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Exploring the relationship between physical activity, beta-amyloid and tau: A narrative review

Belinda M. Brown[a,b,c,*], Jeremiah Peiffer[a,c], Stephanie R. Rainey-Smith[b,c,d]

[a] School of Psychology and Exercise Science, Murdoch University, Murdoch, Western Australia, Australia
[b] Australian Alzheimer's Research Foundation, Sarich Neuroscience Research Institute, Nedlands, Western Australia, Australia
[c] Ageing, Cognition and Exercise Research Group, School of Psychology and Exercise Science, Murdoch University, Murdoch, Western Australia, Australia
[d] School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia, Australia

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ABSTRACT

Several prospective cohort studies have reported an association between higher levels of physical activity and decreased risk of cognitive decline and dementia, years later. To support physical activity as a preventative measure against dementia, including Alzheimer's disease (AD; the most common form of dementia), evidence regarding the underlying mechanisms is vital. Here, we review previous work examining the role of physical activity in modulating levels of AD pathological hallmarks, beta-amyloid (Aβ) and tau (in the brain, cerebrospinal fluid and blood). Robust evidence from transgenic animal studies suggests that physical activity (voluntary wheel running) and exercise (forced wheel running) are implicated in lowering levels of brain Aβ and tau. Nevertheless, evidence from human studies, utilising measurements from positron emission tomography and cerebrospinal fluid biomarkers, is less consistent. Rigorous randomised controlled trials utilising long exercise interventions are vital to further understand the relationship between physical activity and Alzheimer's disease.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative condition, accounting for approximately 70% of dementia cases and is characterised by neuronal loss and cognitive decline. Beta-amyloid (Aβ) plaques and intracellular accumulation of neurofibrillary tangles, comprising hyperphosphorylated tau proteins, are the primary hallmarks of AD, and are proposed to contribute to decline in brain volume and function. Nevertheless, current therapies for the treatment of AD target the symptoms, rather than the underlying pathological processes, which are known to commence decades before the symptoms manifest (Mangialasche et al., 2010). Recent pharmaceutical advances have identified compounds associated with reduced production, enhanced clearance, and degradation of Aβ; however, to date, trials evaluating these compounds have not reached their primary endpoints (Graham et al., 2017). Thus, interest has grown in the investigation of alternative factors that may delay or prevent the onset of AD, or, more specifically, slow the accumulation of AD pathology before the onset of clinical symptoms. One such group of factors are components of lifestyle, including good sleep quality, optimum nutrition and high levels of physical activity or structured exercise.

Physical activity and exercise are both defined as body movement produced by skeletal muscle that results in energy expenditure. However, physical activity can include any type of movement, whereas exercise is a form of physical activity, including planned and structured activities, usually for the purpose of improving or maintaining physical fitness (Caspersen et al., 1985). Indeed, cardiorespiratory fitness is associated with the amount and intensity of physical activity or exercise (Joyner and Lundby, 2018) that an individual undertakes over a prolonged period (DeFina et al., 2015). In this review, we have attempted to distinguish between physical activity and planned exercise interventions, where relevant. Importantly, within animal models we have identified voluntary wheel running as a form of physical activity, and forced running as exercise.

Several prospective cohort studies have examined the relationship between physical activity levels and dementia risk: With consistent reports that higher levels of physical activity are associated with decreased risk of dementia years later (Buchman et al., 2012; Iso-Markku et al., 2015; Larson et al., 2006; Scarmeas et al., 2009; Wang et al., 2014). Numerous potentially protective mechanisms underlying the effect of physical activity on dementia risk have been proposed, including increases in brain-derived neurotrophic factor (BDNF),

* Corresponding author at: College of Science, Health, Engineering and Education, Murdoch University, 90 South Street, Murdoch, Western Australia 6150, Australia.
E-mail address: b.brown@murdoch.edu.au (B.M. Brown).

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Table 1
Summary of animal studies evaluating the effect of exercise on brain Aβ levels.

