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Drug consumption in medication overuse headache is influenced by brain-derived neurotrophic factor Val66Met polymorphism

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Abstract Medication overuse headache (MOH) can be considered a clinical condition at the boundaries between drug addiction and chronic pain disorder. The common 196G > A single-nucleotide polymorphism of BDNF gene, resulting in a valine 66 to methionine (Val66Met), is related with behaviour disorders and substance abuse. With the aim of identifying a worsening factor in MOH, rather than the detection of a specific risk factor for the development of the disease, we investigated whether the presence of a functional BDNF polymorphism might determine clinical differences within a group of 90 MOH patients, particularly in monthly drug consumption, that is the hallmark of disease. Directly comparing MOH patients homozygous for G allele (G/G) with carriers of A allele (non-G/G), we have observed 47 G/G genotypes and 60 non-G/G genotypes. Non-G/G had a higher consumption of monthly drug number (Cohen's $d = 0.76$) than G/G patients. At multiple regression analysis, the Val66Met BDNF polymorphism emerged as a significant independent predictor of analgesic drug consumption (Beta = 0.33, Cohen's $f^2 = 0.134$). These findings showed an influence of examined BDNF polymorphism in the MOH clinical features, supporting the idea that MOH is a substance abuse disorder.

Keywords Brain-derived neurotrophic factor (BDNF) · Genetic polymorphisms · Medication overuse headache (MOH) · Addictive behaviour

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Introduction

Medication overuse headache (MOH) is a chronic headache disorder due to overuse of analgesic medicines, taken to treat a primary headache, and remitted by drug discontinuation [1]. MOH has long been considered as a "biobehavioural" disorder, in which the biological predisposition to develop a chronic headache interacts with an individual behaviour prone to develop a dependence disorder [2, 3]. The molecular basis of MOH are largely unknown, though it has been hypothesized that this subtype of headache could be mediated by cognitive impulsivity, and shares some

pathophysiological mechanisms with drug addiction, including dysfunction of the frontostriatal system and central pain sensitization induced by drug overuse [4]. Based on this hypothesis, there seems to be a role in MOH for BDNF (brain-derived neurotrophic factor), because of its role in central pain sensitization and its relationship with substance-related disorders [5, 6].

BDNF is a member of "neurotrophin" family, a unique group of polypeptide growth factors that influence differentiation and survival of neurons in the developing nervous system. BDNF is involved in long-term potentiation (LTP), and therefore in learning and memory mechanisms. Also, a pathogenic role for BDNF has been shown in pain transduction and sensitization, in epilepsy, and in neuropsychiatric disorders [5].

BDNF gene, mapped to chromosome 11p, encodes for pro-BDNF that is subsequently cleaved in its mature form [5]. Recently, it has been observed that a common $196G > A$ single-nucleotide polymorphism (SNP) of BDNF gene, resulting in a valine at residue 66 to methionine (Val66Met) substitution in pro-BDNF protein, exhibits a functional relevance in that it seems to reduce BDNF activity by altering neurotrophin trafficking [7]. The Val66Met variant affects anatomy, cognition and behaviour in adults [7] and leads to memory impairment [5] and susceptibility to obsessive-compulsive, eating, substance abuse and mood disorders [6, 8–10].

The rationale behind our study derives from two findings, which have been consistently reported in previous researches: (1) overuse of analgesic drugs is a defining feature of MOH and, for this reason, MOH has been related to behavioural syndromes associated with substance abuse [1–3], (2) there is evidence that proneness to use/abuse substances is associated with the allele A of BDNF polymorphism [6].Therefore, we tested the frequency of the Val66Met genotype in a sample of MOH patients, and compared clinical features between individuals homozygous for G allele (G/G) and carriers of the allele A (non-G/G). Aim of this study is to confirm our hypothesis that allele A of the examined BDNF polymorphism interfere with MOH, seeking for clinical and psychiatric differences between the two groups, mainly in the monthly drug consumption, that is both the clinical hallmark of disease, and the feature closest to abuse disorder.

