

## Mismatch negativity in chronic tension-type headache with and without medication-overuse

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### Abstract

**Background:** It is unknown if medication-overuse headache, clinically similar to chronic tension-type headache, has pre-attentive problems which may be related to pain or substance abuse. **Methods:** Auditory frequency deviance elicited mismatch negativity was recorded from 22 patients with chronic tension-type headache, 26 with medication-overuse headache from underlying chronic tension-type headache and 41 healthy volunteers as controls. Their depression and anxiety scores were noted. **Results:** There were no significant differences in the N1 latency or amplitude to both standard and deviant stimuli for the different groups. However, the latency and amplitude of mismatch negativity were significantly shortened and reduced at Fz, Cz, and Pz in medication-overuse headache as compared to chronic tension-type headache and normal subjects. Anxiety levels were elevated in chronic tension-type headache and medication-overuse headache subjects compared to healthy controls but were not correlated with mismatch negativity latency or amplitude in a given group.

**Conclusions:** In medication-overuse headache subjects, the shortened mismatch negativity latency indicates quick involuntary attention switching to auditory change, while its reduced amplitude indicates poor accuracy in discriminating early stimuli, which may be related to medication overuse rather than to the head pain experienced.

### INTRODUCTION

The population-based one-year prevalence of the medication-overuse headache (MOH) ranges between 0.7 to 1.7% in different countries.<sup>1</sup> In terms of its frequency, intensity and duration, MOH behaves more like chronic tension-type headache (CTTH) than chronic migraine.<sup>2-5</sup> Underlying mechanisms of the preexisting headache e.g. migraine or CTTH may contribute to the pathogenesis of MOH.<sup>3,4,6</sup> In CTTH, these include both peripheral (e.g. altered myofascial nociception) and central (e.g. inadequate endogenous pain control) mechanisms while in migraine, there is activation of trigeminovascular system and initiation of cortical spreading depression.<sup>7,8</sup> However, the exact pathophysiology of MOH, especially when evolved from tension-type headache, is not well-understood, with central sensitization and deficits of endogenous pain control suspected of playing a role.<sup>9,10</sup> Moreover, MOH has been assumed to be a type of addiction disorder and its mechanisms may overlap with those that contribute to the drug addiction.<sup>1,11,12</sup>

Neuropsychological studies in migraine have shown various attention deficits in both adult and childhood migraine with and without aura.<sup>13-15</sup> On the other hand, there is also a study which showed no attention deficits in children and adolescents with migraine or tension-type headache.<sup>16</sup> Up to now, there has been no study showing altered attention in MOH. However, other chronic pain disorders such as the rheumatoid arthritis or fibromyalgia have been shown to have impaired selective attention.<sup>17</sup> Drug abusers also have been found to have deficits in cognitive flexibility<sup>18,19</sup> and working memory.<sup>20</sup>

Neurophysiological studies using a cerebral cognitive index, the event-related potential (ERP) P3, have been carried out in migraine and CTTH. For example, reduced P3 amplitude through an active auditory discriminative task was found in migraine<sup>21,22</sup> and in CTTH<sup>22</sup>, and reduced P3 amplitude through a passive auditory paradigm was also found in migraine and CTTH.<sup>23</sup> In addition, the active auditory P3 amplitude was found to be deformed in chronic pain sufferers<sup>24,25</sup>,

and the active visual P3 amplitude was reduced in substance-abuse disorders.<sup>26</sup> There has been no study showing P3 changes in MOH.

Another ERP component, the mismatch negativity (MMN), which occurs approximately 100-250 ms after the onset of a deviant stimulus, acts as an index of involuntary pre-attention, or an involuntary shift of attention.<sup>27-29</sup> MMN latency indicates the speed of involuntary attention switching to stimulus change while its amplitude indicates the extent of allocation of neural resources to pre-attentive process of a stimulus change.<sup>28</sup> MMN was found to be reduced in amplitude in migraine and CTTH.<sup>22,30</sup> Whether or not the MMN morphology is intact in MOH still opens to question. However, MMN amplitude was decreased<sup>31</sup>, and its latency was delayed<sup>32</sup> in chronic pain sufferers. In addition, many studies have shown that MMN was reduced or delayed in addiction disorders.<sup>33-35</sup>

The purpose of the present study was to look for pre-attentive problems in MOH. Based on the previous reports, we hypothesize that MMN would be delayed and reduced in this headache type. However, due to the heterogeneity of MOH, we decided to include only patients whose MOH evolved from CTTH and compared them with patients with CTTH but without MOH. As there is high prevalence of anxiety and depression in MOH<sup>36,37</sup> and CTTH<sup>38-40</sup>, anxiety and depression levels were measured in all our study subjects.