Author (Year)	Animal	Type of exercise	Age exercise commenced	Duration of exercise	Frequency of exercise	Observed effect of exercise on Aβ	Additional mechanistic effects of exercise
Adlard et al. (2005)	TgCRND8, mice	Voluntary wheel running	Short-term: 6 wks Long-term: 1 mo	Short-term: 1 mo Long-term: 5 mos	N/A*	Long-term exercise: Decreased Aβ plaques in frontal cortex and cortex at level of hippocampus. Decreased cortical $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$.	Short-term exercise: Mediates Aβ changes by altering APP processing (decreased αCTFs and βCTFs). No changes to neprilysin and IDE.
Alkadhi and Dao (2018)	Aβ infusion, rats	Treadmill exercise	7 wks	4 wks	Progressive, by fourth week: 15 min. d, 4 d/wk	Prevented increases in $A\beta_{1\text{-}42}$ levels in both CA1 and DG in Aβ rats.	Prevented increases in APP and BACE1.
Choi et al. (2014)	STZ, rats	Treadmill exercise	20 wks	6 wks	30 min. day, 5 d/wk	Decreased Aβ expression.	Decreased inflammatory response reflected by lower levels of TLR4, NF-kb, TNF-α and IL-1 α.
He et al. (2017)	C57BL/6 J and *Thy1-GFP* mice	Voluntary wheel running	14 mos	6 wks	N/A*	Aβ accumulation decreased. Decreased $A\beta_{1\text{-}16}$, $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ in the cortex and hippocampus.	Increased glymphatic clearance but not BBB permeation.
Kang and Cho (2014)	STZ, rats	Treadmill exercise	20 wks	6 wks	30 min. d, 5 d/wk	Decreased Aβ expression.	Activated AKT/GSK3α.
Koo (2017)	NSE/APPsw, mice	Treadmill exercise	12 mos	3 mos	Progressive, last 5 weeks: 60 min. d, 5 d/wk	Decreased Aβ plaques and $A\beta_{1\text{-}42}$ and $A\beta_{1\text{-}40}$ protein levels in the cortex.	Induced activation in SIRT1 which mediated ADAM10 increase. Elevated PGC-1α and reduced BACE1 and C99 levels.
Liu (2013)**	APP/PS1, mice	Treadmill exercise	3 mos	5 mos	30 min. d, 5 d/wk	Reduction in Aβ plaques and tau phosphorylation in the hippocampus.	Decrease in APP phosphorylation and PS1 expression. Signalling mechanism is likely GSK3, rather than CDK5.
Moore et al. (2016)	Tg2576, mice	Treadmill exercise: High intensity (32 m/min) Low intensity (15 m/min)	3 mos	3 mos	60 min. d, 5 d/wk	Dose-dependent decreases in $A\beta_{1\text{-}40}$ (cortex) and $A\beta_{1\text{-}42}$ (cortex and hippocampus).	Dose-dependent increases in neprilysin, IDE, MMP9, LRP1 and HSP70 (all involved in Aβ clearance).
Nichol et al. (2008)	Tg2576, mice	Voluntary wheel running	16 mos	3 wks	N/A*	Decreases in soluble $A\beta_{1\text{-}40}$. No changes in Aβ aggregates or soluble $A\beta_{1\text{-}42}$.	Reductions in TNF-α and IL-1β in the hippocampus.
Nigam et al. (2017)	APP/PS1, mice	Voluntary wheel running	7-9 mos	3 wks	N/A*	Reduced $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ protein levels in the hippocampus.	Increased levels of ADAM10 and sAPPα. Further *in vitro* work in this paper suggests BDNF mediates increases in sAPPα.
Ozbeyli et al. (2017)	Ovariectomy and D-galactose treated, rats	Aerobic (swimming), resistance or combined exercise	6-7 mos	6 wks	60 min. d, 3 d/w	Combined exercise decreased APP mRNA levels. Decreased Aβ in resistance and combined groups.	Increased IGF-1 levels.
Um et al. (2008)	NSE/APPsw, mice	Treadmill exercise	13 mos	16 wks	60 min. d, 5 d/wk	Decreased $A\beta_{1\text{-}42}$ peptides.	Inhibited apoptopic cascades, GLUT-1 and BDNF pathways.
Wolf et al. (2006)	APP-23, mice	Voluntary wheel running	10 wks	11 mos	N/A*	No difference in plaque load.	Down-regulation of neurotrophic factors.
Yu et al. (2013)	D-galactose, rats	Treadmill exercise	2 mos	8 weeks	Progressive, last 2 weeks: 60 min. d, 5 d/wk	Decreased $A\beta_{1\text{-}42}$ levels.	Upregulation of ADAM17 mRNA and downregulation of BACE1 mRNA.
Yuede et al. (2009)	Tg2576, mice	Voluntary or forced wheel running	5 mos	16 wks	60 min. d, 5 d/wk	Voluntary wheel running group had greatest reduction in Aβ plaque, followed by forced group. Soluble $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ did not differ across groups.	
Zhang et al. (2018)	APP/PS1, mice	Treadmill exercise	5 mos	5 mos	30 min. d, 6 d/wk	Reduced Aβ plaque burden (hippocampus and neocortex).	Reduced APP, BACE1 and PS1; amyloidogenic pathway was inhibited.
Zhao et al. (2015)	APP/PS1, mice	Treadmill exercise	Young: 3 mos Old: 12 mos	5 mos	30 min. d, 5 d/wk	Reduction in soluble Aβ levels (young mice) but not Aβ plaque deposition.	

* Frequency of exercise is not consistent in animals undertaking voluntary wheel running.

** Liu et al. examined changes in both Aβ and tau, thus findings are presented in both Tables 1 and 2. Abbreviations: Aβ, beta-amyloid; αCTF, α-C-terminal fragments; ADAM10/17, A disintegrase and metalloprotease domain 10/17; AKT, Ak strain transforming; APP, amyloid precursor protein; BACE1, β-site APP cleaving enzyme 1; BBB, blood-brain barrier; βCTF, β-C-terminal fragment; BDNF, brain-derived neurotrophic factor; CA1, *Cornu Ammonis* area 1; CDK5, Cyclin-dependent kinase 5; d, days; DG, Dentate gyrus; GLUT1, glucose transporter-1; GSK3, Glycogen synthase kinase 3; HSP70, Heat shock protein 70; IDE, insulin-degrading enzyme; IGF-1, Insulin-like growth factor; IL-1α, Interleukin-1α; IL-1β, Interleukin-1 beta; LRP1, Lipoprotein receptor-related protein 1; min, minutes; MMP9, Matrix metalloproteinase 9; mo, month; mRNA, messenger ribonucleic acid; NF-kb, Nuclear factor-kB; NSE, neuron-specific enolase; PGC1-α, Peroxisome proliferator-activated receptor-gamma coactivator-1alpha; PS1, Presenilin 1; SIRT1, sirtuin 1; STZ, Streptozotocin; Tg, Transgenic; TLR4, Toll-like receptor 4; TNF-α, Tumour necrosis factor α; wk, week.

reduction in cardiovascular disease and metabolic syndrome risk, and increased cerebral blood flow (Brown et al., 2013a). Importantly, modulation of the above factors through increases in physical activity is associated with a reduction in risk of a number of dementia types, with AD appearing to be the most responsive (Rovio et al., 2005). It is, therefore, reasonable to hypothesise that alterations in the processing and degradation of Aβ and tau are likely to be vital underlying mechanisms in the association between exercise and AD risk. Indeed, evidence is emerging that physical activity may directly influence proteomic changes that contribute to a delay in the accumulation of AD neuropathology and biomarkers (Burnham et al., 2016). Here, we provide a comprehensive narrative review of animal and human studies that have investigated the role of physical activity in modulating levels of Aβ and/or tau. The aim of this review is to identify the gaps within the literature and provide recommendations for future research.

2. Methods

A computer-based search of PubMed was conducted for all relevant articles published before June 12, 2018. The following search terms were used: (Physical activity OR exercise OR fitness) AND (Alzheimer's disease OR Dementia OR beta-amyloid OR amyloid OR tau). The search was limited to only publications in English.

For studies to be included in Tables 1–3, titles and abstracts were screened by the first-author (BMB) to ensure they met the following criteria: 1) Were conducted on animals or humans (i.e., no in vitro studies were reviewed), 2) Examined the relationship between physical activity/exercise/fitness and measures of Aβ or tau in the brain, cerebrospinal fluid (CSF) or blood, 3) Studies must have independently assessed physical activity/exercise/fitness (i.e., no combined studies with, e.g., cognitive training, diet etc. unless a physical activity only group was utilised). Articles were excluded if they: 1) Were a conference proceeding abstract, 2) A review or theoretical article, 3) Were non-peer reviewed, or a book chapter, or 4) Were a non-English language article. Additional relevant articles, including those undertaking mechanistic work, are referred to throughout this manuscript based on supplementary targeted searches.

