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LINE BISECTION IN MEDICATION-OVERUSE AND CHRONIC TENSION-TYPE HEADACHES

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Abstract

Background: Both medication-overuse headache (MOH) and drug dependence share similar clinical features and the latter displays some deficits in visuospatial attention. The line bisection performance might help to indicate whether there is also a disruption in the visuospatial attention in MOH. Methods: We administered the line bisection test and measured anxiety and depression levels in 21 patients with MOH, 26 patients with chronic tension-type headaches (CTTH) and in 22 healthy volunteers. Results: On average, MOH patients significantly bisected leftward when referring to both frequency and magnitude, whereas the healthy volunteers and CTTH patients bisected slightly rightward. The levels of anxiety and depression were elevated in both MOH and CTTH patients compared to healthy volunteers, but the anxiety / depression levels were not correlated with the line bisection errors in all participants. Conclusions: We found a pronounced pseudoneglect in MOH, which might indicate a relatively hyperactive right or hypoactive left hemisphere, or both, suggesting the disorder's neuropsychological mechanism might overlap with that of drug dependence.

Keywords

• Pseudoneglect • Visuospatial attention • Handedness • Right and left hemisphere • Neuropsychological mechanism

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Introduction

Medication-overuse headache (MOH) is a common public health problem, but its exact pathophysiology is not well understood [1]. Recently, a central sensitization or defective endogenous pain control, and a possible link between drug dependence and MOH have been suggested as probable explanations [2,3]. For example, MOH and substance dependence disorder share some clinical features [4,5], and detoxification is a major treatment strategy for MOH [6-8]. In addition, MOH usually occurs in patients with a history of primary headaches, mainly migraine and tension-type headache. Clinical studies have shown that patients with migraine [9-11] or tension-type headache [11] often display various attention problems. Interestingly, deficits of visuospatial attention have also been documented in drug abusers [12,13]. There are, however, not many studies addressing the problems of attention in MOH.

Moreover, disruptions of visuospatial attention, i.e., the global spatial attention confined to the visual field, are a hallmark of the clinical neurological syndrome known as hemispatial neglect [14]. Line bisection has been employed as a sensitive test for unilateral neglect [15,16]. In this task, lateral deviation from the true centre indicates relative inattention to the contralateral side of space, and a consistent leftward error has been reported in healthy volunteers in the Western world, indicating a relative right cerebral dominance [17]. Nonetheless, patients with right hemispheric lesions usually place the subjective midpoint to the right of the true centre [17]. Using the technique in headache research, Hu *et al.* [18] found that migraine patients bisected slightly rightward, while both chronic tension-type and frequent episodic tension-type headache sufferers bisected significantly leftward.

Interestingly, evidence suggests that the right hemisphere has a higher sensitivity to drug dependence than the left. For example, using electroencephalography, Fingelkurts *et al.* [19] found a right-sided cerebral dominance in patients with opioid dependence; using fMRI, Orr *et al.* [20] found an increased activity in the right hemisphere, including the superior frontal gyrus, inferior frontal gyrus, superior parietal gyrus, and inferior temporal gyrus in patients with cannabis dependence. One might therefore ask whether MOH patients display a right hemispheric dominance when processing visual stimulation. Thus, we hypothesize that MOH patients exhibit a pronounced leftward error in the line-bisection task.

On the other hand, with regards to attack frequency, intensity, and duration, MOH behaves more similarly to chronic tension-type headache (CTTH) than to chronic migraine in clinics [21,22]. In order to exclude the effect of chronic head pain, we have included a group of patients with CTTH. Bearing in mind that patients with generalized anxiety disorder bisected lines significantly leftward [23], and that both anxiety and depression are co-morbid with MOH [24,25] and CTTH [26-28], we have used the Zung Self-Rating Anxiety Scale [29] and the Zung Self-Rating Depression Scale [30] to measure the anxiety and depression levels in our participants.

