INSTITUTO DE PSIQUIATRIA - IPUB

Centro de Ciências da Saúde - CCS

Universidade Federal do Rio de Janeiro

EFEITOS DE DIFERENTES TIPOS DE EXERCÍCIOS AERÓBICOS SOBRE O ESTADO PSICOAFETIVO E VARIABILIDADE DA FREQUÊNCIA CARDÍACA EM PACIENTES COM TRANSTORNO BIPOLAR.

Alberto Souza de Sá Filho

Rio de Janeiro

2017

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Tese de Doutorado submetida ao Corpo Docente do Programa de Pós-Graduação em Psiquiatria e Saúde Mental - PROPSAM do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários para a obtenção do Grau de Doutor em Saúde Mental.

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Tese de Doutorado

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DEDICATÓRIA

Aos meus pais, Luiza Sequeira Ferreira e Alberto Souza de Sá, que sempre incentivaram e ajudaram a percorrer o caminho até o momento.

A minha esposa Celaine que sempre me apoiou em meio a dificuldade dessa jornada.

Ao meu orientador e amigo Sérgio Machado pela tolerância em meio as minhas adversidades e ajuda em diversas etapas.

Aos amigos Eduardo Lattari, Eduardo Portugal, Bruno Viana e muitos outros que participaram ativamente de minha formação, ou que apenas ajudaram com uma única palavra para que pudesse continuar.

RESUMO

A presente tese exibe uma divisão em quatro diferentes artigos, e tem por objetivo em seu primeiro ponto revisar mecanismos fisiopatológicos relativos principalmente ao sistema monoaminérgico, bem como associar respostas agudas e crônicas derivadas do exercício a reduções na gravidade dos sintomas do TB. Neste sentido, uma relevante base de sustentação posiciona o exercício de característica aeróbia como um indutor de benefícios fisiológicos e comportamentais, reduzindo a gravidade dos sintomas. Parece ainda que a melhora no condicionamento cardiorrepiratório ($VO_{2Máx}$) pode ser uma importante via de proteção, na qual propiciaria a redução de tais sintomas. Um segundo ponto importante desenvolvido nesta tese trata especificamente de mecanismos neurobiológicos relativos a fisiopatologia do TB, e suas associações com alterações cognitivas, corticais e de biomarcadores. A literatura atual demonstra que os déficits cognitivos são comumente observados em todas as fases nos pacientes BD, independentemente de um estado remissivo. Esses déficits são atribuídos a mudanças funcionais, estruturais e metabólicas, particularmente na região do córtex pré-frontal, hipocampo e amígdala, juntamente com as conexões entre eles. Além disso, fatores neurotróficos derivados do cérebro ou desequilíbrio entre citosinas pró/anti-inflamatórias podem afetar o funcionamento cognitivo. Além dos pontos supracitados, a presente tese revisa em seu terceiro artigo evidencias específicas da influência do exercício aeróbio e seus efeitos diante do TB, ficando claro que tais respostas apesar de positivas ainda precisam ser melhor delineadas e principalmente controladas, pois problemas metodológicos dificultam a precisão dos resultados. Além do mais, diferentes configurações do exercício aeróbio sequer foram testados. Portanto, afim de contribuir para tais lacunas, o último artigo desta tese visa determinar os efeitos agudos do exercício aeróbio continuo vs. intervalado de alta intensidade sobre os níveis de ansiedade, ativação corporal, repostas afetivas, bem como, sobre alterações na variabilidade da FC (V_{FC}) entre treinados e sedentários, e bipolares. Ficou evidenciado uma redução significativa dos níveis de ansiedade pós exercício comparado a base ($p = 0,001$), existindo tendência do intervalado à promoção melhor perfil de ansiedade comparado ao contínuo. Além disso, o programa de exercício intervalado demonstrou superiores diferenças na ativação quando comparado ao grupo contínuo ($p = 0,000$) para todos os grupos amostrais. As respostas afetivas demonstraram semelhante padrão, sendo significativamente positivas e aumentadas pós exercício contínuo ($p = 0,000$) e intervalado ($p = 0,000$), porém com diferenças significativas entre o modo contínuo vs. intervalado ($p = 0,000$), tendendo o exercício intervalado a um alto TE para os grupos treinados e bipolares. Por fim, as repostas de VFC foram modificadas pós exercício, havendo redução do drive simpático observado a partir da medida RMSSD, LF, e LF/HF ($p = 0,001$), sem significativa reentrada vagal ($p > 0,05$). Não houve diferenças significativas entre grupos pós intervenção com exercício ($p > 0,05$). Conclui-se que existe uma relação inversa entre os níveis de $VO_{2Máx}$ e os sintomas do TB, e que a combinação entre exercício a medicamentos específicos poderiam afetar positivamente a gravidade dos sintomas promovendo influência sobre os sistemas monoaminérgicos, equilíbrio pró/anti inflamatório, e neurotrofinas. Apesar de observarmos redução do drive simpatico em pacientes com TB, o que poderia ser positivo para sintomas da doença, a literatura apenas caminha sob a ótica da aplicação do exercício físico, e pouco se sabe ainda acerca dos efeitos do exercício de característica intervalada nestes pacientes, cabendo investigação extensiva.

Palavras Chave: transtorno bipolar, exercício aeróbio, variabilidade da frequência cardíaca

ABSTRACT

The present thesis shows a division into four different articles, and its first objective is to establish possible pathophysiological mechanisms related mainly to the monoaminergic system, as well as to associate acute and chronic responses derived from exercise to possible reductions in the severity of TB symptoms. In this sense, a relevant support base positions mainly the aerobic exercise as an inducer of physiological and behavioral benefits, reducing the severity of the symptoms. In addition, it seems that the improvement in cardiorespiratory fitness (VO_{2Max}) may be an important protection route, in which it would facilitate the reduction of such symptoms. A second important point developed in this thesis deals specifically with neurobiological mechanisms related to the pathophysiology of TB, and its associations with cognitive, cortical and biomarkers alterations. The current literature demonstrates that cognitive deficits are commonly observed at all stages in BD patients, regardless of a referral status. These deficits are attributed to functional, structural and metabolic changes, particularly in the region of the prefrontal cortex, hippocampus and amygdala, along with the connections between them. In addition, neurotrophic factors derived from the brain or imbalance between pro and anti-inflammatory cytokines may directly affect cognitive functioning. In addition to the aforementioned points, this thesis reviews in its third article the specific evidence on the influence of aerobic exercise and its effects on TB, and it is clear that such responses regarding exercise still need to be better delineated and mainly controlled, since methodological problems accuracy of the results. Moreover, different configurations of aerobic exercise have even been tested. Therefore, in order to contribute to such gaps, the fourth and final article of this thesis aims to determine the acute effects of continuous (moderate) aerobic exercise (vs. high intensity interval on anxiety levels, body activation, affective responses, as well as on changes in HR variability between trained and sedentary participants (controls), and bipolar patients. In this study, there was a significant reduction in post-exercise anxiety levels compared to the baseline ($p = 0.001$), with a tendency of the interval to promote a better anxiety profile compared to the continuous one (moderate TE). In addition, the interval exercise program showed superior differences in activation when compared to the continuous group ($p = 0.000$) for all sample groups. The affective responses showed a similar pattern, being significantly positive and increased after continuous exercise ($p = 0.000$) and interval ($p = 0.000$), but with significant differences between the continuous vs. interval ($p = 0.000$), tending the interval exercise to a high TE for the trained and bipolar groups. Finally, the HRV responses were modified post exercise, with a reduction in the sympathetic drive observed from the RMSSD, LF, and LF / HF measurements ($p = 0.001$), without significant vagal reentry ($p> 0.05$). There were no significant differences between groups post intervention with exercise ($p> 0.05$). It was concluded that there is an inverse relationship between physical conditioning levels and TB symptoms, and that the combination of aerobic exercise with specific medications could positively affect the severity of the symptoms, promoting a significant influence on the monoaminergic mechanisms, pro/anti-balance inflammation, and the production of neurotrophins. Although we observed a reduction of the sympathetic drive in patients with TB, which could be positively related to the symptoms of the disease, the literature only comes from the perspective of the application of physical exercise, and little is known about the effects of the interval exercise in these patients, with extensive research.

Keywords: bipolar disorder, aerobic exercise, heart rate variability

SUMÁRIO

INTRODUÇÃO

O sedentarismo é um problema de saúde publica que acomete cerca de 31% da população mundial. Tal fator de risco é comumente observado em diferentes transtornos mentais, e diretamente associado aos sintomas do transtorno de humor bipolar (TB) [1]. É bem descrito na literatura também que um baixo valor do consumo máximo de oxigênio ($VO_{2Máx}$) [2], representaria um prognóstico negativo para saúde, resultando em mais graves manifestações sintomaticas da doença[1], bem como, maior incidência de comorbidades associadas, e um risco aumentado de mortalidade [3, 4].

É amplamente suportado que alterações no sistema de neurotransmissão monoaminérgico seja uma das principais causas do TB [5-8], e o sedentarismo um dos mecanismos precipitadores de tal fenômeno. No entanto, a essa relação inserem-se outras amplas manifestações fisiológicas, tal como, perda da função autonômica e alterações no balanço simpatovagal, processos inflamatórios generalizados crônicos [9-12], superativações do eixo hipotálamo-pituitária-adrenal (HPA) [13], e a redução da expressão de fatores de crescimento associados a processos neurogênicos [14-17], que por fim culminam na redução da densidade neuronal, e eficiência sináptica [18-21]. Esse espectro negativo do TB parece ocorrer independentemente do momento cíclico da doença. Entretanto, a neuroprogressão é capaz de ser parcialmente atenuada diante do uso de medicamentos específicos como "*Lithium*" [22], e mais contemporaneamente, pela inclusão de rotinas de exercício aeróbio [23-28].

Neste sentido, os efeitos agudos e/ou crônicos promovidos pelo exercício aeróbio ao condicionamento físico são bem definidos e claros na literatura em praticantes saudáveis, porém, sobre a saúde de pacientes com transtorno de humor, ainda que alguns desfechos

possam ser extrapolados, estes precisam de maior fortalecimento. Por exemplo, é consistente a base de evidências que demonstram a promoção de efeitos ansiolíticos e a melhora sobre o estado de humor em pacientes com depressão unipolar moderada [29-31]. Inclusive, o estudo de Blumenthal *et al*.[23] sugere que o exercício aeróbio regular possa se estabelecer como uma estratégia complementar ao tratamento da depressão, uma vez que seus efeitos tenham trazido iguais reduções de sintomas, porém com um tempo de ação mais demorado, comparado a apenas o uso da sertralina, que demonstrou rápida ação. Além disso, parece que apenas uma sessão de exercício aeróbio de moderada intensidade seja capaz de melhor regular mecanismos relativos ao sistema monoaminérgico. Mais especificamente, a síntese e liberação de precussores de 5HT (serotonina) [30, 32], a produção de opióides endogenos, ambos exibindo grande pertinência na regulação do humor, e aumento da expressão e de regulação dos níveis basais de fatores de crescimento derivados de cérebro (BDNF) [14, 17, 33, 34] e do endotélio (VEGF) [35, 36], favorecem a plasticidade e a regulação do metabolismo neuronal.

Segundo esse raciocínio então, faz sentido pensar que o exercício físico em pacientes bipolares poderia exibir o petencial terapeutico necessário para influenciar positivamente os efeitos deletérios proporcionados tanto por comorbidades associadas ao baixo condicionamento físico, quanto aos diretamente atribuídos pelos sintômas da doença[30, 37, 38]. As evidências específicas com pacientes bipolares, apesar de metodologicamente questionáveis, exibem uma tendência a um efeito positivo sobre os sintômas[27, 31, 39], especificamente para o exercício de carácter aeróbio. Ng *et al*.[27] em estudo retrospectivo reportaram redução dos escores das escalas de estresse ($p = 0,01$), ansiedade ($p = 0,002$), e depressão ($p = 0,048$) (DASS) em pacientes com TB participantes de programas de

caminhadas regulares, sem quaisquer alterações sobre as escalas de impressão global clínica (CGI). A mais nova revisão sistemática sobre a influência do exercício e o TB produzido por Aguiar Melo *et al*. [40] conclui que o exercício nestes pacientes foram associado a melhor capacidade funcional, qualidade de vida, e principalmente redução de sintomas depressivos, corroborando com os resultados encontrados por Ng *et al*.[27], assim como, a meta-análise de Pershall *et al*. [25].

Portanto, a partir desses resultados preliminares, e outros transferidos de sintomas e fisiopatologias correlatas, o exercício aeróbio contínuo de intensidade moderada parece ser uma solução de influência direta ou complementar a primeira linha de tratamento [23, 25, 41]. Entretanto, apesar desse entendimento acerca dos benefícios preliminares, existem algumas questões chave a serem questionadas: Será que tal modelo de exercício moderado proporciona uma percepção afetiva positiva a ponto de modificar o estado de humor e favorecer a adesão ao exercício? Além disso, porque diferentes modelos e configuração do exercício aeróbio ainda são pouco explorados até hoje em pacientes com transtornos mentais? Diante da ampla gama de possibilidades e designs que podem ser extraídas de um programa de exercícios aeróbio [42-44], talvez melhores respostas afetivas, de humor, ansiedade, e autonômicas, pudessem ser proporcionada[45].

Uma das alternativas possíveis seria a administração de exercícios de caráter intervalado, possibilitando pequenos períodos de intensidades vigorosas (70-75% do $VO_{2Máx}$), ou próximas ao $VO_{2Máx}$ (90-100% do $VO_{2Máx}$), intercalados com períodos de recuperação[42-44, 46]. A esta estratégia quando em elevadas intensidades, da-se o nome de HIT (do inglês *"high intensity interval training"*)[42, 44, 46]. Tal proposta é capaz de reduzir substancialmente o impacto fisiológico e o esforço percebido decorrente da

magnitude da carga de trabalho, e ainda proporciona superiores ganhos ao condicionamento cardiorrespiratório ($VO_{2Máx}$)[44, 46, 47]. Em apenas curtos períodos de exercício (até 90% menores comparados a estratégia contínua), observa-se a melhora da sensibilidade a insulina em pacientes portadores de diabetes tipo II [48], melhor regulação ponderal da massa corporal em pacientes com síndrome metabólica, e a redução do risco de mortalidade e a reabilitação de pacientes acometidos por doenças coronarianas estáveis. Portanto, esta se estabelece como uma estratégia "tempo-eficiente"[42, 44].

No entanto, apesar de parecer uma estratégia promissora com inúmeros benefícios agregados, merece ser destacado que HIT quando mal alinhado a proporções de tempo x intensidade, pode gerar consequências extremamente negativas, como o estresse mental aumentado, elevação dos níveis de ansiedade, um estado afetivo negativo, humor deprimido, em suma, agravando os sintômas do TB [49]. Por isso, seguindo o entendimento de que a percepção de esforço é delineada sobre a inter-relação entre tempo de estímulo x intensidade, isto é, se proporcionarmos um tempo de estímulo reduzido com elevada intensidade (90-100% do $VO_{2Máx}$), a resposta desse cálculo será uma percepção média de esforço, semelhante a proporcionada por uma intensidade moderada [49]. Então, para tais respostas faz-se necessário a investigação intensiva das influências do modelo HIT sobre a ótica do TB.

OBJETIVOS

Os objetivos da presente tese são estabelecer a relação entre exercício físico de característica aeróbia e o transtorno bipolar (TB), bem como, atualizar sobre a fisiopatologia da doença para que possamos inferir sobre potenciais alterações provenientes do exercício

físico sobre os sintomas e comorbidades relativas ao TB. Por fim, faz-se necessário determinar os efeitos agudos de um protocolo de exercício aeróbio contínuo de moderada intesidade vs. intervalado de alta intensidade (HIT) sobre a redução dos sintômas de ansiedade, nível de excitação corporal, respostas afetivas, além de alterações sobre a variabilidade da frequência cardíaca em praticantes treinados, sedentários, e bipolares.

JUSTIFICATIVA

Embora alguns estudos tenham mostrado os possíveis benefícios do exercício aeróbio em pacintes com TB, a literatura carece de base consistente acerca do efeito do exercício controlado em seu volume e intensidade nesta população. O exercício aeróbio parece interferir positivamente no funcionamento de algumas funções fisiológicas em pacientes com transtornos neuropsiquiátricos, o que fortaleceria essa estratégia como uma importante forma profilática não farmacológica de tratamento para o TB. Mais pesquisas sobre esses temas devem ser realizadas com o intuito de melhorar nossa compreensão sobre a magnitude do efeito principalmente do exercício intervalado controlado em pacientes dessa natureza, justificando o racional teórico e prático do presente estudo.

ARTIGO 1

EXERCISE IS MEDICINE: A NEW PERSPECTIVE FOR HEALTH PROMOTION IN BIPOLAR DISORDER

EXERCISE IS MEDICINE: A NEW PERSPECTIVE FOR HEALTH PROMOTION IN BIPOLAR DISORDER – A NARRATIVE REVIEW

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ABSTRACT

There are many reasons to believe that physical exercise, especially aerobic exercise character exerts significant effects on health promotion and the consequent reduction of the severity of bipolar disorder (BD). In this sense, increased cardiorespiratory fitness (VO_{2max}) can be an important means of protection and a reducing potential of physical and mental damage, ie, comorbidities, however, this variable also has little value outstanding under the mental disorder. Similar effects in reducing the symptoms of the mental disorder (MD) are also reported in the literature compared the action of drugs, the aerobic exercise sessions, demonstrating the potential of exercise in the control and mood stabilization. The exercise seems to induce significant changes in monoaminergic after, and with long-term training, and work with a threshold of exercise can modulate positive effects on mood. We could speculate that exercise may be a way of maintaining euthymia in the case of BD, making it less vulnerable patient to stay longer at a time of neutrality. Future research is needed to adopt a training strategy that is both time efficient in the different areas and adequate for the population in question.

Keywords: Bipolar disorder, monoaminergic system, catecholamines, exercise, high intensity interval training.

INTRODUCTION

The pathophysiology of bipolar disorder (BD) is closely related to changes in physical and neurological status [1-4]. BD patients commonly exhibit changes in cortical pattern [5-11], neuroanatomical [12-18], cognitive [2, 19-22], and hormonal [23, 24], about mood, as well as comorbid conditions that are triggered by stress and physical inactivity [4, 25]. This limiting disease observed spectrum is similar to other mental disorders (MD), and it is usually treated by drug interventions such as lithium in BD. However, there are many reasons to believe that the intervention from exercise to exercise similar to drugs used in patients with MD [26-28], especially anxiolytic and antidepressant effects of exercise effect [29-31].

Assessing the literature extensively, reporting evidence that physical exercise especially the aerobic character, plays an important role in the regulation of the symptoms of BD [26-28, 32-40]. Some associations are proposed between bipolar patients and exercise, and it is observed inverse relationship between the level of physical activity and body mass index, symptoms, and comorbidities [25, 41-43]. These responses are consistently demonstrated in the literature with healthy population and may in part be extrapolated to patients with MD [44, 45]. Despite this understanding, the state of the art so far has weak foundations on the subject, still lacking important evidence to clarify the mechanisms of improvement resulting from the routine practice of an exercise program [3, 26-28, 32, 33, 36, 46-50].

Hypotheses for improving symptoms of BD are constantly tested and postulated, but largely hindered by serious methodological problems of control between dose and response exercise, making the results inconclusive. For example, Ng, Dodd, and Berk [32] observed the effect of 40 min walking in patients with BD on the symptoms of the disease assessed by

scales of anxiety, depression, and stress (DASS) and global improvement (CGI-I and CGI-S). Based improvement of symptoms was observed in the reduction of these scores, results that are similar to other positively favoring treatment with exercise studies. However, the lack of methodological consistency and exercise control reduces the potential for inference on the results.

Regardless of methodological problems, chronic benefits of exercise tended to yield satisfactory results, and the key to curb BD neuroprogression seems to be linked to the regulation of basal levels of brain-derived neurotrophins, such as BDNF [37, 38, 51-54], which consequently impacts on reducing stress via the HPA axis, reducing allostatic load [55], and a synaptic favoritism [35, 53, 56, 57]. However, other physiological mechanisms may put the aerobic exercise as an important modulator of the release and reuptake of monoamine neurotransmitters in the classic type, specially, dopamine (DA), serotonin (5HT) and norepinephrine (NE), possibly present in the pathophysiology of BD and as a reducing physical and mental stress from the release of endogenous opioids [58-64]. The objective of this review was to establish the pattern of response of exercise on the pathophysiology of BD, relating the possible mechanisms, as well as, create hypotheses based on acute and chronic responses of the exercises, and establish future perspectives with the focus of the exercise as an important and innovative model of treatment for BD and MD.

HEALTH PROMOTION BY PHYSICAL EXERCISE FOR BIPOLAR DISORDER

Patients with BD or other MD have a history of severe inactivity and sedentary lifestyle, as well as extensive use of alcohol or drugs [1, 65, 66]. Evidence also suggests a high prevalence of metabolic syndrome among patients with BD [43]. The poor employee life

style, as well as disorders of eating character [25], corroborate expanding the deleterious effects presented in the pathophysiology of the disease as well, exacerbating comorbidities associated with MD [43, 66]. There is then an inverse relationship between level of exercise and multifactor such as body mass index, symptoms, or comorbidities, in patients with MD [25, 42], as in healthy people [44, 45, 67].

