Assessing for unique immunomodulatory and neuroplastic profiles of physical activity subtypes: A focus on psychiatric disorders

Harris A. Eyre [a,b], Bernhard T. Baune [a,*]

[a] *Discipline of Psychiatry, School of Medicine, University of Adelaide, Adelaide, Australia*
[b] *School of Medicine and Dentistry, James Cook University, Townsville, Australia*

A B S T R A C T

Physical activity (PA) is emerging as a safe and effective tool in the prevention and treatment of psychiatric disorders. PA subtypes include aerobic, resistance, flexibility, neuromotor (involving balance, agility and co-ordination), mind–body (e.g. tai chi, qi gong and yoga) and mixed type trainings. Evidence from clinical trials suggests that PA subtypes can have positive clinical effects, however the effects on the symptomatology may vary according to the PA subtype. It therefore stands to reason that various PA subtypes may modulate the immune system and neuroplastic processes differently. This systematic review aims to assess the immunomodulatory and neuroplastic profiles of various PA subtypes, particularly in unipolar depression and age-related cognitive decline (ARCD). The literature suggests several unique immunomodulatory and neuroplastic profiles for PA subtypes (i.e. resistance, aerobic and mind–body) in depression and ARCD. In depression, levels of various cytokines at baseline may predict treatment response to subtypes of PA and pharmacological agents. The pro-neuroplastic effects of resistance and aerobic PA in ARCD may differ due to variances in neurotrophin profiles. At this stage of literature in the field, it is difficult to draw firm conclusions on the specific immunomodulatory and neuroplastic pathways involved in these PA subtypes given of the small number of comparative studies and methodological heterogeneity between studies (e.g. study population age and illness severity, as well as duration and intensity of PA intervention). This important field requires well-designed, high-quality comparative studies to better describe unique immunomodulatory and neuroplastic profiles.

© 2013 Elsevier Inc. All rights reserved.

1. Introduction

Debate is ongoing regarding the differing clinical effects of subtypes of PA in the treatment of psychiatric disorders (Cooney et al., 2013; Hotting and Roder, 2013; Rethorst and Trivedi, 2013; Schuch and de Almeida Fleck, 2013; Voelcker-Rehage and Niemann, 2013). Understanding the neurobiological effects of various PA subtypes may assist in understanding target populations, differences and similarities in clinical efficacy, as well as providing biomarkers to enhance the clinical utility of PA in unipolar depression and ARCD (i.e. across the spectrum of cognitive aging, to Mild Cognitive Impairment (MCI) and Alzheimer's dementia (AD). A comprehensive assessment of the field pertaining to the neuroimmune and neuroplastic effects of PA subtypes has not been published to date.

A significant amount of literature is emerging allowing for a comparison of PA subtypes in unipolar depression and ARCD, however a thorough analyzis of this literature is outside of the scope of this review. A number of studies have examined the effect of various types of PA in ARCD (see Balsamo et al., 2013; Brown et al., 2012; Cassilhas et al., 2007; Davis et al., 2013; Hotting and Roder, 2013; Kramer et al., 1999; Liu-Ambrose et al., 2010; Nagamatsu et al., 2012, 2013; Pitkala et al., 2013; Roig et al., 2013). A number of primary research, meta-analyzes and systematic reviews provide a comparison between subtypes of PA in depression (see Bridle et al., 2012; Chi et al., 2013; Erickson et al., 2013; Krogh et al., 2009, 2011, 2012; Lavretsky et al., 2011; Oh et al., 2013; Penninx et al., 2002; Ravindran and da Silva, 2013; Rimer et al., 2012; Wang et al., 2013).

From a neuroplasticity perspective, data has emerged suggesting aerobic and resistance PA have a more potent neuroplastic effect than other PA subtypes (Voelcker-Rehage and Niemann, 2013). A recent review by Voelcker-Rehage and Niemann (Erickson et al., 2013; Voelcker-Rehage and Niemann, 2013) compares the clinical effect of 'metabolic exercise' (i.e. cardiovascular and resistance training) and co-ordinative PA (i.e. motor fitness, co-ordination and flexibility) on cognitive function and markers of neuroplasticity. The authors present evidence arguing pure metabolic PA has greater effects on brain volume and functional activity, particularly in the prefrontal and hippocampal (HC) areas, as compared to

stretching, toning or relaxation interventions (for primary evidence see Erickson et al., 2011; Ruscheweyh et al., 2011; Voelcker-Rehage et al., 2011); they contribute this effect to differing metabolic demands (Voelcker-Rehage and Niemann, 2013). The recent RCT by Nagamatsu et al. (2012) noted differing neuroplastic effects of resistance PA vs. balance and toning (BAT) PA. Over 6 months, the study examined 86 community-dwelling women aged 70–80 years with probable MCI. Resistance training improved selective attention/conflict resolution, associated memory and regional patterns of functional brain plasticity (right lingual gyrus under functional MRI analysis) compared with BAT. A recent rodent study suggests aerobic and resistance PA have divergent pro-neuroplastic effects (Cassilhas et al., 2012). This study found both types of PA improved learning and spatial memory, resistance PA induced central and peripheral insulin-like growth factor-1 (IGF-1) and AKT in the hippocampus (HC), whereas aerobic PA showed an increase in IGF-1, brain-derived neurotrophic factor (BDNF), TrkB and β-CaMKII (calcium-dependent kinase II) in the HC.

Understanding the immunomodulatory effects of PA subtypes may provide insight into the similarities and differences between neuroplastic and clinical effects (Baune and Eyre, 2012). This is relevant given the positive and negative effects of immune factors (e.g. cytokines and microglia) on neuroplasticity processes and markers (i.e. volumetric analysis, neurogenesis, synaptic plasticity, long-term potentiation/depression (LTP/D)) and symptomatology in unipolar depression and ARCD (for reviews see Eyre and Baune, 2012a; McAfoose and Baune, 2009; Wyss-Coray and Rogers, 2012). A number of examples of comparative studies assessing the immunomodulatory profiles of PA are offered in the literature, and will be reviewed in this paper.

This paper will initially outline the involvement of the immune system in unipolar depression and ARCD. Following this, the systematic review aims to assess the immunomodulatory and neuroplastic profiles of various PA subtypes, particularly in clinical populations with unipolar depression and ARCD.

2. Methods

The literature search for this review was carried out according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines as they apply to systematic reviews (Moher et al., 2009). An electronic search of reputable databases including PubMed, PsychoInfo, OvidSP and ScienceDirect were utilized in the creation of this systematic review. An initial search was conducted using the following keywords: (Immune OR cytokine OR inflammatory OR microglia) OR (neuroplastic* OR neurogenesis OR synap* OR volume) AND (aging brain OR cognition OR Alzheimer's OR cognitive decline OR cognitive dysfunction) OR (depression OR depressive OR stress OR mood disorder). A second search was conducted as above, but with the addition of the following: AND (exercise OR physical activity OR strength OR aerobic OR flexibility OR mind–body). Articles were also obtained by reviewing reference lists of review and research articles. A total of 680 studies were found using these search terms. A total of 316 articles remained after assessment of abstracts for relevance to the aims of this review. Abstracts were also selected based on the year of publication (between 1969 and October 2013), publication in the English language and of peer-reviewed type. Of these, 201 studies were excluded after review of the full text if they did not either directly compare between subtypes of PA or provide data on the neuroplastic/neuroimmune effects of PA subtypes, if they included anecdotal evidence or did not include measurement of clinical information or relevant biomarkers. Where possible, risks of bias across studies has been reported. Finally, 115 articles were utilized in the making of this literature review (Fig. 1 depicts this strategy).

3. Results

3.1. The involvement of the immune system in psychiatric disorders

Prior to investigating clinical and immunological effects of PA subtypes, we will first frame the most up-to-date understanding

Medline, PsycINFO, Google Scholar, ScienceDirect and reference lists

680 articles were identified and 364 were excluded after a review of the body and/or abstracts.

316 articles

201 articles were excluded based on exclusion criteria and relevance.

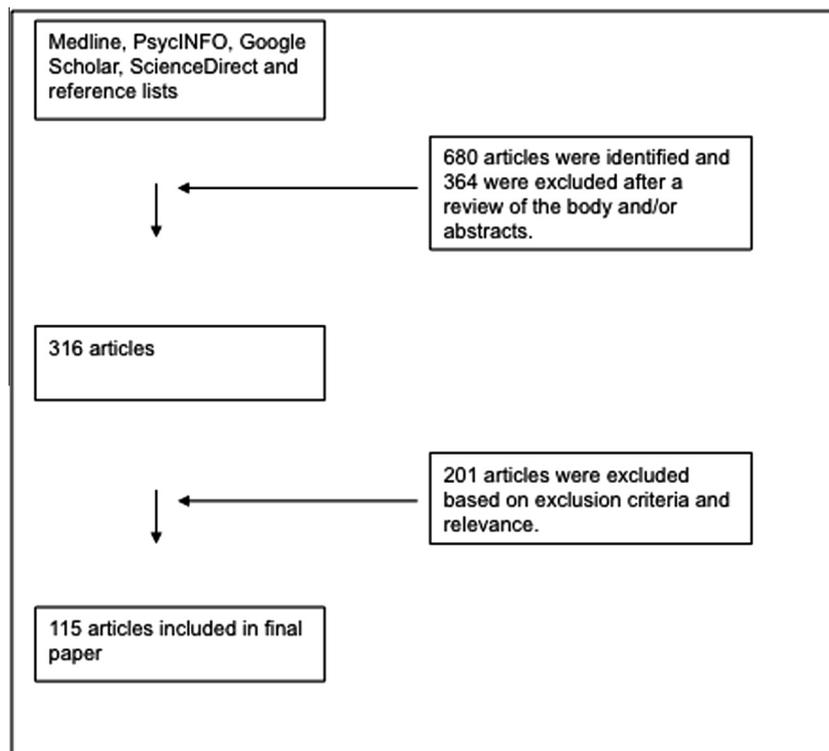115 articles included in final paper

Fig. 1. Study inclusion flowchart.

of immune-related pathophysiology in depression and ARCD. These fields have been extensively reviewed in recent times (Dantzer et al., 2008; Eikelenboom et al., 2012; McAfoose and Baune, 2009; Miller et al., 2009; Tanzi and Bertram, 2005; Wyss-Coray and Rogers, 2012), and will therefore be summarized below.

3.1.1. Depression and the immune system

The most established immune-based model of depression is the inflammatory or cytokine model of depression (Dantzer et al., 2008; McAfoose and Baune, 2009; Miller et al., 2009). This model postulates that a pro-inflammatory state characterized by elevations in pro-inflammatory cytokines (PICs) and reductions in anti-inflammatory cytokines (AIC) are involved in the development of depression-like behavior in animals and clinical depression in humans. In addition, the resulting net pro-inflammatory state, mediated via elevations in tumor necrosis factor (TNF)-α, interleukin (IL)-6, interferon (IFN)-γ and IL-1β, is found to impair HC neuroplasticity (e.g. neurogenesis, synaptic plasticity, LTP), induce glucocorticoid insensitivity of the hypothalamo–pituitary–adrenal (HPA) axis, increase oxidative stress in the HC, reduce serotonin levels and create neurotoxic serotonergic metabolites (i.e. 3-hydroxykynurenine (3-HK) and quinolinic acid (QA)) (Dantzer et al., 2008; Eyre and Baune, 2012b; Leonard and Maes, 2012; Miller et al., 2009; Moylan et al., 2012). From a clinical perspective, a meta-analysis by Dowlati et al. (2010) concludes that the pro-inflammatory state is associated with clinical depression. This study pooled 24 studies involving unstimulated measurements of cytokines in patients meeting DSM criteria for major depression and found significantly higher concentrations of TNF-α and IL-6 in depressed subjects compared with control subjects. These findings were recently replicated for IL-6 (Hiles et al., 2012). Prospective studies have found associations between PIC levels (specifically IL-6, IL-8 and CRP) and incident depressive symptoms (Baune et al., 2012; Rohleder and Miller, 2008; Vogelzangs et al., 2012).

