Evidence for Exercise-Related Plasticity in Functional and Structural Neural Network Connectivity

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Abstract

The number of studies investigating exercise and cardiorespiratory fitness (CRF)-related changes in the functional and structural organization of brain networks continues to rise. Functional and structural connectivity are critical biomarkers for brain health and many exercise-related benefits on the brain are better represented by network dynamics. Here, we reviewed neuroimaging literature to better understand of how exercise or CRF may facilitate and maintain the efficiency and integrity of functional and structural aspects of brain networks in both younger and older adults. Converging evidence suggests that increased exercise performance and CRF modulate functional connectivity of the brain in a way that corresponds to behavioral changes such as cognitive and motor performance improvements. Similarly, greater physical activity levels and CRF are associated with better cognitive and motor function, which may be brought about by enhanced structural network integrity. This review will provide a comprehensive understanding of trends in exercise-network studies as well as future directions based on the gaps in knowledge that are currently present in the literature.

Keywords

Cardiorespiratory Fitness; Exercise; Physical Activity; Resting State fMRI; Diffusion Tensor Imaging; White Matter Fiber Tracts; Cognition

1. Introduction

In addition to the well-documented cardiovascular, musculoskeletal, and metabolic adaptations, accumulating evidence has suggested neuroprotective effects of exercise and cardiorespiratory fitness (CRF) (Hillman et al., 2008). As a valuable tool that can measure

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exercise-related changes in the brain, magnetic resonance imaging (MRI) has gained much popularity for its high spatial resolution allowing for spatially fine measurement of functional and structural changes in the brain after exercise (Scarapicchia et al., 2017). In addition to enabling measurement of changes in regional brain activation or volume, technological advances of MRI have made it possible for researchers to probe the functional and structural networks of the brain (Sporns, 2013). Network connectivity measures are particularly of great interest because many processes in the brain are better represented by network dynamics and interactions facilitated throughout the brain (Petersen & Sporns, 2015; Sporns, 2013). Therefore, it is exceedingly worthwhile to determine how exercise or CRF might help facilitate and maintain the efficiency and integrity of critical brain networks.

Resting state functional connectivity (rsFC) is one measure of brain health that can be assessed using fMRI. This fMRI measure is effective in representing, at a network level, the cooperation between brain regions. The observation of rsFC depends on the correlation of blood-oxygen-level-dependent (BOLD) signals between different brain regions. rsFC is acquired during wakeful rest, in the absence of external stimuli or goal-directed tasks (Ferreira & Busatto, 2013; Raichlen et al., 2016). During rsFC data acquisition, participants rest in a supine position in the MRI scanner for 5 to 10 mins while they typically keep their eyes open with gaze fixated upon a cross-hair (Van Dijk et al., 2010). rsFC data reflects spatially remote, but functionally-coupled brain areas with different temporal characteristics (Sporns, 2013). While regions with positive signal correlations indicate that these regions are highly functionally connected (Fox et al., 2005; Kelly et al., 2008), anticorrelations (i.e., networks that are negatively correlated) may be associated with regulatory interactions between brain networks (e.g., reciprocal modulations, suppression, inhibition, and neurofeedback) (Gopinath et al., 2015). Despite the complexity, observation of rsFC between brain regions characterizes how these regions interact in the forms of direct and indirect networks (Bullmore & Sporns, 2009), providing novel insights into the functional aspect of the brain network (Petersen & Sporns, 2015).

Chronic exercise studies have utilized task-based measurements such as the Flanker task (Colcombe et al., 2004), Stroop task (Wu et al., 2018), verbal fluency task (Nocera et al., 2017), and famous name recognition task (Smith et al., 2013). Other studies have also examined functional and physiological changes throughout the brain after a single session of exercise (also known as acute exercise) using the Flanker task (Won et al., 2019a), Stroop task (Himmelmeier et al., 2019), mnemonic discrimination task (Suwabe et al., 2018), and famous name recognition task (Won et al., 2019b). However, findings using task-based approaches can potentially be confounded by practice effects and task difficulty (Weng et al., 2017) – it can be unclear whether observed changes in brain activation are truly alterations in underlying brain function or are rather driven by other confounding factors during task performance such as age or disease-state (Ferreira & Busatto, 2013; Price & Friston, 1999). In contrast, rsFC metrics are not confounded by age- or disease-related differences in task performance or difficulty due to the absence of behavioral performance (Fox & Greicius, 2010). Further, since rsFC in humans is subsumed within structural brain networks (Greicius et al., 2009; van den Heuvel et al., 2008), it provides a non-invasive proxy measurement of the communication within and between structural brain networks. Lastly, there is high reliability, applicability, and replicability across a wide range of populations for rsFC

findings (Buckner et al., 2009; Meindl et al., 2010; Shehzad et al., 2009), suggesting that rsFC assessment can be applied across children, older adults, and clinical populations alike.

Structural connectivity is an additional measure of brain health that can be acquired by employing diffusion-weighted imaging (DWI). DWI is a variant of conventional MRI that uses the non-Gaussian diffusion properties of water molecules in biological tissue to parse out microstructural tissue properties (Le Bihan et al., 1986). The observation of diffusion-driven displacement of hydrogen atoms has predominantly been used to study the integrity of the brain's white matter (Le Bihan, 2003). White matter primarily consists of myelinated axons, which facilitate the rapid transmission of information between grey matter regions – it is known to comprise approximately 40–50% of total brain volume. Groups of myelinated axons are themselves referred to as fiber tracts and help facilitate communication between neurons in different brain regions (Walhovd et al., 2014).

The structural boundaries provided by myelinated axons and the impact of these boundaries on water diffusion enable Diffusion Tensor Imaging (DTI) (Basser et al., 1994) to be a useful measure of white matter integrity and structural connectivity. Water molecules are more likely to diffuse along, rather than diffuse perpendicular to, healthy white matter fiber tracts. DTI data are acquired by obtaining multiple non-collinear diffusion-weighted images. Using the tensor model, DTI estimates diffusion axes of an ellipsoid (three eigenvectors and three eigenvalues) to define the parallel and perpendicular diffusivity of water within each image voxel (Assaf & Pasternak, 2008; Basser et al., 1994; Pierpaoli et al., 1996). These eigenvectors and eigenvalues are then used to create summative indexes of diffusivity, such as the average or apparent amount of diffusion [mean diffusivity (MD)], the diffusion parallel to the primary diffusion direction [axial diffusivity (AD)], the diffusion perpendicular to the primary diffusion direction [radial diffusivity (RD)], and the directional preference of diffusion [fractional anisotropy (FA)] (Pierpaoli et al., 1996). More specifically, higher FA and AD of white matter fiber tracts indicates greater diffusion along the white matter fiber tracts and is believed to result from physiological differences in fiber tracts such as axon packing, number, density, and size, as well as myelination and myelin thickness (Beaulieu, 2014). Meanwhile, higher MD and RD of white matter suggests higher overall diffusion and increased diffusion perpendicular to the fiber tracts, which is generally associated with worse cognitive performance. Increased perpendicular diffusion is thought to represent a breakdown in fiber tract integrity, an increased level of permeability, and possibly increased glial activity and inflammation in the extracellular space surrounding the fiber tracts (Beaulieu, 2014; Walhovd et al., 2014). Summative metrics are often used in diffusion imaging literature as predictive biomarkers of brain health that compare the microstructural integrity of white matter fiber tracts in a cross-sectional and longitudinal manner.

While considerable research in the exercise and neuroimaging literature has focused on older adults, comparatively little attention has been afforded to younger adults. Yet, young adulthood can be a critical period to adopt and implement lifelong PA or another healthy lifestyle behavior; thus, it is imperative to investigate the relationship between exercise and the brain in early adulthood. In addition, recent research has suggested that just a single bout of exercise can provoke physiological responses associated with improvements in brain

activation and cognition (Hyodo et al., 2012; Suwabe et al., 2018; Won et al., 2017; Won et al., 2019b). Given that single bouts of exercise are the building blocks of exercise training (ET), it is likely that the effects of acute exercise may accumulate over time in response to ET. Therefore, gaining insights into the relationship between the brain and acute and chronic forms of exercise will advance our understanding of the underlying neurophysiological mechanisms behind exercise-induced changes in brain health.

With consideration of both functional and structural connectivity as critical biomarkers of brain health (Bullmore & Sporns, 2009; Rubinov & Sporns, 2010), many exercise neuroimaging studies have investigated the links between exercise or fitness and the functional and structural connectivity of the brain. Stillman et al. (2019) previously reviewed the relationship between ET, fitness, and rsFC in an aging population. Furthermore, Sexton and colleagues (2016) reviewed the associations between fitness or PA and white matter integrity in older adults (Sexton et al., 2016). These previous review papers consistently suggest there is a positive association between exercise and CRF and functional and structural network integrity in older individuals (Sexton et al., 2016; Stillman et al., 2019). Nevertheless, there is still limited work that collectively reviews the effects of acute exercise, non-traditional form of exercise, ET, and fitness across adulthood for both the functional and structural networks of the brain. In addition, prior review papers have primarily focused on cognition-related networks, and exercise-related changes in motor networks have been neglected. Moreover, there is little discussion regarding exercise protocols and fitness measurements used in the studies. To mitigate gaps in the literature and expand upon the previous review papers, we aim to provide an overview on the relationships between functional and structural forms of connectivity and acute exercise, ET, fitness, and PA in both younger and older adults. This review will attend to each of these domains to achieve a richer understanding of the relationships between exercise, fitness, and structural and functional connectivity of the brain in both younger and older adults and this may be crucial to better understand the mechanisms of exercise-driven improvements in brain health in general.

2. Definition of Key Terms

2.1. Physical Activity

By definition, PA refers to any kind of bodily movement that involves skeletal muscle and increases energy expenditure beyond resting energy expenditure (Caspersen et al., 1985). PA encompasses leisure-time activities as well as structured activities that improve health. In the literature, self-report questionnaires (i.e., subjective method) or actigraphy (i.e., objective method) are commonly used to assess the amount of PA completed by individuals. A caveat to be considered, however, is that self-rated PA questionnaires are administered at a single time point and measure PA for a retrospective time period, so they are susceptible to memory distortion-driven inaccuracies.

2.2. Exercise

Exercise is a planned and structured subtype of PA that is aimed at enhancing physical fitness and health (Caspersen et al., 1985). Acute exercise is a single session of exercise, and

in research settings, it is normally administered using a cycle ergometer or treadmill. Many acute exercise studies administer a single session of exercise for   30 mins, immediately after which participants undergo experimental sessions. ET refers to repeated participation in exercise for a prolonged length of time. Most ET studies have a time span of greater than three months and participants typically undergo experiments at baseline and post-intervention. Typically, ET investigations randomize participants into either an aerobic exercise group or a non-aerobic exercise control group (e.g., balance, stretching, and toning) groups.