We would like to emphasize that, although such studies are necessary to get a deeper understanding of the association between MOH and BDNF polymorphism, the present study did not intend to ascertain whether the BDNF polymorphism is a risk factor for the development of MOH, but only an aggravating factor for subjects that have already developed the disorder.

Materials and methods

Subjects and clinical data

Unrelated consecutive MOH patients were enrolled from two Italian University Headache Clinics: the inpatient Headache-Unit of IRCCS "C. Mondino" Institute of Neurology Foundation (Pavia), and Headache Outpatient Department of University of Rome "La Sapienza", among those admitted with a diagnosis of probable MOH [1], to undergo withdrawal from their overused medications. Although revised criteria were formulated for MOH [11], patients' enrolment was started before their statement, thus original ICHD-II version (i.e. in the presence of headache improvement within 2 months after analgesics withdrawal) [1], that is more conservative, was adopted to recruit all patients; a retrospective analysis will also confirm that all enrolled patients fulfilled the revised criteria.

Socio-demographic and clinical data were obtained by anamnesis; consumption of analgesic drugs per month (from here, monthly drug number), days with headache per month (from here, monthly headache days) and days with drug consumption per month (from here, monthly drug days) were self reported by patients through a headache diary, received at the time of first visit. Inclusion criteria were: (a) patient written informed consent, (b) absence of other major medical conditions, (c) absence of psychiatric disorders that could sustain a chronic pain condition (psychotic and/or somatoform disorders), (d) to have accurately completed the last 3-month pre-withdrawal diary, (e) ability to complete the psycho-diagnostic assessment, (f) diagnostic confirmation of MOH after withdrawal. Our Institutional Ethical Committees approved the study, conducted according to Declaration of Helsinki.

Trained interviewers, blinded to headache diagnosis, performed psychiatric assessment. Presence of categorical psychiatric diagnosis was investigated through four modules of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Clinician Version [12]: mood episodes, mood disorders, anxiety disorders, and eating disorders. Moreover, a dimensional assessment was made with the Beck depression inventory (BDI), a self-reported questionnaire to measure the presence and severity of depressive symptoms [13].

Molecular analyses

With the patients' written informed consent, 10 cc of peripheral blood were collected, total genomic DNA purified [14], and genotyping for the BDNF Val66Met-BDNF variant was performed essentially as reported [15]. Genotyping was performed blind to clinical and psychiatric data.

Power calculation and statistical analysis

All data obtained in the three phases of the study (socio-demographic and clinical recordings, psychiatric assessment, and genetic determinations) were merged in a all-comprehensive database by an independent data-manager, which opened the blind and performed the sample size analysis on a preliminary group, to indicate the minimal number of patients needed in the study, and statistical analyses on definitive data.

On the base of initial 36 patients, a sample size analysis was performed to obtain the required number of subjects to fulfil a desired power of 80% with significance level at 5% [16]. Because our primary endpoint was to detect a difference in number of analgesics consumed per month by patients between the two groups (see introduction), we divided G/G from non-G/G subjects and calculated the monthly mean of drug consumption: 21 non-G/G subjects consumed meanly 45.57 doses versus 32.93 doses of 15 G/G subjects ($t = 1.887$, $P = 0.07$, Cohen's $d = 0.65$). These data were used to calculate the sample size. Required sample size resulted to be 87 subjects, respectively, 51 for non-G/G and 36 for G/G group.

Descriptive statistics to compare BDNF genotypes were performed using parametric or, when appropriate, non-parametric tests. A stepwise multiple linear regression analysis was employed to identify significant predictors of the monthly drug number in the entire sample. In addition, to well-know indexes of null hypothesis significance testing, effect size measures were also reported to recognize the value of the degree of association among variables, particularly between BDNF polymorphism group and monthly drug number [17, 18]. Effect sizes were calculated with the phi (φ) coefficient [or, when appropriate, Cramér's V (φ_c)] for χ^2 test, with Cohen's d for Student's t test, with partial Eta squared (η_p^2) for the analysis of variance (ANOVA), and with Cohen's f^2 for multiple regression [19]. Statistical significance was set at 5%.

