

# Cognition Imaging: Neuroimaging for Cognitive Assessments

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# Cognition Imaging in psychiatric disorders

- Psychiatric disorders are associated with complex and disease-specific patterns of cognitive impairment



- provoked by various interacting genetic, epigenetic, developmental and environmental factors.



# Significance

- Studies of psychiatric disorders traditionally focused on emotional symptoms
  - Depression, anxiety and hallucinations
- Cognitive deficits
  - Poorly controlled and highly relevant dimensions of psychiatric disorders
  - Severely compromise quality of life
  - Not just a secondary consequence of perturbed affect
  - Different underlying neurobiological substrates
  - Not usually improved by drugs prescribed for symptoms, and may even be worsened
- Improved treatment should be a major goal in efforts to enhance quality of life for patients
- Close interrelationship between cognition and mood though

# Cognitive Deficits as Diagnostic Symptoms

- Features of **mental disorders** listed **among diagnostic symptoms**
  - e.g. reduced concentration in depression and poor memory in chronic alcoholism
- Focus on **cognitive challenges** based on **classic neuropsychological domains**
  - executive function, memory
- Functional Neuroimaging
  - identifies brain areas which **respond atypically to cognitive challenges**
  - correlates clinical features of mental disorders and **neural basis** of cognitive deficits
  - important biomarker for subtypes of disorders that respond to different treatments
  - new techniques emerging to advance understanding of **disrupted connectivity** underpinning cognitive deficits
  - led to development of **neurobiological models** based on functionally **abnormal networks**

Table 1 | Main characteristics of cognitive impairment in psychiatric disorders, and a comparison with PD and AD\*

	Attention and/or vigilance	Working memory	Executive function	Episodic memory	Semantic memory	Visual memory	Verbal memory	Fear extinction	Processing speed	Procedural memory	Social cognition (theory of mind)	Language	References
<b>Major depression</b>	+(+)	++	++	++	+	+	+(+)	0/+?	++(+)	+	+(+)	+	2,16,19,25,26,36
<b>Bipolar disorder</b>	++(+) M	++	++	++	+	+	++	+?	++	0	++	++	19,23,24,37
<b>Schizophrenia</b>	+++ M	+++ M	+++ M	+++	++	+(+) <sup>M</sup>	+++ M	++	++ <sup>M</sup>	+	+++ M	+++	6,9,19–22
<b>ASD</b>	+++	+	+++	++	+	+	+(+)	+(+)	+++	0/+	+++	+++	8,31,32
<b>ADHD</b>	+++	++	+++	0/+	+	++	++	+	++	+	+	0/+	28,29
<b>OCD</b>	+++(↑)	+(+)	++	+	0/+	+	0/+	++	++	++	+	0/+	12,30
<b>PTSD</b>	+++(↑)	+(+)	+(-)	++	+	+	++(+)	+++	+	0	0/+	0	14,16
<b>Panic disorder</b>	+++(↑)	+	0/+	+	0/+	0/+	+	++	++	0	0	0	16,18
<b>GAD</b>	+	+	0	0	+	+	+	+	0	0	0/+	0	16,17
<b>Parkinson's disease</b>	++	++(+) M	++	+	0/+	+	+	0?	+++	+++	+(-)	+(-)	-
<b>Alzheimer's disease</b>	+(-)	+(-)	+(-)	+++	+++	+++	++(+)	0?	+	+	+	++	-

0, essentially absent; 0/+, poorly documented, ambiguous, mild and/or variable; +, consistently present but not pronounced; ++, a common, marked characteristic; +++, a core, severe and virtually universal characteristic of the disorder; ?, not clearly evaluated; ↑, increase; AD, Alzheimer's disease; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; GAD, generalized anxiety disorder; OCD, obsessive compulsive disorder; PD, Parkinson's disease; PTSD, post-traumatic stress disorder; \*Cognitive deficits in the absence of treatment are depicted. 'M' indicates a cognitive domain specified in the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) programme (BOX 2), in which episodic and semantic memories are subsumed under 'visual or verbal learning and memory'. Social cognition encompasses theory of mind. In rare cases (such as Savant syndrome), autistic individuals display a remarkable increase in declarative memory and processing speed for selected domains of interest. ADHD observations refer to the young; similar symptoms usually persist into adulthood. Individuals with OCD, PTSD and panic disorders show hypervigilance to threatening (intrusive) stimuli, which can disrupt performance of goal-directed tasks. For AD, observations are for a modest degree of progression. Brackets around '+' symbols indicate an intermediate magnitude of deficit: for example, '+(-)' indicates between '+' and '++'.



**Fig. 1. A global view of cognition and its disruption in psychiatric disorders.**

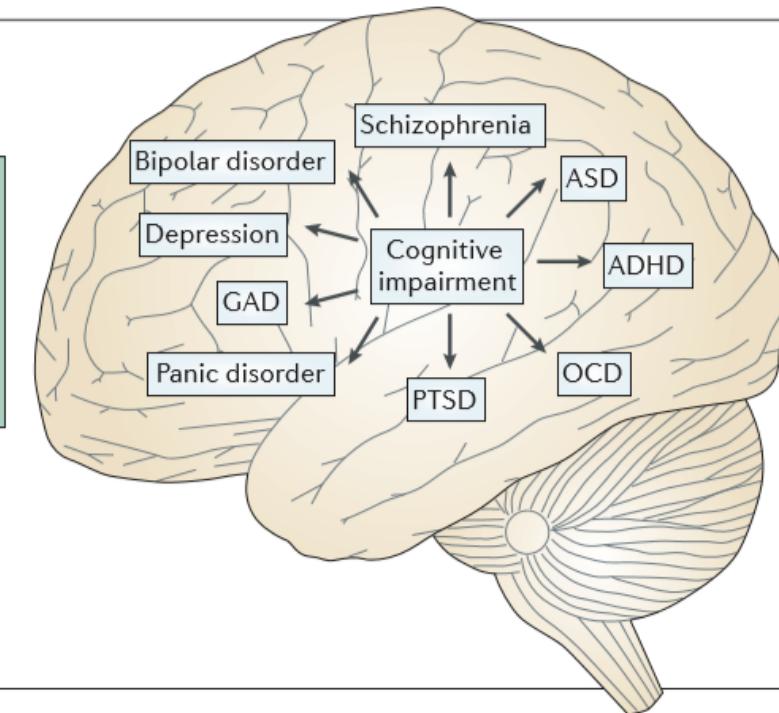
- ADHD, attention deficit hyperactivity disorder
- ASD, autism spectrum disorder
- GAD, generalized anxiety disorder
- LTD, long-term depression
- LTP, long-term potentiation
- OCD, obsessive compulsive disorder
- PTSD, post-traumatic stress disorder

**Universal domains:**

- Attention, working memory, executive function
- Procedural learning and memory
- Speed of processing
- Fear-extinction learning
- Semantic memory

Functional and structural disruption in neurons and/or glia of:

- Cellular signalling
- Gene transcription and mRNA translation
- DNA and/or histone epigenetic codes
- Firing rate and patterns (LTP and LTD)
- Dendritic spines, synaptic plasticity and neurogenesis
- Neuromodulator release



**Higher domains:**

- Episodic memory
- Social cognition
- Theory of mind
- Verbal learning and memory
- Language (use and understanding)

Focal and distributed network perturbation:

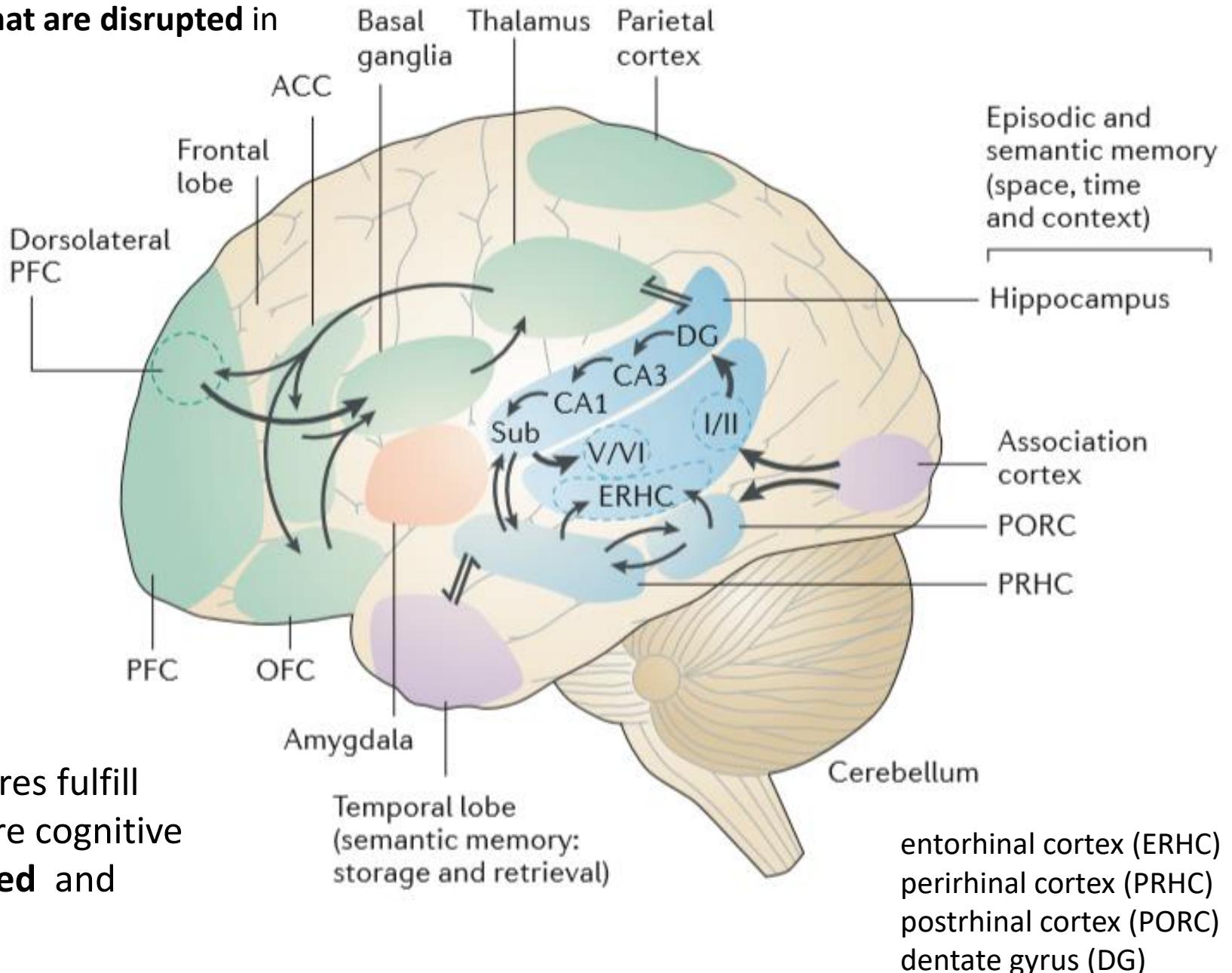
- Interregional dysconnectivity
- Local overconnectivity
- Collapse of small-world configurations
- Disorganization and desynchronization
- Disrupted  $\gamma$ -and  $\theta$ -oscillations

Multiple spatial scales: molecules to cerebral circuits

↔

Multiple time scales: milliseconds to years

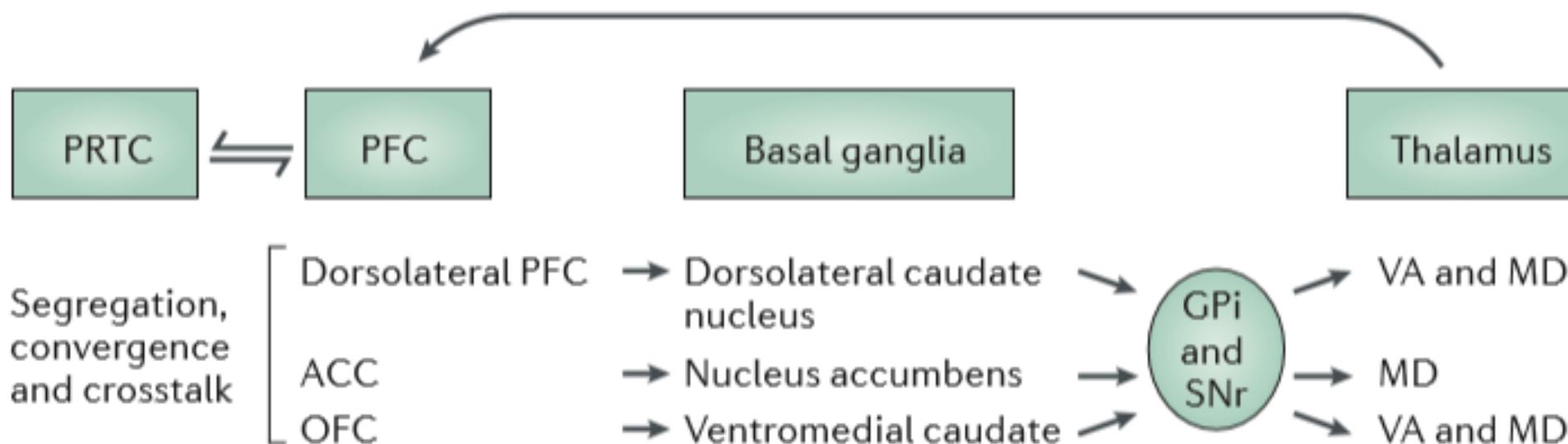
Schematic representation of major cerebral circuits underpinning **core cognitive domains** that are disrupted in psychiatric disorders.



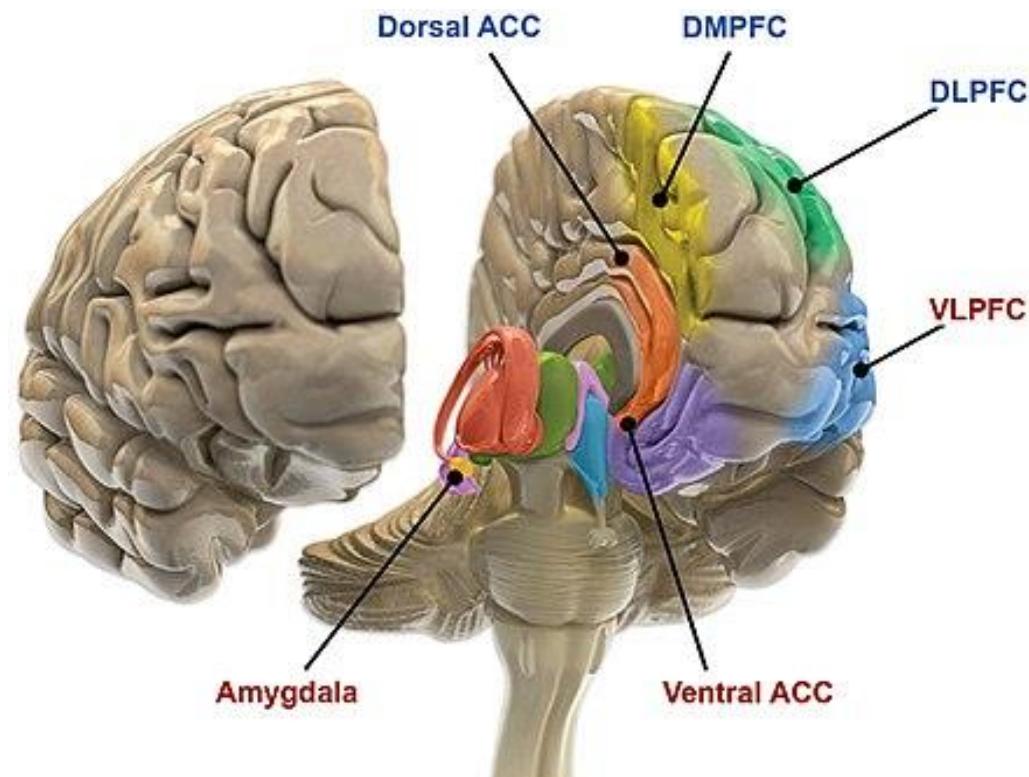
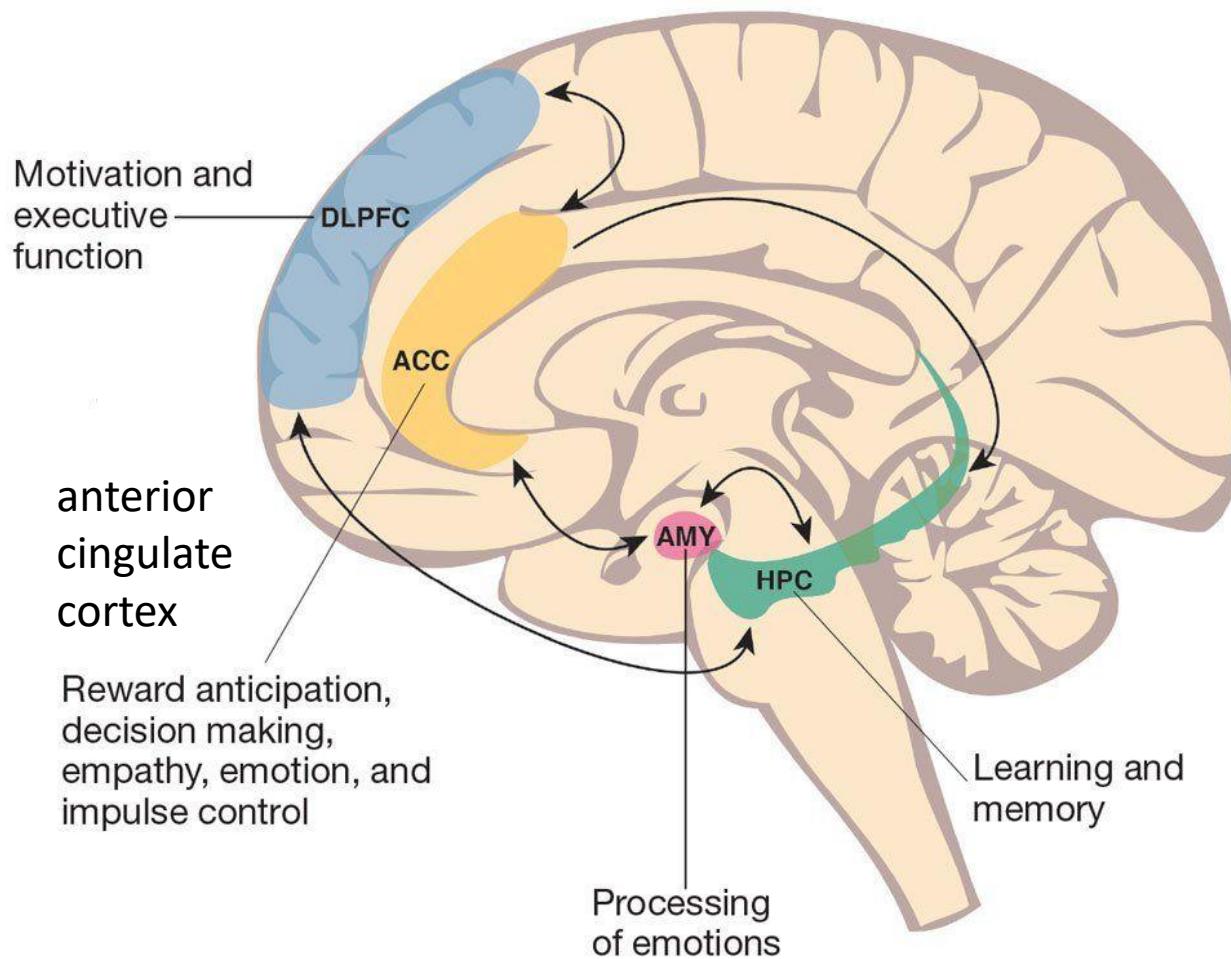
Although individual cerebral structures fulfill **distinctive** roles in the control of core cognitive domains, they operate as **coordinated** and **overlapping networks**.

# Cortico-Thalamo-straital Loop

## a Attention, working memory and executive function



**Figure 1. Corticolimbic system**



DLPFC: Dorsolateral prefrontal cortex

VLPFC: Ventrolateral prefrontal cortex

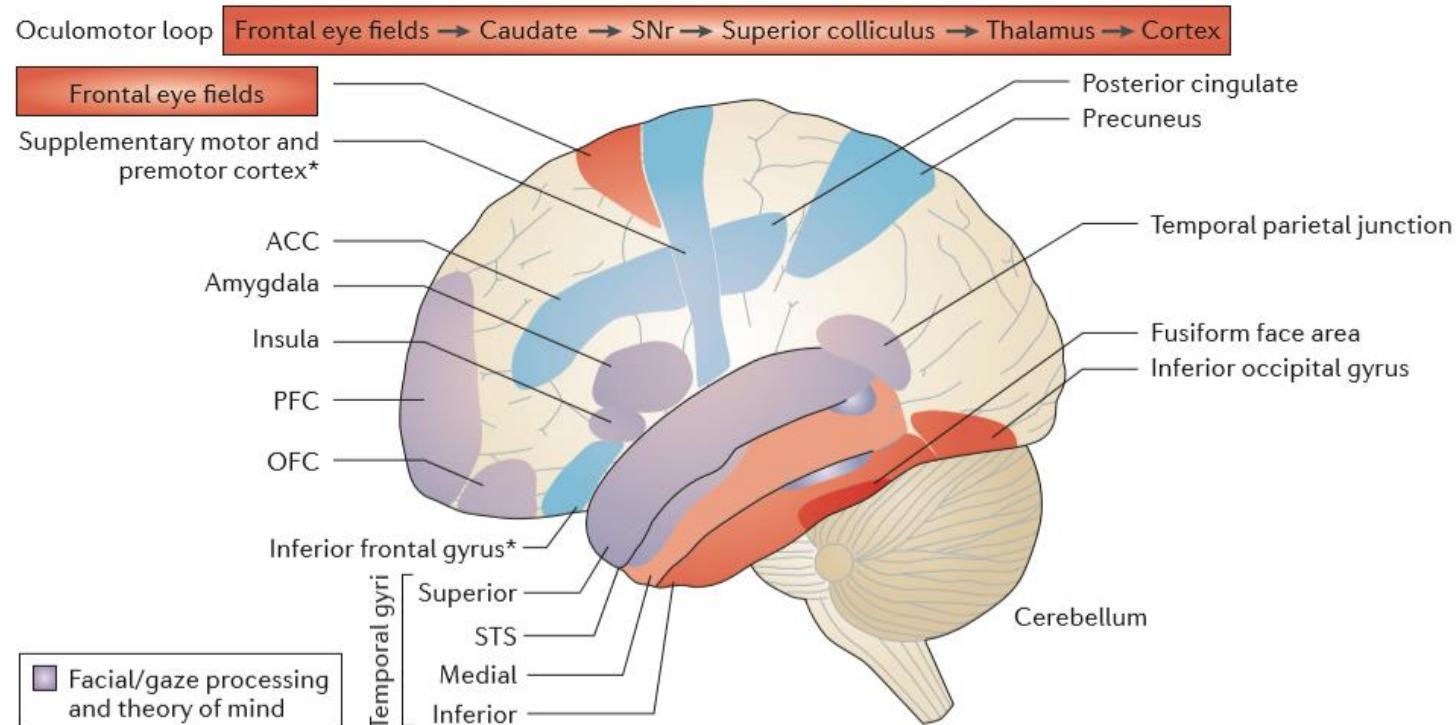
DMPFC: Dorsomedial prefrontal cortex

ACC: Anterior cingulate cortex

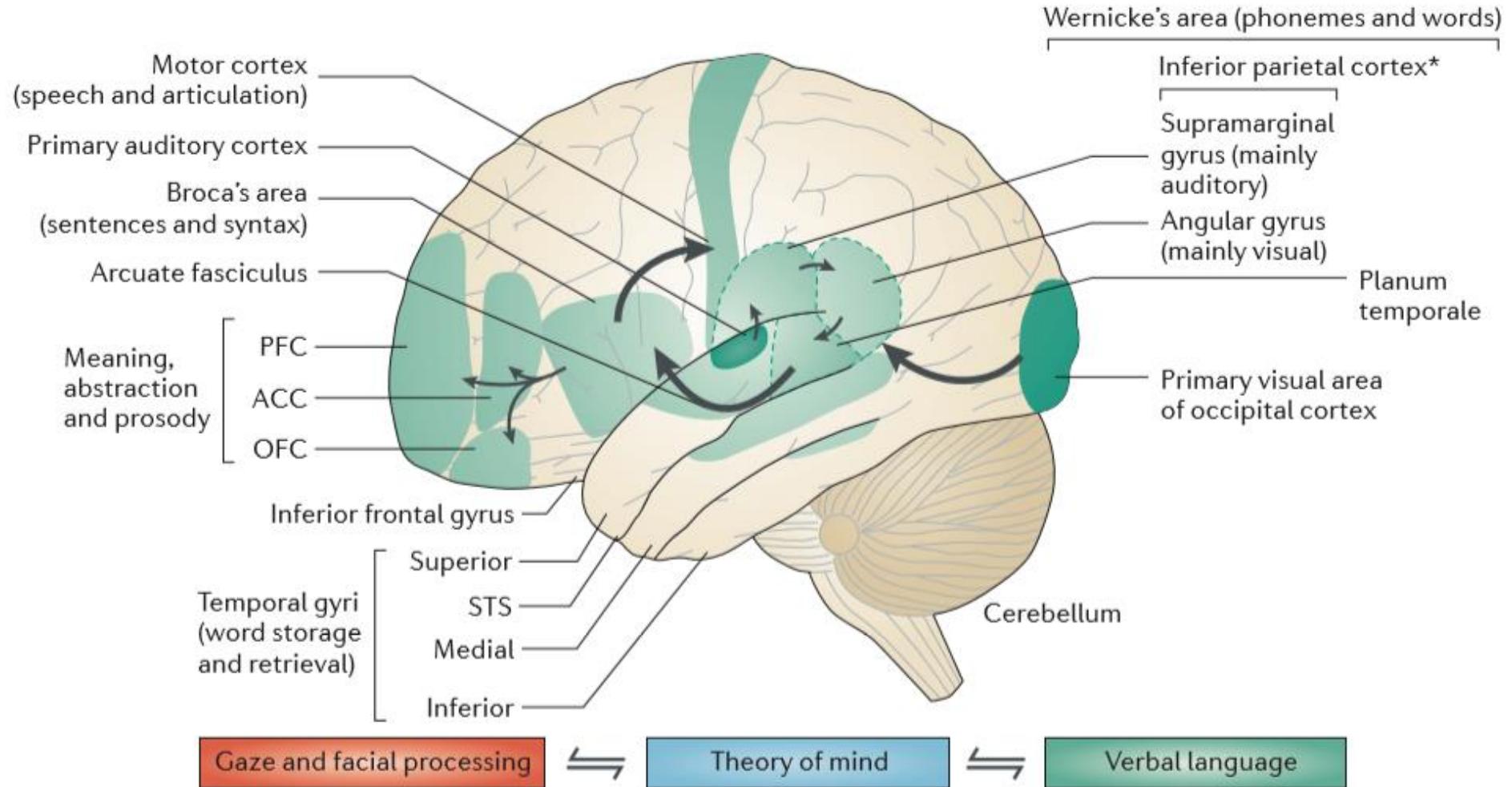
DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; AMY, amygdala;  
HPC, hippocampus.