2.3. Cardiorespiratory Fitness

CRF represents the ability of the cardiorespiratory system to supply and utilize oxygen to large muscle groups during dynamic exercise for prolonged periods of time (Caspersen et al., 1985). The most widely used method to quantify CRF is a Maximal Rate of Oxygen Utilization $\left(\dot{V}O2_{max}\right)$ test, which measures an individual's the highest volume of oxygen uptake and utilization during sustained PA. $\dot{V}O2_{max}$ reflects aerobic capacity, and is typically observed with a plateau of oxygen consumption and the concurrent attainment of other criteria that are indicative of maximal effort. For physically inactive older participants, an alternative and modified submaximal test is often used because the $\dot{V}O2_{max}$ test could come with considerable safety risks. Although exercise level is indeed a factor that contributes to $\dot{V}O2_{max}$, there are other significant moderating factors (e.g., training status, age, and sex) for $\dot{V}O2_{max}$ levels (Guth & Roth, 2013). Thus, it is important to factor in these potential moderators into analyses when investigating the associations between CRF and variables of interest.

3.   Key Functional Brain Networks

3.1.   Executive Function Network

Executive function refers to the execution of goal-oriented behavior and the coordinated action of brain networks and domains in a context-dependent way (Purves et al., 2008). Executive function includes working memory (i.e., temporarily storing and manipulating the information to accomplish complex cognitive tasks), mental flexibility (i.e., the ability to shift between tasks and mental states), set-shifting and updating (i.e., the capacity to monitor and manipulate items in working memory), and inhibitory control (i.e., the ability to suppress habitual responses) (Stuss, 2011). Neuroimaging research has provided evidence that the prefrontal cortex (PFC) in addition to other complementary neural networks play an important role in executive function (Miyake et al., 2000; Purves et al., 2008). The PFC, which composes approximately a third of the human brain, has several subregions linked to executive function, such as the dorsal and ventral aspects of the lateral PFC, the dorsomedial PFC, and the orbitofrontal cortex (Purves et al., 2008). Among these PFC subregions, the dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortex constitute the central executive network (CEN). The CEN has been shown to be important for manipulating and maintaining executive function (Miller & Cohen, 2001; Müller & Knight, 2006; Petrides, 2005). The CEN reflects the PFC's cortico-cortical connections with subcortical areas including the basal ganglia, amygdala, and hippocampus, and thus,

represents the complex multifaceted nature of the PFC's involvement in executive function (Miyake et al., 2000).

3.2. Default Mode Network

The default mode network (DMN) is one of the most widely-studied resting state networks. The DMN reflects the brain's state during rest (i.e., in a task-free environment), during which there is a high degree of connectivity and functional coherence within this network (Buckner et al., 2008). The functional role of the DMN includes memory consolidation, self-referential thought, mind-wandering, and auto-biographical memory (Buckner et al., 2008; Schilbach et al., 2008). Converging evidence identifies a linkage between DMN integrity and cognitive health in older adults. The key nodes of the DMN are the posterior cingulate cortex (PCC) and precuneus. These particular nodes are especially susceptible to disruption associated with healthy aging (Andrews-Hanna et al., 2007) and beta-amyloid aggregation in Alzheimer's disease (Buckner et al., 2008). Thus, a reduction in the DMN rsFC can be indicative of age-related neurodegeneration in older adults (Agosta et al., 2012; Damoiseaux et al., 2008). Pathological and structural changes in the DMN rsFC could also serve as valid and reliable hallmarks not only for aging but also for neuronal and psychological diseases such as autism, schizophrenia, depression, and post-traumatic stress disorder (Lustig et al., 2003; Supekar et al., 2008; Zhang & Raichle, 2010).

3.3. Cingulo-Opercular Network

The cingulo-opercular ('salience') network is anchored in the anterior insula (AI) and the anterior cingulate cortex (Seeley et al., 2007; Sridharan et al., 2008). This network detects incoming stimuli and segregates relevant stimuli to help guide biobehavioral response (Menon & Uddin, 2010). The cingulo-opercular network also initiates switching between the CEN and DMN, thus mediating attentional shifts between exogenous and endogenous events (Menon, 2010). Importantly, the cingulo-opercular network plays a crucial role in affective processing, as well (Menon & Uddin, 2010). It has been reported that there is a relationship between cingulo-opercular network dysfunction and impaired emotion recognition (Rzepa & McCabe, 2016). Further, individuals with major depressive disorder demonstrated reduced cingulo-opercular network rsFC (Tahmasian et al., 2013; Ye et al., 2012).

3.4. Hippocampal Network

The hippocampus is a brain region crucial for memory – unsurprisingly, there is a close correlation between age-related memory decline and deteriorated hippocampal function (Small et al., 2011). According to functional neuroimaging work, there is a distinction in the rsFC of the the anterior versus posterior hippocampus (Kahn et al., 2008). The anterior hippocampus is preferentially connected to the temporal pole and medial prefrontal cortex (Robinson et al., 2016). This anterior hippocampal rsFC has been implicated in memory processes that are related to recalling familiarity and prior occurrence (Yonelinas et al., 2005). In contrast, the posterior hippocampus is connected to the parahippocampal gyrus, fusiform gyrus, and posterior cingulate cortex (Robinson et al., 2016) and posterior hippocampal functional connection has been associated with recalling contextual details about events (Rugg & Vilberg, 2013).

3.5. Cerebellar Network

The cerebellum is a sub-cortical structure that has, for years, been associated with motor control and coordination (Schmahmann, 2019). Importantly, continued research into the cerebellum has highlighted that this structure can contribute to cognitive processes and constitute a brain network that can have consequences towards cognitive and emotional health (Patil et al., 2021). Of note, cerebellar structures have been observed to be topographically arranged in a highly specialized manner where the posterior lobules VI and VII seem to be key hubs of the cerebellar network associated with cognitive health (Stoodley & Schmahmann, 2009). Not surprisingly, cerebellar rsFC, blood flow, and volume have all been observed to be compromised in neurodegenerative diseases such as Alzheimer's Disease (Wang et al., 2007) and can behaviorally manifest during cognitive tasks such as the Stroop test (Kaufmann et al., 2008). Thus, evidence suggests subcortical structures such as the cerebellum may have properties reminiscent of a working network that can contribute towards cognitive health and should be considered in connectivity work.

3.6. Motor Networks

3.6.1. Frontoparietal Network (FPN)—The FPN is a large network essential for allocating neural resources towards attention (Scolari et al., 2015), goal-directed control processes, and motor control (Raichlen et al., 2016; Seitzman et al., 2019). Not surprisingly, studies suggest the FPN to be a key network for the execution of fast adaptive behaviors (Marek & Dosenbach, 2018). Brain structures that give rise to the FPN include the DLPFC, temporo-parietal junction, AI, anterior cingulate cortex, middle temporal gyrus, and anterior inferior parietal lobule (Raichlen et al., 2016; Seitzman et al., 2019; Voss et al., 2010a). This widespread intrinsic functional connection of the FPN extends to the ventral part of cerebellum (e.g., lobules VII/VIII), a sub-cortical structure that has, for years, been associated with motor control and coordination (Brissenden et al., 2016). The FPN contributions towards motor control include facilitation of movement production through segmentation (i.e., the process of parsing contiguous elements into short action sets) (Wymbs et al., 2012) and motor planning through motor imagery (i.e., the process of mentally simulating movement without physically executing it) (Hanakawa et al., 2008; Wu et al., 2009); both of which are particularly important for the correction of complex motor behavior in real-time (Seitzman et al., 2019). In neurological disorders such as Parkinson's disease and Mild Cognitive Impairment (MCI), the FPN rsFC has been observed to be altered (Filippi et al., 2019; Tahmasian et al., 2013). In addition, research in older adults shows that the functional and structural integrity of the FPN is also impaired during normal aging (Andrews-Hanna et al., 2007; Madden et al., 2007). Similar in function as compared to the function of the FPN, the Dorsal Attention Network (DAN) is active during tasks that require voluntary and sustained attention. Housed in the intraparietal sulcus and frontal eye fields, this network is also thought to be negatively impacted by aging (Fox et al., 2006; Tomasi & Volkow, 2012).

3.6.2. Sensorimotor Network (SMN)—The SMN, the first resting state network to be reported by Biswal and colleagues (1995) (Biswal et al., 1995) includes the primary motor (M1) and somatosensory (S1) cortices as well as the supplementary motor area (Rosazza & Minati, 2011; Seitzman et al., 2019). In addition to the anatomical overlap, previous work

has also shown resting state neural activity of the SMN to correspond to neural activity during the execution of motor behavior (De Luca et al., 2005). Thus, the SMN may serve as a proxy to measure the function and integrity of the neural processes responsible for conscious motor behavior (Rosazza & Minati, 2011). In healthy older adults, the SMN rsFC positively associates with performance of a simple motor task performance (Langan et al., 2010). Interestingly, changes in the SMN rsFC in disease states are not linear, and patients with amnestic MCI show a compensatory hyperconnectivity whereas patients with Alzheimer's disease show hypoconnectivity of the SMN (Agosta et al., 2010). Maintaining the integrity of the SMN has important implications for long-term health; as an example illustrating this, impaired SMN integrity across both healthy and pathological aging has been associated with losses in motor function and physical independence that can significantly decrease quality of life (Alzheimer's Disease Association, 2019; Seidler et al., 2010).

4. Fitness, Exercise, and rsFC

4.1. Fitness and rsFC

4.1.1. Summary of the Findings—As well-documented in the literature, regular participation in aerobic exercise and PA has been shown to benefit cognition and brain functions over the human lifespan (Mattson, 2012; Raefsky & Mattson, 2017). Consistent with the literature, cross-sectional studies have consistently found that greater CRF ($\dot{V}O_{2max}$ or $\dot{V}O_{2peak}$) or participation in PA are associated with greater synchrony in networks such as the DMN (Boraxbekk et al., 2016; Voss et al., 2010b; Voss et al., 2016), dorsal attention network (DAN) (Voss et al., 2016), FPN (Raichlen et al., 2016), and hippocampal network (Stillman et al., 2018) in both younger and older adults. Furthermore, a cross-sectional work by Boyne and colleagues (2018) found that greater rsFC between motor network regions was linked to a greater distance walked during a 6-min walk test in healthy adults (Boyne et al., 2018). In a longitudinal study, increased self-reported PA was associated with higher frontal-subcortical network rsFC in older adults at follow-up (Dorsman et al., 2020). A 16-week aerobic exercise intervention study by Flodin and colleagues (2017) corroborates this notion with evidence that training-related increases in fitness levels were associated with an enhancement in rsFC both between the SMN and occipital cortex, and within networks and structures such as the DMN, SMN, and thalamus (Flodin et al., 2017). Taken together, there is evidence supporting the relationship between higher fitness and greater rsFC relevant to a variety of cognitive domains including attention, memory, executive function, and locomotion.

4.1.2. Age-Related Differences—There was no evidence directly comparing the fitness-related age differences in rsFC (e.g., high-fit older adults vs high-fit younger adults; lower-fit older adults vs lower-fit younger adults). In two studies employing both younger and older adults (Voss et al., 2010b; Voss et al., 2016), younger adults were used to highlight the age-related disruption of brain networks and neuroprotective effects induced by higher CRF on the aging brain. Therefore, these between-age group differences do not elucidate how age moderates the link between CRF and rsFC; thus, this knowledge gap should be addressed in future studies.