Experimental procedures

Participants

Altogether 69 Chinese participants were included in the study, their vision was either normal or corrected to normal. Twenty-two

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healthy volunteers (15 women and 7 men; mean age: 34.14 years with 15.67 SD; age range: 19-68 years) were recruited from students and hospital staff. According to the International Classification of Headache Disorders - 2nd edition [22], 26 outpatients (9 women and 17 men; mean age: 28.54 ± 6.93; age range: 19-41) who were diagnosed as suffering from CTTH without medication overuse (code 2.3) with a mean headache duration of 92.01 months (± 98.40 SD), and 21 patients (14 women and 7 men; mean age: 35.43 ± 10.97; age range: 19-54 years), who were diagnosed as suffering from MOH were included in the study. Six MOH patients had abused simple analgesics (paracetamol, code 8.2.3), and 15 abused a combination of analgesics (paracetamol plus salicylates, code 8.2.5.). They had mean headache duration of 90.12 months (± 98.01), which was also roughly the duration of analgesic abuse. There was no significant age (one-way ANOVA, main effect, $F_{[2, 66]} = 2.44$, $P = 0.095$, mean square effect (MSE) = 323.31) nor a difference in level of education (one-way ANOVA, main effect, $F_{[2, 66]} = 1.12$, $P = 0.33$, MSE = 1.67) between groups. There was no significant gender difference between groups ($\chi 2 = 0.71$, $P = 0.40$). In each participant, depression was measured with a four-point evaluation, the Zung 20-item Self-rating Depression Scale [30], and anxiety was measured with another four-point evaluation, the Zung 20-item Self-rating Anxiety Scale [29]. No participants had ingested alcohol, drugs, or medication for at least 72 hours prior to the test. The study was approved by a local ethics committee, and all participants gave their written informed consent to participate in the study.

Handedness was determined using a Chinese translation of the Edinburgh Handedness Inventory [31], which has been used in previous studies [18,23]. Each of the 12 items of the inventory were scored 1, 2 or 3 according to the left-hand, either left or right, or right-preference. All participants scored from 29 to 36 and were considered to be moderate or strong right-handers.

Procedures

All participants were asked to bisect eight lines without measuring or folding the paper. The lines, drawn in black and oriented horizontally, ranged from 95-146 mm in length, and were arranged randomly on a sheet of A4 size paper one below the other, differing in their distances from the sheet margins so that their centres were not in alignment (Figure 1). The response sheet was always centred on participants' mid-sagittal plane. No restrictions were placed on head or eye movements and no time limits were imposed. Participants were instructed to use their right hand to make a mark indicating the centre of the line.

Data analyses and statistics

There are many classical methods to analyze line bisection performance, including the percentage expression of bias errors [32]. Here we used a method developed by Drake and Ulrich [33]. Briefly, the distance of the line bisecting mark was measured from the actual centre to the nearest millimetre. The frequency of directional errors, irrespective of the magnitude, was measured using the Index of Line Bisection Error (Index). This was calculated as (Right - Left) / (Right + Left); positive values indicate errors to the right and negative values indicate errors to the left. The magnitude of line bisection deviation was calculated as the algebraic sum of the distance of marks from the veridical centre. The statistic is called the Net of Line Bisection Errors (Net). Positive values indicate errors to the right and negative values indicate errors to the left.

The mean Index and Net data in the three groups were submitted to one-way ANOVA followed by the least significant difference (LSD) for post-hoc analysis. One-way ANOVA was also used to analyze the levels of anxiety and depression, and the Chi-square test was used to analyze the gender effects on them. The Spearman rank order correlation was used to search for possible relationships between the Index / Net and age, education, anxiety, depression level, or headache duration (in months). A P value less than 0.05 was considered to be significant.

