Effects of physical exercise on depressive symptoms and biomarkers in depression

Trevor Archer

Department of Psychology, University of Gothenburg

Torbjörn Josefsson,

School of Social and Health Sciences, Halmstad University

Magnus Lindwall

Department of Food and Nutrition, and Sport Science; Department of Psychology, University of Gothenburg

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All correspondence should be addressed to:

Torbjörn Josefssson
School of Social and Health Sciences
Halmstad University
Box 823
S-301 18 Halmstad, Sweden
E-mail: Torbjorn.Josefsson@hh.se
Telephone: +46 35-16 71 46
Fax: +46 35-18 61 92

Abstract

Regular physical exercise/activity has been shown repeatedly to promote positive benefits in cognitive, emotional and motor domains concomitant with reductions in distress and negative affect. It exerts a preventative role in anxiety and depressive states and facilitates psychological well-being in both adolescents and adults. Not least, several meta-analyses attest to improvements brought about by exercise. In the present treatise, the beneficial effects of exercise upon cognitive, executive function and working memory, emotional, self-esteem and depressed mood, motivational, anhedonia and psychomotor retardation, and somatic/physical, sleep disturbances and chronic aches and pains, categories of depression are discussed. Concurrently, the amelioration of several biomarkers associated with depressive states: hypothalamic-pituitary-adrenal (HPA) axis homeostasis, anti-neurodegenerative effects, monoamine metabolism regulation and neuroimmune functioning. The notion that physical exercise may function as "scaffolding" that buttresses available network circuits, anti-inflammatory defences and neuroreparative processes, e.g. brain-derived neurotrophic factor (BDNF), holds a certain appeal.

Keywords: depression, symptoms, cognition, emotion, motivation, somatic, biomarkers, exercise, HPA-axis, neurodegeneration, monoamines, neuroimmune function, physical activity

Physical activity confers several physical health benefits and regular exercise has been successfully included in primary prevention, treatment and rehabilitation for many chronic diseases (e.g. cardiovascular disease, diabetes, cancer) as well as for premature mortality (1, 2). It has also become increasingly and firmly associated with lasting improvements in mental and somatic health and psychological well-being (3, 4), and as Boreham and Riddoch (5) put it: "from the cradle to the grave, regular physical activity appears to be an essential ingredient for human well-being" (p. 24). According to Meng and D'Arcy (6), a ten percent increase in the physical activity (PA) of adult Canadians presenting neuropsychiatric disorders would reduce several mental disorders, such as clinical depression, by 167,000 cases, a twenty-five percent reduction would result in 389,000 fewer cases; PA was shown to be more beneficial for men. After adjusting for covariates, physical inactivity was a significant risk factor for common mental disorders with approximately 780,000 cases nationally attributable.

The aim of the present study was to examine the evidence that physical exercise ameliorates symptoms and biomarkers of depressive disorders. In particular, exercise is believed to be effective in preventing depression and also to significantly reduce depressive symptoms in clinical as well as in non-clinical (i.e. not clinical or medical) populations (7, 8). Several correlational analysis studies show that exercise is negatively related to depressive symptoms (e.g. 9, 10). Also, a number of prospective longitudinal studies have found that regular exercise at baseline is related to lower risk for subsequent depression (11, 12, 13), although the relationship between exercise and depression across time may be best viewed as reciprocal (14). Moreover, a considerably large number of intervention studies have by now investigated the effect of various exercise programs on depression and the vast majority of them indicate that exercise significantly reduces depression (e.g. 14, 15, 16). In addition to cross-sectional and/or longitudinal studies, a number of meta-analyses of intervention studies have been published during the last 20 years (3, 17, 18, 19, 20, 21, 22, 23, 24). Under

conditions of prolonged physical inactivity psychological, affective, status tended to deteriorate (25). Blumenthal et al. (26) concluded that exercise was effective in improving depressive symptoms among patients with major depression and offers practical suggestions for helping patients initiate and maintain exercise in their daily lives. In sum, the main results from eight meta-analyses so far show that exercise has an antidepressant effect compared to control conditions that ranges from slightly moderate (g = -0.40) (19) to very large (g = -1.39) (24).

The advantages of physical exercise over pharmaceutical and other approaches, e.g. antidepressant drugs, as an intervention in depressive disorders are manifold in comparison with traditional treatments, i.e. traditional antidepressants, for several reasons: (i) exercise improves the general physical health status (e.g. increased oxygen uptake, decreased blood pressure, and reduced risk for coronary diseases). (ii) Exercise provides a number of benefits in neurocognitive domains (cf. 27). (iii) Physical exercise alleviates the effects of stress and expressions of negative affect and elevates psychological well-being and health (28, 29). (iv) It has been established that the disturbance of neuroimmune functions may contribute to depressive states (30, 31), the unique role of exercise specifically (cf. 32) and generally in this regard (33) ought to be noted. (v) In terms of 'cost-benefit', it is likely that exercise group interventions (often employer-subventioned) ought to be more cost-efficient than individual psychotherapy or drug therapy. (vii) Exercise regimes may be considered also in terms of behavioural schedules whereby the intervention compliance ought to be reinforced through application of the 'schedule-induced behaviour principle'. (viii) Compared with psychotherapy or drug therapy, stigmatizing considerations are absent with exercise regimes. (ix) Both the psychomotor retardation and anhedonia symptom profiles associated with deficits in dopaminergic systems; it has been shown that physical exercise ameliorates both functional, biomarker and quality-of-life aspects (34, 35, 36). (x) Finally, although physical

exercise assumes no direct side-effects compared with traditional antidepressant medication, there exist real risks that individuals with depressive tendencies undergoing depressive episodes may ‘abuse’ varieties of exercise for the purpose of mood-elevation (37).

