Dissecting the pathological circuit substrates of reward and anhedonia subdomains

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INTRODUCTION

Patients with major depressive disorder (MDD) exhibit diverse sets of symptoms that correspond to alteration of different brain networks.

Anhedonia, or the loss of pleasure experience, is a critical pathological affective dimension associated with maladaptive changes to the *reward circuitry* and comprised of clinically-relevant subdomains : e.g. consummatory ('liking') and anticipatory ('wanting') anhedonia.

The *reward network* includes the **nucleus accumbens** (NAcc), considered as major hedonic hotspot, influenced by the dopaminergic circuit of the **ventral tegmental area** (VTA). The **hippocampus** provides contextual information to the NAcc, while the **amygdala** conveys affective influence.

Neuroimaging showed an abnormal cooperation in depression between these subcortical areas, limbic and cortical regions during reward processing (Fossati et al, 2015). In this study, we aim to characterize reward circuit dynamics in patients with MDD by understanding how functional connectivity (FC) patterns of critical hubs explain reward-specific dimensions: anhedonia subtypes and reward constructs extracted from behavior.

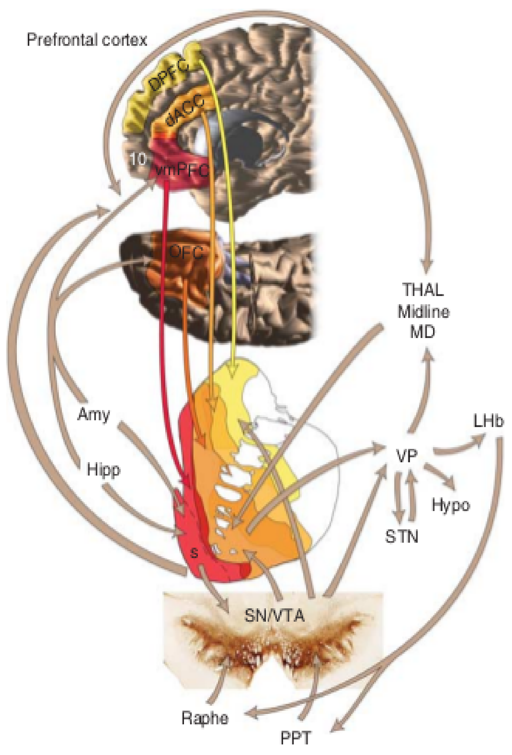


Figure 1. *Incentive salience network (Haber and Knutson,2010)*

METHODS

1. The populations

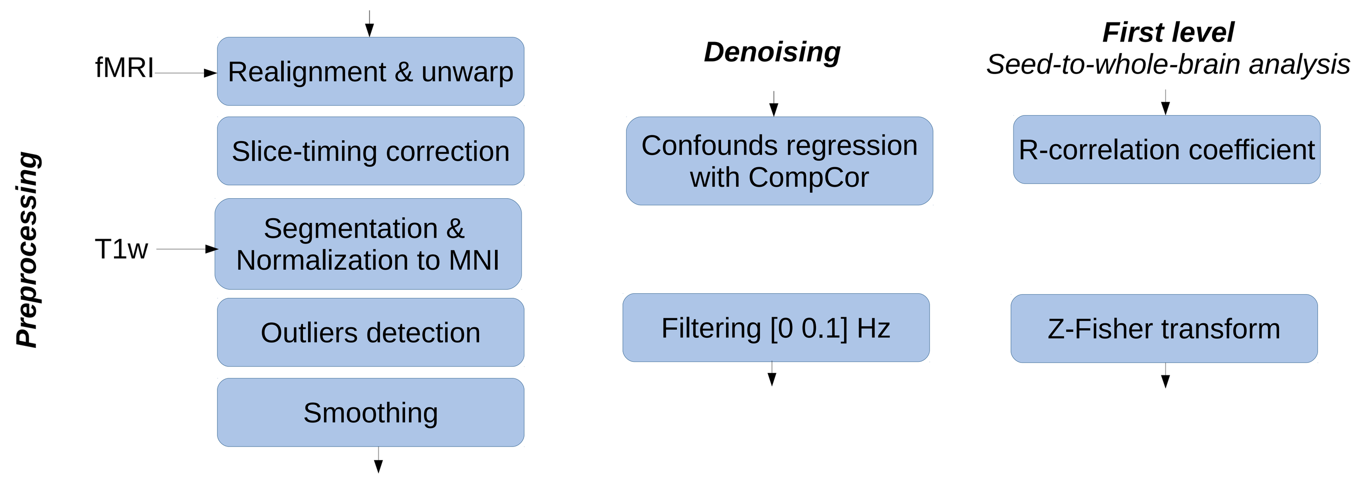
67unipolar patients were included in the study. Clinical measures were reported: the Snaith-Hamilton Pleasure Scale (SHAPS) (high score is associated with more anhedonia), the Temporal Experience of Pleasure Scale (TEPS) as a measure of anhedonia, divided into its anticipatory (ANT) and consummatory (CON) components (high score means less anhedonia).

