

REVIEW ARTICLE

Exercise, Fitness and the Aging Brain: A Review of Functional Connectivity in Aging

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ABSTRACT

Aging is associated with changes in brain structure and function with some brain regions showing more age-related deterioration than others. There is evidence that regional changes in brain structure and function may affect the functioning of other, less- age-sensitive brain regions and lead to more global changes in brain efficiency and cognitive functioning. Fortunately, emerging evidence from health neuroscience suggests that age-related brain changes and associated cognitive declines may not be inevitable. In fact, they may even be reversible. Exercise is a particularly promising health behavior known to induce changes in regional brain structure and function in older adults. However, much less is known about how exercise affects the organization of brain networks in late life. The purpose of this review is to summarize what is known to date regarding the relationships between functional connectivity, exercise, fitness, and physical activity in aging. A critical summary of this literature may reveal novel mechanisms by which physical activity influences brain health, which in turn may be leveraged to improve other aspects of functioning, including physical, cognitive, and mental health in late life.

1. Introduction: Unprecedented increases in life expectancy and the resulting rapid growth in the proportion of older adults in societies across the globe have led to international interest in how to promote healthier aging--i.e., how to ensure all individuals age "successfully." Successful

aging is a descriptor typically used to describe individuals who maintain their cognitive and physical functioning in late life in comparison to their less fortunate counterparts who experience greater deteriorations in these domains (Bowling & Dieppe, 2005).

Individual variability in age-related cognitive decline is linked to variations in the rates of brain structural atrophy (Driscoll et al., 2009; D. Ferreira et al., 2014; Fjell, McEvoy, Holland, Dale, & Walhovd, 2013) and functional activation changes (Grady, 2008; Lustig et al., 2003). In addition, these changes are more pronounced in some brain regions than in others. For example, age-related reductions in gray matter volume of the temporal and prefrontal cortices are associated with poorer memory function (Fjell et al., 2013) and a greater risk for future cognitive impairment (Driscoll et al., 2009). Similarly, greater, more sustained functional brain activation in frontal, temporal, and parietal brain regions during cognitive tasks in older adults has been linked to better working memory performance compared to older adults with less activation in these regions, but both groups perform worse than young adults (Grady, 2008). Further, older adults who exhibit patterns of brain activation more similar to younger adults, tend to perform better on cognitive tasks and have a lower risk of developing cognitive impairment (Spreng, Wojtowicz, & Grady, 2010; Woodard et al., 2010). These findings have provided support for the idea that over-recruitment of certain brain regions in older adults during cognitive tasks is adaptive (Park & Reuter-Lorenz, 2009). That is, since the overactivation in certain brain regions is often associated with better behavioral performance, older adults displaying such a pattern are effectively compensating for brain aging. Nevertheless, not all age-related increases in brain activation can be interpreted as compensatory, and some are

more indicative of neural inefficiency, impending cognitive impairment, and loss of functional independence (Dickerson et al., 2005; Jiang, Petok, Howard, & Howard, 2017; Woodard et al., 2010).

Crucially, regionally-specific structural and functional activation changes in the aging brain do not happen in isolation. There is growing evidence that regional brain changes indirectly affect the functioning of other, less- age-sensitive brain regions and lead to more global changes in brain efficiency (described in more depth in a following section). This realization has led to an increased interest in examining patterns of functional connectivity in aging, or the integrated communication amongst physically disparate brain regions. Studies of functional connectivity can be grouped into two general categories: Those conducted in the resting state (resting state-connectivity) vs. those conducted while individuals perform a task (task-evoked connectivity).

Resting state connectivity patterns are thought to reflect the intrinsic communication patterns amongst groups of brain regions, or networks. This is in contrast to task-evoked connectivity which is the communication amongst the brain regions involved in a particular task. Across both of these types of functional connectivity studies, aging has been associated with a decrease in the efficiency of brain networks (Damoiseaux et al., 2008; La Corte et al., 2016; Madden et al., 2010; Onoda & Yamaguchi, 2013; Sala-Llonch, Bartrés-Faz, & Junqué, 2015; Stanley et al., 2015). In fact, these more global changes in brain efficiency are so pronounced that it is

possible to distinguish older from younger adults using functional connectivity patterns alone (La Corte et al., 2016). This troubling finding begs the question as to whether or not we can do anything to prevent, or at least slow, brain aging.