Given this scenario, it is clear that disciplinary actions based on different domains and needs, are important for the control of physical and mental symptoms of the disease. Therefore, aerobic exercise has been extensively studied and recommended as an intervention for treating co-adjuvant or adjuvant to the BD [3, 32, 33, 40, 48, 49]. Its effects can significantly affect cardiorespiratory [68, 69] and metabolic function (systemic and cerebral metabolism in regions such as the prefrontal cortex, and hippocampus), about mood swings [54, 70], as well as, improved synaptic efficiency or neurogenesis [37, 53, 57, 71]. However, these responses are still inconclusive or underused in patients with different MD and in particular to the BD. In general, the hypotheses studied tend for a positive effect of exercise on regulation of symptoms and health in these patients.

About a distinct perspective of commonly presented in the medical literature, although still little studied in patients with MD [72], it seems that increased cardiorespiratory fitness (VO_{2max}) can be a way of protecting health and reducing potential physical and mental damage. For example, every 1 MET (metabolic equivalent = 3.5 $mL.kg.^{-1}min^{-1}$ increased the maximum oxygen consumption, this can reduce about 13% relative risk of all-cause mortality, and also contribute to improvement of systemic metabolic profile (blood pressure, lipoproteins, glucose). More recently, Whiteman *et al.* [41] demonstrated significant and positive relationship between the level of $VO_{2max,}$ BDNF, cognitive and

memory tasks. The recall, BDNF, brain-derived neurotrophin, exerts great influence on neuronal plasticity [37, 53], mainly on the hippocampal region [57], and is a highly expressed substance through exercise, and dependent on the given intensity. In addition, aerobic exercise act selectively on cognitive process (age-dependent) [73], and people with higher VO_{2max} tend to get higher cognitive performance during and after training [74]. It is observed then that the variable in question should be a more appropriate position with respect to the MD and BD, since it has a direct impact on the disease pathophysiology. Figure 1 shows possible general mechanisms of influence of exercise on mental illness.

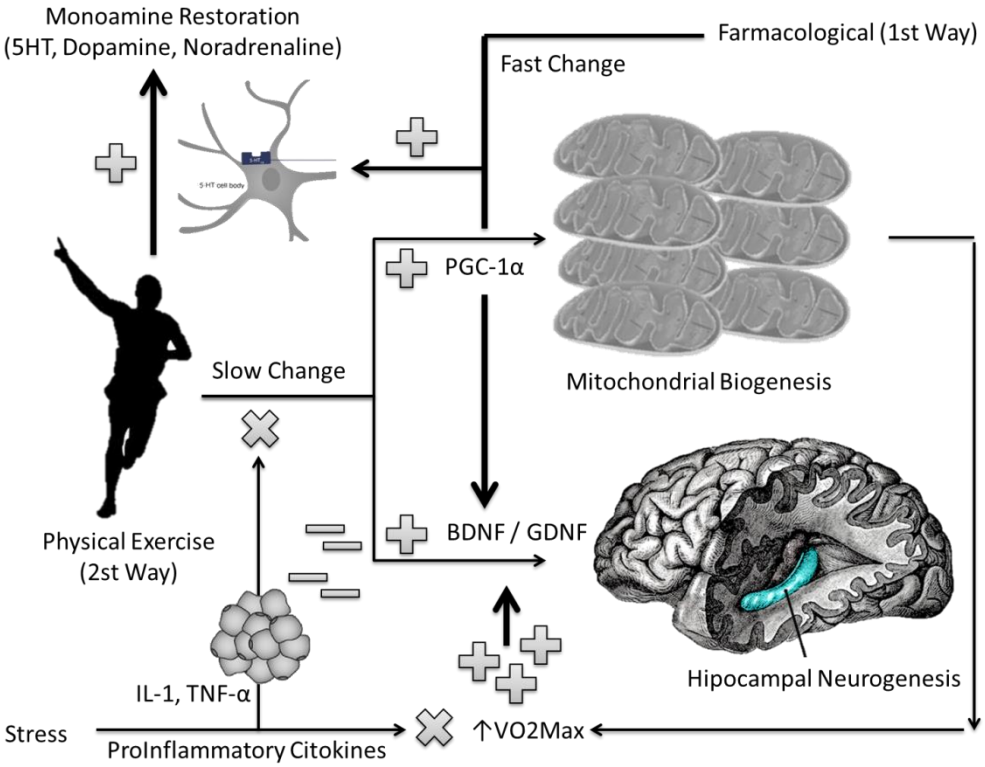

Figure 1. possible general mechanisms of influence of exercise on mental illness.

Moreover, it is known that the lifestyle of people with serious MD contributes to low participation and adherence to training programs. Thus, patients with BD are not normally included with the minimum recommendation proposed by the American College of Sports Medicine (ACSM), 150 min.week $^{-1}$ of moderate aerobic activity or 60 min.week $^{-1}$ of vigorous activity to promote health [75]. An inverse dose-response relationship between the level of exercise practiced and the severity symptoms, and emotional well-being, adds a negative prognosis for health in patients with BD [72]. So, inclusion strategies/progression, and mostly controlled in relation to dose-response, and enabling adherence of patients with BD in aerobic exercise programs strategies is a gap still to be structured.

EXERCISE IN THE CONTEXT OF BIPOLAR DISORDER

The literature reports the benefits of exercise on reducing the symptoms of BD. However, it is commonly observed in several studies a lack of control of the exercise, or the relationship of dose x response, which undermines the consistency of the completion of studies. A meta-analysis of Pearsall *et al.* [27], for example, met a few randomized controlled studies that made use of exercise as therapy in patients with different MD, including BD. The authors observed a moderate effect size (ES) on the levels of physical exercise, however, no significant results were found on the negative *(p* = 0:40) positive symptoms *(p* = 0:12) or. In another study, Ng, Dodd and Berk [32], for example, evaluation scales used for anxiety, depression, and stress (DASS), plus a scale of global improvement (CGI-I and CGI-S). 40 minute walk in patients with BD have provided positive results only in the DASS scores evaluated in the participants (mean ± standard deviation; (base-line) 58.2 ± 25.4> (post-exercise) 23.0 ± 14.9).

More favorable and consistent with the practice of aerobic exercise results are observed in studies focusing on comorbidities, however, the outcomes of the symptoms remain controversial. Daumit *et al.* [48] for example, evaluated weight reduction in patients with BD and subjected 291 patients (22% in the bipolar sample), the group of programs in cognitive and behavioral therapies, food restructuring exercise groups during a follow up of 18 months . By the sixth month, the intervention group reduced 1.8 kg while the control changed only 0.3 kg. Throughout the remainder of treatment, group intervention reduced a total of 3.4 kg, and the control is not changed. Other interventions evaluated changes on the symptoms and comorbidity with bipolar patients and found no significant effects on reducing body weight or any derived variable. Nonetheless, there was improvement of the scores of scales of depression and mania after 20 weeks of intervention with exercise and behavioral therapies (MADRS - *Montgomery Asberg Depression Rating Scale,* YMRS - *Young Mania Rating Scale,* CGI-Mania - *Clinical Global Impression Mania Subscale,* CGI -Depression - *Clinical Global Impression Depression Subscale,* among others) [39]. Table 1 shows the main chronic benefits with exercise intervention.

Based on the presented data, and similar studies with a use of different MD, e.g., unipolar depression, anxiety or schizophrenia, that have particular pathophysiological schemes, it is assumed that the mechanisms responsible of the reduction of symptoms from the intervention exercise are common among themselves. Aerobic exercise enables you to change or improve metabolism specifically on structures such as the pre frontal cortex (PFC) and hippocampus, better regulated monoaminergic pathways, or new synaptic connections (regardless of the specificity of the disease). The BD-specific mechanisms need to be better

understood, and next topic is based on physiological, assumptions and relationships created processes to try to explain and enhance our understanding of the pathophysiology of BD.

Table 1. Studies assessing benefits of exercise interventions in patients with bipolar disorder.

Author	Methods Features				Exercise Features			Outcomes		
	n	Control Group	Med	Therapy	Exercise Protocol	Level of Exercise	Total Weeks	Criteria ACSM	Bipolar Symptoms	Exercise Benefits
Ng, Dodd, and Berk. [32]	49	Y (n=35)	?	N	Walk (40 min)	Free	?	Y	↓	↓Stress, depression and anxiety Symptoms
Sylvia *et al*. [39]	5	N	?	Y (cogitive, lifestyle)	? (30 min) 5x/week	Moderate Effort	± 20 Weeks	Y	↓	↑Mood, ↓weight, cholesterol and triglycerides
Daumit *et al.* [3]	64	Y (n=147)	Y	Y (lifestyle)	?	Moderate Effort	± 72 Weeks	?	?	↓Weight loss
Verhaeghe *et al*. [50]	173	Y (n=50)	Y	Y (social + cognitive)	Walk (30 min) 3x/week	Moderate Effort	± 10 Weeks + 6 month (follow up)	Y	↔	↔ positive symptoms, physical and mental component scores
Van Citters *et al*. [40]	76	N	Y	Y (behavior, lifestyle, psycological)	?	Vigorous Effort	± 36 Weeks	?	↓	↓Waist circumference, blood pressure, exercise time, severity of negative symptoms

Subtitles: Med - medicines; Criteria ACSM - subjects ou studies covered the minimum recomended; Y - yes; N - no; ? - non reported; ↓ - significative reduction on symptoms of BD; ↔ - non significative change; ↑ - significantive increase on mood.

EXERCISE INDUCED-MECHANISMS ASSOCIATED WITH THE PATHOPHYSIOLOGY OF BIPOLAR DISORDER

The state of the art shows that aerobic exercise can provide anxiolytic, antidepressant effects [29, 30], and anti-inflammatory [76], and promote change on the synthesis of monoamine neurotransmitters [61, 63, 77-79] and neurotrophins types during exercise [51, 80-82]. For patients with MD, the studies on the subject show commonly a chronic imbalance in the operating system specific monoamine neurotransmission for each disease [59]. Pharmacological treatment appears to induce the restoration of normal levels of these substances in the brain [83, 84]. Accordingly, considering that the use of specific drugs is the primary route for treatment of MD, this can often cause side effects or the patient is refractory to such medication. Aerobic exercise could be an alternative co-adjuvant, or even the main treatment of the MD without the possible side effects [26]. To prove the positive effects of aerobic exercise, Blumenthal *et al.* [26] compared a 16-week intervention in elderly patients with major depression divided into three groups: a) treated with sertraline, a medication 5HT reuptake inhibitor, b) regular aerobic exercise, c) combination of medication and exercise. The authors reported similar effects between strategies for the decline in depression scores (Hamilton Rating Scale for Depression, Beck depression inventory), however, treatment with medication only promoted faster response for reducing symptoms of depression in patients with greater severity than aerobic exercise. In subjects with less severe symptoms, the combined between aerobic exercise and medication, strategies promoted greater decline on the scores of the depression. Thereafter, the same researcher group conducted a treatment in 156 adults diagnosed with major depression for 4 months, plus 6 months of follow up. Patients were divided in three groups

of similar intervention detailed in previous study (aerobic exercise, sertraline therapy, or a combination of exercise and sertraline), and also showed significant improvement in symptoms of major depression (reduction ranging between 60.4 a 68.8%) after 4 months [85]. After the follow up, interestingly, the findings indicated increased chance of recovery, or lower frequency of depression episodes in patients that participated only the aerobic exercise group compared to treatment with sertraline, and the combined group. Moreover, the chance of relapse during this period also was lower for aerobic exercise group compared to other groups [85].

Trying to explain how aerobic exercise acts to modulate the imbalance monoaminergic regulation, we must first understand that in bipolar, this imbalance is state-dependent, ie, associated with the cycle time of the patient (mania or depression) [86]. It is known that the serotonergic system - 5HT has extensive involvement in the pathophysiology of depression [87, 88], and drugs that increase extracellular concentration of 5HT from inhibition of their reuptake by presynaptic neurons are the first line in the prescription. The exercise seems to induce similar effects, and the intensity of training can exercise some influence gene expression of this substance. Gomez-Merino *et al.* [60], although still controversial, observed significant increases in animal model of 5HIAA (marker of serotonin levels) and extracellular 5HT in the hippocampal region after 90 min of recovery from aerobic exercise. Other studies with animal model showed increases of 47% in the extracellular concentration of 5HT, returning to baseline values after the first hour of recovery [79]. The administration of tryptophan (a precursor of 5HT) 60 min prior to acute exercise appears to promote an increase in the length of exposure to 5HT (100% increase) and 5HIAA (83%) [79].

Obviously, we must evaluate this information cautiously, since this increased availability of 5HT from the exercise, does not necessarily lead to greater interaction "key receiver", and increased the activity of mechanism. However, it can be said that exercise induces an up-regulation of 5HT receptors (subunits 1 and 2), and also a hypersensitivity of the $5HT_2$ receptors, suggesting the operation of the antidepressant mechanism modulated by exercise [46]. Amplifying the positive effects of exercise, it seems that the 5HT neurotransmitters type and neurotrophins such as BDNF are also closely related, and have their signs in order to co-regulate, promoting neuronal plasticity in several brain areas. For better understanding of this mechanism see revision proposed by Mattson and Martin Maudsley [52].

Evidence also supports that dopaminergic system (DA), due to its excitatory nature, also has particular importance for the manic phase, like the noradrenergic system (NA) BD [59]. It is understood that antagonists of DA receptors drugs are known to produce an anti-mania effect, however, when the process of DA and NA are stimulated, for example, by the administration of amphetamine-like effects mania or even psychosis are manifested in healthy subjects, and expanded in euthymic patients [58, 89]. Within this scenario, the literature is still not entirely clear regarding the magnitude or extent of influence of the DA circuit on the BD, however, it appears that both DA and NA neurotransmitters are found in higher concentrations in the basal transition of depression to mania [86].

Historically the behavior of this neurotransmitter DA, as well as 5HT, were studied in the context of central fatigue, the major influence on the ability to perform prolonged exercise [90]. Aerobic exercise seems to induce changes on the functioning of the DA pathways, especially in tasks that require motor control [91]. The DA system in exercise is

highlighted by a high volubility in their concentrations, as well as metabolites DOPAC (3,4-dihydroxyphenylacetic acid) and HVA (homovanilic acid) in regions of the hypothalamus and striatum during and after aerobic exercise [61]. Because we are dealing with a manic state in patients with BD, we will have to agree that an expected positive effect with exercise at this stage of the cycle would be a significant reduction in the levels of DA and NA after exercise, a kind of latency. Acutely literature provides a reduction in post-exercise sympathetic drive, leading by example, lower levels of catecholamines, less sympathetic neural activity via mediation by GABA receptors, and increased activity of the parasympathetic tone [62, 63, 92]. Moreover, subjects with greater physical fitness, tend to more rapid inactivation of plasma catecholamines by sulfation than less trained [63]. Therefore, it is assumed that autonomic changes after acute exercise may contribute to trigger an "anti-mania" state, and the fitness level may be an important factor to be considered.

Within this perspective, extensively analyzing studies of fatigue and exercise there is evidence that in exhaustive or prolonged exercise to fatigue, a reduced sympathetic drive also suppress the levels of DA and NA released in the bloodstream [90]. However, microdialysis studies in animals support an intensity threshold point (3 to 6 m / min - moderate effort) in the release of DA, DOPAC, HVA in the striatum were minimally elevated during exercise [61]. The administration of higher training intensities (above threshold moderate work) led to increased extracellular DA concentrations, remaining free for a longer time [61]. In healthy humans it is still controversial, Wang et al. 2000 [64], twelve volunteers were evaluated using the technique of positron emission tomography (PETscan) and showed unchanged results. The subjects ran at an average speed of 8.7 km / h with 3.3º tilt for 10 to 15 min (average total distance of 4.3 km), with no changes in the availability of D2 receptors

after exercise in the cerebellum and putamen (baseline, 4:17 ± 12:29 - after exercise, 4:22 ± 0.34 - p = 0.06). Additional human studies are needed to clarify the true effect of DA as well, which exercise conditions would be more interesting to such patients.

The connection system in the pathophysiology of BD seems not to extend only to monoaminergic changes, in other words, evidence suggests intimate association with a mutant variant gene (single nucleotide polymorphic region in intron 8) 1-subunit of dopamine transporter (DAT1), suggesting multiple susceptibility functional variations and MD as BD [93, 94]. Friedel et al. [95], adds that the DAT1 polymorphism is associated with other MD, and problems such as attention deficit hyperactivity disorder, commonly seen in patients in the manic state [95].

Finally, one of the most adaptive effects seen with regular aerobic exercise is the reduction of sympathetic drive after a few weeks for the same exercise training intensity [96]. This may be a mechanism of great importance to be considered in a manic state, and along with the production of β-endorphin could favorably contribute to a reduction in euphoria and mania. In short, considering the monoaminergic changes specifically 5HT, DA, and NA during, after, and with exercise in long-term, these may exhibit potential benefits for mood regulation in BD. Furthermore, the long term could speculate that the exercise may be a means of maintaining euthymia making patients less vulnerable to stay longer in a moment of neutrality [26, 85].

FIVE YEARS VIEW

Speculating that the improvement in VO_{2Max} could be an interesting channel to be stimulated, higher growth of this variable is observed when administered higher training intensities (90-100% of VO_{2Max}) in healthy subjects [68, 69, 97], with metabolic syndrome

[98], or in patients with cardiac failure [99]. It is reasonable to think that these higher training stimuli with recovery periods (high-intensity interval training - HIIT) can also be adjusted to improve the physical fitness and health in patients with MD. First it is important to understand that the term high intensity should not necessarily be interpreted as a high effort, since the effort depends on the ratio of intensity vs. time. So, considering the negative effect on the affective state reported in the literature with prolonged exposure to high-intensity stimuli [70], new research can be devised thinking about determining a threshold effort that simultaneously reproduce the physiological benefits of HIIT, also promotes a positive perception of the training. For a better understanding of the HIIT training answers, check the revisions Gibala *et al*. [69], Swain and Franklin [100]. Thus, future studies are needed to clarify this new perspective, however, in other words, knowing that patients with BD have low physical capacity or exercise tolerance [47], adopt a suitable training strategy that is both time efficient and cited in different fields for the population in question, it is still a challenge to researchers.

CONCLUSION

In fact there is still no definitive answer about the effects of exercise on MD, however, combined with aerobic exercise and specific drug strategies seem to lead us to a positive effect in reducing disease severity. The mechanisms for this reduction are multifactorial, and monoaminergic systems are only part of the pathophysiology of MD and BD. Moreover, although still unclear, the monoaminergic responses manifested from exercise in general can adjust the patient with MD to a neutrality, introducing it as an

innovative form of treatment. Future studies are needed to establish a pattern and a more effective dose of training for this population.

Acknowledgements

The authors feel obliged to thank Professor Rodolfo Valentini for the translation, and by the aid in document reviews.

Financial & Competing Interests Disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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ARTIGO 2

NEUROBIOLOGY OF BIPOLAR DISORDER: ABNORMALITIES ON COGNITIVE AND CORTICAL FUNCTIONING AND BIOMARKERS LEVELS

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CNS & Neurological Disorders - Drug Targets, 2016, *15*, 713-722

Neurobiology of Bipolar Disorder: Abnormalities on Cognitive and Cortical Functioning and Biomarker Levels

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Abstract: Bipolar disorder (BD) affects 1 to 1.5% of the world population and consists of at least one manic episode (or hypomanic) associated with depressive episodes, interspersed with periods of euthymic mood. Recurrent crises lead to significant disability in BD patients, and correlates negatively to social and occupational adjustment. Such disability can be explained by a series of events, such as cortical and altered metabolic activity, impairments in cognitive functions, and in core anatomical structures involved in mood modulation. Therefore, our review aims to provide information on the current research related to the pathophysiology of BD. We will review the cognitive and brain functioning, and biomarkers of BD. The current literature shows that cognitive deficits are commonly observed in all phases in BD patients, independent of a remissive state. These deficits are assigned to functional, structural and metabolic changes, particularly in the pre-frontal cortex region, hippocampus and amygdala, along with the connections between them, as well as decreased baseline brain-derived neurotrophic factor levels or imbalance between pro- and anti-inflammatory cytokines, implying a lower physical ability to reestablish from a stressful stimulus. BD patients effectively present a differentiated pattern of cortical, neuroanatomical and functional responses. It is suggested that physiological processes occur differently in bipolar subjects compared to healthy individuals, affecting behavior and brain function in such patients. Future directions are yet necessary to establish the best way to neutralize or reverse these events.

Keywords: Bipolar disorder, brain-derived neurotrophic factor, depression, mania, neuroplasticity.

Received: July 16, 2015 **Revised: February 16, 2016** **Accepted: March 16, 2016**

INTRODUCTION

Bipolar disorder (BD) affects 1 to 1.5% of the world population [1] and consists of at least one manic episode (or hypomanic) associated with depressive episodes, interspersed with periods of euthymic mood [2]. Recurrent crises lead to significant disability in BD patients and correlate negatively to social and occupational adjustment [3]. Such disability can be explained by a series of events, such as, cortical and altered metabolic activity, impairments in cognitive functions, and in core anatomical structures involved in mood modulation [3, 4].

