ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Short communication Acta Neurobiol Exp 2008, 68: 97–102

Mismatch negativity in methamphetamine dependence: A pilot study

Ladislav Hosák[1], Jan Kremláček[2]*, Miroslav Kuba[2], Jan Libiger[1], and Jiří Čížek[1]

[1]Department of Psychiatry, Charles University in Prague, Faculty of Medicine in Hradec Králové, and University Hospital Hradec Králové, Czech Republic; [2]Department of Pathological Physiology, Charles University in Prague, Faculty of Medicine in Hradec Králové, Czech Republic, *Email: jan.kremlacek@lfhk.cuni.cz

The objective of this study was to verify hypothesised changes in event related potentials (visual mismatch negativity, vMMN) in 17 subjects dependent on methamphetamine (MAMP) compared to age and gender matched 17 healthy volunteers. We found a significant correlation between vMMN and duration of methamphetamine abuse (Spearman correlation coefficient r=0.54–0.78; P<0.05). The positive correlation indicates drop of originally more negative response to deviant stimulus, what may indicate a pre-attentive processing enhancement in the first years of MAMP abuse with its decease later on. Accordingly, *post-hoc* analysis revealed significantly stronger vMMN in patients with length of MAMP abuse shorter than 5 years than in paired controls. There were no such differences in abusers with the length of abuse longer than 5 years. The results show that the visual processing on the pre-attentional level can be influenced by long-term MAMP abuse, what can be specifically assessed by vMMN.

Key words: methamphetamine dependence, event related potentials, visual mismatch negativity paradigm, methamphetamine neurotoxicity, pre-attentive visual processing

Methamphetamine (MAMP) is a potent central nervous system stimulant which produces dose-dependent euphoria. MAMP is relatively easy to produce and inexpensive to purchase. MAMP increases the extracellular level of dopamine in the nucleus accumbens involved in the reward system (Izawa et al. 2006). Chronic MAMP use leads to oxidative stress, neurotoxicity and neurodegeneration (Kanthasamy et al. 2006).

The total number of drug users in the world is now estimated at some 185 million people, equivalent to 3% of the global population, or 4.7% of the population aged 15 to 64 years. Amphetamines, primarily MAMP and amphetamine, are used by about 30 million people (United Nations 2004). Dramatic increases in MAMP production and addiction have been reported over the last decade e.g. in North America (Barr et al. 2006), Germany (Hartel-Petri et al. 2005) and the Czech Republic (Csemy et al. 2002).

Correspondence should be addressed to J. Kremláček, Email: jan.kremlacek@lfhk.cuni.cz

Received 8 October 2007, accepted 21 February 2008

Auditory or visual mismatch negativity (MMN) is a component of event related potentials (ERP) that represents an index of sensory memory. Deficits in MMN generation have been repeatedly demonstrated in chronic schizophrenia (Jessen et al. 2001, Baldeweg et al. 2004), and appeared to be quite specific for schizophrenia (Umbricht et al. 2003). However, MMN has never been studied in MAMP dependence. We found no items in the MEDLINE database using the key words “mismatch AND negativity AND methamphetamine” on 13th February 2008.

The aim of our study was to test the hypothesis that subjects dependent on MAMP significantly differ from age- and gender-matched healthy volunteers in the visual mismatch negativity generation.

Seventeen patients (at age 24.4 ± 4.4 years) dependent on MAMP (DSM-IV Code 304.40) who had been treated at the Mental Hospital in Nechanice (part of University Hospital Hradec Králové) in 2005–2006 participated in the study. 17 age- and gender-matched control group of healthy volunteers (24.7 ± 4.7 years, 3 females) who had never used any illegal psychotropic drug (including MAMP) consisted of staff members