# Principal cerebral circuits integrating social cognition and verbal language

The oculomotor loop is modulated by prefrontal and parietal inputs, and guides the direction and speed of voluntary eye movement.

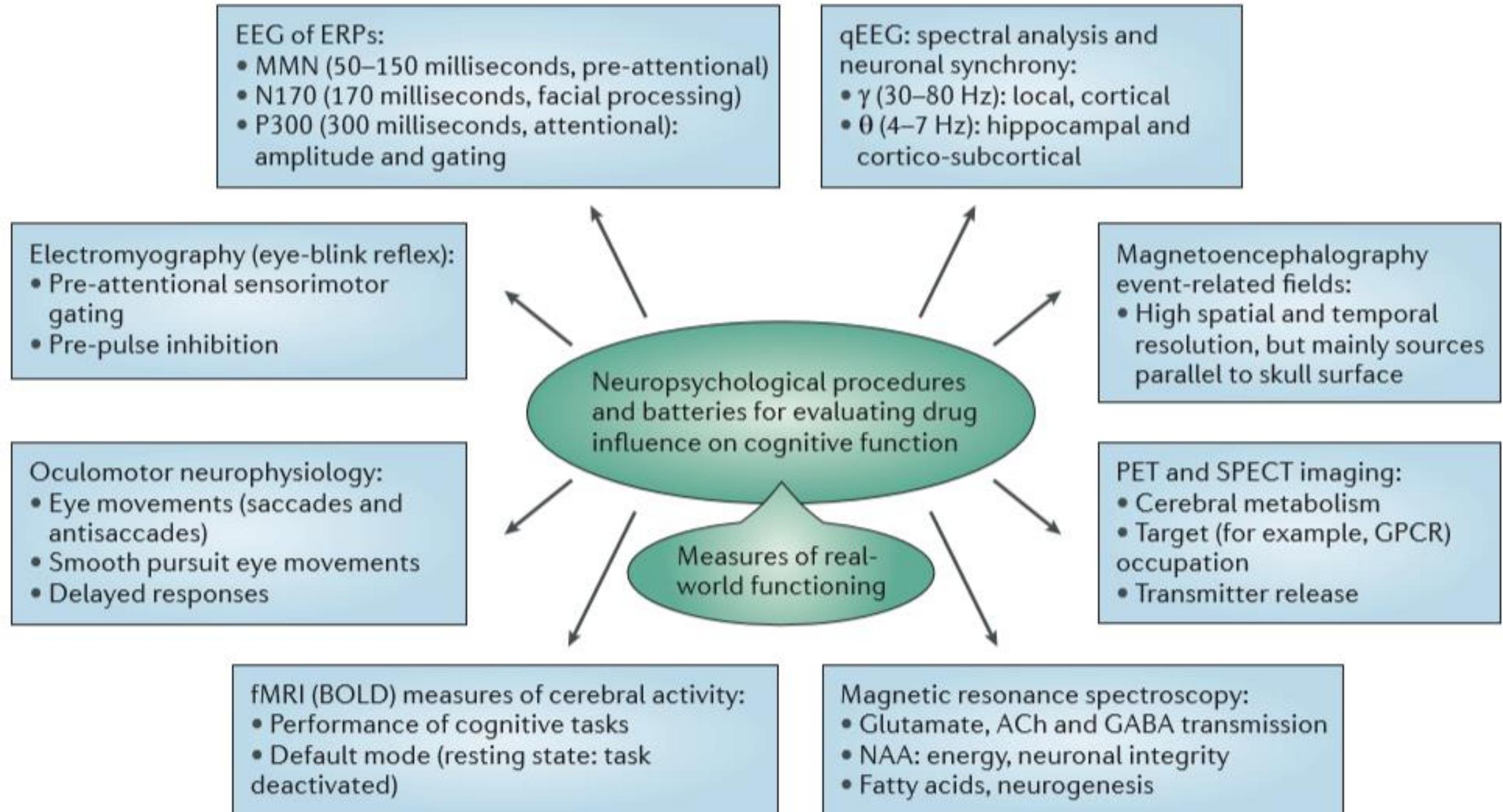


# Principal cerebral circuits integrating social cognition and verbal language



No	Disorder	Impaired EF	Impaired brain regions
1	Schizophrenia	All EFs*, Severe social cognition**	A disturbance of frontocortical–striatal–thalamic loops, together with impaired top-down cognitive control from the cortex, contributes to deficits in attention, working memory and executive function.
2	OCD	Inhibition, Attention, Social cognition	Cortico–striato–thalamo–cortical (CSTC) dysfunction
3	MDD <sup>1</sup>	Decision making, Processing speed, Working memory, Social cognition	
4	Bipolar***	Inhibition, Attention, Social cognition	
5	ADHD	Attention, Working memory, Processing speed, Planning, Social cognition	
6	GAD****	Attention, Working memory	

No	Task name	Executive function target
1	BART	Risk-taking behavior
2	Stop Signal task	Inhibition
3	Paired associate memory task	Memory
4	Spatial capacity task	Working memory
5	Task-switching task	Task switching
6	Stroop task	Inhibition
7	Go/No-Go	Inhibition
8	Delayed-Discounting task	Impulsive behavior
9	Iowa Gambling task	Decision making
10	Dot-Probe	Attentional bias
11	Wisconsin Card sorting task	Task switching
12	N-back	Working memory
13	Tower of London	Planning



# fMRI

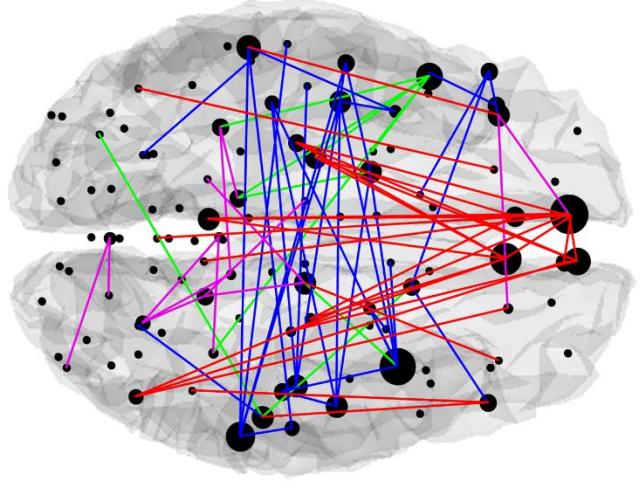
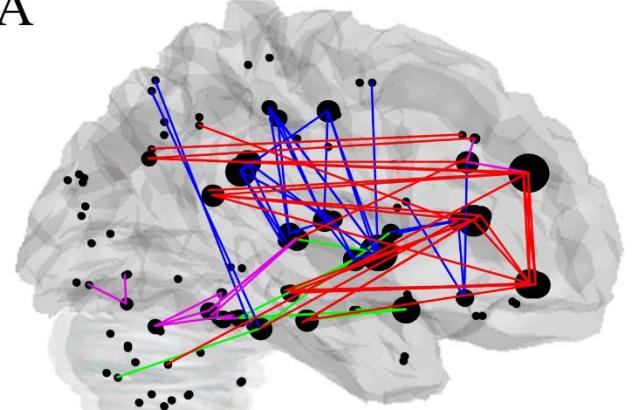
- A technique that exploits the differential paramagnetic properties of oxy- and deoxyhaemoglobin to estimate local cerebral BOLD activity.
- Increased oxygen supply compensates for (and transiently exceeds) energy needs, so the BOLD signal is proportional to neuronal activity.
- Interpretation of data is challenging as BOLD integrates changes both in neurons and in glia, pre- and postsynaptic changes in excitability, as well as local and upstream effects of drugs.
- Furthermore, BOLD signals can be affected by energy balance and haemodynamic parameters.

# Graph theory

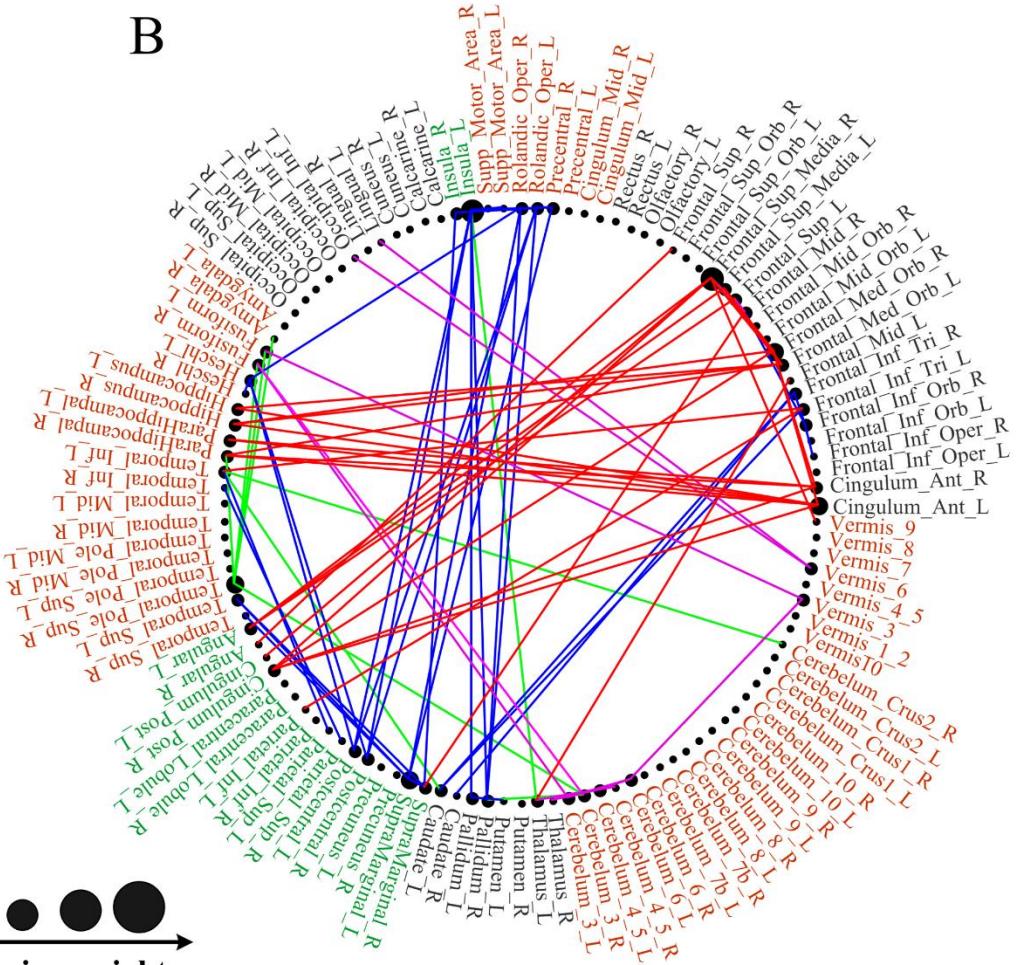
- A mathematical approach for modelling complex networks whereby individual elements, like cerebral regions, neurons or cellular proteins, are considered as ‘nodes’ linked by ‘edges’.
- Brain graphs (derived from neuroimaging data) and cellular graphs (derived from studies of protein networks) reveal non-random topological properties such as modularity (clusters of nodes highly connected to each other) and hubs (nodes with numerous connections).
- These properties help to optimize network function, including cognitive processing.

# Functional Connectivity

A



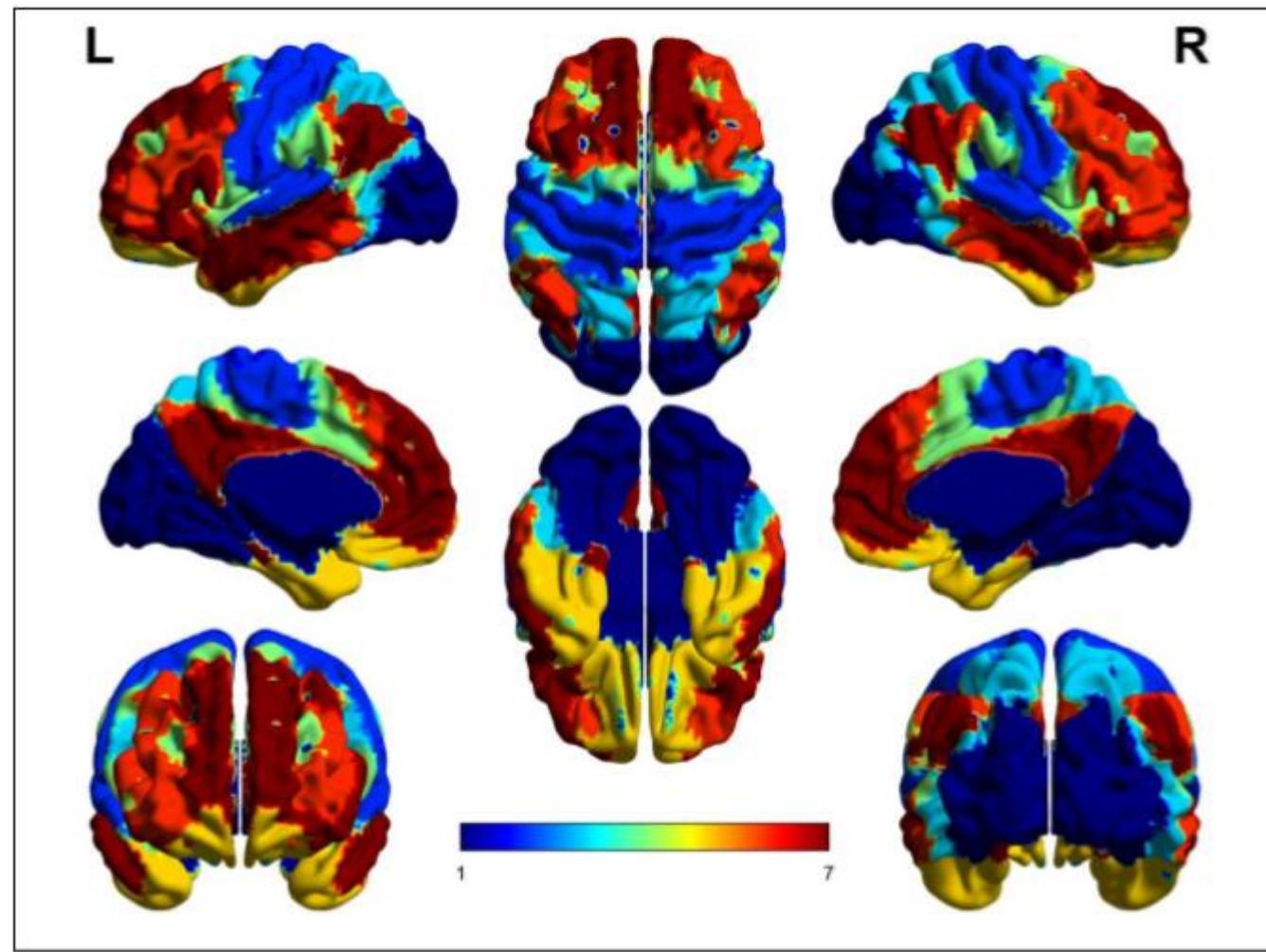
B



region weight

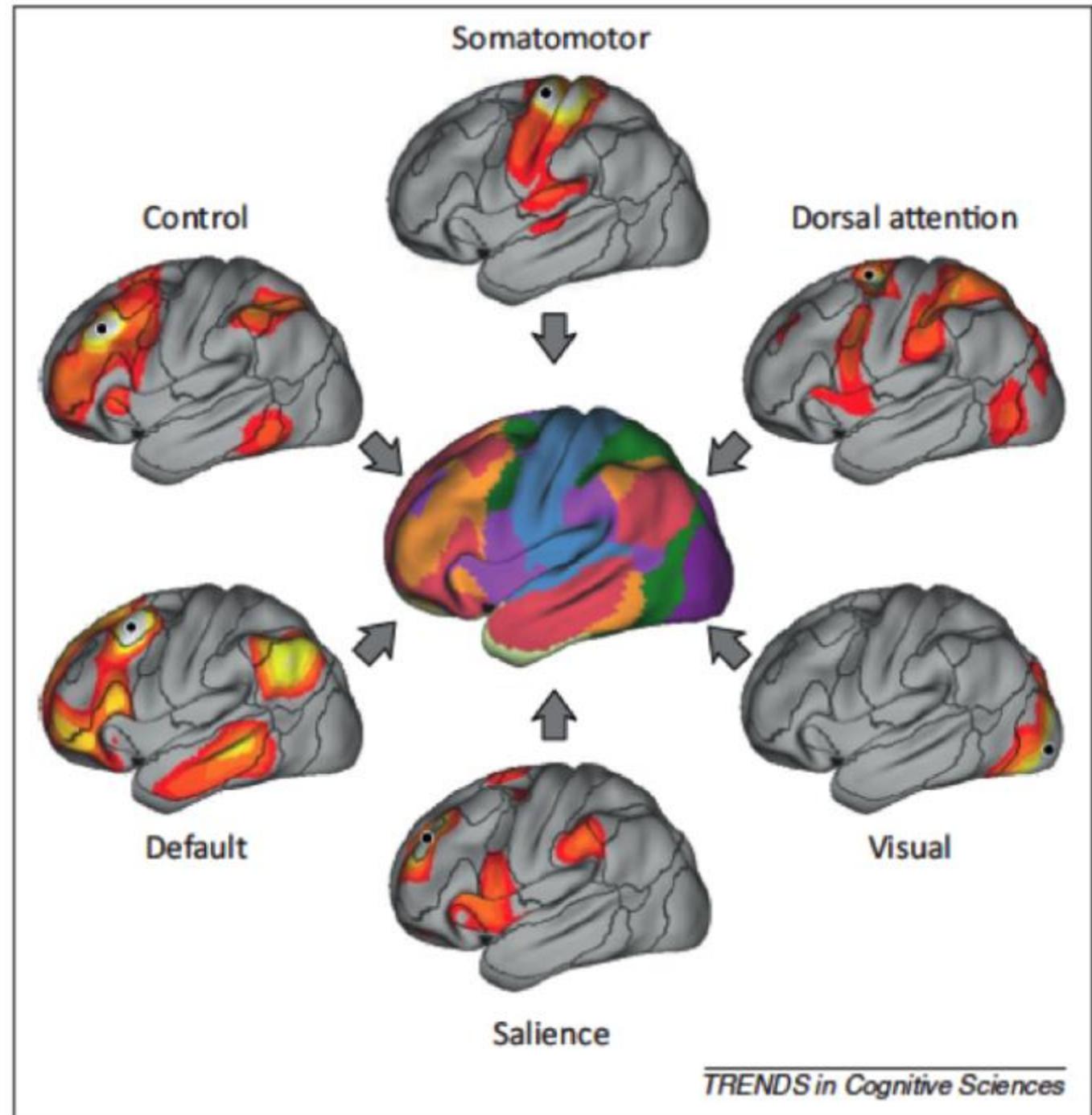
linear + linear - quadratic + quadratic -

Yeo.2011- 7 functional networks



1	Visual
2	Somatomotor
3	Dorsal Attention
4	Ventral Attention
5	Limbic
6	Frontoparietal
7	Default

The human brain is structured with several large-scale networks with widely distributed regions across the cortex and subcortical regions.