Fortunately, emerging evidence from health neuroscience supports the argument that age-related brain changes and associated cognitive declines are not inevitable. In fact, they may even be reversible. This is because we now know that the brain is plastic, even into late adulthood and is therefore amenable to health behaviors. Exercise has been shown to induce changes in regional brain structure and function in older adults (for reviews see Colcombe et al., 2006; Hillman, Erickson, & Kramer, 2008). However, less is known about how exercise affects the organization of brain networks in late life. It is critically important to examine this question because it may reveal novel mechanisms by which physical activity influences brain health, which in turn may be leveraged to improve other aspects of functioning, including physical, cognitive, and mental health.

The number of studies examining the relationship of physical activity and fitness on brain functional networks has exploded over the last several years. However, to date most reviews on physical activity and brain aging are focused on structural aspects of brain health (e.g., gray matter volume). The purpose of this review is to summarize what is known to date regarding the relationships between functional connectivity and exercise, fitness, and physical activity in aging. Because of our choice to focus on

aging, we will not be covering studies that have examined the relationships between exercise and functional connectivity in younger age groups (e.g., children and younger adults), nor will we be covering studies of structural connectivity.

1.1 Patterns of functional connectivity in healthy and pathological aging: Patterns of signal covariation between anatomically distributed brain regions are thought to represent the organization of these regions into distinct functional networks. Examination of how these patterns are modulated by the engagement of various cognitive processes or states has advanced our understanding of the neural mechanisms that support these processes, both in health and disease. The preponderance of studies that have examined functional network organization in the context of healthy and pathological aging have focused on patterns of inter-regional communication that occur at rest in the absence of any deliberate cognitive processing, or when in a “resting” state. Patterns of resting state functional connectivity have been hypothesized to reflect the “intrinsic” network architecture of the brain (Cole, Bassett, Power, Braver, & Petersen, 2014; Fox et al., 2005). Brain regions that are anatomically connected via white matter tracts are more likely to exhibit signal coherence at rest (Greicius, Supekar, Menon, & Dougherty, 2009; Honey et al., 2009). However, even structurally disconnected regions can exhibit strong functional connectivity. Moreover, resting state connectivity has been shown to be stronger in brain networks that are similarly engaged during the performance of tasks

within related domains (Cole et al., 2014; Fox et al., 2005). This suggests that brain regions that participate in overlapping cognitive domains form cohesive functional networks independently of cognitive demands. Connectivity patterns observed at rest may therefore reveal insights about both context-free and context-dependent brain network function in late life.

Normal aging is associated with cognitive decline even in the absence of overt neuropathological processes, with age-related decline being most evident in domains of attention, memory, and executive functioning (Hedden & Gabrieli, 2004; Salthouse, Atkinson, & Berish, 2003; von Hippel & Dunlop, 2005). Research has demonstrated that the cognitive changes that occur in the context of healthy aging are accompanied by alterations in functional network integrity (Andrews-Hanna et al., 2007; Hedden & Gabrieli, 2004; Tomasi & Volkow, 2012), providing some evidence that functional network disruption in non-pathological aging may contribute to the progression of cognitive decline and may therefore yield important insights regarding the neural mechanisms underlying more severe neurodegenerative states. For a more comprehensive review of neural network changes that occur with normal aging (for review see L. K. Ferreira & Busatto, 2013).

The most pronounced age-related changes in functional connectivity have been observed in the default mode network (DMN), a cohesive functional network that is involved in internally-guided and self-referential processes (Greicius, Krasnow, Reiss, & Menon, 2003) and is comprised of regions

that are critical for the cognitive processes most sensitive to aging (e.g., medial prefrontal cortex, posterior cingulate cortex, and the extended hippocampus (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010). In general, the density and strength of functional connections within the DMN has been shown to be reduced in both normal and pathological aging (Damoiseaux et al., 2008; Hafkemeijer, van der Grond, & Rombouts, 2012; Jones et al., 2011; Tomasi & Volkow, 2012). Interestingly, regions comprising the DMN are particularly vulnerable to the neurotoxic processes that give rise to amyloid deposition, one of the neuropathological signatures of Alzheimer's disease (AD) (Buckner, Andrews-Hanna, & Schacter, 2008). Further, amyloid pathology has been associated with reduced DMN coherence in cognitively healthy older adults (Sheline et al., 2010; Sperling et al., 2009), which may indicate that disruption in this network mediates the relationship between amyloid accumulation and subsequent cognitive decline. In support of this hypothesis, DMN integrity has been shown to distinguish individuals with mild cognitive impairment (MCI) who later develop AD from those who do not (Petrella, Sheldon, Prince, Calhoun, & Doraiswamy, 2011), raising the possibility that disruption of the DMN may precede the development of AD and thus represents a preclinical signature of later disease progression. On the other hand, there is evidence that exercise repairs age-related disruptions of the DMN (Boraxbekk, Salami, Wåhlin, & Nyberg, 2016; Voss, Prakash, et al., 2010a), suggesting that this network may preferentially benefit from the

health promoting effects of exercise. These studies highlight the centrality of the DMN in both healthy and pathological brain aging, as well as the potential for exercise to mitigate the deleterious effects of aging on this network.

