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Meeting Report

Proceedings from the Albert Charitable Trust Inaugural Workshop on 'Understanding the Acute Effects of Exercise on the Brain'

Jill N. Barnes[a], Jeffrey M. Burns[b], Marcas M. Bamman[c], Sandra A. Billinger[b], Sue C. Bodine[d], Frank W. Booth[e], Patrice Brassard[f], Tameka A. Clemons[g], Paul J. Fadel[h], Paige C. Geiger[i], Swathi Gujral[j], Jacob M. Haus[k], Scott E. Kanoski[l], Benjamin F. Miller[m], Jill K. Morris[b], Kristin M.S. O'Connell[n], David C. Poole[o], Darleen A. Sandoval[p], J. Carson Smith[q], Russell H. Swerdlow[b], Shawn N. Whitehead[r], Eric D. Vidoni[b] and Henriette van Praag[s,*]

[a]*Department of Kinesiology, University of Wisconsin-Madison, Madison, WI, USA*
[b]*University of Kansas Alzheimer's Disease Research Center, Fairway, KS, USA*
[c]*UAB Center for Exercise Medicine, University of Alabama, Birmingham, AL, USA*
[d]*Department of Internal Medicine, Division of Endocrinology and Metabolism, University of Iowa Carver College of Medicine, Iowa City, IA, USA*
[e]*Department of Biomedical Sciences, University of Missouri, Columbia, MO, USA*
[f]*Department of Kinesiology, Faculty of Medicine, Université Laval, and Research center of the Institut universitaire de cardiologie et de pneumologie de Québec, Québec city, QC, Canada*
[g]*Department of Professional and Medical Education, Meharry Medical College, Nashville, TN, USA*
[h]*Department of Kinesiology, University of Texas at Arlington, Arlington, Texas, USA*
[i]*Department of Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas City, KS, USA*
[j]*University of Pittsburgh School of Medicine, Department of Psychiatry, Pittsburgh, PA, USA*
[k]*School of Kinesiology, University of Michigan, Ann Arbor, MI, USA*
[l]*Human and Evolutionary Biology Section, Department of Biological Sciences, Dornsrife College of Letters, Arts and Sciences, University of Southern California, Los Angeles, CA, USA*
[m]*Aging and Metabolism Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA*
[n]*The Jackson Laboratory, Bar Harbor, ME, USA*
[o]*Departments of Kinesiology, Anatomy and Physiology, Kansas State University, Manhattan, KS, USA*
[p]*University of Colorado, Anschutz Medical Campus, Aurora, CO, USA*
[q]*Department of Kinesiology, School of Public Health, University of Maryland, College Park, MD, USA*
[r]*Vulnerable Brain Laboratory, Department Anatomy and Cell Biology, Schulich School of Medicine and Dentistry, Western University, London, N6A 5C1, Canada*
[s]*Stiles-Nicholson Brain Institute, Charles E. Schmidt College of Medicine, Florida Atlantic University, Jupiter FL, USA*

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*Correspondence to: Henriette van Praag, Stiles-Nicholson Brain Institute, Charles E. Schmidt College of Medicine, Florida Atlantic University, Jupiter FL 33458, USA. E-mail: hvanpraag@health.fau.edu.

Abstract. An inaugural workshop supported by "The Leo and Anne Albert Charitable Trust," was held October 4–7, 2019 in Scottsdale, Arizona, to focus on the effects of exercise on the brain and to discuss how physical activity may prevent or delay the onset of aging-related neurodegenerative conditions. The Scientific Program Committee (led by Dr. Jeff Burns) assembled translational, clinical, and basic scientists who research various aspects of the effects of exercise on the body and brain, with the overall goal of gaining a better understanding as to how to delay or prevent neurodegenerative diseases. In particular, research topics included the links between cardiorespiratory fitness, the cerebrovasculature, energy metabolism, peripheral organs, and cognitive function, which are all highly relevant to understanding the effects of acute and chronic exercise on the brain. The Albert Trust workshop participants addressed these and related topics, as well as how other lifestyle interventions, such as diet, affect age-related cognitive decline associated with Alzheimer's and other neurodegenerative diseases. This report provides a synopsis of the presentations and discussions by the participants, and a delineation of the next steps towards advancing our understanding of the effects of exercise on the aging brain.

Keywords: Alzheimer's Disease, Parkinson's Disease, exercise, cardiorespiratory fitness, blood vessels, mitochondria, cerebrovasculature, neurotrophins, cognition

INTRODUCTION

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease. With the increase in human lifespan [1] the incidence of AD will likely continue to rise in the coming decades. Risk for the disease is increased in individuals with a family member affected by AD or who have apolipoprotein e4 genotype (APOE4) alleles [2], as well as by physical inactivity and associated conditions, such as arterial hypertension and hypercholestremia [3]. The accumulation of amyloid plaques and neurofibrillary tangles in the hippocampus and cortex result in a progressive loss of brain function accompanied by physical and cognitive decline [4]. To date there are no effective treatment options for AD patients, and pharmaceutical trials have generally resulted in failure [5]. Indeed, the recently approved monoclonal anti-amyloid antibody aducanumab has unclear therapeutic efficacy [6]. Therefore, at present lifestyle interventions hold the most promise for delaying or preventing the onset of dementia [7]. In particular, aerobic physical activity, such as walking, running, swimming or cycling, that improves cardiorespiratory endurance is a low-cost and low-risk intervention [8]. In rodents, running enhances adult hippocampal neurogenesis and neurotrophin levels, and memory function [9, 10]. In animal models of AD, exercise improves pathophysiology and cognitive function [11–13]. In humans, longitudinal epidemiological studies suggest that aerobic exercise benefits memory function during normal aging [14], and reduces the incidence of AD [15, 16]. Moreover, randomized controlled trials indicate that aerobic exercise training in older adults can increase brain volume, blood flow, memory, and executive function [17–19], which may delay or prevent AD onset [7, 20, 21].