3.1.2. Age-related cognitive decline and the immune system

Elevated PICs (i.e. TNF-α, IL-6, IL-1β and IFN-γ) have been implicated in impaired cognitive function in clinical and pre-clinical studies (Eikelenboom et al., 2012; McAfoose and Baune, 2009; Tanzi and Bertram, 2005; Wyss-Coray and Rogers, 2012). To this effect, an amyloid-neuroinflammation hypothesis has been recently suggested stating that neurodegenerative changes in LOAD are the result of an uncontrolled, chronic intra-cerebral inflammatory reaction triggered by the accumulation/aggregation of Aβ protein in plaques (Eikelenboom et al., 2012; Tanzi and Bertram, 2005; Wyss-Coray and Rogers, 2012). PICs have been found to enhance the accumulation of Aβ protein plaques, which in turn promote further neuroinflammation leading to progressive neurodegeneration (Eikelenboom et al., 2012; Tanzi and Bertram, 2005; Wyss-Coray and Rogers, 2012). Additional to effects on Aβ proteins, neuroinflammation is found to induce tau protein-based pathology (i.e. neurofibrillary tangles (NFTs)) (Krstic and Knuesel, 2013; Wyss-Coray and Rogers, 2012) and can lead to increases in reactive oxygen species (ROS) (Gavillet et al., 2008; Li et al., 2008; Miller et al., 2009; Salminen et al., 2011; Steele and Robinson, 2012; Tilleux and Hermans, 2007). Neuroinflammation is found to be associated with neurotransmitter dysfunction (i.e. reduced acetylcholine production/function, glutamate-induced excitotoxicity and increased QA production) (Beattie et al., 2002; Butterfield et al., 2007; Guillemin et al., 2005; Hofer et al., 2008; Pavlov et al., 2009; Pickering et al., 2005; Rahman et al., 2009; Reale et al., 2004). Neuroinflammation also enhances neuronal apoptosis and impairs neuroplasticity (i.e. neurogenesis, synaptic function, and LTP) (Baune and Eyre, 2012; McAfoose and Baune, 2009; Yirmiya and Goshen, 2011).

A meta-analysis of 40 studies comparing peripheral blood cytokine concentrations between AD and healthy control subjects found higher levels of IL-6, TNF-α, IL-1β, TGF-β, IL-12 and IL-18 in AD subjects (Swardfager et al., 2010). There was no difference for IL-2, IL-4, IL8 or IFN-γ. A recent study has examined peripheral inflammatory and neuroimaging biomarkers in a cohort 350 of subjects with AD, MCI and elderly normal controls (Leung et al., 2013). After analyzing a panel of 27 cytokines and MRI measures of brain volume, this study found IL-6, TNF-α, IL-1ra, IL-10 and IL-13 inversely correlated with ventricular volume, whole brain volume or entorhinal cortex in AD. An analysis of rate of cognitive decline found increased IL-10 levels associated with Alzheimer's Disease Assessment Scale (ADAS)-cog fast decliners compared with slow decliners, and an increased level of IFN-γ was observed in ADAS-cog intermediate compared to slow decliners. Another recent meta-analysis of 14 studies measuring cerebrospinal fluid cytokine concentrations in AD and healthy control subjects found significantly higher concentrations of TGF-β in AD subjects compared with control subjects (Swardfager et al., 2010). There was no difference between groups for IL-6, TNF-α and IL-1β. A number of prospective studies have found higher levels of PICs (specifically IL-6, CRP and TNF-α) are associated with increase risk of cognitive decline in aging populations (Dik et al., 2005; Engelhart et al., 2004; Koyama et al., 2013; Nilsson et al., 2011; Schmidt et al., 2002; Sundelof et al., 2009; van Himbergen et al., 2012; Yaffe et al., 2004).

4. Immunomodulatory effects of physical activity subtypes

The following sections will examine the immunomodulatory profiles of various subtypes of PA in depression and ARCD. An emphasis will be given to comparative studies, where available. Tables 1 and 2, examine the immune effects of PA subtypes in depression and ARCD, respectively.

4.1. Immunomodulatory effects of physical activity in depression

4.1.1. Comparative studies

There is only one study directly comparing the immunomodulatory and anti-depressive effects of PA subtypes. This clinical trial by Kohut et al. (2006) randomized 87 healthy older adults (64–87 years) to either aerobic (CARDIO) or strength and flexibility (FLEX) training 3 days/week, 45 min/day for 10 months. A subgroup of subjects treated with non-selective $\beta_1\beta_2$ adrenergic antagonists were included to evaluate the potential role of β-adrenergic receptor adaptations as mediators of PA-induced change in inflammation. The study found CARDIO treatment resulted in significant reductions in serum CRP, IL-6 and IL-18 compared to FLEX treatment, whereas TNF-α declined in both groups. Both groups had similar improvements with depressive symptoms (measured by the Geriatric Depression Scale (GDS)) ($F(1,86) = 5.943$, $p = .017$). CARDIO group depressive symptoms changed from 2.5 ± 0.3 at baseline to 1.8 ± 0.7 at end of trial; FLEX depressive symptoms changed from 3.2 ± 0.4 at baseline to 2.8 ± 0.4 at end of trial. Several psychosocial measures (i.e. depression, optimism, and sense of coherence) improved in both groups suggesting that the reduction of CRP, IL-6, and IL-18 in the CARDIO group was not mediated by improvements in psychosocial scores.

4.1.2. Aerobic physical activity studies

To our knowledge, there are two studies examining the effect of aerobic PA (Rethorst et al., 2011, 2012). A recent study by Rethorst et al. (2012) investigated the extent to which inflammatory markers can be used to predict response to exercise treatment after an incomplete response to a selective serotonin reuptake inhibitor

(SSRI). This neuroimmune investigation was conducted with the cohort from the Treatment with Exercise Augmentation for Depression (TREAD) study, a randomized, parallel dose comparison trial (Trivedi et al., 2011). Incomplete response was qualified as having at least moderate residual depressive symptomatology, quantified by a 17-item Hamilton Depression Rating Scale score $\geqslant 14$. This study randomized 73 participants aged 18–70 years to 12 weeks of either 4 or 16 kilocalories per kilogram of body weight per week (KWW), via aerobic PA. The study examined serum IFN-γ, IL-1β, IL-6, TNF-α and made a number of interesting findings. From a clinical perspective, both doses of exercise showed significant improvements over time ($F_{1,121} = 39.9$, $p < .0001$). Adjusted remission rates at week 12 were 28.3% versus 15.5% for the 16-KKW and 4-KKW groups, respectively. There was a trend for higher remission rates in the higher-dose exercise group ($p < .06$). High baseline TNF-α (>5.493 pg/ml) was associated with a greater reduction in depressive symptoms (measured by Inventory for Depressive Symptomatology Clinical (IDS-C)). There was also a significant correlation between reductions of IL-1β and depressive symptoms in the 16 KWW group, but not the 4 KWW group. Otherwise, there was no significant change in cytokine levels following the 12 week PA intervention, and a non-significant association between PA dose and change in cytokine levels. A cross-sectional study by the same authors, Rethorst et al. (2011), examined the relationship between IL-6 and depressive symptoms by participation in moderate-intensity PA in a sample of 97 primary care patients aged >40 years. The patients had a Center for Epidemiological Studies Depression (CES-D) scale of >15 and PA was determined by a questionnaire. In this study, there was no correlation between IL-6 and depressive symptoms and no effect for PA on IL-6 levels ($r = .086$, $p = .40$); however, the association between IL-6 and depressive symptoms was moderated by PA ($p = .02$). In physically inactive subjects, higher depressive symptoms were associated with higher IL-6 levels ($r = .28$, $p = .05$).

4.1.3. Other physical activity studies

A total of five studies have been found investigating the effects of mind–body therapies on the immune system and depressive symptoms, one study examining tai chi (Irwin and Olmstead, 2012) and the others examining an 8-week Mindfulness-Based Stress Reduction course (MBSR) (Carlson et al., 2003, 2007; Fang et al., 2010; Gallegos et al., 2013). An RCT by Irwin and Olmstead (2012) investigated the effects of tai chi chih (TCC) on depressive symptoms and inflammatory markers (IL-6, CRP, sIL-1ra, sIL-6, sICAM, IL-18), as compared to control (health education (HE)). This study involved 83 healthy, non-depressed older adults (aged 59–86) in a 16 week intervention with 9 week follow up. Depressive symptoms were measured by the Beck Depression Inventory.

Table 1
Immunomodulatory effects of various subtypes of physical activity in depression.

Authors	Objective	Study design & demographics	Physical activity details	Depression measures	Immune measures	Results
Comparative exercise studies						
Kohut et al. (2006)	To determine if a long-term exercise intervention among older adults would reduce serum inflammatory cytokines, and if this reduction would be mediated, in part, by improvements in psychosocial factors and/or by β-adrenergic receptor mechanisms	Adults $\geqslant 64$ years. Community-based. Randomised to aerobic or flexibility/strength EXC. 10 months. A subgroup of patients on non-selective $\beta 1\beta 2$-adrenergic antagonists were included	Aerobic (CARDIO) or flexibility/ strength EXC (FLEX). 3 day/week, 45 min/day, 10 months	GDS, PSS, CS, SPS, LOT	ELISA of plasma: CRP, IL-6, TNF-α, IL-18	EXC = ↓ depressive symptoms, ↑ optimism (CARDIO = FLEX) CARDIO EXC = ↓IL-6, IL-18, CRP, TNF-α vs. FLEX FLEX EXC = ↓ TNF-α, no change in IL-6, IL-18, CRP vs. CARDIO. ↓ CRP α ↓ depressive symptoms. No effect for non-selective $\beta 1\beta 2$-adrenergic antagonists
Aerobic exercise studies						
Rethorst et al. (2012)	To examine the extent to which inflammatory markers can be used to predict response to exercise treatment after an incomplete response to an SSRI. To examine how the inflammatory markers change with exercise and if those changes are associated with dose of exercise or changes in symptom severity	Prospective. Randomised. TREAD study. Participants had MDD and were partial responders to an SSRI (i.e. $\geqslant 14$ HRSD-17 following >6 weeks but <6 months of treatment). Excluded if regularly engaging in PA Age 18–70 years 73 participants 12-week	Randomized to either 16 or 4 KWW Aerobic EXC (treadmill or cycle ergometers). Combination of supervised and home-based sessions	Clinician: IDS-C30 Self-rated: IDS-SR30 and HRSD17	ELISA of serum at baseline and 12 weeks. IFN-γ, IL-1β, IL-6, TNF-α	High baseline TNF-α (>5.493 pg ml) α greater ↓ in depression sxs (IDS-C) over 12 weeks ($P < 0.0001$) Sig pos α between Δ IL-1β and Δ depression sxs ($p = 0.04$). For 16KKW not 4 KKW. NS change in cytokine levels following 12 weeks of EXC. NS relationship between EXC dose and change in

