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Review

Role of physical activity and diet on mood, behavior, and cognition

Barbara Strasser[a], Dietmar Fuchs[b,*]

[a] Division of Medical Biochemistry, Biocenter, Medical University, Innsbruck, Austria
[b] Division of Biological Chemistry, Biocenter, Medical University, Innsbruck, Austria

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ABSTRACT

Research on the relationship between physical activity and mental health reveals that physical activity exerts beneficial effects on emotional and cognitive functioning. Studies clearly indicate that aerobic exercise is neuroprotective. It seems that the activity-dependent production of nitric oxide (NO) and the anti-inflammatory effects of regular exercise may play an important role in the production of brain-derived neutrophic factor (BDNF) that occurs in response to exercise. With regard to behavioral functioning, most studies focus on the influence of physical activity on depressive symptoms or affective disorders. Physical exercise upregulates the production of several neurotransmitters which like serotonin are associated with mood enhancement and reduced depressive symptoms. The positive effects of physical activity on anxious mood and anxiety disorders are also well documented. Thereby cytokine-induced effects on nitric oxide formation and activity of indoleamine 2,3-dioxygenase (IDO) as well as the formation of tetrahydrobiopterin (BH_4), cofactor of several amino acids monooxygenases, seem to be special relevance. Improved self-esteem and self-efficacy seem to play an important part. Physical activity also affects the endocrine stress-regulation system: trained people exhibit stronger reactivity and quicker regeneration when faced with stressful events. However, aerobic exercise does not improve mental health in every case, as seen for instance in over-trained athletes associated with fatigue, disturbed mood and signs of depression might emerge. Recent research has provided exciting evidence for the influence of dietary factors on specific molecular systems and mechanisms that maintain mental function, for instance, a diet that is rich in omega-3 fatty acids.

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1. Introduction

The concept of the mind and human thought is not a novel one. Many tentative explanations have been advanced, even in the form of art—notably in Michelangelo's Creation of Adam, in which the borders in the painting are strikingly similar to current anatomical drawings of the brain (Meshberger, 1990). Thales of Miletus (624–546 B.C.), an early Pre-Socratic philosopher, believed that a happy

* Corresponding author.
E-mail addresses: barbara.strasser@umit.at (B. Strasser), dietmar.fuchs@i-med.ac.at (D. Fuchs).

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man was one who was "healthy in body, resourceful in soul and of a readily teachable nature". Hippocrates (460–370 B.C.) had originally proposed that the body must be treated as a whole and not just a series of parts and laid the foundations of the modern theory that thoughts, ideas and feelings, which he proposed to originate in the brain, can influence health and the process of disease. Plato (428–347 B.C.) emphasized the importance of physical exercise for developing the mind and first expressed the required dosage for a human healthy being in a most exact way, never too little and never too much. The Roman poet Juvenal (60–127) composed the phrase "*Mens sana in corpore sano*" to express that only a healthy body can produce or sustain a healthy mind. Its most general usage is to illustrate the hierarchy of needs: with physical and mental health at the root.

Today, modern technologies are available to understand the relationship between mind and body. Recent neurobiological research indicates that for optimal mental health, exercise is essential. However, there is limited mechanistic insight how the human brain is affected by physical activity. Regular exercise typically reduces inflammation (Gleeson et al., 2011a), which as one important consequence is accompanied by slowing-down the expression and activity of tryptophan—degrading enzyme indoleamine 2,3-dioxygenase (IDO) (Gostner et al., 2015). In turn, tryptophan levels rise and its transport into the brain can increase production of neurotransmitter 5-hydroxytryptamin (5-HT, serotonin) and thereby enhance mood.

The purpose of this review is to provide a brief overview on the protective effects of physical activity on cognition and mood and to describe possible neurobiological mechanisms that underlie this relationship. The biological pathways whereby physical activity may benefit the brain include: (1) enhancing neuroplasticity and growth factor expression, (2) promoting an anti-inflammatory state, and (3) serving as a buffer against stress and stress-related disorders and chronic diseases. Another aim of the present review is to provide an update about nutrients influencing the serotonergic system that have potential to increase stress resilience and thereby our well-being.

2. Neurobiological effects of physical exercise

2.1. Brain-derived neurotrophic factor, exercise, and cognition

There is evidence that physical exercise promotes changes in the human brain due to increases in metabolism, oxygenation and blood flow in the brain (Dishman et al., 2006). Studies have shown that physical exercise modulates the major central nervous system (CNS) neurotransmitters such as norepinephrine (noradrenalin) which is associated with alertness, dopamine which plays a major role in reward-motivated behavior, and serotonin which is popularly thought to be a contributor to feelings of well-being and happiness (Lin & Kuo, 2013).

Other neuromodulators that are activated by exercise are trophic factors. One important growth factor that has received much attention is brain-derived neutrophic factor (BDNF) which plays a critical role in integrating behavioral and metabolic responses to various challenging environments, including exercise (Cotman, Berchtold, & Christie, 2007). In particular, BDNF signaling mediates adaptive responses of the nervous, cardiovascular, and energy-regulating organ systems in response to exercise and energy restriction (Rothman, Griffioen, Wan, & Mattson, 2012). Therefore, since the early 1990s, studies have begun to investigate the effects of acute and chronic exercise on the concentrations of BDNF. It was shown that acute exercise, independent of the CNS (Goekint et al., 2008), increased BDNF in the hippocampus, the area that is vital for learning and memory (Vaynman, Ying, Gomez-Pinilla, & Hippocampal, 2004). Activity-dependent production of nitric oxide ($NO^{\bullet}$) may play an important role in the production of BDNF that occurs in response to exercise (Chen, Ivy, & Russo-Neustadt, 2006). It appears that the magnitude of increase in BDNF is intensity dependent with higher BDNF response after intense exercise (above the ventilator threshold) (Ferris, Williams, & Shen, 2007). BDNF possesses the extraordinary capacity to enhance neuronal excitability and synaptic plasticity by interacting with energy metabolism, thereby supporting cognitive abilities (Gomez-Pinilla & Hillman, 2013). Blocking the action of BDNF during exercise has been shown to counteract the enhancing effects of exercise on synaptic plasticity and cognitive function (Gomez-Pinilla, Vaynman, & Ying, 2008). A recent study found that the hippocampus remains plastic in late adulthood and exercise training increased hippocampal volume by 2%, effectively reversing age-related loss in volume by 1–2 years (Erickson et al., 2011). Furthermore, increased hippocampal volume was associated with improved memory function and higher serum BDNF. These results clearly indicate that aerobic exercise is neuroprotective and that starting an exercise regimen later in life is not futile for either enhancing cognition or augmenting brain volume.

Little is known about the effect of resistance training on BDNF and cognition. Although it was shown that 10 weeks of resistance exercise do not significantly increase peripheral BDNF levels in sedentary individuals (Goekint et al., 2010), there is some evidence that strength training increases cognitive performance, especially in the elderly population (Cassilhas et al., 2007). It seems that memory is improved by aerobic and resistance exercise through different molecular mechanisms. An animal study found that endurance training increased BDNF in the brain as well as tyrosine kinase B receptor, while resistance training did not but increased insulin growth factor 1 and its receptor (Cassilhas et al., 2012), triggering the hypothesis that both aerobic and resistance training can employ divergent molecular mechanisms, but achieve similar results on memory and cognition.

