Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine

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The way in which medication overuse transforms episodic migraine into chronic daily headache is unknown. To search for candidate brain areas involved in this process, we measured glucose metabolism with 18-FDG PET in 16 chronic migraineurs with analgesic overuse before and 3 weeks after medication withdrawal and compared the data with those of a control population (n = 68). Before withdrawal, the bilateral thalamus, orbitofrontal cortex (OFC), anterior cingulate gyrus, insula/ventral striatum and right inferior parietal lobule were hypometabolic, while the cerebellar vermis was hypermetabolic. All dysmetabolic areas recovered to almost normal glucose uptake after withdrawal of analgesics, except the OFC where a further metabolic decrease was found. A subanalysis showed that most of the orbitofrontal hypometabolism was due to eight patients overusing combination analgesics and/or an ergotamine-caffeine preparation. Medication overuse headache is thus associated with reversible metabolic changes in pain processing structures like other chronic pain disorders, but also with persistent orbitofrontal hypofunction. The latter is known to occur in drug dependence and could predispose subgroups of migraineurs to recurrent analgesic overuse.

Keywords: PET; orbitofrontal cortex; migraine; addiction; medication overuse headache

Abbreviations: FDG = [18F]fluorodeoxyglucose; FDG-PET = 18F-fluoro-deoxyglucose positron emission tomography; MOH = medication overuse headache; MRI = magnetic resonance imaging; OFC = orbitofrontal cortex; PET = positron emission tomography; rCBF = regional cerebral blood flow; VAS = visual analogue scale

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Introduction

Overuse of acute medication is the most frequent factor associated with the transformation of episodic migraine into chronic daily headache (Matthew et al., 1982). The latter is called ‘medication overuse headache’ (MOH) in the second edition of the International Classification of Headache Disorders (ICHD-II, 2004). It is classified as a secondary headache disorder, which may evolve from any type of primary headache but mainly from episodic migraine. MOH is a disabling health problem, which may affect 1–2% of the general population (Colas et al., 2004) and 15–30% of patients in tertiary care centres worldwide (Schoenen et al., 1989; Bigal et al., 2004).

A causal relationship between medication overuse and the aggravation of primary headache disorders has been questioned (see Tepper et al., 2002 for review). Clinical data, however, showing that MOH is usually rapidly reversible after medication withdrawal (Schoenen et al., 1989; Bahra et al., 2003) and the speed at which MOH develops with increasing intake or disappears after withdrawal varies between triptans, ergotamine or analgesics (Limmroth et al., 2002; Katsarava et al., 2005), indicate that medication overuse is the culprit. After medication withdrawal, amelioration of daily headache is the rule in the majority of patients who...
return to an episodic migraine pattern. In a minority (20%) the headache does not improve within 2 weeks after withdrawal which is a diagnostic criterion of ‘chronic migraine’ in ICHD-II (code 1.2.5; ICHD-II, 2004). Higher relapse rates were found in patients who overused combination analgesics containing codeine or barbiturates (Diener et al., 1989; Pini et al., 1996, 2001; Suhr et al., 1999).

The precise mechanisms underlying the development of MOH are not understood. Various pathophysiological abnormalities have been reported: increased pain after electrical forearm stimulation favouring central sensitization (Fusco et al., 1994), NMDA receptor dysfunction (Nicolodi et al., 1997), low beta-endorphin and opioid levels (Anselmi et al., 1997), increased norepinephrine turnover (Schoenen et al., 1987) or increased inositolphosphate production in platelets suggesting abnormal signal transduction (Hering et al., 1993). Although some of these findings may help to understand the chronic pain, they offer no explanation for several clinical observations suggesting that dependence and predisposition might play a role in MOH sufferers. For instance, up to 30% of patients relapse within 1 year after medication withdrawal (Schoenen et al., 1989; Katsarava et al., 2005); only ~10% of severely affected migraineurs, not all of them, develop MOH (Katsarava et al., 2004) and the syndrome can have a familial character (Couch et al., 1999). There is some evidence for co-morbidity between migraine and substance abuse or dependence (see Radat and Swendsen, 2005 for a review). Clinical and neurological similarities between MOH and drug addiction have been emphasized (see Calabresi and Cupini, 2005 for a review), but there is at present no direct evidence for a common underlying mechanism.