Results

A hundred and seven MOH patients (84 women and 23 men; age, mean ± SD: 46.741 ± 11.36 years) were enrolled in the study. Depending on the type of overused drug, patients were divided into four groups: 29 patients (27.10%) consumed exclusively triptans, 18 (16.82%) exclusively non-steroidal antinflammatory drugs (NSA-IDs); 27 (25.23%) exclusively combination drugs (combination), and 33 (30.84%) associated different types of drugs (association). None of the patients consumed opioid drugs; all types of combination drugs consumed by our patients resulted to contain caffeine. By genotyping entire

MOH population, we identified seven cases of harboured A/A genotype (6.54%), 53 were G/A (49.53%), and 47 were G/G (43.93%). Samples were in Hardy-Weinberg equilibrium ($\chi^2 = 2.460$, $df = 1$, $P = 0.12$ for the null hypothesis).

A preliminary analysis was performed to investigate differences in monthly drug numbers between A/A (mean ± SD 54.86 ± 19.05), A/G (49.06 ± 27.19) and G/G (33.83 ± 14.04) group. Due to small sample size in A/A group, we used the Kruskal–Wallis H test, the Mann–Whitney U test, and the Monte Carlo method, a bootstrapping technique with a resampling process that produces nonparametric significance estimates. The three groups differed statistically (among them) in number of monthly used drug [mean rank: A/A, 76.21; A/G, 61.43; G/G, 42.31; $H = 13.317$, $df = 2$, $P < 0.0001$ (99% confidence interval <0.0001–0.001)]. Pairwise comparisons (significance threshold adjustment with Bonferroni's correction, $P = 0.0167$) showed higher values in A/A [mean rank: A/A, 43.00; G/G, 25.19; $U = 56.000$, $Z = 2.794$, $P_{2\text{-tailed}} = 0.004$ (99% CI 0.003–0.006)] and A/G [mean rank: A/G, 58.82; G/G, 41.12; $U = 804.500$, $Z = 3.046$, $P_{2\text{-tailed}} = 0.002$ (99% CI 0.001–0.003)] when compared with G/G patients, but no difference between A/A and A/G [mean rank: A/A, 37.21; A/G, 29.61; $U = 138.500$, $Z = 1.082$, $P_{2\text{-tailed}} = 0.29$ (99% CI 0.28–0.30)].

Till now obtained results confirmed our decision to consider together carriers of allele A in the non-G/G group: (1) above-mentioned explorative analysis showed that A/A and A/G groups were not different in terms of monthly drug consumption, (2) as expected, a little size of A/A subjects was found, and it makes difficult to perform complex, multivariate statistical analysis with an acceptable degree of reproducibility.

As mentioned, to perform further statistical analyses, the population was divided into two groups: G/G genotype (47 subjects, 43.93%), homozygotes for valine (allele G), and non-G/G genotype (60 subjects, 56.07%), carriers of metionine 66 (allele A), either in heterozygosity or in homozygosity.

Clinical characteristics and descriptive statistics for the two groups are illustrated in detail in Table 1. Non-G/G showed a higher consumption of monthly drug number (non-G/G vs. G/G, mean ± SD: 49.73 ± 26.31 vs. 33.83 ± 14.04; $t = 4.011$, $P < 0.0001$, $d = 0.76$) and longer MOH duration (6.43 ± 7.78 vs. 3.09 ± 3.66; $t = 2.944$, $P = 0.004$, $d = 0.56$) when compared to G/G patients. There were no significant differences between G/G and non-G/G patient groups in terms of other clinical and socio-demographic features. Moreover, no significant associations were found among the two groups and current occurrence of psychiatric disorders.