2.2. The anti-inflammatory effects of exercise

As previously noted, BDNF is regulated by $NO^{\cdot}$ which is, however, highly sensitive to oxidative stress and vascular inflammation (Fig. 1). Reactive oxygen species (ROS)-mediated declines in production and stability of $NO^{\bullet}$ and increases in pro-inflammatory cytokines might inhibit the BDNF pathway, whereas chronic aerobic exercise may attenuate the effects of normal aging on oxidative stress. Thus, NO is believed to have an antioxidative effect on the vasculature, while acute exercise leads to a transient increase in oxidative stress (Pialoux, Brown, Leigh, Friedenreich, & Poulin, 2009). Furthermore, ROS may play a role in the regulation of cerebrovascular function, potentially through its effects on the endothelium. It is hypothesized that increased levels of ROS will increase the permeability of the blood-brain barrier to pro-inflammatory cytokines and interfere with growth factor signaling within the brain (Davenport, Hogan, Eskes, Longman, & Poulin, 2012). Regular exercise leads to a number of favorable adaptations in the vascular system, including decreases in oxidative stress and increases in antioxidative activity, which contributes to improved cerebrovascular function. The anti-inflammatory effects of regular exercise may be mediated via both a reduction in visceral fat mass with a subsequent decreased release in pro-inflammatory adipokines such as leptin, interleukin-6 (IL-6), and tumor necrosis factor (TNF)-α and the induction of an anti-inflammatory environment with each bout of exercise (Gleeson et al., 2011a). Notably, IL-6 can also be classified as a myokine with an endocrinological activity since it contributes to hepatic glucose production during exercise (Febbraio, Hiscock, Sacchetti, Fischer, & Pedersen, 2004). The systemic level of IL-6 increases markedly with exercise, and skeletal muscle is the main source of origin. Muscle contractions

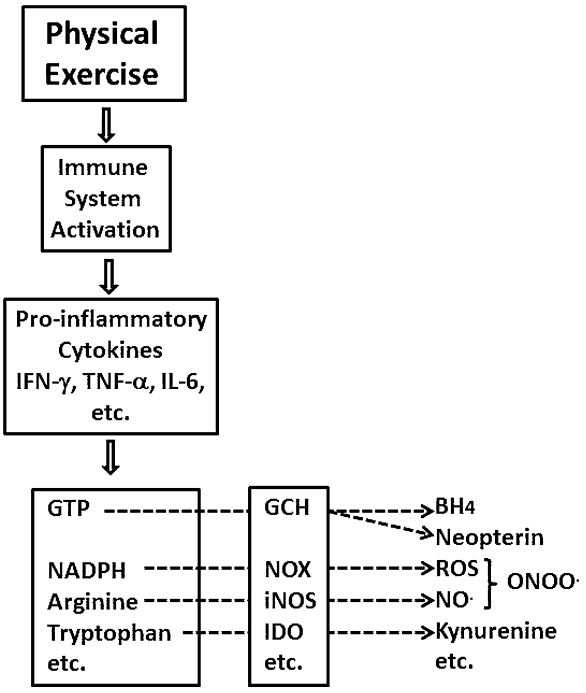

Fig. 1. Physical exercise elicits activation of several immune system compartments and is associated with the enhanced production of pro-inflammatory cytokines such as interferon-γ (IFN-γ) tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). The cytokines up-regulate several enzymes like GTP-cyclohydrolase I (GCH), NADPH oxidase (NOX), nitric oxide ($NO^{\bullet}$) synthase (iNOS) and indoleamine 2,3-dioxygenase (IDO), some products of these are important in host defense and neurotransmission: GCH produced tetrahydrobiopterin (BH_4), cofactor of enzymes involved in the production of $NO^{\bullet}$, serotonin, adrenalin and noradrenalin, and neopterin which serves as a sensitive biomarker of IFN-γ production and forward regulates preferentially pro-oxidative signaling cascades. IDO degrades tryptophan as the first step in the production of kynurenines. iNOS produces $NO^{\bullet}$ acting as a neurotransmitter and vasodilatory as does also kynurenine. Aside from that, $NO^{\cdot}$ suppresses expression and activity of IDO and kynurenine is important for the induction of regulatory T-cells (T_{reg}) slowing down activated T-cells. Alternatively, $NO^{\bullet}$ once produced, may immediately react with superoxide anion $O_2^{\bullet-}$, an important NOX-derived reactive oxygen species (ROS), and generate highly toxic peroxynitrite $ONOO^{-}$.

lead to the production and release into the circulation of IL-6, which appears to have numerous biological effects, including effects on glucose and fat metabolism. In addition, IL-6 mediates anti-inflammatory effects. Acute elevations in IL-6 produced by contracting skeletal muscle down-regulates the production of TNF-α by monocytes and stimulates the release of IL-1 receptor antagonist (IL-1RA) from monocytes and macrophages, thus increasing the circulating concentrations of anti-inflammatory cytokines such as adiponectin and IL-10 from adipose tissue (Pedersen, 2013). However, these effects are also likely to be responsible for the suppressed immunity that makes elite athletes more susceptible to upper respiratory tract infections, although other factors – such as psychological stress, disturbed sleep and negative energy balance – may contribute to immunosuppression in athletes. Athletes engaging in longer periods of intensified training can exhibit decreases in T cell functionality, which appears to be related to elevated circulating stress hormones, particularly cortisol, and alterations in the pro/anti-inflammatory cytokine balance in response to exercise. The consequence is a temporary inhibition on Th1-type cell cytokine production, with a relative dampening of the Th1 (cell-mediated) immune response (Walsh et al., 2011). Typically, free radicals are thought of as perpetrators of cell damage, ageing, even cancer, whereas antioxidants are seen as the defense against these threats. Accordingly, antioxidants are among the most common sports supplements used by amateur and professional athletes. However, there is some evidence that regular intake of relatively high doses of antioxidant vitamins can also reduce the stress response to prolonged exercise (Fischer et al., 2004) and even may increase infection and allergy risks (Burtscher, Pesta, Fuchs, Ledochowski, & Gatterer, 2015; Zaknun, Schroecksnadel, Kurz, & Fuchs, 2012). Such supplements slow-down Th1-type immune activation cascades leading to a suppression of IDO activity, which counteracts immune defense. Thus, excessive supplementation with antioxidant vitamins cannot be recommended because there is little evidence of benefit, while it is known that over supplementation can actually diminish the body's natural antioxidant defense system (Gomez-Cabrera et al., 2008; Ristow et al., 2009).

There are several nutritional and training strategies that can be adopted to limit exercise-induced immunosuppression and minimize the risk of infection. The impact of intensive training stress on immune function can be minimized by adequate sleep (at least 7 h per night is recommended), minimizing psychological stress, avoiding periods of dietary energy restriction, consuming a well-balanced diet that meets energy and protein needs, avoiding deficiencies of micronutrients (particularly iron), ingesting carbohydrate (30–60 g per hour) during prolonged training sessions, and consuming plant polyphenol foodstuffs (e.g., non-alcoholic beer) (Scherr et al., 2012) and *Lactobacillus* probiotics (Gleeson, Bishop, Oliveira, & Tauler, 2011b).

2.3. Hypothalamic–pituitary–adrenal axis, physical fitness, and stress response

The biological mechanisms underlying the relation between physical fitness and stress response are multifactorial and complex. Physical fitness appears to buffer against stress and stress-related disorders by optimizing effects on hormonal stress responsive systems, such as the hypothalamic–pituitary–adrenal (HPA) axis, with the formation of cortisol, and the sympathetic nervous system (SNS), which releases the catecholamines epinephrine (adrenalin) and noradrenalin. Further, as mentioned above, physical fitness promotes an anti-inflammatory state thereby promoting behavioral and metabolic resilience (Hamer, Endrighi, & Poole, 2012).

Progress has been made to understand the association between multiple biological factors (i.e., genetics, nutrition, exercise) and obesity. People who are more responsive to psychological stress are also at an increased risk of developing obesity, particularly abdominal obesity (Björntorp, 2001). However, the precise biological mechanisms underlying the association between psychological stress and obesity still remain unclear. One potential mechanism might relate to immunoregulatory cytokines (Brydon et al., 2008). Leukocyte counts and biomarkers of inflammation, such as cytokines TNF-alpha, IL-6, as well as leptin are increased in obesity and predict the development of the metabolic syndrome (Lee & Pratley, 2005). Leptin is a hormone secreted from adipose tissue that was first discovered to regulate eating, satiety, and body weight. In addition to its function in metabolic control, leptin has been recognized as a more complex hormone involved in regulating stress responses in the HPA axis (Auwerx & Staels, 1998). Stress is known to activate the HPA axis thus increasing glucocorticoid levels which in turn stimulate leptin production. Evidence from several studies suggests that experiences of psychological stress may have the potential effect of increasing leptin levels. Higher serum leptin levels were associated with awareness of higher stress in men (Otsuka et al., 2006), stress-related psychopathological symptoms (Liao, Lee, Lee, & Huang, 2004), and phobic anxiety in women (Brennan et al., 2009). A large population-based study of adults found a 4-fold increased risk for

elevated leptin levels in men suffering from both depressed mood and social isolation (Häfner et al., 2011).

