Medication overuse headache associated with decreased dopamine transporter availability in the left orbitofrontal cortex: A 11CFT PET/MR study

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Research article

Keywords: Medication overuse headache, dopamine transporter, orbitofrontal cortex, PET/MR, functional connectivity

Posted Date: October 21st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-968662/v1

Abstract

Backgrounds

The dysfunction of dopamine in the mesocorticolimbic dopamine system in MOH is unknown. Dopamine transporter (DAT) regulates dopamine clearance and neurotransmission and is sensitive to dopamine levels. A decrease in DAT availability can reflect a decrease in dopamine. To determine DAT availability abnormalities in the mesocorticolimbic dopamine system and explore functional network changes in medication overuse headache (MOH) patients.

Methods

We examined 17 MOH patients and 16 healthy controls (HCs) using integrated positron emission tomography (PET)/magnetic resonance (MR) brain scans with ^{11}CFT, a radioligand that binds to DAT. Standardized uptake value ratio (SUVr) images were compared voxelwise between MOH patients and HCs. Then, the significantly changed cluster ($p < 0.01$, GRF correction) with abnormal DAT availability was selected as a specific seed region to further evaluate altered functional connectivity (FC) in MOH. SUVr and mean FC values from significantly changed regions were extracted, and partial correlation analyses with clinical measures were conducted.

Results

MOH patients had lower SUVr levels in the left rather than right orbitofrontal cortex (OFC) than HCs. There was altered FC between the left OFC and the left superior temporal pole and bilateral calcarine gyri. SUVr levels in the left OFC and the connectivity strength linking the positive brain regions with the left OFC were not correlated with clinical measures in the MOH patients.

Conclusions

MOH is characterized by decreased DAT availability in the left OFC, which might reflect compensatory downregulation due to low dopamine signalling within the mesocorticolimbic dopamine system. In addition, the OFC on both sides may have different functions in the pathogenesis of MOH. Altered intrinsic FC in the left OFC was identified in MOH patients, which may provide a new perspective to understand the pathogenesis of MOH.

Backgroud

Medication overuse headache (MOH) is a chronic daily headache caused by frequent (≥10 days per month or ≥15 days per month, depending on the medication) and long-term (≥3 months) use of medication for acute or symptomatic headache in patients with preexisting primary headache, most commonly migraine [1]. It is recognized as a threat to public health and a disabling condition that causes substantial socioeconomic consequences for society and families [2], ranking 20th in the Global Burden of Disease study in 2015 [3].

Although the molecular underpinnings of MOH remain incompletely understood, various clinical phenomena, such as obsessional drug-taking behaviours, psychological drug dependence or high rates of relapse in MOH patients [4], have been reported, which may imply a common mechanism shared in MOH and drug addiction [5]. Moreover, numerous imaging studies with different modalities in the context of drug addiction research have demonstrated structural and functional alterations in the mesocorticolimbic dopamine system [6, 7]. In addition, dopamine is known as the main neurotransmitter involved in the mesocorticolimbic dopamine system [8]. The ability to directly increase dopamine is considered to be a crucial mechanism underlying drug addiction [8]. Therefore, we speculated that dysfunction of dopamine in the mesocorticolimbic dopamine system might play a central role during the development of MOH. However, there are no studies to date exploring dopamine changes in the mesocorticolimbic dopamine system in the context of MOH research.

The dopamine transporter (DAT) regulates dopamine clearance and neurotransmission and is sensitive to dopamine levels [9]. Clinical and preclinical studies have demonstrated that a decrease in DAT availability was compensatory for the decrease in dopamine signalling [10, 11, 12] and that dopamine synthesis capacity was positively correlated with DAT availability [13]. Thus, a decrease in DAT availability can reflect a decrease in dopamine.

To test the hypothesis that abnormalities in DAT availability were present in the mesocorticolimbic dopamine system with MOH, we performed combined ^{11}CFT (^{11}C-2β-carbomethoxy-3β-(4-fluorophenyl) tropane, a highly selective radiotracer for DAT) positron emission tomography (PET)/magnetic resonance (MR) imaging in MOH patients. Then, the cluster with abnormal DAT availability was selected as a specific seed point to further evaluate altered functional connectivity (FC) in MOH.

Methods

This study was approved by the ethics committee of Chinese PLA General Hospital (S2018-027-02) and registered in the Chinese Clinical Trial Registry (ChicTR1800016773). All subjects provided written informed consent in accordance with the Declaration of Helsinki.