# Focal and distributed network perturbation

- Interregional dysconnectivity
- Local overconnectivity
- Collapse of small-world configurations
- Disorganization and desynchronization
- Disrupted  $\gamma$ -and  $\theta$ -oscillations

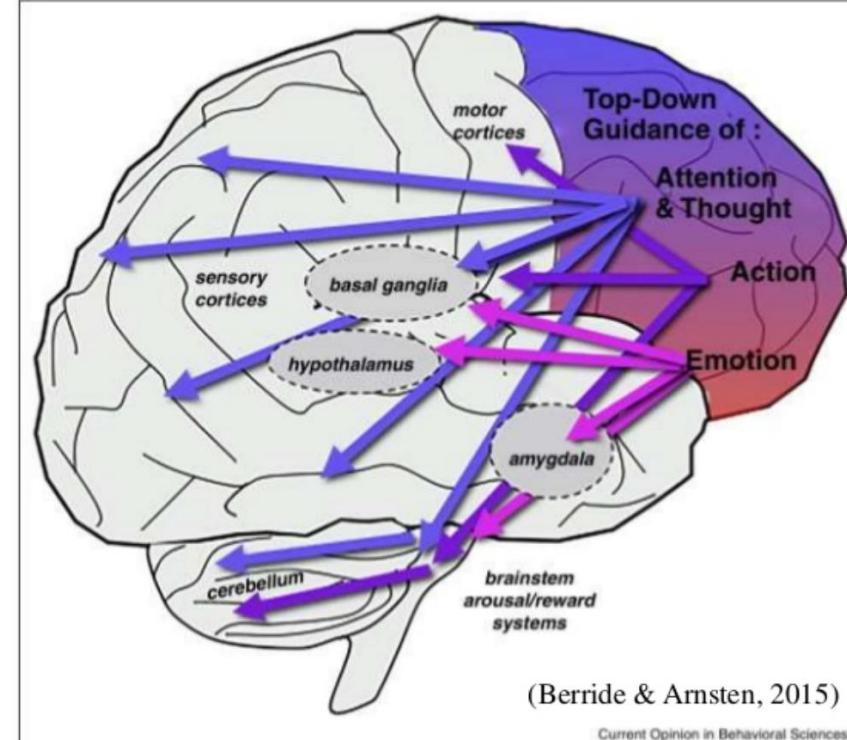
# Cognitive challenges used in functional neuroimaging

- Non-emotional challenges
- Emotional challenges

## The Neural Correlates of Executive Function

Prefrontal Cortex

[ozella.brundidge@gmail.com](mailto:ozella.brundidge@gmail.com) 8/29/2017

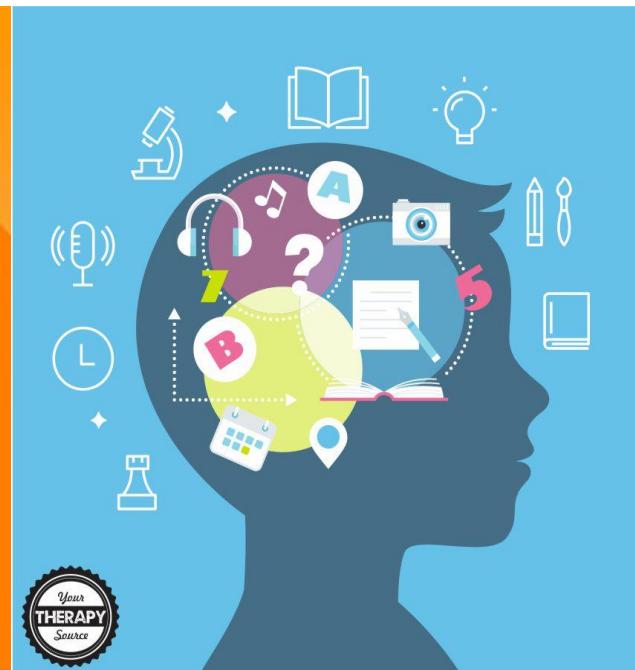
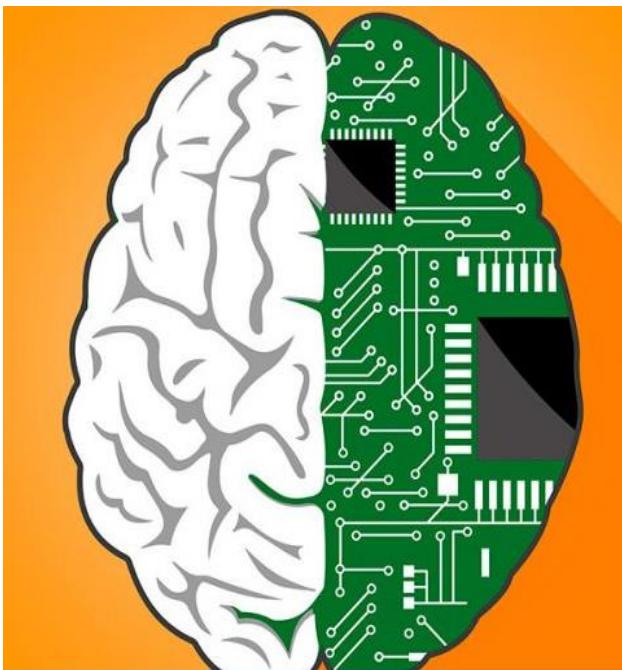


(Berride & Arnsten, 2015)

Current Opinion in Behavioral Sciences

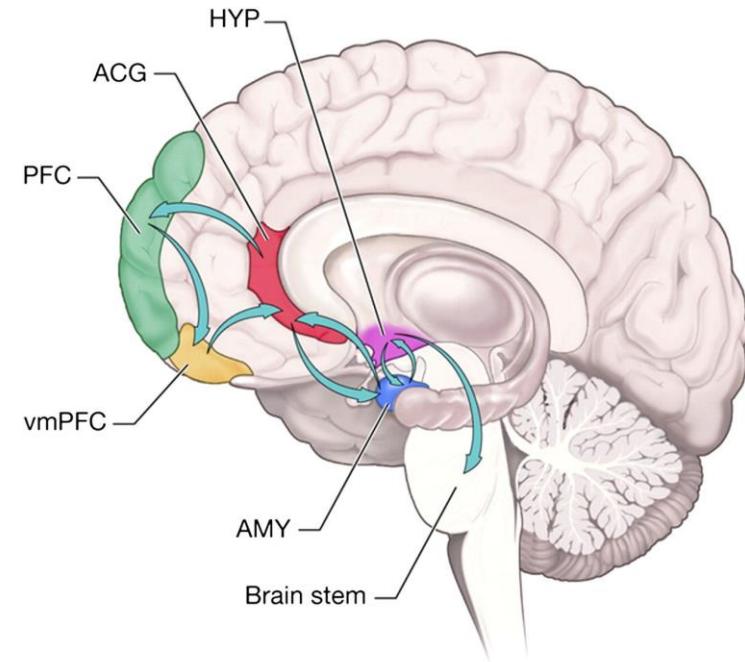
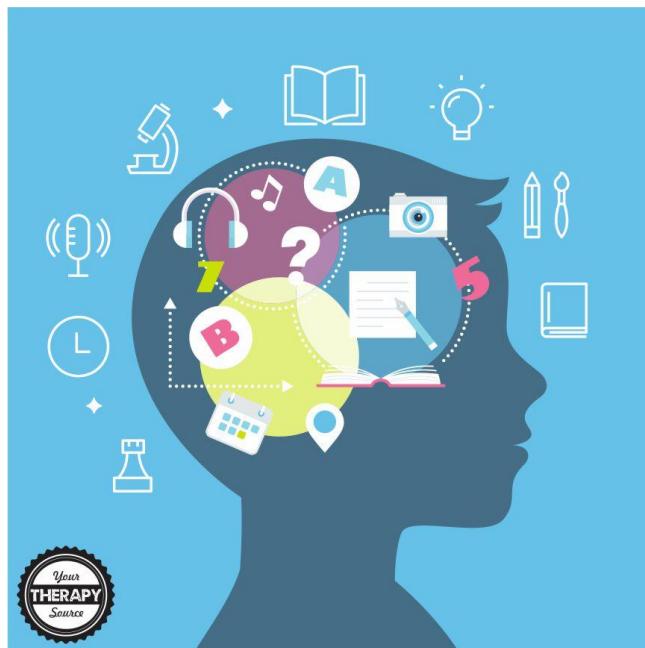
# Cognitive Neuroimaging

- Executive function and working memory
- Memory
- etc.



# COGNITIVE NEUROIMAGING: Executive Function and Working Memory

- Studies examined the **neural substrates** of nonemotional cognitive deficits in psychiatric disorders
  - typically focused on **executive tasks** that depend on **functional integrity** of the **prefrontal cortices**.



# executive function and working memory

- Fitzgerald et al. (2008)

♦ Human Brain Mapping 29:490–501 (2008) ♦

## An fMRI Study of Prefrontal Brain Activation During Multiple Tasks in Patients With Major Depressive Disorder

**Paul B. Fitzgerald,<sup>1,\*</sup> Anusha Sirthiran,<sup>1</sup> Jessica Benitez,<sup>1</sup>  
Zafiris Z. Daskalakis,<sup>2</sup> Tom J. Oxley,<sup>1</sup> Jayashri Kulkarni,<sup>1</sup> and Gary F. Egan<sup>3</sup>**

<sup>1</sup>*Department of Psychological Medicine, Alfred Psychiatry Research Centre, The Alfred and Monash University, Melbourne, Victoria, Australia*

<sup>2</sup>*Centre for Addiction and Mental Health, Clarke Division, Toronto, Ontario, Canada*

<sup>3</sup>*Howard Florey Institute, The University of Melbourne, Victoria, Australia*

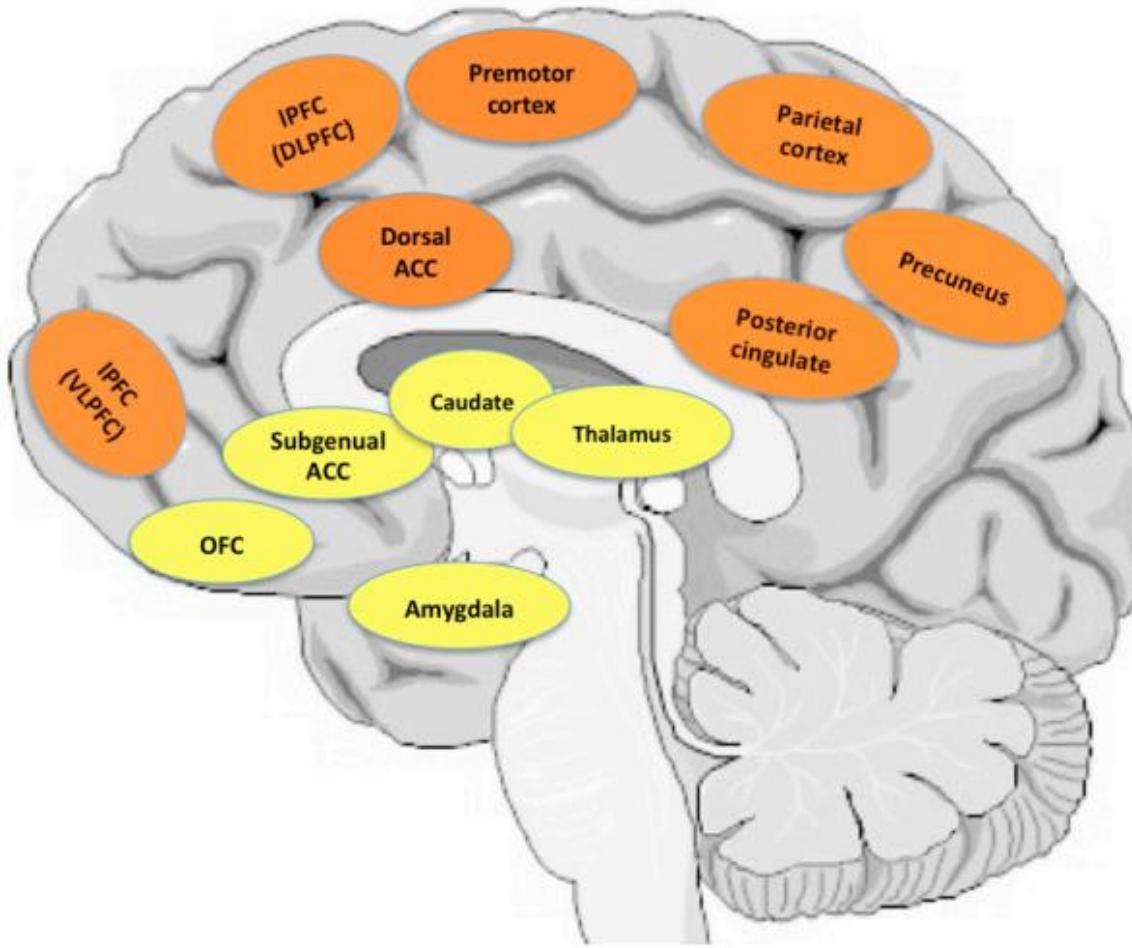
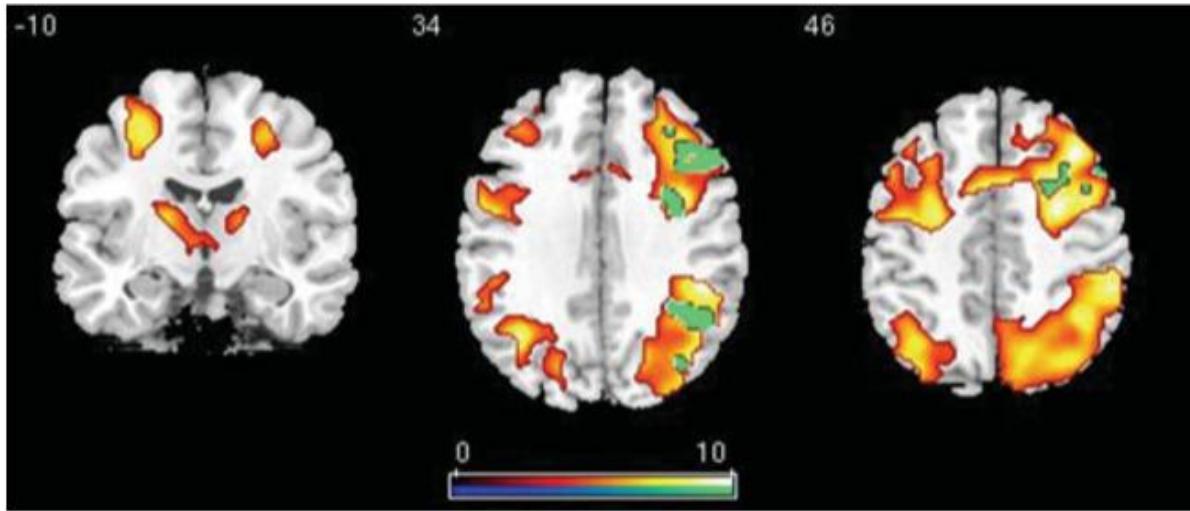


Figure 5.1. Regions of the dorsal and ventral circuit implicated in depression. The regions of the dorsal circuit are represented in orange while the ventral circuit regions are depicted in yellow.

## executive function and working memory

- Fitzgerald et al. (2008)
  - performing a **similar fMRI planning task**
  - **increased activity** for depressed participants in regions including right **VLPFC, DLPFC** and **angular gyrus/cuneus**.
  - performance accuracy was **normal**
    - **increased** cortical activity using an **n-back working memory task** where patients' performance was intact.
    - patients **recruiting additional neuronal resources** to achieve normal performance accuracy.



**Figure I.**

Regions significantly activated in patients compared with controls in the TOL task (blue-green) and *n*-back task (red-yellow) as shown in neurological format (axial slices are  $z = 34$  and  $46$ , coronal slice is  $y = -10$  mm).

### fMRI Activation

### *n*-Back

**Tower of London test**

Target Stacks:

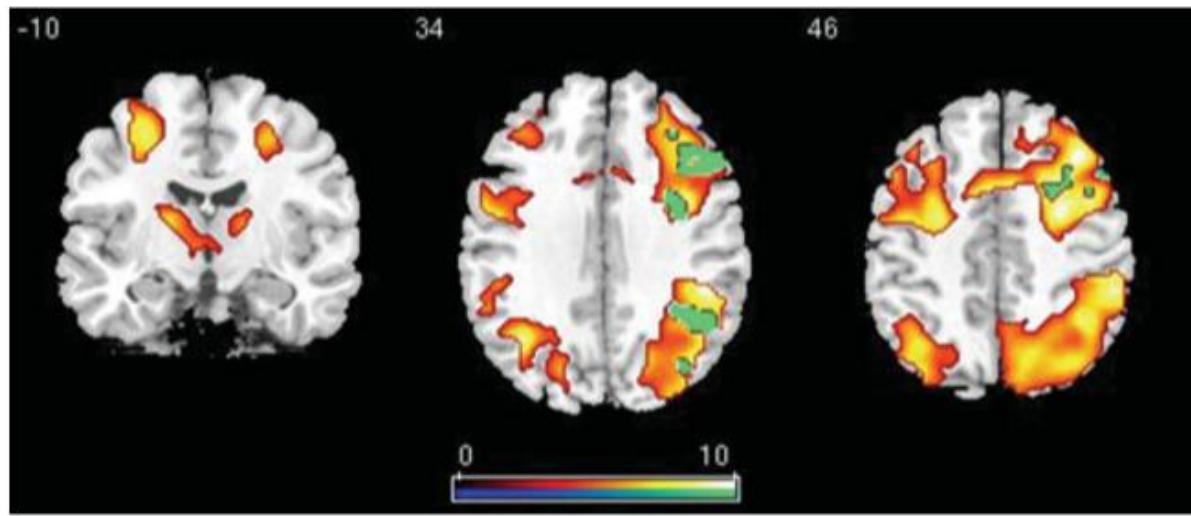
Click on pile to pick up and drop disk

Screenshot of the PEBL psychology software running the Tower of London test

**Purpose** assess executive function

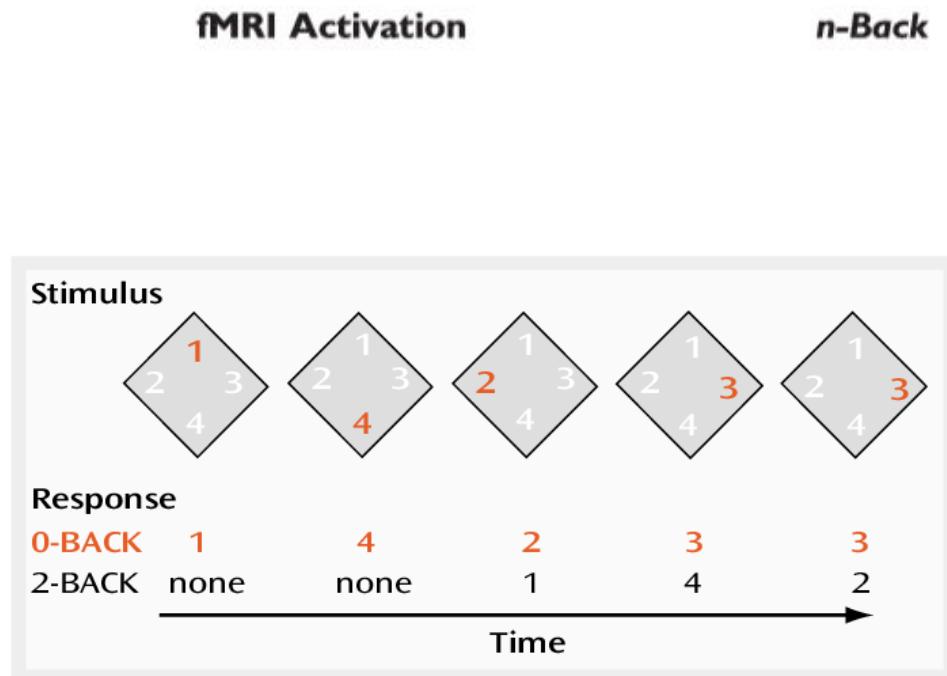
**TABLE II. Regions of greater activation in patients compared to controls in TOL task**

Regions	Co-ordinates (mm)	Cluster size ( $\text{mm}^3$ )	Z-score	$P_{\text{FDR}}$
Right Frontal		1,747		
Inferior frontal gyrus	30 30 2		4.84	<0.016
Middle frontal gyrus	48 20 36		4.67	<0.032
	32 48 18		4.61	<0.040
	44 20 34		4.59	<0.045
Right angular gyrus/cuneus	42 -52 36	503	4.96	<0.009



**Figure 1.**

Regions significantly activated in patients compared with controls in the TOL task (blue-green) and *n*-back task (red-yellow) as shown in neurological format (axial slices are  $z = 34$  and  $46$ , coronal slice is  $y = -10$  mm).



Regions	Coordinates (mm)	Cluster size (mm <sup>3</sup> )	its Z-score
Right frontal			
Middle frontal gyrus	28 18 54	7,767	>10
Inferior frontal gyrus	50 12 16		6.50
Medial frontal gyrus	6 10 4		>10
Anterior cingulate gyrus	6 12 42		7.75
Precentral gyrus	34 -8 54		7.56
Left frontal		3,440	
Medial frontal gyrus	-4 2 60		>10
Anterior cingulate gyrus	-2 8 46		>10
Precentral gyrus	-28 -54 48		>10
Middle frontal gyrus	-28 20 52		7.73
Inferior frontal gyrus	-52 24 16		7.59
Right parieto-temporal			
Inferior parietal lobule	50 -38 34	7,165	>10
Superior temporal gyrus	52 -52 28		>10
Precuneus	18 -66 42		7.22
Orbital gyrus	36 -80 24		>10
Left parieto-temporal			
Cuneus	-38 -62 36	1,979	>10
Inferior parietal lobule	-52 -46 32		6.35
Superior temporal gyrus	-46 -54 28		5.15
Middle temporal gyrus	-58 50 6	461	7.72
Right Thalamus	18 -10 10	971	5.75
Left Thalamus	-18 -14 12		7.29

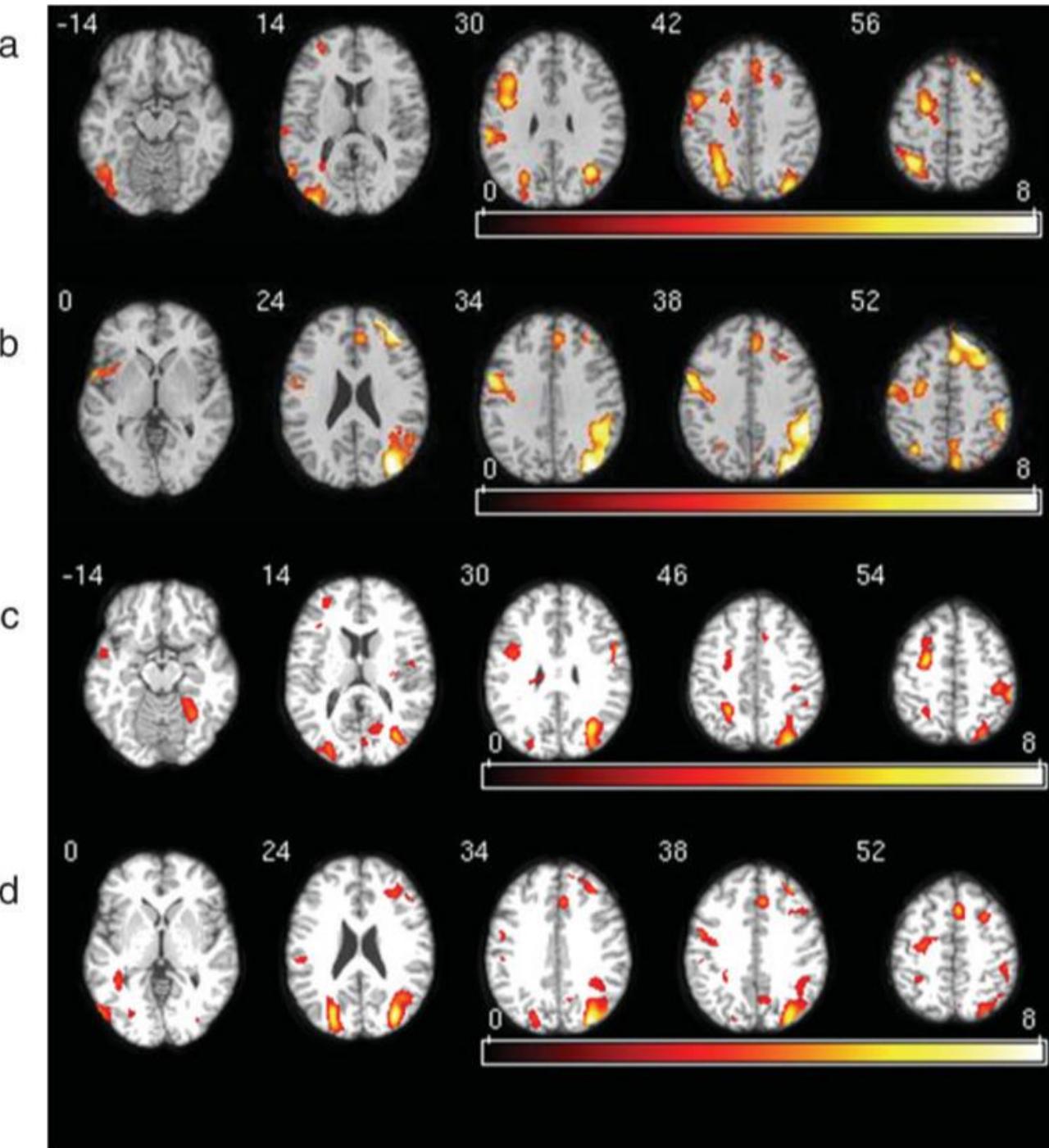
All Z scores are significant at  $P_{corr} < 0.001$ .

**TABLE V. Significant regions, at cluster level threshold  $P_{\text{corr}} < 0.001$  observed in patients compared to controls for the pool data (mean TOL and n-back)**

Regions	Co-ordinate mm	Cluster size ( $\text{mm}^3$ )	Cluster level threshold <sup>a</sup>
Right superior temporal gyrus	42 8 -16 50 -58 20	1,891 579	<0.001 <0.001
Right middle frontal gyrus	44 24 48	1,049	<0.001
Left Sylvian fissure	-42 -32 22	679	<0.001

<sup>a</sup> Corrected for multiple comparisons.

