

Brain areas associated with cognitive dysfunction in bipolar disorder patients: a fMRI meta-analysis

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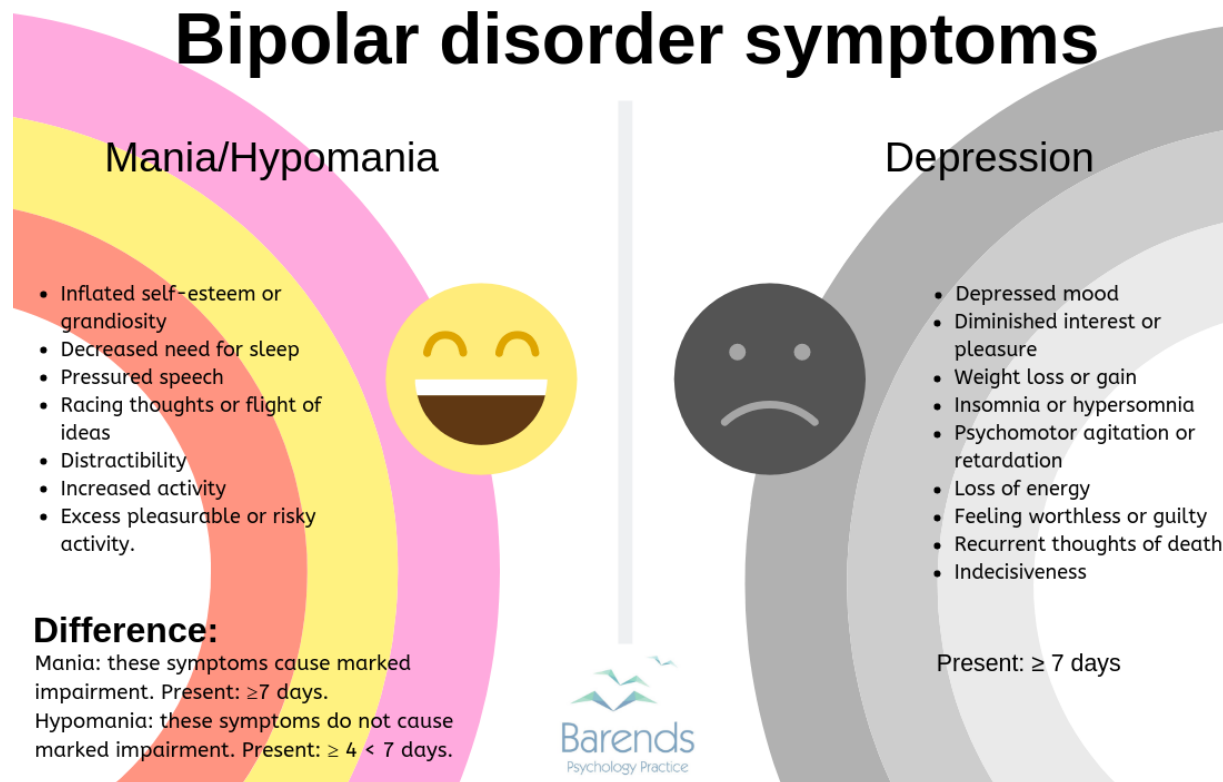
Department of Psychiatry

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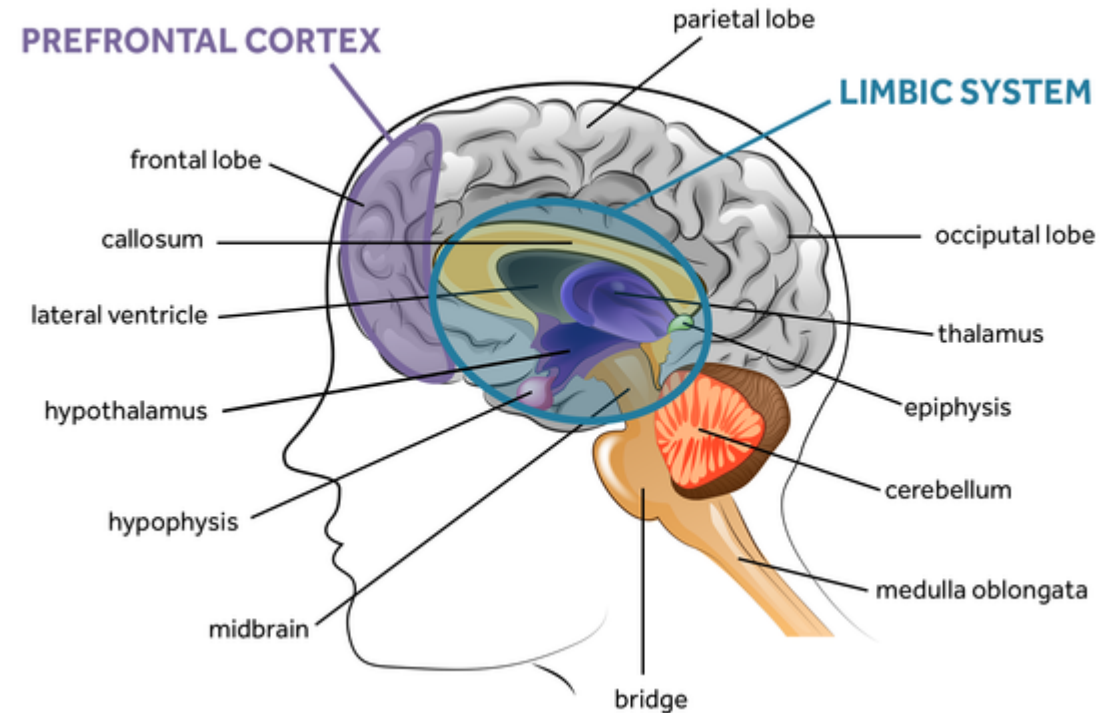
Bipolar disorder

Bipolar disorder is characterized by depressive and manic episodes



Literature

- Disruption of prefrontal networks and the limbic structures, e.g., “fronto-limbic network”.
- Fronto-limbic network is associated with cognitive functioning of three domains: emotion processing, reward processing and working memory.



