ORIGINAL ARTICLE

Comparison of Continuous Performance Test results between subjects dependent on methamphetamine and healthy volunteers

Ladislav Hosak [1], Marek Preiss [2], Jan Bazant [1], Andrea Tibenska [1], David Holub [3], Radka Cermakova [2], Eva Cermakova [4]

[1] Department of Psychiatry, Charles University in Prague, Faculty of Medicine in Hradec Kralove, and University Hospital Hradec Kralove, Czech Republic; [2] Prague Psychiatric Center, and University of New York in Prague, Czech Republic; [3] Mental Health Service for Adults, Douglas, Isle of Man; [4] Computer Technology Center, Charles University in Prague, Faculty of Medicine in Hradec Kralove, Czech Republic.

Correspondence to: Prof. Ladislav Hosak, MD., PhD., Dpt. of Psychiatry, University Hospital, Sokolska 581, 500 05 Hradec Kralove, Czech Republic; TEL: +420 495 832 228; FAX: +420 495 833 041; E-MAIL: hosak@lfhk.cuni.cz

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Abstract

Methamphetamine is a neurotoxic agent. Its chronic abuse may result in cognitive impairment with negative consequences for patients´ treatment and rehabilitation. The aim of the study was to compare Continuous Performance Test (CPT) profiles of subjects dependent on methamphetamine with healthy individuals.

Forty-five hospitalized patients including twenty-nine men at the average age of 25.3±5.4 years dependent on methamphetamine for 6.0±3.3 years were assessed by the Continuous Performance Test. We used the same neurocognitive test for the comparison group of healthy controls (controls N=118, men N=50, average age of 28.1±7.2 years). We applied the Chi-Square Test, Two-Sample T Test, Mann-Whitney U Test and Kolmogorov-Smirnov Test to compare methamphetamine dependent patients with healthy volunteers.

In the Continuous Performance Test, general T scores of commissions were significantly higher (p=0.02; Mann-Whitney U Test), but general T scores of hit reaction time (p<0.001; Mann-Whitney U Test), speed/accuracy scores (p=0.04; Kolmogorov-Smirnov Test) and erratic reaction time scores (p=0.04; Mann-Whitney U Test) were significantly lower in the patients as compared to healthy controls. We ascertained a significant cognitive deterioration in the patients as compared to healthy volunteers even if the average patients´ achievements were within the normal range according to the test norms.

A cognitive impairment was present in the group of patients as compared to healthy controls. Better understanding of neurocognitive impairments in methamphetamine dependent subjects should help to generate modern therapeutic approaches, both pharmacological and psychosocial, to prevent or attenuate the long-term negative consequences of methamphetamine use disorders.

Abbreviations:
Continuous Performance Test (CPT); fluorodeoxyglucose-positron emission tomography (FDG-PET); hir reaction time (HitRT); hit reaction time standard error (HitSE); intravenous (I.V.); Kolmogorov-Smirnov Test (KS); methamphetamine (MA); Mann-Whitney U Test (MWU); standard deviation (S.D.); Two-Sample T Test (TST);

Introduction

United Nations Office on Drugs and Crime estimates that between 13.7 and 52.9 million people worldwide used amphetamine-group substances at least once in 2009 (UNODC 2010). Methamphetamine (MA) abuse is a significant problem in the United States. Approximately 10 million people aged 12 years and older have abused methamphetamine in their lifetimes (http://www.nida.nih.gov/). The number of serious illegal drug abusers amounts to 37 000 in the Czech Republic where the total number of population equals to 10 million. Methamphetamine abusers represent approximately 25 000 subjects in this country (The Government Office of the Czech Republic 2010).

Methamphetamine is a central nervous system stimulant having a high potential for abuse. MA increases the release and blocks the reuptake of the brain neurotransmitter dopamine, which leads to high levels of dopamine in the brain. Dopamine is involved in reward, motivation, experience of pleasure, and motor function. Methamphetamine's ability to release dopamine rapidly in reward regions of the brain, such as ventral striatum, produces the intense euphoria (Drevets *et al* 2001).

Chronic methamphetamine abuse significantly impairs both the brain structure and its functions. Neuronal apoptosis, dopaminergic and serotonergic nerve terminal degeneration, and activation of astroglial and microglial cells are the main consequences of MA neurotoxicity (Schep *et al* 2010). Oxidative stress, hyperthermia, excitotoxicity, and various apoptotic pathways are the factors that are thought to underlie this process (Cadet *et al* 2007).

The Continuous Performance Test (CPT) measures a person´s sustained and selective attention and impulsivity (Conners 2000). Sustained attention is the ability to maintain a consistent focus on some continuous activity or stimuli, and is associated with impulsivity. Selective attention is the ability to focus on relevant stimuli and ignore competing stimuli. This skill is associated with distractibility. Abnormalities in brain functions due to neurotoxic effects of methamphetamine can be measured by CPT (Piper *et al* 2011). The Continuous Performance Test has been repeatedly administered in clinical practice and research in the Czech Republic (Preiss & Kučerová 2006; Kawaciuková 2008; Raszka *et al* 2008).

