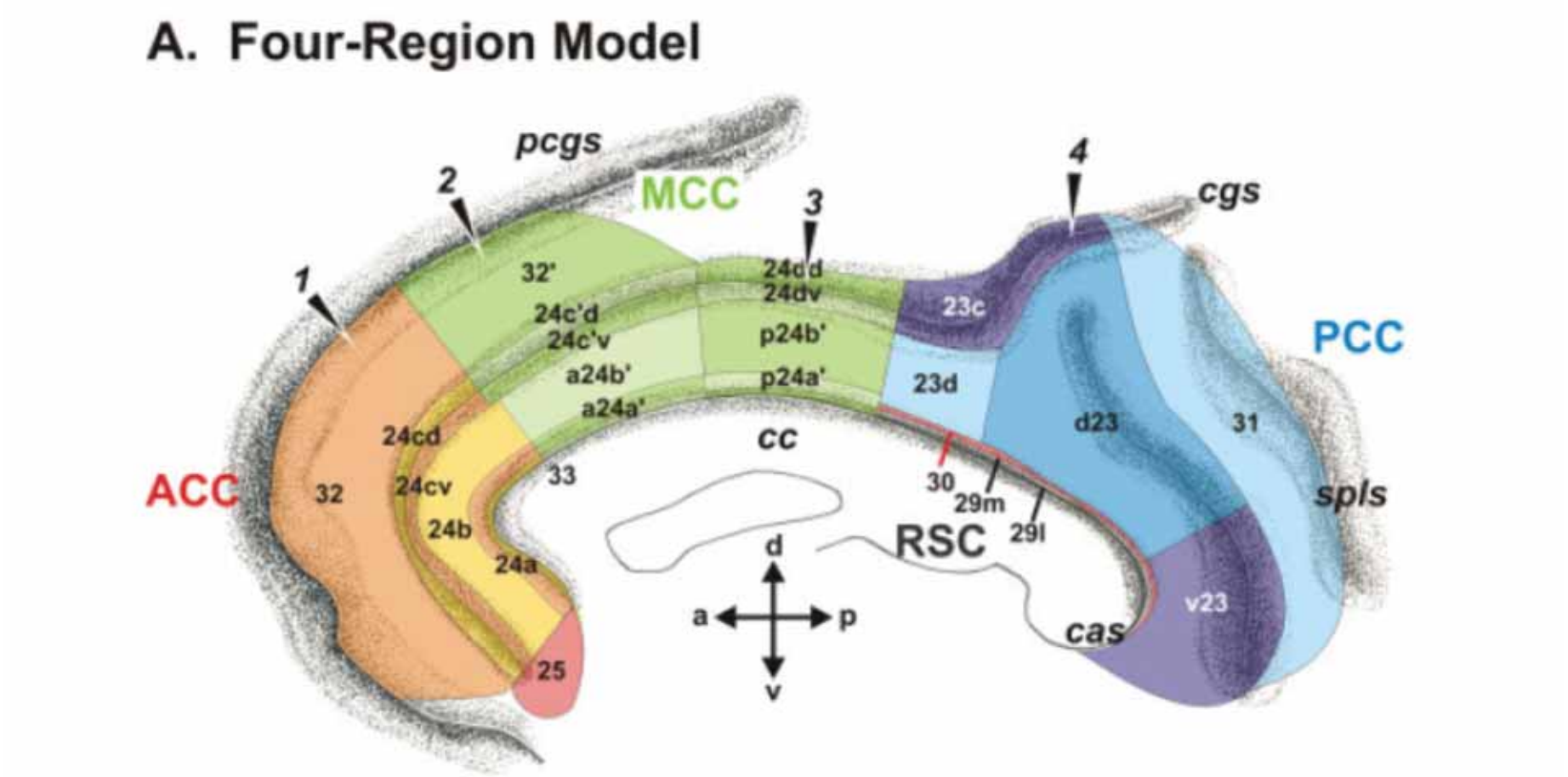
-**Dopaminergic/noradrenergic fibers**
-**Serotonergic fibers**
-**Cholinergic fibers**

All through the cingulum bundle.

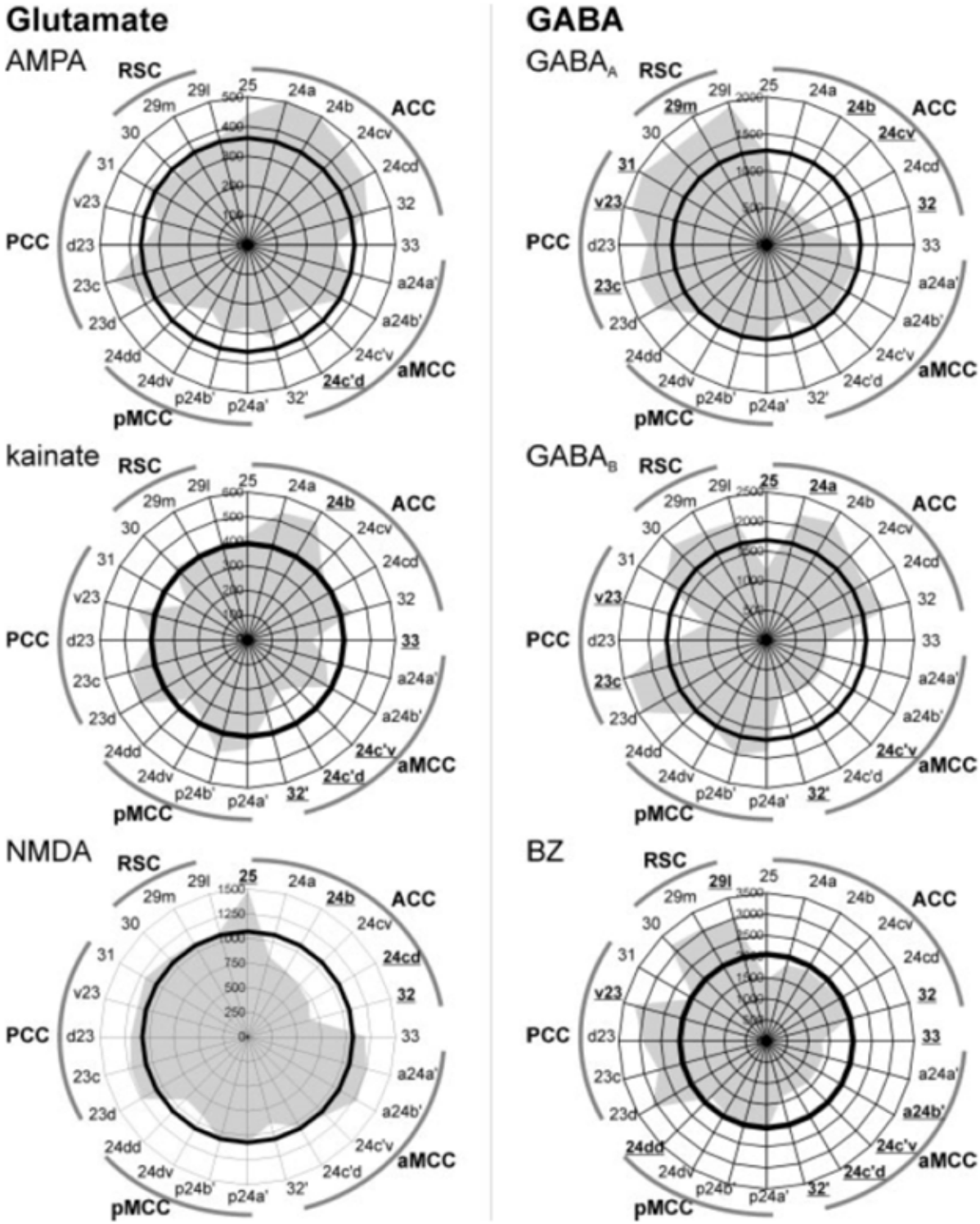
Heilbronner and Haber, (2014).

Receptor mapping using autoradiography in human cingulate cortex

The receptor fingerprints of 15 receptors for classical neurotransmitters distinguished cingulate regions, subregions, and areas.

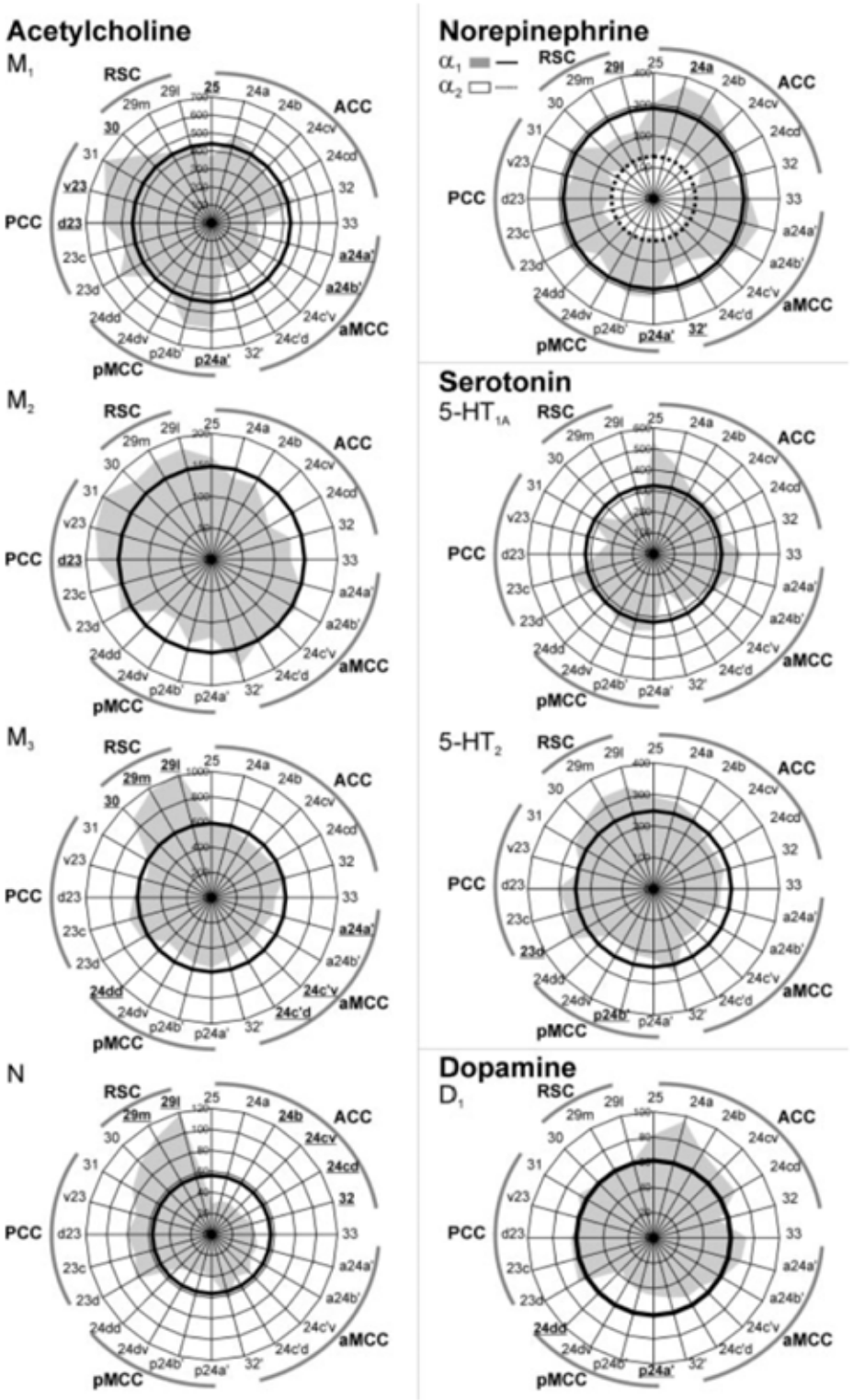


Palomero-Gallagher et al., 2009



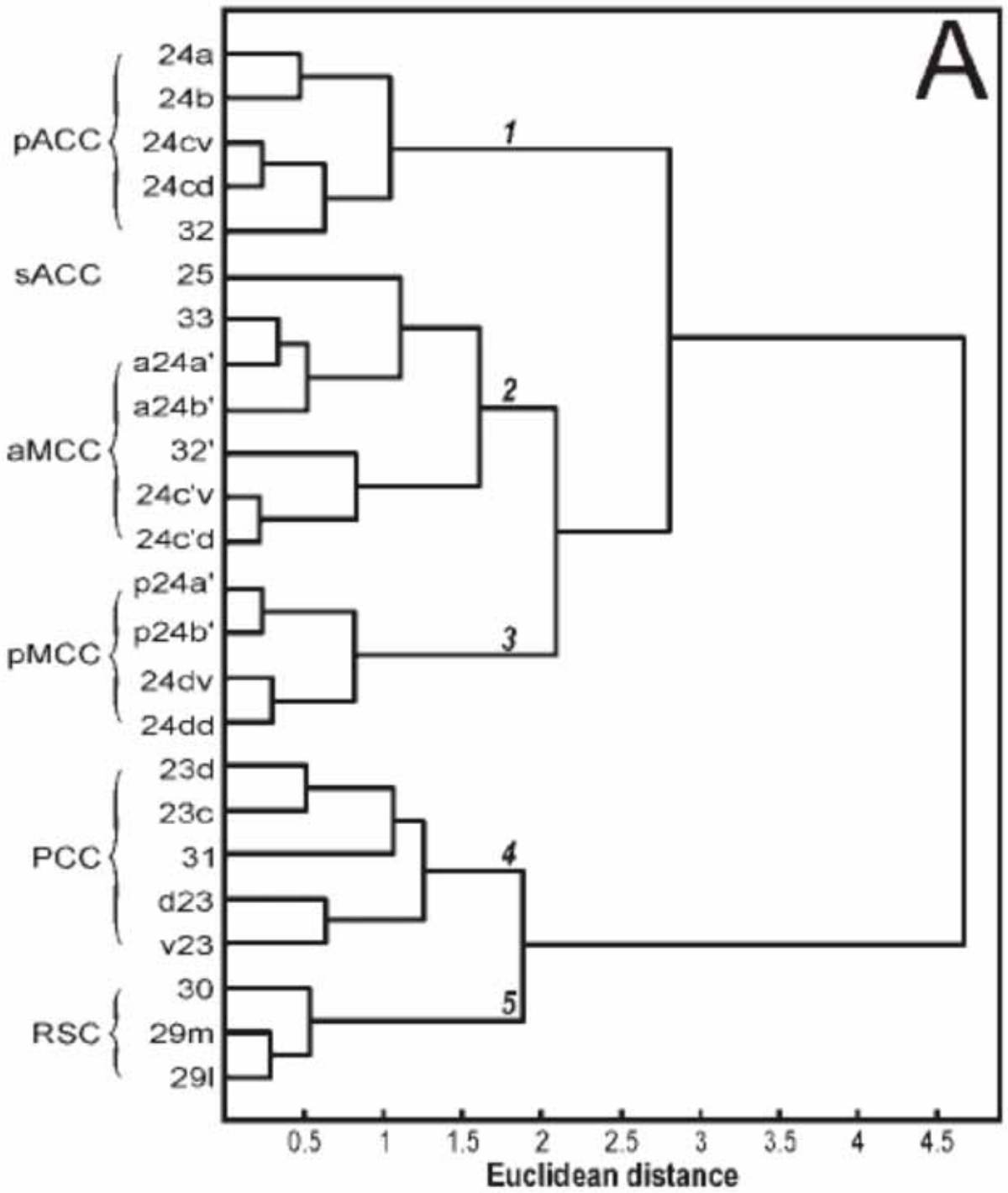
Comparative receptors concentration in each sub-division of cingulate cortex

Palomero-Gallagher et al., 2009



Comparative receptors concentration in each sub-division of cingulate cortex

Palomero-Gallagher et al., 2009



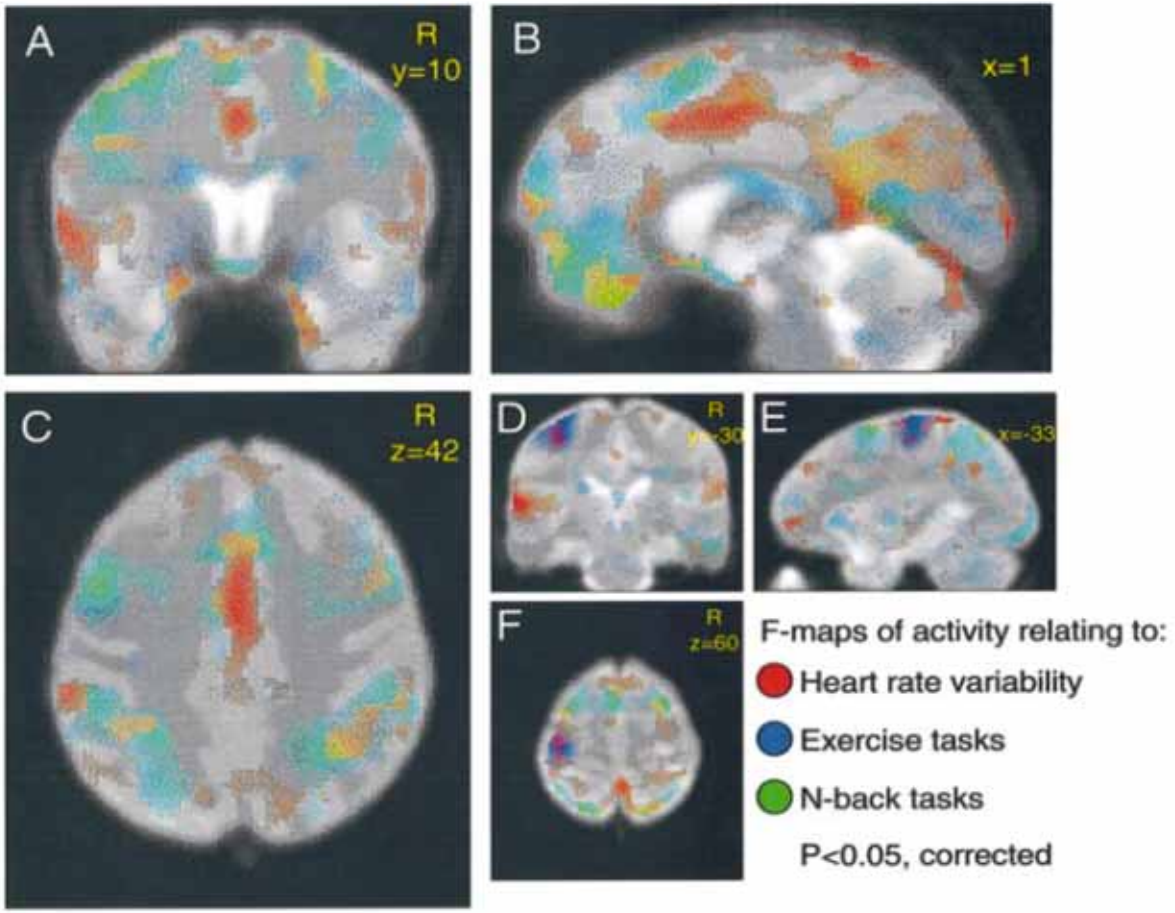
Hierarchical clustering based on receptors profile.

