



Hypothalamic connectivity strength is decreasing with polygenic risk in migraine without aura patients

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ABSTRACT

Migraine is a heritable primary headache disorder which pathophysiology involves altered hypothalamic activity during migraine attacks. To explore the relationship between hypothalamic functional connectivity (HYPT FC) and genetic predisposition characterised by polygenic risk scores (PRS), in migraine, this research examines two types of PRS: one based on all migraine patients (PRS_{ALL}) regardless of their time of diagnosis and other disorders, and another on migraine-first patients (PRS_{FIRST}), whose first diagnosed condition was migraine in their lifetime. In an independent sample of 35 migraine patients and 38 healthy controls, using resting-state functional magnetic resonance (rfMRI, 3T) brain imaging, the study reveals significant hypoconnectivity of hypothalamus with the two investigated PRS scores but with different brain areas. While weakened hypothalamic connections in relations with PRS_{ALL} highlight regions involved in pain modulation, correlation with PRS_{FIRST} emphasizes decreased connections with sensory and integrative brain areas, suggesting a link between migraine-first genetic risk and cortical hyperexcitability. Our results demonstrate that the polygenic risk of different migraine subgroups may advance our insight into the specific genetic and neural underpinnings of migraine, advancing precision medicine approaches in this field.

1. Introduction

Migraine is a prevalent neurovascular disorder that significantly impacts both individuals and society (Headache Classification Committee of the International Headache Society (IHS), 2018). It affects approximately 15 % of the global population and is typically marked by recurring, often severely disabling episodes of intense headache, commonly on one side of the head (Steiner and Stovner, 2023). One of its main characteristics is that it usually worsens with movement and

can be accompanied by nausea, vomiting, photophobia, phonophobia, as well as various physical and mental symptoms. Migraine attacks can last from 4 up to 72 hours and have a profound effect on daily activities and quality of life (Headache Classification Committee of the International Headache Society (IHS), 2018; Magyar et al., 2022).

In the background of the variable symptoms, lies a complex environmental, genetic and neurological interplay (Khan et al., 2021; Ferrari et al., 2022). The pathomechanism of migraine has many aspects, all of which need to be unravelled. A number of well-studied mechanisms

Abbreviations: CGRP, calcitonin gene-related peptide; CSF, cerebrospinal fluid; EPI, echo-planar imaging; FC, Functional connectivity; fMRI, Functional Magnetic Resonance Imaging; FOV, field of view; GWAS, Genome-Wide Association Studies; HYPT, Hypothalamus; ICHD-3, International Classification of Headache Disorders; MNI, Montreal Neurological Institute; PAG, Periaqueductal grey; PRS, Polygenic Risk Score; PRS_{ALL}, All migraine Polygenic Risk Score; PRS_{FIRST}, Migraine-first Polygenic Risk Score; rfMRI, Resting-state Functional Magnetic Resonance Imaging; SNP, single nucleotide polymorphism; TE, echo time; TFE, turbo field echo; TR, repetition time.

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have been identified as potential contributors to migraine, including cortical spreading depolarisation, trigeminovascular activation, central and peripheral sensitisation, the role of calcitonin gene-related peptide (CGRP), the role of intracranial blood vessels, and last but not least the role of the brainstem and genetics (Ferrari et al., 2022). The present study investigates the role of genetics and the hypothalamus (HYPT), including the importance of its functional connections (FC).

Family and twin studies, supported by subsequent population genetics observations, have confirmed that genetics plays a significant role in the pathogenesis of common, non-monogenic migraines. Genetic factors influence the clinical presentation of migraines considerably, accounting for 35–60 % of heritability (Honkasalo et al., 1995; Russell and Olesen, 1995; Grangeon et al., 2023), though they cannot fully explain the manifestation of migraines. Other factors, such as sex, age, hormonal fluctuations, stress, and various additional influences, also contribute to the increased risk of migraines.

A modern approach to uncovering genetic contributors to diseases is genome-wide association studies (GWAS) (Gormley et al., 2016; Choquet et al., 2021; Hautakangas et al., 2022). This method analyses millions of single nucleotide polymorphisms (SNPs) across large cohorts of affected individuals and non-headache controls. SNPs represent variations at a single DNA base pair that differ among individuals. While the impact of one SNP on disease risk is minimal, the cumulative effect of multiple disease-associated SNPs can significantly increase the overall risk. This cumulative genetic predisposition is quantified using a polygenic risk score (PRS) (Cader, 2020; Juhasz et al., 2023). Evidence supports that PRS provides biological validation for the International Classification of Headache Disorders (ICHD-3) and is associated with the severity of migraine burden (Häppölä et al., 2022). These findings underline the role of PRS, as an important genetic biomarker for migraine susceptibility and its clinical manifestations.

However, it is important to investigate how this genetic risk translates into migraine susceptibility. Previous functional magnetic resonance (fMRI) brain imaging studies have shown strong evidence of SNP heritability in brain imaging biomarkers (Elliott et al., 2018). These genetically influenced biomarkers reflect structural and functional variations in the brain. One example for these functional measures is resting-state fMRI, which quantifies spontaneous fluctuations within individual brain regions, and apparent connectivity between brain regions based on co-activity rather than structural tracts (Stephen Smith et al., 2025; Elliott et al., 2018).

Regarding migraine, functional neuroimaging studies suggest that the hypothalamus, midbrain, and limbic areas play a central role in the earliest (premonitory) phase of migraine attacks (Karsan and Goadsby, 2018). Altered hypothalamic activity has been observed up to 24 hours before the headache onset using positron emission tomography (PET) (Maniyar et al., 2014) and fMRI (Schulte and May 2016), during nitroglycerin-triggered migraine attacks (Maniyar et al., 2014; Karsan et al., 2018), trigeminal nociceptive stimulation with ammonia (Schulte et al., 2017b), as well as spontaneous migraine headaches from 24 to 48 hours before the attack (Schulte and May 2016; Schulte et al., 2020). They found an early activation of the HYPT during the premonitory phase of migraine, suggesting that it may be involved in regulating early symptoms (like yawning, increased appetite, thirst, and fatigue) (Schulte and May 2016; Schulte et al., 2017b, 2020; Gollion et al., 2022; Messina et al., 2022). Furthermore, they observed altered functional coupling between the HYPT, spinal trigeminal nuclei, and dorsal pons, visual cortex and limbic system prior to the attack, supporting the role of brainstem-hypothalamic interactions in migraine pathophysiology (Schulte and May 2016; Stankewitz et al., 2021; Gollion et al., 2022; Karsan and Goadsby, 2023). Focusing on interictal (migraine-free) intervals, increased connectivity between the HYPT and frontal pain-processing areas has been noted, while decreased connectivity is seen with visual-processing regions (Messina et al., 2022). HYPT connections with visual cortical areas impact spatial visual and multisensory processing and circadian rhythm regulation (Miana Gabriela et al.,

2018).