## METHODS

### *Participants*

This study was carried out on 89 participants. Forty-one were healthy controls (13 women; mean age, 28.02 years with 8.51 S.D.; age range, 19-51 years) recruited from students, hospital staff and paid volunteers, 22 were CTTH patients without MOH based on the International Classification of Headache Disorders - 2nd edition (ICHD-II)<sup>2</sup> (5 women; mean age, 32.64 ± 10.37; age range, 17-54) with a mean headache duration of 91.22 months (+98.31) while 26 were patients diagnosed to have MOH from pre-existing CTTH (16 women; mean age, 33.08 ± 9.56; age range, 18-54); 8 had abused simple analgesics (paracetamol, code 8.2.3) while 18 abused a combination of analgesics (paracetamol plus salicylates, code 8.2.5.). They had mean headache duration of 90.74 months (± 97.71), which was also roughly the duration of analgesics abuse). A semi-structured interview was performed for each healthy control in order to ascertain that they were not suffering or had not

previously suffered from any recurrent headache or neuropsychiatric problems. There was no significant age difference (one-way ANOVA, main effect,  $F(2, 86) = 3.02, p = 0.054$ , MSE = 261.29) between groups. However, there were more women in the MOH group compared to healthy controls ( $\chi^2 = 5.77, p < 0.05$ ) and CTTH ( $\chi^2 = 7.29, p < 0.05$ ). In each participant, the depression symptoms were measured by a four-point evaluation, the Zung 20-item Self-rating Depression Scale<sup>42</sup>, and anxiety symptoms were measured by another four-point evaluation, the Zung 20-item Self-rating Anxiety Scale.<sup>41</sup> All participants had to be drug or alcohol free for at least 72 hours prior to testing. The study was approved by the ethics committee of the Zhejiang University School of Medicine, and all subjects gave written informed consent to participate in the study.

### *Stimuli and recording parameters*

Participants were seated in an armchair in a quiet room. Binaural tone stimuli of 80 dB SPL (50 ms in duration; rise/ fall times of 5 ms) were delivered through headphones at an inter-stimulus interval of 0.625 s (1.6 Hz). The frequencies of standard (90%) and deviant (10%) tones were 1.1 kHz and 1.2 kHz, respectively. These stimuli were presented in a randomized order. With a pen in their dominant hand, participants were instructed to arrange series of seven randomized digits (selected from 0 to 9) in an ascending order. This approach was chosen to keep attention away from the auditory stimuli. Because of our limited number of amplifier channels, we recorded ERPs with cup electrodes placed at Fz, Cz, and Pz according to the 10-20 System. An earlobe reference was used and a ground electrode was fixed to one arm. Electrode impedance was kept at 10 kΩ. All recordings were made on a Nihon Kohden Neuropack-sigma device using a band-pass of .01-30 Hz, and a sampling rate of 1 kHz. The configuration band rate was set at 9600 bits/s, and the data configuration length was set at 8 bits in the hardware of the device. Connections were set such that a negative activity produced an upward deflection. Bipolar recordings of the electrooculogram (EOG) were made with electrodes at the outer canthus and above the right eye. ERP traces with an EOG of amplitude exceeding ± 100 µV (which indicates blink or ocular movement) were automatically rejected. Only artifact-free sweeps were automatically selected for averaging. About 1100 tones were

delivered in each trial but only 1000 sweeps were finally selected for averaging (the artifact free recordings to 900 frequent and 100 deviant tones were selected for averaging). The sampling epoch was 100 ms pre-stimulus and 500 ms post-stimulus. Both latencies and peak-to-baseline amplitudes of the maximal negative deflection within a specified latency ranges were measured, based on visual inspection. The ERP negative component, N1, to standard or deviant tones, was measured within a latency range of 50-150 ms. MMN was obtained by subtracting standard from deviant tone elicited ERP within a latency range of 100-250 ms.

#### *Statistical Analyses*

Two-way ANOVA was used to analyze the latencies and amplitudes of N1 to standard and deviant tones, and of MMN at the three midline electrodes (Fz, Cz, and Pz) [i.e. group (3) × electrode sites (3)], and to analyze the gender effects on these parameters [i.e., gender (2) × electrode sites (3)]. Whenever a significant main effect was found, a post-hoc Tukey test was performed to evaluate between-group differences for the corresponding parameter. One-way ANOVA was also used to analyze the levels of anxiety and depression, and the independent Student *t* test was used to analyze the gender effects on them. We used the Spearman rank order correlation to search for possible relationships between MMN latency/ amplitude and age, education level, anxiety, depression, and headache history. Regarding MMN latency/ amplitude, only the correlations which were significant at all three midline electrodes, were considered stable and meaningful. A *p* value < 0.05 was considered to be significant.

