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Improvement of Saccadic Functions After Dosing with Methadone in Opioid Addicted Individuals

Short title: Improvement of Saccadic Functions with Methadone

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Abstract

Background: In the current experiment we used the saccadometric test to study the effect of a single therapeutic dose of methadone on the integrity of cortico-subcortical brain functioning.

Methods: In this prospective study we used the Saccadometer System (Advanced Clinical Instrumentation, Cambridge, UK). The saccadometric test was performed before and 1.5 hours

after methadone dosing. We analyzed the following saccadic parameters: latency, duration, amplitude, average and peak velocity, sharpness, skewness, gain, accuracy, Q ratio and number of different types of saccades like: under/overshoot, catch-up, back-up, intrusive saccades, and anticipatory saccades.

Results: The sample consists of 40 objects with an average 18 years of opioid addiction. The mean age is 35.3±7 (80% males and 20% females). The mean period of heroin dependence is 15.3±6.3 years. The mean daily dose of methadone in substitution therapy is 90±26.5mg.

After administration of a single therapeutic dose of methadone there were statistically significant differences in the values of saccade duration and latency when compared to the values before the drug administration. Average duration of saccade was significantly longer [51.40 ±8.75 *ms* vs 48.93 ± 6.91 *ms*, z=2.53, p=0.01] and average latency was significantly longer [198.85 ±52.57 *ms* vs 183.05 ±30.95 *ms,* z=2.09 p<0.03].

Conclusions: This is the first study to test the therapeutic effect of daily methadone dosing on the integrity of the cortico-subcortical brain functions as measured by the saccadometry. More research is needed to explore the effect of illicit opioid use on the integrity of brain structures and functions, and the protective effect of opioid agonist therapy on reversing the damaging effects of illicit opioid use.

Key Words: Saccadic eye movements, methadone, opioid addicts

Introduction:

The term saccades refers to the relatively small, rapid and jerky movements of the eyeballs when they move from one point in the visual field onto another one. The saccadic movements are associated with activation of the brain regions which are responsible for controlling of executive functions. The cortical area known as frontal eye field (FEF) plays an important role in the control of visual attention and eye movements. The activiation of the FEF in response to eye movements (including saccades) has been confirmed by functional neuroimaging studies[1,2]. The frontal gaze center is located bilaterally in Brodmann area 8 (middle frontal gyrus). There is evidence that FEF may be located outside Brodmann area 8 on the contrary to the commonly held believes[3]. Important areas controlling saccadic movements are the dorsolateral prefrontal cortex (DLPFC), supplementary eye field (SEF), and lateral intraparietal area (LIP)[4]. DLPFC is connected functionally by a number of inhibitory connections with the basal ganglia.

It is possible in healthy individuals to move their eyes in many different ways. Healthy individuals are able to follow visual targets while scanning the environment. This occurs as the result of the spontaneous rapid movements (i.e. saccades) when the eyes move continuously (although discretely). These quick, relatively freely saccadic eye movements occur physiologically with great rapidity and frequency. Therefore, identifying abnormalities in saccadic eye movements could be very useful in evaluating organic central nervous system disorders and their treatment[5-7]. Functional neuroimaging studies in humans contributed significantly to the understanding of the neural correlates of saccadic eye movements and various neuropsychiatric disorders[6,7]. Qualitative and quantitative evaluation of saccadic eye movements gives the chance to determine the relationship between mental functions (i.e. motor, emotional,

and cognitive) and the structure of the brain region controlling these functions.

The brain cortical and subcortical strcutures are connected via circuits or loops. An intact structure of these loops is a necessary condition for their efficient functioning according to the concept of motor, emotional and cognitive control carried out by the cortico-subcortical loops[8,9]. The theoretical basis for this study is that heroin addiction could disrupt the the harmony of the cortico-subcortical brain circuits. This is based on the theory explaining the physiological control of the majority of motor, emotional, and cognitive functions[10-11]. Structural and functional changes were found in the ventral striatum of addicted individuals[12-13]. The heroin's short blood life and the lifestyle of the addict which involves poor nutrition, sleep deprivation, environmental hazards, and social stresses could contribute to the disruption of the brain cortical-subcortical structures.