Table 1 (*continued*)

Authors	Objective	Study design & demographics	Physical activity details	Depression measures	Immune measures	Results
						cytokine levels. High TNF-α may predict better outcomes with EXC vs. SSRI ↓ IL-1β α positive depression treatment outcomes
Rethorst et al. (2011)	To determine whether the relationship between IL-6 and depressive symptoms is moderated by participation in moderate-intensity physical activity in a sample of primary care patients	Cross-sectional 97 participants. Family medicine clinic ⩾40 years CES-D >15	Moderate-intensity PA. Measured using modified Community Health Activities Model program for Seniors Activity Questionnaire for Older Adults	CES-D	ELISA of serum. IL-6	Correlation between IL-6 and depressive sxs = NS. Association between IL-6 and depressive symptoms was moderated by PA. Among those who did not engage in mod PA, higher depressive sxs α ↑ IL-6. Association was NS for moderate PA
Neuromotor/flexibility/contemplative exercise studies						
Irwin and Olmstead (2012)	To evaluate the effects of a behavioral intervention, TCC on circulating markers of inflammation in older adults	83 healthy older adults (59–86 years) RCT. 2 arms – TCC, HE. 16 weeks intervention +9 weeks follow up	TCC and HE. Groups of 7–10. TCC 20 min, 3/week	BDI PSQI	ELISA of plasma for IL-6, CRP, sIL-1ra, sIL-6, sICAM, IL-18 *high IL-6>2.46 pg/ml*	- High IL-6 at entry: TCC ↓ IL-6 comparable to those in TCC and HE who had low IL-6 at entry. IL-6 in HE remained higher than TCC and HE with low entry IL-6 - TCC ns Δ cellular markers of inflammation - TCC = ↓ depressive sxs α ↓ IL-6
Carlson et al. (2007)	This study investigated the ongoing effects of participation in a MBSR program on QOL, symptoms of stress, mood and endocrine, immune and autonomic parameters in early stage breast and prostate cancer patients	49 patients with breast cancer and 10 with prostate cancer. Enrolled in 8-week MBSR program. Mean of 54.5 years, SD 10.9 years	MBSR program (relaxation, meditation, gentle yoga, daily home practice)	QL (EORTC QLQ-C30) Mood and stress scales (POMS, SOSI) (all assessed post-intervention, and at 6 and 12 months follow up)	Salivary cortisol levels Immune cell counts Intracellular cytokine production (all assessed post-intervention, and at 6 and 12 months follow up)	Numbers: 59, 51, 47, 41 were assessed pre- and post-intervention and at 6- and 12-month follow-up, respectively Stress: significant improvements over follow-up Cortisol: decreased over follow-up Immune patterns: reduction in Th1 cytokines over the year. Reduced T cell production of PICs
Carlson et al. (2003)	This study investigated the relationships between a MBSR meditation program for early stage breast and prostate cancer patients and	49 patients with breast cancer and 10 with prostate cancer. 50 years of age or older (mean ± SD, 54.5 ± 10.9 years)	8-week MBSR program (relaxation, meditation, gentle yoga and daily home practice)	QL (EORTC QLQ C-30), mood (POMS), stress (SOSI)	Counts of NK, NKT, B, T total, T helper, and T cytotoxic cells, as well as NK and T cell production of TNF, IFN-γ, IL-4, and IL-10 were assessed pre- and	Numbers: 59 and 42 patients were assessed pre- and post-intervention, respectively Stress: significant improvements Immune patterns:

Table 1 (*continued*)

Authors	Objective	Study design & demographics	Physical activity details	Depression measures	Immune measures	Results
	quality of life, mood states, stress symptoms, lymphocyte counts, and cytokine production				post-intervention	• No Δ in number of lymphocytes or cell subsets. • T cell production of IL-4 ↑, IFN-γ ↓. • NK cell production of IL-10 decreased
Fang et al. (2010)	The objectives of this study were to examine changes in psychosocial and immunologic measures in a heterogeneous patient sample following participation in a MBSR program	A single-group, pretest = post-test design was utilized. This pilot study involved 24 participants (aged 28–72 years)	8-week MBSR program.	Distress and QOL measures included the Brief Symptom Inventory-18 and the Medical Outcomes Survey Short-Form Health Survey, respectively	Immunologic measures included NK cell cytolytic activity and CRP. Pre-MBSR and within 2-weeks post-MBSR	Significant improvements in anxiety and overall distress as well as across multiple domains of QOL were observed from baseline to post-MBSR Reductions in anxiety and overall distress were associated with reductions in CRP Patients who reported improvement in overall mental well-being also showed increased NK cytolytic activity from pre- to post-MBSR, whereas patients who reported no improvement in mental well-being showed no change in NK cytolytic activity
Gallegos et al. (2013)	The objectives of this study were to examine the effects of specific MBSR activities (yoga, sitting and informal meditation, body scan) on immune function, circulating IGF-1 concentrations, and positive affect among older adults	Longitudinal analyses of data from subjects in an 8-week MBSR program 100 community-dwelling older adults. ⩾65 years of age	8-week MBSR program	Participants completed a 10-item measure of positive affect at study entry and post-intervention. PANAS, PAS	IL-6 and IGF-1 levels were assayed from blood collected at post-intervention assessments. Participants were immunized post-intervention with keyhole limpet hemocyanin (KLH), and IgM and IgG KLH-specific antibody responses were measured prior to immunization as well as 3 weeks and 24 weeks post-intervention	Affect: greater improvement in positive affect from study entry to post-intervention.IGF-1: • higher post-treatment IGF-1 levels from study entry to post-intervention • Sitting meditation was positively associated with post-treatment IGF-1 • Greater use of body scanning was associated with reduced antigen-specific IgM and IgG 3 weeks post-intervention but not 24 weeks. No associations were found betweenNo associations

Table 1 (continued)

Authors	Objective	Study design & demographics	Physical activity details	Depression measures	Immune measures	Results
						were found between MBSR activities and IL-6 levels

Abbreviations: PA, physical activity; EXC, exercise; GDS, geriatric depression scale; PSS, perceived stress scale; SPS, Stanford Presenteeism scale: LOT, life orientation test: ELISA, enzyme-linked immunosorbent assay; CRP, c-reactive protein; IL, interleukin; TNF, tumor necrosis factor; SSRI, selective serotonin reuptake inhibitor; TREAD, TReatment with Exercise Augmentation for Depression; MDD, major depressive disorder; HRSD, Hamilton Rating Scale for Depression; KWW, kilocalories per kilogram of body weight per week; IFN, interferon; IDS-C, inventory of depressive symptomatology; NS, non-significant; CES-D, center for epidemiological studies – depression scale; TCC, tai chi chih; HE, health education; ICAM, intercellular adhesion molecule; QOL, quality of life; MBSR, mindfulness-based stress reduction; SD, standard deviation; EORTC QLQ-30, European Organisation for Research and Treatment for Cancer QLQ-C30; POMS, profile of mood states; SOSI, symptoms of stress inventory; PIC, pro-inflammatory cytokine; NK, natural killer; IGF-1, insulin-like growth factor-1; PANAS, positive and negative affect schedule.

TCC lasted 40 min and were given 3 times per week for a total 120 min of weekly instruction. HE was also allocated over a 120-min period of instruction per week; hence, an identical amount of instructor time was provided to both intervention groups. This study found subjects with high IL-6 at entry (>2.46 pg/ml) had TCC-induced reductions in IL-6 to levels comparable to those found in TCC and HE subgroups who have low levels of IL-6 at baseline (t's(72) = 0.80, 1.63, p's > 0.01), whereas IL-6 levels in HE remained higher than the TCC and HE subgroups with low baseline IL-6 ($t(72) = 2.47$, $p = 0.02$; $t(72) = 1.71$, $p = 0.09$). Reductions in depressive symptoms in the two groups correlated with decreases of IL-6 ($r = .28$, $p < .05$). TCC did not affect other inflammatory markers.

The studies investigating immune effects of MBSR included varying populations including subjects with breast and prostate cancer (Carlson et al., 2003, 2007) as well as community-dwelling mid and old-age adults (Fang et al., 2010; Gallegos et al., 2013). MBSR is an 8-week secular, multi-faceted stress reduction course which has been extensively published in international scientific literature (Bohlmeijer et al., 2010; Grossman et al., 2004). The MBSR course involves yoga, meditation, body scan and progressive relaxation techniques. A meta-analysis from 2010 (Hofmann et al., 2010) noted 19 studies employing MBSR reported data from measures of depressive symptoms severity, and the ES for the pooled data was Hedges' $g = 0.49$ (95% CI: 0.42–0.56, $p < .01$). A pilot study has examined the immune effects of MBSR in a heterogeneous population, i.e. 24 participants aged between 28 and 72 (Fang et al., 2010). The study utilized the Brief Symptom Inventory 18 and the Medical Outcomes Survey Short-Form and found reductions in anxiety and overall distress were associated with reductions in CRP. A clinical trial comparing specific components of the MBSR program examined a range of immune markers in 100 non-depressed community-dwelling old adults aged >65 years (Gallegos et al., 2013). MBSR had beneficial effects on positive affect ($p < .05$) (measured by the Positive and Negative Affect Schedule). This study failed to find associations between MBSR activities and IL-6 levels, however the study did find higher post-treatment IGF-1 levels than at baseline. Interestingly, IGF-1 has been found to have anti-inflammatory effects when administered intra-cerebral in rodents (Park et al., 2011). In brief, studies in non-depressed subjects with prostate or breast cancer found MBSR did increase T cell production of IL-4 and reduce IL-10 levels while reducing Th1 cytokines (Carlson et al., 2003, 2007).

4.1.4. Additional considerations

Research is suggestive of unique immunomodulatory profiles according to PA subtypes (i.e. resistance, aerobic and mind–body). For example, the RCT by Kohut et al. (2006) suggests aerobic treatment resulted in significant reductions in serum CRP, IL-6 and IL-18 compared to strength and flexibility treatment, whereas TNF-α declined in both groups. Another study compared resistance and aerobic exercise in sedentary, non-depressed adults and found

resistance PA produced a greater reduction in CRP than aerobic PA, 32.8% vs. 16.1%, respectively (Donges et al., 2010). Levels of various cytokines at baseline may predict unique treatment response to subtypes of PA. For example, aerobic PA is shown to be more efficacious with subjects (partial responders to SSRIs) who have a higher baseline TNF-α (>5.493 pg/ml) (Rethorst et al., 2012). Given Eller et al. (Eller et al., 2008) found high baseline TNF-α associated with non-response to an SSRI, the finding by Rethorst et al. (2012) suggests TNF-α as a moderator between SSRI and exercise treatment, and TNF-α levels could be used to recommend exercise rather than medication as part of a personalized treatment algorithm.