Thus, BD patients show particularities in cortical activity compared to other psychiatric illnesses [4, 5], including differences among phases [6-8]. These cortical patterns are closely associated with poor cognitive performance [5], supporting the notion that BD patients exhibit cognitive dysfunction. This problem seems to occur in different cognitive

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1996-3181/16 $58.00+.00

domains, even during periods of clinical remission [3, 9], and may be explained by a significant volume reduction of white and gray matter [10, 11]. Therefore, the chronic state has been consistently attributed to functional and neuroanatomical changes in the cortex and may occur with different magnitudes of impact [4, 10, 12-14].

The prefrontal cortex (PFC) has an important role in BD pathophysiology, and has been also directly involved in changes of cognitive function [10, 15]. Neural connections between PFC and structures such as the hippocampus [16] and amygdala [11, 12] may explain the manifestation of mood events linked to BD, and seem to represent specific features of the disorder. For instance, manic patients have reduced activity of specific portions of PFC and increased reactivity of the amygdala in front of facial expressions of emotion, reflecting a state-dependent excitatory nature. The opposite is also observed in depressive phase of BD.

Moreover, the neurotransmission system and hormonal metabolic abnormalities such as elevated cortisol levels, or reduced levels of neurotrophic factors, are commonly observed in several mental disorders, as well as in BD patients. These changes strongly contribute to the worsening of the disorder, and they are connected to negative disease neuroprogression [17-20]. Thus, it makes sense to believe that a cascade of physiological events is integrated and forms a complex system, supporting concurrent level of damage from the disorder. Therefore, our review aims to provide information on current research related to the pathophysiology of BD. We will review cognitive and brain functioning and biomarkers of BD.

Cognitive Impairments in Bipolar Disorder Patients

Special attention has been given to cognitive deficits in patients with BD, which influence social and behavioral aspects of these subjects [21]. The literature is consistent and unidirectional in presenting cognitive deficits in bipolar patients [3, 9, 15, 22, 23], and that seems to be independent of a remitting phase of the disorder [3]. Martínez-Arán *et al*. [3] and other authors [9] further argue that negative effects over cognitive function do not seem to differ from patient's clinical status (i.e., depression, hypomania/maniac or euthymia).

There is a strong association between some neuropsychological and clinical characteristics presented by bipolar patients and cognitive performance variables. Clark, Iversen and Goodwin [24] suggest negative associations between the number of depressive episodes and poor performance in spatial working memory, California verbal learning test, tower of London problem solving task and tasks of speed process of visual information ($P<0.05$). Similarly, manic episodes are negatively associated to the same California verbal learning test and rapid visual information processing ($P<0.05$). These responses represent a large deficit of sustained attention in bipolar patients [3, 24]. Recurrence, in a large number of episodes, is also negatively correlated to poor cognitive performance [24] making them more vulnerable and increasing the effects of disorder cycles. Cognitive deficit independence during the remission phase of symptoms is mentioned in the meta-analysis of Robinson *et al*. [22]. These authors reported a moderate magnitude of effect size (ES – *"d index"*) (0.5 a 1.0) with important clinical significance on reducing cognitive function in euthymic patients. Thompson *et al*. [23], also presented persistent cognitive reduction on euthymic patients in different psychomotor, executive function, attention, immediate and declarative tests compared to control group. It seems that clinical status is quite independent of the performance in these cognitive domains [3, 9, 22, 25-27].

It is also suggested that patients with psychosis diagnosis in BD are significantly affected with higher cognitive decline compared to bipolar patients without psychotic traits [28]. However, these responses seem still uncertain. Preliminary comparisons demonstrate the existence of cognitive declines of similar magnitude for the same domains previously discussed [29, 30]. In this same meta-analysis of Bora, Yucel and Pantelis [29] the highest ES was found in the Symbol Coding Test – ES = 1.02. Eleven of the cognitive tests (Stroop test, Category Fluency, Verbal Memory Immediate, Wisconsin Card Sorting Test, Continuous Performance Test, Trail Making Test A and B, verbal memory delayed, Wisconsin Card Sorting Test Categories") obtained ES > 0.8 and moderate ES for two of the tests (visual memory e letter fluency) [29].

Exploring Mechanisms

The responsible mechanisms for poor cognitive performance despite not yet totally understood seem to be multifactorial, therefore, related to different functional implications [14], neuroanatomical [31], and regional cerebral blood flow abnormalities [32, 33]. In this sense, the PFC region and its subdivisions are directly affected in its functioning [4, 31, 34] and volume [11, 35, 36], and some areas become inefficiently activated during the cognitive assessment [4]. The changes in cortical activity can be associated to pre-existing cognitive alterations in these patients, loss of functionality, or efficiency of synaptic circuities in question [12, 13, 31]. For example, it was observed that manic patients, who had a poor performance in the Continuous Performance Test (i.e., reduction in attentional functioning), also had a lower volume in PFC and hippocampal areas, indicating an association between cognitive and brain functions [31]. Abnormalities in the activation of the ventral region of PFC observed in functional magnetic resonance imaging (fMRI) during the Color-Word Stroop test", suggest that cognitive processing is different in bipolar subjects when compared to healthy subjects [13].

A strong relationship was established between the cognitive decline and neuroanatomical changes in different brain areas such as hippocampus, amygdala, gray matter, and the PFC, as seen in the longitudinal multicenter study by Mungas *et al*. [37]. The mechanism responsible for the loss of volume or density in a given brain region seems to be related to a reduction in dendritic arborization, loss of myelination or synaptic connections, as observed in other mental disorders such as schizophrenia or Alzheimer disease [38]. These negative outcomes may be explained by a lower serum level of substances related to trophic processes, biomarker promoters of neuronal cell proliferation and survival, i.e., neurogenesis, such as brain-derived neurotrophin

factor (BDNF), or insulin-like growth factor-1 (IGF-1) which also participate of this pathophysiological mechanism [39]. The massive activation of the immune system is also closely linked to this process, and could also explain this cascade of events [40-42] and inhibition of neurogenesis. This relationship will be discussed in more detail below.

In another perspective, cerebrovascular metabolism and regional cerebral blood flow may reflect a neuronal cell deficient and poor nutrition in certain brain areas and seem to suppress the demand of activation on simple or complex cognitive tasks, and are strongly associated with cognitive decline [32, 33]. Dolan *et al*. [33], for example, reported a significant reduction of cerebral blood flow in the left PFC in depressed patients compared to healthy subjects. These authors also maintain the idea that these abnormalities are highly associated with neuropsychological functions. Other findings showed similar reductions in the anterior cingulate cortex, and the left dorsolateral prefrontal cortex [32].

In turn, treatment with specific drugs or engagement in physical exercise can induce the production of substances related to growth and vascular proliferation (e.g. vascular endothelial growth factor - VEGF). VEGF is produced due to the need of oxygen and increased metabolism [43], which is directly associated with improved cognition [43, 44]. In an important recent study conducted by Hohman *et al*. [44], the authors argue that hippocampal volume (p = 0.009), longitudinal hippocampal atrophy (p = 0.01), longitudinal decline of memory (p = 0.01), and reduction in executive function (p = 0.003) are highly associated with the amount of VEGF available in cerebrospinal fluid [44]. In this sense, the bioavailability of VEGF is essential for neurogenic effects [45].

β-amyloid plaque deposition appears to exert a similar influence on cognitive performance in bipolar patients [46, 47], like observed in Alzheimer disease patients [48]. The interaction of VEGF/β-amyloid peptide (1-42) has proven be a predictor of longitudinal memory decline [44]. β-amyloid plaques are formed by the action of β-secretase and γ-secretase cleavage of a transmembrane protein called amyloid precursos protein [49]. The regulation of β-amyloid seems to be influenced by the serum level of growth factors such as IGF-1 and other neurotrophins that are directly linked to neurogenesis [50]. Thus, high concentrations of β-amyloid are inversely related to IGF-1 concentrations [50]. Therefore, within this scenario, an efficient cognitive processing seems contradictory (Fig. **1**).

Cortical and Structural Changes in Bipolar Disorder Patients

PFC plays an important role on different functions, from the synthesis of information to behavioral execution, supported by innumerous connection networks [7, 8]. PFC is, perhaps, the most relevant structure to be studied in order to understand the physiopathology of patients with BP in the different domains of the illness [11, 13]. Abnormalities in the PFC are directly related to emotional and behavioral dysfunctions and poor cognitive performance [11, 51]. Thus, changes in metabolism and regional cerebral blood flow can alter the level of cortical activation in this particular area of interest, and thus modify the interaction with the limbic system [52]. For example, Blumberg *et al*. [13] associated elevated state of positive mood in patients with BD mainly due to reduction in the activation of the PFC right ventral portion. The left portion of the same structure was more activated in depressive patients, both determined via fMRI. Amygdala, in particular, a structure related directly with mood disorders and responsible for emotional processing, although still controversial, exhibits a bilateral reduction in activation in bipolar depressive patients [53]. In contrast, an opposite cortical response occurs in manic patients [8, 53]. It is suggested, generally, that these different responses of PFC, together with other structures, could reflect a specific trait in each BD cycle [13].

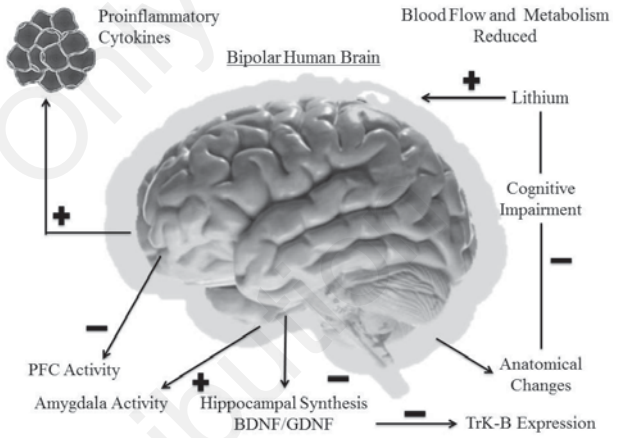

Fig. (1). Typical cortical, neuroanatomical, and biomarker alterations observed in patients with bipolar disorder.

In addition to particular cortical responses, fMRI also show implications on the volume and density of structures such as the hippocampus [16, 31, 36], amygdala [12, 36], hypothalamus [35] and cingulated cortex [11, 54]. This brain general dysfunction does not depend on the clinical state. Considering the field of emotional processing, the amygdala and hippocampus play an important role in BD, and these structures have its volume significantly reduced [12, 36]. Similarly, white and grey matters, mainly in frontal area of the brain, are also reduced on its volume [11]. The abnormality of these structures is associated to a strong genetic predisposition to develop BD and may explain diverse chronic cognitive alterations. Research point toward glial cells reduction, specifically in Broadman area 24, as well as blood flow reduction and cerebral metabolism alterations [55] in unipolar and bipolar depression [56]. All these responses seem to be higher when patients have previous familiar history compared to those who don't have familiar history, which probably makes them more vulnerable to the large spectrum illness symptoms [56].

Mania/Hypomania

Cortical activity in manic patients manifests in different pattern compared to bipolar patients in depressive and euthymic phase [6, 8, 13, 57-60]. As mentioned earlier, PFC

and its subdivisions have a great expressivity on symptoms developed by bipolar patients. There is data convergence toward a cortical activity reduction, mainly in PFC ventral portion in manic patients. The reduction of activity in this portion of the brain reflects mainly an excitatory state [13].

The functional network of cortical connections in manic bipolar patients, exhibits inverse modulation between PFC ventrolateral region and amygdala [8]. Foland *et al*. [8] found in a group of 9 manic and hypomanic patients and 9 healthy subjects, a higher activation of left portion of amygdala and concomitant reduction of PFC ventrolateral region from tests of facial matching of emotional expressions (labeling and emotional perception tasks). Amygdala reactivity seems to be state-dependent, however, these result are still questionable [6, 8]. Additionally, cortical activity increase of the inferior part of anterior frontal gyrus with concomitant reduction of cingulated cortex activity was also task dependent. The alterations in cortical activation pattern in manic patients compared to healthy individuals are shown in Table **1**.

Hippocampal region, also of great interest for BD, plays an important function on mood disorders and cognitive domains of attention, memory and learning. Abnormalities in this structure are consistently expressed both in depressive and bipolar depressive patients [61], however not in manic patients. Although still controversial, literature shows significant association between abnormal hippocampal volume and poor performance in cognitive tests ("Continuous Performance test"- *p=0,002*) [35], especially for smaller attention functioning in manic patients [31].

Drug interventions based on lithium exerts positive effects on both amygdala and hippocampus structures compared to patients who did not use medication [36]. Foland *et al*. examined 49 BD patients (22% manic at the scanning moment) and observed significant increasing of amygdala (*p=0.0258*) and hippocampus (*p=0.0356* – left portion; *p=0.005* – right portion) volumes, for patients who were administered lithium in treatment. In fact, these responses did not depend of the patients' clinical status (*p = 0.23*). Therefore, one must be careful when analyzing studies that did not make a rigorous pharmacological control, because lack of control could derail results extrapolation, given that there is a great influence in cerebral neuroanatomy [36]. The meta-analysis produced by Hajek *et al*. [62] compared patients who were long-term users of lithium to patients without use of the medicament and healthy controls. A smaller hippocampal volume was observed in patients who not used lithium, while a larger volume of both sides of hippocampus was noticed in patients treated with drugs. Lithium seems to protect patients from the deleterious effects of bipolar disorder [36], and this phenomenon is linked to the

Table 1. Cortical Changes in Manic Patients Compared to Healthy Subjects.

Author		Features			Results	
		Sample	Objective	Task	Outcomes	Conclusion
Mazzola-Pomietto *et al*. [57]	A	16 (manics)	Identify brain functional abnormalities in mania	Go-NoGo Task	VLPFC (R/ L) ↓	Response inhibition in mania is associated with a lack of engagement of the bilateral VLPFC
		16 (healthy)			VLPFC (R/ L) ↑	
Altshuler *et al*. [58]	A	11 (manics)	Investigate neural activity in the lateral orbitofrontal cortex in mania	Go-NoGo Task	RL Orbitofrontal Cortex ↓; Hippocampus ↓; Cingulate ↓	Mania is associated with a significant attenuation of task-related activation of RL orbitofrontal function
		13 (healthy)			RL Orbitofrontal Cortex ↑↑↑	
Elliott *et al*. [59]	A	11 (manics)	Investigate the neural activity orbitofrontal in mania	Go-NoGo Task	Orbitofrontal Cortex ↓; VLPFC/VMPFC ↑	Critical role for ventral and medial dysfunction in the pathology of mania
		13 (healthy)			Orbitofrontal Cortex ↔; VLPFC/VMPFC ↔	
Kaladjian *et al*. [60]	C	10 (manics)	Examine the functional changes associated with symptomatic remission in mania	Go-NoGo Task	Amygdala ↑; ↓(after mania);	Decrease in left amygdala responsiveness is a critical phenomenon associated with remission from mania
		10 (healthy)			Amygdala ↔	
Foland *et al*. [8]	A	9 (manics)	Evaluate functional connectivity between VLPFC and amygdala during the cognitive evaluation of affective stimuli	Perceive & label emotion	Amygdala (L)↑; VPFC (R)↓; inferior frontal gyrus ↑; ventral ACC ↓	Bipolar mania suggest that reductions in inhibitory frontal activity in these patients may lead to an increased reactivity of the amygdala
		9 (healthy)			Amygdala (L) ↓; VPFC (R) ↑; inferior frontal gyrus; (R) ACC ?	
Blumberg *et al*. [13]	A	11 (manics)	Characterize state/trait-related functional impairment in frontal systems in bipolar disorder	Strop Task	(R) VPFC ↓	VPFC abnormalities may be associated with specific acute mood states
		20 (healthy)			VPFC ↔	

Subtitles: ↑- increased activation compared to control; ↓- reduced activation compared to control; ↑↑↑ - greater intensity compared to other groups; ↓↓↓ - lower intensity compared to other groups; ↔ - small percentage of activation; VLPFC - Ventral Lateral Prefrontal Cortex; R - Right; L - Left; RL - Right Lateral; VMPFC - Ventromedial Prefrontal Cortex; ACC - Anterior Cingulate Cortex; A - Acute Research; C - Chronic Research; All studies used functional magnetic resonance imaging (fMRI).

increase, or restoration of normal levels of serum concentration of neurotrophins as mentioned before, thereby increasing neuronal resilience and reducing the perception of symptoms [19, 20, 63].

Depression

PFC is also directly implicated in the physiopathology of bipolar depressive patients. Patients with BD, in their depressive phase, exhibit a particular cortical activation pattern in relation to euthymic, manic and unipolar depressive patients [53, 64-68]. Negative mood state observed in depressive patients is associated with altered cortical responses, particularly a hemispheric asymmetry of PFC area, presenting a greater activation in the right side compared to manic patients. However, the ventral portion of the PFC becomes significantly more activated, as well as subcortical regions when observing positive and/or negative emotional expressions, when compared to unipolar depressive patients and healthy controls [64]. Given these characteristics, it is possible to have a differential diagnostic between unipolar and bipolar depression, since unipolar depressive patients have depressed activation in these regions using the same procedure [64].

Abnormal activation of structures related to frontal-subcortical circuit (frontal cortex, striatum, globus pallidus, substancia nigra and thalamus) [69] are directly associated to bipolar depression physiopathology [68]. This circuit is divided in different routes and is responsible for motor activity and some human behaviors, including emotion [69]. The responses of subcortical activation seem clear and some of them are defined as predominant traits in BD, compared to major depression. Lawrence *et al*. [64] showed increased striatal ventral, thalamic, hippocampal and amygdala activation in response to different facial expressions (fear or happiness) while patients with major depression presented less activation in the same areas. Almeida *et al*. [6] observed significant amygdala reactivity when comparing neuroimaging data between groups of patients with bipolar depression, major depression and healthy subjects exposed to faces of happiness (no interaction between depressive groups in amygdala activity), fear and sadness (reactivity in amygdale left portion in BP - $p=0.012$). These patients also tended to exhibit negative and deficient connectivity between the right portion of amygdala and dorsolateral right regions, as well as the right orbitofrontal area of PFC [53]. This directly implies in incapacity to regulate mood and emotions. The alterations in cortical activation pattern in bipolar depressive patients compared to healthy individuals are shown in Table **2**.

In addition to functional alterations observed in the depressive phase of BD, there are also neuroanatomical modifications, mainly in limbic/subcortical regions. According to what happens in the other phases of BD, volumetric relations are normally reduced when compared to healthy subjects [12, 70]. The volumetry of PFC, thalamus, hippocampus, amygdala, pallidal and striatal regions of patients with BD are reduced when compared to healthy subjects, with an effect size moderate to large [12]. Correspondingly, white matter linked to PFC and subcortical regions are also significantly reduced compared to healthy subjects, with moderate to large ES.

Biomarkers in BD Patients

Numerous studies have pointed out a strong and inverse association between BD symptoms and serum levels of some physiological biomarkers [71-74]. As a rule, the biomarkers can express a general neuroprogression of mental disorders, such as in the case of BD, or the degree of deterioration for repeated events related to the symptoms of disease. There are distinct biomarkers represented in the literature, and we can name a few with significant emphasis on BD, i.e., BDNF [20], glial cell line-derived neurotrophic factor (GDNF) [74], cortisol level [75], and cytokines [76]. Concerning BDNF and GDNF, these have an extensive role in the physiopathology of BD, and therefore will be addressed first. In this sense, the neuroanatomical and related brain functional circuit alterations do not comprise the whole set of abnormalities observed in BD. Neurotrophin deregulation in brain structures (hippocampal) and to a lesser extent in other body tissues suggests a mediator of illness progression [19]. Improvement of these biomarkers can reflect a positive and momentary reorganization of the illness course. These neurotrophins are then sustained as orchestrated substances during neuroplasticity, promoting greater synaptic efficiency/ connectivity, dendritic arborization, and are also mediators of important neurotransmitters implicated in the pathophysiology of BD [77].

Reduced circulating levels of BDNF, for example, are commonly observed in patients with BD [71]. Cunha *et al*. [71] compared serum levels of BDNF between bipolar depressive, manic, euthymic and healthy subjects. The results showed a significant reduction of serum concentration of BNDF (ELISA method) for depressive ($p=0.027$) and manic ($p=0.019$) patients, compared to healthy subjects; however, there was no interaction in euthymic and healthy subjects. Similar effects were demonstrated between BDNF levels in bipolar depressive compared to unipolar depressive patients [78]. Finally, a meta-analysis by Fernandes *et al*. [72] demonstrated a significant reduction of serum levels of BDNF in manic bipolar (ES =0.81) and depressive (ES =0.97) patients, but not in euthymics (ES =0.20) in relation to a healthy control group. Despite these consistent data, recent studies contradict previous results [79].