5 sub-divisions

Palomero-Gallagher et al., 2009

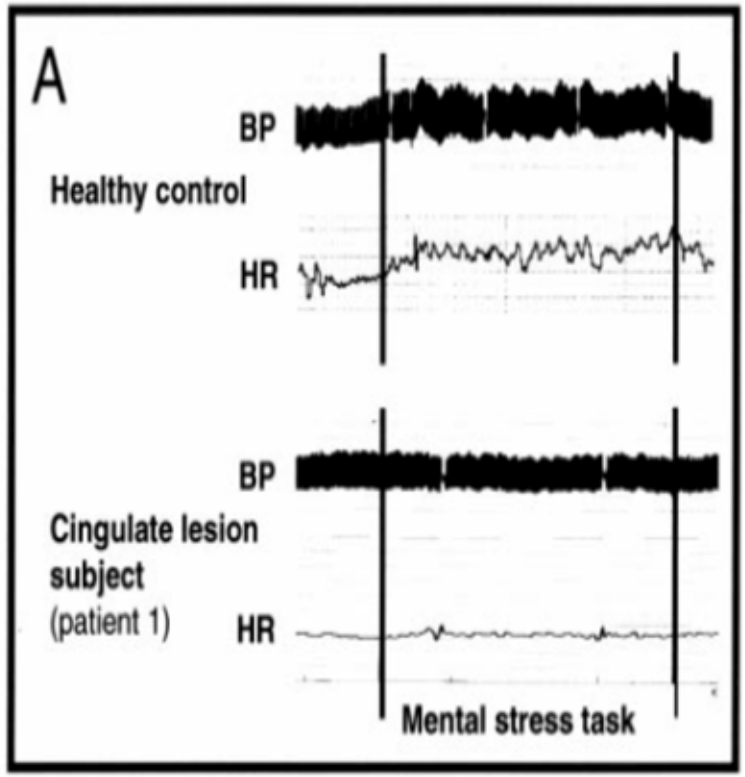
Physiological Correlates

Autonomic state of <u>cardiovascular arousal</u> supported by dorsal ACC during effortful cognitive and motor behavior.
(fMRI and ECG)



Results for 6 health subjects

Damage to ACC affects HR



Critchley et al., (2003)

Other physiological correlates

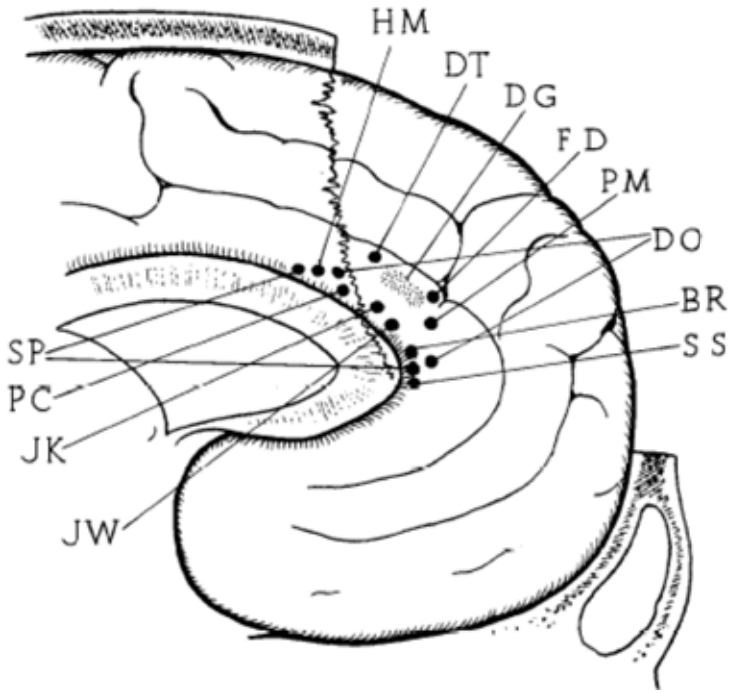
BOLD activity of ACC correlated with **spontaneous breathing** in men.
(Evans et al., 2009)

Electrical stimulation of cingulate cortex in monkeys **increase heart rate** while monkeys are trying to attenuate it after exercise.
(Chefer et al., 1997)

Electric stimulation of anterior cingulate in rats, elicit a **fall in blood pressure.**
(Burns and Wyss, 1985)

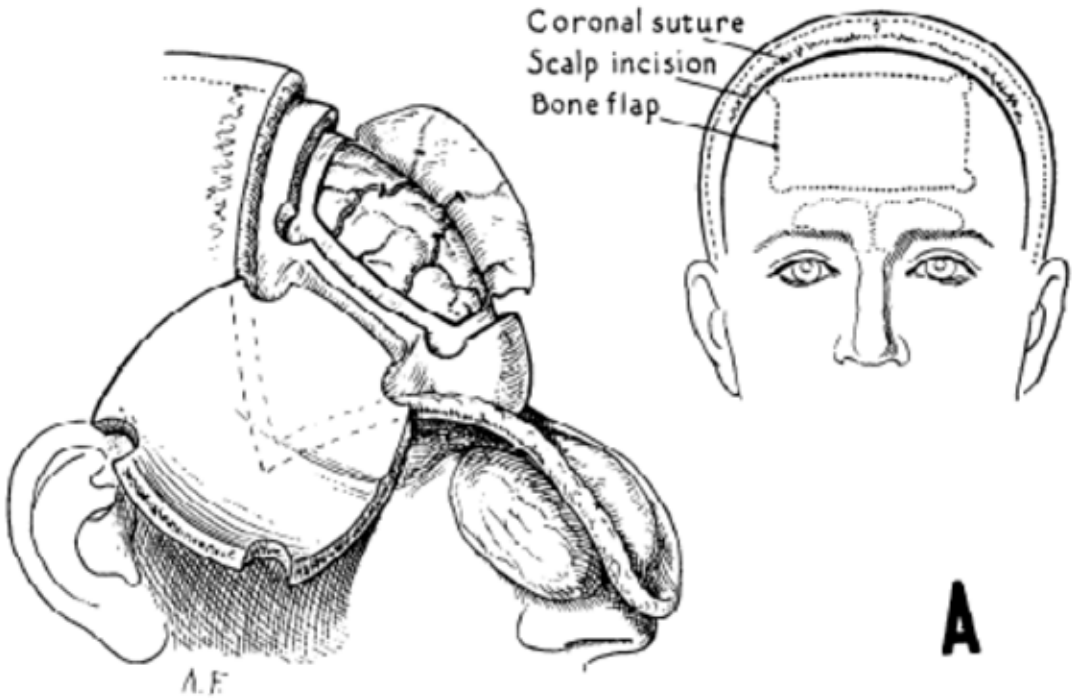
Autonomic and somatic responses after electrical stimulation of cingular gyrus in dogs, such as changes in **blood pressure** and **respiratory rate**, and bladder contractions.
(Kremer, 1947)

Electrical stimulation of anterior cingulate cortex in men produced autonomic effects, such as **increase of blood pressure, pulse rate, respiratory rate.**
(Pool and Ransohoff, 1949)



Sites of electrical stimulation

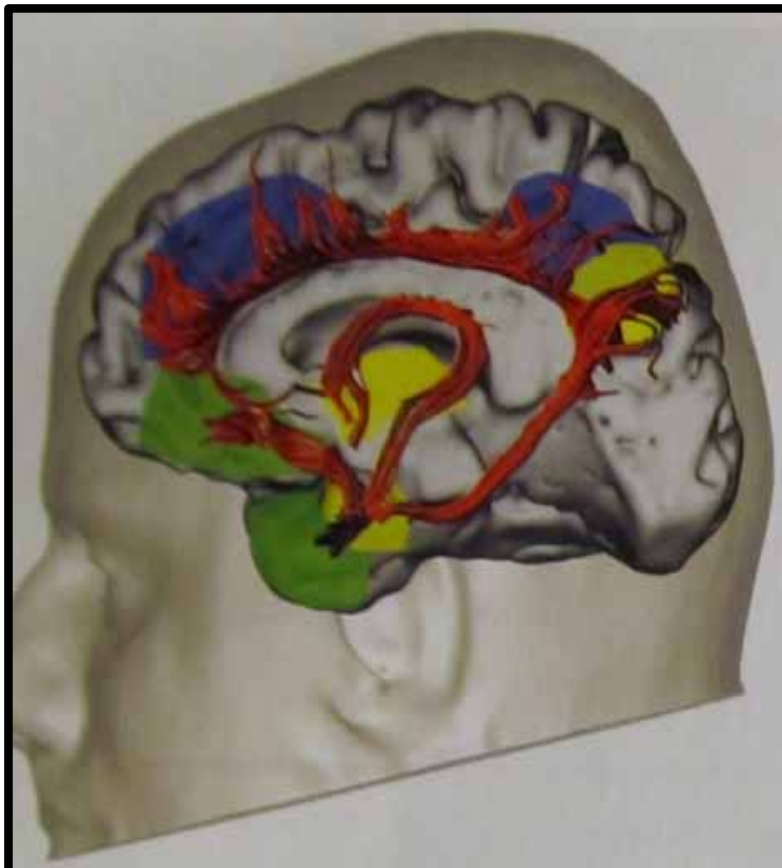
Frontal gyrectomy site



Pool and Ransohoff, (1949)

Behavioral Correlates

Summary



retrosplenial-hippocampal-diencephalic network

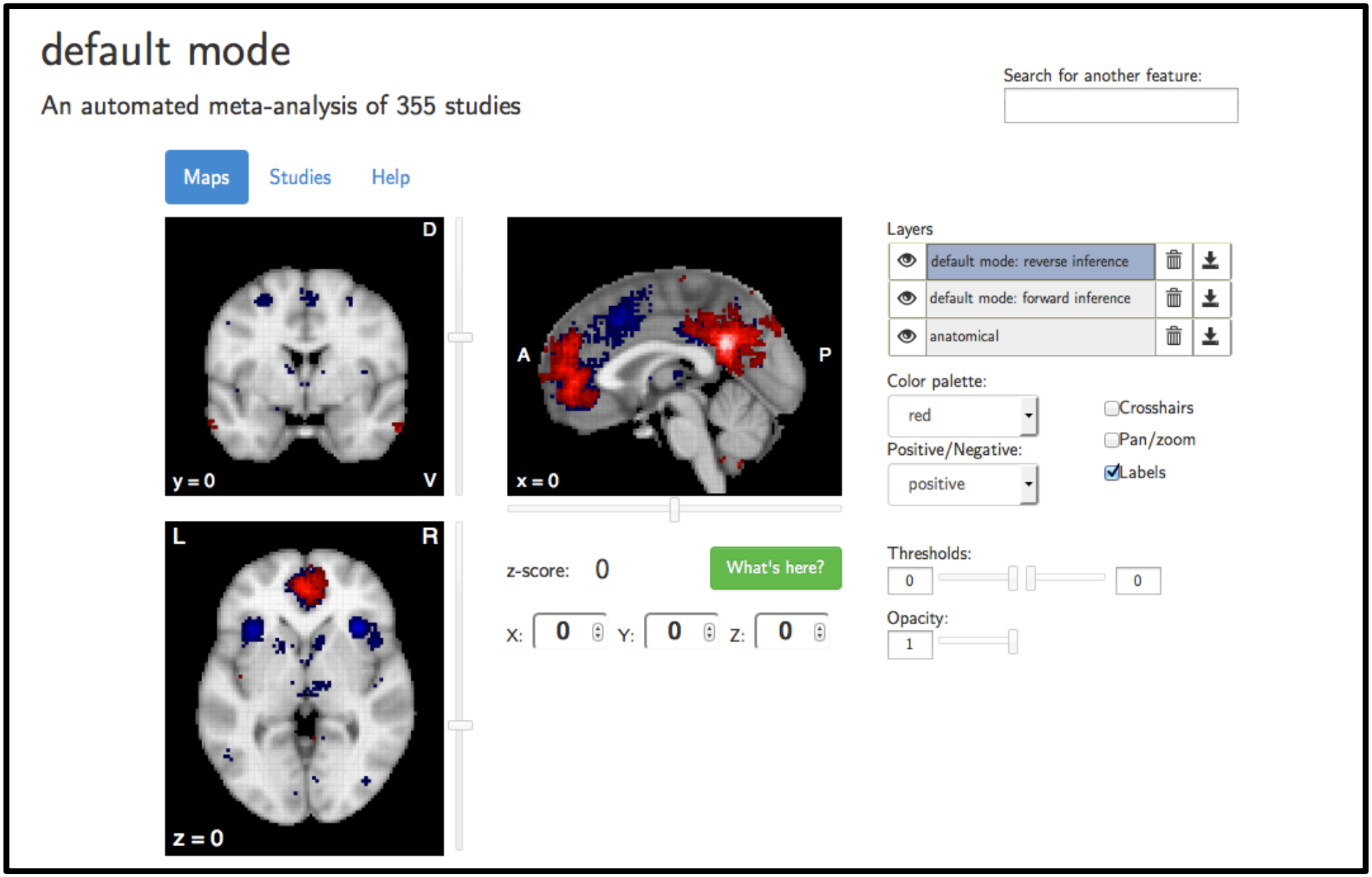
temporal-amygdala-orbitofrontal network

medial 'default network'

Network	Functions	Disorder
Retrosplenial-hippocampal-diencephalic	•spatial orientation •memory	•Amnesias •Korsakoff's syndrome •Mild Cognitive impairment •Alzheimer's disease (early) •Balint syndrome
Temporo-amydgala-orbitofrontal	•Olfactory-gustatory-visceral functions •Multimodal sensory integration •Behavioural inhibition •Outcome monitoring •Object-reward association learning •Memory for temporally complex visual information	•Depression •Temporal lobe epilepsy •Semantic dementia •Alzheimer's Disease (advanced) •Klüver-Bucy syndrome •Geschwind's syndromes •Psychopathy
Default network	•Attention •Mentalizing •Response selection and action monitoring •Autobiographical memory •Self-knowledge •Pain perception •Empathy •Person perception	•Mild Cognitive Impairment •Alzheimer's Disease (early) •Autism •Attention Deficit Hyperactivity Disorder •Schizophrenia •Depression •Anxiety •Obsessive compulsive disorder

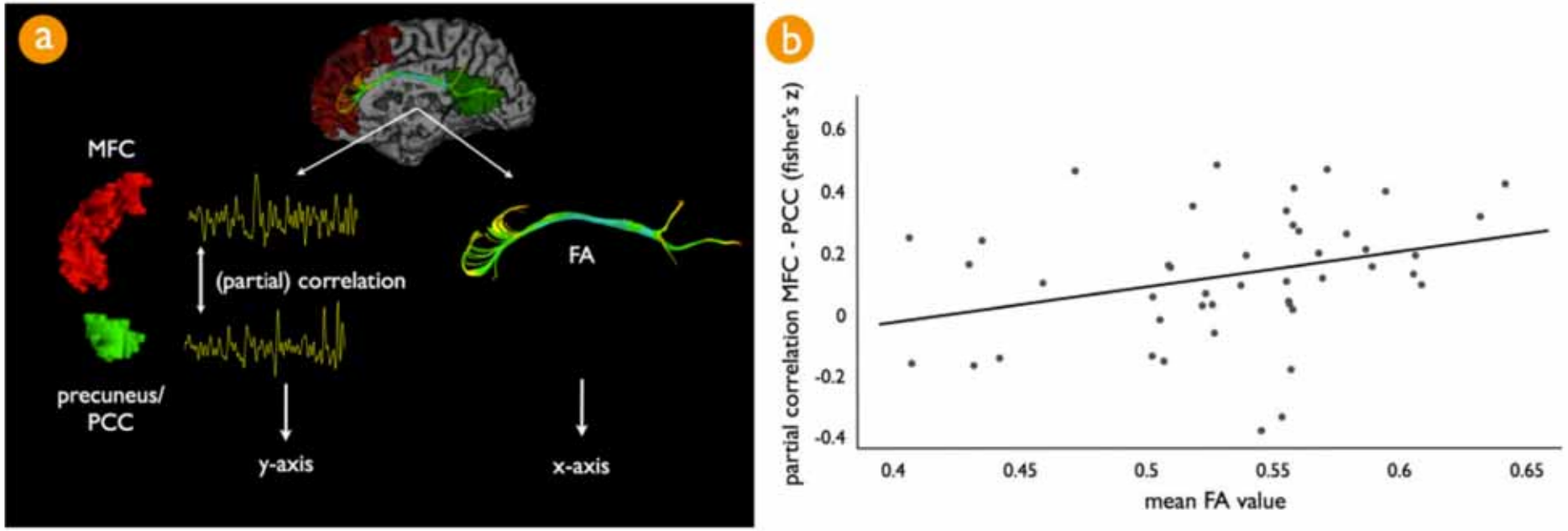
Catani, M., & Thiebaut de Schotten, M. (2012)

DMN is active during resting-state and decreased activity during goal-directed tasks.