4.2. Immunomodulatory effects of physical activity in age-related cognitive decline

4.2.1. Comparative studies

While there are a significant number of clinical studies comparing the efficacy of PA subtypes in ARCD, particularly from the Liu-Ambrose group who compared aerobic, resistance and BAT subtypes (Liu-Ambrose et al., 2010, 2012; Nagamatsu et al., 2012), to our knowledge there are no studies comparing immunomodulatory profiles in this field.

4.2.2. Aerobic physical activity studies

Three studies have been found examining the effects of aerobic PA on immune factors in ARCD (Baker et al., 2012; Pedersen et al., 2012; Swardfager et al., 2011). A study by Baker et al. (2012) aimed to determine whether aerobic PA modulates dietary effects on CSF Aβ, IL-8 and tau levels. This study involved 41 adults with an average age of 68, 18 with normal cognition and 23 with aMCI. The study provided a 4-week dietary intervention of either low saturated fat and GI diet or high saturated fat and GI diet, as well as assessing self-reported PA each week. At baseline, high intensity PA in subjects with normal cognition predicted lower levels of cerebro-spinal fluid (CSF) tau ($r = -0.54$, $p = 0.020$) and IL-8 ($r = -0.70$, $p = 0.025$). High intensity PA in subjects with MCI did not affect IL-8 levels. Diet-induced effects on CSF Aβ(42) during the study were modulated by high intensity PA, and this effect differed between normal cognitive subjects and those with MCI (ANOVA, $p = 0.039$). For normal adults, increased high intensity PA attenuated the effects of the high fat and GI diet on Aβ(42) whereas in MCI, increased high intensity PA potentiated the effects of the low fat and GI diet. This study suggests that PA may interact with diet to alter pathological processes that modify risk of AD. In a cross-sectional study from Swardfager et al. (2011) 88 non-demented, aged subjects with coronary artery disease entering cardiac rehabilitation, aged approx. 62.8 years, were assessed for serum brain-derived neurotrophic factor (BDNF), IL-6 and TNF-α and cardiopulmonary fitness. In this sample, 26 subjects (29.5%) had a depressive episode as determined by a Structured Clinical Interview. Greater cardiopulmonary fitness

Table 2
Immunomodulatory effects of various subtypes of physical activity in age-related cognitive decline.

Authors	Objective	Study design & demographics	Physical activity details	Depression measures	Immune measures	Results
Aerobic exercise studies						
Baker et al. (2012)	To determine whether high intensity physical activity modulates dietary effects on CSF Amyloid Beta levels and other markers of Alzheimers pathology	Interventional study. 41 adults (normal cognition $n = 18$, amnestic MCI $n = 23$) Age approx 68 Low saturated fat/low GI diet (LOW) vs high saturated fat/high GI diet (HIGH), 4 weeks	Self-report 7-d questionnaire Low intensity (HR not increase, breathing light) High intensity (HR increased, breathing moderate/heavy)	Visual memory: brief Visuospatial Memory Test @ baseline and 4 weeks	Lumbar puncture @baseline and 4 weeks (ELISA) Aβ42, total tau protein, p181-tau, IL-8	High PA modulated diet-induced change in Aβ42 Normal- non-significant attenuation of effects of HIGH diet MCI-potentiated effects of LOW diet NORMAL: high PA = ↓tau, ↓IL-8 no sig Δ in p181-tau MCI: high PA = NS Δ in total tau or IL-8 No change in visual memory
Swardfager et al. (2011)	To assess serum BDNF concentrations as a correlate of cardiopulmonary fitness and as a predictor of cognitive performance in people with coronary artery disease	Cross-sectional study: 88 men and women with coronary artery disease (age $n = 62.8 \pm 10.5$ years)	Cardiopulmonary fitness assessed by cycle ergometer to obtain VO2-peak (divided by expected VO2-peak for age)	Processing speed: Digit-symbol coding test Executive function: Trail making test B, Stroop test Memory: Immediate, short and delayed recall (CVLT) Global cognition: MMSE	Serum of IL-6, TNF-α, BDNF (ELISA)	Greater cardiopulmonary fitness associated with ↑ serum BDNF ↑ BDNF assoc with ↑ MMSE ($p < 0.005$) & ↑Digit-Symbol Coding scores ($p = 0.003$) ↑BDNF not sig assoc with ↑TMT-B, Stroop test or CVLT ↓IL-6 assoc with ↓ BDNF ($p = 0.02$)
Pedersen et al. (2012)	To investigate the relationship between cognitive impairment, metabolic deteriorations, low physical fitness, low-grade inflammation and abdominal obesity in middle-aged individuals	Cross-sectional study. 184 community-dwelling individuals (40–65 years). type 2 diabetes and limited co morbidity ($n = 56$), age-matched individuals with impaired glucose tolerance ($n = 56$) as well as age-matched controls with normal glucose tolerance ($n = 72$)	Single-stage, submaximal test of physical fitness (6 min on ergometer bike, workload equivalent to HR 110–150). VO2 max calculated. DXA also performed to assess whole-body fat composition	Memory (RAVLT), processing speed (SDMT, Trail making test A), attention, executive function (Trail making test B, Category Fluency)	Plasma IL-6, TNF-a, CRP	Low scores in processing speed (SDMT and Trail Making A) were associated with high fasting C-peptide, low insulin sensitivity and low fitness level. Low scores in executive functions (Trail Making B and word mobilization) were associated with high levels of C-peptide, decreased beta cell function and low fitness level. Low cognitive function NS assoc with low IL-6
Flexibility/contemplative exercise studies						
Oh et al. (2012)	To examine the effects of Medical Qigong on cognitive function, quality of life and inflammation in cancer patients	Randomised, controlled trial. 81 cancer patients. Standard health care (CONTROL) $n = 44$ vs standard care and medical Qigong (MQ) $n = 37$, 10 weeks (34–86 years)	2 × 90 min sessions/week, 10 weeks 15 min discussion of health issues, 30 min gentle stretching & body movement in standing posture, 15 min movement in seated posture, 30 min meditation and breathing exercises	Self-reported with 2-item cognitive subscale of EORTC-QLQC30 & FACT-Cog @baseline and 10 weeks	Blood CRP: particle-enhanced immunological agglutination	MQ = ↓CRP Increased self-reported cognitive function Improved EORTC QLQC30 scores Improved FACT-Cog scores
Combination exercise studies						
Lin et al. (2012)	To determine whether leisure activities modify the effect of CVDRFs on inflammatory markers on cognition in middle and old age	Secondary-data analysis study from survey of MIDUS 405 middle-aged (40–59) and 342 old-age (60–84) participants	Self-report based on checklist for frequency of social, physical and mental. Physical items included tennis, swimming, golf, mowing etc	BTACT - episodic verbal memory (Immediate-Delayed Word List) - Working memory span (Digits backward) - Verbal fluency (Category fluency) - Inductive reasoning (Number series) - Processing speed (Backward counting)	Serum IL-6, CRP via ELISA	↑CVDRFs α ↓executive function ↑physical activity α ↓IL-6, ↓CRP Older people – ↑PA = attenuated effect of CDRFs on episodic memory

Abbreviations: CSF, cerebrospinal fluid; MCI, mild cognitive impairment; HR, heart rate; BDNF, brain-derived neurotrophic factor; CRP, c-reactive protein; IL, interleukin; TNF, tumor necrosis factor; MMSE, mini mental state examination; CVLT, California Verbal Learning Test; SDMT, Symbol Digit Modalities Test; RAVLT, Rey Auditory Verbal Learning Test; MQ, medical qi gong; EORTC QLQ-30, European Organisation for Research and Treatment for Cancer QLQ-C30; FACT-Cog, Functional Assessment of Cancer Therapy-Cognitive Function; CVDRFs, cardiovascular disease risk factors; MIDUS, Midlife Development in the US; BTACT, Brief test of Adult Cognition by telephone.

was associated with increased BDNF (β = .305, p = .013) and higher serum BDNF was associated with higher MMSE scores ($F(1,87)$ = 15.406, p < .0005) and better performance on the Digit Symbol-Coding Task ($F(1,87)$ = 9.620, p = .003). Cytokine levels did not influence these results. A recent study by Pedersen et al. (2012) has examined cross-sectional associations between cognitive impairment, cardiovascular fitness, plasma IL-6 and TNF-α and abdominal obesity in middle-aged individuals. The study examined 184 community-dwelling individuals with type 2 diabetes mellitus and limited co-morbidity, impaired glucose tolerance and subjects with normal glucose tolerance, aged 40–65 years in a cross-sectional setting. Cardiovascular fitness was determined by a sub-maximal test to determine a VO$_2$max measure. In this study, low aerobic capacity was associated with decreased overall cognitive scores (a composite score of verbal memory, processing speed and executive functions) and increased CRP; there was no association for IL-6 or TNF-α. Furthermore, a low score in processing speed, executive functions and overall cognitive function were related to high fasting C-peptide, as well as low insulin sensitivity, beta-cell function and VO$_2$max.

4.2.3. Resistance physical activity studies

As outlined in the introduction, there are a number of studies comparing the clinical and neuroplastic effects of aerobic, resistance and BAT PA types. However, to our knowledge there are no studies examining the immunomodulatory effect of resistance PA in ARCD. This field would therefore benefit from clinical trials also analysing immune biomarkers.

4.2.4. Other physical activity studies

There is one study which assesses the effects of mind–body PA on cognitive function in ARCD. This RCT by Oh et al. (2012) was conducted on 81 cancer patients and compared medical qi gong with standard health care for 10 weeks. Subjects had cancer and an expected survival >12 months, were aged 34–86 years and self-reported cognitive function was measured by the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog). The medical qi gong program involved a group class, conducted over 10 weeks with two identical supervised 90-min session per week. Over 10 weeks, subjects who partook in the active group showed increases in self-reported cognitive function (mean difference (MD) = 4.70, $t(43)$ = −2.254, p = 0.029),as well as reductions in CRP levels (MD = −0.72, $t(45)$ = 2.092, p = 0.042). Beavers et al. (2010) provides an analysis of the immunomodulatory effects of exercise interventions in aging and general medical conditions (i.e. heart disease, diabetes, metabolic syndrome, obesity). This review finds large population-based cohort studies consistently show an inverse association between markers of systemic inflammation and physical activity or fitness status, and data from several small-scale intervention studies support that exercise training diminishes inflammation. However, data from large, RCTs designed to definitively test the effects of exercise training on inflammation are limited, and results are inconclusive.

5. Neuroplastic effects of subtypes of physical activity

The following sections will examine the neuroplastic profiles of various subtypes of PA in depression and ARCD. An emphasis will be given to comparative studies, where available.

5.1. Neuroplastic effects of physical activity in depression

5.1.1. Comparative studies

To our knowledge only one study compares markers of neuroplasticity between PA subtypes in depression (Pereira et al., 2013). An RCT study by Pereira et al. (2013) has examined the effect of 3 weeks of aerobic and resistance PA on plasma BDNF levels in 451 inactive, community-dwelling older women (65–89 years). Both protocols lasted 10 weeks, and 30 sessions (1-h sessions) in total were performed 3 times a week under the direct supervision of physical therapists. Both groups had significant pre- and post-intervention GDS improvements (p = .001). Pre-post changes in the aerobic group were 3.21 ± 2.71 and 2.67 ± 2.4, respectively; pre-post changes in the resistance group were 3.76 ± 3.04 and 2.91 ± 2.56, respectively. BDNF level reductions were only significant for resistance PA subjects and there was a difference between BDNF plasma levels between groups (p = .009).