So far, only one study investigated the role of psychological stress on leptin levels in children. In this population-based study, leptin levels were associated with psychological stress, in particular peer problems in ten year old children (Kohlboeck et al., 2014). Since obese children have higher plasma leptin concentrations than their normal-weight peers this would suggest that body fat rather than peer problems in children are related with elevated leptin levels. However, it is currently unclear whether the psychological stress/leptin relationship is a result of overweight and obesity, or whether this relationship is due to increased reactivity of the HPA axis in children with psychological stress. Furthermore, the pathways by which physical fitness affect the psychological stress/leptin relationship remains still unclear.

There is some evidence that vigorous physical activity and fitness moderates the levels of leptin concentrations, regardless of relevant confounders including total body fat (Jiménez-Pavón et al., 2012). Acute exercise activates the HPA axis in a dose-dependent manner, such that the intensity of the exercise, as well as the duration, determines the magnitude of the stress response. For example, low-intensity exercise minimally activates and strenuous exercise (>70% VO_{2max}) markedly activates the HPA axis as well as the sympathetic nervous and immune system (Luger et al., 1987). This blunting appears to contribute to reduced emotional, physiological and metabolic reactivity as well as increased positive mood and well-being (Karatsoreos & McEwen, 2011). Typically, upon termination of exercise, these systems return to baseline. However, prolonged or insufficient activation of the systems can cause metabolic dysregulation of the HPA axis and immune dysfunction/inflammation and can lead to the development of various chronic diseases (Dhabhar, 2009). Thereby, the kynurenine pathway is induced and the ratio of kynurenine to tryptophan (Kyn/Trp) concentrations reflects the tryptophan breakdown rate and elevation of which is often linked with conditions of inflammation (Capuron et al., 2011). However, tryptophan metabolism and obesity-related immune mediated inflammation differs markedly between juveniles and adults. While childhood obesity seems to be dominated by a Th2-driven activation, an accelerated production of Th1-type cytokines may pave the way for later atherosclerotic endpoints (Mangge et al., 2014).

Several studies demonstrate significant relationships between cytokine-induced alterations of tryptophan and kynurenine and the occurrence of neuropsychiatric symptoms that are associated with a variety of chronic inflammatory conditions (Mangge et al., 2014). Pro-inflammatory cytokines can influence virtually every pathophysiological domain relevant to depressive symptomatology, including neuroendocrine function, neurotransmitter metabolism and neuroplasticity, and ultimately influence behavioral resilience and well-being (Maes et al., 2009; Miller, Maletic, & Raison, 2009). Disturbed metabolism of tryptophan affects biosynthesis of serotonin, and it appears to be associated with an increased susceptibility for mental disorders (Widner, Laich, Sperner-Unterweger, Ledochowski, & Fuchs, 2002).

3. Benefits of exercise on mood and mental disorders

Van, raag, Christie, Sejnowski, and Gage (1999) showed for the first time in animals that running is a potential enhancer of cognitive and behavioral functions. From the findings of studies undertaken to date, it would appear that exercise may reduce both depression and anxiety and improve wellbeing. Three recent systematic reviews confirm the potential benefit of exercise of people with depression (Rethorst, Wipfli, & Landers, 2009; Rimer et al., 2012; Robertson, Robertson, Jepson, & Maxwell, 2012). However, when the analysis was limited to high quality studies with long-term follow-up, not all reviews support the role of exercise in the treatment of depression (Cooney et al., 2013; Krogh, Nordentoft, Sterne, & Lawlor, 2011). It appears that moderate-intensity exercise programs (≈65% VO_{2max}) result in improved behavioral, affective, mood or anxiety responses (Ekkekakis & Petruzzello, 1999). Intriguingly, the antidepressant effects of exercise can far outlast the period of exercise (Babyak et al., 2000). Although much of this research has examined the effects of aerobic exercise on mental health outcomes, resistance exercise also produces many physiological and psychological benefits (O'Connor, Herring, & Caravalho, 2010). A growing body of literature has identified anxiolytic effects of resistance exercise in a diverse range of populations after both single-bout sessions and long-term training. This research has shown that strength training at a low to moderate intensity (<70% 1RM) produces the most reliable and robust decreases in anxiety (Strickland & Smith, 2014). It seems that changes in body mass (fat loss, lean body mass increase) may be an effective strategy for reducing an inflammatory milieu. Based on a recent meta-analysis, chronic resistance training significantly reduced resting levels of inflammation biomarker C-reactive protein (CRP) by 25% independently from weight loss in sedentary adults (Strasser, Arvandi, & Siebert, 2012). Thus, physical exercise could be a potent stimulus to improve pro-inflammatory cytokines by lowering them and thereby enhancing, e.g., tryptophan levels (Gleeson et al., 2011a; Capuron et al., 2011).

During acute exercise, the entry of tryptophan into the CNS through the blood–brain barrier is favored by increased muscle use of branched-chain amino acids (BCAAs) and elevated plasma fatty acids, as this elevates the ratio of unbound tryptophan to BCAA. This increases the amount of tryptophan crossing the blood–brain barrier, consequently leading to higher serotonin concentrations in the brain. Increases in brain serotonin concentration and overall activity have been associated with increased physical and mental fatigue during endurance exercise (Meeusen, Watson, Hasegawa, Roelands, & Piacentini, 2006).

The stimulation of the monoamine system is dependent on exercise intensity. Strenuous exercise results in formation of ROS. When ROS levels exceed the buffering capacity of the cell, synaptic plasticity and cognitive function are compromised. Failure to maintain energy homeostasis can affect the cellular machinery associated with cognitive function, and increase the risk for mental disorders. Chronic moderate exercise, which has the capacity to reestablish cellular homeostasis, that is, energy metabolism and buffer ROS, can help to maintain cognitive function and mental disorders (Gomez-Pinilla & Hillman, 2013).

Animal and human studies have shown that aerobic exercise can stimulate brain serotonin activity and trigger parallel elevations in tryptophan availability in blood. Exercise elevates the levels of tryptophan 4-mono-oxygenase, the enzyme involved in the rate-limiting step in the synthesis of serotonin, and sends projections to the hippocampus that can influence hippocampal activity (Dey, Singh, & Dey, 1992). It has also been found that running can increase the levels of tryptophan in the hippocampus (Meeusen et al., 1996). The increased availability of tryptophan might enhance serotonin production and reduce depressive symptoms in adults who have been diagnosed with mild to moderate major depressive disorder (Dunn, Trivedi, Kampert, Clark, & Chambliss, 2005).

Little attention has been paid thus far to the influence of chronic exercise on serotonergic activity. A recent study in senior men found marked transient elevations in plasma tryptophan availability to the brain in response to exercise, both before and after 16 weeks of aerobic training. However, the maximum values for plasma tryptophan supply to the brain attained during exercise were lower following training than at baseline (Melancon, Lorrain,

& Dionne, 2014). The underlying reason for the smaller increase in brain serotonin activity may be explained by the existence of an intimate link between serotonergic activity and SNS activities (Chaouloff, 1993). Thus, post-training exercise stress might increase SNS activity to a lower extent compared with baseline; hence, less plasma tryptophan was made available to the brain and less brain serotonin was released. It should be noted that the antidepressant effect of an acute session of exercise is likely to be small and short-lived (Krogh et al., 2011). Thus the potential benefits can be realized only if exercise is performed on a regular basis.

New findings suggest that exercise affects tryptophan metabolism specifically within muscle, and peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1 α in rats. PGC-1α transcriptional coactivators play an important role in regulation of muscle kynurenine aminotransferase (KAT) enzyme expression, which modulates plasma kynurenine levels to, in turn, influence hippocampal neuronal plasticity and to alleviate stress-induced depression (Agudelo et al., 2014). The kynurenine pathway is considered important for depression (Schwarcz, Bruno, Muchowski, & Wu, 2012). In addition, elevated PGC-1α1 in muscle improves insulin metabolism, which may convey antidepressant-like effects (Oxenkrug, 2013). The study by Agudela et al. demonstrates that skeletal muscle PGC-1α1 overexpression can counteract depression and acts as an exercise-mimetic that modulates paracrine factors and this may open up avenues to new therapeutic approaches (Moon & van Praag, 2014).