4.1.3. Network-Behavior Associations—Voss et al. (2010) demonstrated that greater PCC-frontal medial cortex (FMC), medial temporal gyrus-medial frontal gyrus, and medial frontal gyrus-FMC rsFC were associated with better executive function (e.g., Wisconsin Card Sorting Test) and spatial memory task performance (Voss et al., 2010b). Moreover, greater rsFC mediated the relationship between higher CRF $\left(\dot{V}O_{2max}\right)$ and better executive function performance, suggesting that rsFC may be an important mediator in the relationship between CRF and executive function performance. Although the association between CRF and hippocampal network rsFC was measured by Stillman et al. (2018), hippocampal-dependent cognitive performance was not included in the analyses. Hence, it remains unknown if hippocampal rsFC mediates the relationship between CRF and memory performance.

4.1.4. Methodological Considerations—Sample size varies across fitness-rsFC studies (N=22 to 225). With regard to the measurement of fitness, while four studies used a standardized CRF test ($\dot{V}O_{2max}$ test) (Raichlen et al., 2016; Stillman et al., 2018; Voss et al., 2010b; Voss et al., 2016), one study utilized a composite fitness score that encompasses body mass index (BMI), waist circumference, grip strength, and blood pressure (Boraxbekk et al., 2016), another study utilized self-reported PA (Dorsman et al., 2020) and an additional study used the 6-min walk test (Boyne et al., 2018) – a sub-maximal exercise test often used to assess cardiorespiratory capacity (Burr et al., 2011). With respect to the rsFC analysis method, there were not large inconsistencies across investigations, as seed-based analysis, independent component analysis (ICA), and network-based analysis were consistently used to examine rsFC (Table 1).

4.2. Acute Exercise and rsFC

4.2.1. Summary of the Findings—Acute exercise-rsFC study findings consistently suggest the linkage between a single exercise session and altered functional brain networks related to motor behaviors (Rajab et al., 2014), cognitive function (Weng et al., 2017), and emotion regulation (Alfini et al., 2020). Specifically, according to an acute exercise study in younger adults, a single bout of aerobic exercise was associated with increases in rsFC of key SMN hubs including the pre- and post-central gyri, thalamus, and secondary somatosensory (S2) region when compared to a non-exercise control group (Rajab et al., 2014). According to work by Weng and colleagues (2017), relative to motor-driven cycling, a single session of active cycling was related to increased integration of affect-reward, hippocampal, cingulo-opercular, and right ECN in both younger and older adults (Weng et al., 2017). Alfini and colleagues (2020) reported a decreased emotion regulation-related network rsFC (i.e., cingulo-opercular functional network) in response to a single cycling exercise session compared to a seated-rest control session among older adults (Alfini et al., 2020). Of note, there is evidence to suggest that acute changes in rsFC from a single session of exercise may be dependent on the intensity of the exercise stimulus (Schmitt et al., 2019). In healthy trained younger adults, a single bout of low-intensity treadmill running (i.e., < 35% lactate threshold) increased rsFC of cognitive and attentional processing networks, while an acute bout of high-intensity treadmill running (i.e., > 20% lactate threshold) promoted an increases in rsFC of affective networks concomitant with decreases in sensorimotor rsFC (Schmitt et al., 2019). Collectively, findings invariably support the

view that an acute bout of exercise is a stimulus that provokes physiologic responses within functional brain networks.

4.2.2. Age-Related Differences—In Weng et al. (2017), older adults (66.3±1.0 years), when compared to their younger counterparts (23.2±0.7 years), demonstrated a greater increase in attention and reward-related, hippocampal, and right FPN rsFC in response to a single exercise session (Weng et al., 2017). Additionally, an acute bout of exercise induced greater increases in rsFC between the sensorimotor area and right dorsal anterior cingulate in older adults when compared to younger adults. rsFC between the SMN and dorsolateral prefrontal cortex was also significantly lower in older adults relative to younger adults following acute exercise. Hence, Weng et al. (2017) suggests that age is a moderating factor in the relationship between acute exercise and functional networks and that impacts of acute moderate-intensity exercise are preferentially focused on the networks that have a propensity to decrease in rsFC with age (Andrews-Hanna et al., 2007; Damoiseaux et al., 2016). Since only a single age group was used for the other studies (younger adults in the Rajab et al. (2014) and older adults in the Alfini et al. (2020)), little is known about whether there are age-related disparities in acute exercise effects on motor and emotion regulation brain networks. Future studies should explore the possible differences between age groups in the relationship between acute exercise and rsFC.

4.2.3. Network-Behavior Associations—While Alfini et al. (2020) demonstrated the link between greater exercise-related reduction in the cingulo-opercular network and enhanced positive affect, it remains to be determined if rsFC alterations underlie cognitive and motor performance changes following a single exercise session. This study also showed that acute exercise-induced decrease in rsFC between the left hippocampus and cingulo-opercular network mediated the acute exercise-related increase in positive affect among older adults with greater disturbance in sleep (i.e. higher wake after sleep onset) (Alfini et al., 2020). This result opens up the possibility that acute exercise may interact with lifestyle factors (e.g., sleep) when influencing affect or cognitive function. Thus, there is a need for further investigations of possible mediators or moderators of acute exercise effects on rsFC outcomes.

4.2.4. Methodological Considerations—From an experimental design standpoint, while three studies measured rsFC both at baseline and upon completion of the exercise (Rajab et al., 2014; Schmitt et al., 2019; Weng et al., 2017), one study assessed rsFC only after intervention (Alfini et al., 2020). Three studies employed a within-subject design (Alfini et al., 2020; Schmitt et al., 2019; Weng et al., 2017) and one study used a no-intervention control group (Rajab et al., 2014). Different forms of control conditions (e.g., passive motor-driven cycling (Weng et al., 2017) and seated-rest (Alfini et al., 2020)) were used throughout the findings. In regards to exercise mode, three studies (Alfini et al., 2020; Rajab et al., 2014; Weng et al., 2017) used cycling exercise and one study used treadmill exercise (Schmitt et al., 2019). While two studies reported 65–70% maximal heart rate (HR_{max}) (Rajab et al., 2014; Weng et al., 2017) as a measurement of exercise intensity, two other studies utilized RPE (Borg rating of perceived exertion (Borg, 1998)) (Alfini et al., 2020) and lactate threshold (Schmitt et al., 2019). Despite these inconsistencies, there

was a consistency in the exercise duration (25–30 min) across studies. Finally, different rsFC analysis methods were employed across acute exercise-rsFC investigations, with dual regression (Rajab et al., 2014; Schmitt et al., 2019), a data-driven approach and averaged across multiple regions of theoretically-defined networks (e.g., DMN) (Weng et al., 2017), and seed-based (Alfini et al., 2020) approaches all being utilized (see Table 2).

4.3.   Aerobic Exercise Training and rsFC

4.3.1.   Summary of the Findings—Twelve studies examining the relationship between aerobic ET and rsFC underscore that chronic exercise results in altered rsFC across ages, as well as in both sedentary and clinical (e.g., overweight, MCI) populations. Converging evidence has shown ET to have global effects on brain networks from the DMN to cerebellar rsFC. Multiple studies point towards a general pattern of enhanced functional coherences within brain networks in response to ET. For instance, ET was associated with increased DMN (Chirles et al., 2017; McGregor et al., 2018; Voss et al., 2010a), hippocampal network (Burdette et al., 2010; Flodin et al., 2017; Tozzi et al., 2016; Won et al., 2021a), ECN (Prehn et al., 2019), cerebellar rsFC (Won et al., 2021b), between-networks (SMN and DMN) (McGregor et al., 2018), and rsFC modularity (Baniqued et al., 2018). Additionally, improvements in CRF stemming from ET may facilitate improvements in rsFC between areas such as the SMN and occipital cortex, and within networks such as the DMN, SMN, and thalamus (Flodin et al., 2017). Conversely, some studies reported decreased rsFC after ET [e.g., decreased DMN (Chirles et al., 2017; McFadden et al., 2013), SMN (Flodin et al., 2017), and PCC between network rsFC (Legget et al., 2016)]. As such, ET-related changes in rsFC may not be generalizable or congruent across all investigations. Although interpretation of decreased rsFC is typically challenging, ET-related decreased rsFC co-occurred with decreased fat mass and hunger ratings (McFadden et al., 2013), increased CRF (Flodin et al., 2017; Legget et al., 2016), and cognitive stability in older adults (Chirles et al., 2017). Together, these rsFC-behavior relationships suggest that ET-elicited reduction in rsFC may in some cases be beneficial for behavior.

4.3.2.   Age-Related Differences—Little is known about whether ET-induced changes to rsFC are different among different age groups. This field of research has primarily focused on older adults (> 60 years) (Baniqued et al., 2018; Burdette et al., 2010; Chirles et al., 2017; Flodin et al., 2017; McGregor et al., 2018; Prehn et al., 2019; Voss et al., 2010a; Won et al., 2021a; Won et al., 2021b), especially given that rsFC may serve as an important biomarker to understand the aging brain. Evidence suggests an age-related loss of specificity of large-scale networks (such as within the DMN, SMN, FPN, FE) where chronic participation in exercise may be beneficial (Zhang et al., 2020). Indeed, McGregor et al. (2018) found that a 12-week cycling intervention in older adults (73.5±6.8 years) was associated with improvements in rsFC between the anterior DMN and the left SMN, as well as consolidation within the SMN (from bilateral pre- to lateralized in dominant hemisphere post-). This notion is given credence by Voss and colleagues (2010) whose work found that following a 12-month walking intervention, there were distinct patterns of ET-elicited enhanced rsFC in the large-scale networks susceptible to the aging process (e.g., DMN, FE, and FP networks) in older adults (67.3±5.8 years) and furthermore, the

ET-induced strengthened rsFC within these networks were comparable to those of younger adults (23.9±4.4 years) (Voss et al., 2010a).

Research in middle-aged adults also reports ET to improve rsFC between motor areas and the parahippocampal gyrus, the mid-cingulate cortex and motor cortex as well as between the parahippocampal gyrus and right middle occipital lobe, left thalamus, and left inferior occipital lobe (Tozzi et al., 2016). Thus, while little work has been done to directly compare age-related differences in rsFC in response to ET, evidence suggests that regular engagement in ET may be an ancillary tool to maintain the integrity of large-scale networks throughout the lifespan. Additional studies in middle-aged and younger adults may elucidate potential moderating effects of age in the relationship between ET and rsFC. More middle-aged and younger adult studies may also highlight possible ways by which early adoption of healthy lifestyle behaviors (e.g., ET) engender health benefits towards brain network integrity in late adulthood.

4.3.3. Network-Behavior Associations—ET-induced changes in rsFC occur concomitant to ET-related salutary cognitive and behavioral changes [e.g., memory (Won et al., 2021a), executive function (Baniqued et al., 2018; Voss et al., 2010a; Won et al., 2021b), psychomotor speed (McGregor et al., 2018)), mental health (Tozzi et al., 2016), food intake (McFadden et al., 2013), and CRF (Flodin et al., 2017)]. The evidence from these investigations illustrates that a functional brain network may serve as a neurophysiological mechanism for long-term exercise-related cognitive and behavioral changes. Furthermore, there is an association between ET-induced increase in hippocampal perfusion and rsFC (Burdette et al., 2010). Based on this evidence, it is plausible to speculate that ET-elicited modulation in rsFC may not occur independently, but may rather occur in concert with modulation of other metrics of brain function. It is also noteworthy that training-induced improvements in CRF $(\dot{V}O_{2max})$ led to changes in rsFC after completion of training (Flodin et al., 2017; Legget et al., 2016). This hints that ET-related improvements in CRF may be a key driving factor for the ET-related behavioral changes – this is also supported by results from cross-sectional studies (Voss et al., 2010b; Voss et al., 2016). These studies, however, did not assess behavioral measures, and future studies are needed to clarify the potential mediating role of aerobic fitness in the relationship between ET and behavioral changes.