5.1.2. Studies applying other physical activity modes

There is an emerging literature outlining differing neural effects of mind–body therapies in adult populations, and these populations may suggest a utility in depression. Use of diffusion tensor imaging reveals short-term meditation (4-weeks of integrative body-mind training) enhances white matter neuroplasticity in the anterior cingulate cortex, a part of the brain network related to self-regulation, versus relaxation training controls (Tang et al., 2012). Additionally, long-term meditators have also been observed to have larger HC than controls (Luders et al., 2013); short-term meditation tasks are associated with reducing automatic emotional responding via the insula (Paul et al., 2013). A recent study of TCC practitioners (Wei et al., 2013) has found, compared with controls, significantly thicker cortex in precentral gyrus, insula sulcus and middle frontal sulcus in the right hemisphere and superior temporal gyrus and medial occipito-temporal sulcus and lingual sulcus in the left hemisphere. Moreover, thicker cortex in left medial occipito-temporal sulcus and lingual sulcus was associated with greater intensity of TCC practice.

An emerging literature comparing MBSR vs. aerobic PA in social anxiety disorder reveals distinct neural effects of MBSR (Goldin et al., 2012, 2013). Such studies are outside the score of this review, and require translation to the depression field.

5.2. Neuroplastic effects of physical activity in age-related cognitive decline

5.2.1. Comparative studies

To our knowledge there are two studies investigating neuroplasticity markers between PA subtypes in ARCD. The recent RCT by Nagamatsu et al. (2012) noted differing neuroplastic effects of resistance PA vs. BAT. In this six-month randomized trial (EXercise for Cognition and Everyday Living; EXCEL), 86 community-dwelling women aged 70–80 years old were randomly allocated to twice-weekly resistance training (RT), twice-weekly aerobic training (AT), or twice-weekly balance and tone training (i.e. control group) (BAT). Participants were classified as having probable MCI if they scored <26/30 on the Montreal Cognitive Assessment and had subjective memory complaints. Compared with the BAT group, the RT group significantly improved performance on the Stroop Test (p = 0.04) and the associative memory task (p = 0.03). Compared with the BAT group, resistance training also led to functional changes in three regions of cortex – the right lingual (p = 0.03) and occipital-fusiform (p = 0.02) gyri, and the right frontal pole (p = 0.03) – during the encoding and recall of associations. As outlined previously, a recent rodent study suggests aerobic and resistance PA have divergent pro-neuroplastic effects (Cassilhas et al., 2012). This study found both types of PA improved learning and spatial memory, resistance PA induced central and peripheral insulin-like growth factor-1 (IGF-1) and AKT in the hippocampus (HC), whereas aerobic PA showed an increase in IGF-1, brain-derived neurotrophic factor (BDNF), TrkB and β-CaMKII (calcium-dependent kinase II) in the HC.

5.2.2. Physical activity studies of resistance training

An RCT by Liu-Ambrose et al. (2012) examined the effect of 12-months of resistance training (once- or twice-weekly) vs. BAT on fMRI-based neuroplasticity measures in 52 community-dwelling senior women, with a baseline Mini Mental State Examination (MMSE) score of ⩾24. Investigators found twice-weekly resistance training led to functional changes in 2 regions of cortex previously associated with response inhibition processes (assessed via flanker tast) – the anterior portion of the left middle temporal gyrus and the left anterior insula extending into lateral orbital frontal cortex. These hemodynamic effects co-occurred with improved task performance. The data suggest that RT improved flanker task performance via an increased engagement of response inhibition processes when needed; and a decreased tendency to prepare response inhibition as a default state. This effect of RT was only observed among those who trained twice weekly; participants of the once-weekly RT did not demonstrate comparable response profiles, both in behavioral performance and hemodynamic activity in cortex.

5.2.3. Aerobic physical activity studies

Reviews by Erickson et al. (2013) and Hayes et al. (2013) summarize data from cross-sectional, longitudinal, observational studies and RCTs consistently show higher fitness levels are associated with larger brain volumes, and participation in only modest among of physical activity are sufficient for increasing gray matter volumes in select brain regions (e.g. HC).

5.2.4. Other physical activity studies

A recent small, cross-sectional study by Froeliger et al. (2012) examined gray matter volume (GMV) differences and cognitive failures between hatha yoga meditation practitioners and control subjects. The study involved 7 healthy hatha yoga meditation practitioners, 7 healthy hatha yoga and meditation-naïve controls between the ages of 18 and 55 years. Practitioners reported maintaining an active and ongoing modern hatha yoga practice (>45-min/day, 3–4 times/week, >3 years (M = 9.4; SD = 2.4)) and engaging in mindfulness meditation on average 7 days per week (0) over the course of the previous 5.6 years (4.2). The matched control group reported no current or past dedicated meditation or yoga practice. This study found practitioners exhibited greater GMVin frontal, limbic, temporal, occipital, and cerebellar regions; whereas the CG had no greater regional greater GMV. In addition, the yoga group reported significantly fewer cognitive failures on the Cognitive Failures Questionnaire, the magnitude of which was positively correlated with GMV in numerous regions identified in the primary analysis. Finally, GMV was positively correlated with the duration of yoga practice.

6. Discussion

PA is emerging as an important intervention in the prevention and treatment of common psychiatric disorders, including depression and ARCD (Eyre et al., 2013). Emerging evidence suggests there may be unique biological profiles of PA subtypes, and a greater understanding of these profiles may assist in increasing PA efficacy by personalizing treatment approaches. With this in mind, this systematic review aims to assess the immunomodulatory and neuroplastic profiles of various PA subtypes, particularly in unipolar depression and ARCD. As outlined in a previous review, it is likely the immune effects of PA have a significant impact upon neuroplastic changes from PA (Baune and Eyre, 2012).

6.1. Biological factors underlying possible immunomodulatory and neuroplastic profiles of physical activity

Biological factors which may underlie immunomodulatory and neuroplastic profiles of PA subtypes include specific effects on adipose tissue, muscle, blood vessels, vagal tone and the brain as discussed below. Fig. 2 outlines these dynamic interactions.

PA subtypes appear to have differing effects on adipose tissue deposits, and this may in turn affect immunomodulatory profiles. A study comparing 10 weeks of aerobic and resistance PA with control in 103 sedentary adults has found resistance training reduces CRP to a greater extent than aerobic training (Donges et al., 2010). The resistance group significantly improved total-body fat mass as compared with the aerobic group, measured by dual-energy X-ray absorptiometry (DEXA) scanning. The aerobic group exhibited greater reductions in intra-abdominal fat mass and total body mass as compared to the resistance group. A rodent study (Cohen et al., 2013) has found differing leukocyte and macrophage phenotype compositions between white subcutaneous and various types of white visceral fat (i.e. peritoneal serous fluid, parametrial, retroperitoneal and omental). Serous visceral fluid was comprised almost entirely of CD45(+) leukocytes (>99%), while omental fat contained less, but still almost twofold more leukocytes than para-metrial and retroperitoneal (75%, 38% and 38% respectively; $p < 0.01$). Parametrial fat was composed primarily of macrophages, whereas retroperitoneal fat more closely resembled omental fat, denoted by high levels of B1 B-cell and monocyte populations. Further, omental fat harbored significantly higher
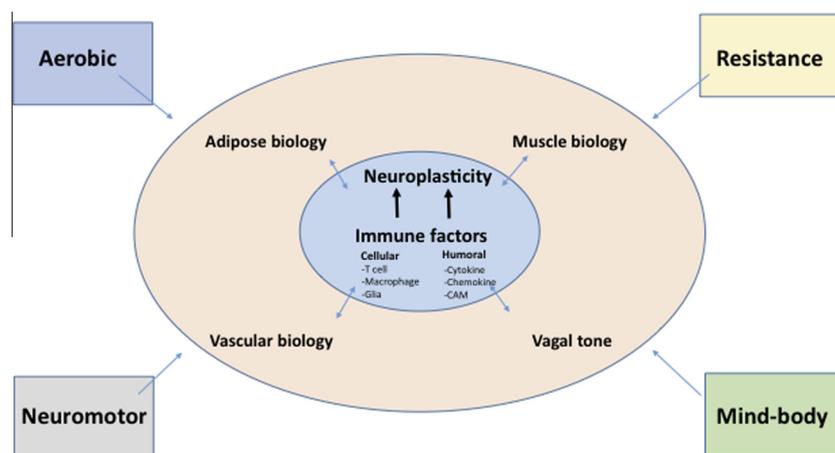
Fig. 2. Assessing for unique immunomodulatory and neuroplastic profiles of various types of physical activity: a focus on psychiatric disorders This figure illustrates the hypothetical biological factors to be considered when investigating the immunomodulatory and neuroplastic profiles of PA subtypes. The differing PA subtypes may impact uniquely upon adipose, muscle and vascular biology, as well as vagal tone, and these effects may in turn affect immune factors which may affect neuroplasticity.

proportions of T-cells than the other tissues, consistent with its role as a secondary lymphoid organ. In another rodent study (Kawanishi et al., 2010), aerobic exercise was shown to inhibit M1 macrophage infiltration into adipose tissue as well as inducing macrophage phenotype switching from M1 to M2.

Changes in muscle physiology may belie the unique immunomodulatory profiles of PA subtypes. In 14, young untrained health male subjects, skeletal muscle biopsies were analyzed prior to, immediately after, and in the recovery period following resistance PA, aerobic PA and control intervention (Moller et al., 2013). Resistance exercise, but not aerobic exercise, increased inhibitory κB protein kinase complex (Iκκ)β phosphorylation (a key regulator of NF-κB), possibly suggesting Iκκβ can influence activation of mammalian target of rapamycin complex 1 (mTORC1). mTORC1 is considered a principal mediator of muscular adaptations to exercise and integrates signals from mitogenic growth factors, cellular stressors, and/or nutrients to regulate protein synthesis (Ma and Blenis, 2009).

A differential effect of PA subtypes on acute, neuroprotective myokine release is unclear. A rodent study by Funk et al. (2011) demonstrates that PA can offer significant protection to the HC in a chemical-induced injury model (via trimethyltin (TMT)) that involves TNF receptor signaling. PA attenuated TMT-induced changes such as loss of DG neurons and microglial activation. Furthermore, PA was accompanied by a significant elevation in IL-6 and IL-1ra mRNA levels and repressed elevations in PICs and chemokines (CCL2 and CCL3). Interestingly, the investigators identified a functional role for IL-6 in neuroprotection given mice deficient in IL-6 (IL-6 knock-out) were not responsive to the neuroprotective effects of PA on the HC. The effects of PA and TMT on IL-6 downstream signal events differed at the level of STAT3 activation. The beneficial effects of acute spikes in IL-6 with PA is clearly a significant factor in the anti-inflammatory effect of PA. In a human study by Starkie et al. (2003), 3 h of cycling blunted the endotoxin-induced increase in circulating TNF-α levels, and this effect was mimicked by an IL-6 infusion.

Vagal tone may be differentially regulated by PA subtypes, and this may impact upon the anti-inflammatory effects of PA (Lujan and DiCarlo, 2013). Baroreceptor sensitivity, a marker of vagal tone, was found to be affected more by 6 weeks of yoga than 6 weeks of aerobic exercise (Bowman et al., 1997). Yoga affected only α-index at high frequency, but not mid frequency while aerobic PA did not affect either frequency.