In a literature review (Meredith *et al* 2005) it was shown that abusers of MA or amphetamine, compared to cocaine and heroin abusers, demonstrate deficits on tests of executive function, which suggests frontal dysfunction. Marked impairment in the neurocognitive functioning of MA-dependent patients persists into abstinence. These impairments diminish the ability of MA abusers to benefit from psychosocial treatment.

The aim of the study was to compare CPT profiles of Czech subjects dependent on methamphetamine with healthy individuals.

Subjects and methods

Participants

Patients dependent on methamphetamine (DSM-IV Code 304.40), who were hospitalised and treated at the Addiction Treatment Unit in Nechanice in 2007–2010, agreed to participate in the investigation. Addiction to substances other than MA (apart from nicotine) was an exclusion criterium. The participants did not have any withdrawal symptoms at the time of neurocognitive testing, which was assessed by a qualified psychiatrist. The patients must have abstained from methamphetamine for one month at least. We obtained demographic and clinical data on the patients via a chart review. The Addiction Treatment Unit in Nechanice is an inpatient facility with 50 beds designated to treat alcohol and illicit drugs addictions and pathological gambling. The expected duration of hospitalization is three months. The prevailing method of treatment is psychotherapy.

Healthy volunteers were enrolled by the staff of the Prague Psychiatric Center. They must have had no medical record related to psychiatry or neurology. This was assessed by the direct questioning of the research worker. The group of healthy volunteers was predominantly composed of medical students, other students, employees of the Prague Psychiatric Center (nurses, physicians, technicians), and their relatives.

Neurocognitive assessment

We assessed both the patients and healthy volunteers by the computerized CPT test (Conners 2000). The examination was performed in a quiet testing room. During the test, the examinee is asked to watch the screen which turns black, and letters start to appear in different intervals in the middle of the screen. The respondent is told to click a mouse button as soon as possible anytime when any letter appears with the exception of letter X. When X appears, the examinee is instructed to hold back without any response. There are four main scores that are used in the CPT: *Correct Detection* indicates the number of times the client responded to the target stimulus. Higher rates of correct detections indicate better attentional capacity. *Reaction Times* measure the amount of time between the presentation of the stimulus and the client's response. *Omission Errors* indicate the number of times the target was presented, but the client did not respond to it. High omission rates indicate that the subject is either not paying attention to stimuli (distractibility) or has a sluggish response. *Commission Errors* indicate the number of times the client responded but a non-target stimulus was presented. A fast reaction time and a high commission error rate point to difficulties with impulsivity. A slow reaction time with high commission and omission errors indicates inattention in general. The client's scores are compared with the normative scores relevant for age and gender.

Statistical analysis

We used the NCSS 2007 statistical software to test the differences between the patients and healthy volunteers in demographic variables and the CPT results (Chi-Square Test, Two-Sample T Test, non-parametric Kolmogorov-Smirnov Test, and Mann-Whitney U Test). We calculated T scores of CPT variables to establish the position of every subject in his or her study subgroup regarding age, gender and duration of education (http://everything2.com/). Spearman´s rank correlation coefficient was used to look for a correlation between the CPT results of the patients and the duration of their MA abuse.

Ethical issues

The study was approved by the Ethics Committees of the Faculty of Medicine in Hradec Kralove and Prague Psychiatric Center. The protocol for the research project conforms to the provisions of the Declaration of Helsinki in 1975 as revised in 1983. The patients as well as the healthy volunteers voluntarily signed their „informed consent". The anonymity of all participants is preserved.

Tab. 1. Selected demographic and clinical data on the patients dependent on methamphetamine (N=45).

Variable	Option	N	%
Education	Junior high school	12	27
	Apprenticeship	21	46
	High school	12	27
Employment	Paid job	22	48
	Unemployed	18	40
	Students	5	12
Marital status	Single	37	82
	Divorced	7	16
	Married	1	2
Housing	With parents or grandparents	31	69
	Independent housing	8	18
	With a partner	4	9
	Homeless	2	4
Criminal behavior in the history	Yes	17	38
	No	28	62
Mode of MA application	I.V.	35	78
	Sniffing	10	22
Common MA dose in one application	0.5 gram	19	42
	1 gram	8	18
	Other doses	18	40
Frequency of MA application	Once a day	20	44
	Several times a day	5	12
	Less frequently than once a day	20	44

Results

MA dependent patients

Forty-five Czech Caucasian individuals (men N=29) at the average age of 25.3±5.4 years (range 18–37 years) dependent on MA were administered the Continuous Performance Test. The average time span of MA abuse was 6.0±3.3 years (range 1–13 years). Their average duration of education was 11.7±1.4 years (range 8–15 years). Other demographic and clinical data on the patients are stated in ***Table 1***. Four other methamphetamine dependent patients were not included into the study because of symptoms of depression with hypoprosexia.