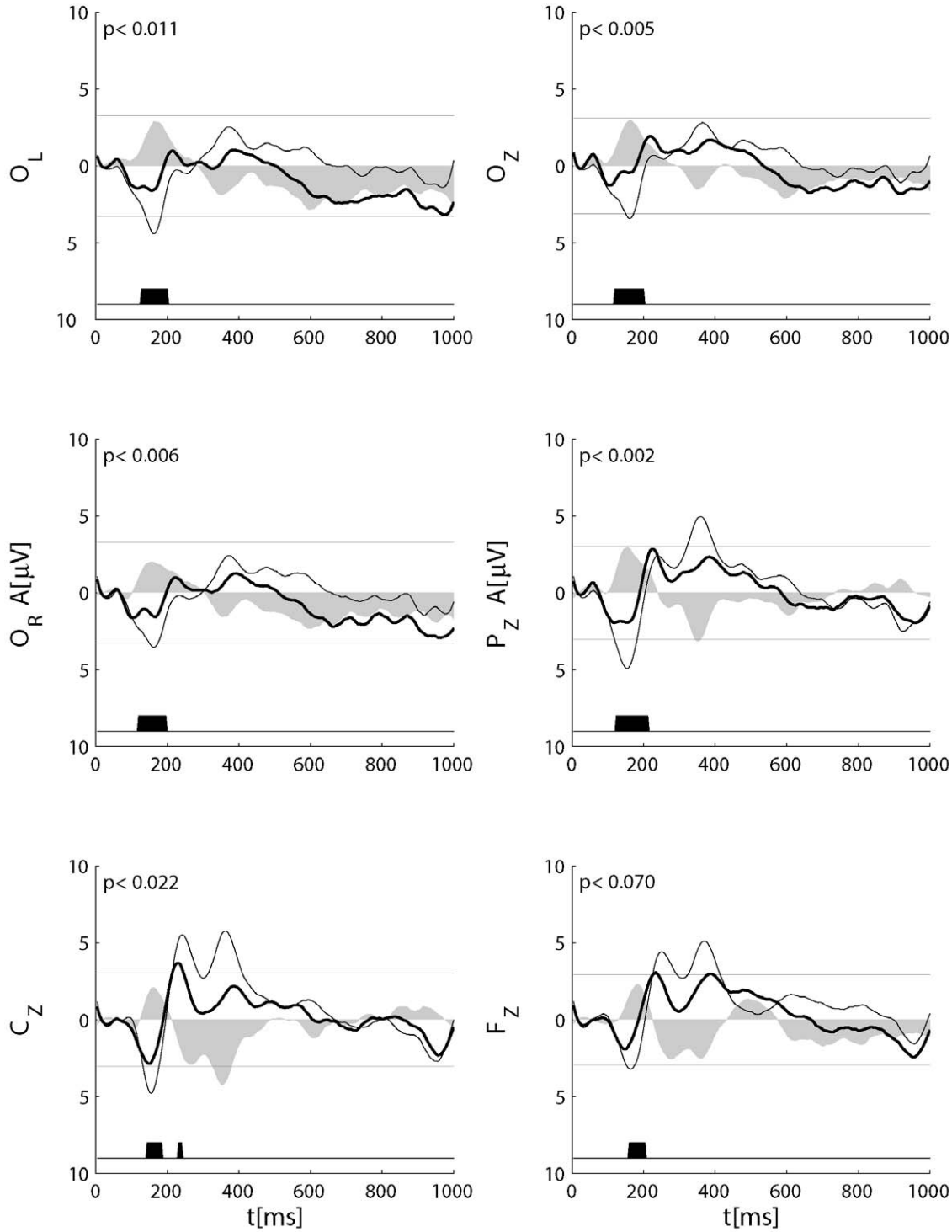

Fig. 1. The grand averages of the ERP responses of 17dependent subjects. The thick lines represent response to standard stimulus the thin curves were recorded as response to deviant stimulus. The gray area marks difference between ERP to standard and deviant stimuli. The derivation is indicated along vertical axis. The overall curves difference in interval 120–240 ms assessed by PC1 method (Achim 2001) is typed in the left upper corner of the plot. The statistical difference of point-vice paired *t*-test is depicted in bottom part of each plot as a black area for interval 120–240 ms. The gray area exceeding variability of the signal illustrated by two lines around the zero amplitude gives similar information. The variability was determined as 2.5 of standard derivation of the first 60 ms of ERP difference.

and students at the Faculty of Medicine in Hradec Králové. The study was approved by the local Ethics Committee and performed in accordance with the ethical standards laid down in the 2004 Declaration of Helsinki. All subjects signed informed consent forms prior to their inclusion in the study.

The average duration of MAMP abuse in patients (intravenous in all cases) was 5.3 ± 2.7 years. They stopped using of MAMP 3.8 ± 1.1 weeks before they entered the study.