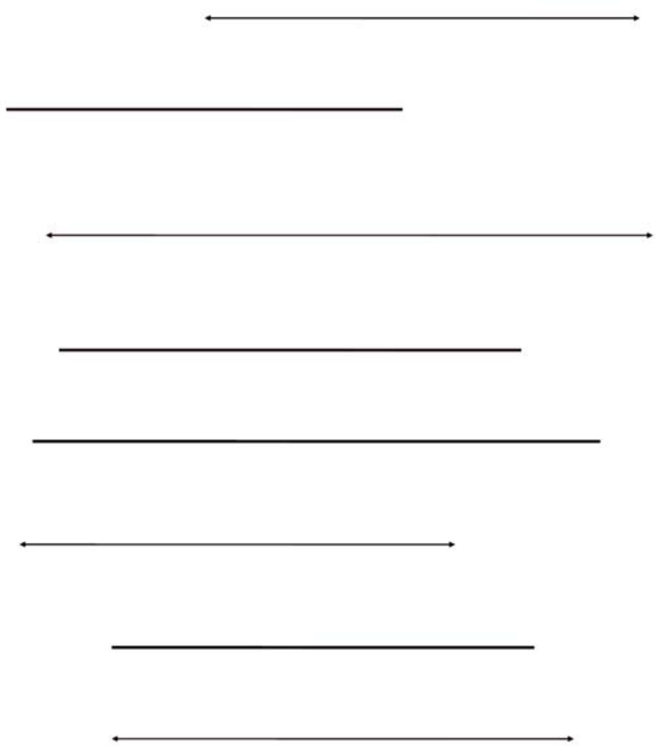

Figure 1. The eight lines placed horizontally on a sheet of A4 size paper used for participants to bisect without measuring or folding the paper.

Results

There were significant differences between three groups of participants in the mean anxiety (group effect, $F_{[2, 66]} = 6.72$, $P < 0.01$, MSE = 631.92) and depression scores (group effect, $F_{[2, 66]} = 5.37$, $P < 0.01$, MSE = 558.60). The post-hoc LSD test detected that anxiety levels in both CTTH (41.08 ± 10.47; P < 0.01; 95% CI: 4.65 to 15.87) and MOH (37.19 ± 10.71; P < 0.05; 95% CI: 0.46 to 12.28) were higher than that in the healthy controls (30.82 ± 7.49), and depression levels in both CTTH (33.12 ± 11.61; P < 0.01; 95% CI: 3.53 to 15.33) and MOH (30.76 ± 11.69; P < 0.05; 95% CI: 0.87 to 13.30) were also higher than those in the healthy controls (23.68 ± 6.058).

On average, MOH patients bisected leftward, whereas the healthy participants and CTTH patients bisected slightly rightward. When referring to Index, ANOVA detected statistical significance among the three groups (main effect, $F_{[2, 66]} = 4.70$, $P < 0.05$, MSE = 1.70). The LSD test detected that MOH (-0.37 ± 0.618) bisected significantly more leftward than healthy controls (0.09 ± 0.53; P < 0.05; 95% CI: -0.83 to -0.09) and CTTH did (0.13± 0.64; P < 0.01; 95% CI: -0.85 to -0.15) (Figure 2). When referring to Net, ANOVA also detected statistical significance among the three groups (main effect, $F_{[2, 66]} = 4.69$, $P < 0.05$, MSE = 9.40). Again, the LSD test detected that MOH (-1.02 ± 2.00) bisected significantly more leftward than healthy controls (0.18 ± 0.87; P < 0.01; 95% CI: -2.06 to -0.34), as did CTTH (0.04 ± 1.20 P < 0.05; 95% CI: -1.9 to -0.24) (Figure 3).

In 69 participants, there was significant correlation between their age and Index (r = -0.25, P < 0.05) or Net (r = -0.25, P < 0.05). However, there was no significant correlation between their education level and Index (r = 0.15, P = 0.22) or Net (r = 0.20, P = 0.11), nor between their SAS score and Index (r = -0.03, P = 0.80) or Net (r = -0.01, P = 0.93), nor between their SDS score and Index (r = -0.06, P = 0.63) or Net (r = -0.15, P = 0.21). There was no correlation either between Index (in MOH, n = 21, r = 0.14, P = 0.54; in CTTH, n = 26, r = 0.14, P = 0.49) or Net (in MOH, n = 21, r = -0.10, P = 0.66; in CTTH, n = 26, r = 0.024, P = 0.24) and headache duration (in months).