Healthy volunteers

The healthy volunteers comprised one hundred and eighteen Czech Caucasian individuals (men N=50) at the average age of 28.1±7.2 years (range 18–50 years), not dependent on any illicit substance or alcohol, and suffering from no serious physical or mental disorder. The average duration of education was 14.4±2.3 years (range 9–18 years). All healthy volunteers met the inclusion criteria, and were involved into the study.

A demographic comparison of the patients vs healthy controls

The gender distribution and the average age were significantly different in the patients vs healthy controls, with more males in the patient group (p=0.01; Chi-Square Test) as well as the average age of the patients being younger (p=0.006; Kolmogorov-Smirnov Test). The total time of education was significantly longer in healthy volunteers in comparison to the patients (p=0.001, Two-Sample T Test).

Results of the CPT in MA dependent patients vs healthy controls

General T scores of commissions were significantly higher (p=0.02; Mann-Whitney U Test), and general T scores of hit reaction time (p<0.001; Mann-Whitney U Test), speed/accuracy (p=0.04; Kolmogorov-Smirnov Test) and erratic reaction time (p=0.04; Mann-Whitney U Test) were significantly lower in the patients as compared to healthy controls. The rest of the recorded CPT items were not significantly different between the patients and control subjects (***Table 2***). The patients were quicker on average as against the controls (hit reaction time, HitRT), but they more frequently responded to a nontarget, and had a less cautious response style (speed/accuracy, Beta). The MA dependent subjects were also more concerned with responding to all targets and less concerned about whether their responses were correct. This manner can be described as "cognitive impulsivity". The patients tended to have an increase in reaction time, as the time between targets increased. The average achievements of the patients are mostly situated in the normal range (average T scores are about 50, and S.D.s approximately equal to 10,

Tab. 2. Differences in CPT between individuals dependent on methamphetamine and healthy volunteers (T scores).

Variable	Mean±S.D. Controls (N=118)	Mean±S.D. Patients (N=45)	Median Min-Max Controls (N=118)	Median Min-Max Patients (N=45)	*p*-value (test)
General-TScore-Omissions	50.5±9.7	48.2±7.4	47 (41-104)	45 (41-74)	0.4 (KS)
General-TScore-Commissions	52.9±10.8	56.8±8.9	52 (33-89)	56 (38-78)	0.02 (MWU)
General-TScore-HitRT	45.9±7.5	37.4±9.2	46 (24-73)	36 (13-62)	0.000 (MWU)
General-TScore-HitSE	44.6±7.8	45.3±9.6	45 (23-67)	45 (24-80)	0.9 (MWU)
General-TScore-VarSE	46.4±8.2	46.8±9.9	45 (31-72)	46 (30-83)	1.0 (MWU)
General-TScore-DPrime	52.9±9.5	56.4±6.4	54 (17-71)	57 (41-69)	0.1 (KS)
General-Tscore-Beta	48.9±9.1	45.9±2.6	47 (42-100)	46 (42-54)	0.04 (KS)
General-TScore-Perseverations	50.4±11.2	56.8±23.8	47 (45-130)	47 (45-173)	0.2 (KS)
General-TScore-HitRTBlock	48.3±7.5	46.5±9.2	48 (28-69)	46 (22-65)	0.2 (TST)
General-TScore-HitSEBlock	48.6±9	50±8.3	48 (29-72)	49 (28-78)	0.6 (MWU)
General-TScore-HitRTIsi	44.9±8.3	44.9±9	44 (19-72)	45 (30-71)	1.0 (MWU)
General-TScore-HitSEIsi	48.4±8.6	45.6±8.6	47 (30-75)	45 (28-70)	0.04 (MWU)

CPT – Continuous Performance Test; KS – Kolmogorov-Smirnov Test; MWU – Mann-Whitney U Test; S.D. – standard deviation; TST – Two-Sample T Test; General-TScore-Omissions – T score of omissions (omissions are a number of targets to which the individual did not respond); General-TScore-Commissions – T score of commissions (commissions are a number of times the individual responded to a nontarget); General-TScore-HitRT – T score of hit reaction time (hit reaction time is a mean response time in milliseconds for all target responses over all six times); General-TScore-HitSE – T score of hit reaction time standard error (a high score means highly variable reactions); General-TScore-VarSE – T score of variability of standard error (amount of variability the individual shows in relation to his/her own standard error); General-TScore-Dprime – T score of attentiveness (how well the individual discriminates between targets and nontargets); General-TScore-Beta – T score of speed/accuracy (high values reflect a cautious response style); General-TScore-Perseverations – T score of perseverations (a response that occurs less than 100 ms following a stimulus); General-TScore-HitRTBlock – T score of vigilance (a high score indicates a loss of vigilance); General-TScore-HitSEBlock – T score of reaction time (a high score indicates a less consistent reaction time, a loss of vigilance); General-TScore-HitRTIsi – T score of slowing of reaction time (a high score indicates a slowing of reaction time); General-TScore-HitSEIsi – T score of erratic reaction time (a high score indicates a more erratic reaction time)