Chen et al., *Bipolar disorders*, 2011; 13, pp. 1–15.

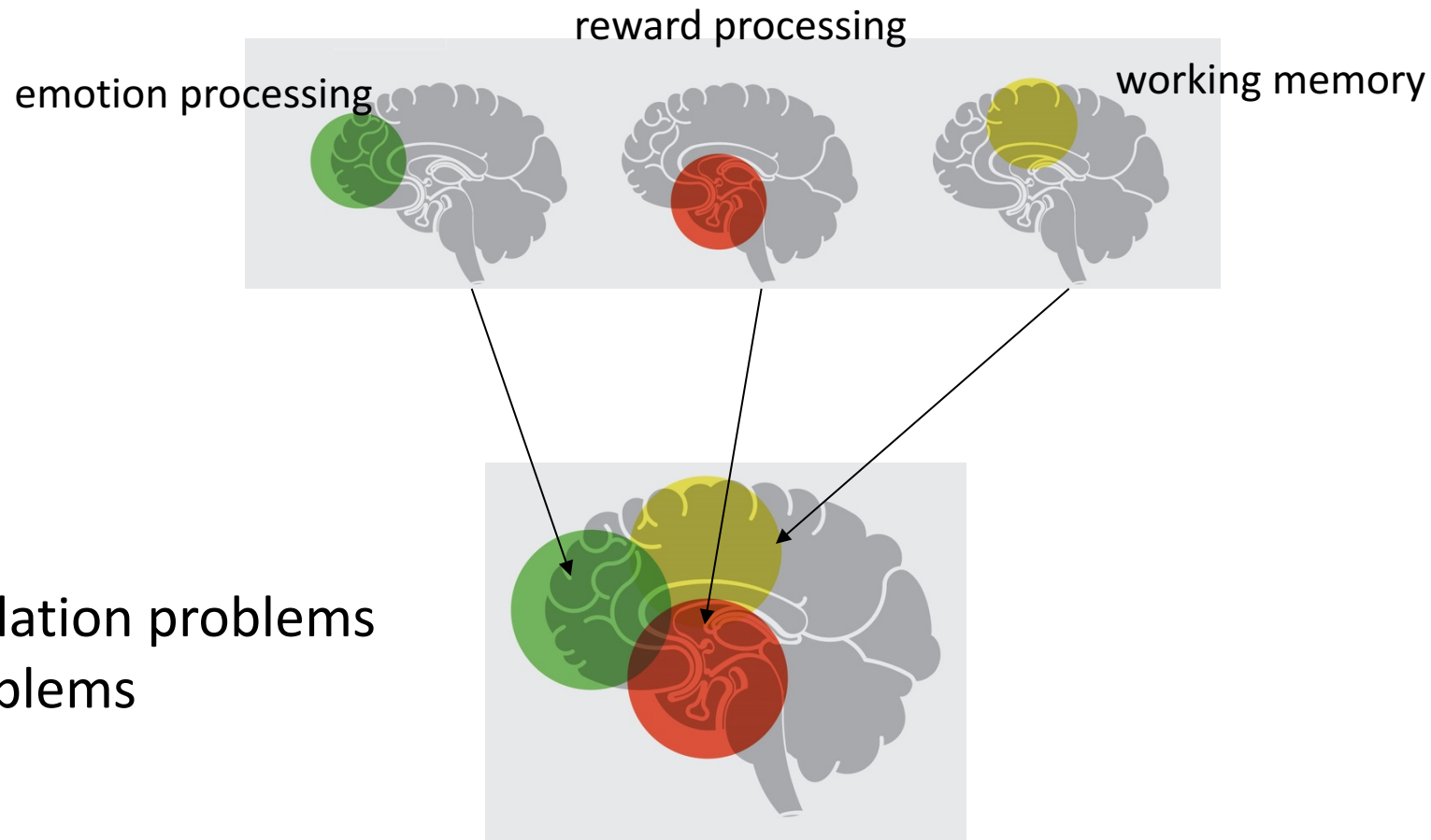
Strakowski et al., *Mol Psychiatry*, 2005; 10, pp. 105–116.

Aim of the study

- Up-to-date fMRI meta-analysis on bipolar disorder compared to healthy controls
- Brain functioning within three cognitive domains: emotion processing, reward processing and working memory.



