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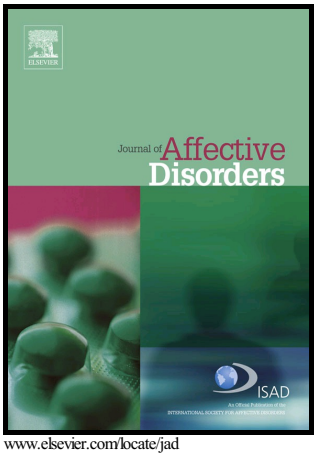

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TITLE: Impact of physical exercise on catechol-O-methyltransferase activity in depressive patients: A preliminary communication

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Abstract

Background: Catechol-O-methyltransferase (COMT) is a catabolic enzyme involved in the degradation of bioactive molecules including the neurotransmitters epinephrine, norepinephrine, and dopamine. Higher COMT activity in depressive patients in comparison to non-depressed individuals has been reported. The effect of aerobic exercise on depressive patients has been studied and a number of researchers and clinicians believe it to be effective in the treatment of depression and to be involved in several molecular underlying mechanisms. However, the effect of physical exercise on this enzyme activity is unknown, and it remains to be elucidated if chronic exercise changes COMT activity. This randomized control trial evaluates the effects of chronic exercise on peripheral COMT (S-COMT) activity in women with depressive disorder.

Methods: Fourteen women (aged: 51.4±10.5 years) diagnosed with depression (according to International Classification of Diseases-10) were randomized to one of two groups: pharmacotherapy plus physical exercise (n=7) or only pharmacotherapy (n=7). The aerobic exercise program was supervised, lasting between 45-50 min/session, three times/week for 16 weeks. Erythrocyte soluble COMT were assessed prior to and after the exercise program.

Results: Exercise group when compared to a control group presented a significant decrease (p=0,02, r= -0,535) in S-COMT activity between baseline and post-intervention.

Limitations: These data are preliminary outcomes from a small sample and should be replicated.

Conclusions: Chronic exercise therapy combined with pharmacotherapy leads to significant decrease in S-COMT activity. Our results provide evidence that exercise interferes with S-COMT activity, a molecular mechanism involved in depression.

Keywords: Enzymes, Depression, Aerobic exercise, Catechols, Women.

1. Introduction

It is well known that unipolar depression is a debilitating disease that has a substantial negative impact on quality of life, morbidity/mortality, and cognitive function (Behr et al., 2012). Major depressive disorder (MDD) is not only characterized by intense dysregulation of affect and mood (Villanueva, 2013) but it is also linked with other abnormalities, namely in cognitive dysfunction (memory, executive function, processing speed and attention) (Carvalho et al., 2014). MDD has been consistently associated with catecholaminergic dysfunction (Opmeer et al., 2013), especially with a decrease in dopamine neurotransmission (Hasler et al., 2008). New studies have revived interest in the enzyme catechol-O-methyltransferase (COMT), one of the key modulators of the dopaminergic levels in the prefrontal cortex (PFC) of the human brain (Sengupta et al., 2008). COMT is an important enzyme for inactivation and metabolism of catechols, including dopamine, norepinephrine, estrogens and other catechol compounds (Chen et al., 2011). Two main COMT protein isoforms are known: a membrane bound form (MB-COMT), which is predominantly expressed in brain neurons and a soluble cytoplasmic (S-COMT), which is more abundant in peripheral tissues (Mannisto and Kaakkola, 1999). The COMT enzyme activity is encoded for the COMT gene (Antypa et al., 2013) and has a genetically polymorphic with a tri-modal distribution (Val/Val genotype, Val/Met genotype, and Met/Met genotype) (Hosak, 2007). Evidence from clinical investigations on the role of the COMT supports the finding that abnormal catecholamine transmission has been linked to the pathogenesis of disorders in mood, which include MDD (Massat et al., 2005).