It is unclear if methadone maintenance treatment improves cortical brain functions. We reported in a previous study that a therapeutic dose of methadone could improve the integrity of the cortico-subcortical brain functioning and enhancing the ability of making healthy decisions in opioid addicted individuals[14]. However, we used a subjective test (i.e. Iowa Gambling Task) to study this hypothesis. In the current experiment we used an objective test (i.e. saccadometric test) to study the effect of a therapeutic dose of methadone on the integrity of cortico-subcortical brain functioning in individuals with history of heroin addiction.

Methods:

Subjects were recruited to this study from an Opioid Substitution Clinic in Świecie nad Wisłą (Poland) and Substitution Clinic in Warsaw (Poland). The inclusion criteria include: fulfilling the

criteria of Diagnostic and Statistical Manual of Mental Disorders-fourth edition (DSM-IV) of opioid dependence, age ranging between 18-65 years, written informed consent of the subject to participate in the study, and subjects being stable on methadone maintenance for at least two weeks before starting the test. Exclusion criteria include: head and/or eyes injuries, history of psychotic illness, history of cognitive or memory disturbance, history of traumatic brain injury, senile dementia, Alzheimer's disease, untreated depression and/ or anxiety, pregnancy and/or breast-feeding, surgery and/or painful medical procedure planned during the period in which study will be carried out, being on antidepressants, antiepileptic, or myorelaxant drugs with dose modification for less than two weeks prior to the test, currently or in the past four weeks being treated with monoamine oxidase inhibitors, metastases to the central nervous system, neuromuscular diseases, advanced cardiovascular, kidney or liver disease, lack of cooperation during the test, illicit drugs use, alcohol withdrawal or intoxication at the time of the study, and any conditions which, according to the researcher may prevent completion of the tests.

Forty six subjects were screened and 40 met all inclusion and exclusion criteria. After consenting for participation in the study each subject was scheduled for two sessions of saccadometry testing before and after dosing with methadone. Before administration of methadone two tests were performed: Latency test and Antisaccades test. Both tests were repeated approximately 1.5 hours after administration of methadone. Saccadometer System (Ober Consulting Poland) was used allowing the measurement of the eyeball's position with 1ms (1000*Hz*) time resolution. Forty (n=40) subjects finished Latency Task correctly before and after administration of methadone, and thirty four (n=34) subjects performed correctly Antisaccades Task before and after administration of methadone. The paper presents only the results of subjects who correctly

performed the test.

The study protocol and consent were reviewed and approval by Nicolaus Copernicus University's Bioethical Commission at Medical College in Bydgoszcz, Poland in accordance with Polish and international law (no. KB/416/2008).

Outcome measures:

- Average duration of saccade before and after administration of a therapeutic dose of methadone.

- Average latency of saccade before and after administration of a therapeutic dose of methadone.

- Average saccade amplitude before and after administration of a therapeutic dose of methadone.

- Average peak saccade velocity before and after administration of a therapeutic dose of methadone.

Statistics:

LatencyMeter version 4.14 (Ober Consulting Poland) application was used for data acquisition system to Saccadometer and to calculate averages, standard deviations and standard errors of all saccades recorded during a single test. The following parameters were analyzed saccades, correct and incorrect**:**

- The overall number of saccades recorded during a single test (max. 50 saccades).
- The mean latency of saccades
- Average efficiency of processing latency of saccades divided into correct and incorrect.
- The average duration of saccades

- The average peak velocity of saccades

STATISTICA 64 version 10 (Stat Soft, Inc. - license number JLV110D131518AR-S) was used for data analysis. To examine possible differences between subjects - before and after administration of methadone - we conducted samples dependent- t-tests. P value less than 0.05 was considered statistically significant.