Observational studies indicate moderate to high intensity aerobic activity of at least 150 minutes per week may be needed for cognitive benefits in middle-aged and older adults [22, 23]. To better understand the outcomes and mechanisms underlying effects of exercise on human brain function, objective measures of physical activity capacity such as peak oxygen consumption (VO_2peak) and cardiorespiratory fitness (CRF) are very important [24]. Research has shown that increased CRF is associated with a larger hippocampal volume and better cognitive function scores in normal aging adults [25], improved functional connectivity in the default mode network [26], and is linked to a reduction in brain atrophy in patients with AD [27]. Similarly, randomized controlled trials suggest that higher intensity exercise, which results in increased CRF, is the optimal approach to improvement and maintenance of memory function in older adults [28–30]. In late-middle-aged adults with increased risk for AD due to family history and APOE4 status, six months of aerobic exercise training increased CRF in correlation with enhanced executive function [31]. Indeed, there is increasing evidence that CRF is an important indicator of brain health both during normal aging and in AD patients [32]. In addition, randomized controlled trial data suggest aerobic exercise may influence brain structure and function in older adults both with and without AD. In early AD, exercise-related increases in VO_2peak are associated with improved memory performance and reduced hippocampal atrophy over 6 months [33]. **Jeff Burns** and colleagues showed that in older adults without cognitive impairment, a dose-response relationship likely exists between aer-

obic exercise and cognition, beginning with low doses (75 mins/week) and with increased benefits at higher doses (150 and 225 mins/week) in those who adhered to the exercise protocol [29]. Maximizing CRF may be an important therapeutic target for achieving cognitive benefits [34].

In a study of the benefits of acute exercise in chronic stroke survivors (>6 months post-stroke), **Swathi Gujral** and colleagues showed that an acute bout of exercise in chonic stroke survivors and age-matched controls had broad-based cognitive benefits (i.e., processing speed, memory, global cognition), regardless of intensity (low or moderate) or modality (aerobic or stretching). However, only aerobic exercise resulted in attentional and executive functioning benefits specifically in chronic stroke survivors but not in age-matched controls.

The link between exercise, CRF, cognition and dementia was discussed in this Workshop by **Jeff Burns, Swathi Gujral, Eric Vidoni and Jill Morris.**

CEREBROVASCULATURE

The mechanisms underlying the association between CRF and brain health remain under investigation. In a healthy brain, cerebral blood flow is augmented in response to a vasodilatory stimulus. Exercise modulates the cerebrovasculature, which may allow for better cerebral perfusion, delivery of oxygen, nutrients, neurotrophins, and other factors that may promote brain function. In animal studies, acute bouts of running increase cerebral blood flow (CBF) in several brain regions, including the hippocampus [35], and chronic voluntary wheel running enhances angiogenesis, neurogenesis and spatial memory function [36]. On the other hand, in mouse models of AD, cerebral hypoperfusion and inflammation are associated with memory impairment [37]. Similarly, cerebrovascular reactivity to CO_2 is impaired in patients with mild cognitive impairment [38]. Reductions in global CBF and cerebrovascular reactivity may lower blood flow to critical areas of the brain and augment neurological disease burden [39]. In a collaborative study resulting from the Workshop, **Jill Barnes, Sandra Billinger** and **Patrice Brassard** combined data sets to show that middle cerebral artery blood velocity (MCAv) declines across the lifespan with older women showing the most rapid decline after the 6th decade of life [40]. Therefore, interventions are necessary to maintain CBF and cerebrovascular reactivity, and to potentially reduce or delay the onset of cognitive decline or Alzheimer's disease. In humans, exercise may counteract the age-related decline in CBF [41] and cerebrovascular reactivity [42, 43] findings supported by a collaborative paper that resulted from the Workshop [44]. In addition, gadolinium contrast imaging in humans revealed hippocampal perfusion changes after long-term exercise in young [45] and older adults [46]. However, questions remain with regard to the exercise modality, intensity, duration of the intervention as well as the types of measurements used to assess CBF and cerebrovascular reactivity. In the Workshop various aspects of exercise effects on the cerebral vasculature was discussed by **Jill Barnes, Paul Fadel, Jill Morris and Shawn Whitehead.**

Cross-sectional studies examining the influence of habitual exercise on cerebrovascular function have reported conflicting results [43, 47–49]. The majority of studies assessing habitual aerobic exercise effects on cerebrovascular function have been performed in older adults. Furthermore, the underlying mechanisms by which exercise may impact the cerebral circulation remains unclear. To address these gaps in the literature, the **Barnes** lab designed a study to examine cerebrovascular function, determined as cerebrovascular reactivity to CO_2, in healthy young adults who were either aerobically trained, resistance trained, or untrained. This is the first study to date, to evaluate cerebrovascular reactivity in resistance trained individuals and to directly compare across different modes of exercise. Contrary to the hypothesis, there was no difference in cerebrovascular reactivity to CO_2 between untrained, aerobic trained, or resistance trained healthy young adults. The results suggest that exercise mode does not influence cerebrovascular reactivity in healthy young adults, but may influence resting cerebral hemodynamics in this population [50].