An emerging multidisciplinary literature has documented the beneficial influence of physical activity on selective aspects of brain function (Hillman et al., 2008). Thus, physical exercise (PE) has been regarded as a useful non-pharmacological intervention strategy to improve cognitive function. In this context, physical activity engendered through aerobic exercise, in particular, benefits executive control processes of cognition in several domains such as in selective attention, planning, organizing, multitasking, inhibition, and working memory (Hotting and Roder, 2013; Kubesch et al., 2003) Despite knowing that aerobic exercise can enhance cognitive functioning by modulating particular aspects of brain functioning, there are a multitude of questions which remain to be answered, namely the mechanisms underlying this modulating effect (Stroth et al., 2010). It is possible that the effect of aerobic exercise on cognitive functions is partly mediated by dopaminergic modulation. One mechanism that accounts for up-regulation of dopamine in the brain has been associated to exercise inducing higher levels of serum calcium, which is transported to the brain (Lin and Kuo, 2013). Calcium ions in brain functions activate tyrosine hydroxylase through a calmodulin-dependent system (Sutoo et al. , 1991). Calmodulin is a calcium-binding protein, which is involved in many calcium-dependent enzyme activities, and in the synthesis and release of several neurotransmitters, including in dopamine synthesis (Sutoo et al., 2001). Subsequently, the increased dopamine levels lead to behavioral and physiologic changes. Nevertheless, assessing central dopamine levels in humans is problematic since dopamine cannot cross the blood–brain-barrier (Volkow et al., 1996). On the systemic level, an enzyme related to dopamine metabolism – the COMT could be used as an

indicator of central dopamine availability. Animal studies have shown that the COMT enzyme, by catabolizing dopamine regulates its neurotransmission in brain areas, exerting influence on general levels of dopamine (Bilder et al., 2004). Indeed, COMT, one of the main modulators of the dopaminergic levels, has been documented as one of the potential moderators of the effect of PE on neurocognitive function (Leckie et al., 2012). Surprisingly, few studies have examined whether the COMT moderates the effect of chronic physical activity on neurocognitive function. Indeed, the majority of the studies have focused on COMT polymorphisms and no information on COMT activity has been described. Given the higher prevalence of depression in women, we set out to investigate the potential impact of exercise on S-COMT activity in depressive women.

2. Methods

The protocol was performed according to the Declaration of Helsinki, and the Ethics Committee of Centro Hospitalar de São João approved it (11th of March, 2013) with ethics reference number 112/13. All participants signed an informed consent prior to beginning the trial.

2.1 Participants

Fourteen women (mean age: 51.4±10.5) participated in this randomized control trial (RCT); seven patients engaged in moderate intensity exercise plus their usual pharmacological therapy (exercise group), and the other seven patients took their usual pharmacological therapy but were not assigned to any exercise (control group).

2.2 Inclusion Criteria

Eligible patients had to fulfill the following inclusion criteria: (1) women aged 18-65; (2) able and willing to provide informed consent and accept randomized group assignment; (3) with current diagnosis of: F33.1 (recurrent depressive disorder, moderate current episode), F34.1 (dysthymia) confirmed by a psychiatrist according to ICD-10 (International Classification of Diseases, 10th revision); (4) physically fit to do exercise confirmed in writing by general practitioners; (5) normal ECG; (6) patients had to be sedentary (involved in sports activity for less than 1 hour per week).

2.3 Exclusion Criteria

The exclusion criteria were: (1) psychiatric co-morbidities; (2) current participation in other RCTs; (3) medical background indicating significant medical constraints; (4) current active alcohol/drug abuse or dependence; (5) pregnancy or planning to become pregnant in the next year; (6) taking beta-blocking medication; (7) change of pharmacological therapy during PE program; (8) change of drug therapy in the 6 weeks preceding the PE program; (9) exhibiting significant exacerbation of symptoms; (10) less than 60% of attendance of sessions; (11) undergoing complementary therapies.

2.4 Trial design

This trial was randomized and two-armed. The patients, physical training teacher, general practitioners, psychiatrists, or researchers performing the outcome assessment were not blinded in relation to treatment allocation. However, the laboratory technician who analyzed the blood samples was blinded in relation to patients.

These patients were randomized following a 1:2 scheme to one of two groups: aerobic exercise (n=7) and control (n=7). Randomization was implemented with sequentially numbered opaque, sealed envelopes.