Decrease in BDNF levels implies a lower physical ability to reestablish from a stressful stimulus, i.e. allostasis [19]. An increased allostatic load seems to maintain cortisol levels chronically more elevated in BD patients [19]. Naturally, cortisol concentrations are higher in the daytime [80], and changes occur throughout the day and in response to stressful stimuli. This is a physiological response commonly observed and activated via the hypothalamic/pituitary/adrenal axis, which mediates the secretion of adrenocorticotropic hormone and cortisol release by the adrenal cortex. This path is chronically activated in BD patients [75] and it is possible to establish an association between BDNF and cortisol levels and the concept of allostasis. Apparently, BDNF concentration is also increased mainly during daytime, along with cortisol levels following the circadian cycle [80]. This event can be explained as a co-regulation between these two variables in order to establish homeostasis. Increasing circulating levels of BDNF may provide a lower allostatic load and consequently a better regulation of existing cortisol.

Table 2. Cortical Changes in Depressive Bipolar Patients Compared to Healthy Subjects.

Author		Features			Results	
		Sample	Objective	Task	Outcomes	Conclusion
Almeida *et al*. [6]	A	15 (depressed)	Evaluate abnormal amygdala activity during positive and negative emotion processing	Perceive & label emotion	Amygdala ↑ (mild and neutral facial expressions)	Abnormally elevated (L) amygdala activity to mild sad and neutral faces might be a depression-specific marker in BD
		15 (healthy)			Amygdala ↔	
Lawrence *et al*. [64]	A	15 (depressed)	Compare responses within subcortical and prefrontal cortical regions to emotionally salient material	Perceive & label emotion	Ventral striatal ↑; thalamic ↑↑(fear); hippocampal ↑↑ (sad); VLPFC ↑↑ (happy)	BD patients demonstrated increased subcortical and ventral prefrontal cortical responses to both positive and negative emotional expressions
		15 (healthy)			Amygdala/hippocampus ↔; Thalamus ↑ (fear); parahippocampal gyrus ↑; VLPFC↔	
Vizueta *et al*. [53]	A	21 (depressed)	Examined neural activity in response to negative emotional faces during an emotion perception task	Perceive & label emotion	VLPFC (L/R) ↑; amygdala ↑; right orbitofrontal cortex ↑	BD depression is characterized by reduced regional orbitofrontal and limbic activation compared to healthy subjects
		21 (healthy)			VLPFC (L/R) ↑↑↑; amygdala ↑↑↑; right orbitofrontal cortex ↑↑↑	
Blumberg *et al*. [13]	A	10 (depressed)	Characterize state- and trait-related functional impairment in frontal systems in BD	Stroop Task	cVPFC ↑; rVPFC (L) ↓;	BD is associated with a trait abnormality in VPFC (L)
		20 (healthy)			cVPFC ↔; rVPFC (L) ↔;	
Diler *et al*. [65]	A	12 (depressed)	Identify differential patterns of neural activity in BD vs UD underlying response inhibition in adolescent	Go/ NoGo Task	Superior temporal (L) ↑; caudate (L) ↑; ACC (L) ↑	BD and UD shared similar neural responses in depression during response inhibition, but different to healthy control
		10 (healthy)			Superior temporal (L) ↔; caudate (L) ↔; ACC (L) ↔	
Perlman *et al.* [66]	A	21 (depressed)	Examine functional integration between the bilateral amygdala and PFC integrity of neural circuitry supporting abnormal emotion processing in depressed BD	Perceive & label emotion	Amygdala (R) ↑(fearful); VLPFC/VMPFC ↓	Differences in recruitment of amygdala–PFC circuitry support implicit emotion processing between remitted depressed BD and depressed-BD
		31 (remitted)			Amygdala (L/R) ↑ (all emotional conditions); VLPFC/ VMPFC ↓	
		25 (healthy)			Amygdala (L/R) ↔	
Marchand *et al*. [67]	A	14 (depressed)	Determine if the task activates structures of interest in depressed BD when euthymic	Paced motor; Stroop Task	Bilateral striatum ↑; ACC (R) ↑; medial frontal gyrus ↑	This finding provides evidence that the motor task may provide information about both state and trait functional abnormalities in BD
		14 (euthymic)			Bilateral striatum ↑↑↑; ACC (R) ↑↑↑; medial frontal gyrus ↑↑↑	
Marchand *et al*. [68]	A	14 (depressed)	Test the utility of a paced motor activation to evaluate FSC circuit function in BD depression	Paced motor; Stroop Task	Thalamus ↓; globus pallidus ↓; putamen ↓; DLCPF/Orbitofrontal ↓	This study supports the role of FSC circuit dysfunction in BD depression
		15 (healthy)			Thalamus ↑; globus pallidus ↑; putamen ↑; DLCPF/Orbitofrontal ↑(All in motor task)	

Subtitles: ↑- increased activation compared to control; ↓- reduced activation compared to control; ↑↑↑ - greater intensity compared to other groups; ↓↓↓ - lower intensity compared to other groups; ↔ - small percentage of activation; VLPFC - Ventral Lateral Prefrontal Cortex; DLCPF - Dorso Lateral Cortex Prefrontal; R - Right; L - Left; RL - Right Lateral; VMPFC - Ventromedial Prefrontal Cortex; ACC - Anterior Cingulate Cortex; cVPFC - Caudal Ventral Prefrontal Cortex; rVPFC - Rostral Ventral Prefrontal Cortex; FSC - Frontal-Subcortical. A - Acute Research; C - Chronic Research; All studies used functional magnetic resonance imaging (fMRI).

The use of mood stabilizing drugs such as lithium and valproate seem to increase the concentration of BDNF [81, 82], and positively affect BD symptoms by a second messenger mechanism, more specifically, inducing increased

intracellular signaling via G protein (Gs) expression, and increasing interaction with neurotransmitters linked to mood changes [83]. For example, it seems that the serotonin and neurotrophins, such as BDNF are also closely related, and signal in order to co-regulate the promotion of neuronal plasticity in several brain areas [84]. Increased expression of BDNF TrkB receptors is also caused by antidepressant drugs and mood stabilizers, which may favor BDNF/TrkB interaction and in turn, the cascade of physiological reactions.

Similar to effects produced by BDNF, GDNF seems to correlate negatively with BD symptoms (r = *-0.54*) [74], and a possible protector effect has been discussed, although there is no consensus so far [74, 85]. This neurotrophic factor is capable of promoting neuronal cell survival and differentiation of dopaminergic neurons, in addition to a high-affinity for dopamine capitation (?) [86]. Dopaminergic circuits are a direct participant of the mechanisms related to mood control. The reduction of dopamine is inversely related to depressive symptoms and its increase is directly associated to mania [87], and consequently GDNF is also an important piece of the puzzle to be investigated [86].

There is some evidence showing that circulating levels of GDNF are changed in BD, but not in the euthymic phase [74]. However, these findings have been debated [85]. Barbosa *et al*. [74] presented significant reduction in serum levels of GNDF in 35 manic patients (mean ± SD; 34.09 ± 48.80 pg/mL - $p \leq 0.05$) in comparison to 35 euthymic patients (mean ± SD; 76.74 ± 95.26 pg/mL - $p \leq 0.05$). In contrast, Rosa *et al*. [85] showed a significant increase of GNDF levels in depressive ($p=0.004$) and manic ($p=0.001$) patients, while euthymic patients matched the control group. Perhaps the difference between methods has generated these conflicting results [74, 85]. Another possibility is the use of pharmacological substances such as mood stabilizers (e.g., valproate and lithium), that possibly increase BDNF and GDNF concentrations.

Finally, it is known that the imbalance between pro- and anti-inflammatory cytokines is involved in the physiopathology of BD [42, 76]. Changes in the profile of certain cytokines, such as tumor necrosis factor alpha (TNF-α) and C-reactive protein, as well as interleukin 1 and interleukin 6, are commonly associated to mood disorders and others psychiatric disorders [76]. Evidence also supports a higher content of free pro-inflammatory cytokines in BD patients, compared to healthy subjects, thus demonstrating a severe inflammatory reaction in these subjects. According to Goldstein *et al*. [88], the chronic inflammatory process is directly related to expression of polymorphic genes and the increase of these pro-inflammatory substances. This sustained effect has an adverse impact in the neuroregenerative ability, or the resilience of important brain areas such as hippocampus, and can also contribute to the neuroprogression of the illness [40]. It is suggested that induction of the inflammatory process through excessive activation of brain microglia mediates the suppression of neurogenic effects in hippocampus, and similarly, blocking the microglial response by tetracycline restores cells in the subgranular region after 35 days [40]. Therefore, a higher concentration of circulating cytokines is implicated in an increase in neurotoxicity [89]. In this state of chronic inflammation, as noted in BD, macrophages remain in the brain to maintain a setting of continuous inflammatory signaling, and this mechanism may be responsible for demyelination, cell adhesion, as well as apoptosis of neurons and glial cells [89]. Thus, the continued use of drugs such as lithium (> than 3 months) seems to act as a braking mechanism for this deterioration process. These drugs appear to act by cross interaction signaling pathways such as adenylate cyclase, tyrosine phosphorylation, and phosphatoinositides, and therefore patients treated do not exhibit the same level of circulating pro-inflammatory cytokines compared to untreated patients [90, 91].

Certain cytokines can vary according to the cycles of the BD (e.g., manic, depressive or euthymic phase) [42]. In that sense there is a state-dependent concentration of different cytokines. The concentration of TNF-α, for example, does not differ across phases of the BD patient [92], although greater immune activation can be sustained during the exchange of depressive to mania cycle [93]. Independently, significantly higher levels of TNF-α are reported in bipolar patients, compared to control group ($p<0.05$) [42]. Similar results are reported by Usmani *et al*. [94], who observed a significant difference in the content of TNF-α in bipolar patients (99.86 ± 10.22 pg/ml), compared to healthy subjects (8.88 ± 2.84 pg/ml), independent of gender ($p>0.05$). On the other hand, interleukin-1 and interleukin-6 are significantly different between depressive bipolar patients (16.85 ± 3.17, e 3.67 ± 1.32pg/ml, respectively) and manic patients (9.54± 2.40 pg/ml, and not reported values, respectively), which in turn were different from the control group (17.65 ± 0.48, e 1.21 ± 0.22 pg/ml, respectively). Interleukin-2 seems to respond to the same pattern as TNF-α, differing only between bipolar and healthy controls.

CONCLUSION

The state of art demonstrates well-defined directions about the pathophysiology of BD. Different modifications are presented and some special traits resulting from the disease can be extracted, for example in cortical activity and on different neuropsychological and motor tasks, differing from patients with other psychiatric disorders. These changes are often associated with pre-existing changes, indicating the relationship between the cognitive decline mechanisms, functional and neuroanatomical changes, as well as abnormal neurotrophic and pro-inflammatory responses. It is, therefore suggested that physiological processes occur differently in bipolar subjects compared to healthy, affecting behavior and brain functions in such patients. Despite the progress, future directions are yet necessary to stablish the best way to neutralize or reverse these events.

LIST OF ABBREVIATIONS

BD = Bipolar Disorder

BDNF = Brain-Derived Neurotrophic Factor

ES = Effect Size

fMRI = Functional Magnetic Resonance Imaging

GDNF = Glial Cell Line-Derived Neurotrophic Factor

IGF-1 = Insulin-Like Frowth Factor 1

PFC = Prefrontal Cortex

TNF-α = Tumor Necrosis Factor Alpha

VEGF = Vascular Endothelial Growth Factor

CONFLICT OF INTEREST

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

ACKNOWLEDGEMENTS

Declared none.

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ARTIGO 3

POTENTIAL THERAPEUTIC EFFECTS OF PHYSICAL EXERCISE FOR BIPOLAR DISORDER

Potential Therapeutic Effects of Physical Exercise for Bipolar Disorder

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Abstract: Cognitive deficits are observed in a variety of domains in patients with bipolar disorder (BD). These deficits are attributed to neurobiological, functional and structural brain factors, particularly in prefrontal cortex. Furthermore, cortical alterations in each phase (mania/hypomania, euthymia and depression) are also present. A growing basis of evidence supports aerobic exercise as an alternative treatment method for BD symptoms. Its benefits for physical health in healthy subjects and some psychiatric disorders are fairly established; however evidence directly addressed to BD is scant. Lack of methodological consistency, mainly related to exercise, makes it difficult accuracy and extrapolation of the results. Nevertheless, mechanisms related to BD physiopathology, such as hormonal and neurotransmitters alterations and mainly related to brain-derived neurotrophic factors (BDNF) can be explored. BDNF, specially, have a large influence on brain ability and its gene expression is highly responsive to aerobic exercise. Moreover, aerobic exercise trough BDNF may induce chronic stress suppression, commonly observed in patients with BD, and reduce deleterious effects caused by allostatic loads. Therefore, it is prudent to propose that aerobic exercise plays an important role in BD physiopathological mechanisms and it is a new way for the treatment for this and others psychiatric disorders.

Keywords: Bipolar disorder, brain-derived neurotrophic factor, depression, exercise, mania, neuroplasticity.

INTRODUCTION

Bipolar disorder (BD) affects 1 to 1.5% of the world population [1] and consists of recurrent manic and depressive episodes, interspersed with periods of euthymic mood [2]. BD patients exhibit cognitive dysfunction in a variety of domains, even during periods of clinical remission [3, 4]. In this sense, the prefrontal cortex (PFC) is an important part of the pathophysiology of BD, and has a leading role on several cognitive functions [5, 6]. Such functions have significant impairments that correlate negatively with social and occupational adjustment [3]. Its chronicity has been consistently attributed to functional and neuroanatomical changes in the cortex that occurs in different magnitudes [5, 7-10].

Given this scenario, the literature starts speculating that programs of physical exercise could act as an important adjuvant and no pharmacological strategy for the treatment of patients with BD [11-14]. Physical exercise, specially aerobic exercise, is recognized for modulate an affective behavior in healthy subjects in moderate intensities of effort

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1996-3181/15 $58.00+.00

[15, 16], modify cerebral activity [17], promote neurogenesis [18], and improve cognitive function [15]. Despite little consistent, significant reduction of symptoms are found with the practice of aerobic exercise in bipolar patients [12, 19-21], and its effects related to exercise begin to be established in the literature [13]. Ng *et al*. [12], for example, observed in 24 patients diagnosed with BD, inserted in a walking group (effort not controlled), an improvement in the Depression Anxiety and Stress Scale (DASS – *p=0.005)* and all its subscales (Depression *p=0,048*, Anxiety *p=0,002*, and Stress *p=0,01*), compared to 74 bipolar patients who not participated in walking group.

In this sense, mechanisms sustaining improvement and insertion of aerobic exercise in lifestyle of patients with BD would be related to alterations in hormonal responses [22], neurotransmitters, such as monoamines, and physiological biomarkers produced by the brain, such as the brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF) [22, 23]. Although understanding these mechanisms, the evidence still lacks of consistent data that supports the link between remission and BD symptoms to programs of aerobic exercise. Thus, this review paper aims to show the experimental advances of aerobic exercise that can become available as clinical applications in the coming years for bipolar disorder.

The literature search was conducted using the databases PubMed, ISI Web of Knowledge and PsycInfo using the following terms and their combinations: "aerobic exercise", "bipolar disorder", "mechanism", "manic/hippomanic", "depressive", "electroencephalogram", "functional magnetic resonance imaging", "cognitive function", "biomarkers". All articles were published between 1980 and 2015 and in English. Additional references were identified through hand search of the possessed articles. Due to the lack of randomized clinical trials on the issue, we decided to select any study, *i.e.*, open and controlled studies, case reports, and cohort and observational studies.

EFFECTS OF AEROBIC EXERCISE ON BIPOLAR DISORDER

Benefits and/or General Adaptations of the Exercise for Health Promotion – Initial Contextualization

The American College of Sports Medicine (ACSM) recommends an accumulation of at least 150 minutes of moderate aerobic activity (50-55% VO_2 of reserve – VO_{2R}) weekly or 60 minutes of vigorous activity (70-75% VO_{2R}) weekly, for health promotion. The result of this summation is observed, primarily, in physical, metabolic and systemic state, providing protection over risk factors associated to coronary artery disease (lipid profile, body mass control, changes in resting glucose and blood pressure) [24]. It is also known that an increase of only 1 MET (1 metabolic equivalent = 3,5 mL/kg/min) in cardiorespiratory fitness (VO_{2Max}) represents an decrease in relative in mortality of about 13%, independent of any type of disease previously installed, such as coronary artery disease (CAD) [25, 26].

In addition to physical health, mental health aspects should also be emphasized 22, 25, 74]. The promotion of morphological and functinal changes in several brain areas (PFC, hippocampus) [27], and the formation of new neuronal synapses [28] may reduce the deleterious effects to the brain associated to age and different psychiatric disorders. In this sense, evidence tends to demonstrate positive effects on reducing the severity of symptoms related to illnesses such as BD [12, 20, 21, 29]. Moreover, significant positive modifications in mood with the practice of aerobic exercises [15, 20] and the cognitive function [27] are considered, and these benefits are observed in both healthy subjects and in patients with different psychiatric disorders. Bipolar patients, regardless of their clinical status, have low cardiorespiratory fitness and resistance exercise [13], as well, diverse deleterious effects to functional and structural ability of the brain [3, 4, 6, 8, 10, 23, 30-34]. Therefore, it is prudent to propose that cardiorespiratory conditioning, that is, improvement of VO_{2Max} is an important pathway for the treatment of different psychiatric disorders, given that their physiopathological mechanisms can be minimized and/or reorganized.

Relationship Between Exercise and Bipolar Disorder

The current state of art exposes results that confront the real benefit of controlling bipolar illness with programs of aerobic exercises [12-14, 16, 19-21, 27, 35-40]. Few studies were published about this particular topic and these fail to methodological controlling the relation of "*dose x response*" and/or in several times, there isn't any control. This is a factor that makes the results inconsistent and impossible for future comparisons.

For example, Ng, Dodd and Berk [12] evaluated the effects of walking exercise on acute treatment of BD. Twenty four participants diagnosed with BD joined to the program and 74 not participants with the same psychiatric profile were compared. The main results showed a significant reduction on BD symptoms evaluated with *Depression Anxiety Stress Scales* (DASS; mean ± standard deviation of participants; $58.2 \pm 25.4 > 23.0 \pm 14.9$). These results should be analyzed careful as well as those reported by Van Citters *et al*. [39]. The authors produced a pilot study using a specific program of diet reeducation, social behavior and fitness, called SHAPE, with different psychiatric disorders. Within this program, participants performed aerobic activities such as swimming and walking, or strength training or yoga. The criteria of training duration and intensity were adjusted according to an initial observation of the participant's physical state and evaluation scales of psychiatric progress were carried out. Reduction of the severity of symptoms, such as depression, was an important result to be noted (*p =0.003*) after 9 months follow up, in addition to benefits related to comorbidity in these patients. Other satisfactory results with effect sizes varying from moderate to high were found in different mania and depression scales and an improvement (mean %) of BD symptoms (MADRS – *Montgomery Asberg Depression Scale* (-23%); YMRS – *Young Mania Rating Scale* (27%) ; CGI *Mania – Clinical Global Impression Mania Subscale* (43%); *CGI Depression – Clinical Global Impression Depression Subscale* (22%); CGI *Overall – Clinical Global Impression Overall Bipolar Illness* (-16%); LIFE-RIFT – *Longitudinal Interval Range Impaired Functioning Tool* (-22%)) [38].

In contrast, a meta-analysis of Pearsall *et al*. [21] summarizes the possible effects obtained with exercise in a modest and not significant response over the physical activity level in patients with psychiatric disorders, such as bipolar, without effects on negative symptoms of depression ($p = 0.43$) and anxiety ($p = 0.14$). These results should be interpreted carefully given that the control of the relation "dose x response" is questioned in almost all studies. Moreover, and inadequate stimulus may tend to extremes, or to a result without effects in BD symptoms, or the stimulus may be interpreted as an stressor agent, contributing to the relapse of the symptoms [41]. An high intensity of exercise, though still uncertain, seems to be associated to a positive association with BD symptoms [42] and more precisely, to a negative effect on mood [43]. Contextualizing this data, after performing aerobic exercise to exhaustion, cortisol concentrations remain high for hours while BDNF concentrations are reduced to baseline values in a small amount of time [22] (Table **1**).

Possible Exercise Mechanisms that Influence Bipolar Disorder

Despite of inconsistencies and limitations, there is a tendency to obtain positive results with exercise practice [11, 12, 16, 36, 38, 39]. The improvement mechanism of the severity of BD symptoms may be connected to stress reduction from physiopathology agent's characteristics of the illness. Chronic stress caused by the imbalance between pro-inflammatory cytokines, changes in corticosteroid and reduction of BDNF levels, create a propitious ambient to increased allostatic charges and consequent reduction of cerebral neuroplasticity [19]. Therefore, subjects that practice appropriated periods of exercise (threshold around 20 – 30 min) may produce appropriated results on anxiety and reduction of stress reactivity in long term [43].

Chronic stress is also suggested as the most precipitator of mood disorders, given that a great sensitivity to stress is related to recurrent episodes [44]. This fact can be explained also by a defective modulation of monoaminergic systems [45, 46], such as observed in different psychiatric disorders. Several theories support a possible influence of mechanisms of dopaminergic transport [46] or GABAergic influence on physiopathological characteristics of BD [19]. This last, in special, has an important influence on gene expression of BDNF by hippocampus during exercise, influencing directly the basal levels of this substance [19].