This general pattern of weakened functional connectivity with age has also been observed in other networks. Global disruptions of both short (Supekar, Menon, Rubin, Musen, & Greicius, 2008) and long range (Sanz-Arigitia et al., 2010; Stam, Jones, Nolte, Breakspear, & Scheltens, 2007) connections throughout the brain have been documented in AD. Further, there is evidence of network-specific disruptions in functional coherence with aging. For instance, the density of long range connections within the dorsal attention network (DAN) has been shown to be reduced in non-pathological aging (Tomasi & Volkow, 2012). Reduced connectivity strength between nodes of the DAN has also been observed in individuals with frontotemporal dementia (Filippi et al., 2013) and AD (Li et al., 2012). This network is comprised of regions of visual and parietal cortex and directs adaptive orientation of attention in response to salient changes in the environment (Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013; Vossel, Geng, & Fink, 2014). Disrupted communication within this network may underlie impairments in attention that occur with age. Similarly, research has demonstrated that the integrity of the salience network, a large-scale network anchored in the anterior insula and dorsal anterior cingulate cortex (Menon,

2015), is compromised in both normal and pathological aging. Evidence suggests that signal coherence in the salience network declines with increasing age among cognitively healthy older adults, with more severe disruptions of this network being associated with worsened executive functioning (Onoda, Ishihara, & Yamaguchi, 2012). Further, individuals with AD exhibit more pronounced disruptions in this network relative to similarly aged individuals without cognitive impairments (Brier et al., 2012). The salience network is involved in the detection of salient events in the environment and the coordination of responses to those events, and is thus fundamental to numerous cognitive and affective processes (Menon, 2015). Given these functions, it is possible that weakening of communication within this network contributes to age-related disturbances in both cognitive and psychological functioning.

Overall, these findings suggest that disruption of large-scale functional networks is a feature of both normal and pathological aging. In light of evidence suggesting that reduced intra- and inter-network signal coherence may underlie the development and progression of cognitive impairments in older adults, it is imperative to identify interventions that may slow or reverse these functional changes. Exercise interventions represent a promising approach to mitigate these neurofunctional changes to promote healthy brain aging.

1.2 Definitions: Before we begin summarizing the studies examining the relationship of functional connectivity to

exercise, fitness, and physical activity in aging, we will first define how the field distinguishes between these related, yet distinct terms. *Physical activity* (PA) is the most encompassing of the terms as it refers to any bodily movement of the skeletal muscles that produces energy expenditure (Caspersen, Powell, & Christenson, 1985). PA therefore includes structured activities aimed at improving health (e.g., jogging), as well as leisure activities that involve movement and thus, inadvertently, energy expenditure (e.g., gardening, grocery shopping). In the context of research, PA can be assessed via self-report--i.e., asking people how much PA they partake in during a typical time period--or, via objective PA monitoring using person-worn devices such as accelerometers. Given that people, particularly older adults, are notoriously inaccurate at reporting their own PA levels (Colbert, Matthews, Havighurst, Kim, & Schoeller, 2011), objective PA measurements are considered the gold standard. However, there are some self-report questionnaires designed to more accurately detect PA levels in older adults (Harada, Chiu, King, & Stewart, 2001), and self-report is frequently the only option in larger, epidemiological studies due to the practical limitations of objectively monitoring very large samples over time.

Exercise is a specific form of PA that is planned, structured, and repetitive. Exercise is a behavior that is designed to improve one's physical fitness, but these two terms are not equivalent. In this review, we will use the term exercise only when referring to structured PA training conducted in the

context of a randomized clinical trial (RCT). In RCTs, (typically) sedentary participants are randomly assigned to partake in either an aerobic exercise or non-aerobic or no-contact control intervention. Because of the random assignment that occurs in RCTs, it is more likely that any changes in brain or behavior are attributable to exercise and not to other confounding factors. *Physical fitness* is a term that can refer to either physical (e.g., muscular or cardiorespiratory strength) or functional (e.g., skill level) attributes (Caspersen et al., 1985). However, for the purposes of this review we will use the term fitness to refer solely to *cardiorespiratory fitness*, which refers to the ability of the cardiovascular system to supply oxygen to the skeletal muscles during sustained PA. The gold standard for assessing this type of fitness is via a *Maximal Volume of Oxygen (VO₂max) test*, which measures the maximum rate of oxygen consumption during exercise of increasing intensity. Changes in VO₂max are often a main outcome of exercise RCTs. However, it should be noted that while engaging in exercise increases VO₂max, there are also other factors (e.g., genetics, gender) that can contribute to variation in VO₂max levels (Guth & Roth, 2013). For this reason, studies assessing associations with fitness cannot attribute any detected relationships to changes in exercise, per se, because fitness is a measure *related* to exercise behavior, but is not a measurement of the behavior itself.

