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ANALYSIS OF THE ANTIDEPRESSANT POTENTIAL OF PHYSICAL EXERCISE PRACTICE, MEDIATED BY NEUROPLASTICITY, IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: A SYSTEMATIC REVIEW ARTICLE

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Abstract: Introduction: Major Depressive Disorder is a common mental disorder, characterized by high incidence, disability and fatality, culminating in a significant burden on society. Changes in brain plasticity may be a reason for Depression, and recent studies show that physical exercise plays a positive role in depression. **Goal:** In order to better understand the antidepressant effect of exercise and changes in brain plasticity, the present study explores the relationship between depression, brain plasticity and the positive role of physical exercise in treatment. Methodology: Given the above, related literature was retrieved using specific descriptors from the Cochrane Central Register of Controlled Trials (CENTRAL) database, MEDLINE, Embase, China National Knowledge Infrastructure (CNKI) and PubMed. **Result:** Increased exercise was negatively correlated with the risk of depression, that is, clinical trials demonstrate that aerobic, resistance and mind-body exercises can improve depressive symptoms. Evidence indicates that exercise remodels brain structure, activates related brain areas, promotes behavioral adaptation, and maintains the integrity of the hippocampus and white matter. Although exercise has benefits in brain neuroprocessing, slowing cognitive degradation in depressed patients, the intensity and long-term effects still need to be clarified. **Conclusion:** Therefore, future research is crucial to establish accurate exercise prescriptions aimed at improving depressive symptoms.

Keywords: Brain plasticity; Major Depressive Disorder; Physical exercise; Neuroplasticity.

INTRODUCTION

Depression is a common mental disorder, with high morbidity, disability and mortality. According to the World Health Organization (WHO), there are around 350 million people with depression worldwide (World Health Organization, 2017). Those affected experience persistent feelings of sadness and loss of pleasure in activities, in addition to associated physical comorbidities (CORREL et al, 2017). Among the different hypotheses proposed to explain the pathophysiology of Major Depressive Disorder, the "monoaminergic hypothesis" was initially validated, with the development of monoaminergic antidepressants. Based on this hypothesis, an impairment of the monoaminergic systems (serotonin, noradrenaline and dopamine) was considered a primary event for the appearance of affective and cognitive symptoms in depression (HIRSCHFELD, 2000). Therefore, most antidepressant medications were developed according to this hypothesis, representing a useful therapeutic tool (LOPEZ-MUNOZ; ALAMO, 2009), but hampered by side effects, dependence, high cost and low patient adherence. In this sense, drug treatment, in general, is not completely satisfactory, significantly affecting patients' quality of life (KONG et al, 2014), with an approximate rate of 40% of depressed patients who do not respond adequately to treatment. (DERUBEIS et al, 2005; DIMIDJIAN et al, 2006), as well as high recurrence rates, greater than 60% (HARDEVELD et al, 2010), probably because additional emerging factors involved in the pathophysiology of the disorder, such as chronic stress and neuroinflammation, must be considered for the appropriate treatment of the pathology (CARACI et al, 2018b).

A meta-analysis recently conducted by Kirsch and colleagues on the effect of antidepressants showed that these medications do not have a clinically significant effect on

mild, moderate or severe depression compared to placebo. A small significant effect was detected only for patients scoring very high on the Hamilton Depression Rating Scale, so the authors concluded that there appears to be little evidence to support the prescription of antidepressant medications for anyone except patients with depression. more severe unless alternative treatments have failed to provide benefit (KIRSCH et al., 2008).

The brain is continually balancing two conflicting demands: it must retain sufficient structural integrity to maintain adequate neurotransmission and function efficiently, while remaining malleable enough to restructure and adapt to changing environmental demands. The dynamic nature of the brain is supported by the concept of neuroplasticity, which refers to the brain's ability to reorganize itself in response to internal and/or external influences (KANDOLA et al., 2016). Adult neurogenesis therefore refers to the growth of new neurons in the adult brain and, a priori, reports of neurogenic activity in adults were met with skepticism because it was assumed that this phenomenon was limited to the developmental period (RAKIC, 1985). However, the legitimacy of adult neurogenesis in certain areas of the brain has since gained widespread acceptance, so that it is now clear that some regions of the adult mammalian brain contain populations of active progenitor cells that can give rise to new neurons and glial cells. (CAMERON; MCKAY, 1999; GOULD et al., 1999).

To some extent, brain disorders can be considered diseases of neuroplasticity (KRYSTAL et al., 2009), as such, stimulating neuroplasticity is becoming a popular approach aimed at counteracting pathological damage (KAYS; HURLEY; TABER, 2012). In relation to Major Depressive Disorder, the pathological effects of stress on the hippocampus contributed to the development of the so-called "neurotrophic hypothesis", according to which neurotrophic factors play a fundamental role in the etiology of depression (ALTAR, 1999; DUMAN; LU, 2012; JAGGAR et al., 2019). This hypothesis suggests that depression derives from decreased neurotrophic support, resulting in neuronal atrophy, decreased hippocampal neurogenesis and loss of glial cells (DUMAN; MONTEGGIA, 2006). On the other hand, the mechanism of action of antidepressant medications may involve the promotion of neurogenesis (BREZUM; DASZUTA, 1999; MALBERG; DUMAN, 2003).

DEFICITS

in neuroplasticity and corresponding deficits in the ability to respond adaptively to the environment are observed both in depressed humans and in rodent models of depression-like behavior and thus may be a central mechanism underlying the disorder (PRICE; DUMAN, 2020).In this sense, a diversity of structural and functional deficits in neuroplasticity underlying depression-like behavioral states can be observed in rodents after exposure to stress (e.g., anhedonia-like behavior, tested using the sucrose preference test; anxiety type, indexed by the novelty suppressed eating; and despair behavior, observed during the forced swimming test) (WANG et al., 2017). These neuroplasticity deficits include decreased long-term potentiation and/or increased long-term depression, decreased expression of synaptic proteins, impaired brain-derived neurotrophic factor (BDNF) signaling, decreased synaptogenesis/atrophy of existing synapses, and decreased neurogenesis/ neuron atrophy, resulting in dysfunction of corticolimbic circuits and expression of disadaptive behavioral strategies (PRICE; DUMAN, 2020; LIU et al., 2017; DUMAN et al., 2016). In contrast, effective antidepressant

therapies have been shown to reverse many of these deficits, emphasizing the relevance of these studies to depression and providing some of the strongest evidence to date that impairments in neuroplasticity may be a central mechanism underlying depression (MALBERG et al., 2000; MODA-SAVA et al., 2019).

