Neurocognition and depression: Which Future?

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Neurocognitive deficit at the core of depressive disorder. Why?

Present in 92% of depressive states

Present in more 70% of the cases of remission during MDD

Are concerning a much wider brain connectivity network than « mood » itself

The domain of Neurocognition

« Cold » Cognitions

Attention

Memory

Executive function

« Hot Cognitions »

Anytime emotions (ie positive or negative stimuli)

are interfering with cognitive functions.

Social cognitions (depending on both processes)

Attention deficit in MDD

Effortful attention is impaired (during acute states and even in remission)

Impairment in **processing speed** * is interfering

Normal performance in automatic processing

(Cohen, 2001; Landro, 2001; Kelp, 2008; Simons, 2009)

Memory impairment in MDD

Verbal short-term memory is **NOT** impaired (indexed recall and recognition)

Verbal delayed memory (retrieval) impaired*

Visuo-spatial memory (immediate and long term) is impaired*

Working memory (verbal and visuo-spatial) is impaired*

(Fleming, 2004; Bora, 2013; Fossati, 2016)

At the core of cognitive impairment: Executive function (EF) deficit

Executive function refers to cognitive processes that **control and integrates** other cognitive activities (at a lower level) in order to reach a goal

The challenge: dealing with **novelty and treating new information**

The way to address this challenge: selecting strategies (outcome: planning)

(Miyake 2000; Chamberlain, 2006; Hammar, 2009)

The process (how our EF is performed in daily life)

Updating information (coding and monitoring new information)

Inhibiting incorrect responses (in general automatic responses)

Shifting to the right strategy and using feed-back for adjustment

Planning and sequencing complex actions (monitoring performance and modifying behaviour)

These different components can be **implemented only if WORKING MEMORY is actively maintaining or manipulating** information

(Miyake, 2000; Friedman 2008)

How to test EF in practice?

Updating information: **n-back task, DSST***

Inhibiting incorrect responses: **Stroop test**

Set-shifting: **T**rail **M**aking **T**est* **B**, **WCST, DSST*, LSST*, Fluency**

Planning strategies (including sequencing**): Tower** of London

Working Memory * Tasks (maintaining and manipulating information): verbal: **digit span** forward; backward; visual: **visual span** forward, backward. Operation span

Major EF deficit in Depression

HR Snyder, Psychol Bull, 2014. Metaanalysis of 113 studies

- Deficit evidenced **for all the components of EF**
- Patients with MDD were significantly impaired on all tasks requiring updating
- Patients with MDD were significantly impaired on all inhibition measures
- Patients with MDD were significantly impaired on all measures taping shifting between tasks
- **Patients with MDD were impaired on all working memory tasks**
- **Data adjusted for age, severity, medication, comorbidity, IQ**
- Speed impairment as a confounding variable can not explain the EF deficit

Hot cognitions characteristics in depression
(compared to controls)

Negative bias for positive stimuli recall

Positive bias for negative stimuli recall

Negative emotions are better memorized

(Roiser and Sahakian, 2013; Hammer, 2014, 2016).

Autobiographical memory characteristics in depression

Excessive self-focus

Engaging oneself in self-referential processing

Excessive categorical memory

“Spectator shifting”

(Northoff, 2006;2007; Lemogne, 2006; Fossati, 2013; Polosan and Fossati, 2016)

Impairment in Social cognition

Lack of empathy

Lack of contextualization (Theory of mind)

(Thoma, 2011; Wolkenstein, 2011)

Take Home messages: a summary of cognitive abnormalities in MDD

Non specific impairments with effortful tasks

Slowed processing speed can not be considered as an explanatory factor

Negative emotional biases are evidenced for all tasks

All components of EF* are impaired (including the **common EF**: working memory)

Autobiographical memory characteristics are suggestive of a vulnerability to depression

Immediate future: digital assessment of neurocognitive function in depression
(drugs with new mechanisms of action*)

Since all EF components are impaired, including common EF, EF assessment is the key target:

TMT, LSST, DSST (includes attention and speed processing)

Working Memory (verbal and visuo-spatial)

Follow up of treatment efficacy, assessment of relapse risk

*** indicated tests used in Vortioxetine clinical trials**

Future avenues for research in Depression

How can be explained the **negative interferences in information processing?**

EF deficit being at the core not only of cognitive symptoms but of the depressive illness as well, **what are the mechanisms common to EF deficit and MDD?**

What are the relationships between **EF deficit and self-referential excessive processing?**

Can EF and hot cognitions be considered as the **central therapeutic targets** in MDD?

Negative Interferences

Emotional Network

Role of the network:

- **Integration of Emotions (emotional salience, emotionnal biases)**

Dysfunctional in:

- **Depression**
- **Anxious states**

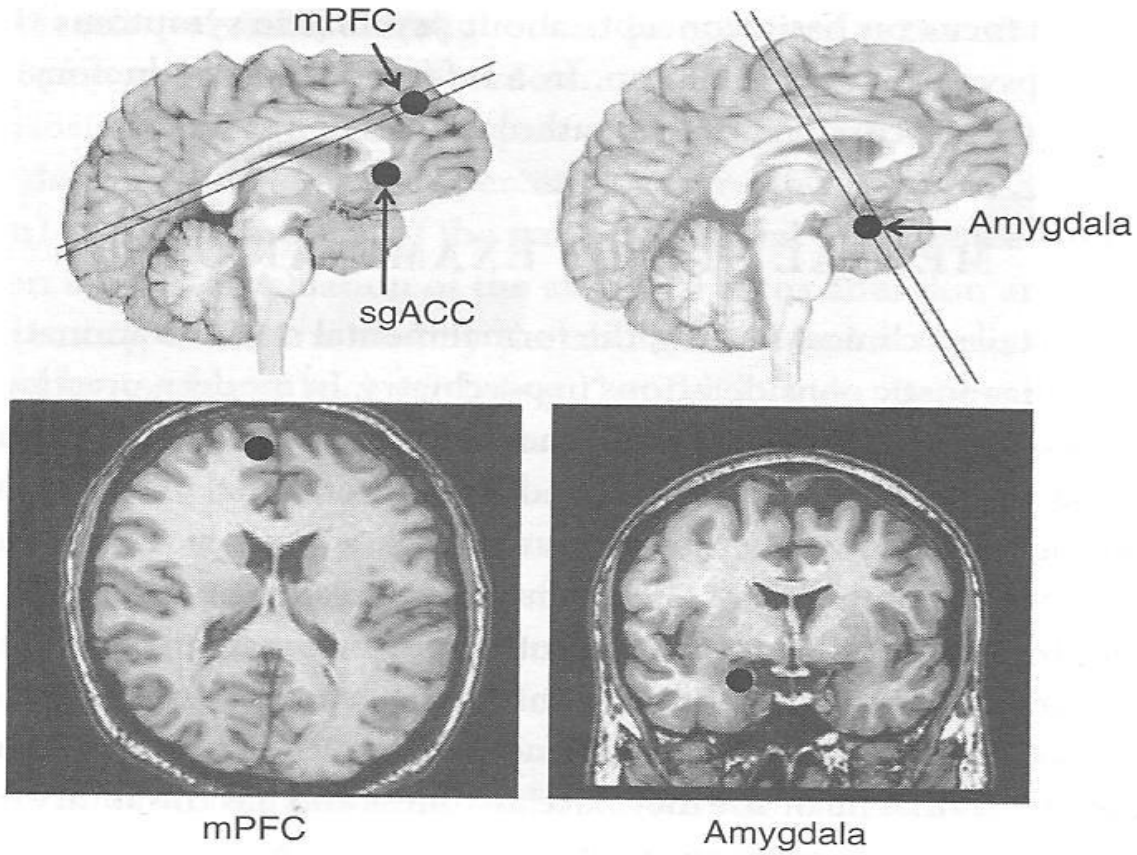
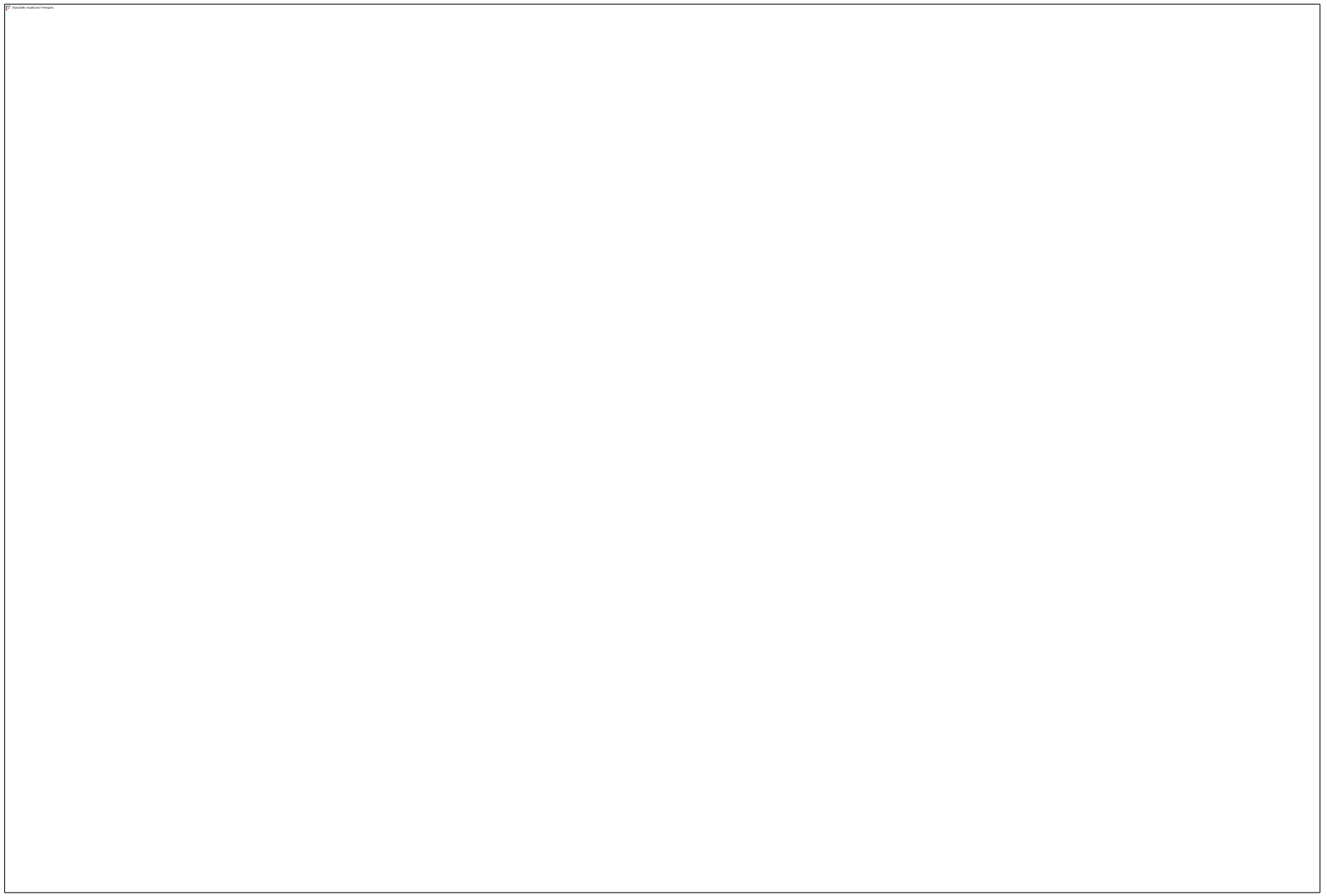
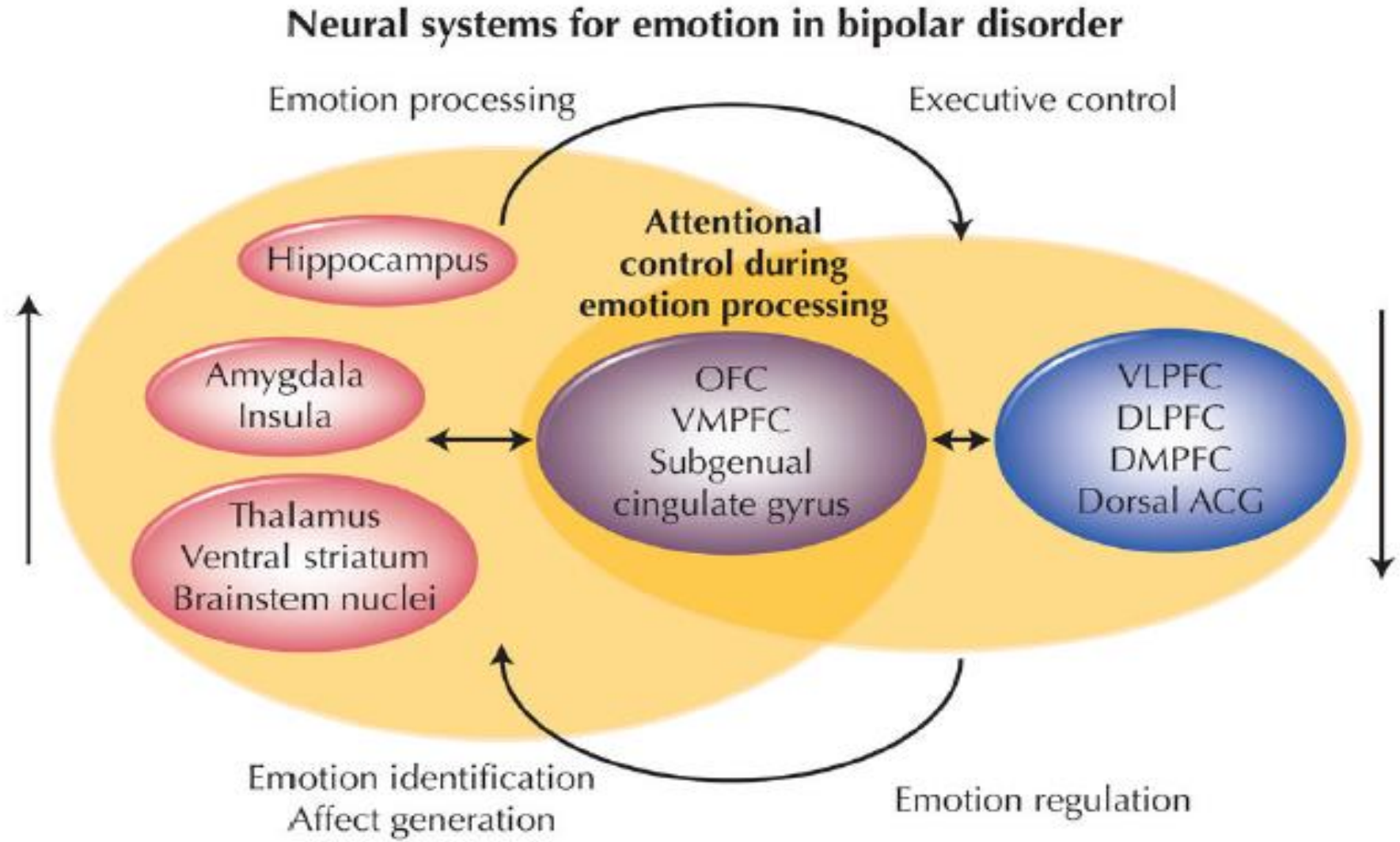


Figure 1-2 Key regions in emotional processing. The images depict key regions involved in emotional processing, including the subgenual anterior cingulate cortex (sgACC), medial prefrontal cortex (mPFC), and amygdala. The lines through the brain reconstructions indicate the approximate locations that are shown in the radiologic images. (Adapted from Damasio, 2005, with permission.)