Based on the above observations in this study, we investigated whether interictal resting-state HYPT FC in migraine is associated with the PRS of migraine. We performed statistical analyses to compare different polygenic risk scores and evaluate their respective relationships with resting-state fMRI connectivity patterns. One PRS was calculated by a GWAS (Gormley et al., 2016) involving all migraine patients who reported having migraines or were diagnosed with them, while another was based on a GWAS by Torok et al. (Torok et al., 2024), involving migraine-first patients whose first diagnosis in their lifetime was migraine. This distinction between migraine-first and all migraine patients is important because of the potential comorbidity of migraine with other disorders, such as major depression (Minen et al., 2016; Baksa et al., 2017; Zhang et al., 2019). Studies suggest that the presence of comorbid depression can affect the relevance and impact of genetic findings related to migraine and indicate that heritability estimates may vary depending on the presence of comorbid depression (Minen et al., 2016; Baksa et al., 2017; Anttila et al., 2018; Zhang et al., 2019; Grangeon et al., 2023). These findings support the idea that migraine-first patients may have a more distinct genetic profile. To our knowledge, no other studies investigating the potential relationship between PRS and fMRI connectivity in migraine. Thus our study presents a unique way to understanding the mechanism that translate genetic risk to migraine.

2. Methods

2.1. Participants

The study included 35 patients with episodic migraine without aura and 38 non-migraine, healthy controls. Prior to the study, participants' mental health was assessed through an interview with trained researchers, using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). None of the participants had any other internal, neurological, or psychiatric disorders. We also implemented several controls for lifestyle-related confounders. Participants were instructed to abstain from alcohol for 72 hours prior to the fMRI scan, and to avoid caffeine and smoking for at least 4 hours before scanning. They did not use any migraine preventive medications for at least 3 months prior to the study, and remained medication-free during the examination period, except contraceptives. Moreover, they have not used any acute pain medications for at least 48 hours prior to the fMRI scan. The diagnosis of episodic migraine without aura was confirmed by headache specialists based on the diagnostic criteria of the ICHD-3 (Headache Classification Committee of the International Headache Society (IHS), 2018). The number of headache days per month in migraine patients did not exceed the threshold for chronic migraine (≥ 15 days), and they did not experience visual, sensory, or other aura-related symptoms.

The study protocol received approval from the Scientific and Research Ethics Committee of the Medical Research Council (Budapest, Hungary, 23,609–1/2011-EKU, 23,421–1/2015-EKU). The entire study was conducted in accordance with the Declaration of Helsinki, with the informed consent obtained from all participants.

2.2. Imaging: resting-state functional magnetic resonance imaging (fMRI)

2.2.1. Data acquisition and preprocessing

Participants underwent a 6-minute resting-state fMRI, during which they were instructed to close their eyes, relax but remain awake. Prior to the resting state session, a T1-weighted 3D turbo field echo (TFE) sequence with a resolution of $1 \times 1 \times 1 \text{ mm}^3$ was used to acquire high-resolution structural images, using a 3T MRI scanner (Achieva 3T, Philips Medical System). Imaging data were collected with the following parameters: repetition time (TR)=2,500 ms, echo time (TE)=30 ms, field of view (FOV)= $240 \times 240 \text{ mm}^2$, and resolution of $3 \times 3 \times 3 \text{ mm}^3$, using a T2*-weighted echo-planar imaging (EPI) pulse sequence.

The images were preprocessed as described by Gecse et al. (Gecse et al., 2021, 2022) to obtain analysable data. T1-weighted images were processed using FreeSurfer version 5.3 (Harvard University) (Fujihara and Takei, 2018) for non-uniform intensity correction, intensity normalization, and structural segmentation. White matter, grey matter, and cerebrospinal fluid (CSF) were separated, and brain volume was extracted. Spatial normalization was performed with ANTs, aligning brain volumes to a 2 mm isotropic MNI152 template (Dadar et al., 2021).

The first four volumes were removed from fMRI scans to allow the scanner's magnetic field to stabilize. Motion correction was conducted using MCFLIRT from FSL (version 6) (Jenkinson et al., 2012), and functional images were coregistered to structural images before transformation into MNI152 space. The CompCor technique (Behzadi et al., 2007) extracted the first five principal components from white matter and CSF time series. Spatial filtering was applied using FSL SUSAN (Smith and Brady, 1997) with a 6 mm FWHM Gaussian kernel.

Motion-related signals were corrected using ICA-AROMA (Pruim et al., 2015), and 24 motion-related nuisance variables were regressed, derived from rigid body transformation parameters and the five principal components capturing noise variance (white matter and CSF) (Friston et al., 1996). Finally, temporal band-pass filtering (0.009–0.08 Hz) was applied. Further details on the processing pipeline can be found in Gecse et al. (2021), (2022).

2.2.2. Resting-State functional connectivity analysis

A seed-based connectivity analysis was conducted to generate individual connectivity maps, focusing on the FC of the HYPT. The HYPT coordinates were identified based on literature data. MNI space coordinates of the left HYPT (LHYPT): $x = -6$, $y = -6$, $z = -12$ (Schulte et al., 2017a; Dumkrieger et al., 2019). The analysis was conducted with both left and right HYPT coordinates, but only the analysis using the LHYPT coordinate yielded significant results in all analyses. After defining the seed regions, the time-averaged hypothalamic data of each subject was correlated with data from all other brain voxels using Pearson correlation. The resulting values were transformed into Z-scores using Fisher's transformation. The individual Z maps were used in second-level analyses in Statistical Parametric Mapping (SPM12) software package (implemented in Matlab 2016a (Math Works, Natick, MA)).

