Interactions Between Stress and Physical Activity on Alzheimer's Disease Pathology

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Interactions between stress and physical activity on Alzheimer's disease pathology

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\textsuperscript{c} Biomedical Science Department, Missouri State University, Springfield, MO, USA

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder for which there is currently no effective treatment. The increasing social, physical, and economic burden of AD for both patients and caregivers is becoming a major public health concern in many areas of the world. The complexity of the disease, involving multiple pathological changes, interactions with risk-associated genes, and effects of behavioral or environmental modifiers have made finding a successful treatment difficult. Multifactorial treatment strategies will likely be necessary to provide a significant benefit to both patients and caregivers.

It is generally accepted that physical activity decreases the risk of developing AD and many other disorders that occur with age (Adlard and Cotman, 2004; Kennedy et al., 2017; Paillard et al., 2015). Higher rates of reported exercise are correlated with improved AD biomarkers in cognitively normal older adults (Liang et al., 2010). However, some forms of physical activity can induce stress and the effects of intensity, duration, frequency, and mode of activity needed to maximize health benefits are not fully understood. Psychological stress is associated with increased risk of many disorders and has been repeatedly shown to exacerbate symptoms and accelerate disease onset in AD (Baglietto-Vargas et al., 2015; Cernansky et al., 2006; Dong et al., 2004; Selye, 1955). Conversely, mild stress can be beneficial, particularly for cognitive function (Bos et al., 2014). The circumstances under which stress or physical activity occur may determine its effects on AD pathology.

Acute stress activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), which increases the release of glucocorticoids (GCs) and catecholamines (Smith and Vale, 2006). These molecules then initiate a neuroendocrine response, mobilizing lipids, glucose, and other resources to facilitate cognitive and physical demands of a “fight or flight” challenge. In conditions of acute psychological stress, these neuroendocrine responses are not tied to an increased metabolic demand. In chronic stress, this prolonged activation of the stress system has been linked to a large number of comorbidities ranging from metabolic dysfunction and cardiovascular...
disorders, to cognitive dysfunction and psychological disorders, such as depression (McEwen, 2017). The effects of psychological stress are likely to be exaggerated in the presence of physical inactivity due to lack of use of the physiological and metabolic products produced in preparation for the body's anticipated physical response to a threat. For example, increasing pro-inflammatory cytokines to help repair tissue damage due to physical exertion is counterproductive in the absence of the tissue damage and may lead to aberrant responses in the system (Flesner and Crane, 2017). Several of these physiological changes associated with chronic stress are also risk factors for AD (Mayeux and Stern, 2012).

Chronic physical activity may play a protective role in stress system dysregulation and increase resistance to stress-related disorders (Tatsoulis and Fountoulakis, 2006). A recent review by Nation et al. (2011) carefully outlines the effects of stress and exercise specifically on the neurovascular system in AD, and highlights the importance of uncovering the mechanisms and interactions involved in the effects of exercise and stress on AD pathophysiology so that new behavioral and/or pharmacological strategies can be developed for effective treatment of the disease. Many studies have examined the effects of stress or exercise on AD neuropathology or cognitive function independently, but few have analyzed the interactions between stress and exercise on the pathophysiology and cognitive symptoms of the disease. The goal of this review is to evaluate the interaction between physical activity and stress on AD pathophysiology in the context of forced versus voluntary physical activity. Does physical activity promote stress resistance or resilience (or both) to AD pathology? Do parameters of physical activity such as intensity or duration matter such that there is a threshold to counteract the negative effects of psychological stress on AD pathology?

2. Physical activity terminology and characteristics

Physical activity refers to any movement of the body resulting from skeletal muscle contraction that elevates total body energy expenditure above that at rest (Caspersen et al., 1985). Physical activity encompasses a wide variety of endeavors, including walking around the block, gardening, mowing the lawn, or running several miles. Caspersen et al. (1985) suggest that physical activity can be categorized in multiple ways, for the purposes of this review we categorized physical activity as acute or chronic (Fig. 1). Acute physical activity refers to one bout or session, such as walking to the store or a long bicycle ride, and can be subdivided into normal daily physical activity and exercise. Chronic physical activity refers to a structured, repetitive regimen carried out over weeks, months, or years intended to improve physiological or physical health, and can be subdivided into exercise training and sub-exercise training. Exercise training refers to chronic physical activity with a goal of increasing physical fitness above that of a sedentary individual (e.g. improved cardiovascular or muscle endurance, muscle strength, or flexibility). Exercise training regimens must be of sufficient intensity (physically taxing), duration (length of time exercise is performed), and frequency (number of exercise bouts performed) to overload the body and increase function. For a chronic physical activity regimen to meet the criteria of exercise training an increase in a physiological function must be demonstrated (referred to as an exercise training effect). Examples of an exercise training effect would be an increase in maximum oxygen consumption, an increase in the activity of a skeletal muscle mitochondrial enzyme associated with the Krebs cycle or electron transport chain (e.g. citrate synthase), or an increase in muscle strength. Sub-exercise training chronic physical activity refers to a structured regimen where the intensity, duration, and frequency are not at a high enough level to change physical fitness above that of a sedentary individual, such as a casual daily walk.

3. Studies of the effects of physical activity in mouse models of AD: can we determine the effects of stress?

Environmental factors influence disease onset and progression in AD, and being able to uncover the experience-dependent mechanisms for modifying the course of the disease is important to provide treatment guidelines and predict the success of therapeutic interventions. Studies of the effects of physical activity in animal models of AD have primarily used two methods: voluntary running on a wheel (Table 1) or running at a fixed speed on a treadmill (Table 2). Forced exercise, typically in the form of treadmill running, has been shown to increase biomarkers of the stress response in rodents (Moraska et al., 2000; Svensson et al., 2016; Yanagita et al., 2007). Due to the findings by Dong et al. (2008, 2004) and others (Baglietto-Vargas et al., 2015; Carroll et al., 2011) that chronic stress exacerbates AD pathology in mouse models, it is important to determine the influence of stress in forced exercise studies. Treadmill running provides a measure of control over exercise intensity and duration not available in voluntary running conditions; however, the psychological stress component could possibly counteract some of the positive benefits of chronic physical activity. Presumably voluntary exercise results in less stress on the mouse than forced exercise and comparison of voluntary and forced exercise in exercise training and sub-exercise training regimens can provide insight into the opposing relationship that psychological stress and physical activity have on biomarkers of AD.