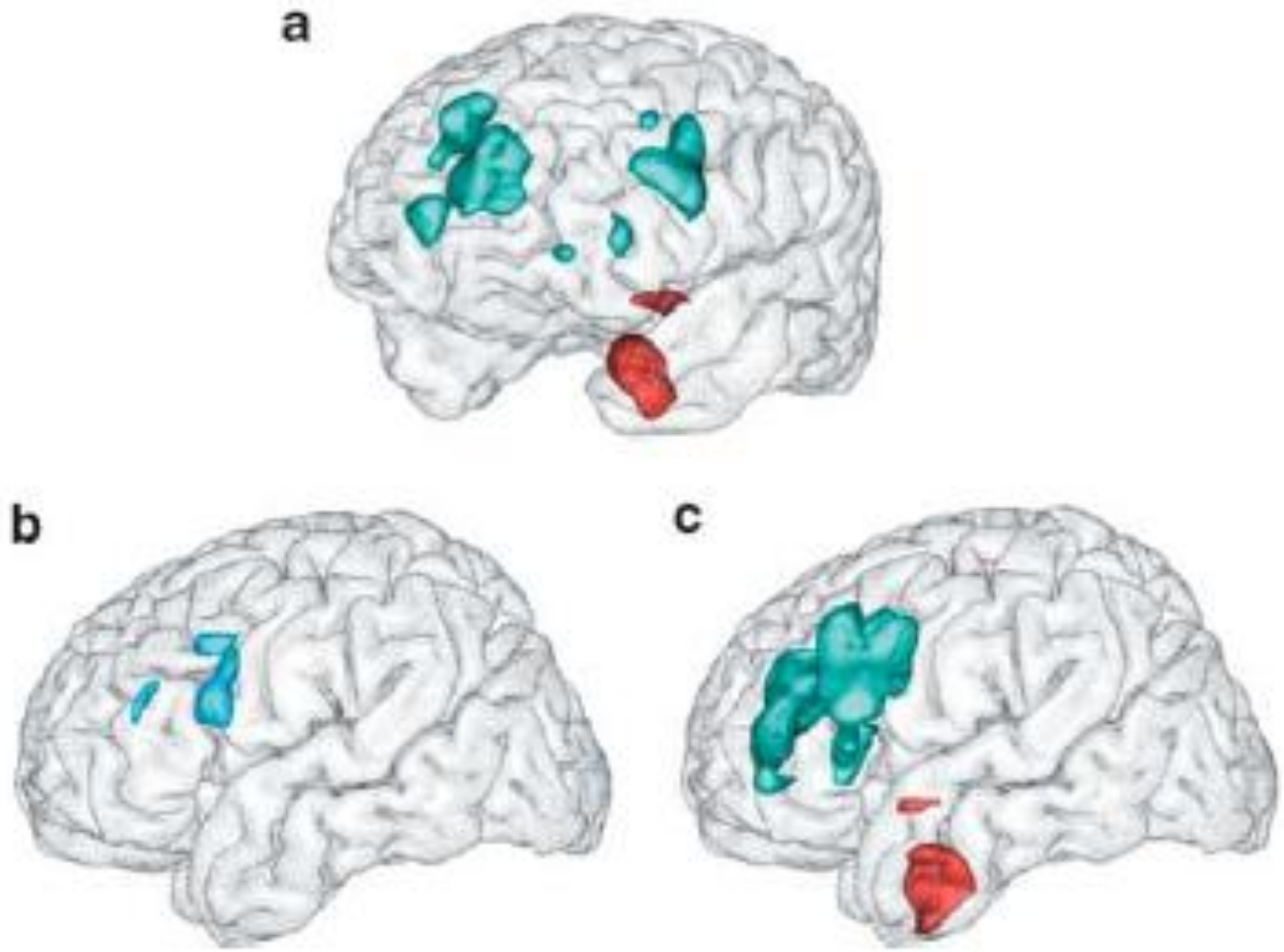




Keener MT. Current Psychiatry report, 2007

BASELINE CEREBRAL GLUCOSE METABOLISM (CGM) IN RESPONDERS AND NON-RESPONDERS (PET)

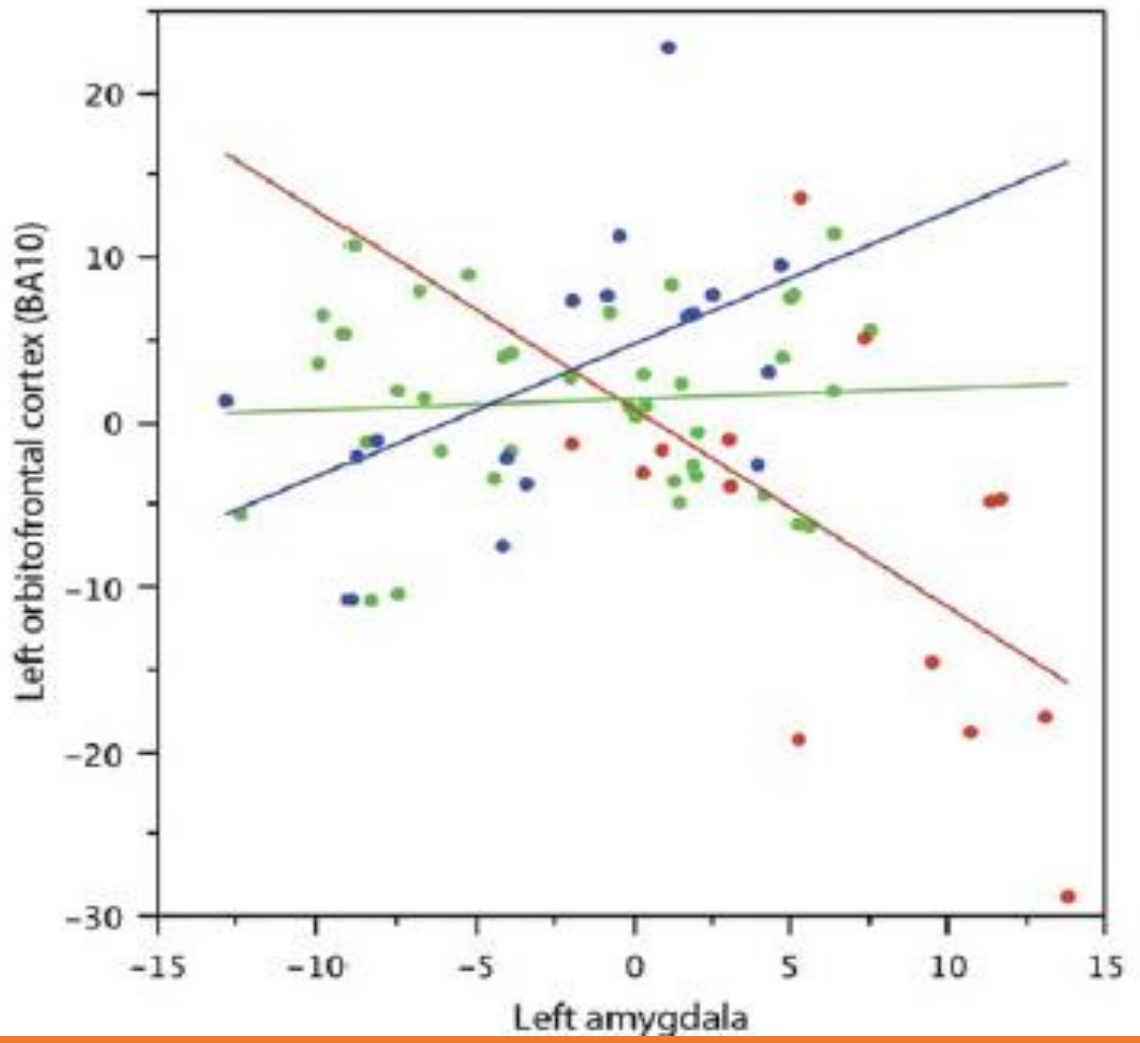
ML. Paillière-Martinot, Neuropsychopharmacology, 2011



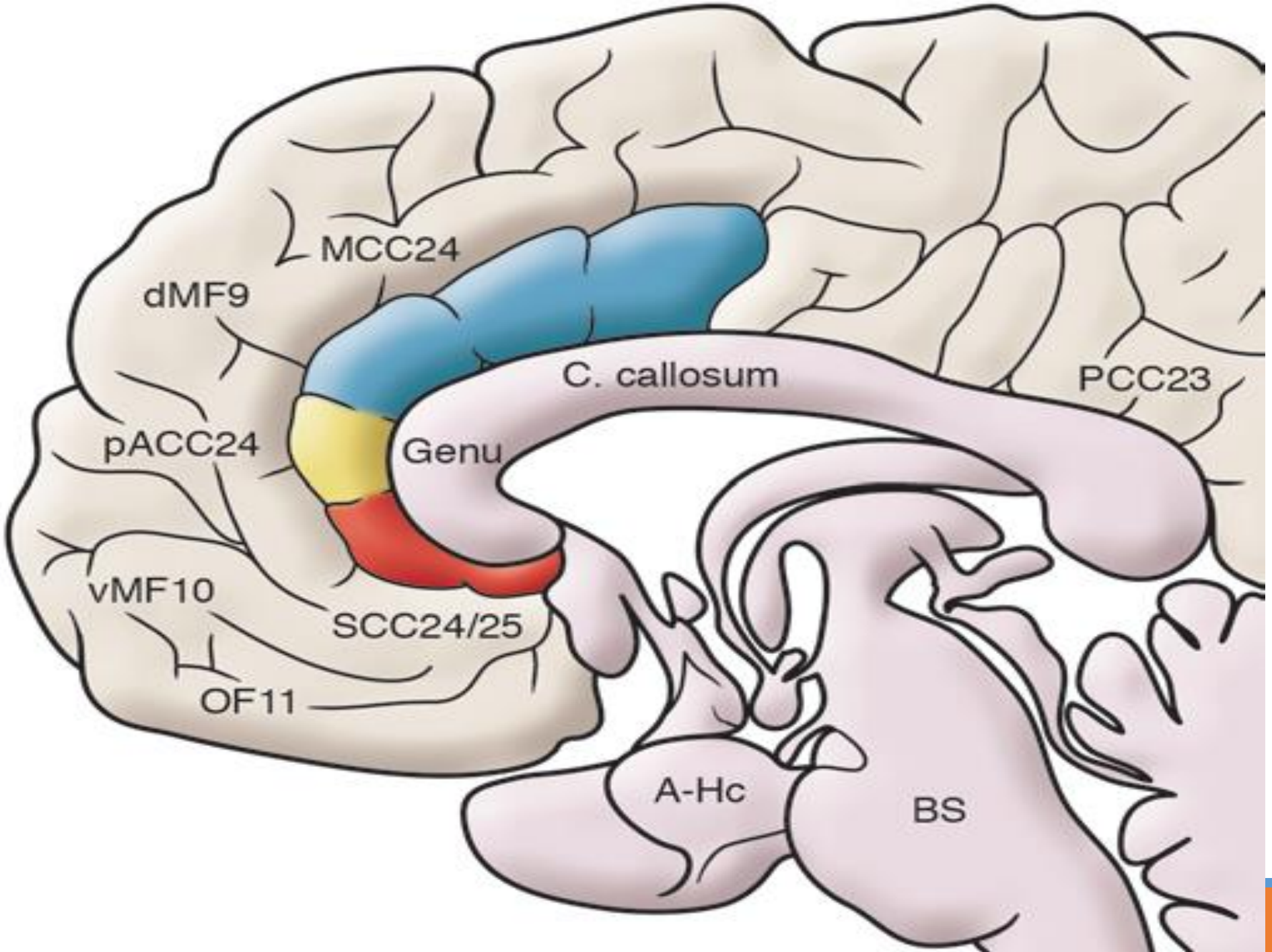
b: Responders c: Non-responders (in this group ↘ in left DLPF and ↗ in left amygdala)