2.3. Polygenic risk score calculations

2.3.1. All migraine GWAS (PRS_{ALL})

In order to calculate all migraine PRS (PRS_{ALL}), Gormley et al.'s (Gormley et al., 2016) GWAS meta-analysis of migraine was utilised, in which 44 independent single nucleotide polymorphisms (SNPs) were identified that significantly associated with migraine risk ($P < 5 \times 10^{-8}$).

The primary meta-analysis was conducted using all available migraine samples from the International Headache Genetics Consortium IHGC, regardless of how participants were selected. They analysed summary statistics from 22 GWAS (23andMe, ALSPAC, ATM, B58C, DeCODE, EGCUT, Health 2000, HUNT, NFBC, NTR/NESDA, Rotterdam, Swedish Twins, Tromsø, Twins UK, WGHS, Young Finns, Danish HC, Dutch MA, Dutch MO, Finnish MA, German MA, German MO)(Gormley et al., 2016).

All datasets consisted of unrelated individuals of European descent. The case group included both individuals diagnosed with migraine by healthcare professionals and those who self-reported their condition through questionnaires (Gormley et al., 2016). In this analysis no distinction was made between migraineurs with and without aura. Patients with other medical conditions prior to, during or after their migraine diagnosis were not excluded from the analysis. A total of 59,674 people with migraine and 316,078 people without (control group) were included.

2.3.2. Migraine-first GWAS (PRS_{FIRST})

GWAS for migraine-first patients (PRS_{FIRST}) was calculated following a methodology published in a recent article by Torok et al. (Torok et al., 2024). The term migraine-first refers to individuals who are diagnosed with migraine as their initial medical condition in their lifetime.

GWAS were conducted, including a total of 199,929 individuals. Patients who had migraine as their first diagnosed condition ($N = 6,139$) were identified based on the date of their initial migraine diagnosis, and healthy controls ($N = 193,790$) were defined as individuals, with no history of migraine in their lifetime, and without any recorded diseases at the same age when the migraine-first patients received their diagnosis.

2.3.3. PRS calculations on the hungarian target sample

For the PRS calculations in the Hungarian target sample ($N = 73$) we used LDpred2 (Privé et al., 2020) (R package versions: bigsnpr v1.12.2, bigstatsr v1.5.). We calculated PRS_{ALL} and PRS_{FIRST} on the target sample, using beta values from Gormely et al. (Gormley et al., 2016) GWAS and Torok et al. (Torok et al., 2024) results.

2.4. Statical analysis

The descriptive statistics were calculated by using SPSS 29.0.1.0 (IBM Corp., Armonk, NY, USA, SPSS Statistics for Windows). Independent T-tests were used to investigate the difference in PRS_{ALL} and PRS_{FIRST} scores between migraine and control groups. We examined the effect of PRSs on hypothalamic connections using multiple regression model in Matlab 2016 (Math Works, Natick, MA, USA) using SPM12 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK; <https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). First, we investigated the effect of PRS_{ALL} and PRS_{FIRST} on HYPT connectivity in the whole population (migraine and control subjects). Then, post-hoc analyses were conducted in the migraine and control groups separately. The primary significance level was set at $p < 0.001$ with a minimum cluster size of 10 contiguous voxels. Our results survived the cluster-level correction for multiple comparisons using the recommended settings of SPM12 (https://www.fil.ion.ucl.ac.uk/spm/doc/spm12_manual.pdf) with **Family-Wise Error (FWE) correction** $p_{FWE} < 0.05$. All analyses were corrected for sex, age, and motion.

3. Results

3.1. Descriptive statistics of the investigated subjects

In our study migraine patients and healthy controls did not differ significantly in age ($U = 682.500$, $p = 0.378$) or sex ($\chi^2 = 3.223_a$, $p = 0.073$) (see Table 1). Significant differences were observed between migraine and control groups in PRS_{ALL} ($p = 0.030$) and PRS_{FIRST} ($p = 0.048$) scores. The PRS_{ALL} scores were negative in both groups,

Table 1
Descriptive statistics of our subjects. Data are expressed as mean value $\pm$ standard deviations. N: number of participants. PRS_{ALL}: Polygenic Risk Score in all migraine patients. PRS_{FIRST}: Polygenic risk score in migraine-first patients.

N	Migraineurs 35	Controls 38	Statistical test	p-value
Gender (N)	Female $N = 27$ Male $N = 8$	Female $N = 22$ Male $N = 16$	$\chi^2 = 3.223_a$	0.073
Age (years)	26.00 ± 4.595	25.21 ± 4.491	$U = 682.500$	0.378
PRS _{ALL}	-0.928 ± 0.294	-0.794 ± 0.222	$T = -2.211$	0.030
PRS _{FIRST}	0.142 ± 0.260	0.021 ± 0.255	$T = 2.015$	0.048
Age of first migraine (years)	14.09 ± 6.393			
Migraine attacks in a month	3.367 ± 3.115			

indicating that neither the migraine nor the control group carried genetic risk based on Gormley et al.'s (Gormley et al., 2016) GWAS meta-analysis. In fact this risk was significantly lower in the migraine group (see Table 1 and Fig. 1). In contrast, PRS_{FIRST} scores (calculated from genetic data of migraine patients, whose first diagnosed disorder was migraine) were significantly higher in migraine patients, predicting migraine in our population substantially better.

Fig. 1/A displays the PRS_{ALL} scores based on Gormley et al.'s (Gormley et al., 2016) GWAS meta-analysis. The PRS_{ALL} scores of migraine and control patients are in the negative range, and controls have significantly higher PRS_{ALL} scores ($p = 0.030$).

Fig. 1/B displays the PRS_{FIRST} scores based on GWAS by Torok et al.'s (Torok et al., 2024). The PRS_{FIRST} scores are distributed in both the negative and positive ranges. The PRS_{FIRST} scores in migraineurs are significantly higher ($p = 0.048$).