2. MRI acquistion

All subjects were scanned with the same sequences :
- T1w : TR = 2530 ms, TE = 1.69 ms, TI = 1100 ms, slice thickness = 1mm,
- resting-state fMRI: TR = 3000 ms, TE = 30 ms, flip angle = 85°, slice thickness = 3mm.

MRI processing pipeline

SPM12-based CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012)



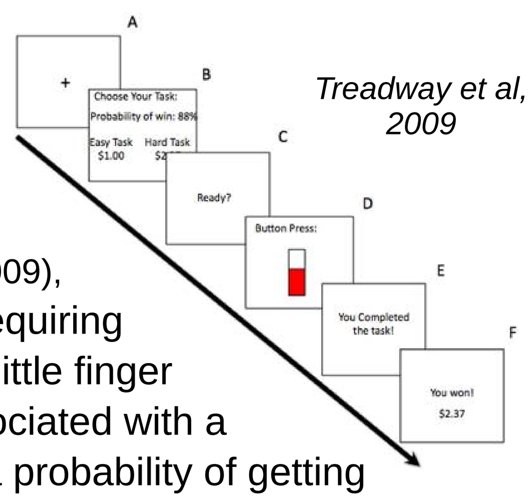
Seeds

The VTA seeds were drawn manually, whereas the NAcc, amygdala and hippocampus come from the Harvard-Oxford atlas (Makris et al 2006 ; Frazier et al, 2005 ; Desikian et al, 2006 ; Goldstein et al, 2007).

Reward tasks

Effort Expenditure Reward Task

59 patients completed the effort task. They were asked to fill a bar by pressing on a keyboard with one finger (Treadway et al, 2009), for the easy task, using their index dominant index finger and requiring 30 presses within 7s, or the hard task, with their non-dominant little finger requiring to press 100 times within 21s. The hard task was associated with a reward within 1.24-4.30$, the easy one with a 1$ reward, with a probability of getting it either 12%, 50% or 88%.

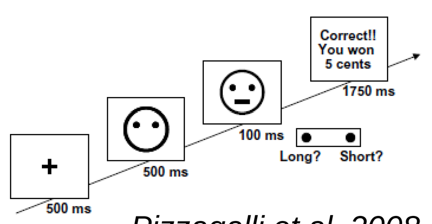


Treadway et al, 2009

We classified the patients into three groups according to which model best fitted their behavior: in the Subjective Value (SV) group, participants took into account reward probability and magnitude to make their choice, in the Reward Magnitude (RM) group just the magnitude, and others were classified in the Bias group (Cooper et al, 2019). We assessed the FC differences between groups with a one-way ANCOVA controlling for age and gender.

The Probabilistic Reward Task

57 patients performed the Probabilistic Reward Task (PRT) (Pizzagalli et al, 2008). They had to discriminate smiley faces with either long (13 mm) or short mouths (11.5mm). The correct identification of one stimulus was associated with a higher reward, without their knowledge.



Pizzagalli et al, 2008

The task is divided in two blocks : during the first one they were supposed to learn the bias, that would be learnt during block 2. The sum of the biases over the two blocks was integrated in a GLM model to assess its FC correlates, regressing out age and gender.