CORRELATIONS BETWEEN REGIONAL CGM IN LEFT FRONTAL BA10 AND LEFT AMYGDALA: RESPONDERS AND NON-RESPONDERS (TMS).

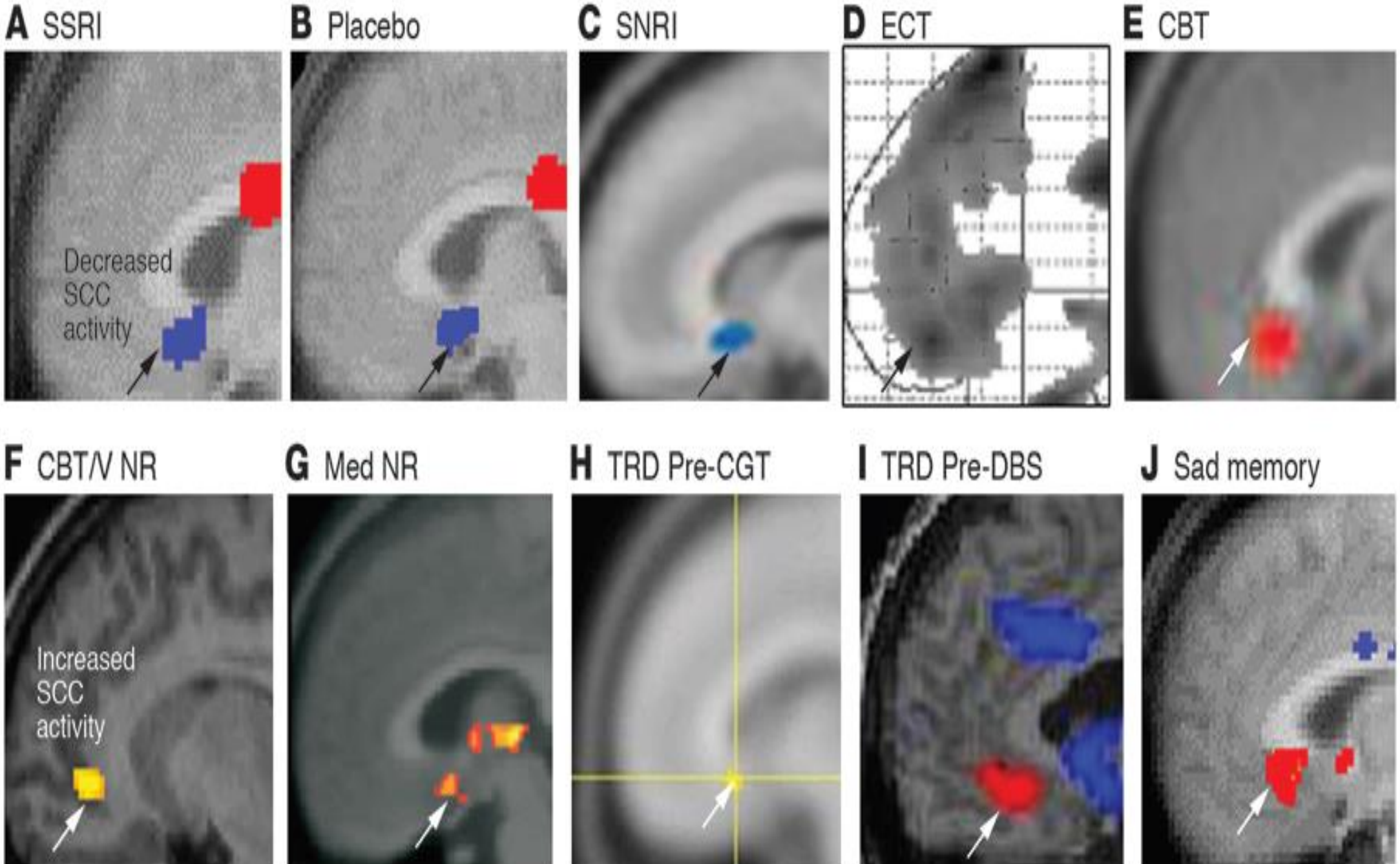
ML. Paillière-Martinot, Neuropsychopharmacology, 2011



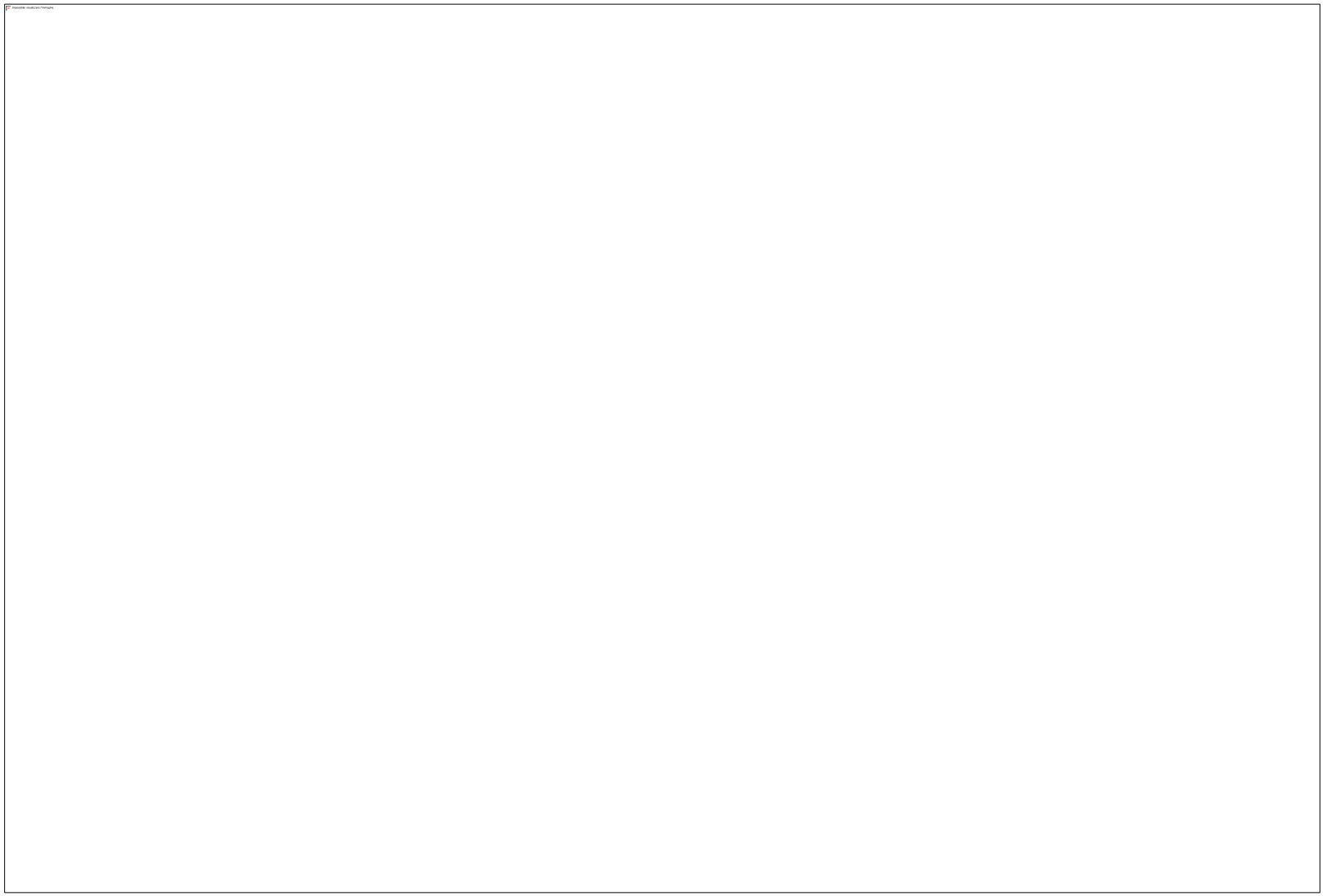
In red: Non-responders


MCC24
dMF9
C. callosum
PCC23
pACC24
Genu
vMF10
SCC24/25
OF11
A-Hc
BS

(H Mayberg, 2009)