Functional imaging studies in acute and chronic pain have demonstrated that multiple brain areas contribute to the various facets of pain processing and that they are interconnected within the so-called ‘pain network’ (see Peyron et al., 2000 for a review). Regarding migraine, much interest was aroused by the finding of ictal regional cerebral blood flow (rCBF) increases in the upper brain stem (Weiller et al., 1995; Bahra et al., 2001; Afridi et al., 2005), but the identified areas may also be involved in other chronic pain syndromes (Kupers et al., 2000) and in experimental hyperalgesia (Iadarola et al., 1998; Zambreanu et al., 2005). Drug dependence and addiction are also accompanied by metabolic changes in several brain regions. In particular, the dysfunction found in the orbitofrontal cortex (OFC) and the striato–thalamo–orbitofrontal circuit has been emphasized in abuse disorders (London et al., 2000; Volkow et al., 2004).

We hypothesized therefore that, in MOH, metabolic abnormalities might be found in brain areas belonging to the pain network including brain stem nuclei but also in those that are involved in drug dependence. To verify this hypothesis we performed 18F-fluoro-deoxyglucose positron emission tomography (FDG-PET) in migraine patients with longstanding MOH and compared the results to a PET data bank of healthy volunteers.

**Materials and methods**

**Subjects**

The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège. Written informed consent was obtained from all patients and from all control subjects according to the Declaration of Helsinki.

**Control population**

The control population consisted of drug-free, healthy volunteers without any significant medical, surgical or psychiatric history. Control subjects were devoid of any neurological disorder including recurrent headache. FDG-PET data were obtained from 68 subjects (30 females and 38 males; mean age 45 ± 21 years).

**Patient population**

We prospectively selected 16 migraine patients suffering from chronic daily or almost daily headache with repeated daily or almost daily intake of acute anti-migraine drugs (13 females and 3 males, mean age 42.5 ± 11 years). They fulfilled the ICHD-II criteria (ICHD-II, 2004) for MOH and had a mean monthly symptomatic migraine drug intake of 105 tablets or suppositories. Eight patients were overusing non-narcotic analgesics, chiefly paracetamol (code 8.2.3); six were taking combination analgesics (paracetamol–codeine and/or aspirin–paracetamol–caffeine) (code 8.2.5); two were using an ergotamine-caffeine preparation (code 8.2.1). Before evolving into chronic daily headache and MOH, all patients had had a clear history of episodic migraine without aura (n = 15) or with aura (n = 1) since adolescence (mean age of the first migraine attack: 15 ± 3 years) (ICHD-II codes 1.1 and 1.2.1). Mean duration of headache was 28 ± 12 years and mean duration of MOH 7 ± 6 years.

Subjects with any other serious organic or psychiatric disease were excluded. Before inclusion, all patients were tested on the Hamilton rating scale for depression and only those who had a normal score (≤10) were considered for the study.

In the patients, FDG-PET was performed before (Scan 1) and ~3 weeks after analgesic or ergotamine withdrawal (Scan 2). The acute anti-migraine drugs were stopped abruptly immediately after Scan 1 and withdrawal symptoms were prevented during the two following weeks with oral acamprosate (333 mg three times daily), which was interrupted at least 7 days before Scan 2. If necessary, ibuprofen (600 mg/day) was allowed twice per week and an oral or subcutaneous triptan once per week for disabling headache. Scan 2 was performed at an interval of at least 72 h after and before a migraine attack and symptomatic medication intake. We checked by telephone interview that the patient remained attack-free for at least 72 h after Scan 2. Prophylactic anti-migraine therapy was started only after Scan 2.