Abnormal brain functioning



Emotion and reward processing

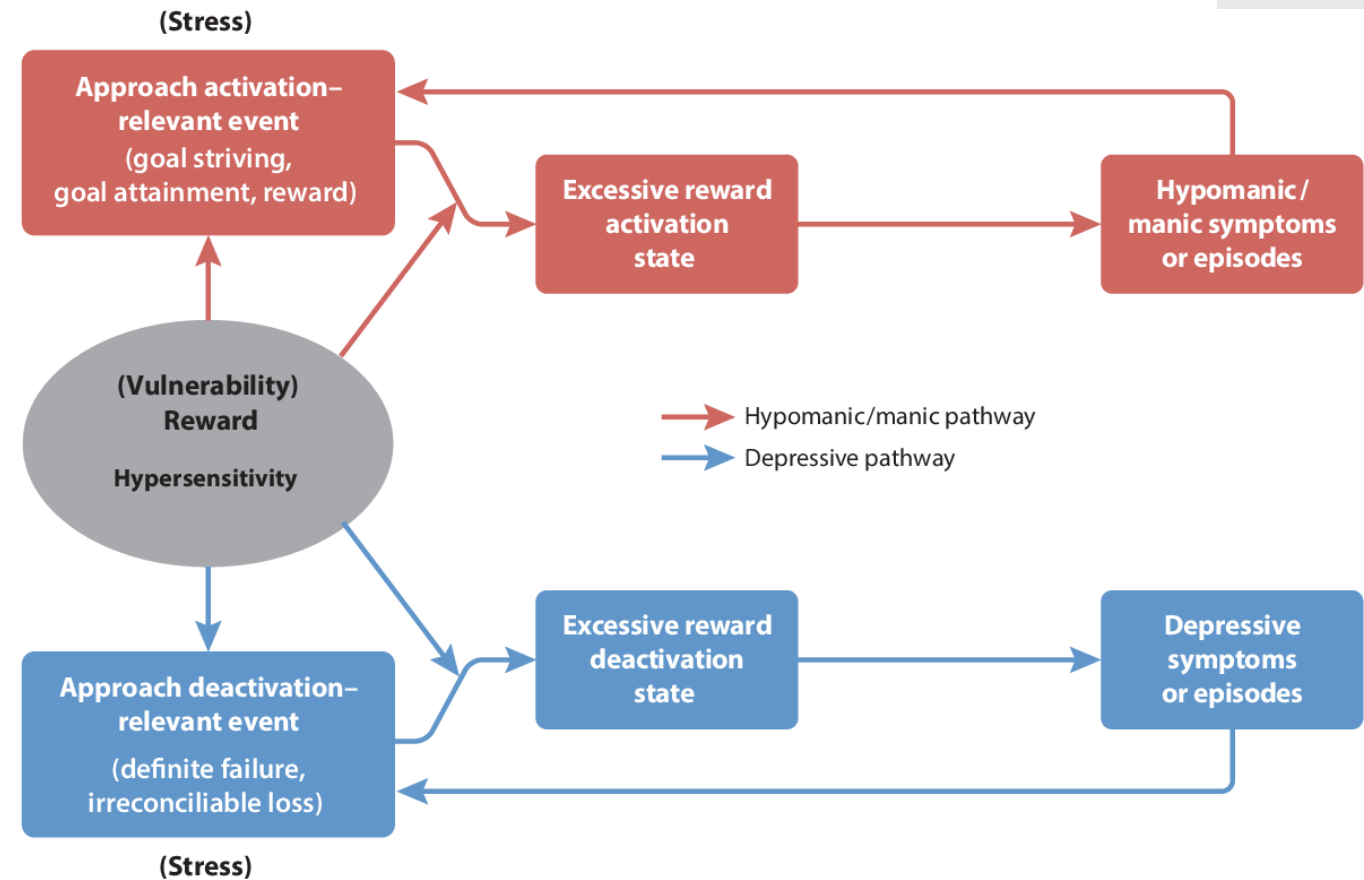


Behavioral Approach System (BAS)

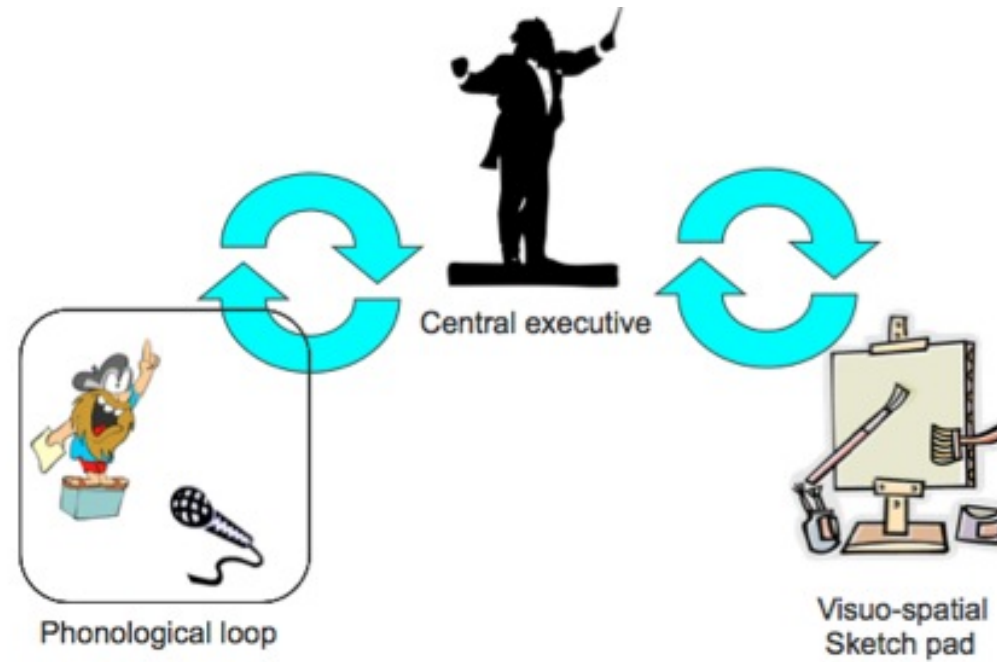
Regulates our responses to rewards

Overactive: impulsivity

Controlled by **dopaminergic pathways** and parts PFC and the limbic system including **amygdala** (Pickering and Smillie 2008)