In order to understand the complex and multilevel effects of exercise on depression, and to be able to develop a broad foundation for the understanding of the mechanisms, how they function, and how they interact to affect the individual, it is important to integrate both the effects of exercise on the specific symptoms of depression as well as its influence on the identified biomarkers of depression. The utility of categorizing symptoms of depression on the basis of cognitive, emotional, motivational and somatic, according to the formulations of Beck (38) has been discussed previously (39); utilizing the trans-diagnostic approach emergent in clinical psychology (40, 41, 42), neurobiological and psychopathological processes may be addressed (43). Although there have been previous attempts to outline the various mechanisms of exercise on depression and integrate the various candidates (e.g., 44, 45), no previous account, to our knowledge, has incorporated both the effects of exercise on specific key symptoms of depression as well as on key biomarkers. Figure 1 present a modeled account of symptoms and biomarkers of depressions that have been shown to be ameliorated by physical exercise. Applying this type of model as illustrative, the impact of exercise schedules on different symptoms and biomarkers of depressive disorder is outlined; concurrently, each of four groups of symptom categories, cognitive, emotional, motivational and somatic symptoms, and each the four chosen biomarkers of the disorder, HPA-axis homeostasis, neurodegenerative effects, monoamine metabolism effects and neuroimmune functioning, are highlighted separately. Thus, from each of the four symptom categories two symptoms of disorder were selected and from each of the four biomarker categories five to ten biomarkers were selected.