Statistical analysis

The effect of anhedonia dimensions and the task features on the FC were computed using a general linear model, regressing out age and gender as covariates of non-interest. Clusters significance on the whole-brain was assessed using a height threshold of p<0.001 and a cluster threshold of 0.05 FDR-corrected. Significant clusters were characterized anatomically with the Harvard-Oxford atlas and functionally with the YEO networks (Yeo et al, 2011).

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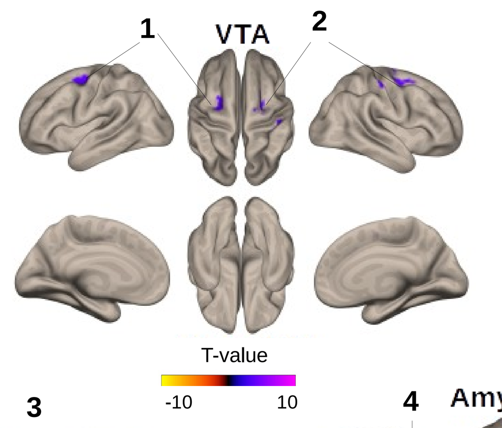
RESULTS

1. Correlations with anticipatory anhedonia (TEPS-ANT)

1

Anatomical parcellation	Functional parcellation
39% in Superior Frontal gyrus (Left)	88% in Dorsal Attention
17% in Precentral Gyrus (Left)	

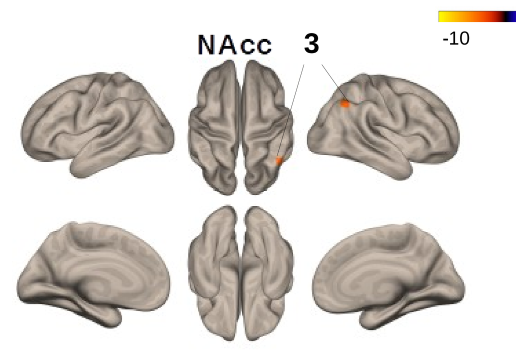


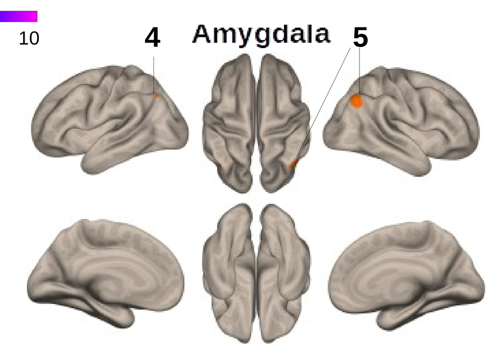
2

Anatomical parcellation	Functional parcellation
28% in Precentral Gyrus (Right)	36% in Dorsal Attention
21% in Superior Frontal Gyrus (Right)	19% in Somatomotor

3

Anatomical parcellation	Functional parcellation
71% in Lateral Occipital Cortex (Right)	83% in DMN
25% in Angular Gyrus (Right)	17% in FPN





4

Anatomical parcellation	Functional parcellation
56% in Lateral Occipital Cortex (Left)	45% in DMN

5

Anatomical parcellation	Functional parcellation
98% in Lateral Occipital Cortex (Right)	64% in DMN
	20% in FPN

Figure 3. *T-values of the clusters significantly correlating with TEPS-ANT and their characterization using the YEO networks (function) and the Harvard-Oxford atlas (anatomy).*

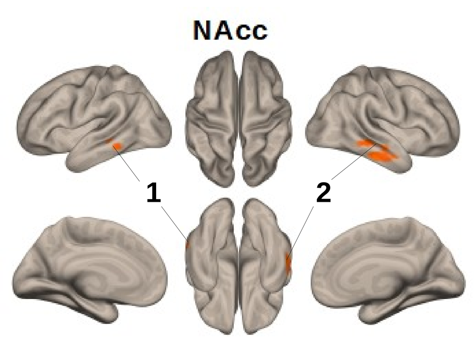
2. Correlations with consummatory anhedonia (TEPS-CON)

1

Anatomical parcellation	Functional parcellation
36% in Middle Temporal Gyrus, posterior (Left)	58% in DMN
9% in Inferior Temporal Gyrus, posterior (Left)	9% in FPN