## **RESULTS**

The mean anxiety scores were significantly different between the three groups of participants (group effect,  $F(2, 86) = 35.18$ ,  $p < 0.001$ ,  $MSE = 3384.98$ ). The post-hoc Tukey test showed that anxiety levels in MOH ( $41.96 \pm 10.58$ ,  $p < 0.05$ ) and CTTH ( $39.27 \pm 13.15$ ,  $p < 0.05$ ) are higher than in the healthy volunteers ( $28.66 \pm 6.79$ ). In general, anxiety in women ( $36.50 \pm 13.45$ ) were similar to men ( $38.53 \pm 12.91$ ) ( $t = -0.65$ ,  $p = 0.52$ ). The mean depression scores were however, not significantly different between the three groups of participants (group effect,  $F(2, 86) = 2.84$ ,  $p = 0.064$ ,  $MSE = 321.18$ ). Depression levels in MOH ( $32.12 \pm 11.50$ ) and

in CTTH ( $31.18 \pm 12.60$ ) were similar to that in the healthy volunteers ( $26.34 \pm 8.77$ ). However, women ( $33.47 \pm 14.03$ ) scored significantly higher ( $t = 3.04$ ,  $p < 0.01$ ) than men ( $26.60 \pm 7.28$ ) on depression.

All participants showed clear N1 components to both standard and deviant tones at each electrode site. The MMN peak was distinct enough to be separated from the original N1 peaks to both standard and deviant tones in all participants (Figure 1). There were no significant differences between the groups for N1 latencies to standard (group effect,  $F(2, 86) = 1.24$ ,  $p = 0.29$ ,  $MSE = 778.85$ ) or deviant (group effect,  $F(2, 86) = 2.28$ ,  $p = 0.11$ ,  $MSE = 1819.49$ ) tones, or for N1 amplitudes to standard (group effect,  $F(2, 86) = 0.77$ ,  $p = 0.47$ ,  $MSE = 6.65$ ) or deviant (group effect,  $F(2, 86) = 0.27$ ,  $p = 0.76$ ,  $MSE = 5.18$ ) tones (Table 1). In general, men and women displayed similar N1 morphologies to both standard and deviant tones ( $F(1, 87) = 0.42 \sim 1.21$ ;  $p: 0.27 \sim 0.52$ ; MSN:  $3.89 \sim 606.10$ ).

By contrast, mean MMN latencies were significantly different between the three groups of participants (group effect,  $F(2, 86) = 7.65$ ,  $p < 0.001$ ,  $MSE = 6648.04$ ; electrode effect,  $F(2, 172) = 0.67$ ,  $p = 0.51$ ,  $MSE = 2.53$ ; group × electrode interaction effect,  $F(4, 172) = 0.08$ ,  $p = 0.99$ ,  $MSE = 0.30$ ). Post-hoc Tukey test showed that latencies in MOH were significantly shortened at the midline electrodes compared to healthy controls (all *P* values < 0.01) and CTTH patients (all *P* values < 0.001) respectively (Table 1). Women had similar MMN latencies compared to men when recorded at the three electrodes ( $F(1, 87) = 0.002$ ,  $p = 0.97$ ,  $MSE = 1.99$ ). Mean MMN amplitudes were also significantly different between the three groups of participants (group effect,  $F(2, 86) = 7.78$ ,  $p < 0.05$ ,  $MSE = 63.86$ ; electrode effect,  $F(2, 172) = 37.29$ ,  $p < 0.001$ ,  $MSE = 45.57$ ; group × electrode interaction effect  $F(4, 172) = 1.35$ ,  $p = 0.25$ ,  $MSE = 1.65$ ). Post-hoc Tukey test showed that amplitudes in MOH at the three midline electrodes were significantly lower compared to healthy controls (all *P* values < 0.05) and CTTH (all *P* values < 0.05) respectively (Table 1). In general, women displayed similar MMN amplitudes compared to men at the three midline electrodes ( $F(1, 87) = 0.17$ ,  $p = 0.20$ ,  $MSE = 27.00$ ).