Patients filled in headache diaries for the whole study period, starting at least 3 weeks before Scan 1 up to at least Scan 2. Moreover, the intensity of headache at the time of each FDG-PET recording was measured on a 0–10 point visual analogue scale (VAS). The paired t-test was used to compare the VAS ratings between Scans 1 and 2, as well as the number of headache days between the 3-week run-in period and the 3-week interval between the two scans.

**Data acquisition**

**Positron emission tomography**

PET data were obtained on a Siemens CTI 951 16/32 scanner (Siemens, Erlangen) ~15–20 mm above the canthomeatal...
PET in medication overuse headache

line and in 2D mode. A transmission scan was performed to allow a measured attenuation correction. Data were reconstructed using a Hanning filter (cutoff frequency: 0.5 cycle/pixel) and corrected for attenuation and background activity. Resting cerebral metabolism was studied after intravenous injection of 5–10 mCi (185–370 MBq) $[^{18}F]$fluorodeoxyglucose (FDG). Subjects were scanned, eyes closed, with minimal environmental noise.

Magnetic resonance imaging

High resolution T1-weighted structural MRI (voxel size: 0.96 × 0.96 × 1.35 mm) was performed within 5 days after the PET study in each patient (1.5 T Magnetom imager, Siemens, Erlangen).

Data analysis

Data were analysed using statistical parametric mapping (SPM2 version; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (version 6.1, Mathworks Inc., Sherborn, MA). Images were spatially normalized into a standard stereotactic space (Talairach and Tournoux) using the MNI PET template (Montreal Neurological Institute) and smoothed using a 12 mm full-width-half-maximum (FWHM) isotropic kernel. PET data were co-registered with T1-weighted MRI scan.

The design matrix included the 16 patient scans recorded before drug withdrawal, the 16 patient scans recorded after drug withdrawal and the 68 control scans. Global activity normalization was performed by proportional scaling. For each scanning session, an analysis identified brain regions where resting glucose metabolism was significantly lower or higher in the patient than in the control group. The resulting set of voxel values for each contrast, constituting an SPM of the $t$-statistic (SPM(t)) was transformed to the unit normal distribution (SPM(Z)) and thresholded at $P = 0.001$ ($Z > 3.09$). Given our a priori knowledge of the involvement of areas related to chronic pain and drug dependence, results were thresholded at small-volume-corrected $P < 0.05$ (20 mm diameter sphere centred on peak voxels).

Results

Clinical data

According to their headache diary, all patients completely stopped the intake of analgesics as soon as Scan 1 was performed. During the 3-week period preceding medication withdrawal and Scan 1, the mean number of headache days was 19.4 ± 2.3; during the subsequent 3-week period from withdrawal up to Scan 2 this number was significantly reduced (11.9 ± 4.3; $P = 0.001$). By contrast, at the time of PET data acquisition, the mild headache most patients reported did, on average, not differ in severity between Scan 1 (VAS 2.9 ± 2.0) and Scan 2 (VAS 2.1 ± 1.7; $P = 0.08$). There were no drop-outs between Scans 1 and 2, and none of the subjects had a migraine attack within 72 h after Scan 2.

Imaging data

On FDG-PET Scan 1 performed while patients were still experiencing MOH, areas that were significantly less metabolically active in patients, compared with controls ($P < 0.001$), were identified in the bilateral thalami (ventral posterior lateral part), bilateral insula/ventral striatum and right posterior parietal lobule (Brodmann’s area 40) (Fig. 1). At lower threshold ($P < 0.005$) the orbitofrontal and anterior cingulate cortices were also hypometabolic ($P < 0.003$ and $P < 0.002$, respectively). In contrast, the cerebellar vermis showed a significant increase in metabolic activity in patients, compared with controls, during Scan 1 (Fig. 2).