We directly evaluated the effects of intensity-matched forced and voluntary chronic physical activity regimens on the cognitive and pathological changes in a transgenic AD mouse model and found that both forms of chronic physical activity decreased plaque count and increased hippocampal volume, but only mice in the voluntary group performed better on a cognitive task (Yuede et al., 2009). Psychological stress in forced exercise bouts can be due to the physical discomfort of the shock stimulus at the back of the treadmill belt designed to motivate the mice to run, or by the emotional distress associated with having to run at a constant predetermined speed. To differentiate between those two forms of stress we included a group that received the foot shock only, but did not run. Interestingly, we did not find a significant impairment in our shock-only control group suggesting that the shock exposure the forced exercise group received during treadmill running was not a strong enough stressor to have an effect on AD pathology. However, the animals in the forced exercise group did not achieve all of the same benefits as the animals in the voluntary exercise group indicating a qualitative difference between the physical activity regimens. We concluded that it was more likely that the psychological stress associated with the forced exercise mitigated some of the beneficial effects.

Exercise training is a chronic physical activity regimen of sufficient intensity, duration, and frequency to increases physical fitness. Sub-exercise training is a chronic physical activity regimen that is not of sufficient intensity, duration, or frequency to improve physical fitness, but may reduce psychological stress and improve psychological health.
<table>
<thead>
<tr>
<th>Model (Strain and Gender)</th>
<th>Physical Activity Type</th>
<th>Intensity (estimated) and Duration</th>
<th>Frequency</th>
<th>Major AD Outcomes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TgCRND8 Female</td>
<td>Wheel running</td>
<td>3.7-6.0 m/min 12 h/day</td>
<td>7 days/week 5 months</td>
<td>↓ amyloid plaque ↑ MWM</td>
<td>Adlard et al., 2005</td>
</tr>
<tr>
<td>APP23 Female</td>
<td>Wheel running</td>
<td>Multiple animals per cage w/single running wheel</td>
<td>Beginning at 10 weeks of age Ending at 11 months of age</td>
<td>MWM (ns) Amyloid plaque (ns)</td>
<td>Wolf et al., 2006</td>
</tr>
<tr>
<td>APPsw Male or Female not specified</td>
<td>Wheel running</td>
<td>Multiple animals per cage w/single running wheel</td>
<td>Beginning at 6 weeks of age Ending at 9 months of age</td>
<td>MWM (ns) RAWM (ns) Cortisol (ns) Cytokines (ns) Amyloid plaque (ns) Synaptophysin (ns)</td>
<td>Cracchiolo et al., 2007</td>
</tr>
<tr>
<td>Tg2576 Male or Female not specified</td>
<td>Wheel running</td>
<td>2.4 m/min 12 h/day</td>
<td>7 day/week Age ranged from 16 to 18 months at beginning of treatment</td>
<td>↓ soluble Aβ40 Aβ42 (ns) ↑ TNF-α and IL-1β</td>
<td>Nichol et al., 2008</td>
</tr>
<tr>
<td>Tg2576 Male and Female</td>
<td>Wheel running</td>
<td>12 h/day Distance run not reported</td>
<td>3 weeks in 16-18 month old mice</td>
<td>↑ RAWM although performance similar to group with locked wheel</td>
<td>Nichol et al., 2007</td>
</tr>
<tr>
<td>Tg2576 Male or Female not specified</td>
<td>Wheel running</td>
<td>12 h/day Distance run not reported</td>
<td>7 days/week Age ranged from 15 to 19 months at beginning of treatment</td>
<td>Insoluble Aβ40 and Aβ42 (ns) ↑ RAWM both reference and working memory</td>
<td>Parachikova et al., 2008</td>
</tr>
<tr>
<td>TgCRND8 Male</td>
<td>Wheel running</td>
<td>2.0 m/min 12 h/day Animals housed individually</td>
<td>7 days/week Treatment from 80 to 150 days of age (10 weeks)</td>
<td>NOR (ns) Barnes maze (ns) Spontaneous behavior (ns) Corticosterone (ns) Amyloid plaque (ns) ↑ adult hippocampal neurogenesis (ns)</td>
<td>Richter et al., 2008</td>
</tr>
<tr>
<td>Tg2576 Male and Female</td>
<td>Wheel running</td>
<td>10.9 m/min/60 min/day</td>
<td>5 day/week 16 weeks From 5 to 9 months of age</td>
<td>↑ MWM ↑ sensorimotor function ↓ dark-light box test ↓ phosphorylated tau</td>
<td>Yuede et al., 2009</td>
</tr>
<tr>
<td>APP23 Female</td>
<td>Wheel Running</td>
<td>12 h/day</td>
<td>7 days/week 2 groups: Animals had access to running for 10 days one group was 6 months of age the other was 18 months of age</td>
<td>↑ MWM ↑ dark-light box test (ns) Boissier’s 4 hole board test (ns) Soluble Aβ (ns) Amyloid plaque (ns)</td>
<td>Mirochnic et al., 2009</td>
</tr>
<tr>
<td>THY-Tau22 Male</td>
<td>Wheel Running</td>
<td>12 h/day Distance run not reported</td>
<td>7 days/week 9 months from 3 to 12 months of age</td>
<td>↑ Y-Maze ↓ pathological tau species Astrogliosis (ns) Inflammation (ns) Cholinergic neurons (ns) BDNF (ns)</td>
<td>Belarbi et al., 2011</td>
</tr>
<tr>
<td>3xTg-AD Male and Female</td>
<td>Wheel running</td>
<td>12 h/day Distance run not reported</td>
<td>7 days/week 2 groups: One month beginning at 3 months of age 6 months beginning at 1 month of age</td>
<td>↑ MWM ↑ dark-light box test (ns) Boissier’s 4 hole board test (ns) Soluble Aβ (ns) Amyloid plaque (ns) ↓ oxidative stress</td>
<td>García-Mesa et al., 2011</td>
</tr>
<tr>
<td>3xTg-AD male</td>
<td>Wheel running</td>
<td>4.0 m/min 12 h/day</td>
<td>7 days/week 6 months from 6 to 12 months of age</td>
<td>↑ MWM ↑ sensorimotor function ↓ dark-light box test ↑ Boissier’s 4 hole board test ↓ oxidative stress ↓ amyloid plaque</td>
<td>García-Mesa et al., 2012</td>
</tr>
<tr>
<td>SAMP8 Female</td>
<td>Wheel running</td>
<td>0.55 m/min/12 h/day</td>
<td>7 days/week 8 weeks from 6 months of age to 8 months of age</td>
<td>↑ growth factors in plasma and cortex Plasma triglycerides (ns)</td>
<td>Cosín-Tomás et al., 2014</td>
</tr>
</tbody>
</table>
particularly on cognition, realized by the voluntary exercise group.