4.3.4. Methodological Considerations—Many ET research studies employed supervised treadmill walking exercise or stationary cycling, while one study utilized spin cycling (McGregor et al., 2018). Although the intensity of aerobic ET was consistent throughout studies (moderate-intensity; 60–75% HR_{max}), training duration (6 weeks to 12 months) and frequency (2 to 4 times/week) varied across the literature. Another source of variability was type and presence of control group. Most studies used a non-aerobic ET (e.g., balance and toning) or a non-exercise control group [e.g., health education and maintaining exercise habit), but some studies lacked a control group (Chirles et al., 2017; Legget et al., 2016; McFadden et al., 2013; Tozzi et al., 2016; Won et al., 2021a; Won et al., 2021b) and other reports used small sample size (< N=12) (Burdette et al., 2010; Legget et al., 2016; McFadden et al., 2013)]; thus, results from the studies that lack a control group or have a small sample size should be interpreted with caution.

While there is relative consistency in findings across the studies, there is less consistency regarding the rsFC analytic approach methodology [e.g., seed-based analysis (Chirles et al., 2017; Flodin et al., 2017; McGregor et al., 2018; Prehn et al., 2019; Won et al., 2021a; Won et al., 2021b), ROI-ROI (Voss et al., 2010a), BOLD fluctuation (Tozzi et al., 2016), graph theory methods (Burdette et al., 2010; Tozzi et al., 2016), ICA (McFadden et al., 2013), between network analysis (Legget et al., 2016), network-based analysis (Tozzi et al., 2016), and modularity analysis (Baniqued et al., 2018; Burdette et al., 2010)]. The diversity of analytic approaches across the reports is likely attributable to the relatively recent emergence of many different rsFC analytical methods. It is worth noting that differences in analytic methods should be taken into consideration in the interpretation of the converging evidence (Table 3).

4.4. Non-Traditional ET/PA and rsFC

4.4.1. Summary of the Findings—In agreement with aerobic ET studies, non-traditional training investigations have shown to modulate rsFC, as well. For example, in a quasi-experimental intervention, Ji and colleagues (2017) found an increased right putamen and pallidum rsFC in response to a 6-week home-based Wii-fitness exercise program (Ji et al., 2017). Magon et al. (2016) and Demirakca et al. (2016) suggested that motor coordination and balance ET alter rsFC of the motor and visual/somatosensory areas. Moreover, other non-traditional ET interventions such as mind-body exercises (e.g., Tai-Chi and Badunjin) in older adults may also enhance cognitive function which co-occurred with alterations in rsFC within networks such as the SMN, ECN and hippocampal network – networks that are particularly prone to substantial age-related deterioration (Tao et al., 2016, Tao et al., 2017).

4.4.2. Age-Related Differences—There were no between-age group comparisons among the non-traditional of ET/PA ET studies.

4.4.3. Network-Behavior Associations—Ji et al. (2017) reported that the striatum-thalamus rsFC that was increased after a 6-week Wii fitness program corresponded with improved executive function performance. The thalamus has been consistently observed as one of the nodes that are affected by exercise (Flodin et al., 2017; Rajab et al., 2014; Tozzi et al., 2016). The thalamus is a key component of the DMN (Wang et al., 2014) and ascending reticular activating system (Maldonato, 2014), which are responsible for consciousness and vigilance (Kinomura et al., 1996). Therefore, increased thalamus rsFC and associated improvement in cognitive function is well-supported and more evidence is needed to explore the contribution of thalamic pathways to exercise-related changes in rsFC. In another study, training-induced reduction in rsFC between the DLPFC and putamen accompanied an increased mental control score in older adults who completed Tai-Chi or Badunjin training (Tao et al., 2017). The other study showed that the increase in the rsFC between the bilateral hippocampus and medial prefrontal gyrus following Tai-Chi training was significantly associated with improvement in memory performance among older individuals (Tao et al., 2016). Collectively, Tai-Chi training may be an ameliorative intervention for cognitive function in older adults that might help by modifying the functional networks of the brain.

4.4.4. Methodological Considerations—Although Demirakca et al. (2016) demonstrated that life kinetik training modified balance-related rsFC, the duration of training was short (~12 sessions; 1 hour/week) and documentation regarding the intervention is relatively unclear. Moreover, no intervention (e.g., non-exercise or active control) was administered to individuals in the control group and it remains equivocal whether the gap between pre- and post-intervention rsFC scans in the control group was comparable to that of the training group. Similarly, Magon et al. (2016) and Ji et al. (2017) utilized a relatively short intervention period (e.g., 6 weeks) and the correlation between performance and rsFC was not reported in Magon et al. (2016). Hence, interpretation of the results from these investigations may require extra caution due to weaknesses in study design and lack of rsFC-performance associations. In contrast, two Tai-Chi studies (Tao et al., 2016, 2017) had a relatively longer intervention (e.g., 12 weeks), a non-exercise control group, and well-supervised interventions. Importantly, both of these Tai-Chi studies elucidate cognition-rsFC relationships, suggesting that changes in rsFC may act as a neural mechanism underlying the Tai-Chi related changes in cognitive function.

It is important to point out that none of the non-aerobic ET studies documented exercise intensity. As reported earlier, evidence from Schmitt et al. (2019) demonstrated exercise intensity is a major factor that needs to be accounted for in exercise studies. Hence, establishing target exercise intensity (using HR or RPE) is necessary, since not doing so renders it unknown whether the participants in each study performed the exercise at similar or different intensities – variance in exercise intensity between studies could possibly play as a confounding factor for the results. Documenting exercise intensity is also useful and necessary since it would help set up future replicate studies. Lastly, seed-based approach was the most frequently used analysis method throughout the studies (Ji et al., 2017; Magon et al., 2016; Tao et al., 2016; Tao et al., 2017), but a seed-to-voxel approach (Demirakca et al., 2016), and, ICA (Magon et al., 2016) were used in other studies (Table 4).

5. Exercise, Fitness, and Structural Connectivity

5.1. Fitness and Structural Connectivity

5.1.1. Summary of Findings—Although numerous studies support the positive impact that PA and CRF has upon cognition and gray matter preservation in older adults (Angevaren et al., 2008; Erickson et al., 2010; Zhu et al., 2014), the moderating effects of fitness do not appear to be restricted to gray matter. Indeed, improvements in CRF are associated with maintenance of white matter volume and reductions in white matter lesions in older adults (Sexton et al., 2016). White matter volume and lesion studies, however, are incapable of ascertaining microstructural changes that may lead to improvements in brain structure and function. Due to the inherent limitations of structural MRI techniques, our understanding of the benefits of CRF for the brain has been predominantly restricted to the macrostructural level. Despite this limitation, a growing number of DTI studies have begun to parse out the link between CRF/PA and microstructure.

Studies focusing on the relationship between CRF and structural connectivity in healthy adults suggest a consistent positive relationship between CRF and PA levels with white matter integrity (represented by higher FA and lower MD and RD values). In particular,

this relationship appears to most consistently exist for association fiber tracts such as the cingulum (Chen et al., 2020; Marks et al., 2011; Marks et al., 2007; Oberlin et al., 2016; Smith et al., 2016; Tian et al., 2014; Tseng et al., 2013), superior and inferior longitudinal fasciculus (Smith et al., 2016; Tseng et al., 2013), and uncinate fasciculus (Maltais et al., 2020; Marks et al., 2007; Strömmer et al., 2020), which link the temporal, parietal, occipital, and frontal lobes. Several studies have also reported relationships between CRF and the corpus callosum, the primary commissural fiber tract (Johnson et al., 2012; Oberlin et al., 2016) and projection fiber tracts such as the fornix, thalamic radiation, anterior corona radiata, cerebral peduncle, and internal capsule (Chen et al., 2020; Oberlin et al., 2016; Smith et al., 2016; Tseng et al., 2013). While limited, recent work also provides evidence for a positive relationship between CRF and the integrity of large motor and sensory fiber tracts in older adults (Harasym et al., 2020). A link between greater CRF and greater white matter integrity in the superior and inferior longitudinal fasciculus of individuals with MCI has also been supported (Teixeira et al., 2016), suggesting that higher CRF moderates structural integrity across cognitive status. A few studies have failed to identify a significant relationship between fitness and white matter fiber tract integrity (Burzynska et al., 2014; Tian et al., 2014), but the overall body of work does suggest a strong and consistent link between the maintenance of PA levels and CRF and preserved white matter fiber tract integrity. Furthermore, while most of the research conducted thus far has focused on PA and CRF in particular, there are a couple of recent studies in healthy older adults that suggests long-term participation in other forms of PA such as Tai-Chi, which focuses on mind body connections, may be related to greater white matter integrity of the corpus callosum (Yao et al., 2019) and greater structural network efficiency (Yue et al., 2020). However, more research is needed to compare and determine which particular modalities of PA may be associated with better structural connectivity.

5.1.2. Age-Related Differences—Several recent large cohort studies found that relationships between white matter integrity and PA and fitness exist across younger, middle aged, and older adults. For example, young athletes have been reported to have higher FA within large white matter fiber tracts such as the left corticospinal fiber tract (B. Wang et al., 2013). In another younger adult investigation, higher CRF measures were positively associated with higher whole-brain FA (Opel et al., 2019). While in active older adults, higher indices of CRF appear to be positively associated with FA in association and projection fiber tracts along the posterior to anterior gradient, which is generally the direction of deterioration experienced with older age (Chen et al., 2020; Hayes et al., 2015; Oberlin et al., 2016; Tseng et al., 2013). There are several studies that have compared this relationship in younger and older adults. Marks et al. (2007) (Marks et al., 2007) found a significant positive relationship between CRF (measure based on age, sex, BMI, and self-reported PA) and FA of the uncinate fasciculus and cingulum fiber tracts across age. Meanwhile, Strömmer et al. (2020), found that higher self-reported PA levels mediated the negative relationship between age and lower FA in the corpus callosum, uncinate fasciculus, external capsule, and anterior limb of the external capsule in participants aged 18–87 years old (Strömmer et al., 2020). Hayes et al. (2015) reported that high fit older adults (60–90% $\dot{V}O_{2max}$ ACSM classification) had similar FA values compared to the younger adults in several posteriorly located fiber tracts known to deteriorate by aging.

Tarumi and colleagues (2021) found that fitter middle-aged adults (< 65 years old) had higher FA in numerous white matter fiber tracts and CRF $(\dot{V}O_{2max})$ was positively associated the FA of the corpus callosum, superior longitudinal fasciculus, fronto-occipital fasciculi, uncinate fasciculus, and cingulum across younger and middle-aged adults (Tarumi et al., 2021). Finally, Wolf and colleagues (2020) found that an association between PA and white matter microstructure was restricted to high age within a sample of healthy older adults (Wolf et al., 2020). Overall, it appears that the relationship between fitness and white matter integrity, while existing across the lifespan, may be stronger in older adults – therefore, maintaining CRF may be an especially important factor in preserving structural networks in the aging brain.