No correlation was found between MMN latency or amplitude at a given electrode site and education, anxiety and depression levels in the healthy controls ( $n = 41$ ,  $r: -0.17 \sim 0.27$ ),

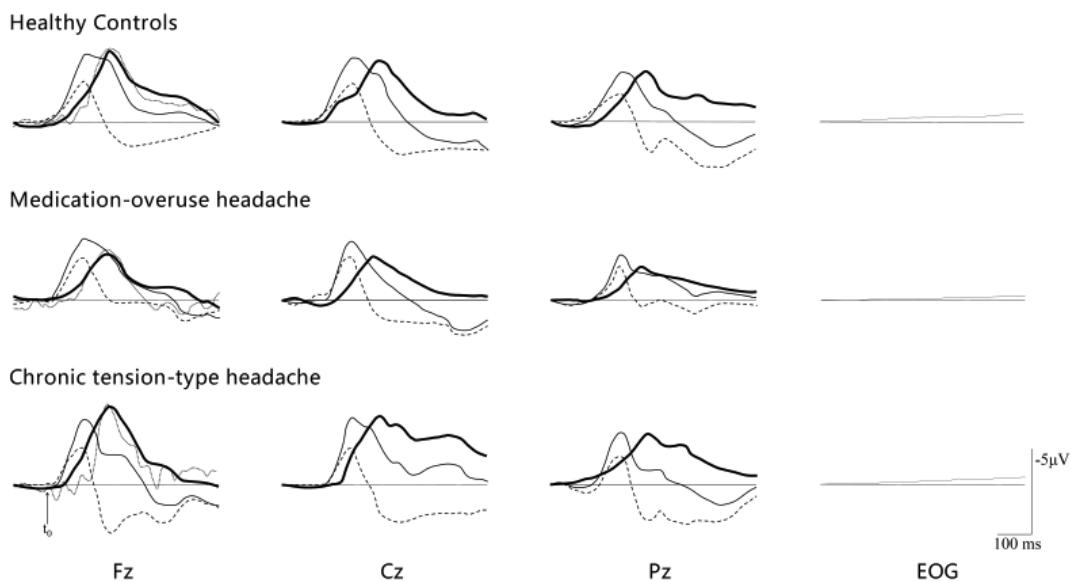


Figure 1. Superimposed grand averages of ERPs elicited by deviant (thin solid lines), and standard (dashed lines) tones, of difference waveforms (MMNs, thick solid lines) at three midline electrodes, and of electrooculogram (EOG) in the healthy volunteers ( $n = 41$ ), medication-overuse headache ( $n = 26$ ) and chronic tension-type headache ( $n = 22$ ) patients. Dotted lines in the left column stand for the representative MMNs at Fz in each group respectively.

MOH ( $n = 22$ , r:  $-0.20\sim0.32$ ), or CTTH ( $n = 26$ , r:  $-0.37\sim0.35$ ) groups. There was also no correlation between MMN latency or amplitude at a given electrode and duration of headache in MOH (months) ( $n = 26$ , r:  $-0.01\sim0.22$ ) or in CTTH ( $n = 22$ , r:  $-0.15\sim0.17$ ) group.

## DISCUSSION

We found that MMN latencies were shortened and its amplitudes were reduced at the three midline electrodes in MOH rather than in CTTH patients, which partly confirmed our hypothesis. The anxiety levels were higher in both MOH and CTTH, which were consistent with previous reports about the MOH<sup>36,37</sup> and CTTH.<sup>38-40</sup> In general, women were more depressed than men did, which were also in line with the previous documentation.<sup>43</sup> The deformed MMN morphology in MOH was not correlated with education, anxiety or depression level, or with the duration of headache, suggesting a unique pathology in this headache type.

Partly contrary to our hypothesis, the shortened MMN latency found in MOH suggested that the involuntary attention switching to auditory change was accelerated in the disorder. This finding was similar to the reports in paranoid schizophrenia<sup>44</sup> and in paranoid personality disorder.<sup>45</sup> In clinics, some patients with chronic alcohol dependence as well as those who overuse of the non-steroidal

anti-inflammatory drugs are also diagnosed with personality disorders including paranoid type disorders.<sup>46-49</sup> Furthermore, a shortened MMN was found in paranoid schizophrenia with frequent nicotine use.<sup>50</sup> This effect seems not to be due to head pain itself since we found a normal MMN latency in CTTH, nor due to a chronic general pain experience since latency was prolonged in chronic pain conditions.<sup>32</sup>

As expected, MMN amplitudes were reduced in MOH compared to those in the healthy controls or CTTH, which might imply lower discrimination accuracy to stimulus change, or decreased neural activity of pre-attention to the change in MOH. This was similar to documented findings to chronic pain sufferers<sup>31</sup>, and substance abusers.<sup>33-35</sup> Again, this effect seems not due to head pain itself since we found normal MMN amplitudes in CTTH. Whether or not reduced MMN amplitude in MOH was the result of chronic analgesic overuse remains to be determined. Considering that many studies have suggested that MMN is a functional index of the N-methyl-D-aspartate-receptor (NMDAR)<sup>29</sup>, and that an increased extracellular level of glutamate seems to play a key role in the MOH<sup>11</sup>, future studies addressing the NMDAR in MOH patients would help to clarify this speculation.