Table 1 Table shows descriptive socio-demographic, headache, and psychiatric data for the entire study sample

	Non-G/G (n = 60; 56.07%)	G/G (n = 47; 43.93%)	Statistics		
Gender					
Women	47 (43.93%)	37 (34.58%)	$\chi^2 = 0.002$	$P = 0.96$	$\varphi = 0.005$
Men	13 (12.15%)	10 (9.35%)			
Age (years)	47.57 ± 11.47	44.94 ± 11.15	$t = 1.192$	$P = 0.24$	$d = 0.23$
Education (years)	12.34 ± 4.40	12.59 ± 4.09	$t = -0.262$	$P = 0.79$	$d = -0.06$
Employment					
Yes	38 (35.51%)	32 (29.91%)	$\chi^2 = 0.263$	$P = 0.61$	$\varphi = -0.050$
No	22 (20.56%)	15 (14.02%)			
Age of primary headache onset (years)	16.20 ± 7.42	15.32 ± 7.14	$t = 0.620$	$P = 0.54$	$d = 0.12$
Primary headache duration (years)	32.07 ± 11.96	30.43 ± 14.28	$t = 0.647$	$P = 0.52$	$d = 0.13$
Age of MOH onset (years)	41.53 ± 11.82	42.66 ± 12.64	$t = 0.475$	$P = 0.64$	$d = -0.09$
MOH duration (years)	**6.43 ± 7.78**	**3.09 ± 3.66**	**$t = 2.944$**	**$P = 0.004$**	**$d = 0.56$**
Monthly headache days	24.82 ± 6.07	25.89 ± 5.70	$t = -0.935$	$P = 0.35$	$d = -0.18$
Monthly drug number	**49.73 ± 26.31**	**33.83 ± 14.04**	**$t = 4.011$**	**$P < 0.0001$**	**$d = 0.76$**
Monthly drug days	23.63 ± 6.14	22.17 ± 6.46	$t = 1.195$	$P = 0.24$	$d = 0.23$
Drug type					
Triptans	18 (16.82%)	11 (10.28%)	$\chi^2 = 0.707$	$P = 0.87$	$\varphi_c = 0.081$
NSAIDs	10 (9.35%)	8 (7.48%)			
Association	17 (15.89%)	16 (14.95%)			
Combination	15 (14.02%)	12 (11.21%)			
Current psychiatric diagnosis					
Present	45 (42.06%)	34 (31.78%)	$\chi^2 = 0.096$	$P = 0.76$	$\varphi = 0.030$
Absent	15 (14.02%)	13 (12.15%)			
Current mood diagnosis					
Present	27 (25.23%)	22 (20.56%)	$\chi^2 = 0.035$	$P = 0.85$	$\varphi = -0.018$
Absent	33 (30.84%)	25 (23.36%)			
Current anxiety diagnosis					
Present	32 (29.91%)	24 (22.43%)	$\chi^2 = 0.054$	$P = 0.82$	$\varphi = 0.023$
Absent	28 (26.17%)	23 (21.50%)			
Current eating diagnosis					
Present	6 (5.61%)	2 (1.87%)	$\chi^2 = 1.257$	$P = 0.26*$	$\varphi = 0.108$
Absent	54 (50.47%)	45 (42.06%)			
Current double psychiatric diagnosis					
Present	18 (16.82%)	15 (14.02%)	$\chi^2 = 0.045$	$P = 0.83$	$\varphi = -0.021$
Absent	42 (39.25%)	32 (29.91%)			
BDI (score)	13.15 ± 8.53	12.09 ± 8.73	$t = 0.634$	$P = 0.53$	$d = 0.12$

Continuous data are expressed as mean ± SD, whereas categorical data are frequencies and percentages of total subjects. Differences between non-G/G and G/G patients, with bivariate statistics results, are also illustrated. *Bold* entries represent the statistical significant differences

MOH medication overuse headache, *BDI* beck depression inventory, *Monthly drug days* number of days per month in which patient assumed at least one dose of drug to treat headache, *Drug type* triptans (exclusively one, or more, types of triptan), NSAIDs (exclusively one, or more, type of non steroidal antinflammatory drugs), association (use of different types of drug in association); combination (drugs of combination, with more active ingredients)

* Fisher's exact test, two-tailed: $P = 0.46$

A two-way analysis of covariance (ANCOVA) was employed to investigate the group effect (two between-subject factors: "genotype", non-G/G vs. G/G; "drug type", triptans vs. NSAIDs vs. association of drugs vs. drugs of combination) on monthly drug number (dependent variable); monthly headache days and monthly drug days were used as covariate in this analysis to reduce the error variance. The ANCOVA model was highly significant ($F_{9,97} = 7.149$,