Participants

Patients who were admitted to the international headache centre in the neurological department of Chinese PLA General Hospital between July 2018 and August 2019 and diagnosed with MOH were potential participants. Patients who agreed to participate in the study were asked to keep a headache diary for at least one month before final enrolment. All enrolled patients were fully evaluated by two headache specialists (Dr. Zhao Dong and Dr. Shengyuan Yu). The inclusion criteria for MOH were as follows: (1) were 18–65 years of age; (2) had a migraine history before medication overuse; (3) met the MOH diagnostic criteria based on the International Classification of Headache Disorders–3rd edition (ICHD-3); (4) were without anxiety and depression (i.e., a total score of > 6 points on the Hamilton Anxiety scale or a total score of > 8 points on the Hamilton Depression scale); (5) had no sleep disorders (i.e., a total score of > 5 points on the Pittsburgh Sleep Quality Index); and (6) had not received preventive treatment for MOH within the 3 months before

enrolment. The exclusion criteria for the patients with MOH were as follows: (1) other secondary headaches; (2) comorbid disease requiring long-term use of a pain reliever; and (3) failure to meet the MOH diagnostic criteria after keeping a headache diary for one month. Healthy controls (HCs) were matched for age and sex. All HCs were recruited by advertisements on WeChat social media and completed a one-month follow-up before final enrolment. The inclusion criteria for HCs were as follows: (1) drug-free and (2) no psychiatric or neurological disorders, including recurrent headache. The exclusion criteria for both groups were pregnancy and contraindications for PET/MR scanning. The study design is outlined in Figure 1.

After PET/MR scans, all MOH patients were prescribed preventive medications, and their intake of acute medication for headache was reduced to < 10 days/30 days. All enrolled MOH patients were followed up by telephone or face-to-face consultation. Treatment outcomes were subjectively defined as “satisfactory” when a patient felt > 50% improved or “poor” when improvement was < 50% or the patient felt unchanged [14]. Relapse was defined based on the MOH diagnostic criteria in the ICHD-3.

Image acquisition

^{11}CFT PET/MR was performed at least 12 hours after the last intake of analgesics. The subjects underwent PET/MR after an injection of 3.70–5.55 MBq/kg ^{11}CFT. Emission scans were acquired 35 minutes after the injection using an integrated PET/MR scanner (Biograph mMR, Siemens, VB20P). PET images were obtained in list mode for 10 minutes. PET images were reconstructed by a high-definition method with 21 subsets and 3 iterations. Images were postfiltered with a 2-mm Gaussian filter, and the image matrix size was 344. Attenuation correction was performed using UTEμmap. MR images were acquired on the integrated PET/MR scanner at the same time using a T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence [repetition time =1900 ms, echo time =2.44 ms, flip angle=9°, field of view = 250 mm * 250 mm, matrix= 256 x 256, slice thickness=1.0 mm, and voxel size= 1.0 x 1.0 x 1.0 mm].

Resting-state functional magnetic resonance imaging (fMRI) was obtained using a gradient echo-planar imaging sequence (repetition time = 3000 ms, echo time = 30 ms, flip angle = 90°, slice thickness = 3.0 mm, slice gap = 0, field of view = 210 mm * 210 mm, matrix = 70 x 70, and voxel size= 3.0 x 3.0 x 3.0 mm), and 184 transverse, continuous echo-planar imaging functional volumes were acquired.

Data processing

Images were analysed using Statistical Parametric Mapping (SPM12 version; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK; http//www.fil.ion.ucl.ac.uk/spm) and Data Processing and Analysis for Brain Imaging [15] (DPABI_V6.0_210501) running in MATLAB (version 6.1, Mathworks Inc., Sherborn, MA).

PET image processing

Images were spatially normalized into Montreal Neurological Institute (MNI) space using 12-parameter affine transformation and subsequent nonlinear registration methods and resliced to 2 mm^3. These normalized images were then smoothed using an 8-mm^3 full-width at half-maximum (FWHM) Gaussian kernel. The cerebellum was selected as the reference region. DAT availability was measured by the standardized uptake

value ratio (SUVr). Voxelwise SUVr images were obtained by dividing the SUV value of the cerebellum. Whole-brain voxelwise analysis was conducted between MOH patients and HCs. The significantly changed regions were generated at the threshold of $P < 0.01$ with Gaussian random field (GRF) correction. Furthermore, the mean SUVr of the significantly changed region was calculated.

Resting-state functional connectivity (RSFC)

The RSFC analysis was performed in DPABI as follows: (1) removal of the first ten volumes; (2) slice timing; (3) spatial normalization; (4) spatial smoothing (FWHM = 8 mm) using SPM12; (5) selection of seed regions based on the PET results; and (6) calculation of FC of seed regions using DPABI. The time courses of the seed regions were extracted, and Pearson's correlation coefficients were used to calculate FC between the extracted time course and the averaged time course of the whole brain in a voxelwise manner. (7) The individual r-maps were normalized to Z-maps using Fisher's R-to-Z transformation. (8) Abnormal clusters based on statistical parametric mapping were generated as binary masks, and connectivity strength of the altered brain region was extracted based on Z-maps. Significance was set at P<0.05 with GRF correction. (9) Finally, the mean FC value in each significantly changed region was extracted.

Statistical analysis

Numerical results are presented as the means (±SD) or medians with interquartile ranges. Age was compared with a *t* test, and sex ratio was compared with Fisher's exact test. The SUVr and mean FC values of the cluster that showed a significant group difference were further extracted to perform partial correlation analysis with clinical measures (headache duration, medication overuse duration, pain intensity, headache frequency, and treatment outcomes). For the clinical measures, partial correlations were run in the MOH group only. Age and sex were used as covariates in all correlation analyses. These statistics were processed using IBM SPSS 26, and statistical significance was set at $P < 0.05$.