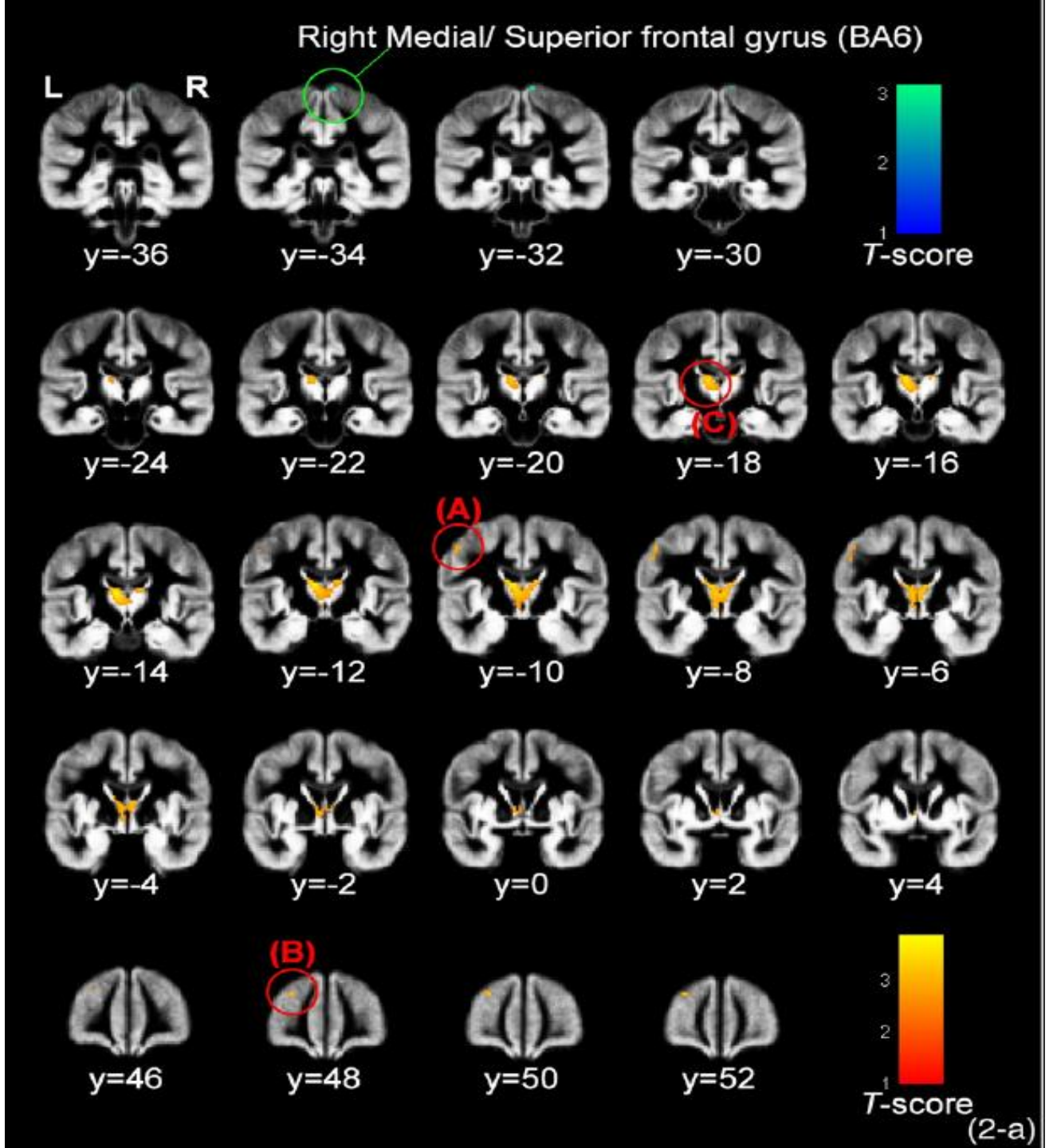
Executive Deficit



Main Volumetric Data in Depression

(Price JL, Drevets WC, Neuropsychopharmacology Review, 2010)

Brain region	Gray matter volume Dep *vs* Con	Cell counts, cell markers Dep *vs* Con
Dorsal medial/anterolateral PFC (BA9)	↓	↓
Frontal polar C (BA 10)		↓
Subgenual anterior cingulate C	↓	↓
Pregenual anterior cingulate C	↓	↓
Orbital C/ventrolateral PFC	↓	↓
Posterior cingulate	↓	
Parahippocampal C	↓	↓ BD
Amygdala	↓/↑[b]	↓ MDD
Ventromedial striatum	↓	
Hippocampus	↓	↓ BD
Superior temporal G/temporopolar C	↓	
Medial thalamus		



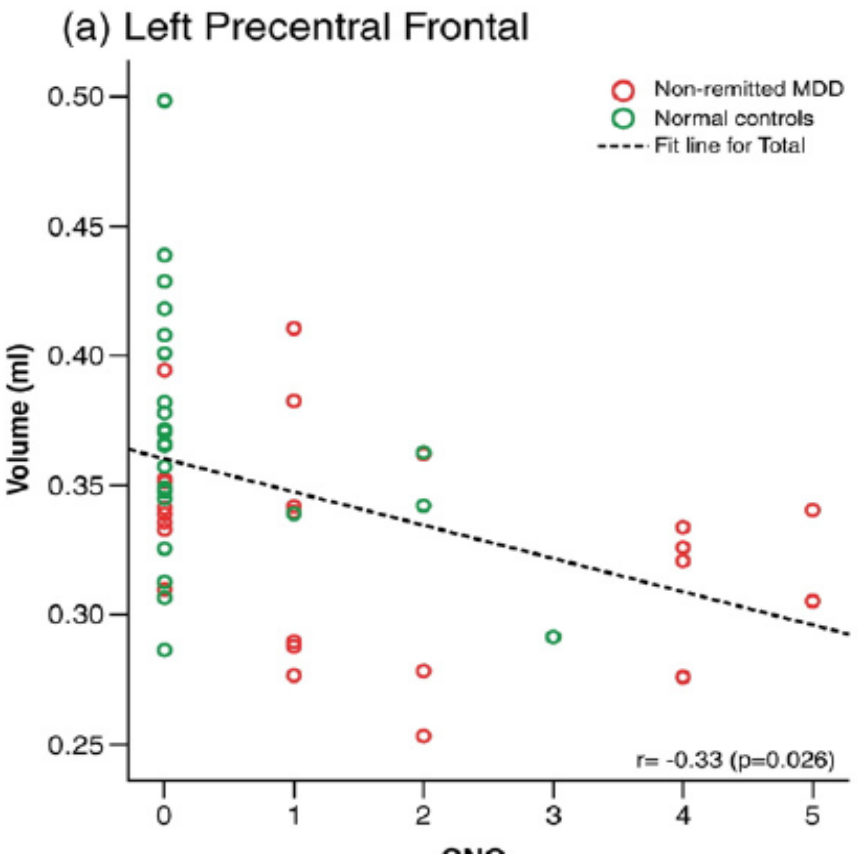
REDUCTION OF GMV: NON REMITTED DEPRESSIVES VS CONTROLS

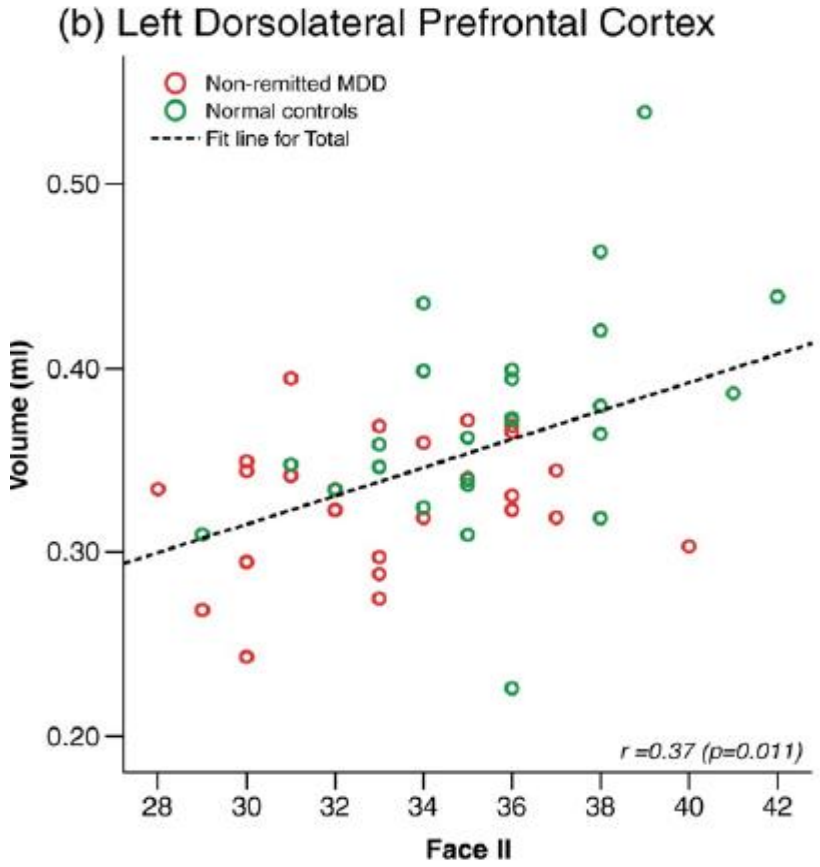
A: Left precentral-gyrus
B: Left dorso-lateral PFC
C: Thalamus