respectively). The exception is a decreased hit reaction time in the patients which is related to their impulsivity. It is evident that a cognitive deterioration in the CPT variables is present in the group of patients, in spite of the fact that their achievement is in the normal span range according to the test norms.

The CPT results of the patients did not correlate with the duration of their methamphetamine abuse (Spearman´s rank correlation coefficient from –0.51 to 0.33).

Discussion

The demographic dissimilarities between the patients and healthy controls, related to gender distribution, age and duration of education, were eliminated by using demographically corrected normative data (T scores) (Conners 2000). In the CPT test, the patients were quicker, but they responded to a nontarget significantly more frequently and had a less guarded response style as against healthy volunteers. The MA dependent subjects were more concerned with responding to all targets and less concerned about whether their responses were correct. Under the term of „cognitive impulsivity", we understand the situation when the patient is not able to analyse the stimulus properly, and suppress his reaction if the letter X appears. This is caused by the accelerated speed of the patient´s reactions. Our finding that the CPT results of the patients did not correlate with the duration of their methamphetamine abuse can be explained by the fact that the duration of MA abuse was relatively long in the study subjects, and such a correlation would be more probable at an earlier stage of this mental disorder. We can state that a significant cognitive deterioration was revealed in the patients group as compared to the healthy controls, even if the measurable performance of the patients occurred in the standard range according to the CPT test norms. Our CPT findings may be related to the anterior cingulate cortex in MA dependence (Salo *et al* 2002).

Having used the PubMed computer database on September 8th, 2011 (key words: continuous AND performance AND test AND methamphetamine), we only found one fully relevant article. Piper *et al* (2011) studied abnormalities in parentally rated executive function in methamphetamine/polysubstance exposed children in the U.S. The authors used a battery of established tests, including the Wechsler Abbreviated Scale of Intelligence, Conner´s Continuous Performance Test II, Behavioral Rating Inventory of Executive Function, the

CMS Family Pictures, Dot Location tests, and Memory Island to assess the effects of prenatal drug exposure on neurobehavioral performance. Participants were 7 to 9 year old children who either had (N=31) or had not (N=35) been exposed to methamphetamine/polysubstance during pregnancy. Compared to unexposed children, exposed children showed more problems in parental ratings of executive function, including behavioral regulation and metacognition.

The fluorodeoxyglucose-positron emission tomography (FDG-PET) data found by Kim *et al* (2009) in 24 abstinent methamphetamine dependent patients and 21 age-matched control subjects suggest that MA dependent patients have dose-dependent frontal hypometabolism and frontal executive dysfunction.

As for amphetamine short-term neuropsychological effects, Fleming *et al* (1995) studied 17 healthy individuals in the U.S. They received a single oral dose of dextroamphetamine. There was a decreased reaction time on the Continuous Performance Test. The results also suggest that cognitive abilities of persons who may have relatively high dopaminergic tone are disrupted by amphetamine, while those with relatively low dopaminergic tone may have their performance enhanced.

Positive allosteric modulation of the metabotropic glutamate receptors mGlu5 may actually enhance cognition and potentially reverse some of the cognitive deficits associated with chronic drug use (Olive 2010). Inhibitors of acetylcholinesterase such as galantamine can enhance cognitive function (e.g., sustained attention) in abstinent psychostimulant users (Sofuoglu *et al* 2011). Atypical antipsychotic drugs may also improve some domains of cognition via their action on serotonergic 5-HT1A, 5-HT2A and 5-HT7 receptors, which has already been proved in schizophrenia (Meltzer & Massey 2011).

There are several limitations of the present study. We do not compare the test results of a concrete patient with a healthy control subject in the practice of clinical psychology, but only use standard values described in the test norm. In this way, the method of our study does not fully reflect the actual clinical practice. Our results may also have been influenced by premorbid characteristics of the patients.

The strength of our results is given by a homogenous study sample concerning ethnicity and a narrowly specific diagnosis in the patients.

Conclusions

We found a significant cognitive deterioration in the patients group as compared to the healthy controls using the Continuous Performance Test. Better understanding of neurocognitive impairments in methamphetamine dependent subjects may help to generate modern therapeutic and rehabilitation approaches, both pharmacological and psychosocial, to prevent or attenuate the long-term negative consequences of MA use disorders in the future.

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