During acute exercise of mild to moderate effort, cortisol and BDNF concentrations was not significantly altered, but not for high intensities [22]. High cortisol concentration is normally co-regulated by BDNF concentration and both follow a linear increase pattern [47]. However, in bipolar patients, initial BDNF concentration is normally depressed [23] which may mitigate the co-regulator and protection effect of BNDF. Despite of acutely after exercise the BDNF concentrations come back closely to baseline values [22], chronically the main benefits on symptoms severity are primarily associated to basal BNDF concentrations.

As explained, high basal concentrations of this substance are deeply connected to neuroplasticity and cerebral neurogenic capacity [11, 19, 40] and these responses extend

Table 1. Papers that investigated the chronic effect of the exercise in patients with bipolar disorder.

Article	General Features				Sample Features						Exercise Features					Results			
	Control	Random	Evaluation	Patient	n	Group	Age	Gender	Med	Instrument	Exercise: Modality	Exercise: Time	Exercise: Intensity	Times a week	Follow-up	Instrument	Absolut	Δ	ES
Ng, Dood & Berk, [12]	Yes	Not	(ICD-10)	Bipolar (100%)	14	Exercise	43.6 (15.0)	M + F	?	CGI-S, CGI-I, DASS Scale & Sub-scales	Walk	40 min	Free	?	24 month	CGI-S	4.2 ± 1.0 > 2.5 ± 1.2	40.5%	1.7
																CGI-I	Non-reported	-	-
																DASS Depres	24.0 ± 12.4 > 7.2 ± 7.3	70.0%*	1.4
																DASS Stress	19.4 ± 12.3 > 9.2 ± 7.2	52.6%*	0.8
																DASS Anxiety	14.8 ± 11.2 > 6.6 ± 4.5	55.4%*	0.7
					35	Non-exercise	43.9 (18.5)	M + F	?		-	-	-	-		CGI-S	4.3 ± 0.8 > 2,4 ± 0,8	44.2%	2.4
																CGI-I	Non-reported	-	-
																DASS Depres	27.3 ± 12.3 > 13.7 ± 12.8	49.8%	1.1
																DASS Stress	25.3 ± 9.3 > 17.1 ± 11.6	32.4%	0.9
																DASS Anxiety	18.2 ± 8.9 > 13.8 ± 8.9	24.2%	0.5
Van Citters, et al. [39]	Not	Not	DSM-IV	Bipolar (19%)	76	Exercise Diet Relax Yoga	43.5 (11.4)	M+ F	?	(SF-12 MCS) (SF-12 PCS) CESD, RSES SANS	Walk, Swimming	20-60 min	Free	3-5 times	9 month	SF-12 MCS	32.2 ± 12.0 > 36.4 ± 13.4	13.0%*	0,30
																SF-12 PCS	44.7 ± 12.5 > 44.3 ± 11.1	0.9%	0
																CESD	28.6 ± 13.0 > 26.0 ± 15.4	9.1%	0.2
																RSES	53.3 ± 18.5 > 57.4 ± 18.4	7.7%	0.2
																SANS	2.4 ± 0.7 > 2.3 ± 0.6	4.2%*	0.1
Sylvia, et al. [38]	Not	Not	MINI-Plus CGI-BP	Bipolar (100%)	5	Diet Exercise Lifestyle Changes Cognitive Work	44.0 (16.0)	M + F	?	MADRS YMRS (CGI-BP M, D, O) (LIFE-RIFT)	?	30 min	Moderate Effort (% non-reported)	5 times	5 month	MADRS	17.2 ± 5.2 > 13.2 ± 10.1	23.3%*	0.8
																YMRS	4.4 ± 2.0 > 5.6 ± 3.9	27.3%*	0.6
																CGI-BP M	1.4 ± 0.9 > 2.0 ± 0.7	42.9%*	0.6
																CGI-BP D	3.6 ± 0.6 > 2.8 ± 1.3	22.2%*	1.3
																CGI-BP O	3.8 ± 0.5 > 3.2 ± 0.8	15.8%*	1.2
																LIFE-RIFT	12.0 ± 3.1 > 9.4 ± 2.1	21.7%*	0.8
Verhaeghe, et al.	Yes	Yes	DSM-IV	Bipolar (24%)	123	Exercise Social Cognitive	44.2 (12.5)	M + F	Yes	(SF36 PCS) (SF36 MCS) (BSI PST)	Walk	30 min	Moderate Effort	3 times	2.5 month + 6 month	SF36 PCS	40.4 ± 7.7 > 39.4 ± 7.5	2.5%	0.1
																SF36 MCS	35.6 ± 8.7 > 34.8 ± 7.9	2.2%	0.1
																BSI PST	27.6 ± 12.6 > 25.3 ± 12.8	8.3%	0.2
					50	Control	46.6 (11.9)	M + F	Yes		-	-	-	-		SF36 PCS	41.2 ± 5.9 > 40.2 ± 7.8	2.4%	0.2
																SF36 MCS	35.8 ± 7.9 > 35.3 ± 7.4	1.4%	0.1
																BSI PST	26.5 ± 13.8 > 24.0 ± 14.5	9.4%	0.2

Subtitles: * - Significant Difference; ES - Effect Size; Med - Medications; ICD-10 - International Statistical Classification of Deseases and Related Health Problems; CGI S - Clinical Global Impression Severity; CGI I - Clinical Global Impression Improvement; DASS - Depression Anxiety Stress Scale; Mental Health Functioning - (SF-12 MCS); Psysical Health Functioning - (SF-12 PCS); Depression - (CESD); Self-Efficacy - (RSES); Negative Symptoms (SANS); MINI-Plus - Mini International Neuropsychiatric Interview; CGI-BP - Clinical Impression-Bipolar; MADRS - Montgomery Asberg Depression Rating; YMRS - Young Mania Rating Scale; CGI-BP M - Clinical Impression-Bipolar Mania; CGI-BP D - Clinical Impression-Bipolar Depression; CGI-BP O - Clinical Impression-Bipolar Overall; LIFE-RIFT - Longitudinal Interval Follow-up Evaluation Range Impaired Functioning Tool; SF36 PCS - Physical component score; SF36 MCS - Mental component score; BSI PST – Brief Symptom Inventory Positive Symptom Total.

to different BD domains, including cognition [35]. Exercise effects on cerebral neurotrophins were demonstrated by Seifert *et al*. [37] in a cycling training program aiming 600 kcal/day (±70% FC maximum/ ±60 min of exercise), during 3 months. The authors observed significant increases in arterial BDNF concentration in rest (baseline – 58 ± 106; follow-up – 206 ± 108 $ng.100g^{-1}.min^{-1}$), for the training group ($p<0.05$). The Control group was included just on a diet program (similar energy cost of exercise), but not reaching significant improvement. Exercise acts increasing gene expression of BDNF and messenger RNA in diverse body cells, including in muscular cells, but mainly in the hippocampal region [19].

Regarding cognition, BDNF can be an important key to cognitive recovery [18, 48]. The mechanism is associated mainly to synaptic plasticity changes, namely, better transmission and/or new synaptic connections [28]. It is demonstrated possible long term synaptic potentiating localized in hippocampal area, which is traduced in a better memory [18, 48]. Evidences suggest that effects produced by the relation between BDNF and new neurons formation may favor cognitive domains of adult learning [49].

Pharmacological administration helps maintaining and/or reducing cognitive deficit on bipolar subjects [50]. In these patients, treatment with lithium is the first treatment option and has significant effects on increasing volume of amygdala and hippocampus [51], neuroanatomical structures fundamental for cognitive performance and affective state [50]. Aerobic exercise seems to have similar effect on neuroanatomical organization and cognitive function in healthy subjects [27] and in different psychiatric disorders [52, 53].

Despite this understanding, little is known about aerobic exercise influence on different cognitive domains of BD. Exercise is recognized for inducing an increase in cerebral volume and consequently is associated to cognitive function changes. Colcombe *et al*. [27] implemented tree weekly sessions of 60 minutes training, initiating at 40 – 50% of heart rate reserve (H_{RR}) and progressing along six months to prescribed intensities of 60 – 70% of H_{RR}. The authors reported significant increases, mainly in white and grey matters, localized at PFC (right inferior frontal gyrus - $p \leq 0.05$) and temporal cortex (left superior temporal gyrus - $p \leq 0.05$). PFC region plays an important role in BD physiopathology and in motor control, attention and executive function [8]. Thus, larger changes in cerebral volume can bring important cognitive gains in long term.

CONCLUSION

Strong evidence in literature suggests using aerobic exercise as an important prophylactic strategy of actuation similar to pharmacology, aiming a reduction on symptoms severity and BD treatment in long term. Neurotrophins, mainly BDNF, obtained increasing relevance in what concerns aerobic exercise benefits. Complementary studies should be applied using different exercise protocols and controlled "dose x response" to evaluate better strategies for the symptoms treatment. Despite possible positive responses to exercise on BD symptoms, results still remain inconclusive and should be interpreted and implemented carefully.

LIST OF ABBREVIATIONS

ACSM	=	American College of Sports Medicine
BD	=	Bipolar Disorder
BDNF	=	Brain-Derived Neurotrophic Factor
CHD	=	Coronary Heart Disease
DASS	=	Depression Anxiety and Stress
ES	=	Effect Size
fMRI	=	Functional Magnetic Resonance Imaging
GDNF	=	Glial Cell-Derived Neurotrophic Factor
PFC	=	Prefrontal Cortex
VO_{2Max}	=	Maximal Oxygen Consumption

CONFLICT OF INTEREST

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

ACKNOWLEDGEMENTS

Declared none.

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Received: August 7, 2014 **Revised: April 9, 2015** **Accepted: April 23, 2015**

PMID: 26556085

ARTIGO 4

PODE O EXERCÍCIO INTERVALADO PROMOVER SUPERIORES RESPOSTAS PSICOAFETIVAS E ALTERAR O BALANÇO SIMPATOVAGAL EM PACIENTES BIPOLARES, PESSOAS TREINADAS E SEDENTÁRIAS

PODE O EXERCÍCIO INTERVALADO PROMOVER SUPERIORES RESPOSTAS PSICOAFETIVAS E ALTERAR O BALANÇO SIMPATOVAGAL EM PACIENTES BIPOLARES, PESSOAS TREINADAS E SEDENTÁRIAS

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RESUMO

Os objetivos do presente estudo foram determinar os efeitos agudos do exercício aeróbio continuo (moderado) vs. intervalado de alta intensidade sobre os níveis de ansiedade, ativação corporal, repostas afetivas, bem como, sobre alterações na variabilidade da FC (V_{FC}) entre participantes treinados e sedentários, e pacientes bipolares. A amostra foi composta de 8 participantes treinados aeróbiamente, 8 sedentários, e 8 pacientes diagnosticados com TB. Foram realizados três visitas ao laboratório. Os pacientes com TB passaram por prévia avaliação, definindo a gravidade dos sintomas para TB. Os treinados e sedentários iniciaram prontamente a coleta de dados após assinatura do termo de consentimento. Todos os participantes foram submetidos na primeira visita a uma bateria de procedimentos antropométricos, avaliação da pressão arterial, bem como, um teste de esforço submáximo para definição das cargas de trabalho. Nas vistas dois e três os sujeitos foram divididos aleatóriamente à realizar um exercício aeróbio contínuo e intervalado. Anterior ao início do exercício, as escalas psicoafetivas foram aplicadas na seguinte ordem: SUDs de ansiedade; ativação corporal (excitação); de sensação. Após, todos foram submetidos a um exame de V_{FC} de olhos fechados por 10 min com respiração espontânea. Após exatamente 3 minutos do término da execução do exercício, uma nova medida de de V_{FC} foi realizada e todas as escalas foram novamente respondidas em ordem. Para as análises das variáveis dependentes, escalas de ansiedade, ativação corporal, sensação, foram utilizados um modelo ANOVA de medidas repetidas de três entradas (3 x 2 x 2) com medidas repetidas para momento (pré e pós). Os dados de V_{FC} foram analisados a partir das diferenças das médias pré e pós exercício (contínuo vs. intervalado) com uma ANOVA de medidas repetidas de duas entradas (2 x 2). A magnitude do tamanho do efeito (TE) foi também determinada. Todos os grupo reduziram significativamente as respostas de ansiedade pós exercício comparado a base (p = 0,001), existindo tendência do intervalado à promoção melhor perfil de ansiedade comparado ao contínuo (TE moderado). A ANOVA demonstrou diferenças significativas entre o nível de ativação corporal pré e pós exercício contínuo (p = 0,000), bem como, para o exercício intervalado (p = 0,000). O programa de exercício intervalado demonstrou diferenças quando comparado ao grupo contínuo (p = 0,000). No entanto, não houve diferenças para ativação corporal entre grupos (p = 0,088). Todas as respostas perceptivas em função dos exercícios prescritos foram significativamente positivas e aumentadas pós exercício contínuo (p = 0,000) e intervalado (p = 0,000). Da mesma forma existiu diferenças significativas entre o modo contínuo vs. intervalado (p = 0,000), tendendo o exercício intervalado a um alto TE para os grupos treinados e bipolares. Para V_{FC}, não houve diferenças significativas na condição pré, tanto contínuo, quanto intervalado (p > 0,05). Não houve diferenças significativas entre grupos pós intervenção com exercício (p > 0,05), no entanto, houve redução do drive simpático observado a partir da medida RMSSD, LF, e LF/HF (p = 0,001), sem significativa reentrada vagal (p > 0,05). Ambos os exercícios foram eficientes para promover redução dos níveis de ansiedade, elevação do afeto positivo, e promover alterações do balanço simpatovagal para todos os participantes. Nossos resultados sugerem que exercício intervalado desencadeou melhores resultados principalmente para o TB comparado ao exercício contínuo, podendo ser incluída como estratégia para fracionar o impacto do exercício e favorecer a adesão ao treinamento.

Palavras Chave: Frequência cardíaca, respostas afetivas, exercício intervalado

INTRODUÇÃO

É bem estabelecido na literatura que pacientes com transtornos de humor bipolar (TB), em geral, possuem alterações estruturais e funcionais significativas no sistema nervoso central [1-9], podendo se agravar decorrente do tempo em que a doença se inicia, bem como, em função de hábitos comportamentais como o sedentarismo, e o abuso de álcool, fumo e drogas [10, 11]. Tal perspectiva, traz consigo comorbidades associadas, como por exemplo, elevados níveis de ansiedade [12-14], que por sua vez exibem significativa relação com alterações no balanço simpatovagal, demonstrado a existência de pobre regulação autonômica em pacientes psiquiátricos [15, 16].

Recentemente, pesquisas tem apresentado um novo cenário de tratamento para pacientes com TB. O exercício aeróbio, agora, parece se comportar como uma interessante via complementar de intervenção, capaz de alterar agudamente o sistema monoaminérgico de neurotransmissão, altamente ligado a psicopatologia dos disturbios de humor, bem como, aumentar a expressão de fatores tróficos e seus receptores específicos [17-21]. Em pessoas saudáveis é bem documentado que apenas uma sessão de exercício aeróbio é capaz de melhorar a modulação simpatovagal, associado a menores índices de riscos cardiovasculares e mortalidade por infarto [22, 23]. O padrão de tais respostas são também delineados dentro do espectro do TB em diferentes momentos do ciclo (depressão, mania, eutimia) a partir da medida não invasiva de variabilidade da frequência cardíaca (V_{FC}) [15, 16], no entanto, os efeitos agudos do exercício aeróbio sobre componêntes da V_{FC} são pouco articulados. Além disso, a aplicação de diferentes modelos de intervenção aeróbia, como por exemplo, a partir do exercício aeróbio intervalado, permanece ainda no campo das inferências, sem quaisquer informações acerca de como o cérebro de pacientes interpretaria

os estímulos em intensidade diferenciada, afetando diretamente a adesão ao exercício.

Portanto, é pertinente então, determinar os efeitos agudos do exercício de característica continua de moderada intensidade vs. intervalado de alta intensidade sobre os níveis de ansiedade, ativação corporal, repostas afetivas, bem como, sobre alterações na V_{FC} entre participantes controle treinados e sedentários, e pacientes bipolares. Como hipótese, acreditamos que os níveis de ansiedade serão significativamente reduzidos nos pacientes com TB, sem quaisquer alterações significativas nos participantes treinados e sedentários. É esperado também que as respostas de ativação corporal sejam superiores nos exercícios de característica intervalada, sem distinção entre grupos. As percepções afetivas serão positivas para todos os grupos de participantes e para todos os modelos de exercício, sendo apresentadas superiores respostas para o exercício intervalado. Por fim, a as variáveis relativas a V_{FC} quando comparado todos os grupos de participantes pré exercício, apresentarão significativas diferenças entre treinados vs. sedentários, treinados vs. bipolares, sem diferenças entre sedentários vs. bipolares. Para as demais comparações, todos os grupos apresentarão significativo aumento da V_{FC} pós exercício, sem diferenças significativas entre grupos.

MÉTODOS

O presente estudo utilizou como referência os pressupostos descritos pelo "*International Committee of Medical Journal Editors"* (ICMJE) e respeitou todos os ítens propostos no guideline "*Consolidated Standards of Reporting Trials"* (CONSORT) for reporting parallel group randomised trials. Todos os procedimentos foram realizados em acordo com a Declaração de Helsinki e incluídos no clinical trial registration of the U.S.

National Institutes of Health (ClinicalTrials.gov; NCT02498730).

Participantes da Amostra

A amostra foi composta de 8 participantes treinados aeróbiamente (contemplavam um nível 2-3x superior às exigências propostas pelo Colégio Americano de Medicina do Esporte – ACSM para prática de exercícios físicos), 8 participantes sedentários (não realizavam quaiquer tipos de exercícios físicos), bem como, 8 pacientes com diagnóstico de TB (em fase eutimica). Os participantes foram convidados a partir de chamadas feitas na internet e no CIPE do IPUB/UFRJ. Foram incluídos indivíduos treinados e sedentários de ambos os gêneros, com idade entre 18 e 65, e pacientes medicados e com diagnóstico de TB tipo II conforme critérios da "*Structured Clinical Interview for DSM-IV* (SCID; First *et al*, 1997) e *American Psychiatric Association*. Foram excluídos comorbidades psiquiátricas como sinais e sintomas psicóticos, doenças neurológicas, epilepsia, retardo mental, além de pacientes com transtornos do tipo: obsessivo-compulsivo, personalidade grave, ou possuem diagnóstico de problemas cardíacos. Todos os pacientes assinaram o termo de consentimento livre e esclarecido (ANEXO IV).

O estudo foi previamente aprovado pelo comitê de ética da Universidade Federal do Rio de Janeiro (#045.2015 - ANEXO I). A Tabela 1 conterá as características antropométricas, de composição corporal, variáveis fisiológicas e de desempenho do grupo investigado. A Tabela 2 apresenta os medicamentos adminstrados ao pacientes bipolares.

Tabela 1. Característica da amostra

Variáveis	Treinados	Sedentários	Bipolares
#	Média ± DP	Média ± DP	Média ± DP
Variáveis Antropométricas			
Idade (anos)	30,6 ± 8,7	42,4 ± 11,9	46,6 ± 10,4
Massa (kg)	75,3 ± 11,8	78,0 ± 16,0	85,5 ± 16,8
Estatura (cm)	176,6 ± 9,9	161,4 ± 11,2	166,3 ± 8,3
Gordura (%)	12,4 ± 8,3	27,0 ± 10,7	25,8 ± 11,3
RCQ (-)	0,79 ± 0,04	0,85 ± 0,08	0,88 ± 0,09
Variáveis Fisiológicas			
FC Repouso (bpm)	62,1 ± 8,1	81,1 ± 11,1	81,0 ± 10,4
PA Sistólica (mmHg)	124,0 ± 15,2	124,3 ± 12,4	130,8 ± 14,4
PA Diastólica (mmHg)	76,3 ± 7,9	81,8 ± 15,2	82,0 ± 9,7
$VO_{2Máx}$ ($mL.kg.^{-1}min^{-1}$)	53,4 ± 6,4	32,1 ± 4,9	25,8 ± 8,1
$V_{VO2Máx}$ (km/h)	14,8 ± 1,8	-	-
$INC_{VO2Máx}$ (%)	-	13,3 ± 2,0	8,5 ± 5,2
Escalas Psiquiátricas			
Hamilton Depressão	-	-	5,3 ± 4,4
Young Mania	-	-	1,0 ± 1,4

Legenda: DP = desvio padrão; RCQ = relação cintura quadril; FC = frequência cardíaca; $V_{VO2Máx}$ = velocidade associada ao consumo máximo de oxigênio; $INC_{VO2Máx}$ = inclinação associada a intensidade de ocorrência do consumo máximo de oxigênio.