Significance of differences tests:

- Parametric test: Dependent T-Test for Paired Samples - for variables with distribution close to normal (Normality was checked by Kolmogorov–Smirnov & Lilliefors test for normality) and homogeneous variances (checked by Levene's Test for Homogeneity of Variances)
- Nonparametric test: Wilcoxon Matched-Pairs Signed-Ranks Test

Results:

The sample consists of forty objects with an average 18 years of opioid addiction. The average age of subjects is 35.3±7 (80% males and 20% females). The average period of heroin dependence is 15.3±6.3 years. The average daily dose of methadone in substitution therapy is 90±26.5mg.

Latency Task:

Table 1 summarizes the results of the latency task. The average latency of correct saccades before the administration of methadone was 183.05 (±30.95) *ms.* After a single therapeutic dose of methadone the average latency of correct saccades was 198.85 (±52,57) *ms.* The difference is statistically significant (z=2.09, p=0.03).

The average processing performance (promptness) of correct saccades before the administration of a single therapeutic dose of methadone was 5.96 (±0.77) *Hz*. The average processing performance (promptness) of correct saccades after the administration of a single therapeutic dose of methadone was 5.65(±0.78) *Hz*. The difference is statistically significant (t=2.93, p=0.005).

The average correct saccades duration before administration of a single therapeutic dose of methadone was 48.93(± 6.91) *ms*. The average correct saccades duration after administration of a single therapeutic dose of methadone was 51.40(±8.75) *ms*. The difference is statistically significant (z=2.53, p=0.01).

The average correct saccades peak velocity (PSV) value before administration of a single therapeutic dose of methadone was 416.30 (±65,30) deg/s. The average correct saccades peak velocity value after administration of a single therapeutic dose of methadone was 391.48(±64.25) deg/s. The difference is statistically significant (t=3.22, p=0.002).

Antisaccades task:

Table 2 summarizes the results of the antisaccades task. The average correct saccades number before administration of a single therapeutic dose of methadone was 25.18(±11.79). The average correct saccades number after administration of a single therapeutic dose of methadone was 30.50(±12.53). The difference is statistically significant (z=2.997, p=0.0027).

The average incorrect saccades number before administration of a single therapeutic dose of methadone was 17.18 (±10.28). The average incorrect saccades number after administration of a

single therapeutic dose of methadone was 13.00 (±10.97). The difference is statistically significant (z=2.778, p=0.005).

The average processing performance (promptness) of correct saccades before administration of a single therapeutic dose of methadone was 4.14 (±1.10) *Hz*. The average processing performance (promptness) of correct saccades after administration of a single therapeutic dose of methadone was 3.70 (±0.65) *Hz*. The difference is statistically significant (t=2.09, p=0.04).

The average incorrect saccades promptness before administration of a single therapeutic dose of methadone was 5.21 (±1.30) *Hz*. The average incorrect saccades promptness after administration of a single therapeutic dose of methadone was 4.68(±1.32) *Hz*. The difference is statistically significant (t=2.09, p=0.04).

Discussion

Our results confirm the changes in the dynamics of the saccade, as well as changes in the latency of response to a stimulus after a single therapeutic dose of methadone. In our study it was observed that after administration of methadone, dynamic parameters such as saccade latency and asymmetry of the reaction of these parameters (depending on the direction of the eye movements) are different from the value before the drug administration. We conclude, based on these data, that methadone can improve the harmonization of the cognitive, motor and emotional brain functions in opioid addicted individuals. Methadone could reduce the damaging effect of illicit heroin use on brain structures and functions. Some studies reported that heroin could damage certain brain regions, which may interrupt the cortico-subcortical circuits. A brain imaging study reported that opioid-dependent subjects had lower baseline dopamine (DA) type 2

receptors (D2R) in the left caudate nucleus compared with normal subjects[15]. They also found that opioids-dependent subjects demonstrated higher DA release after cue-exposure in the right putamen than controls. This study suggests the possibility of the damage in the circuit connecting cortical and subcortical structures as a result of heroin use. Another imaging study found a statistically significant positive correlation between the fractional anisotropy (FA) values in the right orbito-frontal white matter (WM), right parietal WM and poor performance on the Iowa Gambling Task (IGT) in heroin addicted individuals[16]. The extent and severity of WM integrity deficits in heroin addicts was associated with the duration of heroin dependence[17]. Furthermore, it was suggested that the abnormal WM microstructure may correlate with poor decision-making in those individuals. In another study there was a positive correlation between the mean regional homogeneity in the medial orbito-frontal-cortex (OFC) and the performance level in the IGT[18]. These studies suggest that heroin use may damage the integrity of the brain cortico-subcortical connections leading to changes in the functions of these circuits. These changes could disrupt the harmonization and integrity of the cognitive, motor and emotional brain functions.

