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EFEITOS DO EXERCÍCIO AERÓBIO SOBRE A ANSIEDADE E ATIVIDADE CORTICAL EM PACIENTES COM TRANSTORNO DE PÂNICO

JOSÉ EDUARDO LATTARI RAYOL PRATI

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2017

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Tese de Doutorado submetida ao Programa de Pós-graduação em Psiquiatria e Saúde Mental (PROPSAM), do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro - UFRJ, como parte dos requisitos necessários para à obtenção do título de Doutor em Saúde Mental.

Orientador: Sérgio Eduardo de Carvalho Machado

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Primeiramente a Deus, pois sem ele nada seria possível.

Aos meus pais, José de Arimathea (*in memorian*) e Sandra Lattari, por tudo que me proporcionaram na vida.

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RESUMO

Transtorno de Pânico (TP) pode ser caracterizado pela presença de ataques de pânico (AP) recorrentes e inesperados, onde pelo menos um dos ataques foi seguido de um mês (ou mais) de uma preocupação persistente acerca de novos ataques e suas consequências, além de gerar uma mudança comportamental relacionada aos ataques. Esse transtorno mental gera importantes consequências funcionais, sendo que, dentre os diversos transtornos de ansiedade, o TP e o Transtorno de Ansiedade Generalizada são os que apresentam maiores custos aos sistemas de saúde. Embora existam métodos de tratamento seguros e eficazes, como a farmacoterapia e a terapia cognitivo-comportamental (TCC), altas taxas de pacientes refratários ao tratamento são relatadas, aproximadamente 20%. Em detrimentos disto, novos tratamentos têm sido propostos, tal como o exercício físico. O exercício físico tem sido utilizado como importante ferramenta coadjuvante no tratamento do TP, demonstrando que o exercício pode proporcionar efeitos ansiolíticos de forma aguda e crônica. Contudo, não há nenhuma evidência conclusiva da eficácia do exercício, aguda e crônica, sobre a gravidade do TP e sintomas de ansiedade global nesses pacientes. Até o presente momento, nenhuma revisão sistemática foi realizada sobre o tema. Nesta tese, são apresentados 2 estudos. O estudo 1 avaliou-se por meio de uma revisão sistemática os efeitos das intervenções do exercício sobre a gravidade do pânico, a ansiedade global e os sintomas de depressão de pacientes com TP. Os resultados demonstraram que o exercício, por meio de uma única sessão, aumenta imediatamente os sintomas relacionados ao pânico, mas permite reduzir os ataques de pânico e a ansiedade provocados artificialmente. Não há evidências claras que indiquem que os programas de exercícios regulares reduzem os sintomas relacionados ao pânico, mas parece que esta intervenção é eficaz para melhorar as medidas globais de ansiedade e a depressão. No estudo 2, investigaram-se os efeitos de uma única sessão do exercício aeróbio sobre os sintomas de ansiedade e os efeitos de uma intervenção do exercício aeróbio sobre a gravidade e os sintomas relacionados ao TP, além das mudanças na assimetria frontal do córtex cerebral. Os pacientes foram divididos em dois grupos: exercício aeróbio e controle. No grupo exercício aeróbio os pacientes realizaram exercício aeróbio com frequência de duas vezes semanais e 12 sessões totais. O protocolo de exercício aeróbio foi realizado com duração total de 25 minutos e intensidade de 50-55% da frequência cardíaca de reserva. O grupo controle foi recomendado ao paciente somente a dar continuidade no tratamento farmacológico previamente estabilizado, pelo mesmo período de tempo que o grupo de exercício aeróbio, em um formato de banco de espera. O exercício aeróbio aumentou

a ansiedade imediatamente após uma sessão única de exercício e demonstrou que após um período de intervenção de exercício aeróbio ocorreram diminuições na ansiedade global e nos sintomas de depressão, bem como aumento no consumo máximo de oxigênio. Nenhuma alteração foi observada na gravidade do TP e na assimetria frontal do córtex cerebral. A seguinte tese concluiu que uma única sessão de exercício é capaz de promover aumento nos níveis de ansiedade, particularmente por escores somáticos. Quanto a intervenção de um protocolo de exercício, parece ser possível obter melhores nos níveis de ansiedade global e sintomas comórbidos depressivos.
Palavras-chave: Exercício aeróbio. Transtorno de Pânico. Ansiedade.

ABSTRACT

Panic Disorder (PD) can be characterized by recurrent and unexpected panic attacks (PAs), where at least one of the attacks was followed by a month (or more) of a persistent concern about new attacks and their consequences, in addition to generate behavioral change related to the attacks. This mental disorder generates important functional consequences, and among the various anxiety disorders, PD and generalized anxiety disorder are the ones that present the highest costs to health systems. Although safe and effective treatment methods such as pharmacotherapy and cognitive-behavioral therapy (CBT) exist, high rates of treatment-refractory patients are reported, approximately 20%. In detriment of this, new treatments have been proposed, such as physical exercise. Physical exercise has been used as an important adjuvant tool in the treatment of PD, demonstrating that exercise can provide acute and chronic anxiolytic effects. However, there is no conclusive evidence of the efficacy of acute and chronic exercise on the severity of PD and overall anxiety symptoms in these patients. To date, no systematic review has been conducted on the subject. In this thesis, two studies are presented. Study 1 was evaluated through a systematic review of the effects of exercise interventions on the severity of panic, overall anxiety and depression symptoms of patients with PD. The results showed that exercise, through a single bout, immediately increase panic-related symptoms, but reduces artificially induced panic attacks and anxiety. There is no clear evidence to indicate that regular exercise programs reduce panic-related symptoms, but it appears that this intervention is effective in improving overall anxiety and depression. In study 2, we investigated the effects of a single bout of aerobic exercise on the symptoms of anxiety and the effects of an aerobic exercise intervention on the severity and symptoms related to PD, as well as the changes in frontal asymmetry of the cerebral cortex. The patients were divided into two groups: aerobic exercise and control. In the aerobic exercise group the patients performed aerobic exercise with frequency of twice weekly and 12 total sessions. The aerobic exercise protocol was performed with a total duration of 25 minutes and intensity of 50-55% of the reserve heart rate. The control group was recommended to the patient only to continue the pharmacological treatment previously stabilized, for the same period of time as the aerobic exercise group, in a waiting bank format. Aerobic exercise increased anxiety immediately after a single bout exercise and demonstrated that after a period of aerobic exercise intervention there were decreases in global anxiety and depression symptoms as well as increased maximal oxygen consumption. No change was observed in the severity of PD and in frontal asymmetry of the cerebral cortex. The following

thesis concluded that a single bout exercise is capable of promoting increase in anxiety levels, particularly by somatic scores. Regarding the intervention of an exercise protocol, it seems to be possible to obtain better levels of global anxiety and depressive symptoms.

Keywords**:** Aerobic exercise. Panic Disorders. Anxiety.

LISTA DE SIGLAS

TP = Transtorno de Pânico

AP = Ataque de pânico

TCC = Terapia cognitivo-comportamental

% = Porcentagem

SUMÁRIO

Introdução

O Transtorno de Pânico (TP) pode ser caracterizado pela presença de ataques de pânico (AP) recorrentes e inesperados, onde pelo menos um dos ataques foi seguido de um mês (ou mais) de uma preocupação persistente acerca de novos ataques e suas consequências, além de gerar uma mudança comportamental relacionada aos ataques. Essa perturbação não pode ser consequência dos efeitos psicológicos de uma substância (ex.: medicamento) ou de outra condição médica. Além disso, essa perturbação não pode ser mais bem explicada por outro transtorno mental (APA, 2000).

A prevalência estimada é de 1,7% da população (de Jonge, 2016), sendo cerca de duas vezes mais comum nas mulheres do que nos homens (APA, 2000). Geralmente começa no final da adolescência, com idade de início entre 20 e 30 anos (APA, 2000), sendo reportado em pesquisa recente iniciando por volta dos 32 anos (de Jonge, 2016).

Importantes consequências funcionais acometem os pacientes com TP. Cerca de 80,4% das pessoas com TP apresentaram ao longo da vida algum transtorno mental comórbido (de Jonge et al., 2016), como a depressão (Tilli et al., 2012), abuso de substâncias e suicídio (Markowitz, 1989). Além do transtorno mental, o TP está associado a comorbidades clínicas como dor torácica (Soares-Filho et al., 2009), doença arterial coronariana (Lynch et al., 2003), perda de produtividade, bem-estar, contato social e auto-realização (Marciniak et al., 2004). Os custos relacionados com o TP são altos, demonstrando que dentre os diversos transtornos de ansiedade, o TP e o Transtorno de Ansiedade Generalizada (TAG) são os que apresentam maiores custos aos sistemas de saúde (Konnopka et al., 2009).

Os tratamentos mais utilizados em pacientes com TP são através da farmacoterapia e terapia cognitivo comportamental (TCC). A combinação dessas duas formas de tratamento parece apresentar melhores resultados quando comparada ao tratamento isolado (Furukawa et al., 2007). Apesar disso, na literatura encontrou-se um estudo que não identificou diferença após sete meses de interrupção de uma combinação de benzodiazepínico com TCC e o TCC de forma isolada (Watanabe et al., 2009). Além disso, terapia combinada também pode acarretar em maiores desistências ao tratamento comparado a TCC de forma isolada (Furukawa et al., 2007). Muito embora existam tratamentos eficazes e seguros, como medicamentos e psicoterapia, muitos pacientes com TP não respondem a este modelo tradicional de tratamento (Holt et al., 2007). Em detrimentos disto, novos tratamentos têm sido propostos, tal como o exercício físico.

Um grande número de estudos têm utilizado o exercício físico como importante ferramenta coadjuvante no tratamento do TP (Strohle et al., 2006; Strohle et al., 2009; Esquivel et al., 2008; Broocks et al., 1998; Meyer et al., 1998). A modalidade de exercício físico mais utilizado em pacientes com TP é o exercício aeróbio (Strohle et al., 2006; Strohle et al., 2009; Esquivel et al., 2008; Broocks et al., 1998; Meyer et al., 1998). Estas pesquisas tem demonstrado que o exercício aeróbio pode proporcionar efeitos ansiolíticos por meio de uma única sessão de exercício (Strohle et al., 2009; Esquivel et al., 2008) e por um protocolo de treinamento aeróbio (Broocks et al., 1998; Meyer et al., 1998). Parece que após uma única sessão de exercício aeróbio, o número de ataques de pânico em experimentos induzidos foi menor comparado a uma condição de repouso (Strohle et al., 2009; Esquivel et al., 2008). Por meio de um protocolo de treinamento aeróbio, somente dois estudos sugerem que o exercício aeróbio diminui os níveis de ansiedade global com esses pacientes (Broocks et al., 1998; Meyer et al., 1998).

De particular interesse em nosso estudo foi investigar as alterações ocorridas no córtex cerebral mediante a intervenção do exercício aeróbio. Baseando-se no modelo proposto por Davidson (1990), o hemisfério frontal esquerdo é dominante para o processamento de emoções positivas e comportamentos de abordagem, enquanto que o hemisfério frontal direito é dominante para o processamento de emoções negativas e comportamentos de retirada. Pacientes com depressão maior (Jesulola et al., 2015) e ansiedade social (Beaton et al., 2008) apresentaram elevações relativas significativas na atividade do cérebro frontal direito quando avaliadas durante estados de repouso ou períodos de provocação emocional aguda, apoiando essas previsões teóricas (Coan et al., 2004). Em uma pesquisa realizada por Moscovitch et al. (2011) foi observado, em pacientes com Transtorno de Ansiedade Social (TAS), que o menor índice de assimetria frontal pré-tratamento estava relacionado com maiores níveis de ansiedade. Após o tratamento com TCC ocorreu uma mudança no índice de assimetria frontal, favorecendo maior ativação do córtex frontal esquerdo, e diminuição nos níveis de ansiedade.

Algumas lacunas foram estabelecidas na presente tese. Até o momento, a literatura é inconclusiva sobre os efeitos de uma única sessão de exercício sobre a gravidade do TP e os níveis de ansiedade (Strohle et al., 2009; Esquivel et al., 2008; Rief & Hermanutz, 1996). Além disso, pouco se sabe sobre os efeitos de um protocolo de treinamento aeróbio sobre as mesmas medidas de desfechos, citadas anteriormente. No estudo de Wedekind e colaboradores (2010) o exercício aeróbio comparado a um grupo controle (relaxamento) apresentou somente tendências de melhoras, na quarta semana de intervenção, quanto a gravidade do TP e níveis de ansiedade global. Outra pergunta a ser respondida na presente

tese foi à capacidade do exercício aeróbio em alterar o índice de assimetria frontal. Nesta tese, como todo trabalho inédito, foi necessário supor certas hipóteses. Pelo fato do exercício aeróbio influenciar na ativação cortical (Petruzzello e Tate, 1997; Woo et al., 2010), postulou-se que este tipo de intervenção pudesse favorecer maiores índices de assimetria frontal cortical (maior ativação do córtex frontal esquerdo e/ou menor ativação do córtex frontal direito) associados com maiores reduções nos níveis de ansiedade e sintomas de depressão.

O primeiro artigo foi uma revisão sistemática. Neste artigo avaliou-se os efeitos das intervenções do exercício sobre a gravidade do pânico, a ansiedade global e os sintomas de depressão de pacientes com transtorno de pânico. Foram exploradas as características clínicas e sócio-demográficas dos pacientes, as características dos protocolos de exercício, os efeitos agudos e crônicos dos exercícios.

O segundo artigo foi um estudo piloto experimental. Neste artigo investigaram-se os efeitos agudos do exercício aeróbio sobre os sintomas de ansiedade e os efeitos crônicos do exercício aeróbio sobre a gravidade e os sintomas relacionados ao TP, além das mudanças na assimetria frontal do córtex cerebral. Os pacientes foram divididos em dois grupos: exercício aeróbio e controle. No grupo exercício aeróbio os pacientes realizaram exercício aeróbio com frequência de duas vezes semanais e 12 sessões totais. O protocolo de exercício aeróbio foi realizado com duração total de 25 minutos e intensidade de 50-55% da frequência cardíaca de reserva, segundo recomendações do Colégio Americano de Medicina Esportiva (ACSM, 2010). O grupo controle foi recomendado ao paciente somente a dar continuidade no tratamento farmacológico previamente estabilizado. Nesse estudo, foi investigado tanto o efeito agudo quanto o efeito crônico do exercício aeróbio. De forma aguda, investigaram-se os níveis de ansiedade gerados pelo exercício aeróbio. Cronicamente, procurou-se investigar os efeitos do exercício aeróbio sobre a gravidade do pânico, os níveis de ansiedade global, os sintomas de depressão e assimetria frontal cortical em pacientes com TP.

Portanto, a presente tese teve como objetivos, (1) Avaliar, através de uma revisão sistemática, os efeitos das intervenções do exercício sobre a gravidade do pânico, a ansiedade global e os sintomas de depressão de pacientes com transtorno de pânico, (2) investigar os efeitos agudos do exercício aeróbio sobre os sintomas de ansiedade e os efeitos crônicos do exercício aeróbio sobre a gravidade e os sintomas relacionados ao TP, além das mudanças na assimetria frontal do córtex cerebral.

Justificativa

Uma pesquisa envolvendo 20 países, com uma população de 142,949 pessoas, a prevalência para o TP foi de 1,7% da população (de Jonge, 2016). Esse transtorno que acomete grande parte a população está associado a diversas comorbidades como a depressão (Tilli et al., 2012), abuso de substâncias e suicídio (Markowitz, 1989), dor torácica (Soares-Filho et al., 2009) e doença arterial coronariana (Lynch et al., 2003). Além disso, também está associado a perda de produtividade, bem-estar, contato social e auto-realização (Marciniak et al., 2004), sendo os custos relacionados ao TP o segundo mais alto gerado aos sistemas de saúde comparados entre os diferentes transtornos de ansiedade (Konnopka et al., 2009).