Working memory



Model of Baddeley & Hitch, 1974

Aim of the study

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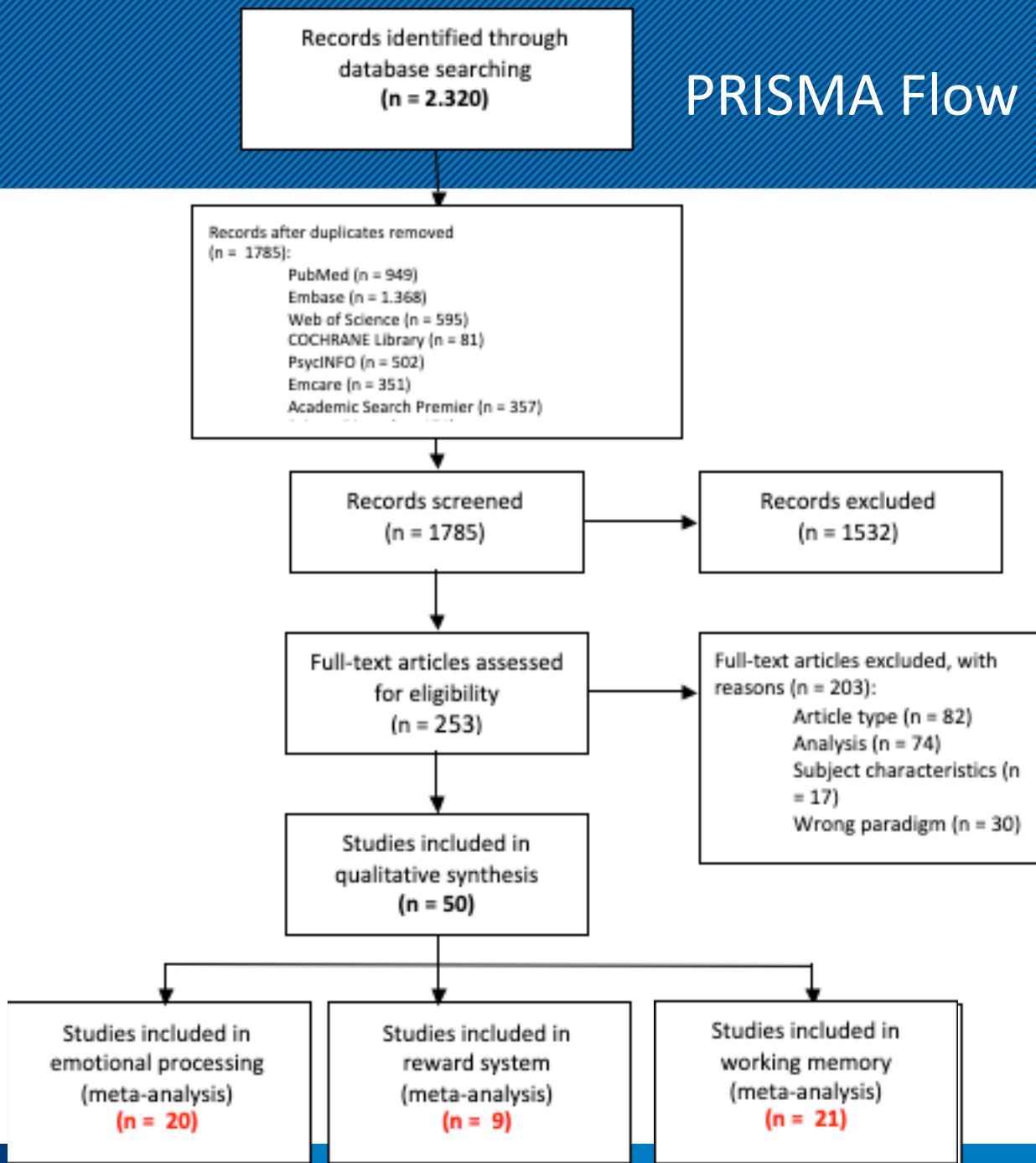


Literature search

Inclusion criteria:

- Articles written in English
- Human subjects between 18 and 65 years old
- Only fMRI studies with ‘whole brain’ analysis
- Bipolar patients versus healthy controls

PRISMA Flow Diagram



Total subjects included:
1034 bipolar disorder
1027 healthy controls

Method

- The activation likelihood estimation (ALE)
- Brainmap -> programma GingerALE
Differences in activation in brain regions for each paradigm (i.e. emotion processing, working memory and reward processing) separately between the two groups.
- Contrasts for each domain:
Bipolar disorder > Healthy controls
Healthy controls > Bipolar disorder
- Multiple comparison using the Family Wise Error Rate (FWER) Voxel level at $p = 0.05$ with threshold permutations of 1000

Result emotion processing

- 20 studies
- 316 patients with bipolar disorder and 369 healthy controls

BD > HC

Hyperactivation

Significantly increased activation in

- left **hippocampus**: socio-emotional process and production of affective states
- left **amygdala** : the emotional generation (i.e. perception and arousal), identification of emotional stimuli and emotion regulation.
- left and right superior **temporal gyrus**: social and emotion including face processing and recognition