We concluded in a previous study that a therapeutic dose of methadone could improve faulty decisions in individuals with long history of opioid addiction[14]. We showed in that study that the time to making a healthy decision was significantly shorter as a result of administration of methadone. Our current study may confirm our hypothesis about the protective effect of methadone on the integrity of the cortico-subcortcial brain circuits. Wang et al[19] concluded in a recent brain imaging study that long term methadone maintenance treatment may improve heroin-craving response by modulating the impaired function in the bilateral dorsal striatum

caused by former heroin use. This study may also support our hypothesis about the protective effect of methadone on brain structures and functions in former heroin addicts.

Our current study has the advantage of using an objective testing to confirm this hypothesis. The exact mechanism for the therapeutic effect of methadone on improving the brain cortico-subcortical connections is not clearly understood. Chronic activation of the noradrenergic system has shown to be associated with damaging effects in the brain[20]. Chronic exposure to opioid withdrawal during active heroin use can create a state of chronic stress, which may damage brain structures. One possible theory is that methadone could prevent the opioid withdrawal symptoms and reduce the stress associated with opioid withdrawal. Methadone has shown to reduce the opioid withdrawal syndrome[21]. Methadone is long acting and a single daily dose could block the opioid withdrawal syndrome all day. Normalization of the noradrenergic activity in the cortico-subcortical brain circuits can explain the therapeutic effect of methadone on brain functions. In addition to the acute effect of a therapeutic dose of methadone on improving brain functions, it seems that methadone could also have long term therapeutic effects. Methadone blocks the euphoric effects, reduces the reward reinforcing properties and craving for opioid use. It reduces the risk of HIV[22-26] and other infectious diseases associated with intravenous illicit opioid use, particularly hepatitis B and C but also bacterial infections like endocarditis[27]. Methadone can directly reduce the damage to the brain structures and functions in opioid addicts due to its protecting effect on the cortico-subcortical brain structures. It can also reduce this risk indirectly by reducing craving for opioids and by reducing the risk of HIV and other infections.

This study has some limitations including the small sample size, relying on one method (saccadometry) only for testing the integrity of the cortico-subcortical brain functions and lack of

a control group. We also could not replicate the results when the saccadometry was performed in two clinics in two different cities in Poland (we present the results from one clinic only). The difference in the methadone dosing patterns between the prescribers in these two clinics, the difference in patient's demographics or presence of other confounding factors like recent smoking or illicit drug use could explain the inability to replicates the results in the two clinics. A multicenter randomized controlled study is needed to confirm our results. It would be helpful in future studies to include functional neuroimaging techniques to correlate with the results of the saccadometry before and after methadone dosing. Another limitation is that multiple testing (pre and post methadone dose) might affect outcomes irrespective of the effects of methadone.

However, this is the first study to test the therapeutic effect of daily methadone dosing on the integrity of the cortico-subcortical brain functions as measured by the saccadometry. More research is needed to explore the effects of illicit opioid use on the integrity of brain structures and functions, and the protective effects of opioid agonist therapy on reversing the damaging effects of illicit opioid use.

In summary while short acting opioids like heroin may disrupt the brain cortical-subcortical strcutures it seems that long acting opioids like methadone may have a protecting effect on brain functions in heroin addicted individuals.