A recent review by Roque et al. (2013) outlines evidence to suggest PA minimizes vascular damage produced by obesity, hypertension, diabetes, dyslipidemia and metabolic syndrome. PA training reduces endothelial dysfunction, altered vascular structure and/or increased vascular stiffness. Mechanisms underlying these changes include reduced inflammation and pro-inflammatory adipokines, improved nitric oxide availability, increased antioxidant production. Further research is required to understand unique vascular modifying profiles of PA subtypes.

6.2. Methodological limitations

In the unipolar depression literature, although the collated studies are suggestive of PA subtype-specific immunological and neuroplastic changes, it is not possible to draw firm conclusions on the neurobiological profiles. This is given the small number of comparative studies and methodological heterogeneity between studies (e.g. study population age and illness severity, as well as duration and intensity of PA intervention). Furthermore, as stated in the most recent Cochrane review assessing the clinical effects of Exercise in Depression, by Cooney et al. (2013), measures need to be taken to enhance the methodological robust nature of this field. Cooney et al. (2013) suggests clinical evidence is of moderate

quality. They suggest significant study bias, heterogeneity and outcome reporting bias. They also suggest additional large-scale high-quality studies where all participants at the time of recruitment were diagnosed through clinical interview as having depression, adhered closely to an exercise regimen as a sole intervention and were further assessed through diagnostic clinical interview post intervention. Further work is required to improve the understanding of the biology of such PA related immunomodulatory profiles.

There are no studies examining the immunomodulatory effects of PA subtypes in this area. Additionally, there is no prospective data on the immunomodulatory effects of aerobic and resistance PA. Given this, in addition to the heterogeneity of study participants it is not possible to draw firm conclusions as to the immunomodulatory effects of PA subtypes in ARCD. Current literature suggests unique neuroplastic profiles for PA subtypes in ARCD. Again, further comparative studies and less methodological heterogeneity is required in future research to reach more definite conclusions. While aerobic, resistance and mind–body interventions (e.g. yoga) enhance neuroplasticity, as shown in neuroimaging studies investigating the HC, it is unclear if the magnitude of this effect is similar across the PA subtypes.

This review does not include the substantial literature arising from rodent studies. Relating to this current paper which compares the neuroplastic and neuroimmune effects PA subtypes, there is only one rodent study comparing aerobic and resistance training (see Cassilhas et al., 2012). Therefore, more comparative studies are required in the rodent literature. We recommend rodent studies to be considered in the future given the relatively high-throughput of these studies and the ability to more readily access brain tissue. Studies in the rodent literature have recently been reviewed by our group (Eyre et al., 2013).

6.3. Future directions

A number of future directions should be considered in order to advance this field of research. These include a need to develop comparative studies examining aerobic, resistance, neuromotor and mind–body exercise from clinical, neuroplasticity and immune perspectives in depression and ARCD. Creating such comparative studies will also assist in minimizing methodological heterogeneity by standardizing PA interventions, duration, intensities and study populations. Moreover, rodent models can be utilized to assist in understanding the immunomodulatory differences between aerobic and resistance training – the study by Cassilhas et al. (2012) provides a useful model for such a study. The age of subjects is important to consider in PA interventions examining immunomodulatory, neuroplastic and clinical effects in depression. The immune profiles seen in adolescent, adult and late-life depression may differ across age groups and need further attention (see for review Mills et al., 2013; Taylor et al., 2013). Clinical trials examining neuropsychological effects of PA should include concurrent immune biomarkers analysis. Other immune markers and investigative methodologies should be utilized in future comparative studies. For example, a recent RCT of omega-3 polyunsaturated fatty acids revealed effects on leukocyte phenotype (Rizzo et al., 2012). Further, in vivo microglial imaging techniques utilizing positron emission tomography are available and have been utilized in ARCD and depression (see primary studies Hannestad et al., 2013; Kreisl et al., 2013). Finally, given the pro- and anti-neuroplastic effects of cellular and humoral immune factors (Eyre and Baune, 2012b), efforts should be made to understand how possible immunomodulatory profiles of PA subtypes may be involved in unique neuroplastic profiles.

7. Conclusion

While PA subtypes appear to have unique immunomodulatory and neuroplastic profiles in depression and ARCD, the current paucity of comparative studies and methodological heterogeneity between studies make the exact nature of these profiles unclear. This field requires high quality comparative studies to better identify unique immunomodulatory and neuroplastic profiles.

Conflict of interest

All authors declare that there are no conflicts of interest.

References

Baker, L.D., Bayer-Carter, J.L., Skinner, J., Montine, T.J., Cholerton, B.A., Callaghan, M., Leverenz, J.B., Walter, B.K., Tsai, E., Postupna, N., Lampe, J., Craft, S., 2012. High-intensity physical activity modulates diet effects on cerebrospinal amyloid-beta levels in normal aging and mild cognitive impairment. J. Alzheimers Dis. 28, 137–146.

Balsamo, S., Willardson, J.M., Frederico Sde, S., Prestes, J., Balsamo, D.C., Dahan da, C.N., Dos Santos-Neto, L., Nobrega, O.T., 2013. Effectiveness of exercise on cognitive impairment and Alzheimer's disease. Int. J. Gen. Med. 6, 387–391.

Baune, B., Eyre, H., 2012. Novel perspectives on the role of immune biomarkers in exercise and depression. Brain Behav. Immun. 26, 512.

Baune, B.T., Smith, E., Reppermund, S., Air, T., Samaras, K., Lux, O., Brodaty, H., Sachdev, P., Trollor, J.N., 2012. Inflammatory biomarkers predict depressive, but not anxiety symptoms during aging: the prospective Sydney memory and aging study. Psychoneuroendocrinology 37, 1521–1530.

Beattie, E.C., Stellwagen, D., Morishita, W., Bresnahan, J.C., Ha, B.K., Von Zastrow, M., Beattie, M.S., Malenka, R.C., 2002. Control of synaptic strength by glial TNFalpha. Science 295, 2282–2285.

Beavers, K.M., Brinkley, T.E., Nicklas, B.J., 2010. Effect of exercise training on chronic inflammation. Clin. Chim. Acta 411, 785–793.

Bohlmeijer, E., Prenger, R., Taal, E., Cuijpers, P., 2010. The effects of mindfulness-based stress reduction therapy on mental health of adults with a chronic medical disease: a meta-analysis. J. Psychosom. Res. 68, 539–544.

Bowman, A.J., Clayton, R.H., Murray, A., Reed, J.W., Subhan, M.M., Ford, G.A., 1997. Effects of aerobic exercise training and yoga on the baroreflex in healthy elderly persons. Eur. J. Clin. Invest. 27, 443–449.

Bridle, C., Spanjers, K., Patel, S., Atherton, N.M., Lamb, S.E., 2012. Effect of exercise on depression severity in older people: systematic review and meta-analysis of randomised controlled trials. Br. J. Psychiatry 201, 180–185.

Brown, B.M., Peiffer, J.J., Martins, R.N., 2012. Multiple effects of physical activity on molecular and cognitive signs of brain aging: can exercise slow neurodegeneration and delay Alzheimer's disease? Mol. Psychiatry 18, 864–874.

Butterfield, D.A., Reed, T., Newman, S.F., Sultana, R., 2007. Roles of amyloid beta-peptide-associated oxidative stress and brain protein modifications in the pathogenesis of Alzheimer's disease and mild cognitive impairment. Free Radic. Biol. Med. 43, 658–677.

Carlson, L.E., Speca, M., Patel, K.D., Goodey, E., 2003. Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress, and immune parameters in breast and prostate cancer outpatients. Psychosom. Med. 65, 571–581.

Carlson, L.E., Speca, M., Faris, P., Patel, K.D., 2007. One year pre-post intervention follow-up of psychological, immune, endocrine and blood pressure outcomes of mindfulness-based stress reduction (MBSR) in breast and prostate cancer outpatients. Brain Behav. Immun. 21, 1038–1049.

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. Med. Sci. Sports Exerc. 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.

Chi, I., Jordan-Marsh, M., Guo, M., Xie, B., Bai, Z., 2013. Tai chi and reduction of depressive symptoms for older adults: a meta-analysis of randomized trials. Geriatr. Gerontol. Int. 13, 3–12.

Cohen, C.A., Shea, A.A., Heffron, C.L., Schmelz, E.M., Roberts, P.C., 2013. Intra-abdominal fat depots represent distinct immunomodulatory microenvironments: a murine model. PLoS One 8, e66477.

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 Syst. Rev. 9 (CD004366).

Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9, 46–56.

Davis, J.C., Bryan, S., Marra, C.A., Sharma, D., Chan, A., Beattie, B.L., Graf, P., Liu-Ambrose, T., 2013. An economic evaluation of resistance training and aerobic training versus balance and toning exercises in older adults with mild cognitive impairment. PLoS One 8, e63031.

Dik, M.G., Jonker, C., Hack, C.E., Smit, J.H., Comijs, H.C., Eikelenboom, P., 2005. Serum inflammatory proteins and cognitive decline in older persons. Neurology 64, 1371–1377.

Donges, C.E., Duffield, R., Drinkwater, E.J., 2010. Effects of resistance or aerobic exercise training on interleukin-6, C-reactive protein, and body composition. Med. Sci. Sports Exerc. 42, 304–313.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., Lanctot, K.L., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatry 67, 446–457.

Eikelenboom, P., Hoozemans, J.J., Veerhuis, R., van Exel, E., Rozemuller, A.J., van Gool, W.A., 2012. Whether, when and how chronic inflammation increases the risk of developing late-onset Alzheimer's disease. Alzheimer's Res. Ther. 4, 15.

Eller, T., Vasar, V., Shlik, J., Maron, E., 2008. Pro-inflammatory cytokines and treatment response to escitalopram in major depressive disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 32, 445–450.

Engelhart, M.J., Geerlings, M.I., Meijer, J., Kiliaan, A., Ruitenberg, A., van Swieten, J.C., Stijnen, T., Hofman, A., Witteman, J.C., Breteler, M.M., 2004. Inflammatory proteins in plasma and the risk of dementia: the rotterdam study. Arch. Neurol. 61, 668–672.

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. Proc. Natl. Acad. Sci. USA 108, 3017–3022.

Erickson, K.I., Gildengers, A.G., Butters, M.A., 2013. Physical activity and brain plasticity in late adulthood. Dialogues Clin. Neurosci. 15, 99–108.

Eyre, H., Baune, B.T., 2012a. Neuroimmunomodulation in unipolar depression: a focus on chronobiology and chronotherapeutics. J. Neural Transm. 119, 1147–1166.

Eyre, H., Baune, B.T., 2012b. Neuroplastic changes in depression: a role for the immune system. Psychoneuroendocrinology 37, 1397–1416.

Eyre, H., Papps, E., Baune, B.T., 2013. Treating depression and depression-like behavior with physical activity: an immune perspective. Front. Psychiatry/ Front. Res. Found. 4, 3.

Fang, C.Y., Reibel, D.K., Longacre, M.L., Rosenzweig, S., Campbell, D.E., Douglas, S.D., 2010. Enhanced psychosocial well-being following participation in a mindfulness-based stress reduction program is associated with increased natural killer cell activity. J. Altern. Complement. Med. 16, 531–538.