3. Beta-amyloid and amyloid precursor protein processing

The amyloid cascade hypothesis is the primary theory underlying the initiation of pathology accumulation in AD (Hardy and Higgins, 1992). Aβ peptides aggregate to form extracellular amyloid plaques, contributing to neuronal death and decline in cognitive functions. The longer, and more fibrillar isoform of Aβ, $A\beta_{1\text{-}42}$, is the primary constituent of amyloid plaques (Masters and Beyreuther, 1995). *Post-mortem* assessment of AD brains has identified that amyloid plaques are first observed in the cingulate cortex, followed by the temporal and parietal cortices and the caudate. In the later stages of this neuropathological process, plaques are found in the occipital, sensory and motor brain regions (Thompson et al., 2007). Within studies of living humans, measurements of Aβ in the CSF and brain (via positron emission tomography; PET, with Aβ binding ligands) have proved sensitive and specific in identifying individuals with AD, and correlate highly with *post-mortem* quantified amyloid plaques (Ikonomovic et al., 2008). Using the biomarker modalities described above, research has demonstrated that brain Aβ begins accumulating up to two decades before the onset of clinical symptoms (Villemagne et al., 2013).

Aβ is produced from the amyloid precursor protein (APP), which is cleaved via one of two competing pathways: the non-amyloidogenic and amyloidogenic pathways (Verdile et al., 2004). APP is cleaved by β-site APP cleaving enzyme 1 (BACE1) and γ-secretase to produce the Aβ peptide ($A\beta_{1\text{-}40}$ or $A\beta_{1\text{-}42}$). BACE1 is considered a biomarker for the early detection of AD and is also a target for a number of therapeutic compounds (Yan and Vassar, 2014). Cleavage of APP by α-secretase (such as A Disintegrin and metalloproteinase domain-containing protein 10; ADAM10) contributes to the production of non-amyloidogenic fragments (soluble APPα; sAPPα), which are believed to be involved in the modulation of neurite growth and neuronal excitability (for an overview of APP processing enzymes and products see Chow et al., 2010).

Pertinent to the current review, various animal models of AD can be utilised to model disease course, and subsequently, gain a greater understanding of factors that may modify the pathological cascade usually observed in AD. Either transgenic or infusion models are typically used to ensure rapid accumulation of Aβ in the brain. Nevertheless, the length of time from birth/infusion until peak pathology accumulation can vary across models (Janus et al., 2000); and thus model type is an important consideration across the reviewed studies below.

3.1. The role of physical activity and exercise in modulating Aβ levels

3.1.1. Animal studies

In the current review, we identified studies that have examined the role of physical activity (i.e., voluntary wheel running) and exercise (i.e., forced wheel running) in modulating brain Aβ in AD animal models (Table 1; Fig. 1). The methodologies utilised across the seventeen studies reviewed here were diverse: numerous animal models were used, including a variety of transgenic and infusion models, and the age of the animals at intervention commencement varied (6 weeks to 16 months). Importantly, the length of the administered interventions also differed largely across studies, from 3 weeks through to 11 months. Unsurprisingly, given the protracted nature of brain Aβ deposition, studies that reported an effect of physical activity or exercise on brain Aβ plaque load were more likely to be those utilising a longer intervention (i.e. greater than 3 months; Adlard et al., 2005; Koo et al., 2017; Liu et al., 2013; Yuede et al., 2009; Zhang et al., 2018). Studies utilising relatively shorter interventions (i.e. < 3 months) did report an effect on Aβ; however, this was more frequently in the form of alterations to soluble Aβ (including $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$) protein levels and mRNA expression, both of which are subject to more acute fluctuations in levels (Alkadhi and Dao, 2018; Choi et al., 2014; He et al., 2017; Kang and Cho, 2014; Nichol et al., 2008; Ozbeyli et al., 2017; Um et al., 2008; Yu et al., 2013; Zhao et al., 2015). However, the relationship between intervention length and type of Aβ alteration was not consistent across all studies; for example, Zhao et al. (2015) administered five months of exercise to a group of younger (3 months) and older (12 months) mice, and observed a reduction in soluble Aβ levels in the young mice, yet no changes in soluble or brain plaque load in the older mice.

Despite the widely varying methodologies used across the reviewed studies, only one study reported no effect of exercise on brain Aβ protein levels or plaque load (Wolf et al., 2006). A reason for these discordant findings could be due to the use of a long intervention (11 months), and compared with other studies reviewed here, the animals were older at brain Aβ quantification (13 months). It is possible that exercise delays or reduces Aβ deposition, rather than entirely inhibiting it, and thus may reflect the importance of exercise being undertaken within a 'preclinical' period (i.e. before the onset of symptoms). Furthermore, Um et al (2008) quantified Aβ at ~17 months and observed an effect of exercise on reduced $A\beta_{1\text{-}42}$ deposition. What is considered 'preclinical' likely varies across animal models, and the particular transgenic models used by Um et al and Wolf et al must be considered. Wolf et al utilised the APP-23 mouse model, within which, brain Aβ deposition is usually observed by 6 months; Um et al however, utilised the NSE/APPsw mouse model, in which brain Aβ deposition is usually apparent by approximately 12 months (Janus et al., 2000). It is possible that AD pathology was too advanced within the mouse model utilised by Wolf et al, for an environmental factor, such as exercise, to influence disease course. To understand the relationship between exercise and Aβ in early to late stage disease, a meta-analysis modelling the effect of exercise across the disease course in varying disease models should be

Table 2
Summary of animal studies evaluating the effect of exercise on brain tau levels.