Results

A total of 21 eligible MOH patients and 17 HCs were enrolled. One patient failed to meet the MOH diagnostic criteria after review of a headache diary that was kept for one month. Three patients failed to complete ^{11}CFT PET/MR scanning because of the impact of COVID-19. One HC had contraindications for PET/MR scanning. Then, 33 participants (17 patients with MOH and 16 HCs) completed ^{11}CFT PET/MR. The majority of patients (16/17, 94.1%) overused combination analgesics (94.1%), and only one overused triptan (1/17, 5.9%). Finally, we included 16 patients who overused combination analgesics for further analysis (Fig. 1). At the two-year follow-up, 11 MOH patients (11/16) reported satisfactory improvement, and 3 of them (3/11) relapsed within 1 year.

Participant characteristics

Participant information is displayed in Table 1. The average age of the MOH patients (13 F/3 M) was 45.9 ± 7.3 (mean ± SD) years, with an average duration of headache of 22.9 ± 8.4 years and medication overuse of 3.1 ± 2.9 years. The mean headache frequency and headache intensity were 22.9 ± 6.9 attacks per month and 7.6 ± 1.0 (visual analogue scale 1–10), respectively. The mean age of the HCs (12 F/4 M) was 43.1 ±

6.7 years. Three patients had a nonmigraine-like headache attack when PET scans were performed. Age and sex showed no significant differences between the two groups ($P > 0.05$). Clinical details are provided in Table 2.

Table 1
Participant characteristics

Characteristic	MOH (n=16)	Control (n=16)	*P*-value
Sex (n, %)			0.669
Male	3 (18.8%)	4 (25.0%)	
Female	13 (81.2%)	12 (75.0%)	
Age (years) Mean±SD	45.9 ± 7.3	43.1 ± 6.7	0.263
HAMD	3.5 ± 0.8	3.1 ± 1.0	
HAMA	3.0 ± 1.2	2.5 ± 0.9	
PSQI	2.5 ± 0.8	2.4 ± 0.9	
Headache duration (years) Mean±SD	22.2 ± 8.5	-	
Headache frequency (days/month) Median (P_{25}, P_{75})	20(15,30)	-	
Pain intensity (VAS) Median (P_{25}, P_{75})	8(7,8)	-	
Medication overuse duration (years) Median (P_{25}, P_{75})	3(0.6,4.5)	-	
Dosage frequency (days/month) Median (P_{25}, P_{75})	30(18.5,30)	-	
Abbreviations: HAMD = Hamilton Depression scale; HAMA = Hamilton Anxiety scale; MOH = medication overuse headache; PSQI = Pittsburgh Sleep Quality Index; VAS = visual analog scale;			

Table 2
Clinical characteristics of MOH patients (n=17)

Patient	Age (years)	Sex	Headache duration (years)	Medication overuse duration (years)	VAS	HAMD	HAMA	PSQI	Medication type
NO.1	56	F	10	4	7	3	1	3	Combination analgesics
NO.2	54	M	44	4	8	4	2	2	Combination analgesics
NO.3	45	F	15	8	7	2	3	3	Combination analgesics
NO.4	45	F	15	0.5	8	3	3	2	Combination analgesics
NO.5	46	F	26	10	7	4	2	3	Combination analgesics
NO.6	47	F	16	0.25	7	2	4	1	Combination analgesics
NO.7	38	M	25	0.6	10	4	5	2	Combination analgesics
NO.8	35	M	18	0.5	7	4	1	3	Combination analgesics
NO.9	30	F	20	5	6	3	4	4	Combination analgesics
NO.10	48	M	12	3	8	3	3	2	Triptan
NO.11	53	F	30	3	8	4	3	1	Combination analgesics
NO.12	50	F	30	3	8	4	2	3	Combination analgesics
NO.13	48	F	15	5	7	3	3	3	Combination analgesics
NO.14	47	F	30	3	8	5	4	3	Combination analgesics
NO.15	48	F	23	0.5	7	3	4	2	Combination analgesics
NO.16	54	F	25	1	8	4	5	2	Combination analgesics
NO.17	39	F	24	0.7	9	4	2	3	Combination analgesics

Patient	Age (years)	Sex	Headache duration (years)	Medication overuse duration (years)	VAS	HAMD	HAMA	PSQI	Medication type

Abbreviations:

HAMD = Hamilton Depression scale; HAMA = Hamilton Anxiety scale;

MOH = medication overuse headache; PSQI = Pittsburgh Sleep Quality Index; VAS = visual analog scale;

Imaging data

The SUVr in the left orbitofrontal cortex (OFC; Brodmann 11) was significantly lower in the 16 MOH patients who overused combination analgesics than in the HCs ($P^{GRF} < 0.01$) (Fig. 2). The partial correlation analysis demonstrated no significant correlations between the SUVr in the left OFC and the clinical measures in the patients with MOH.

We subsequently set the left OFC as the seed region to compute RSFC to identify the altered resting-state functional architecture in the MOH patients compared with the HCs. There was decreased RSFC between the left OFC and the left superior temporal pole (Brodmann 28) and increased RSFC between the left OFC and the bilateral calcarine gyri (Brodmann 17; primary visual cortex) (Fig. 3). There were no significant correlations between the connectivity strength linking the positive brain regions and the left OFC and clinical measures in the MOH patients.