Froeliger, B., Garland, E.L., McClernon, F.J., 2012. Yoga meditation practitioners exhibit greater gray matter volume and fewer reported cognitive failures: results of a preliminary voxel-based morphometric analysis. Evid. Based Complement. Altern. Med. 2012, 821307.

Funk, J.A., Gohlke, J., Kraft, A.D., McPherson, C.A., Collins, J.B., Jean Harry, G., 2011. Voluntary exercise protects hippocampal neurons from trimethyltin injury: possible role of interleukin-6 to modulate tumor necrosis factor receptor-mediated neurotoxicity. Brain Behav. Immun. 25, 1063–1077.

Gallegos, A.M., Hoerger, M., Talbot, N.L., Krasner, M.S., Knight, J.M., Moynihan, J.A., Duberstein, P.R., 2013. Toward identifying the effects of the specific components of mindfulness-based stress reduction on biologic and emotional outcomes among older adults. J. Altern. Complement. Med. 19, 787–792.

Gavillet, M., Allaman, I., Magistretti, P.J., 2008. Modulation of astrocytic metabolic phenotype by proinflammatory cytokines. Glia 56, 975–989.

Goldin, P., Ziv, M., Jazaieri, H., Gross, J., 2012. Randomized controlled trial of mindfulness-based stress reduction versus aerobic exercise: effects on the self-referential brain network in social anxiety disorder. Front. Hum. Neurosci. 6, 295.

Goldin, P., Ziv, M., Jazaieri, H., Hahn, K., Gross, J.J., 2013. MBSR vs aerobic exercise in social anxiety: fMRI of emotion regulation of negative self-beliefs. Soc. Cogn. Affect. Neurosci. 8, 65–72.

Grossman, P., Niemann, L., Schmidt, S., Walach, H., 2004. Mindfulness-based stress reduction and health benefits. A meta-analysis. J. Psychosom. Res. 57, 35–43.

Guillemin, G.J., Brew, B.J., Noonan, C.E., Takikawa, O., Cullen, K.M., 2005. Indoleamine 2,3 dioxygenase and quinolinic acid immunoreactivity in Alzheimer's disease hippocampus. Neuropathol. Appl. Neurobiol. 31, 395–404.

Hannestad, J., Dellagioia, N., Gallezot, J.D., Lim, K., Nabulsi, N., Esterlis, I., Pittman, B., Lee, J.Y., O'Connor, K.C., Pelletier, D., Carson, R.E., 2013. The neuroinflammation marker translocator protein is not elevated in individuals with mild-to-moderate depression: a [C]PBR28 PET study. Brain Behav. Immun. 33, 131–138.

Hayes, S.M., Hayes, J.P., Cadden, M., Verfaellie, M., 2013. A review of cardiorespiratory fitness-related neuroplasticity in the aging brain. Front. Aging Neurosci. 5, 31.

Hiles, S.A., Baker, A.L., de Malmanche, T., Attia, J., 2012. A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: exploring the causes of heterogeneity. Brain Behav. Immun. 26, 1180–1188.

Hofer, S., Eisenbach, C., Lukic, I.K., Schneider, L., Bode, K., Brueckmann, M., Mautner, S., Wente, M.N., Encke, J., Werner, J., Dalpke, A.H., Stremmel, W., Nawroth, P.P., Martin, E., Krammer, P.H., Bierhaus, A., Weigand, M.A., 2008. Pharmacologic cholinesterase inhibition improves survival in experimental sepsis. Crit. Care Med. 36, 404–408.

Hofmann, S.G., Sawyer, A.T., Witt, A.A., Oh, D., 2010. The effect of mindfulness-based therapy on anxiety and depression: a meta-analytic review. J. Consult. Clin. Psychol. 78, 169–183.

Hotting, K., Roder, B., 2013. Beneficial effects of physical exercise on neuroplasticity and cognition. Neurosci. Biobehav. Rev. http://dx.doi.org/10.1016/j.neubiorev.2013.04.005 [Epub ahead of print].

Irwin, M.R., Olmstead, R., 2012. Mitigating cellular inflammation in older adults: a randomized controlled trial of tai chi chih. Am. J. Geriatr. Psychiatry 20, 764–772.

Kawanishi, N., Yano, H., Yokogawa, Y., Suzuki, K., 2010. Exercise training inhibits inflammation in adipose tissue via both suppression of macrophage infiltration and acceleration of phenotypic switching from M1 to M2 macrophages in high-fat-diet-induced obese mice. Exerc. Immunol. Rev. 16, 105–118.

Kohut, M.L., McCann, D.A., Russell, D.W., Konopka, D.N., Cunnick, J.E., Franke, W.D., Castillo, M.C., Reighard, A.E., Vanderah, E., 2006. Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of beta-blockers, BMI, and psychosocial factors in older adults. Brain Behav. Immun. 20, 201–209.

Koyama, A., O'Brien, J., Weuve, J., Blacker, D., Metti, A.L., Yaffe, K., 2013. The role of peripheral inflammatory markers in dementia and Alzheimer's disease: a meta-analysis. J. Gerontol. A Biol. Sci. Med. Sci. 68, 433–440.

Kramer, A.F., Hahn, S., Cohen, N.J., Banich, M.T., McAuley, E., Harrison, C.R., Chason, J., Vakil, E., Bardell, L., Boileau, R.A., Colcombe, A., 1999. Ageing, fitness and neurocognitive function. Nature 400, 418–419.

Kreisl, W.C., Lyoo, C.H., McGwier, M., Snow, J., Jenko, K.J., Kimura, N., Corona, W., Morse, C.L., Zoghbi, S.S., Pike, V.W., McMahon, F.J., Turner, R.S., Innis, R.B., Biomarkers Consortium P.E.T.R.P.T., 2013. In vivo radioligand binding to translocator protein correlates with severity of Alzheimer's disease. Brain 136, 2228–2238.

Krogh, J., Saltin, B., Gluud, C., Nordentoft, M., 2009. The DEMO trial: a randomized, parallel-group, observer-blinded clinical trial of strength versus aerobic versus relaxation training for patients with mild to moderate depression. J. Clin. Psychiatry 70, 790–800.

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. J. Clin. Psychiatry 72, 529–538.

Krogh, J., Videbech, P., Thomsen, C., Gluud, C., Nordentoft, M., 2012. DEMO-II trial. Aerobic exercise versus stretching exercise in patients with major depression-a randomised clinical trial. PLoS One 7, e48316.

Krstic, D., Knuesel, I., 2013. Deciphering the mechanism underlying late-onset Alzheimer disease. Nat. Rev. Neurol. 9, 25–34.

Lavretsky, H., Alstein, L.L., Olmstead, R.E., Ercoli, L.M., Riparetti-Brown, M., Cyr, N.S., Irwin, M.R., 2011. Complementary use of tai chi chih augments escitalopram treatment of geriatric depression: a randomized controlled trial. Am. J. Geriatr. Psychiatry 19, 839–850.

Leonard, B., Maes, M., 2012. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. Neurosci. Biobehav. Rev. 36, 764–785.

Leung, R., Proitsi, P., Simmons, A., Lunnon, K., Guntert, A., Kronenberg, D., Pritchard, M., Tsolaki, M., Mecocci, P., Kloszewska, I., Vellas, B., Soininen, H., Wahlund, L.O., Lovestone, S., 2013. Inflammatory proteins in plasma are associated with severity of Alzheimer's disease. PLoS One 8, e64971.

Li, J., Ramenaden, E.R., Peng, J., Koito, H., Volpe, J.J., Rosenberg, P.A., 2008. Tumor necrosis factor alpha mediates lipopolysaccharide-induced microglial toxicity to developing oligodendrocytes when astrocytes are present. J. Neurosci. 28, 5321–5330.

Lin, F., Friedman, E., Quinn, J., Chen, D.-G., Mapstone, M., 2012. Effect of leisure activities on inflammation and cognitive function in an aging sample. Arch. Gerontol. Geriat. 54 (3), e398–e404.

Liu-Ambrose, T., Nagamatsu, L.S., Graf, P., Beattie, B.L., Ashe, M.C., Handy, T.C., 2010. Resistance training and executive functions: a 12-month randomized controlled trial. Arch. Intern. Med. 170, 170–178.

Liu-Ambrose, T., Nagamatsu, L.S., Voss, M.W., Khan, K.M., Handy, T.C., 2012. Resistance training and functional plasticity of the aging brain: a 12-month randomized controlled trial. Neurobiol. Aging 33, 1690–1698.

Luders, E., Kurth, F., Toga, A.W., Narr, K.L., Gaser, C., 2013. Meditation effects within the hippocampal complex revealed by voxel-based morphometry and cytoarchitectonic probabilistic mapping. Front. Psychol. 4, 398.

Lujan, H.L., DiCarlo, S.E., 2013. Physical activity, by enhancing parasympathetic tone and activating the cholinergic anti-inflammatory pathway, is a therapeutic strategy to restrain chronic inflammation and prevent many chronic diseases. Med. Hypotheses 80, 548–552.

Ma, X.M., Blenis, J., 2009. Molecular mechanisms of mTOR-mediated translational control. Nat. Rev. Mol. Cell. Biol. 10, 307–318.

McAfoose, J., Baune, B.T., 2009. Evidence for a cytokine model of cognitive function. Neurosci. Biobehav. Rev. 33, 355–366.

Miller, A.H., Maletic, V., Raison, C.L., 2009. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol. Psychiatry 65, 732–741.

Mills, N.T., Scott, J.G., Wray, N.R., Cohen-Woods, S., Baune, B.T., 2013. The role of cytokines in depression in adolescents: a systematic review. J. Child Psychol. Psychiatry 54, 816–835.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6, e1000097.

Moller, A.B., Vendelbo, M.H., Rahbek, S.K., Clasen, B.F., Schjerling, P., Vissing, K., Jessen, N., 2013. Resistance exercise, but not endurance exercise, induces IKKbeta phosphorylation in human skeletal muscle of training-accustomed individuals. Pflugers Arch. 465, 1785–1795.

Moylan, S., Maes, M., Wray, N.R., Berk, M., 2012. The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. Mol. Psychiatry 18, 595–606.

Nagamatsu, L.S., Handy, T.C., Hsu, C.L., Voss, M., Liu-Ambrose, T., 2012. Resistance training promotes cognitive and functional brain plasticity in seniors with probable mild cognitive impairment. Arch. Intern. Med. 172, 666–668.

Nagamatsu, L.S., Chan, A., Davis, J.C., Beattie, B.L., Graf, P., Voss, M.W., Sharma, D., Liu-Ambrose, T., 2013. Physical activity improves verbal and spatial memory in older adults with probable mild cognitive impairment: a 6-month randomized controlled trial. J. Aging Res. 2013, 861893.

Nilsson, K., Gustafson, L., Hultberg, B., 2011. C-reactive protein level is decreased in patients with Alzheimer's disease and related to cognitive function and survival time. Clin. Biochem. 44, 1205–1208.

Oh, B., Butow, P., Mullan, B., Clarke, S., Beale, P., Pavlakis, N., Lee, M., Rosenthal, D., Larkey, L., Vardy, J., 2012. Effect of medical Qigong on cognitive function, quality of life, and a biomarker of inflammation in cancer patients: a randomized controlled trial. Support. Care Cancer 20, 1235–1242.