2

Anatomical parcellation	Functional parcellation
35% in Middle Temporal Gyrus, posterior (Right)	44% in DMN
13% in Inferior Temporal Gyrus, posterior (Right)	24% in FPN



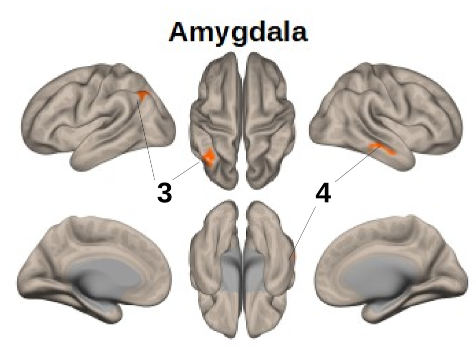


Figure 4. *T-values of the clusters significantly correlating with TEPS-CON.*

3

Anatomical parcellation	Functional parcellatin
74% in Lateral Occipital Cortex, superior (Left)	64% in DMN
6% in Angular Gyrus (Left)	13% in FPN

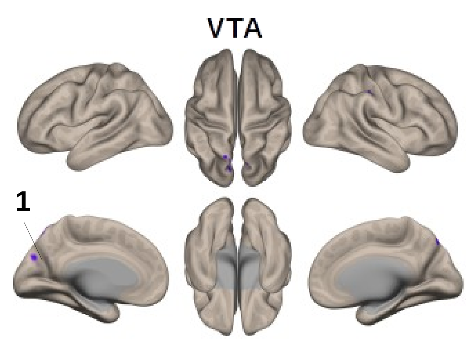
4

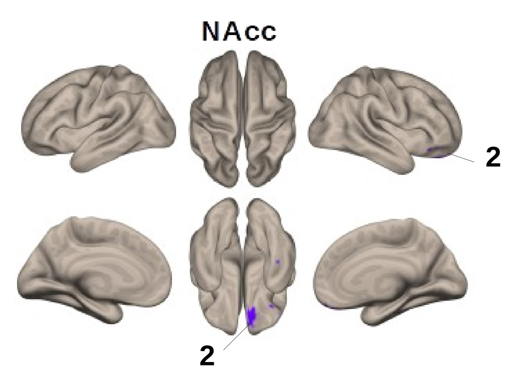
Anatomical parcellation	Functional parcellation
77% in Middle Temporal Gyrus, posterior (Right)	76% in DMN
7% in Middle Temporal Gyrus, anterior (Right)	13% in FPN

3. Differences between TEPS-ANT and TEPS-CON

1

Anatomical parcellation	Functional parcellatin
56% in Cuneal Cortex (Left)	55% in Visual
44% in Precuneus (Left)	25% in FPN





2

Anatomical parcellation	Functional parcellatin
59% in Frontal Pole (Right)	81% in Limbic
17% in Frontal Medial Cortex	9% in DMN

Figure 5. *T-values of the clusters for which TEPS-ANT > TEPS-CON was significant.*