Discussion

To the best of our knowledge, this is the first PET/MR study to examine abnormalities in DAT availability in the brains of MOH subjects, and decreased DAT availability in the left OFC was observed. We also found that there was altered FC between the left OFC and the left superior temporal pole and the bilateral calcarine gyri.

We excluded possible potential confounding factors, including depression, anxiety, and sleep disturbance, in our study for the following reasons. First, a previous study found that DAT availability in the striatum was lower in individuals with psychiatric comorbidities such as major depressive disorder [9]. Moreover, recent findings have indicated that the mesocorticolimbic pathway comprising the ventral tegmental area and the nucleus accumbens is involved in controlling sleep and wakefulness [16]. Rodent studies have also revealed that ventral tegmental area dopamine neurons play a wake-regulatory role [16]. We believe it is worth evaluating the impact of medication overuse and chronic headache on DAT availability in the mesocorticolimbic dopamine system. However, the strict recruitment criteria resulted in the relatively small sample size in our study because MOH-associated psychiatric comorbidities are very common.[17] In addition, previous studies in China showed that combination analgesics were the most commonly overused medications [14, 18]. In contrast, overuse of triptans is very rare in China, as was found earlier in other regions [19, 20, 21]. Therefore, patients overusing combination analgesics were enrolled in the final analysis in the present study.

We first found that MOH patients exhibited decreased DAT availability in the OFC, which is involved in both drug addiction and pain processing. The OFC has been suggested to play a key role in drug addiction by behavioural and pharmacological studies [7]. A previous FDG-PET study also found persistent hypometabolism in the OFC in MOH patients before and 3 weeks after detoxification and therefore confirmed that MOH was related to drug addiction [22]. In addition, dopamine is a vital neurotransmitter involved in drug addiction, and previous studies have verified that patients with drug addiction present abnormalities in the dopamine pathway [8]. Taken together, the reduction in DAT availability in the OFC observed in our study could be interpreted as direct evidence that drug addiction is involved in the pathogenesis of MOH. On the other hand, the decreased DAT availability of the OFC could also be related to pain processing (Fig. 4). Glutamatergic projections from the ventrolateral OFC to the periaqueductal grey (PAG) are involved in antinociception in rats [23]. The projection neurons could be inhibited by GABAergic neurons, which in turn are inhibited by opioids or dopamine [24]. Lower DAT availability in the OFC in MOH patients implied lower dopamine transmitter levels in the OFC. Reductions in dopamine would reduce the inhibition of GABAergic neurons, which increases the activation of GABAergic neurons and decreases activity in the PAG. The PAG is the region with primary control over descending pain modulation and pain relief [25]. Thus, lower dopamine levels in the OFC decreasing the activity in the PAG could result in decreased inhibitory pain modulation and facilitate the process of central sensitization, leading to chronic headaches [23]. Therefore, we speculate that the OFC is involved in the pathogenesis of MOH, which may be related to its roles in both addiction and pain.

We observed decreased DAT availability located in the left rather than right OFC in MOH patients, which may reveal functional differences. Previous studies with MOH patients demonstrated that cortical thickness was lower in the left prefrontal cortex [26], and the grey matter in the left OFC was nonsignificantly decreased [27], implying that there may be a difference between the left and right OFC in the pathogenesis of MOH. Lopez-Persem et al. first identified an asymmetrical response of the lateral OFC to reward in human and nonhuman primates [28]. A Neurosynth meta-analysis suggested that value-guided and motivational processes might be supported more by the left OFC, while the right OFC has a greater role in emotional and affective processes [28]. In addition, a recent voxel-based morphometry study revealed that individuals with more grey matter volume (GMV) in the left OFC tended to be less impulsive and more goal-directed [29], which helps individuals make better decisions. Therefore, it is understandable that dysfunction of the left OFC may make patients more prone to overuse analgesics. Taken together, we speculate that the left OFC might play a more important role than the right OFC in the pathogenesis of MOH, which provides a precise target for the treatment of MOH in the future.

The partial correlation analysis demonstrated no significant correlations between the left OFC SUVr and the clinical measures in patients with MOH after correcting for age and sex. Because only 3 MOH patients relapsed during the two-year follow-up, we did not perform an analysis between MOH relapse and left OFC SUVr. Although previous studies have demonstrated that cortical volume [30] and metabolism [22] in the OFC were related to treatment response and relapse, these studies used different imaging methods to investigate the correlation between aspects of the OFC and clinical measures; thus, the results may not be directly comparable. Further studies are needed to explore the potential factors that affect the reduction in DAT in the OFC.