Although functional neuroplasticity cannot be directly tested in the living human brain, post-mortem studies of depression have evidenced reductions in markers of neuroplasticity, including reduced BDNF and decreased synapse and synapse-related gene expression (KANG et al., 2012; SEN; DUMAN; SANACORA, 2008). Furthermore, neuroimaging studies in depressed individuals reveal hypofunction and loss of gray matter volume in key corticolimbic structures, including the prefrontal cortex (PFC) and hippocampus, as well as decreased functional integration in these regions and their associated networks (DISNER et al., 2011; SIEGLE et al., 2007).

Given the above, a stimulus as peripheral as physical exercise has been shown to have a strong influence on the induction of neuroplasticity (VOSS et al., 2013). Given its general benefits for physical health, low-risk profile and relative ease of implementation, exercise appears to be a promising therapeutic target for a variety of brain pathologies (WARBURTON; NICOL; BREDIN, 2006; HASKELL et al., 2007). The finding that exercise increases the rate of adult neurogenesis in the hippocampus of mice and rats also suggests a mechanism for the alleged therapeutic effect of exercise in Major Depressive Disorder (VAN PRAAG; KEMPERMANN; GAGE, 1999; VAN PRAAG et al, 1999).

In view of the above, studies confirm that, in a non-pharmacological way, exercise can help alleviate depressive symptoms, with an efficiency comparable to drug therapy and other psychological interventions (HARVEY et al, 2018). However, there are different conclusions about the effect of different types of exercise on depression (CERVENKA; AGUDELO; RUAS, 2017; MALHI; MANN, 2018; LI et al, 2018.). Thus, when considering the results of several large-scale meta-analyses which have recently suggested that the efficacy of antidepressant medications is only marginally different from that of a placebo (LEUCHT et al., 2009; RIEF et al., 2009) and, at the same time, evaluating that the commonly used medicinal approaches are not designed to achieve neuroplasticity, but rather to remedy other aspects of the psychiatric disorder, such as dysfunctional neurotransmitter systems, so as not to induce any lasting changes in brain plasticity (RIEF, 2015), becomes It is relevant to systematically address the effectiveness and applicability of physical exercise as a therapy capable of promoting brain plasticity and, consequently, mitigating, in the long term, the symptoms of Major Depressive Disorder.

Based on this question, the present study proposes to analyze and outline the impacts of different types of physical exercise on neuronal plasticity, in order to provide more information about the antidepressant action induced by physical exercise.

METHODOLOGY

TYPES OF STUDIES

Randomized clinical trials evaluating the correlation between physical exercise and the reduction of depressive symptoms in patients diagnosed with Major Depressive Disorder were eligible for inclusion.

TYPES OF PARTICIPANTS

Adults over the age of 18 and diagnosed with Major Depressive Disorder confirmed using one of the following methods: Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), Bech-Rafaelsen Melancholy Scale (BRMS), Depression Inventory Beck-II (BDI-II), Patient Health Questionnaire-9 (PHQ-9), International Classification of Diseases (ICD-10), Hamilton Depression Scale (HDRS/ HAMD), Geriatric Depression Scale (GDS), Beck and Kettle Questionnaire, Mini-International Neuropsychiatric Interview (MINI), Quick Inventory of Depressive Symptoms (QIDS) or Mini Mental State Examination (MMSE).

TYPES OF INTERVENTIONS

Practice aerobic exercise, resistance exercise and mind-body exercise. Different intensities, frequency and duration of the three types of exercise were considered for analysis.

TYPES OF OUTCOME MEASURES

The primary parameter for evaluating the clinical improvement of patients diagnosed with Major Depressive Disorder was remission of the disease or reduction in scores on diagnostic tests and questionnaires for the disorder, such as the Bech-Rafaelsen Melancholy Scale (BRMS)., Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), Beck Depression Inventory-II (BDI-II), Patient Health Questionnaire-9 (PHQ-9), International Classification of Diseases (ICD-10), Hamilton Depression Scale (HDRS/ HAMD), Geriatric Depression Scale (GDS), Beck and Kettle Questionnaire, Mini-International Neuropsychiatric Interview (MINI), Quick Inventory of Depressive Symptoms (QIDS), Mini Mental State Examination (MMSE)), Depression Rating Scale for aerobic exercise, resistance exercise and mind-body exercise. Different intensities, frequency and duration of the three types of Montgomery and Asberg (MADRS), Center for Epidemiological Studies Depression Scale (CES-D) and Cornell Scale for Depression (CSDD) were considered.

SEARCH METHODS FOR IDENTIFYING STUDIES

Studies identified from electronic searches in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, China National Knowledge Infrastructure (CNKI) and PubMed were included. In order to compose the study, the following descriptors were used - included in the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH) - isolated and/or combined in Portuguese and English: "depression", "depressive disorder", "exercise", "brain plasticity" and "brain function" through the adoption of the Boolean operator AND. For the development of this systematic review, the research question was prepared using the PICO strategy and the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) document were used, which aims to guide the dissemination of reviews systematic and meta-analyses in the area of health and which can be accessed via the link: https://prisma-statement.org//documents/PRISMA%20Portugese%20checklist.pdf. Furthermore, a manual search was carried out using the references of all included studies for more studies.

DATA COLLECTION AND ANALYSIS

STUDY SELECTION

Two reviewers (LN, LA) independently screened the titles and abstracts for inclusion of all potential studies identified as a result of the search. Full-text study reports were then retrieved and two reviewers (LN, LA) independently examined the full texts to identify studies for inclusion, with subsequent recording of reasons for exclusion of ineligible studies. Any disagreements were resolved through discussion or consultation with a third review author (BG). Duplicates were identified and excluded. No language restrictions or publication status were used. Finally, the selection process was recorded in a PRISMA flow diagram.

DATA EXTRACTION AND MANAGEMENT

A data collection form was used for study characteristics and outcome data that were tested. Two reviewers (LN, LA) independently extracted the following characteristics from the included studies.