5.1.3. Fiber Tract Integrity-Behavior Associations—While some cross-sectional works focusing on fitness and structural connectivity failed to incorporate behavioral measures, many studies have focused on establishing a relationship between aging, white matter, behavior, and cognition (Gujral et al., 2018; Madden et al., 2009; Vernooij et al., 2009). Among older adults, there is compelling evidence for a correlation between white matter integrity and behavioral and cognitive factors such as adherence to PA (Gujral et al., 2018). For example, in a secondary analysis of an intervention study, Gujral and colleagues (2018) found that individuals with greater baseline FA in the corpus callosum, right external capsule, and superior longitudinal fasciculus were more likely to adhere to a 1 year exercise program (Gujral et al., 2018). Moreover, Oberlin et al. (2016) provided evidence that greater CRF was associated with higher FA in a diverse network of white matter fiber tracts (e.g., the anterior corona radiata, anterior internal capsule, fornix, cingulum, and corpus callosum) in older adults. Further, FA of these white matter fiber tracts positively mediated the relationship between cardiorespiratory fitness and spatial memory performance in both groups of subjects (Oberlin et al., 2016).

Meanwhile, two recent large observational studies have found that white matter integrity may mediate the relationship between PA and fitness with cognitive performance. For example, Opel et al. (2019) found that higher whole-brain white matter FA mediated the positive relationship between 2-min walk test score and global cognition in younger adults. Strömmer et al. (2020) found that higher self-reported PA levels mediated the negative relationship between age and structural connectivity by preserving white matter integrity of several anterior fiber tracts (e.g., the genu of corpus callosum, uncinate fasciculus, external capsule, and anterior limb of external capsule) across age groups (18–87 years). There are few studies that have empirically tested whether the association between fitness or PA and white matter fiber tract integrity is behaviorally relevant. The scarce studies that have provided this type of evidence suggest that fitness-related preservation of white matter integrity may be associated with benefits to various cognitive domains across the lifespan (Oberlin et al., 2016; Opel et al., 2019; Strömmer et al., 2020). Due to the limited number of studies, there is a need for more evidence that incorporates additional cognitive measures, determines which white matter fiber tracts are most strongly related to fitness, and identifies which cognitive domains these specific white matter fiber tracts might preserve or even promote through higher fitness and/or PA levels.

5.1.4. Methodological Considerations—Findings were gathered with the use of a wide variety of fitness and physical activity measurements, such as the 2-min walk test (Opel et al., 2019), max duration treadmill test (Zhu et al., 2015), $\dot{V}O_{2peak}$ and $\dot{V}O_{2max}$ (Harasym et al., 2020; Herting et al., 2014), 1-min HR recovery (Johnson et al., 2012), and subjective measures of self-reported PA (Strömmer et al., 2020). Additionally, Wang et al. (2013) compared athletes to non-athletes but failed to take measures of fitness, and instead, greater CRF in athletes was assumed. As a result, these findings must be taken with caution in interpretation as no direct link between CRF and FA is demonstrated, but rather assumed based on the differences between group backgrounds.

With regard to analysis methods, it is important to consider that white matter fiber tract integrity measures are particularly sensitive to the underlying processing and analysis methods utilized (Soares et al., 2013). Although some of the studies employed well-established and standardized analysis methods for obtaining whole-brain white matter fiber tract integrity (Burzynska et al., 2014; Hayes et al., 2015; Johnson et al., 2012; Oberlin et al., 2016; Opel et al., 2019; Smith et al., 2016; Teixeira et al., 2016; Tseng et al., 2013), such as fiber tract based spatial statistics (TBSS) (Smith et al., 2006), many of the studies limited their analyses to specific white matter fiber tracts and utilized different processing steps such as analyzing fiber tracts through hand drawn (Marks et al., 2011; Marks et al., 2007) or atlas based ROIs (Chen et al., 2020; Harasym et al., 2020; Tian et al., 2014; Tian et al., 2014) (Table 5). These well-established and standardized methods limit the analysis to specific white matter fiber tracts and could lead to inconsistency in the literature regarding the location of white matter fiber tracts that are associated with CRF or PA levels.

5.2. ET and Structural Connectivity

5.2.1. Summary of Findings—There is reason to suspect that exercise interventions impact microstructural connectivity based on limited prior intervention work. There have been eight studies examining the impact of exercise interventions on white matter microstructure in cognitively normal older adults and older adults with MCI/subjective memory complaints (6 randomized control trials, 1 nonrandomized intervention, 1 no control group). With this in mind, most studies reviewed here highlight that while ET-related changes to brain microstructure may appear, our understanding of such changes is still limited (Rektorova et al., 2020; Tarumi et al., 2020; Voss et al., 2013). For example, Rektorova et al. (2019) report that following a six month supervised dance intervention and in relation to baseline levels, individuals in the ET group saw an increase in RD and MD within the sensorimotor, cingulate, and insular cortices, but no significant group differences in RD and MD were observed between the intervention and control group (Rektorova et al., 2020).

Further, while Voss and colleagues (2013) found a trend towards percentage change increase in prefrontal FA in a walking intervention group (Voss et al., 2013) and Tarumi and colleagues (2020) found individual CRF gains to be associated with preserved WM fiber tract integrity (MD, AD) in the prefrontal cortex (Tarumi et al., 2020), only one study of the eight exercise intervention-structural connectivity investigations found a significant impact of exercise intervention on structural connectivity (Burzynska et al., 2017). Therefore,

there is little current support for a change in white matter microstructure following an exercise intervention in older adults (Burzynska et al., 2017), and some findings need to be interpreted with caution (Rektorova et al., 2020). This is in line with many recent reviews and meta-analyses that support very subtle, if any, structural brain changes following exercise interventions in older adults (Firth et al., 2018; Gogniat et al., 2021; Sexton et al., 2016). The results from Burzynska et al. (2017) are also in agreement with meta-analyses that have provided support for the greatest cognitive improvement associated with exercise interventions to be found with multicomponent training (e.g., combination of aerobic and resistance training, dance, and Tai-Chi (Colcombe & Kramer, 2003; Smith et al., 2010)) as compared to other types of exercise.

5.2.2.   Age-Related Differences—At the time of the present review, there is no study directly investigating the age-related differences in ET-related effects on structural connectivity. The lack of age-related investigation highlights the need for more studies examining the impact of exercise interventions on structural connectivity prior to old age, especially given that examining the impact of exercise in midlife has been shown to be important for brain health (Barha & Liu-Ambrose, 2020; Rovio et al., 2010).

5.2.3.   Fiber Tract Integrity-Behavior Associations—Burzynska and colleagues (2017) utilized the Virginia Cognitive Aging Battery to assess changes in cognitive functioning (fluid abilities, processing speed, memory, vocabulary) following an exercise intervention (Burzynska et al., 2017). Baseline fornix FA was positively associated only with processing speed and not for memory, vocabulary or reasoning. However, there was neither a Group (Dance vs Walking vs Walking + Nutrition vs BAT) x Time (pre vs post ET) interaction for processing speed nor a correlation between training-related change in speed and change in FA. While these results confirm previous associations of white matter microstructure and cognitive function in aging and suggest that the fornix may play a role in processing speed, there was no indication that exercise intervention had an impact on cognitive performance (Burzynska et al., 2017).

5.2.4.   Methodological Considerations—The studies varied greatly in their participant demographics, size, intervention content, and duration (see Table 6). While all studies included participants who were cognitively healthy, a majority of the studies included older adults with an average age below 70 years old. Three studies included participants with subjective cognitive complaints/MCI (Fissler et al., 2017; Tarumi et al., 2020; Venkatraman et al., 2020). Sample sizes for the exercise intervention groups ranged from 12 to 49 for the exercise intervention groups. While a majority of the studies utilized an aerobic training intervention (all walking), others used a multi-modal approach to exercise, including combining aerobic, strength, coordination, and balance (Fissler et al., 2017) and dance (Burzynska et al., 2017; Rektorova et al., 2020). Intervention length ranged from 10 weeks (Fissler et al., 2017) to 24 months (Venkatraman et al., 2020) with all interventions including a session frequency of more than once per week and a progressively increasing intensity over time.

While the studies varied in their analytic method, all studies but one (Fissler et al., 2017) utilized TBSS to quantify white matter microstructure. Importantly, the study by Burzynska

and colleagues (2017) had some methodological differences compared to the other studies that should be considered (Burzynska et al., 2017). One striking difference was that this study had more participants in the overall study and in the exercise intervention (i.e., dance) group than any of the other included studies, indicating that this study might be the most powered. Furthermore, in addition to being on the higher end of session frequency (i.e., 3/week), the dance intervention used was unique in that the authors' described it as having a physical, cognitive, and social component to it, which the dance intervention of another study (Rektorova et al., 2020) did not seem to incorporate to the same extent (cognitive training components), if at all (social components). Overall, most of the studies included a mix of *a priori* ROIs and exploratory analyses with an emphasis on areas impacted by aging (Table 6).

6. Potential Mechanisms

6.1. Exercise, Fitness, and rsFC

Although the mechanisms by which exercise and fitness may facilitate functional network integrity are not completely understood, it is known that regular participation in exercise is associated with enhanced skeletal muscle capillarization and mitochondrial function in the brain (Kayes & Hatfield, 2019). Enhanced mitochondrial function and mitochondrial density in the brain are instrumental for synaptogenesis (i.e., growth of new synapses) (Steib et al., 2014) and long-term potentiation (Bettio et al., 2019). These ET-related adaptations lead to enhanced transport of oxygen and brain metabolism (Davenport et al., 2012; Dustman et al., 1984), which subsequently helps induce synaptic strengthening and construction of a stronger and resilient capacity within the neural networks (Reuter-Lorenz & Park, 2014). The ET-related adaptations are also thought to result in efficient upregulation and expression of neurotrophic factors [e.g., brain-derived neurotrophic factors and nerve growth factor (Neeper et al., 1995, 1996)] and neurotransmitters [e.g., norepinephrine and dopamine (Hattori et al., 1994)]. This neural adaptation to ET promotes neuronal signaling, proliferation of new neurons into brain networks, reduced oxidative stress and, in turn, strengthens the functional network integrity (Voss et al., 2016).

6.2. Exercise, Fitness, and Structural Connectivity

The precise mechanisms by which exercise and fitness might afford benefits to structural connectivity and white matter integrity remains to be fully characterized. White matter myelination via mature oligodendrocytes is known to enhance the efficiency and speed of axonal conduction, while demyelination leads to reduced efficiency in neural transmission that can impair neural circuits and facilitate cognitive impairment (Peters, 2009; Peters & Sethares, 2002). A recent animal study found that wheel-running preserved white matter myelination, matured oligodendrocyte cells, and increased both peripheral brain derived growth factors and white matter capillary density (Chen et al., 2020). Moreover, exercise greatly reduced levels of neurite outgrowth inhibitor-A (Nogo-A) in the white matter, which is a myelination-suppressing cytokine that can be expressed by mature oligodendrocytes. This suggests that exercise may preserve oligodendrocytes and myelinated fiber tracts by inhibiting Nogo-A expression in white matter to thus preserve structural connectivity and facilitate better signal transmission. Exercise itself has been associated with increased

angiogenesis, cerebral perfusion, capillary density, and upregulation of VEGF, all of which may preserve or even enhance white matter microstructure (Anderson et al., 2010; Lucas et al., 2012; Morland et al., 2017; Thomas et al., 2020).