- Hemispheric predominance during
  - n-back task for (a) controls and (b) patients
  - TOL task for (c) controls and (d) patients
- The images are displayed in the neurological format and the z coordinate in millimeter



# Executive function and working memory

- Similarly
- Harvey et al. (2005)



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**NeuroImage**

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[www.elsevier.com/locate/ynimng](http://www.elsevier.com/locate/ynimng)  
NeuroImage 26 (2005) 860–869

## Cognitive control and brain resources in major depression: An fMRI study using the *n*-back task

Philippe-Olivier Harvey,<sup>a,b</sup> Philippe Fossati,<sup>b,c,\*</sup> Jean-Baptiste Pochon,<sup>a</sup> Richard Levy,<sup>a</sup> Guillaume LeBastard,<sup>b</sup> Stéphane Lehéricy,<sup>a</sup> Jean-François Allilaire,<sup>b,c</sup> and Bruno Dubois<sup>a</sup>

<sup>a</sup>Inserm U610, Pitié-Salpêtrière Hospital, Paris, France

<sup>b</sup>Service de Psychiatrie d'Adultes, Pitié-Salpêtrière Hospital, Paris, France

<sup>c</sup>CNRS UMR 7593, Pitié-Salpêtrière Hospital, 47-83, Bd de l'Hôpital 75651, Paris, France

Received 2 December 2004; revised 16 February 2005; accepted 21 February 2005

Available online 8 April 2005

# Executive function and working memory

- Similarly
- Harvey et al. (2005)
  - **increased lateral prefrontal and ACC responses** in depressed participants performing an **n-back task**
  - No performance deficits
  - Increased activity caused by '**cortical inefficiency**'.
    - a neural manifestation of the greater effort required to maintain normal performance.

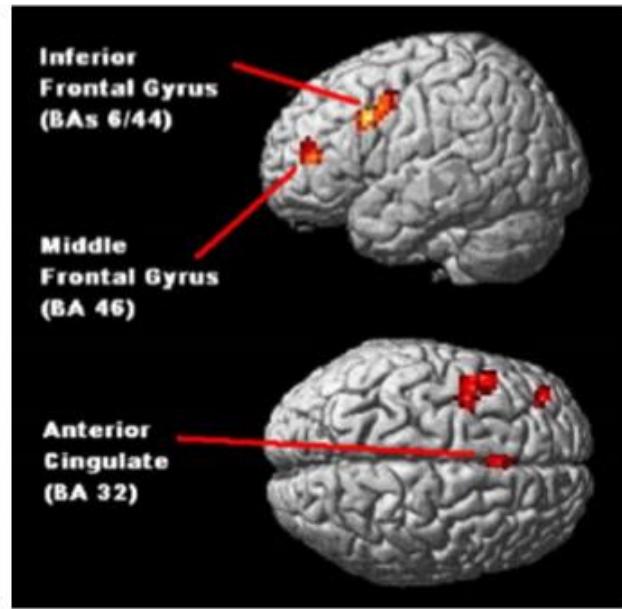
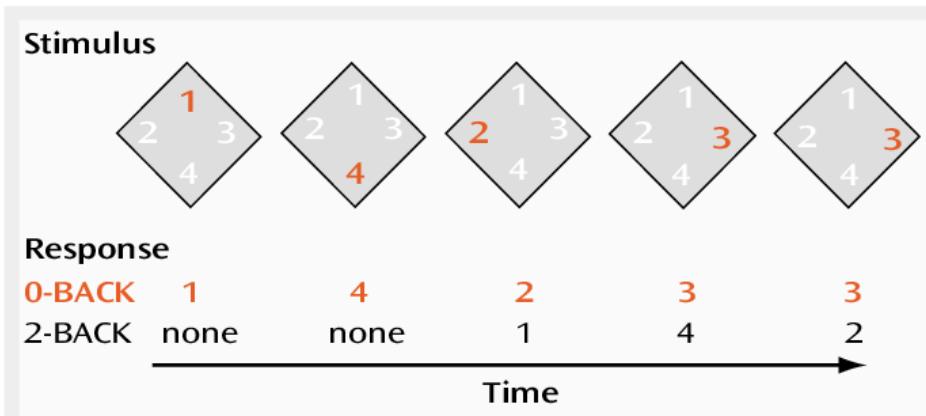


Fig. 2. Statistical parametric maps of brain regions (two-sample  $t$  test;  $n$ -back vs. 0-back) showing significantly more activation in depressed patients compared to healthy subjects during the  $n$ -back task. The coordinates and  $t$  values for maximal activation in these clusters were  $x = -45, y = 12, z = 33$  ( $t = 4.89$ ) for the left inferior frontal gyrus,  $x = -36, y = 42, z = 12$  ( $t = 4.84$ ) for the left middle frontal gyrus and  $x = -3, y = 24, z = 39$  ( $t = 4.12$ ) for the ACC. Statistical threshold of  $P < 0.001$  (uncorrected) on the single-voxel level and  $P < 0.05$  (corrected) on the cluster level.



P.-O. Harvey et al. / NeuroImage 26 (2005) 860–869

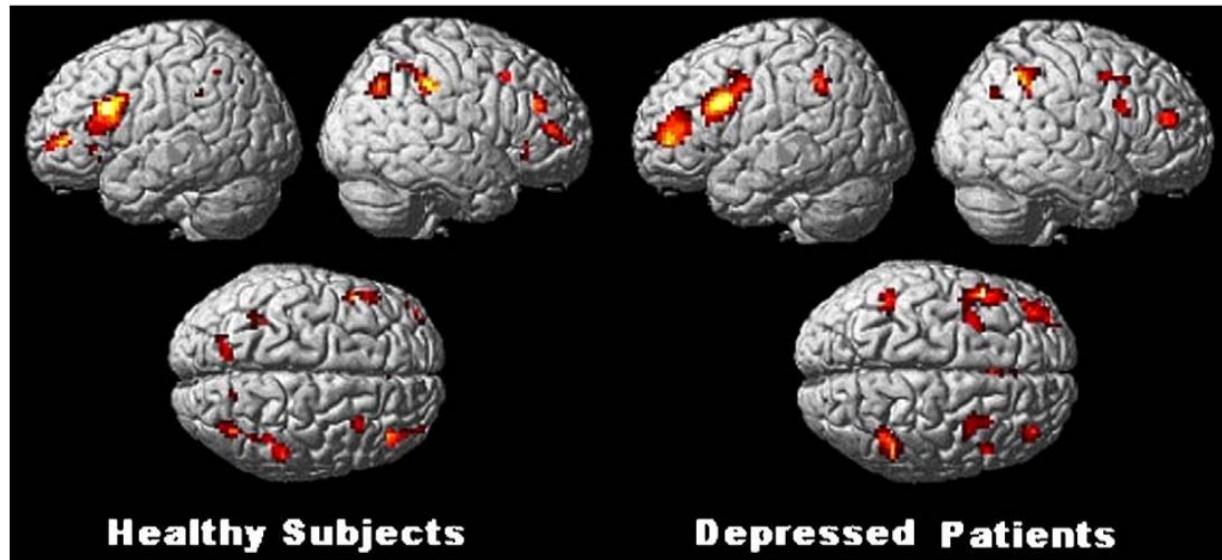


Fig. 1. Brain activations during the  $n$ -back working memory task (1-2-3-back vs. 0-back) in healthy subjects (left) and depressed patients (right). Statistical parametric maps of brain regions (one-sample  $t$  test for each group of 10 subjects) showing significant activation at a statistical threshold of  $P < 0.001$  (uncorrected) on the single-voxel level and  $P < 0.05$  (corrected) on the cluster level. For coordinates related to the peak voxel of each cluster, see Table 2.

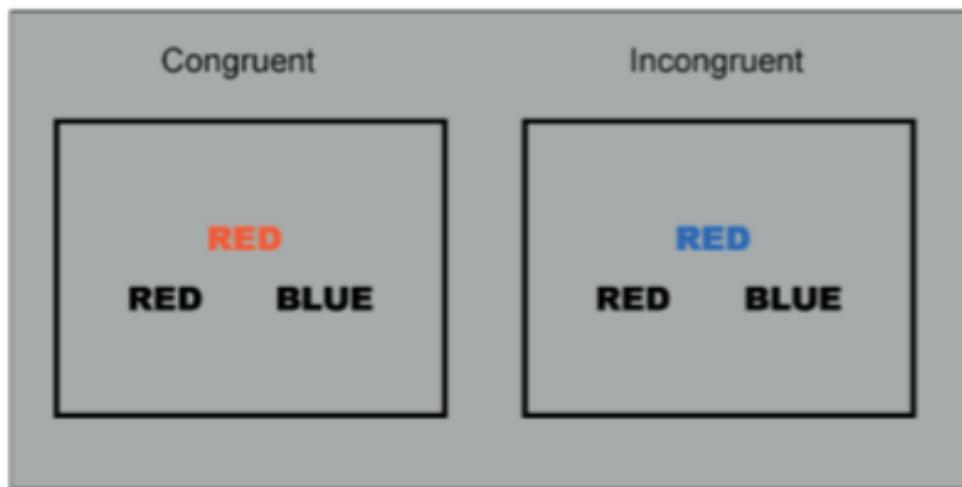
## executive function and working memory

- Wagner et al. (2006)
  - reported enhanced cortical (VLPFC and rostral ACC) activation in depressed patients performing a Stroop cognitive control task at normal levels.

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### **Cortical Inefficiency in Patients with Unipolar Depression: An Event-Related fMRI Study with the Stroop Task**

Gerd Wagner, Esther Sinsel, Thomas Sobanski, Sabine Köhler, Varvara Marinou, Hans-Joachim Mentzel, Heinrich Sauer, and Ralf G.M. Schlösser



In psychology, the Stroop effect is the delay in reaction time between congruent and incongruent stimuli.

Figure 1. Display screen of the Stroop task as used in the present study.

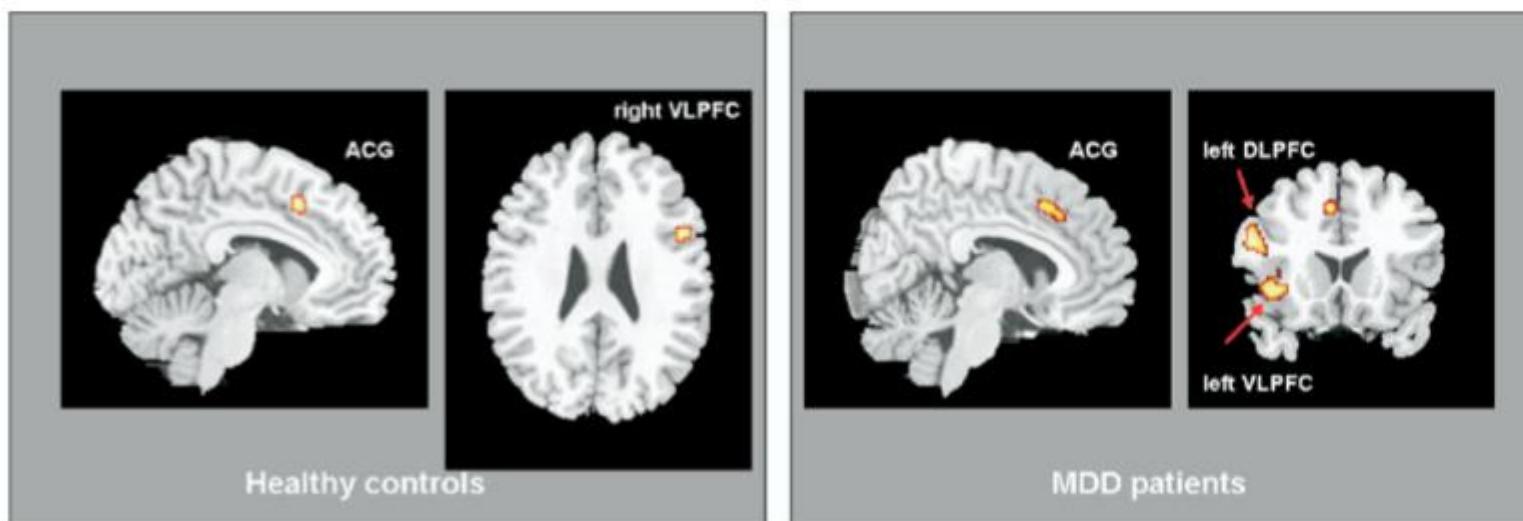


Figure 3. Incongruent > congruent condition ( $p < .001$ , cluster size  $> 19$ ). Control subjects activated stronger in dorsal ACG and right VLPFC. Patients showed an increased BOLD signal in dorsal ACG, left VLPFC, and DLPFC. ACG, anterior cingulate gyrus; VLPFC, ventrolateral prefrontal cortex; BOLD, blood oxygenation level-dependent; DLPFC, dorsolateral prefrontal cortex.

## Executive function and working memory

- Langenecker et al. (2007)
  - successful response inhibition in depressed subjects was associated with enhanced cortical activation.

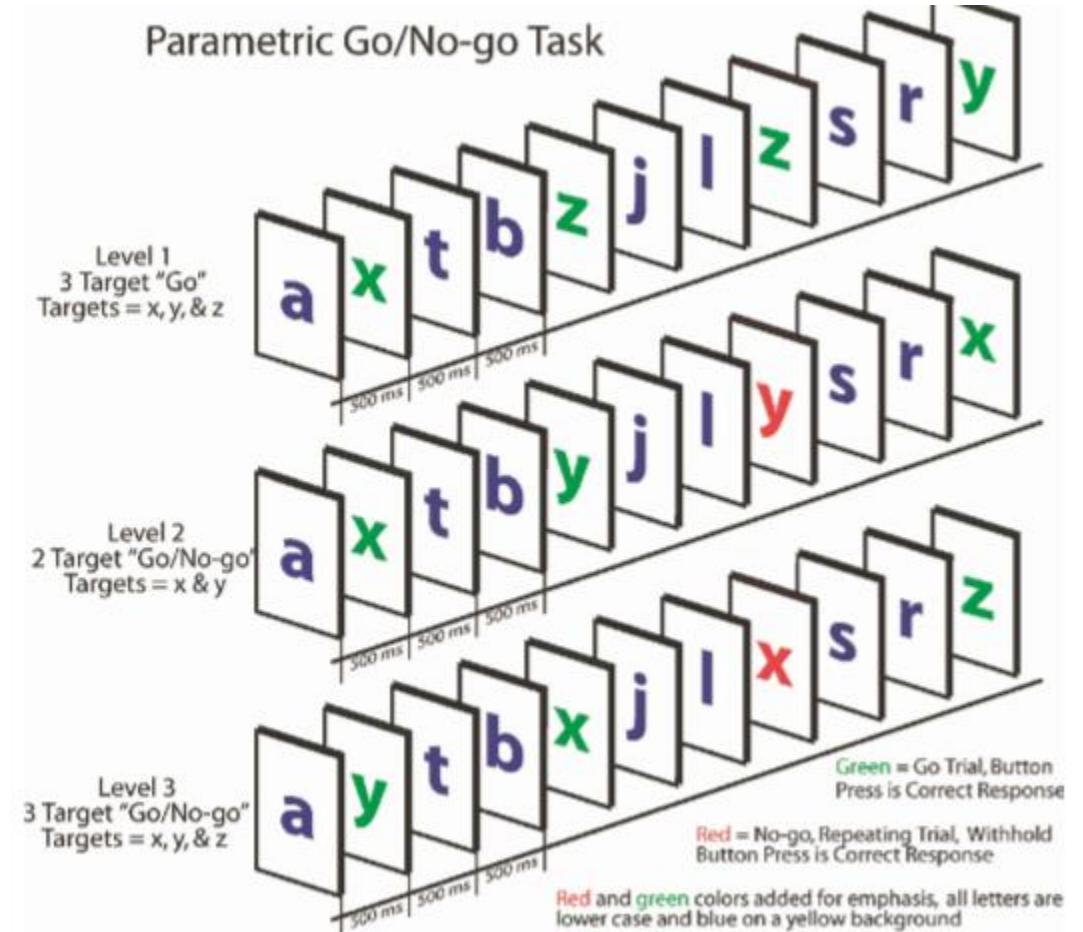
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### **Frontal and Limbic Activation During Inhibitory Control Predicts Treatment Response in Major Depressive Disorder**

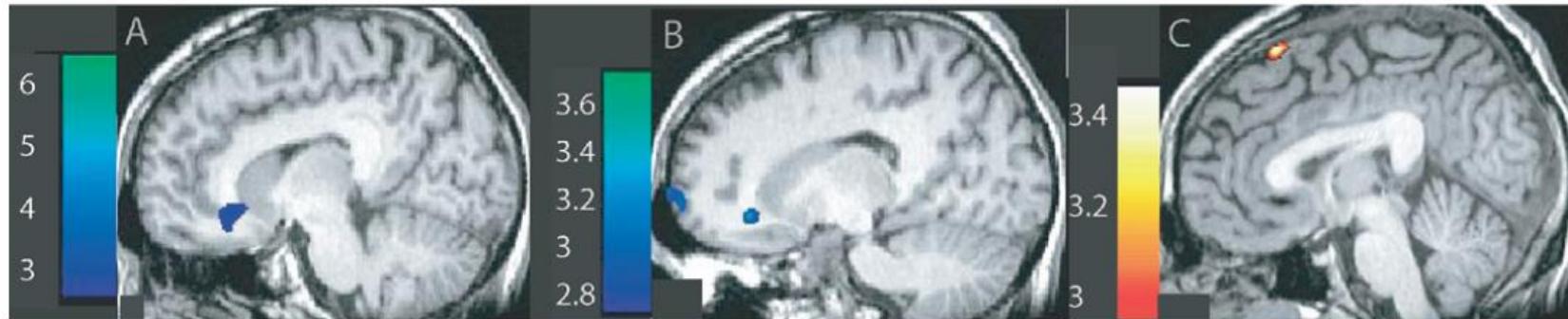
Scott A. Langenecker, Susan E. Kennedy, Leslie M. Guidotti, Emily M. Briceno, Lawrence S. Own, Thomas Hooven, Elizabeth A. Young, Huda Akil, Douglas C. Noll, and Jon-Kar Zubieta

# Parametric Go/No-go (PGNG)

- 3 levels of difficulty, the latter two of which include set shifting and inhibitory control.
- Measurement of behavioral inhibition (correct lure rejections)
- Measures attention (hits) and set-shifting, processing speed, and correct (rejections) and incorrect (commissions) responses to lure trials as a part of inhibitory control



- A significant interaction among response time (control subjects better), hits (control subjects better), and **rejections (patients better)**.
- MDD:
- **Greater activation** in frontal and anterior temporal areas during correct rejections (inhibition).
  - during successful inhibitory events
    - in bilateral inferior frontal and left amygdala, insula, and nucleus accumbens
  - during unsuccessful inhibition (commission errors)
    - in rostral anterior cingulate
    - predicted post-treatment improvement in depression symptoms.
- **Greater activation in MDD**
  - necessary to achieve **behavioral performance** equivalent to control subjects
  - predictive of better treatment response in MDD



**Figure 4.** Figure demonstrating statistically greater activation in the major depressive disorder (MDD) group compared with the control group for correct (rejections, panel **A**, blue, Left 10 mm) and incorrect (commissions, panel **B**, blue, Left 17 mm) inhibitory trials. The figure also illustrates statistically greater activation in the control group compared with the MDD group for incorrect (commissions, panel **C**, red, right 2 mm) inhibitory trials. The viewing threshold on these images was relaxed to  $T > 2.8, p < .003$ , cluster  $> 10 \text{ mm}^3$  for ease in viewing.

# COGNITIVE NEUROIMAGING: Executive function and working memory

- Walter et al. (2007)



Journal of Affective Disorders 101 (2007) 175–185



Research report

Increased left prefrontal activation in patients with unipolar depression: An event-related, parametric, performance-controlled fMRI study

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Available online 2 January 2007

# Executive function and working memory

- Walter et al. (2007)
  - assessed patients' neural response to correct trials only in a working memory task
  - increased DLPFC activation was not seen with incorrect trials
    - suggesting that matched performance is associated with increased cortical response

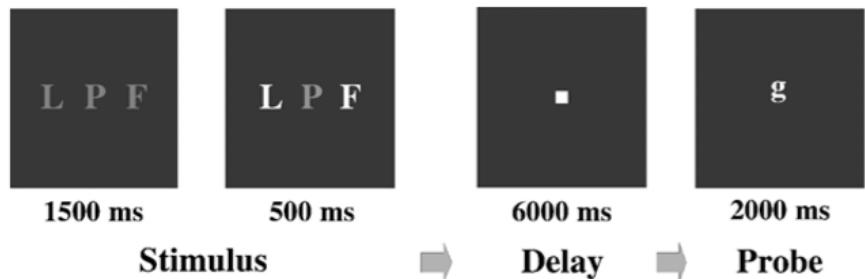


Fig. 1. Activation paradigm, exemplarily shown for a trial of Load 2. In the stimulus period, three capital grey letters appeared on a black screen from which either one, two or three letters turned bright at the end of the stimulus period. For the following delay period, subjects were instructed to focus only on the letters having turned bright and to memorize only the letter(s) which directly followed in the alphabet ('manipulated set'). In the probe period a lower-case letter was presented, and subjects had to indicate whether it was or was not part of the manipulated set. The control condition consisted of three grey X's calling for a stereotype button press during the presentation of a small x in the target period, thus forming a motor task without mnemonic requirements relative to the load conditions.

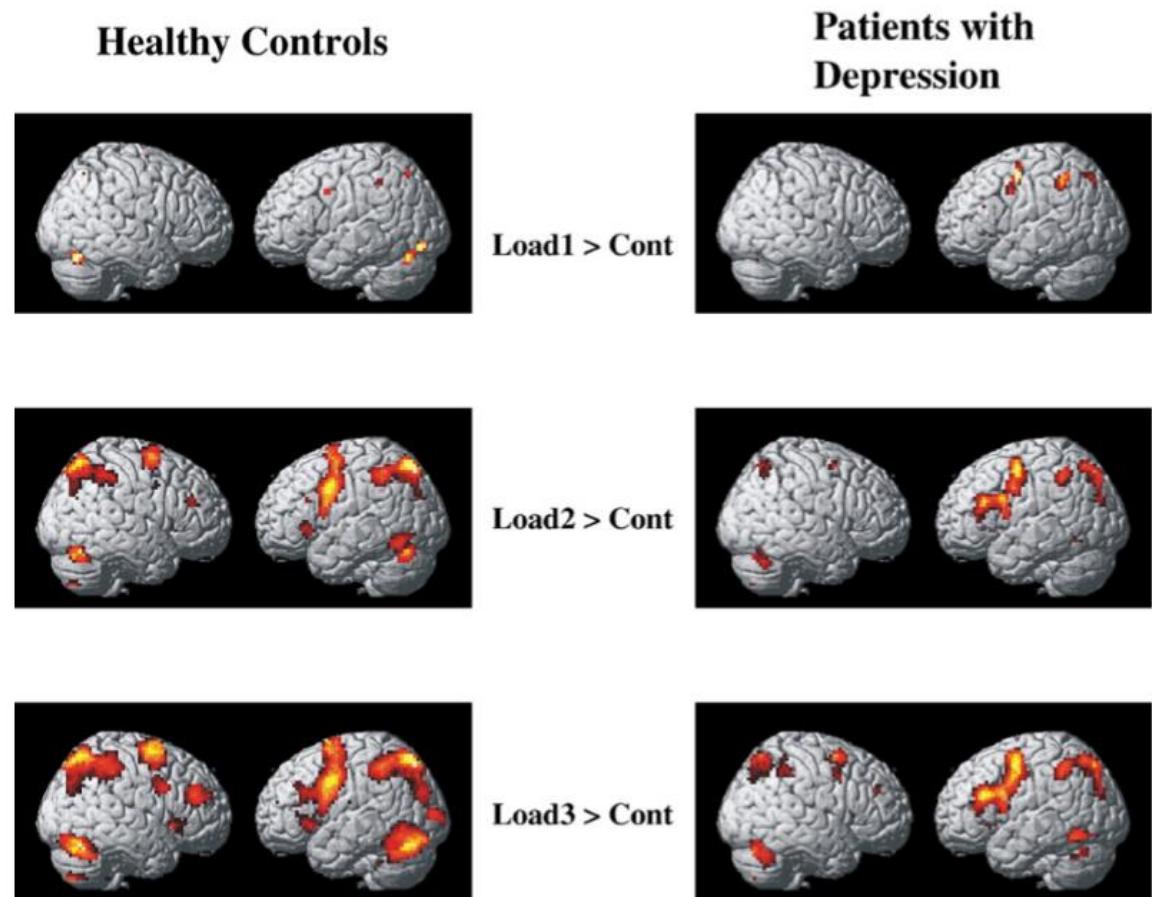


Fig. 2. Main effects of load versus control condition within groups, analysis of correct trials only. 2nd level ANOVA,  $p < 0.05$  FWE corrected.