| Table 1 Coordinates of peak voxels defined in the stereotactic space of Talairach and Tournoux |
|---------------------------------------------------|---------------------------------------------------|----------------|----------------|
| Region                                             | Coordinates                                      | $Z$            | $P$            |
|                                                   | $X$                              | $Y$              | $Z$ | $P_{SVC}$ |
| Scan 1 < controls                                  |                                                  |                |                |
| Left thalamus                                     | –12                               | –22              | 2    | 3.86      | <0.001 | <0.05 |
| Right thalamus                                    | 16                                 | –24              | 0    | 3.64      | <0.001 | <0.05 |
| Left insula/ventral striatum                      | –30                               | –10              | –4   | 3.87      | <0.001 | <0.05 |
| Right insula/ventral striatum                     | 36                                 | –6               | –4   | 3.47      | <0.001 | <0.05 |
| Right posterior parietal cortex                    | –42                               | –40              | 48   | 3.35      | <0.001 | <0.05 |
| Scan 1 > controls                                  |                                                  |                |                |
| Cerebellum (vermis)                               | 6                                 | –52              | –6   | 4.75      | <0.001 | <0.05 |
| Scan 2 < controls                                  |                                                  |                |                |
| OFC                                                | –6                                | 32               | –24  | 4.05      | <0.001 | <0.05 |

$Z$ scores are for the peak voxel in each region. The coordinates and statistics for hypometabolic (Scan 1 < controls) and hypermetabolic (Scan 1 > controls) regions before analgesic withdrawal are shown, as are those for the hypometabolic region after analgesic withdrawal (Scan 2 < controls). Only voxels with $P < 0.001$ are shown; * = cluster level corrected $P < 0.05$; $P_{SVC}$ = small volume corrected $P$ using a sphere with 20 mm radius.
Exclusive masking analysis revealed that thalamic, insular, parietal and cerebellar areas, dysmetabolic in Scan 1, resumed near-normal glucose metabolism in Scan 2, except the left thalamus, where this normalization was less pronounced. During the second scan, 3 weeks after analgesic withdrawal, the only area less metabolically active in patients than in controls was the OFC bilaterally (Brodmann’s area 11) (Fig. 3). There were no areas with significantly higher metabolism (Table 1).

We found no abnormal areas in the brain stem or hypothalamus on either scan.

Analyses directly comparing patients’ scans obtained during medication overuse state to post-withdrawal state confirmed these findings (see insets Figs 1–3). However, given the limited number of patients studied, this approach yielded lower levels of significance (uncorrected $P < 0.05$).

Finally, a separate analysis searched for differences between the eight mono-compound non-narcotic analgesics overusers (Patient group A) as compared to the eight combination analgesics overusers (Patient group B). Pre- and post-withdrawal orbitofrontal hypometabolism was significantly more pronounced in the latter group (Fig 3B inset). This subgroup analysis did not reveal analgesia-type-related brain dysfunction in brain regions other than the identified orbitofrontal cortex.

Discussion

To the best of our knowledge, this is the first functional imaging study in MOH. We observed metabolic changes in several brain areas that are recognized as being involved in pain processing and found to be hypo- or hyperactive in
chronic pain disorders or in experimental pain. In addition, glucose metabolism was abnormal in the medial orbitofrontal cortex, which may be related to dependence on the analgesic drugs and the high recurrence rate associated with MOH. We will discuss both abnormalities in turn.