3.2. The effect of PRS on functional connectivity of hypothalamus

Analysing the total population (migraine and control subjects combined), a negative correlation was found between PRS scores and HYPT connectivity. Specifically, in relation to PRS_{ALL}, decreased HYPT connections were found with the anterior cingulum (a component of the limbic system), the medial superior frontal gyrus (which is implicated in self-monitoring and working memory (Luu et al., 2000; Boissgueheneuc et al., 2006)) and the medial orbitofrontal gyrus (involved in reward evaluation and receiving stimuli from olfactory and gustatory pathways (Rolls, 2017, 2019)) as PRS scores increased (Table 2, Fig. 2/A). These regions are also key component to the pain matrix and play a role in the top-down control of pain perception (Price, 2000; Tracey, 2008; Urien and Wang, 2019).

A negative correlation was found between PRS_{FIRST} and HYPT FCs with the inferior occipital gyrus, cerebellum, and fusiform gyrus (Table 3, Fig. 2/B). This suggests alterations in areas responsible for visual perception and processing, as well as sensory integrative functions (Wang et al., 2022). (Table 3).

Fig. 3.

3.3. Post-hoc analyses

3.3.1. Migraine group

When analysing the migraine group separately, we observed similar trends between the HYPT connectivity and PRS scores as in the total

Table 2
Hypothalamic connectivity in correlation with the polygenic risk score based on all migraine diagnosis (PRS_{ALL}) in the combined healthy and migraine group.

Brain Regions	p (FWE)	Cluster size (voxel)	peak T	MNI coordinates		
				x	y	z
Anterior Cingulum_L	5.761E-05	379	5.025	-6	42	2
Meidal Superior Frontal gyrus L			4.464	-12	66	8
Medial Orbitofrontal gyrus L			4.399	-10	64	-2

FWE: Familywise error correction MNI: Montreal Neurological Institute L: Left side R: Right side.

population analysis but in more extended areas.

Examining PRS_{ALL} in migraineurs we found negative correlation between PRS_{ALL} scores and HYPT connectivity with regions of the limbic system, such as the hippocampus, the anterior and posterior cingulate, as well as regions involved in reward-related decision-making, such as the medial orbitofrontal gyrus (Rolls et al., 2020). Additionally, regions associated with memory, perception, and pain responses, such as the precuneus (Borsook et al., 2015), and sensory processing regions, such as the lingual gyrus, were also impacted (Table 4, Fig. 4/A).

Investigating PRS_{FIRST} scores, negative correlation was found between PRS_{FIRST} scores and HYPT connectivity with regions responsible for visual perception, including the inferior and medial occipital gyri and the lingual gyrus, as well as the supplementary motor area (which has been shown to function as an interface between the emotional and motor system, modulating emotional perception and in fear conditioning (Dobos et al., 2021)) and the cerebellum (which presumably fulfils integrative functions in migraines (Wang et al., 2022)), and regions involved in sensory-motoric innervations, such as the paracentral gyrus (Patra et al., 2021) (Table 5., Fig. 4/B).

Fig. 5.

3.3.2. Control group

Separately analysing the control group, we did not find any significant correlation between the HYPT connectivity and none of the PRS scores. study revealed significant differences in genetic risk scores (PRS) calculated based on two different cohorts and their relationship with HYPT connectivity patterns in migraine patients and controls. While PRS_{ALL}, calculated from all migraine-associated genetic data, did not

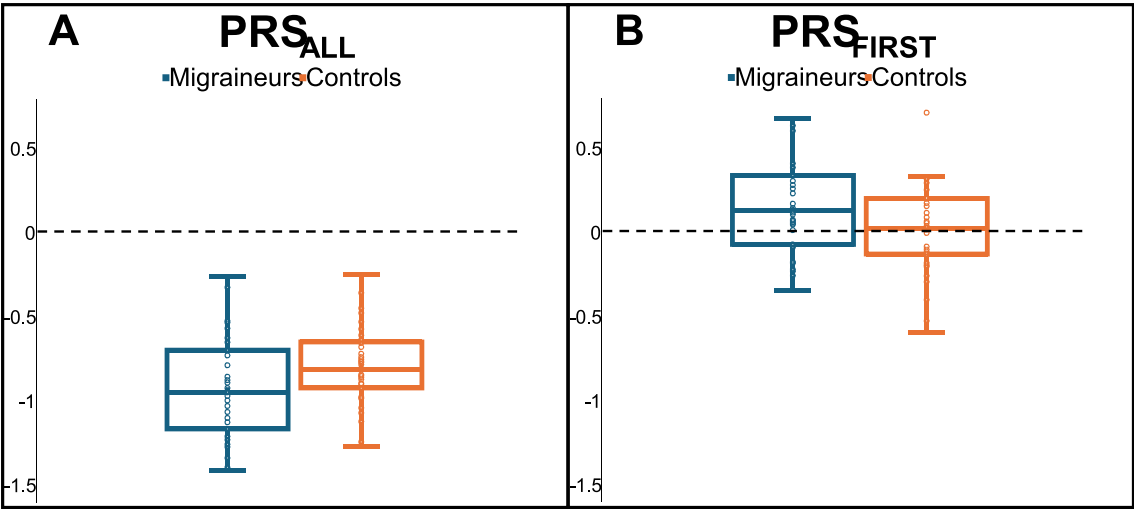


Fig. 1. Boxplot of migraineur's and control's PRS_{ALL} (A) and PRS_{FIRST} (B) scores. Lines display the median, boxes denote the interquartile range, and whiskers demonstrate the maximum and minimum values (excluding outliers) of PRS scores in the migraine and control groups. Dots represent the individual data points. Blue: Migraine patients; Orange: Healthy controls; PRS: Polygenic Risk Score.