Diversas formas de tratamento têm sido propostas, destacando-se o tratamento farmacológico e a TCC. Contudo, muito embora esses tratamentos apresentem resultados eficazes e seguros, muitos dos pacientes com TP não respondem a este modelo tradicional de tratamento (Holt et al., 2007). Assim, outras formas de tratamento têm sido utilizadas, destacando-se o exercício físico como coadjuvante no tratamento do TP.

As pesquisas que utilizaram o exercício físico como tratamento para o TP têm demonstrados resultados conflitantes quanto a melhora e nenhuma resposta sobre a gravidade de transtorno e níveis de ansiedade global (Strohle et al., 2009; Esquivel et al., 2008; Broocks et al., 1998). Assim, este tese justifica-se com o objetivo de avaliar, por meio de duas pesquisas realizadas, os efeitos do exercício físico sobre a ansiedade em pacientes com TP. Além disso, também foi interesse desta tese investigar se o exercício aeróbio irá influenciar em uma medida de atividade cortical, a assimetria frontal. Os maiores índices dessa medidas tem sido relacionado com maiores reduções nos níveis de ansiedade em pacientes com Fobia Social (Moscovitch et al., 2011)

Artigo 1

Aerobic exercise in panic disorder patients: a systematic review

Aerobic exercise in panic disorder patients: a systematic review.

Running title: Exercise in panic disorder

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ABSTRACT

Background: In the last few decades exercise has been explored as a potential tool to reduce symptoms experienced by patients with anxiety disorders, including panic disorder. *Objective:* This systematic review aims to assess the effects of exercise interventions on panic severity, global anxiety and depression symptoms of patients with panic disorder. *Methods:* A systematic literature search was conducted on PubMeb, ISI Web of Science and Cochrane Central Register of Controlled Trials using search terms regarding panic disorder and exercise (aerobic, strength training, etc). Study selection and data extraction procedures were independently completed in a standardized manner by two researchers. Effect sizes were computed for every included trial whenever it was possible. *Results:* A total of 9 trials were included in this review: 3 acute exercise studies and 6 trials with regular exercise programs. Results from acute studies suggest that exercise immediately increases panic-related symptoms, but allows to reduced artificially induced increase panic attacks and anxiety. There is not clear evidence indicating that regular exercise programs reduce panic-related symptoms, but it seems that this intervention is effective to improve global anxiety measures and depression. Moreover, other interventions (pharmacotherapy or psychotherapy) seem to achieve larger improvements in comparison to exercise, but differences are quite small. *Conclusion:* In conclusion, physical exercise was associated with immediately increases panic-related symptoms, but reduced increase panic attacks and anxiety. Regular exercise programs showed that this intervention is effective to improve global anxiety measures and depression. The literature still needs to establish the exercise modality, duration, frequency and intensity of the physical exercise required to promote positive effects in individuals with PD.

Keywords: Exercise, Aerobic exercise, Anxiety, Depression, Panic Disorder.

1.Background

Panic disorder (PD) is characterized by the presence of recurrent panic attacks, with at least one of them being sudden and followed by at least one month of persistent concern about a new attack or concerns about its effects.(Association, 1994). Lifetime prevalence of PD estimates were 1.7% with a median age of onset of 32 years and some 80.4% of persons with lifetime PD had a lifetime comorbid mental disorder (de Jonge et al., 2016). PD is about twice as common in women than in men (DSM-V) and usually begins in late adolescence or early adulthood, with an average onset between 20 and 30 years (Association, 1994).

Long term PD is associated with a decrease in productivity, well-being, social contact and self-realization (Marciniak et al., 2004). In addition, comorbidities such as chest pain (Soares-Filho et al., 2009), coronary artery disease (Lynch and Galbraith, 2003) and other psychiatric comorbidities such as depression (Tilli et al., 2012), substance abuse and suicide are common in these patients (Markowitz et al., 1989). Most of the costs related with and anxiety disorders and their treatment were linked to PD and generalized anxiety disorder (Konnopka et al., 2009). The most common forms of treatment in PD patients are pharmacotherapy and cognitive-behavioral therapy (CBT). Drugs used are tricyclic antidepressants, monoamine oxidase inhibitors, selective inhibitors of serotonin reuptake and benzodiazepines. CBT interventions include exposure (interoceptive and exteroceptive), cognitive restructuring, breathing training and relaxation training.

Due to the chronic nature of anxiety disorders, new treatment strategies are being introduced, such as the use of physical exercise and some research has shown the anxiolytic effects of exercise, both acutely (Esquivel et al., 2008; Strohle et al., 2009) and chronic (Broocks et al., 1998; Meyer et al., 1998). Acutely, exercise seems to have an antipanic and anxiolytic protective effect in patients with PD (Esquivel et al., 2008; Strohle et al., 2009). Despite the possible benefits of physical exercise, patients with panic disorder have low level of physical activity (Belem da Silva et al., 2014). Thereby, the practice of physical exercise should be encourajed. Gaudlitz et al. (2015) showed that of the exercise an additional benefit to CBT in treatment of the disease. Perhaps, the specific effects of somatic symptoms of anxiety experienced during exercise is one of the great factors for the low level of physical activity (Belem da Silva et al., 2014)

Few studies support the hypothesis that physical exercise has chronic anxiolytic effects (Hovland et al., 2013; Meyer et al., 1998). In general, most studies have supported an

association between the acute effects of exercise and a reduced state anxiety, but failed to completely explain the relationship between the chronic effect of exercise, physical fitness and anxiety traits (Petruzzello et al., 1991). In recent reviews, exercise has been suggested that exercise may be clinically effective, or at least as an adjunct to established treatment, whether by psychotherapy or pharmacotherapy (Asmundson et al., 2013; Jayakody et al., 2014; Strohle, 2009). Most published studies have important methodological errors regarding exercise prescription (Strohle, 2009). The short duration of the studies and the inconsistency in the selection of patients with PD regarding adequate diagnostic weakens the results of several studies. The use of different anxiety measures can further limit the generalizability of their findings. Moreover, the lack of valid control groups is also found. Finally, for some disorders, such as PD, exercise can be helpful, but is often falsely perceived as harmful. To our knowledge, have meta-analyse published with regard to exercise effects on anxieties in individuals with anxiety disorders (Jayakody et al., 2014) but none on diagnosed clinical PD alone.

This systematic review aims to assess the effects of exercise interventions on panic severity, global anxiety and depression symptoms of patients with panic disorder.

2.Methods

This systematic review was designed and reported accordingly to the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

2.1.Eligibility criteria

The eligibility criteria for study inclusion were established according to the PICOS strategy:

- Population: participants must be primarily diagnosed with panic disorder with or without agoraphobia using gold standard criteria such as the Diagnostic Statistics Manual of Mental Disorders (Association, 1987, 1994, 2000), and the International Classification of Diseases (Organization, 1992). Participants may present secondary comorbid disorders associated (e.g. depression, social phobia, generalized anxiety disorder, etc).
- Intervention: any sort of acute or regular exercise intervention (e.g. aerobic, strength or multimodal training) aiming to reduce panic-related and anxiety symptoms in patients with panic disorder. Exercise interventions combined with other treatment procedures were also included.

- Comparators: exercise interventions must be compared to active or waiting control groups, treatment-as-usual and/or alternative interventions (e.g. pharmacotherapy, psychotherapy).
- Outcomes: primary outcomes were measures related to panic severity (frequency and intensity of panic attacks, standardized panic-related scales) and global anxiety (e.g. Hamilton Anxiety Rating Scale, Beck Anxiety Inventory, etc). Measures related to depressive symptoms were defined as a secondary outcome (e.g. Hamilton Rating Scale for Depression, Beck's Depression Inventory, etc).
- Study Design: randomized and non-randomized trials, using either cross-over or parallel group designs, comparing an intervention(s) encompassing exercise with a group(s) without exercise. Non-blinded trials were included as it is impractical to expect blinding of patients and personnel who participated in the exercise programs.

2.2. Search strategy and selection of studies

A systematic literature search was conducted through February 22, 2017 using the following databases: PubMeb, ISI Web of Science (Web of Science Core Collection) and Cochrane Central Register of Controlled Trials (CENTRAL). Search terms were defined accordingly to population (panic disorder) and intervention (exercise), based on previous systematic reviews on the field. The following search query was used:

("anxiety disorders"[MeSH] OR anxiety disorder[All Fields] OR "panic"[MeSH] OR "panic"[All Fields] OR panic disorder*[All Fields] OR panic attack*[All Fields] OR agoraphobia*[All Fields] OR phobic disorder*[All Fields]) AND ("exercise"[MeSH] OR exercis*[All Fields] OR "exercise therapy"[MeSH] OR "physical fitness"[MeSH] OR physical fit*[All Fields] OR physical activit*[All Fields] OR aerobic training*[All Fields] OR resistance training*[All Fields] OR strength training*[All Fields] OR weight-lift*[All Fields] OR weight-bear*[All Fields] OR muscle stretch*[All Fields])*

Medical subject headings (MeSH) terms were removed from the query for the search using the Web of Science database. Included reports and important reviews regarding exercise and anxiety disorders were manually screened for additional relevant studies. Experts on the field, including authors from the included reports, were also requested to suggest any additional trials in order to ensure that the review was as comprehensive and up-to-date as possible. Only studies published in English were included.

After merging search results and discarding duplicates, two researchers (EL and CC) independently screened titles and abstracts in order to identify relevant studies. Full-text articles of the included reports were retrieved and independently assessed for eligibility by the two researchers according to the previously described criteria. A consensus meeting was performed in case of disagreement regarding any report and a third researcher (SM) completed the decision when required. When it was not possible to retrieve full-text articles, authors were contacted using email and Research Gate in order to provide the required report. After three failed attempts to obtain response from the respective authors, the report was excluded from analysis. Some reports were seemingly published based on data from the same trials. Corresponding authors were contacted in order to confirm whether these reports were actually produced from different trial or not.

2.3. Data extraction and processing

Data extraction was independently completed in a standardized manner by two researchers (EL and CC) and a consensus meeting was held to review the collected data. Data extracted from the included trials included: general characteristics (title, authors and publication date), sociodemographic characteristics (age and gender), clinical information (diagnosis, symptom severity, duration of illness, medication), description of exercise intervention (exercise modality, length, frequency, duration and intensity) and study design (sample size, control intervention, follow-up, drop-out rate, outcome measures).

Descriptive statistics regarding relevant outcome measures (mean change from baseline and standard deviation of the change or post-intervention means and standard deviation) were extracted in order to compute effect sizes. If there was no information available, corresponding and senior authors were contacted by email and Research Gate. If the authors were not able to provide the required information or if they did not reply after three attempts to contact them, descriptive statistics were obtained through the graphs provided in the full-text articles using the Plot Digitize software. This method to extract data has been proven as reliable and accurate method to extract data for systematic reviews (Jelicic Kadic et al., 2016). In the trial of Wedekind et al. (2010) there was no graphical data regarding standard deviation of the change and the baseline value was used to replace it and compute effect size. Furthermore, some of the included trials encompassed patients with other primary psychiatric disorder in their analysis. Thereby, authors were contacted in order to provide descriptive statistics only including patients primarily diagnosed with panic disorder.

Although some of the authors accomplished to do so, other researchers did not reply to this request which led to the exclusion of these trials.

The most commonly used formula to compute effect sizes is the *Cohen's d* but it has a slight bias as it overestimates effect size in small samples. Thereby, as most included studies had a small sample size, effect sizes were computed using the *Hedges' g* which removes this bias using a simple correction (formula 1 & 2), yielding an unbiased estimate of the effect size (Hedges, 1981).

$$Hedges'g = \left(\frac{\overline{X}\text{exercise} - \overline{X}\text{control}}{SDwithin}\right) \times J = \left(1 - \frac{3}{4df - 1}\right) \qquad (1)$$

$$SDwithin = \sqrt{\frac{(n1-1)SD1^2 + (n2-1)SD2^2}{n1+n2-2}} \qquad (2)$$

SDwithin = within-groups standard deviation, pooled across groups; df = degrees of freedom; n1 = sample size exercise; SD1 = standard deviation exercise; n2 = sample size control; SD2 = standard deviation control

Hedges' g was individually calculated for every relevant outcome measure in each included trial. For trials with more than 2 groups, this calculation was completed for each comparison between exercise and another condition. *Hedges' g* was preferentially calculated using change from baseline and standard deviation of the change. When the authors did not report or provide these measures, changes scores and standard deviation of the change were calculated using baseline and post-intervention values, using the following formula:

$$\overline{X}change = \overline{X}pos - \overline{X}pre \qquad (1)$$

$$SDchange = SEchange \times \sqrt{n} = \sqrt{\left(\frac{SDpre^2}{n} + \frac{SDpos^2}{n}\right) \times (1 - r)} \times \sqrt{n} \qquad (2)$$

n = number of participants included for analyzes; r = within-individual correlation (between before and after condition)

As there was no information regarding the within-individual correlation for any of the studies, the *r* value of 0.5 was used to compute the standard deviation of the change as suggested by Follmann et al. (1992). *Hedges' g* was computed so that positive values indicated superior treatments effects of exercise in comparison to the control or alternative treatment group. Furthermore, effect sizes were classified as trivial (d <0.19), small (d = 0.20-

0.49), moderate (d = 0.50-0.79), large (d = 0.80-1.29) and very large (> 1.30) (Rosenthal, 1996).

2.4. Assessment of risk of bias in included studies

Risk of bias was judged based on the criteria described on the *Cochrane Handbook for Systematic Reviews of Interventions*, version 5.1.0 (Higgins and Green, 2011). The following criteria were evaluated:

- Selection bias: Random sequence generation (inadequate randomization procedures) and allocation concealment (inadequate concealment of allocations prior to assignment).

- Performance bias: blinding of participants and personnel (knowledge of the allocated interventions by participants and personnel).

- Detection bias: blinding of outcome assessments (knowledge of the allocated interventions by outcome evaluators).

- Attrition bias: incomplete outcome data (amount, nature or handling of incomplete data).

- Reporting bias: selective outcome reporting (differences between reported and unreported findings).

- Other bias

Two researchers (EL and CC) independently assessed the included trials, rating each of the previously described factors with low, high, or unclear risk of bias according to the criteria defined by Higgins and Green (2011). Again, a consensus meeting was performed in order to discuss rating disagreements and a third researcher (SM) ensured the final decision when required.

3. Results

3.1. Study selection

Study selection flow chart is presented in Figure 1. A total of 2581 records were identified (1451 on PubMed, 875 on Web of Science and 291 on CENTRAL), from which 601 duplicate citations were removed, leaving a total 1980 records. After screening titles and abstracts, 1935 records were excluded because they did not meet the eligibility criteria. Thereby, a total of 45 full-text articles were assessed for eligibility. Eleven studies were excluded because they did not present any kind of comparator group. Four studies were not

experimental research (commentary, cross-sectional, or retrospective) and 3 articles did not include participants with PD. There was also one record excluded because it was not written in English language and another one that had no full-text available, even after contacting the authors.

It is important to notice that several trials included for full-text reading enrolled participants with other anxiety disorders rather than panic disorder. Thereby, the authors were contacted in order to provide the required information only for patients with panic disorder. Although 2 authors provided the necessary information, 4 trials had to be excluded as the authors were not able to provide the requested data or did not reply.

A total of 21 records were included in this review. However, several records report different analysis and/or outcomes from the same trials, which led to a total of 9 trials to be analyzed in this review:

-Broocks et al.(1998): Publications regarding this trial also include Broocks et al. (Broocks et al., 1998; Broocks et al., 2003; Broocks et al., 1997), Bandelow et al. (Bandelow et al., 2000), Meyer et al. (Meyer et al., 1998);

- Esquivel et al.(2008): Preliminary findings published in Esquivel et al. (Esquivel et al., 2006).

- Gaudlitz et al.(2015): Other outcomes from the same trial presented in Plag et al. (Plag et al., 2014)

- Hovland et al. (2013)

- Ma et al. (2017)

- Merom et al. (2008)

- Rief & Hermanutz (1996)

- Strohle et al. (2009): Other outcomes from the same trial presented in Strohle et al. (Strohle et al., 2010)

- **Wedekind et al. (2010):** Other outcomes from the same trial presented in Wedekind et al. (Wedekind et al., 2008).