Further functional analysis revealed that there was altered FC between the left OFC and the left superior temporal pole and the bilateral calcarine gyri. Previous structural MRI studies demonstrated that the left temporal pole showed increased GMV in MOH patients with chronic migraine [31]. One diagnosis classification study of migraine proposed that the structural characteristics (such as cortical thickness and volume) of the temporal pole could serve as one of the principal classifiers [32], indicating that the temporal cortex might play a crucial role in the pathogenesis of migraine and MOH. Furthermore, functional MRI coupled with noxious thermal stimulation revealed that the temporal polar region was also associated with an increased frequency of migraine attacks [33]. Therefore, decreased FC between the left OFC and left temporal polar cortex confirmed in our study may suggest associated dysfunction in pain modulation present in MOH patients. Cortical spreading depression may originate from the visual cortex [34, 35, 36] and can activate trigeminal nociception and thus trigger headache [36]. Previous studies have found higher local gyrification in the right occipital pole [26] and decreased GMV in occipital areas in MOH patients compared with controls [31], indicating the involvement of the visual cortex in MOH. In a rat model of MOH, exposure to sumatriptan for two weeks produced long-lasting increased susceptibility to evoked cortical spreading depression [37]. In addition, the visual cortex has been demonstrated to be involved in the mesocorticolimbic dopamine system [38, 39]. Decreased GMV and altered functional activity in the visual cortex have been reported in patients with dependence problems such as gambling disorder and cocaine addiction [40, 41]. Therefore, we speculate that increased FC between the left OFC and bilateral visual cortex was correlated with the development of MOH through its role in drug addiction and headache. Unfortunately, we did not find any significant correlation between the connectivity strength linking the positive brain regions with the left OFC and the clinical measures in the MOH patients.

A number of potential limitations need to be considered. First, the sample size of the MOH patients was relatively small because of strict enrolment criteria. Second, as 94.1% (16/17) of the MOH patients overused combination analgesics in our present study, it was difficult to perform a subgroup analysis to differentiate the effects of different analgesics on DAT availability in the OFC. Moreover, we did not enrol patients with chronic migraine without medication overuse, because it was difficult to recruit “pure” chronic migraine patients without anxiety, depression, sleep disorders or medication overuse [42, 43]. Therefore, it is difficult to directly answer the question of whether the decreased DAT availability in the left OFC was secondary to protracted drug self-administration, chronic headache or both. Finally, due to the influence of COVID-19 and the patient’s willingness to participate in the re-examination, most of the MOH patients who successfully abstained from the drug did not complete the re-examination with ^{11}CFT PET/MR, resulting in unclear changes in the DAT in the OFC after withdrawal.

Conclusions

The reduction in DAT availability in the left OFC in MOH patients who overused combination analgesics provides in vivo molecular imaging evidence that the left OFC, as a part of the mesocorticolimbic dopamine system, directly participates in the pathogenesis of MOH, and this study may cast light on an underlying pharmacological and behavioural treatment target for those with MOH. In addition, the OFC on both sides may have different functions in the pathogenesis of MOH. Altered intrinsic FC with the left OFC was identified in MOH patients, which provides a new perspective to understand the pathogenesis of MOH.

Abbreviations

^{11}CFT: ^{11}C-2β-carbomethoxy-3β-(4-fluorophenyl) tropan; DAT: dopamine transporter; FC: functional connectivity; FWHM: full-width at half-maximum; GRF: Gaussian random field; GMV: grey matter volume; HCs: healthy controls; ICHD-3: International Classification of Headache Disorders–3rd edition; MOH: medication overuse headache; OFC: orbitofrontal cortex; PAG: periaqueductal grey; RSFC: resting-state functional connectivity; SUVr: standardized uptake value ratio.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Chinese PLA General Hospital (S2018-027-02) and registered in the Chinese Clinical Trial Registry (ChicTR1800016773). All subjects provided written informed consent in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

All data generated and analyzed during the current study will be available from the corresponding authors on reasonable request.

Competing interests

The authors declared that they have no competing interests.

Funding

This work was supported by grants from the National Natural Science Foundation of China (grant 81771200, 82071226), and Beijing Natural Science Foundation Essential Research Project (Z170002).

Author contributions

Zhao Dong, Shengyuan Yu, and Huanxian Liu contributed to conception and design of the study, Jiajin Liu, Baixuan Xu and Shuping Sun contributed to acquisition of data,Binbin Nie contribute to analysis of data, Wei Dai contributed to drafting a significant portion of the figures.

Acknowledgements

We thank all patients and healthy volunteers who took part in the study.