2. Associations with fitness and physical activity (cross sectional work): Initial evidence supporting a link

between cardiorespiratory fitness, PA, and functional network integrity comes from a handful of cross-sectional studies in which fitness or PA levels were examined in relation to functional connectivity (Veldsman et al., 2017; Voss, Erickson, et al., 2010b; Voss et al., 2016). These studies predominantly focused on the age-vulnerable large scale resting state networks, described above. For example, using a seed-based approach centered on the posterior cingulate, Voss and colleagues (2010b) demonstrated that in comparison to a group of 32 young adult controls, 120 healthy older adults showed overall reduced functional connectivity within the DMN. While increasing age was associated with DMN disruption, older adults with high levels of aerobic fitness displayed patterns of DMN connectivity comparable to that of the young adults (Voss, Erickson, et al., 2010b). In addition, metrics of both specific and global DMN connectivity were found to mediate the relationship between fitness and executive control performance (Wisconsin Card Sorting Task (WCST) Perseverative Errors) in the sample (Voss, Erickson, et al., 2010b). These results support the argument that higher fitness levels may help mitigate the effects of normal aging on large scale age-vulnerable networks, such as the DMN.

A similar relationship was observed between fitness, DMN and DAN connectivity, and executive functioning in another sample of 189 healthy older adults (Voss et al., 2016). This study further extended previous findings by demonstrating that associations between fitness and connectivity of age-vulnerable large-scale networks can be

observed independently of current PA levels in older adults. However, PA levels *do* appear to explain variance in the connectivity of large-scale networks in other populations. For example, an association between objectively measured physical activity and functional connectivity of the dorsal attention network (DAN) was detected in a sample of 62 stroke survivors (Veldsman et al., 2017). A similar relationship for DMN connectivity was observed in a longitudinal study of healthy older adults using self-reported PA accumulated over the previous decade (Boraxbekk et al., 2016). In addition, fitness-related DAN connections were associated with improvements in attentional processes in the stroke patient sample (Veldsman et al., 2017). These findings suggest that variability in aerobic fitness and PA is associated with functional connectivity which can explain variability in cognitive performance of both healthy older adults, as well as in stroke survivors. However, due to the correlational nature of these studies, it is not possible to determine directionality of these associations. Fortunately, a number of RCTs have included measures of functional connectivity, and so it is possible to more definitively determine the direction of these associations.

3. Effect of exercise interventions on functional network organization:

To date, there have been 9 studies to use an intervention framework (eight RCTs, one non-randomized intervention) to examine the effect of exercise on functional connectivity in older adults. One additional

study examined the effects of functional connectivity metrics (i.e., modularity) on future responsiveness to an exercise RCT (Baniqued et al., 2017). Across these studies, there is considerable heterogeneity in the size, content, and duration of these interventions (**Table 1**). Across studies, there was a wide distribution in participant age, ranging from 50 - 88 years ($M_{age} = 69.93$, $SD = 4.60$). With the exception of one study (Chirles et al., 2017), all participants were cognitively healthy, and all studies excluded individuals with major medical conditions that might limit their ability to safely participate in an exercise program. Sample sizes tended to be small (mean $N = 47.66$, $SD = 45.99$), particularly when considering that samples were further divided by condition. Mean trial duration was 5.25 months ($SD = 3.03$), with the longest trial lasting 12 months and the shortest just six weeks. Intervention conditions primarily consisted of a combination of supervised and unsupervised walking sessions titrated so that participants reached 50-80% of their maximum heart rate, though several interventions also included other aerobic activities in their exercise protocols, such as cycling (McGregor et al., 2018; Prehn et al., 2017), dancing (Voss et al., 2019), and/or jogging (Flodin, Jonasson, Riklund, Nyberg, & Boraxbekk, 2017). One study employed a commercially available video game designed to enhance fitness that included a variety of both aerobic (dancing, running in place) and strength (e.g., yoga) exercises, with participants completing all exercise sessions independently in their own homes. The majority of RCTs ($n = 5$) included an

active control condition that mimicked the exercise condition in all aspects (e.g., number and duration of weekly sessions, amount of social contact) except in the non-aerobic nature of the activities prescribed. Further, most interventions included elements designed to maximize adherence to exercise protocols (e.g., PA monitoring with actigraphy) and ensure that participants' heart rate reached the targeted aerobic zone (e.g., using heart rate monitoring). However, few studies reported adherence and compliance statistics.