Author (Year)	Animal	Type of exercise	Age exercise commenced	Duration of exercise	Frequency of exercise	Observed effect of exercise on tau	Additional mechanistic effects of exercise
Belarbi et al. (2011)	THY-Tau22, mice	Voluntary wheel running	3 mos	9 mos	N/A*	Reduced hippocampal tau pathology. No changes in phosphorylated tau levels.	Upregulation of NPC1 and NPC2 (involved in degradation of pathological tau species).
Elahi et al. (2016)	Tg601, mice	Treadmill exercise	19 mos	3 wks	30 min. d, 5 d/wk	Increased levels of insoluble tau. Increased phosphorylation of tau at C-terminus.	
Gratuze et al. (2017)	hTau + high fat diet, mice	Voluntary wheel running	6 mos	2 mos	N/A*	Reduced tau phosphorylation.	No effect on tau kinase activation or expression, nor tau phosphatases.
Jeong and Kang (2018)	High fat diet, rats	Treadmill exercise	6 mos	2 mos	30 min. d, 5 d/wk	Reduced hyperphosphorylation and aggregation of tau.	
Kang and Cho (2015)	Tg-NSE/*htau23*, mice	Treadmill exercise	18 mos	3 mos	20 min. d, 5 d/wk	Reduced hyperphosphorylation and aggregation of tau.	Abnormal mTOR phosphorylation (known to be involved in hyperphosphorylation of tau) was improved.
Leem et al. (2009)	Tg-NSE/*htau23*, mice	Treadmill exercise: Intermediate and high-intensity groups	16 mos	3 mos	60 min. d, 5 d/wk	Decreased phosphorylated tau.	
Liu et al. (2013)**	APP/PS1, mice	Treadmill exercise	3 mos	5 mos	30 min. d, 5 d/wk	Reduced tau phosphorylation in the hippocampus.	Decrease in APP phosphorylation and PS1 expression. Signalling mechanism is likely GSK3, rather than CDK5.
Ohia-Nwoko (2014)	P301S tau, mice	Treadmill exercise	7 mos	3 mos	40 min. d, 5 d/wk	Reduced full length and hyperphosphorylated tau in the spinal cord and hippocampus.	

* Frequency of exercise is not consistent in animals undertaking voluntary wheel running.

** Liu et al. examined changes in both Aβ and tau, thus findings are presented in both Tables 1 and 2. Abbreviations: APP, Amyloid precursor protein; CDK5, Cyclin-dependent kinase 5; d, days; GSK3, Glycogen synthase kinase 3; hTau, human tau; min, minutes; mo, month; mTOR, mechanistic target of rapamycin; NPC1, Niemann-Pick type C disease 1; NPC2, Niemann-Pick type C disease 2; NSE, neuron-specific enolase; PS1, Presenilin 1; Tg, Transgenic; wk, week.

Table 3
Human studies evaluating the relationship between physical activity/exercise and brain, cerebrospinal fluid and plasma levels of Aβ and tau.

Author (Year)	Cohort details	Cohort age (years) (mean ± SD)	PA/Exercise	Aβ/tau level measured	Relationship/effect observed
Baker (2010)	Glucose intolerant (n = 28)	Intervention: 71.0 ± 7.5 Control: 66.0 ± 6.0	Intervention: 6 mos of aerobic exercise	Plasma Aβ	Trend level decease in plasma $Aβ_{1-42}$ in aerobic group. No changes in plasma $Aβ_{1-40}$.
Baker et al. (2012)	Cognitively normal (n = 18) and MCI (n = 23)	High PA: 68.3 ± 7.2 Low PA: 68.9 ± 7.9	High intensity self-reported PA (hi-PA)	CSF Aβ and tau	Increased hi-PA in cognitively normal predicted lower CSF tau.
Brown et al. (2013b)	Cognitively normal (n = 546 for plasma Aβ; n = 116 for PET)	69.6 ± 6.8	Self-reported PA	PET Aβ and plasma $Aβ_{1-40}$ and $Aβ_{1-42}$	Lower levels of brain Aβ in highest tertile of PA (*APOE* ε4 carriers only). Lower levels of plasma $Aβ_{1-42/1-40}$ in highest tertile of PA (non-carriers of *APOE* ε4 only).
Brown et al. (2017)	Presymptomatic ADAD mutation carriers (n = 139)	High PA: 33.7 ± 9.3 Low PA: 38.6 ± 9.4	Self-reported exercise	CSF Aβ and tau, and PET Aβ	No relationship between exercise and CSF Aβ, tau and brain Aβ burden. In accumulators of Aβ only, an association between Aβ burden and exercise was observed.
Brown (2018)	Cognitively normal (n = 43)	High PA: 76.9 ± 7.6 Low PA: 74.9 ± 6.2	Self-reported PA	PET tau	Lower levels of brain tau were observed in higher PA group.
de Souto Barreto (2015)	Cognitively normal (n = 128) and MCI (n = 140)	74.7 ± 4.2	Self-reported PA	PET Aβ	No association between PA and Aβ levels.
Head (2012)	Cognitively normal (n = 201)	*APOE* ε4+: 65 ± 10.0 *APOE* ε4-: 68 ± 10.0	Self-reported PA	PET Aβ	Sedentary *APOE* ε4 carriers had highest levels of brain Aβ.
Law (2018)	Cognitively normal (n = 85)	64.3 ± 5.4	Actigraphy-quantified PA	CSF Aβ and tau	Time spent in moderate PA was associated with higher $Aβ_{1-42}$, lower total tau/$Aβ_{1-42}$ and lower phosphorylated tau/$Aβ_{1-42}$. Time spent in light and vigorous PA was not associated with any markers.
Liang (2010)	Cognitively normal (n = 69)	70 ± 10.0	Self-reported PA	PET Aβ and CSF Aβ and tau	Brain Aβ was higher in non-exercisers. CSF tau and phosphorylated tau were lower in exercisers, but association was not significant after controlling for covariates.
Okonkwo (2014)	Cognitively normal (n = 186)	High PA: 60.1 ± 6.1 Low PA: 59.4 ± 6.9	Self-reported PA	PET Aβ	Age x physical activity interaction was observed for brain Aβ burden: those who were physically active experience attenuated Aβ increases with age.
Steen Jensen et al. (2016)	Alzheimer's disease (n = 53)	Intervention: 68.1 ± 6.8 Control: 69.2 ± 3.9	Intervention: 16 wks of moderate-high intensity PA	CSF Aβ and tau	No effect of exercise intervention on CSF levels of Aβ and tau.
Stillman et al. (2017)	Cognitively normal (n = 149)	79.5 ± 3.1	Self-reported PA	Plasma Aβ	Higher PA at baseline predicted lower levels of plasma $Aβ_{1-42}$ 9-13 years later.

