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COMPARISON OF WISCONSIN CARD SORTING TEST RESULTS BETWEEN CZECH SUBJECTS DEPENDENT ON METHAMPHETAMINE VERSUS HEALTHY VOLUNTEERS

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SUMMARY

Background: *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 Wisconsin Card Sorting Test profiles of Czech subjects dependent on methamphetamine with healthy individuals.*

Subjects and methods: *Forty-three hospitalized Czech Caucasian patients including twenty-seven men at the average age of 25.3±5.2 years dependent on methamphetamine for 6.2±3.3 years were assessed by the Wisconsin Card Sorting Test. We used the same neurocognitive test for the comparison group of healthy controls with the same ethnicity (N=52, men N=28, average age of 38.7±12.1 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.*

Results: *All recorded Wisconsin Card Sorting Test parameters were significantly different in the group of methamphetamine dependent patients versus healthy volunteers (P=0.04-0.006; Mann-Whitney U Test, Two-Sample T Test). The results showed a higher error rate and a smaller achievement quality in the patients as against healthy subjects. We ascertained a significant cognitive deterioration in the patients as compared to healthy volunteers even if the average patients´ achievements were in the normal range according to the test norms.*

Conclusions: *A cognitive impairment was present in the group of patients as compared to healthy controls. Better understanding of neurocognitive symptoms 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.*

Key words: *methamphetamine dependence – neurotoxicity – cognitive impairment – Wisconsin Card Sorting Test*

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INTRODUCTION

The 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 (United Nations Office on Drugs and Crime 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 (National Institute on Drug Abuse 2011). The number of serious illegal drug abusers amounts to 37 000 in the Czech Republic where the total number of the population equals to 10 million. Methamphetamine abusers represent about 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 the ventral striatum, produces 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, Slaughter & Beasley 2010). Oxidative stress, hyperthermia, excitotoxicity, and various apoptotic pathways are factors that are thought to underlie this process (Cadet et al. 2007).

The Wisconsin Card Sorting Test (WCST) can reveal perseverative errors in patients addicted to illicit drugs, and thus measure neurocognitive impairment induced by these substances in the brain (Henry, Minassian & Perry 2010, Henry et al. 2011, Woicik et al. 2011). Perseverative Errors are highly relevant for clinical assessment because this type of error is considered to be an indicator of frontal lobe dysfunction (Heaton et al. 1993, Steinmetz et al. 2010). The Wisconsin Card Sorting Test has been validated and repeatedly used in the Czech Republic (Kawaciuková 2008, Preiss & Kučerová 2006, 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 such as the Wisconsin Card Sorting Test, which suggests frontal dysfunction. Marked impairment in the neurocognitive functioning of MA-dependent patients persists into abstinence. MA-dependent patients in early abstinence perform markedly worse than controls on measures of attention and psychomotor speed, and verbal learning and memory, as well as on fluency-based measures of executive function such as set shifting and inhibition. Apart from dopaminergic and serotonergic nerve terminal degeneration, deficiency in cellular energy production in orbitofrontal and dorsolateral prefrontal cortex may also be responsible for attention deficits in MA abusers. Chronic MA users experience impairments in memory and learning, psychomotor speed, and information processing. These impairments diminish the ability of MA abusers to benefit from psychosocial treatment.

The aim of the study was to compare WCST 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 for the treatment of alcoholics, drug abusers, and pathological gamblers. The expected duration of hospitalization is three months in the case that the patient does not finish his or her treatment prematurely (i.e. unsuccessfully). The prevailling 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 research worker by an immediate request. The group of healthy volunteers was composed of employees of two non-psychiatric hospitals, one government institution, one theatre, and one car repair service in Prague. They were physicians, nurses, managers, assistants, car mechanics, actors, dramaturgists, technicians and cleaning women.

Neurocognitive assessment

We assessed both the patients and healthy volunteers by the computerized WCST test (Heaton & PAR Staff 2003). The examination was performed in a quiet testing room. The basic idea of the WCST is that participants match response cards to key cards according to a nonspecified matching rule, which changes every time when 10 (out of a maximum of 128) response cards have been sorted correctly. The test yields a number of psychometric scores: Firstly, the total number of correctly matched response cards (or *Total Correct*), which is an indicator of overall performance. Secondly, *Percentage of Errors* as an alternative indicator of overall performance. This score is computed by dividing the total number of incorrectly sorted response cards by the total number of response cards sorted and multiplying this value by 100 percent. Thirdly, *Perseverative Errors* which occur when a participant continues sorting response cards according to a matching rule after it has been changed.

Statistical analysis

We used the NCSS 2007 statistical software to test the differences between the patients and healthy volunteers in demographic variables and the WCST results (Chi-Square Test, Two-Sample T Test, non-parametric Kolmogorov-Smirnov Test, and Mann-Whitney U Test).

We calculated T scores of WCST variables to establish the position of every subject in his study subgroup regarding gender, age and duration of education (Everything2 2011).

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 1995 as revised in Tokyo 2004. The patients as well as the healthy volunteers voluntarily signed their „informed consent“. The anonymity of all participants is preserved.