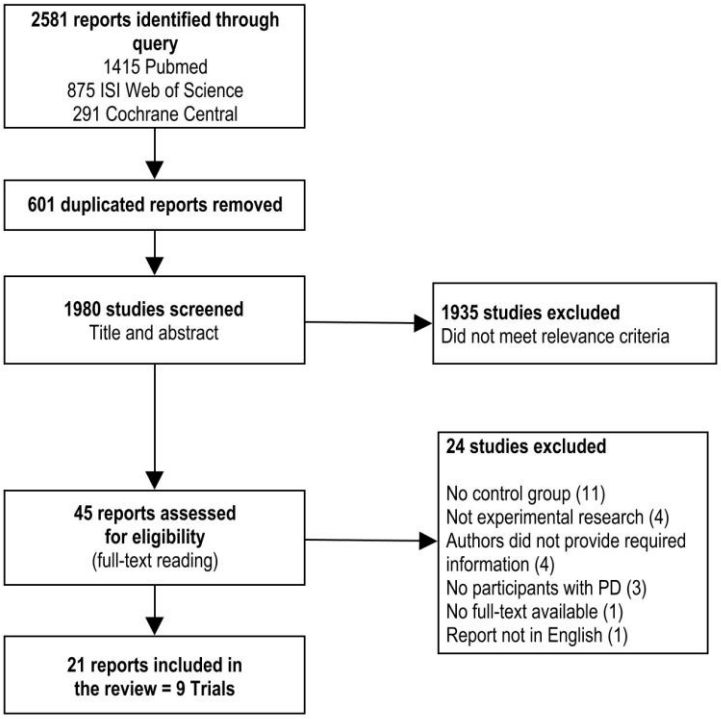

Fig. 1. Flowchart for study selection

3.2. Participants

Sociodemographic and clinical characteristics of the participants in the included studies are described in Tables 1. There's a total of 40 patients with PD that participated in the acute exercise trials, with no drop-outs in any of the included studies. Regarding regular exercise programs, exercise groups had sample sizes between 13 and 27, with a total of 128 participants among studies. There was a total of 26 drop-outs in the exercise groups (20.31%), a rate slight lower displayed by the compared interventions/groups (23.33%). In most exercise and control groups, participants' average age was between 30 and 40 years old, with the youngest group being the light-exercise control group of Esquivel et al. (Esquivel et al., 2008) and the oldest the traditional care control group of Ma et al. (Ma et al., 2017). Regarding gender, most studies had more female participants than male (as expected) as only the clomipramine group from Broocks et al. (Broocks et al., 1998) had more men than women.

Diagnostic procedures were quite consistent across studies, with every trial using some version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), although some

authors cross-validated the diagnosis with the *International Classification of Diseases* (ICD-10). Every trial also used some sort of validated clinical interview, with 6 studies using the *Structured Clinical Interview for DSM* and 3 trials using the *Mini-International Neuropsychiatric Interview* (MINI). PD severity was not reported by four of the studies (Esquivel et al., 2008; Ma et al., 2017; Merom et al., 2008; Rief and Hermanutz, 1996), as one trial did not use any sort of standardized procedures (Hovland et al., 2013). However, the remaining trials reported symptom severity at baseline using the Panic and Agoraphobia Scale (PAS), with average values from each group ranging from 20.5 to 29.4, suggesting moderate panic-related symptoms. It also important to notice that only two studies (Broocks et al., 1998; Hovland et al., 2013) reported illness duration, a factor that may clearly play role in treatment response. There were two different approaches to medication intake before and during the trial. There were three studies in which participants had to stop medication before the trial (Broocks et al., 1998; Strohle et al., 2009; Wedekind et al., 2010). Other authors opted to allow for medication intake during the trial (mainly antidepressants), but the participants could no change medication until they finished the intervention period (Gaudlitz et al., 2015; Hovland et al., 2013; Rief and Hermanutz, 1996). The remaining three trials did not provide information regarding the medication of patients with PD.

Table 1- Included studies description: Sociodemographic and clinical characteristics of participants

Study Authors	Sample Size	Drop-outs	Diagnosis	Age (Mean & SD)	Gender (% Male)	Panic Severity (Mean & SD)	Duration of Illness (Years/Mean & SD)	Medication
Acute Exercise								
Esquivel et al. (2008)	EX = 10 LEX = 8	None	DSM-IV ICD-10 (MINI)	EX = 30.1 (8.9) LEX = 29.1 (8.0)	39%	Not reported	Not reported	Not reported
Rief & Hermanutz (1996)	EX/R = 20 (cross-over)	None	DSM-III-R (SCID)	41.5 (11.2)	20%	Not reported	Not reported	Tricyclic and tetracyclic antidepressants for at least 2 weeks (n=3)
Ströhle et al. (2009)	EX/R = 12 (cross-over)	None	DSM-IV ICD-10 (MINI)	31.9 (7.62)	25%	PAS = 24.20 (16.28)	Not reported	No medication for at least 10 days before the trial
Regular Exercise Programs								
Broocks et al. (1998)	EX = 16 CMP = 15 PLA = 15	EX = 5 (31%) CMP = 0 (0%) PLA = 4 (27%)	DSM-III-R & ICD-10 (SCID)	EX = 31.8 (9.5) CMP = 33.9 (9.2) PLA = 34.8 (6.8)	EX = 38% CMP = 73% PLA = 40%	*PAS* EX = 28.5 (9.1) CMP = 24.4 (6.4) PLA = 23.2 (7.4)	EX = 3.1 (2.1) CMP = 4.1 (4.6) PLA = 6.9 (7.9)	No medication for at least 3 weeks before the trial (only promethazine in case of panic attacks)
Gaudlitz et al. (2015)	EX+CBT = 27 MV+CBT = 31	EX+CBT = 5 (19%) MV+CBT = 12 (39%)	DSM-IV ICD-10 (MINI)	EX+CBT = 35.4 (12.6) MV+CBT = 36.2 (8.9)	EX+CBT = 50% MV+CBT = 45%	*PAS* EX+CBT = 20.5 (9.0) MV+CBT = 20.62 (10.4)	No reported	*Antidepressants, beta-blockers or anxiolytics* EX+CBT = 7 MV+CBT = 8
Hovland et al. (2013)	EX = 17 CBT = 19	EX = 0 CBT = 1 (5%)	DSM-IV-TR (SCID)	EX = 38.1 (8.6) CBT = 37.8 (8.9)	EX = 12% CBT = 26%	*Panic-related distress/disability (0-8)* EX = 6.53 (1.42) CBT = 6.79 (1.32)	EX = 12.3 (10.7) CBT = 8.2 (8.1)	EX: SSRIs (7) and benzodiazepines (3) CBT: SSRIs (6) and benzodiazepines (n=2)
Ma et al. (2016)	EX = 14 TC = 10	None	DSM-IV-TR (SCID)	EX = 39.86 (8.34) TC = 44.00 (8.45)	EX = 21% TC = 20%	Not reported	Not reported	No specific information for PD participants
Merom et al. (2008)	EX+CBT = 13 ED+CBT = 13	EX+CBT = 6 (46%) ED+CBT = 5 (38%)	DSM-IV (SCID)	No specific information for PD participants	No specific information for PD participants	Not reported	Not reported	Not reported
Wedekind et al. (2010)	EX+PAR = 21 RT+PAR = 17 EX+PLA = 20 RT+PLA = 17	EX+PAR = 5 (24%) RT+PAR = 4 (24%) EX+PLA = 5 (25%) RT+PLA = 1 (6%)	DSM-IV & ICD-10 (SCID)	EX+PAR = 31.3 (9.1) RT+PAR = 36.0 (9.7) EX+PLA = 29.8 (7.8) RT+PLA = 30.3 (5.8)	EX+PAR = 40% RT+PAR = 46% EX+PLA = 27% RT+PLA = 12%	*PAS* EX+PAR = 26.3 (8.1) RT+PAR = 27.4 (9.2) EX+PLA = 29.4 (8.9) RT+PLA = 25.7 (5.4)	No reported	No medication for at least 2 weeks before the trial (only promethazine in case of panic attacks during the trial)

EX: exercise; LEX: light exercise; DSM: Diagnostic and Statistical Manual of Mental Disorders; MINI: Mini-International Neuropsychiatric Interview; R: Rest; SCID: Structured Clinical Interview for DSM; ICD: International Classification of Diseases; PAS: Panic and Agoraphobia Scale; CMP: clomipramine group; PLA: placebo group; MV: Movement Group; CBT: cognitive-behavioral therapy; SSRI: Selective Serotonin Reuptake Inhibitors; TC: Traditional Care; PD: Panic Disorder; ED: education group; PAR: paroxetine; RT: relaxation training

3.3. *Exercise protocols and control groups*

The characteristics of the included exercise protocols and respective control groups are described in Table 2. Regarding studies assessing the effects of acute exercise, it is interesting to notice that the authors selected different study designs. While Esquivel et al. (Esquivel et al., 2008) opted to develop a parallel group trial with an active control group of very-light exercise, the others two trials used a cross-over design, where participants completed an exercise condition and a rest period (Rief and Hermanutz, 1996; Strohle et al., 2009). Furthermore, session duration was quite discrepant across single bout studies, with sessions lasting from 2 to 30 minutes.

Studies with regular exercise programs also presented different characteristics between each other. Interestingly, four out of six studies developed home-based exercise programs mainly requiring walking and running, although Ma et al. (Ma et al., 2017) also used other activities (dance, tai-chi, yoga). Furthermore, most programs developed aerobic training activities, although two studies (Hovland et al., 2013; Ma et al., 2017) utilized multimodal programs encompassing other procedures such as strength training, sports, dance, among others. Intervention length was quite similar among studies, ranging from 8 to 12 weeks, with an average of 10 weeks across trials. Session duration was either 30 or 45 minutes, except in the program of Hovland et al. (Hovland et al., 2013) where each session lasted 90 minutes. Most of the programs included 3 sessions per week, although Ma et al. (Ma et al., 2017) and Merom et al. (Merom et al., 2008) home-based programs stimulated participants to work out 5 times per week. Finally, exercise intensity was labeled as moderate or vigorous in all included trials, although there were only 2 trials which clearly defined aerobic training intensity (Gaudlitz et al., 2015; Hovland et al., 2013).

It is also important to highlight that on 3 of the included trials exercise was combined with other treatments procedures such as group CBT (Gaudlitz et al., 2015; Merom et al., 2008) and paroxetine or placebo pills (Wedekind et al., 2010). Furthermore, there was a wide range of control interventions in the included studies, namely traditional care, clomipramine treatment or placebo pills, CBT, relaxation training, educational meetings, and movement sessions.

Table 2: Included studies description: Interventions characteristics

Study Authors	Exercise Modality	Intervention Length	Frequency (sessions per week)	Session Duration	Intensity	Control Intervention(s)
Acute Exercise Trials						
Esquivel et al. (2008)	Aerobic Exercise (Bicycle Ergometer)	Single Bout Between-Group Design		3 min. warm-up + 15 min. at target heart rate (or exhaustion)	80 - 90 % HR_{max}	**Very-Light Exercise** 1 W per kg at 70 rpm
Rief & Hermanutz (1996)	Aerobic Exercise (Bicycle Ergometer)	Single Bout Cross-Over Design		2 min.	75 watts	**Rest (5 min.)**
Ströhle et al. (2009)	Aerobic Exercise (Treadmill)	Single Bout Cross-Over Design		30 min.	70% VO_2Max	**Rest (30 min.)**
Regular Exercise Programs						
Broocks et al. (1998)	Home-Based Aerobic Exercise (Outdoors Walking/Running)	10 weeks	3x / week	45 min.	**Outdoors Route** *Week 1:* Walking *Week 2-6:* Short Running Periods *Week 7-10:* Running	**Clomipramine Group** (*Week 1* - 37.5 mg; *Week 2* - 75 mg; *Week 3-10* - 112.5 mg) **Placebo Group**
Gaudlitz et al. (2015)	Aerobic Exercise (Treadmill) combined with Group CBT	8 weeks	3x / week	30 min.	70% VO_2Max	**Group CBT** (one weekly 90 min. session) combined with **Movement Group** (e.g. light stretching)
Hovland et al. (2013)	Group-Based Multimodal Exercise	12 weeks	3x / week	90 min. (including introduction, warm-up, stretching)	**3 Session Types** *Walking/Running* (60 - 80 HR_{max}) *Strength Circuit Training* *Sports & Games*	**CBT** (one weekly 2-hour session)
Ma et al. (2017)	Home-Based Multimodal Exercise Program	12 weeks	5x / week	30 min.	Moderate to Vigorous (tai-chi, yoga, aerobic dance, 30-min. walking)	**Traditional Care**
Merom et al. (2008)	Home-Based Aerobic Exercise (Walking) combined with Group CBT	8 weeks	At least 5x / week	30 min.	Moderate (participants educated on HR and exercise intensity)	**Group CBT** (one weekly 90 min. session) combined with **Educational Meetings** (healthy eating)
Wedekind et al. (2010)	Home-Based Aerobic Exercise (Outdoors Walking/Running) combined with Paroxetine or Placebo	10 weeks	3x / week (one group session with trainer)	45 min.	**Outdoors Route** *Week 1:* Walking *Week 2-6:* Short Running Periods *Week 7-10:* Running	**Relaxation** (one weekly session of autogenic training and home-based relaxation) combined with **Paroxetine** (*Week 1-2* - 20 mg; *Week 3-10* - 40 mg) or **Placebo**

HR_{max}: maximum heart rate; VO_2Max: maximum oxygen uptake; CBT: Cognitive-Behavioral Therapy;

3.4. Effects of acute exercise in patients with PD

This review only included 3 studies assessing the effects of acute exercise on patients with panic disorder. The findings provided by these trials are quite difficult to compare as the authors selected very different designs. Rief & Hermanutz (Rief and Hermanutz, 1996) compared 2-minutes of exercise and 5-minutes of rest which were performed only a few minutes apart in a cross-over design. However, interestingly enough, both conditions led to increased anxiety scores in patients with PD, with no significant differences between them. The trials developed by Esquivel et al. (Esquivel et al., 2008) and Ströhle et al. (Strohle et al., 2009) are much more similar, as both trials assessed panic and/or anxiety levels after each experimental condition (exercise vs control) and after the induction of panic-related symptoms (35% CO_2 inhalation and cholecystokinin tetrapeptide injection, respectively). Although these studies have some differences (parallel group vs cross-over design; active exercise control vs rest; intensity and duration; panic-induction method) both displayed similar findings. First, both studies found that exercise induced an immediate increase in panic-related symptoms, especially somatic symptoms. However, a single bout of exercise was also able to assure that the artificially induced increase in panic-related symptoms and anxiety was reduced, with effects sizes ranging from 0.8 to 1.57. Furthermore, pooled results from both studies suggest that the panic attack rate after symptom induction was significantly lower in the exercise conditions (5 in 22 – 22.7%) compared to the control conditions (14 in 20 – 70%) (Table 3).

Table 3. Major Findings and Effect Size Analysis (*Hedges' g)*.