4. Forced versus voluntary chronic physical activity: does intensity matter?

The results of studies employing physical activity in mouse models of AD are largely positive (Tables 1 and 2), however there are studies reporting little to no improvement in AD pathology or cognitive benefit of the physical activity regimen (Cracchiolo et al., 2007; Giménez-Llort et al., 2010; Richter et al., 2008; Wolf et al., 2006). Mice in all of these studies have increased physical activity, though it is difficult to determine exactly how much exercise training the animals received. To date, only two studies using mouse models of AD have assessed an exercise training effect (Lin et al., 2015; Moore et al., 2016). It is conceivable that the stress involved in treadmill running in animal models is enough to counteract the beneficial effects of chronic physical activity if the intensity, duration, and frequency are below a critical threshold. Currently, it is not possible to differentiate the studies listed in Tables 1 and 2 as to whether they represent significant exercise training or sub-exercise training chronic physical activity regimens. Since voluntary exercise is often studied by giving mice unrestricted access to a running wheel in their cage and reporting total distance, it is difficult to precisely determine exercise intensity. We attempted to estimate intensity based on the parameters reported in the studies of voluntary exercise in animal models of AD in Table 1. We calculated speed by dividing the total distance reported by the amount of time the animal likely ran on the running wheel each day. In the studies where distance was reported, most exercise intensities ranged from roughly 0.55–6 m/min each day, however we note that these are likely an underestimation of the actual intensity. If a mouse utilizes the running wheel during the 12 h dark cycle but only runs for a total of 4 h, their intensity would be higher than we estimate. From our own experience, we found that when given access to a running wheel for only 1 h a day, Tg2576 mice voluntarily ran at an average speed of 10.9 m/min over 6 min (minutes in 12h). This likely underestimates intensity slightly as the mice do not run constantly for the full 12 h dark cycle.

3. Several studies reported in this summary employed multiple groups as part of larger enrichment studies. For these studies, we only report exercise duration as 12 h/day. Therefore, in this summary we report exercise duration as 12 h/day.

## Table 1 (continued)

<table>
<thead>
<tr>
<th>Model (Strain and Gender)</th>
<th>Physical Activity Type</th>
<th>Intensity (estimated) and Duration</th>
<th>Frequency</th>
<th>Major AD Outcomes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>3xTgAD Male or Female Not specified</td>
<td>Wheel running</td>
<td>12 h/day distance not reported</td>
<td>7 days/week for 6 months from 1 to 7 months of age</td>
<td>†Neuroprotective factors</td>
<td>Revilla et al., 2014</td>
</tr>
<tr>
<td>3xTgAD female</td>
<td>Wheel running</td>
<td>3.3 m/min 12 h/day</td>
<td>7 days/week 3 months from 12 to 15 months of age</td>
<td>†MWM</td>
<td>García-Mesa et al., 2016</td>
</tr>
<tr>
<td>APPswe/PS1ΔE9 Male or Female not specified</td>
<td>Wheel Running</td>
<td>12 h/day Distance run not reported</td>
<td>7 days/week 10 weeks beginning at 5 months of age</td>
<td>†MWM</td>
<td>Tapia-Rojas et al., 2016</td>
</tr>
<tr>
<td>TgGRND8 Male or Female not specified</td>
<td>Wheel Running</td>
<td>13.75 m/min 12 h/day</td>
<td>7 days/week Two groups: 1 month or running from 3 to 4 months of age 2 months of running from 3 to 5 months of age</td>
<td>†neurogenesis 1 month group: Y-Maze †neurogenesis 2 month group: Y Maze</td>
<td>Maliszewska-Cyna et al., 2016</td>
</tr>
</tbody>
</table>

Abbreviations: MWM = Morris Water Maze, NOR = Novel Object Recognition, RAWM = Radial Arm Water Maze, BDNF = Brain Derived Neurotrophic Factor, APP = Amyloid Precursor Protein.

Clarifications:
1. In our experience mice exposed to running wheels 24 h per day, 7 days per week run in the wheel almost constantly during the 12 h dark cycle and almost not at all during the light cycle. Therefore, in this summary we report exercise duration as 12 h/day.
2. We estimated daily exercise intensity (speed) in studies that reported average distance run by dividing distance (meters) by 720 min (minutes in 12h). This likely underestimates intensity slightly as the mice do not run constantly for the full 12 h dark cycle.
3. Several studies reported in this summary employed multiple groups as part of larger enrichment studies. For these studies, we only report findings comparing the group that only had access to a running wheel to the group receiving no enrichment.
Table 2
Summary of studies investigating chronic forced physical activity in transgenic mouse models of Alzheimer's disease.