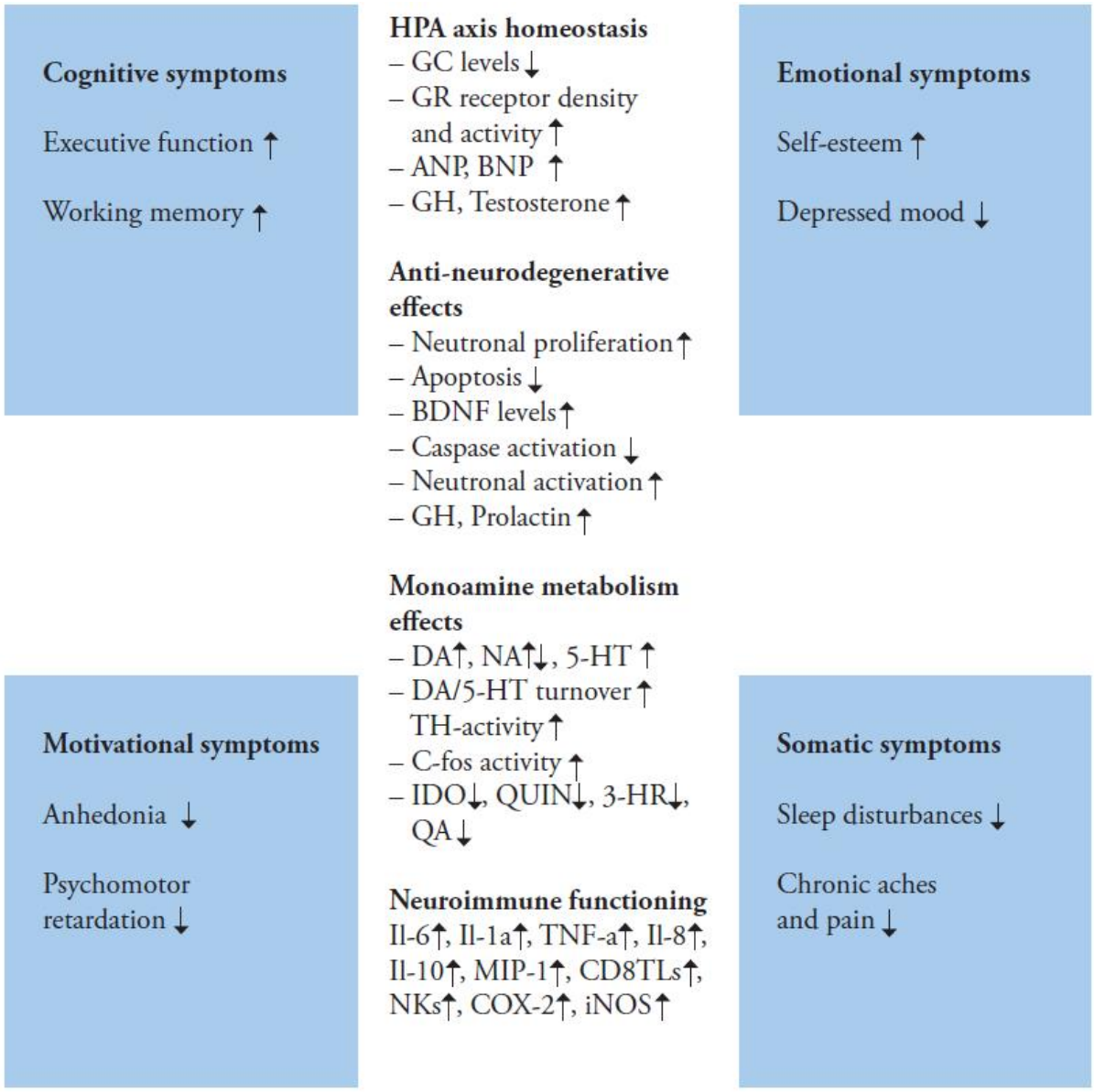

Figure 1. The influence of physical exercise interventions upon symptoms and biomarkers of depressive disorders. Note: ↑: upregulation/increase; ↓: downregulation/decrease; HPA: hypothalamic-pituitary-adrenal; GC: glucocorticoid; GR: glucocorticoid receptor; ANP: atrial natriuretic peptide; BNP: brain natriuretic peptide; GH: growth hormone; BDNF: brain-derived neurotrophic factor; GH: growth hormone; DA: dopamine; NA: noradrenaline; 5-HT: serotonin; TH: tyrosine hydroxylase; c-fos: protein encoded by *FOS* gene; IDO: indoleamine-pyrrole 2,3-dioxygenase; QUIN: quinolinic acid; 3-HR: QA: QFT ethanol;Il-6, -8, -10: Interleukin-6, -8, -10; Il-1β: Interleukin-1β; TNF-α:

Effect of exercise on depressive symptoms

Among the major symptoms of depressive order must be considered depressed mood, low self-esteem, irritability, neurocognitive deficits and difficulties concentrating, anhedonia, psychomotor retardation, increased tiredness, and abnormalities in sleep and

appetite (e.g. 46). Depressed patients often present with complaints such as weight loss, appetite changes, sleep disturbances, pain, psychomotor agitation or retardation, decreased sexual drive, loss of energy, and somatic complaints (47). Exercise generally alleviates emotional symptoms: McKercher et al. (48) showed that moderate levels of ambulatory activity, i.e. walking as opposed to cycling/swimming/resistance, physical activity (≥ 7500 steps/day) gave a 50% lowered prevalence of depressive symptoms compared with sedentary individuals (≤ 5000 steps/day) among young adult women. The distinction between physical activity during leisure time and work time contexts was marked: relatively low durations of physical activity (≥ 1.25 hours/week) were associated with a 45% lower prevalence of depression compared with sedentary individuals whereas high durations of work physical activity (≥ 10 hours/week) were a two-fold higher prevalence of the disorder compared with sedentary work schedules (0 hours/week). Among adult patients (950 men and 1045 women) presenting major depression, those physically active individuals seemed to differ in their depression symptom profiles from those physically inactive/sedentary (49), with a lowered likelihood of insomnia, at risk for suicide and fatigue. Physical exercise has proved beneficial for several conditions that induce consequences that include depression, such as aging and Alzheimer's disease (50), Parkinson's disease (35) and traumatic brain injury (25, 27).

Cognitive symptoms

The manifest benefits of physical exercise for cognitive functions appear critical for children, adolescents, adults, older adults and individuals presenting affect affliction (51, 52, 53, 54, 55), with improvements in both executive function (56, 57) and working memory capacity (58, 59). Sedentary conditions and physical inactivity, unless prescribed through rest and recovery, are generally detrimental to neurocognitive performance (60). During aging, endurance exercise protects against cognitive decline, particularly with regard to working

memory and executive function (61); in both healthy aged and mild Alzheimer's disease the relationships between depressive symptom clusters and neuropsychological performance ought to be noted (62). In aged and older aged individuals presenting dementia-depression comorbidity, exercise alleviated these deficits, e.g. in executive functioning (63). Finally, Hars et al. (64) found that six months of once weekly music-based multitask training, including sessions of physical exercise, was associated with improved cognitive function and decreased anxiety in community-dwelling older adults, compared with non-exercising controls.

Kramer et al. (65) have shown that the enhanced performance on executive functioning tests and improved reaction times were linked to rate of oxygen consumption during walking exercise by healthy older adults. McAuley et al. (66) obtained higher levels of executive function and use of self-regulatory strategies one month into an exercise program for older adults (mean age: 66.4 years) which enhanced beliefs in exercise capabilities, resulting in higher compliance. In another study of older adults, McGough et al. (67) showed that physical performance speed was associated with executive function after adjustment was made for age, sex, and age-related factors in sedentary older adults with mild cognitive impairment. Deficits in executive functioning in depressive disorders are well-documented; the utility of exercise intervention both in the disorder and in depression that accompanies other conditions, e.g. dementia, has also been observed (68, 69, 70). Moderate physical exercise ameliorates single-prolonged stress-induced cognitive, light-dark and elevated maze learning tasks, and other behavioral and biomarker deficits in male Wistar rats (71).

There are three possible mechanisms through which exercise may enhance cognition: (i) increased cellular oxygen saturation (72) and angiogenesis (73), (ii) enhanced monoamine metabolism, e.g. noradrenaline and serotonin, thereby facilitating information-processing (74, 75), and (iii) upregulation of neurotrophins, including brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF-I), vascular endothelial growth

factor (VEGF) and basic fibroblast growth factor (bFGF), that facilitate neuronal survival, proliferation and dendritic arborization (76, 77). Exercise increases brain volume in brain regions associated with executive functioning with prolonged low-moderate intensity endurance effects probably preferable to acute high intensity resistance exercise (78). The aspect of exercise level sufficiency indicates that intense rather than moderate levels enhance neurotransmitter levels and executive performance (79).