7. Recommendations for Future Research

7.1. Need for More Acute Exercise Studies

The number of acute exercise study is still relatively scarce and our understanding of the effects of an acute bout of exercise on functional or structural connectivity of the brain is far from conclusive. It is speculated that effects elicited by acute exercise presumably accumulate over time in response to chronic exercise to bolster the connection and capacity of brain networks (Won et al., 2019b). Based on this mechanism, neural adaptations after daily bouts of exercise may mediate ET-induced enhancement of rsFC. Therefore, transitional investigations need to characterize the relationship between acute and chronic exercise for mechanistic understanding about the effects of exercise on the brain networks.

Furthermore, future works should also evaluate whether acute exercise-induced functional changes underlie acute exercise-induced behavioral changes. The literature indicates that a single exercise session leads to performance improvements in cognitive tasks that involve memory (Etnier et al., 2016; Hyodo et al., 2012; Suwabe et al., 2018), executive function (Kamijo et al., 2009; Won, et al., 2017; Won et al., 2019a), and attention (Budde et al., 2008). Nevertheless, it remains to be conclusively demonstrated that changes in functional brain network are a causal mechanism or mediator of acute exercise-elicited cognitive changes, which should be further examined in the future.

No work to date has explored the relationship between an acute bout of exercise and white matter fiber tract integrity because commonly used techniques such as TBSS are thought to be insensitive to small acute microstructural changes. However, a recent study found that an acute bout of aerobic exercise may alter hippocampal gray matter microstructure in older adults (Callow et al., 2021a). Therefore, future acute exercise studies should consider quantifying both functional and microstructural changes that occur in both white and gray matter following a single exercise session.

7.2. Need for Investigating the Effects of Different Forms and Intensities in ET Studies

Although the effects of motor/balance training and mind-body exercise (e.g., Tai Chi) on functional and structural connectivity have been explored, other types of non-aerobic ET (e.g., resistance training) also have been known to impact brain function (Gothe et al., 2019; Herold et al., 2019). It is becoming increasingly apparent that both an acute bout of resistance exercise and resistance training are associated with improvement in executive function performance (Coetsee & Terblanche, 2017; Liu-Ambrose et al., 2012; Tsai et al., 2014; Vonk et al., 2019). Resistance training has also been shown to modulate functional activation during an associative memory task (Nagamatsu et al., 2012) and increase PCC gray matter volume in MCI individuals (Suo et al., 2016). Moreover, resistance training promotes expression of brain-derived neurotrophic factors and insulin like growth factor-1 (Herold et al., 2019). Hence, it is reasonable to hypothesize that resistance training could

robustly contribute to functional and structural network integrity. Still, little is known about the effects of resistance training on functional and structural brain networks. This knowledge gap therefore provides an intriguing avenue for future exercise-connectivity investigations.

As shown by Schmitt et al. (2019), distinct intensities of acute exercise can differentially affect network signaling dynamics. Based on this evidence, it is plausible to hypothesize that different intensities of chronic exercise could differentially impact functional and structural connectivity; therefore, future studies need to assess the relationship between chronic exercise with different intensities and changes in brain connectivity. Additionally, the effects of training cessation on brain networks should be investigated. Prior work has shown that a 10-day ET cessation was associated with reduced neural efficiency during a memory task (Won et al., 2020) and decreased cerebral and hippocampal blood flow in older distance runners (Alfini et al., 2016). Given these substantial alterations in the brain function following such a short-term ET cessation, it may be that cessation of exercise is associated with alterations in functional and structural brain connectivity. Further investigation of ET cessation will help establish a more complete understanding of the significance of continuous participation in ET to maintain brain networks' integrity.

7.3. Experimental Design Considerations

For future ET studies, stronger experimental effects could likely be achieved by having a non-exercise control condition. In this review, absence of non-exercise (or active) control conditions was observed in several ET studies (Chirles et al., 2017; Legget et al., 2016; McFadden et al., 2013; Won et al., 2021a; Won et al., 2021b), warranting caution in the interpretation of the results. Although pretest-posttest designs are commonly used to examine intervention effects over time, lack of non-exercise control group obscures the possible effects induced by the passage of time or other nonspecific intervention. Thus, future ET studies need to include a non-exercise (or active) control condition, carefully document control intervention protocol, and identically match the duration and frequency of the control intervention to the exercise protocol.

Next, future investigations should extend the sample to a broader range of populations to enhance reproducibility and generalizability of the findings, which will help to identify new strategies for intervention. Another benefit of extending the sample variability is investigation of possible individual differences that might moderate the relationship between exercise or CRF and functional and structural connectivity. The number of younger adult investigations still remain limited when compared to the quantity of studies of older individuals. Characterizing the multi-dimensional nature of age-related changes in patterns of brain network by studying younger adults is of interest (Cole et al., 2010; Hayasaka & Laurienti, 2010). Thus, studying younger adults could provide an explanatory examination of the effects of exercise on brain networks that is complementary to older adult studies.

Moreover, it is also imperative for future studies to consider other factors (e.g., genetics, sleep, or hydration status) that could significantly moderate the relationship between exercise and structural and functional brain networks. In addition, to enhance reliability and replicability of neuroimaging findings, a complete report of results including null findings and clarifying which analyses are ad hoc, explanatory, or hypothesis-driven will

be helpful for future investigations or meta-analyses (Ioannidis et al., 2014; Poldrack et al., 2017). Future studies examining the association between exercise and large-scale network communication at integrative hubs will contribute to understanding individual responsivity to exercise. The relationship between structural and functional connectivity or relationship with other metrics of brain function (e.g., blood flow) should be assessed to broaden our understanding about how brain functions are modulated by exercise.

7.4. Data Analysis Considerations

In the perspective of data analysis, fMRI and DWI data must undergo careful quality control procedures to avoid significant errors and bias in results and thus have an improved reproducibility of findings. Future rsFC studies need to employ a stringent voxel-wise threshold (e.g., $p = 0.001$), because a lenient voxel-wise threshold (e.g., $p = 0.01$) increases the possibility of cluster-level false positive rate (Woo et al., 2014). For structural connectivity analysis, we have found that there is less support for the impact of exercise interventions on white matter fiber tract integrity, presumably due to inconsistencies with respect to the extent and location of these effects. Since DWI signal is sensitive to tissue microstructure (Assaf & Pasternak, 2008; Walhovd et al., 2014), it is critical for future structural connectivity work to utilize additional brain imaging measures that examine neurite properties (i.e., orientation dispersion, neurite density) using multi-shell diffusion imaging scans (e.g., High Angular Resolution Imaging or Estimating Neurite Orientation and Dispersion Parameters) (Zhang et al., 2012) and control for cerebrospinal fluid and free water signal contamination (Henf et al., 2018). Additionally, some studies have explored ET-related changes in hippocampal gray matter diffusivity (Kleemeyer et al., 2016; Thomas et al., 2016), and one recent study found increased cortical gray matter MD in healthy older adults and individuals with MCI following a 12-week exercise intervention, which was associated with improvements in verbal fluency and memory performance (Callow et al., 2021b). This indicates that the effects of exercise on DWI within hippocampal and other gray matter regions is an important area of future study.

8. Conclusions

Taken together, acute exercise, ET, and greater CRF consistently demonstrated altered motor, cognitive function, and emotion regulation-related rsFC changes in both younger and older adults. Importantly, the exercise/fitness-related alterations in rsFC were associated with corresponding motor function, cognition, and mental health changes, implicating rsFC alteration as a possible mechanism underlying the relationship between exercise/fitness and behavior changes. Further, greater PA levels and CRF are associated with better motor and cognitive function which may be mediated by enhanced white matter microstructural integrity. However, studies have failed to provide evidence for ET-related improvements in structural connectivity. Future investigations should focus on having a large sample size to increase statistical power, finding moderators in the relationship between exercise/ fitness and functional and structural connectivity of the brain, and gaining insights into neurophysiological mechanisms that derive exercise-induced changes in functional and structural brain networks.

Acknowledgements

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Highlights

- Regular participation in exercise and higher fitness modulate functional connectivity of the brain.

- Exercise-related changes in functional connectivity corresponds to behavioral changes such as cognitive and motor performances improvements.

- Greater physical activity levels and fitness are associated with better motor and cognitive function, mediated by enhanced white matter microstructural integrity.

Table 1.

A summary of investigations examining the relationship between fitness and functional connectivity.

Author, year	Participant		Fitness assessment	Analysis Method	Results	Network(s) Implicated
	n, Subjects	Mean age (year)				
Voss, 2010	32 YA and 120 OA	YA: 24.1±5.1 OA: 66.5±5.7	$\dot{V}O_{2max}$	SBC (seed: PCC/rsp)	1) Link between ↑ FIT and ↑ FC between PCC and MFG 2) Link between the ↑ DMN and ↑ EF performance 3) ↑ FIT mediated the link between ↑ rsFC and ↑ EF performance	DMN
Boraxbekk, 2016	118 OA	61.5	BMI, WC, GS, resting SBP and DBP	ICA	Association between ↑ PA score and ↑ DMN rsFC	DMN
Voss, 2016	36 YA and 189 OA	YA: 22.1±3.0 OA: 65.1±4.4	$\dot{V}O_{2max}$, PA/ health history assessment	1) ICA 2) NBS 3) Target ROI selection	1) Link between ↑ FIT and ↑ DMN and DAN 2) No relationship between PA history and rsFC	1) DMN 2) DAN
Raichlen, 2016	11 ATH and 11 NATH YA	ATH: 21.5±2.4 NATH: 20.6±1.1	BMI, MET, $\dot{V}O_{2max}$	SBC (seed: Bi APC, IPL, PCC, MPC, MC)	1) ↑ FPN and ↓ DMN in ATH > non-ATH 2) Dose-response relationship between PA and rsFC	1) FPN 2) DMN
Boyne, 2018	119 MAA	41±19	6MWT	1) SBC (seed: MLR, CLR) 2) Target ROI selection	1) Link between ↑ 6MWT distance and ↑ rsFC between MLR-R SFG and PC 2) Link between ↑ 6MWT distance and ↑ rsFC between the CLR and the M1F	SMN
Stillman, 2018	50 YA	25.2±5.1	$\dot{V}O_{2max}$	SBC (seed: Bi anterior/ posterior HIP)	1) Link between ↑ FIT and HIP rsFC 2) No significant relationship between FIT and caudate rsFC	HPN
Dorsman, 2020	212 OA	73.3±6.2	Self-reported PA	Within and between network analysis	Longitudinal association between ↑ PA and ↑ fronto-subcortical network	FPN

Notes: OA, older adults; YA, younger adults; MAA, middle-aged adults; ATH, athlete; NATH, non-athlete; $\dot{V}O_{2max}$, maximal oxygen consumption; BMI, body mass index; WC, waist circumference; GS, grip strength; PA, physical activity; MET, metabolic equivalent of task; 6MWT, 6-min walk test; SBC, seed-based correlation analysis; PCC/rsp, posterior cingulate cortex/retrosplenial cortex; ICA, independent components analysis; NBS, network-based statistic; Bi, bilateral; APC, anterior prefrontal cortex; IPL, inferior parietal lobule; MPC, medial prefrontal cortex; MC, motor cortex; MLR, midbrain locomotor region; CLR, cerebellar locomotor region; HIP, hippocampus; FIT, fitness; MFG, medial frontal gyrus; DMN, default-mode network; EF, executive function; rsFC, functional connectivity; DAN, dorsal attention network; FPN, frontoparietal network; R, right; SFG, superior frontal gyrus; PC, paravermal cerebellum; M1F, primary motor cortex foot area; SMN, sensorimotor network; HPN, hippocampal network.