**Abnormal metabolism in the pain network**

Our finding of an abnormal glucose metabolism before medication withdrawal in areas belonging to the pain network is in line with several imaging studies performed in other pain disorders. For example, bilateral blood flow changes have been described in ventral posterior lateral thalamus, posterior parietal cortex (Brodman’s area 40), insula/ventral striatum and anterior cingulate cortex in chronic neuropathic pain (Talbot et al., 1991; Hsieh et al., 1995; Iadarola et al., 1995), migraine attacks (Weiller et al., 1995; Bahra et al., 2001; Matharu et al., 2004; Afridi et al., 2005) and after painful stimuli in healthy volunteers (Coghill et al., 1994). These areas are involved in various aspects of pain processing: respectively in sensory discrimination, cognitive and attentional dimensions, emotional dimensions (Jones and Derbyshire, 1995; Coghill et al., 2001) and unpleasantness (Rainville et al., 1997). In most studies, as in ours, changes predominate in the right-sided posterior parietal cortex, which has been attributed to the role of the right hemisphere in the emotional

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**Fig. 2** (A) Hypermetabolic area before analgesic withdrawal in migraineurs projected on transverse sections of a normalized brain MRI template. Z-values are distances relative to the anterior-posterior commissural plane. For display, results were thresholded at \( P < 0.01 \).

(B) Plots of size effects (parameter beta estimates; centred arbitrary units) from SPM analyses, in selected voxels (ns = not significant; *, \( P < 0.05 \); **, \( P < 0.001 \)).

**Fig. 3** (A) Hypometabolic area 3 weeks after analgesic withdrawal in migraineurs projected on transverse sections of a normalized brain MRI template. Z-values are distances relative to the anterior-posterior commissural plane. For display, results were thresholded at \( P < 0.01 \).

(B) Plots of size effects (parameter beta estimates; centred arbitrary units) from SPM analyses, in selected voxels (*, \( P < 0.05 \); **, \( P < 0.001 \)). The inset shows results for patients overusing simple non-narcotic analgesics (subgroup A) compared to patients overusing combination analgesics (subgroup B) before (A-1, B-1) and after (A-2, B-2) drug withdrawal.
aspects of pain and behaviour (Coghill et al., 2001) and was also found during cluster headache attacks (Hsieh et al., 1996).

Many of the abovementioned studies have shown increased regional blood flow in areas of the pain network, while all of them were hypometabolic, and thus probably hypoactive, before withdrawal in our study of MOH. In fact, blood flow reduction was also reported in chronic neuropathic and central pain (Iadarola et al., 1995; Jones and Derbyshire, 1995; Hsieh et al., 1996) and attributed to inhibitory compensation, supposed to counterbalance the excessive excitatory inputs in pain-processing nuclei during long lasting pain (Iadarola et al., 1995). The patients we recorded had suffered from chronic, almost daily, headache for an average of 7 years, offering sufficient time for such a compensatory mechanism to develop. Whether deactivation of certain pain-processing areas could have been instrumental in the persistence of their headache remains to be determined. That this may be the case is suggested by the metabolic normalization of most areas after analgesic withdrawal and the parallel decrease in headache activity between the two scans. The metabolic change between Scans 1 and 2 cannot be explained by different pain levels at the time of the recordings, as VAS values were similar.

There were no metabolically abnormal brain stem areas in our study, which contrasts with reports in episodic (Weiller et al., 1995; Bahra et al., 2001; Afridi et al., 2005) or chronic migraine (Matharu et al., 2004). There may be several explanations for this difference. First, our patients were not recorded during full-blown attacks of episodic migraine or during exacerbations of chronic migraine but during interval headaches of mild intensity (mean VAS 2.9 on Scan 1 and 2.1 on Scan 2). The migrainous nature may be the crucial factor for the ictal demonstration of brain stem activations, if they have a primary role in pathogenesis; pain intensity may be more relevant if they are secondary phenomena. Moreover, whereas all previous studies showing brain stem activations in migraineurs used H215O labelled PET which measures CBF, our study was based on FDG-PET which reflects longer lasting metabolic neurono-glial changes.

We found increased glucose metabolism in the cerebellar vermis in MOH before, and normalization of metabolism after analgesic withdrawal. Although typically activated in chronic ongoing neuropathic pain (Iadarola et al., 1995) and in experimental acute phasic pain (Casey et al., 1994), the involvement of the cerebellar vermis was more recently emphasized in cognitive processing and suspected in drug addiction (see below). The cerebellum could thus play a pivotal role in MOH because it is involved both in pain processing and drug dependence.