Tabela 2. Medicamentos administrados aos pacientes bipolares

Paciente	Medicamento	Dose	Quantidade
1	Lithium	300 mg	(2 manhã e 2 noite)
	Rivotril	2 mg	1 (noite)
2	Lithium	300 mg	(1 manhã e 2 noite)
	Lamotrigina	100 mg	(1,5 noite)
	Fenargan	25 mg	(0,5 manhã e 1 noite)
3	Lithium	300 mg	(2 manhã e 3 noite)
	Neuroleptil	10 mg	(1 noite)

	Rivotril	2 mg	(1 noite)
4	Lithium	300 mg	(1 manhã e 2 noite)
	Lamotrigina	100 mg	(2 noite)
	Olanzapina	2,5 mg	(2 noite)
5	Risperidona	2 mg	???
	Carbomazepina	200 mg	(1 manhã e 1 noite)
	Diazepam	20 mg	(1 noite)
6	Lithium	300 mg	(2 manhã e 3 noite)
	Rivotril	2 mg	(1 noite)
7	Não Reportado	???	???
8	Sertralina	50 mg	(1 noite)

Design Experimental

Foram realizados um total de três visitas ao laboratório. Todos os pacientes com TB passaram por prévia avaliação em local anexo ao laboratório de pesquisa, onde foram aplicadas as escalas de sintomas para TB, para posterior enquadramento nas características estudo. Os participantes treinados e sedentários não foram submetidos a esta etapa, e portanto, iniciaram prontamente a coleta de dados. Após a inclusão no estudo, os participantes foram submetidos na primeira visita a uma bateria de procedimentos antropométricos, avaliação da pressão arterial, bem como, um teste de esforço submáximo para definição das cargas de trabalho. Nas vistas posteriores (dois e três) os sujeitos foram divididos aleatóriamente à realizar um exercício de característica contínua e intervalada, alternando conforme a entrada, e os grupos.

Dentro das vistas experimentais (dois e três), foram realizados anterior ao início do exercício, a aplicação das escalas psicoafetivas na seguinte ordem: escala SUDs de ansiedade; escala de ativação corporal (excitação); escala de sensação. Após verificação, todos foram submetidos a um exame de variabilidade de FC (V_{FC}) de olhos fechados por 10

min (sentados em posição de conforto e em ambiente escuro) e com respiração espontânea. Em seguida, deu-se início aos procedimentos de exercício (protocolo descrito na sessão de exercício). Após exatamente 3 minutos do término da execução do exercício, uma nova medida de de V_{FC} foi realizada nas mesmas condições ditadas anteriormente por 10 min. Todas as escalas foram novamente respondidas em mesma ordem de acontecimentos. A Figura 1 representará o desenho experimental de pesquisa.

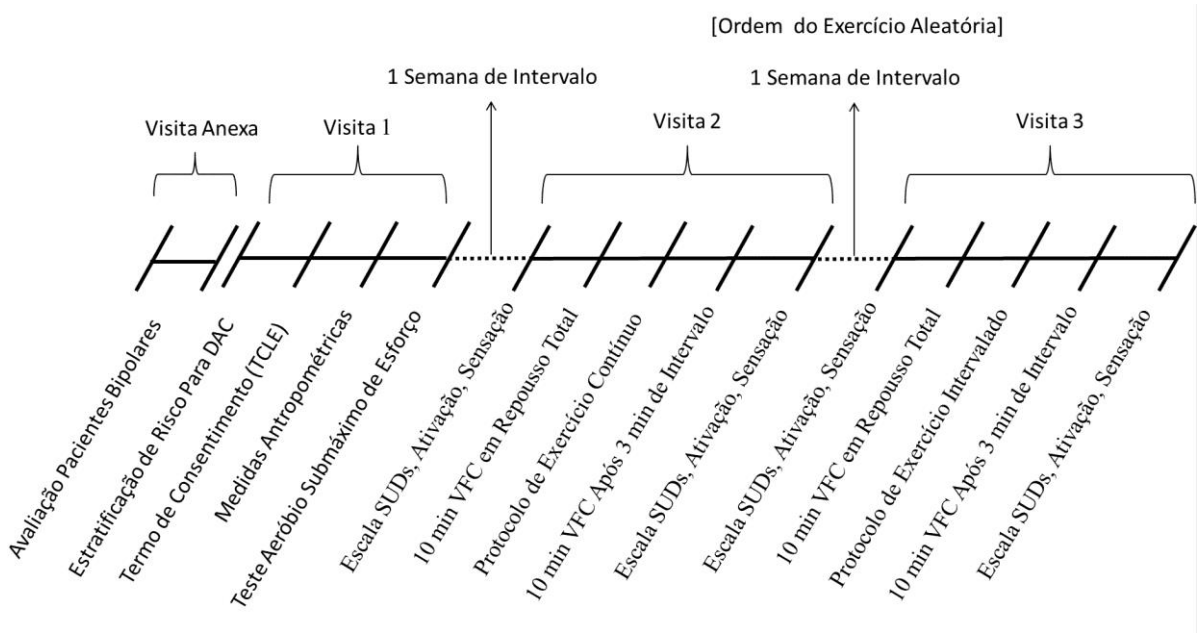


Figura 1. Desenho Experimental

Procedimentos

Avaliação de Sintomas do TB

Para fazer o enquadramento dos pacientes no presente estudo, cada sujeito foi avaliado por duas diferentes escalas: Hamilton para sintomas depressivos, e Young para avaliação do estado maníaco [24, 25]. Estes instrumentos consistem em uma entrevista

diagnóstica semi-estruturada. A escala de Hamilton para depressão é composta por 21 ítens pontuados em uma escala Likert que varia em uma pontuação de 0 a 2 ou 0 a 4 de acordo com a severidade dos sintomas. Já a escala de Young para mania é composta por 11 ítens investigados a partir de entrevista clínica subjetiva, onde cada ítem é classificado quanto sua severidade, graduando de 0 a 4 (humor elevado, atividade psicomotora, interesse sexual, sono, linguagem, aparência e discernimento), a excessão dos ítens: irritabilidade, fala, conteúdo, e comportamento agressivo, os quais possuem classificação de 0 a 8.

Antropometria e Medidas Fisiológicas de Repouso

Foram realizados medidas de espessura de dobras cutâneas a partir do protocolo de três dobras (peitoral, abdome e coxa) conforme descrito por Jackson e Pollock, [22], assim como, as medidas perimétricas de cintura, abdômen, e quadril. Após a predição da densidade corporal, foi determinado o percentual de gordura através da equação de Siri, (1961). Também serão coletados dados sobre a freqüência cardíaca de repouso (FC_{rep} - Polar® 810i), e pressão arterial em repouso (PA) por um esfigmomanômetro (Wan Med®), além da massa corporal e a estatura (Sanny®, Brasil).

Avaliação Cardiopulmonar Submáxima ($VO_{2Máx}$)

Em um ambiente calmo e com temperatura controlada (20 a 22º), todos os participantes aferiram sua FC de repouso (FC_{Rep}) durante 6 min precedentes ao teste. O aquecimento consistiu em uma caminhada na esteira rolante a 5,0 $km \cdot h^{-1}$ a 1% de inclinação durante um período de 3 min. A partir desse estágio inicial, foram administrados incrementos de 2% sobre a inclinação (aprox. 1 MET) a cada minuto objetivando o alcance

da intensidade mínima de 55% da FC de reserva (FC_{Res}). Depois de alcançado a intensidade proposta, a inclinação e a velocidade então foram mantidas inalteradas por 6 min para possibilitar o alcance do estado de equilíbrio. O objetivo é alcançar um mínimo de 65% da FC_{Res}.

A FC e a percepção subjetiva de esforço (PSE) variando 0 (nenhum esforço) e 10 (máximo absoluto) foram registradas nos 10 s finais de cada minuto. A média de FC entre o 5º e 6° minutos da fase estável foi utilizada para a estimativa do $VO_{2Máx}$. O $VO_{2Máx}$ foi estimado a partir da equação metabólica de caminhada proposta pelo ACSM [26], conforme adaptação sugerida por Oliveira et al. [27] para esteira rolante, juntamente com a equação de preditiva definida por Swain et al. [28]. A confiabilidade da medida para esteira rolante foi estabelecida previamente por Santos et al. [29].

Quadro 1. Formula de predição do $VO_{2Máx}$ proposta por Swain *et al*. (2004), e adaptada por Oliveira *et al*. (2013).

$VO_{2Máx} = [(0,1 \times velocidade) + (1,8 \times velocidade \times inclinação) + 3,5] \div [(FC_{Carga} - FC_{Rep}) \div (FC_{Máx} - FC_{Rep})] + 3,5$
Onde: $VO_{2Máx}$ - consumo máximo de oxigênio em $mL \cdot kg^{-1} \cdot min^{-1}$; Velocidade - em $m \cdot min^{-1}$; Inclinação - em valores centesimais; FC_{Carga} - média da FC entre o 5º e o 6º min em estado estável; $FC_{Repouso}$ - FC após 10 min de repouso; $FC_{Máx}$ – estimada pela equação 220 – idade.

Escalas de Avaliação Psicoafetivas.

Todas as escalas são de fácil entendimento e foram devidamente respondidas por autoseleção de valores graduados pelos próprios participantes e pacientes bipolares.

Escala de Ansiedade (SUDS). A escala SUDS de ansiedade utiliza-se de um padrão linear de resposta variando de "0" onde representaria ausência de ansiedade, ou "10" representando um nível de ansiedade máxima (ANEXO III-A)

Escala de Ativação Corporal (Felt Arousal Scale). Utilizada com objetivo de avaliar o nível de excitação auto percebida decorrente das três condições pré e pós exercício físico realizado. Essa escala varia linearmente de 1 = pouco ativado, até 6 = muito ativado, com seus valores intermediários (ANEXO III-B).

Escala de Sensações (Feeling Scale). A escala de sensações tem por objetivo verifica a dimensão das respostas afetivas determinada pelo nível de sensação positiva, neutra, ou negativa, proporcionada pelo exercício aeróbio, sendo distribuídos em uma escala ordinal de dois polos, variando de zero (0) como uma posição neutra; +1 = razoavelmente bom a +5 = muito bom; -1 = razoavelmente ruim, até o -5 = muito ruim (ANEXO III-C).

Avaliação do Comportamento Afetivo Relativo ao Exercício. O afeto foi avaliado pelo modelo circumplexo, estrutura bidimensional onde se posicionam valores dos processos psicologicos obtidos de respostas emocionais de excitação (ativação) e afetiva (agradabilidade). Então, a apartir dessas escalas de sensações e ativação, foi criado um modelo cartesiano

representativo com quatro divisões que demonstrará se o sujeito se encontrará em um quadrante de categorias emocionais relacionadas a serenidade, calma, conforto, relaxamento e sonolencia (em caso de baixa excitação e valor afetivo positivo), ou em uma categoria emocional de alegria, felicidade, encantamento, surpresa e estimulação (alta excitação e afeto positivo). Ja quando o nivel de excitação for alto e a valencia afetiva negativa, as caracteristicas emocionais sao relacionadas a um estado furioso, aflito, irritado, frustrado, tenso, medroso, aticado e em panico. Por fim, quando o nivel de excitacao for baixo e a valencia afetiva for negativa, caracterizam-se os estados emocionais de triste, deprimido, melancolico, entediado, abatido, e cansado.

Avaliação Autonômica de Variabilidade da Frequência Cardíaca (V_{FC})

Os dados de V_{FC} foram determinados em períodos de 10 minutos de repouso antes e após a sessão de exercício, e armazenados no monitor de FC, e posteriormente transmitidos ao computador para serem registrados em software específico (*RS800* Perfomance de Precisão versão 4.01.029, *Polar*, Finlândia). A V_{FC} armazenada de cada participante foi importada para um software específico (Kubios HRV – Heart Rate Variability Analysis – Version 3.0.2, 2017), e analisado sob o domínio do tempo e da frequência, extraindo os seguintes dados derivados: SDNN (desvio padrão dos intervalos RR normal-a-normal); RMSSD (raiz quadrada das diferenças dos sucessivos intervalos RR); LF (banda de frequência baixa - 0.04-0.15 Hz); HF (banda de frequência alta - 0.15-0.4 Hz); e Razão LF/HF. Os dados referêntes ao domínio foram transformados em escala logarítmica para normalização dos dados para posterior comparação pré e pós exercício.

Sessão de Exercício Aeróbio Contínuo e Intervalado de Alta Intensidade (HIT)

Ambos os procedimentos de exercício contínuo e intervalados foram iniciados em um aquecimento padrão de 5 min de caminhada a 40% $VO_{2Máx}$. Para o exercício de característica contínua os participantes iniciaram a parte específica a 65% do $VO_{2Máx}$ e mativeram tal intensidade durante um período de 12 min, e posteriormente finalizando com 3 min de volta a calma. Para o exercício HIT os participantes realizaram um total de 6 estímulos de tempo igual a 45 seg, com recuperação de 1 min e 15 seg. A intensidade dos estímulos foram ajustadas a um patamar correspondente a 100% do $VO_{2Máx}$ e a recuperação 40% deste percentual. Ao final, foi estabelecido uma volta a calma de intensidade livre durante 3 min. O tempo total de exercício para ambos os grupos foi de 20 min e o trabalho total foi igualado entre os grupos. As intensidades tanto para o exercício contínuo, quanto para o exercício intervalado foram definidas e ajustadas por conversão metabólica utilizando como referência o $VO_{2Máx}$ obtido previamente, e calculado a partir das equações de predição para corrida e caminhada descrita pelo ACSM, [26] (Tabela 4). Como critério de finalização do protocolo, foi estabelecido o alcance da totalidade dos estímulos, ou a exaustão voluntária máxima. A FC e a PSE será gravada durante todas as sessões de treinamento e serão realizadas em uma esteira Imbramed modelo ATL (MODELO Professional, USA). O programa de treinamento é descrito na Tabela 3.

Tabela 3. Programas de treinamento HIT.

	Estímulo		Recuperação	
Momento	Duração	Intensidade	Duração	Intensidade
Aquecimento	5,0 min	40% $VO_{2Máx}$	-	-
Específico	6x 45 seg	100% $VO_{2Máx}$	1 min 15 seg	40% $VO_{2Máx}$

Volta Calma	Livre	-	3,0	Livre

Tabela 4. Determinação da carga de trabalho de exercício a partir da equação de conversão proposta pelo ACSM.

$Velocidade = (VO_{2Máx} – 3,5) / 0,2$
Onde: $VO_{2Máx}$ - consumo máximo de oxigênio a partir da predição Velocidade - em $m \cdot min^{-1}$

Análise Estatística

Foram realizados análises de homocedasticidade e normalidade dos dados. Para análise das variáveis antropométricas e fisiológicas de base, foi utilizado uma ANOVA Univariada, com posterior aplicação do Post Hoc de Tuckey para observara as diferenças entre grupos. Para as análises das variáveis dependentes, escalas de ansiedade, ativação corporal, sensação, foram utilizados um modelo ANOVA de medidas repetidas de três entradas (3 x 2 x 2) com medidas repetidas para momento (pré e pós). Os dados de V_{FC} foram analisados a partir das diferenças das médias pré e pós exercício (contínuo vs. intervalado) com uma ANOVA de medidas repetidas de duas entradas (2 x 2). Um teste de Post Hoc Tuckey apresentou a diferença entre grupos. A magnitude do tamanho do efeito (TE) foi determinada para sustentar os resultados analisados, e foi classificado segundo sugerido por Cohen (*d*). Todas as análises serão realizadas no programa SPSS (v. 17, SPSS Inc., Chicago, USA), considerando um nível de significância de $p = 0,05$.

RESULTADOS

Primeiramente, quando observamos as características da amostra, o seguinte cenário nos é apresentado na Tabela 5.

Tabela 5. Variáveis antropométricas e fisiológicas

Variáveis	Comparações		
	T x S	T x B	S x B
Idade	*p* = 0,084	*p* = 0,0015*	*p* = 0,696
Massa	*p* = 0,929	*p* = 0,377	*p* = 0,586
Altura	*p* = 0,015*	*p* = 0,377	*p* = 0,581
% Gordura	*p* = 0,024*	*p* = 0,039*	*p* = 0,970
RCQ	*p* = 0,348	*p* = 0,063	*p* = 0,596
PA Sistólica	*p* = 0,999	*p* = 0,599	*p* = 0,621
PA Diastólica	*p* = 0,605	*p* = 0,578	*p* = 0,999
FC Repouso	*p* = 0,003*	*p* = 0,003*	*p* = 0,999
FC Máxima	*p* = 0,084	*p* = 0,015*	*p* = 0,696
$VO_{2Máx}$	*p* = 0,000*	*p* = 0,000*	*p* = 0,016*

Legenda: T = grupo treinados; S = grupo sedentários; B = grupos bipolar; RCQ = relação cintura quadril; PA = pressão arterial; FC = frequência cardíaca; $VO_{2Máx}$ = consumo máximo de oxigênio.

Respostas de Ansiedade Diante do Exercício

Ao analizarmos os três grupos amostrais individualmente, todos os grupo demonstraram redução significativa nas respostas de ansiedade pós treinamento comparado a condição de base (*p* = 0,001). Além disso, existiu também uma tendência do treinamento intervalado à promoção de uma melhor perfil de ansiedade comparado ao treinamento contínuo. O TE forneceu significativa sustentação a essas respostas, a excessão do grupo de participantes sedentários (T = -0,54 vs. -0,68; S = -0,87 vs. -0,55; B = -1,09 vs. -1,62, respectivamente para o exercício continuo vs. intervalado). Houve diferenças significativas entre os grupos de treinados x bipolares (*p* = 0,000), e sedentários x bipolares

(p = 0,000), no entanto, nenhuma diferença foi observada entre os grupos treinados vs. sedentários para redução da ansiedade (p = 0,766). Em adendo, o impacto da redução da ansiedade para o grupo Bipolar foi superior a todos os outros grupos. A Tabela 6 abaixo demonstra mais detalhadamente as respostas de ansiedade com seus respectivos valores estatísticos.

Tabela 6. Perfil de Ansiedade Pré e Pós Exercício

	Treinados				Sedentários				Bipolares			
Exercício	Contínuo		Intervalado		Contínuo		Intervalado		Contínuo		Intervalado	
Momento	Pré	Pós	Pré	Pós	Pré	Pós	Pré	Pós	Pré	Pós	Pré	Pós
Média	0,25	0,00	0,63	0,00	0,50	0,00	1,13	0,38	3,50	2,00	3,29	0,86
DP	0,46	0,00	0,92	0,00	0,58	0,00	1,36	0,74	1,38	1,79	1,50	1,07
TE		-0,54		-0,68		-0,87		-0,55		-1,09		-1,62

Legenda: DP = desvio padrão da média; TE = tamanho do efeito (Cohen index)

Respostas de Ativação Corporal e a Escala de Sensação.

A ANOVA demonstrou diferenças significativas entre o nível de ativação corporal pré e pós exercício contínuo (p = 0,000), bem como, para o exercício intervalado (p = 0,000). Além disso, o programa de exercício intervalado demonstrou significativa diferenças quando comparado ao grupo contínuo (p = 0,000). No entanto, não houve diferenças significativas para ativação corporal entre grupos (p = 0,088). A tabela 7 demontra os resultados de média e desvio padrão obtidos para todos os grupo de exercício e condições. Em adendo o TE novamente apresentou uma tendência mais acentuada para o modo de exercício intervalado, a excessão do grupo Sedentário que obteve maior magnitude do efeito.

Tabela 7. Ativação Corporal Pré e Pós Exercício

	Treinados				Sedentários				Bipolares			
Exercício	Contínuo		Intervalado		Contínuo		Intervalado		Contínuo		Intervalado	
Momento	Pré	Pós	Pré	Pós	Pré	Pós	Pré	Pós	Pré	Pós	Pré	Pós
Média	2,10	3,88	2,38	5,75	1,25	3,25	2,00	5,38	2,83	4,83	2,43	5,14
DP	1,10	0,83	1,06	0,46	0,50	0,50	1,20	0,74	1,17	2,04	0,98	1,07
TE		1,55		3,18		4,00		2,82		1,71		2,78

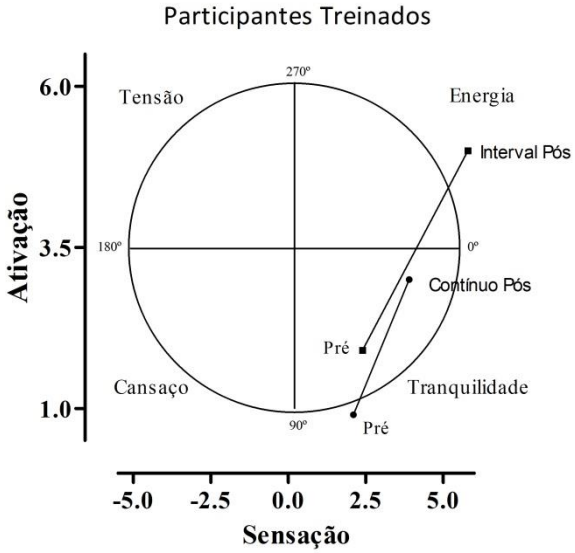
Legenda: DP = desvio padrão da média; TE = tamanho do efeito (Cohen index)

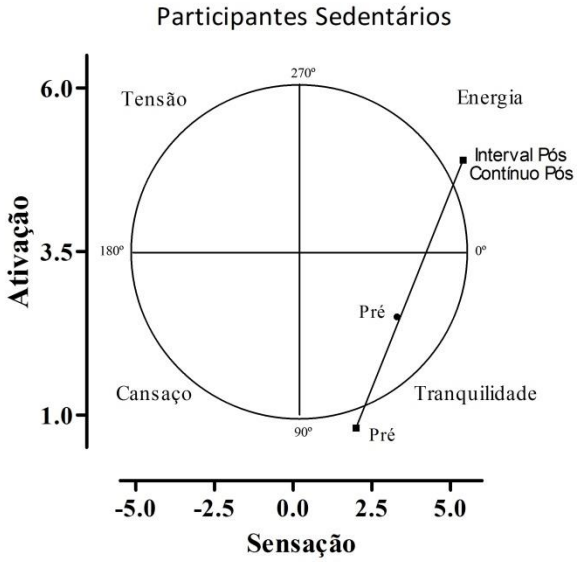
Quando analisamos as escalas de sensação, todas as respostas perceptivas em função dos exercícios prescritos foram significativamente positivas e aumentadas pós exercício contínuo (p = 0,000) e intervalado (p = 0,000). Da mesma forma existiu diferenças significativas entre o modo contínuo vs. intervalado (p = 0,000), tendendo o exercício intervalado a uma alta magnitude do efeito para os grupos treinados e bipolares, segundo a classificação de Cohen (TE = 1,37 vs. 1,59. O grupo de sendetários interessantemente obtiveram superiores respostas de TE para o exercício inervalado quando comparados aos demais grupos (TE = 2,50 vs. 3,54, respectivamente para contínuo e intervalado). Quando avaliamos os grupos, os mesmos não diferiram significativamente (*p* = 0,289). A tabela 8 apresenta as médias e desvio padrão de todas as condições e grupos investigados. Além disso, por inspeção visual, observamos de acorco com o modelo circumplexo na Figura 3, que o participantes transitaram somente no quadrantes de tranquilidade e energia, sem apresentar fadiga ou desgaste decorrente dos exercícios.