Neurosynth.org

Mean FA of dorsal cingulum positively correlated with rs-functional correlation of PCC and ACC (DMN)



Van den Heuvel et al., (2008)

Behavioral functions ascribed to ACC

Table 3
Summary terms for behavioral functions ascribed to anterior cingulate cortex in neuroimaging and review studies using healthy participants.

Summary	Term studies
Attention	Bush et al. (2000); Carlson et al. (2012); Killgore and Yurgelun-Todd (2004); Mohanty et al. (2007); Pardo et al. (1990); Weissman et al. (2005).
Conflict, feedback, error, or performance monitoring	Botvinick et al. (2004); Eisenberger et al. (2003); Holroyd and Coles (2002); MacDonald et al. (2000); Mies et al. (2011); Milham et al. (2003); Nee et al. (2011); Roberts and Hall (2008); Smith and Jonides (1999); van Veen et al. (2001); Zang et al. (2003).
Maintenance of set	Dosenbach et al. (2007).
Goal-directed behavior	Dosenbach et al. (2007); Grabenhorst and Rolls (2011); Schulz et al. (2011).
Working memory	Haxby et al. (2000); Smith and Jonides (1999).
Inhibition	Guo et al. (2011).
Autonomic control	Critchley et al. (2003); Devinsky et al. (1995); Farrell et al. (2008); Seeley et al. (2007); Williamson et al. (2006)
Homeostatic incongruence	Bie-Olsen et al. (2009); Freedman et al. (2006); Seeley et al. (2007); Tataranni et al. (1999); von Leupoldt et al. (2009).
Emotional concomitants of physical and/or social pain	Eisenberger and Lieberman (2004); Lorberbaum et al. (1999); Peyron et al. (2000); Price (2000).
Encoding of the pleasant/averseness of stimuli	Grabenhorst et al. (2010); Grabenhorst and Rolls (2011); Hayes and Northoff (2011); Lindgren et al. (2012); Wallis and Kennerley (2010).
Response selection	Bie-Olsen et al. (2009); Devinsky et al. (1995); Grabenhorst et al. (2010); Karama et al. (2002); Milham et al. (2003); Peyron et al. (2000); Price (2000); Redoute et al. (2000); Schulz et al. (2011); Shackman et al. (2011); van Veen et al. (2001); von Leupoldt et al. (2009); Weston (2012).

Gasquoine, (2013)

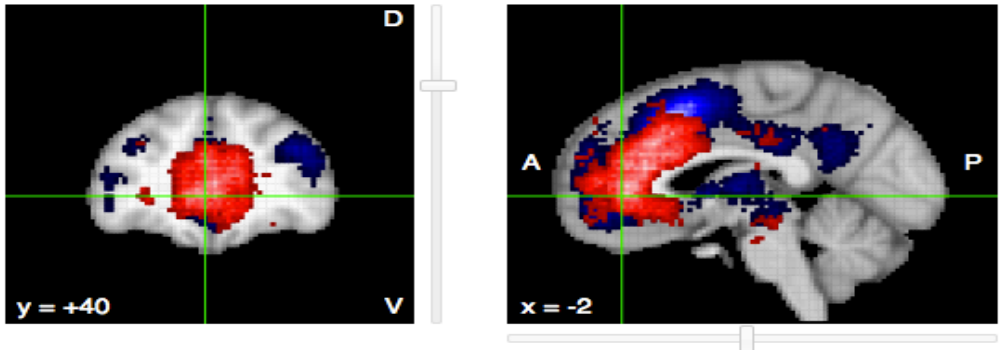
Just for curiosity

anterior cingulate

An automated meta-analysis of 1433 studies

Search for another feature:

Maps Studies Help



Layers

- anterior cingulate: reverse
- anterior cingulate: forward
- anatomical

Color palette: red

Positive/Negative: positive

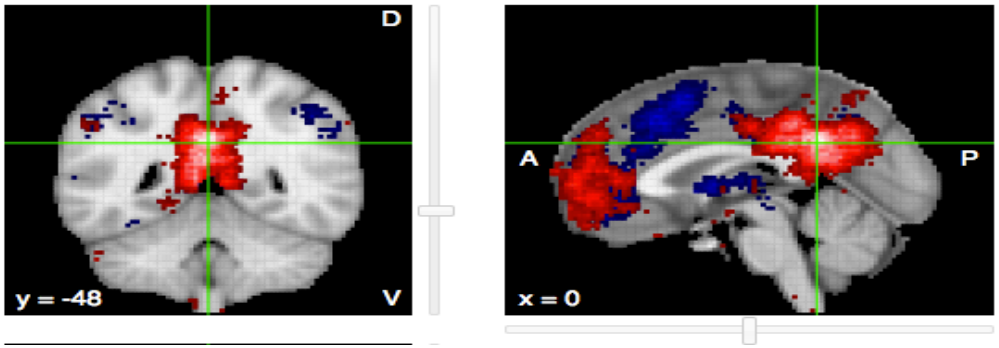
Crosshairs
Pan/zoom
Labels

posterior cingulate

An automated meta-analysis of 615 studies

Search for another feature:

Maps Studies Help



Layers

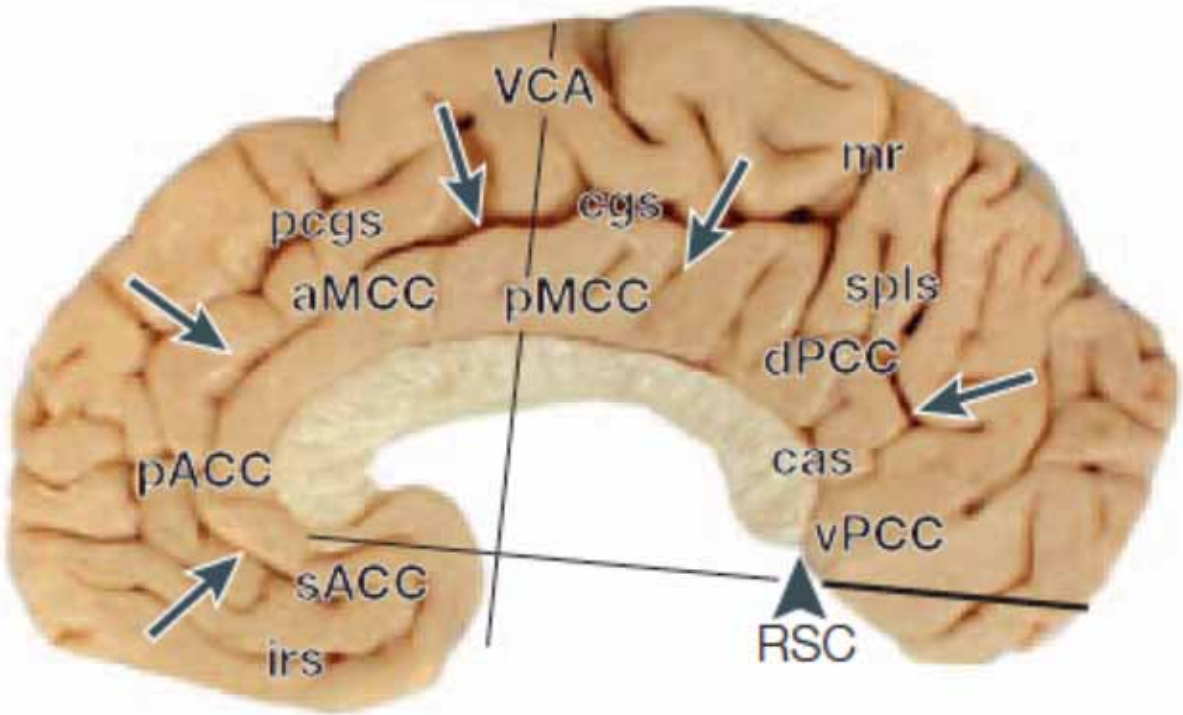
- posterior cingulate: reverse
- posterior cingulate: forward
- anatomical

Color palette: red

Positive/Negative: positive

Crosshairs
Pan/zoom
Labels

Behavior and cingulate cortex subdivision



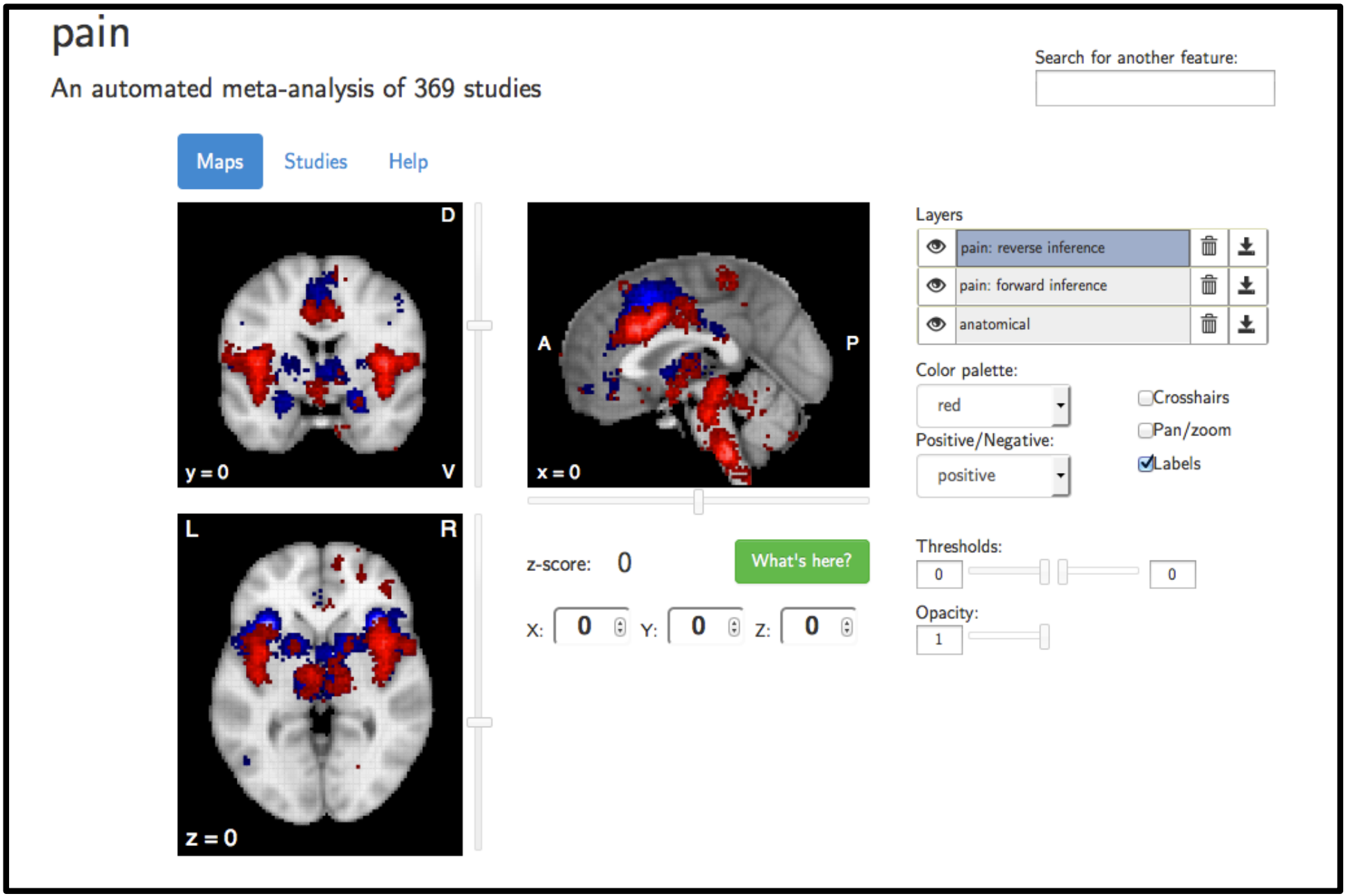
ACC: emotion
- sACC, visceral integration

MCC: response selection
- aMCC, fear-avoidance
- pMCC, skeletomotor orientation

PCC: personal orientation
- dPCC, visuospatial orientation
- vPCC, self-relevance assessment

RSC: memory formation/access

Vogt, (2005)