Physical exercise was also observed to affect metabolism of pteridine derivatives such as neopterin and 5,6,7,8-tetrahydobiopterin (BH_4) (Tilz et al., 1993). Neopterin represents a sensitive indicator of macrophage activation and oxidative stress in humans (Murr et al., 1999) and BH_4 is necessary cofactor of several aromatic amino acid monooxygenases such as tryptophan 5-hydroxylase that is primary in the biosynthesis of serotonin, as well as phenylalanine and tyrosine hydroxylases that comprise the first enzymatic steps in the biosynthesis of dihydroxyphenylalanine (DOPA), adrenalin and noradrenalin and also of $NO^{\cdot}$ synthases (Werner-Felmayer, Golderer, & Werner, 2002). Consequently, physical exercise upregulates the production of several relevant neurotransmitters (Fig. 1) which like serotonin and noradrenalin are not only important for the neuropsychiatric performance of individuals. $NO^{\bullet}$ and kynurenine are also relevant in blood pressure regulation and coagulation via platelet activating factor (PAF) (Watschinger and Werner, 2013; Wang et al., 2010). However, it has to be considered that the increase of the neurotransmitters and their precursors is only a consequence of short time physical exercise. Repeated physical exercise without sufficient periods of recovery bears the risk of prolonged cytokine-induced depletion of tryptophan (Widner et al., 2002) and diminution of phenylalanine hydroxylase activity and $NO^{\cdot}$ production because of the reduced half-life of BH_4 during oxidative stress conditions (Neurauter et al., 2008) that finally may even result in deficiency of these neurotransmitters.

Aside from that it has to be kept in mind that an overwhelming increase of serotonin not necessarily is solely associated with mood enhancement. In patients treated with selective serotonin reuptake inhibitors (SSRI) or with serotonin receptor agonists occasionally the appearance of adverse symptoms has been observed which were summarized as the so-called serotonin syndrome (Boyer & Shannon, 2005). It may well indicate that there are not only positive consequences of an enhanced availability of serotonin, rather it could also be involved in the precipitation of adverse symptoms when the exercise-induced upregulation of serotonin production goes above a certain threshold. Especially in the case of a too high training intensity as compared with the training status without sufficient periods of recovery, physical and psychic exhaustion associated with fatigue, disturbed mood and signs of depression might emerge.

4. The effects of nutrients on mood and cognition

Current epidemiological data are in favor of a protective role of certain micronutrients (B vitamins also related to homocysteine metabolism, the anti-oxidant vitamins C and E, flavonoids, polyunsatured omega-3 fatty acids, vitamin D) and macronutrients (fish) in the prevention of cognitive decline and dementia (Gillette-Guyonnet, Secher, & Vellas, 2013). Some factors have been targeted by interventions tested in randomized controlled trials, but many of the results are conflicting with observational evidence only. A major problem with the study of diet is that it is really particular nutrients within food that influence our brains, rather than the foods themselves. A second problem is that the impact of individual nutrients is likely to be mediated by other factors, such as the nutrient's baseline level in the body, or the presence or absence of other nutrients (Morris, 2012). Likewise other factors that are independent of diet, such as age, genetics, and the level of physical activity, are likely to influence the effect of nutrition on health (Dauncey, 2009).

4.1. Neuropsychiatric effects of diet

Given the complex relationship between food and nutrition and the brain, and the imprecision of self-report measures, diet is often characterized in cohort studies in broad terms. One relative common distinction that is used is between the so-called Mediterranean Diet (MD) and the Western Diet. The former involves the high intake of fruit, vegetables, fish, cereals and unsaturated fats (e.g., the type of fat that tends to be found in nuts and seeds). In contrast, the Western Diet involves the frequent consumption of foods with high levels of saturated fats, such as red meats, dairy products as well as other processed foods such as convenience foods. Studies tend to show that those who have diets that more closely resemble the MD have lower instances of both dementia and mild cognitive impairment, even after confounding factors like age, socio-economic status and physical activity (Sofi, Abbate, Gensini, & Casini, 2010). More specifically it has been shown that high intake of fruit and vegetables, as well as omega-3 fats (dietary rather than through supplements) predict a reduced likelihood of dementia (dementia levels in those with diets high in fruit and vegetables being 2.6%, compared with 5.7% for those with diets poor in fruit, vegetables and omega-3 rich oils) (Barberger-Gateau et al., 2007). Furthermore, adherence to a MD may affect Alzheimer disease (AD) risk and subsequent disease course (Scarmeas, Stern, Tang, Mayeux, & Luchsinger, 2006): Higher adherence to the MD appears to be associated with lower mortality in AD and these associations seem not to be mediated by CRP, fasting insulin, or adiponectin (Gu, Luchsinger, Stern, & Scarmeas, 2010).

The neuropsychiatric effects of diet are not just restricted to dementia however. There is increasing evidence that diets high in saturated fat and sugars may contribute to behavioral problems in children and adolescents, including attention deficit hyperactivity disorder (ADHD) (Kohlboeck et al., 2012; Howard et al., 2011). Similarly artificial food additives, such as the colourings and preservatives commonly added to confectionery and soft drinks, appear to increase hyperactivity in children (Schab & Trinh, 2004). For example in a double-blind placebo trial it was found that children regularly given a drink containing additives became more hyperactive than those given a placebo drink with the same frequency (McCann et al., 2007). This effect was present in both 3 year old and 8 year old children, suggesting that the influence of additives is not restricted to one particular stage of development.

Some evidence indicates that the supply of long-chain (LC) polyunsaturated fatty acids (PUFAs), docosahexaenoic acid (DHA), and arachidonic acid to the developing fetus influences neurodevelopment. LC-PUFAs are biochemically involved in the development of the brain and neuronal structures and are also involved in numerous neuronal processes, ranging from effects on membrane fluidity, signal transduction, to gene expression regulation (Schuchardt, Huss, Stauss-Grabo, & Hahn, 2010). With this information as background, the main objective of the LISAplus study was to assess the effect of fatty acids in cord blood serum on children's behavioral difficulties at the age of 10 year (Kohlboeck et al., 2011). Higher concentrations of DHA reduced hyperactivity/inattention scores, higher LC-PUFA and arachidonic acid concentrations reduced emotional symptoms scores, and higher concentrations of EPA were related with higher scores for conduct problems. An appropriate fatty acid supply to the developing fetus may therefore be essential for optimal long-term behavioral outcomes in children.

Evidence also exists that deficiencies in a variety of vitamins and minerals within the body may encourage depressive symptoms. For example double-blind placebo trials consistently show that thiamine (B1) supplements improve mood while other studies have suggested that low levels of vitamins B6 and E are implicated in depression (Soh, Walter, Baur, & Collins, 2009). Moreover, it was postulated that abnormalities in phospholipid fatty acid composition may play a role also in psychiatric disorders, including depression, changing membrane fluidity and, consequently, influencing various neurotransmitter systems, which are believed to be related to the pathophysiology of major depression (Hibbeln & Salem, 1995). The question is whether a diet rich in n-3 PUFAs or omega-3 PUFA supplementation would reduce depressive symptoms. Previous meta-analytic studies reported a general positive effect of omega-3 PUFA intake on ameliorating symptoms of depression (Freeman et al., 2006; Lin & Su, 2007). On the other hand, incongruent results have been reported in other systematic revisions of the literature (Appleton et al., 2006) and in an updated analysis (Rogers et al., 2008). The reasons for such variability in these findings depend on the significant heterogeneity among studies examined, weakening the results of the analyses. Moreover, nutrients that are known to be beneficial to human health when consumed in food often fail to produce positive results when consumed in supplementary form, an effect that is most likely due to the absence (in supplements) of naturally co-existing chemicals that facilitate the body's uptake of the nutrient when it is consumed via foods. However, the effect of diet on mood may be self-reinforcing as depressed individuals often turn to comfort eating (Macht, 2008), which is likely to involve foods that are high both in carbohydrates and saturated fats, and which in turn may promote obesity which could further depress mood and self-esteem over the long term. Ingestion of carbohydrates increases the plasma tryptophan leading to increased serotonin synthesis in the brain and alleviating depression. Such is the case for carbohydrate craving during depression that often leads to obesity and vice versa (Shabbir et al., 2013). Obesity in turn regulates mood due to metabolic disturbances. Metabolic disturbances further alter brain-signaling systems leading to a bi-directional vicious cycle of Mood, food, and obesity (Singh, 2014).