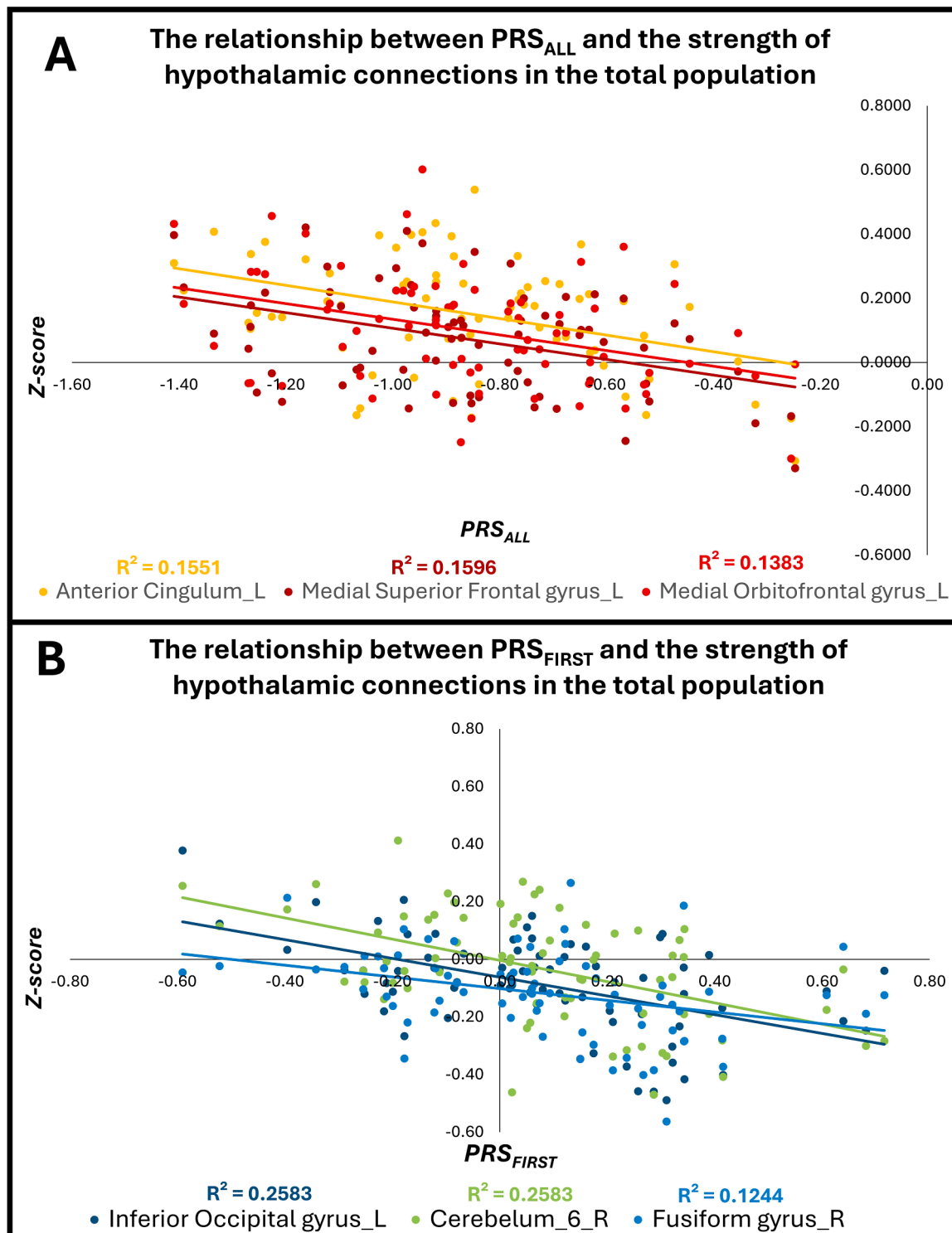


Fig. 2. The correlation between the polygenic risk scores, and hypothalamic connectivity based on all migraine (PRS_{ALL}) and migraine first (PRS_{FIRST}) in the total population ($p_{FWE} < 0.05$). Z-score shows the strength of the connections between hypothalamus and the depicted regions. In Fig. 2/A, the hypothalamic connections of the total population are shown as a function of PRS_{ALL} . In Fig. 2/B, the hypothalamic connections of the total population are shown as a function of PRS_{FIRST} . L: Left side; R: Right side.

predict migraine diagnosis in our study, PRS_{FIRST} , derived from patients whose first diagnosis was migraine, aligned better with our population and accurately predicted migraine diagnosis. Despite these differences, both PRS scores correlated with a weakened connectivity pattern of HYPT albeit in different brain regions. PRS_{FIRST} highlighted altered HYPT connectivity with sensory and motor integrative regions,

suggesting its relevance in cortical hyperexcitability and sensory processing abnormalities in migraine-first patients. In contrast, PRS_{ALL} were associated with connectivity alterations between HYPT and regions involved in pain modulation and nociception.

Our study was the first to investigate the effect of PRS on HYPT connectivity to determine how the genetic predisposition for migraine

Table 3
Hypothalamic connectivity in correlation with the polygenic risk score based on migraine first diagnosis (PRS_{FIRST}) in the combined healthy and migraine group.

Brain Regions	p (FWE)	Cluster size (voxel)	peak T	MNI coordinates		
				x	y	z
Inferior Occipital gyrus_L	0.01753	173	5.660	-30	-82	-4
Cerebellum 6_R	0.000303	342	5.219	16	-58	-16
Fusiform gyrus_R			3.726	30	-70	-4

FWE: Familywise error rate MNI: Montreal Neurological Institute L: Left side R: Right side.

could be related to FC alterations in migraine related brain networks. Investigating the PRS_{ALL} score in the total population, negative correlation was found between PRS_{ALL} and HYPT connectivity with regions involved in pain perception and modulation, such as the anterior cingulate, the medial orbitofrontal, and the medial superior frontal gyri. According to previous studies, these regions have a role in descending pain modulation, either in facilitation or inhibition of nociception (Price, 2000; Tracey, 2008; Zhuo, 2017; Urien and Wang, 2019). Post-hoc analysis revealed that the correlation between PRS and HYPT connectivity is only significant in migraine patients, but not in healthy controls. In addition, separately analysing migraine patients, we observed additional decreased HYPT connectivity with the hippocampus, the paracentral lobule, the lingual gyrus and the precuneus in relations with PRS_{ALL}. Hippocampus contributes to the significant elements of the pain connectome, having a role in top-down pain control, via projections from the anterior cingulum to the periaqueductal grey in animals (Urien and Wang, 2019).

Based on a recent extensive review (Schramm et al., 2023), our findings regarding the hypoconnectivity of HYPT with anterior cingulate gyrus, lingual gyrus, and regions of the prefrontal cortex in migraine patients compared to controls align with the previous literature. However, there is conflicting evidence regarding the HYPT-hippocampus FC in migraine, showing both increased and decreased connectivity between these regions in migraineurs compared to controls (Schramm et al., 2023). Inconsistent results in migraine resting state brain imaging could be related to methodological differences (e.g. different paradigms or scanner settings) but also to heterogeneity of patients. For example, it has been demonstrated that hypothalamic connectivity with several brain regions changes throughout the migraine cycle, with the weakest connectivity during the migraine attack and gradually increasing

connectivity interictally until the next attack (Stankewitz et al., 2021). Our results support that migraine patients genetically predisposed to hypoconnectivity of HYPT interictally.