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Figures

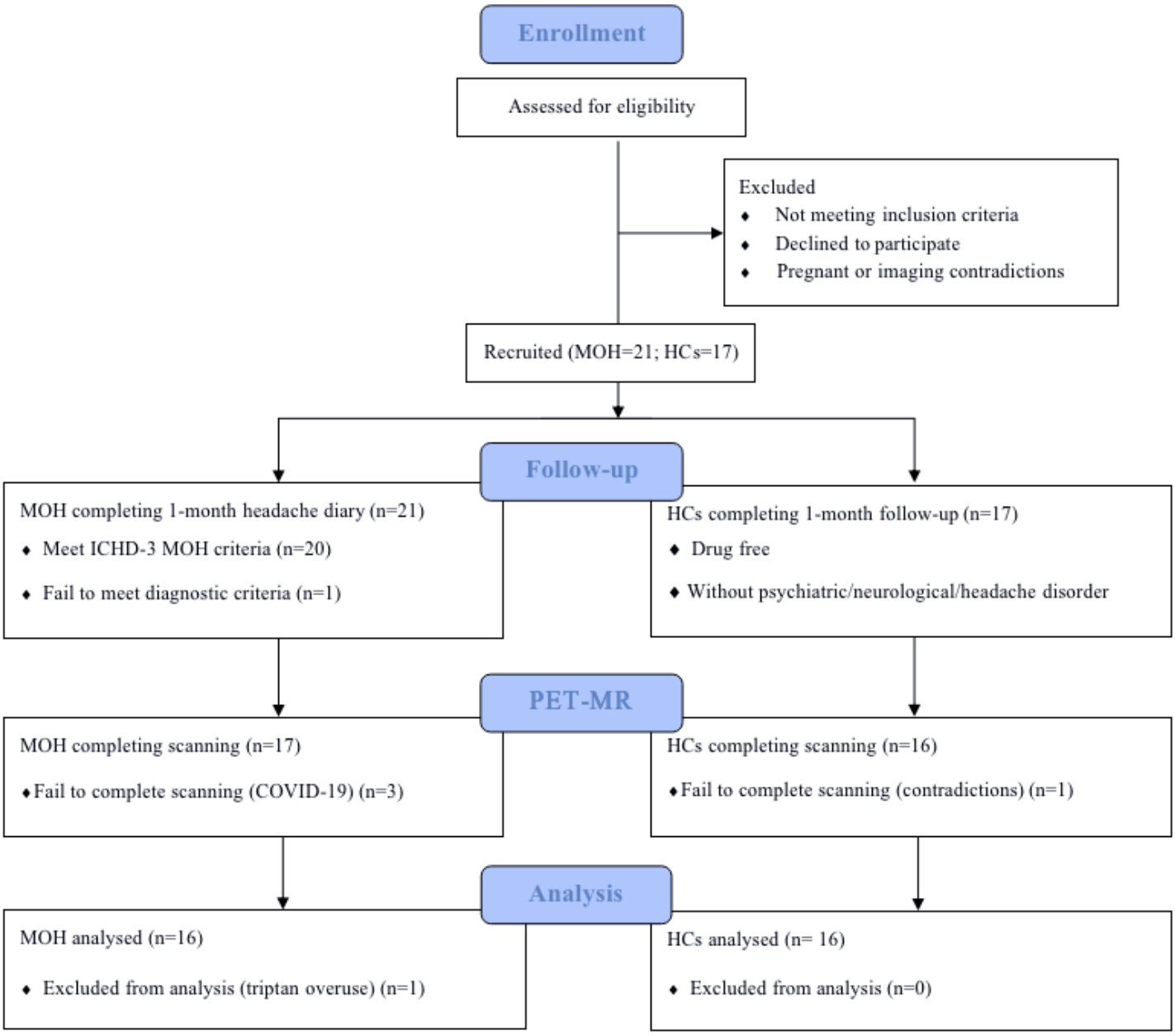
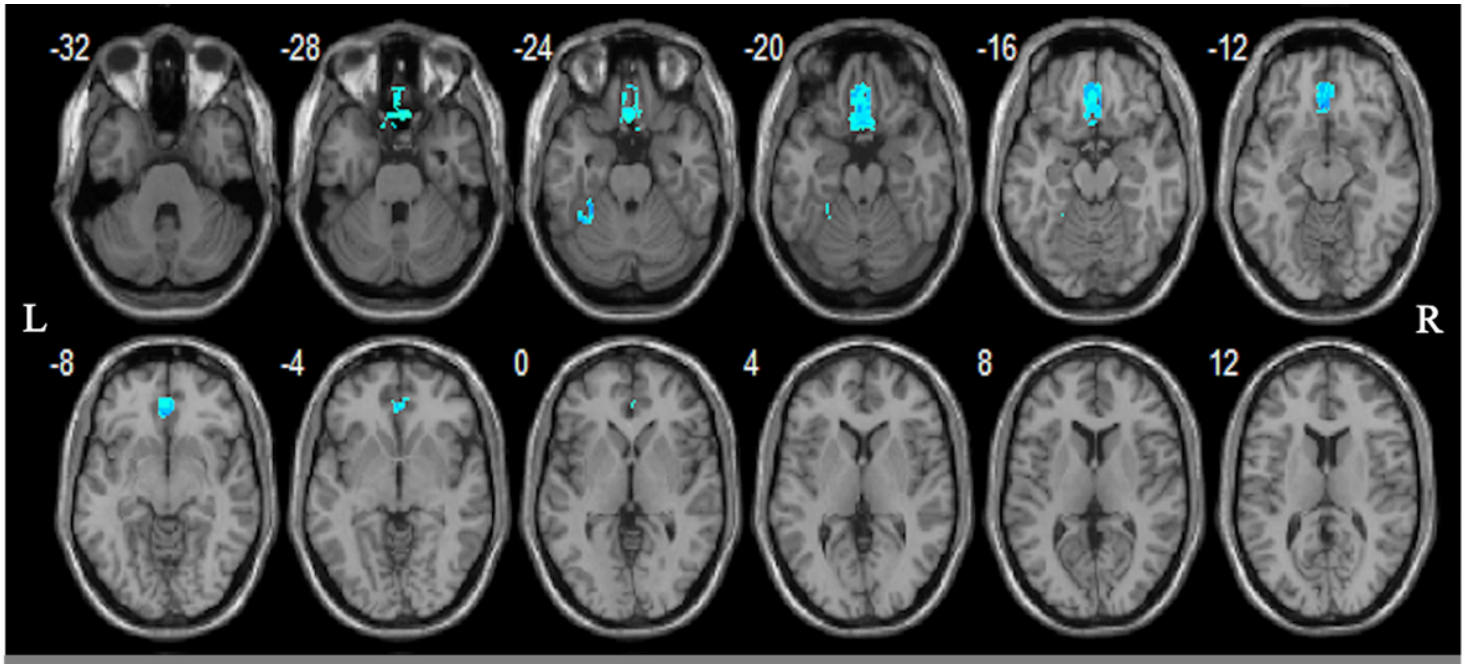