Taken together, the co-existence of shortened latency and reduced amplitude of MMN in MOH, suggests central sensitization when receiving

**Table 1: Latencies and amplitudes (mean  $\pm$  S.D.) of N1 to both standard and deviant tones and MMN at the three midline electrode sites in the healthy volunteers (Healthy, n = 41), medication-overuse headache (MOH, n = 26) and chronic tension-type headache (CTTH, n = 22) patients.**

	Healthy controls	MOH	CTTH
<b>Latency (ms)</b>			
<b>N1-deviant</b>			
Fz	109.54 $\pm$ 17.21	103.58 $\pm$ 18.95	101.50 $\pm$ 13.79
Cz	108.73 $\pm$ 16.55	102.04 $\pm$ 18.35	100.91 $\pm$ 12.67
Pz	109.29 $\pm$ 17.11	101.54 $\pm$ 17.44	101.14 $\pm$ 12.56
<b>N1-standard</b>			
Fz	105.44 $\pm$ 13.09	100.31 $\pm$ 16.92	100.77 $\pm$ 15.03
Cz	104.90 $\pm$ 13.14	99.58 $\pm$ 16.31	101.14 $\pm$ 15.15
Pz	105.37 $\pm$ 13.11	99.69 $\pm$ 16.65	101.86 $\pm$ 15.87
<b>MMN</b>			
Fz	177.10 $\pm$ 15.59	163.85 $\pm$ 19.42**	181.82 $\pm$ 16.24
Cz	176.63 $\pm$ 16.10	163.50 $\pm$ 19.27**	181.68 $\pm$ 16.22
Pz	176.63 $\pm$ 16.16	163.54 $\pm$ 18.96**	181.73 $\pm$ 17.08
<b>Amplitude (<math>\mu</math>V)</b>			
<b>N1-deviant</b>			
Fz	-5.09 $\pm$ 3.36	-4.60 $\pm$ 3.10	-4.50 $\pm$ 2.68
Cz	-4.83 $\pm$ 2.86	-4.37 $\pm$ 2.75	-4.62 $\pm$ 2.25
Pz	-3.73 $\pm$ 2.37	-3.35 $\pm$ 2.21	-3.58 $\pm$ 1.96
<b>N1-standard</b>			
Fz	-3.09 $\pm$ 2.10	-3.18 $\pm$ 2.09	-2.6 $\pm$ 1.48
Cz	-2.90 $\pm$ 1.90	-3.21 $\pm$ 1.92	-2.53 $\pm$ 1.50
Pz	-2.13 $\pm$ 1.73	-2.53 $\pm$ 1.71	-1.95 $\pm$ 1.13
<b>MMN</b>			
Fz	-5.32 $\pm$ 2.25	-3.42 $\pm$ 2.91**	-5.42 $\pm$ 2.79
Cz	-4.58 $\pm$ 2.41	-3.22 $\pm$ 2.19**	-4.72 $\pm$ 3.09
Pz	-3.78 $\pm$ 1.68	-2.47 $\pm$ 1.97**	-3.51 $\pm$ 2.91

Note: \* p < 0.05 vs. healthy controls; # p < 0.05 vs. CTTH

an external stimuli and subsequent excessive inhibition of that stimulus in this disorder. These results, on one hand, support the speculation that there is sensitization of central nociceptive neurons following repeated peripheral stimulation in the development of chronic pain in MOH<sup>10</sup>, but on the other hand, are also in line with a neuroimaging study in MOH which showed that cerebral areas (including frontal and parietal regions) linked with the pain network are hypometabolic during medication overuse.<sup>51</sup>

One should also bear in mind the limitations of our study design. Firstly, we recorded ERPs with only three midline scalp electrodes, which are less sensitive in detecting regional brain activity. Secondly, although MOH evolving from migraine is less frequent, enrolment of a group of these patients in a future study would make a nice comparison. Thirdly, we did not measure personality traits of participants in our study to determine whether some who were paranoid-

prone. Fourthly, as there were more women in the MOH group, a future study with equal numbers of men and women would be helpful to reduce the possible effect of gender differences.

In conclusion, using an auditory frequency deviance, we found shortened and reduced MMN which might indicate an early but insufficient neuronal mobilization for discriminating an acoustic change at the early stage in medication-overuse headache.

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