To address another aspect of patients' heterogeneity, in our study we rigorously included only episodic migraine patients without aura or any other somatic or mental disorders. Thus, it is not surprising that a PRS score calculated based on genetic variants of non-selected migraine patients, including those with comorbidities (PRS_{ALL}), had a low predictive value in our homogeneous population. However, the PRS_{FIRST} score, which was calculated based on a dataset containing migraine patients' data, whose first ever diagnosis was migraine, was significantly elevated in our migraine group, and predicted the migraine diagnosis better compared to PRS_{ALL} score. Thus, based on this result, we also expected that the two different PRS scores reflect different brain mechanisms that contribute to migraine.

Indeed, investigating the effect of PRS_{FIRST} on HYPT connectivity, we did not observe significant alterations in any of the previous connections with regions having a role in the top-down control of pain. Instead, in the total population negative correlation was observed between PRS_{FIRST} and HYPT connectivity with regions involved in sensory processing, cortical hyperexcitability and dysfunctions affecting sensory integration, further supporting that genetically determined hypoconnectivity of the HYPT is an important feature of migraine.

The decreased HYPT connectivity with occipital gyrus and the

Table 4
Hypothalamic connectivity correlated with the polygenic risk score based on all migraine diagnosis (PRS_{ALL}) in the migraine group.

Brain Regions	p (FWE)	Cluster size (voxel)	peak T	MNI coordinates		
				x	y	z
Hippocampus_L	0.009651	176	4.949	-24	-10	-24
Anterior Cingulum_R	3.65E-11	1147	4.756	4	34	14
Medial Orbitofrontal gyrus_R			4.695	8	66	-4
Posterior Cingulum_L			4.463	-10	44	22
Precuneus_L	0.02110	150	4.097	-4	-56	8
Posterior Cingulum_L			3.620	-4	-42	10
Lingual gyrus_L			4.271	-8	-40	2

FWE: Familywise error rate MNI: Montreal Neurological Institute L: Left side R: Right side.

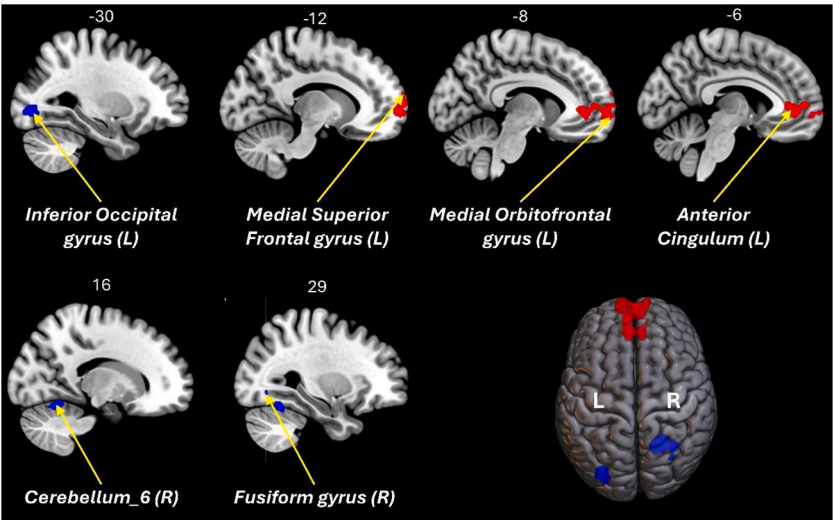


Fig. 3. Significant regions connected with the hypothalamus in the total population in correlation with PRS scores (pFWE<0.05). Red: regions with weakening hypothalamic connections with increasing PRS_{ALL}. Blue: regions with weakening hypothalamic connections in correlation with PRS_{FIRST}. L: Left side; R: Right side.