Hippocrates, father of modern medicine, said: "Let your food be your medicine and your medicine be your food". Typical nutrients that impact mood are – beside omega-3 fatty acids – chocolate (increases pleasant feeling, reduces tension, and results in good mood via serotonin and cannabinoid receptors signaling) (Jenny et al., 2009; Parker et al., 2006), caffeine (enhances alertness and increases anxiety) (Rossi et al., 2010), and micronutrients, such as thiamine (plays a role in emotion, mood states, and cognitive functioning) (Benton, Griffiths, & Haller, 1997), iron (deficiency results in depressed mood and lethargy) (Benton & Donohoe, 1999), and folic acid (deficiency is associated with depressed mood) (Young, 2007). These mood food compounds possess the ability to improve tryptophan availability as a source for serotonin production in the human brain. Consequently, mood might be enhanced after intake of such beverages. Since serotonergic mechanisms may reduce obesity by accelerating the onset of satiety and beside suppressing excessive snacking of carbohydrate-rich foods (Steinert et al., 2014), eating foods high in tryptophan or supplementation with tryptophan while dieting could be helpful in improving mood and cognition status and preventing uncontrolled weight gain or neuropsychiatric symptoms (Silber & Schmitt, 2010).

4.2. Biological mechanisms

Due to the complexities in identifying the contribution of different nutrients, it has proven difficult to identify the exact mechanisms by which the under or overabundance of certain nutrients might affect the brain. However, two interrelated systems are thought to be most vulnerable to dietary factors; the neuroinflammatory response of brain neurons, and the processes surrounding insulin signaling within the brain (Parrott & Greenwood, 2007). It is thought that the beneficial effect of diets high in fruit and vegetables may partly be due to the polyphenols present in plant matter working to limit neuroinflammation in the brain. In terms of the second system, insulin is involved in regulating the uptake of glucose by neurons, as well as maintaining their function and structure (Sebastião et al., 2014). Diets that are high in saturated fats appear to promote insulin resistance which reduces the body's ability to utilize insulin (hence the association between obesity and type 2 diabetes). In turn, negative impacts take place on the ability of neurons to function properly and to adapt to changes in the signaling patterns of other connecting neurons. This leads to reduced neural plasticity and an increased likelihood of chronic, maladaptive neuroinflammation, both of which are likely to interfere with normal cognitive functioning. This may be the mechanism by which frequent consumption of junk foods leads to a greater risk of dementia (De la Monte, 2014).

Inflammatory factors have been shown to significantly modulate the metabolism of neurotransmitters known to be important in the regulation of mood and cognitive processes, including serotonin, noradrenalin, and dopamine (Capuron et al., 2011). Data also indicates significant relationships between cytokine-induced alterations of tryptophan and kynurenine metabolism and the occurrence of neuropsychiatric symptoms. In particular, the kynurenine pathway of tryptophan breakdown is activated by stress via tryptophan 2,3-dioxygenase (TDO) as well as directly by inflammatory factors via IDO (Gibney et al., 2013; Liu et al., 2013). Tryptophan conversion to kynurenine under pro-inflammatory and stress conditions is linked to neuroinflammation and considered to contribute to the pathogenesis of mood disturbances and depression (Schwarcz et al., 2012; Widner et al., 2002). Depressive mood appears to modulate nutrition behavior and, vice versa, serotonergic foods rich in carbohydrates improve mood by increasing tryptophan and serotonin in the brain (Fernstrom & Wurtman, 1971), which may contribute to overeating and weight gain. Another reason for increasing the consumption of serotonergic foods such as soya beans, cereals, nuts and bananas arises from the recognition that well-being and happiness, described by the Greek philosopher Aristotle (384–322 B.C.) in the *Nicomachean Ethics* as the "best, the finest, the most pleasurable thing of all" (Aristotle, 2004), are important, both as factors protecting against mental and physical disorders and in their own right (Delamothe, 2005).

References

Agudelo, L. Z., Femenía, T., Orhan, F., Porsmyr-Palmertz, M., Goiny, M., Martinez-Redondo, V., Correia, J. C., Izadi, M., Bhat, M., Schuppe-Koistinen, I., Pettersson, A. T., Ferreira, D. M., Krook, A., Barres, R., Zierath, J. R., Erhardt, S., Lindskog, M., & Ruas, J. L. (2014). Skeletal muscle PGC-1α1 modulates kynurenine metabolism and mediates resilience to stress-induced depression. *Cell*, *159*, 33–45.

Appleton, K. M., Hayward, R. C., Gunnell, D., Peters, T. J., Rogers, P. J., Kessler, D., & Ness, A. R. (2006). Effects of n-3 long-chain polyunsaturated fatty acids on depressed mood: systematic review of published trials. *The American Journal of Clinical Nutrition*, *84*, 1308–1316.

Aristotle. (2004). Nicomachean Ethics. In: Hugh Treddenick (Ed.), London: Penguin.

Auwerx, J., & Staels, B. (1998). Leptin. *Lancet*, *351*, 737–742.

Babyak, M., Blumenthal, J. A., Herman, S., Khatri, P., Doraiswamy, M., Moore, K., Craighead, W. E., Baldewicz, T. T., & Krishnan, K. R. (2000). Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. *Psychosomatic Medicine*, *62*, 633–638.

Barberger-Gateau, P., Raffaitin, C., Letenneur, L., Berr, C., Tzourio, C., Dartigues, J. F., & Alpérovitch, A. (2007). Dietary patterns and risk of dementia: the Three-City cohort study. *Neurology*, *69*, 1921–1930.

Benton, D., & Donohoe, R. T. (1999). The effects of nutrients on mood. *Public Health Nutrition*, *2*, 403–409.

Benton, D., Griffiths, R., & Haller, J. (1997). Thiamine supplementation mood and cognitive functioning. *Psychopharmacology (Berlin)*, *129*, 66–71.

Björntorp, P. (2001). Do stress reactions cause abdominal obesity and comorbidities? *Obesity Reviews*, *2*, 73–86.

Boyer, E. W., & Shannon, M. (2005). The serotonin syndrome. *The New England Journal of Medicine*, *352*, 1112–1120.

Brennan, A. M., Fargnoli, J. L., Williams, C. J., Li, T., Willett, W., Kawachi, I., Qi, L., Hu, F. B., & Mantzoros, C. S. (2009). Phobic anxiety is associated with higher serum concentrations of adipokines and cytokines in women with diabetes. *Diabetes Care*, *32*, 926–931.

Brydon, L., Wright, C. E., O'Donnell, K., Zachary, I., Wardle, J., & Steptoe, A. (2008). Stress-induced cytokine responses and central adiposity in young women. *International Journal of Obesity (London)*, *32*, 443–450.

Burtscher, M., Pesta, D., Fuchs, D., Ledochowski, M., & Gatterer, H. (2015). Methodological considerations when evaluating the effectiveness of dietary/supplemental antioxidants in sport. In M. Lamprechter (Ed.), *Antioxidants in Sport Nutrition* (pp. 203–220). Boca Raton, London, New York: CRC Press, Taylor and Francis Group (chapter 13).

Capuron, L., Schroecksnadel, S., Féart, C., Aubert, A., Higueret, D., Barberger-Gateau, P., Layé, S., & Fuchs, D. (2011). Chronic low-grade inflammation in elderly persons is associated with altered tryptophan and tyrosine metabolism: role in neuropsychiatric symptoms. *Biological Psychiatry*, *70*, 175–182.

Cassilhas, R. C., Viana, V. A., Grassmann, V., Santos, R. T., Santos, R. F., Tufik, S., & Mello, M. T. (2007). The impact of resistance exercise on the cognitive function of the elderly. *Medicine & Science in Sports & Exercise*, *39*, 1401–1407.