Cheng-Ta Li
Neuroimage, 2010

REDUCTION OF GMV: NON REMITTING DEPRESSIVES VS CONTROLS

Correlations with cognitive tasks

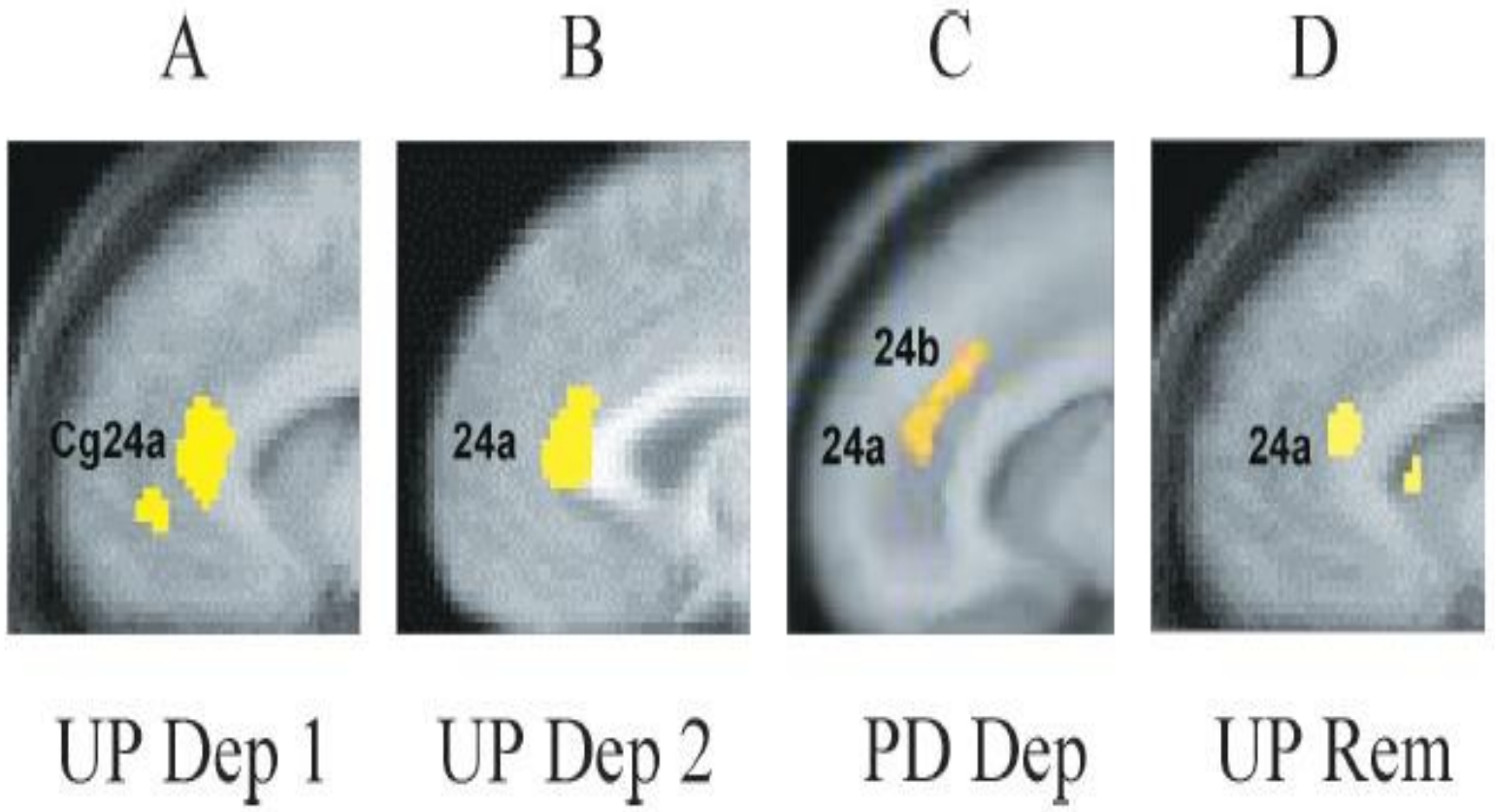




Cheng-Ta Li
Neuroimage, 2010

PREDICTIVE VALUE OF BASAL ROSTRAL CINGULATE (CG24a) METABOLISM: Responders vs Non-Responders

HS Mayberg, BMB, 2003



Summary of summary: characteristics of TRD

Reduced GMV in left DLPFC

Incapacity to decrease the activity of

- **Amygdala**
- **Subgenual regions**
- **Habenula**
- **OFC**
- **Reduced hippocampal volume (posterior)**

A central network for depression?

Default Mode Network

Role of the network:
Self-Centered Mental Activity

- Biographical Memory
- Experience-based anticipation
- Social abilities
- Theory of mind

Dysfunctional in:
- **Psychotic states**
- **Depression**

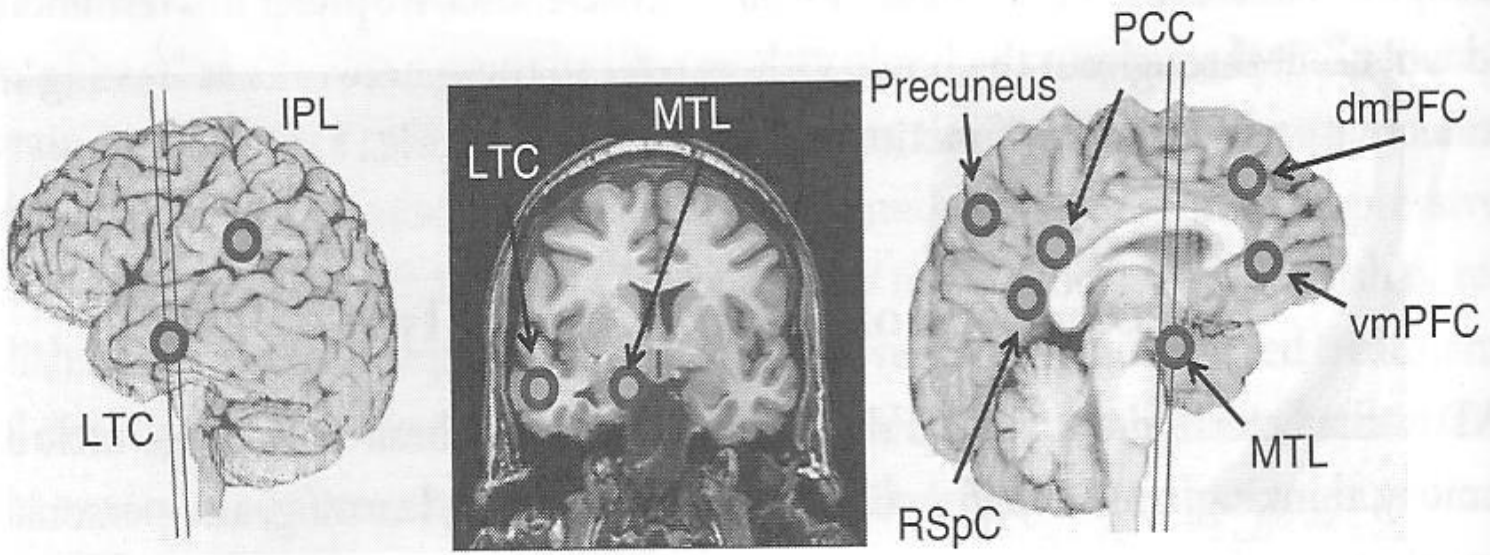
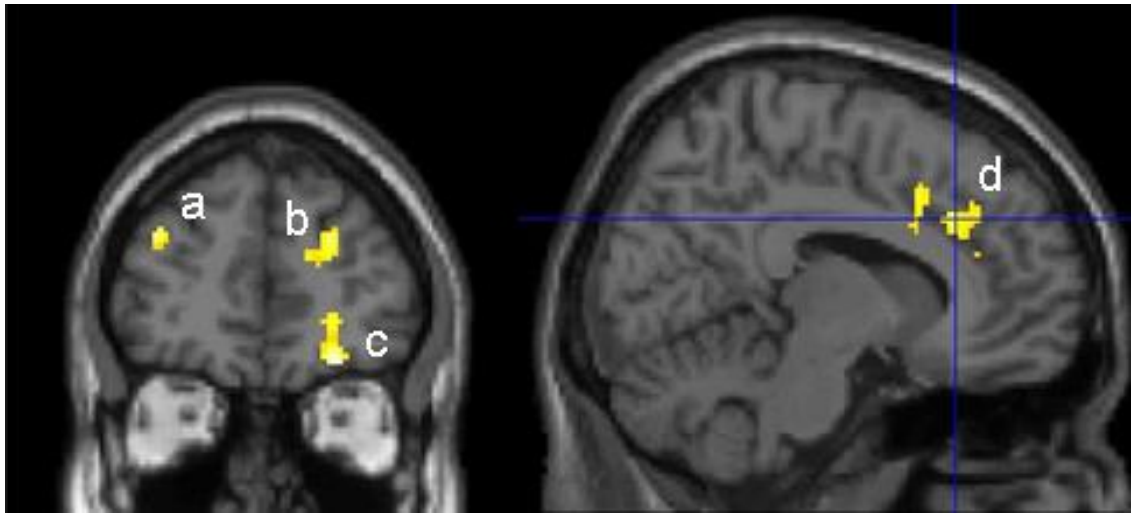