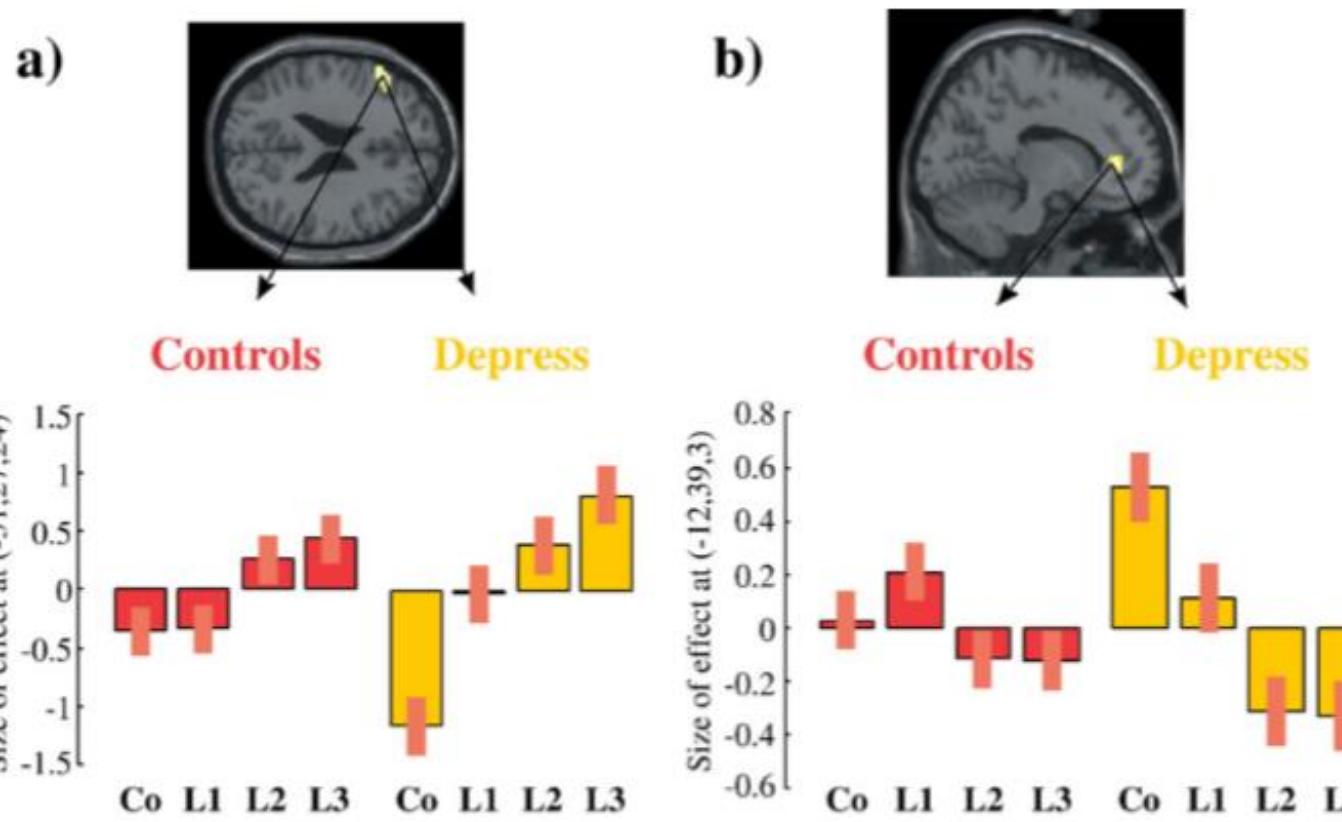


Fig. 3. Mean activation effects (estimated beta parameters, 95% confidence interval) of the contrast 'all loads against control condition' in the dorsolateral prefrontal (BA 46) and medial prefrontal cortex (BA 24), analysis of correct trials only. Red: Healthy control subjects; Ochre: Patients with depression. The activation effects were extracted from the 2nd level between-group ANOVA (most significant voxel of group differences,  $p < 0.001$  at the voxel,  $p < 0.05$  at the cluster level).

## Executive function and working memory

- Several other studies: Matsuo et al., 2007; Walsh et al., 2007
  - **prefrontal hyperactivity** associated with **intact performance on working memory**
- By contrast
- Patients with **impaired performance**, as in the Elliott et al. (1997a) study, **reduced neuronal response** is typically observed in cortical regions.
- Okada et al. (2003)
  - found **reduced activity in left VLPFC** in depressed patients during a **verbal fluency task** on which they also **performed poorly**.

# COGNITIVE executive function and working memory

- Hugdahl et al. (2004)

## Article

### Brain Activation Measured With fMRI During a Mental Arithmetic Task in Schizophrenia and Major Depression

**Kenneth Hugdahl, Ph.D.**

**Bjørn Rishovd Rund, Ph.D.**

**Anders Lund, Ph.D., M.D.**

**Arve Asbjørnsen, Ph.D.**

**Jens Egeland, Ph.D.**

**Lars Ersland, Ph.D.**

**Nils Inge Landrø, Ph.D.**

**Atle Roness, Ph.D., M.D.**

**Kirsten I. Stordal, Ph.D.**

**Kjetil Sundet, Ph.D.**

**Tormod Thomsen, Ph.D.**

**Objective:** The authors used functional magnetic resonance imaging (fMRI) to investigate brain activation in patients with schizophrenia and major depression while they performed two tasks—a vigilance task and a mental arithmetic task—that differed in cognitive complexity.

**Method:** In the vigilance task, the participants had to press a response button whenever a specific number was seen on a screen inside the MR scanner. In the mental arithmetic task, the participants had to add two consecutive numbers and press the response button whenever the sum was 10. fMRI was performed with a 1.5-T MR scanner. Twelve patients with recurrent nonpsychotic unipolar major depression, 12 patients with schizophrenia, and 12 healthy comparison subjects were included in the study.

**Results:** Performance data showed that the patients were impaired relative to the

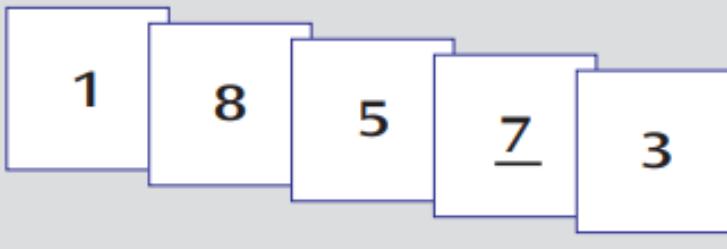
comparison subjects and showed no difference in performance between the patient groups. The patients with schizophrenia, but not those with major depression, had less activation in prefrontal brain regions, relative to the comparison participants. However, subtracting brain activation during the vigilance task from activation during the mental arithmetic task showed that the schizophrenia patients had activation in parietal areas.

**Conclusions:** A double dissociation of parietal and frontal lobe activation was found for the schizophrenia patients and the depression patients. The greater parietal lobe activation in the patients with schizophrenia may reflect a compensatory strategy for the failure to recruit cognitive processes that involve frontal lobe areas when solving a mental arithmetic task.

# COGNITIVE NEUROIMAGING: Executive function and working memory

- Hugdahl et al. (2004)
  - **impaired performance** and **decreased right inferior parietal activity** in depressed participants during an **arithmetic task**
  - impaired performance is associated with reduced cortical function
  - normal performance can be achieved through enhanced cortical function

Run 1: "Press on number 7"



Run 2: "Add each consecutive number to the previous one, and press when the sum is 10"

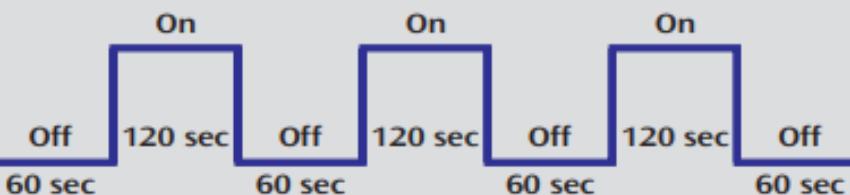
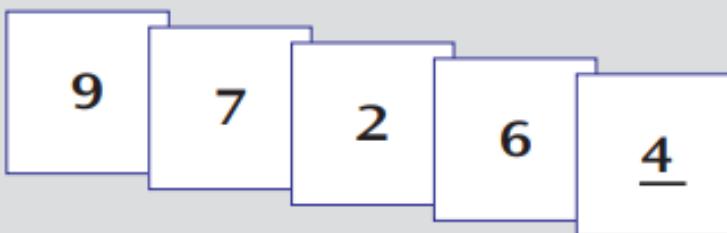
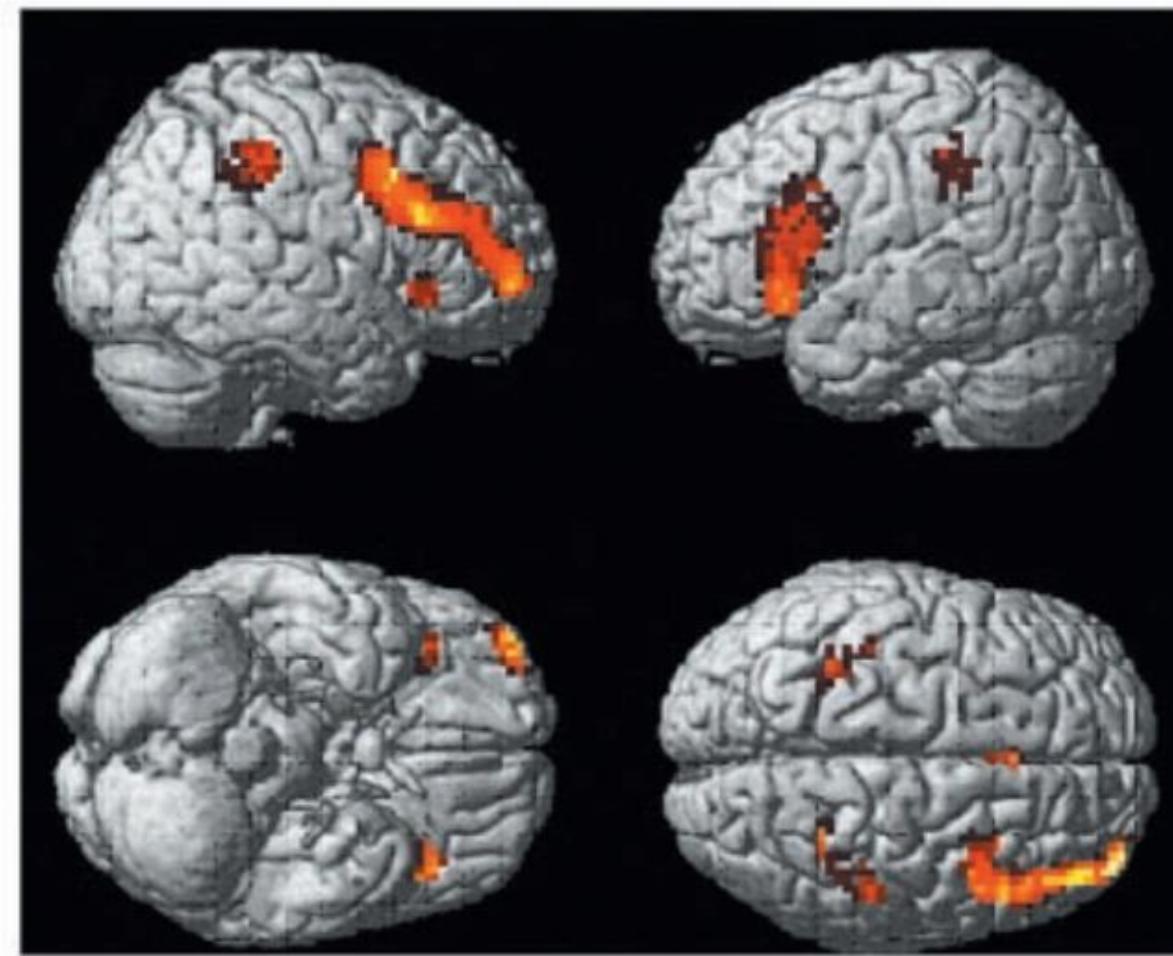
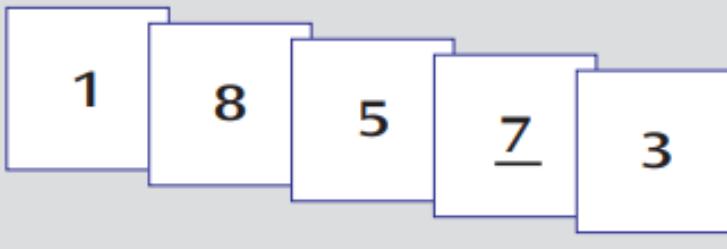


FIGURE 2. Brain Regions With Significant Activation During Performance of Mental Arithmetic, Relative to Performance of a Visual Perception and Vigilance Task, in Healthy Comparison Subjects (N=12)



<sup>a</sup> Run 1 tested participants' visual perception and vigilance. Run 2 tested number manipulation and simple mental arithmetic in addition to visual perception and vigilance. The lower panel shows the time course for the "on" and "off" blocks in the boxcar design for each run. Stimuli were presented during the "on" blocks. During the "off" blocks, the participants were instructed to relax and not to think about the digits seen during the "on" blocks. The first 10 volume images (from the first "off" block) in each run were discarded before data analysis. See Method section for further details.

Run 1: "Press on number 7"



Run 2: "Add each consecutive number to the previous one, and press when the sum is 10"

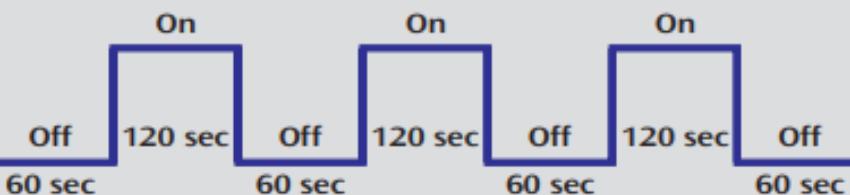
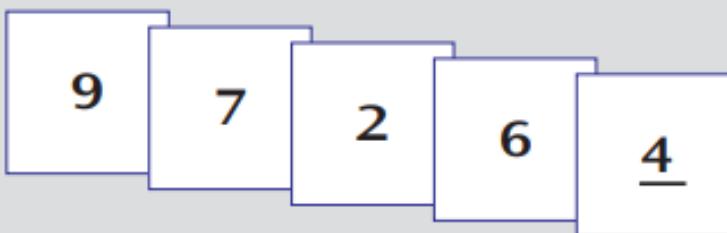
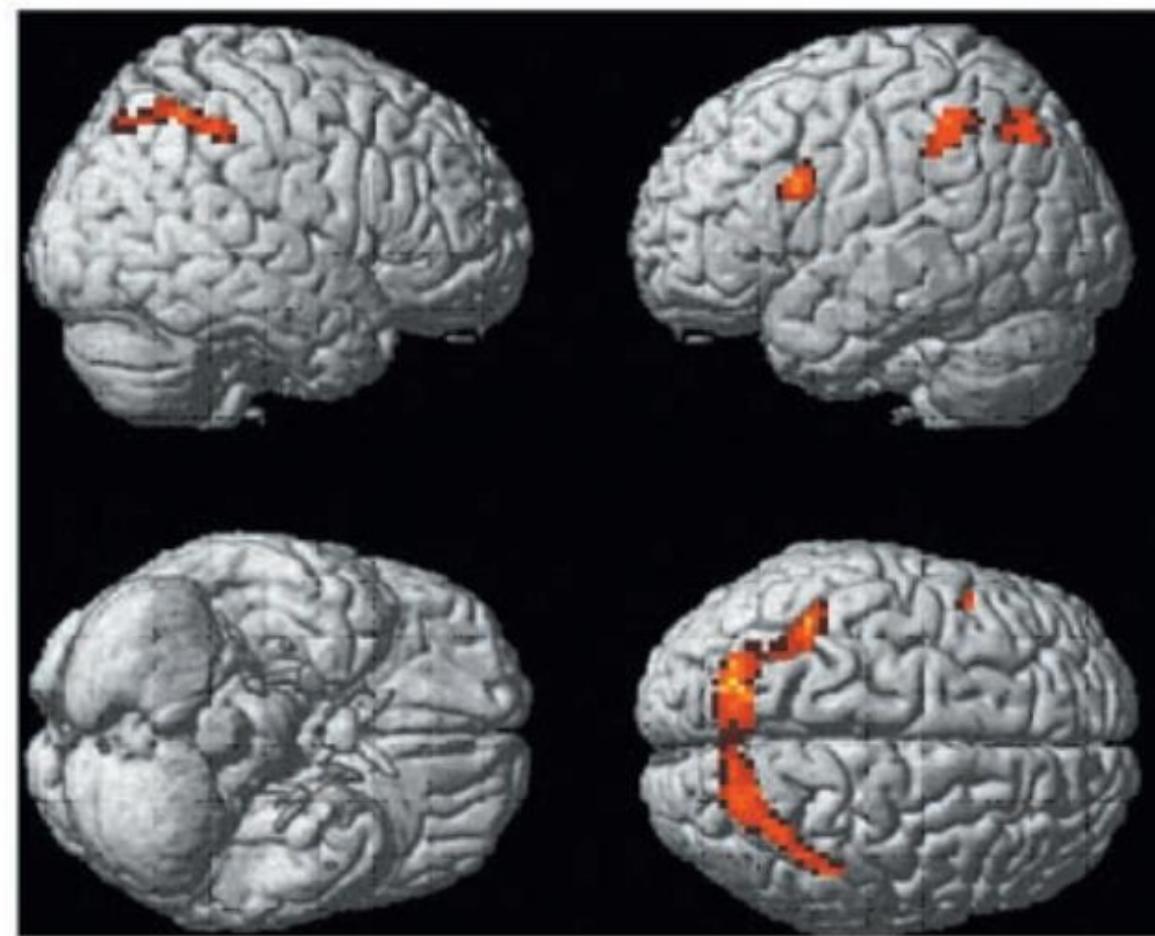


FIGURE 4. Brain Regions With Significant Activation During Performance of Mental Arithmetic, Relative to Performance of a Visual Perception and Vigilance Task, in Patients With Major Depression (N=12)



<sup>a</sup> Run 1 tested participants' visual perception and vigilance. Run 2 tested number manipulation and simple mental arithmetic in addition to visual perception and vigilance. The lower panel shows the time course for the "on" and "off" blocks in the boxcar design for each run. Stimuli were presented during the "on" blocks. During the "off" blocks, the participants were instructed to relax and not to think about the digits seen during the "on" blocks. The first 10 volume images (from the first "off" block) in each run were discarded before data analysis. See Method section for further details.

# Executive function and working memory

- Barch et al. (2003)

## ORIGINAL ARTICLES

### Working Memory and Prefrontal Cortex Dysfunction: Specificity to Schizophrenia Compared with Major Depression

Deanna M. Barch, Yvette I. Sheline, John G. Csernansky, and Abraham Z. Snyder

# Executive function and working memory

- Barch et al. (2003)
  - **attenuated activity** in depressed participants to both word and face versions of an n-back task
    - in bilateral thalamus, right precentral gyrus and right parietal cortex
    - despite **no behavioral deficit** being observed.
  - Why not observed in the prefrontal cortex even with the performance was at ceiling.
    - Hyperfrontality associated with intact performance is only observed for **more challenging versions of tasks**.
  - These **discrepancies** highlight the importance of careful characterization of the **relationship between task difficulty, performance and brain response**.
  - It is also possible that differences in
    - patient demographics, severity of illness and medication status

# Memory

- One of the commonest cognitive symptoms reported by patients.
- A need for a full exploration of neural correlates of memory dysfunction
- Memory dysfunction reported most frequently in elderly patients with depression, and functional imaging studies are needed to relate this structural pathology in the hippocampus and to compare memory problems in late life depression with those observed in other conditions (mild cognitive impairment or early Alzheimer's disease).

# Memory

- **Memory problems** are one of the most common cognitive symptoms reported by psychiatric patients
- few fMRI studies of memory in depression.
- Bremner et al. (2004)

## Article

### Deficits in Hippocampal and Anterior Cingulate Functioning During Verbal Declarative Memory Encoding in Midlife Major Depression

J. Douglas Bremner, M.D.

Meena Vythilingam, M.D.

Eric Vermetten, M.D.

Viola Vaccarino, M.D., Ph.D.

Dennis S. Charney, M.D.

**Objective:** Prior studies showed that subjects with major depression have deficits in hippocampal-based verbal declarative memory (e.g., recall of a paragraph) and in hippocampal and prefrontal cortical functioning and structure. The purpose of the present study was to assess hippocampal and prefrontal functioning during performance of a verbal declarative memory task in subjects with midlife major depression.

**Method:** Subjects with midlife major depression ( $N=18$ ) and healthy subjects ( $N=9$ ) underwent positron emission tomogra-

phy imaging during a control task and verbal encoding of a paragraph.

**Results:** During the verbal memory encoding task the comparison subjects, but not the subjects with depression, activated the right hippocampus and prefrontal cortex (anterior cingulate), as well as the cuneus and cerebellum.

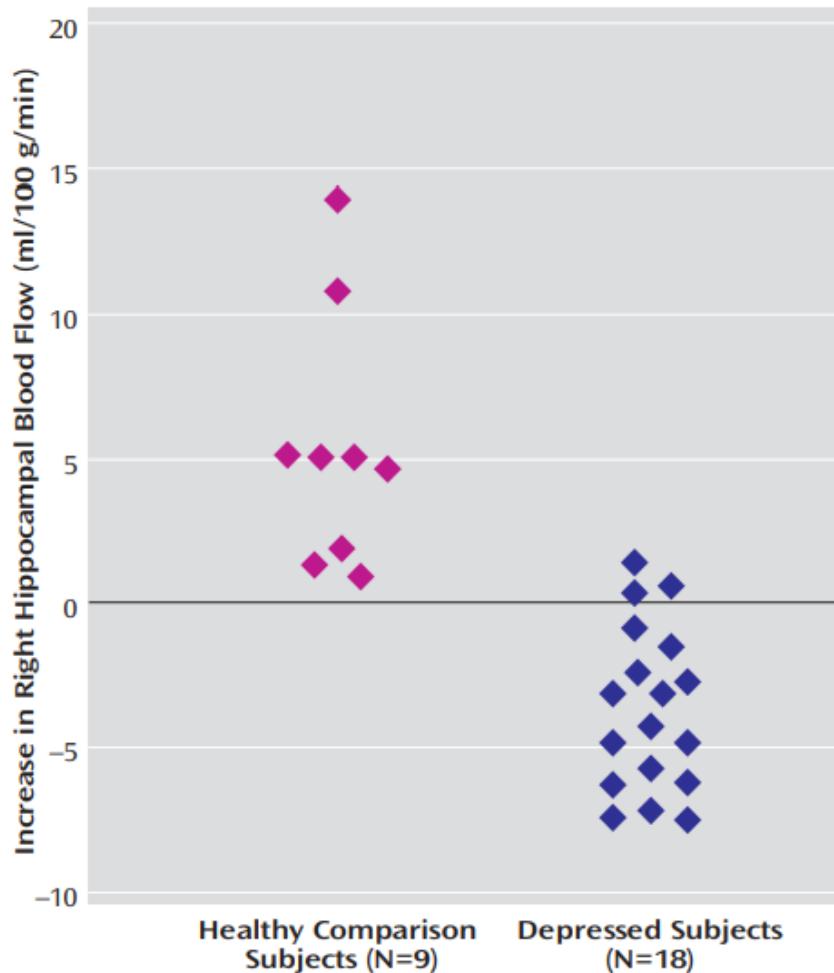
**Conclusions:** These results are consistent with a failure of hippocampal and anterior cingulate activation in depression, and they support the hypothesis of deficits in hippocampal and anterior cingulate functioning in depression.