3. Intervention

3.1 Exercise group

The aerobic group program consisted of 45-50 min per session, three times a week, for a total of 16 weeks. Sessions were supervised in the presence of a Physical Training Teacher. The patients carried pulse monitors (Polar FT1, Finland) during every session to ensure they exercised in the prescribed pulse interval. A rate of perceived exertion was used (Borg scale) in order to have a measure of the subjective intensity of exercise. This program was initiated with 10 minutes of general low-intensity warm-up, and then patients performed 30 minutes of aerobic, followed by 5 minutes of low-intensity period. The aerobic exercise involved aerobic traditional games, indoor and outdoor natural circuit workout with resistance bands, jump rotes, fitness balls, brisk walking and dancing. The intensity was gradually increased, being the average intensity of heart rate maximum (HRmax) for the four months 67%, 75%, 75% and 77% (RPE=12-13), respectively.

3.2 Control group

The control group comprised seven patients that continued their usual pharmacological therapy but were not assigned to any PE.

4. Outcome measures

All patients were evaluated for anthropometric parameters, functional assessment, depressive symptoms, and blood analysis at baseline and at the end of the PE intervention (16 weeks). Patients met with a psychiatrist throughout the study to assess symptomatology and medication tolerance. The dose of medication was kept constant in both groups. Patients were medicated with selective serotonin reuptake inhibitor (SSRIs); fluoxetine, escitalopram, sertraline and paroxetine. When convenient, benzodiazepines diazepam, lorazepam and estazolam were used as anxiolytic or hypnotics.

4.1 Psychiatric evaluation

Assessment procedures were performed in relation to psychiatric evaluation, where patients were considered eligible if referred to by a psychiatrist and fulfilled the ICD-10 criteria.

4.2 Physical functioning

To assess physical functioning, a performance battery was used: distance walked in six minutes, time to sit and stand from a chair in 30 seconds, and seated medicine ball throw.

4.3 Physical examination

Physical examination was carried out with the Tanita BC-418 Segmental Body Composition Analyzer, which was used to complete the body composition profile including weight and body mass index (BMI).

4.4 S-COMT assay

The analysis of the soluble COMT activity in erythrocytes was carried out as following: firstly, blood samples (5 mL) were collected in tubes containing ethylenediamine tetraacetic acid (EDTA) and plasma was separated by centrifugation (4°C, 1500 g); then, red blood cells were washed with three times the cell volume of cold 0.9% NaCl. The procedure was repeated in triplicate. The washed cells were immediately stored at -80°C until the enzymatic assay. After melting, the washed cell samples were haemolyzed with four times the cell volume of cold 1 mM sodium phosphate buffer (pH 7.4), vortex-mixed, and left to stand in an ice bath for 10 min, before centrifugation (20 min, 4°C, 20000 g) to separate MB-COMT from S-COMT. The supernatant was used immediately for the measurement of soluble COMT enzyme activity. In addition, an aliquot of the supernatant was diluted (1:100) with 0.9% NaCl and stored at -20°C before measurement of the protein content.

The COMT assay was performed essentially according to the method of Schultz, Nissinen and Kaakkola (Schultz et al., 1989) with minor modifications (Souteiro et al., 2013). The incubation mixture contained 300 µL enzyme preparation, 375 µL incubation medium, and 75 µL 10 mM (final concentration 1 mM) adrenaline as the enzyme substrate. The final 750 µL reaction volume contained 100 mM sodium phosphate buffer (pH 7.8), 2 mM $MgCl_2$, and 200 µM S-adenosyl-L-methionine. The samples were incubated in a water bath at 37°C for 60 min. The tubes were transferred to ice, and the reaction was stopped by adding 75 µL of ice-cold 2 M perchloric acid. After 10 min, the samples were centrifuged for 10 min at 4°C at 5400 g, and 500 µL aliquots of the supernatant filtered on 0.22-µm pore size Spin-X filter tubes (Costar) were used for the assay of metanephrine by means of high performance liquid chromatography with electrochemical detection.

S-COMT activity was expressed as the amount of metanephrine formed (in pmol) per mg of protein in the sample, per hour (pmol/mg prot/h), by the action of COMT on a single adrenaline concentration (1000 µM).