$P < 0.0001$) and explained more than one-third of variance (adjusted $R^2 = 0.343$). The "drug type" effect was not significant ($F_{3,97} = 0.383$, $P = 0.77$, $\eta_p^2 = 0.011$) whereas the "genotype" effect was statistically considerable ($F_{1,97} = 12.487$, $P = 0.0006$, $\eta_p^2 = 0.114$); the interaction effect of "genotype" × "drug type" was also significant ($F_{3,97} = 2.776$, $P = 0.04$, $\eta_p^2 = 0.079$) (Fig. 1). Among the covariate, monthly drug days was highly significant ($F_{1,97} = 16.918$, $P < 0.0001$, $\eta_p^2 = 0.149$) but there was no effect of monthly headache days ($F_{1,97} = 0.043$, $P = 0.84$, $\eta_p^2 = 0.000$). Pairwise comparisons [Fisher's least square difference (LSD); significance threshold adjustment for multiple comparison test with Bonferroni's correction (0.05/8): $P = 0.00625$] showed no genotype difference in patients who consumed triptans ($P = 0.74$) and NSAIDs ($P = 0.16$); on the contrary, when compared with G/G, non-GG patients had a statistically higher consumption of drug both among those that used association of drugs ($P = 0.009$; this value, however, did not reach the adjusted threshold of significance) and among consumers of drugs of combination ($P < 0.0001$).

As showed in Table 2, in the multiple regression analysis, the Val66Met BDNF polymorphism (Beta = 0.33, $t = 3.669$, $P < 0.0001$, $f^2 = 0.134$) and the BDI score (Beta = 0.19, $t = 2.090$, $P < 0.04$, $f^2 = 0.037$) emerged as significant, independent predictors of the monthly drug consumption in MOH patients. No further variables, considered as possible predictors, entered the regression model (see Table 2).

Discussion

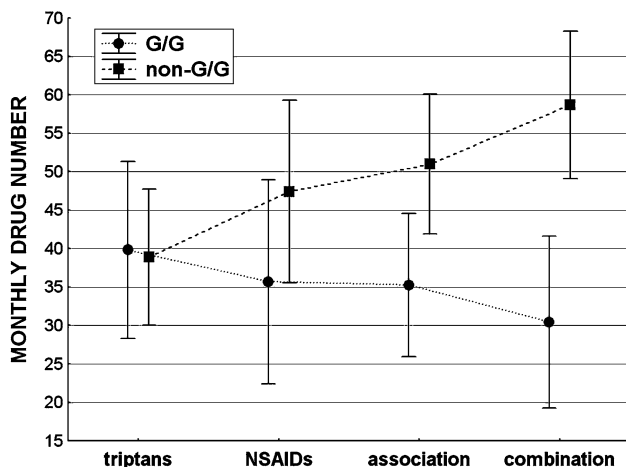Consistent with our working hypothesis, monthly drug consumption in MOH patients resulted to be influenced by the examined BDNF polymorphism (Fig. 2), both if univariate, and both if multiple regression analyses (to control the association for such possible confounding factors) are performed. The relationship between monthly drug consumption and Val66Met polymorphism was also confirmed by effect size calculation (medium effect at t test, small to medium effect at regression analysis). The fact that a unique BDNF SNP could account for these observed

Table 2 Results of stepwise multiple regression analysis: BDNF polymorphism (G/G genotype) and BDI score (depressive symptoms) are the predictors of monthly drug number in MOH patients

Variable	Beta	t	P
BDNF gene	**0.33**	**3.669**	**<0.0001**
BDI	**0.19**	**2.090**	**<0.04**
MOH duration	0.12	1.242	0.22
Drug type	0.08	0.917	0.36
Gender	0.08	0.908	0.37
Employment	−0.07	−0.754	0.45
Current psychiatric diagnosis	0.05	0.532	0.60
Age of headache onset	−0.02	−0.167	0.87
Age	0.01	0.123	0.90