We recorded the electroencephalographic activity of both patients and controls in the mismatch negativity paradigm. The visual stimuli consisted of two low contrast (10%) horizontal sinusoidal gratings – with a low spatial frequency (0.1 c/deg) outside the central 15 deg of the stimulus field, and a high spatial frequency (1 c/deg) inside the central 5 deg. The test paradigm was specifically designed to elicit the visual MMN (vMMN) and was based on a similar study by Tales and coauthors (1999). It involved presenting a standard stimulus for 88% of the recording time and a random deviant stimulus for 6% of the time. To ensure that the subjects did not pay attention to these stimuli, they were given a task of responding to a target random stimulus that was presented in the central visual field for 6% of the time. The subjects had to press a handheld button whenever the target stimulus appeared. The standard and deviant stimuli with opposite directions of motion were presented as a fast motion (50 deg/s) in the peripheral visual field for 200 ms. The opposite direction of motion was the only difference between the standard and deviant stimuli. A stationary pattern was displayed during the interstimulus interval of 600 ms. Correct visual fixation was checked via a near-infrared camera located in the test room.

We recorded the responses from six unipolar electrode derivations. The active electrodes were positioned on the scalp at midline above the frontal (F_Z), central (C_Z), parietal (P_Z) and occipital (O_Z) lobes. Two lateral occipital electrodes were placed 5 cm to the right and to the left of O_Z (O_R and O_L, respectively). The right earlobe (A_2) served as a reference. Each subject underwent one EEG recording session consisting of four blocks, each presenting 170 stimuli. During offline processing, 40 single ERP sweeps were averaged

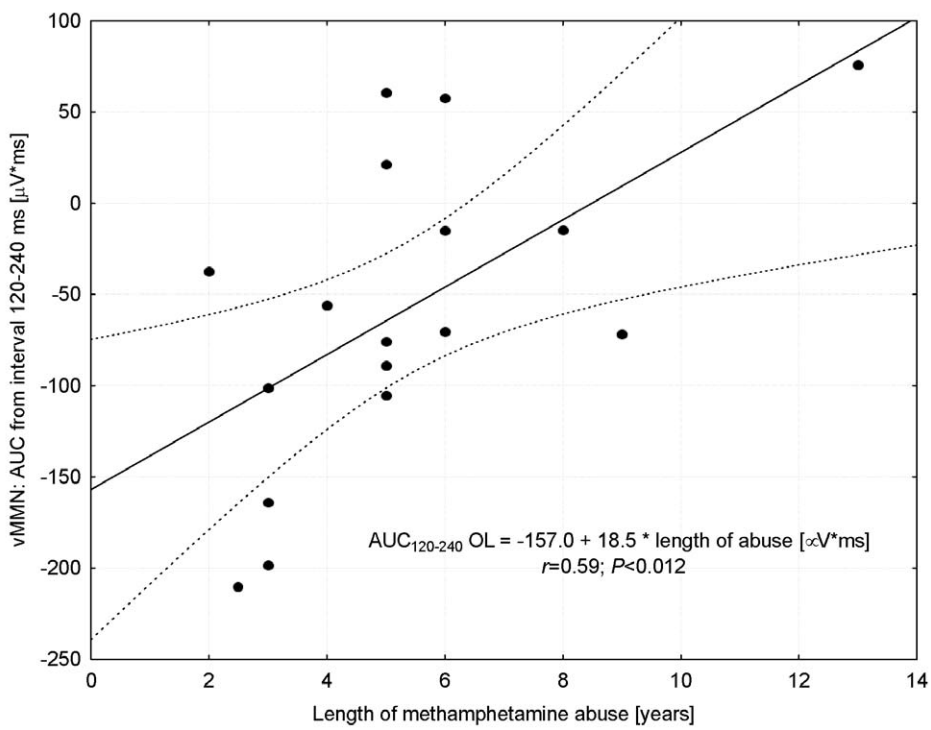

Fig. 2. Correlation between the duration of methamphetamine abuse and the vMMN in 17 methamphetamine dependent individuals (AUC, area under curve computed from left occipital electrode in the time interval 120–240 ms). Negative values indicate mismatch negativity as an index of sensory memory. Transition to less negative or even positive values identifies mismatch negativity deficit (cognitive impairment).