1. Methods: study design, total study duration, study location and study date
2. Participants: number, average age, inclusion and exclusion criteria
3. Interventions: intervention and comparison
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported
5. Observations: funding for the study and notable conflicts of interest of the study authors.

Two reviewers (LN, LA) independently extracted outcome data from the included studies and any disagreements were resolved by consensus or involving a third review author (BG). Subsequently, the data was transferred to the Review Manager 5 software.

ASSESSMENT OF RISK OF BIAS IN INCLUDED STUDIES

Two reviewers (LD, LA) independently assessed the risk of bias for each study using the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions. The risk of bias was assessed according to the following domains.

1. Random sequence generation
2. Allocation Concealment
3. Blinding of participants and staff
4. Blinding of outcome assessment
5. Incomplete results data
6. Selective reporting of results
7. Another bias

Finally, each potential source of bias was classified as high, low or unclear, a judgment explained in the "Risk of bias" table.

RESULTS AND DISCUSSION

Figure 1: PRISMA 2020 Flowchart for new systematic reviews that include searches in databases, protocols and other sources.

Source: written by the authors themselves.

Initially, the search strategy identified 7,329 potential scientific publications in the selected databases. After excluding duplicates and ineligible articles, 3,087 articles were found. Subsequently, a preliminary analysis of the article titles was carried out, excluding 2,972 articles. In this way, 115 articles were selected, of which, after reading the publication summaries, 92 were excluded, as they did not answer the guiding research question.

Finally, 23 articles remained, which made up the sample of the study. In order to present a characterization of the selected scientific articles, table 1 was prepared. An overview of the publications was prepared with regard to reference, sample, age, gender, exercise prescription and main result of each study.

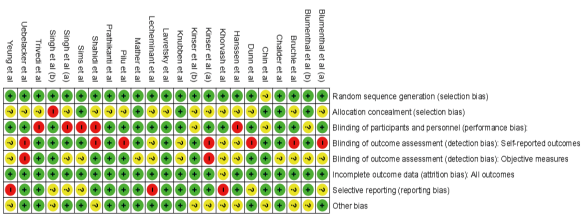

Figure 2: Risk of Bias Summary

Source: written by the authors themselves using the RevMan software

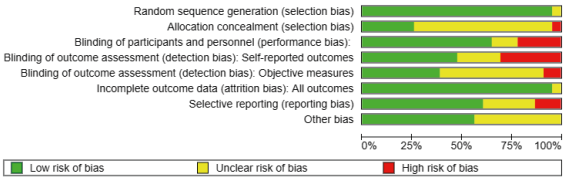

Figure 3: Risk of Bias Chart

Source: written by the authors themselves using the RevMan software

The analysis of the selected studies allows us to identify great variability regarding intervention aspects, so that research differs, significantly in relation to the modality and characteristic of the proposed physical activity, intensity, frequency and durability of evaluation, as explained in Table 1. In this sense, in order to systematize the evaluations, the twenty-three studies are distributed into three large categories of exercise modality: "aerobic exercise", "resistance exercise" and "mind exercise". body". In the first category, seven studies were allocated (CHALDER et al., 2012; DUNN et al., 2005; BLUMENTHAL et al., 1999; KNUBBEN et al., 2007; BLUMENTHAL et al., 2007; HANSSEN et al., 2017; TRIVEDI et al., 2011); nine studies were designated for the "resistance exercise" category (MATHER et al., 2002; PILU et al., 2007; BRUCHLE et al., 2021; SIMS et al., 2006; SINGH et al., 2001; LECHEMINANT et al., 2014; CHIN et al., 2004; SINGH et al., 2005; KHORVASH et al., 2012), while in the third category there are seven studies (SHAHIDI et al., 2011; KINSER et al., 2013; KINSER et al., 2014; UEBELACKER et al., 2017; PRATHIKANTI et al., 2017; YEUNG et al., 2017; LAVRETSKY et al., 2011).

Of the twenty-three studies included, nine were from the United States of America (BLUMENTHAL et al., 1999; BLUMENTHAL et al., 2007; TRIVEDI et al., 2001; KINSER et al., 2013; KINSER et al., 2014; PRATHIKANTI et al., 2017; YEUNG et al., 2017; LAVRETSKY et al., 2012; DUNN et al., 2005), four from Germany (SINGH et al., 2001; KNUBBEN et al., 2007; BRUCHLE et al., 2021; SINGH et al., 2005), one from Switzerland (HANSSEN et al., 2007), one from Australia (SIMS et al., 2006), one from Scandinavia (LECHEMINANT et al., 2014), one from Netherlands (CHIN et al., 2004), one from the United Arab Emirates (KHORVASH et al., 2012), three from England (UEBELACKER et al., 2017; CHALDER et al., 2012; MATHER et al., 2002), one from Italy (PILU et al., 2007) and one from Iran (SHAHIDI et al., 2011).

All twenty-three studies listed for the sampling field of this review were randomized clinical trials, of which eighteen had two arms (MATHER et al., 2002; KNUBBEN et al., 2007, HANSSEN et al., 2017; TRIVEDI et al., 2011; BRUCHLE et al., 2021; SIMS et al., 2006; SINGH et al., 2001; LECHEMINANT et al., 2014; CHIN et al., 2004; KHORVASH et al., 2012; KINSER et al., 2013; KINSER et al., 2014; UEBELACKER et al., 2017; PRATHIKANTI et al., 2017; YEUNG et al., 2017; LAVRETSKY et al., 2012; CHALDER et al., 2012; PILU et al., 2007), three had three arms (BLUMENTHAL et al., 1999; SINGH et al., 2005; SHAHIDI et al., 2011), one had four arms (BLUMENTHAL