Study Authors	Treatment condition	Control Condition	Follow-Up	Panic-Related Outcomes	Global Anxiety Outcomes	Depression Outcomes
Acute Exercise						
Esquivel et al. (2008)	Aerobic Exercise (n=10)	Very-Light Exercise (n=8)	Single Bout Parallel Group	PSL (0.99) **Panic attacks** EG: 1 in 10 / CG: 5 in 8	VAAS (1.57)	None
Rief & Hermanutz (1996)	Aerobic Exercise (n=20)	Rest (n=20)	Single Bout Cross-Over	None	VAAS (0.05)	None
Ströhle et al. (2009)	Aerobic Exercise (n=12)	Rest (n=12)	Single Bout Cross-Over	API (1.51) API Somatic Subcore (1.09) API Anxiety Subcore (0.80) **Panic attacks** EG: 4 in 12 / CG: 9 in 12	None	None
Regular Exercise Programs						
Broocks et al. (1998)	Home-Based Aerobic Exercise (n=11)	Clomipramine (n=15) Placebo (n=11)	None	*EG vs Placebo* PAS Observer Rating (1.35) PAS Patient Rating (1.33) *EG vs Clomipramine* PAS Observer Rating (-0.37) PAS Patient Rating (-0.49)	*EG vs Placebo* HARS (1.61) BAI (1.40) *EG vs Clomipramine* HARS (-0.11) BAI (0.22)	*EG vs Placebo* MADRS (1.06) BDI (0.79) *EG vs Clomipramine* MADRS (-0.26) BDI (0.11)

Gaudlitz et al. (2015)	Aerobic Exercise plus CBT (n=22)	Control (Movement) plus CBT (n=19)	5 months	PAS Patient Rating (0.25 / FU: 0.32)	HARS (0.01 / FU: 0.38) BAI (0.35 / FU: 0.40)	HRSD (0.18 / FU: 0.14)
Hovland et al. (2013)	Multimodal Exercise (n=17)	Group CBT (n=18)	6 and 12 months	Panic-related Distress - Patient (-0.37 / FU1: -0.31 / FU2: -0.65) Panic Frequency - Patient (-0.34 / FU1: -0.24 / FU2: -0.60 Panic-related Distress - Clinician (-0.18 / FU1: -0.20) Panic Frequency - Clinician (0.23 / FU1: 0.28)	BAI (-0.52/-0.41-/0.33) STAI State (-0.19/-0.30/0.08) STAI Trait (-0.23/-0.15/-0.26)	BDI-II (-0.38/-0.31/-0.35)
Ma et al. (2016)	Home-Based Exercise (n=14)	Usual Care (n=10)	3 months	None	STAI State (0.45 / FU: 0.55) STAI Trait (0.72 / FU: 0.77)	*None*
Merom et al. (2008)	Home-Based Walking plus Group CBT (n=7)	Education plus Group CBT (n=8)	None	None	*DASS-21 Anxiety (0.91)*	*DASS-21 Depression (0.90)*
Wedekind et al. (2010)	Home-Based Exercise plus Placebo (n=15) Home-Based Exercise plus Paroxetine (n=16)	Relaxation Training plus Placebo (n=16) Relaxation Training plus Paroxetine (n=13)	None	EG plus Paroxetine vs RT plus Paroxetine PAS Observer Rating (-0.14) EG plus Placebo vs RT plus Placebo PAS Observer Rating (0.29) PAS Observer & Patient Rating No significant differences between exercise and relaxation groups	*HARS & BAI* No significant differences between exercise and relaxation groups	*MADRS & BDI* No significant differences between exercise and relaxation groups

EG: exercise group; CG: control group; PSL: DSM-IV Panic Symptom List; VAAS: Visual Analogue Anxiety Scale; PAS: Panic and Agoraphobia Scale; HARS: Hamilton Anxiety Rating Scale; BAI: Beck Anxiety Inventory; MADRS: Montgomery-Asberg Depression Rating Scale; BDI: Beck Depression Inventory; CBT: Cognitive-Behavioral Therapy; FU: Follow-Up; HRSD: Hamilton Rating Scale of Depression; State and Trait Anxiety Inventory; DASS-21: Depression Anxiety Stress Scale; RT: Relaxation Training

3.5. Effects of regular exercise in patients with PD

Main findings and effect sizes regarding regular exercise programs are presented in Table 3. Four of the regular exercise trials included some sort of measure of panic-related symptoms. Only one trial reported clear effects of exercise on panic symptomatology, with large effects in comparison to placebo pills (Broocks et al., 1998) (*Hedges' g =1.33 and 1.35*). Other authors only reported small effect sizes of exercise (Gaudlitz et al., 2015; Wedekind et al., 2010) (*Hedges' g* =0.29 – 0.32) and Broocks et al. (Broocks et al., 1998) actually described that clomipramine treatment was marginally superior to exercise (*Hedges' g =0.37 – 0.49).* Finally, the study from Hovland et al. (Hovland et al., 2013) comparing CBT and exercise actually had discrepant findings on several panic-related measures. CBT was slightly more effective than exercise on panic-related distress (clinician and patients ratings) and panic frequency (patients ratings) immediately after training (*Hedges' g =018 – 0.37)* and

on the follow-up periods (*Hedges' g =0.20 -0.65).* However, exercise was somewhat more effective on panic-frequency (clinician ratings; *Hedges' g =0.23 and 0.28),* suggesting that there are not a big difference in treatment effects between these interventions.

Every included regular exercise trials included some measure of anxiety symptoms. There were four studies suggesting that exercise is effective to reduce anxiety in patients with panic-disorder (Broocks et al., 1998; Gaudlitz et al., 2015; Ma et al., 2017; Merom et al., 2008), with effects ranging from trivial to very large (*Hedges' g =0.01 – 1.61).* Furthermore, two of these trials (Gaudlitz et al., 2015; Ma et al., 2017) also reported small to moderate effects of exercise even after the follow-up assessment (*Hedges' g =0.38 – 0.77)*. Conversely, Wedekind et al. (Wedekind et al., 2010) did not found any significant differences the exercise and controls. The difference between exercise and clomipramine on anxiety-related symptoms also seems to be trivial (*Hedges' g = -0.11 and 0.22)* and CBT seems to be slightly more effective immediately after the intervention (*Hedges' g = 0.19 – 0.52)* and after the follow-up period *(Hedges' g =0.15 – 0.41).*

Finally, five of the included studies using regular exercise programs also had depression-related outcome measures and results were quite discrepant across trials. Wedekind et al. (Wedekind et al., 2010) found no significant differences between groups using exercise intervention and relaxation training and Gaudlitz et al. (Gaudlitz et al., 2015) only reported trivial effects of exercise plus CBT in comparison to the control group (*Hedges' g = 0.18; Follow-up = 0.14)*. Conversely, there were also two trials suggesting moderate to large effects of exercise in the depressive symptoms of patients with panic disorder (*Hedges' g* = 0.79 – 1.06). It is also interesting to compare the effects of exercise with other interventions on depressive symptoms. Both CBT and clomipramine treatment seem to be slightly more effective than exercise (Broocks et al., 1998; Hovland et al., 2013), although effect sizes favoring these interventions are either small or trivial (*Hedges' g =0.26 – 0.38*).

3.6. Risk of bias assessment

Risk of bias assessment for each included trial is presented on Table 4. Only three trials provided sufficient information about the way allocation sequence was generated (Hovland et al., 2013; Ma et al., 2017; Merom et al., 2008). Furthermore, only one trial had adequate allocation concealment procedures and was classified with low risk of bias (Hovland et al., 2013). Thereby, there is a significant risk of selection bias on most of the included trials in this systematic review.

Regarding blinding, all the studies have a high risk of performance bias, as it is not possible to assure blinding of participants and personnel in trials using exercise interventions. However, there was a low risk of bias regarding blinding of outcome assessment in many of the included trials as some authors had evaluators blinded to group allocation (Gaudlitz et al., 2015; Strohle et al., 2009) and other only included self-report scales as outcome measures (Esquivel et al., 2008; Ma et al., 2017; Merom et al., 2008; Rief and Hermanutz, 1996). Hovland et al. (Hovland et al., 2013) included both clinician ratings and self-report measures, but the evaluators was not blind to the experimental conditions.

All studies were judged as being at low risk of selective reporting bias. Although none of the trials had a protocol, it seems unlikely that any of the authors did not report relevant outcome measures. The risk of attrition bias was low in most of the included trials (Esquivel et al., 2008; Hovland et al., 2013; Ma et al., 2017; Rief and Hermanutz, 1996; Strohle et al., 2009). Attrition rates were not significantly different between groups in most trials, ranging from 0% to 46% in the exercise condition and from 0% to 39% in the control groups. However, there were a few trials were differences in drop-out rates were quite substantial (Broocks et al., 1998; Gaudlitz et al., 2015) and other studies where studies did not clearly describe why participants dropped-out. Finally, two studies were also classified with unclear risk of other bias as they did not describe if participants included in the trial were enrolled in some sort of regular exercise during the study (Rief and Hermanutz, 1996; Strohle et al., 2009).

Table 4. Risk of Bias Assessment

Study Authors	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Acute Exercise							
Esquivel et al. (2008)	Unclear	Unclear	High	Low (self-report measures)	Low	Low	Low
Rief & Hermanutz (1996)	High	High	High	Low (self-report measures)	Low	Low	Unclear
Ströhle et al. (2009)	Unclear	Unclear	High	Low	Low	Low	Unclear
Regular Exercise Programs							
Broocks et al. (1998)	Unclear	Unclear	High	Unclear	High	Low	Low

Gaudlitz et al. (2015)	Unclear	Unclear	High	Low	High	Low	Low
Hovland et al. (2013)	Low	Low	High	High (clinician ratings) Low (self-report measures)	Low	Low	Low
Ma et al. (2017)	Low	Unclear	High	Low (self-report measures)	Low	Low	Low
Merom et al. (2008)	Low	Unclear	High	Low (self-report measures)	Unclear	Low	Low
Wedekind et al. (2010)	Unclear	Unclear	High	Unclear	Unclear	Low	Low

4. Discussion

The aim this study was to assess the effects of exercise interventions on panic severity, global anxiety and depression symptoms of patients with panic disorder. Results from acute studies suggest that exercise immediately increases panic-related symptoms, but allows to reduced artificially induced increase panic attacks and anxiety. There is not clear evidence indicating that regular exercise programs reduce panic-related symptoms, but it seems that this intervention is effective to improve global anxiety measures and depression.

This review shows that evidence about the effects of physical exercise on panic disorder is scarce. Acute exercise induced an immediate increase in somatic symptoms panic-related (Esquivel et al., 2008; Strohle et al., 2009). In anxiety symptoms subscore, no difference was observed between exercise and rest after conditions, and the greatest increase in total API after exercise was reflected by somatic symptoms scores (Strohle et al., 2009). Perhaps this is the main factor for the smaller involvement of PD patients with exercise. In fact, these patients, compared to healthy subjects, presented low cardiorespiratory fitness and higher ratings of perceived exertion during physical exercise, which did not seem to be related to the psychological variables (Caldirola et al., 2011). Corroborating with our hypothesis, patients with high somatic anxiety showed a significantly higher prevalence of low level of physical exercise as compared to those with low somatic anxiety. Somatic symptoms of anxiety were the only important predictors of low level of physical exercise (Belem da Silva et al., 2014). However, patients with PD should be encourajed to practice regular physical exercise. Rief and Hermanutz demonstrated that patients with PD had elevated anxiety scores

after exercise, but also after rest (Rief and Hermanutz, 1996). Esquivel et al. also showed that Visual Analogue Anxiety Scale and the DSM-IV Panic Symptom List (neurovegetative symptomatology) were smaller in patients that performed moderate/hard exercise in contrast to those that performed very-light exercise (Esquivel et al., 2008). In addition to the possible reduction in anxiety levels, acute aerobic exercise may promote anti-panic action. Our results suggest that the panic attack rate after symptom induction was significantly lower in the exercise conditions (22.7%) compared to the control conditions (70%) in two studies (Esquivel et al., 2008; Strohle et al., 2009). Current studies have centered on mechanisms related to the atrial natriuretic peptide (Strohle et al., 2010), brain-derived neurotrophic factor (Strohle et al., 2006), and the serotonergic system (Greenwood and Fleshner, 2011).

In relation to the regular practice of aerobic exercise, our results showed that there is not clear evidence indicating reduces panic-related symptoms, but it seems that this intervention is effective to improve global anxiety measures and depression. Only one Study demonstrated improvements in severity of panic disorder seen through of effect size (very large) (Broocks et al., 1998). Broocks et al also demonstrated that aerobic exercise compared to placebo pill status was efficient in reducing overall anxiety levels (HAM-A and BAI) (Broocks et al., 1998). Aerobic exercise was prescribed with a progression of walking and running over the weeks, being performed for 45 minutes, 3 times weekly and lasting for 10 weeks. Intensity of exertion was not controlled during training. Ma et al. divided the patients with PD into two groups: Home-Based Multimodal Exercise Program and traditional care (Ma et al., 2017). The Home-Based Multimodal Exercise Program was performed with exercises of tai-chi, yoga, aerobic dance, 30-min of walking. These exercises were performed 5 times a week and lasting for 12 weeks. The results showed reduced in state and trait anxiety for the exercise group. However, despite the beneficial results of the exercise on anxiety levels, no benefit was demonstrated in the Wedekind et al. (Wedekind et al., 2010). The exercise routine was prescribed similarly by Broocks et al.(Broocks et al., 1998).

It is premature to speculate that only exercise intervention will promote improvements in the severity of panic disorder, anxiety levels and depression symptoms in patients with PD. Corroborating with our hypothesis, patients with PD who were treated with clomipramine presented greater reductions in anxiety and disease severity compared to those who underwent exercise intervention (Broocks et al., 1998). CBT was also more effective in reductions in anxiety and disease severity compared to those who underwent exercise intervention (Hovland et al., 2013). However, exercise intervention associated with CBT has been an

excellent option to contribute to the improvement of anxiety symptoms. Gaudlitz et al. divided the patients into two experimental groups: aerobic exercise plus CBT and control plus CBT (Gaudlitz et al., 2015). Aerobic exercise was prescribed with 30 minutes, 70% of VO_2max, 3 times weekly and lasting for 8 weeks. The control group performed light stretching movements. Both groups performed one session for weekly with 90 minutes per session. The results showed favorable the exercise plus CBT compared to control plus CBT for levels of anxiety and severity of disease. Merom et al. divided the patients into two experimental groups: walking plus CBT and control plus CBT (Merom et al., 2008). Aerobic exercise was prescribed with 30 minutes, 5 times weekly and lasting for 8 weeks. The intensity of exertion was moderate, based in the perceived of heart rate. The control group performed educational meetings for healthy eating. The results showed favorable the walking plus CBT compared to control plus CBT for depression and anxiety.

Several limitations should be acknowledged. It is observed that the methodological outlines of the presented involved attempts at analysis based on both the effects of acute physical exercise and chronic physical exercise. In addition, variations in exercise intensity, type of exercise, and types of instruments to assess anxiety demonstrate difficulties in reaching more definitive conclusions. The literature still needs to establish the exercise modality, duration, frequency and intensity of the physical exercise required to promote positive effects in individuals with PD.

In conclusion, physical exercise was associated with immediately increases panic-related symptoms, but reduced artificially induced increase panic attacks and anxiety. Regular exercise programs showed that this intervention is effective to improve global anxiety measures and depression. However, evidence was insufficient to infer a cause-effect relationship and randomized trials are suggested.

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CONFLICT OF INTEREST

The authors state none conflict of interest

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Artigo 2

Effects of aerobic exercise on anxiety symptoms and cortical activity in patients with panic disorder

Effects of aerobic exercise on anxiety symptoms and cortical activity in patients with panic disorder: a pilot study.

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Abstract

Background: The effects of the aerobic exercise on anxiety symptoms in patients with Panic Disorder (PD) remain inconclusive. To investigate the possible changes in frontal asymmetry activity can contribute for understanding the relationship between exercise, brain and anxiety. **Objective:** To investigate the acute effects of aerobic exercise on the symptoms of anxiety and the chronic effects of aerobic exercise on severity and symptoms related to PD, besides the changes on frontal brain asymmetry. **Method:** Ten patients with PD (DSM-IV-TR) were divided in two groups, Exercise group (EG; n=5) and Control group (CG; n=5), in a randomized order. At baseline and post-intervention, they were submitted of the psychological evaluation through of Panic Disorder Severity Scale (PDSS), Beck Anxiety Inventory (BAI), and Beck Depression Inventory-II (BDI-II), frontal brain asymmetry, and determining the maximal oxygen consumption (VO_2max). On the second visit, the patients of EG being submitted to the aerobic exercise (treadmill, 25 minutes, and 50-55% of heart rate reserve) and the CG remained seated for the same period of time. Both groups were submitted a psychological evaluation with Subjective Units of Distress Scale (SUDS) at baseline, immediately after (Post-0), and after 10 minutes of the rest pause (Post-10). The patients performed 12 sessions of aerobic exercise with 48-72 hour interval between sessions. **Results:** EG increased immediately after the SUDS and showed chronic decreased in BAI and BDI-II as well as increased in VO_2max (Post-intervention). **Conclusion:** Aerobic exercise can promote increase in anxiety acutely and regular aerobic exercise promotes reductions in anxiety levels.