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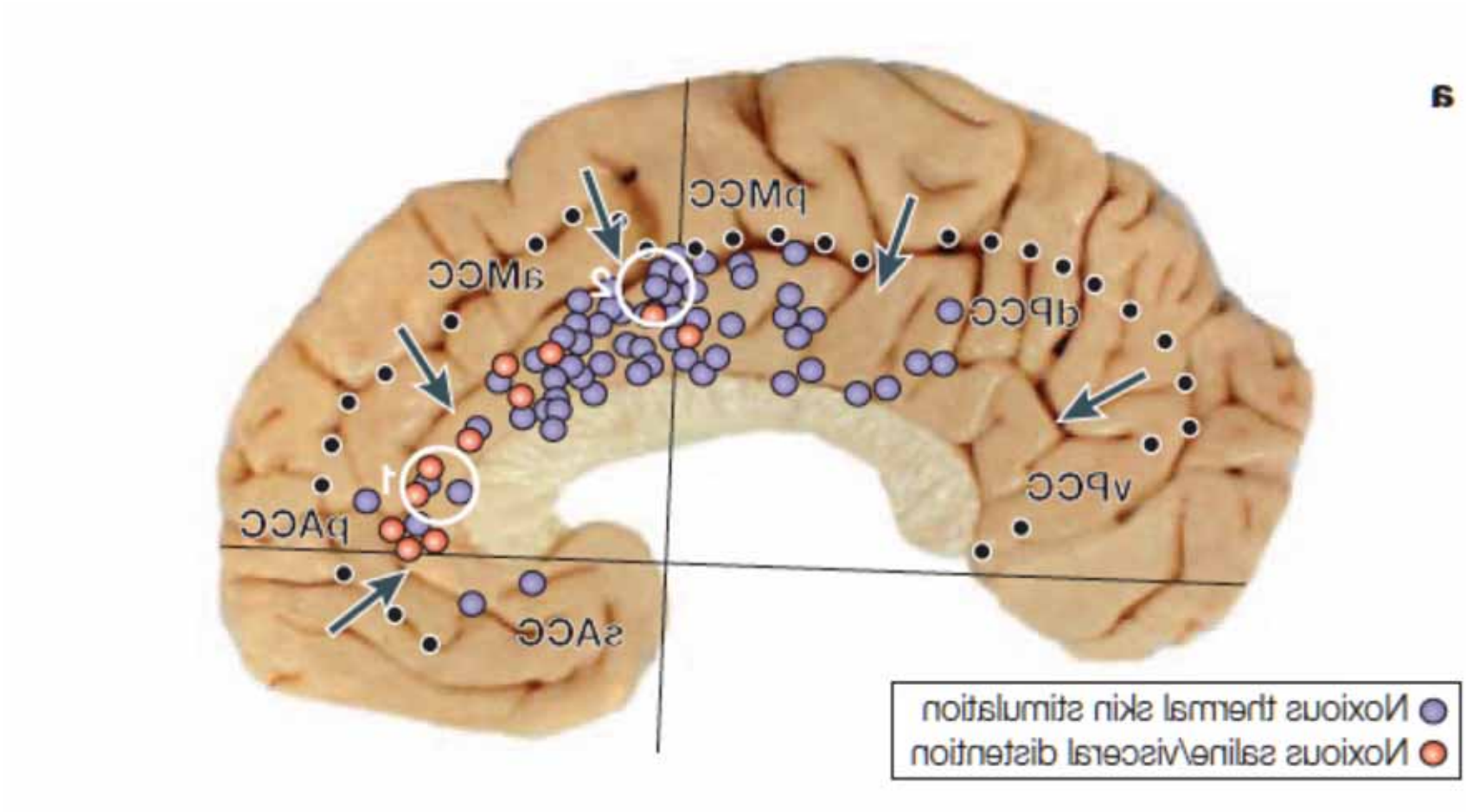
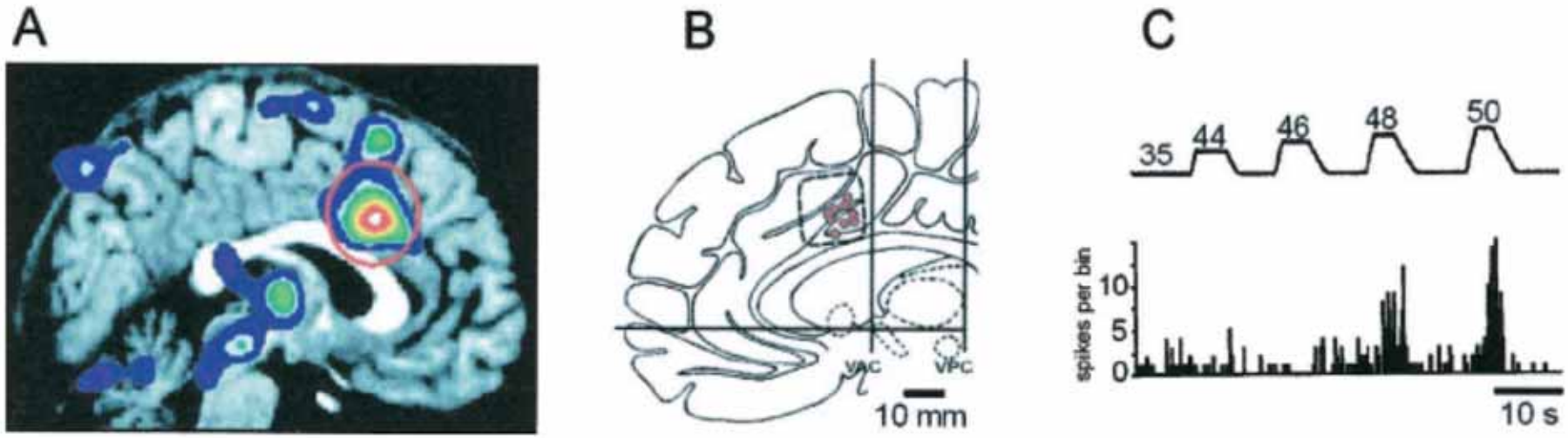
Activation sites of pain in Anterior Cingulate Cortex



Summary of 40 studies showing peak activation sites.
purple -> thermal skin stimulation
red -> saline/visceral distention

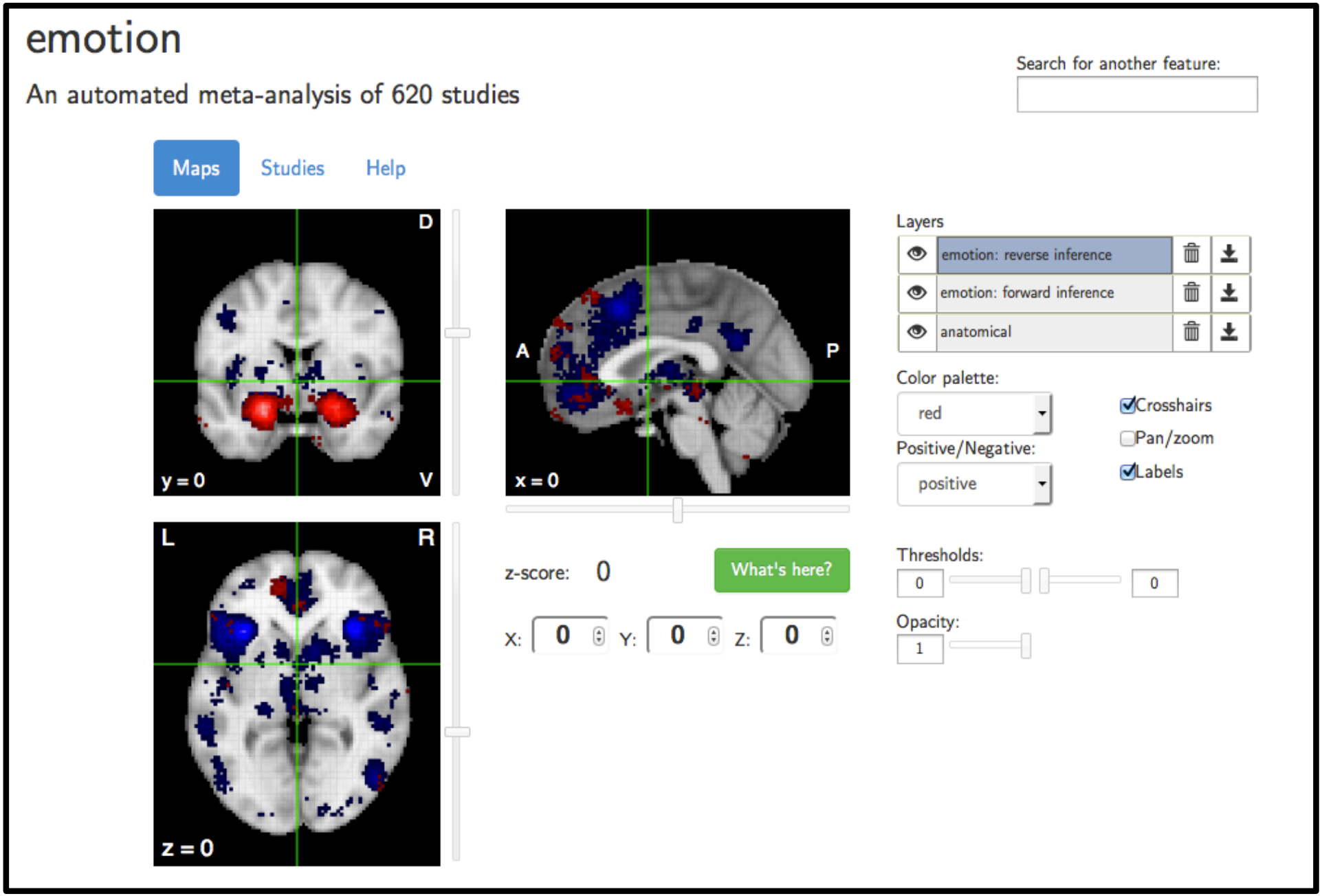
Vogt, (2005)

Neurons in ACC respond selectively to painful stimuli



a. PET -> painful thermal and mechanical stimuli
b. Location of neurons recorded
c. Neural firing rate related to thermal painful stimuli

Schnitzler and M. Ploner (2000)
Hutchinson et al., (1999)
Rainville et al., (1997)



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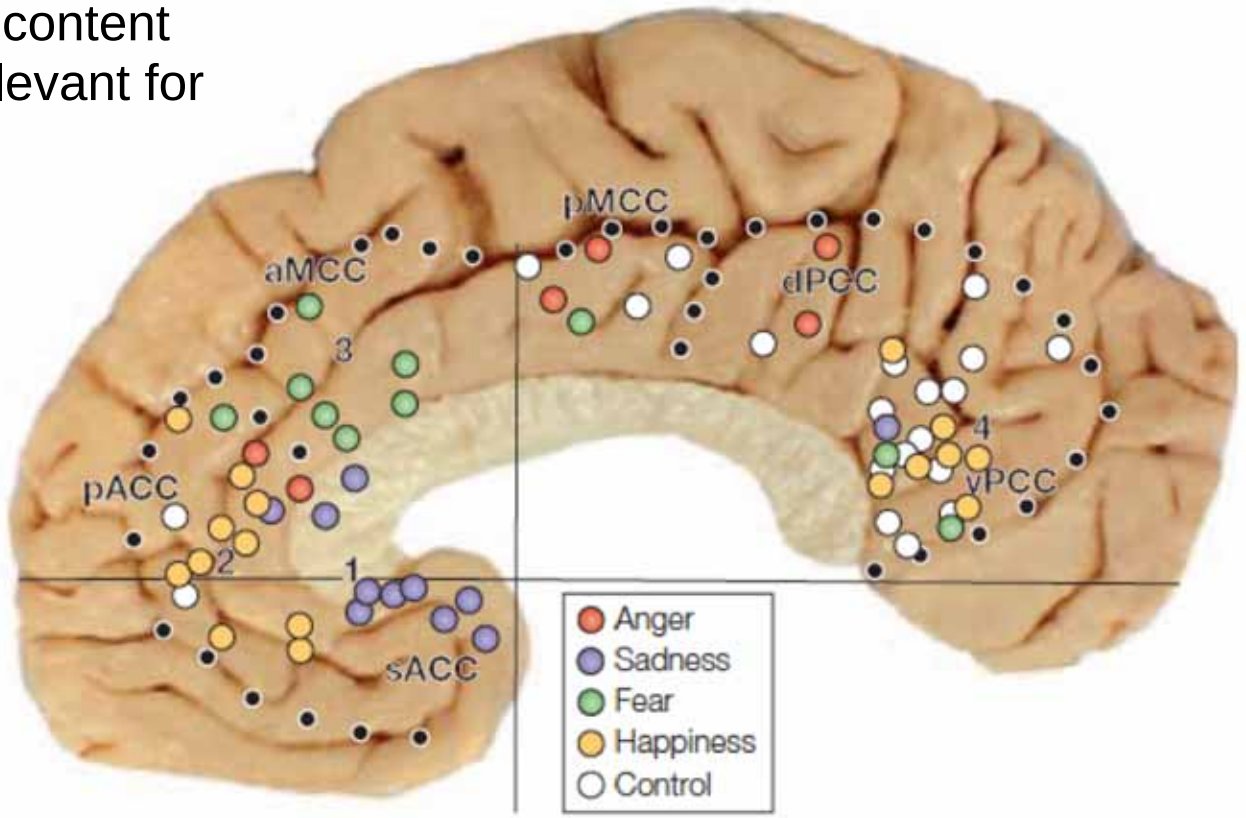
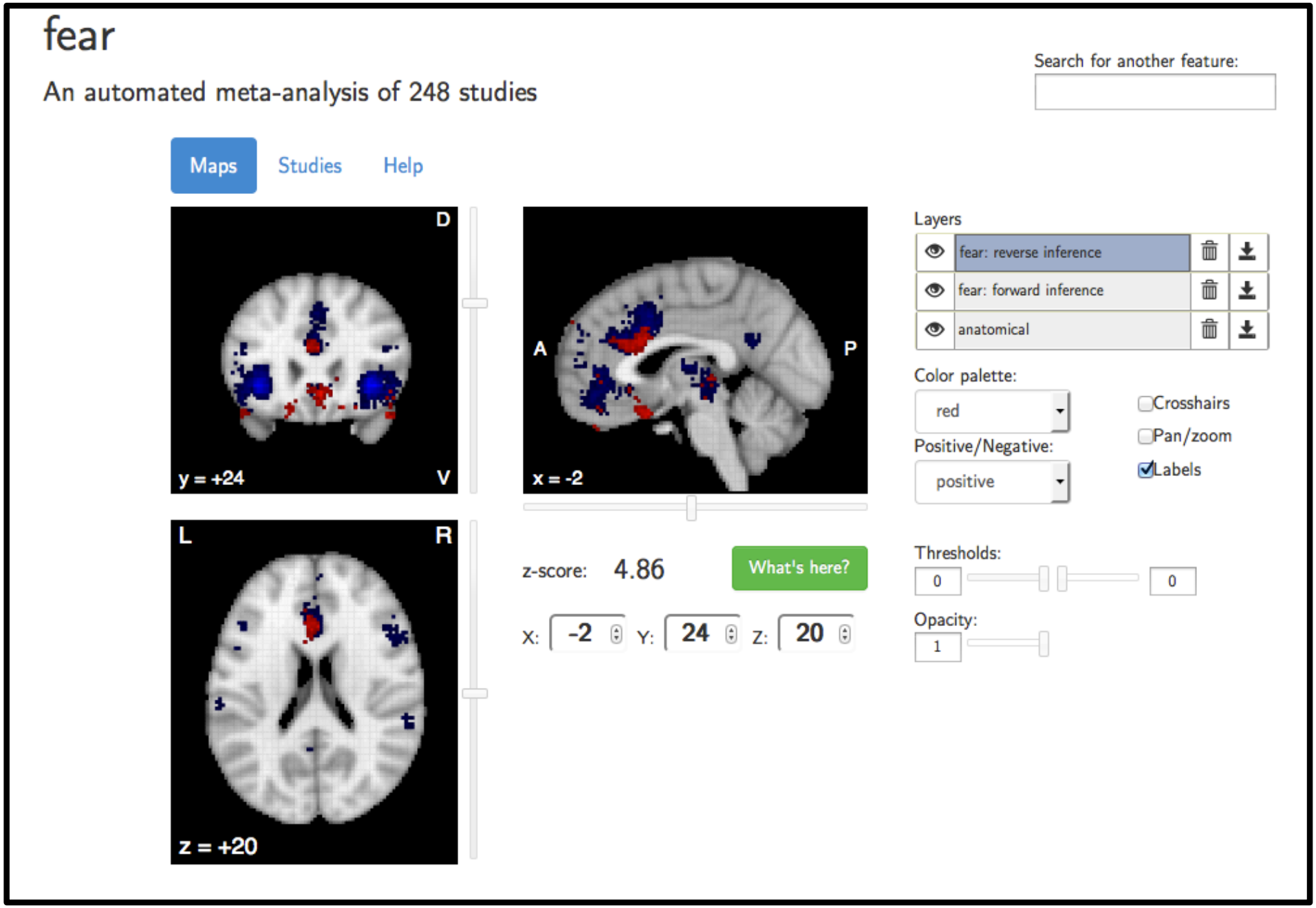
Cingulate Cortex and emotion peak activation sites

"Emotion is processed in different areas according to the *memory valence, autonomic associations and sensory driving* that are necessary for the internal content and behavioural output relevant for each class of emotion."