Figure 2-1 Key nodes of the default mode network. The figure depicts key structures involved in the default mode network as defined by Marc Raichle, Randy Buckner, and others. The highlighted regions include the lateral temporal cortex (LTC), inferior parietal lobule (IPL), precuneus, retrosplenial cortex (RSpC), posterior cingulate cortex (PCC), dorsomedial PFC (dmPFC), ventromedial PFC (vmPFC), and medial temporal lobe (MTL), including the hippocampus. The line through the brain reconstructions indicate the approximate location that is shown in the radiologic image. (Adapted from Damasio, 2005, with permission.)

Hyperactivity of the « self-reference » network in patients before treatment (vs controls) (self reference task)

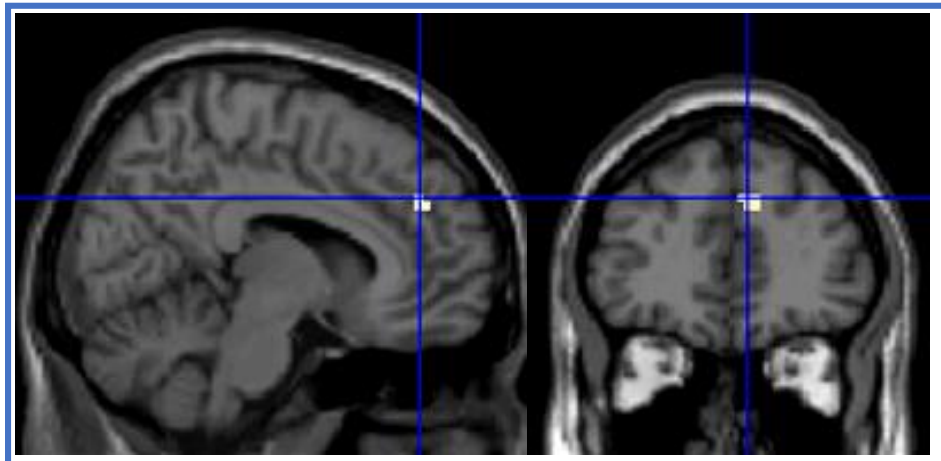


(a) Right DLPFC, (b) right DLPFC , (c) right VLPFC droit, (d) dorsal ACC

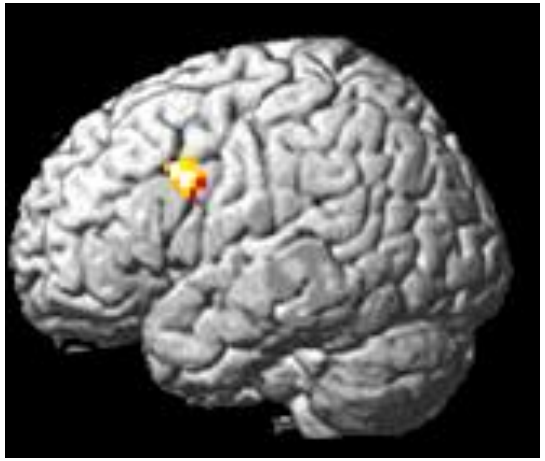
Fossati et al, European Psychiatry, Volume 28, Supplement 1, 2013

Self reference and depression

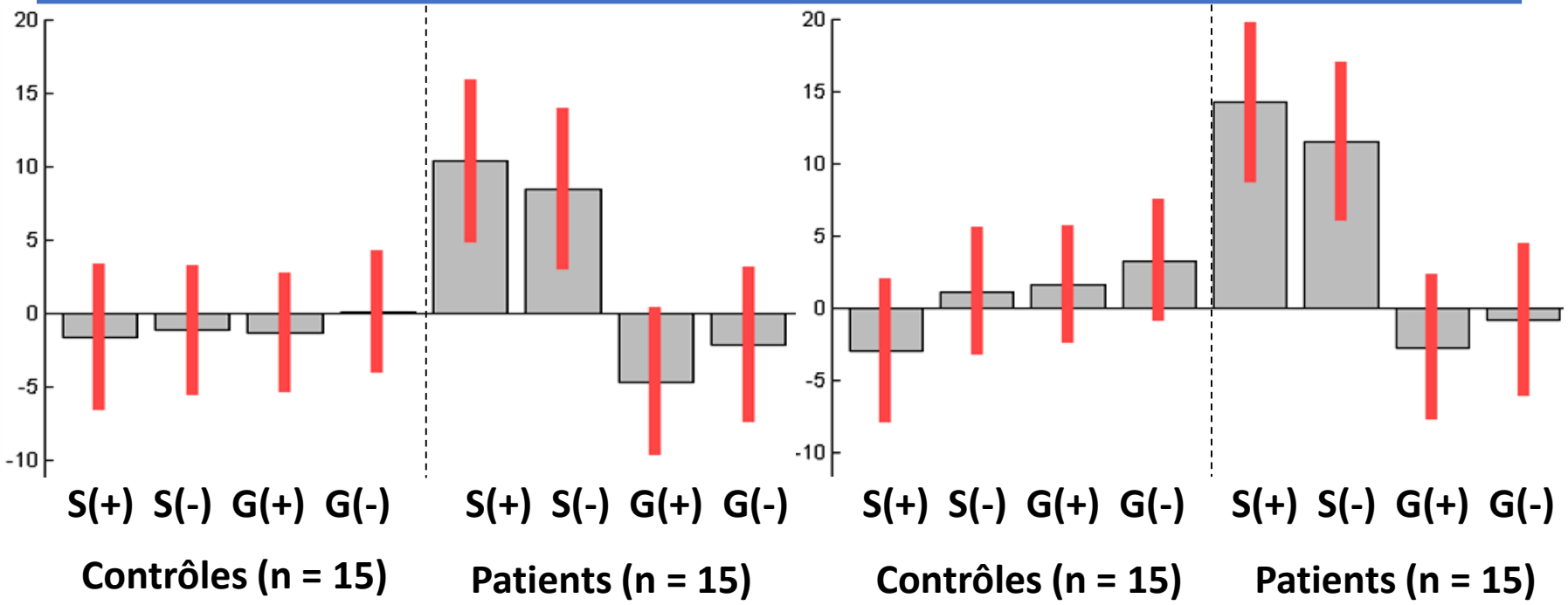
Lemogne et al, SCAN, 2009



Gyrus frontal dorsomedian
(9, 42, 33)



Gyrus frontal inférieur gauche
(-42, 9, 36)



Impossible valuations formalgma.

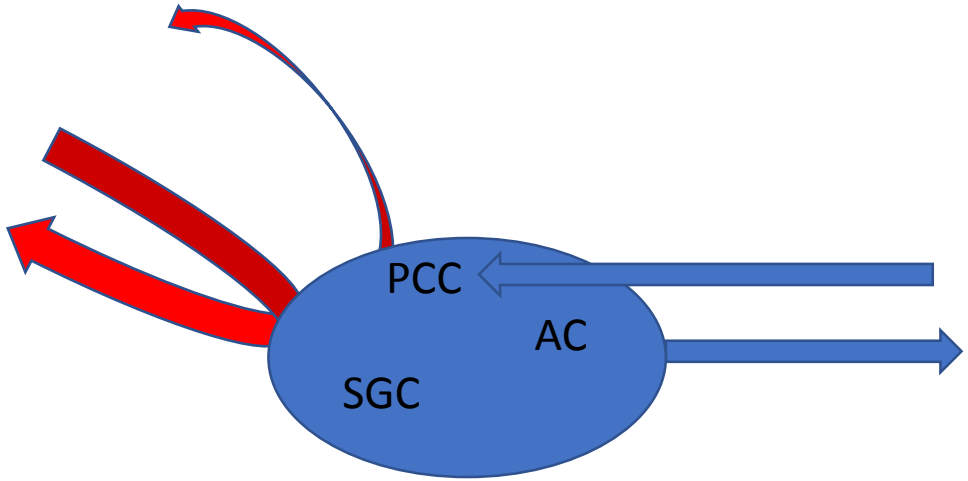
Cingulate Cortex Modulation: a new key?