Table 2.

A summary of investigations examining the relationship between acute exercise and functional connectivity.

Author, year	n (E/C), Subjects	Mean age (year)	Condition (E/C)	Duration	Intensity	Analysis Method	Results	Network(s) Implicated
	Participant							
Rajab, 2014	30 (15/15), YA	E: 26.1±4.3 C: 27±6.5	E: semirecumbent CYE C: no exercise	25 min	70% of HR$_{max}$	Dual regression	↑ Co-activation between secondary somatosensory and thalamus and in motor function regions after E > C	SMN
Weng, 2017	26 (26/0), 12 YA/14 OA	YA: 23.2±0.7 OA: 66.3±1	E: CYE C: passive, motor driven CYE	30 min	65% of HR$_{max}$	1) Data-driven approach 2) Averaged multiple regions of theoretically defined networks	1) ↑ integration of affect-reward, HIP, CO, and R ECN after AEX across age 2) ↑ attention-reward network, hippocampal and FPN intensity in OA > YA	1) HPN 2) CO 3) ECN
Schmitt, 2019	25 (25/0), trained male YA	27.1±4.0	E1: treadmill E2: treadmill	30 min	low intensity (< 35% LT) high intensity (> 20% LT)	Dual regression	↑ R affective and reward network, R FPN and sensorimotor rsFC after low-intensity > high-intensity acute EX	FPN
Alfini, 2020	32 OA	66.3±7.3	E: CYE C: seated-rest	30 min	15 RPE	SBC (seed: Bi AI)	1) ↓ connectivity between CO and HIP and CB after AEX 2) ↓ CO-hippocampal network mediated the relationship between exercise-related ↑ positive affect and ↑ disturbance in sleep	CO

Notes: E, exercise condition or group; C, control condition or group; OA, older adults; YA, younger adults; CYE, cycling exercise; HR$_{max}$, maximal heart rate; LT, lactate threshold; RPE, ratings of perceived exertion; SBC, seed-based correlation analysis; Bi AI, bilateral anterior insula; HIP, hippocampus; CO, cingulo-opercula network; R, right; ECN, executive control network; AEX, acute exercise; FPN, frontoparietal network; rsFC, functional connectivity; CB, cerebellum; SMN, sensorimotor network; HPN, hippocampal network.

Table 3.

A summary of investigations examining the relationship between aerobic ET and functional connectivity.

Author, year	Participant n (E/C), Subjects	Mean age (year)	Intervention (E/C)	Frequency and duration	Intensity	Analysis Method	Results	Network(s) Implicated
Voss, 2010	97 (65/32), 65 OA / 32 YA	YA: 23.9± 4.4 OA E: 67.3±5.8 OA C: 65.3±5.2	E: Walking C: Flexibility, BAT	3/W for 12M, 5 min increments weekly to 40 min	50–75% HR_{max}	ROI-ROI	1) ↑ DMN and FPN rsFC after walking intervention 2) Link between ↑ ET-related DMN rsFC and ↑ EF 3) ↑ DMN and FPN after BAT	1) DMN 2) FPN
Burdette, 2011	11 (6/5), OA	E: 77.6±5 C: 74±2.5	E: Walking & Cycling C: HE and stretching	4/W for 4M, 150 min/week	RPE from 12 to 14	Graph Theory methods, Modularity, ROI (HIP)	Link between ET-related ↑ HIP rsFC and ↑ HIP CBF	HPN
McFadden, 2013	11, obese adults	38.2±9.5	E: Walking	Frequency X, 6M, 15–20 min ↑ to 40–60 min	500/kcal day at 75% $\dot{V}O_{2max}$	ICA	Link between ET-related ↓ DMN rsFC and ↓ fat mass/ hunger ratings	DMN
Legget, 2016	11, obese adults	38.2±3.2	E: Walking	Frequency X, 6M, 15–20 min ↑ to 40–60 min	500/kcal day at 75% $\dot{V}O_{2max}$	BNC	1) ↓ PCC BNC after ET 2) Link between ET-induced ↑ FIT and ↓ PCC BNC	DMN
Tozzi, 2016	38 (19/19), MAA	E: 42.8±13.8 C: 45.1±13.3	E: Treadmill & Cycling C: Maintain Exercise Habits	2/W for 4M, 1 hour	↑ (max 30 W/min) up to the target intensity	Graph Analysis, NBS (seed: R PRHIP), BOLD Fluctuation	Link between ET-related ↑ rsFC between R PRHIP and L STG and ↓ TMD	HPN
Chirles, 2017	32 (32/0), 16 OA / 16 MCI	MCI: 79.6±6.8 HC: 76.1±7.2	E: Walking	4/W for 3M, 30 min	50–60% HRR	SBC (seed: PCC/ precuneus)	1) ↑ ET-induced DMN rsFC in MCI 2) ↓ ET-related DMN rsFC in HC	DMN
Flodin, 2017	47 (22/25), OA	E: 68.4±2.5 C: 69.1±3.0	E: Walking C: BAT	3/W for 4M, 30–60 min	40 to 80% of HR_{max}	SBC (seed: Bi HIPP, Bi PRHIP and PCC)	Link between ET-related ↑ FIT and ↑ HIP rsFC (BOLD signal fluctuation), ↑ DMN, and ↓ thalamus-sensorimotor network	1) HPN 2) DMN 3) SMN
Baniqued, 2017	128 (34/33/42/40), OA	E1: 64.8±4.5 E2: 64.5±4.4 E3: 65.5±4.5 C:65.5±4.4	E1: Walking E2: Walking + Supplement E3: Dance C: BAT	3/W for 12M, 5 min ↑ weekly to 40 min	50–75% HR_{max}	Modularity	Link between ↑ baseline rsFC modularity and ET-related ↑ in EF in walking, walking+nutritional supplement, and SSS groups	1) DMN 2) ECN 3) CO 4) DAN
McGregor, 2018	37 (19/18), sedentary OA	73.5±6.8	E: Spin Cycling C: BAT	3/W for 3M, 45 min	started at 50%–75% of HRR	SBC (seeds: Bi M1 and anterior DMN)	1) EX > C: ↑ rsFC between SMN and anterior DMN 2) Positive association between ET-related ↑ SMN-DMN rsFC and ↑ HRR PSM speed	1) SMN 2) DMN

Author, year	Participant n (E/C), Subjects	Mean age (year)	Intervention (E/C)	Frequency and duration	Intensity	Analysis Method	Results	Network(s) Implicated
Prehn, 2019	29 (11/18), overweight OA	E: 69±5 C: 65±6	E: Cycling C: BAT	2/W for 4M, 45 min	40% of the AT and ↑ to max 30 W/min	SBC (seeds: Bi DLPFC)	1) EX > C: ↑ rsFC between DLPFC and SPL/precuneus 2) C > EX: ↑ rsFC between L DLPFC and MSFG	ECN
Won, 2021a	32 (32/0), 16 OA / 16 MCI	77.0±7.6	E: Walking	4/W for 3M, 30 min	50–60% HRR	SBC (seeds: anterior and posterior HIP)	Link between ET-related ↑ rsFC between HIP and R PC and ↑ memory	HPN
Won, 2021b	35 (35/0), 17 OA / 18 MCI	78.0±7.1	E: Walking	4/W for 3M, 30 min	50–60% HRR	SBC (seeds: cerebellum)	Link between ET-related ↑ rsFC between CB and R IPL and ↑ phonemic fluency	CBN

Notes: OA, older adults; YA, younger adults; MAA, middle-aged adults; MCI, mild cognitive impairment; E, exercise group; C, control group; HC, healthy control; BAT, balance and toning; HE, health education; A&B, aerobic and balance training; WL, weightlifting; M, months; W, week; HR_{max}, maximal heart rate; $\dot{V}O_{2max}$, maximal oxygen consumption; HRR, heart rate reserve; ROI, region of interest; ICA, independent components analysis; BNC, between network connectivity; NBS, Network Based Statistics; BOLD, blood oxygen level dependent; R, right; PRHIP, parahippocampal gyrus; SBC, seed-based correlation analysis; PCC, posterior cingulate cortex; Bi, bilateral; AT; anaerobic threshold; rsFC, functional connectivity; DMN, default-mode network; FEN, fronto-executive network; EF, executive function performance; FPN, frontoparietal network; ET, exercise training; HIP, hippocampus; CBF, cerebral blood flow; L, left; STG, superior temporal gyrus; TMD, mood disturbance; FIT, fitness; BOLD, blood oxygen level dependent; SMN, sensorimotor network (hub region: motor cortex (left M1)); PSM, psychomotor; DLPFC, dorsolateral prefrontal cortex; SPL, superior parietal lobule; MSFG, medial superior frontal gyrus; CB, cerebellum; IPL, inferior parietal lobule; HPN, hippocampal network; ECN, executive control network; CO, cingulo-opercula network; DAN, dorsal attention network; CBN, Cerebellum Network.

Table 4.

A summary of investigations examining the relationship between aerobic non-traditional ET/PA and functional connectivity.

Author, year	Participant n (E/C), Subjects	Mean age (year)	Intervention (E/C)	Frequency and duration	Intensity	Analysis Method	Results	Network(s) Implicated
Magon, 2016	28 (14/14), OA	E: 62.3±5.4 C: 61.8±5.3	E: slackline training C: no intervention	3/W for 1.5M, 30 min		1) ICA 2) SBC (seed: THL, BG)	↓ BG rsFC after training in a subgroup of participants with ↑ slackline performance	SMN
Demirakca, 2016	32 (21/11), MAA	E: 48±9 C: 49±8	E: life kinetik training C: no intervention	1/W for 4M, 1H		seed to voxel (seed: MA, SMA, VA, AA, FC)	E > C: ↑ rsFC between motor and visual/ somatosensory area, primary sensory area and ACC, and PAC and CB	SMN
Ji, 2017	24 (12/12), OA	70±7.78	E: Wii Fit C: no training	7/W for 1.5M, 30 min		SBC (seed: PCC/ precuneus)	Link between ET-related ↑ rsFC between putaman and thalamus and ↑ in EF	DMN
Tao, 2017[a]						SBC (seed: Bi DLPFC)	1) Tai Chi group: ↓ rsFC between DLPFC and L SFG/ACC 2) Badunjin group: ↓ rsFC between DLPFC and L putamen/ insula	ECN
Tao, 2017[b]	57 (36/21), OA	E1: 62.3±4.5 E2: 62.3±3.8 C: 59.7±4.8	E1: Tai Chi E2: Badunjin C: HE	5/W for 3M, 1H	No information	SBC (seed: Bi HIP)	1) ↑ rsFC between bilateral HIP and MPFG 2) Link between Tai Chi training-related ↑ HIP rsFC and ↑ memory	HPN

Notes: OA, older adults; YA, younger adults; MAA, middle-aged adults; TC, Tai-Chi; W, walking; E, exercise group; C, control group; HE, health education; W, week; M, month; H, hour; yrs, years; ICA, independent component analysis; SBC, seed-based correlation analysis; THL, thalamus; BG, basal ganglia (including caudate, putamen, and globus pallidus); MA, motor area; SMA, sensorimotor area; VA, visual area; AA, auditory area; FC, frontal cortex area; PCC, posterior cingulate cortex; Bi, bilateral; DLPFC, dorsolateral prefrontal cortex; HIP, hippocampus; TAN, topological attributes of network; rsFC, functional connectivity; ACC, anterior cingulate cortex; PAC, primary auditory cortex; CB, cerebellum; L, left; SFG, superior frontal gyrus; MPFC, medial prefrontal gyrus; SMN, sensorimotor network; DMN, default-mode network; ECN, executive control network; HPN, hippocampal network.