Tabela 8. Escala Afetiva de Sensação Pré e Pós Exercício

	Treinados				Sedentários				Bipolares			
Exercício	Contínuo		Intervalado		Contínuo		Intervalado		Contínuo		Intervalado	
Momento	Pré	Pós	Pré	Pós	Pré	Pós	Pré	Pós	Pré	Pós	Pré	Pós
Média	0,88	3,00	1,88	5,00	0,25	2,50	0,75	4,88	2,00	3,17	0,71	4,00
DP	1,55	1,07	1,96	0,00	0,50	0,58	1,16	0,35	1,00	2,23	1,25	1,53
TE		1,37		1,59		2,50		3,54		0,58		2,62

Legenda: DP = desvio padrão; TE = tamanho do efeito





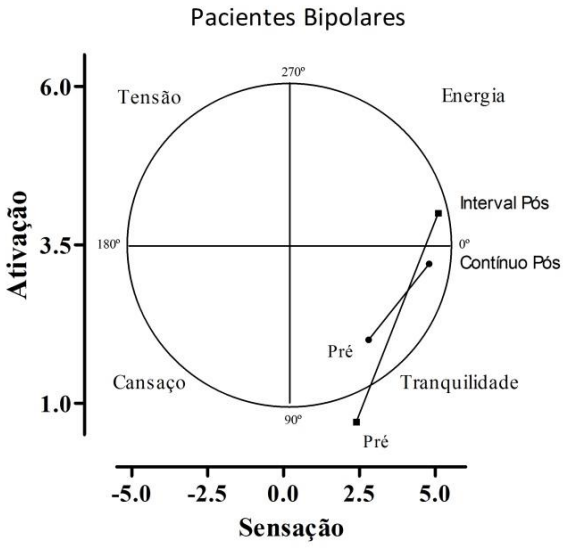


Figura 3. Modelo Cirumplexo Observacional do Comportamento Diante dos Exercícios Contínuos e Intervalados.

Variabilidade da Frequência Cardíaca (V_{FC})

Os resultados de V_{FC} foram expressos por média e desvio padrão e são devidamente apresentados nas tabelas 9 e 10. A Figura 4 nos apresenta o comparativo do TE observado em cada grupo. Não houve diferenças significativas na condição pré exercício, tanto contínuo, quanto intervalado para todas as variáveis contra todos os grupos da amostra (p > 0,05).

Tabela 9. Comparativo de Médias e DP dos dados de V_{FC} diante do Exercício Contínuo.

Variáveis	Pré Exercício Contínuo						Pós Exercício Contínuo					
	Treinados		Sedentário		Bipolares		Treinados		Sedentário		Bipolares	
	(M)	(DP)	(M)	(DP)	(M)	(DP)	(M)	(DP)	(M)	(DP)	(M)	(DP)
SDNN (ms)	45,7	18,2	19,2	4,4	31,9	33,0	22,5	4,7	9,9	3,7	16,9	20
RMSSD (ms)	53,0	34,2	15,1	3,4	30,4	28,7	17,8	7,1	6,13	3,0	18,1	26
LF (Pot Log)	6,81	0,53	5,40	0,63	5,39	1,67	5,71	0,5	4,19	0,84	3,90	0,9
HF (Pot Log)	6,33	1,33	4,39	0,12	5,10	2,00	4,34	0,9	1,96	0,67	3,36	2,0
LF/HF (ms^2)	2,94	3,15	3,173	2,18	2,17	2,66	6,26	6,0	12,60	8,70	4,00	6,1

Legenda: M = média; DP = desvio padrão; SDNN = ; RMSSD = ; LF = baixa frequência; HF = alta frequência; LF/HF = razão entre os componêntes de baixa e alta frequência.

Tabela 10. Comparativo de Médias e DP dos dados de V_{FC} diante do Exercício Intervalado.

Variáveis	Pré Exercício Intervalado						Pós Exercício Intervalado					
	Treinados		Sedentários		Bipolares		Treinados		Sedentários		Bipolares	
	(M)	(DP)	(M)	(DP)	(M)	(DP)	(M)	(DP)	(M)	(DP)	(M)	(DP)
SDNN (ms)	49,7	19,8	34,4	20,8	37,9	31,3	16,8	5,0	23,7	16,8	12,8	6,9
RMSSD (ms)	52,5	32,9	39,6	34,4	42,7	34,9	12,1	4,4	24,3	21,5	12,4	8,6
LF (Pot Log)	6,91	0,9	5,73	0,9	5,61	1,5	4,90	0,9	4,96	1,61	3,85	1,6

HF (Pot Log)	6,46	1,2	5,73	1,9	5,76	1,8	3,49	1,2	4,33	2,40	3,18	2,1
LF/HF (ms^2)	2,13	1,7	2,34	3,0	1,13	0,9	5,31	3,6	2,95	2,86	5,74	10,9

Legenda: M = média; DP = desvio padrão; SDNN = ; RMSSD = ; LF = baixa frequência; HF = alta frequência; LF/HF = razão entre os componêntes de baixa e alta frequência.

Os dados foram comparados a partir das diferenças de médias entre pré e pós exercício (contínuo e intervalado). Seus respectivos valores estatísticos são apresentados na Tabela 11.

Tabela 11. Valores Estatísticos Comparativos entre as Variáveis Referentes ao Domínio do Tempo.

	Domínio do Tempo		Domínio da Frequência		
	SDNN	RMSSD	LF	HF	HF/LF
	(ms)	(ms)	(Pot Log)	(Pot Log)	(ms^2)
Grupo					
T x S	*p*=0,123	*p*=0,131	*p*=0,125	*p*=0,090	*p*=0,574
T x B	*p*=0,564	*p*=0,285	*p*=0,897	*p*=0,638	*p*=0,755
S x B	*p*=0,311	*p*=0,591	*p*=0,114	*p*=0,205	*p*=0,415
Treino					
T	*p*=0,040*	*p*=0,379	*p*=0,006*	*p*=0,028*	*p*=0,845
S	*p*=0,426	*p*=0,548	*p*=0,643	*p*=0,209	*p*=0,206
B	*p*=0,050*	*p*=0,050*	*p*=0,284	*p*=0,050*	*p*=0,289

Legenda: *p* = valor estatístico produzido pela ANOVA de medidas repetidas a partir das comparações das médias das diferenças pré e pós exercício entre tipos de treinamento; T x S = grupo Treinado x Sedentário; T x B = grupo Treinado x Bipolares; S x B = grupo Sedentários x Bipolares; T = Treinados; S = Sedentários; B = Pacientes Bipolares.

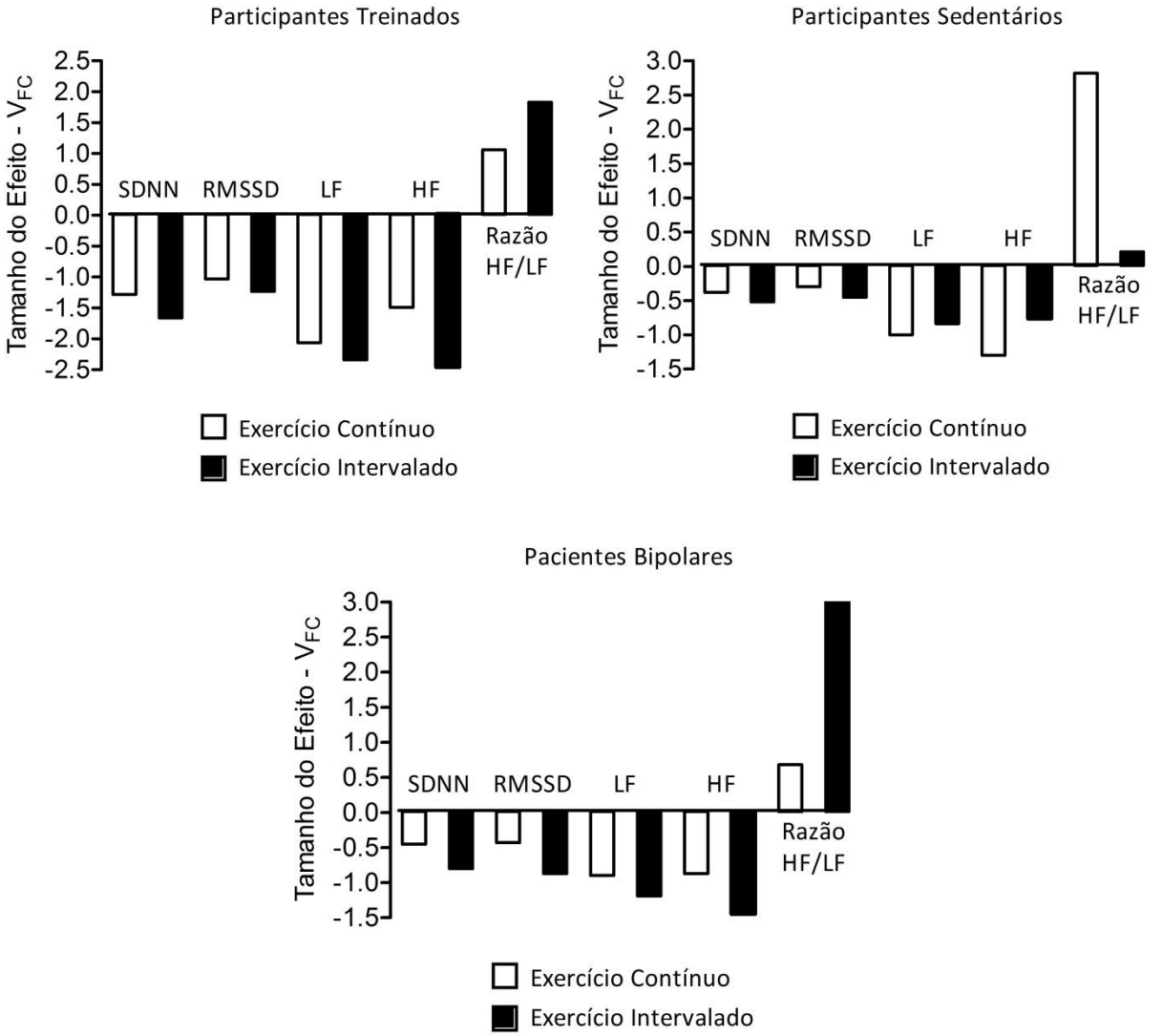


Figura 4. Comparativo dos valores de TE entre exercício contínuo vs. intervalado

DISCUSSÃO

O presente estudo é pioneiro em examinar os efeitos agudos do exercício aeróbio contínuo de moderada intensidade e intervalado de alta intensidade (HIT) sobre parâmetros psicoafetivos e autonômicos, na perspectiva principalmente do transtorno bipolar (foco em questão). Primeiramente, o protocolo HIT foi o ponto chave de nossa investigação. Propor uma nova configuração de prescrição aeróbia, que apesar da intensidade administrada (100% do $VO_{2Máx}$), fracionasse o impacto fisiológico, proporcionando respostas afetivas

favoráveis a adesão ao exercício, fornecem importante sustentação e valor inovativo aos achados deste estudo. Tal perspectiva quando consideramos especialmente a população bipolar, pouquissimo condicionada e refratárias ao exercício, parece-nos agora passível de inclusão como uma interessante via de tratamento para redução dos sintomas da doença, e das comorbidade normalmente associadas a esses transtornos.

Apesar dos benefícios já apontados ao tradicionais exercícios aeróbios de endurance [30, 31], tanto para pessoas saudáveis quanto pacientes com TB [32-35], atualmente projeta-se na literatura a ampliação do entendimento de aspectos relativos a intensidade ideal para melhora da saúde, e da potência aeróbia máxima ($VO_{2Máx}$), importante marcador do risco relativo de mortalidade por doenças cardiovasculares [23, 36]. Então, Quando comparamos protocolos de menor intensidade ao HIT, em pessoas saudáveis, os resultados são promissores ao sustentar o uso de intensidades de exercício próximas ou superiores ao $VO_{2Máx}$, verificando aumentos significativamente maiores principalmente para o $VO_{2Máx}$, e em um menor tempo de trabalho (estratégia tempo-eficiente). [37-41] [40, 42, 43]. Além disso, tais efeitos de melhora parecem exibir comportamentos semelhantes dentre níveis distintos de condicionamento físico, mas não há evidências na literatura que nos forneça base a respeito da aplicação do modelo intervalado de exercício e seus efeitos com TB, inviabilizando comparações diretas.

Um segundo ponto em questão em nosso estudo, foi a proposição de um meio de controle razoavelmente preciso para prescrição do exercício aeróbio, uma vez que metodologicamente os estudos realizados com pacientes bipolares são relativamente questionáveis [17-19, 44]. Então, a padronização dos estímulos, sejam eles contínuos ou

intervalados, nos possibilita obter também respostas padronizadas sob a ótica da ciência e da prática clínica. Em nosso estudo, todos os estímulos de exercício foram balanceados para gerar um mesmo impacto fisiológico, e os resultados apesar da maximização das diferenças entre as intensidades selecionadas, as mesmas proporcionaram uma percepção de esforço atenuadas e semelhantes entre as modalidades (3,5 ± 0,5 vs. 4,0 ± 0,8, em uma escala de 0 a 10, respectivamente para exercício contínuo, e exercício intervalado em pacientes bipolares). Atribuímos a essa resposta de esforço atenuada alguns dos resultados obtidos. Por exemplo, nossa hipótese inicial de efeito ansiolítico do exercício foi aceita além das expectativas, sendo observados reduções significativas para todos os grupos pós exercício, e superior impacto sob o grupo de TB no exercício intervalado (3,5 ± 1,3 vs. 2,0 ± 1,7 - TE = -1,09 vs. 3,2 ± 1,5 vs. 0,8 ± 1,0 – TE = -1,62; respectivamente para pré e pós exercício contínuo vs. intervalado). A literatura carece de informação acerca dos efeitos do exercício intervalado e suas respostas ansiolíticas especificamente em pacientes bipolares, no entanto, quando analisamos tais respostas em estímulos intervalados com diferentes transtornos mentais, Wu et al. [45] demonstraram a efetividade de um programa HIT em 22 pacientes após 8 semanas de exercício. Eles observaram significativa redução nos escores de ansiedade “BAI - Beck Anxiety Inventory” (13,67 ± 13,83 para 10,06 ± 11,18, p = 0,003), e depressão “BDI – Beck Depression Inventory” (19,56 ± 15,28 para 15,89 ± 14,33, p < 0,001) pós treinamento.

Quando observamos modelos de exercícios contínuos moderados, aqui em nosso estudo tratado como uma forma de controle, diferentes revisões e meta-análises já nos apresentavam relativa efetividade e significativa redução dos níveis de ansiedade [14, 46]. Além disso, parece ser claro uma associação inversa entre altos níveis iniciais de ansiedade e

níveis de atividade física [47, 48], e apesar de não nos tratarmos à responder esta pergunta, em nosso estudo foram encontrados baixíssimos níveis de $VO_{2Máx}$ nos pacientes com TB (treinados: 53,4 ± 6,4; sedentários: 32,1 ± 4,9; bipolares: 25,8 ± 8,1), ao mesmo tempo que elevados níveis de base de ansiedade foram também observados, estando em linha com observado na literatura [47, 48].

O conceito de respostas afetivas gira em torno de como o cérebro humano percebe e fornece significado a um determinado estímulo sensorial externo, ou decorrentes de alterações do ambiente fisiológico interno, mediando um comportamento facilitatório capaz de estimular os sistemas de recompensas por vias dopaminérgicas, ou um comportamento negativo, compreendido pelo mesmo como um ambiente de tensão, medo, ou ansiedade [20, 49]. Isto posto, as evidências dispostas na literatura acerca do modelo HIT de exercício são muito claras afirmando que as respostas afetivas decorrentes do exercício de alta intensidade são percebidas negativamente pelo nosso cérebro [50-52], desfavorecendo a adesão ao exercício e criando um ambiente de alta ativação corporal e alta tensão, em resumo, um ambiente hostil. Em posse dessas informações, o protocolo de exercício HIT realizado pelos três grupos de participantes foi preparado de forma que não obtivessemos os efeitos já esperados na literatura. Em nosso estudo, as respostas afetivas foram significativamente positivas para todos os grupos, e com maior magnitude justamente pelo modelo HIT de exercício (sedentários contínuo: 0,2 ± 0,5 vs. 2,5 ± 0,5 – TE = 2,50; sedentários intervalado: 0,7 ± 1,1 vs. 4,8 ± 0,3 – TE = 3,54; bipolares contínuo: 2,0 ± 1,0 vs. 3,17 ± 2,2 – TE = 0,58; bipolares intervalado: 0,7 ± 1,2 vs. 4,0 ± 1,5 – TE = 2,62; respectivamente pré e pós exercício), o que vai contra o exposto na literatura [50, 51]. Uma das recomendações da liteatura para obtenção de positivas respostas afetivas, é uma utilização prioritária do

metabolismo aeróbio [20]. E diferentemente do que é posicionado por alguns autores, HIT enquadra-se numa zona de transição entre ambos os sistemas aeróbios e anaeróbios (*crossover*) [38, 53-55]. Então, o que foi ajustado principalmente em nosso protocolo de exercício HIT, foi impedir que os estímulos realizados em alta intensidade, transitassem em uma zona anaeróbia por longos períodos de tempo. Esse efeito sugere que o fracionamento dos estímulos em períodos pequenos de exercício, possa ser uma importante saída para manutenção do exercício aeróbio regular, e consequentemente, a melhora de indicadores relativos a saúde [17, 21, 56, 57]. Ao visualizarmos os modelos gráficos circumplexos, observamos claramente que todos os sujeitos transitaram sob o quadrante da tranquilidade e da energia para todos os tipos de treinamento, sem um alto nível de estresse, o que configura a manutenção do Afeto Ativado Positivo (AAP).

Apesar dos importantes achados observados no campo do afeto, quando analisamos as respostas de V_{FC}, nossos resultados conflitam parcialmente com o padrão encontrado na literatura. Em primeira análise, tanto as variáveis fisiológicas representantes do domínio do tempo (SDNN e RMSSD), e da frequência (LF, HF, razão HF/LF) não demonstraram diferenças significativas pré exercício quando comparados os diferentes grupos testados (treinados vs. sedentários; treinados vs. bipolares; sedentários vs. bipolares), o que difere dos padrões encontrados para os referêntes grupos ($p > 0,05$). É de consenso que pessoas treinadas exibem supeiror V_{FC} em repouso quando comparado a grupos de pessoas sedentárias ou menos treinadas, denotando maior influência do drive neural parassimpático. Contrariamente, disfunções autonômicas tem sido reportadas tanto para pessoas sedentárias quanto para pacientes com transtornos mentais diversos [15, 16]. No entanto, Cohen et al. [58] observaram valores superiores de HF, bem como, reduzidos valores de

SDNN e razão LF/HF em 39 pacientes bipolares em seu estado eutímico, comparado aos controles saudáveis. Em outro estudo do mesmo grupo [59] quando foram comparados 32 pacientes bipolares caracterizados como eutímicos, utilizando métodos de análises da V_{FC} não lineares, desta vez nenhuma diferença significativa foi apontada para VFC em comparação aos controles saudáveis. Voss, Baier, Schulz, e Bar [60] sugerem a aplicação de métodos não lineares como interessante estratégia para análise da VFC em pacientes bipolares, apesar de não existir consenso na literatura.