Reference	Sample	Age (years)	Gender	Exercise prescription	Main result
Aerobic exercise					
CHALDER et al	361	18-69	Male Female	Vigorous or moderate activity for 150 minutes per week, in sessions of at least 10 minutes	BDI ↓
DUNN et al	80	20-40	Male Female	Treatment with aerobic exercise with variations in energy expenditure (17.5kcal/kg/week or 7.0kcal/kg/week) or placebo control exercise	HDRS ↓
MATHER et al	86	>60	Male Female	Fitness and stretching exercise, 2x per week for 10 weeks	HAMD ↓
BLUMENTHAL et al	156	≥50	Male Female	Supervised aerobic exercise program, 3x per week, for 16 weeks	HAMD ↓ BDI ↓
KNUBBEN et al	20	49±13	Male Female	Walk for 15 minutes, 5 times a day, for 10 days	BRMS ↓ CES-D ↓
BLUMENTHAL et al	202	≥40	Male Female	Supervised aerobic exercise (walking or running) for 45 minutes, 3x a week, for 16 weeks	HAMD ↓
HANSSEN et al	34	37,8	Male Female	Cycling for 35 minutes, 3x a week, for 4 weeks	BDI-II ↓
TRIVEDI et al	122	18-70	Male Female	Running + cycling, 2-3 times a week, for 12 weeks	HDRS ↓
Resistance exercise					
PILU et al	30	40-60	Female	Two 60-minute physiological strengthening classes per week taught by a qualified instructor	HAMD ↓ GAF ↓ CGI ↓
BRUCHLE et al	50	18-65	Male Female	Instructor-led resistance or strength training activity for 60 minutes, 3x per week, for 3 weeks	HAMD ↓
SIMS et al	32	≥65	Male Female	Moderate-intensity strengthening exercise 3x per week for 10 weeks	GDS ↓
SINGH et al	32	71,3 ± 1,2	Male Female	Supervised weight lifting exercises for 10 weeks	BDI-II ↓
LECHEMINANT et al	30	26,9 ± 5,1	Female	Instrument resistance movement, 8-12 times per group, 3 groups, 2x per week, for 18 weeks	CES-D ↓

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et al., 2007) and one had five arms (DUNN et al., 2005). Of the eighteen two-arm analyses, exercise was compared to health education lectures or usual medical care in thirteen studies (MATHER et al., 2002; SIMS et al., 2006; SINGH et al., 2001; CHIN et al., 2004; KHORVASH et al., 2012; KINSER et al., 2013; KINSER et al., 2014; UEBELACKER et al., 2017; PRATHIKANTI et al., 2017; YEUNG et al., 2017; LAVRETSKY et al., 2012; CHALDER et al., 2012; PILU et al., 2007); in four other studies, the control group was considered to have a lower exercise intensity (HANSSEN et al., 2017; TRIVEDI et al., 2011), considered a placebo, or in a different modality, such as stretching, flexibility and relaxation exercises (KNUBBEN et al., 2007; LECHEMINANT et al., 2014); finally, a study considered cognitive activities of logic and concentration in the control group (BRUCHLE et al., 2021). In turn, of the three studies with three arms, one compared exercise versus exercise associated with usual pharmacotherapy for depression versus usual pharmacotherapy alone (BLUMENTHAL et al., 1999); another evaluated a high-intensity training program versus a low-intensity training program versus usual medical care (SINGH et al., 2005); while the latter evaluated laughter yoga versus aerobic exercise versus usual medical care (SHAHIDI et al., 2011). The four-arm study compared home exercise versus supervised exercise versus usual pharmacological therapy versus placebo (BLUMENTHAL et al., 2007). Finally, the five-arm study evaluated four different exercise intensities versus placebo control flexibility exercise (DUNN et al., 2005).

Regarding the previous diagnosis and assessment of the severity of the depressive symptoms of the patients evaluated in the studies included in this review, in addition to the Diagnosis carried out in a clinical interview according to the ICD-10 or criteria from the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV), the Hamilton Rating Scale for Depression was used in seven studies (BLUMENTHAL et al., 1999; TRIVEDI et al., 2011; BRUCHLE et al., 2021; YEUNG et al., 2017; LAVRETSKY et al., 2012; DUNN et al., 2005; PILU et al., 2007). Similarly, the Beck Depression Inventory was used for pre-test assessment in six studies (BLUMENTHAL et al., 2007; HANSSEN et al., 2017; SINGH et al, 2001; KHORVASH et al., 2012; PRATHIKANTI et al., 2017; CHALDER et al., 2012). For the same purpose, scores on the Geriatric Depression Scale were also reported (MATHER et al., 2002; SIMS et al., 2006; CHIN et al., 2004; SINGH et al., 2005; SHAHIDI et al., 2011), on the Bech-Rafaelsen Melancholy Scale (KNUBBEN et al., 2007), on the Center for Epidemiological Studies Depression Scale (LECHEMINANT et al., 2014), on the Patient Health Questionnaire (KINSER et al., 2013; KINSER et al., 2014) and the Rapid Inventory of Depressive Symptoms (UEBELACKER et al., 2017).

Finally, in relation to the outcomes analyzed by the studies, all included remission of depressive symptoms or reduction in scores on the Major Depressive Disorder assessment tools. However, the parameters considered for clinical improvement based on the scales, as well as the use of different scales for this purpose, make it difficult to systematically analyze these results globally.

CHANGES IN BRAIN PLASTICITY IN PATIENTS WITH DEPRESSION

Major Depressive Disorder (MDD) presents a complex pathophysiology that has recently been partially elucidated (CARACI et al., 2018a). In this sense, several factors contribute to explaining this pathophysiology of MDD, such as chronic stress, reduced synaptic plasticity, impaired adult hippocampal neurogenesis and hippocampal

neurodegeneration, in addition to the known dysregulation of the monoaminergic system.

(JAGGAR et al., 2019; VU, 2019). The importance of chronic stress in the disorder is supported by epidemiological studies which highlight its central role in this pathology (PITTENGER; DUMAN, 2008); in fact, stressful life events contribute to the development of the disease (CZEH; LUCASSEN, 2007). Chronic stress impairs the negative feedback of glucocorticoids (GR) in the hypothalamic-pituitary-adrenal (HPA) axis, resulting in elevated cortisol levels (DeKLOET et al., 2005). Excess GR can induce neuronal death in the hippocampus (YU; HOLSBOER; ALMEIDA, 2008) and dysfunction in the prefrontal cortex (PFC), areas related to the cognitive symptoms of depression (KRISHNAN; NESTLER, 2008). Stress also reduces the synthesis of the neuronal factor BDNF (NOWACKA; OBUCHOWICZ, 2013), crucial for the maintenance of dendritic spines (VIGERS et al., 2012). Low levels of BDNF are associated with dendritic atrophy, neuronal apoptosis and inhibition of neurogenesis in Major Depressive Disorder (NOWACKA; OBUCHOWICZ, 2013). This reduction is evidenced in the hippocampus and PFC of animal models of depression (SMITH et al., 1995; DUMAN; MONTEGGIA, 2006; FILHO et al., 2015), as well as in depressed patients (THOMPSON et al., 2011; REINHART et al., 2015). Stress also impairs TGF-β1 signaling in different regions of the brain in MDD, so that a correlation is observed between reduced plasma levels of TGF-β1, severity of depressive symptoms and resistance to treatment (SUTCIGIL et al., 2007; CARACI et al., 2018a).