Given the methodological variations noted above, it is perhaps not surprising that there is also heterogeneity in the observed effects of exercise on indices of network integrity. Nevertheless, some general patterns seem to emerge, namely that engagement in exercise is associated with increased functional coherence within several networks. For instance, exercise has been shown to enhance resting connectivity within the DMN (Flodin et al., 2017; Voss, Prakash, et al., 2010a) as well as cross-network connectivity between nodes of the DMN and regions situated within other networks (e.g., sensorimotor network: McGregor et al., 2018; Chirles et al., 2017; executive control network: Prehn et al., 2017). However, other studies observed reductions in DMN coherence with exercise (Ji, Zhang, Potter, Zang, Steffens et al., 2017) or found no effect of exercise on intra- or inter-network connectivity of the DMN (Voss et al., 2019). Cross-study methodological heterogeneity may explain these inconsistencies. For instance, the intervention conducted by Ji et al. (2017) was the shortest in duration (six

weeks), and employed a fitness game that included both aerobic and strength exercises. It is possible that non-aerobic exercise exerts unique effects on DMN connectivity compared to aerobic exercise. Indeed, there is evidence that improvements in aerobic fitness levels may mediate some proportion of the effects of exercise on DMN connectivity (Flodin et al., 2017; McGregor et al., 2018), indicating that aerobic exercise may contribute more robustly to functional network integrity compared to other non-aerobic forms of exercise. Further, one study found evidence to suggest that the magnitude and direction of the relationship between exercise and DMN connectivity is dependent on premorbid cognitive status (Chirles et al., 2017). Specifically, 16 individuals with MCI exhibited enhanced whole-brain connectivity with the posterior cingulate cortex (PCC) and precuneus following 12 weeks of exercise, while a comparison group of 16 cognitively healthy older adults showed reduced connectivity of the PCC following the training period (Chirles et al., 2017). As such, it is possible that cognitive status at the start of an exercise program may moderate the effect of exercise on functional network organization, though the functional implications of these differences are not yet clear. Additional research using an RCT approach will be necessary to explore whether and how exercise-induced changes in functional network organization relates to changes in cognitive functioning for individuals with varying levels of premorbid cognitive impairment.

The effects of exercise on functional network organization are not limited to the DMN. For instance, the largest RCT to examine the effects of exercise on functional network organization in the context of aging found that 12 months of moderate intensity walking enhanced coherence in the salience and dorsal attention networks (Voss et al. 2019). Some of the effects of aerobic exercise on network organization were augmented by nutritional supplementation (Voss et al., 2019), suggesting that combined diet and exercise may exert synergistic effects on network signaling dynamics. Moreover, the degree of network modularity at baseline predicted improvements in executive functioning following the intervention (Baniqued et al., 2017), providing evidence that pre-existing network characteristics may influence their plasticity. Healthy brain networks are highly modular (Bullmore & Sporns, 2009; Meunier, Lambiotte, Fornito, Ersche, & Bullmore, 2009), and modularity decreases with age (Meunier, Achard, Morcom, & Bullmore, 2009). However, although the results reported by Baniqued et al. (2017) suggest that age-related decline in modularity may reduce sensitivity of individuals' brain networks to intervention, additional research is necessary to determine whether the reverse is also true--i.e., whether exercise alters indices of network modularity.

Interestingly, the salutary effects of exercise on these networks were not observed among individuals in an active comparison group that combined cognitive enrichment and exercise using dance training (Voss et al.,

2019). As the authors acknowledged, it is possible that cognitive enrichment in the form of dance instruction may have limited the time and intensity of the dancing itself, which may have interfered with functional network restructuring observed in the walking groups. Notably, though, the dancing group exhibited changes in structural connectivity within the fornix (Burzynska et al., 2017), which may indicate that exercise-induced changes in structural connectivity precede changes in functional connectivity. However, the nature and timing of the effects of exercise on structural vs. functional connectivity have yet to be resolved, and warrant further research.