Table I

Spearman correlation	Electrode derivations					
	O_L	O_Z	O_R	P_Z	C_Z	F_Z
vMMN (120–240 ms) vs. length of abuse	0.61#	0.69#	0.78#	0.54#	0.31	0.01
vMMN (120–240 ms) vs. age	0.41	0.55#	0.37	0.49#	0.19	0.1

Correlation between length of MAMP abuse or age and visual mismatch negativity (expressed as area under curve [μV*ms] for time interval 120–240 ms from the stimulus onset) in 17 patients. (#) Significant correlations.

for each stimulus condition. The full description of the recording and analysis was published elsewhere (Kremláček et al. 2006).

Statistical analysis of the vMMN recordings was based on the differences in the ERPs recorded to the standard and deviant stimuli (area under the difference curve) in interval 120–240 ms. We used the Wilcoxon matched-pairs non-parametric test to assess the difference between the groups and the Spearman correlation to find dependencies of the measured values on the length of abuse in the group of patients. A significance level of 5% ($P \leq 0.05$) was used for all statistical tests.

The grand averages of 17 patients' responses to standard and deviant stimuli are shown on the Fig. 1. The comparison of vMMN median yielded only one significant difference between the MAMP dependent patients and the control subjects. The patients' vMMN was stronger than controls' one in parietal derivation for time interval 120–240 ms (P=0.017; Wilcoxon Matched Pairs Test) (Table II). The only significant difference out of 6 comparisons (6 derivations) could represent a random effect due to multiple statistical testing.

However, we observed a significant positive correlation (Spearman correlation coefficient r=0.54–0.78; P<0.05) between the duration of MAMP abuse and the vMMN in the group of dependent individuals (valid for occipital derivations) (Table I; Fig. 2). The positive correlation indicates drop of originally more negative response to deviant stimulus, what may indicate a preattentive processing enhancement in the first years of MAMP abuse with its decease later on.

Beside this correlation we also observed another positive significant correlation of the vMMN to patients' age (Spearman correlation coefficient r=0.49–0.55; P<0.05; Table I). A possibility of spurious correlation between length of MAMP abuse and vMMN, because of causal relation of abuse duration and patient age (Spearman r=0.44, n=17), was, however, rejected because of non-significant correlation between vMMN and age in the control group.

The vMMN dependency on MAMP abuse duration can be the reason why vMMN medians between group of patients and controls did not differ significantly. We performed *post-hoc* analysis in median split groups (with respect to the MAMP abuse dura-

Table II

Subjects	Active EEG electrodes – vMMN area under curve [μV*ms] ± SD					
	O_L	O_Z	O_R	P_Z	C_Z	F_Z
Dependent (n=17)	–58.6 ± 85.0	–60.6 ± 78.4	–48.6 ± 62.3	–58.6 ± 72.2	–19.6 ± 58.6	–29.1 ± 73.1
Controls (n=17)	–13.5 ± 55.2	–16.9 ± 67.3	–25.0 ± 66.4	–10.5 ± 61.3	17.0 ± 74.9	–17.0 ± 69.7
P (Wilcoxon Matched Pairs Test)	NS	NS	NS	0.017#	NS	NS

Visual mismatch negativity in 17 subjects dependent on methamphetamine in comparison with healthy volunteers (time interval 120–240 ms from the stimulus onset). (#) Significant correlation; (NS) not significant.

tion) and we found significantly more negative response to the deviant stimulus ($P<0.05$ for O_L, O_Z, P_Z derivations) in subgroup with length of abuse shorter than 5 years compared to the paired controls. The rest of group (n=11, abuse of MAMP longer than 5 years) did not differ from controls in this respect.

These findings might be explained by a facilitation of an attentional processing in the starts of MAMP abuse (Nordahl et al. 2003) or it can arise from different temperament and character inventory of the population of MAMP abusers, what can also influence the electroencephalographic activity (Hansenne 1999).

The underlying mechanism for the long term effect of MAMP to the pre-attentional visual processing might be related to changes in dopamin, norepinephrin or serotonin levels. The evidence of decreased dopamine levels in MAMP abusers and also the modulation of electroencephalographic activity (wave P300) related to attention by dopaminergic system (Kahkonen et al. 2002) would correspond to our findings. However, recent findings show insensitivity of the pre-attentive activity (MMN) to dopamine or norepinephrine changes (Leung et al. 2007). The only effect on MMN was observed after the serotonin levels modulation (Kahkonen et al. 2005, Oranje et al. 2007). Quantification of the serotonin effect was not subject of this study, therefore, the question concerning an underlying mechanism of relation between the long term abuse of MAMP and the vMMN remains to be solved in a future study.