In addition to hyperactivation of the HPA axis, immune dysregulation and neuroinflammation are central to the pathophysiology of depression (CARACI et al., 2010), with an impact on the global activity of monoaminergic systems (CARACI et al., 2018a). Regarding neuroinflammation, pro-inflammatory cytokines, called interleukin (IL)-1β and tumor necrosis factor-α (TNF-α) increase, while anti-inflammatory cytokines (IL-10, IL-4 and TGF-β1) increase. decrease in animal models and patients with Major Depressive Disorder (YOU et al., 2011; FAROOQ et al., 2017; CARUSO et al., 2019).

Structural magnetic resonance studies show a reduction in hippocampal volume in depressed patients compared to controls (SHELINE et al., 1996), a change also evidenced in post-mortem studies (STOCKMEIER et al., 2004). From this perspective, it is observed that stress hormones (corticosteroids) from the adrenal gland affect the hippocampus, decreasing neurogenesis (GOULD; TANAPAT, 1999; WESTENBROEK et al, 2004), and playing a crucial role in decreasing hippocampal volume in MDD (BROWN; RUSH; MCWEN, 1999; SAPOLSKY, 2000). The hippocampus has receptors for adrenal steroids and is involved in the negative feedback cycle of the HPA axis, suggesting that abnormalities in this system may contribute to a decrease in hippocampal volume (GOULD; TANAPAT, 1999).

Based on the analysis of evidence that points to this relationship between depression and brain function, studies using functional magnetic resonance imaging (fMRI), event-related potentials (ERP) and spontaneous electroencephalograms (EEG) identify abnormalities in the main brain regions of patients with depression (SCHMAAL et al., 2016), including the frontal lobe, cingulate gyrus, hippocampus, striatum and white matter (ZHANG et al., 2018). Reductions in brain volume, neuronal loss and a decrease in neurotrophic factor are linked to depressive episodes (CAMPBELL; MACQUEEN, 2004). Therefore, the hippocampus, central to the regulation of stress and mood, has

reduced volumes, which highlights structural changes in patients with depression, as well as abnormal emotional regulation, elucidating the functional impacts on the disorder (GEERLING; GERRITSEN, 2017).

Furthermore, depression also affects the synaptic connections of the hippocampus, as seen in autopsy studies, which show that patients with depression had impaired plasticity of hippocampal neurons, manifested as a decrease in the density of the hippocampal gray matter and a reduction in the nerve fibers and hippocampal neurogenesis (SEXTON; MACKAY; EBMEIER, 2013), in addition to a decrease in the volume of nerve cells and a reduction in the density of glial cells in the prefrontal cortex (RAJKOWSKA et al., 1999). Brain dysfunction is reflected in changes in neurological activity during cognitive tasks, such as attention and memory tasks (LV et al., 2010; WERNER et al., 2009). In summary, the complex pathophysiology of MDD involves chronic stress, dysregulation of the immune system, neuroinflammation, and structural and functional changes in the brain. The interaction between these factors contributes to the understanding of the mechanisms underlying depression.

EFFECTS OF EXERCISE ON BRAIN PLASTICITY IN PATIENTS WITH DEPRESSION

Physical activity as a complementary strategy to the traditional treatment of depression has demonstrated the ability to reduce the risk of relapse, increase adherence to pharmacological treatment and promote the management of side effects, obtaining a success rate of 60-80% (NEUMEYER-GROMEN et al., 2004; SILVEIRA et al., 2013). Physical activity triggers beneficial effects on pre- and postnatal brain development (GOMES; ARIDA, 2015), stimulating neurogenesis and synaptic plasticity by increasing the synthesis and release of BDNF (WALSH; TSHAKOVSKY, 2018), in addition to reducing hyperactivation of the HPA axis (NABKASORN et al., 2006). Notably, during exercise, BDNF expression is induced, with a consequent increase in hippocampal neurogenesis, contributing to improvements in learning, memory and mood (PEDERSEN, 2019). Furthermore, physical activity can increase the plasma concentration of TGF-β1, as observed in response to running exercise (1h on a treadmill) (HEINEMEIER; LANGBERG; KJAER, 2003).

The connection between exercise and specific brain structures has an impact on depressive emotion by restructuring the brain, so animal studies suggest that exercise can improve hippocampal structures affected by Major Depressive Disorder. For example, Chen and colleagues subjected rats to unpredictable chronic stress and administered a 4-week treadmill exercise regimen (20 minutes per session), resulting in a significant increase in the total length and total volume of capillaries in the dentate gyrus regions of the hippocampus. (CHEN et al., 2017). Furthermore, recent research investigated the effect of aerobic exercise on BDNF expression in the hippocampal dentate gyrus and its relationship with spatial learning and memory in rats with chronic stress. The results showed that rats in the exercise group showed a significant increase in BDNF neurons and in certain regions of the hippocampus ($p<0.05$), suggesting that structural changes in hippocampal regions may be associated with the brain structure affected in depression, reinforcing the contribution of targeted exercise therapy to this disorder (CUI et al., 2018).

Regarding the impact of physical exercise on the functions of brain regions related to Major Depressive Disorder, Silveira and collaborators investigated the relationship

between EEG changes and exercise in elderly patients with depression through a 6-month aerobic exercise regimen (two Times a week). The results showed that the patients' P3, P4, T5, T6, O1, and O2 regions exhibited lower θ wave frequencies than the healthy control group, and after exercise, these frequencies increased and HAMD scores decreased ($p=0.001$), suggesting an improvement in cortical activation and depressive symptoms (SILVEIRA et al., 2010).