There is also evidence that hippocampal connectivity is modified with exercise (Burdette et al., 2010; Flodin et al., 2017; Voss, Prakash, et al., 2010a), an effect that is consistent with and extends previous research demonstrating that exercise promotes hippocampal growth (Erickson et al., 2009, 2011) and improves hippocampal-dependent cognitive processes (Erickson et al., 2011). Moreover, hippocampal connectivity to posterior nodes of the DMN was shown to mediate the relationship between exercise and improvements in executive functioning (Voss, Prakash, et al., 2010a). Another study demonstrated that exercise-related reductions in signal coherence within the frontoparietal network was associated with faster performance on motor tasks (Hsu, Best, Wang, Voss, Hsiung et al., 2017). These studies provide some initial support for the hypothesis that exercise-induced changes in functional network organization are not merely

coincident to enhanced functioning but may actually represent a mechanism by which such improvements occur. It is important to note, however, that other studies did not find an association between functional network organization and cognitive functioning (Voss et al., 2019). Moreover, although many of the intervention studies conducted comprehensive cognitive assessments, they were likely underpowered to detect such relationships, highlighting the need for additional research with larger sample sizes that examine the functional consequences of network reorganization following an exercise program.

Table 1. Studies examining the relationship between physical activity, fitness, and exercise on functional connectivity in aging.

Author	Design	Variable(s) of interest	Sample Size (MRI sample if different than overall)	Mean Age (SD, or range if SD not reported)	Control condition	Intervention	Intervention duration
Baniqued, 2017	RCT	fitness, resting functional connectivity, cognition	43 (control), 46 (dance), 35 (walk), 39 (walk +)	Control: 65.85 (4.29); Dance: 65.66 (4.62); Walk: 65.49 (4.67); Walk +: 64.62 (4.1)	Flex/Tone/Balance	Dance, Walk, Walk+nutritional supplement	6 months
Burdette, 2010	RCT	fitness, resting functional connectivity	11 (6 Exercise; 5 Controls)	77.6 (5.0) Exercise; 74.0 (2.5) Education Controls	Healthy aging education; Cognitive training	Walking	4 months
Chirles, 2017	Training	exercise, resting connectivity	32 (16 MCI, 16 cognitively healthy) sedentary older adults	60-88; 79.6 (6.8) MCI; 76.1 (7.2) healthy controls	No control group	Walking	12 weeks
Flodin, 2017	RCT	fitness, resting functional connectivity, cognition	47 (22 Exercise; 25 Active Controls)	68.4 (2.6); 69.2 (3.01)	Stretch/Tone	Aerobic walking/jogging/cycling	6 months
Hsu, 2017	RCT (quasi)	fitness	21 (12 Exercise; 9 Controls); all participants had subcortical ischemic vascular cognitive impairment	69.9 (9.2) No Contact Controls; 72.0 (8.6) Exercise	Usual Care	Walking	6 months
Ji, 2017	RCT (quasi)	fitness, resting connectivity, cognition, psychological function	24 (12 Exercise; 12 Waitlist Control)	73.0 (8.0) Controls; 67.0 (6.4) Exercise	Waitlist	Wii fit (aerobic, balance, weight lifting, and yoga)	6 weeks

McGregor, 2018	RCT	fitness, resting functional connectivity, motor function	37 (19 Aerobic Exercise; 18 Stretch/Tone Controls)	73.5 (6.8)	Stretch/Tone	Cycling	12 weeks
Prehn, 2017	RCT	fitness	29 (18 Exercise; 11 Stretch/Tone Controls)	65 (6) Controls; 69 (5) Exercise	Stretch/Tone	Cycling	6 months
Voss, 2010a	RCT	fitness, resting functional connectivity, cognition	65 (30 Exercise; 35 Flex/Tone/Balance Controls)	65.37 (5.24) Controls; 67.30 (5.80) Exercise	Flex/Tone/Balance	Walking	12 months
Voss, 2019	RCT	fitness, resting functional connectivity, cognition	43 (control), 46 (dance), 35 (walk), 39 (walk +)	Control: 65.85 (4.29) Dance: 65.66 (4.62) Walk: 65.49 (4.67) Walk +: 64.62 (4.1)	Flex/Tone/Balance	Dance, Walk, or Walk+ nutritional supplement	6 months
Boraxbekk, 2016	longitudinal	self-reported PA, resting functional connectivity	196	64.6 (25-100)	n/a	n/a	n/a
Veldsman, 2016	cross-sectional	objective PA, resting connectivity, cognition	130 (68 stroke; 62 CN)	67.0 (12.6)	n/a	n/a	n/a
Voss, 2010b	cross-sectional	fitness, resting functional connectivity, cognition	120	66.5 (5.7)	n/a	n/a	n/a
Voss, 2016	cross-sectional	fitness, objective PA	189 OA; 36 YA	65.1 (4.4)	n/a	n/a	n/a

4. Discussion: In this review, we summarized the existing literature examining the relationship between functional connectivity, exercise training,

fitness, and PA in aging. Since 2010, there have been 14 studies on this topic, with 79% of these studies (11/14) published within the last 3 years. Collectively, the results from

these studies suggest that physical activity is an effective way to preserve or strengthen connectivity within large-scale brain networks known to be disrupted in both normal and pathological aging.