Summary of 23 studies showing peak activation sites during simple emotions

Vogt, (2005)



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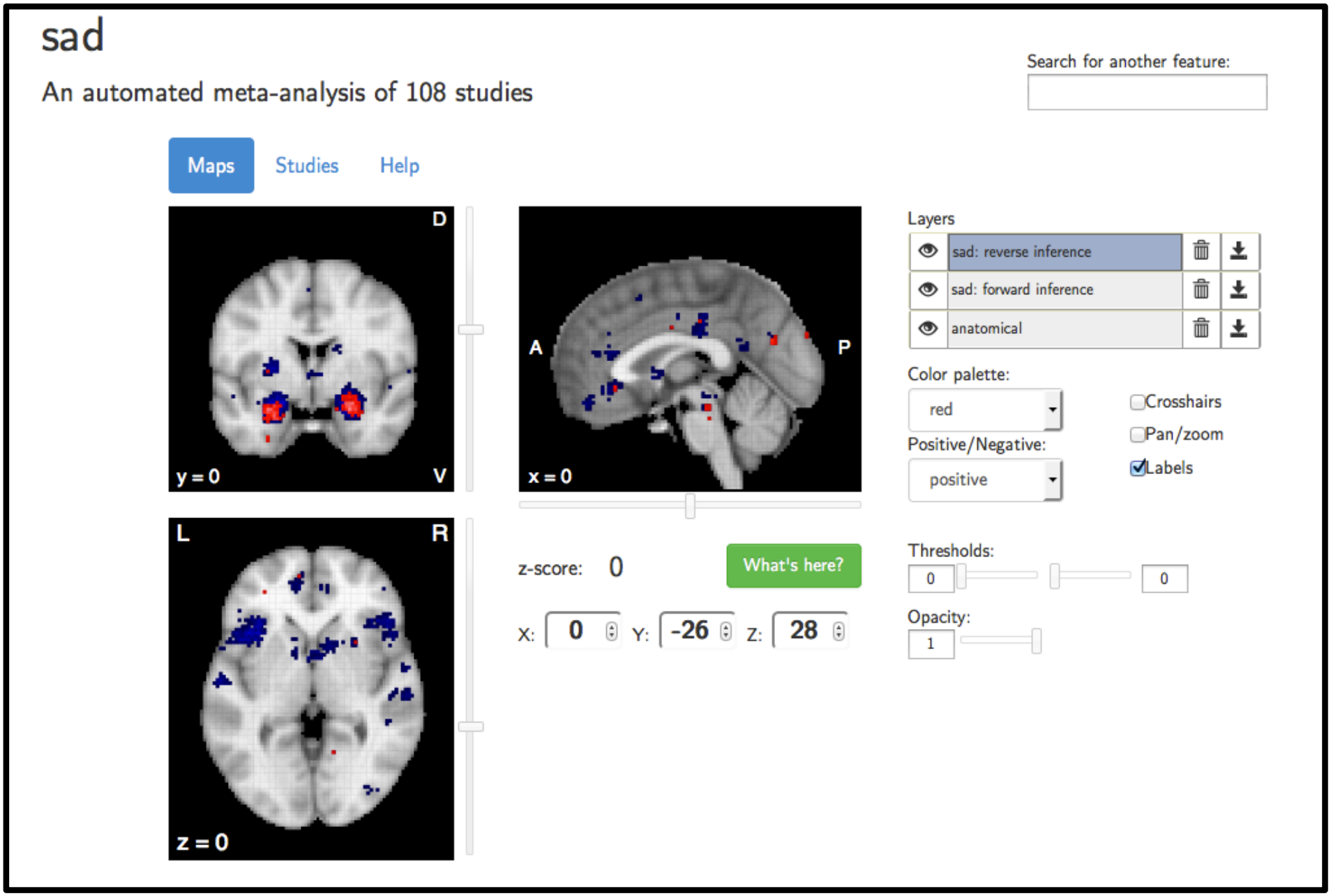

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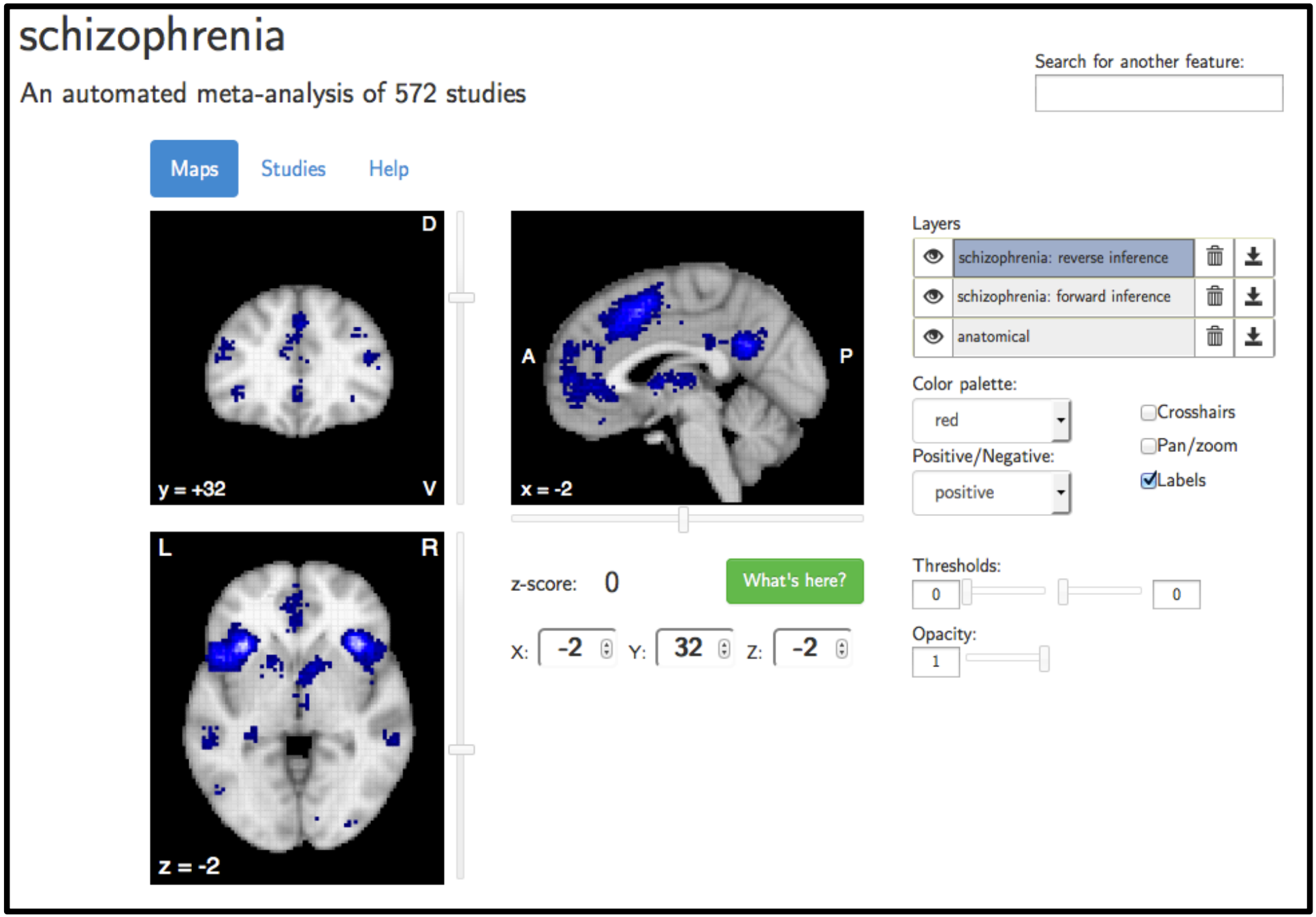
Clinical Pathologies



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Schizophrenia

-Consistent functional activation of **ACC** in **auditory hallucination**, together with medial temporal regions in neuroimaging studies (Allen et al., 2008).

-Decreased volume of ACC.
(Honea et al., 2005)

-Report of micro-structural changes in the anterior and posterior cingulum.
(Fujiwara et al., 2007).

In a 4 section partition of the cingulum
-FA reduction and RD increase in the rostral portion of the *left anterior cingulum (aCGC)*
-RD increase in the anterior segment of the *left middle cingulum (mCGC)*
(Abdul-Rahman et l., 2011)

Decreased FA in patients with schizophrenia in anterior and posterior cingulum.

Difference between groups is higher in anterior cigulum.

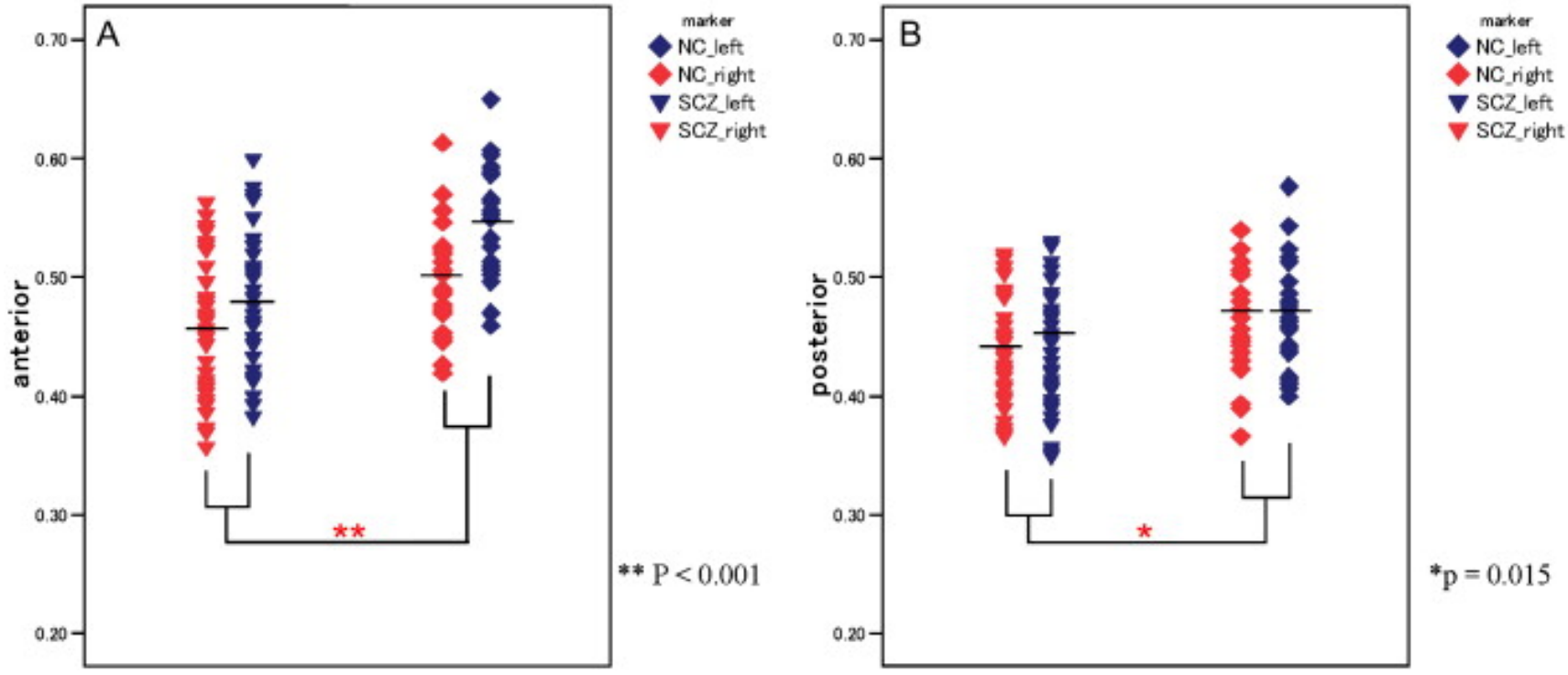
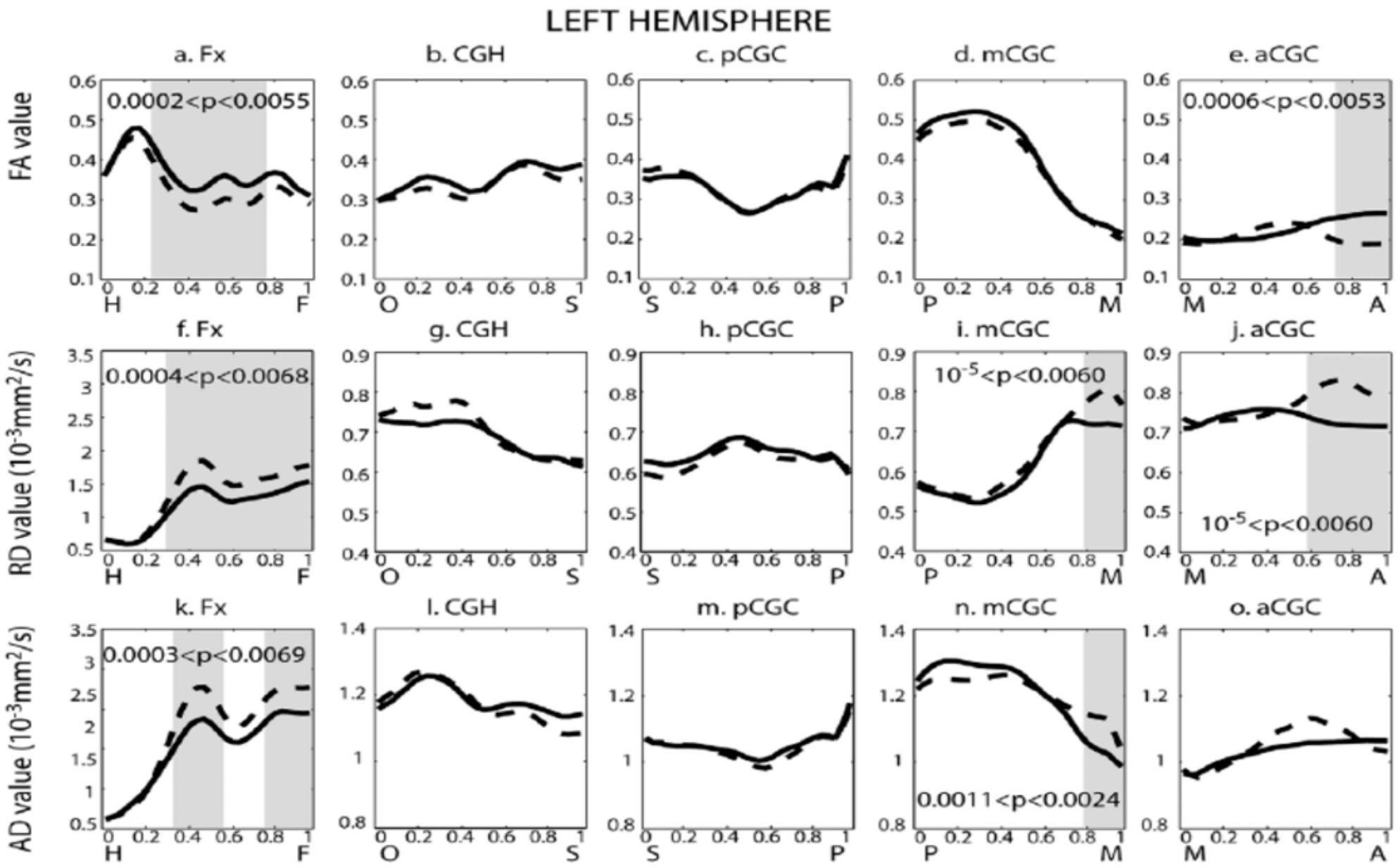


Fig. 2 A, B. Fractional anisotropy in the anterior (A) and posterior (B) cingulum bundles in normal controls and patients with schizophrenia. Abbreviations; SCZ = schizophrenia, NC = normal control.

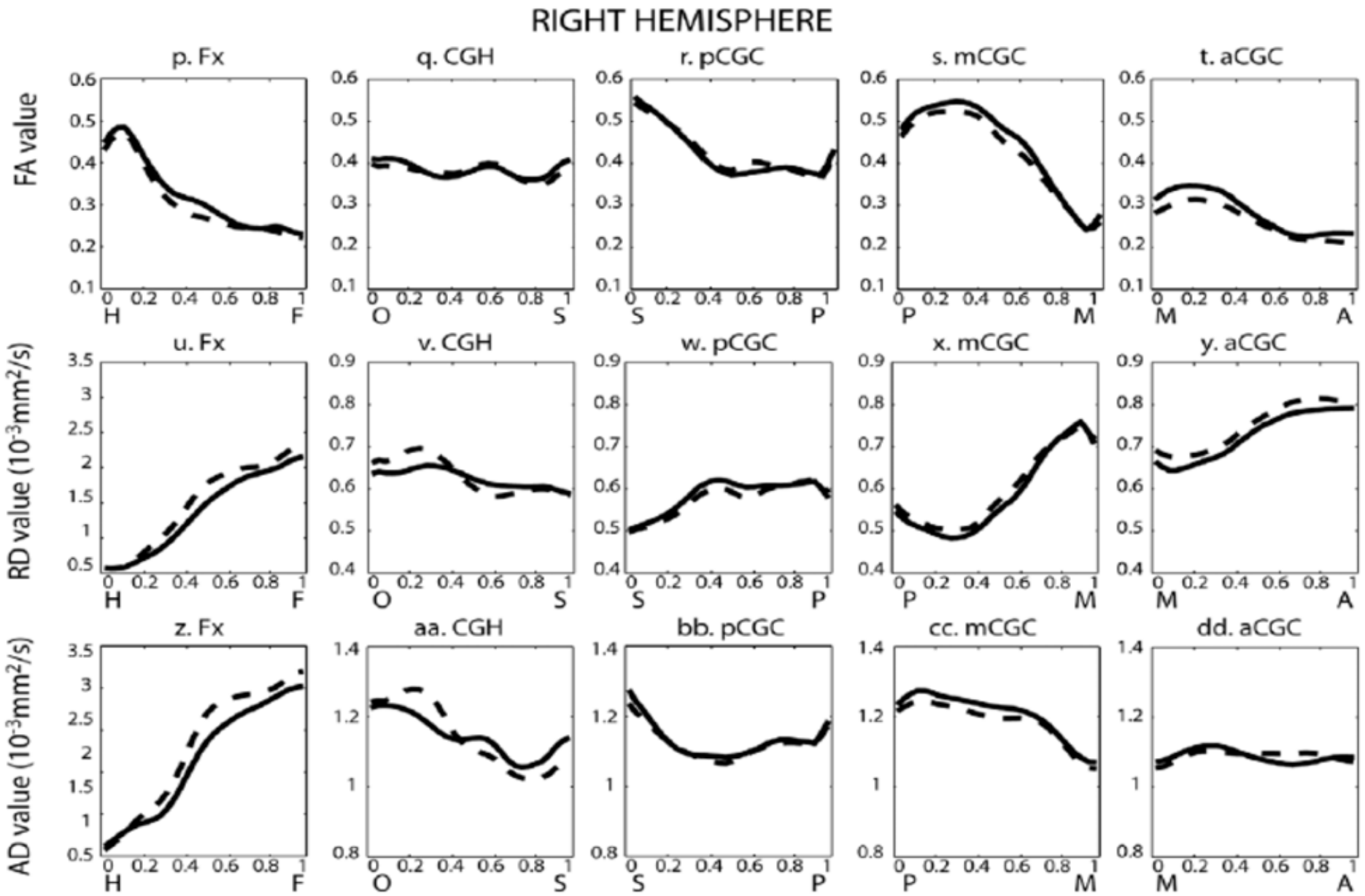
Fujiwara et al., (2007)