4. Anhedonia results summary

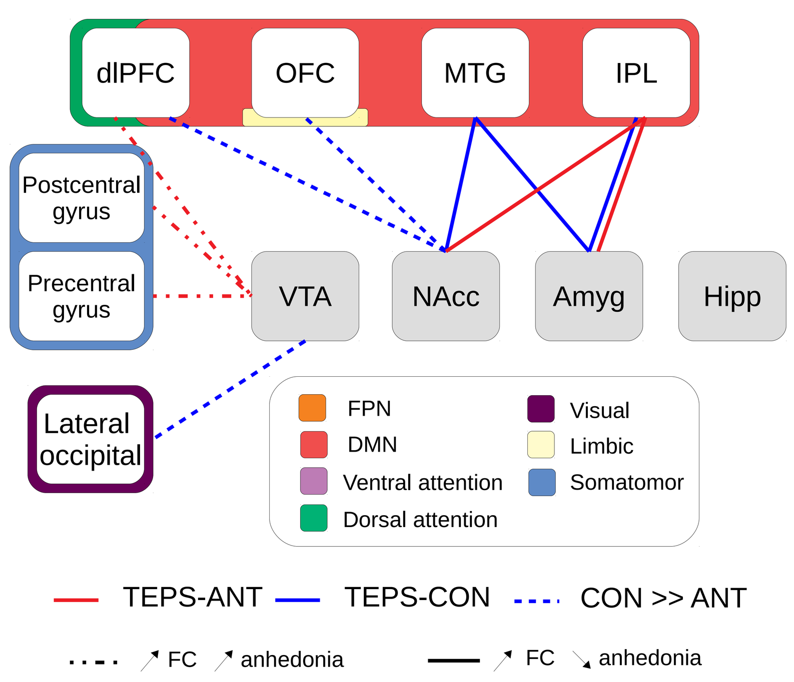


Figure 6. *Summary of the significant results between the four seeds and areas gathered by networks (YEO).*

FC between the NAcc and the amygdala seeds and **Default-Mode Network (DMN)** nodes were associated with less anticipatory and consummatory anhedonia (areas in the middle temporal gyrus and inferior parietal lobule).

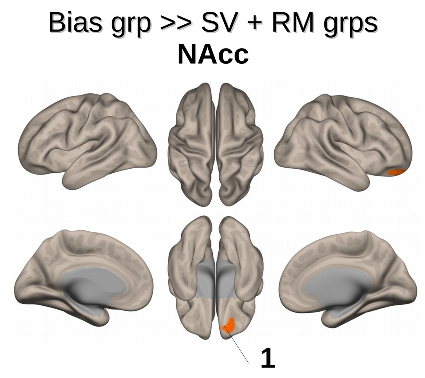
FC between the VTA, **somatomotor** and **dorsal attention** areas correlated with more anhedonia.

Consummatory was dissociated from anticipatory anhedonia in **limbic** and **visual** areas.

5. The Effort Expenditure Reward Task

Groups statistics:
- 63 % in the SV group
- 7 % in the RM group
- 31 % in the Bias group

These groups did not significantly differ in anhedonia scores (SHAPS, TEPS) or age.
Due to the discrepant number, the SV and RM groups were put together and compared to the Bias group.

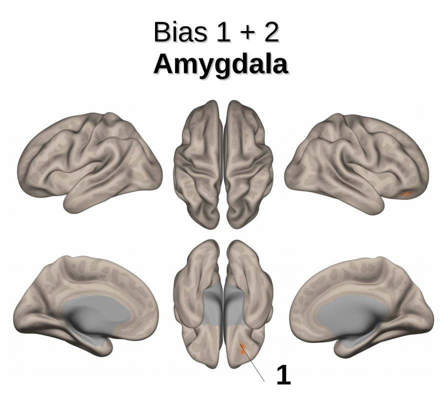


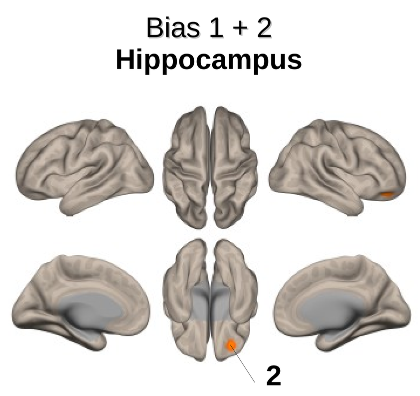
1

Anatomical parcellation	Functional parcellation
88% in Frontal Pole (Right)	36% in FPN
	27% in Limbic

6. The Probabilistic Reward Task

No correlates of Bias 2-1 but of the Bias 1+2 (less clear measure of learning).





1

Anatomical parcellation	Functional parcellation
28% in Frontal Pole (Right)	29% in FPN

2

Anatomical parcellation	Functional parcellation
69% in Frontal Pole (Right)	18% in FPN

CONCLUSIONS

We found that more FC between reward structures and *high-order networks*, i.e. the DMN at the interplay with the FPN, correlated with less anhedonia. A DMN less centered on itself can thus be associated with less anhedonic symptoms.

Visual, *limbic*, *dorsal attention* areas preferentially associated with consummatory than anticipatory anhedonia, and logically rather associated with the *immediate pleasure experience*.

Behavioral tasks highlighted the role of a *FPN-limbic area* in distinguishing types of behavior in the effort task, and in integrating reward bias in the learning task.