0.0 0.3

HC > BD

Hypoactivation

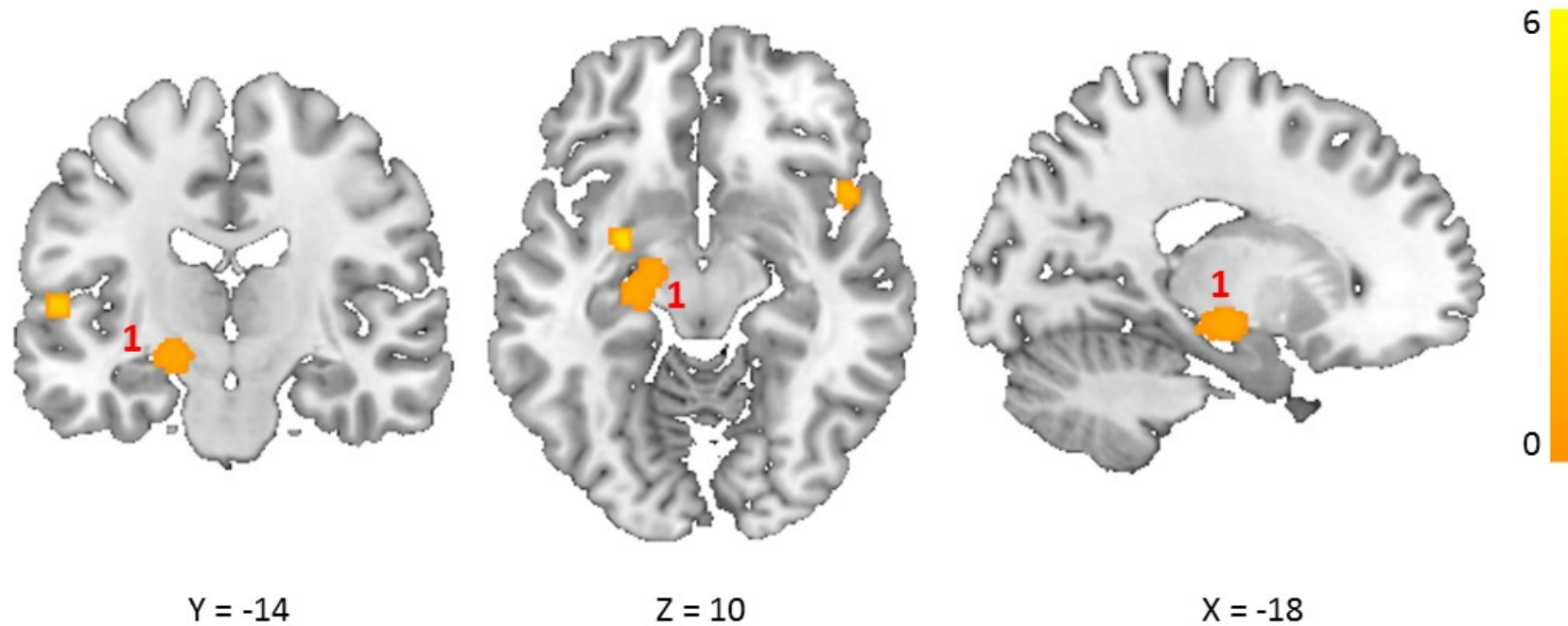
- right **Inferior frontal gyrus (IFG)**: inhibition and attentional control

Phillips et al., Biol. Psychiatry, 2013; 54, pp. 515-528

Banks et al., Soc. Cogn. Affect. Neurosci., 2007; 2, pp. 303-312,

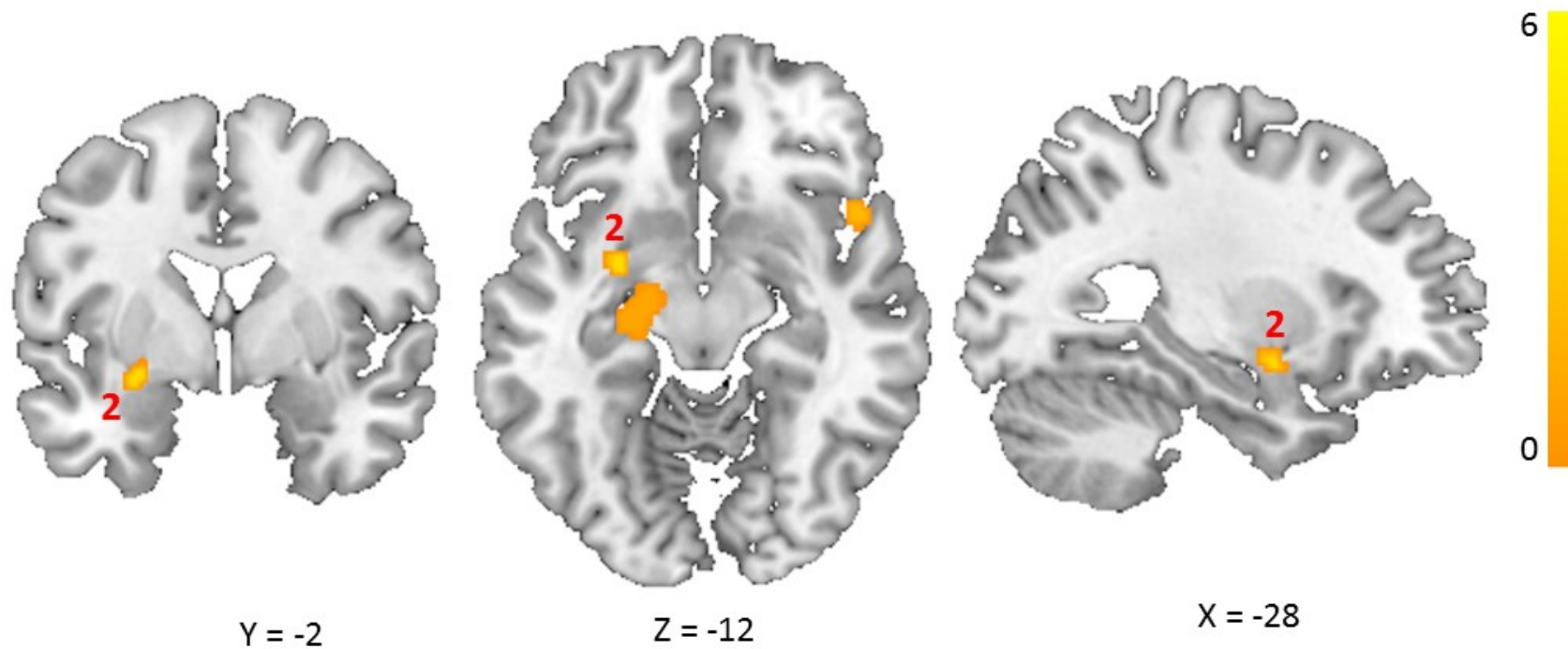
Hampshire et al., Biol. Psychiatry, 2010; 50, pp. 1313-1319