Furthermore, patients with depression are characterized by a decline or impairment in execution skills, attention and memory, and the impact of exercise on cognitive abilities is also evident. In this sense, thirty patients with depression were divided into a yoga group (8 weeks, 3 times a week) and a conventional drug treatment group; all participants completed a letter cancellation test (LCT), trail creation test (TAT), forward digital span test (FDS), and reverse digital span test (RDS). The results showed that LCT and RDS improved significantly only in the yoga group ($p < 0.05$), indicating that yoga can benefit the attention and memory of depressive patients (SHARMA et al, 2006). Similarly, Viola and colleagues discovered that aerobic exercise for 4 weeks (3 times a week and 45 minutes at a time) can improve working memory, processing speed, visual learning function and psychopathological symptoms of depressive patients (OERTEL- KNOCHEL et al, 2014).

Therefore, physical activity stimulates neurogenesis and synaptic plasticity through the synthesis and release of BDNF, promoting positive physiological changes, such as the release of endorphins and monoamines, an increase in the plasma concentration of TGF-β1 and a reduction in cortisol levels, which can It also acts as an "anti-inflammatory factor" by increasing IL-10 levels and suppressing the production of TNF-α. Furthermore, adequate exercise positively impacts hippocampal and white matter volume, promoting hippocampal regeneration, activating prefrontal cortex function, and eventually improving brain neuroprocessing efficiency and delaying cognitive degradation in patients with depression. In summary, depression influences brain structure and functions, while exercise can effectively protect brain plasticity and promote neuronal health. The aforementioned actions combined give exercise an antidepressant and modulating effect on mechanisms involved in the pathophysiology of depression.

AEROBIC EXERCISE

Aerobic exercise is based on aerobic metabolism, large muscle group, long duration and regular rhythm, and has great health benefits (JONES; CARTER, 2000). Numerous studies have revealed a good antidepressant effect of aerobic exercise, based on its ability to alter monoamine neurotransmitters, increasing the levels of 5-HT and noreprinephrine, reducing the level of cortisol and, consequently, leading to the relief of depressive symptoms (NIEUWENHUIJSEN et al. al., 2014). Furthermore, aerobic exercise was associated with an increase in the concentration of neuroactive substances in the central nervous system of depressive rats and the activation of brain BDNF (TAHERICHADORNESHIN et al., 2017), as well as an increase in beta-endorphin (BENDER et al., 2007).

Mather and colleagues published the results of a study focused on the effect of exercise as an adjunct to antidepressants in reducing depression in a sample of 86 patients over the age of 60 with poor response to antidepressant therapy alone. Participants were randomly assigned to either an exercise class group (muscle strengthening and stretching twice a week for 10 weeks) or a control group with health education lectures twice a week.

Patients were evaluated at the beginning of the study, after 10 weeks and after 37 weeks using the HAMD-17; Because the study focused on a specific population (i.e., a group that did not respond to initial treatment), the general convention in antidepressant therapy trials of considering a ≥50% reduction in the HAMD-17 score as defining a response was modified by the authors, who assumed that a ≥30% reduction in the HAMD-17 score associated with exercise participation could be of clinical interest. At 10 weeks, a significantly greater proportion of the intervention group (55% versus 33%) experienced a greater than 30% decline in depression according to the HAMD-17 (p=0.05), concluding that as exercise was associated with an improvement in depressive symptoms, these patients with poorly responsive Depressive Disorder must be encouraged to participate in aerobic exercise activities (MATHER et al., 2002).

Similarly, Blumenthal and colleagues conducted a randomized controlled trial to establish the effectiveness of an aerobic exercise program (three supervised exercise sessions per week, in a group) compared to Sertraline (50-200 mg) or combined treatment (exercise in association with Sertraline) in Major Depressive Disorder. The study sample consisted of 156 depressed volunteers aged 50 years or older (average age 57 years). After 16 weeks of treatment, all groups exhibited statistically and clinically significant reductions in HAMD and BDI-II scores, with no statistical difference between groups (p=0.67), concluding that, although antidepressants may facilitate a more rapid initial therapeutic response, faster than exercise, at the end of treatment, physical exercise was equally effective in reducing depression (BLUMENTHAL et al., 1999). Subsequently, in a new randomized controlled study of 202 adults diagnosed with major depression, Blumenthal and colleagues randomly assigned participants to one of four conditions: supervised group exercise, home exercise, antidepressant medication (Sertraline 50-200mg /day), or placebo pill, and discovered that 30-minute sessions, three times a week for four months, had an effect similar to an antidepressant (p=0.514). So that after four months of treatment, 41% of participants achieved remission, defined as no longer meeting the criteria for Major Depressive Disorder and a HAMD score < 8 (BLUMENTHAL et al., 2007).

Although several studies have shown that aerobic exercise has a better antidepressant effect than traditional medicine, the dose-response to aerobic exercise remains ambiguous. Systematic reviews have shown that moderate-intensity aerobic exercise for at least 9 weeks, 3-4 days a week, can effectively reduce the risk of depression (STANTON; REABURN, 2014). Previous studies have shown that long-term exercise appears to be more effective compared to short-term exercise. However, one study showed that aerobic training intensity of 80% of maximum heart rate (MHR) in a short training period (10 days) could substantially improve symptoms of depression (KNUBBEN et al., 2007).

With the same aim, the study by Dunn and others sought to evaluate whether exercise is an effective treatment for mild to moderate major depressive disorder and the dose-response relationship of exercise and reduction of depressive symptoms, through the randomization of 80 adults aged between 20 and 45 years in treatment groups with aerobic exercise with variations in total energy expenditure or placebo control exercise. In this sense, a reduction in HRSD scores of 47% was observed for exercise intensity compatible with public health recommendations (17.5kcal/kg/week), 30% for low intensity exercise (7.0kcal/ kg/week) and 29% for the control group (3 days/week of flexibility

exercises), concluding that high-intensity aerobic exercise is an effective treatment for mild to moderate Major Depressive Disorder. However, lower dose exercise is comparable to the placebo effect (DUNN et al., 2005).