Cassilhas, R. C., Lee, K. S., Fernandes, J., Oliveira, M. G., Tufik, S., Meeusen, R., & de Mello, M. T. (2012). Spatial memory is improved by aerobic and resistance exercise through divergent molecular mechanisms. *Neuroscience*, *202*, 309–317.

Chaouloff, F. (1993). Physiopharmacological interactions between stress hormones and central serotonergic systems. *Brain Research Reviews*, *18*(1), 1–32.

Chen, M. J., Ivy, A. S., & Russo-Neustadt, A. A. (2006). Nitric oxide synthesis is required for exercise-induced increases in hippocampal BDNF and phosphatidylinositol 3′ kinase expression. *Brain Research Bulletin*, *68*, 257–268.

Cooney, G. M., Dwan, K., Greig, C. A., Lawlor, D. A., Rimer, J., Waugh, F. R., McMurdo, M., & Mead, G. E. (2013). Exercise for depression. *Cochrane Database of Systematic Reviews*, *9*, CD004366.

Cotman, C. W., Berchtold, N. C., & Christie, L. A. (2007). Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends in Neurosciences*, *30*, 464–472.

Dauncey, M. J. (2009). New insights into nutrition and cognitive neuroscience. *Proceedings of the Nutrition Society*, *68*, 408–415.

Davenport, M. H., Hogan, D. B., Eskes, G. A., Longman, R. S., & Poulin, M. J. (2012). Cerebrovascular reserve: the link between fitness and cognitive function? *Exercise and Sport Sciences Reviews*, *40*, 153–158.

De la Monte, S. M. (2014). Relationships between diabetes and cognitive impairment. *Endocrinology Metabolism Clinics of North America*, *43*, 245–267.

Delamothe, T. (2005). Happiness. *British Medical Journal*, *331*, 1489–1490.

Dey, S., Singh, R. H., & Dey, P. K. (1992). Exercise training: significance of regional alterations in serotonin metabolism of rat brain in relation to antidepressant effect of exercise. *Physiology & Behavior*, *52*, 1095–1099.

Dhabhar, F. S. (2009). Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection and immunopathology. *Neuroimmunomodulation*, *16*, 300–317.

Dishman, R. K., Berthoud, H. R., Booth, F. W., Cotman, C. W., Edgerton, V. R., Fleshner, M. R., Gandevia, S. C., Gomez-Pinilla, F., Greenwood, B. N., Hillman, C. H., Kramer, A. F., Levin, B. E., Moran, T. H., Russo-Neustadt, A. A., Salamone, J. D., Van Hoomissen, J. D., Wade, C. E., York, D. A., & Zigmond, M. J. (2006). Neurobiology of exercise. *Obesity*, *14*, 345–356.

Dunn, A. L., Trivedi, M. H., Kampert, J. B., Clark, C. G., & Chambliss, H. O. (2005). Exercise treatment for depression: efficacy and dose response. *American Journal of Preventive Medicine*, *28*, 1–8.

Ekkekakis, P., & Petruzzello, S. J. (1999). Acute aerobic exercise and affect: current status, problems and prospects regarding dose-response. *Sports Medicine*, *28*, 337–374.

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., Kim, J. S., Heo, S., Alves, H., White, S. M., Wojcicki, T. R., Mailey, E., Vieira, V. J., Martin, S. A., Pence, B. D., Woods, J. A., McAuley, E., & Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences of the United States of America*, *108*, 3017–3022.

Febbraio, M. A., Hiscock, N., Sacchetti, M., Fischer, C. P., & Pedersen, B. K. (2004). Interleukin-6 is a novel factor mediating glucose homeostasis during skeletal muscle contraction. *Diabetes*, *53*, 1643–1648.

Fernstrom, J. D., & Wurtman, R. J. (1971). Brain serotonin content: increase following ingestion of carbohydrate diet. *Science*, *174*, 1023–1025.

Ferris, L. T., Williams, J. S., & Shen, C. L. (2007). The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. *Medicine & Science in Sports & Exercise*, *39*, 728–734.

Fischer, C. P., Hiscock, N. J., Penkowa, M., Basu, S., Vessby, B., Kallner, A., Sjöberg, L. B., & Pedersen, B. K. (2004). Supplementation with vitamins C and E inhibits the release of interleukin-6 from contracting human skeletal muscle. *The Journal of Physiology*, *558*, 633–645.

Freeman, M. P., Hibbeln, J. R., Wisner, K. L., Davis, J. M., Mischoulon, D., Peet, M., Keck, P. E. Jr., Marangell, L. B., Richardson, A. J., Lake, J., & Stoll, A. L. (2006). Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *The Journal of Clinical Psychiatry*, *67*, 1954–1967.

Gibney, S. M., McGuinness, B., Prendergast, C., Harkin, A., Connor, T. J., & Poly, I. (2013). C-induced activation of the immune response is accompanied by depression and anxiety-like behaviours, kynurenine pathway activation and reduced BDNF expression. *Brain Behavior and Immunity*, *28*, 170–181.

Gillette-Guyonnet, S., Secher, M., & Vellas, B. (2013). Nutrition and neurodegeneration: epidemiological evidence and challenges for future research. *British Journal of Clinical Pharmacology*, *75*, 738–755.

Gleeson, M., Bishop, N. C., Stensel, D. J., Lindley, M. R., Mastana, S. S., & Nimmo, M. A. (2011a). The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nature Reviews Immunology*, *11*, 607–615.

Gleeson, M., Bishop, N. C., Oliveira, M., & Tauler, P. (2011b). Daily probiotic's (*Lactobacillus casei* Shirota) reduction of infection incidence in athletes. *International Journal of Sport Nutrition and Exercise Metabolism*, *21*, 55–64.

Goekint, M., Heyman, E., Roelands, B., Njemini, R., Bautmans, I., Mets, T., & Meeusen, R. (2008). No influence of noradrenaline manipulation on acute exercise-induced increase of brain-derived neurotrophic factor. *Medicine & Science in Sports & Exercise*, *40*, 1990–1996.

Goekint, M., De Pauw, K., Roelands, B., Njemini, R., Bautmans, I., Mets, T., & Meeusen, R. (2010). Strength training does not influence serum brain-derived neurotrophic factor. *European Journal of Applied Physiology*, *110*, 285–293.

Gomez-Cabrera, M. C., Domenech, E., Romagnoli, M., Arduini, A., Borras, C., Pallardo, F. V., Sastre, J., & Viña, J. (2008). Oral administration of vitamin C decreases muscle mitochondrial biogenesis and hampers training-induced adaptations in endurance performance. *The American Journal of Clinical Nutrition*, *87*, 142–149.

Gomez-Pinilla, F., & Hillman, C. (2013). The influence of exercise on cognitive abilities. *Comprehensive Physiology*, *3*, 403–428.

Gomez-Pinilla, F., Vaynman, S., & Ying, Z. (2008). Brain-derived neurotrophic factor functions as a metabotrophin to mediate the effects of exercise on cognition. *European Journal of Neuroscience*, *28*, 2278–2287.

Gostner, J. M., Becker, K., Sperner-Unterweger, B., Überall, F., Fuchs, D., & Strasser, B. (2015). Role of tryptophan metabolism in mood, behavior, and cognition. In S. Mittal (Ed.), *Targeting the Broadly Pathogenic Kynurenine Pathway*Springer.

Gu, Y., Luchsinger, J. A., Stern, Y., & Scarmeas, N. (2010). Mediterranean diet, inflammatory and metabolic biomarkers, and risk of Alzheimer's disease. *Journal of Alzheimer's Disease*, *22*, 483–492.

Häfner, S., Zierer, A., Emeny, R. T., Thorand, B., Herder, C., Koenig, W., Rupprecht, R., & Ladwig, K. H. (2011). KORA study investigators. Social isolation and depressed mood are associated with elevated serum leptin levels in men but not in women. *Psychoneuroendocrinology*, *36*, 200–209.

Hamer, M., Endrighi, R., & Poole, L. (2012). Physical activity, stress reduction, and mood: insight into immunological mechanisms. *Methods in Molecular Biology*, *934*, 89–102.

Hibbeln, J. R., & Salem, N. Jr. (1995). Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy. *The American Journal of Clinical Nutrition*, *62*, 1–9.