<table>
<thead>
<tr>
<th>Model (Strain and Gender)</th>
<th>Physical Activity Type</th>
<th>Intensity and Duration</th>
<th>Frequency</th>
<th>Major AD Outcomes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSE/APPsw Male or Female not specified</td>
<td>Treadmill running</td>
<td>13.2 m/min, 0% grade 1 h/day</td>
<td>5 days/week</td>
<td>↑ MWM ↓ Aβ42 deposition ↓ BDNF and GLUT-1 ↑ HSP70 ↑ SOD and catalase ↓ pro-apoptotic proteins</td>
<td>Um et al., 2008</td>
</tr>
<tr>
<td>NSE/APPsw Male or Female not specified</td>
<td>Treadmill running</td>
<td>13.2 m/min, 0% grade 1 h/day</td>
<td>5 days/week 16 weeks Beginning at 13 months of age</td>
<td>↑ MWM ↓ Aβ42 deposition ↓ BDNF and GLUT-1 ↓ pro-apoptotic proteins</td>
<td>Cho et al., 2010</td>
</tr>
<tr>
<td>NSE/APPsw Male or Female not specified</td>
<td>Treadmill running</td>
<td>12 m/min, 0% grade 1 h/day 5 days/week</td>
<td></td>
<td>↑ MWM ↓ Aβ42 deposition ↓ tau phosphorylation ↓ BDNF, NGF, CREB ↑ HSP70 ↑ MAPK signaling ↑ neuronal apoptosis</td>
<td>Um et al., 2011</td>
</tr>
<tr>
<td>NSE/APPsw Male or Female not specified</td>
<td>Treadmill running</td>
<td>12 m/min, 0% grade 1 h/day</td>
<td>3 months 5 days/week</td>
<td>↑ MWM ↓ Aβ42 deposition ↓ BACE-1 activity (β-secretase) ↓ ER stress ↓ amyloid plaque ↓ soluble Aβ ↓ guanidine extracted soluble Aβ ↓ amyloid plaque in old mice (ns) ↑ BDNF → ↑ Aβ42, Aβ42 (ns in females, improved ratio in males) Tau (ns)</td>
<td>Kang et al., 2013</td>
</tr>
<tr>
<td>3xTg-AD Male and Female</td>
<td>Treadmill running</td>
<td>4.2 m/min, 0% grade 30 min/day</td>
<td>5 days/week 5 weeks beginning at 6 months of age</td>
<td>Corner test (ns) Dark-Light box test (ns) MWM (ns) T-Maze (ns) ↑ Aβ42, Aβ42, Aβ42 (ns in females, improved ratio in males) ↑ BDNF, NGF, CREB ↑ HSP70 ↑ MAPK signaling ↑ neuronal apoptosis</td>
<td>Gimenez-Llort et al., 2010</td>
</tr>
<tr>
<td>APP/PS1 Male or Female not specified</td>
<td>Treadmill running No electric shock motivation</td>
<td>5-11 m/min, 0% grade 30 min/day</td>
<td>5 days/week 5 months from 3 to 8 months of age</td>
<td>↑ MWM ↓ synaptic plasticity, LTP ↓ BDNF mRNA ↓ amyloid plaque ↓ soluble Aβ ↓ APP (ns) ↓ sAPP α ↓ sAPP β ↓ hyperphosphorylated tau ↓ amyloid plaque in old mice (ns) ↑ microglial activation</td>
<td>Liu et al., 2011</td>
</tr>
<tr>
<td>APP/PS1 Female</td>
<td>Treadmill running No electric shock motivation</td>
<td>5-11 m/min, 0% grade 30 min/day</td>
<td>5 days/week 5 months from 3 to 8 months of age</td>
<td>↑ MWM ↓ synaptic plasticity, LTP ↓ BDNF mRNA ↓ amyloid plaque ↓ soluble Aβ ↓ APP (ns) ↓ sAPP α ↓ sAPP β ↓ hyperphosphorylated tau ↑ MWM ↑ amyloid plaque (ns) ↑ microglial activation</td>
<td>Liu et al., 2013</td>
</tr>
<tr>
<td>APPswe/PS1dE9 Male</td>
<td>Treadmill running Gentle tail touching motivation no electric shock</td>
<td>Gradual distance increase 70-300 m/day with gradual speed increase from 5 to 8 to 10-15 m/min</td>
<td>6 days/week 5 months beginning at 4 months of age</td>
<td>↑ MWM ↑ amyloid plaque ↑ guanidine extracted soluble Aβ40 and Aβ42 ↑ UTP</td>
<td>Xiong et al., 2015</td>
</tr>
<tr>
<td>APP/PS1 Male</td>
<td>Treadmill running No electric shock motivation</td>
<td>5-11 m/min, 0% grade 30 min/day</td>
<td>5 days/week 5 months 2 groups; one beginning at 3 months of age the other beginning at 12 months of age</td>
<td>↑ MWM ↑ amyloid plaque ↑ guanidine extracted soluble Aβ40 and Aβ42 ↑ UTP</td>
<td>Zhao et al., 2015</td>
</tr>
<tr>
<td>APP/PS1 Male</td>
<td>Treadmill running Gentle tail touching motivation no electric shock</td>
<td>Week 1: 5 m/min, 0% grade 10 min/day</td>
<td>5 days/week 5 weeks 2 groups; one beginning at 7 months of age the other at 24 months of age</td>
<td>↑ MWM ↑ amyloid plaque ↑ guanidine extracted soluble Aβ40 and Aβ42 Few amyloid plaques detected in SED or EX BDNF (ns)</td>
<td>Ke et al., 2011</td>
</tr>
<tr>
<td>APP/PS1 Male</td>
<td>Treadmill running Gentle tail touching motivation no electric shock</td>
<td>Time increased by 10 min each day</td>
<td>5 days/week 5 weeks 2 groups; one beginning at 7 months of age the other at 24 months of age</td>
<td>↑ MWM ↑ amyloid plaque ↑ guanidine extracted soluble Aβ40 and Aβ42 Few amyloid plaques detected in SED or EX BDNF (ns)</td>
<td>Ke et al., 2011</td>
</tr>
<tr>
<td>APP/PS1 Male</td>
<td>Treadmill running Gentle tail touching motivation no electric shock</td>
<td>11 m/min 30 min/day 0% grade</td>
<td>5 days/week 20 weeks; from 3 months of age to 8 months of age</td>
<td>↑ MWM ↑ amyloid plaque ↑ guanidine extracted soluble Aβ40 and Aβ42 Few amyloid plaques detected in SED or EX BDNF (ns)</td>
<td>Bo et al., 2014</td>
</tr>
</tbody>
</table>

(continued on next page)
IHaskins et al., 2016). Additionally, lower intensity treadmill running, 4.2 m/min, did not result in significant changes in pathology female 3xTg mice, although subtle benefits on Aβ40/42 ratio were found in male mice (Giménez-Llort et al., 2010) suggesting exercise intensity may play a role in the magnitude of the benefits on AD pathology.