Abbreviations: Aβ, beta-amyloid; ADAD, autosomal dominantly inherited Alzheimer's disease; *APOE,* apolipoprotein E; *APOE* ε4+, carriers of the apolipoprotein E ε4 allele; *APOE* ε4-, non-carriers of the apolipoprotein E ε4 allele CSF, cerebrospinal fluid; MCI, mild cognitive impairment; mo, month; PA, physical activity; PET, positron emission tomography; wk, week.

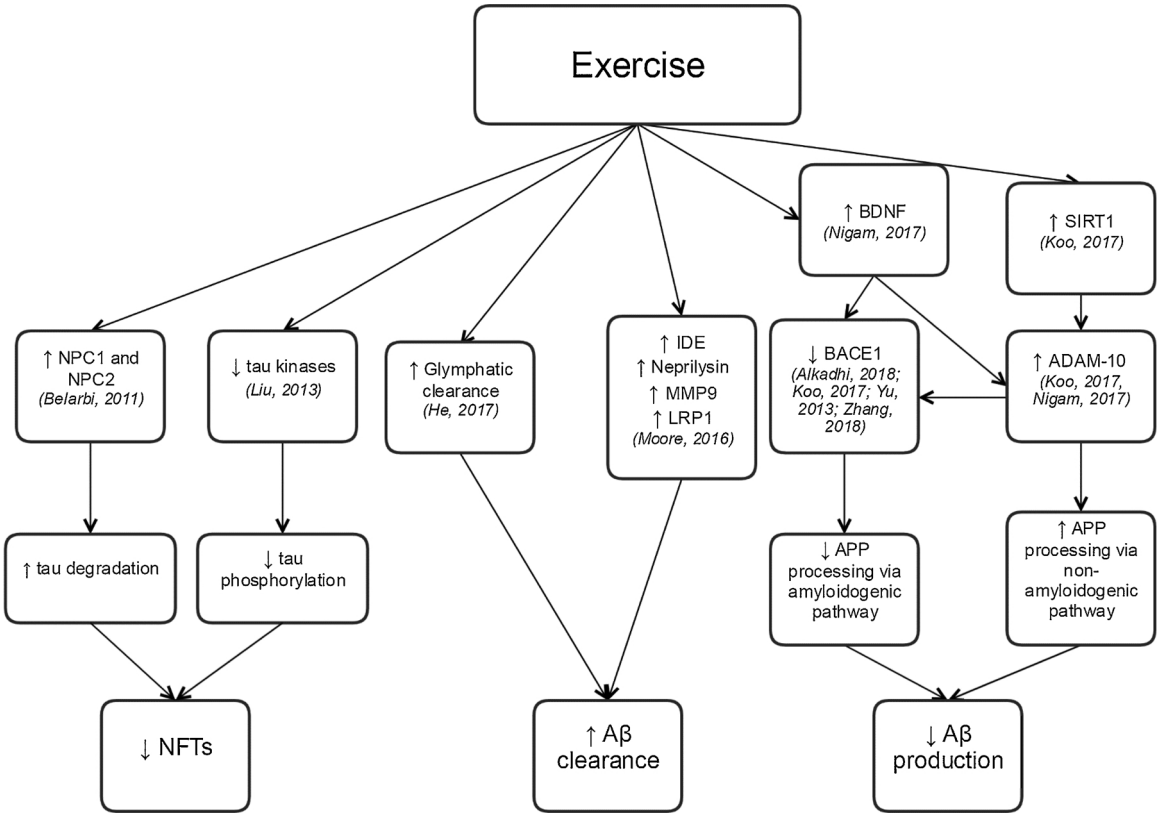

Fig. 1. Events that may underlie the effect of exercise on brain Aβ and tau, based on reviewed literature. Abbreviations: Aβ, beta-amyloid; ADAM-10, A disintegrin and metalloproteinase domain-containing protein 10; APP, amyloid precursor protein; BACE1, β-site APP cleaving enzyme; BDNF, brain-derived neurotrophic factor; IDE, Insulin-degrading enzyme; LRP1, Lipoprotein receptor-related protein 1; MMP9, Matrix metalloproteinase 9; NFTs, neurofibrillary tangles; NPC1, Niemann-Pick type C disease 1; NPC2, Niemann-Pick type C disease 2; SIRT1, Sirtuin 1.

conducted.

Whether increased Aβ production or decreased Aβ clearance, or both, is the primary contributor to the development of AD is still under debate (Selkoe and Hardy, 2016). Evidence from animal studies suggests that exercise may contribute to both the inhibition of Aβ production and enhancement of Aβ clearance in the brain. Indeed, alterations in APP cleavage enzymes and fragments have been observed in exercising transgenic mice (Adlard et al., 2005; Alkadhi and Dao, 2018; Koo et al., 2017; Liu et al., 2013; Zhang et al., 2018). Reduced levels of BACE1 (Alkadhi and Dao, 2018; Koo et al., 2017; Yu et al., 2013; Zhang et al., 2018) and increased ADAM-10 (Koo et al., 2017) have been observed following exercise, suggesting a respective decrease in APP processing via the amyloidogenic pathway and increase in APP processing via the non-amyloidogenic pathway. It has been proposed that both brain-derived neurotrophic factor (BDNF) and sirtuin 1 are mechanisms modulating levels of BACE-1 and ADAM-10, respectively (Koo et al., 2017; Nigam et al., 2017); both BDNF and sirtuin 1 have been shown to be increased following exercise in animal models (Ferrara et al., 2008; Wrann et al., 2013).