Emotional symptoms

Feelings of worthlessness, low self-esteem/self-worth and a depressed mood are according to DSM-IV key emotional symptoms of depression. Exercise has documented effect on global self-esteem and more specifically physical self-esteem (self-esteem linked to the body and physique). Early reviews (80, 81) of experimental studies indicated that participation in exercise program was linked to increased self-esteem scores. Mirroring the above-mentioned positive relation between sport/exercise and body image, Sonstroem (81) found in a narrative review of 16 studies that participation in exercise programmes was linked to increased self-esteem scores. However, as only 10 studies included control groups, only four studies had a randomized design, and half the studies contained 20 or fewer participants in the experiment group, the result of this review should be interpreted with caution.

Fox (82) conducted an extensive meta-analysis of studies on exercise and self-esteem since 1970. Fox, compared to Sonstroem (81), focused specifically on randomized control trials (RCTs). In the meta-analyses, 36 RCT's were found. In addition to this, 44 non-randomised studies were identified for further consideration. The results showed that 78% of the RCTs demonstrated a significant positive change specifically in physical self-esteem. Also, the effects of exercise were larger for individuals with previously low self-esteem. A more recent meta-analysis by Spence and colleagues (83) further examined the effect of

exercise on self-esteem and included 113 studies. Overall they found that participation in exercise lead to a small, but significant, improvement in self-esteem. The effect of exercise on self-esteem also seem to apply for children and adolescents. Ekeland, Heian, and Hagen (84) reviewed 23 randomly controlled trials with children and young people between the ages of 3 and 20 years. The review indicates that exercise has positive short-term effects on self-esteem in children and young people and it might be a useful intervention in improving levels of self-esteem, with the added health benefits of children taking more exercise.Overall, it seems that exercise has a small but significant effect of general self-esteem. However, an important notion is that the small but significant effects of exercise on general self-esteem may mask larger effects on more domain specific aspects of self-esteem, such as physical self-esteem (82, 85).

Several meta-analyses and reviews have found that exercise is associated with increased mood and affect (86, 87, 88, 89). For example, Arent and colleagues (89), using data pertaining to statistical 158 effect sizes from 32 studies on older adults, found that exercise intervention was associated with improved mood in elderly, both in terms of negative affect and positive affect. For example, Sylvia et al (90) observed a mood-specific relationship between exercise frequency and polarity such a fashion that depression was associated with lesser degrees of exercise and mania with greater amounts of exercise in individuals presenting bipolar disorder.

Motivational symptoms

Motivational symptoms in depressive disorder include a general inability to experience enjoyment and pleasure, reduced reward learning and may be assessed through expressions of psychomotor retardation and anhedonia (91, 92). Anhedonia, an inability to experience pleasure, presents a core symptom of major depressive disorder and has been

observed both under clinical (93) or laboratory conditions (94, 95, 96). The rewarding and anti-anhedonic effects of running exercise have been observed (97). For example, in a cross-sectional study of college students using regression analyses, Leventhal (98) found that measures of anhedonia were associated inversely with (i) walking frequency, moderate-intensity physical activity frequency and duration, and (ii) vigorous-intensity physical activity frequency and duration. As several animal laboratory studies have shown, PA constitutes a major natural reward (99), as demonstrated through spontaneous running wheel activity (100, 101), bar-pressing for access to running wheel (102), and the development of place preference to environments associated with after-effects of running bouts (103, 104). Greenwood et al. (105) tested the notion that voluntary physical exercise was rewarding with induction of plastic changes in gene transcription factors that modulate dopaminergic and opioidergic neurotransmission in the mesolimbic reward pathway. Using young adult male Fischer 344 rats, that were given voluntary access to running wheels over six wheels, it was observed that the running activity had rewarding properties, as assessed through place preference conditioning to environments associated with exercise, and increased λFosB/FosB immunoreactivity in the nucleus accumbens. In comparison with the sedentary condition, running activity increased tyrosine hydroxylase mRNA levels in the ventral tegmental area, delta opioid receptor mRNA levels in the shell of the nucleus accumbens and reduced levels of dopamine-D2 receptor mRNA in the core of the nucleus accumbens. Thus, running is rewarding and alters gene transcription in reward pathways. Trivedi et al. (106) have argued that neurobiological evidence provides plausible mechanisms by which exercise could positively affect treatment outcomes with regard to several symptoms including sleep disturbance, cognitive function, mood, weight gain, quality of life, and anhedonia. Swimming training exercise to Wistar rats prtotected depressive rats from an anhedonic state, increased

testosterone blood concentrations, increased interleukin-10 and total BDNF and induced a severe loss of body mass (107).

Psychomotor retardation is observed in individuals afflicted by neurodevelopmental disruptions that affect the motivation of these individuals and expressed through interference of the regular participation in movement, physical activities and sports (108). Physical exercise proved beneficial for symptoms of psychomotor retardation in depressed patients with Alzheimer's disease (109 Mizukami).