<table>
<thead>
<tr>
<th>Model (Strain and Gender)</th>
<th>Physical Activity Type</th>
<th>Intensity and Duration</th>
<th>Frequency</th>
<th>Major AD Outcomes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>APP/PS1 Male</td>
<td>Treadmill running</td>
<td>10 m/min 20 min/day 0% grade</td>
<td>5 days/week 4 months; from 6 months of age to 10 months of age</td>
<td>↑ MWM ↑ White matter capillary length and volume White matter capillary surface area (ns)</td>
<td>Zhang et al., 2017</td>
</tr>
<tr>
<td>APPswe/PS1dE9 Male and Female</td>
<td>Treadmill running</td>
<td>Acclimation at 10 m/min 20-60 min/day first 4 weeks gradually increasing to 12 m/min 1 hr/day 0% grade</td>
<td>5 days/week for 9 weeks beginning at 6 weeks of age</td>
<td>↑ Conditioned fear memory ↑ dendritic complexity ↑ BDNF signaling pathways ↑ LRP1 ↓ Aβ40 and Aβ42 ↓ Amyloid plaque ↓ APP ↓ Presenilin 1 ↓ CTFβ ↓ ADAM10/17 (%) ↓ BACE1 (%) ↓ IDE (%) ↓ Neprilysin (%) ↓ phosphorylated tau ↑ PSD-95 and synaptophysin BDNF and NGF (ns)</td>
<td>Lin et al., 2015</td>
</tr>
<tr>
<td>NSE/htau23 Male or Female not specified</td>
<td>Treadmill running</td>
<td>Acclimation at 9 m/min for 20 min/day Gradual increase from 12 m/min for 30 min/day to 14.4 m/min for 50 min/day 0% grade</td>
<td>5 days/week for 12 weeks</td>
<td>↑ GSK-3β ↓ tau and phospho-tau ↑ MWM</td>
<td>Kang and Cho, 2015</td>
</tr>
<tr>
<td>TgNSE/hPS2m Male or Female not specified</td>
<td>Treadmill running</td>
<td>12 m/min 1 h/day 0% grade</td>
<td>5 days/week for 3 months from 24 months of age</td>
<td>↑ anti-apoptotic factors ↑ insulin signaling pathways ↑ COX-2 ↑ BDNF ↑ HSP70 Improvement in blood and brain inflammatory chemokines in the 3x/week group, but not the 1x/week group</td>
<td>Koo et al., 2013</td>
</tr>
<tr>
<td>3xTg-AD Male</td>
<td>Forced Wheel running</td>
<td>8 m/min 1 h/day 0% grade</td>
<td>2 groups: 1x/week or 3x/week for 12 weeks from 2.5 to 6 months of age</td>
<td>↓ soluble Aβ40 and Aβ42 HI &gt; LOW &gt; SED ↓ numerous Aβ clearance proteins HI &gt; LOW &gt; SED</td>
<td>Haskins et al., 2016</td>
</tr>
<tr>
<td>Tg2576 Male and Female</td>
<td>Treadmill running</td>
<td>10.9 m/min, 0% grade 1 h/day</td>
<td>5 day/week 16 weeks From 5 to 9 months of age</td>
<td>↓ amyloid plaque Soluble Aβ (ns) NOR (ns) ↑ hippocampal volume ↓ soluble Aβ40 and Aβ42 HI &gt; LOW &gt; SED</td>
<td>Yuede et al., 2009</td>
</tr>
<tr>
<td>Tg2576 Male</td>
<td>Treadmill running</td>
<td>Low Intensity group: 15 m/min 0% grade</td>
<td>5 days/week 3 months</td>
<td>↓ hippocampal volume ↓ soluble Aβ40 and Aβ42 HI &gt; LOW &gt; SED</td>
<td>Moore et al., 2016</td>
</tr>
<tr>
<td></td>
<td>Hi Intensity group: 32 m/min 10% grade</td>
<td>1 h/day</td>
<td>5 days/week 3 months</td>
<td>From 3 to 6 months of age</td>
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Abbreviations: MWM = Morris Water Maze, APP = Amyloid Precursor Protein, BDNF = Brain Derived Neurotrophic Factor, HSP = Heat Shock Protein, CTF = C Terminal Fragment, SOD = Superoxide Dismutase, LTP = Long Term Potentiation, NGF = Nerve Growth Factor, ROS = reactive oxygen species.
group as our focus was to evaluate the potential negative effects of psychological stress associated with forced exercise. We subsequently evaluated the effects of exercise intensity (keeping duration and frequency constant) on AD pathology. In pilot studies, we discovered that Tg2576 mice running at 15 m/min on a level treadmill for 60 min/day, 5 days/week, for 8 weeks had an increased citrate synthase activity, whereas mice running at 10 m/min for the same duration and frequency only had a trend towards an increase in citrate synthase activity. We further discovered that most Tg2576 mice were capable of running at a speed of 32 m/min on a 10% incline for 1 h. These investigations indicated that the running speeds previously utilized by ourselves and others to investigate the effects of chronic physical activity on AD pathology were relatively low, and that running speeds of around 10 m/min are near the threshold separating sub-exercise training from exercise training in transgenic model of AD.

We then evaluated the effect of exercise training intensity on soluble Aβ concentrations by comparing Tg2576 mice running at 32 m/min on a 10% incline for 60 min/day, 5 days/week, for 12 weeks (from 3 to 6 months of age) to a sedentary group, and a group running at 15 m/min on a level treadmill for the same duration and frequency. The exercise training effect (citrate synthase activity) was significantly greater in the high intensity group compared to the low intensity group, and the low intensity group was greater than the sedentary group demonstrating a dose-dependent exercise training effect. In both the cortex and hippocampus, soluble Aβ42 and Aβ40 were decreased in an exercise training dose-dependent manner, and proteins involved in Aβ clearance (neprilysin, insulin degrading enzyme, MMP9, LRP1, and HSP70) were all increased in a dose-dependent manner. We have followed up using the same groups, but continuing the exercise regimen for 12 months ending at 15 months of age. Improvements in pathological markers of AD also remained high for at least 13 h following the stressful experience. Blocking action potentials during restraint stress blocked the increase in Aβ suggesting that increased neuronal activity in the hippocampus during restraint stress was driving the increase in extracellular Aβ levels. Administration of corticotrophin releasing factor (CRF), but not corticosterone, mimicked the effects of restraint stress on extracellular Aβ indicating that this effect occurred through the actions of CRF in the brain.

To determine if exercise training could protect against this effect of acute psychological stress on Aβ levels in the brain, we measured Aβ before, during, and after acute restraint stress in 4 month old female APP/PS1 mice following 8 weeks of treadmill running at an intensity of 15 m/min, 60 min/day, 5 days a week. We used the same techniques for stress, microdialysis, and Aβ quantification as reported in Kang et al., 2007 and all methods and procedures were conducted in accordance with the guidelines established by the IACUC and Animal Studies Committee at Washington University School of Medicine. Interestingly, the stress-induced effect on extracellular Aβ levels in the hippocampus was prevented, not just diminished, in the exercise trained female mice compared to sedentary female mice (Fig. 2A). Aβ levels fluctuate around baseline for the entire 15 h period following stress, while Aβ levels in the sedentary mice continued to rise significantly above baseline following acute restraint stress. In addition, baseline Aβ levels in the hippocampus of exercise trained mice were significantly lower, by 42%, than those in sedentary mice (Fig. 2B). To establish a

5. Does chronic physical activity protect against the effects of acute psychological stress in AD?

Acute stress has rapid effects on the levels of Aβ in the mouse brain. Kang et al. (2007) tested the effects of acute restraint stress on Aβ in Tg2576 mice. Using a microdialysis technique to measure soluble Aβ in the brain (Cirrito et al., 2003), they found that acute restraint stress significantly increased Aβ levels in the hippocampus, and levels remained high for at least 13 h following the stressful experience. Blocking action potentials during restraint stress blocked the increase in Aβ suggesting that increased neuronal activity in the hippocampus during restraint stress was driving the increase in extracellular Aβ levels. Administration of corticotrophin releasing factor (CRF), but not corticosterone, mimicked the effects of restraint stress on extracellular Aβ indicating that this effect occurred through the actions of CRF in the brain.

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6. Does chronic physical activity provide resistance or resilience to stress in AD?