Surprisingly, the number of cross-sectional or longitudinal studies on this topic was far fewer ($N = 4$) than RCTs ($N = 8$), or non-randomized studies involving exercise training ($N = 1$). Nonetheless, all four of the existing cross-sectional/correlational studies report results consistent with the idea that more PA (as measured via self-report or objective monitoring; Boraxbeek *et al.*, 2016; Veldsman *et al.*, 2017) or higher fitness levels (Voss, Erickson, *et al.*, 2010b; Voss *et al.*, 2016) are linked to stronger connectivity within the default mode and dorsal attention networks in late life. Further, stronger connectivity within these networks was unanimously associated with better cognitive performance in older adults across the 3 studies that assessed cognition (Veldsman *et al.*, 2017; Voss, Erickson, *et al.*, 2010b; Voss *et al.*, 2016). Despite their correlational nature, the consistency of the overall positive fitness/PA - functional connectivity relationship across studies employing a diversity of functional connectivity techniques (e.g., seed-based, graph theory, ICA), cognitive outcomes (WCST, simple and choice reaction time, one-back), and populations (healthy older adults, stroke survivors) is remarkable and suggests a fairly robust relationship between these variables. Moreover, the presence of longitudinal evidence (Boraxbeek *et al.*, 2016) hints at a directional association between physical activity and functional

connectivity in which prior physical activity levels may precede variability in functional network strength later in life.

The exercise intervention literature more firmly supports a causal link between exercise behavior and functional connectivity in aging. Although the specific networks found to be influenced by exercise varied across studies, all 9 interventions observed changes in functional network organization amongst individuals who engaged in exercise compared to those who did not. DMN coherence was most often shown to be modified by exercise (Chirles *et al.*, 2017; Flodin *et al.*, 2017; McGregor *et al.*, 2018; Voss, Prakash, *et al.*, 2010a), an intriguing finding given that this network also appears to be most sensitive to the deleterious effects of aging relative to other large scale networks (Buckner *et al.*, 2008; Damoiseaux *et al.*, 2008; Hafkemeijer *et al.*, 2012; Jones *et al.*, 2011; Petrella *et al.*, 2011; Sheline *et al.*, 2010; Sperling *et al.*, 2009). Exercise-induced changes in functional network organization were also observed in the dorsal attention (Voss *et al.*, 2019), salience (Voss *et al.*, 2019), and frontal executive networks (Voss, Prakash, *et al.*, 2010a), each of which support cognitive processes known to decline with age (e.g., decision making, attentional control, conflict monitoring, inhibitory control, emotion recognition and regulation (Menon, 2015; Vessel *et al.*, 2014). Finally, hippocampal connectivity was found to be enhanced by exercise, an observation that is consistent with animal and human literature demonstrating that hippocampal structure and function are preferentially affected by

exercise (Erickson et al., 2009, 2011). Together, these studies provide evidence that exercise alters functional organization of networks that have been implicated in age-related pathology, which suggests that restoration of network integrity may represent one mechanism by which exercise promotes healthy cognitive aging.

4.1 Limitations: Despite these promising findings, there are several remaining questions that cannot be resolved based on the available evidence. First and foremost is the extent to which altered functional network organization following an exercise program ameliorates or slows age-related decline in functioning (e.g., cognitive, physical, socioemotional). As described above, there are some data to suggest that exercise-related changes in functional connectivity mediate improvements in cognitive and motor processes. However, few studies have examined the functional consequences of altered network organization, and those that have tended to focus on changes in cognitive performance at the exclusion of other potentially important functional domains (e.g., mood, mobility). Further, the majority of studies (12 of 15) only included cognitively healthy older adults, leaving open the question of whether the observed effects of exercise will generalize to individuals with MCI or more severe cognitive impairment. Indeed, there is some evidence that premorbid cognitive status moderates the effect of exercise on functional network organization (Chirles et al., 2017). Additional research is necessary to explore the efficacy of exercise on functional network organization at various

stages in the progression of cognitive decline to determine whether the benefits of exercise persist even at more severe stages of decline, as well as the most optimal time to intervene. Moreover, given the heterogeneity in the size and duration of the interventions reviewed herein, it is unclear how reliable or robust the observed patterns are. It will be imperative to examine the effect of exercise on functional network organization in the context of a large, well-controlled RCT.