Somatic symptoms

Somatic/physical symptoms of depressive disorder include loss of appetite, tiredness and fatigue, major sleep problems, alterations in pain thresholds and problems associated with sexual behaviour. Most patients presenting depressive disorders, many of them elderly, complain of insomnia expressed through difficulties falling/staying asleep, early morning awakenings and non-restorative sleep (110, 111, 112). There is a bidirectional relationship between sleep disturbances and mood disorders with the former predictive of individuals at higher risk for development of depression. Patients presenting major depressive disorder show a higher prevalence of alpha-delta sleep associated with daytime sleepiness (113). Sleep disturbances and affective problems are presented also by the elderly, nursing home and assisted-living residents and patients with pulmonary hypertension presenting depressiveness (114, 115, 116, 117). Several studies attest to the benefits of physical activity and exercise upon sleep quality in both the elderly and those individuals presenting mood disturbance (16, 118, 119). Richards et al. (120) found that a combination of high-intensity strength training + 45-min walking exercise and individualized social activity increased markedly total nocturnal sleep time, sleep efficiency and non-rapid eye movement sleep in nursing home and assisted living residents. In 17 sedentary older middle-aged (mean age: 61.6 ± 4.3 years) presenting

insomnia, 16 weeks of moderate level aerobic physical activity improved sleep quality on the Pittsburgh Sleep Quality Index, sleep latency, sleep duration, sleep efficiency and daytime dysfunction compared to controls (121). Catecholamine depletion has been shown consistently to be associated with sleepiness in both healthy volunteers (122) and depressed patients (123, 124). Meyers et al. (125) have found a link between dopamine depletion and sleepiness independent of the brain reward system. Several studies show that physical exercise affects catecholamine metabolism and turnover positively in a variety of ways (126, 127, 128). In young cancer patients, physical activity improved fatigue, sleep-wake cycle disturbances and depressiveness (129). Finally, the interventional and convalescent properties of exercise in affective conditions presenting sleep disorders are emphasized (130, 131).

Chronic aches and pain: these complaints, in combination with fatigue, present 'often-experienced' physical symptoms reported by depressed individuals. Depression is commonly associated with chronic pain (132, 133, 134), particularly in elderly individuals (135). Chronic pain patients typically display reduced activity level attributed to pain and implying a positive correlation between exercise or activity and pain complaints. Chronic non-malignant aches and pain involve both sensory (nerve) and affective (cognitive/emotional) experiences. These symptoms express those types of pain lasting beyond the normal time duration required for any insult/injury to any body part to heal. Whereas one month may be referred to as subchronic three to four months and above constitutes a chronic period. Several studies have shown that physical exercise generally induces modest positive effects upon physical symptoms of depression (e.g. 136, 137). Akyol et al. (138) demonstrated in a randomized, controlled clinical trial that 40 female patients presenting bilateral primary knee osteoarthritis that received isokinetic exercise training, 3 days/week over four weeks, expressed improvements in pain, depressive symptoms, disability walking distance, muscle strength and quality of life. Isokinetic exercises, apparatus and methods, introduced by Perrine (139), are

generally performed at a dynamic preset fixed speed (ranging from 1 degree per second to approximately 1000 degrees per second) with resistance that is accommodating throughout the 'range of motion' (ROM) thereby allowing the propensity for objective measurement of muscle strength. Finally, whole body physical fitness, employing exercise programs, alleviated pain, anxiety and depression in patients with chronic neck pain (140).

Clinical depression may be linked also with lack of compliance with cancer treatment and reduced survival (141), and in turn affects negatively physical and psychological health of survivors. Several factors are contributory: poor adjustment to specific somatic symptoms (e.g. sexual, bowels, fatigue), symptom severity, frequency and duration (pain, fatigue), treatments factors (surgery, scars) or poor prognosis (142, 143, 144). Physical exercise offers an intervention that provides symptom relief for depression in cancer survivors (145 Fleishman, 2004). Several meta-analytic studies in this context concerning depression and cancer have shown moderate to large effects sizes (146, 147, 148, 149, 150). Larger effects may be obtained for programs that were supervised or partially supervised, performed outside the home environment, and taking up at least 30 minutes in duration (151). Those results complemented other studies showing that exercise is associated with reduced pain and fatigue and with improvements in quality of life among cancer survivors (152, 153, 154). Hicks et al. (155) have found that the presence of depressive symptoms, poor self-rated health and adherence to an adaptive physical activity program were the best predictors of improved pain status, with adherence being the strongest predictor [odds ratio: 13.88 (95% confidence interval: 8.17, 23.59)]. Improved physical function, longer pain duration, and positive rating of the trainer were all positively associated with adherence to the adaptive physical activity program whereas poor self-rated health and further distance from the gym were inversely associated.