Physical activity has been shown to be protective against several stress-related psychiatric disorders (King et al., 1993; Taylor et al., 1985) even though acute exercise can be similar to acute stress in that it stimulates the SNS and HPA axis. The stress response is a physiological reaction to environmental changes that can be positive and proadapative or negative and maladaptive (Musazzi et al., 2017). Chronic exercise training can have adaptive effects on the homeostatic regulation of the system that may improve resistance and/or resilience to psychological and physical stress and therefore be protective or preventative against disease. In contrast, chronic stress results in several maladaptive changes that can accelerate or potentiate disease (Fig. 3). Among other things, acute exercise increases pro-inflammatory cytokines, increases oxidative stress, and increases cortisol/corticosterone. When combined with physical activity in a chronic manner, this response can train the body to adapt or be more resilient to psychological and physical stress, or counteract inflammatory or other negative physiological effects of AD, leading ultimately to protection or slowing of the disease progression (Caivalcante et al., 2017; Pedersen and Saltin, 2006).

As defined in Flesher et al. (2011) stress resistance refers to an increase in the duration and/or intensity of a stressor needed to cross the threshold from adaptive to maladaptive responses to psychological stress. Stress resilience, in contrast, refers to facilitated recovery after stressor exposure. Individuals who are stress resistant are able to endure higher levels of psychological or physical stress before experiencing negative consequences, while individuals who are more resilient are able to bounce back more quickly following a stressful experience. Monika Flesner's laboratory has done many elegant studies defining the impact of physical activity on psychological stress in rats. Six weeks of physical activity in the form of voluntary wheel running has stress-buffering effects on the immune system of male rats (reviewed in Flesher, 2005), inflammatory cytokines (Speaker et al., 2014), anxiety-related behaviors and social avoidance (Greenwood et al., 2003). Studies by Greenwood et al. (2013) evaluated the importance of the controllability of chronic physical activity on neural circuits involved in stress resistance. While voluntary exercise is a natural reward and is a motivator for some people, the amount of control a person has over their physical activity may have similar aspects to forced exercise. For example, if a person does not enjoy running, do they experience the same benefits as someone who does? Greenwood and colleagues have attempted to dissect this by making the degree of controllability over wheel running a variable in their studies. Both voluntary and forced wheel running protected against stress-induced behavioral changes in rats. They also found dopamine reward-related plasticity enhanced in both voluntary and forced running conditions, and these changes in plasticity contribute to stress resistance independent of the controllability of the chronic physical activity (Herrera et al., 2016). In fact, despite the apparent markers of chronic stress in the forced wheel running rats, benefits from the physical activity were still evident in behavioral responses and neurochemical pathways involved in stress resistance. The differences in intensity and duration of exercise as well as the amount of psychological stress perceived with either type of exercise, forced or voluntary, may play a role in which functional or physiological domain positive effects are conferred. So, thresholds for the intensity of physical activity to provide psychological stress resistance or resilience may differ depending on the physiological or behavioral outcome of interest.

Environmental enrichment has been shown to more quickly reduce plasma corticosterone levels in mice following acute restraint stress, suggestive of a stress resistance effect (Meijer et al., 2007). It appears that some aspects of acute or subthreshold voluntary physical activity promotes stress resiliency, while chronic physical activity may promote resistance. Stress resistance and resilience are dependent on multiple genetic and environmental factors, and the mechanisms of stress resiliency are important to uncover for identifying new approaches for the treatment of stress-related disorders, including AD.

7. What are the possible mechanisms for the stress-buffering effects of exercise training on AD pathology?

7.1. Improved Aβ clearance

A variety of stressors (both physical and psychological) can induce the upregulation of heat shock proteins (HSPs), which are designed to protect the cell against stress-induced oxidative, heat, and cytokine insult (Kiang and Tsokos, 1998). HSPs have also been reported to prevent protein aggregation and refold damaged proteins (Moseley, 1997). Voluntary physical activity increases levels of HSPs in the rat brain, and particularly in response to acute psychological or physical stress (Campisi et al., 2003). Since exercise training increases levels of HSP70 in a dose-dependent manner, this is one possible mechanism for physical activity to confer stress resilience or resistance to AD by promoting clearance of Aβ or other proteins/debris from the brain. Exercise intensity dependent increases in mRNA levels in the hippocampus and cortex for Aβ clearance factors such as; neprilysin, HSP70, LRP1, and LRP2 have also been shown (Moore et al., 2016) as well as, increases in protein levels in the cortex and hippocampus for neprilysin, insulin degrading enzyme (IDE), MMP9, LRP1, and HSP70. In addition to changes in receptors and enzymes, another factor that may contribute to clearance efficiency is cerebral blood flow. Chronic stress decreases local cerebral blood flow in the rat hippocampus (Endo et al., 1999), and region-specific increases in cerebral blood flow have been reported following physical activity of moderate intensity (approximately 60% maximal oxygen uptake) in humans (Ide and Secher, 2000; Ogoh and Ainslie, 2009). An overall improvement in global or regional cerebral blood flow could minimize the effects of hypoperfusion in AD, which may also promote clearance of Aβ and other AD related proteins.

7.2. Improved neuroprotection

Brain-derived neurotrophic factor (BDNF), which is highly
expressed in brain regions involved in AD, has many beneficial effects on cognition and synaptic plasticity (Fumagalli et al., 2006). Chronic stress has been shown to reduce BDNF levels, particularly in the hippocampus, in several animal models (Aleisa et al., 2006; Schaaf et al., 2000; Smith et al., 1995). Higher serum levels of BDNF are correlated with lower risk for developing dementia (Aisen, 2014; Laske et al., 2011). Higher serum levels of BDNF are correlated with lower risk for developing dementia (Aisen, 2014; Laske et al., 2011). In humans, acute exercise causes an increase in BDNF in peripheral blood that is directly correlated with exercise intensity (Dinoff et al., 2017), and chronic exercise training results in higher resting levels of BDNF in circulation in both men and women (Dinoff et al., 2016). Stem cell production is modulated by homeostasis to keep pace with physiological demands such as exercise (Nakada et al., 2011), so physical activity and exercise training may prevent the age-related decline in neurogenesis and impaired HPA axis homeostasis. Keeping these homeostatic mechanisms intact for a longer time would slow aspects of disease progression driven by disrupting metabolism and HPA axis function. Adlard and Cotman (2004) reported that voluntary physical activity protected against a stress-induced decrease in hippocampal BDNF, and that corticosterone directly modulates alterations in hippocampal BDNF. Short term (5 days of 30 min/day at 15 m/min) treadmill exercise in rats also increased BDNF, which was suppressed by chronic (2hr/day) immobilization stress (Fang et al., 2013). Immobilization stress reduced synaptic markers, which was reversed by treadmill exercise. Voluntary physical activity (wheel running) did not have a significant effect on neurogenesis and LTP until 56 days of running (Patten et al., 2013), suggesting it may take longer to reach a physiological benefit with voluntary physical activity compared to exercise training. It is well established that physical activity and exercise training increase hippocampal BDNF (Cotman and Berchtold, 2002; van Praag et al., 2005, 1999) and given the correlations with BDNF and dementia risk in humans, increasing hippocampal BDNF through exercise is another pathway through which exercise can buffer the effects of stress in AD.