Although there were no differences in cerebrovascular reactivity between healthy adults with different modes of exercise, acute exercise is known to cause shifts in vascular function, and this may be dependent on exercise intensity. Specifically, the function of the peripheral blood vessels is acutely improved after a single bout of moderate intensity aerobic exercise in young adults, and it was hypothesized that the cerebral circulation would respond in a similar manner. Previous studies have shown that CBF during exercise is highest at moderate intensities, but is lower at near-maximal exercise [51]. Yet, it is still unclear what exercise "dose" is necessary to improve CBF and cerebrovascular reactivity after exercise. There-

fore, a study to assess cerebral and peripheral vascular function after an acute bout of aerobic exercise at low (30% VO_2max) and high (70% VO_2max) intensity was conducted in young healthy adults. Data from the **Barnes** lab show that carotid artery blood flow increased immediately after high intensity exercise, whereas there was no change in carotid artery blood flow after low intensity exercise. This study will help inform future exercise protocols to improve cerebrovascular health in young adults, and then extend this protocol to middle-aged and older adults. This information will help determine the aerobic exercise dose that may be needed to improve cerebrovascular function, promote brain health, and reduce the risk of cognitive decline (Fig. 1).

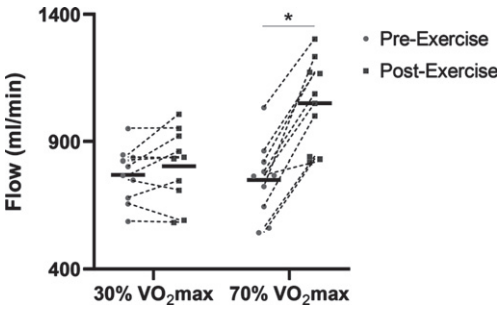

Fig. 1. Preliminary data showing common carotid artery flow differences before (Pre-Exercise) and immediately after (Post-Exercise) 30 minutes of treadmill-based exercise in $n = 10$ young adults (4M:6F). The common carotid artery blood flow was significantly increased Post-Exercise with the 70% VO2max treadmill exercise. * $P < 0.05$ vs. Pre-Exercise.

In related work to understand the cerebrovascular dynamic response during an acute bout of exercise, **Sandra Billinger, David C. Poole** and colleagues developed a novel method for measuring cerebrovascular response from rest to moderate-intensity exercise in the middle cerebral artery (MCA) [52–54]. The resolution of the MCAv kinetic response has provided unique information for age- and sex-differences with a blunted response in older adults when compared to their younger counterparts (Fig. 2). For those with chronic conditions, the MCAv kinetic response may provide valuable insight into cerebrovascular function. For instance, stroke in the MCA negatively affects the MCAv kinetic response and those with stroke differ compared to age-and sex-matched sedentary individuals. Future work is needed to understand which exercise parameters (frequency, intensity, time and type) possess the greatest influence on cerebrovascular health. The downstream consequences, specifically in the capillary bed, of these slowed kinetics and reduced blood flow amplitude in response to increased metabolic demands have not been resolved, as described below.

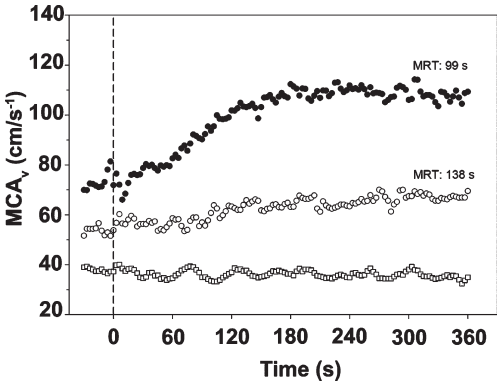

Fig. 2. Typical middle cerebral artery velocity (MCAv) at rest and response following the onset of moderate intensity exercise (dashed vertical line, time 0). Solid circles are from a representative young healthy subject, Subject 2. Hollow circles are from an older healthy subject (Subject 20). Hollow squares are from stroke patient (Subject 201) using the ipsilateral MCA. By comparison, note very slow mean response time (MRT) and low amplitude of response in the older subject and absence of any response in the stroke patient [52].

Effective blood-tissue oxygen delivery depends not only on bulk arterial blood flow but crucially on the capillary distribution of that flow. **David C. Poole** and colleagues have developed a contemporary model of capillary function that replaces extant Kroghian-based models, which more accurately describes oxygen transport especially in muscle and brain [55–58], (Fig. 3). Disease processes that impair red blood cell (RBC) distribution within the capillary bed, such as homogenization of flow, longitudinal recruitment of capillary surface area, capillary hematocrit and glycocalyx function, may restrict blood-tissue oxygen transport as much as a substantial reduction in bulk blood flow. However, present diagnostic approaches that permit clinicians to visualize large arteries and measure blood perfusion regionally cannot assess capillary distribution of that flow. Thus, accurate capillary hemodynamic models are desperately needed to provide insights into the impact of ageing, vascular risk factor and diseases such as Alzheimer's disease (AD) on capillary function and oxygen transport (Fig. 4) over and above their impact on bulk blood supply [59, 60]. That large vessel alterations are absent in AD has resulted in the prevailing view that vascular impediments are not involved in its etiology: This despite the common risk factors for AD as for stroke and cardiovascular disease. Counter to this notion, capillary

hemodynamic derrangements, that impair brain oxygen transport, were found in AD patients [61, 62]. These observations highlight a clear and pressing urgency for application of realistic capillary functional models (Fig. 3), in the steady-state and across metabolic transients, to the brain in health and disease. Key questions that such models will usefully address are listed in Table 1. Development of better visualization techniques and models, likely combined with machine learning, to better understand the role of microvascular dysfunction and oxygenation deficits in AD and other diseases is crucial for this undertaking.