Effects of exercise on biomarkers for depression

The vulnerability of individuals to chronic, sustained and repetitive stress is an important predisposing or predetermining factor for depressive illness, dysregulation of HPA axis function, promoting apoptosis and neurodegeneration and disrupting neuroimmune functioning (156, 157, 158, 159). Chronic stress, whether during adulthood or adolescence, may induce a vulnerable phenotype through maladaptive epigenetic changes that renders predisposed individuals liable to symptoms and biomarkers of the disorder (50, 160, 161, 162, 163). Blugeot et al. (164) have shown that this type of stress induced, in "vulnerable" laboratory rats (42%) persistent reduced levels of serum and hippocampal BDNF, reduced hippocampal volume and neurogenesis, CA3 dendritic retraction and reduced spine density, and amygdala neuron hypertrophy; a subsequent mild stressor evoked elevated corticosterone levels and a "depressive" phenotype. Severe depression is associated with increased microglial quinolinic acid (QUIN) in regions of the anterior cingulate cortex (165). Indoleamine-pyrrole 2,3-dioxygenase (IDO) that degrades tryptophan to kynurenine derivatives is implicated in depressive disorders (166, 167), in particular cognitive aspects (168). QFT ethanol is implicated in depression through inhibition of the 5-HT transporter (169). The manifest gains from exercise have been shown under laboratory conditions of some severity: early adverse experiences due to maternal separation induce neuronal cell death, depressiveness and neurocognitive deficits. Baek et al. (170) showed that treadmill exercise, presented postnatally, increased cognitive performance and alleviated depressiveness in the rat pups in the maternal separation group. Serotonin synthesis and TPH expression in the dorsal raphe nuclei and cell proliferation in the hippocampal dentate gyrus were significantly decreased due to maternal-separation; postnatal treadmill exercise increased 5-HT synthesis, the TPH expression, and the cell proliferation. Apoptotic neuronal cell death in the hippocampal dentate gyrus was significantly elevated by maternal-separation exercise

suppressing the apoptosis. Postnatal treadmill exercise alleviated maternal separation-induced depression and cognitive deficits through suppression of apoptotic neuronal cell death and by enhancing cell proliferation. Some of the major effects of exercise contributing to an antidepressant outcome include: altered blood flow (171), prevention of helplessness/behavioral depression (172), depressive symptoms following stroke (173), relief from symptoms in patient groups (174 Dimeo et al., 2001), and prevention and treatment of depressive disorders through mechanisms modulating chronic stress, neurodegeneration, monoamine integrity and immune responses (175).

HPA axis homeostasis

Sustained high serum glucocorticoid levels in depressive individuals (176) can elicit atrophic changes in hippocampal subregions (177) that contribute reduced hippocampal volume observed in postmorten brains of depressed patients (178), with dire consequence for negative HPA feedback. Antidepressant treatment elevates glucocorticoid receptor concentrations, restores HPA negative feedback and normalizes HPA function and cortisol levels (179). Stranahan et al. (180) have argued that HPA axis regulation through running exercise, offering a voluntary and controllable stressor with a distinct temporal profile, activates several systems related to the stress response whereas other mechanisms exist to reduce the reactivity to this stressor, with possible crosstalk between running and other forms of stress. Acute exercise affects concentrations of both testosterone and cortisol (181), thereby activating the HPA axis (182). Acute high intensity exercise increases cortisol levels (183, 184) but sustained exercise reduces the stress response (185, 186). The associations between activity-related salivary and plasma steroid hormones (cortisol, testosterone, and dehydroepiandrosterone (DHEA)), as well as growth hormone (GH) levels as a function of the type, duration, and intensity of the exercise reflect real benefits for disorders defined by

chronic stress and negative affect (187, 188). The putative protective effects of testosterone and DHEA in several conditions, including depression, have been considered (e.g. 189) whereas GH exerts important influences (cf. 190).

Physical exercise counteracts HPA dysregulation through modulatory effects of chronic stress on hippocampal functions. Elevated corticosteroids, expressing stress, exert profound effects on hippocampal structure and function with detrimental influences through altered expression of hippocampal brain-derived neurotrophic factor (BDNF) (191), suppression of neuronal differentiation of proliferating cells in the adult hippocampus (192) and suppressed neurogenesis (193). Several antidepressant effects of activity appear to be mediated through restoration of hippocampal integrity (194). A procedure consisting of repeated corticosterone injections to rodents over 14 days has been established as an animal model for examining the role of stress in depressive disorders (195). Yau et al. (196) observed that repeated corticosterone treatment caused a graded increase in depression-like behavior and impaired spatial learning linked to reduced hippocampal cell proliferation and BDNF levels. Running exercise reversed these effects in rats treated with low or moderate levels of corticosterone but not in those treated with high levels. Running increased neuronal differentiation in both vehicle and corticosterone treated rats, increased dendritic length and spine density in rats treated with a moderate dose of corticosterone. They authors suggested that exercise-induced restoration of hippocampal neurogenesis and dendrite remodelling are necessary ingredients to counteract chronic stress and biomarkers of depression.

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) hormones are implicated in HPA axis regulation through reduction of corticotrophin-releasing hormone (CRH), arginine vasopressin (AVP), adrenocorticotrophic hormone (ACTH) and cortisol (197, 198, 199). Circulating levels of ANP increase during exercise (200) with further increases in both ANP and BNP, as well as oxytocin, occurring as exercise intensity increased (201, 202).

Wisén et al. (203) observed lower concentrations of ANP and BNP during rest and exercise in patients with major depressive disorder accompanied by a decreased dynamic response to maximal exercise. It is likely that the high levels of hormones in depression are in part due to reduced levels of these hormones. Thus, and potential ANP-BNP elevating effects of exercise ought to be beneficial for symptoms of depression (204).

Anti-neurodegenerative effects

Proteins and peptides associated with health promotion and neuronal survival are released by physical exercise in humans (205, 206). These molecules, in particular BDNF, pertain to essential centrally-active growth factors implicated in conditions of affective/emotional dysregulation, e.g. aging and depression, that are linked to reductions (207, 208); BDNF, vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF), all produced by exercise regimes, are involved intimately in neuronal integrity (209, 210, 211). VEGF mRNA levels in hippocampus were significantly increased both in olfactory bulbectomised (an animal model of depression) and control rats following combined exercise and environment enrichment (212). Using the chronic unpredictable rat model of depression, Wen et al. (213) found an overactivation of the mitochondria in the raphe nuclei, an indication of oxidative stress leading to neurotoxicity (214); physical exercise suppressed the mitochondrial overactivation.