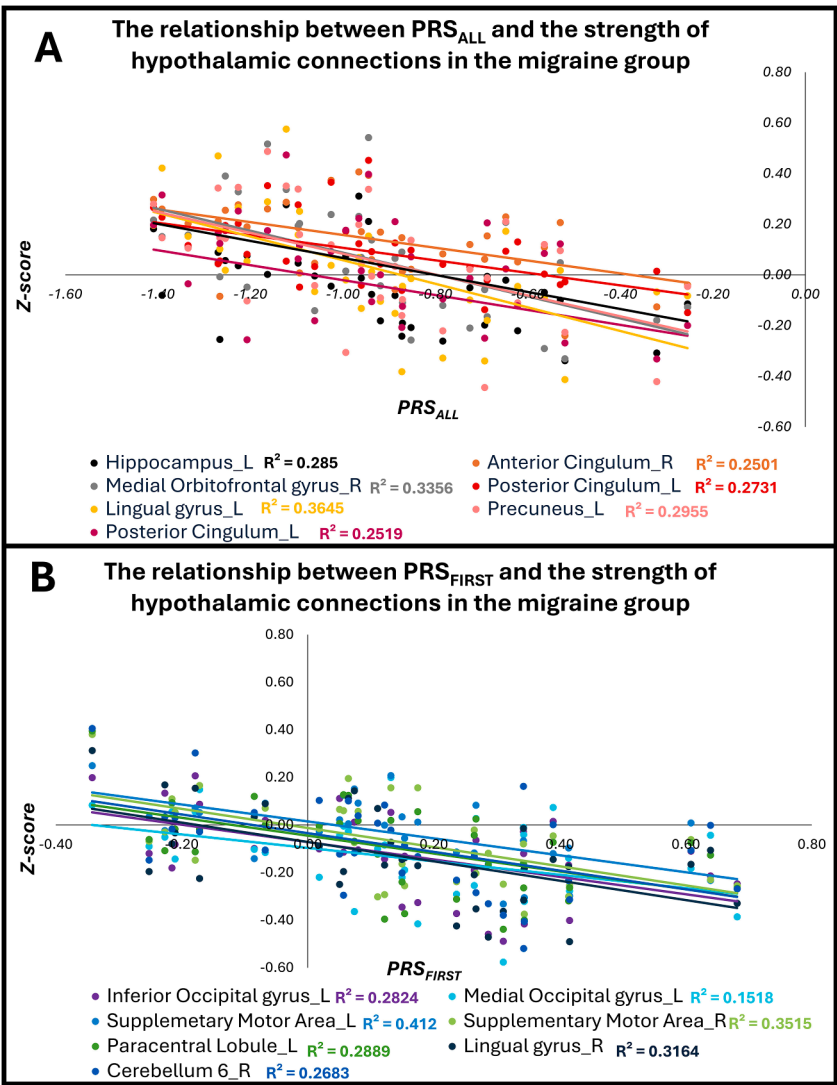


Fig. 4. The correlation between the polygenic risk scores, based on all migraine (PRS_{ALL}) and migraine first (PRS_{FIRST}) diagnosis, with the strength of hypothalamus connectivity and the strength of hypothalamic connections in the migraine group (pFWE<0.05). Z-score shows the strength of the connections between hypothalamus and the depicted regions. In Fig. 4/A, the hypothalamic connections of the migraine group are shown as a function of PRS_{ALL}. In Fig. 4/B, the hypothalamic connections of the migraine group are shown as a function of PRS_{FIRST}. L: Left side; R: Right side.

Table 5
Hypothalamic connectivity in correlation with the polygenic risk score based on migraine first diagnosis (PRS_{FIRST}) in the migraine group.

Brain Regions	p (FWE)	Cluster size (voxel)	peak T	MNI coordinates		
				x	y	z
Inferior Occipital gyrus_L	5.761E-05	379	5.805	-30	-82	-4
Medial Occipital gyrus_L			3.797	-28	-84	6
Supplementary Motor Area_L	0.0003711	300	5.544	-10	4	50
Supplementary Motor Area_R			4.642	2	-14	62
Paracentral Lobule_L			4.552	-2	-18	68
Lingual gyrus_R	3.146E-06	514	4.885	16	-60	-12
Cerebellum 6_R			4.767	34	-56	-22

FWE: Familywise error rate MNI: Montreal Neurological Institute L: Left side R: Right side.

cerebellum regarding PRS_{FIRST} remained consistently significant when investigating both the total population and only migraine patients. Several studies have shown altered connectivity of the HYPT with these regions in migraine (Chong et al., 2020; Coppola et al., 2020). Functional and structural connectivity between the HYPT and occipital brain regions in patients with episodic or chronic migraine emphasizes the involvement of visual areas in migraine pathophysiology and progression, through connecting the visual, thalamic, hypothalamic, and trigeminovascular pathways (Messina et al., 2022). Previous studies also found altered connection between HYPT and the cerebellum in migraineurs, however it's hypothalamic connectivity was elevated in migraine patients compared to controls (Moulton et al., 2014; Wang et al., 2022; Schramm et al., 2023), whereas we observed weakening connections as migraine-first genetic risk increased, suggesting that genetic predisposition to hypoconnectivity of HYPT might be better captured in a more homogeneous interictal migraine population, such as ours.

Post-hoc analyses revealed additional significantly decreased HYPT connectivity with regions responsible for integrating sensory input with motor and cognitive functions in migraine patients in association with PRS_{FIRST}. The supplementary motor area, the paracentral gyrus and the lingual gyrus were also significantly less connected with HYPT

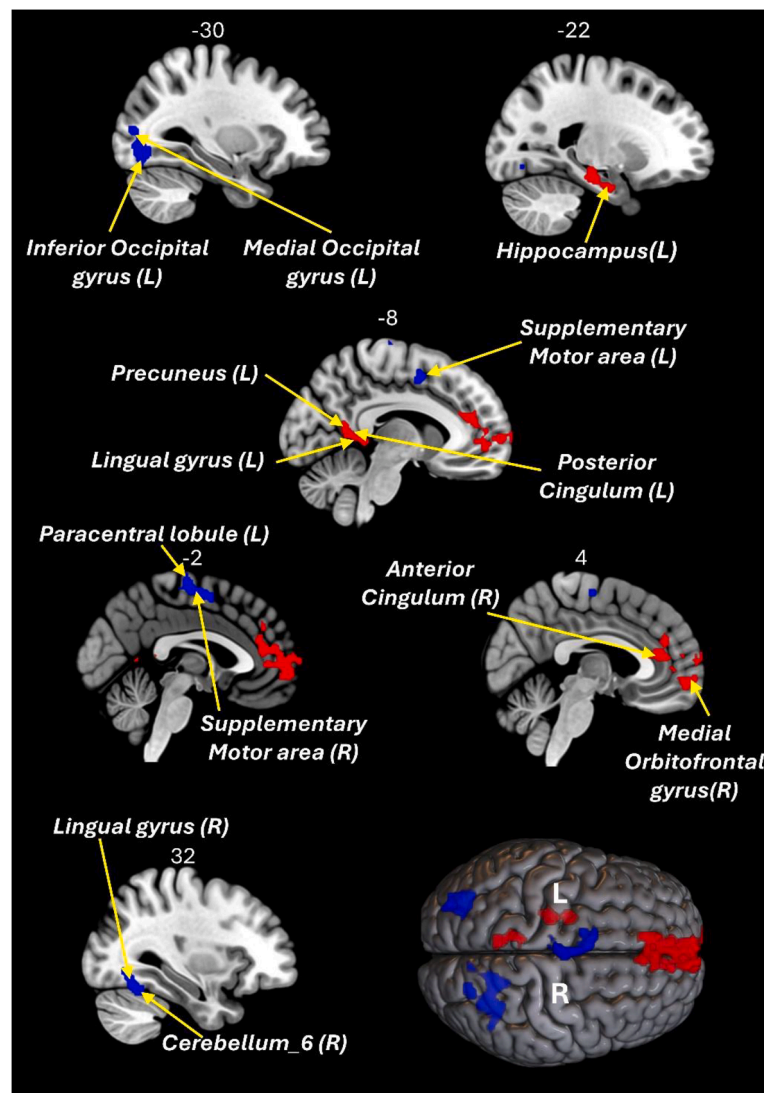


Fig. 5. Significant regions ($p_{FWE} < 0.05$) connected with the hypothalamus in migraineurs in correlation with PRS scores. Red: regions with weakening hypothalamic connections with increasing PRS_{ALL} . Blue: regions with weakening hypothalamic connections in correlation with PRS_{FIRST} . L: Left side; R: Right side.

regarding the migraine-first genetic risk. The relevance of these findings in migraine is supported by studies demonstrating altered hypothalamic connections with the lingual and fusiform gyri and the supplementary motor area in migraineurs. Moreover, these connections showed a decreased hypothalamic connectivity in migraineurs compared to healthy controls (Moulton et al., 2014; Schramm et al., 2023; Li et al., 2024), similarly to our findings.