The available research has also focused predominantly on examining exercise-induced changes in *intrinsic* functional connectivity, with very little research exploring how and whether exercise modulates network organization during the performance of specific tasks. Importantly, patterns of connectivity observed at rest may differ from patterns observed in the context of particular cognitive demands, with these dissociable patterns potentially mediating distinct aspects of functioning. Along these lines, all but one of the studies examining the relation between functional connectivity and exercise in aging focused on resting state connectivity, specifically within large-scale networks known to be disrupted with age. However, exercise is known to have regionally-specific effects on brain structure and function (Baek, 2016; Erickson, Leckie, & Weinstein, 2014). Thus, it may be the case that studies of functional connectivity in aging are actually underestimating the effects of exercise on network integrity since task-specific networks, or those centering specifically on exercise-sensitive regions, have not been examined in late life samples

(but see Stillman et al., 2018 for a relevant study in younger adults).

Finally, there is a dearth of studies examining the effects of exercise-related functional connectivity changes on non-cognitive outcomes in aging (e.g., mood, mobility). This represents a significant gap in our understanding of how exercise can best be used to promote successful aging. For example, depressed mood is associated with cognitive decline and dementia onset (Bassuk, Berkman, & Wypij, 1998; Geerlings et al., 2000), and has been shown to be responsive to the effects of exercise (Schuch et al., 2016). Moreover, depression is characterized by disruptions of the DMN (Hamilton, Farmer, Fogelman, & Gotlib, 2015), one of the primary networks implicated in age related cognitive decline that is also known to be sensitive to the effects of exercise (Chirles et al., 2017; Flodin et al., 2017; McGregor et al., 2018; Voss, Prakash, et al., 2010a). Given these associations, it is reasonable to hypothesize that exercise-induced changes in DMN coherence may yield improvements in mood independently of or in concert with improvements in cognitive functioning. Late-life depression is challenging to treat and accelerates decline in other aspects of functioning (Knöchel et al., 2015; Yuan et al., 2017), highlighting the need for additional research exploring the mechanisms by which exercise might impact mood outcomes in late life.

4.2 Future directions: While there is strong and consistent evidence that physical activity increases functional connectivity within certain large-scale networks in late

life, it is clear that the field is still in its infancy. As such, there are many questions that remain to be examined. Related to the limitations above, for example, the intervention characteristics (e.g, type and dosage of exercise) necessary to maximize effects on functional network integrity are still unknown. It will be important for the field to better standardize exercise interventions, as well as to more consistently report intervention outcomes such as adherence (% attendance and drop-out) and compliance (i.e., to heart rate goals). In addition, at least one study reported that the relationship between functional connectivity and exercise is bidirectional (Baniqued et al., 2017). That is, functional connectivity patterns may *predict* subsequent PA behavior or responsiveness to exercise interventions. In fact, using such a “brain as predictor” approach may be crucial to designing more personalized treatments as it may help identify individuals who would benefit most from exercise interventions, and identify key barriers to exercise adherence (Stillman & Erickson, 2018).

It will also be informative to examine the functional consequences of network reorganization following exercise. There is preliminary evidence that exercised-induced changes in functional connectivity may enhance cognitive functioning (Voss, Prakash, et al., 2010a), but few studies have examined this question. Therefore, it is unclear whether changes in network organization are coincidental to engagement in exercise or whether they represent a potential mechanistic pathway linking exercise to improved cognitive functioning.

Relatedly, it has yet to be determined whether exercise-related changes in network organization influence other processes known to affect and be affected by aging, including mood, motor functions, and general quality of life. It will also be important to explore the extent to which alterations in network coherence mediate the health benefits of exercise (e.g., improved glucose regulation, reduced inflammation). Addressing these questions will provide a more complete understanding of the (likely interactive) mechanisms by which exercise promotes successful aging.

Finally, additional research is necessary to determine whether exercise modifies network signaling dynamics during the performance of specific tasks that engage processes known to be disrupted in aging. There is evidence that task-evoked network connectivity may be dependent on intrinsic functional connectivity (Cole et al., 2014), suggesting that exercise-induced changes in network organization at rest may subsequently provoke changes during active cognitive processing that are relevant to behavioral performance. Alternatively, it may be possible to distinguish patterns of task-evoked connectivity from those observed at rest, with these dissociable patterns being related to distinct aspects of function. Comparison of the effects of exercise on task-dependent and intrinsic network organization has the potential to yield novel insights regarding the pathways through which exercise promotes brain health.

5. Conclusion: In summary, exercise may be an effective method to strengthen the

connectivity of intrinsic functional networks and preserve cognitive functioning in late life. However, there is still much to understand in terms of the intervention parameters optimal for eliciting changes in functional connectivity, how exercise might influence task-specific functional networks, as well as which population characteristics that might moderate these effects.

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