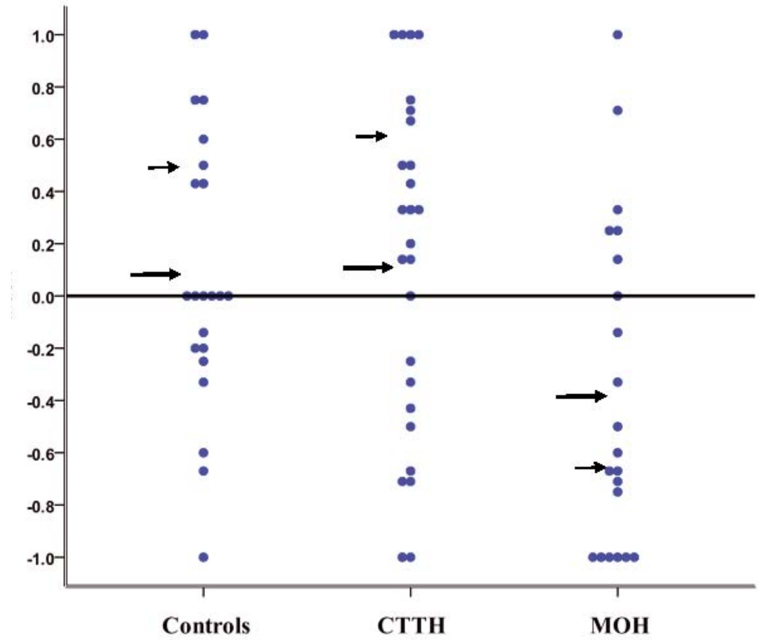

Figure 2. Scatter plot of the Index of errors in line bisection in healthy participants (Controls, n = 22), chronic tension-type headache (CTTH, n = 26), and medication overuse headache (MOH, n = 21) patients. Positive values indicate the rightwardness relative to the true centre, negative values indicate the leftwardness. Big arrows indicate the mean Index, small arrows indicate the standard deviation of the Index. For statistics, see text.

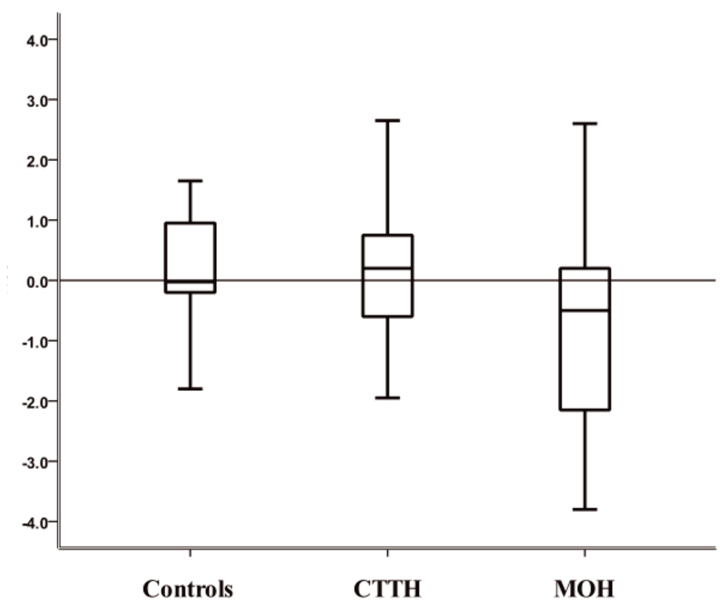

Figure 3. Box and Whisker plot of individual Net line bisection errors in healthy participants (Controls, n = 22), chronic tension-type headache (CTTH, n = 26), and medication overuse headache (MOH, n = 21) patients. Bars: minimum and maximum values; box: quartile; line within box: median value. Positive values indicate the rightwardness relative to the true centre, negative values indicate the leftwardness. For statistics, see text.