Hyperactivation emotion processing



1 = left hippocampus

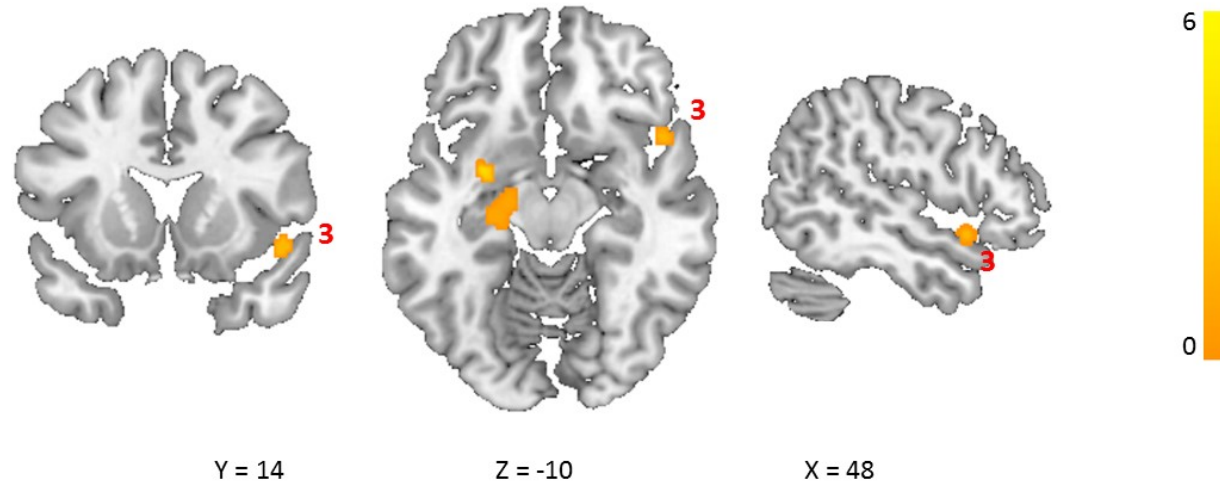
Hyperactivation emotion processing



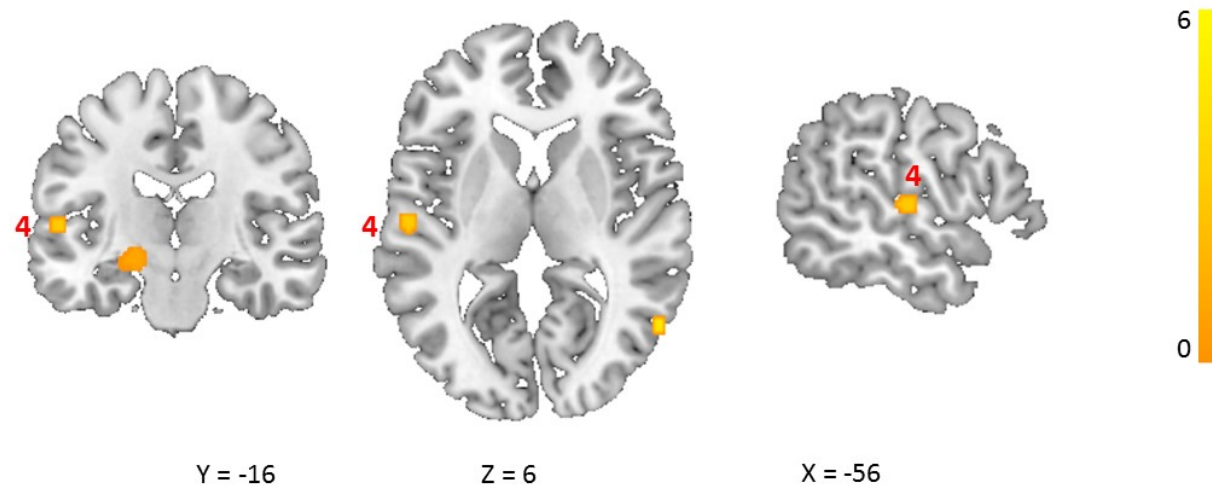
2 = left amygdala

Hyperactivation emotion processing

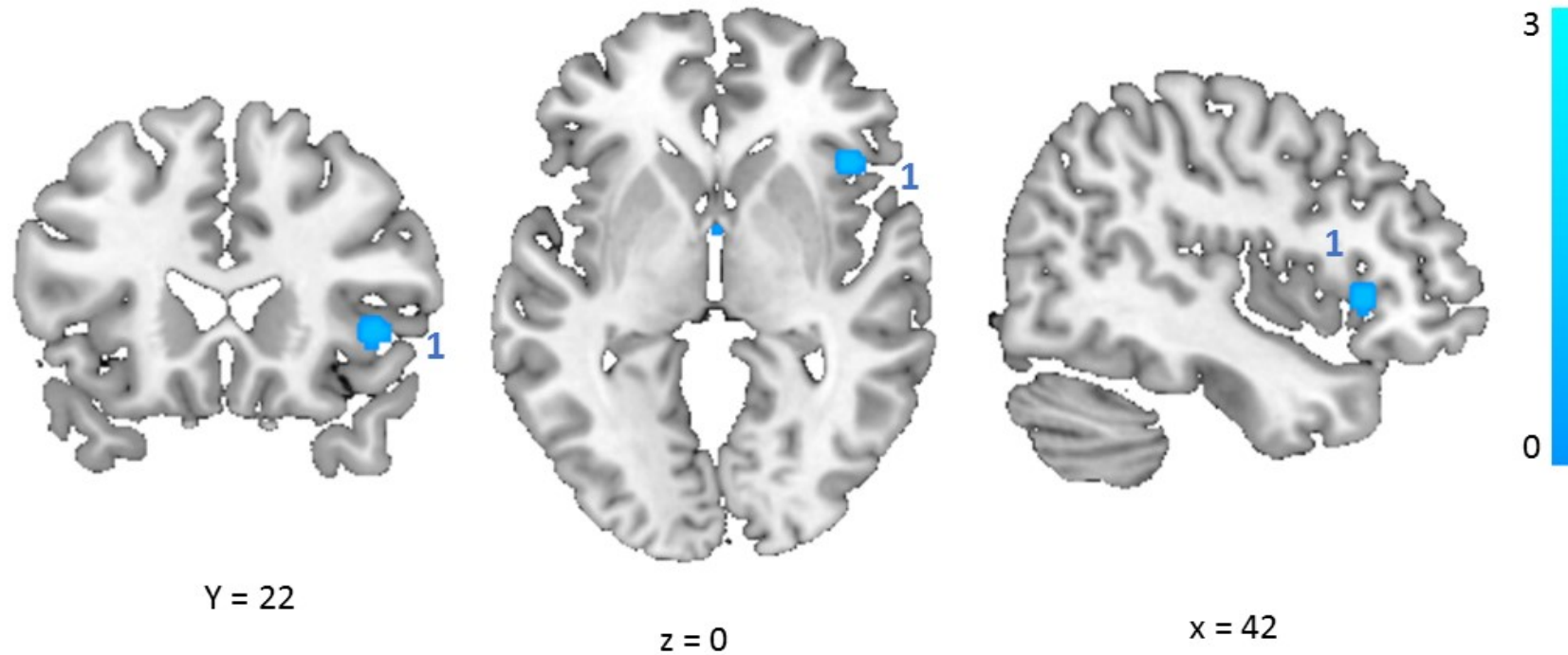
3 = right anterior temporal cortex



4 = left anterior temporal cortex



Hypoactivation emotion processing