Por fim, quando analisamos o padrão de resposta das variáveis de V_{FC} pós sessão em nosso estudo, estes parecem em linha com outros estudos já previamente publicados. Por exemplo, em participantes saudáveis, Heffernan et al. [61], observaram reduzidas alterações tanto em HF quanto LF transformado em função logarítmica, e aumentos significativos na razão LF/HF após o exercício aeróbio de característica contínua. Em pacientes com TB pouco se sabe sobre o tema, principalmente diante das manifestações decorrentes do exercício HIT. Quando outros trasntornos mentais são avaliados diante do modelo intervalado de exercício, James et al. [62] apresentaram reduções significativas na V_{FC} 1h após a realização do exercício, porém não para 72h após. Foram demonstrados reduzidos valores de SDNN: 75 > 57 ms - 57 > 83 ms; potência de LF: 3640 > 1961 ms^2 - 1961 > 4839 ms^2; potência de HF: 886 > 191 ms^2 - 191 > 635 ms^2; razão LF/HF: 14 > 21; 21 > 14, respectivamente para 1h após exercício e 72 após, sugerindo que de alguma forma o efeito principal do exercício HIT para a retomada parassimpática seja retardado por mais de 1h. Hautala et al. [63] sugeriram que o fluxo vagal cardíaco permaneceria atenuado por varias horas após prolongado exercício vigoroso, e o tempo de recuperação vagal dependeria da capacidade cardiorrepiratória individual. Em nosso estudo, apesar da distância percorrida ser completamente diferentes

do investigado no estudo de Hautala et al. [63], efeito semelhante se manifestou para todos os grupos e para todos os modelos de exercício, independendo da intensidade proposta. Apesar disso, o que ficou claramente evidenciado foi a forte redução do “drive” simpático, o que já era esperado.

Limitações

Mudanças no padrão respiratório poderiam representar um fator interveniente em nosso estudo, uma vez que não foram padronizados o número de ciclos respiratórios por minuto, e é conhecido que a respiração sinusal afetaria o fluxo autonômico sem necessariamente significar uma resposta direta do exercício. A V_{FC} mensurada por nós, foi gravada em um ambiente calmo e escuro, de temperatura controlada entre 21 e 23º C, com os participantes de olhos fechados quase que totalmente livre de estímulos sensoriais auditivos externos. Portanto, essa limitação ocorreu de forma proposital devido a necessidade de se realizar outras análises fisiológicas integradas, que não poderiam por sua vez concorrer com a estimulação sensorial de quaisquer tipo. Mesmo diante deste cenário, nossos resultados de V_{FC} exibiram suporte na literatura cinetífica podendo ser considerados válidos.

CONCLUSÃO

Ambos os exercícios de característica contínua moderada, e intervalado de alta intensidade (HIT) foram eficientes para promover significativa redução dos níveis de ansiedade, elevação do afeto positivo, e promover principalmente alterações do balanço simpatovagal para todos os grupos de participantes, reduzindo substancialmente o drive

simpático. Além do mais, nossos resultados sugerem ainda que o modelo intervalado de exercício foi capaz de desencadear melhores resultados fisiológicos principalmente para o grupo de pacientes bipolares quando comparados ao exercício contínuo, podendo ser posicionado com uma estratégia para fracionar o impacto fisiológico do exercício e favorecer a adesão ao treinamento.

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CONCLUSÃO GERAL

De fato parece existir na literatura uma relação inversa entre os níveis de condicionamento físico e os sintomas de diferentes transtornos mentais, inclusive o transtorno bipolar. A combinação entre exercício aeróbio a medicamentos específicos poderiam afetar positivamente os sintomas da doença, e promover significativa influência sobre os mecanismos fisiolpatológicos, tal como, sistema monoaminérgico, equilíbrio pró/anti inflamatório, e as neurotrofinas. Apesar desse entendimento, a literatura apenas caminha sob a ótica da aplicação do exercício físico. Por exemplo, pouco se sabe ainda acerca dos efeitos do exercício de característica intervalada, que em pessoas saudáveis exibem potenciais benefícios no condicionamento cardiorrespiratório. Nossas investigações agudas corroboram dessas expectativas, apresentando-nos resultados promissores que favorescem aspectos psicoafetivos e a adesão ao exercício. Entretanto, essa investigação ainda é parte pequena de uma contrução incipiente, cabendo extensiva investigação.

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ANEXO I – CARTA DE ACEITE DO COMITÊ DE ÉTICA

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

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: EFEITOS DA PRÁTICA DE EXERCÍCIO AERÓBIO SOBRE O CONDICIONAMENTO CARDIORRESPIRATÓRIO, ATIVIDADE CORTICAL, FUNCIONAMENTO COGNITIVO EM PACIENTES COM TRANSTORNO BIPOLAR

Pesquisador: Sergio Eduardo de Carvalho Machado

Área Temática:

Versão: 4

CAAE: 40438115.8.0000.5263

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

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.177.291

Data da Relatoria: 10/08/2015

Apresentação do Projeto:

conforme parecer anterior

Objetivo da Pesquisa:

conforme parecer anterior

Avaliação dos Riscos e Benefícios:

conforme parecer anterior

Comentários e Considerações sobre a Pesquisa:

conforme parecer anterior

Considerações sobre os Termos de apresentação obrigatória:

O pesquisador respondeu satisfatoriamente a todos os itens pendentes.

Informa que a equipe que participará da avaliação nos termos deste protocolo serão:

O médico cardiologista Gastão Luiz Fonseca Soares-Filho CRM (52 41932-6),

Os exames de EEG serão conduzidos pelo Dr. David Sender CRM 52-96113-2

O protocolo de exercícios aeróbicos será acompanhado pelos profissionais de Educação Física Alberto Souza de Sá CREF-1 021708 G/RJ.

A avaliação psicológica será realizada pela psicóloga Bárbara Cristina da Costa Monteiro CRP

Endereço: Av. Venceslau Brás, nº 71, 2º andar - FDS
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ANEXO II – ESCALAS DE AVALIAÇÃO DE SEVERIDADE DOS SINTÔMAS

a) HAMD - Escala de Hamilton para Depressão

1. **Humor deprimido**: 0. Ausente; 1. relatado apenas ao inquirir-se; 2. relato verbal e espontâneo; 3. evidente na expressão facial, postura e choro; 4. relato verbal e não verbal, quase que exclusivamente esses sentimentos.

2. **Sentimento de culpa**: 0. Ausente; 1. auto-recriminação; 3. idéias de culpa ou "ruminação"; 3. idéias delirantes de culpa; 4. alucinações ameaçadoras.

3. **Suicídio**: 0. Ausente; 1. não vale a pena viver; 2. deseja estar morto; 3. idéias ou ameaças de suicídio; 4. tentativas de suicídio.

4. **Insônia inicial**: 0. Ausente; 1. mais de 30 min; 2. dificuldades freqüentes.

5. **Insônia intermediária**: 0. Ausente; 1. agitação e inquietação; 2. deambulação.

6. **Insônia terminal**: 0. Ausente; 1. volta a dormir; não retorna a dormir.

7. **Trabalhos e atividades**: 0. Sem dificuldades; 1. idéias de incapacidade; 2. perda de interesse; 3. redução do tempo dedicado; 4. abandono.

8. **Retardo**: 0. Ausente; 1. discreto; 2. evidente; 3. entrevista difícil; 4. estupor.

9. **Agitação**: 0. Ausente; 1. inquietação; 2. mexe as mãos/cabelos; 3. movimenta-se bastante; 4. movimenta-se incessantemente.

10. **Ansiedade psíquica**: 0. Sem dificuldades; 1. tensão subjetiva e irritabilidade; 2. preocupa-se com trivialidades; 3. atitude apreensiva; 4. expressa tremores.

11. **Ansiedade somática**: 0. Ausente; 1. leve; 2. moderada; 3. grave; 4. incapacitante.

(sintomas gastrintestinais, cardiovasculares, respiratórios, etc).

12. **Sintomas gastrintestinais**: o. Ausente; 1. perda de apetite; 2. dificuldade a comer.

13. **Sintomas somáticos gerais**: 0. Ausentes; 1. sensação de peso, cansaço, dor; 2. sintoma nítido.

14. **Sintomas genitais**: 0. Ausente; 1. leve; 2. grave.

15. **Hipocondria**: 0. Ausente; 1. preocupado; 2. preocupa-se constantemente; 3. lamenta-se, pede ajuda; 4. idéias delirantes hipocondríacas.

16. **Juízo**: 0. Reconhece que está deprimido; 1. reconhece, porém atribui à má alimentação, clima, etc; 2. nega estar doente.

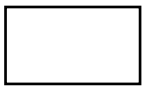
17. **Perda de peso**: 0. Ausente; 1. relato ou mais de 0,5 Kg/semana; 2. comprovada ou mais de 1 Kg/semana.

18. **Variação durante o dia** : 0. Ausente; [ ] pior pela manhã; [ ] pior pela noite. * Quando presente: 1. leve; 2. grave.

19. **Despersonalização/Desrealização**: 0. Ausente; 1. leve; 2. moderado; 3. grave; 4. incapacitante.

20. **Sintomas paranoides**: 0. Ausente; 1. suspeição; 2. idéias de referência; 3. delírios de referência e perseguição.

21. **Sintomas obsessivos e compulsivos**: 0. Ausente; 1. leve ; 2. grave.

ESCORE TOTAL: 

b) Escala de Young para Mania

Item - definição	Graus
01. Humor e afeto elevados Este item compreende uma sensação difusa e prolongada, subjetivamente experimentada e relatada pelo indivíduo, caracterizada por sensação de bem-estar, alegria, otimismo, confiança e ânimo. Pode haver um afeto expansivo, ou seja, uma expressão dos sentimentos exagerada ou sem limites, associada a intensa relação com sentimentos de grandeza (euforia). O humor pode ou não ser congruente ao conteúdo do pensamento.	(0) Ausência de elevação do humor ou afeto (1) Humor ou afeto discreta ou possivelmente aumentados, quando questionado (2) Relato subjetivo de elevação clara do humor; mostra-se otimista, auto-confiante, alegre; afeto apropriado ao conteúdo do pensamento (3) Afeto elevado ou inapropriado ao conteúdo do pensamento; jocoso (4) Eufórico; risos inadequados, cantando (X) Não avaliado
02. Atividade motora - energia aumentada Este item compreende a psicomotricidade - e expressão corporal - apresentada pelo paciente, incluindo a sua capacidade em controlá-la, variando desde um grau de normalidade, até um estado de agitação, com atividade motora sem finalidade, não influenciada por estímulos externos. O item compreende ainda o relato subjetivo do paciente, quanto à sensação de energia, ou seja, capacidade de produzir e agir.	(0) Ausente (1) Relato subjetivo de aumento da energia ou atividade motora (2) Apresenta-se animado ou com gestos aumentados (3) Energia excessiva; às vezes hiperativo; inquieto (mas pode ser acalmado) (4) Excitação motora; hiperatividade contínua (não pode ser acalmado) (X) Não avaliado
03. Interesse sexual Este item compreende idéias e/ou impulsos persistentes relacionados a questões sexuais, incluindo a capacidade do paciente em controlá-los. O interesse sexual pode restringir-se a pensamentos e desejos não concretizados, em geral verbalizados apenas após solicitação, podendo chegar até a um comportamento sexual frenético e desenfreado, sem qualquer controle ou crítica quanto a riscos e normas morais.	(0) Normal; sem aumento (1) Discreta ou possivelmente aumentado (2) Descreve aumento subjetivo, quando questionado (3) Conteúdo sexual espontâneo; discurso centrado em questões sexuais; auto-relato de hipersexualidade (4) Relato confirmado ou observação direta de comportamento explicitamente sexualizado, pelo entrevistador ou outras pessoas (X) Não avaliado

04. Sono

Este item inclui a redução ou falta da capacidade de dormir, e/ou a redução ou falta de necessidade de dormir, para sentir-se bem-disposto e ativo.

(0) Não relata diminuição do sono
(1) Dorme menos que a quantidade normal, cerca de 1 hora a menos do que o seu habitual
(2) Dorme menos que a quantidade normal, mais que 1 hora a menos do que o seu habitual
(3) Relata diminuição da necessidade de sono
(4) Nega necessidade de sono
(X) Não avaliado

05. Irritabilidade

Este item revela a predisposição afetiva para sentimentos/emoções como raiva ou mau-humor, apresentados pelo paciente frente a estímulos externos. Inclui baixo-limiar à frustração, com reações de ira exagerada, podendo chegar a um estado constante de comportamento desafiador, querelante e hostil.

(0) Ausente
(2) Subjetivamente aumentada
(4) Irritável em alguns momentos durante a entrevista; episódios recentes (nas últimas 24 horas) de ira ou irritação na enfermaria
(6) Irritável durante a maior parte da entrevista; ríspido e lacônico o tempo todo
(8) Hostil; não cooperativo; entrevista impossível
(X) Não avaliado

06. Fala (*velocidade e quantidade*)

Este item compreende a velocidade e quantidade do discurso verbal apresentado pelo paciente. Inclui sua capacidade de percebê-lo e controlá-lo, por exemplo, frente a solicitações para que permaneça em silêncio ou permita que o entrevistador fale.

(0) Sem aumento
(2) Percebe-se mais falante do que o seu habitual
(4) Aumento da velocidade ou quantidade da fala em alguns momentos; verborréico, às vezes (com solicitação, consegue-se interromper a fala)
(6) Quantidade e velocidade constantemente aumentadas; dificuldade para ser interrompido (não atende a solicitações; fala junto com o entrevistador)
(8) Fala pressionada, ininterruptível, contínua (ignora a solicitação do entrevistador)
(X) Não avaliado

07. Linguagem - Distúrbio do pensamento

Este item refere-se a alterações da forma do pensamento, avaliado pelas construções verbais emitidas pelo paciente. O pensamento pode estar mais ou menos desorganizado, de acordo com a gravidade das alterações formais do pensamento, descritas a seguir:

- *Circunstancialidade*: fala indireta que demora para atingir o ponto desejado, mas eventualmente vai desde o ponto de origem até o objetivo final, a despeito da superinclusão de detalhes;
- *Tangencialidade*: incapacidade para manter associações do pensamento dirigidas ao objetivo - o paciente nunca chega do ponto inicial ao objetivo final desejado;
- *Fuga de idéias*: verbalizações rápidas e contínuas, ou jogos de palavras que produzem uma constante mudança de uma idéia para outra; as idéias tendem a estar conectadas e, mesmo em formas menos graves, podem ser difíceis de ser acompanhadas pelo ouvinte;
- *Ecolalia consonante*: repetição automática de palavras ou frases, com entonação e forma que produzem efeito sonoro de rima;
- *Incoerência*: fala ou pensamento essencialmente incompreensíveis aos outros, porque as palavras ou frases são reunidas sem uma conexão com lógica e significado.

(0) Sem alterações
(1) Circunstancial; pensamentos rápidos
(2) Perde objetivos do pensamento; muda de assuntos freqüentemente; pensamentos muito acelerados
(3) Fuga de idéias; tangencialidade; dificuldade para acompanhar o pensamento; ecolalia consonante
(4) Incoerência; comunicação impossível
(X) Não avaliado

08. Conteúdo

Este item compreende idéias e crenças apresentadas pelo paciente, variando, de acordo com a intensidade, de idéias novas e/ou incomuns ao paciente, ideação supervalorizada (ou seja, crença falsa, intensamente arraigada, porém susceptível à argumentação racional), a delírios (crenças falsas, baseadas em inferências incorretas sobre a realidade, inconsistentes com a inteligência e antecedentes culturais do paciente, e que não podem ser corrigidas pela argumentação). Conteúdos comumente encontrados no paciente maníaco, incluem:

- *Idéias místicas*: de conteúdo religioso;
- *Idéias paranóides*: crença de estar sendo molestado ou perseguido;
- *Idéias de grandeza*: concepção exagerada da própria importância, poder ou identidade, incluindo posses materiais, qualidades incomuns e relacionamentos especiais com personalidades famosas ou entidades místicas;
- *Idéias de referência*: crença de que o comportamento dos outros tem relação consigo próprio ou de que eventos, objetos ou outras pessoas possuem um significado particular e incomum para si.

(0) Normal
(2) Novos interesses e planos compatíveis com a condição sócio-cultural do paciente, mas questionáveis
(4) Projetos especiais totalmente incompatíveis com a condição sócio-econômica do paciente; hiper-religioso
(6) Idéias supervalorizadas
(8) Delírios
(X) Não avaliado

09. Comportamento disruptivo agressivo

Este item compreende a atitude e as respostas do paciente ao entrevistador e à situação da entrevista. O paciente pode apresentar-se desconfiado ou irônico e sarcástico, mas ainda assim respondendo aos questionamentos, ou então não cooperativo e francamente agressivo, inviabilizando a entrevista.

(0) Ausente, cooperativo
(2) Sarcástico; barulhento, às vezes, desconfiado
(4) Ameaça o entrevistador; gritando; entrevista dificultada
(6) Agressivo; destrutivo; entrevista impossível
(X) Não avaliado

10. Aparência

Este item compreende a apresentação física do paciente, incluindo aspectos de higiene, asseio e modo de vestir-se.

(0) Arrumado e vestido apropriadamente
(1) Descuidado minimamente; adornos ou roupas minimamente inadequados ou exagerados
(2) Precariamente asseado; despenteado moderadamente; vestido com exagero
(3) Desgrenhado; vestido parcialmente; maquiagem extravagante
(4) Completamente descuidado; com muitos adornos e adereços; roupas bizarras
(X) Não avaliado

11. Insight (*discernimento*)

Este item refere-se ao grau de consciência e compreensão do paciente quanto ao fato de estar doente. Varia de um entendimento adequado (afetivo e intelectual) quanto à presença da doença, passando por concordância apenas frente à argumentação, chegando a uma negação total de sua enfermidade, referindo estar em seu comportamento normal e não necessitando de qualquer tratamento.

(0) Insight presente: espontaneamente refere estar doente e concorda com a necessidade de tratamento
(1) Insight duvidoso: com argumentação, admite possível doença e necessidade de tratamento
(2) Insight prejudicado: espontaneamente admite alteração comportamental, mas não a relaciona com a doença, ou discorda da necessidade de tratamento
(3) Insight ausente: com argumentação, admite de forma vaga alteração comportamental, mas não a relaciona com a doença e discorda da necessidade de tratamento
(4) Insight ausente: nega a doença, qualquer alteração comportamental e necessidade de tratamento
(X) Não avaliado

ANEXO III – ESCALAS DE ANSIEDADE, ATIVAÇÃO, PSICOAFETIVAS

a) Escala de Ansiedade (SUDS)

Em uma escala de 0 (nenhuma ansiedade) a 10 (extrema ou terrível ansiedade), como está a sua ansiedade neste momento?

ANTES DO TESTE

0	1	2	3	4	5	6	7	8	9	10

DEPOIS DO TESTE

0	1	2	3	4	5	6	7	8	9	10

b) Escala de Ativação Corporal (Felt Arousal Scale)

6	Muito ativado
5	
4	
3	
2	
1	Pouco ativado

c) Escalas de Sensação (Felling Scale)

+5	Muito bom
+4	
+3	Bom
+2	
+1	Razoavelmente bom
0	Neutro
-1	Razoavelmente ruim
-2	
-3	Ruim
-4	
-5	Muito ruim

ANEXO IV – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Projeto: Alterações Psicoafetivas e de Variabilidade da Frequência Cardíaca Diante do Exercício Aeróbio Contínuo e Intervalado de Alta Intensidade (Hit) em Pacientes Bipolares, Pessoas Treinadas, e Sedentárias.

Declaração de Idade: Eu declaro que tenho mais que 18 anos e que participarei por livre vontade do projeto de pesquisa conduzido pelo Prof. Ms. Alberto Sá, Prof. Dr. Sergio Machado e Prof. Dr. Antônio 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 do exercício aeróbio contínuo vs. intervalado sobre os níveis de ansiedade, perfil psicoafetivo, bem como a variabilidade da frequência cardíaca em pessoas treinadas, sedentárias, e pacientes bipolares.

Detalhamento da técnica: As avaliações dos níveis de ansiedade, e psicoafetivas, são mensurados por aplicação de escalas numérica simples de resposta autopercebida por quem participa das tarefas físicas. A variabilidade da frequencia cardíaca trata-se apenas um método seguro, indolor, e não invasivos de mapeamento da atividade elétrica do coração. Por fim, o exercício apesar das diferentes intensidades utilizadas (moderada vs. alta), o esforço administrado será caracterizado como distânte do máximo.

Procedimentos: Os participantes realizarão 3 visitas ao laboratório. Todos serão aleatoriamente distribuídos entre os 2 tipos de exercício, contínuo de moderada intensidade, e intervalado de alta intensidade. Todos os pacientes deverão estar medicados no momento inicial da pesquisa. Os participantes serão submetidos inicialmente a aplicação das escalas de ansiedade, ativação corporal, e afetivas. A análise de variabilidade da frequencia cardíaca será realizada logo após em um ambiente calmo e de olhos fechados por 10 min. Os pacientes então participarão de um período de exercício aeróbio de no máximo 20 min. Por fim, todos os pacientes realizarão novamente as avaliações realizadas no início da visita.

Confidencialidade: Eu entendo que todas as informações coletadas no estudo são confidenciais e que nomes não serão divulgados, e que a informação será utilizada 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 ao exercício.

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). Av. Venceslau Brás, 71 – Fundos – Botafogo – Rio de Janeiro, RJ. CEP 22.290-2140. Fone: (21) 2295-5549 ramal: 235 – celular: 91567006 – email: secm80@gmail.com.

_____ _____

Nome do participante Data de nascimento

_____

Assinatura do participante

Rio de Janeiro, _____ de _____ de 2017