Howard, A. L., Robinson, M., Smith, G. J., Ambrosini, G. L., Piek, J. P., & Oddy, W. H. (2011). ADHD is associated with a Western dietary pattern in adolescents. *Journal of Attention Disorders*, *15*, 403–411.

Jenny, M., Santer, E., Klein, A., Ledochowski, M., Schennach, H., Ueberall, F., & Fuchs, D. (2009). Cacao extracts suppress tryptophan degradation of mitogen-stimulated peripheral blood mononuclear cells. *Journal of Ethnopharmacology*, *207*, 75–82.

Jiménez-Pavón, D., Ortega, F. B., Artero, E. G., Labayen, I., Vicente-Rodriguez, G., Huybrechts, I., Moreno, L. A., Manios, Y., Béghin, L., Polito, A., De Henauw, S., Sjöström, M., Castillo, M. J., González-Gross, M., & Ruiz, J. R. (2012). HELENA study group. Physical activity, fitness, and serum leptin concentrations in adolescents. *Journal of Pediatrics*, *160*, 598–603.e2.

Karatsoreos, I. N., & McEwen, B. S. (2011). Psychobiological allostasis: resistance, resilience and vulnerability. *Trends in Cognitive Sciences*, *15*, 576–584.

Kohlboeck, G., Glaser, C., Tiesler, C., Demmelmair, H., Standl, M., Romanos, M., Koletzko, B., Lehmann, I., & Heinrich, J. (2011). LISAplus study group. Effect of

fatty acid status in cord blood serum on children's behavioral difficulties at 10 y of age: results from the LISAplus Study. *The American Journal of Clinical Nutrition*, *94*, 1592–1599.
Kohlboeck, G., Sausenthaler, S., Standl, M., Koletzko, S., Bauer, C. P., von Berg, A., Berdel, D., Krämer, U., Schaaf, B., Lehmann, I., Herbarth, O., & Heinrich, J. (2012). GINI-plus and LISA-plus study groups. Food intake, diet quality and behavioral problems in children: results from the GINI-plus/LISA-plus studies. *Annals of Nutrition and Metabolism*, *60*, 247–256.
Kohlboeck, G., Romanos, M., Tiesler, C., Koletzko, S., Kratzsch, J., Thiery, J., Bauer, C. P., von Berg, A., Berdel, D., Hoffmann, B., Schaaf, B., Lehmann, I., Herbarth, O., & Heinrich, J. (2014). GINI-plus study group; LISA-plus study group. Peer problems are associated with elevated serum leptin levels in children. *Psychological Medicine*, *44*, 255–265.
Krogh, J., Nordentoft, M., Sterne, J. A., & Lawlor, D. A. (2011). The effect of exercise in clinically depressed adults: systematic review and meta-analysis of randomized controlled trials. *Journal of Clinical Psychiatry*, *72*, 529–538.
Lee, Y. H., & Pratley, R. E. (2005). The evolving role of inflammation in obesity and the metabolic syndrome. *Current Diabetes Reports*, *5*, 70–75.
Liao, S. C., Lee, M. B., Lee, Y. J., & Huang, T. S. (2004). Hyperleptinemia in subjects with persistent partial posttraumatic stress disorder after a major earthquake. *Psychosomatic Medicine*, *66*, 23–28.
Lin, T. W., & Kuo, Y. M. (2013). Exercise benefits brain function: the monoamine connection. *Brain Sciences*, *3*, 39–53.
Lin, P. Y., & Su, K. P. (2007). A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. *Journal of Clinical Psychiatry*, *68*, 1056–1061.
Liu, W., Sheng, H., Xu, Y., Liu, Y., Lu, J., & Ni, X. (2013). Swimming exercise ameliorates depression-like behavior in chronically stressed rats: relevant to proinflammatory cytokines and IDO activation. *Behavioural Brain Research*, *242*, 110–116.
Luger, A., Deuster, P. A., Kyle, S. B., Gallucci, W. T., Montgomery, L. C., Gold, P. W., Loriaux, D. L., & Chrousos, G. P. (1987). Acute hypothalamic–pituitary–adrenal responses to the stress of treadmill exercise. Physiologic adaptations to physical training. *The New England Journal of Medicine*, *316*, 1309–1315.
Macht, M. (2008). How emotions affect eating: a five-way model. *Appetite*, *50*(1), 1–11.
Maes, M., Yirmyia, R., Noraberg, J., Brene, S., Hibbeln, J., Perini, G., Kubera, M., Bob, P., Lerer, B., & Maj, M. (2009). The inflammatory & neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression. *Metabolic Brain Disease*, *24*, 27–53.
Mangge, H., Summers, K. L., Meinitzer, A., Zelzer, S., Almer, G., Prassl, R., Schnedl, W. J., Reininghaus, E., Paulmichl, K., Weghuber, D., & Fuchs, D. (2014). Obesity-related dysregulation of the tryptophan-kynurenine metabolism: role of age and parameters of the metabolic syndrome. *Obesity*, *22*, 195–201.
McCann, D., Barrett, A., Cooper, A., Crumpler, D., Dalen, L., Grimshaw, K., Kitchin, E., Lok, K., Porteous, L., Prince, E., Sonuga-Barke, E., Warner, J. O., & Stevenson, J. (2007). Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial. *Lancet*, *370*, 1560–1567.
Meeusen, R., Thorré, K., Chaouloff, F., Sarre, S., De Meirleir, K., Ebinger, G., & Michotte, Y. (1996). Effects of tryptophan and/or acute running on extracellular 5-HT and 5-HIAA levels in the hippocampus of food-deprived rats. *Brain Research*, *740*, 245–252.
Meeusen, R., Watson, P., Hasegawa, H., Roelands, B., & Piacentini, M. F. (2006). Central fatigue: the serotonin hypothesis and beyond. *Sports Medicine*, *36*, 881–909.
Melancon, M. O., Lorrain, D., & Dionne, I. J. (2014). Changes in markers of brain serotonin activity in response to chronic exercise in senior men. *Applied Physiology, Nutrition, and Metabolism*, *39*, 1250–1256.
Meshberger, F. L. (1990). An interpretation of Michelangelo's Creation of Adam based on neuroanatomy. *Journal of the American Medical Association*, *264*, 1837–1841.
Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biological Psychiatry*, *65*, 732–741.
Moon, H. Y., & van Praag, H. (2014). Muscle over mind. *Cell Metabolism*, *20*, 560–562.
Morris, M. C. (2012). Nutritional determinants of cognitive aging and dementia. *Proceedings of the Nutrition Society*, *71*, 1–13.
Murr, C., Fuith, L. C., Widner, B., Wirleitner, B., Baier-Bitterlich, G., & Fuchs, D. (1999). Increased neopterin concentrations in patients with cancer: indicator of oxidative stress. *Anticancer Research*, *19*, 1721–1728.
Neurauter, G., Schröcksnadel, K., Scholl-Bürgi, S., Sperner-Unterweger, B., Schubert, C., Ledochowski, M., & Fuchs, D. (2008). Chronic immune stimulation correlates with reduced phenylalanine turn-over. *Curr Drug Metabol*, *9*, 622–627.
O'Connor, P. J., Herring, M. P., & Caravalho, A. (2010). Mental health benefits of strength training in adults. *American Journal of Lifestyle Medicine*, *4*, 377–396.
Otsuka, R., Yatsuya, H., Tamakoshi, K., Matsushita, K., Wada, K., & Toyoshima, H. (2006). Perceived psychological stress and serum leptin concentrations in Japanese men. *Obesity*, *14*, 1832–1838.
Oxenkrug, G. (2013). Insulin resistance and dysregulation of tryptophan-kynurenine and kynurenine-nicotinamide adenine dinucleotide metabolic pathways. *Molecular Neurobiology*, *48*, 294–301.
Parker, G., Parker, I., & Brotchie, H. (2006). Mood state effects of chocolate. *Journal of Affective Disorders*, *92*, 149–159.
Parrott, M. D., & Greenwood, C. E. (2007). Dietary influences on cognitive function with aging: from high-fat diets to healthful eating. *Annals of the New York Academy of Sciences*, *1114*, 389–397.
Pedersen, B. K. (2013). Muscle as a secretory organ. *Comprehensive Physiology*, *3*, 1337–1362.
Pialoux, V., Brown, A. D., Leigh, R., Friedenreich, C. M., & Poulin, M. J. (2009). Effect of cardiorespiratory fitness on vascular regulation and oxidative stress in postmenopausal women. *Hypertension*, *54*, 1014–1020.
Rethorst, C. D., Wipfli, B. M., & Landers, D. M. (2009). The antidepressive effects of exercise: a meta-analysis of randomized trials. *Sports Medicine*, *39*, 491–511.
Rimer, J., Dwan, K., Lawlor, D. A., Greig, C. A., McMurdo, M., Morley, W., & Mead, G. E. (2012). Exercise for depression. *Cochrane Database of Systematic Reviews*, *7*, CD004366.
Ristow, M., Zarse, K., Oberbach, A., Klöting, N., Birringer, M., Kiehntopf, M., Stumvoll, M., Kahn, C. R., & Blüher, M. (2009). Antioxidants prevent health-promoting effects of physical exercise in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 8665–8670.
Robertson, R., Robertson, A., Jepson, R., & Maxwell, M. (2012). Walking for depression or depressive symptoms: a systematic review and meta-analysis. *Mental Health and Physical Activity*, *5*, 66–75.
Rogers, P. J., Appleton, K. M., Kessler, D., Peters, T. J., Gunnell, D., Hayward, R. C., Heatherley, S. V., Christian, L. M., McNaughton, S. A., & Ness, A. R. (2008). No effect of n-3 long-chain polyunsaturated fatty acid (EPA and DHA) supplementation on depressed mood and cognitive function: a randomised controlled trial. *British Journal of Nutrition*, *99*, 421–431.
Rossi, S., De, C., hiara, V., Musella, A., Mataluni, G., Sacchetti, L., Siracusano, A., Bernardi, G., Usiello, A., & Centonze, D. (2010). Effects of caffeine on striatal neurotransmission: focus on cannabinoid CB1 receptors. *Molecular Nutrition & Food Research*, *54*, 525–531.
Rothman, S. M., Griffioen, K. J., Wan, R., & Mattson, M. P. (2012). Brain-derived neurotrophic factor as a regulator of systemic and brain energy metabolism and cardiovascular health. *Annals of the New York Academy of Sciences*, *1264*, 49–63.
Scarmeas, N., Stern, Y., Tang, M. X., Mayeux, R., & Luchsinger, J. A. (2006). Mediterranean diet and risk for Alzheimer's disease. *Annals of Neurology*, *59*, 912–921.
Schab, D. W., & Trinh, N. H. (2004). Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials. *Journal of Developmental & Behavioral Pediatrics*, *25*, 423–434.
Scherr, J., Nieman, D. C., Schuster, T., Habermann, J., Rank, M., Braun, S., Pressler, A., Wolfarth, B., & Halle, M. (2012). Nonalcoholic beer reduces inflammation and incidence of respiratory tract illness. *Medicine & Science in Sports & Exercise*, *44*(1), 18–26.
Schuchardt, J. P., Huss, M., Stauss-Grabo, M., & Hahn, A. (2010). Significance of long-chain polyunsaturated fatty acids (PUFAs) for the development and behaviour of children. *European Journal of Pediatrics*, *169*, 149–164.
Schwarcz, R., Bruno, J. P., Muchowski, P. J., & Wu, H. Q. (2012). Kynurenines in the mammalian brain: when physiology meets pathology. *Nature Reviews Neuroscience*, *13*, 465–477.
Sebastião, I., Candeias, E., Santos, M. S., de Oliveira, C. R., Moreira, P. I., & Duarte, A. I. (2014). Insulin as a bridge between type 2 diabetes and Alzheimer disease—how anti-diabetics could be a solution for dementia. *Frontiers in Endocrinology*, *5*, 110.
Shabbir, F., Patel, A., Mattison, C., Bose, S., Krishnamohan, R., Sweeney, E., Sandhu, S., Nel, W., Rais, A., Sandhu, R., Ngu, N., & Sharma, S. (2013). Effect of diet on serotonergic neurotransmission in depression. *Neurochemistry International*, *62*, 324–329.
Silber, B. Y., & Schmitt, J. A. (2010). Effects of tryptophan loading on human cognition, mood, and sleep. *Neuroscience & Biobehavioral Reviews*, *34*, 387–407.
Singh, M. (2014). Mood, food, and obesity. *Frontiers in Psychology*, *5*, 925.
Sofi, F., Abbate, R., Gensini, G. F., & Casini, A. (2010). Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. *The American Journal of Clinical Nutrition*, *92*, 1189–1196.
Soh, N., Walter, G., Baur, L., & Collins, C. (2009). Nutrition, mood and behaviour: a review. *Acta Neuropsychiatrica*, *21*, 214–227.
Steinert, R. E., Luscombe-Marsh, N. D., Little, T. J., Standfield, S., Otto, B., Horowitz, M., & Feinle-Bisset, C. (2014). Effects of intraduodenal infusion of -tryptophan on ad libitum eating, antropyloroduodenal motility, glycemia, insulinemia, and gut peptide secretion in healthy men. *The Journal of Clinical Endocrinology & Metabolism*, *99*, 3275–3284.
Strasser, B., Arvandi, M., & Siebert, U. (2012). Resistance training, visceral obesity and inflammatory response: a review of the evidence. *Obesity Reviews*, *13*, 578–591.
Strickland, J. C., & Smith, M. A. (2014). The anxiolytic effects of resistance exercise. *Frontiers in Psychology*, *5*, 753.
Tilz, G. P., Domej, W., Diez-Ruiz, A., Weiss, G., Brezinschek, R., Brezinschek, H. P., Hüttl, E., Pristautz, H., Wachter, H., & Fuchs, D. (1993). Increased immune activation during and after physical exercise. *Immunobiology*, *188*, 194–202.
Van, P., raag, H., Christie, B. R., Sejnowski, T. J., & Gage, F. H. (1999). Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proceedings of the National Academy of Sciences of the United States of America*, *96*, 13427–13431.
Vaynman, S., Ying, Z., Gomez-Pinilla, F., & Hippocampal, B. D. N. F. (2004). mediates the efficacy of exercise on synaptic plasticity and cognition. *European Journal of Neuroscience*, *20*, 2580–2590.
Walsh, N. P., Gleeson, M., Shephard, R. J., Gleeson, M., Woods, J. A., Bishop, N. C., Fleshner, M., Green, C., Pedersen, B. K., Hoffman-Goetz, L., Rogers, C. J., Northoff,