1 = right Inferior frontal gyrus

Results reward processing

- 9 studies
- 215 patients with bipolar disorder and 213 healthy controls

BD > HC

Brodmann area 47 -> the orbitofrontal cortex (OFC).

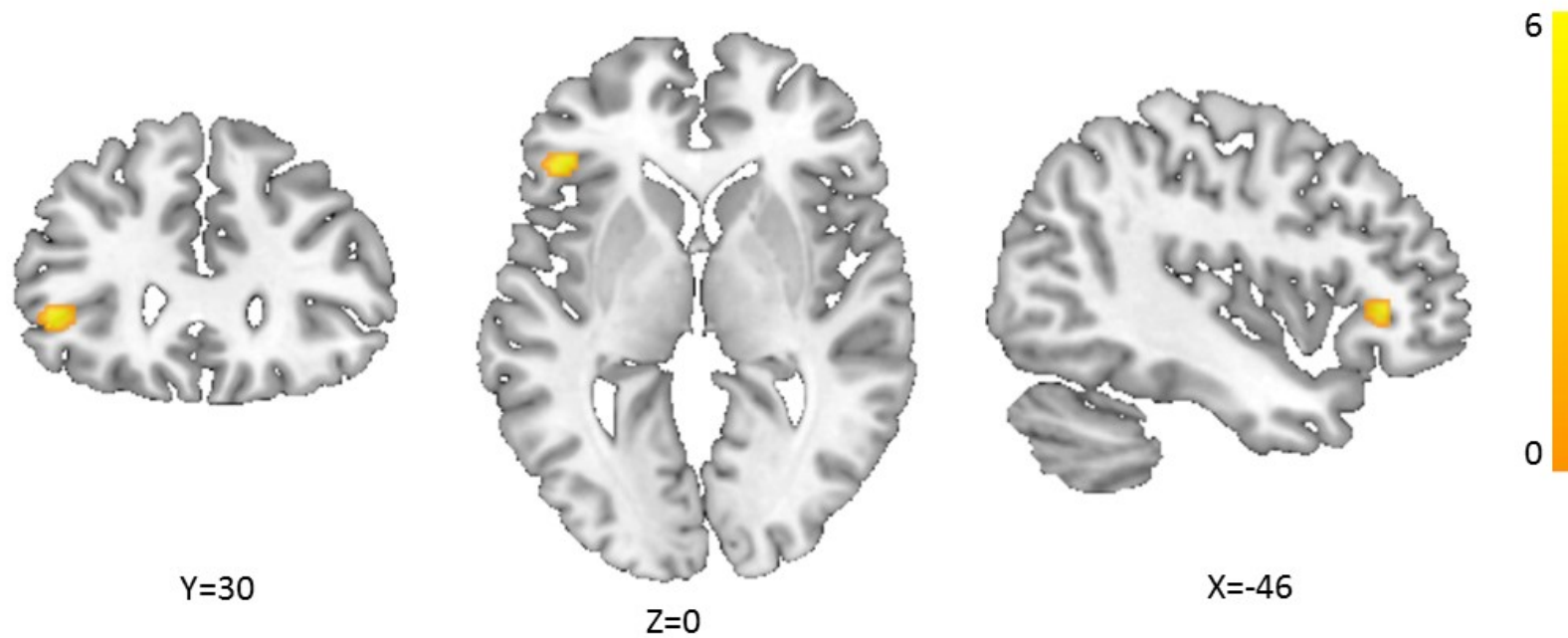
OFC activity is an important region for pleasure coding as well as reward outcome, and subregions of OFC are involved in processing the experience of hyperhedonia.