4.5 Statistical analysis

Descriptive statistics (means, standard deviation) were used to summarize socio-demographic, functional assessment and anthropometric variables. The kinetic parameters, maximum velocity (Vmax) and Michaelis-Menten constant (KM) values were calculated from non-linear regression

analysis by using the Graphpad Prism Software package (version 6.0) for Mac OSX. All dependent variables were tested for normality according to the Shapiro-Wilks method. The measures showed significant deviations from a normal distribution. Consequently, our data do not meet the requirements of parametric tests. Thus, to allow for comparison in clinical characteristics at baseline and after 16 weeks, between two arms of the trial, non-parametric Mann-Whitney test was used. Furthermore, to determine changes from baseline to endpoint (16 weeks) in the exercise and control groups non-parametric Wilcoxon test was used. We analyzed data with IBM SPSS statistics software (version 21.0). A P-value of less than 0.05 was taken as significant. Likewise, effects were examined using magnitude-based inferences (Hopkins et al., 2009). According to Fritz et al. (2012), the z value can be used to calculate an effect size for Mann-Whitney and Wilcoxon nonparametric tests, through the following formula, $r=z/\sqrt{N}$. Thus, the effect size r was performed using the software package effect size calculators PolyU. Cohen's guidelines for r are that a large effect is .5, a medium effect is .3, and a small effect is .1 (Cohen, 1988).

5. Results

5.1 Participants and baseline values

Fourteen patients were eligible for randomization, and seven patients were allocated to the exercise group and the other seven to the control group. Mean age of patients was 51,43 (SD=10,54). In relation to anthropometric parameters, average weight was 73,49 kg (SD=10,98) and a mean body mass index (BMI) of 30,51 kg/m^2 (SD=5,06).

Furthermore, the majority of patients (78,60%) had the diagnosis of dysthymia (F34.1) whereas the others had recurrent depressive disorder (F33.1), (21,4%). Fluoxetine was the most commonly used SSRI (64,30%), followed by sertraline (21,4%). The analysis between the groups, using the Mann–Whitney test, showed no significant difference in the baseline characteristics in all analyzed variables (table 1).

5.2 Mean changes from baseline to last observation

After 16 weeks of exercise therapy, when both groups are compared, all physical functioning parameters had significant improvements in the exercise group in relation to the control group (table 2). Post intervention scores in distance walked in six minutes were 591,00±67,57 meters for the exercise group, and 375,57±49,83 meters for the control group, differing significantly (p=0,001, r= -0,802). Likewise, post intervention scores in seated medicine ball throw test were 3,42±0,29 for the exercise group, and 2,76±0,54 for the control group, showing a significant difference (p=0,026, r= -0,535). Similarly, post intervention scores in time to sit and stand from a chair in 30 seconds test were 26,29±3,50 seconds for the exercise group and 17,43±6,68 seconds for the control group, and differed significantly (p=0,014, r= -0,535).

At a single concentration of substrate (1000 μ M of adrenaline) in the end of PE intervention, S-COMT activity was significantly higher (p=0,02, r= -0,535) in control patients (8,79±4,95 pmol/mg prot/h) than in exercise patients (2,71±1,68 pmol/mg prot/h).

There were no significant differences between the two groups, after 16 weeks in weight (p=1,000, r=0,000) and BMI (p=0,902, r=0,000) (table 2) variables.

6. Discussion

The aim of this RCT was to assess the effects of 16 weeks of PE (chronic exercise) on the S-COMT activity in a sample composed of depressive patients. The main finding of this study has provided evidence that chronic PE changes S-COMT activity. Indeed, after the intervention, patients in the experimental group (pharmacotherapy plus exercise) evidenced a significant decline in S-COMT activity whereas the control group (only pharmacotherapy) evidenced no changes in this enzyme (figure 1). In this trial, the patients in the exercise group significantly increased physical fitness, which confirms the efficacy of the exercise intervention.