In addition to reducing Aβ production, there is evidence that physical activity enhances Aβ degradation/clearance (He et al., 2017; Moore et al., 2016b). Most recently, six weeks of voluntary wheel running was found to be associated with Aβ clearance in the brain by accelerating interstitial fluid (ISF) drainage (He et al., 2017). The influence of physical activity on the glymphatic system mirrors a proposed mechanism by which good quality sleep is associated with Aβ reduction (Xie et al., 2013), highlighting the idea that lifestyle factors may have common underpinning mechanisms and should be investigated in parallel. Other studies have investigated the role of exercise in Aβ degradation: Moore et al (2016a) demonstrated an intensity dose-dependent increase in the Aβ proteases insulin-degrading enzyme (IDE), matrix metallopeptidase 9 (MMP-9), neprilysin, and low density lipoprotein receptor-related protein 1 (LRP1), indicating that high-intensity exercise may be more effective than low-intensity exercise in enhancing Aβ degradation. Nevertheless, these results are not supported by Adlard et al. (2005) who reported reduced Aβ in the brains of mice following 5 months of voluntary wheel running, independent of changes to IDE and neprilysin. The difference between voluntary and forced wheel running may explain these disparate findings, as it is unlikely that the intensity of each intervention was similar; thus, differences in the degradation of Aβ, through the induction of Aβ proteases would be expected. Future research into the effect of exercise, and more specifically exercise intensity, on Aβ degradation/clearance is required.

In addition to the Adlard et al (2005) and Moore et al (2016a) studies detailed above, the current review includes numerous studies that utilised voluntary wheel running (Adlard et al., 2005; He et al., 2017; Nichol et al., 2008; Yuede et al., 2009) and forced exercise (Alkadhi and Dao, 2018; Choi et al., 2014; Koo et al., 2017; Moore et al., 2016a; Zhang et al., 2018). One study compared the effects of *both* forced and voluntary wheel running on brain Aβ levels and reported animals undertaking voluntary wheel running had significantly reduced Aβ plaque burden, compared with animals that had undergone forced exercise (Yuede et al., 2009). However, both groups had less plaque burden than a control (i.e., brain Aβ reductions: voluntary wheel running > forced wheel running > control). Stress is likely to mitigate the relationship between physical activity/exercise and Aβ, and, importantly, forced exercise is associated with increasing levels of hypothalamic corticotropin-releasing factor (a hormone involved in the stress response; Yanagita et al., 2007). Interestingly, mental stress associated with continuous running without being able to stop was a greater contributor to stress in animal models than the initial foot shock

used to induce running (Yuede et al., 2009). Based on this study alone, it would appear that exercise (i.e., forced wheel running) is not as potent at reducing Aβ as physical activity (i.e., voluntary wheel running). Paradoxically; however, the ability to deliver high-intensity exercise (for example in Moore et al (2016)) within an animal model may only be possible when forced.

3.1.2. Human cohorts

When compared with animal studies, human studies provide less compelling evidence of an effect of physical activity or exercise in modulating Aβ levels (Table 3; Fig. 1). Given the inability to *directly* quantify brain Aβ plaques in human cohorts (i.e. this can only be achieved *post-mortem*), the use of gold-standard measurements, such as PET imaging with Aβ binding ligands and CSF Aβ, provide the strongest opportunities to evaluate the relationship between exercise and brain Aβ levels *ante-mortem*. Studies utilising Aβ PET scanning in cognitively normal older adults have shown higher levels of self-reported physical activity are associated with lower levels of Aβ (Brown et al., 2013b; Head et al., 2012; Liang et al., 2010; Okonkwo et al., 2014). Nevertheless, the largest study to date (n = 268) examining the relationship between physical activity and PET-quantified Aβ in humans reported no association between self-reported physical activity and brain Aβ (de Souto Barreto et al., 2015). It is important to note however, that de Souto Barreto et al. (2015) utilised a cohort comprising both individuals with subjective memory complaints (SMC) and mild cognitive impairment (MCI): It is possible the combination of two different clinical groups may have contributed to their negative findings. Indeed, Aβ PET imaging data derived from the Australian Imaging, Biomarkers and Lifestyle Study of Ageing suggests individuals with SMC have significantly lower brain Aβ burden (mean neocortical Pittsburgh Compound B SUVR: 1.5), compared with those with MCI (mean neocortical Pittsburgh Compound B SUVR: 1.96; Rowe et al., 2010). It is also possible that the presence of objective memory impairment (i.e., MCI) may decrease the accuracy of self-reported physical activity, further confounding the findings. Thus, by studying individuals likely to be further along the AD trajectory (i.e. individuals with AD pathology and reaching MCI diagnostic criteria), it may be more difficult to discern a relationship between physical activity and brain Aβ. Indeed, as hypothesised above in the review of animal literature, an effect of exercise on Aβ levels may become more unlikely later in the disease course.

Given the small detectable changes in PET-quantified brain Aβ over short periods (Villemagne et al., 2013), measurements of soluble forms of Aβ in CSF fractions may provide a more dynamic indication of the relationship between physical activity and Aβ in human populations. Nevertheless, observational studies in cognitively normal cohorts have reported conflicting results. Utilising actigraphy, an inverse relationship has been observed between time spent in moderate physical activity and higher CSF Aβ (reflection of lower brain Aβ load; Law et al., 2018), while other studies utilising self-reported physical activity data describe no association between physical activity and CSF Aβ (Baker et al., 2012; Brown et al., 2017). Nevertheless, these studies were conducted on relatively small sample sizes, and thus, larger observational studies with CSF Aβ measurements should consider conducting similar analyses. The only exercise intervention in AD individuals (to the Authors' knowledge) also reported no effect of exercise on CSF levels of Aβ (Steen Jensen et al., 2016). It is plausible however, that levels of CSF Aβ in this clinical population were too low for exercise to induce a detectable change, as by the time a diagnosis of AD has been reached, the majority of Aβ has been sequestered into plaques within the brain (Jack et al., 2013). These fluctuations are also influenced by *APOE* genotype (presence or absence of the *APOE* ε4 allele; Ju et al., 2016); thereby representing another factor which requires consideration when interpreting the relationship between exercise and isoforms of Aβ in CSF.

ELISA-measured plasma Aβ has also been evaluated in relation to physical activity and exercise, with higher baseline levels of physical activity associated with lower levels of plasma $A\beta_{1\text{-}42,}$ measured 9–13 years later (Stillman et al., 2017), and a decreased trend in plasma $A\beta_{1\text{-}42}$ observed following a six month aerobic intervention (Baker et al., 2010). It is important to note however, that the authors acknowledge that the plasma Aβ measurements within the outlined studies had high levels of variability: this issue may potentially be attenuated in the future through the utilisation of high-performance blood-based Aβ assays (validated against PET measures of Aβ) using mass spectrometry (Nakamura et al., 2018).