In the Dementia Risk and Dynamic Response to Exercise clinical trial **Eric Vidoni** and colleagues are characterizing the acute exercise response in cerebral perfusion, and circulating neurotrophic factors in older adults with and without APOE4, the strongest genetic predictor for sporadic, late onset AD. Older adults will undergo single bouts of a moderate intensity exercise intervention. Pre- and post-exercise CBF will be examined using arterial spin labeling, as well as blood-based neurotrophic factors. Indeed, it is very important to accurately measure circulating factors that are responsive to acute exercise. Some of the most dynamic biomarkers, such as neurotrophins, are markedly affected by draw timings and post blood draw processing [63]. Moreover, **Jill Morris** and colleagues have shown that medication use can markedly affect mitochondrial bioenergetic outcomes, which may add another dimension to trial design in cognitively impaired individuals [64]. It is expected that APOE4 carriers will have poor CBF regulation and will demonstrate blunted neurotrophic response to exercise. Accurately understanding the acute effects of aerobic exercise on cognitive function and brain health is especially important for those at a higher genetic risk of Alzheimer's disease (Fig. 5).

Exercise modality may also have effects on human cerebrovascular function [65]. In particular, **Patrice Brassard** addressed the growing interest in high-intensity interval training (HIIT) because of its efficacy in improving cardiovascular and metabolic functions, both in healthy individuals and in people with chronic disease. However, there are important knowledge gaps regarding the impact of acute and chronic HIIT on cerebrovascular function. For example, high-intensity exercise is usually associated with rapid elevations in arterial blood pressure, which could be directly transmitted to the brain without efficient neuroprotective mechanisms. Unless countered by the neuroprotective influences of sympathetic activation or cerebral autoregulation, these acute and repeated surges in blood pressure could potentially increase the risk of hyperperfusion injury predisposing to stroke or blood–brain barrier breakthrough (reviewed in [65, 66]). Recent research shows that the acute cerebral artery blood velocity response to a high-intensity exercise bout is biphasic in young fit individuals: a rapid elevation in cerebral artery blood velocity relative to baseline is followed by a return toward baseline values at the completion of exercise [67, 68]. Both of these studies also reported large elevations in cerebral artery blood velocity during the recovery period following high-intensity exercise. These results suggest that cerebral blood vessels of young fit individuals are challenged during and after a bout of high-intensity exercise. Further research is needed to evaluate how the cerebral vessels respond to rapid surges in blood pressure during and following high-intensity exercise in patients with cardiovascular and cerebrovascular diseases. Knowledge gaps also exist regarding the chronic effects of HIIT on the cerebrovascular function as recently highlighted in a systematic review [69]. Studies reported either no training effect (aerobic exercise training of varied nature and intensity including high-intensity exercise) on cerebral autoregulation in healthy older sedentary participants [70], or a subtle reduction in dynamic cerebral autoregulation following 6 weeks of HIIT to exhaustion in young endurance-trained men [71]. Further research showed an acute increase in MCAv during HIIT, in particular in women, which will further understanding the long-term implications of HIIT on cerebrovascular function in health and disease [72].

Another important consideration in studying cerebral vasculature is race. American Non-Hispanic Black (BL) individuals have a greater prevalence of cerebrovascular and neurocognitive conditions including cognitive dysfunction, and AD, relative to other racial groups. Although it is known that long-term exercise is important for cognitive function and overall brain health, the impact of race remains incompletely understood. This is important because the increased blood flow response leads to elevations in shear stress, a primary stimulus to improve vascular health. Recently, **Paul Fadel** and colleagues studied forearm blood flow responses to acute bouts of moderate and high-intensity rhythmic handgrip exercise and found that these were lower in young, healthy BL compared to White (WH) men, indicating a reduced peripheral vascular responsiveness [73]. Additional research found that BL men have an overall blunted