Oh, B., Choi, S.M., Inamori, A., Rosenthal, D., Yeung, A., 2013. Effects of qigong on depression: a systemic review. Evid. Based Complement. Altern. Med. 2013, 134737.

Park, S.E., Dantzer, R., Kelley, K.W., McCusker, R.H., 2011. Central administration of insulin-like growth factor-I decreases depressive-like behavior and brain cytokine expression in mice. J. Neuroinflamm. 8, 12.

Paul, N.A., Stanton, S.J., Greeson, J.M., Smoski, M.J., Wang, L., 2013. Psychological and neural mechanisms of trait mindfulness in reducing depression vulnerability. Soc. Cogn. Affect. Neurosci. 8, 56–64.

Pavlov, V.A., Parrish, W.R., Rosas-Ballina, M., Ochani, M., Puerta, M., Ochani, K., Chavan, S., Al-Abed, Y., Tracey, K.J., 2009. Brain acetylcholinesterase activity controls systemic cytokine levels through the cholinergic anti-inflammatory pathway. Brain Behav. Immun. 23, 41–45.

Pedersen, M., Pedersen, K.K., Bruunsgaard, H., Krabbe, K.S., Thomsen, C., Færch, K., Pedersen, B.K., Mortensen, E.L., 2012. Cognitive functions in middle aged individuals are related to metabolic disturbances and aerobic capacity: a cross-sectional study. PLoS One 7.

Penninx, B.W., Rejeski, W.J., Pandya, J., Miller, M.E., Di Bari, M., Applegate, W.B., Pahor, M., 2002. Exercise and depressive symptoms: a comparison of aerobic and resistance exercise effects on emotional and physical function in older persons with high and low depressive symptomatology. J. Gerontol. B Psychol. Sci. Soc. Sci. 57, P124–P132.

Pereira, D.S., de Queiroz, B.Z., Miranda, A.S., Rocha, N.P., Felicio, D.C., Mateo, E.C., Favero, M., Coelho, F.M., Jesus-Moraleida, F., Gomes Pereira, D.A., Teixeira, A.L., Maximo Pereira, L.S., 2013. Effects of physical exercise on plasma levels of brain-derived neurotrophic factor and depressive symptoms in elderly women-a randomized clinical trial. Arch. Phys. Med. Rehabil. 94, 1443–1450.

Pickering, M., Cumiskey, D., O'Connor, J.J., 2005. Actions of TNF-alpha on glutamatergic synaptic transmission in the central nervous system. Exp. Physiol. 90, 663–670.

Pitkala, K.H., Poysti, M.M., Laakkonen, M.L., Tilvis, R.S., Savikko, N., Kautiainen, H., Strandberg, T.E., 2013. Effects of the Finnish Alzheimer disease exercise trial (FINALEX): a randomized controlled trial. JAMA Int. Med. 173, 894–901.

Rahman, A., Ting, K., Cullen, K.M., Braidy, N., Brew, B.J., Guillemin, G.J., 2009. The excitotoxin quinolinic acid induces tau phosphorylation in human neurons. PLoS One 4, e6344.

Ravindran, A.V., da Silva, T.L., 2013. Complementary and alternative therapies as add-on to pharmacotherapy for mood and anxiety disorders: a systematic review. J. Affect. Disord. 150, 707–719.

Reale, M., Iarlori, C., Gambi, F., Feliciani, C., Salone, A., Toma, L., DeLuca, G., Salvatore, M., Conti, P., Gambi, D., 2004. Treatment with an acetylcholinesterase inhibitor in Alzheimer patients modulates the expression and production of the pro-inflammatory and anti-inflammatory cytokines. J. Neuroimmunol. 148, 162–171.

Rethorst, C.D., Trivedi, M.H., 2013. Evidence-based recommendations for the prescription of exercise for major depressive disorder. J. Psychiatr. Pract. 19, 204–212.

Rethorst, C.D., Moynihan, J., Lyness, J.M., Heffner, K.L., Chapman, B.P., 2011. Moderating effects of moderate-intensity physical activity in the relationship between depressive symptoms and interleukin-6 in primary care patients. Psychosom. Med. 73, 265–269.

Rethorst, C.D., Toups, M.S., Greer, T.L., Nakonezny, P.A., Carmody, T.J., Grannemann, B.D., Huebinger, R.M., Barber, R.C., Trivedi, M.H., 2012. Pro-inflammatory cytokines as predictors of antidepressant effects of exercise in major depressive disorder. Mol. Psychiatry 18, 1119–1124.

Rimer, J., Dwan, K., Lawlor, D.A., Greig, C.A., McMurdo, M., Morley, W., Mead, G.E., 2012. Exercise for depression. Cochrane Database Syst. Rev. 7 (CD004366).

Rizzo, A.M., Corsetto, P.A., Montorfano, G., Opizzi, A., Faliva, M., Giacosa, A., Ricevuti, G., Pelucchi, C., Berra, B., Rondanelli, M., 2012. Comparison between the AA/EPA ratio in depressed and non depressed elderly females: omega-3 fatty acid supplementation correlates with improved symptoms but does not change immunological parameters. Nutr. J. 11, 82.

Rohleder, N., Miller, G.E., 2008. Acute deviations from long-term trait depressive symptoms predict systemic inflammatory activity. Brain Behav. Immun. 22, 709–716.

Roig, M., Nordbrandt, S., Geertsen, S.S., Nielsen, J.B., 2013. The effects of cardiovascular exercise on human memory: a review with meta-analysis. Neurosci. Biobehav. Rev. 37, 1645–1666.

Roque, F.R., Hernanz, R., Salaices, M., Briones, A.M., 2013. Exercise training and cardiometabolic diseases: focus on the vascular system. Curr. Hypertens. Rep. 15, 204–214.

Ruscheweyh, R., Willemer, C., Kruger, K., Duning, T., Warnecke, T., Sommer, J., Volker, K., Ho, H.V., Mooren, F., Knecht, S., Floel, A., 2011. Physical activity and memory functions: an interventional study. Neurobiol. Aging 32, 1304–1319.

Salminen, A., Ojala, J., Kaarniranta, K., Haapasalo, A., Hiltunen, M., Soininen, H., 2011. Astrocytes in the aging brain express characteristics of senescence-associated secretory phenotype. Eur. J. Neurosci. 34, 3–11.

Schmidt, R., Schmidt, H., Curb, J.D., Masaki, K., White, L.R., Launer, L.J., 2002. Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia aging study. Ann. Neurol. 52, 168–174.

Schuch, F.B., de Almeida Fleck, M.P., 2013. Is exercise an efficacious treatment for depression? A comment upon recent negative findings. Front. Psychiatry/Front. Res. Found. 4, 20.

Starkie, R., Ostrowski, S.R., Jauffred, S., Febbraio, M., Pedersen, B.K., 2003. Exercise and IL-6 infusion inhibit endotoxin-induced TNF-alpha production in humans. FASEB J. 17, 884–886.

Steele, M.L., Robinson, S.R., 2012. Reactive astrocytes give neurons less support: implications for Alzheimer's disease. Neurobiol. Aging 33 (423), e413–e421.

Sundelof, J., Kilander, L., Helmersson, J., Larsson, A., Ronnemaa, E., Degerman-Gunnarsson, M., Basun, H., Lannfelt, L., Basu, S., 2009. Systemic inflammation and the risk of Alzheimer's disease and dementia: a prospective population-based study. J. Alzheimers Dis. 18, 79–87.

Swardfager, W., Lanctot, K., Rothenburg, L., Wong, A., Cappell, J., Herrmann, N., 2010. A meta-analysis of cytokines in Alzheimer's disease. Biol. Psychiatry 68, 930–941.

Swardfager, W., Herrmann, N., Marzolini, S., Saleem, M., Shammi, P., Oh, P.I., Albert, P.R., Daigle, M., Kiss, A., Lanctôt, K.L., 2011. Brain derived neurotrophic factor, cardiopulmonary fitness and cognition in patients with coronary artery disease. Brain Behav. Immun. 25, 1264–1271.

Tang, Y.Y., Lu, Q., Fan, M., Yang, Y., Posner, M.I., 2012. Mechanisms of white matter changes induced by meditation. Proc. Natl. Acad. Sci. USA 109, 10570–10574.

Tanzi, R.E., Bertram, L., 2005. Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective. Cell 120, 545–555.

Taylor, W.D., Aizenstein, H.J., Alexopoulos, G.S., 2013. The vascular depression hypothesis: mechanisms linking vascular disease with depression. Mol. Psychiatry 18, 963–974.

Tilleux, S., Hermans, E., 2007. Neuroinflammation and regulation of glial glutamate uptake in neurological disorders. J. Neurosci. Res. 85, 2059–2070.

Trivedi, M.H., Greer, T.L., Church, T.S., Carmody, T.J., Grannemann, B.D., Galper, D.I., Dunn, A.L., Earnest, C.P., Sunderajan, P., Henley, S.S., Blair, S.N., 2011. Exercise as an augmentation treatment for nonremitted major depressive disorder: a randomized, parallel dose comparison. J. Clin. Psychiatry 72, 677–684.

van Himbergen, T.M., Beiser, A.S., Ai, M., Seshadri, S., Otokozawa, S., Au, R., Thongtang, N., Wolf, P.A., Schaefer, E.J., 2012. Biomarkers for insulin resistance and inflammation and the risk for all-cause dementia and Alzheimer disease: results from the Framingham heart study. Arch. Neurol. 69, 594–600.

Voelcker-Rehage, C., Niemann, C., 2013. Structural and functional brain changes related to different types of physical activity across the life span. Neurosci. Biobehav. Rev. http://dx.doi.org/10.1016/j.neubiorev.2013.01.028 [Epub ahead of print].

Voelcker-Rehage, C., Godde, B., Staudinger, U.M., 2011. Cardiovascular and coordination training differentially improve cognitive performance and neural processing in older adults. Front. Hum. Neurosci. 5, 26.

Vogelzangs, N., Duivis, H.E., Beekman, A.T., Kluft, C., Neuteboom, J., Hoogendijk, W., Smit, J.H., de Jonge, P., Penninx, B.W., 2012. Association of depressive disorders, depression characteristics and antidepressant medication with inflammation. Transl. Psychiatry 2, e79.

Wang, C.W., Chan, C.L., Ho, R.T., Tsang, H.W., Chan, C.H., Ng, S.M., 2013. The effect of qigong on depressive and anxiety symptoms: a systematic review and meta-analysis of randomized controlled trials. Evid. Based Complement. Altern. Med. 2013, 716094.

Wei, G.X., Xu, T., Fan, F.M., Dong, H.M., Jiang, L.L., Li, H.J., Yang, Z., Luo, J., Zuo, X.N., 2013. Can taichi reshape the brain? A brain morphometry study. PLoS One 8, e61038.

Wyss-Coray, T., Rogers, J., 2012. Inflammation in Alzheimer disease – a brief review of the basic science and clinical literature. Cold Spring Harb. Perspect. Med. 2, a006346.

Yaffe, K., Kanaya, A., Lindquist, K., Simonsick, E.M., Harris, T., Shorr, R.I., Tylavsky, F.A., Newman, A.B., 2004. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA 292, 2237–2242.

Yirmiya, R., Goshen, I., 2011. Immune modulation of learning, memory, neural plasticity and neurogenesis. Brain Behav. Immun. 25, 181–213.