Increased levels of reactive oxygen species in the brain occur as we age and play a role in many chronic diseases, including AD. Chronic stress accelerated AD pathology and increased markers of oxidative stress in Tg2576 mice (Lee et al., 2009). While high levels of acute physical activity increase oxidative stress, chronic physical activity regimens have been shown to decrease the activity of enzymes that generate oxidation, and increase the activity of antioxidant enzymes such as SOD1 and SOD3 (reviewed in Kojda and Hambrecht, 2005). In AD transgenic mouse models this has been demonstrated to occur with both voluntary (García-Mesa et al., 2016, 2012, 2011) and forced (Bo et al., 2014; Cho et al., 2010; Um et al., 2008) chronic physical activity. While it remains to be determined if exercise training after damage from oxidative stress has occurred can successfully repair damage, it appears that exercise training prior to the development of AD pathology may provide resistance to the negative effects of oxidative stress in AD, as well as protect against stress-induced increases in oxidative stress in the brain.

### 7.3. Improved homeostatic functions

Peripheral insulin resistance is associated with impaired cognition and lower hippocampal volume (Rasgon et al., 2011), and alterations in insulin sensitivity and insulin signaling occur in individuals with AD (reviewed in Stanley et al., 2016). Increasing glucose in the blood and brain increases extracellular Aβ in the brains of APP/PS1 mice (Macarley et al., 2015). Acute stress increases glucose in the blood/brain to mobilize resources for the fight or flight response, while chronic stress leads to insulin resistance and impaired glucose metabolism. Exercise training results in multiple beneficial adaptations in skeletal muscles to increase glucose transporters and improve overall glucose control. The effects of exercise on glucose regulation have been...
shown to be intensity dependent with higher intensity exercise resulting in more significant changes in glucose regulation or insulin sensitivity (Malin et al., 2016). Improved regulation of glucose metabolism improves whole body homeostasis which ultimately protects against the effects of stress and the development/progression of AD through multiple pathways.

A review by Nation et al. (2011) lays out the involvement of both stress and exercise on the neurovascular system in AD. The well-documented effects of exercise and physical fitness on the cardiovascular system have important indications for exercise training in the prevention and treatment of AD. The more common sporadic form of AD is closely associated with vascular disease, with many major risk factors for cardiovascular disease also being recognized as risk factors for AD (Martins et al., 2006). Many of the physiological processes shown to be impaired in AD are improved with increased physical activity. Furthermore, many of the physiological processes shown to be altered with chronic stress are factors that worsen cardiovascular disease and AD. Therefore, there is a close relationship between the cardiovascular and stress systems and both play a role in the development and progression of AD. Physical fitness to improve the cardiovascular system appears to directly counteract the effects of stress on AD pathology.

Exercise has been shown to provide resistance to stress-induced immune impairment, particularly in response to a challenge (Fleschner, 2005). The immune response regulation is impaired in AD (Marx et al., 1999) and exercise may benefit AD in this regard by strengthening the immune system, as well as suppressing the immune response to stress (stress resistance) in the first place. Studies in aged animals show that areas of the brain, particularly the hippocampus, have an exaggerated immune response with prolonged elevation of pro-inflammatory cytokines following an immune challenge (Barrientos et al., 2015, 2012), suggesting regulation of the immune system in the brain decreases with age. Physical activity has become increasingly recognized as a potential intervention to reduce chronic inflammation (Arikawa et al., 2011; Di Raimondo et al., 2013; Glessen et al., 2011). Resistance to stress-induced suppression of immune function was not observed in conditions of forced exercise, however (Fleschner, 2005), suggesting that the negative effects of stress occurring at the same time as physical activity may suppress benefits on immune system regulation. Future studies to determine if the benefits in immune function are exercise intensity dependent or if duration of physical activity is a more critical factor for modulating immune responses to stress in AD will be important.

Sleep disturbances and circadian rhythm dysfunction are tightly linked with the development and progression of AD (reviewed in Musiek et al., 2015). Many studies have found impairments in the sleep-wake cycle increase cognitive and pathophysiological changes in AD mouse models (Holth et al., 2017; Kang et al., 2009; Roh et al., 2014). Studies of the effects of exercise in animals and humans have shown increased sleep quality (Lancel et al., 2003, 2001; Netzer et al.; Torsvall et al., 1984), while chronic stress shortens duration of sleep and disrupts sleep maintenance resulting in overall reduced sleep quality (Cheeta et al., 1997). Long term physical activity changes sleep physiology (Lancel et al., 2003), with wheel running mice showing fewer, but longer sleep episodes compared to sedentary controls indicating better sleep consolidation. Voluntary physical activity in rats also prevented stress-induced disruptions in sleep quality (Thompson et al., 2016). McCurry et al. (2011) studied the effects of 30 min of continuous walking/day for at least 4 days/week on the effect of sleep in patients with AD. They found that physical activity resulted in significantly less total wake time and better sleep efficiency after six months of intervention. The type of exercise or the stress involved may play a role in the degree of influence exercise has on sleep. Improving sleep quality is beneficial in AD and determining mechanisms to protect the brain from stress-induced sleep dysfunction could be an important intervention strategy.

7.4. Improved regulation in neurotransmitter systems

Stress and exercise also affect several neurotransmitter systems. Glucocorticoids influence synaptic plasticity by altering glutamate receptor density and function in the hippocampus, amygdala and prefrontal cortex (de Kloet et al., 2002; Yuen et al., 2011). GCs enhance calcium influx through NMDA receptors, which underlies both LTP and LTD (Tse et al., 2011). This has an acute effect of memory enhancement (Yuen et al., 2011), however chronic over-excitation or excessively high corticosterone concentrations lead to reduced LTP and memory impairment (Zhang et al., 2012). Exercise can induce changes in regulation of the glutamatergic system that together with upregulation of neurotrophic factors may be protective against excitotoxicity associated with over-activation of the glutamatergic system caused by stress (Dietrich et al., 2005). Exercise, and mild stress, increase noradrenaline release which stimulates phosphorylation of the AMPA receptor subtype GluR1 and mobilizes GluR1-containing receptors to the synapse, therefore enhancing LTP (Hu et al., 2007). Repeatedly activating the NE system through physical activity may protect against psychological stress by producing a habituation-like effect on the system. For example, chronic physical activity induced an adaptation in the locus coeruleus that helped constrain activity in this brain region during exposure to non-exercise stressors such as shock (Dishman et al., 1997; Greenwood et al., 2003).