The Apolipoprotein E (*APOE*) ε4 allele is the strongest known genetic risk factor for sporadic onset AD (Corder et al., 1993): Carriage of the *APOE* ε4 allele is associated with higher rates of Aβ aggregation, reduced clearance of Aβ from the brain, increased rate of cognitive decline and neuronal vulnerability (Mahley et al., 2006; Villemagne et al., 2013). Based on this, the examination of *APOE* ε4 as a moderating factor between lifestyle factors, such as physical activity, and Alzheimer's disease risk is of great interest. Indeed, in the investigation of AD pathological hallmarks, two studies reported the relationship between habitual levels of physical activity and brain Aβ to exist only in carriers of the *APOE* ε4 allele, suggesting higher levels of physical activity (as determined by greater weekly MET min^{-1}) may be associated with mitigating the increased risk of Aβ deposition conferred by *APOE* ε4 carriage (Brown et al., 2013b; Head et al., 2012). Furthermore, an *APOE* genotype-dependent relationship between plasma $A\beta_{1\text{–}42/1\text{–}40}$ and physical activity levels was observed; whereby physically active non-carriers of the *APOE* ε4 allele had significantly lower plasma $A\beta_{1\text{–}42/1\text{–}40}$, than their inactive counterparts (Brown et al., 2013b). These studies bring into focus the need for consideration of *APOE* genotype as a moderating factor in future exercise intervention trials: Such studies will be vital in determining the optimum levels of activity needed for each genotype to attain the greatest benefit.

Clearly, the field of exercise and Aβ in human cohorts requires rigorous evaluation in large exercise intervention trials with longitudinal follow-up. Cohort inclusion criteria and demographics (e.g. age, *APOE* genotype, disease stage, etc.) will also be a vital consideration when examining the role of exercise in modulating Aβ. As demonstrated in the animal studies reviewed here, it is possible that exercise will only be effective in reducing Aβ deposition within an early preclinical period. Thus, individuals already experiencing pronounced decline in cognitive function (i.e. individuals with MCI, or early AD) may be too advanced in the disease course for exercise to alter Aβ levels. We are not however suggesting that exercise is unimportant in individuals with objective cognitive impairment; evidence suggests that exercise is associated with alterations in neurotrophic factors and neurotransmitters, and this is likely to mediate enhancement in cognition following exercise even in individuals with MCI and AD. Furthermore, exercise is effective at reducing falls risk and improving mood, which both have the potential to enhance quality of life and reduce carer burden.

4. Tau

Tau is a microtubule-associated protein which is important for maintaining the functional and structural integrity of neurons. Tau proteins are biologically important for axonal transport and microtubule polymerisation (Buee et al., 2000). Intracellular aggregation of either hyperphosphorylated or abnormally phosphorylated tau forms tau pathology, which is identified in a number of neurodegenerative conditions, including AD (Benzing et al., 1993). In AD, intracellular neurofibrillary tangles, comprised of hyperphosphorylated tau, first form within the entorhinal cortex and hippocampus, before reaching the neocortical regions (Braak and Braak, 1995), and are associated with the development of clinical symptoms in AD (Giannakopoulos et al., 1997). Tau kinases, including Glycogen synthase kinase 3 (GSK3) and Cyclin-dependent kinase 5 (CDK5), have been demonstrated to play a vital role in the phosphorylation of tau, and represent a mechanistic

target in the relationship between exercise and brain tau (Dolan and Johnson, 2010).

4.1. The role of exercise in modulating tau levels

4.1.1. Animal studies

Our review of the literature identified numerous animal studies that have reported reductions in brain tau phosphorylation and tau pathology following physical activity and exercise (Table 2; Fig. 1). It is important to note that many of the reviewed studies utilised tau transgenic models, i.e. models of tauopathies (Belarbi et al., 2011; Elahi et al., 2016; Gratuze et al., 2017; Kang and Cho, 2015; Leem et al., 2009; Ohia-Nwoko et al., 2014), whereas only one reviewed study utilised a model of AD (Liu et al., 2013). Thus, many of the findings summarised below are relevant to all tauopathies, rather than AD alone.

Decreases in tau phosphorylation (Gratuze et al., 2017; Jeong and Kang, 2018; Kang and Cho, 2015; Leem et al., 2009; Liu et al., 2013; Ohia-Nwoko et al., 2014) and decreases in hippocampal tau pathology (Belarbi et al., 2011; Jeong and Kang, 2018; Kang and Cho, 2015) have been observed in studies utilising interventions ranging from 2 to 5 months and 2–9 months; respectively. From these findings, it is unclear whether particular aspects of interventions (i.e. length, intensity, bout duration) play an important role in the effect of physical activity and exercise on brain tau. It could be hypothesised that higher intensity running may elicit a more beneficial effect in terms of tau reduction; however, studies utilising both forced running (Jeong and Kang, 2018; Kang and Cho, 2015) and voluntary wheel running (i.e. likely at a lower intensity; Belarbi et al., 2011; Gratuze et al., 2017) observed effects on both phosphorylation and aggregation. It is possible that any consistent aerobic exercise over a certain duration (e.g. 2 months) elicits reductions in tau in animal models. Nevertheless, one study reported *increases* in both insoluble tau levels and phosphorylation of tau at the C-terminus following exercise (Elahi et al., 2016). It is important to note however, that Elahi and colleagues utilised the oldest animals (19 months), and the shortest duration of exercise (3 weeks), compared with the other reviewed studies. These two factors alone may have contributed to their disparate findings, the animals may have had pathology too advanced to be mitigated by exercise, and indeed the exercise itself was likely too short in duration to decrease the level of brain tau. Furthermore, the authors provide data to suggest that increases in exercise-induced neuroinflammation were associated with the observed increases in tau. Nevertheless, the relationship between exercise, inflammation and neurodegenerative processes is complex: both increases in inflammatory markers and decreases in inflammatory markers are linked to decreased AD pathology, and there are varying (i.e. increases followed by decreases) adaptive inflammatory responses to exercise (Nichol et al., 2008; Parachikova et al., 2008). It is also important to consider that a range of techniques were used to detect brain tau across the reviewed studies: western blotting (Elahi et al., 2016; Kang and Cho, 2015; Leem et al., 2009; Liu et al., 2013), enzyme-linked immunsorbent assays (Belarbi et al., 2011), sarkosyl extraction (Gratuze et al., 2017), and immunofluorescence (Ohia-Nwoko et al., 2014). However, due to the wide range of methods utilised, it is unclear how this varying methodology could influence the reported results.