Significant predictors are in bold

Stepwise model summary: adjusted $R^2 = 0.137$, $F_{2,104} = 9.424$, $P < 0.0001$, $f^2 = 0.181$

Stepwise model change statistics: first step, variable entered = BDNF gene, R^2 change = 0.118, $F_{1,105}$ to enter/to remove = 14.030, $P < 0.0001$, $f^2 = 0.134$; second step, variable entered = BDI, R^2 change = 0.036, $F_{1,104}$ to enter/to remove = 4.368, $P < 0.04$, $f^2 = 0.037$

MOH medication overuse headache, *BDNF* brain-derived Neurotrophic factor, *BDI* beck depression inventory

Fig. 1 Interaction effect of "genotype" × "drug type" on monthly drug number. Markers (*black circles* and *squares*) indicate mean, *vertical bars* denote 0.95 confidence intervals
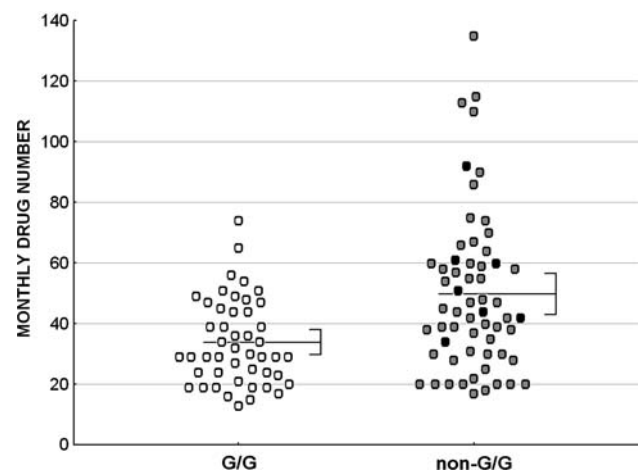

Fig. 2 Monthly drug number in G/G and non-G/G patients. Each *circle* represents an individual patients. In non-G/G group, the *black circles* show A/A patients, the *grey ones* with *black ring* A/G patients. *Horizontal bars* indicate mean. *Vertical bars* denote 0.95 confidence intervals

effects is noteworthy, because drug consumption is a multifactorial variable, surely influenced by many other genetic and environmental factors.

MOH can be considered as a clinical condition at the boundaries between drug addiction and chronic headache. The hypothetical involvement of BDNF in the pathophysiology of MOH was suggested by: (1) the association between the Val66Met polymorphism and drug abuse disorders, (2) the role of BDNF in modulating central and peripheral pain. In this study group, non-G/G patients showed a more severe clinical picture, because they had used a higher number of analgesic drugs in the previous 3 months, and had longer disease duration. Showing for the first time a role in MOH, our findings confirm that somehow the examined BDNF polymorphism is involved, as an independent factor, in pathophysiology of this headache condition. Although it might sound too approximate, considering the association between Met66 pro-BDNF and a reduced BDNF activity [7], it is tempting to speculate that in MOH a lower BDNF activity is a worsening factor. If MOH is regarded as a drug abuse disorder, our data would agree with previous reports of an association between the Val66Met polymorphism and substance addition [6]. The proneness to abuse (i.e. to have an impulse dyscontrol), previously reported in non-G/G subjects, would be expressed in MOH patients by higher drug consumption. In light of this hypothesis, the monthly drug consumption could be considered as an important marker of MOH severity. In fact, although the defining factor in MOH is the number of days with drug intake, the variability of this value theatrically ranges from 10 to 30; on the contrary, a hypothetic upper limit for variability of monthly drug consumption does not exist and patients could be distributed on a wider range that better reflects their proneness to abuse (and/or headache severity).