There is also evidence that the serotonergic system is severely affected in AD and that increasing serotonergic signaling can reduce Aβ levels in the brain (Cirrito et al., 2011; Fisher et al., 2016; Li et al., 2017; Sheline et al., 2014). Stress affects many aspects of the serotonergic system with regulation by GCs depending on the brain region and type of stressor involved. Greenwood et al. (2005) reported hyperactivation of serotonergic neurons in response to acute stress, which could lead to depletion of serotonin under chronic conditions. Regular aerobic physical activity has been shown to increase serum levels of serotonin in humans (Fumoto et al., 2010). Increasing serotonin in the brains of APP/PS1 mice, either directly or through receptor signaling mechanisms, resulted in a significant decrease in Aβ levels (Cirrito et al., 2011). Taken together, increasing serotonin regulation in the brain through physical activity may protect against stress-induced depletion of serotonin and improve cognitive and pathophysiological features in AD.

8. Summary and conclusions

Humans are constantly bombarded by physicians and the media with challenges to reduce psychological stress and increase physical activity to improve health and reduce risk of chronic disease, including AD. For some individuals, however, both the thought and act of daily exercise imposes psychological stress. It is clear that stress increases the risk and exacerbates the symptoms of AD (Dong and Csernansky, 2009). It is equally clear that chronic physical activity decreases AD risk (Intlekofer and Cotman, 2013). Given that acute exercise can both cause stress and be protective against AD when incorporated into a chronic exercise training regimen, this interaction has been investigated in an attempt to elucidate the net effect of these two opposing forces on the disease process.

Voluntary wheel running has been utilized in transgenic mouse models of AD to investigate the effects of chronic physical activity on AD related outcomes in the absence of psychological stress that can accompany an exercise bout. Taken collectively, the results of these studies (summarized in Table 1) suggest that chronic voluntary physical activity is beneficial in enhancing physiological parameters and cognitive function associated with reduced AD risk. However, not all studies confirm this, and the effects are subtle in most of the studies that do support this concept. One likely factor causing the discrepancy in these studies is that exercise intensity is directly related to the magnitude of the effect of physical activity on improving AD-related outcomes, and
there is an intensity threshold below which the effects are not realized. While mice run great distances in wheel running paradigms, the average intensity at which they run is typically very low compared to treadmill running regimens. Establishing physiological training effects in these regimens will be important for determining where this threshold lies.

Treadmill running introduces the element of psychological stress into the paradigm as the mouse must keep up with the set speed of the treadmill and, in most cases, must avoid a small electrical shock if it does not maintain the treadmill speed. Our study (Yuede et al., 2009) directly comparing wheel running vs. treadmill running of the same intensity, duration, and frequency demonstrated that when psychological stress is removed from the chronic physical activity condition, AD-related outcomes are improved to a greater degree than when psychological stress is present. However, treadmill running did result in improved AD outcomes over sedentary mice indicating that the benefits of forced exercise outweighed the negative effects of the psychological stress associated with the activity. When taken collectively, studies that employed treadmill running as the sole chronic physical activity treatment (summarized in Table 2) suggest that the benefits of physical activity outweigh the detrimental effects of psychological stress on AD outcomes. As with wheel running, this conclusion is not universally supported by all studies and, of course, the results are more subtle than robust. Treadmill running intensity overall was greater than that estimated in the wheel running studies (4.2–32.0 m/min), but training effects with both types of running might actually be relatively low as a significant increase in citrate synthase levels as an objective marker of exercise training was found at higher intensities (Lin et al., 2015; Moore et al., 2016). Tg2576 mice running at 15 m/min had modest improvement in AD outcomes similar to those of previous studies employing treadmill running. However, mice running at 32 m/min on a 10% grade, a much greater intensity than other treadmill running studies, showed robust improvement in several pathophysiological markers of AD (Moore et al., 2016). Both groups had elevated soleus muscle citrate synthase activity demonstrating a greater exercise training effect in the high intensity group compared to the low intensity group. These results provide strong evidence for a dose-response of exercise training on AD risk outweighing the negative impact of the stress involved in forced treadmill exercise. Differences in intensity, which is rarely measured directly by something such as citrate synthase activity, between exercise studies relating to AD may also account for apparent inconsistent findings in the literature.

Future studies are needed into the effects of the quantity (intensity, duration, and frequency) of chronic physical activity on AD outcomes as well as the thresholds needed to induced stress resistance or resilience and the mechanisms associated with those outcomes. Health benefits from chronic physical activity regimens could result directly from physical activity enhancing cell, tissue, and organ function or it could come indirectly from the acute bouts of physical activity within the chronic regimen resulting in reducing psychological stress, i.e., taking a walk on a nature trail is a good way to “blow off steam.” Theoretically, exercise training would primarily provide health benefits by directly enhancing health associated with enhanced physiological function, while sub-exercise training physical activity regimens would primarily act by relieving psychological stress.

Many epidemiological studies support the idea that increased physical activity can slow the progression of AD and other neurodegenerative disorders (Beckett et al., 2015; Lautenschlager et al., 2008; Reynolds et al., 2016). A report by Norton et al. (2014) found that 21% of AD cases in the US could be attributed to physical inactivity, making chronic physical activity a powerful tool for decreasing AD risk. While psychological stress is clearly associated with declines in AD, the benefits from chronic physical activity may outweigh the amount of stress associated with the regimen. A study by Ridgel et al. (2009) evaluated the effects of forced and voluntary exercise on motor function in individuals with Parkinson’s disease and found that only the individuals who were forced to achieve an exercise intensity that was higher than their voluntary exercise rate showed significant disease symptom-modifying benefits from the intervention. Although the ideal physical activity regimen for individuals with AD has yet to be clearly described, there is increasing evidence that improving muscle strength, balance, and aerobic capacity will provide valuable health benefits to counteract the pathophysiology of the disease.

The effects of acute exercise and stress have many overlapping components that allow for dissecting out positive stress and negative stress on the system. The opposing effects of stress and exercise allow us to identify mechanisms that can determine vulnerability or resistance to AD. Of course, these mechanisms do not occur in isolation and many interactions could either enhance or diminish the positive effects of exercise on stress in AD. The effects of stress on the system and the circuitry involved in the stress response differ between males and females, and is more recently becoming the focus of many important studies determining the risk of stress on the development of AD (Bangasser et al., 2017). It is also possible that the effects of exercise on the neuroendocrine system are different for males and females. The effects of physical activity in AD can be viewed as a multi-target drug, especially in counteracting the well-documented negative effects of stress on the disease. These interactions need to be studied further to fully understand the frequency, intensity, and duration of physical activity required as well as the timing performed in relation to stress to determine the optimal guidelines to target different aspects of the disease.

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