Sub-regional white matter differences in Schizophrenia as measured by FA, RD and AD



Abdul-Rahman MF et al., (2011)

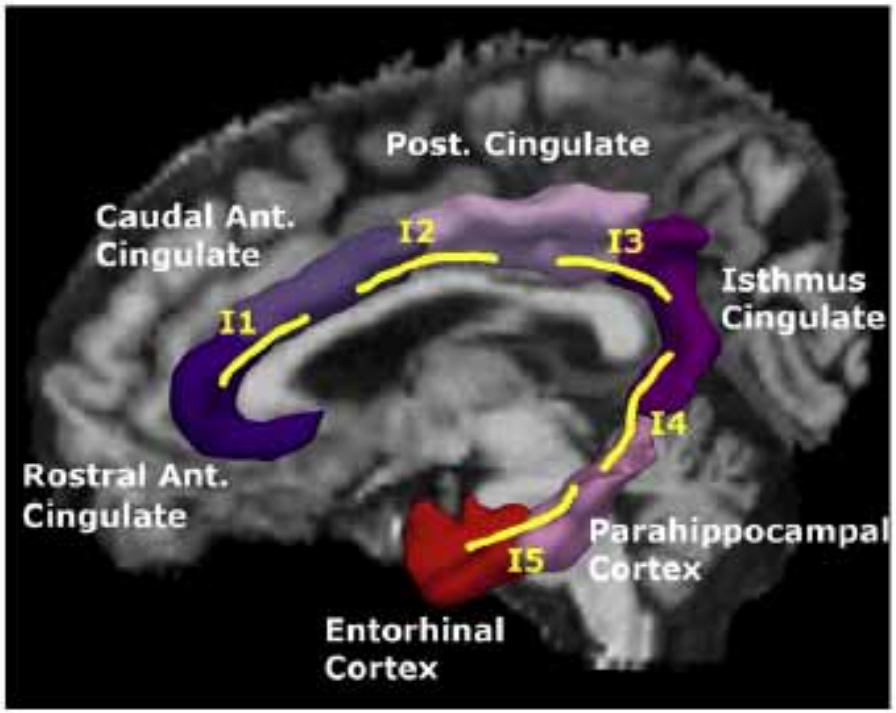
Sub-regional white matter differences in Schizophrenia as measured by FA, RD and AD

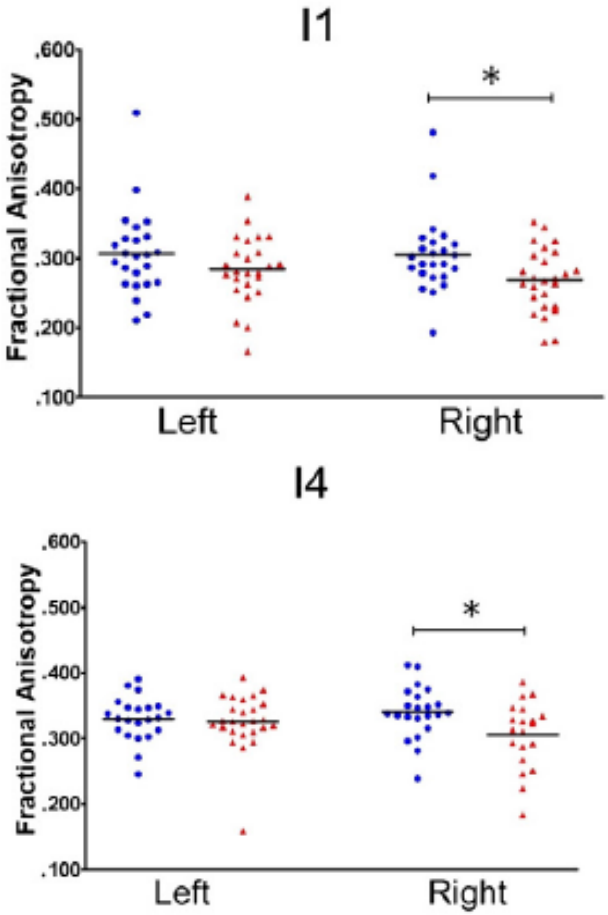


Abdul-Rahman MF et al., (2011)

In a 5 sub-section partition of the cingulum

Significant ($p < 0.05$) FA difference in :
-Fibers connecting the rostral and caudal anterior cingulate gyrus (right I1)
-Fibers connecting the isthmus of the cingulate gyrus with the parahippocampal cortex (right I4).





Blue= control
Red =schizophrenia

Whitford et al., (2004)

Anterior Cingulate Cortex and Schizophrenia

The WM differences in Anterior Cingulum suggests a damage in the connection between ACC and Prefrontal Cortex, an area involved in executive function.

FA reductions in Anterior Cingulum correlated with deficits in executive function in patients with schizophrenia.
(Nestor et al., 2004)

Also, patients with lesions in the ACC after cingulotomy, show deficits of attention and executive function.
(Benes, 1993).

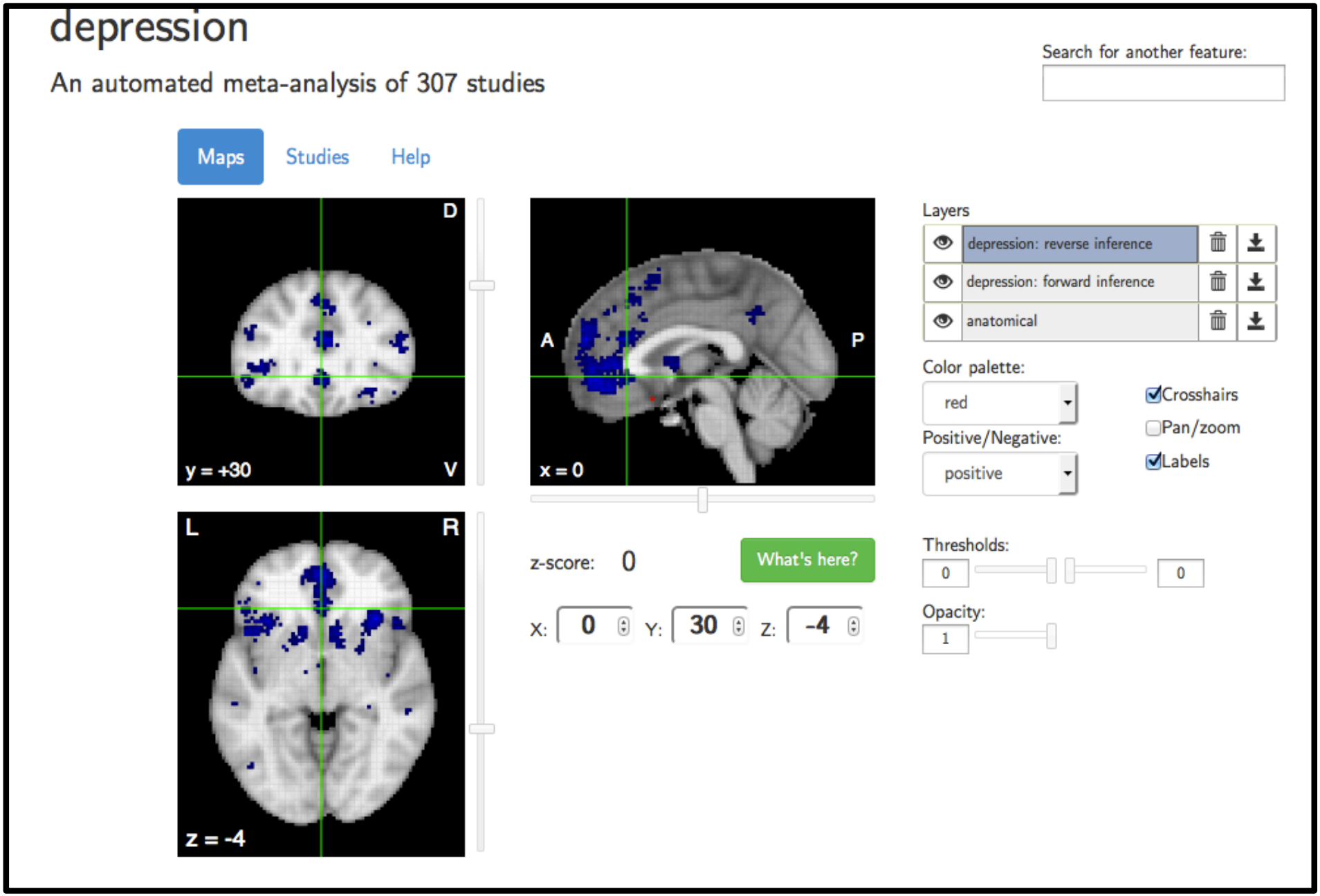
Schizophrenia --> damage in ACC --> deficit in cognitive function

And the Posterior Cingulate Cortex ?

Abnormal metabolism in patients with schizophrenia.
(Andreasen et al., 1997 and Haznedar et al., 1997)

Negative correlation between cerebral blood flow and Schneirder's first rank symptoms in schizophrenic patients (eg. Auditory hallucinations, thought insertion, thought withdrawal)
(Franck et al., 2002)

"Pathology of PCCs has been hypothesized to cause internally generated thoughts or actions to be imbued with abnormal perceptual qualities and misattributed to external agencies."
(Suzuki et al., 2005).



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Depression and subgenual cingulate region (SACC)

(Mayberg et al., 2005)

SACC metabolically overactive in depressed patients.

Reduced activation with antidepressants or direct brain stimulation of WM.

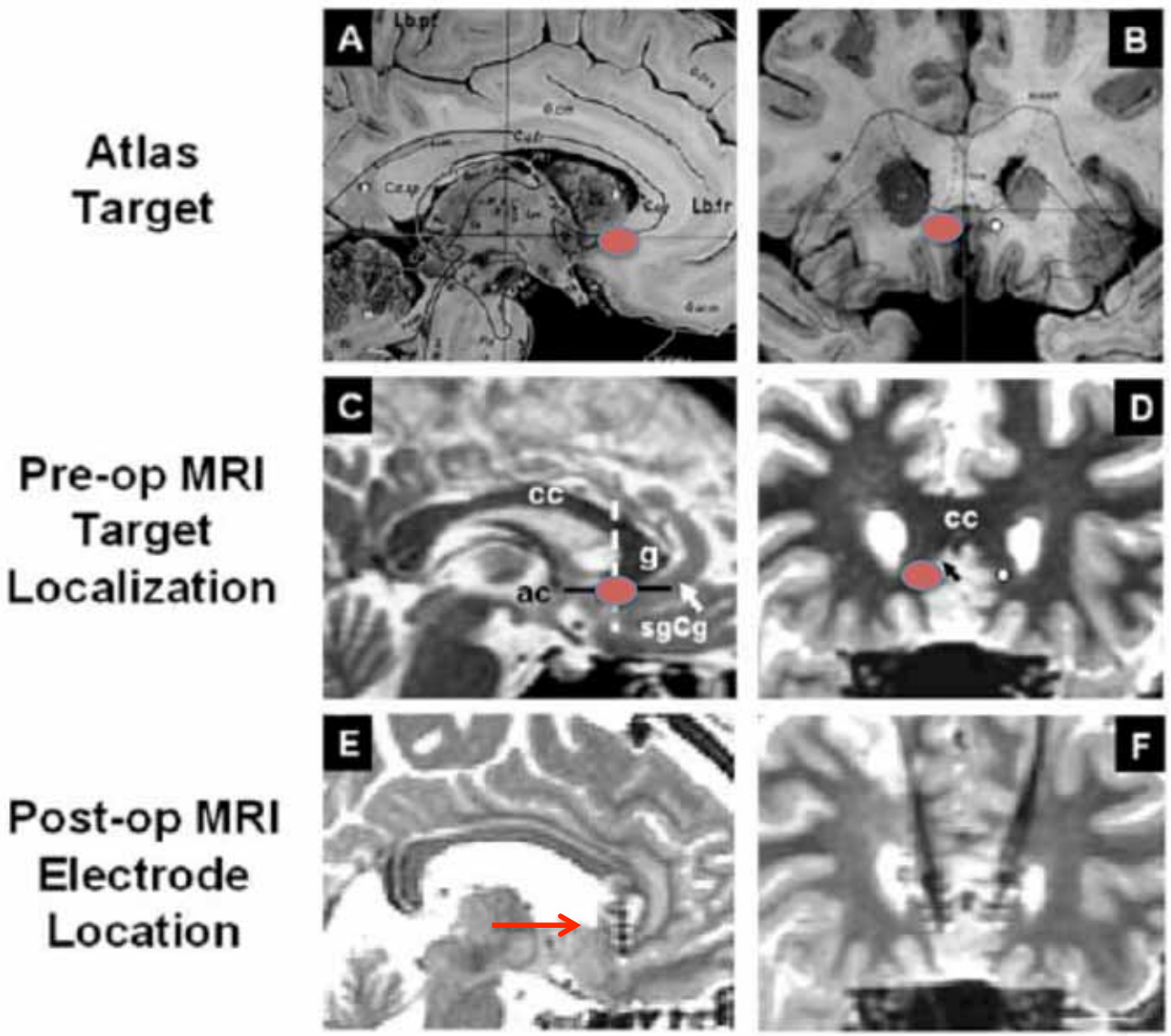
This direct brain stimulation also increase metabolism of dorsal cingulate cortex and other prefrontal areas.

Striking and sustained remission of depression in four of six patients.

What is so special about SACC?

SACC has monosynaptic connections with specific frontal, limbic, subcortical, and brainstem sites involved in mood regulation, depression, and the antidepressant response.
(Riva-Posse et al., 2014)

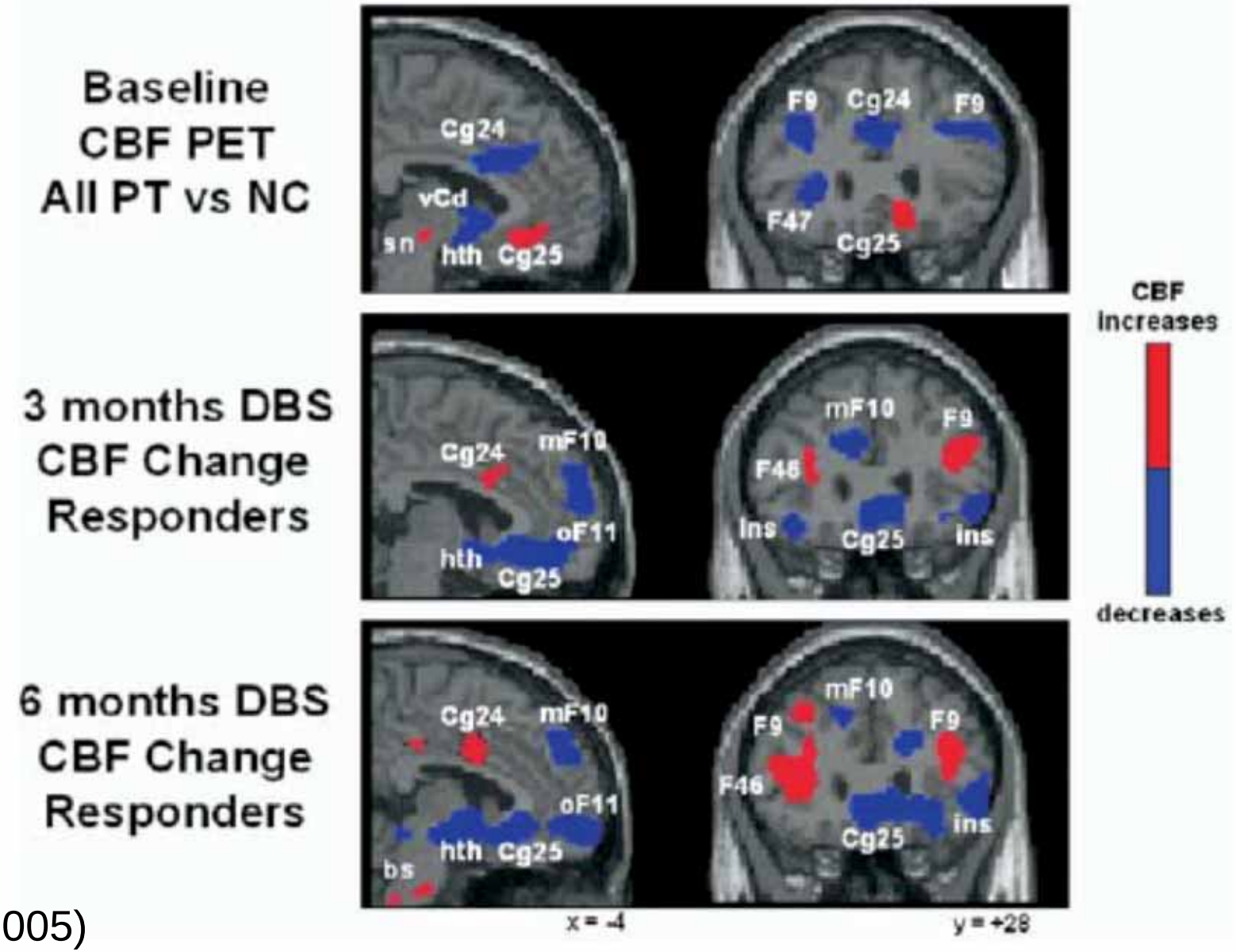
Placement of Deep Brain Stimulation Electrode in subgenual white matter