Table 5.

A summary of investigations examining the relationship between fitness and structural connectivity.

Author, year	Participant		Fitness assessment	Analysis Method	Results
	n, Subjects	Mean age (year)			
Marks, 2007	13 YA and 15 OA	YA: 24±3 OA: 69.6±4.7	age, sex, BMI, and self-reported PA.	Seven hand drawn ROIs	Link between ↑ CRF and ↑ FA in UF and CM for OA and YA
Marks, 2011	15 OA	66±6	$\dot{V}O_{2max}$	Hand drawn CM ROIs	Link between ↑ CRF and ↑ FA of left middle cingulum
Johnson, 2012	26 OA	64.8±2.8	$\dot{V}O_{2max}$, total time on treadmill, 1-min HR recovery	TBSS	Link between ↑ FIT and ↓ RD of the CC
Liu, 2012	9 AC and 6 INAC OA	AC: 62.1±2.6 INAC: 72.3±2.7	$\dot{V}O_{2max}$	Automated Voxel-Wise analysis	Link between ↑ CRF and ↑ FA in tracts connecting prefrontal and parietal brain regions
Tseng, 2013	10 MA and 10 SED OA	MA: 72.2±5.3 SED: 74.5±4.3	$\dot{V}O_{2max}$	TBSS	MA > SED OA 1) ↑ FA in R SCR, both sides of SLF, R IFOF, and L ILF 2) ↓ MD of L PTR and L cingulum HIP
Wang, 2013	13 YA EG, 14 YA	EG: 20.5±3.2 YA: 22.3±2.7	No information	Tractography, Global and Regional network analysis	1) ↑ anatomical connection density in sensorimotor, attentional and default mode systems in EG. 2) ↑ FA in bilateral CST of EG.
Burzynska, 2014	88 low fit OA	65±4	$\dot{V}O_{2max}$ and 7-day actigraphy data	TBSS	1) Link between ↑ SED time and ↓ FA of PRHIP WM 2) No link between SC and FIT
Tian, 2014[a]	276 OA	83±2.7	10-year PA history questionnaire	TOIA	No difference in WM tracts between AC and SED groups
Tian, 2014[b]	164 OA	82.9±2.6	400-meter walk test	TOIA	Link between ↑ FIT and ↑ FA of CM
Tian, 2015	90 OA	87.4±2.3	number of steps	TOIA	Link between ↑ PA and ↑ FA in WM frontal and temporal areas
Hayes, 2015	32 YA and 27 OA	YA: 21.1±3.1 OA: 63.4±6.4	$\dot{V}O_{2max}$	TBSS	1) Link between ↑ PA and whole brain ↑ FA 2) FA mediates positive relationship between CRF and global cognition
Zhu, 2015	565 MA	81.3±2.5	MDT (5 year prior)	TOIA	Link between ↑ FIT and ↑ FA (individual tracts not analyzed)
Oberlin, 2016	Study 1: 113 OA Study 2: 154 OA	Study 1: 66.1±5.7 Study 2: 65.6±4.6	$\dot{V}O_{2max}$	TBSS	1) Link between ↑ FIT and ↑ FA in ACR, AIC, fornix, CM, and CC 2) FA mediated the link between FIT and spatial memory
Smith, 2016	88 OA with APOE-ε4 (LRHP: 21, LRLP: 33, HRHP: 20, HRLP: 14)	LRHP: 76±4.7 LRLP: 73.5±4.7 HRHP: 73.1±4.4 HRLP: 74±4.2	SBAS	TBSS	1) Link between ↑ PA and ↑ FA and ↓ RD in the SLF, SS, GCC, fornix, IC, and CR for APOE-ε4 carriers 2) Opposite trend in APOE-ε4 noncarriers 1) Link between ↑ FIT and ↑ FA in LF, FOF, and CC 2) Link between ↑ FIT and ↓ MD and RD in LF, FOF, and CC Link between ↑ HWT and ↓ whole brain AD and RD and cognition ↑ FA predictive of PA adherence No link between PA and FA or MD
Teixeira, 2016	22, OA with aMCI	68.5	$\dot{V}O_{2max}$	TBSS	1) ↓ PA ↑ MD of uncinate fasciculus over time Link between ↑ FIT and ↑ whole brain FA ↑

| Author, year | Participant | | Fitness assessment | Analysis Method | Results |
	n, Subjects	Mean age (year)			
Best, 2017	141 OA	82.5±2.5	Self-reported 10-year walking time	Whole Brain TOIA	
Gujral, 2018	105 OA	66.6±5.7	PASE	TBSS	
Maltais, 2019	277 OA	74.7 + 3.9	Self-report questionnaire	TBSS	
Opel, 2019	1048 YA	28.8±3.7	2-min walk test	TBSS	
Chen, 2020	56 OA	59.1±4.3	$\dot{V}O_{2max}$	TOIA	FIT linked to ↑ FA in R CM, HIP, and L CP
Harasym, 2020	24 PM women	59.5±3.5	$\dot{V}O_{2max}$	TBSS	Link between ↑ CRF and ↑ FA of S1
Strömmer, 2020	399, YA and OA	Range from 18–87	Self-reported PA levels	TOIA	1) ↑ PA mediates relationship between ↑ age and ↓ FA in the GCC, UF, and EC 2) ↑ FA of GCC mediated relationship between ↓ age and ↑ RT
Wolf, 2020	44 OA	69+7.3	7-day actigraphy data	TBSS	1) No associations between PA and MD or FA 2) Interaction between PA and ↑ age linked to global MD
Tarumi 2021	30 MT, 30 MS, and YA	YA: 32±6 MT: 54±4 MS: 54±4	$\dot{V}O_{2max}$	TBSS	1) ↑ FA in the GCC, SCR, ACR, AIC, LF, FOF, UF, CM, and fornix in the MA group compared to MS. 2) Link between ↑ FIT and ↑ FA in both MA and YA groups

Notes: OA, older adults; YA, younger adults; AC, active; INAC, inactive; MA, master athletes; MT, middle aged trained, MS, middle aged sedentary, SED, sedentary; EG, elite gymnasts; APOE-ɛ4, apolipoprotein E epsilon 4 allele; LRHP, Low Risk (non--APOE-ɛ4 carrier) High PA; LRLP, Low Risk (non--APOE-ɛ4 carrier)-Low PA; HRHP, High Risk (APOE-ɛ4 carrier)-High PA; HRLP, High Risk-Low PA; PM, post-menopausal; TC, Tai Chi group; W, walking group; BMI, body mass index; aMCI, amnestic mild cognitive impairment; PA, physical activity questionnaire; CRF, cardiorespiratory fitness; $\dot{V}O_{2max}$, maximal oxygen consumption; MDT, maximal duration treadmill test; SBAS, Stanford Brief Activity Survey; PASE, Physical Activity Scale for the Elderly; ROI, region of interest; CM, cingulum; TBSS, tract based spatial statistics; TOIA, tract of Interest analysis; FA, fractional anisotropy; CC, corpus callosum; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; UF, uncinate fasciculus; R, right; SCR, superior corona radiata; SLF, superior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus; L, left; ILF, inferior longitudinal fasciculus; PTR, posterior thalamic radiation; HIP, hippocampus; PRHIP, parahippocampal; WM, white matter; SC, structural connectivity; FIT, fitness; ACR, anterior corona radiata; AIC, anterior internal capsule; CP, cerebral peduncle; SS, sagital stratum; GCC, genu of corpus callosum; IC, internal capsule; CR, corona radiata; LF, longitudinal fasciculus; FOF, fronto-occipital fasciculus; CST, corticospinal tract; HWT, historic walking time; S1, somatosensory region; EC, external capsule; RT, response time.

Table 6.

A summary of investigations examining the relationship between aerobic/non-traditional ET and structural connectivity.

Author, year	Participant n (E/C), Subjects	Mean age (year)	Intervention (E/C)	Frequency and duration	Intensity	Analysis Method	Results
Voss, 2013	75 (35/35), 70 OA	64.8±4.4	E: Walking C: BAT	3/W for 1Y 40 min	50–75% HRR	TBSS	No effect of intervention
Burzynska, 2017	174 (49/40/42/43), OA	65.4 ± 4.4	E1: Dance E2: Walking E3: Walking + Nutrition C: BAT	3/W for 6M 1 hr	HR, RPE	TBSS	↑ FA Fornix Dance group compared to all other groups
Fissler, 2017	39 (12/11/16), OA	E: 74.2 C1: 71.4 C2: 70.5	E: MMT C1: 50h computer C2: Waitlist controls	2/W for 10W 1 hr	Adapted at individual level	TIFT	No effect of intervention
Clark, 2019	25 (25/0), OA	67.1±7.9	Walking	3/W for 6M 20–45 min	30–70% HRR	TBSS	No effect of intervention
Rektorova, 2019	62 (31/31), OA	E: 68 C: 67.2	E: Dance C: Life as usual	3/W for 6M 1 hr	Medium physical load intensity	TBSS	No effect of intervention
Venkatraman, 2020	79 (unclear distribution information), OA	72	E: Walking C: Usual Care	24M 150 min/W	Increased over 8 Ws	TBSS	No effect of intervention
Tarumi, 2020	36 (20/16)	E: 66±7 C: 67±7	E: Walking C: SAT	3–4/W for 1Y 25–35 min	75–90% HRR	TBSS	No effect of Intervention

Notes: OA, older adults; YA, younger adults; E, exercise group; C, control group; BAT, balance and toning; SAT, stretch and toning; MMT, multimodal training program (aerobic, strength, coordination, balance, and flexibility elements and was designed in the form of an imaginary journey); Y, year; W, week; M, month; hr, hour; HRR, heart rate reserve; TBSS, tract based spatial statistics; FA, fractional anisotropy; ROI, region of interest; AD, axial diffusivity; RD, radial diffusivity; MD, mean diffusivity; WM, white matterTIFT, tensor imaging and fiber tracking.