In summary, there is a remarkable difference between the correlations of PRS_{ALL} and PRS_{FIRST} with HYPT rFC. The analyses using all migraine genetic risk (PRS_{ALL}) highlighted regions involved in descending pain modulation and nociception. In contrast, PRS_{FIRST} , emphasized hypothalamic connections with regions of altered sensory processing and cortical hyperexcitability. These findings underscore that distinct genetic risk profiles are able to pinpoint different brain mechanisms that can contribute to migraine pathophysiology, and thus may be useful biomarkers for selecting more homogeneous patient populations to improve precision treatment approaches including both pharmacological and non-pharmacological interventions. Previous work suggests that combining PRS with neuroimaging features may help stratify patients into subgroups with distinct pathophysiological profiles and treatment responses (Ashina et al., 2021). For instance, PRS has been linked to clinical features such as age of onset and severity, and

when paired with imaging metrics could potentially guide the selection of targeted therapies. Furthermore, as suggested by (Juhász et al., 2023), integrating imaging and genomic data using machine learning techniques may allow for even more precise identification of responders to specific treatments. While further validation and replication are needed, our findings contribute to the translational potential of using PRS and functional imaging biomarkers to inform personalized migraine care.

4. Limitations

Our study was conducted with several limitations in mind. For instance, our population was highly selected, that limits the generalisability of our results, especially since migraine is a heterogeneous condition. Our control group was free from any disease, and our migraine cohort consisted of individuals with episodic migraines who had no comorbidities, did not take migraine preventive medications and had not experience aura symptoms. Even so, these strict selection criteria provide a more homogeneous population to investigate, and thereby increasing the potential to shed light on different pathophysiological aspects of migraines.

Another limitation was the definition of the seed region. We relied on existing literature to guide us in the identification of HYPT coordinates.

Based on the literature, we divided the HYPT into two regions: the left and right HYPT. Analysis of these regions yielded distinct results no connected regions were found with the right seed, while several significant regions emerged from the left HYPT seed that very well correspond with the previous literature. These findings underscore the sensitivity of the seed region definition in seed-to-voxel analysis.

Regarding the use of PRS, we acknowledge that while it is a widely used and scalable tool for estimating cumulative genetic risk, it does not fully capture the complex and multifactorial nature of migraine genetics. PRS represents only the additive effects of common single nucleotide polymorphisms (SNPs) identified through genome-wide association studies (GWAS). It does not account for gene-gene interactions, rare variants, structural changes (e.g., CNVs, insertions, deletions), epigenetic factors, or post-translational modifications. These unaccounted factors contribute to the so-called missing heritability. Nevertheless, we argue that PRS remains a valuable measure for genetic susceptibility, especially when used in clinically homogeneous samples, as supported by our current study. In fact, recent work has shown that applying PRS to a more refined, migraine-first population without comorbidities significantly improves SNP-based heritability estimates and reduces background noise (Torok et al., 2024). Furthermore, although PRS does not represent the full spectrum of genetic risk, it may help reveal distinct biological mechanisms when derived from GWAS performed on specific population subtypes.

Finally, the reproducibility of fMRI findings represents an inherent limitation. Reproducibility in neuroimaging research faces challenges such as small effect sizes, variability in acquisition protocols, and analytical flexibility. Replicating fMRI findings typically requires very large sample sizes to achieve sufficient statistical power, and subtle differences in preprocessing or analysis pipelines can yield divergent outcomes even within the same dataset. Although we carefully addressed these issues through rigorous preprocessing, hypothesis-driven analysis, and transparent reporting of our methodology, external replication in larger and more diverse cohorts will be necessary to confirm the robustness and generalizability of our findings (Botvinik-Nezer and Wager, 2023; Schramm et al., 2025).

5. Conclusion

This study highlights the critical role of genetic predisposition in shaping hypothalamic connectivity patterns associated with migraine. By comparing two polygenic risk scores (PRS_{ALL} and PRS_{FIRST}), the findings reveal distinct brain connectivity alterations linked to different genetic profiles. PRS_{ALL} underscores the hypoconnectivity of HYPT with regions in pain modulation, whereas PRS_{FIRST} reveals weakened connections in sensory and integrative networks, supporting its relevance in cortical hyperexcitability and sensory dysfunction in migraine-first patients. These results emphasize the importance of refined patient group filtering for uncovering specific genetic and neurological pathways underlying migraine.

Furthermore, the distinct connectivity patterns provide valuable insights into the functional diversity of migraine-related brain networks, advancing both personalized therapeutic strategies and our understanding of migraine. The study also sheds light on the limitations of the use of broad genetic risk models like PRS_{ALL} in populations with different, potentially more homogeneous characteristics. By demonstrating the value of integrating genetic and neuroimaging approaches, this research paves the way for further exploration of the interplay between genetics, and FC in migraine. Ultimately, these findings reinforce the significance of tailored approaches in migraine management, highlighting the importance of well-defined genetic and brain imaging biomarkers that can be used in precision treatment strategies.

CCRediT authorship contribution statement

Anna Németh: Writing – original draft, Visualization, Formal

analysis. **Kinga Gecse:** Writing – review & editing, Supervision. **Dóra Török:** Writing – review & editing, Formal analysis. **Dániel Baksa:** Writing – review & editing. **Dóra Dobos:** Writing – review & editing. **Csaba Sándor Aranyi:** Methodology. **Miklós Emri:** Methodology. **György Bagdy:** Writing – review & editing, Funding acquisition, Conceptualization. **Gabriella Juhász:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization.

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Data availability

The data that has been used is confidential.

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