Previous studies have attempted to evaluate BDNF role in headache disorders. In particular, it has been demonstrated an increased level of BDNF in cerebrospinal fluid (CSF) of patients with a chronic daily headache (with or without drug overuse), in comparison to healthy controls [20]. Furthermore, it has been shown a reduced level of platelet BDNF in the interictal phase of episodic migraineurs and cluster headache patients, in comparison to healthy controls [21]. More recently, a BDNF elevation in CSF was demonstrated both in chronic migraine and in fibromyalgic patients [22]. These three studies were much different from our research for two reasons: the use of diverse classification criteria in the first study; in general, the different study designs, with the lack of relations among BDNF levels, clinical markers of disease severity, and the patients' BDNF genotype. However, these findings showed the involvement in chronic pain pathophysiology of BDNF up regulation, and might support indirectly our

hypothesis that in MOH patients a BDNF hypo-activity, related to Val66Met polymorphism, does not influence pain severity, but impulsive behaviour.

To the best of our knowledge, Val66Met polymorphism was never tested on pain modulation. Pending specific studies on this topic, only speculations could be made about the chance that the higher drug intake is a consequence of putative BDNF-mediated higher pain sensitivity, or not. However, the pain modulation is linked to BDNF release and up-regulation [23, 24], whereas Val66Met polymorphism is related with a reduction of BDNF activity [7]. These observations, though indirectly, might lend support the idea that BDNF influence on MOH is played in terms of impulsivity modulation, as in other drug abuse disorder [4], and not pain hypersensitivity.

Moreover, a recent paper analysed influence of Val66-Met polymorphism on episodic migraine. Examined polymorphism resulted neither associated to development of migraine (comparing polymorphism frequency in a population of episodic migraineurs with a healthy control group), nor associated with differences in terms of clinical characteristics (within the only migraine group) [25]. Consistent with these data, because Val66Met polymorphism seems to be unable to influence development and clinical features of migraine, we suppose that observed worsen effect of polymorphism on MOH is likely driven by the A allele related proneness to abuse [6], and, in turn, that the monthly drug consumption in MOH patients is not necessarily the expression of headache severity.

As reported above, we have also recorded the type of drug consumed by each patient and they were segregated in four groups: triptans, NSAIDs, association of different type of drugs and drugs of combination. It is noteworthy that differences between G/G and non-G/G emerged only in the fourth group (drugs of combination, all containing caffeine), and a trend was also found for the association of drugs. If one consider that non-G/G subjects are supposed to have a BDNF hypoactivity [7], and that BDNF is a kind of biological reward for presynaptic neurons [5], our observations could mean that the lack of reward induces non-G/G subjects in the continue search of different type of drugs, or in caffeine seeking (for its psychotropic effect). None of the patients reported to use drugs containing opioids; therefore, we cannot confirm our hypothesis with this class of drugs.

Severity of depressive symptoms (as measured by BDI score) was found as another independent predictor of drug consumption in MOH patients. The role of depression in headaches has been previously reported and discussed elsewhere [26, 27]. Although a relation between depression and Val66Met polymorphism was frequently found [10], in this study the G/G and non-G/G groups neither differ statistically for the severity of depressive symptoms, nor were

they associated significantly with a psychiatric disorder. Maybe these associations are covered in our population by already described relationship between MOH and psychiatric comorbidity that could not be further increasable by examined polymorphism. Moreover, observed lack of association suggests that this BDNF polymorphism and depression might have an effect on MOH monthly drug consumption through different and unrelated mechanisms.

In summary, our results showed an influence of BDNF polymorphism Val66Met on drug consumption in MOH patients. The polymorphism is likely not related to severer forms of headache, but with a BDNF hypoactivity, in turn related to substance abuse behaviour, consistent with observed higher caffeine seeking. Therefore, aggravating effect of examined polymorphism in MOH patients could be driven by its proneness to develop an impulsivity dyscontrol, the cornerstone of any substance abuse disorder. In other words, we suppose that MOH is not only a very severe headache, but also a complicated bio-behavioural disorder, not dissimilar to a kind of addictive disorder, preferentially developed by some migraineurs, aggravated by conditions unrelated to previous headache clinical features; however, related to behavioural impulsivity dyscontrol, as other substance abuse disorders.

Moreover, we would like to highlight that analysis of SNPs within functionally related genes appears as a good tool in headache research to identify mechanisms potentially involved in disease pathogenesis.

Conflict of interest   None.

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