Figure 1

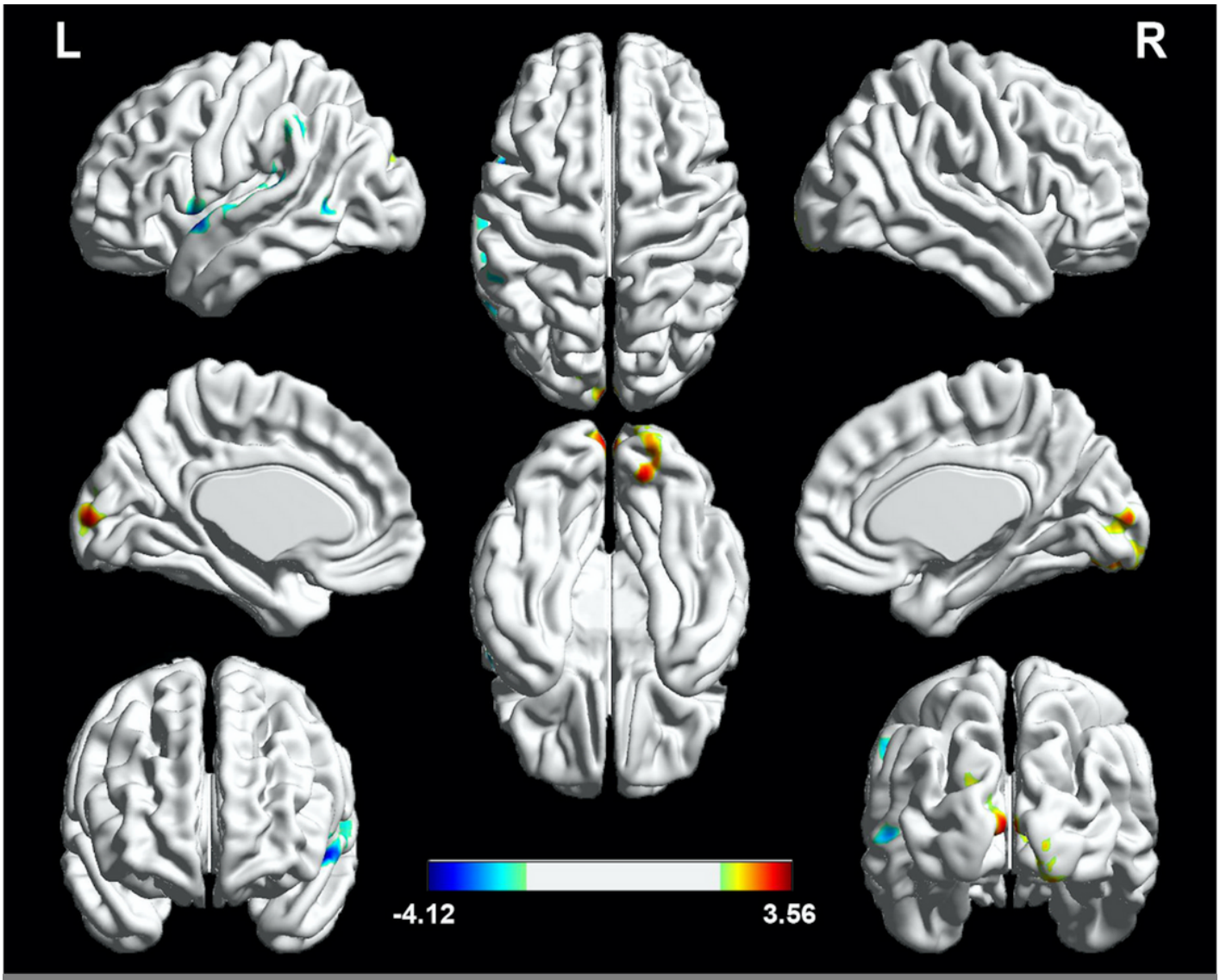
Study design. MOH = medication overuse headache; HCs = healthy controls.



Region	Voxels	MNI			T	p^{GRF}
		X	Y	Z		
OFC_L (Brodmann11)	781	-2	30	-12	-5.0317	<0.01

Figure 2

Area in which the standardized uptake value ratio (SUVr) was lower in MOH patients than in controls. The region of decreased 11CFT SUVr in the MOH patients compared to the controls is shown in blue. Group differences in cortical 11CFT SUVr projected on transverse sections of a normalized brain MRI template. MNI = Montreal Neurological Institute, X, Y, Z coordinates of the primary; GRF = Gaussian random field; MOH: medication overuse headache; OFC_L = left orbitofrontal cortex.