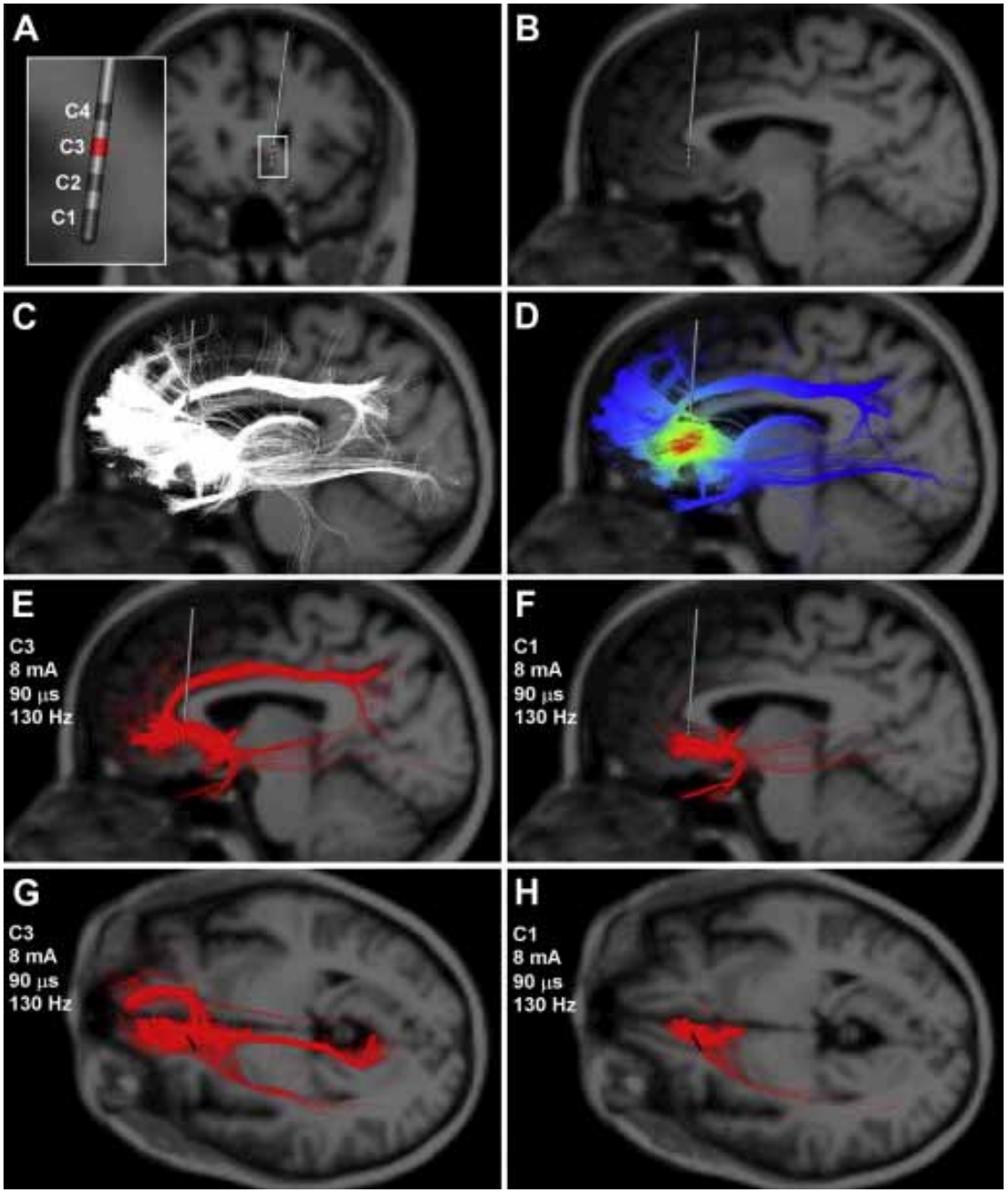
Mayberg et al., (2005)

Changes in resting-state Cerebral Blood Flow (CBF) after DBS

-Decrease in subgenual ACC (Cg25)
-Increase in dorsal ACC (Cg24)



Mayberg et al., (2005)

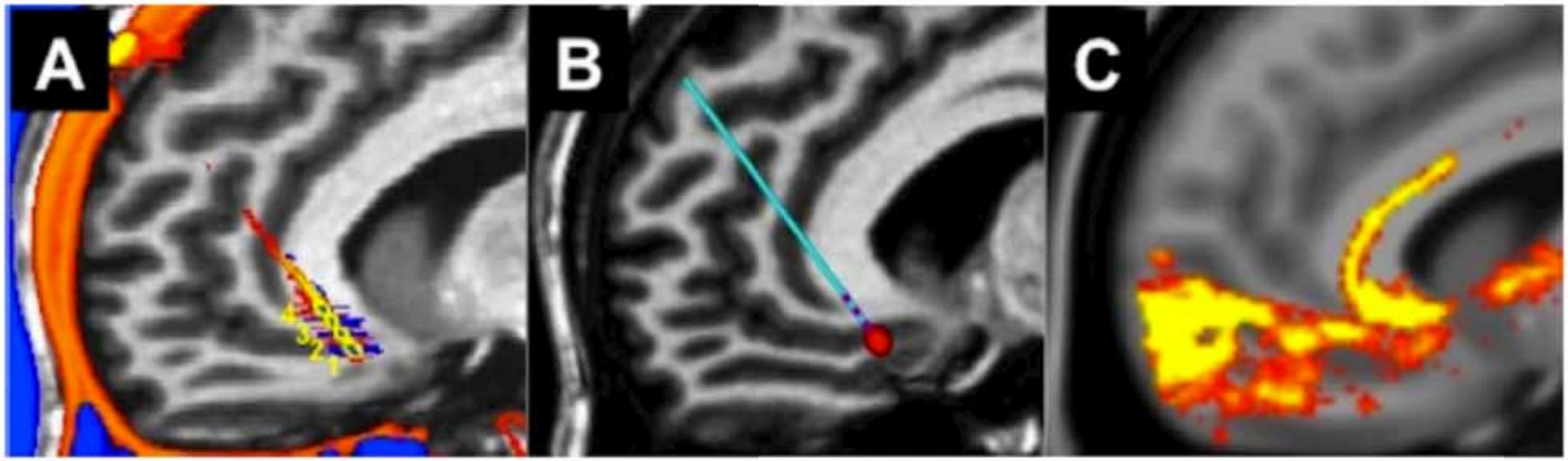


Pathways predicted by activation models to be necessary for successful DBS depression treatment.

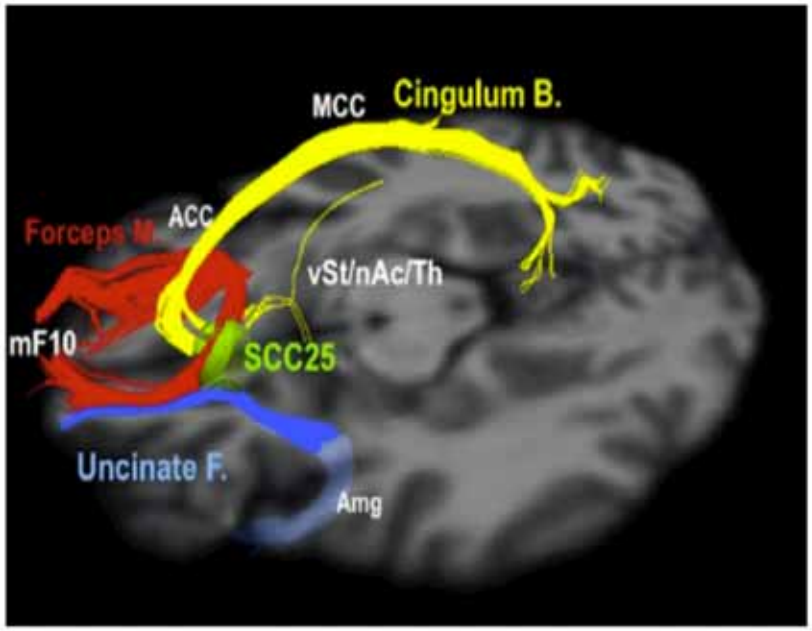
Tractography based activation models show that activation of a critical mass of a unique combination of cortical, sub-cortical, and cingulate pathways may be necessary for therapeutic benefit.

Lujan et al., (2013)

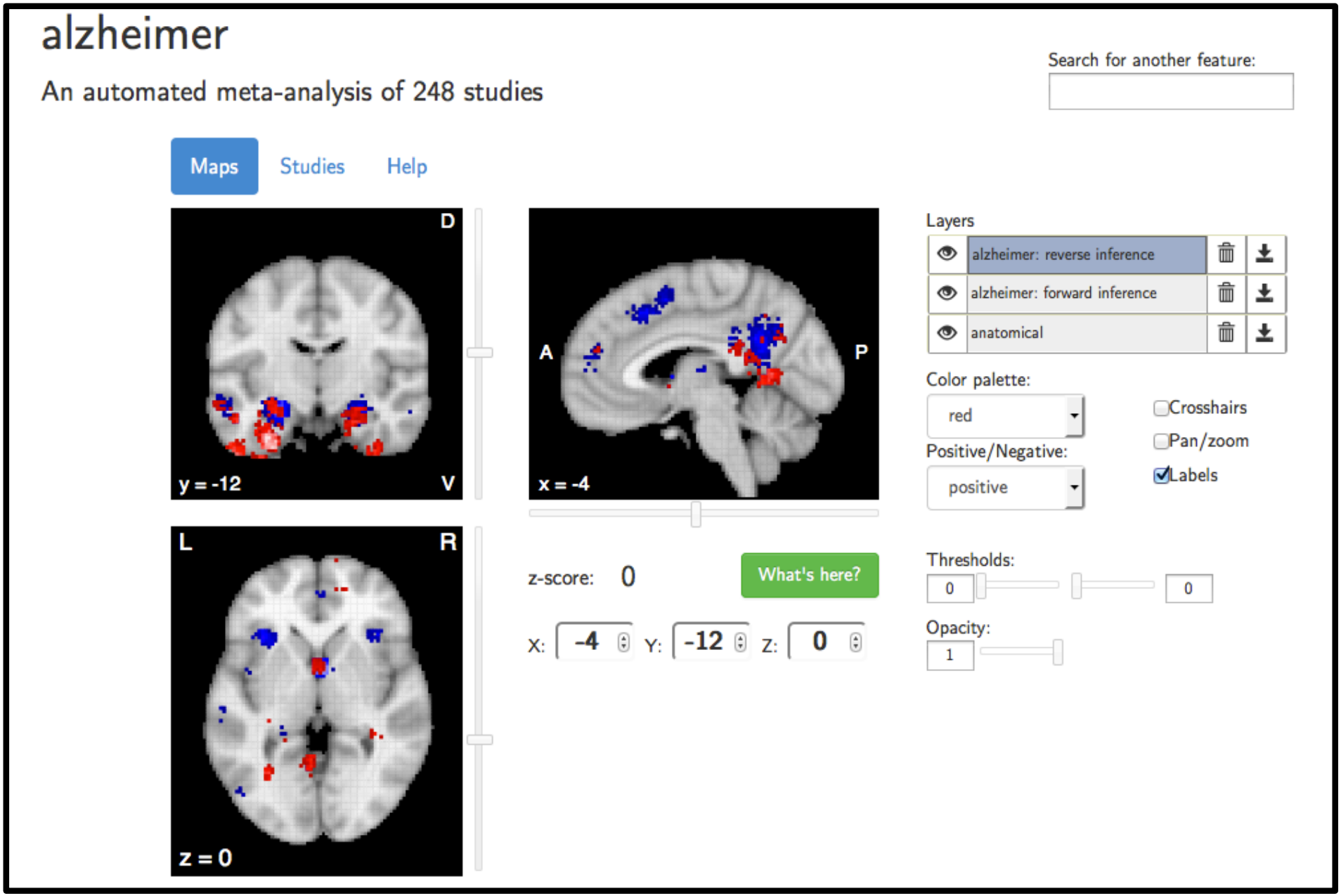
Pathways predicted by activation models to be necessary for successful DBS depression treatment.



Contact point of DBS electrode that achieve “activation” in the three bundles were associated with conversion of non-responders to responders.



Riva-Posse et al., (2014)



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Alzheimer's disease

(Bozzali et al., 2012)

Parahippocampal, posterior cingulate and precuneus have a faster rate of atrophy in pre-symptomatic Alzheimer´s disease patients (autosomal dominant mutation carriers).

In AD, **clusters of reduced GM** in
-Posterior Cingulate Cortex
-Anterior Cingulate Cortex
-Hippocampal/Parahippocampal

-Widespread **reduced FA and increased MD** in the cingulum of AD and MCI patients.

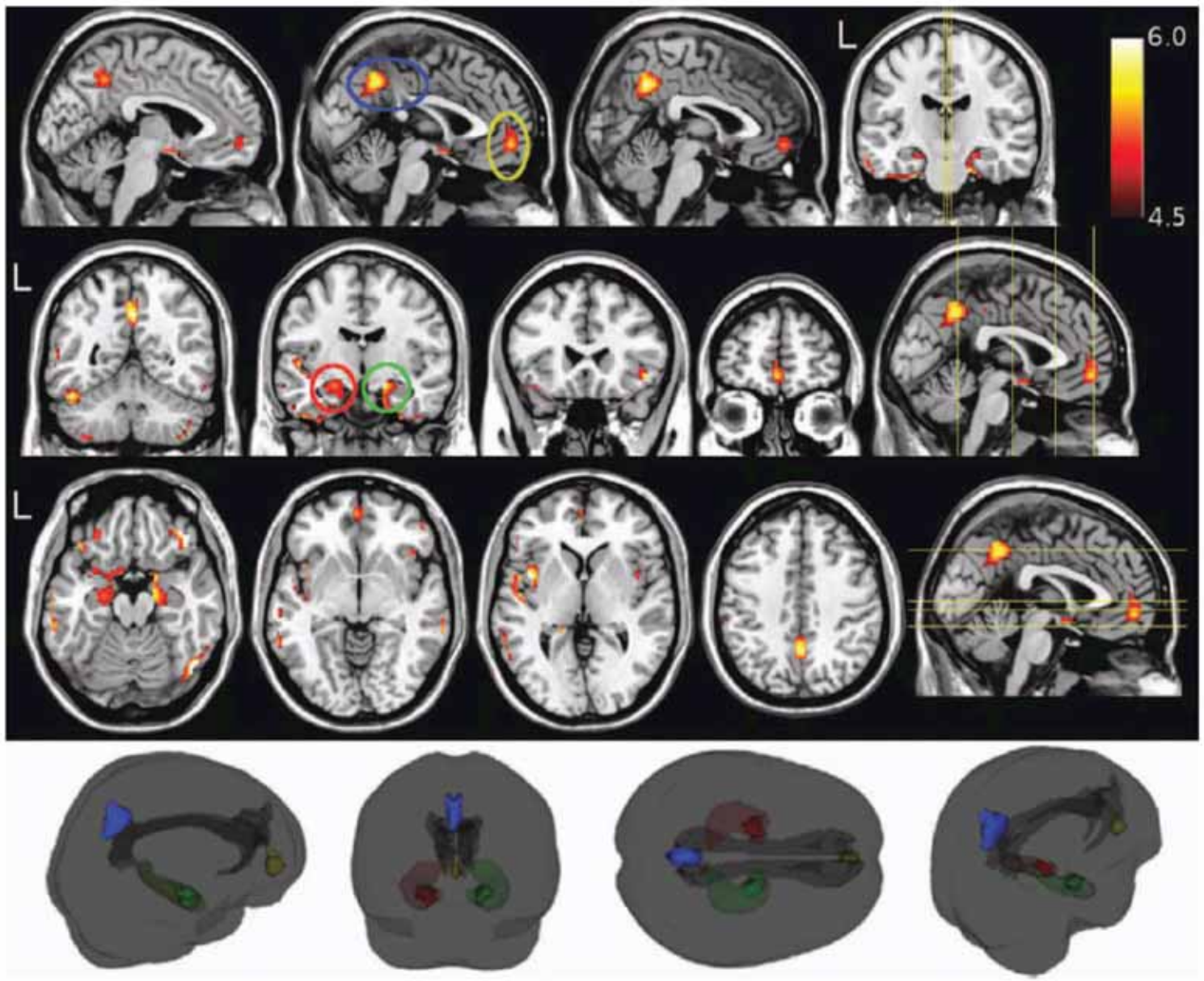
Brain deafferentation though the cingulum is likely to play a remarkable role in progressive development of cognitive impairment in AD.