Keywords: Exercise, Aerobic exercise, anxiety, EEG frontal asymmetry, Anxiety Disorders, Panic Disorder

INTRODUCTION

The Panic Disorder (PD) can be characterized by recurrent and unexpected panic attacks (PAs) where at least one of the attacks was followed by a persistent concern about new attacks and their consequences for a period of a month or more (1). Lifetime prevalence of PD estimates were 1.7% with a median age of onset of 32 years and some 80.4% of persons with lifetime PD had a lifetime comorbid mental disorder (2). Besides mental disorder, the PD is associated with clinical comorbid (3), loss of productivity, well-being, social contact and self-realization (4), causing considerable cost-of-illness (5).

First-line treatments for these disorders are selective serotonin reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, the calcium channel modulator pregabalin, tricyclic antidepressants (6), and benzodiazepines(7). However, long-term tolerability issues associated with antidepressants and benzodiazepines exposure should also be carefully considered (8). Besides that, 20% of the patients with PD are unresponsive to standard treatments (9). Potential treatment options for patients with PD are considered as Cognitive Behavioural Therapy (CBT) and other variants of behaviour therapy (6), yet physical exercise (10) .

The aerobic exercise has been used in patients with PD demonstrating acute anxiolytic and antipanic effects (11, 12). Esquivel et al. (11) compared two conditions of aerobic exercise, high intensity versus low intensity, on the antipanic effects after inhaling 35% of carbon dioxide (CO_2). The reactions of panic attacks to CO_2 were lower in patients who underwent high intensity aerobic exercise compared to low intensity. Research has also demonstrated the capacity of aerobic exercise to minimize anxiety symptoms in patients with PD after the use of substances that induce a PAs such as caffeine (13), cholecystokinin-tetrapeptide (CCK-4) (14), and CO_2 (11). However, other studies showed that aerobic exercise induces an increase in anxiety in patients with PD (14, 15). Rief and Hermanutz (15) found that aerobic exercise, lasting two minutes and intensity of 75 watts, was sufficient to promote an increase in anxiety in patients with PD. Strohle et al. (14) also demonstrated that 30 minutes of aerobic exercise, with an intensity of 70% of maximal oxygen consumption (VO_2max), generated an increase in anxiety. This alteration was present in the somatic symptoms (14), showing that patients with PD are more vulnerable to experiencing somatic symptoms after aerobic exercise (15). However, Martinsen et al. (16) showed that twenty-four hospitalized patients with panic disorder completed supramaximal exercise tests (3-minute

steady-state exercise test and workload at 110%) and all experienced high values of lactate (10.7 mmol/L), but only 1 patient experienced a panic attack during the exercise testing. Thus, the acute effect generated by aerobic exercise on anxiety symptoms in patients with PD remains inconclusive.

Another question persists if aerobic exercise promotes, in the long term, anxiolytic effect in patients with PD (17). Meyer et al. (17) submitted the patients to three experimental groups, clomipramine, aerobic exercise or placebo. They showed that treatment with clomipramine was more effective in disease severity and anxiety symptoms compared to aerobic exercise. The aerobic exercise was more effective in anxiety symptoms compared to placebo only at the end of the study (week 10). Bandelow et al. (18) evaluated three treatment modalities: running, clomipramine or placebo. Treatment efficacy was measured with the Panic and Agoraphobia Scale (P & A) and other rating scales. According to the P & A and other scales, both exercise and clomipramine led to a significant decrease of symptoms in comparison to placebo treatment. Again the clomipramine was significantly more effective and improved anxiety symptoms significantly earlier than exercise. In a study carried by Wedekind et al. (19) patients with PD were submitted to four experimental groups, aerobic exercise with paroxetine, relaxation with paroxetine, aerobic exercise with placebo, or relaxation with placebo. The results showed that response and remission rates only in the paroxetine group. No improvement was observed in the aerobic exercise. Thus, the ability of aerobic exercise to promote long-term improvements in anxiety in patients with PD is questioned.

Of particular interest to the present study are models that link frontal brain asymmetry to individual differences in affective style. This frontal asymmetry particularly postulated within the alpha frequency band (8-12 Hz) is the main base of Davidson model (20). The model proposed by Davidson et al. demonstrates that left frontal areas of the brain mediating the experience of positive emotions and approach behaviors, and right frontal areas of the brain mediating the experience of negative emotions and withdrawal behaviors were associated with higher activation of the right frontal cortex and positive affective responses were associated with higher activation of the left frontal cortex (20). These patterns of frontal electroencephalographic (EEG) asymmetry may serve as an index of risk for a variety of emotion-related disorders. Patients with major depression (21) and social anxiety (22, 23) have been shown significant relative elevations in right frontal brain activity when assessed

during resting states or periods of acute emotional provocation, supporting these theoretical predictions (24).

Until now no studies to date have investigated patterns of change in frontal EEG activity among individuals with PD before and after aerobic exercise. In health subjects, Petruzzelo and Tate who showed that the frontal asymmetry was predictive of positive affect immediately after exercise using the intensities close to the ventilatory threshold (70% of VO_2max) (25). However, the frontal asymmetry measured followed by aerobic exercise conditions, was influenced by the exercise intensities in three (45%, 60% and 75% VO_2max), and associated with an increase in the vigor imposed no differences between three intensities (26). Although no studies to date have investigated patterns of change in frontal EEG activity among individuals with PD before and after aerobic exercise, Lattari et al.(27) demonstrated that aerobic exercise did not change the frontal asymmetry in health subjects.

Thus, the acute and chronic effects generated by aerobic exercise on anxiety symptoms in patients with PD remain inconclusive. In addition, the intensity of effort that promotes anxiolytic effects remains unanswered. Acutely, the intensity of aerobic exercise has been reported objectively (11, 14, 15), but it is not known until now whether it causes an increase or decrease in anxiety in patients with PD. Chronically, research used this variable in an arbitrary form (19, 28), only one study that determined the intensity of effort in an objective form (10). Details on the intensity, frequency and duration may further support the clinical administration of the exercise in patients with panic disorder (29). Of particular interest to the present study is the investigation patterns of change in frontal EEG activity among individuals with PD before and after aerobic exercise and to evaluate predictions on levels of anxiety.

Besides, the study had the following objectives: 1) To investigate the acute effects of aerobic exercise on the symptoms of anxiety; 2) To investigate the chronic effects of aerobic exercise on severity and symptoms related to PD, besides the changes on frontal brain asymmetry. Our hypothesis for acute effects is that exercise compared to resting condition will provide further increases in anxiety immediately after, with significant reductions after 10 minutes of recovery. The regular practice of aerobic exercise will have greater reductions in severity and symptoms related to PD, as well as a increase in frontal asymmetry compared to control group.

METHODS

Patients

The recruited patients had a diagnosis of PD in according to the current Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (unexpected PAs in the last month) (1). The patients had to be symptomatic by Panic Disorder Severity Scale ("PDSS") (> 10 points, moderately ill). Diagnoses were made by an experienced psychologist using the Structured Clinical Interview for DSM-IV-TR. The exclusion criteria were: pregnancy, lactation, severe medical illness, organic brain damage, bipolar affective disorder, severe major depression, psychotic symptoms, alcohol or drug abuse, anorexia or bulimia nervosa, and regular aerobic exercise. The patients were sedentary and for participation in aerobic exercise, patients were requested to have an authorization from the cardiologist. Patients were not allowed to undergo additional psychological treatment during the study. Patients were to have continued treatment with any psychotropic drugs at least two weeks before baseline. The patients were in regular use with the selective serotonin reuptake inhibitors (fluoxetine, paroxetine, and citalopram) and/or benzodiazepines (clonazepam and alprazolam). Ten patients were eligible for the study in accordance with the inclusion and exclusion criteria. Each patient was clarified of all the experimental procedures and signed a written consent form, with the experiment was approved by the institutional ethics committee of the Federal University of Rio de Janeiro. The characteristics of the patients are shown in table 1.

Procedures

On the first visit (1^{st} day) to the Panic and Respiration of Laboratory, the patients were submitted to a battery of psychological evaluation (diagnosis of PD with DSM-IV-TR, Panic Disorder Severity Scale, Beck Anxiety Inventory, and Beck Depression Inventory II), recording the electroencephalographic activity (resting EEG asymmetry), and determining the maximum oxygen consumption (VO_2max) (Baseline). Ten patients were included and randomly assigned to two groups, Exercise group (n=5) and Control group (n=5).

On the second visit (2^{nd}) to the laboratory, the patients of exercise group were submitted to the single bout aerobic exercise (seen in the “Single Bout Exercise”). Patients in the control group remained seated comfortably in an armchair for the same period of time. Both groups were submitted a psychological evaluation with Subjective Units of Distress Scale (SUDS) at baseline, immediately after (Post-0), and after 10 minutes of the rest pause (Post-10). These experimental procedures were performed to verify the acute effects of aerobic exercise on anxiety symptoms.

During the chronic experimental phase, patients performed 12 sessions of intervention protocol of aerobic exercise (2nd to 13th day). The intervention protocol of aerobic exercise was performed with 48-72 hour rest interval between sessions. At the end of the chronic experimental phase (14th day), the same evaluations of the first visit (1st day) to the laboratory were performed, with the exception of DSM-IV-TR (Post-intervention). The psychologist evaluations were made by an experienced psychologist. Recording the electroencephalographic activity, and evaluation of the VO_2max was made by an experienced physical education professional. The aerobic exercise sessions also was accompanied by the same physical education professional. Patients in the control group were instructed not to exercise during the chronic experimental phase and remained on medication. The experimental procedures are shown in figure 1.

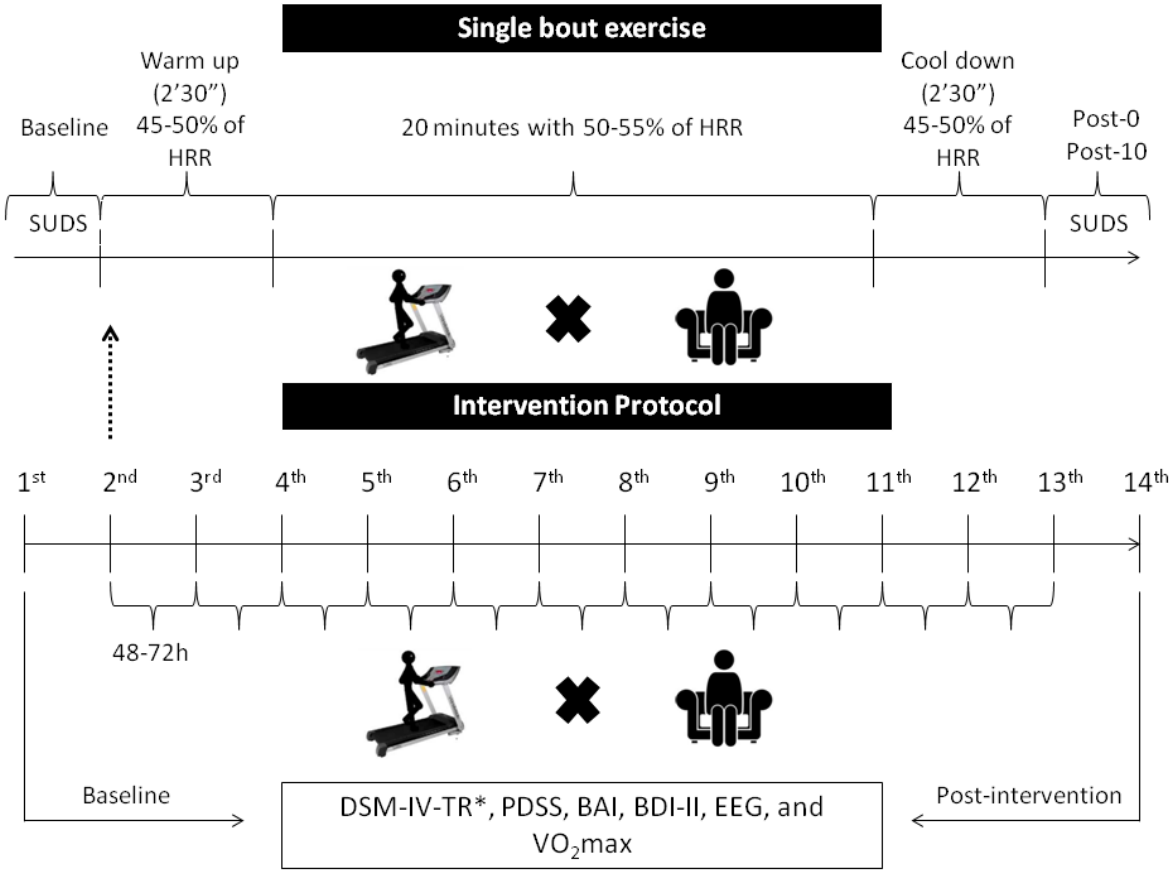

Figure 1- Schematic representation of the experimental procedures. *Assessed only at the baseline

Single bout exercise

All patients performed the training routine without interruptions and in the same calibrated treadmill (INBRAMED, Brazil). The patients performed 12 sessions with 48-72

hours of the interval each session. They received information about the training procedures and also were encouraged to work until the end of the set time, but advised that they could also abort the training session to signal complications or fatigue. The intensity settings occurred at 45-50% of HRR for warm up, 50-55% of HRR for training and 45-50% of HRR for cool down. The warm up and cool down were performed with two minutes and thirty seconds, respectively. For aerobic training was performed twenty minutes of duration. The aerobic exercise had a total duration of 25 minutes. This prescription of aerobic exercise is in agreement with the American College of Sports Medicine (30).

Panic Disorder Severity Scale (PDSS)

The Panic Disorder Severity Scale (PDSS) is a questionnaire developed for measuring the severity of panic disorder (31).The PDSS consists of seven items that assess: 1) Panic frequency; 2) Distress during panic; 3) Panic-focused anticipatory anxiety; 4) Phobic avoidance of situations; 5) Phobic avoidance of physical sensations; 6) Impairment in work functioning; 7) Impairment in social functioning.

Each item is rated on a 5-point scale, which ranges from 0 to 4. The total scores range from 0 to 28.

Subjective Units of Distress Scale (SUDS)

A Subjective Units of Distress Scale (SUDS) is a scale of 0 to 10 for measuring the subjective intensity of disturbance or distress currently experienced by an individual. The anxiety level has been measured with the Subjective Units of Distress Scale (SUDS) in patients with panic disorder (32-34).

Beck Anxiety Inventory (BAI)

The Beck Anxiety Inventory (BAI) is a 21-question multiple-choice self-report inventory that is used for measuring the severity of anxiety (35). Each answer is scored on a scale value of 0 (not at all) to 3 (severely). The BAI has been used as secondary outcomes of the anxiety in patients with panic disorder after aerobic exercise program (10, 28).

Beck Depression Inventory-II (BDI-II)

The Beck Depression Inventory-II (BDI-II) is a 21-question multiple-choice self-report inventory that is used for measuring the severity of depressive episodes (36). Each answer is scored on a scale value of 0 (not at all) to 3 (severely).