# COGNITIVE NEUROIMAGING: Memory

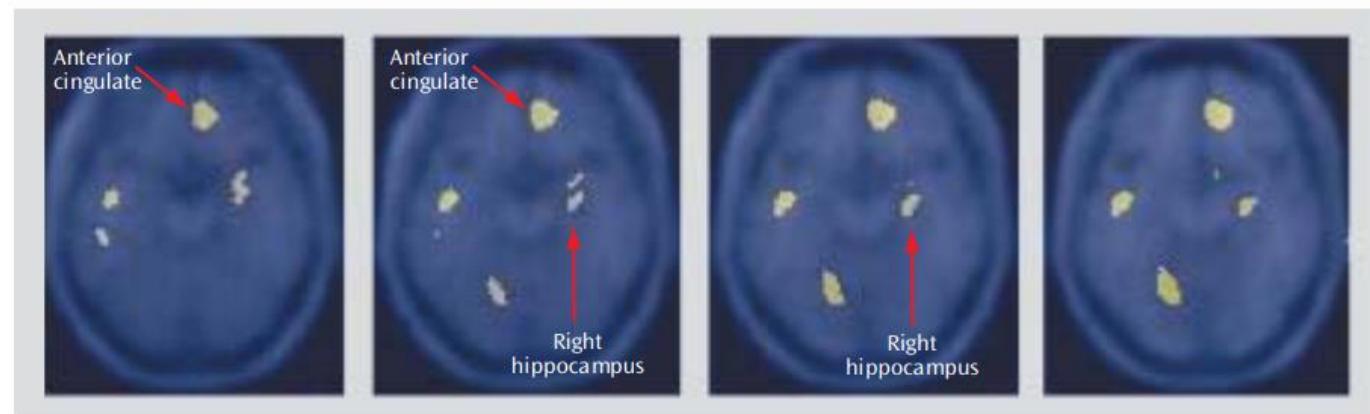
- Bremner et al. (2004) (PET Study)
  - conceptual memory encoding of a neutral paragraph
  - reduced in
    - hippocampal, amygdala and ACC activation
  - increased in
    - right frontal gyri activation
  - Support the hypothesis of failure of hippocampal and anterior cingulate functioning in depression

## PET Findings

**FIGURE 2. Increased Right Hippocampal Blood Flow During a Verbal Memory Encoding Task in Healthy Subjects (N=9) and Subjects With Depression (N=18)<sup>a</sup>**

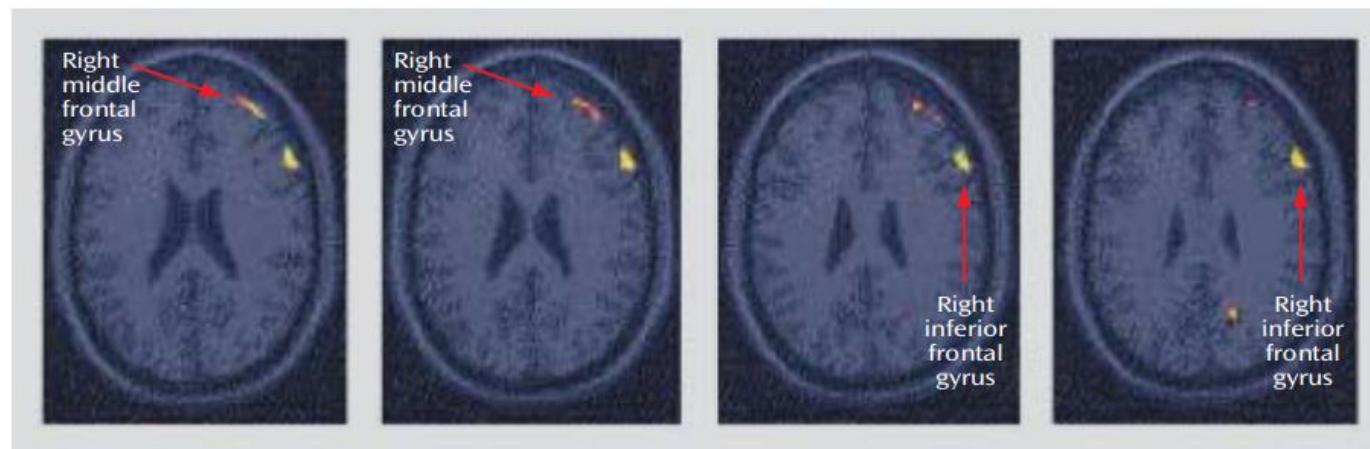


**FIGURE 1. Statistical Parametric Map Overlaid on an MRI Template Showing Brain Areas of Greater Increases in Blood Flow During a Verbal Memory Encoding Task in Healthy Subjects (N=9) Than in Subjects With Depression (N=18)<sup>a</sup>**



<sup>a</sup> Areas of greater increases in blood flow included the hippocampus ( $x=26, y=-14, z=-10$ ) and anterior cingulate ( $x=12, y=26, z=0$ ) ( $p<0.001$ ).

**FIGURE 3. Statistical Parametric Map Overlaid on an MRI Template Showing Brain Areas of Greater Decreases in Blood Flow During a Verbal Memory Encoding Task in Healthy Subjects (N=9) Than in Subjects With Depression (N=18)<sup>a</sup>**



<sup>a</sup> Areas of greater decreases in blood flow included the right middle and inferior frontal gyri ( $p<0.001$ ).

# Memory

- By contrast,
- Werner et al. (2009)

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Research report

Functional MRI study of memory-related brain regions in patients with depressive disorder

Natalie S. Werner <sup>a,b,\*</sup>, Thomas Meindl <sup>c</sup>, Julia Materne <sup>a</sup>, Rolf R. Engel <sup>a</sup>, Dorothea Huber <sup>d,e</sup>, Michael Riedel <sup>a</sup>, Maximilian Reiser <sup>c</sup>, Kristina Hennig-Fast <sup>a,b</sup>

<sup>a</sup> Clinic of Psychiatry and Psychotherapy, Ludwig-Maximilians-University Munich, Germany

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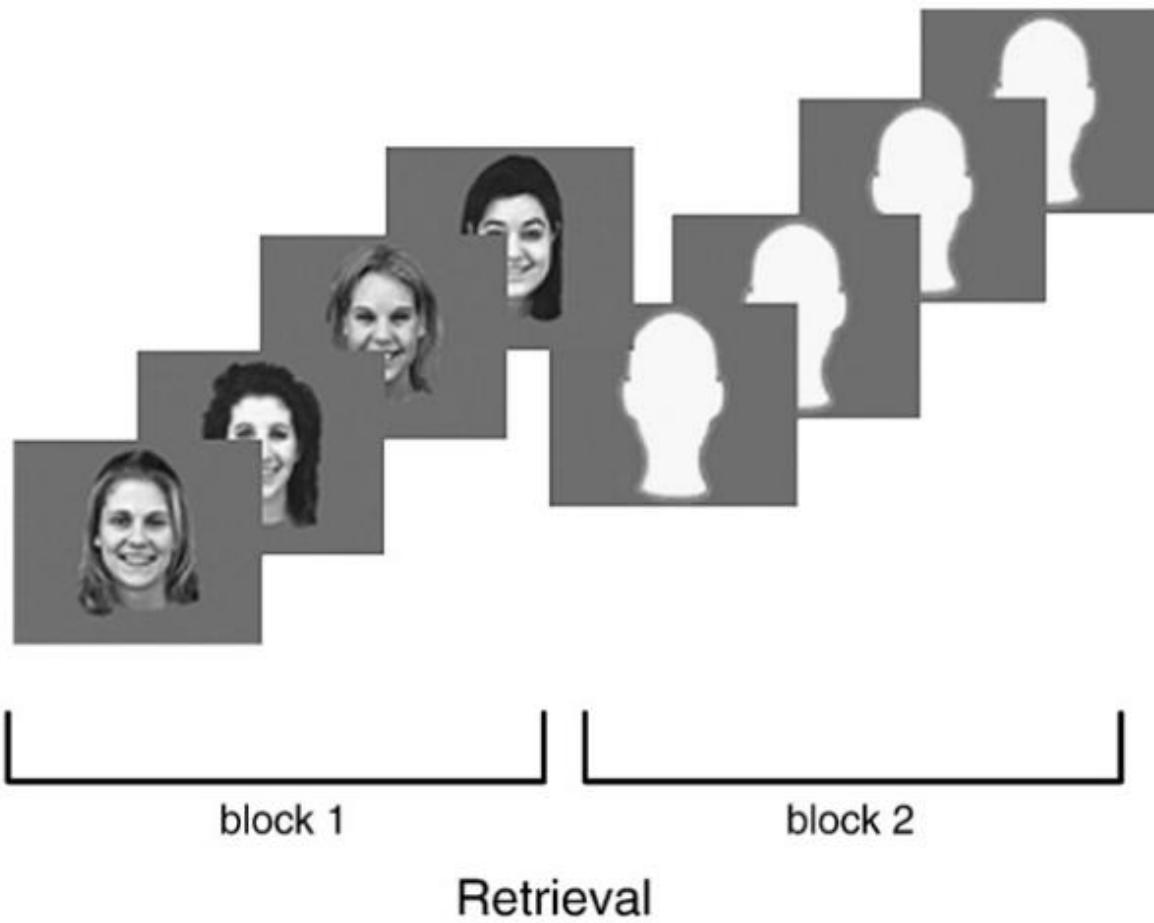
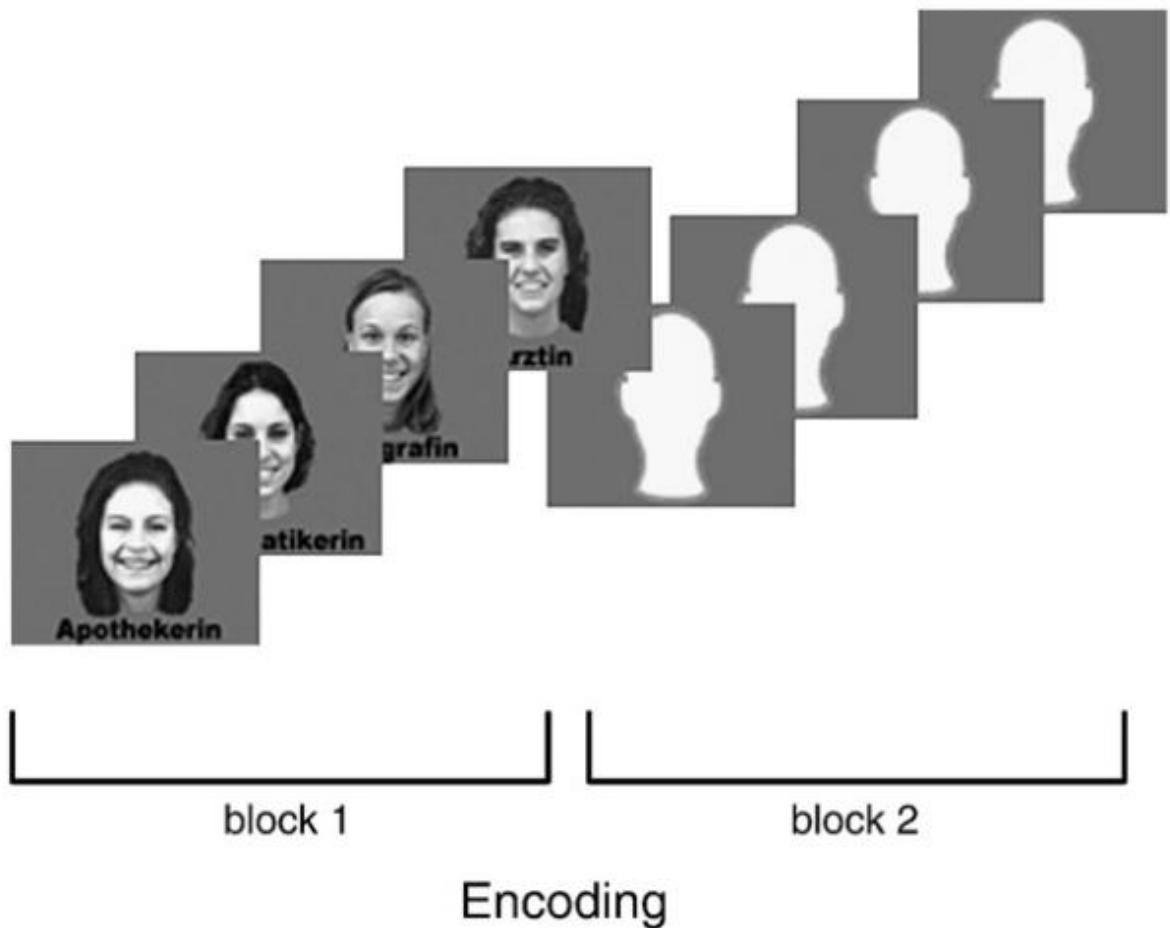
<sup>c</sup> Institute for Clinical Radiology, Ludwig-Maximilians-University Munich, Germany

<sup>d</sup> Clinic of Psychosomatic Medicine and Psychotherapy, Technical University Munich, Germany

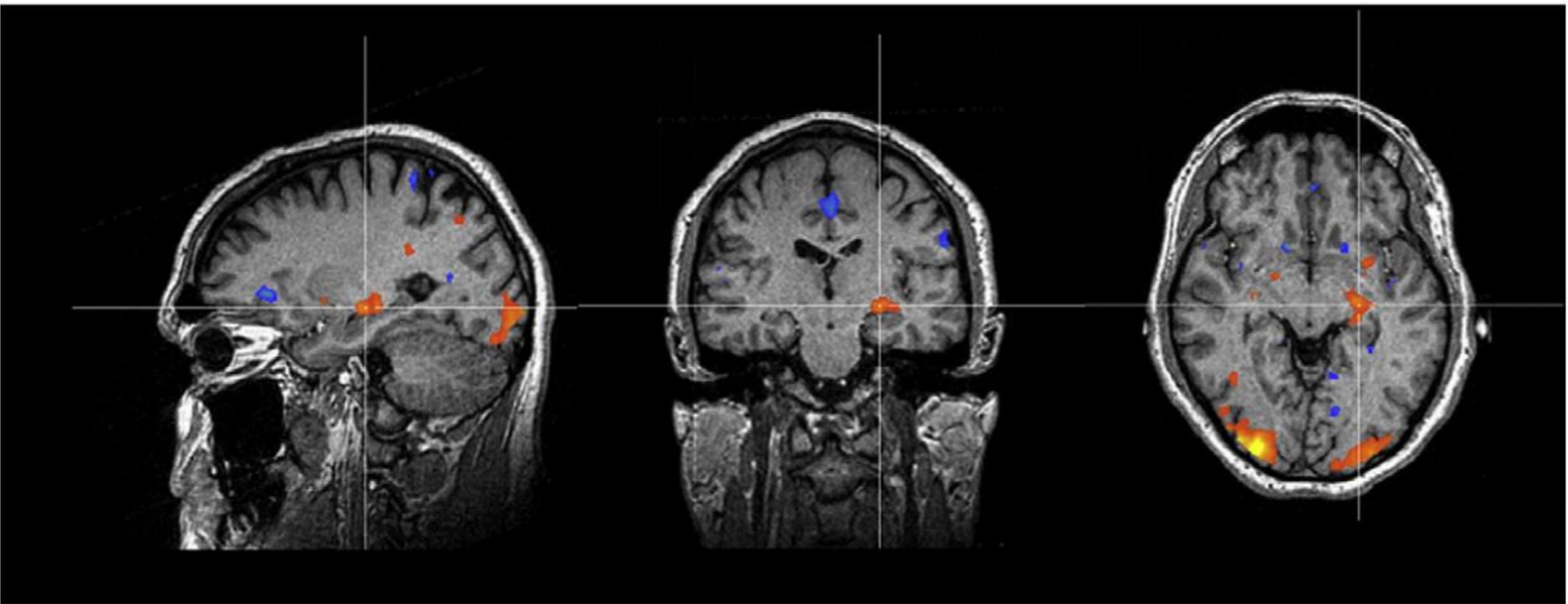
<sup>e</sup> Clinic of Psychosomatic Medicine and Psychotherapy, Municipal Clinics Munich, Germany

# COGNITIVE NEUROIMAGING: Memory

- Werner et al. (2009)
  - **increased parahippocampal activity at encoding**
  - **decreased activity in frontal and parietal regions during both encoding and retrieval.**
  - Performance was **unimpaired**.
  - Discrepancy reflect differences in patient characteristics, in particular their medication status
    - Bremner's patients were unmedicated; Werner's were mostly receiving antidepressants.

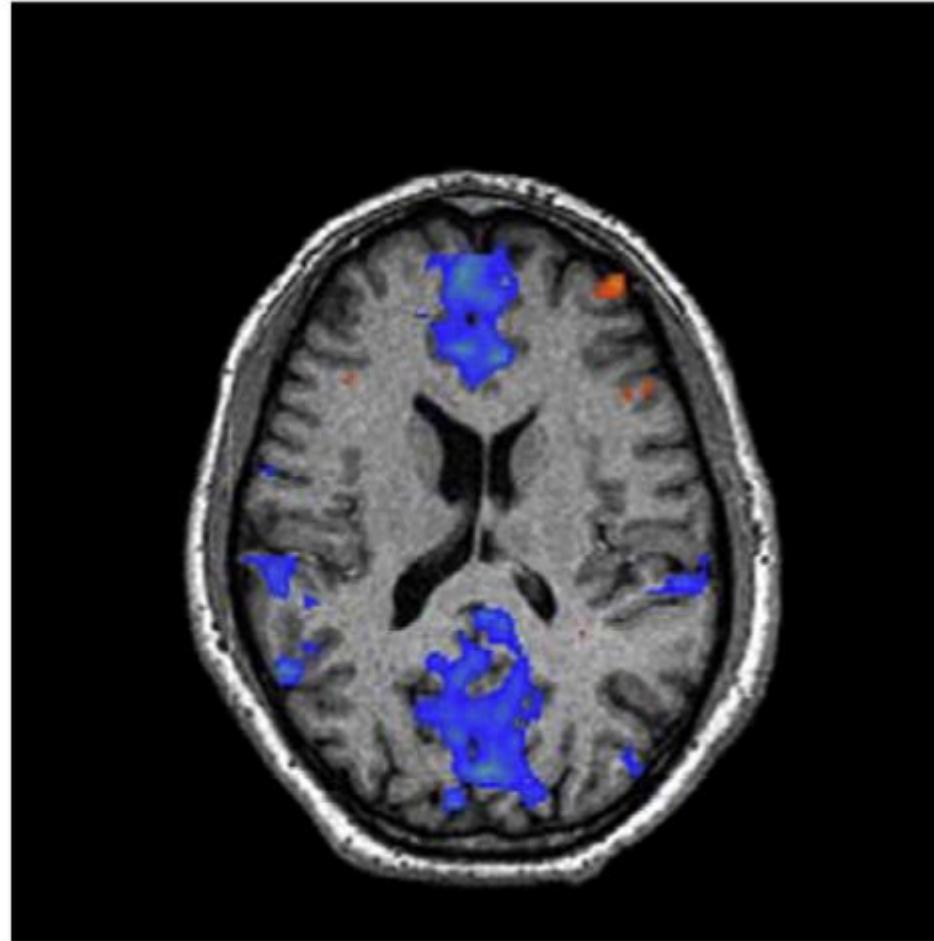


**Fig. 1.** Experimental design. During encoding (left), blocks of face-profession pairs and blocks of head templates were presented alternately. During retrieval (right), blocks of faces without profession and blocks of head templates with unequal ear size were presented alternately. Each stimulus was presented for 5 s.



**Fig. 2.** Increased parahippocampal activation in depressive patients relative to control participants during encoding ( $q < 0.05$ , FDR corrected, Talairach coordinates  $x = -24, y = -19, z = -6$ , red areas display increased activity and blue areas decreased activity in depressive patients).

- Structural hippocampal pathology discussed in depression **subtypes**
- Represents an **important confound in memory studies.**



**Fig. 3.** Decreased activation in frontal and parietal regions in depressive patients relative to control participants during encoding ( $q < 0.05$ , FDR corrected, Talairach coordinate  $z = 17$ , red areas display increased activity and blue areas decreased activity in depressive patients).

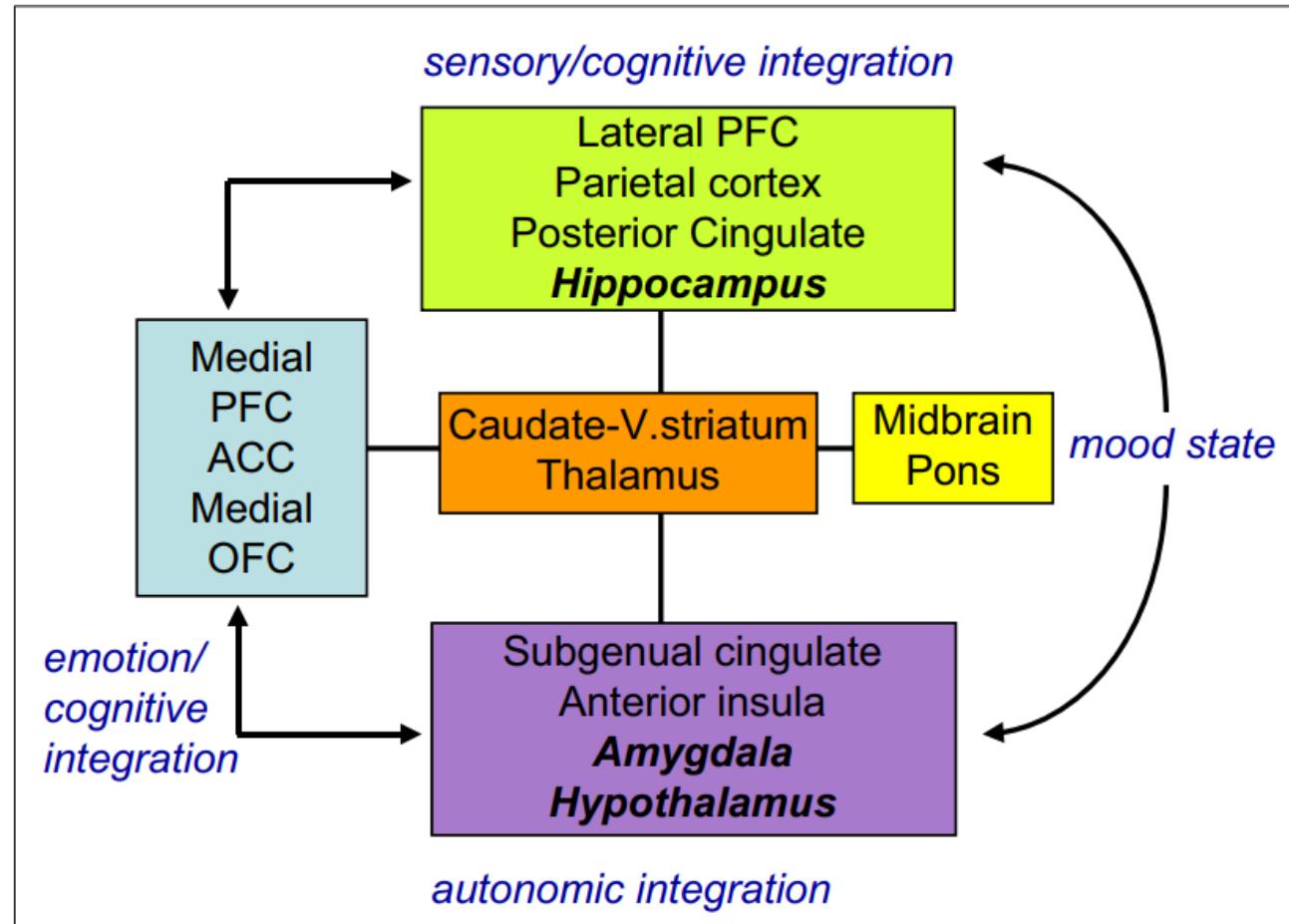
# NETWORK MODELS

- literature highlights the **complexity** inherent in understanding the **functional neuroanatomy of impaired cognition**
  - with various discrepancies and interpretational issues still unresolved.
  - Further research in well-characterized samples needed to resolve these issues fully.
- Strong support for the theory in MDD:
  - normally performing depressed patients show hyper response within lateral frontal regions
  - impaired performance is accompanied by hypo-response.
- Typically interpreted as representing inefficient cognitive processing within **prefrontal regions**.

## Limbic-cortical dysregulation model.

Interconnected regions are grouped into four ‘compartments’ relating to particular cognitive/ behavioral functions. Within compartments there may be a segregation between areas (shown in plain and italic text) showing an inverse relationship on different imaging paradigms.

These interactions are dysfunctional in depression and modulated by successful treatment.



This model has diagnostic value and a role in predicting treatment response (Mayberg, 2002, 2003).

Network models of depression, directly generated from functional neuroimaging results, can be tested explicitly using new connectivity analysis techniques.