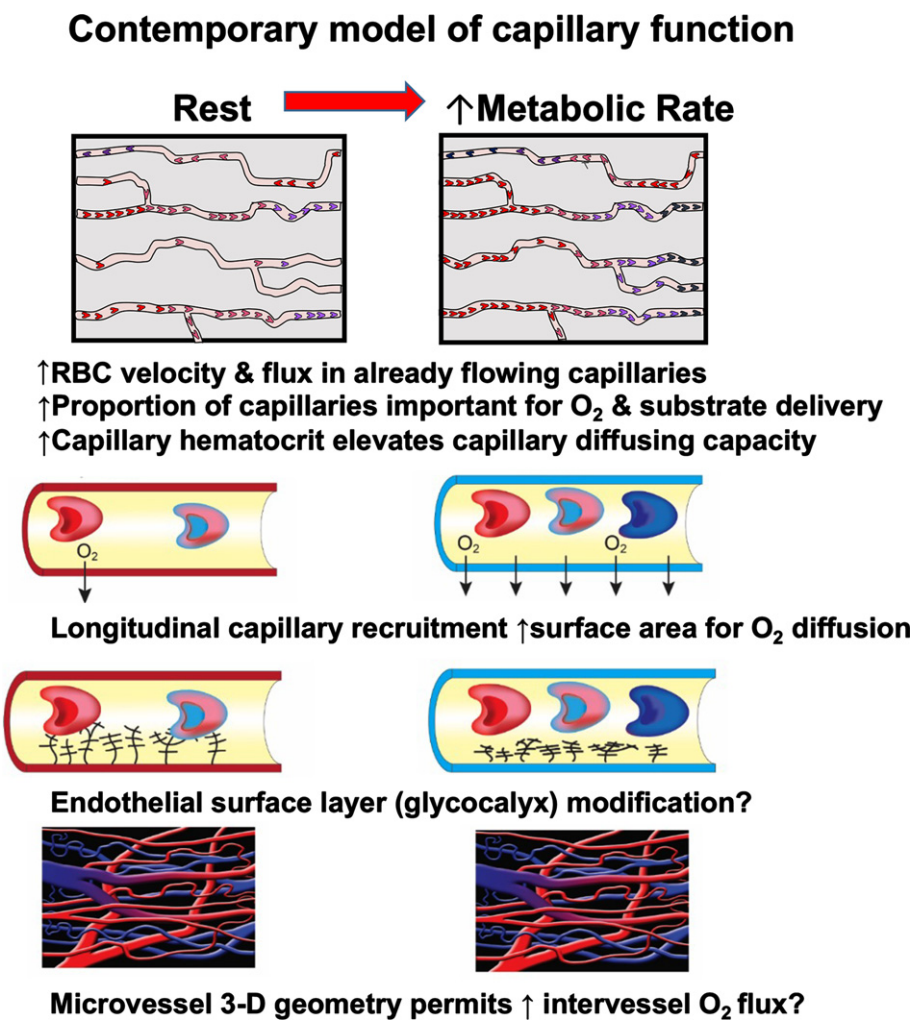

Fig. 3. Contemporary model of brain capillary function developed in skeletal muscle [54] that demonstrates key features of the capillary bed crucial for blood-tissue O_2 (and other substrates) exchange. It is anticipated that further development of these more accurate capillary function models will provide invaluable insights into dysfunction in diseases such as Alzheimer's and dementia.

Table 1
Brain Microcirculation: Pressing questions

How does brain capillary RBC flux and distribution change from rest-↑metabolic rates in health and disease?
Is the necessary homogenization of capillary hematocrit across units impacted in disease?
How does this affect blood-tissue O_2/substrate delivery?
What is the distribution of PO_2 s across the capillary, interstitium and intracellular space at rest and during ↑ metabolic rates in health and disease?
What might be the role of pericytes in re-distributing RBC distribution?
How can regular exercise improve brain capillary function to improve O_2 delivery?
What is the best exercise format – resistance, endurance and what frequency, duration and intensity?

Key questions pertaining to brain microcirculation that the model of capillary function shown in Figure 3 could address.

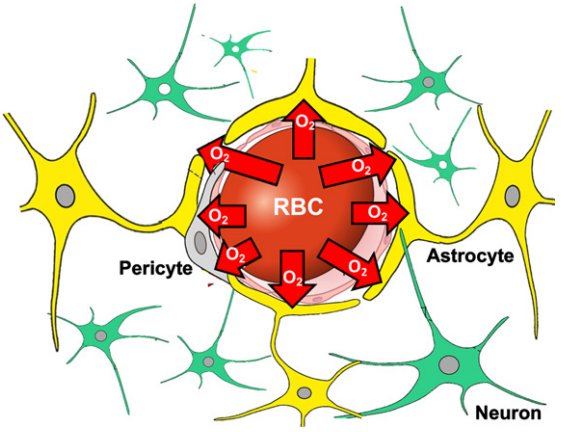

Fig. 4. Geometry of oxygen (O_2) diffusion from red blood cell (RBC) in brain capillary to neurons, astrocytes and pericytes. Effective O_2 supply is dependent upon adequate capillary RBC flux and its distribution as well as capillary hematocrit (generally lower than systemic hematocrit) as it determines capillary O_2 diffusing capacity [144].

ability to rapidly vasodilate in the peripheral circulation at the onset of exercise compared with young WH men [74]. Whether these reduced hyperemic responses to exercise are also present in BL women remains unclear. Heightened peripheral vasoconstriction and reduced vasodilation under resting conditions, highlight peripheral vascular differences in young BL compared to WH individuals. In studies performed mainly in WH individuals, cerebral blood flow increases during acute bouts of aerobic exercise. Whether this occurs in BL individuals is unknown. The impact of race on cerebral hemodynamics in response to acute exercise remains to be studied.

There is emerging evidence for a relationship between AD and cerebrovascular disease. Research presented by **Shawn Whitehead** proposes that white matter inflammation plays a role in linking vascular risk factors and cognitive impairment. Changes to brain volume and white matter integrity can be measured by magnetic resonance imaging (MRI) but may only be visible upon irreversible damage to neurons and axons. Through the application of positron emission tomography (PET) and radio labelled ligands targeting specific proteins, it may be possible to quantify physiological events, such as inflammation and synaptic degeneration, prior to manifestation of the aforementioned damage. Changes to the white matter, in particular chronic activation of microglia, in aging and following cerebrovascular stress, stroke and prodromal AD are related to cognitive impairment. Using a combination of behavioral testing, focused on executive dysfunction, live animal imaging with PET/MRI and brain histopathology, it is suggested that the vascular contribution to chronically activated microglia within the white matter may be prevented or ameliorated by exercise.

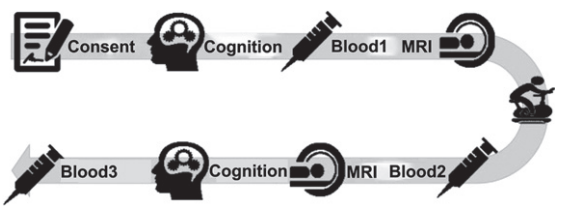

Fig. 5. Example of study flow for assessing markers of the acute effects of exercise using both MRI and blood-based biomarkers by **Eric Vidoni** and colleagues NCT04009629.