RESULTS

MA dependent patients

Forty-three Czech Caucasian patients (men N=27) at the average age of 25.3±5.2 years (range 17-37 years) dependent on methamphetamine were examined by the Wisconsin Card Sorting Test. The average time span of methamphetamine abuse was 6.2±3.3 years (range 1-13 years). The average duration of education was 11.4±1.7 years (range 8-13 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.

Table 1. Selected demographic and clinical data on the patients dependent on methamphetamine (N=43)

Variable	Option	N	%
Education	Junior high school	13	30
	Apprenticeship	18	42
	High school	12	28
Employment	Paid job	22	51
	Unemployed	17	40
	Students	4	9
Marital status	Single	35	82
	Divorced	7	16
	Married	1	2
Housing	With parents or grandparents	29	67
	Independent housing	8	19
	With a partner	4	9
	Homeless	2	5
Criminal behavior in the history	Yes	18	42
	No	25	58
Mode of MA application	I.V.	34	79
	Sniffing	9	21
Common MA dose in one application	0.5 gram	20	47
	1 gram	8	19
	Other doses	15	34
Frequency of MA application	Once a day	20	47
	Several times a day	5	11
	Less frequently than once a day	18	42

Table 2. Differences in the WCST results between individuals dependent on methamphetamine and healthy volunteers (T scores)

Variable	Mean±S.D. Controls (N=52)	Mean±S.D. Patients (N=43)	Median Min-Max Controls (N=52)	Median Min-Max Patients (N=43)	P (test)
Errors	45.1±11.3	51.5±11.2	45 (20-66)	53 (21-77)	0.007 (TST)
Errors-p	45.2±11.1	51.2±10.4	45 (21-67)	53 (23-71)	0.008 (TST)
Pers-Resp	49.1±14.2	57.7±16.1	48.5 (20-80)	54 (21-80)	0.01 (MWU)
Pers-Resp-p	48.8±13.3	56.9±15.9	47 (20-80)	53 (21-80)	0.02 (MWU)
Pers-Errors	47.9±13.6	56.3±15.5	47.5 (20-80)	54 (24-80)	0.006 (TST)
Pers-Errors-p	48±13.6	55.1±14.8	45 (20-95)	52 (23-80)	0.02 (MWU)
Nonpers-Errors	44.5±11.2	49.9±9.8	46 (21-63)	52 (20-66)	0.01 (MWU)
Nonpers-Errors-p	45.4±10.4	49.7±9.2	48.5 (23-66)	52 (20-63)	0.04 (MWU)

MWU – Mann-Whitney U Test; S.D. – standard deviation; TST – Two-Sample T Test; WCST – Wisconsin Card Sorting Test
Errors – total number of all errors; Errors-p – percent errors ("density" or concentration of perseverative errors in relation to overall test performance); Pers-Resp – perseverative responses (persisting on stimuli characteristic that is incorrect); Pers-Resp-p – percent perseverative responses; Pers-Errors – perseverative errors; Pers-Errors-p – percent perseverative errors; Nonpers-Errors – nonperseverative errors (responses that do not match the perseverated-to principle); Nonpers-Errors-p – percent nonperseverative errors

Healthy volunteers

The healthy volunteers comprised fifty-two Czech Caucasian subjects (men N=28) at the average age of 38.7±12.1 years (range 20-59 years), not dependent on any illicit substance or alcohol, and suffering from no serious physical or mental disorder. The average duration of education was 13.3±2.4 years (range 8-19 years). Five other healthy volunteers did not meet the inclusion criteria, and were not involved into the study.

A demographic comparison of the patients vs healthy controls

The gender distribution was comparable (P=0.4; Chi-Square Test) in the MA dependent patients vs healthy subjects, but the patients were significantly different from healthy controls in average age where the patients were younger (P=0.001; Kolmogorov-Smirnov Test). The patients were also less educated (P=0.01; Kolmogorov-Smirnov Test).

Results of the WCST in MA dependent patients vs healthy controls

All recorded WCST parameters were significantly different in the group of MA dependent patients versus healthy volunteers (P=0.04-0.006; Mann-Whitney U Test, Two-Sample T Test; Table 2). The results show a higher error rate and a smaller achievement quality in the patients as against healthy subjects, when the total average patients´achievement was found in the normal range (mean T scores approach to 50, and S.D.s to 10, respectively). We can sum up that a significant cognitive deterioration was revealed in the patients group as compared to healthy controls, even if the performance of the patients occurred in the standard range. The patients significantly differed from control subjects in their overall abilities to react flexibly to a new situation, utilize new information and previous experiences, formulate a logical conception, maintain set, and learn. The results were not significantly different due to gender (Two-Sample T Test). We did not find a correlation between the duration of methamphetamine abuse and the WCST results in the patients (Spearman´s rank correlation coefficients -0.02-0.21 for individual WCST subtests), probably due to the chronicity of MA abuse in our study sample.