Physical exercise improves the efficiency of the capillary system and increases the oxygen supply to the brain, thus enhancing metabolic activity and oxygen intake in neurons, and increases neurotrophin levels and resistance to stress. Regular exercise and an active lifestyle during adulthood have been associated with reduced risk and protective effects for mild cognitive impairment (215). Syu et al. (216) have observed that acute severe exercise immediately increased the oxidative stress, cytosolic ROS and glutathione oxidation, and

sequentially accelerated the reduction of mitochondrial membrane potential, the surface binding of annexin-V, and the generation of mitochondrial ROS chronic moderate exercise upregulated glutathione level, retarded spontaneous apoptosis and delayed mitochondria deterioration. Exercise stimulates growth hormone (GH) and prolactin release (217). The former stimulates growth, cell reproduction and regeneration whereas the latter promotes proliferation of oligodendrocyte precursor cells that differentiate into glial oligodendrocytes.

Monoamine metabolism effects

Since monoamine neurotransmitters (serotonin, norepinephrine, and dopamine) are dysregulated in major depression, it is implied that there has occurred a breakdown in normal homeostatic mechanisms. The actions of forces that develop when a homeostatic mechanism has been subjected to prolonged neuropharmacological perturbation may restore equilibrium (218). Matsui et al. (219) have shown that in the cerebral cortex of male Wistar rats levels of methoxyhydroxyphenol (MHPG), the main noradrenaline metabolite, and 5-Hydroxyindole acetic acid (5-HIAA), the main serotonin metabolite, were increased markedly by 120 min of running; the elevation of these monoamine levels was negatively correlated with glycogen levels which decreased significantly in five brain regions (cerebellum, cerebral cortex, hippocampus, brainstem and hypothalamus).

Both DA turnover and tyrosine hydroxylase activity were markedly increased through exercise (220). The pharmacomimetic effects of exercise are well-documented (221) and contribute to its alleviatory effects upon depressive symptoms (222). Greenwood and Fleshner (223) have shown that voluntary exercise decreased the incidence of stress-related psychiatric disorders in humans and prevented serotonin-dependent behavioral consequences of stress in rodents. Their evidence supports the notion that exercise increases stress resistance by producing neuroplasticity at multiple sites of the central serotonergic system thereby limiting

the behavioral impact of acute increases in serotonin during stressor exposure. Greenwood et al. (224) showed that there exists a time-dependent relationship between serotonergic pathways and running exercise whereby observed changes in mRNA regulation in a subset of raphe nuclei were involved in the stress resistance produced by wheel running and the antidepressant-anxiolytic effects of physical activity. Hendriksen et al. (225) demonstrated that voluntary running wheel exercise reduced anxiety in rats subjects to posttraumatic stress disorder, an effect independent of memory loss due to trauma. Behavioral recovery was accompanied by hippocampus cell proliferation, reduced tissue levels of noradrenaline and increased turnover of serotonin in prefrontal cortex and hippocampus. In both younger and older adults, physical exercise increased cerebral oxygenation and uptake of lactate and glucose although the older group had reduced cerebral perfusion and maximal exercise capacity, cerebral oxygenation and uptake of lactate and glucose were similar during exercise in young and older individuals (226).

Neuroimmune functioning

Dysregulation in the neuroimmune functioning of depressed patients has been established (227, 228, 229), and both symptoms of depression (230, 231, 232, 233) and genetic linkage (234, 235) have been linked to cytokine markers. There is an increase in pro-inflammatory cytokines in patients presenting major depression that is related to HPA overactivity and illness severity (236, 237). It has been observed also that depressed patients who attempted suicide had elevated levels of IL-6 in the cerebrospinal fluid (CSF) (238); increased symptotic severity was linked to higher levels of IL-6 in the CSF. As described by Loftis et al. (30), neuroimmune mechanisms have been assigned an essential role in the development and expression of depressive symptoms and the neural circuits involved (239). Cizza et al. (240) observed that proinflammatory cytokines, neuropeptide Y, substance P and

calcitonin-gene-related peptide were all significantly higher in premenopausal female patients presenting major depressive disorder, whereas vasoactive intestinal peptide, a marker for parasympathetic activity, was significantly lower compared to controls. Inflammation induces also metabolites with potential excitotoxic effects, e.g. kynurenic acid and quinolinic acid (241). Dantzer et al. (242) have presented the notion of inflammation-induced depression as a clinical entity that provides insights regarding the interactions between peripheral and brain mechanisms underlying the different stages in the etiopathogenesis of the disorder (240, 243).

The highly integrated and synergistic responses of the brain and CNS in combination with continuous efficiency of the overall immune system provide the mechanisms underlying the general state of exercise-related psycho-physical well-being (244). In both the 18 major depressive disorder patients and the 18 healthy controls, Hallberg et al. (245) reported exercise-induced significant changes in the plasma levels of inflammatory substances. It was observed that IL-8, IL-6 and TNF-α increased whereas IL-4 decreased during the challenge in both groups. In laboratory studies, Leem et al. (246) have shown that the neuroinflammatory response characterized by activated astroglia and microglia was significantly repressed in the exercised Tg mice, that over-express human Tau23, in an exercise intensity-dependent manner. In parallel, chronic exercise in Tg mice reduced the increased expression of TNF-α, IL-6, IL-1β, COX-2 (cyclooxygenase-2, involved in inflammation and pain), and iNOS (nitric oxide synthase). Finally, treadmill exercise for 10 days after TBI increased the number of calbindin-stained Purkinje neurons and suppressed formation of reactive astroyctes (247). Astrocytes, microglia and T cells all exert anti-inflammatory and neuroprotective functions (32).