SLEEP

Diffusion weighted imaging has been used by **J. Carson Smith** and colleagues to show acute exercise induces microstructural plasticity within the hippocampus [75]. Hippocampal diffusion was elevated following an acute bout of exercise compared to seated rest; an effect not observed in a whole-brain average or in other control regions. Additional work showed that large-scale brain networks interact with acute exercise related effects on executive function and mood. The default mode network (DMN), where beta-amyloid aggregates in Alzheimer's disease, the executive control network (ECN), which promotes inhibitory control and dual-task capabilities, and the salience network (SN, also called the cingulo-opercular network), which helps direct attention, is sensitive to emotion, and shows hyperactivation in mood disorders, all interact to support goal directed behavior. Using functional MRI, Smith and colleagues showed that aging-related changes in sleep may benefit from acute exercise through its impact on brain networks that regulate mood states [76]. Thirty minutes of moderate-intensity aerobic exercise increased positive affect and also reduced functional connectivity between the cingulo-opercular network and the hippocampus. Both of these effects after exercise were greater among older adults who showed greater sleep disturbance, measured by wrist actigraphy. Moreover, the exercise-related decrease in functional connectivity was found to mediate the correlation between greater sleep disturbance and exercise-related improvement in positive mood.

Another study found that older adults with a longer total sleep time showed greater improvements in executive function after acute exercise, and this effect was mediated by greater volume of the caudate nucleus [77]. The effect of acute exercise on improvement in executive function has also been shown to be related to greater activation of the ECN during the performance of incongruent conditions on the Flanker task [78]. In summary, acute exercise seems to produce complex interactive effects among large-scale brain networks that regulate both mood and cognitive function in older adults, with greater exercise-related effects on mood in poor sleepers, and greater exercise-related effects on executive function in better sleepers.

ENERGY METABOLISM

Supply of energy in the form of ATP, produced from glucose by oxidative phosphorylation in mitochondria, and by aerobic glycolysis in the cytoplasm is needed for brain function. With aging there are deficits in brain energy metabolism. In particular, mitochondria are critically important for cell energy metabolism, calcium homeostasis, cell genesis, cell death and synaptic plasticity [79]. In the brains of AD patients, mitochondria have structural and functional deficits [80] and mitochondrial dysfunction may further AD pathology [81]. AD, and metabolic conditions such as diabetes, are associated with an upregulation in inflammatory markers leading to deficient microglial and astrocytic activation [82] which may affect mitochondrial function [83]. Aerobic exercise upregulates markers of mitochondrial biogenesis in aged mice [84] and reduces markers of inflammation [9, 85]. How different cell types, e.g. hippocampal progenitor cells [86], neurons, astrocytes, are affected by the effects of exercise on mitochondrial biogenesis remain to be defined and are being studied using novel genomic and proteomic approaches [87]. **Russell Swerdlow, Jacob Haus and Benjamin Miller discussed aspects of these topics during the Workshop.**

Proteostatic quality control mechanisms fail with age, resulting in the accumulation of damaged and dysfunctional proteins, including mitochondrial proteins [88, 89]. Protein breakdown and synthesis (collectively referred to as protein turnover) is the primary mechanism to mitigate accumulation of damaged proteins. Protein turnover is one of the most energetically costly cellular processes [90]. In turn maintaining efficient energy production relies on the maintenance of mitochondrial proteostasis. Therefore, targeting mitochondrial proteostasis and preserving cellular energetics may have significant benefits for tissue function. Aerobic exercise improves cognitive function in older individuals and those who exercise have reduced risk for developing neurodegeneration [91]. The protective benefits of exercise on cognition are well-established, but the underlying mechanisms are relatively unknown. In peripheral tissues, aerobic exercise stimulates mitochondrial turnover [92], increases antioxidant capacity and reduces accumulation of reactive oxygen species damage [93]. The limited research on the topic suggests these adaptations occur in the brain as well [94]. **Benjamin Miller** and colleagues are currently studying the impact of exercise on mitochondrial protein turnover in the brain. Key methodological developments include the ability to measure synthesis rates of individual proteins using stable isotopes and proteomic approaches, and cell-specific (e.g. neuron versus astrocyte) measurements of turnover [87].

Lactate is a myometabolite produced via exercise that could potentially mediate molecular changes in non-muscle tissues, including mitochondrial biogenesis and turnover in the brain. Lactate can signal through the hydroxycarboxylic receptor (HCAR1), and is also provided to neurons by myelin and myelin-forming cells (oligodendrocytes) by coupling monocarboxylate transporters (MCT) 1 and 2 to neuronal processes [95, 96]. In research by **Russell Swerdlow** and colleagues, C57BL/6 mice underwent seven weeks of treadmill exercise sessions at intensities intended to exceed the lactate threshold. In liver, mRNA levels of gluconeogenesis-promoting genes increased. Peroxisome-proliferator-activated receptor-γ coactivator-1α (PGC-1α) expression increased, PGC-1β expression decreased, and overall gene expression changes favored respiratory chain down-regulation. In brain, PGC-1α and PGC-1β were unchanged but PGC-1 related coactivator (PRC) expression and mtDNA copy number increased. Brain TNF-α expression fell, and vascular endothelial growth factor (VEGF)-A expression rose. In adjunct experiments, exogenously administered lactate was found to reproduce some but not all observed liver and brain changes. Thus, lactate, an exercise byproduct, could mediate some of exercise's extra-muscular effects (including the brain), and lactate itself can act as a partial exercise mimetic [84, 97]. Indeed, these findings are supported by studies

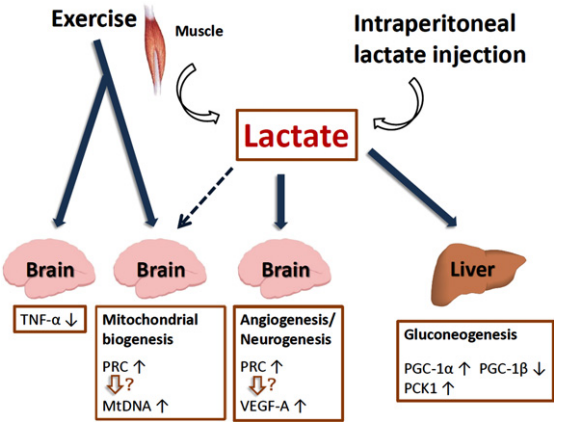

Fig. 6. Lactate plays a role in adult neurogenesis, hippocampal BDNF expression, mitochondrial biogenesis and reduction of inflammation.

showing that lactate plays a role in adult neurogenesis, hippocampal BDNF and VEGF-A expression, and learning and memory [98–100] (Fig. 6).