Declaration of Interest: Dr Fareed received an honorarium from Oraxo, AB pharmaceutical company for serving on a clinical advisory board to assist with research ideas. Dr Fareed was a Consultant to Reckitt Benckiser pharmaceutical company for serving with a group of key opinion leaders to assist with a study design. The other authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

Bioethics approval: To conduct the study, the consent of the Bioethics Commission at Medical College in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland was obtained (Consent no. KB/416/2008)

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Table 1: Results of Latency Task of Saccadometry Before and After Administration of Methadone (N=40)

Test	Value Before Methadone	Value After Methadone	Statistics	P Value
Average number correct saccades (SD)	45.6(±7.34)	45.9 (±6.63)	z=0.235	0.81
Average incorrect saccades (SD)	0.53(±1.04)	0.53(±0.88)	z=0.149	0.88
Average latency of correct saccades (SD)	183.05 (±30.95) *ms*	198.85 (±52.57) *ms*	z=2.09	0.03
Average latency of incorrect (SD)	310.29 (±297.05) *ms*	467.2 (±343.15)	z=1.75	0.07
Average processing performance of correct saccades (SD)	5.96 (±0.77) *Hz*	5.65(±0.78) *Hz*	t=2.93	0.005
Average processing	8.14(±6.58) *Hz*	5.92(±5.88) *Hz*	t= - 0.64	0.89

performance of incorrect saccades (SD)				
Average correct saccades duration (SD)	48.93(± 6.91) *ms*	51.40(±8.75) *ms*	z=2.53	0.01
Average incorrect saccades duration (SD)	41.43 (±13.17) *ms*	49.71(±14.86) *ms*	z=1.752	0.07
Average correct saccades amplitude (SD)	9.95 (±0.43) *deg*	9.85 (±0.43) *deg*	t=1.4	0.16
Average incorrect saccades amplitude (SD)	6.59 (±4.40) *deg*	7.90(±3.15) *deg*	t= - 0.43	0.69
Average correct saccades peak velocity (SD)	416.30 (±65,30) *deg/s*	391.48(±64.25) *deg/s*	t=3.22	0.002
Average incorrect	290.79(±143.35) *deg/s*	328.36 (±54.08) deg/s	t=0.298	0.78

saccades peak velocity (SD)				

SD = standard deviation, ms = millisecond, Hz = hertz, deg = degree, s = second

Table 2: Results of Antisaccades Task of Saccadometry Before and After Administration of Methadone (n=34)

Test	Value Before Methadone	Value After Methadone	Statistics	P Value
Average number correct saccades (SD)	25.18(±11.79)	30.50(±12.53)	z=2.997	0.0027
Average incorrect saccades (SD)	17.18 (±10.28)	13.00 (±10.97)	z=2.778	0.005
Average latency of correct saccades (SD)	293.44 (±74.21) *ms*	333.71(±136.19) *ms*	Z=0.86	0.39
Average latency of incorrect (SD)	280.67(±165.67) *ms*	287.23(±139.77) *ms*	Z=0.99	0.33
Average processing performance of correct saccades (SD)	4.14 (±1.10) *Hz*	3.70 (±0.65) *Hz*	t=2.09	0.04
Average processing	5.21 (±1.30) *Hz*	4.68(±1.32) *Hz*	t=2.09	0.04

performance of incorrect saccades (SD)				
Average correct saccades duration (SD)	67,17(±20.89)*ms*	79.11(±23.58)*ms*	z=0.99	0.32
Average incorrect saccades duration (SD)	52.74(±11.57)*ms*	54.37(±13.33)*ms*	z=0.91	0.36
Average correct saccades amplitude (SD)	10.6(±1.8)*deg*	10.4(±1.5)*deg*	t=0.63	0.53
Average incorrect saccades amplitude (SD)	9.06(±1.98) *deg*	8.6(±1.9)*deg*	t=1.44	0.15
Average correct saccades peak velocity (SD)	336.29(±73.9) *deg/s*	317.34(±77.13) *deg/s*	t=0.72	0.48
Average incorrect	358.29(±99.9) *deg/s*	330.03(±85.4) *deg/s*	t=1.77	0.09

saccades peak velocity (SD)				

SD = standard deviation, ms = millisecond, Hz = hertz