HC > BD

No activation

Berridge et al., Neuron, 2015; 6, pp. 646-664

Hyperactivation reward processing



4 = left orbitofrontal cortex

Result working memory

- 21 studies
- 503 patients with bipolar disorder and 445 healthy controls

BD > HC

Brodmann area 32 -> the anterior cingulate cortex (ACC)

Attentional and memory processes

Hyperactivation in ACC is associated with increased task difficulty and the prediction of error likelihood

Brodmann area 10 -> the (orbito)frontal cortex

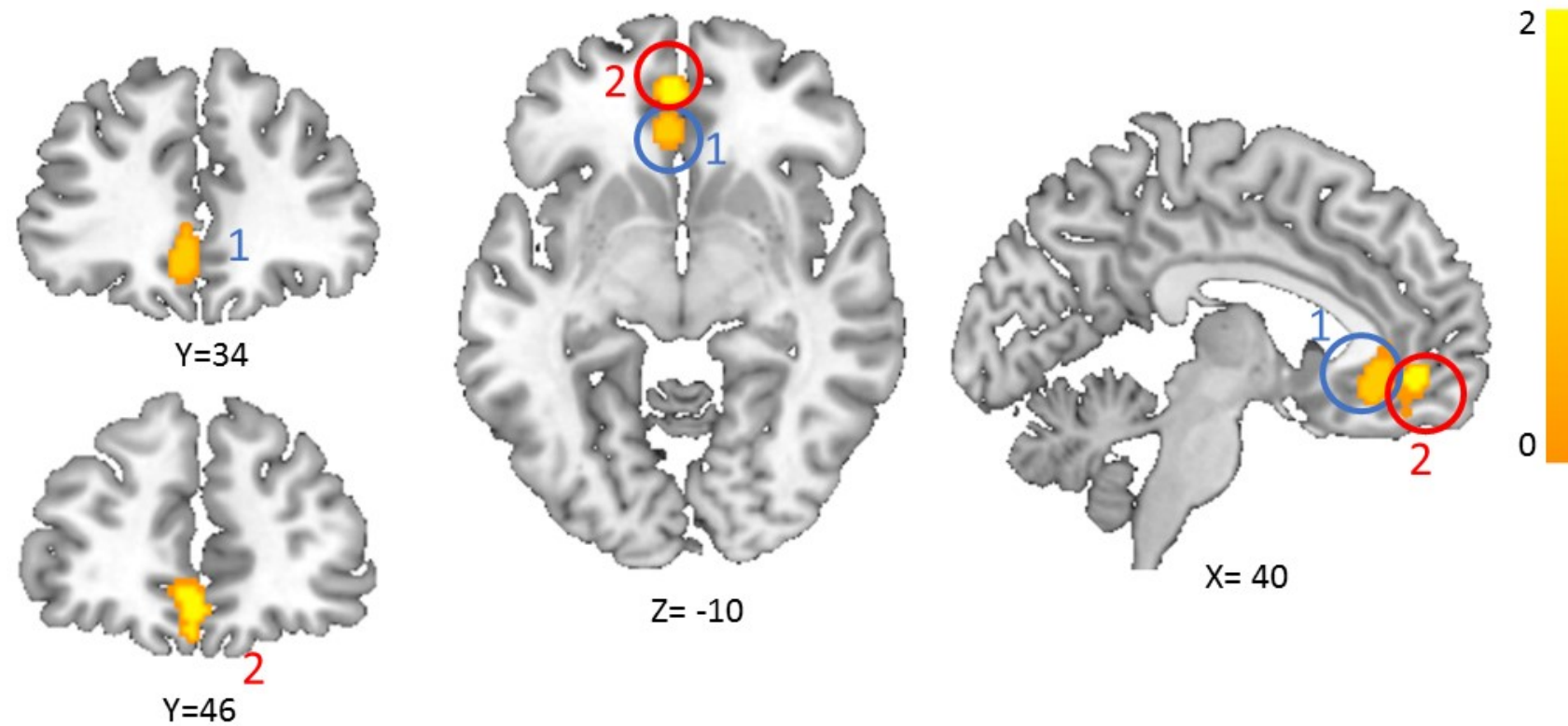
integration information in higher level cognitive processes and working memory :
problem-solving, planning, reasoning and working memory

HC > BD

No activation

Lenartowicz et al., J. Cogn. Neurosci, 2005; 17, pp. 026-1042

Hyperactivation working memory



1 = left Anterior cingulate
2 = left orbitofrontal cortex

Discussion

Emotion processing:

Hyperactivation: hippocampus, amygdala, temporal pole

“Oversensitive” but **dysfunctional** to identify emotional stimuli and the production of affective states.

Hypoactivation: IFG

Does not inhibit > difficulties to regulate emotions

Discussion

Reward processing:

Hyperactivation: OFC

“Oversensitive” for reward and pleasure cues.

dysregulations in motivational functions are involved in the reward system and may explain the mood shifts and lability in BD patients

OFC is involved in the reward system of the hypersensitivity model > Supports BAS theory for bipolar disorder.

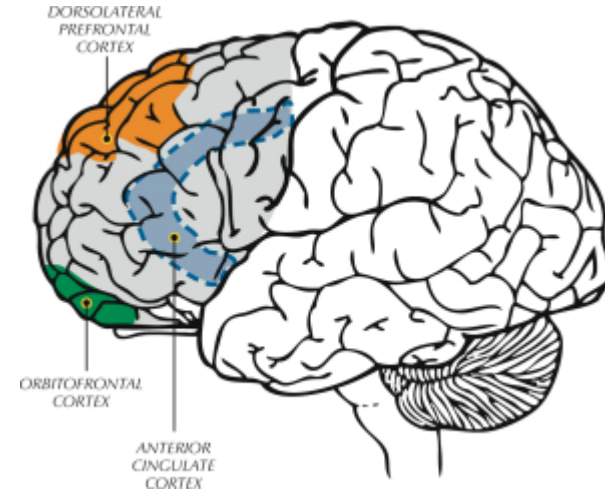
Discussion

Working memory:

Hyperactivation: ACC and OFC

ACC and OFC: part of executive functions.

“The "cortical inefficiency" model”: greater neuronal activation is required despite achieving lower performance



Conclusion

- Disturbances in different brain areas: cognitive functions
- Most of regions are part of the so-called fronto-limbic network which is hypothesized to be affected in bipolar disorder as a result of the expression of bipolar candidate genes.

Questions

Thanks to Dr. Max de Leeuw!
Thank you for your attention!

Questions?