# CONNECTIVITY ANALYSES

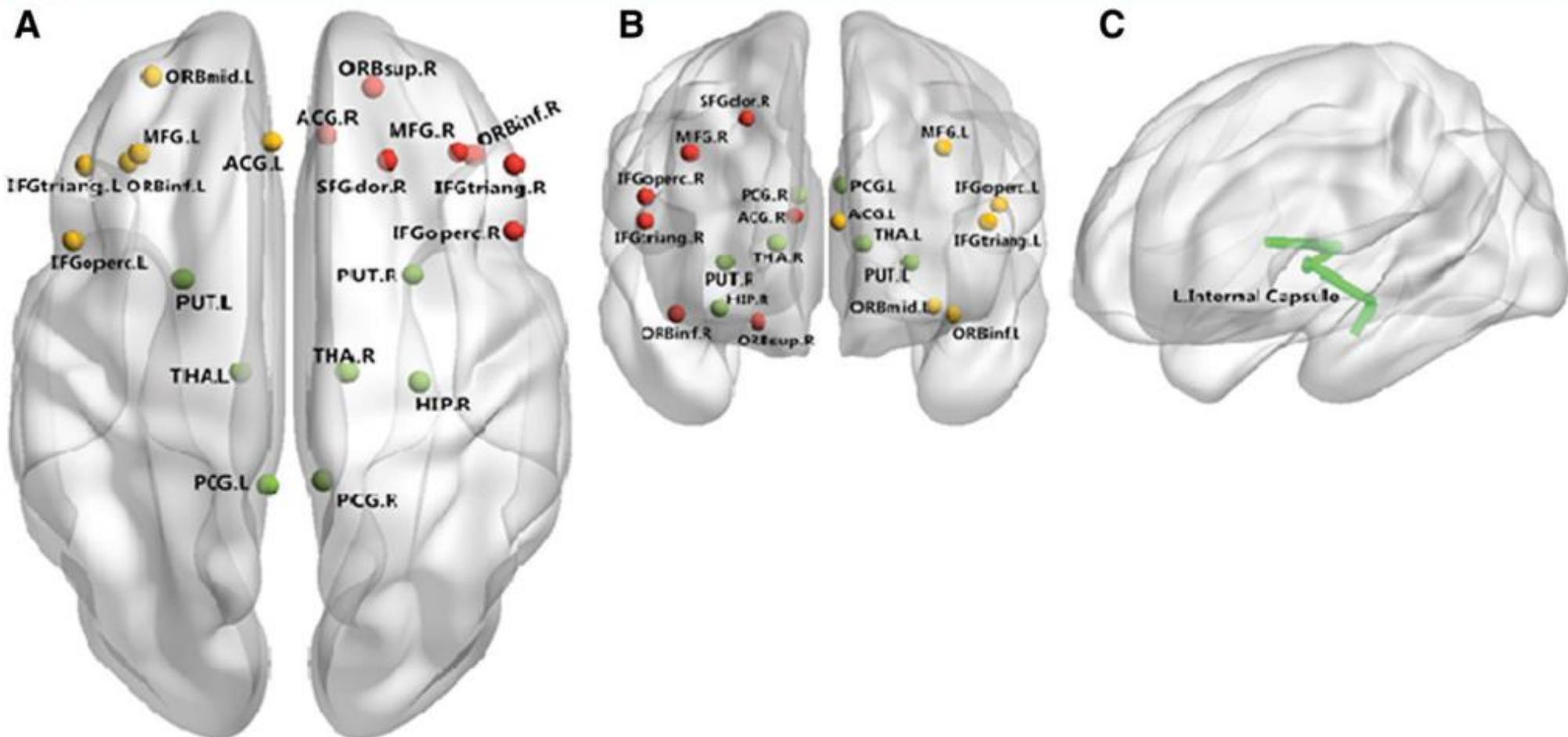
- Several studies have explored functional **coupling of the amygdala and prefrontal regions**
- Matthews et al. (2008)
  - **reduced functional coupling of the amygdala and supragenual ACC during emotion processing associated with increasing severity of depression.**
- Similarly
- Chen et al. (2008)
  - **increased functional coupling of amygdala and ACC during face emotion processing following antidepressant treatment** (i.e. as symptom severity was reduced).

# CONNECTIVITY ANALYSES

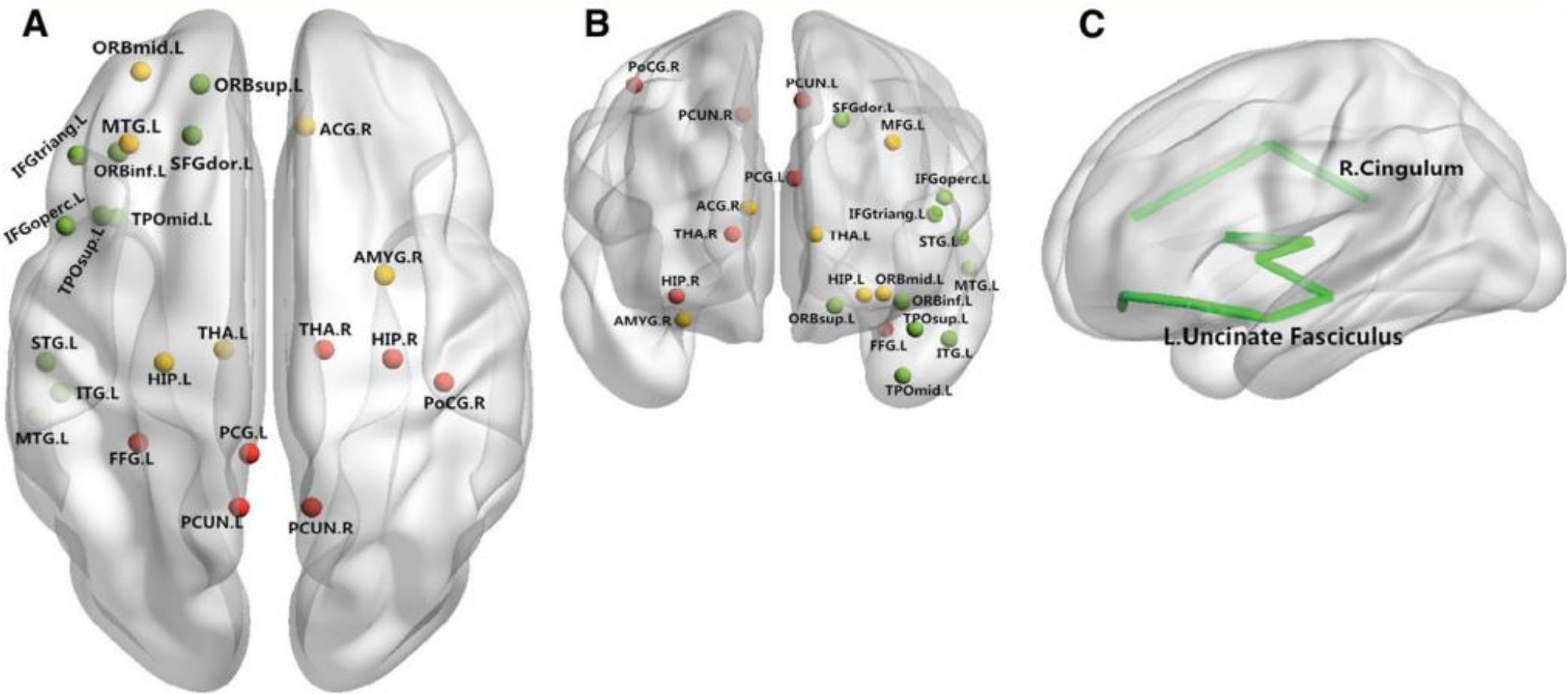
- Siegle et al. (2007)
  - **enhanced amygdala response during emotional tasks**
  - **reduced DLPFC response during executive tasks**
  - **decreased functional coupling** between amygdala and DLPFC
- highlighting the importance of the cognitive challenge in exploring connectivity

# CONNECTIVITY ANALYSES

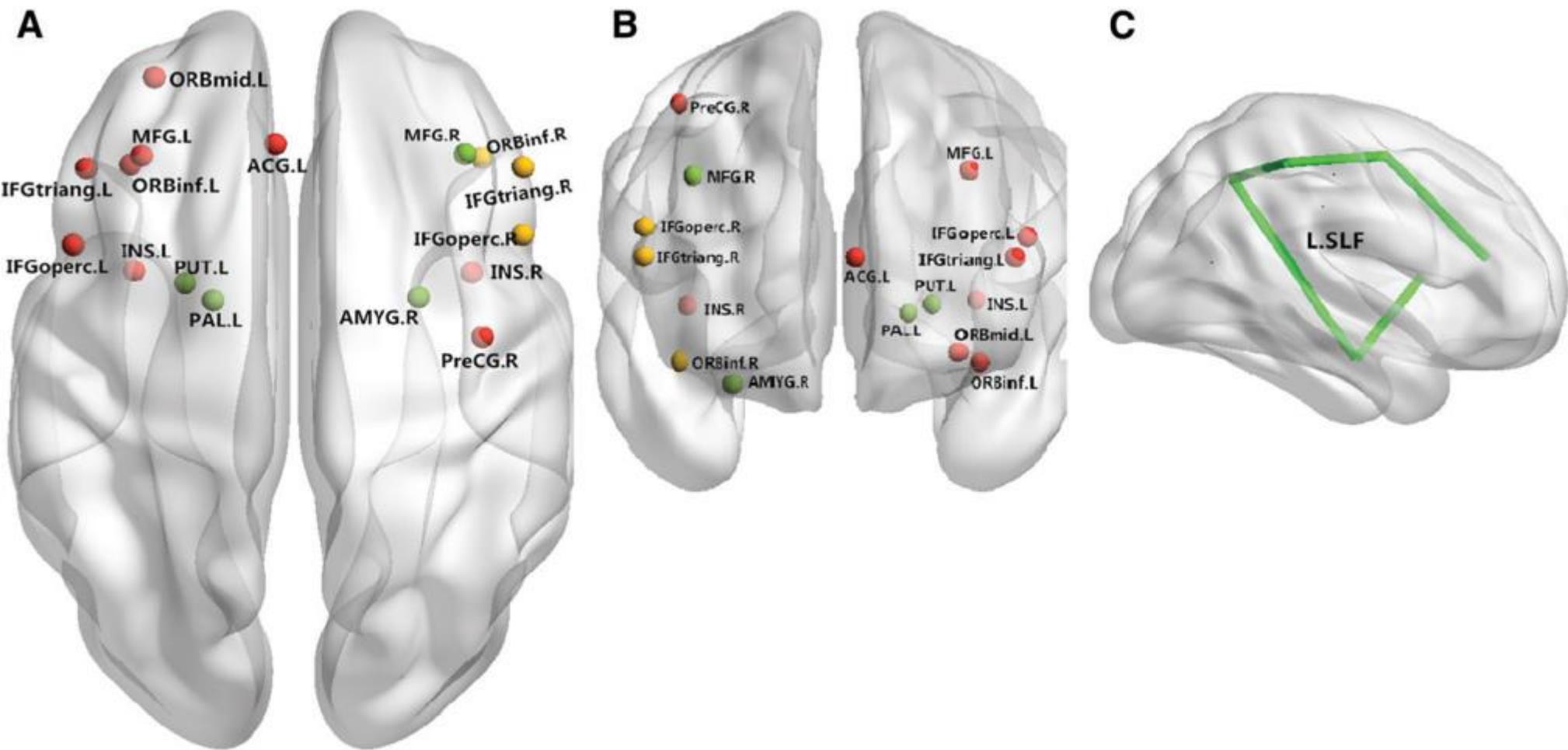
- A more comprehensive approach to connectivity
- to use **structural equation modelling** and **dynamic causal modelling** to explore changes in a pre-specified network of regions.
- Schlosser et al. (2008)
  - connectivity associated with a **cognitive control task** (Stroop)
  - enhanced task-related input from the **dorsal to rostral ACC** in subjects with depression
  - a **failure to downregulate rostral ACC** function in an inhibitory control context.

**Figure 1**

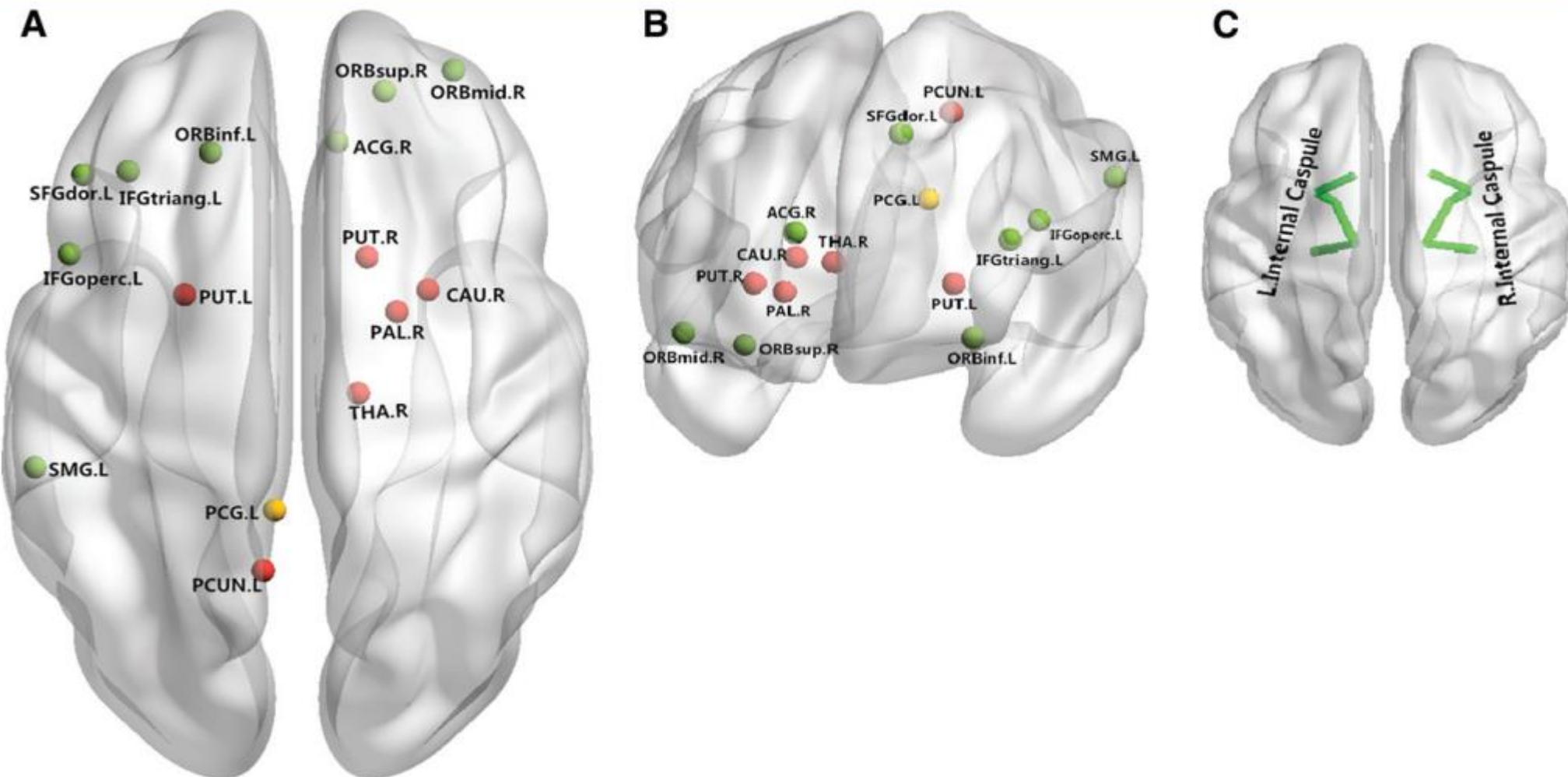
**Figure 1:** Neural networks involved in patients with MDD mainly include the medial frontal cortex, temporal cortex, and superior occipital cortex. Both anatomic and functional changes are shown in the, *A*, superior view and, *B*, anterior view. Red and yellow spots represent changes in gray matter volume and function, respectively, and green spots identify regions with both functional and anatomic changes. *C*, Main white matter bundles (green line), with changes of integrities revealed by DT imaging. *ACG.L* = left anterior cingulate gyrus; *ACG.R* = right anterior cingulate gyrus; *HIP.R* = right hippocampus; *IFGoperc.L* = left inferior frontal gyrus, pars opercularis; *IFGoperc.R* = right inferior frontal gyrus, opercular part; *IFGtriang.L* = left inferior frontal gyrus, pars triangularis; *IFGtriang.R* = right inferior frontal gyrus, triangular part; *MFG.L* = left middle frontal gyrus; *MFG.R* = right middle temporal gyrus; *ORBinf.L* = orbital part of left Inferior frontal gyrus; *ORBinf.R* = orbital part of right inferior frontal gyrus; *ORBmid.L* = orbital part of left middle frontal gyrus; *ORBsup.R* = orbital part of right superior frontal gyrus; *PCG.L* = left posterior cingulate gyrus; *PCG.R* = right posterior cingulate gyrus; *PUT.L* = left lenticular nucleus, putamen; *PUT.R* = right lenticular nucleus, putamen; *SFGdor.R* = right superior frontal gyrus, dorsolateral; *THA.L* = left thalamus; *THA.R* = right thalamus.

**Figure 2**

**Figure 2:** Neural networks involved in schizophrenia mainly include the prefrontal cortex, temporal cortex, and thalamus. Both anatomic and functional changes are shown in the, *A*, superior view and, *B*, anterior view. Red and yellow spots represent changes in gray matter volume and function respectively; green spots indicate regions with both functional and anatomic changes. *C*, Main white matter bundles (green line), with changes of integrities revealed by DT imaging. *ACG.R* = right anterior cingulate gyrus; *FFG.L* = left fusiform gyrus; *HIP.L* = left hippocampus; *HIP.R* = right hippocampus; *IFGperc.L* = left inferior frontal gyrus, pars opercularis; *IFGtriang.L* = left inferior frontal gyrus, pars triangularis; *ITG.L* = left inferior temporal gyrus; *MFG.L* = left middle frontal gyrus; *MTG.L* = left middle temporal gyrus; *ORBinf.L* = orbital part of left inferior frontal gyrus; *ORBmid.L* = orbital part of left middle frontal gyrus; *ORBsup.L* = orbital part of left superior frontal gyrus; *PCG.L* = left posterior cingulate gyrus; *PCUN.L* = left precuneus; *PCUN.R* = right precuneus; *PoCG.R* = right postcentral gyrus; *SFGdor.L* = left superior frontal gyrus, dorsolateral; *STG.L* = left superior temporal gyrus; *THA.L* = left thalamus; *TPOmid.L* = left temporal pole, middle temporal gyrus; *TPOsup.L* = left temporal pole, superior temporal gyrus.

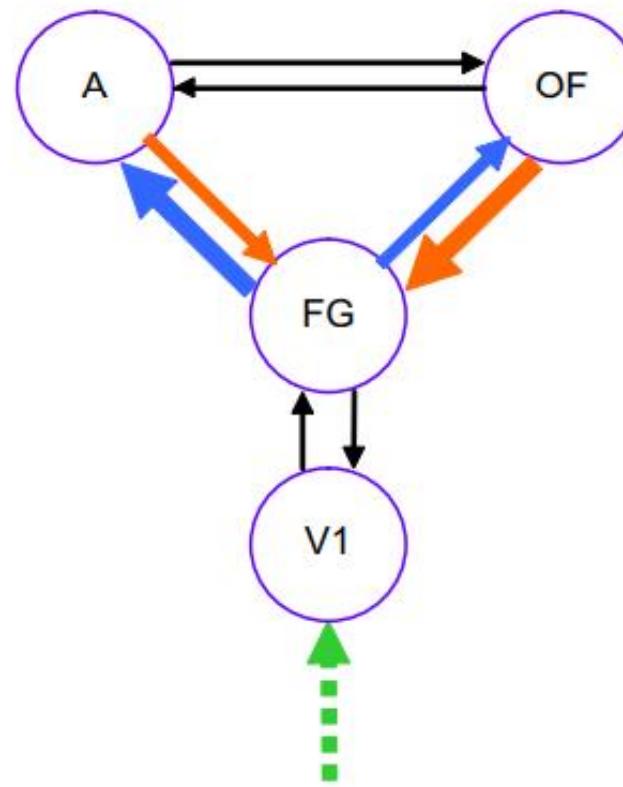
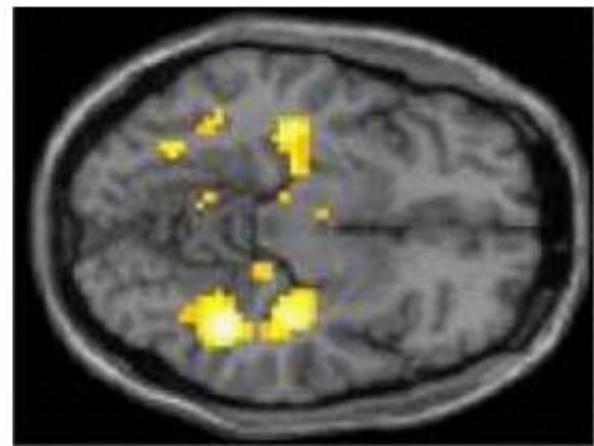
**Figure 3**

**Figure 3:** Neural networks involved in BD mainly include the inferior frontal cortex and limbic areas. Both anatomic and functional changes are shown in the, *A*, superior view and, *B*, anterior view. Red spots and yellow spots represent changes in gray matter volume and function, respectively; green spots indicate regions with both functional and anatomic changes. *C*, Main white matter bundles (green line), with changes of integrities revealed by DT imaging. *ACG.L* = left anterior cingulate gyrus; *AMYG.R* = right amygdala; *IFGoperc.L* = left inferior frontal gyrus, pars opercularis; *IFGoperc.R* = right inferior frontal gyrus, pars opercularis; *IFGtriang.L* = left inferior frontal gyrus, pars triangularis; *IFGtriang.R* = right inferior frontal gyrus, pars triangularis; *INS.L* = left insula; *INS.R* = right insula; *L.SLF* = left superior longitudinal fasciculus; *MFG.L* = left middle frontal gyrus; *MFG.R* = right middle frontal gyrus; *ORBinf.L* = orbital part of left inferior frontal gyrus; *ORBinf.R* = orbital part of right inferior frontal gyrus; *ORBmid.L* = orbital part of left middle frontal gyrus; *PAL.L* = left lenticular nucleus, pallidum; *PreCG.R* = right precentral gyrus; *PUT.L* = left lenticular nucleus, putamen.

**Figure 4**

**Figure 4:** Neural networks involved in ADHD mainly include the superior frontal cortex, inferior frontal cortex, and basal ganglia. Both anatomic and functional changes are shown in the, *A*, superior view and, *B*, anterior view. Red and yellow spots represent changes in gray matter volume and function, respectively; green spots indicate regions with both functional and anatomic changes. *C*, Main white matter bundles (green line), with changes of integrities revealed by DT imaging. *ACG.R* = right anterior cingulate gyrus; *CAU.R* = right caudate nucleus; *IFGoperc.L* = left inferior frontal gyrus, opercular part; *IFG triang.L* = left inferior frontal gyrus, triangular part; *ORB inf.L* = orbital part of left inferior frontal gyrus; *ORBmid.R* = orbital part of right middle frontal gyrus; *ORB.sup.R* = orbital part of right superior frontal gyrus; *PAL.R* = right lenticular nucleus, pallidum; *PCG.L* = left posterior cingulate gyrus; *PCUN.L* = left precuneus; *PUT.L* = left lenticular nucleus, putamen; *PUT.R* = right lenticular nucleus, putamen; *SFGdor.L* = left superior frontal gyrus; *SMG.L* = left supramarginal gyrus; *THA.R* = right thalamus.

Goulden et al., (2009)  
abnormalities when dynamic causal modelling is applied to remitted depressed patients performing a face processing task



**FIGURE 3 | Sad face processing in remitted depressed patients.** The left panel shows attenuated bilateral hippocampus and fusiform signal in patients compared to controls. The right panel shows altered connectivity in patients obtained via dynamic causal modelling. The model tested was a right hemisphere model comprising primary visual cortex (V1), fusiform gyrus (FG),

Amygdala (A) and orbitofrontal cortex (OFC). Connections shown in blue are stronger in patients (significant at  $p < 0.05$  corrected for boldest arrow) while those in orange are weaker in patients (significant at  $p < 0.05$  corrected for boldest arrow). Data acquired at the Wellcome Trust Clinical Research Facility, Manchester (Thomas et al., submitted; Goulden et al., 2009).