Discussion

We found that patients with MOH bisected significantly more leftward than the healthy controls did, which confirmed our hypothesis. Our healthy volunteers on the other hand, bisected slightly rightward, which is consistent with previous reports in Chinese participants [18]. Our patients with CTTH bisected rightward, although non-significantly, which was not consistent with the findings of Hu *et al.* [18]. The reason for the discrepancy is unclear, the different levels of anxiety co-morbid with CTTH in two different studies might account for it, since anxiety is indeed related to leftward bisection errors [23]. Unfortunately, the previous study [18] did not measure the anxiety levels in their CTTH patients. In the current study, we also found that both anxiety and depression levels were higher in CTTH and MOH, which is consistent with previous reports [24-28]. Moreover, age correlates with the line bisection errors found in the current study were consistent with many previous reports [17], implying an age-related decrease of activation in right hemisphere to allocate for spatial attention. The leftward line bisection error in MOH was, however, not correlated with the education, anxiety, or depression levels of the participants. This effect does not seem to be due to chronic head pain, since we found a slightly rightward line bisection error in CTTH. All these findings might suggest a unique neuropsychological mechanism in MOH, different from the one in CTTH.

Studies have shown that the leftward bisection error implies a relatively hyperactive right hemisphere, a relatively hypoactive left hemisphere, or both [34,35]. Indeed, the pivotal role played by the right hemisphere in visuospatial attention and the performance of line bisection tasks has been established by functional magnetic resonance imaging (fMRI) [36-38] and electrostimulation mapping [39] studies. Therefore, a relatively higher degree of right-hemispheric activity might exist in MOH. Interestingly, scholars have demonstrated a right-hemispheric dominance in opioid-dependence [19] and in non-substance-dependent gambling by electroencephalography [40], and in cannabis-dependence by whole-brain voxelwise fMRI approaches [20]. Similar results are described in patients with obsessive-compulsive behaviors, such as nicotine-dependent patients, by performing lateralized left- (lexical decisions) and right- (facial decision task) hemispheric dominant tasks [41]. Right hemisphere dominance is also found in over-eating behavior [42-44], which is considered a behavioral addiction [45,46]. This pattern of hemispheric dominance is also depicted in patients with Parkinson's disease and pathological gambling, by perfusion single-photon emission computed tomography [47]. Further, the obsessive-compulsive trait represents a major risk of headache chronification and drug dependence [48,49]. These findings thus support the leftward line bisection errors found in MOH, since some MOH patients present both medication overuse and obsessive-compulsive behaviors in clinics [50,51].

Although we were not aiming to describe the neurobiological bases for visuospatial attention deficits in MOH patients, previous neuroanatomical and neurobiochemical results conducted elsewhere might help to explain our current findings. For instance, a significant right lateralization of the perisylvian network, including the posterior and inferior sylvian areas, and the temporo-parietal junction, is engaged in visuospatial attention in humans [52]. In healthy adults the genetic markers of dopaminergic receptors adequately predict the direction of spatial attentional bias [53], irrespective of a non-spatial attention load [54]. In cocaine, or other drug abusers, dopaminergic neurotransmitters play a very important role in visuospatial attention [55,56]. MOH patients also present dysfunctions in the mesocorticolimbic dopamine-circuit [57], which has been consistently implicated in drug dependence [58]. Furthermore, genetic predisposition to MOH is traced to the polymorphisms of dopamine-related genes [59,60]. Taken together, these findings point to a common neurobiological substrate for both MOH and drug dependence disorders.

One should also bear in mind the limitations of our study design. First, although we did not detect significant age differences in the current design, age was significantly correlated with the line bisection performance in all participants, and we therefore cannot completely rule out the age effect in MOH. Second, enrolling more controls, such as migraineurs, pain sufferers, or patients with drug dependence would help in elucidating the specificity of right hemispheric dominance in MOH. Nevertheless, our results denote relatively hyperactive right hemispheric activity, hypoactive left hemispheric activity, or both in MOH patients, and suggest a similarity in cerebral functions for MOH and drug dependence.

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Regarding research work described in the paper, each co-author declares that there is no conflict of interest, and has conformed to the Helsinki Declaration concerning human rights and informed consent, and has followed recommended policies and procedures concerning the treatment of human participants in research.

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: WW. Acquisition of data: JZ, QG, HF, EY and HT. Analysis and interpretation of data: JZ and QG. Writing the draft of the manuscript: JZ and WW. Critical revision of the manuscript for important intellectual content: WW. Statistical analysis: JZ and QG. Administrative, technical, and material support: WW. Study supervision: WW.

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