Habenular nuclei in different phases of Major Depressive Disorder: an MRi volumetric study

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Introduction

Habenular nucleus (HbN) is an epithalamic structure involved in stress-response, anxiety and reward-processing. It receives frontolimbic and hippocampal afferences and also projects inhibitory fibers to the brainstem monoaminergic nuclei, thus it might play an important role in the pathophysiology of Major Depressive Disorder (MDD)[1].

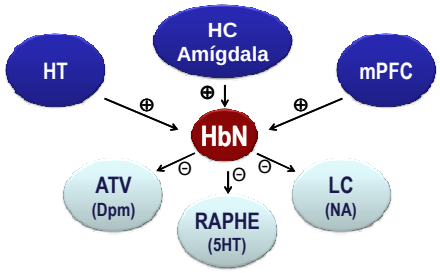

Fig. 1: Habenular connections (extracted from [2])
HT:Hipothalamus, HC: Hipocampus, mPFC: Medial Prefrontal Cortex, VTA: Ventrotegmental area, LC: Locus Coeruleus, Dpm: Dopamine, 5HT: Serotonin, NA: Noradrenalin.

Prior studies[1,2,3] have reported functional and volumetric abnormalities in MDD, however, habenular volume has been hardly compared between different stages of depressive disease leaving apart processes related with chronicity and treatment resistance.

We **aimed** to investigate whether habenular volume differed between patients with MDD in distinct stages of the illness and healthy controls. We hypothesized that chronic/treatment-resistant depression would associate smaller habenular volumes.

Methods

Sample was composed by 61 outpatients with MDD (DSM-IV) in different stages of illness and 34 healthy controls. All participants were right-handed and groups were comparable in age, sex and educational level (Table).

	Healthy Controls (n=34)	First Episode MDD (n=21)	Remitted-Recurrent MDD (n=20)	Chronic MDD (n=20)	F/χ^2	p
Age (years)	47,5	44,4	47,1	48,8	1,22	0,31
Gender (M/F)	11/25	8/14	2/18	4/17	4,87	0,18
TIV (cm^3)	1119,4	1154,1	1134,5	1084,8	0,90	0,44
HDRS§	2,0	15,5	4,1	20,8	92,64	<0,01
Age at onset (years)†	--	43,5	29,8	26,3	23,81	<0,01
Duration (months)‡	--	5,6	206,8	275,0	38,16	<0,01
Medication Load◊	--	2,6	2,8	4,9	11,47	<0,01

There were expected significant differences according to the study design:
§Chron>FE>Rem-Rec=HC / †Chron=Rem-Rec<FE / ‡FE<Rem-Rec=Chron / ◊Chron>Rem-Rec=FE

M/F= Male/Female; HDRS=Hamilton Depression Rating Scale; TIV=Total Intracranial Volume

High-resolution 3D-MPRAGE images were acquired on a **3T** *Philips Achieva* **MR scanner** with 8 receive-channel head-coil (TR=6.7ms;TE=3.2ms;170 slices; Voxel size=0.89x0.89x1.2mm; FOV=256x256x204mm).

HbN were **manually delineated** (*itk-SNAP 2.4*) by two researchers blinded to clinical data. Inter-rater kappa coefficients were 0.83 (p=0.006) and 0.8 (p=0.01) for right and left habenula, respectively. Total, grey matter (GM) and white matter (WM) habenular volumes were calculated for each participant (*Matlab-SPM8*).

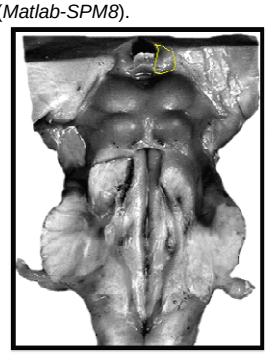

Fig. 2: Posterior view of Brain Stem
Right Habenula, outlined in yellow

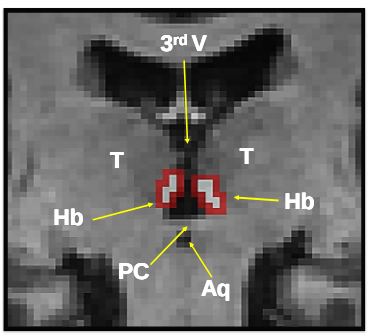

Fig. 3: Coronal MRi section of the Habenula
Hb=Habenula, PC=Posterior commissure, Aq=aqueduct, T=Thalamus, 3rd V=3rd Ventricle

Results

Total habenular volume did not show significant differences among groups.

A **significant group effect** was observed in **right habenular WM volume** (MANOVA: F= 3,199; df=3,91; p=0.027), but not for the rest of comparisons. Post-hoc comparisons showed that patients with a **first-episode had higher WM volume** in the **right HbN** as compared to healthy controls (p=0.007)* and to chronic patients (p=0.015)**. Similar findings were seen for the left HbN, but the differences did not reach statistical significance (Fig. 4).

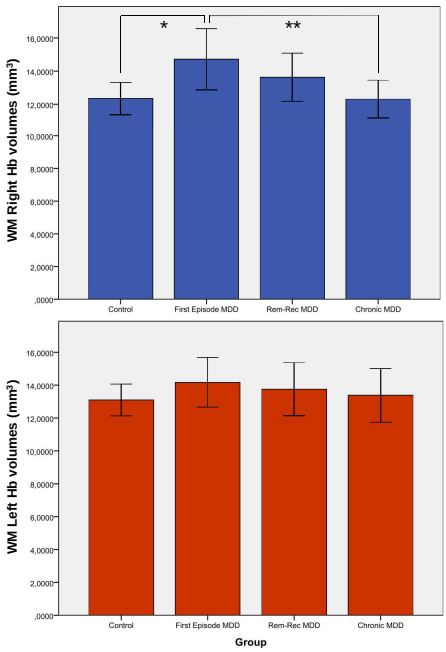

Fig. 4: Habenular White Matter (WM) volume comparison
Patients with a first-episode MDD showed higher right volumes than healthy controls and than patients with chronic MDD (↑ of **19.3%** and **19,6%**, respectively)

Conclusions

- Our findings of abnormalities in WM volume provide some evidence for the **potential involvement of the habenula in MDD**.
- We observed **higher habenular WM volumes** in patients with a **first-episode** than in healthy controls and patients with chronic/treatment-resistance MDD.
- This WM hypertrophy could be related to the habenular hyperactivity described among patients with depression by functional MRi studies[2] and might be part of the **neural substrate** of MDD **in early stages**.
- The smaller WM volumes observed in later phases of the illness, especially in chronic patients, suggest that changes in WM volumes within this structure might play a **role in the treatment response**. In fact, HbN has been targeted for Deep Brain Stimulation in treatment-resistant MDD[1].
- **Limitations:**
  - Cross-sectional design: is small WM habenular volume a vulnerability marker for treatment-resistance? Would a progressive atrophy occur along the course of the illness (perhaps due to an overuse of the structure)?
  - Patients were on medication.
  - HbN is a little structure highly attached to surrounding nuclei, which makes it more difficult to find further potential differences (specially in gray matter).

References

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No potential conflict of interest