Resting EEG asymmetry

The EEG signal was recorded by Neurosoft (Medical Instruments, São Paulo, Brazil) of 19 channels. Nineteen monopolar electrodes were placed in the frontal areas (Fp1, Fp2, Fz, F3, F4, F7 and F8), central (Cz, C3 and C4), temporal (T3, T4, T5 and T6), parietal (Pz, and P3 P4) and occipital (O1 and O2) according to the International System 10/20 protocol (37). Two other electrodes (A1 and A2) were positioned in the earlobes with reference function (bi-auricular). The EEG suffers 0.05 Hz analog filtering (high pass) and 500 Hz (low-pass). EEG Sampling Rate is 5000 Hz and noise level is less than 0.3 μV. We used a digital notch filter 60 Hz and high-pass filters also on 0.5 Hz and low pass at 35 Hz.

The impedance levels of each electrode were observed, which should be between 5 and 10 KOhms (KΩ). The analyzes of EEG were performed in Neuron-Spectrum.NET-3 software. Initially, the artifacts were automatically removed, as spikes and sharp waves. In addition, the estimation of signal components by Independent Component Analysis (ICA) was applied to minimize artifacts. A visual inspection of the data to remove artefacts was performed, such as sweating and muscle tension.

Through Fast Fourier Transform (FFT), that refers to a signal analysis that repeats itselve at regular time intervals, can set how much energy (power) is in each frequency band. The spectral absolute power was used with 1-s window for time of EEG, free of artifacts (spectral resolution of 0.25 Hz). The digital EEG systems of Neuron-Spectrum-3 series allow EEG recording in standard ranges delta, theta, alpha, beta and gamma. Epochs were extracted in the alpha frequency band (8-14Hz). The log transformation was applied (natural log ln) on the power values, since the power of the EEG not have a normal distribution between subjects. This procedure results in a near normal distribution. EEG data were analyzed by cortical asymmetry according to Davidson hypothesis (20). The basic mathematical calculation to compute the asymmetry was expressed by the equation: Resting EEG Asymmetry = InF4- InF3; the choice of fronto-medial electrodes counterparts (F4-F3) was based on the prevalence of this measure in the literature related to exercise and association between asymmetry with reduced in anxiety scores (22, 23).

Determination of the maximal oxygen consumption (VO_2max)

For determination of VO_2max, a submaximal protocol was used as used by Oliveira et al. (38). For this, the patients remained seated for 10 min of rest, in a calm and refrigerated environment (20° - 21°C). After 10 minutes of rest, the resting heart rate (HRrest) was measured by a specific monitor (model RS800, Polar®, Finland). The maximal heart rate (HRmax) was also determined by the following equation: 220 – age (years).

The purpose of the test is to achieve the intensity corresponding to approximately 65% of heart rate reserve (HRR). To determine the HRR, the equation was used: (HRmax - HRrest) x intensity + HRrest. Once hit, this intensity of effort is maintained for 6 minutes, characterizing a steady-state. It is expected that the end of this stage the FC was stabilized at approximately 70% of HRR. Intensity corresponds to the intensity that the patient should have reached during the test (65% of HRR) and maintain in steady state (70% of HRR) (39). The submaximal protocol was performed with an initial warm up of 3 minutes on a treadmill (INBRAMED, Brazil), with a metabolic increment equivalent to 1 MET per minute, provided by the manipulation in the inclination of treadmill.

The VO_2 was obtained by the walking equation: VO_2 = [0,1 (speed) + 1.8 (speed) (inclination / 100) + 3.5], in which the speed is given in m/min. Finally, the VO_2max was predicted by the equation: VO_2max = [(VO_2 - 3.5) / %HRR + 3.5], in which VO_2max is expressed in $mL.kg^{-1}.min^{-1}$(30).

Statistical Analysis

Descriptive statistics (mean and standard deviation) were calculated for age, body weight, height, SUDS, PDSS, BAI, BDI-II, VO_2max, and resting EEG asymmetry. At baseline, independent samples t-tests were used to verify the differences between the two groups (Exercise group vs Control group). A 2 × 2 mixed factor analysis of variance was used to test for differences between control group and exercise group (between-group effects) and differences between baseline, immediately after (Post-0), and 10 minutes post-intervention (Post-10) (within-group effects) for SUDS. A 2 × 2 mixed factor analysis of variance was used to test for differences between control group and exercise group (between-group effects) and differences between baseline post-intervention (within-group effects) for PDSS, BAI, BDI-II, VO_2max, and resting EEG asymmetry. Post-hoc analysis was performed using the Bonferroni to assess the effects within each group. Assumptions of the homogeneity of variance and residual normality were tested by using the Levene's and Shapiro–Wilk tests respectively. If assumptions were not met, change scores for those outcome measures were computed. Depending on the normality of the data, change scores for each group were compared by using independent samples t-test or Mann–Whitney U tests. Analyses were led separately for all the outcome variables including Panic SUDS, PDSS, BAI, BDI-II, VO_2max, and resting EEG asymmetry. The level of significance was set at $p \leq 0.05$.

Effect size analysis for each group was calculated by using Cohen's d. The following measures were used: PDSS, BAI, BDI-II, VO_2max, and resting EEG asymmetry. Given that the calculation was for within group effects, we correlated both means and used Morris & DeShon's (40) equation. Calculations were completed by using the G*POWER software (version 3.1). Effect sizes were classified as trivial (d <0.19), small (d = 0.20-0.49), moderate (d = 0.50-0.79), large (d = 0.80-1.29) and very large (> 1.30) (41).

RESULTS

At baseline, there were no significant group differences regarding age, body weight, height, SUDS, PDSS, BAI, BDI-II, VO_2max, and resting EEG asymmetry ($p > 0.05$), with the exception of the body weight (p=0.03). Thereby, it can be assumed that participants in both groups were similar in relevant variables at the moment the intervention began (Table 1).

Table 1. Descriptive data of the groups at baseline.

Variables	Baseline		
	Exercise group (n=5) (M±SD)	Control group (n=5) (M±SD)	P
Age	36.4±3.5	42±8.4	0.20
Body weight (kg)	81±13.6	64±4.2	0.03*
Height (cm)	168.6±7.1	167.6±5.5	0.81
SUDS	2.4±1.1	2.2±0.8	0.76
PDSS	13.8±2.4	13.2±3.4	0.76
BAI	29.6±7.4	24.2±9.1	0.33
BDI-II	21.6±10.7	21.2±11.3	0.95
VO_2max	35.4±2.7	32.2±2.2	0.08
Resting EEG asymmetry	-0.0295	-0.0130	0.75

Legend- Kg= kilogram; cm= centimeter; SUDS= Subjective Units of Distress Scale; PDSS= Panic Disorder Severity Scale; BAI= Beck Anxiety Inventory; BDI= Beck Depression Inventory-II; VO_2max= maximum consumption oxygen in $mL.kg^{-1}.min^{-1}$;*Difference between groups at baseline.

SUDS

Mixed analysis of variance analysis showed significant group by time interaction ($p = 0.026$), and also significant main effects for time ($p = 0.001$) for SUDS. Post-hoc analysis revealed a significant increase in SUDS in the exercise group after the intervention compared to baseline (p=0.04) and after 10 minutes of the rest pause ($p = 0.003$) (Figure 2). There were no significant differences between the exercise and control groups at baseline (Exercise group=2.4±1.1 vs Control group= 2.2±0.8, p=0.76), immediately after (Exercise group=3.8±0.8 vs Control group= 2.6±1.8, p=0.21) and after 10 minutes of the rest pause (Exercise group=1.6±0.5 vs Control group= 2.2±1.0, p=0.30).

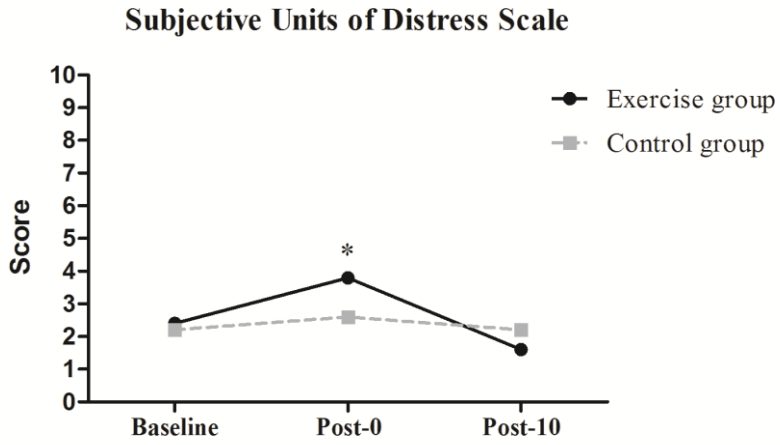

Figure 2- Acute effects of exercise on SUDS.
Legend- *Exercise group- Immediately after > Baseline (p=0.04) and 10 minutes after (p=0.003).

PDSS

The results showed no significant group by time interaction (p=0.41) and no significant main effects for time (p=0.18) for PDSS. Descriptive data are shown in table 2.

BAI

Mixed analysis of variance analysis showed significant group by time interaction (p=0.02), and main effects for time (p=0.02) for BAI. Post-hoc analysis revealed a significantly decreased score in BAI in the exercise group post-intervention compared to baseline (p=0.005) (Figure 3).

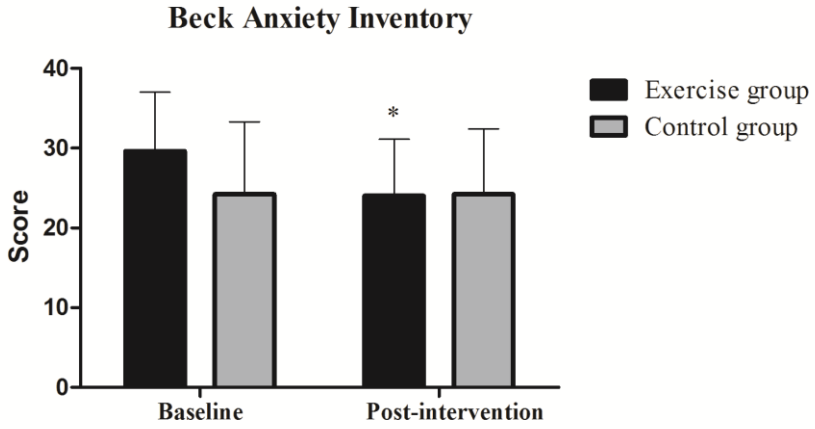

Figure 3- Between and within-group comparisons for BAI.
Legend- *Exercise group- Post-intervention < Baseline (p=0.005).

Independent samples t-test for change scores indicated significant between-group differences regarding BAI (p = 0.02) (Figure 4). Moreover, only the exercise group showed very large effect size (1.40) within group. Descriptive data are shown in table 2.

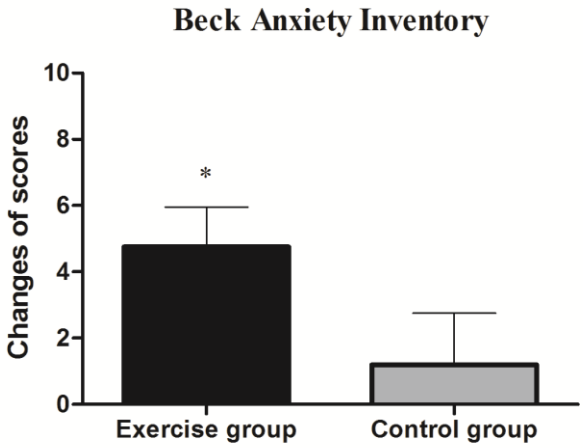

Figure 4- Independent samples t-test for changes scores in BAI.
Legend- *Greater reductions in the exercise group compared to the control group (p=0.02).

BDI-II

Mixed analysis of variance analysis showed significant group by time interaction (p = 0.04), and no significant main effects for time (p = 0.09) for BDI-II. Post-hoc analysis revealed a significantly decreased score in BDI-II in the exercise group post-intervention compared to baseline (p=0.01) (Figure 5). Mann–Whitney's U test for change scores no showed between-group differences for BDI-II (p = 0.09). However, only the exercise group showed large effect size (1.06) within group. Descriptive data are shown in table 2.

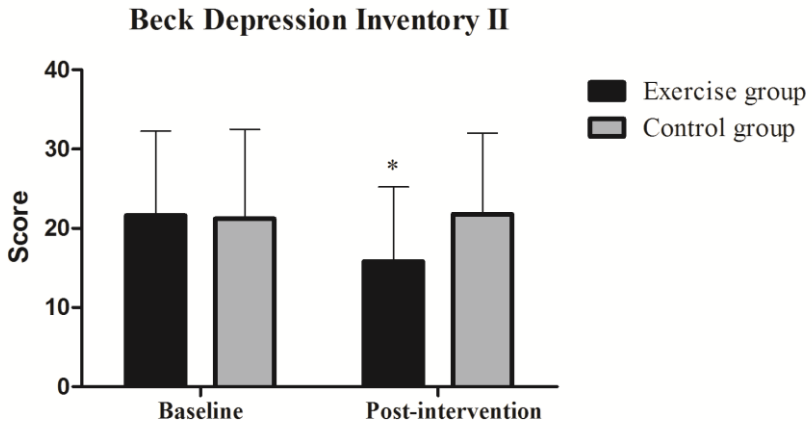

Figure 5- Between and within-group comparisons for BDI-II.
Legend- *Exercise group- Post-intervention < Baseline (p=0.01).

VO_2max

Mixed analysis of variance analysis showed significant group by time interaction ($p < 0.001$), and also significant main effects for time ($p < 0.001$) for VO_2max. Post-hoc analysis revealed a significant increase in VO_2max in the exercise group post-intervention compared to baseline ($p < 0.001$). In addition, VO_2max was greater in the exercise group compared to the control group in post-intervention ($p=0.005$) (Figure 6).

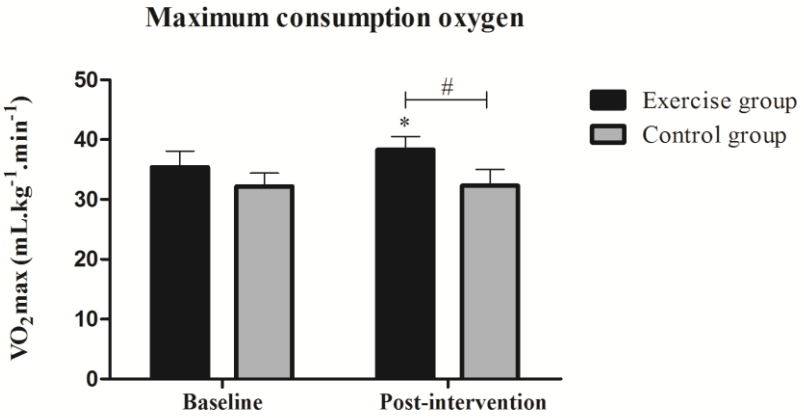

Figure 6- Between and within-group comparisons for VO_2max.
Legend- *Exercise group- Post-intervention < Baseline ($p=0.01$); #Exercise group > Control group in post-intervention

Independent samples t-test for change scores indicated significant between-group differences regarding VO_2max ($p < 0.001$) (Figure 7). Besides, results of the effect size between ($d= 2.43$) and within groups (4.15) showed very largely, favorable of the exercise group. Descriptive data are shown in table 2.

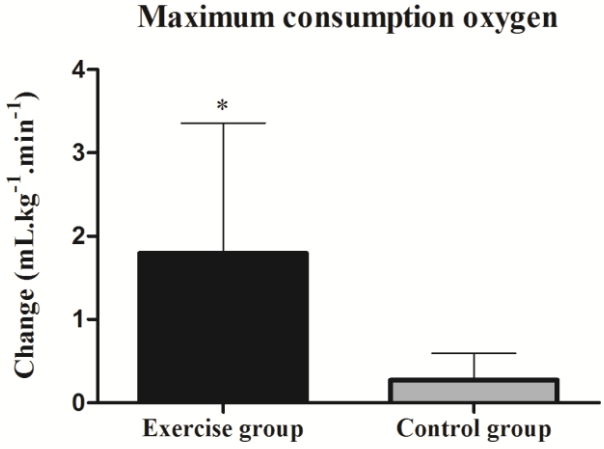

Figure 7- Independent samples t-test for changes in VO_2max.
Legend- *Exercise group > Control group ($p < 0.001$).