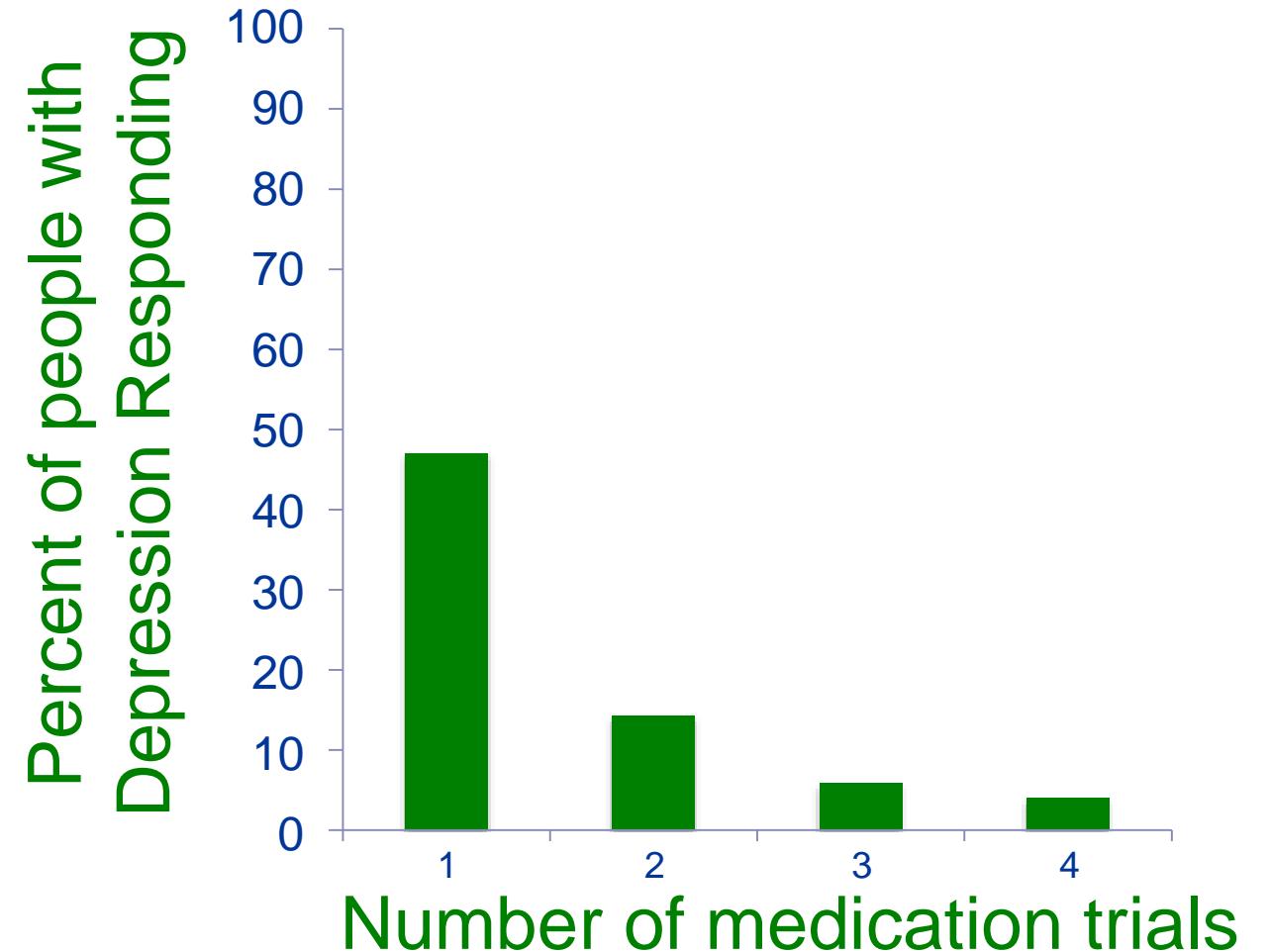
# Clinical Implications of Cognitive Imaging

- Literature
  - suggested important relationships between **clinical features and functional response to cognitive challenges.**
  - reported correlations with **severity**
  - reported changes in **response to treatment.**
  - discrepancies between studies may also point to **distinct functional response profiles in different subtypes** of the diseases.
- To illustrate the potential of neuroimaging cognition to clinical approaches.

# Remitted Studies as a Model for Trait Effects

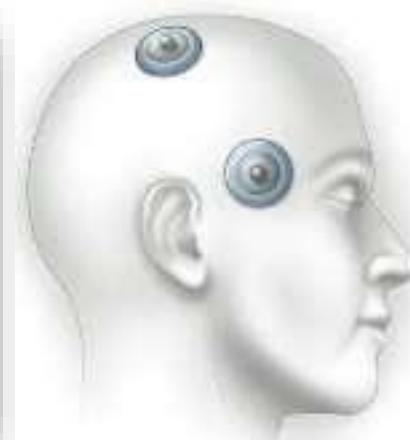
- Studying the neuronal basis of cognitive function in remitted patients
- Provides a model for considering which abnormalities may represent trait effects or vulnerability markers.
- Takamiet al. (2007)
  - a cross-sectional study
  - **attenuated ACC activity to a verbal fluency task** in elderly remitted depressives who had **experienced multiple previous episodes**, though not in those who had experienced only a single episode.
- By contrast
- Hugdahl et al. (2007)
  - used a longitudinal design to show that with remission, **inferior frontal gyrus superior and inferior parietal lobule** activity to a mental arithmetic task normalized in recurrent depressive participants.

- Majority do not respond to first-line treatments
- Diminishing returns from medication switches

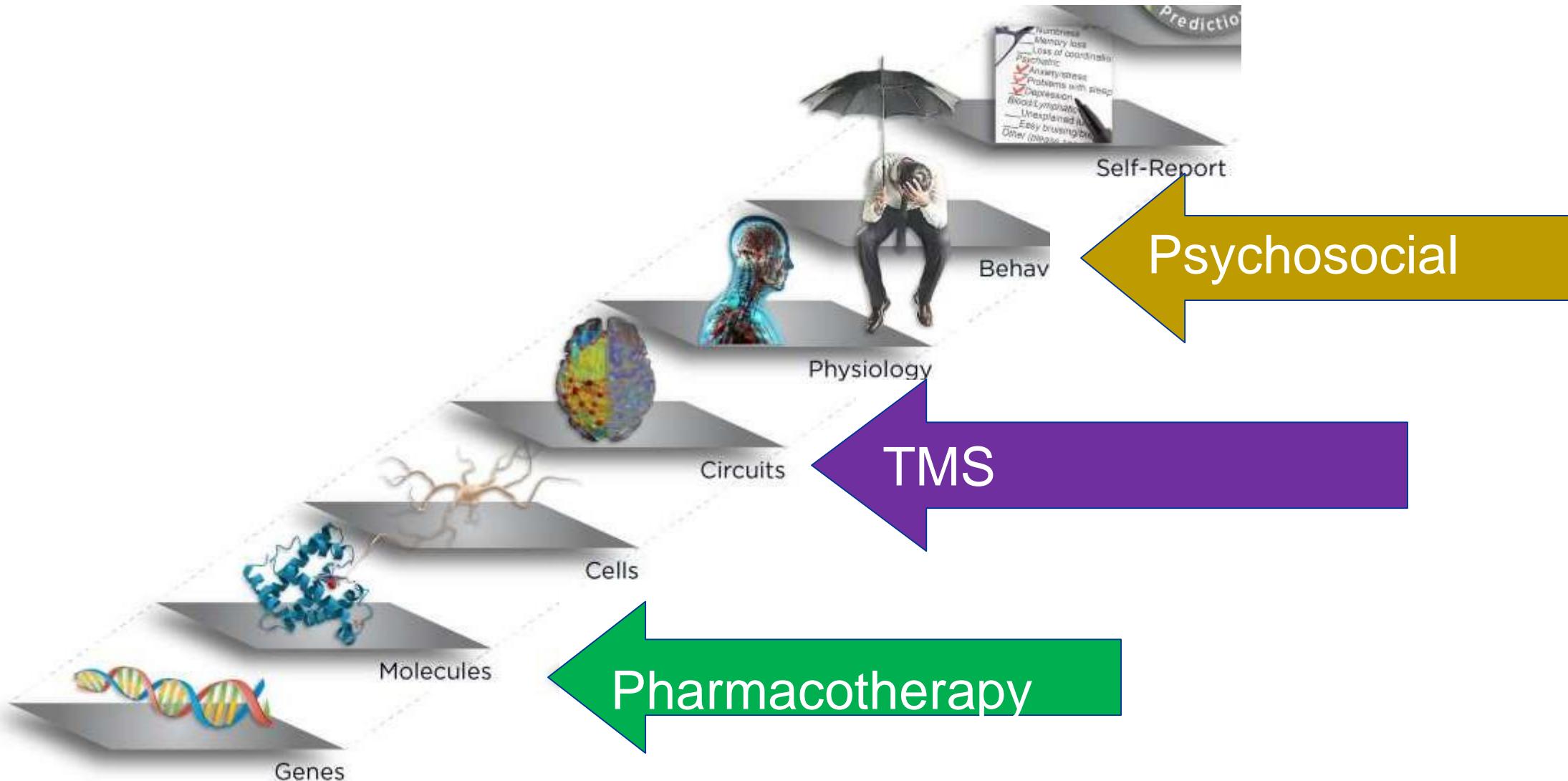


- Psychotherapy
- Pharmacology
- Brain Stimulation
  - Electroconvulsive Therapy (ECT)
  - Transcranial magnetic Stimulation (TMS)

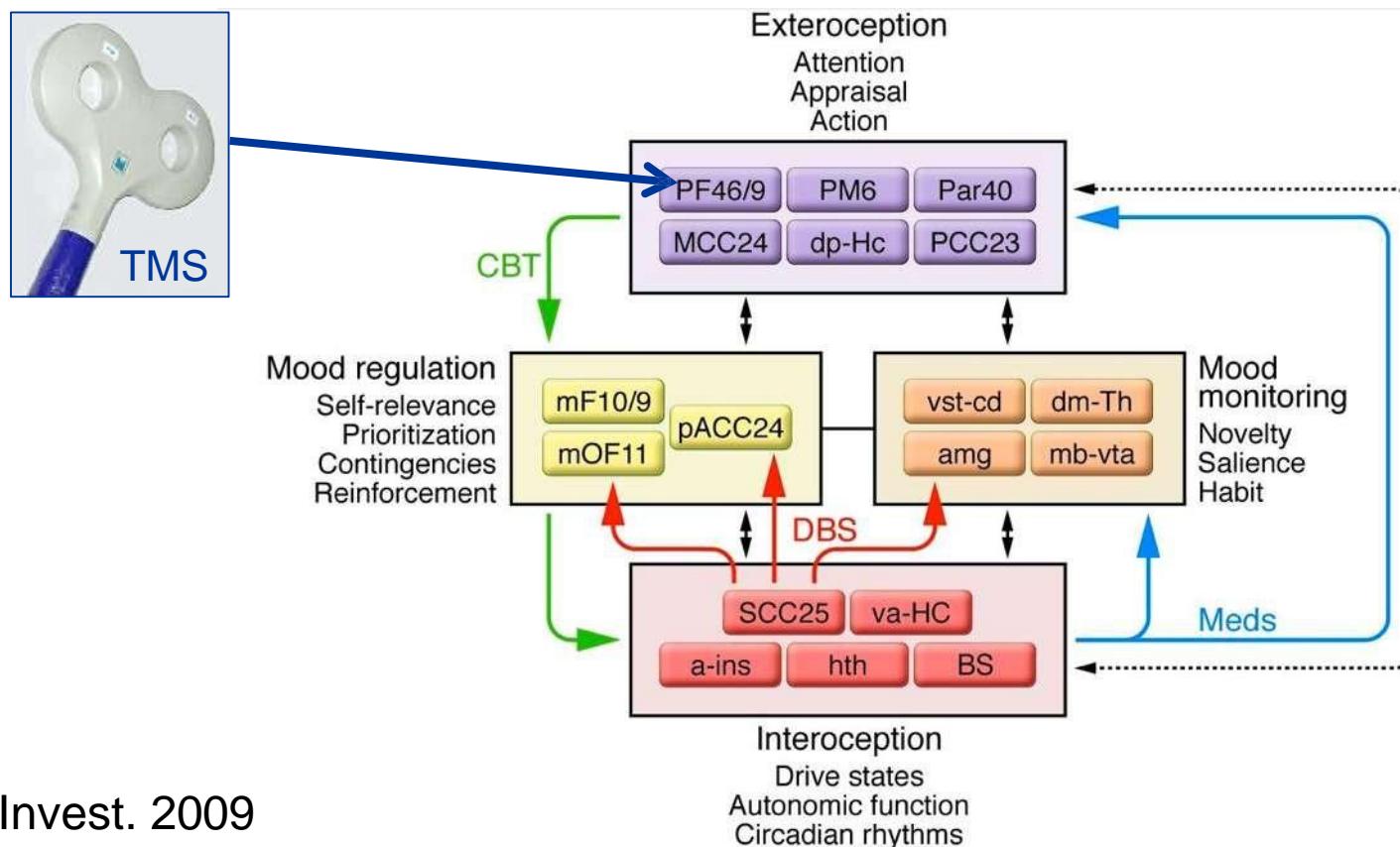
Unlike **tDCS** which utilizes a maximum current of 2 mA, **ECT** uses extremely high current levels (around 800 mA) which induces an intentional, controlled, short-term seizure.



- Complementary to Pharmacological and Psychosocial Interventions



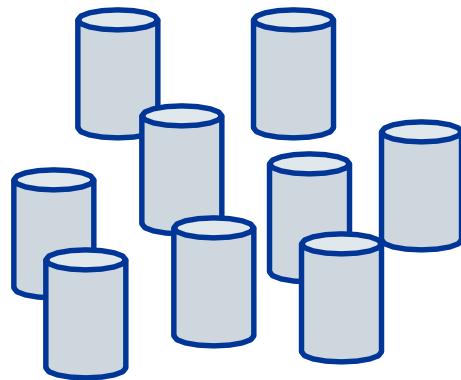
- Complementary to Pharmacological and Psychosocial Interventions
- Translates knowledge of circuitry into therapeutic targets



Therapeutic approach	Influence on emotional symptoms*	Influence on cognitive impairment*	Psychiatric disorders targeted
Currently available pharmacotherapy	+ →	-/0/+	Schizophrenia, depression, bipolar disorder, anxiety disorders
Deep-brain stimulation or electroconvulsive therapy	+ →	0/-	Major depression
Repetitive transcranial magnetic stimulation	0/+ →	0/+	Mainly depression (autism, schizophrenia)
Cognitive behavioural therapy	+ →	0	Mainly depression (anxiety disorders)
Cognitive remediation therapy	0/+ ← +		Mainly schizophrenia (depression)
Exposure therapy for desensitization	0/+ ← +		Post-traumatic stress disorder, obsessive compulsive disorder, phobias, social anxiety disorders
Improved drugs (alone and in combination with above strategies)	+ ↔ +		Dependent on mechanism of action

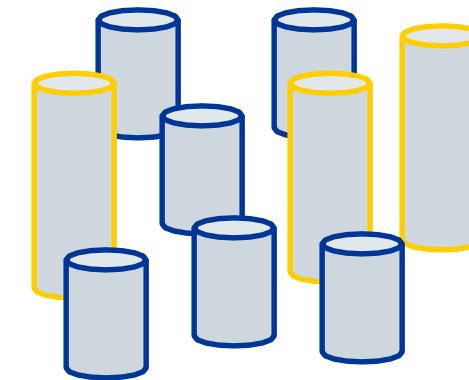
\*The '+' symbol corresponds to improvement; the '-' symbol corresponds to worsening; and '0' corresponds to no marked change.

neural ensemble at “rest”

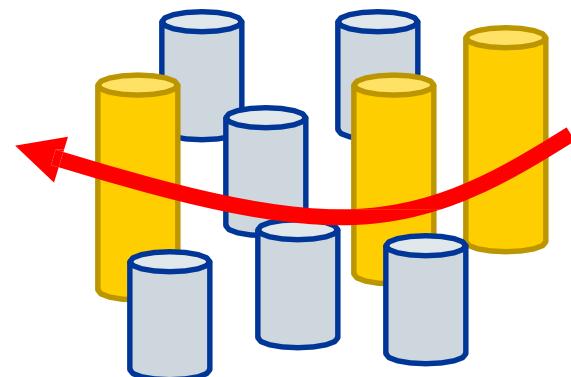


Represents means of providing a “functional focality” to nonfocal interventions

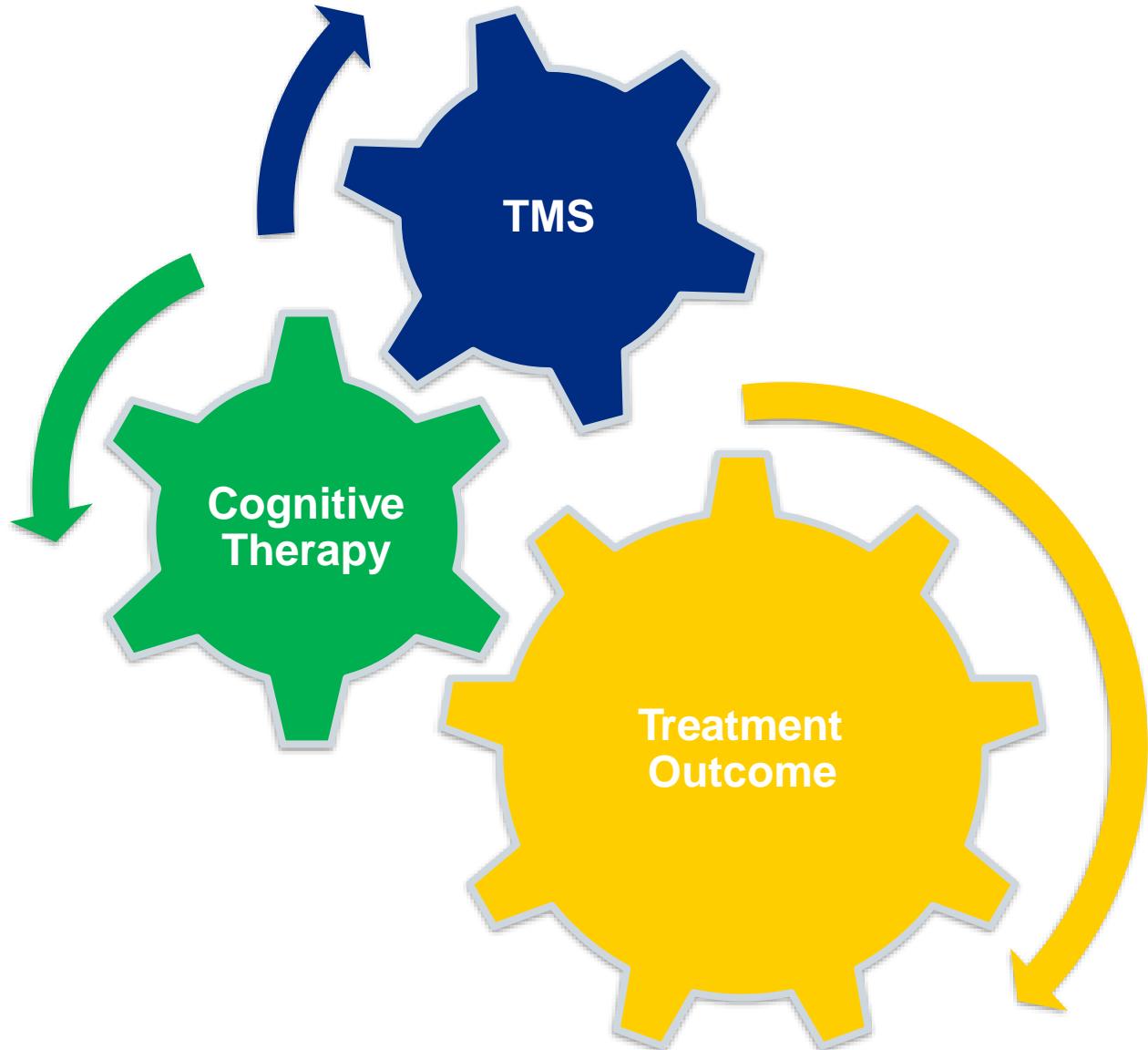
neural ensemble activation via behavior



Neurostim effects maximized at activated neurons



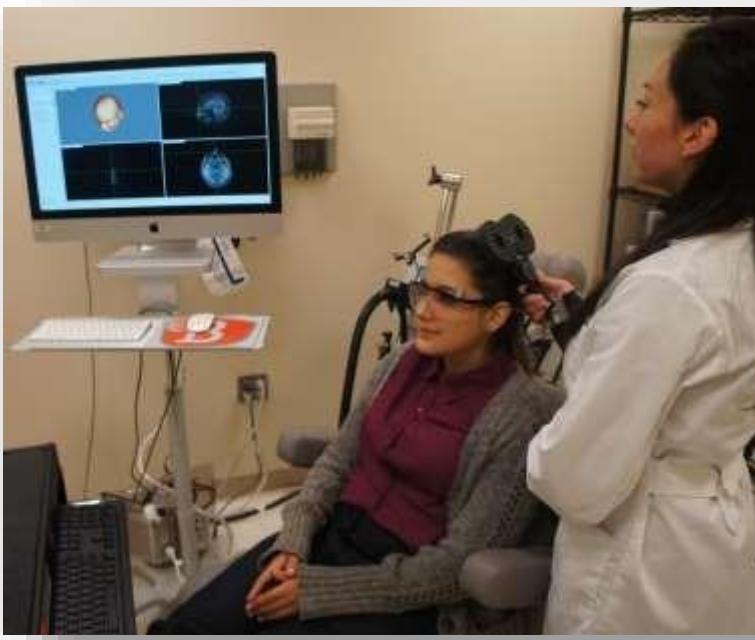
Stimulate the circuit while it's activated



- **Goal:** Leverage state-dependency of TMS effects to enhance antidepressant efficacy
- **Approach:** Administer cognitive therapy to activate the network at the same time as TMS is applied to enhance network function



## Individual fMRI- Targeted



Activate + Identify  
individual DLPFC  
location using fMRI

Neuronavigate  
TMS to  
individualized  
Target

Therapist CBT  
concurrent with  
TMS

# Treatment Effects on Cognition

- An exciting role for brain imaging measures in the development of new algorithms for diagnosis and management of the patients (Mayberg, 2007).
- Possible to identify cognitive neuroimaging biomarkers that can predict which patients are likely to respond to a particular intervention for a particular patient.
- Possible to identify which patients are more likely to relapse after treatment.

# FUTURE DIRECTIONS

- A number of inconsistencies in the literature on imaging cognition
- A need for more comprehensive reporting in imaging studies
  - characterization of the cognitive challenges
  - clear clinical characterization of the patients
    - medication status of patients, duration of illness, number of previous episodes and any co-morbidity may all contribute to differences between studies.
  - carefully characterize controls and match them as closely as possible to the patient sample
    - common for academic researchers to recruit controls among university staff and students, who may not represent a typical population sample.

# Other Modalities

- Research should report subject characteristics and relationships between BOLD response and performance as comprehensively as possible to facilitate cross-study comparisons.
- MEG and EEG provide greater temporal resolution than fMRI, which may be important in studying processes like emotional arousal or inhibition (McNeely et al., 2008; Moratti et al., 2008).
- Combining them with fMRI may help explain some of the discrepancies in the literature.
  - For example, Wacker et al. (2009) combined fMRI and resting EEG to assess responses in reward systems associated with anhedonia.
  - Anhedonia was associated with reduced response to reward (fMRI) but also increased resting state activity in the nucleus accumbens (EEG).

# Longitudinal studies and Systematic studies

- **Longitudinal studies** in this area will also be critical in understanding how abnormalities relate to response to different treatments and long-term prognosis
- Modern **connectivity** techniques to test network dysfunction hypotheses of disorders by non-emotional and emotional cognitive neuroimaging
- Systematic studies to explore how **genetic and environmental factors** interact in conferring vulnerability and resilience to mental disorders
- Neuroimaging biomarkers of disorder vulnerability and effective treatment
  - realizing the potential of functional imaging in diagnosis and management

Thank you  
for your attention!