Seed region	Anatomic region	Voxels	MNI			T	p^{GRF}
			X	Y	Z		
OFC_L (Brodmann11)	bilateral calcarine gyrus	500	0	-96	6	3.5623	<0.05
	left Superior temporal pole	648	-51	9	-6	-4.1163	<0.05

Figure 3

Altered RSFC in the left OFC. Decreased RSFC between the left OFC and the left superior temporal pole (blue), and increased RSFC between the left OFC and the bilateral calcarine gyri (red) in the MOH patients compared to the controls. RSFC = resting-state functional connectivity; OFC_L = left orbitofrontal cortex; MNI = Montreal Neurological Institute, X, Y, Z coordinates of the primary; GRF = Gaussian random field; MOH = medication overuse headache.

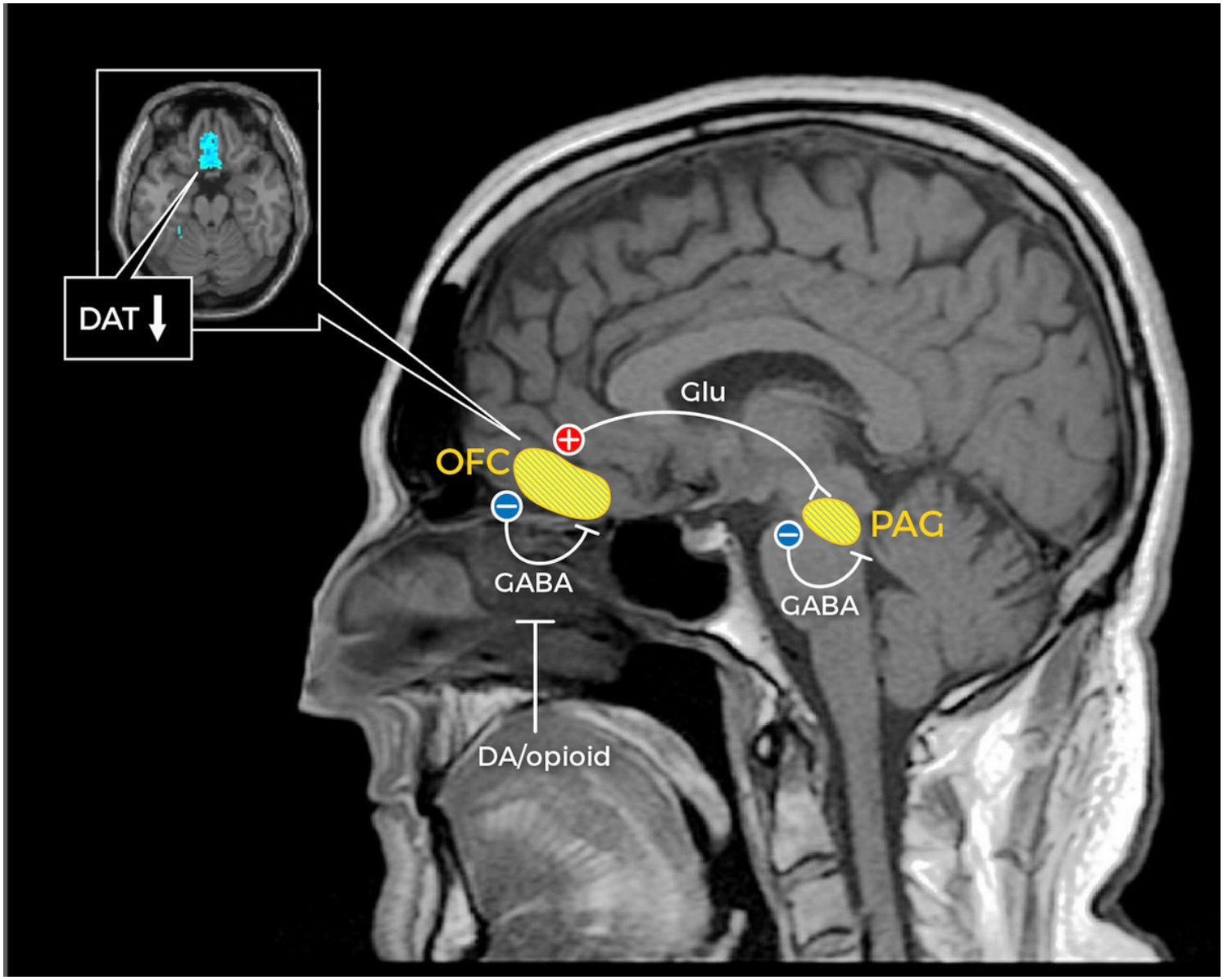


Figure 4

Schematic diagram of chronic headache caused by low availability of dopamine transporters. Glutamatergic projections from the ventrolateral OFC to the periaqueductal grey are inhibited by GABAergic neurons, which in turn is inhibited by opioids or dopamine. DA = dopamine; DAT = dopamine transporter; GABA = Gamma-aminobutyric acid; Glu = glutamic acid; OFC = orbitofrontal cortex; PAG = periaqueductal grey.

Supplementary Files

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- STROBEchecklistcrosssectional.docx