H., Abbasi, A., & Simon, P. (2011). Position statement. Part one: immune function and exercise. *Exercise Immunology Review*, *17*, 6–63.
Wang, Y., Liu, H., McKenzie, G., Witting, P. K., Stasch, J. P., Hahn, M., Changsirivathanathamrong, D., Wu, B. J., Ball, H. J., Thomas, S. R., Kapoor, V., Celermajer, D. S., Mellor, A. L., Keaney, J. F. Jr., Hunt, N. H., & Stocker, R. (2010). Kynurenine is an endothelium-derived relaxing factor produced during inflammation. *Nature Medicine*, *16*, 279–285.
Watschinger, K., & Werner, E. R. (2013). Alkyl glycerol monooxygenase. *IUBMB Life*, *65*, 366–372.
Werner-Felmayer, G., Golderer, G., & Werner, E. R. (2002). Tetrahydrobiopterin biosynthesis, utilization and pharmacological effects. *Current Drug Metabolism*, *3*, 159–173.
Widner, B., Laich, A., Sperner-Unterweger, B., Ledochowski, M., & Fuchs, D. (2002). Neopterin production tryptophan degradation and mental depression: what is the link? *Brain Behavior and Immunity*, *16*, 590–595.
Young, S. N. (2007). Folate and depression—a neglected problem. *Journal of Psychiatry & Neuroscience*, *32*, 80–82.
Zaknun, D., Schroecksnadel, S., Kurz, K., & Fuchs, D. (2012). Potential role of antioxidant food supplements, preservatives and colorants in the pathogenesis of allergy and asthma. *International Archives of Allergy and Immunology*, *157*, 113–124.