EXPLORING THE CENTRAL EFFECT OF ANTI CGRP-MONOCLONAL ANTIBODIES IN MIGRAINE PATIENTS: A RESTING-STATE FUNCTIONAL MRI STUDY

Federica Genovese[1,2,3], Roberta Messina[1,2,3], Ilaria Cetta[1,2,3], Alessandro Visentini[1,2,3], Laura Zanandrea[2,3], Bruno Colombo[2], Massimo Filippi[1,2,3]

1. Neuroimaging Research Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy. 2. Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy. 3. Vita-Salute San Raffaele University, Milan, Italy.

INTRODUCTION and AIMS

- Previous MRI studies considered mainly brain changes over time in patient treated with anti-CGRP mAb. [1,2] Only two MRI randomized controlled trials (RCTs) have compared the effects of mAbs with placebo. [3,4]
- Evidence showed that erenumab modulates brain networks involved in migraine (e.g., thalamus, cerebellum, periaqueductal gray (PAG)) and that such changes are linked to clinical improvement. [3]
- Direct comparisons between treated and untreated patients are still lacking. To address this gap, we used resting state functional MRI (RS fMRI) to compare mAbs-treated (*mAbs group*), untreated (*non-mAbs group*) patients and healthy controls (HC). We also evaluated associations between drug-induced changes and clinical response.

METHODS

- We conducted a prospective, single-center, longitudinal, observational cohort study, including 48 migraine patients: 37 mAbs (44% receptor-targeting, 56% ligand-targeting), 11 non-mAbs and 33 matched HC.

Figure 1. Study design. Legend: assessment of questionnaires; the headache diary; the adverse events; the 3T MRI scan; and the treatment with mAbs

- Clinical and MRI evaluations were performed at baseline and after three and twelve months (**Fig. 1**). HC were assessed at a single time-point
- **Clinical data:** monthly headache days (MHDs), monthly migraine days (MMD), acute medication use days (AMD) and pills (AMP), pain intensity, patients' disability, headache impact, and presence of cutaneous allodynia.
- **3-Tesla MRI scan:** RS fMRI, 3D T1-weighted, T2-weighted and FLAIR sequences at each follow-up.

ANALYSIS

- **Clinical data**: Normality was tested with Kolmogorov-Smirnov and Shapiro-Wilk tests. Depending on distribution, Mann-Whitney, Fisher, or t-tests were applied to compare groups. Longitudinal changes were evaluated with generalized estimating equations (GEE) and full factorial models. Significance was set at p<0.05.
- **RS Functional Connectivity** (RS FC) was analyzed using a seed-to-voxel approach based on 11 regions of interest (ROIs): the bilateral cerebellum, PAG, pons, thalamus, hypothalamus, and spinal trigeminal nucleus (STN) (Fig. 2). Whole-brain voxel-wise analyses were performed using general linear models in SPM12. Results were thresholded at p<0.004 FWE- and Bonferroni-corrected.

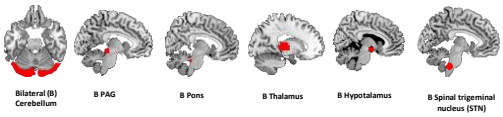


Figure 2. Selected ROIs.

RESULTS

	Healthy Controls	Migraine Patients		mAb *vs* non-mAb
	(HC) (n = 33)	mAbs Group (n = 37)	non-mAbs Group (n = 11)	*p value*
Age	38.2 (15.30)	49 (12.35)	39 (15.8)	0.980
Sex (F/M)	23 (70%) - 10 (30%)	27 (73%) - 10 (27%)	9 (82%) - 2 (18%)	0.951
MHD	-	19 (8.2)	9 (8.7)	**0.002**
MMD	-	18 (8.1)	9 (8.7)	**0.003**
AMP	-	22 (22.4)	10 (12.9)	**0.038**
AMD	-	16 (9.8)	8 (7.1)	**0.016**
MIDAS score	-	73 (67)	29 (37.8)	**0.015**
HIT-6 score	-	65 (5)	60 (10.5)	0.099
NRS score	-	8 (1.3)	7 (1.6)	**0.044**
ASC-12 score	-	6 (5)	4 (3.8)	0.282

Table 1. Clinical characteristics (mean, SD) of subjects enrolled in the study and comparisons between groups of patients at baseline.

mAbs vs HC at baseline (Fig. 3)

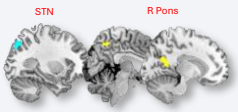


Fig. 3. ↓ RS FC between the STN and the left (L) precuneus (blue); ↑ RS FC between right (R) pons and the L precuneus and calcarine cortex (yellow).

Non-mAbs vs HC at baseline (Fig. 4)

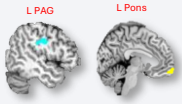


Fig 4. ↓ RS FC between the L PAG and the L supramarginal gyrus (blue); ↑ RS FC between the L pons and the ipsilateral orbitofrontal cortex (yellow).

mAbs *vs* non-mAbs groups at baseline (Fig. 5).

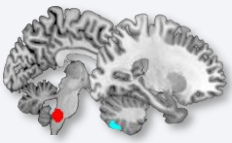
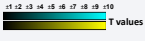


Fig. 5. ↓ RS-FC between L STN – L Cerebellum in mAbs *vs* non-mAbs groups at baseline

mAbs *vs* non-mAbs groups at 3 months (Fig. 6).

Fig .6. ↑ RS FC between L STN – L Cerebellum after 3 months in mAbs *vs* non-mAbs



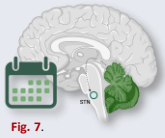


Fig. 7.

Clinical correlations (mAbs *vs* non-mAbs) (Fig. 7).

- At baseline, ↓ L STN–cerebellum RS FC correlated with higher MHD, MMD, AMP, AMD.
- At three months, the ↑ of RS FC between L STN–cerebellum correlated with clinical improvement (p<0.05)

CONCLUSIONS

- **Patients eligible for mAbs** showed **alterations in pain networks**, suggesting a **more severe migraine phenotype**.
- Compared to untreated, **patients treated with mAbs** exhibited **greater clinical improvement** and **reorganization within the STN network**, supporting **central effects of mAbs beyond the natural disease course**.

REFERENCES

1. Ziegeler et al., Neurology. 2020
2. Schwedt et al., J Headache Pain 2022
3. Filippi et al., J Neurol 2023
4. Basedau et al., J Headache Pain 20225