Hojman et al. (248) have found that post-exercise serum inhibited mammary cancer cell proliferation and induces the apoptosis of these cells. Wang and Weng (249) concluded that 15% O_2 (hypoxic) exercise training reduces terminally differentiated natural killer cells (NK)

subsets and up-regulated the expression of activating molecules and cytotoxic granule proteins in NKs, thereby enhancing the capacity of anti-nasopharyngeal carcinoma cells (NPCs) cytotoxicity by NKs. De Lima et al. (250) have shown that Walker 256 tumor-bearing rats that were allowed exercise (anaerobic) presented more tumor cell apoptosis, a higher tumor content of lipid peroxides, pro-apoptotic protein expression balance, and reduced tumor weight and cell proliferation ex vivo, compared with sedentary rats, thereby accounting for the lower tumor growth observed in the exercised rats. The exact mechanisms how exercise affects the brain are not fully understood and the literature lacks of well-designed studies concerning the effects of exercise training on depressive disorders. But the observed antidepressant actions of exercise are strong enough that it already can be used as an alternative to current medications in the treatment of depressive disorders (251).

The scaffolding effects of exercise on mental health

The exact mechanisms how exercise affects the brain are not fully understood and the literature lacks of well-designed studies concerning the effects of exercise training on depressive disorders. Nevertheless, the observed antidepressant actions of exercise are strong enough that it already can be used as an alternative to current medications in the treatment of depressive disorders (251). The notion of physical exercise as a “scaffolding” to buttress damage experienced under such conditions as traumatic brain damage and aging provokes the metaphor of transient measures, external to the buildings, that provides for construction, reconstruction and maintenance but not the buildings themselves. Scaffolding provides a normal process that continues across the lifespan involving that application and development of complementary, alternative neural circuits to achieve a particular cognitive goal (252); it is protective of cognition in the aging (or disabled) brain and is reinforced by physical exercise and cognitive engagement (which is harnessed during exercise. Under conditions of traumatic

brain injury the notion of scaffolding suggests that exercise buttresses, more or less dependent on extent of injury, the surviving adaptive and neuroreparative processes (25, 253). Studies in transgenic mice and primary human skeletal myocyte studies have shown the critical influence of exercise-responsive transcriptional co-activator PGC-1α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha, which regulates the genes controlling energy metabolism), in coordinating intramuscular lipid-droplet-programming leading to mitochondrial remodeling. PGC-1α regulates also mitochondrial biogenesis and function. In this regard, translational studies that compared individuals who exercised physically with sedentary individuals have identified a dramatically strong association between the expression of intramuscular lipid droplet genes and enhanced insulin action in the exercising individuals (254). In the context of depressive disorders, the notion of scaffolding suggests that exercise/activity mobilizes available and alternative neural and neuroimmune circuits that may initiate and/or consolidate neuroreparative and anti-inflammatory processes, such as BDNF.

Conclusions and directions for future research

Despite proper understanding of how exercise affects brain integrity and a paucity of well-designed, standardized studies on the exercise intervention on depressive disorders, the consensus of an impressive plethora of existing evidence reinforces the notion of the antidepressant actions of exercise implying that PA ought to be incorporated as a major alternative to traditional medication (see also, 251), albeit with special focus upon mild-to-moderate levels of the disorder and with patient willingness and compliance (18). The understanding of the mechanisms underlying the effects of exercise on depression constitutes an essential step in the direction of the broad use of exercise as an alternative treatment of depression in the field. In the present review paper, we have based our discussion in a model

that highlights the effects of exercise on key depressive symptoms, and on key biomarkers of depression, rather than on depression as a global outcome. In this regard, stress, intense or chronic, and likely both, is a major agent. Fleshner et al. (255) have proposed an hypothesis outlining a mechanism through which physical exercise, as opposed to sedentary living, promotes stress robustness in the face of intense uncontrollable stress. According to this notion, individuals with a sedentary existence respond to an intense acute uncontrollable stressor with excessive 5-HT and NA activity and/or prolonged down-regulation of the CX3CL1-CX3CR1 axis resulting in activation and proliferation of hippocampal microglia with consequent hippocampal-dependent memory deficits and reduced neurogenesis. Contrastingly, physically active individuals respond to the same stressor with constrained 5-HT and NA activity and a rapidly recovering CX3CL1-CX3CR1 axis responses resulting in the quieting of microglia, and protection from negative cognitive and neurobiological effects of stress. The CX3CL1-CX3CR1 expressing microglia have an important role in limiting neuroinflammatory and neurodegenerative damage in brain cells. The merit of this more detailed approach, focusing on the various and specific effects of exercise on the different facets of symptom-profiles and biomarkers that buttress depressive conditions, concerns the provision for increased understanding of the general process and the perception of existing overall patterns through a more meticulous scrutinization of the far-reaching processes involved.

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