Few studies have explored the role of the COMT gene in regulating the dopaminergic function on the cognitive functions through exercise. However, to our knowledge, no RCT has investigated the effect of chronic exercise in COMT enzyme activity in patients with depressive disorders, specifically in a sample composed of women. COMT activity is a particularly interesting mechanism involved in depressive disorders as it is higher in erythrocytes of depressive patients in comparison to healthy ones (Fahndrich et al., 1980; Puzynski et al., 1983). In addition, a decreased level of endogenous dopaminergic neurotransmission might make a significant contribution to depressive disorder (Pearson-Fuhrhop et al., 2014). So, if exercise decreases COMT activity, it is possible that it increases dopamine availability. Furthermore, the sample focused only on a female population, as several previous studies have well documented the fact that females have higher incidence rates of MDD than males (Kessler, 2003). Moreover, females have major lifetime prevalence of minor states such as dysthymia (Parker et al., 2014), which is a chronic, low-grade form of depression that increases the risk for MDD (Griffiths et al., 2000). In addition, the female patients with endogenous depression revealed a significantly higher COMT activity than males (Fahndrich et al., 1980). Additionally, estrogens fluctuation in females might be a biological risk factor which can lead to the occurrence of depression symptoms during critical periods, such as menopause, pre-menstrual period, postpartum (Lokuge et al., 2011). Indeed, this study highlights the evidence that there might be interactions between exercise and S-COMT, however, the true causes for the changes in enzyme activity responses to exercise require further clarification. One study (Stroth et al., 2010) that assessed whether variants of the COMT gene would be moderated by engaging in a running training for 17 weeks in a sample of healthy individuals showed that there are benefits associated with physical activity on cognitive flexibility and cognitive control, which are dependent on the COMT genotype. Moreover, Val/Val runners when compared to Met/Met runners had greater cognitive performance increment. Nevertheless, there are a limited number of studies on this matter and the pathways by which this effect occurs are controversial. Moreover, some of the limitations of this study included the absence of information with regard

to the possible changes in COMT activity in human erythrocytes and lack of randomization of the study population.

As far as methodological strengths are concerned, our study followed a randomized design, compliance to the exercise program was high (83.3%), laboratory staff was blinded to patient allocation, and patients were referred to by psychiatrists, who provide a high level of external validity. Furthermore, all patients were medicated at the time of inclusion, which was kept constant throughout the study, and thus increases the homogeneity of the sample. However, the small sample size should be considered a shortcoming of this study. Consequently, the results should be replicated in a large sample with the aim to validate the observed association between exercise and COMT activity. Hence, the results and the effect sizes observed in this study should be interpreted with caution. Additionally, little is known about the physiology of this relationship and it is important to note that the COMT enzyme is an indicator of relative central dopamine availability. Therefore, it should be stressed that it is difficult to make a definitive interpretation. At the same time, we need to bear in mind that in the present study, only the effect of exercise in S-COMT activity was investigated, i.e. MB-enzyme activity was not measured. Furthermore, no statement on the impact of exercise in cognitive function can be made on the basis of the present data. Nonetheless, there are several studies in humans reporting positive effects of exercise on cognitive function in both depressive patients (Kubesch et al., 2003) and healthy individuals (Hotting and Roder, 2013). However, this article provides a key contribution to better understand the role of exercise as an underlying modulation factor on the brain monoamine system. Indeed, the effects of COMT cannot be disregarded and must be taken into account when studying the effects of exercise on monoamine systems. Most importantly, future RCTs should analyze the effects of the dose-response of exercise in COMT activity as well as other potential moderators.

7. Conclusion

To our knowledge, this is the first study that assessed the effects of chronic exercise in S-COMT activity in depressive females. In fact, combining a 16-week PE program with pharmacotherapy leads to a decrease in S-COMT activity. In this way, our findings support the hypothesis of a relation between S-COMT activity and exercise. Thus, this has opened up new paths to understand the potential of the exercise as a therapeutic complementary intervention in the treatment of depressive disorder.

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Author contributions
Author Lara S. F. Carneiro carried out the literature search and statistical analysis, wrote the first draft of the manuscript under the supervision of authors Professor José Vasconcelos-Raposo and Professor Maria Paula Mota, Author Professor Maria Augusta Vieira-Coelho identified potentially eligible patients for the clinical trial, conducted the clinical assessment of screened patients and coordinated sample, processing and prepared it for analysis. Author Engineer Paula Serrão performed experiments. Author Professor António Manuel Fonseca provided critical input to the manuscript. All authors contributed to and approved the final manuscript.