DISCUSSION

The demographic dissimilarity between the patients and healthy controls, related to age and education, was eliminated by using demographically corrected normative data (T scores) (Heaton & PAR Staff 2003). Our WCST results show a significantly higher error rate and a smaller achievement quality in the MA dependent patients as compared to healthy controls. 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 WCST test norms. If the Bonferroni correction is used by reason of multiple testing, the difference between the patients and healthy controls in perseverative errors remains at a statistically significant level (P<0.00625), and there is a trend towards statistical significance for the differences in the total number of all errors and percent errors.

Simon et al. (2002) examined cognitive functions of 40 MA abusers, 40 cocaine abusers and 80 non-using controls in the U.S. Both MA and cocaine abusers were impaired on cognitive measures, but the type and degree of impairments were different. On the Wisconsin Card Sorting Test, total errors, perseverative responses, perseverative errors and failure to maintain set were all significantly worse (P=0.04-0.02), with lower scores for the MA group than for the comparison group. These impairments were not present in the cocaine group. The perseverative errors on the WCST are considered to be sensitive to frontal function. It is possible that the MA group has an impairment in frontal function that is not shared by the group of cocaine participants. Another explanation may be a significant proportion of Attention Deficit Hyperactivity Disorder (ADHD) subjects in the MA abusers as against non-users. A third possibility is that the MA group has more attentional problems than does the cocaine group. There were no significant differences between the performance of either the MA and cocaine groups and their comparison groups on the percent of conceptual level response and learning to learn measures of the WCST. These exceptions are consistent with a drug associated impairment of specific abilities, rather than a generalized lessening of cognitive capacity. The results suggest that MA abusers would have trouble organizing information from more than one source and have difficulty switching points of view.

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.

Groups of subjects whose primary drugs of abuse was amphetamine (N=23) or heroin (N=22) were compared, together with age- and IQ-matched control subjects (N=22) by Ornstein et al. (2000) in the U.K. The study consisted of a neuropsychological test battery. The chronic amphetamine abusers were signifycantly impaired in performance on the extra-dimensional shift task, which is formally equivalent to the category shift as a core component of the Wisconsin Card Sorting Test. In contrast, the heroin abusers were impaired in learning the normally easier intra-dimensional shift component. The results indicate that chronic drug use may lead to distinct patterns of cognitive impairment that may be associated with dysfunction of different components of cortico-striatal circuitry. The results are consistent with evidence that amphetamine abuse is associated with loss of serotonin from the orbitofrontal cortex. WCST is a widely used assessment of cognitive set-shifting that requires shift of attention set from one perceptual category to another (e.g. shape to number) and which is attributed to prefrontal cortex integrity. Amphetamine abuse can lead to cognitive deficits through lasting effects on cortico-striatal circuitry. These deficits may add to the difficulties of rehabilitating amphetamine abusers, and lead to further drug abuse.

According to the review by Verdejo-García et al. (2004), the neuropsychological status of the patient has a mediating role on treatment outcomes. MDMA (3,4-methylenedioxymethamphetamine; Ecstasy) is a synthetic, psychoactive drug that is chemically similar to methamphetamine. Some evidence has suggested the existence of executive functioning deficits as a result of MDMA use. The impairments of the executive functions are linked to the orbitofrontal cortex. Neuropsychological impairments in amphetamine abusers may diminish the quality of their decision-making

processes, e.g. in learning and assimilating the contents and objective of the therapeutic programs. Potential findings related to these issues may optimize the efficacy of the therapies. Evidence from magnetic resonance imaging (MRI) studies shows significant morphological reductions in prefrontal and temporal brain areas in cocaine and amphetamine abusers. This is also supported by findings from functional neuroimaging studies. There is some evidence that the cognitive impairments detected in substance abusers are not static, but rather experience dynamic improvements once abstinence is initiated. Neuropsychological rehabilitation strategies as well as cognitive medication can help in this sense.

Our WCST results are in accordance with the literature. The WCST basically measures executive dysfunction, but subjects with a decreased attention and working memory may also have a problem in this task. Methamphetamine dependent patients performed significantly worse in WCST as compared to the healthy population. The patients had significantly decreased attention and executive functions, and thus had problems with the ability to focus and maintain attention in some activities, and difficulty in flexibly reacting to new situations and changes. This is routinely reflected in a clinical observation of the MA dependent patients, and the disorderliness of their lives. Our results suggest that methamphetamine damages brain dopaminergic circuits in their structure and function, and induces prefrontal hypofunction, which is manifested in a poor performance in the applied neuropsychological test. The WCST findings may be associated with an impairment in a dorsolateral subcortical circuit (Preiss & Kučerová 2006).

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 (e.g., amisulpride, aripiprazole, asenapine, clozapine, olanzapine, quetiapine, or risperidone) 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. Hence, the method of our study does not fully reflect the actual clinical practice. Our results may have been influenced by premorbid characteristics of the patients, e.g. Attention Deficit Hyperactivity Disorder during the childhood, or living in an environment with insufficient social support.

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

Assessments of cognitive functions in MA dependent patients including other examination techniques such as brain imaging, electroencephalography, or genetics, and evaluation of the influence of cognitive medication or psychosocial rehabilitation on these cognitive impairments is a target for future research.

CONCLUSION

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

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