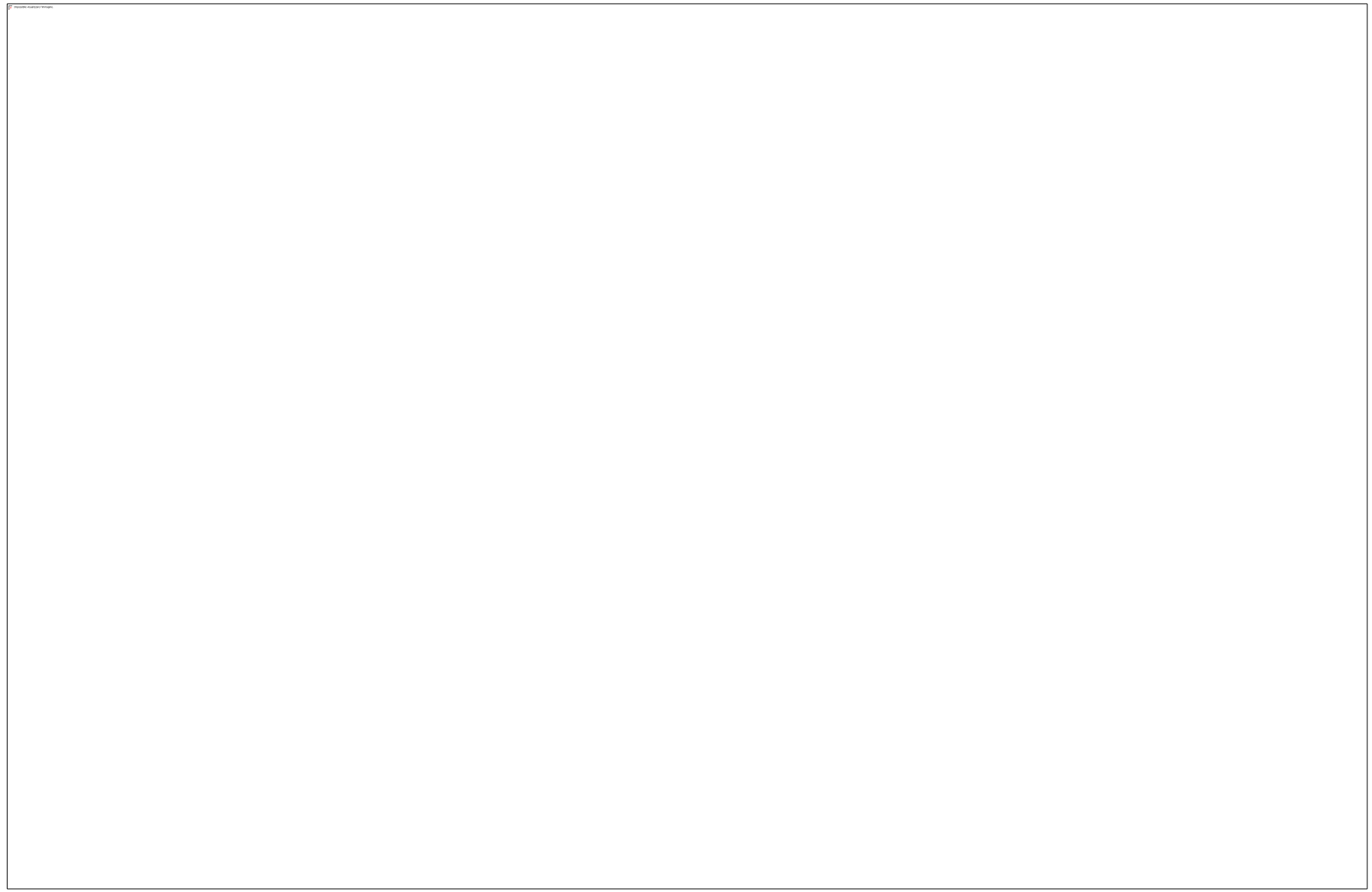
Cg 25 subgenual region: deep brain stimulation and CBT

Cg 24a rostral region: activity increased in responders (Med.)

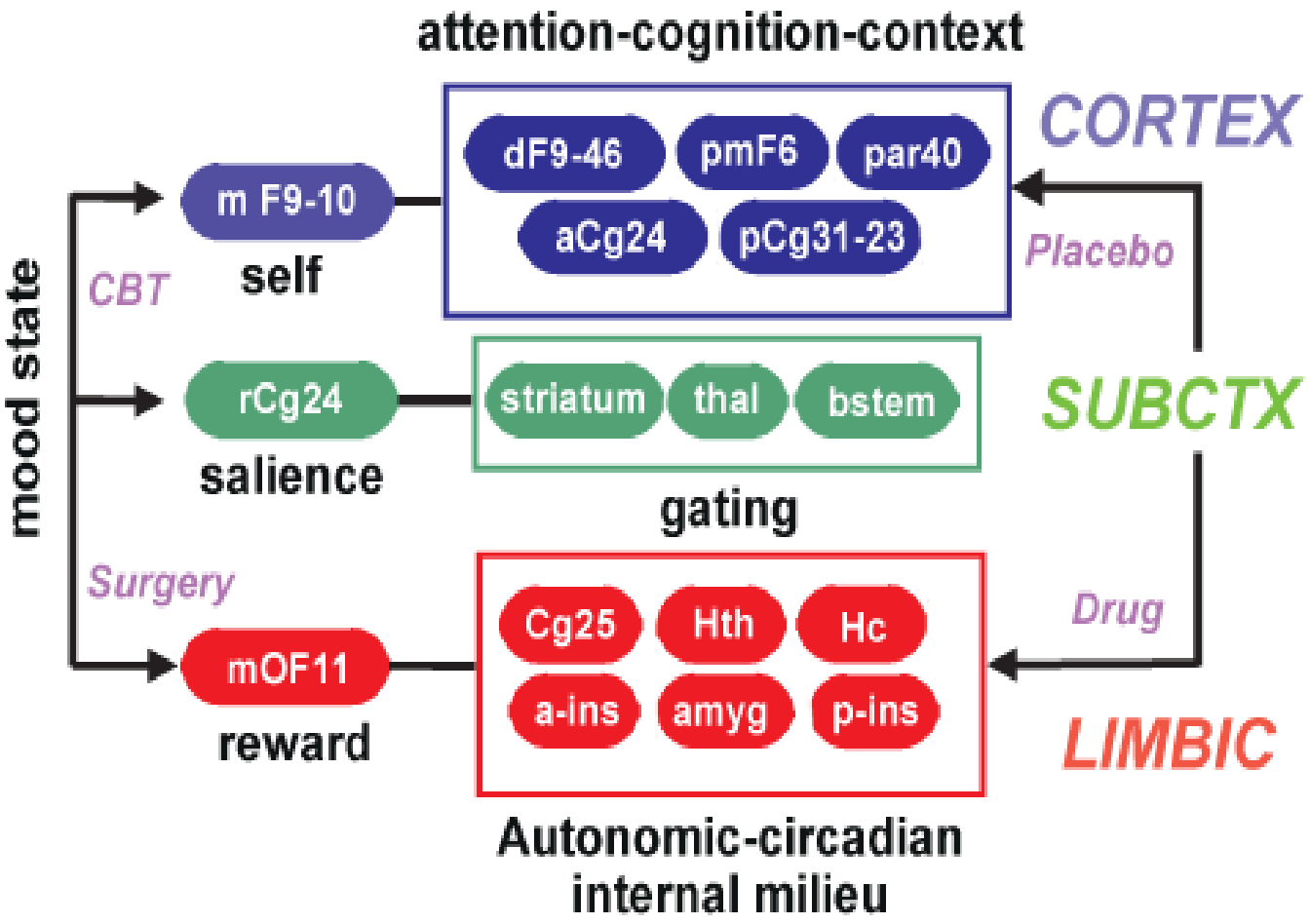
Anterior cingulate: key for executive function

Posterior cingulate: default mode and modulation of autobiographical memory


PCC
AC
SGC



Limbic-Cortical Dysregulation Model



HS Mayberg, BMB, 2003