Abnormal metabolism in the cerebellar vermis and orbitofrontal cortex

Besides its role in motor control and procedural memory the cerebellum is known to be involved in cognitive performances that do not necessarily imply motor activity (Allen et al., 1997). The cerebellar vermis is activated in depressed patients and related to a negative mood-related affective component (Dolan et al., 1992). Although a depressive mood may play a facilitating role in chronic daily headache and MOH, it was not a likely confounding factor in our study, since we excluded patients with a score of ≥10 on the Hamilton depression scale of which the average score in our group of subjects was 3.6 ± 2.3. Interestingly, an increase in cerebellar glucose metabolism has also been found after administration of an ‘ecstasy’ analogue (Schreckenberger et al., 1999) and in cue-elicited cocaine craving (Grant et al., 1996).

The changes observed in OFC metabolism could specifically be related to drug dependence in MOH. There is indeed convincing evidence from FDG-PET, behavioural and pharmacological studies that the OFC plays a crucial role in drive and compulsive behaviour and that its abnormal activation within the striato–thalamo–orbitofrontal circuit underlies the maladaptive behaviour of substance abuse, including expectancy, craving and impaired decision making (see for reviews London et al., 2000 and Volkow et al., 2004). For instance, the medial OFC is hypometabolic in substance abusers after protracted withdrawal but hypermetabolic shortly after drug intake or during craving in proportion to the intensity of the craving (London et al., 1990, Volkow et al., 1991). In our study, the OFC hypoactivity could thus have been partially masked during the first scan because the recordings were performed some time (at least 12 h) after the last intake of analgesics. This probably induced some craving and metabolic activation, as described in cocaine abusers (Volkow et al., 1991). Although the brain dysfunction is likely to vary in severity between MOH and drug addiction, we speculate that the OFC hypometabolism found in analgesic-abusing migraineurs 3 weeks after withdrawal is related to their dependence on the analgesic compound and that its persistence will predispose them to relapsing drug overuse, a frequent clinical finding (see Introduction).

Persistence of OFC hypometabolism for several months after withdrawal is well known in substance abusers, including in alcoholics (London et al., 2000; Volkow et al., 2004). It is thought to be responsible for reactivation of compulsive drug intake after prolonged periods of drug abstinence as a result of activation of reward circuits (nucleus accumbens, amygdala) by exposure either to the drug or to drug-conditioned stimuli (London et al., 2000). There is, furthermore, recent evidence (Robinson et al., 2004) that exposure to amphetamine, cocaine, nicotine or morphine produces persistent structural changes of dendritic trees and spines in brain regions involved in incentive motivation and reward, reflecting lasting reorganization of synaptic connectivity and possibly contributing to persistent behavioural abnormalities. The hypothesis that the persistence of OFC hypoactivity long after drug withdrawal predisposes a subgroup of migraine patients to a relapse of MOH can be tested in prospective studies. The finding in our subanalysis that the OFC hypometabolism is clearly more pronounced in patients overusing combination
pathogenesis of MOH. Both merit a more detailed study. It is likely that genetic liability and drug effects on the brain region in drug overuse. Up to now, only certain poly-
genesics may suggest that part of the metabolic change is drug
dependent. There is no published information on specific
genetic abnormalities in patients suffering from MOH. How-
ever, one may speculate that some of the neurotransmitters
controlling the OFC and the striato–thalamo–orbitofrontal
pathway could be suitable targets for genetic investigation.
The OFC receives dopaminergic innervation from the ventral
tegmental area and its hypoactivity in drug abusers is in pro-
portion to the availability of dopamine D2 receptors in the
striatum (Volkow et al., 2001 and 2004). A polymorphism in
the D2 dopamine receptor gene is more prevalent in certain
migraineurs (Peroutka et al., 1997; Del Zompo et al., 1998),
and a polymorphism in the D4 dopamine receptor might be
more frequent in migraine with aura patients developing
MOH (Montagna et al., 2003). The OFC receives significant
serotonergic innervation, and thus serotonin abnormalities
which are thought to play a pivotal role in migraine patho-
genesis could also contribute to the abnormal function of this
brain region in drug overuse. Up to now, only certain poly-
morphisms of the serotonin transporter have been reported to
be more frequent in migraineurs than in controls (Ogilvie et
al., 1998), but there are no data in MOH. To summarize,
it is likely that genetic liability and drug effects on the
striato–thalamic–orbitofrontal pathway cooperate in the
pathogenesis of MOH. Both merit a more detailed study.