Resting EEG asymmetry

The results showed no significant group by time interaction (p=0.43) and no significant main effects for time (p=0.46) for resting EEG asymmetry. Descriptive data are shown in table 2.

Table 2. Between and within-group comparisons and effect size analysis for all outcome measures.

Variables	Exercise group (EG)		Control Group (CG)		Effect sizes		
	Baseline (M±SD)	Post-intervention (M±SD)	Baseline	Post-intervention (M±SD)	Between-group	Within EG	Within CG
PDSS	13.8±2.4	13.0±2.0	13.2±3.4	13.0±3.3	0	0.75	0.18
BAI	29.6±7.4	24.0±7.1	24.2±9.1	24.2±8.2	0.02	1.40	0
BDI-II	21.6±10.7	15.8±9.4	21.2±11.3	21.8±10.2	-0.61	1.06	0.21
VO_2max	35.4±2.7	38.3±2.2	32.2±2.2	32.3±2.7	2.43	4.15	0.16
Resting EEG asymmetry	-0.0295±0.08	-0.0280±0.04	-0.0130±0.07	-0.0553±0.05	-0.60	0.02	0.51

Legend- PDSS= Panic Disorder Severity Scale; BAI= Beck Anxiety Inventory; BDI= Beck Depression Inventory-II; VO_2max= maximum consumption oxygen in $mL.kg^{-1}.min^{-1}$.

DISCUSSION

The aim of study was to verify the acute effects of aerobic exercise on the symptoms of anxiety and to investigate the chronic effects of aerobic exercise on severity and symptoms related to PD, besides the changes caused on frontal brain asymmetry. Acute effects of exercise provided increases in anxiety immediately after and significant reductions after 10 minutes of recovery. The regular practice of aerobic exercise generated greater reductions in symptoms related to PD, BAI and BDI-II. However, no changes were demonstrated in PDSS and frontal EEG asymmetry in both groups.

In fact aerobic exercise can promote increase in anxiety acutely and other researches corroborated our findings (14, 15). Rief and Hermanutz (15) submitted patients with PD to two experimental conditions, exercise and control. The exercise was performed in the cycle ergometer, with duration of two minutes and intensity of 75 watts. The results showed that patients with PD had elevated anxiety scores after physical activation, but also after rest. Strohle et al.(14) also investigated the effects of quiet rest or an aerobic treadmill exercise on

antipanic and anxiolytic activity in patients with PD. The aerobic exercise was performed in treadmill, 30 min at an intensity of 70% of VO_2max. The results showed that somatic anxiety subscore were higher after exercise compared to rest and no results have been demonstrated for anxiety symptoms subscore. It is expected that some somatic symptoms increase during exercise and that responses of increase in anxiety levels are linked to this factor, as corroborated by the study of Strohle et al.(14). In our findings, this increase in anxiety may be related to possible changes in somatic symptoms. However, although aerobic exercise has promoted increased levels of anxiety, exercise exposure may provide antipanic protective effect. Strohle et al. (14) showed that CCK-4-induced panic attacks were less frequent after prior exercise (Exercise= 4 patients, 33.3% and Rest= 9 patients, 75%). Compared to prior rest, exercise resulted in a significantly reduced CCK-4-induced increase of the total Acute Panic Inventory (API) score and the anxiety subscore. Esquivel et al. (11) also demonstrated the protective effect of exercise for panic attacks and levels of anxiety. Patients participated in two experimental conditions, moderate/hard exercise (to reach and sustain on the cycloergometer 80 and 90% of their maximal heart rate for 15 minutes with or until exhaustion) or a very-light exercise (15 minutes, 1watts per kg, and 20 at 70 rpm, control group). Panic reactions to CO_2 were smaller in patients that performed moderate/hard exercise in contrast to those that performed very-light exercise.

Due to therapeutic potential of acute aerobic exercise, this intervention non-pharmacological was investigated also chronically. Our results showed that aerobic exercise reduced anxiety after 12 training sessions and data of randomized controlled trials suggest higher sizes for the effect of exercise on anxiety (42). Bandelow et al.(18) submitted the patients to three treatment conditions: clomipramine, placebo and aerobic exercise (walking or running). Both exercise and clomipramine led to a significant decrease of anxiety symptoms in according to the P&A and HAM-A, in comparison to placebo treatment. Clomipramine was significantly more effective than aerobic exercise. Similar results were found in the Broocks et al. (28) and Meyer et al. (17). Although the anxiolytic and antipanic effects of exercise have already been empirically observed, the mechanisms of action involved remain to be elucidated. Several plausible mediators have been set forward to explain the antipanic and anxiolytic effects of exercise. Current studies have centered on mechanisms related to the brain-derived neurotrophic factor (43), atrial natriuretic peptide (12), and the serotonergic system (44).

Wedekind et al. (19) showed no improvement in anxiety due to regular aerobic exercise. In this study, the patients were divided into four experimental groups: aerobic

exercise with paroxetine, relaxation with paroxetine, aerobic exercise with placebo, or relaxation with placebo. The results showed that response and remission rates were higher in the groups using paroxetine, regardless of whether exercise or relaxation, compared to placebo groups. The aerobic exercise showed a trend of improvement compared to the relaxation group, seen only in the fourth week. It is still necessary to establish the duration, frequency and intensity of aerobic exercise that promotes the beneficial organic adaptations to patients with PD. In our research, the aerobic exercise protocol was established according to the ACSM recommendations (30) and the control over aerobic exercise intensity has been subjective in others studies (17-19). The intensity settings at 50-55% of HRR for training and twenty minutes of duration is recommended for sedentary subjects and low cardiorespiratory fitness (30). Patients with PD showed lower VO_2max, as well as lower exercise tolerance (45). With this, our training prescription seems appropriate.

In addition to reductions in anxiety levels, our research demonstrated that regular aerobic exercise provided an increase in VO_2max and reductions in depression scores. These results suggest that regular aerobic exercise, in comparison with control group, is associated with significant clinical improvement in patients suffering from panic disorder. Martinsen et al.(46) reported the results of a protocol of 1 hour of AE at 70% of VO_2max, 3 times a week for 8 weeks, in which they observed a significant increase in VO_2max with significant reductions in the depression scores.

Our hypothesis was not confirmed for regular practice of aerobic exercise increase in resting EGG asymmetry compared to control group. No change in resting EEG frontal asymmetry was observed in our results. To date, no study has investigated the changes in resting EEG asymmetry caused by aerobic exercise chronically. Lattari et al. (27) showed that acute aerobic exercise no change the resting EEG asymmetry.

A limitation of our study design is that it is not possible to establish true double-blind conditions. Besides, our results should be interpreted with caution due to the sample size. However, our research was innovative in the most appropriate control of aerobic training. In addition, it was the first study to investigate the effects of aerobic exercise on resting EEG asymmetry in patients with PD.

CONCLUSION

It is concluded that aerobic exercise can promote increase in anxiety acutely. However, regular aerobic exercise promotes reductions in anxiety levels. In addition, the regular practice of aerobic exercise promotes other interesting improvements such as maximal oxygen consumption and reductions in the symptoms of depression. The hypothesis of resting EEG asymmetry be present in the exercise group in post-intervention has not been confirmed. Future research should further examine how the frontal asymmetry is associated with changes in anxiety after the regular practice of aerobic exercise.

LIST OF ABBREVIATIONS

PD= Panic Disorder

PAs= Panic attacks

CBT= Cognitive Behavioural Therapy

CO_2= carbon dioxide

CCK-4= cholecystokinin-tetrapeptide

P & A = Panic and Agoraphobia Scale

VO_2max = maximal oxygen consumption

EEG= electroencephalographic

BAI= Beck Anxiety Inventory

BDI-II= Beck Depression Inventory-II

PDSS= Panic Disorder Severity Scale

SUDS= Subjective Units of Distress Scale

μV= MicroVolts

Hz= hertz

KΩ= KOhms

FFT= Fast Fourier Transform

ACSM= American College of Sports Medicine

API= Acute Panic Inventory

rpm= rotations per minute

HAM-A= Hamilton Anxiety Scale

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Conclusão

De acordo com nossos objetivos iniciais estabelecidos através de dois estudos, podemos concluir esta tese da seguinte forma: (1) No estudo 1, revisão sistemática, uma sessão de exercício provoca de forma imediata aumento nos sintomas relacionados ao pânico, porém também foi capaz de reduzir os ataques de pânico e sintomas de ansiedade induzidos por testes provocativos de ataques de pânico. Em relação a prática regular do exercício, não há evidências claras que indiquem redução nos sintomas relacionados ao pânico, mas parece que esta intervenção é eficaz para melhorar as medidas globais de ansiedade e a depressão, (2) Em relação ao estudo 2, pesquisa experimental, foi confirmado a hipótese de que o exercício aeróbio aumenta a ansiedade imediatamente após o exercício. Também foi demonstrado que a prática regular do exercício aeróbio provocou uma diminuição na ansiedade global, nos sintomas de depressão, bem como aumento no consumo máximo de oxigênio após a intervenção. Nossa hipótese que o exercício aeróbio iria alterar a medida de assimetria frontal do córtex cerebral não foi confirmada. Sendo assim, nenhuma relação entre exercício, assimetria frontal e ansiedade foi verificada.

No primeiro estudo foram abordados os benefícios do exercício físico como possível forma de tratamento no transtorno de pânico. Entre os diversos tratamentos sugeridos aos pacientes com TP, destacam-se o farmacológico e a TCC. Apesar da eficácia do tratamento farmacológico, muitos pacientes não são responsivos, sendo que 20% permanecem sintomáticos (Holt et al., 2007). Combinar as formas de tratamento, TCC e benzodiazepínicos, apresentou bons resultados na diminuição da sintomatologia da doença (Furukawa et al., 2007), porém sem diferença em um acompanhamento em longo prazo (Watanabe et al., 2009). Assim, o exercício físico surgiu como um possível tratamento no auxílio aos pacientes com transtorno de pânico. Ao revisarmos a literatura de forma sistemática, pode-se verificar que uma sessão de exercício aeróbio provocou aumento nos sintomas relacionados ao TP. Porém, esse aumento parece ser provocado por sintomas somáticos, o que é passível de uma resposta “normal” do exercício físico. Por mais que ocorra aumento nos sintomas de ansiedade, o exercício aeróbio demonstrou seu benefício com uma ação antipânico em resposta a testes provocativos de ataques de pânico (Strohle et al., 2009; Esquivel et al., 2008). Os exercícios aeróbios comparados a uma condição de repouso foram mais eficazes em reduzir o número de ataques de pânico realizados por testes provocativos que utilizaram colecistocinina (Strohle et al., 2009) e dióxido de carbono (Esquivel et al., 2008). Assim, uma única intervenção de exercício aeróbio demonstrou promissores resultados

quanto ao tratamento do transtorno de pânico. Em face desses resultados, o exercício físico foi realizado de forma regular para verificar seus possíveis efeitos sobre a sintomatologia do TP. Contudo, ao revisarmos a literatura, não se pode tirar conclusões definitivas sobre eficácia do exercício físico no TP. Ainda assim, esta intervenção foi eficaz para melhorar as medidas globais de ansiedade e a depressão.

Já no segundo estudo investigaram-se os efeitos agudos do exercício aeróbio sobre os sintomas de ansiedade e os efeitos crônicos do exercício aeróbio sobre a gravidade e os sintomas relacionados ao TP, além das mudanças na assimetria frontal do córtex cerebral. Como esperado, o exercício aeróbio agudo aumentou a ansiedade imediatamente após o exercício. No exercício crônico, nossos achados também foram de acordo com a literatura, onde se verificou melhorias nos níveis de ansiedade global e sintomas de depressão, assim como nenhuma alteração quanto a gravidade do TP. Nossa hipótese do exercício alterar a assimetria frontal cortical não foi confirmada.

Essa pesquisa experimental foi inovadora ao estabelecer um protocolo adequado de exercício aeróbio a pacientes com TP. Para prescrição do treinamento foi utilizado as recomendações do Colégio Americano de Medicina Esportiva (2010). Esse protocolo utiliza como parâmetros a aptidão cardiorrespiratória e nível de treinamento de um sujeito saudável. Foi adotado este protocolo pelo fato de pacientes com TP apresentarem consumo máximo de oxigênio semelhante a controles saudáveis (Ramos et al., 2014). Além disso, existiu normalidade em parâmetros fisiológicos (frequência cardíaca máxima e ponto ótimo cardiorrespiratório) em testes aeróbios máximos e submáximos. Pelo fato de não existir, até o momento, um protocolo específico de exercício aeróbio para pacientes com TP, nosso protocolo pode ser o passo inicial para que isso aconteça. Ao evitar o exercício físico, esses pacientes apresentam baixa aptidão cardiorrespiratória e maior percepção subjetiva de esforço durante o exercício físico, o que não pareceu estar relacionada com as variáveis psicológicas (Caldirola et al., 2011). Os sintomas somáticos de ansiedade são os únicos preditores importantes para o baixo nível de atividade física (Belem da Silva et al., 2014).

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Anexo I- Outras produções relevantes

1- **Lattari E,** Campos C, LAMEGO MK, et al. Can transcranial direct current stimulation improve muscle power in individuals with advanced resistance training experience? Journal of Strength and Conditioning research 2017 (aceito para publicação).

2- **Lattari E,** PORTUGAL E, JUNIOR RSM, et al. Acute Affective Responses and Frontal Electroencephalographic Asymmetry to Prescribed and Self-selected Exercise. Clinical Practice and Epidemiology in Mental Health 2016; 12: 108-19.

3- Lamego MK, **Lattari E,** Sá-Filho AS, et al. Aerobic exercise reduces anxiety symptoms and improves fitness in patients with panic disorder. Medical Express 2016; 3: 1-6.

4- **Lattari E,** Andrade ML, Filho AS, et al. Can transcranial direct stimulation improves the resistance strength and decreases the rating perceived scale in recreational weight-training experience? Journal of Strength and Conditioning Research.2016; 30(12): 3381-87.

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8- Machado S, **Lattari E**, Paes F, et al. Mental Practice Combined with Motor Rehabilitation to Treat Upper Limb Hemiparesis of Post-Stroke Patients: Clinical and Experimental Evidence. Clinical Practice and Epidemiology in Mental Health 2016; 12: 9-13.

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12- Portugal EMM, **Lattari E,** Santos TM, et al. Affective responses to prescribed and self-selected strength training intensities. Perceptual and Motor Skills 2015; 121 (2): 465-81.

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14- **Lattari E,** Paes F, Machado A, et al. Chronic effects of aerobic exercise on panic disorder: a systematic review of randomized and non-randomized trials. Medical Express 2015; 2:.M150602.

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16- Machado S, **Lattari E,** Sá-Filho AS, et al. Is mental practice an effective adjunct therapeutic strategy for upper limb motor restoration after stroke? A systematic review and meta- analysis.. CNS & Neurological Disorders. Drug Targets 2015; 14:.567-75.

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18- Monteiro Junior RS, Cevada T, Oliveira BR, **Lattari E**, et al. We need to move more: neurobiological hypotheses of physical exercise as a treatment for Parkinson's disease. Medical Hypotheses 2015; 85: 537-41.

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1-Machado S, **Lattari E,** Kahn JP. Possible Mechanisms Linking Panic Disorder and Cardiac Syndromes In: Panic Disorder: Neurobiological and Treatment Aspects.1ª ed.: Springer, 2016, p. 185-202.

2- Machado S, **Lattari E.** Papel do exercício físico no tratamento da depressão maior em idosos In: Atividade Física e Envelhecimento Humano.1 ed., Rio de Janeiro: H.P. Comunicações Editora, 2015, v.1, p. 57-94.