Conflict of interest
All authors report no conflict of interest.

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Table 1- Baseline data from patients allocated to exercise and control group.

	Exercise (N=7)	Control (N=7)	p value
Demographic			
Age (years), mean (SD),	55,00±7,02	47,86±12,70	0,274
Anthropometric parameters, mean (SD),			
Weight, kg	74,29±12,63	72,69±10,00	0,871
Body mass index, kg/m^2	31,33±6,25	29,69±3,85	0,902
Functional assessment, mean (SD),			
Walk test, 6 minute	459,14±88,25	369,29±30,37	0,073
Medicine ball throw, seated	2,69±0,26	2,93±0,28	0,165
Chair stand test, 30 second	19,86±2,67	18,43±5,53	0,483
Depression characteristics, n (%)			
Recurrent depressive disorder	1 (14,3)	2 (28,6)	
Dysthymia	6 (85,7)	5 (71,4)	
Symptom severity, mean (SD),			
BDI-II	45,29±10,47	44,86±13,37	0,925
COMT activity			
Vmax (pmol/mg prot/h)	8,59±7,82	9,33±5,32	0,710

Abbreviation: BDI=Beck Depression Inventory.

Table 2. Post intervention outcome from patients allocated to exercise and control groups, after 4 months of exercise intervention.

	Exercise (N=7)	Control (N=7)	p value
Anthropometric parameters, mean (SD),			
Weight, kg	72,76±12,90	71,41±11,54	1,000
Body mass index, kg/m^2	30,72±6,52	29,11±4,23	0,902
Functional assessment, mean (SD),			
Walk test, 6 minute	591,00±67,57	375,57±49,83	0,001
Medicine ball throw, seated	3,42±0,29	2,76±0,54	0,026
Chair stand test, 30 second	26,29±3,50	17,43±6,68	0,014

Highlights

- Chronic exercise versus pharmacotherapy leads to decrease in S-COMT activity.
- Exercise interferes with S-COMT activity, a molecular mechanism of depression.
- The study provides an understanding of physiological mechanisms.
- Physiological mechanisms mediate relation between exercises and monoamine system.

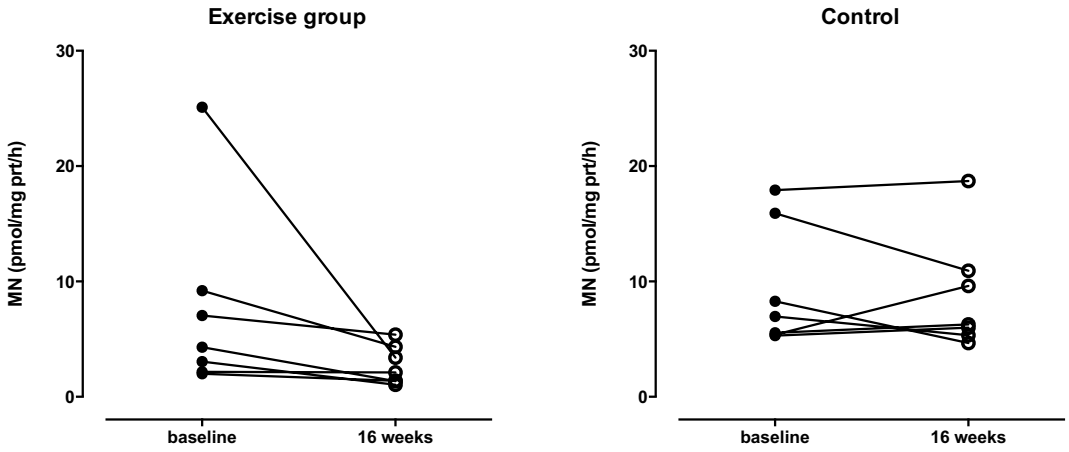

Figure 1- Erythrocyte S-COMT activity (pmol/mg prot/h) in exercise group and controls at baseline and at the end of physical exercise program (W16).
Exercise group-p=0,0156 within group by Wilcoxon test.
Controls-p=0,8125 within group by Wilcoxon test.