Lower GM volume in regions connected through cingulum in Alzheimer's patients.

-ACC

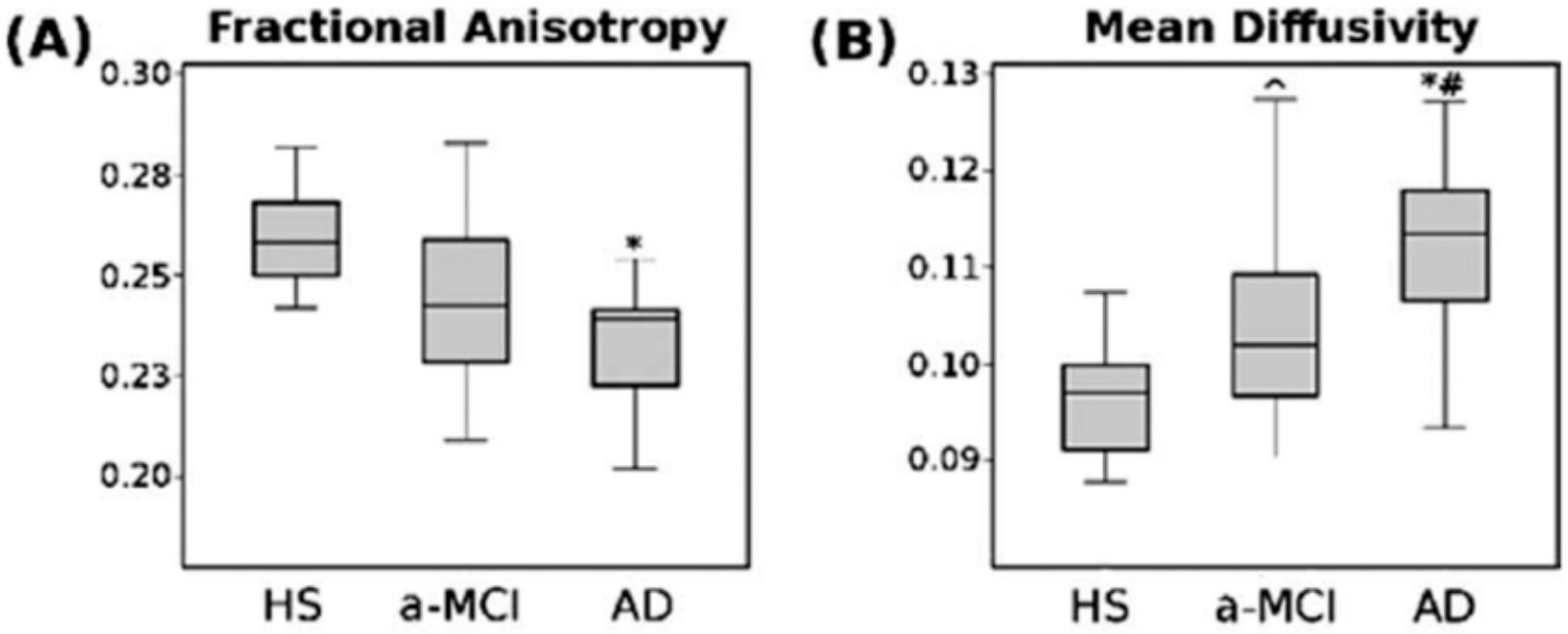
-PCC/ precuneus

-MTL



Bozzali et al., (2012)

Widespread reduced FA and increased MD in the cingulum of AD and MCI patients.



The cingulum plays a relevant role in explaining the spread of Alzheimer's from the ***medial temporal lobe*** to the rest of the brain, and the progressive development of ***cognitive impairment***.

Bozzali et al., (2012)

Reduced FA and increased MD in the *posterior cingulum* of Alzheimer's disease patients

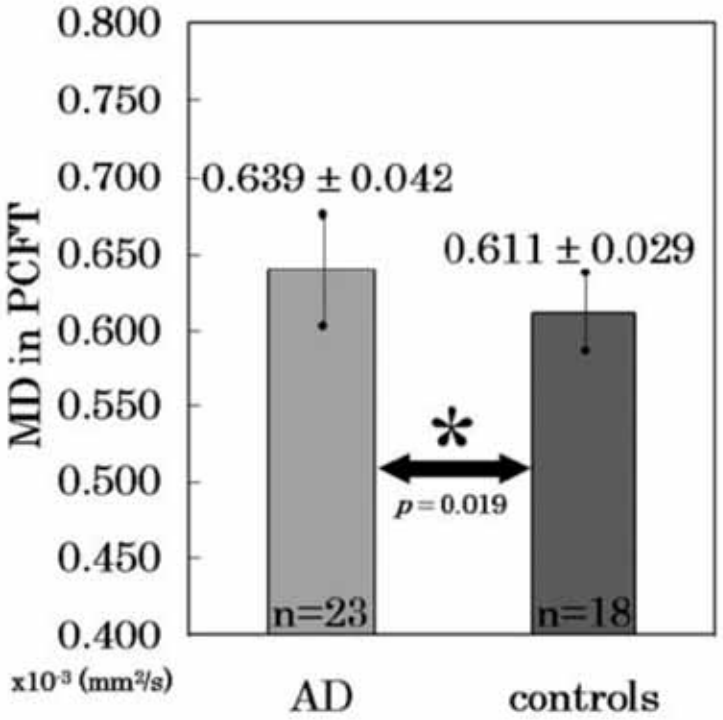


Fig. 2. Mean diffusivity (MD) values in the PCFTs of patients with Alzheimer's disease (*AD*) and normal controls. Measured MD in PCFTs was significantly higher in patients with AD than in normal controls

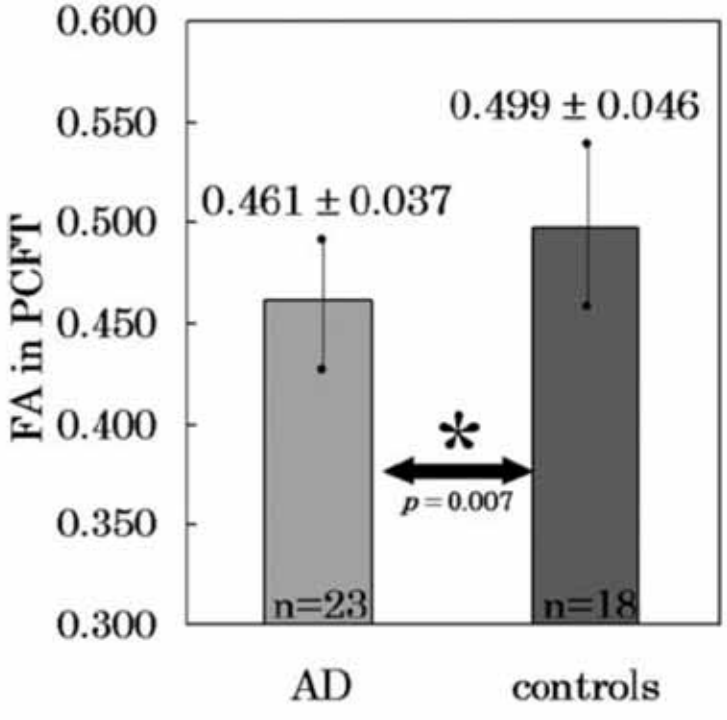


Fig. 3. Fractional anisotropy (FA) values in the PCFTs of patients with AD and normal controls. Measured FA in PCFTs was significantly lower in patients with AD than in normal controls

Nakata et al., (2008)

Cingulotomy reflects the multiple roles of ACC

- Damage to the supracallosal fibres of the cingulum bundle.
  - -Intractable pain
  - -Anxiety disorders
  - -Depressive disorders
  - -Obsessive-compulsive disorders

Table 1 Combined outcomes per procedure for neurosurgical procedures for mental disorder (Spangler *et al*, 1996)

Operation	*Success rate, %*		
	All conditions	*MAD*	*OCD*
Anterior capsulotomy	67	55	45
Anterior cingulotomy	61	65	56
Subcaudate tractotomy	37	34	33
Limbic leucotomy	67	78	61

MAD, major affective disorder; OCD, obsessive–compulsive disorder

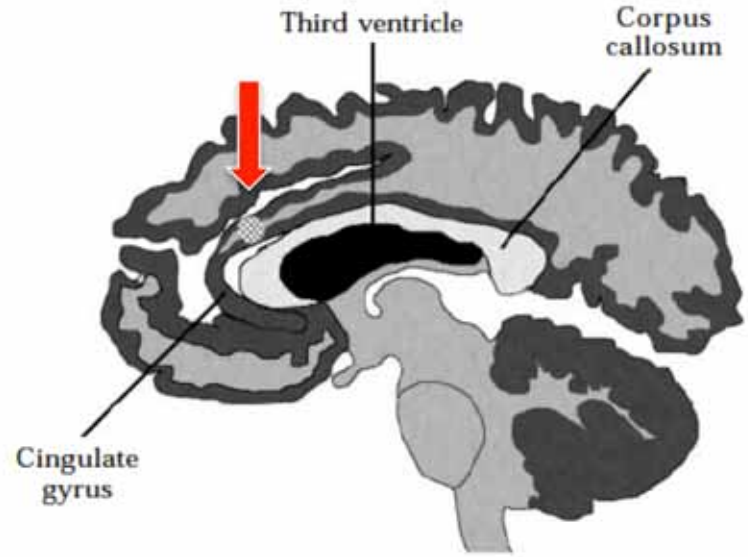
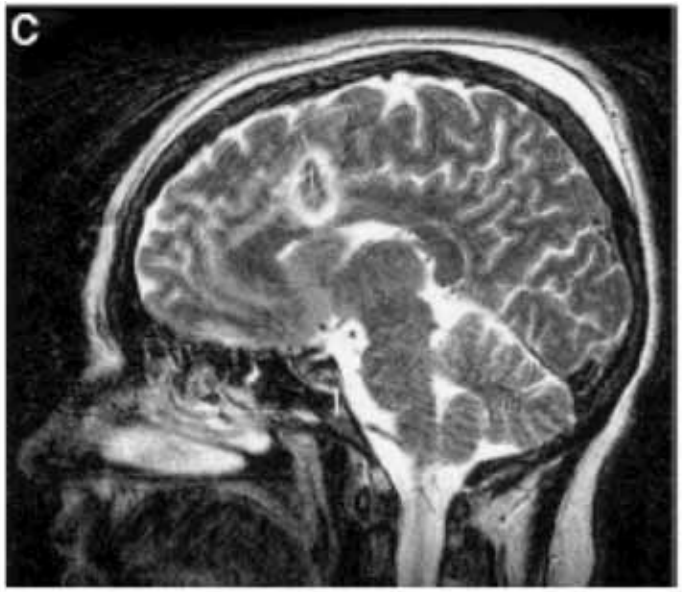
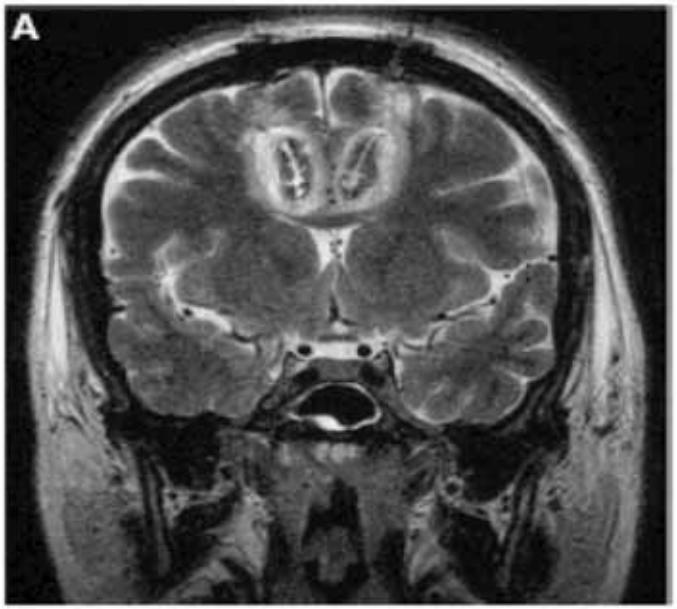


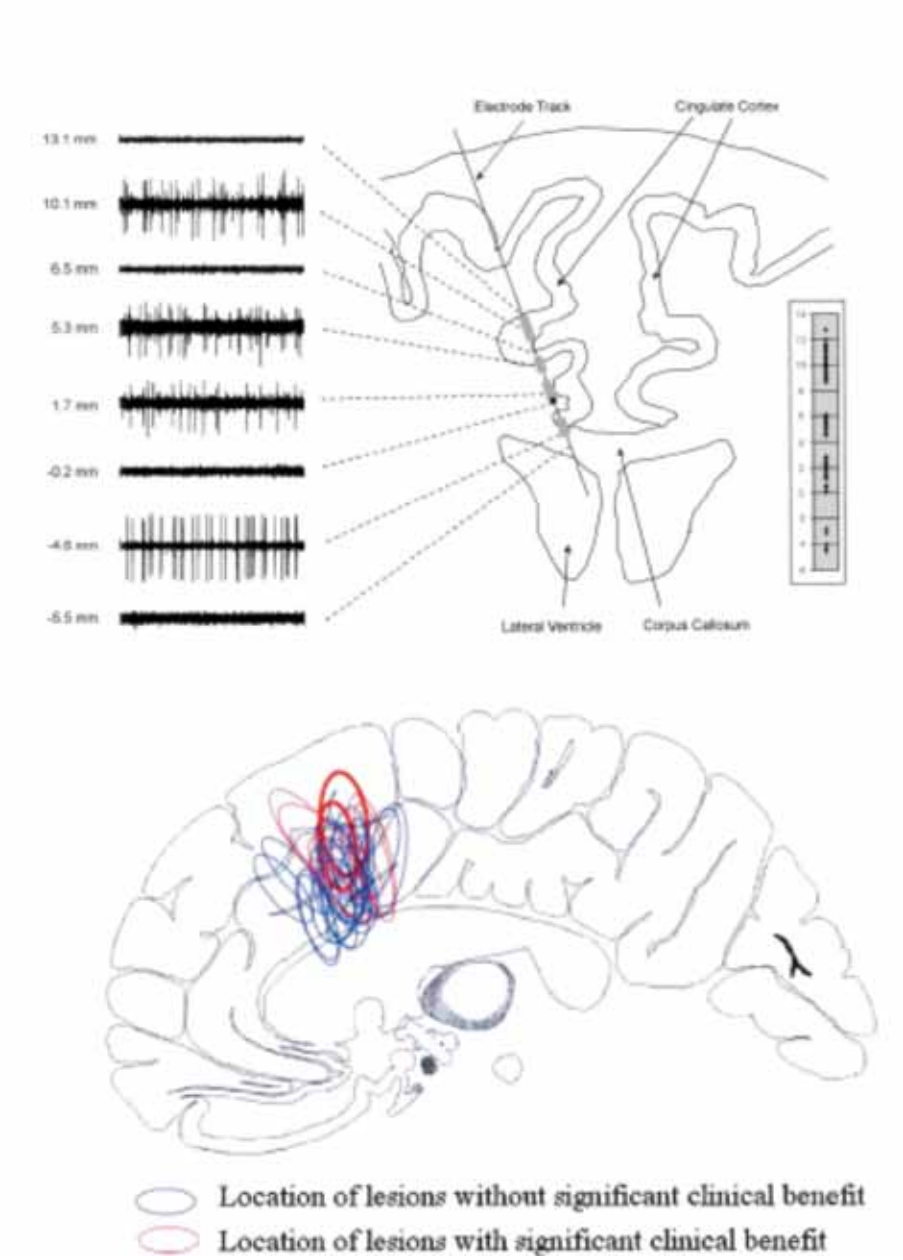
Fig. 2 Sagittal section through human brain, showing a cingulotomy lesion (cross-hatched area).

Christmas et al., (2004)

Importance of the location of the cingulotomy for successful clinical benefit in OCD







Richter et al., (2004).

Thanks for your attention