Hanssen et al evaluated the effects of continuous high-intensity aerobic training compared to moderate-intensity exercise for 4 weeks in 34 patients diagnosed with unipolar depression. At the end of the study, patients were evaluated using the BDI-II index, which showed a change from moderate to mild depression in patients undergoing high-intensity exercise, and a change from severe to moderate depression in participants in the exercise group. of moderate intensity (HANSSEN et al., 2017). Trivedi et al explored the effects of 12 weeks of high-intensity walking and cycling (16 kcal/kg/week) and low-intensity walking and cycling (4 kcal/kg/week) on depression, and the Hamilton Depression Scale (HDRS) showed that both achieved significant improvement in Major Depressive Disorder ($p<0.001$), however, intensive exercise was more conducive to reducing depression levels (TRIVEDI et al., 2011).

In contrast to the aforementioned studies, the randomized clinical trial by Chalder and collaborators, carried out with 361 adults aged between 18-69 years, with the objective of evaluating self-reported symptoms of depression, assessed using the Beck Depression Inventory after four months intervention with facilitated physical activity, concluded that the addition of physical exercise to usual care did not improve depressive symptoms ($p=0.68$) or reduce the use of antidepressants compared to usual care alone ($p=0.44$) (CHALDER et al., 2012).

Current evidence indicates that high-intensity aerobic exercise is superior to low-intensity aerobic exercise for treating depression. Due to different forms of aerobic exercise and individual differences, methods for assessing exercise intensity differ between studies. Absolute indices and relative indices are considered, and the ranges of low, moderate and high intensity exercise are also different, which makes it difficult to provide meaningful information about the effective intensity of exercise for the treatment of depression (GARBER et al., 2011). Therefore, more precise and strict limits are needed to determine the intensity of aerobic exercise in the treatment of depression, and more systematic studies must be conducted to explore the dose-response effect of aerobic exercise intensity in depressed people.

RESISTANCE EXERCISE

Resistance exercise is characterized by the muscle against resistance, being an effective way to increase strength, volume and muscular endurance. Resistance exercise can not only slow muscle degeneration, promote metabolism, and effectively reduce age-related falls and fractures, but also alleviate anxiety and other mood disorders (KRYGER; ANDERSEN, 2007; EDGREN et al., 2012). Regarding its antidepressant role, evidence was found that resistance exercise can be used separately or together as a treatment for Major Depressive Disorder (GORDON; MCDOWELL; LYONS; HERRING, 2017).

Lecheminant and collaborators applied progressive resistance exercises (twice a week for 18 weeks) to 60 postpartum depressed women; patients chose nine major muscle groups to exercise according to their own exercise intensity. The results showed that the CES-D was significantly reduced in the resistance exercise group, with an increase in the participants' self-efficacy ($p=0.016$) (LECHEMINANT et al., 2014).

In a study conducted exclusively on women, Pilu and others compared the effectiveness of strengthening physical activity plus drug

therapy with drug therapy alone. In this sense, patients who practiced physical activity had their HAMD, GAF and CGI scores improved from T0 to T8 after 8 months, all differences were statistically significant. In contrast, in the control group, the HAMD score improved moderately, but the difference between T0 and T8 did not reach statistical significance, the GAF score remained unchanged and the CGI score moderately reduced without any statistically significant difference (PILU et al., 2007).

Similarly, Bruchle and colleagues conducted a randomized clinical trial with 50 hospitalized patients who met the clinical criteria for Major Depressive Disorder as defined by the international classification of diseases (ICD-10: F32, F33) and aged between 18 and 65 years. In this vein, we investigated the effects of a 3-week physical activity program in comparison to a control intervention. Before and after interventions, severity of clinical symptoms was tested using self-rated (BDI-II) and investigator (HAMD-17) scales, transcranial magnetic stimulation (TMS) protocols were used to test motor excitability, and paired associative stimulation (PAS) was used in order to test neuronal plasticity. Thus, it was concluded that the severity of psychological/affective symptoms of depression (monitored using the BDI-II) is highly correlated with the amount of plasticity and that physical activity as an intervention can normalize deficient neuroplasticity and, consequently, reduce clinical symptoms of depression (BRUCHLE et al., 2021).

In this sense, positive results were also observed in the study by Singh and colleagues, who carried out a randomized controlled study with 32 community-dwelling patients with major depression or dysthymia (average age of 71,3 years), for 30 weeks and with a 26-month follow-up. Participants were assigned to the intervention (10 weeks of supervised weight-bearing exercise followed by 10 weeks of unsupervised exercise) or control group, attending educational lectures for 10 weeks. The BDI-II was significantly reduced at 20 weeks and 26 months of follow-up in the exercise group compared to the control ($p<0.05$ and $p=0.001$, respectively) (SINGH et al., 2001).

However, some other research has presented inconsistent conclusions. Chin and collaborators randomly divided 173 elderly people into a resistance exercise group, a functional exercise group, a combined exercise group and a control group; and the resistance exercise group received moderate-intensity training of 45-60 minutes twice a week - the GDS showed that neither resistance exercise nor functional training could significantly improve depression in older adults living in long-term care facilities ($p >0.05$) (CHIN et al., 2004). From the same perspective, Sims and collaborators carried out a study with 32 depressed volunteers aged 65 years or over, randomly assigned to an intervention group (three sessions per week, for 10 weeks, of moderate-intensity strengthening exercise) or in a brief counseling control group. Analyzes of follow-up data after ten weeks revealed no significant differences between the GDS scores of the intervention and control groups. However, at the six-month follow-up, there was a trend towards lower GDS scores in the intervention group, but this finding did not reach significance ($p=0.08$) (SIMS et al., 2006).

Regarding the comparative analysis of different exercise intensities, Singh and collaborators allocated 60 participants into two intervention groups of high-intensity (80%1RM) and low-intensity (20%1RM) resistance exercises (60 minutes, three times a week), and a control group of standard treatment prescribed by the responsible physician, in order to evaluate the effects on mild depression in the elderly after 8 weeks.

The authors concluded that the high-intensity training group obtained a better response, assessed using the HAMD score, than the low-intensity or control group (p=0.03) (SINGH et al., 2005).

Considering that the antidepressant effect of resistance exercise may be through the regulation of monoamine transmitters and neuroimmunological indicators, Khorvash and colleagues reported that resistance exercise for 10 weeks (twice a week for 90 minutes) effectively improved depressive symptoms (P<0.001) and reduced C-reactive protein in 60 depressed university students evaluated (KHORVASH et al., 2012).