Cognitive dysfunction is an emerging chronic complication of diabetes mellitus type 2, which was discussed by **Jacob Haus** and colleagues. The long-term risk of dementia, and progression of mild cognitive impairment (MCI) to dementia, increases in patients with diabetes. Even with prediabetes, there is an increased risk of dementia which is not related to the future development of diabetes. While the mechanisms for these trends are unclear, diabetes-related cognitive decline has been linked to the formation of advanced glycated end products (AGEs) and their receptors (RAGE). AGEs are a heterogenous class of chemical protein adducts that form spontaneously between amino acids and reactive carbonyl groups, such as sugar aldehydes, that disrupts protein charge and function. Circulating AGEs and other damage associated molecular pattern (DAMP) molecules (i.e. amyloid beta, HMGB1, S100 s) bind to RAGE which induces chronic inflammatory signaling. AGE formation and RAGE expression both increase under conditions of hyperglycemia and oxidative stress. Conversely, a number of inflammatory transmembrane cell surface proteins, such as RAGE, also exist as soluble forms (i.e. soluble RAGE, sRAGE) which suggests that their cleavage and release from the cell surface may be a regulatory mechanism. Individuals with metabolic derangement (i.e insulin resistance, elevated BMI, or increased fat mass) concurrent with cognitive impairment, present with aberrant sRAGE profiles [101]. These findings are consistent with prior reports demonstrating decreased plasma sRAGE in individuals with cognitive impairment, obesity, insulin resistance and type 2 diabetes [102–104] and further supports the protective role of sRAGE in inflammatory diseases. In addition, both acute and chronic exercise appears to be effective in attenuating AGE burden and reducing RAGE expression in metabolic tissues of patients with type 2 diabetes and prediabetes [105–107]. RAGE/sRAGE is a potential therapeutic target for the treatment of diabetes-associated cognitive decline and modulation of neuronal plasticity with exercise.

PERIPHERAL ORGAN-BRAIN CROSSTALK

There is increasing evidence that peripheral organs such as muscle, liver and the gut microbiome play a role in the effects of exercise on the brain. Skeletal muscle is of particular interest, it makes up more than 45% of total body weight, and is important for general health and wellness because of its primary role in movement, as well as in the control of systemic functions such as glucose homeostasis, thermoregulation and fat metabolism. Muscle adapts to a variety of signals to modify its size and function throughout life; however, the adaptability of muscle to increased loading is diminished with age. With aging and neurodegenerative conditions there is a loss of muscle mass and motorneuron function [108] as a result of deleterious changes to multiple components of the neuromuscular system. The degree to which loss of function and mass is triggered by motoneurons or muscle is unclear and is under investigation in the laboratory of **Sue Bodine**. In particular, the extent to which exercise can modify these changes during normal aging and in neurodegenerative conditions remain to be determined [108]. This is also important given that studies have shown that muscle weakness (sarcopenia) often coincides with cognitive decline [109]. Interestingly, recent research by **Marcas Bamman** and colleagues pertaining to Parkinson's Disease, the most common motor neurodegenerative disease, shows that HIIT improves muscle, neuromuscular function and motor function as well as indices of brain neural activity, including increased substantia nigra and frontal activity as measured by fMRI, cognition, and emotional well-being [110]. These findings indicate that exercise is a powerful form of regenerative medicine [111]. However, it should be considered that exercise modality, strength or endurance, can produce distinct behav-

ioral and neural plasticity phenotypes accompanied by differential gene expression in peripheral organs and the brain. Another consideration is the motivation to exercise. **Frank Booth** and colleagues have shown that signaling pathways within the rat nucleus accumbens may mediate voluntary wheel running motivation [112].

The benefits of exercise may be communicated to the brain via factors secreted from peripheral organs, comprehensively referred to as exerkines [113]. These include myokines [114, 115] such as VEGF [116] irisin [117–119] and Cathepsin B [30, 120–122] as well as the myometabolite lactate [98]. In addition, hepatokines (insulin-like growth factor ([123], clusterin [124], glycerophosphoryl diester phosphodiesterase-like protein [125]), adipokines [126], and blood platelets [127] derived from runners have been shown to play a role in neural plasticity or cognition [128–130]. Conversely, an unhealthy, high-fat and sugar diet can result in metabolic disturbances in the gut microbiome that impair learning and memory [131]. The human gut microbiome consists of billions of gut microbes that can communicate with the central nervous system [132, 133]. Changes and reduction in the diversity of gut microbiome composition have been observed in AD patients, and have been suggested to play a role in inflammatory processes associated with the disease [134–137]. Exercise training in humans increases the microbiome diversity [138], and contributes to delaying the progression of AD in a mouse model [139]. Another form of inter-organ crosstalk is being studied by **Paige Geiger** and colleagues who hypothesize that tissue crosstalk via transfer of extracellular vesicles (EV; exosomes and microvesicles) could underlie the benefits of exercise in AD patients. Recent studies of EVs have implicated these bilayer-phospholipid enclosed vesicles as key regulators of cell behavior and physiology, including nerve regeneration, synaptic function and behavior. Importantly, rodent studies have demonstrated that intracerebrally administered EVs can scavenge amyloid-β-peptide (Aβ) and these EVs can be deposited in microglia for degradation. Thus, interventions that enhance EV generation, secretion, or Aβ-scavenging could benefit AD patients. Recent findings suggest aerobic exercise improves EV clearance of Aβ in isolated neuronal cells, increases EV number in human serum, and that EVs carrying enhanced amounts of heat shock proteins (HSPs) may clear Aβ through a novel, microglial-independent pathway [129]. This research suggests a novel mechanism of 'exercise-enriched'