The mechanisms by which exercise positively influences tau phosphorylation and tau pathology are not well understood in the current literature. One of the animal studies described above has provided evidence that the tau kinase GSK3, but not CDK5, plays a mediating role in the relationship between exercise and tau phosphorylation (Liu et al., 2013). However, Gratuze et al (2017) reported no effect of voluntary wheel running on a number of tau kinases (GSK3, CDK5, c-Jun N-terminal kinases (JNK) and Calmodulin-dependent protein kinase II (CamKII)) nor phosphatases (shown to dephosphorylate tau in vitro) in their animals. A deficiency in two cholesterol binding proteins, Neimann-Pick disease, type C1 (NPC1) and type C2 (NPC2), has been shown to induce tau pathology (Klunemann et al., 2002). Interestingly, upregulation of NPC1 and NPC2 mRNA was observed by Belarbi and colleagues in their mice following voluntary wheel running, demonstrating another potential mechanism through which exercise reduces tau pathology (Belarbi et al., 2011). Given the large number of potentially mediating factors (i.e. various kinases and phosphatases), this field requires further extensive research.

4.1.2. Human cohorts

The literature examining the relationship between physical activity and tau in humans is sparse (Table 3). Similar to the gold-standard measurement of Aβ in human cohorts, tau quantification is marred by inaccessibility and relative invasiveness. Nevertheless, quantification of phosphorylated tau in CSF is considered a core biomarker for AD, and is routinely utilised in clinical trials (Hampel et al., 2010). In addition, there have been recent advances in the use of tau-binding tracers coupled with PET imaging: tau PET has recently been validated against *post-mortem* histopathological brain tissue (Lemoine et al., 2017).

Liang et al. (2010) found lower self-reported exercise levels to be associated with higher CSF total tau and phosphorylated tau in a group of cognitively healthy older adults; however, when this association was adjusted for covariates (age, gender and education), the relationship was no longer significant. As both tau levels and physical activity levels are highly correlated with advancing age, it is likely that the reported unadjusted association was confounded by participant age. In an investigation of cognitively normal and MCI individuals, Baker et al. (2012) found self-reported high-intensity physical activity to be associated with lower CSF tau in the healthy group only: It is possible that the MCI group may have not been undertaking exercise of a sufficient intensity or volume to detect a relationship with CSF tau. Objectively quantified physical activity (actigraphy) has also been utilised to evaluate the relationship between habitual physical activity levels and CSF biomarkers of AD (Law et al., 2018); a lower ratio of total tau/$A\beta_{1-42}$ and phosphorylated tau/$A\beta_{1-42}$ (indicative of less cerebral pathology) was observed in those that spent the most time undertaking moderate physical activity. Interestingly no association was observed between time spent in vigorous physical activity and the CSF biomarkers; however, this likely reflects the low levels of vigorous physical activity undertaken within this cohort of cognitively normal late-middle-aged adults, and thus the analysis between vigorous physical activity and CSF biomarkers may not have been adequately powered. Recently, Brown et al (2018) demonstrated lower levels of PET-quantified tau in cognitively normal older adults reporting the highest levels of physical activity; however, it is important to note that even those with “higher” levels of tau in the brain were not reaching what we understand to be pathological levels of this protein. With these very recent advances in tau neuroimaging, the relationship between exercise and brain tau in human populations will likely be a highly studied topic in coming years.

5. Discussion

This review has highlighted consistent evidence from animal studies that physical activity and exercise likely modulate levels of Aβ and tau (Fig. 1). However, data from human cohorts is relatively limited and less consistent. It is likely that exercise levels in animal studies are of a high volume, and may not mirror exercise that is being undertaken by ‘high exercisers’ (in observational human studies) nor that being administered in human intervention studies. In addition, it’s important to consider what we have termed ‘duration of exercise to lifespan ratio’; which would play an important role in the differing evidence presented in animal versus human studies. Understandably, the study of exercise in humans is more complex than animal models, with a myriad of factors contributing to the risk and rate of pathology accumulation in AD. Nevertheless, with such striking evidence from animal models, it is clear that this association needs further, thorough examination in humans.

Based on the available evidence, it appears that exercise in animal studies is required to be undertaken within a ‘preclinical’ period, i.e.

before the peak of AD pathology, in order to yield the greatest benefit. Through the utilisation of PET imaging, we know that Aβ begins to accumulate up to two decades before the onset of clinical symptoms in humans. It is during this period we believe that lifestyle factors, such as exercise, will be most effective in decreasing the risk of AD and associated pathology markers. The studies reviewed here support the hypothesis that a 'window of opportunity' exists in humans for the prevention or attenuation of Aβ and tau accumulation (Sperling et al., 2011).

To demonstrate a definitive role for exercise in modulating levels of brain Aβ and tau, high-level evidence from large-scale randomised controlled trials are required. Current AD pharmaceutical trials utilise Aβ PET imaging as an endpoint; however, based on current evidence, it is unlikely that exercise will be potent enough to contribute to detectable changes in Aβ accumulation over short periods, particularly as we know Aβ accumulates slowly over a number of years. Currently, the best option for determining the effect of exercise on Aβ and tau requires the utility of long-term interventions with multiple timepoints. Multimodal lifestyle change studies are currently underway, for example the FINGER trial (Kivipelto et al., 2013), and may be key in understanding how lifestyle can contribute to long-term brain changes in individuals we know to be at increased risk of AD. The combination of measures from both CSF and PET scans would also provide the optimum setting to clearly understand this relationship.

Here, we have summarised consistent evidence from animal studies, supported by some human studies, that exercise plays a role in altering the accumulation of Aβ and tau pathology. Nevertheless, for exercise to be accepted as a mechanism for the reduction of cognitive decline and dementia risk, robust high-level evidence from human research is vital. Future studies should consider gold-standard tau and Aβ measurements as outcome measures in specifically designed exercise-focussed randomised controlled trials.

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Competing interest

None.

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