Our report demonstrates sensitivity of ERP to long-term methamphetamine abuse with agreement to previous studies (Iwanami et al. 1998). We additionally brought a new evidence for relation of the visual preattentional processing (visual MMN) to the length of methamphetamine abuse.

This work was supported by the Czech Ministry of Education (VZ MSM 0021620820) and the Czech Ministry of Health (VZ MZO 00179906).

REFERENCES

Achim A (2001) Statistical detection of between-group differences in event-related potentials. Clin Neurophysiol 112: 1023–1034.

Baldeweg T, Klugman A, Gruzelier J, Hirsch SR (2004) Mismatch negativity potentials and cognitive impairment in schizophrenia. Schizophr Res 69: 203–217.

Barr AM, Panenka WJ, MacEwan GW, Thornton AE, Lang DJ, Honer WG, Lecomte T (2006) The need for speed: an update on methamphetamine addiction. J Psychiatry Neurosci 31: 301–313.

Csemy L, Kubicka L, Nociar A (2002) Drug scene in the Czech Republic and Slovakia during the period of transformation. Eur Addict Res 8: 159–165.

Hansenne M (1999) P300 and personality: an investigation with the Cloninger's model. Biol Psychol 50: 143–155.

Hartel-Petri R, Rodler R, Schmeisser U, Steinmann J, Wolfersdorf M (2005) Increasing prevalence of amphetamine- and methamphetamine-induced psychosis (in German). Psychiatr Prax 32: 13–17.

Iwanami A, Kuroki N, Iritani S, Isono H, Okajima Y, Kamijima K (1998) P3a of event-related potential in chronic methamphetamine dependence. J Nerv Ment Dis 186: 746–751.

Izawa J, Yamanashi K, Asakura T, Misu Y, Goshima Y (2006) Differential effects of methamphetamine and cocaine on behavior and extracellular levels of dopamine and 3,4-dihydroxyphenylalanine in the nucleus accumbens of conscious rats. Eur J Pharmacol 549: 84–90.

Jessen F, Fries T, Kucharski C, Nishimura T, Hoenig K, Maier W, Falkai P, Heun R (2001) Amplitude reduction of the mismatch negativity in first-degree relatives of patients with schizophrenia. Neurosci Lett 309: 185–188.

Kahkonen S, Ahveninen J, Pekkonen E, Kaakkola S, Huttunen J, Ilmoniemi RJ, Jaaskelainen IP (2002) Dopamine modulates involuntary attention shifting and reorienting: an electromagnetic study. Clin Neurophysiol 113: 1894–1902.

Kahkonen S, Makinen V, Jaaskelainen IP, Pennanen S, Liesivuori J, Ahveninen J (2005) Serotonergic modulation of mismatch negativity. Psychiatry Res 138: 61–74.

Kanthasamy A, Anantharam V, Ali SF, Kanthasamy AG (2006) Methamphetamine induces autophagy and apoptosis in a mesencephalic dopaminergic neuronal culture model: role of cathepsin-D in methamphetamine-induced apoptotic cell death. Ann N Y Acad Sci 1074: 234–244.

Kremláček J, Kuba M, Kubová Z, Langrová J (2006) Visual mismatch negativity elicited by magnocellular system activation. Vision Res 46: 485–490.

Leung S, Croft RJ, Baldeweg T, Nathan PJ (2007) Acute dopamine D(1) and D(2) receptor stimulation does not modulate mismatch negativity (MMN) in healthy human subjects. Psychopharmacology (Berl) 194: 443–451.

Nordahl TE, Salo R, Leamon M (2003) Neuropsychological effects of chronic methamphetamine use on neurotransmitters and cognition: a review. J Neuropsychiatry Clin Neurosci 15: 317–325.

Oranje B, Jensen K, Wienberg M, Glenthoj BY (2007) Divergent effects of increased serotonergic activity on psychophysiological parameters of human attention. Int J Neuropsychopharmacol: 1–11.

Tales A, Newton P, Troscianko T, Butler S (1999) Mismatch negativity in the visual modality. Neuroreport 10: 3363–3367.

Umbricht D, Koller R, Schmid L, Skrabo A, Gruebel C, Huber T, Stassen H (2003) How specific are deficits in mismatch negativity generation to schizophrenia? Biol Psychiatry 53: 1120–1131.

United Nations (2004) 2004 World Drug Report. United Nations, Office on Drugs and Crime.