Conclusions

Our FDG-PET study of chronic analgesic overuse headache in
migraineurs shows, on the one hand, that brain regions
belonging to the pain network are hypometabolic and rapidly
reactivated after withdrawal of the analgesic compound. The
cerebellar vermis is, by contrast, hypermetabolic before the
analgesic withdrawal. We propose that these changes are
consequences of the headache and may contribute to its
chronification. The OFC, on the other hand, shows persistent
hypometabolism after drug withdrawal, more so in patients
overusing combination analgesics. Considering the available
data on metabolic changes and role of the OFC in substance
abuse, we speculate that its hypoactivity in MOH favours
ongoing medication overuse and predisposes the patient to
a relapse of MOH. Hypoactivity of the OFC may be induced by
the repeated drug intake, but it could also reflect an
underlying, genetically determined, liability to medication
overuse. If confirmed, the orbitofrontal dysfunction may
have implications for the pharmacological and behavioural
management of MOH, for the prevention of recurrence after
drug withdrawal and for the detection of patients at risk of
developing MOH.

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References

Afridi SK, Matharu MS, Lee L, Kabie H, Friston KJ, Frackowiak RS, et al. A
PET study exploring the laterality of brainstem activation in migraine using
Allen G, Buxton RB, Wong EC, Courchesne E. Attentional activation of the
Serum beta-endorphin increase after intravenous histamine treatment of
Bahra A, Matharu MS, Bucal C, Frackowiak RS, Gooddy PJ. Brainstem
Bahra A, Walsh M, Menon S, Gooddy PJ. Does chronic daily headache arise
de novo in association with regular use of analgesics? Headache 2003; 43:
179–90.
Bigal ME, Rapoport AM, Sheffeld FD, Tepper SJ, Lipton RB. Transformed
migraine and medication overuse in a tertiary headache centre—clinical
Calabresi P, Cupini LM. Medication overuse headache; similarities with drug
Casey KL, Minoshima S, Berger KL, Koepp RA, Morrow TJ, Frey KA.
Positron emission tomography analysis of cerebral structures activated
specifically by repetitive noxious heat stimuli. J Neurophysiol 1994; 2:
802–7.
Coghill RC, Gilron I, Iadarola J. Hemispheric laterization of somatosensory
Distributed processing of pain and vibration by the human brain. J Neurosci
Colas R, Munoz P, Temprano R, Gomrez C, Pascual J. Chronic daily headache
with analgesic overuse: epidemiology and impact on quality of life. Neurology
Couch JR, Samuel S, Stewart KW, Leviston CL. The chronic daily headache
(CDH) with tension and migraine features: a final common pathway of
Association between dopamine receptor genes and migraine without aura
Diener HC, Dichgans J, Scholz E, Geiselhart S, Gerber WD, Bille A.
Analgesic-induced chronic daily headache: long-term results of withdrawal therapy.
Dolan RJ, Bench CJ, Brown RG, Scott LC, Friston KJ, Frackowiak RS.
Regional cerebral blood flow abnormalities in depressed patients with
Fusco BM, Colantoni O, Giaconova M. Alteration of central excitation
circuits in chronic headache and analgesic misuse. Headache 1997; 37:
486–91.