Anexo II- Termo de Consentimento Livre e Esclarecido

Projeto: Influência do exercício aeróbico na atividade cortical, funções executivas e variabilidade da frequência cardíaca em pacientes transtorno de pânico

Declaração de Idade: Eu declaro que tenho mais que 18 anos e que participarei por livre vontade do projeto de pesquisa conduzido pelo Prof. Dr. Sergio Machado e Prof. Dr. Antonio Egidio Nardi do Laboratório de Pânico e Respiração – Instituto de Psiquiatria – IPUB/UFRJ.

Objetivo: Eu entendo que o objetivo deste projeto é investigar os efeitos agudo e crônico do exercício aeróbico nos sintomas de pânico, funções cognitivas e atividade cerebral.

Detalhamento da técnica: A avaliação neuropsicológica e a atividade eletroencefalográfica (EEG) são métodos seguros, indolores e não invasivos de mapeamento da atividade cognitiva e elétrica cerebral, respectivamente. Portanto, são mecanismos de investigação das atividades corticais. Já o exercício aeróbico é uma forma segura e não invasiva de intervenção física.

Procedimentos: Os pacientes serão randomicamente divididos em 2 grupos, um de exercício aeróbico de intensidade moderada e outro de intensidade baixa. Todos os pacientes poderão ser medicados ou não. No momento inicial, os pacientes serão submetidos a um exame de EEG em repouso de olhos fechados por 5 minutos, a um exame de potencial evocado visual e a uma avaliação psicológica e neuropsicológica. Durante o período de 12 semanas de tratamento com 3 sessões de exercício aeróbico por semana, os pacientes serão avaliados a cada 2 semanas, realizando novamente um EEG em repouso, um exame de potencial evocado e avaliação psicológica. Após o período de tratamento, os pacientes realizarão os mesmos exames e avaliações que no momento inicial. Além disso, será realizado um acompanhamento de 1 e 3 meses, onde os pacientes realizarão novamente todos os exames e avaliações.

Confidencialidade: Eu entendo que todas as informações coletadas no estudo são confidenciais e que meu nome não será divulgado em momento algum. Entendo ainda que toda e qualquer informação será utilizada somente para fins acadêmicos.

Riscos e benefícios: O desenvolvimento deste projeto e minha participação não me trarão qualquer benefício financeiro. Porém, a prática de atividade física proporcionará benefícios salutares, como por exemplo, melhora da capacidade aeróbica. No entanto, a realização do protocolo de exercício aeróbico pode causar leves dores musculares e fadiga no início do protocolo com posterior adaptação.

Liberdade para interromper a participação: A qualquer momento posso pedir para interromper minha participação na realização do presente estudo sem penalização alguma e que, se assim eu desejar, a responsável pelo estudo irá fornecer os resultados da minha participação em uma oportunidade futura.

Identificação dos responsáveis pelo estudo:

Profº. Dr. Sergio Machado. Laboratório de Pânico e Respiração – Instituto de Psiquiatria – (IPUB/UFRJ). Email: secm80@gmail.com.

Comitê de Ética do IPUB/UFRJ. Av. Venceslau Brás, 71 – 2º andar - FDS – Botafogo – Rio de Janeiro, RJ. CEP 22.290-2140. Fone: (21) 3873-5510.

_____ _____

Nome do participante Data de nascimento

_____

Assinatura do participante

Rio de Janeiro, _____ de _____ de _____

Anexo III- Parecer de aprovação do Comitê de Ética e Pesquisa

INSTITUTO DE PSIQUIATRIA
DA UNIVERSIDADE FEDERAL
DO RIO DE JANEIRO/ IPUB/

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: INFLUÊNCIA DO EXERCÍCIO AERÓBICO NA ATIVIDADE CORTICAL, FUNÇÕES EXECUTIVAS E VARIABILIDADE DA FREQUÊNCIA CARDÍACA EM PACIENTES COM TRANSTORNO DE PÂNICO

Pesquisador: Sergio Eduardo de Carvalho Machado

Área Temática: Novos procedimentos terapêuticos invasivos;

Versão: 1

CAAE: 19560713.8.0000.5263

Instituição Proponente: Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro/ IPUB/

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 512.995

Data da Relatoria: 20/08/2013

Apresentação do Projeto:

Estudo exploratório sobre a influência do exercício aeróbico moderado (comparado ao de baixa intensidade) sobre a atividade cortical, função executiva e variabilidade da freqüência cardíaca em pacientes voluntários com diagnóstico de transtorno do pânico. Projeto realizado em laboratório do IPUB/UFRJ, redigido de forma clara.

Objetivo da Pesquisa:

Avaliar os efeitos hipoteticamente positivos de um protocolo de exercícios aeróbios moderados sobre as três variáveis mencionadas. Os voluntários serão divididos em 2 grupos randomizados, que farão exercícios moderados OU leves, durante 12 semanas, e serão submetidos, a cada 2 semanas e ao final do período, a EEG de repouso, exame de potencial evocado visual e avaliação psicológica e neurológica.

Avaliação dos Riscos e Benefícios:

Riscos - os voluntários estarão sob acompanhamento médico (medicamentoso ou não), e serão excluídos pacientes de risco para atividade física. O risco do desconforto muscular é mencionado. A realização repetida do EEG e avaliação psicológica pode trazer desconforto emocional aos pacientes.

Endereço: Av. Venceslau Brás, nº 71, 2º andar - FDS
Bairro: Botafogo **CEP:** 22.290-140
UF: RJ **Município:** RIO DE JANEIRO
Telefone: (21)3873-5510 **Fax:** (21)2543-3101 **E-mail:** comite.etica@ipub.ufrj.br

Benefícios - a prática do exercício aeróbico sob orientação médica é supostamente benéfica para todos os pacientes, e, segundo a literatura mencionada no projeto, especificamente nos pacientes com transtorno de pânico. Os voluntários do grupo controle farão exercícios aeróbicos leves, beneficiando-se desta atividade.

Comentários e Considerações sobre a Pesquisa:

Trata-se de pesquisa que atende aos requisitos éticos e pode ser aprovada por este Comitê. É necessário que o pesquisador informe, adicionalmente, onde e como será realizado o recrutamento dos voluntários, de forma mais clara e objetiva do que está no texto do projeto.

Considerações sobre os Termos de apresentação obrigatória:

TCLE adequado. Recomenda-se que não se utilize jargão técnico no TCLE, mas o documento, no geral, é claro e adequado.

Recomendações:

Encaminhar ao CEP documento adicional detalhando a forma de recrutamento dos 40 voluntários da pesquisa.

Conclusões ou Pendências e Lista de Inadequações:

Projeto adequado às exigências do CONEP. Termos de apresentação obrigatória adequados. Necessário encaminhar esclarecimento sobre FORMA DE RECRUTAMENTO dos voluntários.

Projeto aprovado.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Sim

Considerações Finais a critério do CEP:

Projeto relatado em reunião do CEP (novembro de 2013). O pesquisador deve acrescentar informações mais detalhadas sobre o RECRUTAMENTO dos 40 voluntários da pesquisa.

O presente projeto, seguiu nesta data para análise da CONEP e só tem o seu início autorizado após a aprovação pela mesma.

Benefícios - a prática do exercício aeróbico sob orientação médica é supostamente benéfica para todos os pacientes, e, segundo a literatura mencionada no projeto, especificamente nos pacientes com transtorno de pânico. Os voluntários do grupo controle farão exercícios aeróbicos leves, beneficiando-se desta atividade.

Comentários e Considerações sobre a Pesquisa:

Trata-se de pesquisa que atende aos requisitos éticos e pode ser aprovada por este Comitê. É necessário que o pesquisador informe, adicionalmente, onde e como será realizado o recrutamento dos voluntários, de forma mais clara e objetiva do que está no texto do projeto.

Considerações sobre os Termos de apresentação obrigatória:

TCLE adequado. Recomenda-se que não se utilize jargão técnico no TCLE, mas o documento, no geral, é claro e adequado.

Recomendações:

Encaminhar ao CEP documento adicional detalhando a forma de recrutamento dos 40 voluntários da pesquisa.

Conclusões ou Pendências e Lista de Inadequações:

Projeto adequado às exigências do CONEP. Termos de apresentação obrigatória adequados. Necessário encaminhar esclarecimento sobre FORMA DE RECRUTAMENTO dos voluntários.

Projeto aprovado.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Sim

Considerações Finais a critério do CEP:

Projeto relatado em reunião do CEP (novembro de 2013). O pesquisador deve acrescentar informações mais detalhadas sobre o RECRUTAMENTO dos 40 voluntários da pesquisa.

O presente projeto, seguiu nesta data para análise da CONEP e só tem o seu início autorizado após a aprovação pela mesma.

COMISSÃO NACIONAL DE
ÉTICA EM PESQUISA

PARECER CONSUBSTANCIADO DA CONEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: INFLUÊNCIA DO EXERCÍCIO AERÓBICO NA ATIVIDADE CORTICAL, FUNÇÕES EXECUTIVAS E VARIABILIDADE DA FREQUÊNCIA CARDÍACA EM PACIENTES COM TRANSTORNO DE PÂNICO

Pesquisador: Sergio Eduardo de Carvalho Machado

Área Temática: Novos procedimentos terapêuticos invasivos;

Versão: 2

CAAE: 19560713.8.0000.5263

Instituição Proponente: Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro/ IPUB/

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 526.601

Data da Relatoria: 27/01/2014

Apresentação do Projeto:

O presente protocolo foi enquadrado como pertencente à(s) seguinte(s) Área(s) Temática(s) Especial(is): "Novos procedimentos terapêuticos invasivos.

No documento intitulado "PB_RELATORIO_PESQUISA_195.607.pdf", item introdução, lê-se: "Pacientes com transtorno de pânico (PD) apresentam uma variabilidade de frequência cardíaca (VFC) reduzida e uma hipoatividade no córtex préfrontal (CPF), a qual afeta negativamente o funcionamento das funções executivas. Tanto a angustia causada pelo pânico como a duração do episódio são inversamente proporcionais às medidas de VFC e de inibição cognitiva Devido a redução da ativação autonômica em pacientes com pânico, esses pacientes apresentam um modelo de controle cardíaco alterado caracterizado pela redução da VFC. Alguns estudos demonstram que há uma ligação entre o controle da regulação vagal cardíaca e a ativação de áreas do CPF eachou uma associação entre a VFC e atividade neuronal em áreas do córtex pré-frontal ventro medial (CPF vm). O CPF é uma área cerebral associada com as funções executivas, tais como sustentação da atenção, alternância cognitiva, memória de trabalho, inibição comportamental. Dessa forma, a redução na atividade dessa região compromete suas funções. Portanto, a VFC parece refletir na atividade do CPF. A função executiva parece mais sensível do que as outras

funções cognitivas ao treinamento aeróbio. A hipótese de função executiva foi proposta com base em evidências que o exercício aeróbico seletivamente melhora o desempenho de idosos em tarefas de funções executivas e leva a um aumento correspondente na atividade do córtex pré-frontal. Enquanto a maioria dos achados, até agora, apoia os benefícios relacionados ao exercício do funcionamento executivo dentro de populações saudáveis envolvendo adultos mais velhos, novas evidências apontam que a prática regular de exercícios aeróbicos também pode ser benéfico para esse funcionamento na idade adulta jovem. Dado o aumento do sedentarismo da sociedade ocidental, é de grande interesse que os profissionais de saúde investiguem cuidadosamente a relação entre exercício e funcionamento executivo ao longo da vida. Tem sido estabelecido que pacientes com TP tem um padrão alterado no controle cardíaco, caracterizado por a variabilidade da frequência cardíaca reduzida. A VFC de pacientes com TP é reduzida tanto em condições de repouso quanto em ataques de pânico, o que indica que a TD está associada com controle cardíaco anormal em ambos estados tônico e fásico. A VFC parece refletir a integração da frequência cardíaca (FC), as emoções e as funções cognitivas de ordem superior exigidas para a execução de uma conduta flexível e dirigida a uma meta. Embora uma variedade de fatores influenciem a FC e a VFC, o sistema nervoso autônomo (SNA) é considerado a mais importante delas, através do qual o ramo parassimpático exerce um controle inibitório tônico sobre o coração através do nervo vago. Uma série de estudos tem relacionado o controle de regulação vagal cardíaco com a ativação de áreas do córtex pré-frontal. Em recente meta-análise, encontraram associações significativas entre a VFC e a atividade neuronal em áreas do CPF ventromedial. O CPF é a região cerebral mais associada à funções executivas, como atenção sustentada e dividida, memória de trabalho, inibição e flexibilidade mental geral. Consequentemente, uma redução na atividade do CPF estaria relacionada à déficits nas funções executivas. Como a VFC parece refletir a atividade do CPF, seriam esperadas associações entre a VFC e medidas de funcionamento executivo. Até o momento, existem muitas evidências mostrando que há alterações relacionadas com desempenho na VFC durante a avaliação de habilidades executivas, e que a VFC diminui durante essas avaliações."

Objetivo da Pesquisa:

"Devido a escassez de evidências, o objetivo do presente estudo é verificar os efeitos agudos e crônicos de um protocolo de exercício aeróbico de intensidade moderada sobre a VFC, funcionamento executivo e atividade cerebral em pacientes com TP. Mais especificamente: 1 - Investigar os efeitos agudos e crônicos do exercício aeróbico de intensidade moderada sobre a

VFC em pacientes com TP comparados ao grupo controle. 2 - Verificar os efeitos do exercício aeróbico de intensidade moderada sobre o funcionamento executivo em pacientes com TP comparados ao grupo controle. 3 - Investigar os efeitos agudos e crônicos do exercício aeróbico de intensidade moderada sobre a atividade cerebral em pacientes com TP comparados ao grupo controle. 4 - Correlacionar os achados da VFC, do funcionamento executivo e atividade cerebral com a prática de exercício aeróbico de intensidade moderada em pacientes com TP comparados ao grupo controle. 5 - Analisar se existe uma relação linear entre a prática de exercício aeróbico de intensidade moderada e a VFC, funcionamento executivo e atividade cerebral em pacientes com TP comparados ao grupo controle."

Avaliação dos Riscos e Benefícios:

Conteúdo não analisado pela CONEP.

Comentários e Considerações sobre a Pesquisa:

O presente estudo mostra que pacientes com transtorno de pânico (PD) apresentam uma variabilidade de frequência cardíaca (VFC) reduzida e uma hipoatividade no córtex pré-frontal (CPF), que afeta negativamente o funcionamento das funções executivas. Devido a redução da ativação autonômica em pacientes com pânico, esses pacientes apresentam um modelo de controle cardíaco alterado.

O desenho do presente estudo é verificar os efeitos agudos e crônicos de um protocolo de exercício aeróbico de intensidade moderada sobre a VARIABILIDADE DA FREQUÊNCIA CARDÍACA (VFC), funcionamento executivo e atividade cerebral em pacientes com TRANSTORNO DE PÂNICO (TP). Portanto, de acordo com a resolução CNS 466/2012, o desenho do estudo, faz com que o protocolo em análise não se enquadre na área temática "Novos procedimentos terapêuticos invasivos".

Considerações sobre os Termos de apresentação obrigatória:

Não se aplica.

Recomendações:

Não se aplica.

Conclusões ou Pendências e Lista de Inadequações:

Diante do exposto, a CONEP entende que o protocolo de pesquisa em tela não se enquadra na Área Temática Especial "Novos procedimentos terapêuticos invasivos" (considerando as informações do item IX.4 da Resolução CNS nº 466/2012), não cabendo a sua análise ética à

COMISSÃO NACIONAL DE ÉTICA EM PESQUISA

CONEP, mas apenas ao CEP.

Situação do Parecer:

Devolvido

Considerações Finais a critério da CONEP:

Diante do exposto, a Comissão Nacional de Ética em Pesquisa - CONEP - delibera pela devolução do protocolo de pesquisa ao Comitê de Ética em Pesquisa - CEP, por não se enquadrar em nenhuma das áreas temáticas descritas no item IX.4 da Resolução CNS nº 466/2012.

Situação do Parecer: Devolvido.

BRASILIA, 11 de Fevereiro de 2014

Assinador por:
Jorge Alves de Almeida Venancio
(Coordenador)

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