Although resistance exercise has been proven to have an antidepressant effect, it is more difficult to implement into a tangible exercise plan compared to aerobic exercise. Furthermore, long-term follow-up studies and detailed descriptions of exercise intensity and type are still needed to elucidate the therapeutic effects of resistance exercise in Major Depressive Disorder.

MIND-BODY EXERCISE

Yoga and Taijiquan, also known as mind-body exercises, are very accessible and emphasize the integration of body, spirit and external environment, improving overall health through slow body movements, deep breathing and meditation (CHANG et al., 2010). Mind-body exercise can help reduce negative emotions, alleviate fatigue, improve sleep quality and prevent cardiovascular and cerebrovascular diseases (KINSER; GOEHLER; TAYLOR, 2012; YANG et al., 2019), as growing studies demonstrate that mind-body exercise can alleviate symptoms of depression. A meta-analysis of twelve randomized controlled trials concluded that yoga had significantly better antidepressant effects than routine care, relaxation, and aerobic exercise (CRAMER et al., 2013). Another systematic review indicated similar short-term effects between yoga and antidepressants for depressive symptoms (CRAMER et al., 2017).

Given the above, in order to better elucidate this effect, Kinser and colleagues recruited 15 female patients with depression for Hatha Yoga training for 8 weeks (once a week, 75 minutes), while the control group received health education and, it was concluded that the Patient Health Questionnaire-9 (PHQ-9) scores reduced in both groups (KINSER et al., 2013). However, the one-year follow-up of this study found significant improvement in depression in patients engaged in long-term regular yoga (P<0.05) (KINSER; ELSWICK; KORNSTEIN, 2014). Following the same perspective, other more recent research, with a potentially difficult to treat group of participants, that is, patients with persistent depressive symptoms despite antidepressant treatment, found, after 10 weeks, no significant difference in depressed women between the group of 10 weeks of yoga and the health education group (P=0.36), but after 6 months, the PHQ-9 score decreased in more than 50% of women in the yoga group, i.e., it is suggested that yoga had a longer lasting effect when compared to health education (UEBELACKER et al., 2017). Notably, the subjects in the aforementioned studies had moderate or severe depression; in contrast, when considering individuals with less pronounced depressive symptoms, Prathinkanti and colleagues found that BDI-II scale scores decreased significantly in patients with moderate and mild depression who received yoga for 8 weeks compared to mindfulness exercise (p=0,34) (PRATHIKANTI et al., 2017).

Similarly, Yeung and colleagues observed the effect of Yang's Taijiquan on patients with depression and noted that the patients' HAMD score was reduced by 50% (p<0.05) after 12

weeks (twice a week, 60 minutes) (YEUNG et al., 2017). Lavretsy and collaborators used Escitalopram in 73 sixty-year-old patients with depression and divided them into Taijiquan groups (20 standard movements, 10 times, once a week) and a health education group. The results showed that Escitalopram combined with Taijiquan decreased the HDRS score and significantly improved the cognitive function of patients with depression, suggesting a synergistic effect between Taijiquan and antidepressants in improving depressive symptoms (LAVRETSKY et al., 2011).

In order to analyze the clinical applicability of an alternative yoga modality, Shahidi and collaborators compared the effectiveness of Kataria Laughter Yoga (a yoga modality developed in India) and group exercise therapy in reducing depression in seventy women evaluated by Geriatric Depression Scale (score > 10). The analysis revealed a significant difference in the decrease in depression scores of the yoga and exercise therapy group compared to the control group ($p<0.001$ and $p<0.01$, respectively). There was no significant difference between the yoga and exercise therapy groups, concluding that the yoga intervention is at least as effective as the group exercise program in improving depressive symptoms (SHAHIDI et al., 2011).

CONCLUSION

To determine and understanding the antidepressant effect of physical exercise in individuals diagnosed with Major Depressive Disorder, based on changes in brain plasticity, was the central objective of the present study.

It is known that several factors, including biological, psychological and social environments are involved in the development of depression, in this sense, in recent years, the effects of exercise on depression and brain plasticity have become the focus of research. Patients with depression present different degrees of impairment in brain structure and function, reflected through changes in the structures of the hippocampus, frontal lobe, temporal lobe, cerebellum and other regional functions and different neuroimaging techniques and neuroelectrophysiological techniques have revealed changes in brain plasticity in depression.

On the other hand, physical exercise is capable of reconstructing brain structure, activating related brain regions and promoting adaptive changes in behavior, as well as having a positive effect on maintaining hippocampal volume and the integrity of white matter volume, improving processing efficiency. neurological and delaying the degradation of cognitive function, highlighting the positive effect of exercise on brain plasticity in patients with depression. Exercise is supposed to act on depression from a variety of neurobiological effects, such as increased levels of endorphins and monoamines or reduced levels of cortisol in the brain. Since it was hypothesized that depressive disorders may be associated with decreased hippocampal neurogenesis, laboratory research has shown that exercise promotes adult hippocampal neurogenesis and triggers dendritic remodeling, and such an exercise-related effect appears to be very stronger than that determined by antidepressant drugs.

Due to the variety of samples, characteristics of the intervention and control groups, duration of trials, main assessment and follow-up, a direct comparison between studies is difficult. However, despite methodological differences, the vast majority of selected studies showed significant positive findings in terms of reduction in depressive symptoms obtained by exercisers when compared to controls. Given the above, aerobic exercise, resistance exercise and mind-body exercise can alleviate depressive symptoms

and reduce depression levels, which suggests that different exercise patterns can be adopted according to different patients. However, the intensity and long-term effect of exercise have not been clearly established and remain current research questions.

Thus, despite the heterogeneity of studies, the present systematic review concluded that physical exercise has a significant impact on improving depressive conditions. Therefore, intensifying existing treatment approaches through exercise-based interventions may promote hippocampal function and alleviate cognitive deficits in Major Depressive Disorder. Furthermore, the incorporation of non-pharmacological measures into clinical treatment can also promote a series of other benefits for the patient's well-being, such as limiting the risk of adverse side effects. Therefore, although more studies of high methodological quality are needed in order to produce cohesive scientific evidence of exercise as an effective treatment for depression, the promising findings of this intervention in depressive patients must be viewed carefully, considering the low cost and benefits of this intervention for global health.

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