Fig. 7. Exercise can increase HSP content in EVs that travel to the brain and impact protein aggregation. HSP: heat shock proteins; EV: Extracellular Vesicles, Aβ: β-Amyloid.

EVs to prevent or delay the development of AD by mitigating protein aggregation, inflammation and cognitive decline (Fig. 7).

Research pertaining to interactions between peripheral tissues and the brain was discussed by **Marcas Bamman, Sue Bodine, Frank Booth, Paige Geiger, Henriette van Praag.**

DIET AND BRAIN FUNCTION

The hypothalamus is considered as the main locus of the control of feeding behavior [140]. Neurons expressing the neuropeptide agouti-related peptide (AgRP) in the arcuate nucleus of the hypothalamus are essential for sensing and responding to metabolic signals; increased activity of these neurons is associated with increased food seeking and hunger. AgRP neurons also play a critical role in "top-down" regulation of insulin sensitivity and energy expenditure, thus the appropriate coupling of neuronal activity to metabolic need is likely critical for the maintenance of healthy body weight and metabolic function. **Kristen O'Connell** and colleagues have demonstrated that consumption of a 'Western' diet is associated with hyperexcitability and leptin resistance in AgRP neurons, resulting in persistent activation and decoupling of neuronal activity with metabolic state, contributing to obesity and associated comorbidities. Successful therapeutics for improving metabolic health and body weight will likely restore the coupling between AgRP neuronal excitability and metabolic state. Common weight control interventions (low-fat diet, intermittent fasting, exercise) may play a role in restoring AgRP neuronal excitability. Importantly, composition of the diet plays a more important role than calorie intake therein [141].

The detrimental effects of a high-fat diet go beyond disruption of hypothalamic physiology. In addition to promoting obesity and associated comorbidities, excessive consumption of saturated fatty acids and refined sugars – hallmark dietary components of a Western diet – are associated with cognitive impair-

ments in both humans and in experimental animal models [142]. Recent work by **Scott Kanoski** and colleagues has identified the juvenile and adolescent periods of development as particularly vulnerable stages for learning and memory impairments associated with Western diet consumption in rats. More specifically, free access to a Western diet during these early life developmental periods yields long-lasting deficits in learning and memory processes that rely on the integrity of the hippocampus. These effects appear to be based, in part, on dietary-induced changes in the microbiome. These memory deficits and microbiome changes persist well into adulthood despite a dietary intervention of switching the animals to a healthy control diet for an extended period of time [131]. Whether exercise can reverse or attenuate the gut dysbiosis and long-lasting cognitive impairments associated with early life Western diet consumption is under investigation.

Many signals that communicate nutrient status to the brain originate in the gastrointestinal (GI) tract. Nutrient entry into the GI tract initiates a myriad of physiological responses including secretion of several GI peptides that have paracrine, endocrine, and neuroendocrine action, and that function to aid in the processing and systemic assimilation of nutrients. The small intestine is richly innervated by the autonomic nervous system (ANS), but also contains an enteric nervous system (ENS) and many of the GI peptides secreted in response to a meal either have receptors expressed on local innervation or within the central nervous system (CNS). This has contributed to the idea that a "gut-brain axis" is integral to regulating feeding and body mass. Interestingly, **Darleen Sandoval** and colleagues have shown that many of the GI peptides that are secreted in response to meal, are also increased with stress. Glucagon like peptide-1, (GLP-1), predominantly secreted from specialized endocrine cells within the distal gut, is increased in response to various types of stress, including exercise [143]. Mice devoid of GLP-1 have impaired exercise capacity suggesting an important physiological role for GLP-1 in exercise performance. However, the exact function of GLP-1 during stress is unclear. Recent work has focused on understanding the source and function of GLP-1 and GLP-1 receptor signaling that increases with stress.

After food intake, amylin (a fibrillogenic protein), is co-secreted with insulin from pancreatic beta cells. **Tameka Clemons** and colleagues will study the impact of vigorous physical exertion and extended periods of time without food on uncoupling proteins and amylin interaction. Amylin has been shown to function in metabolism through its influence on glucose homeostasis, which includes sending satiety signals to the brain, inhibiting glucagon secretion and delaying gastric emptying. Amylin has also been proposed to have an impact on beta-amyloid. Alzheimer's disease brains have been shown to have amyloid plaque formation and decreased expression of certain isoforms of uncoupling proteins (UCP). UCP are mitochondrial transporter proteins that create proton leaks across the inner mitochondrial membrane resulting in the dissipation of energy in the form of heat. UCP2 is expressed in pancreatic beta cells, which suggests an additional metabolic role for uncoupling proteins.

The role of diet was highlighted by **Kristen O'Connell, Scott Kanoski, Darleen Sandoval and Tameka Clemons.**

DISCUSSION AND NEXT STEPS

The Albert Trust Workshop provided new knowledge and discussion on the effects of exercise on cognitive function in the young and elderly. Some points of further discussion and collaboration were raised that included, but were not limited to the following items:

1. Optimizing exercise duration, type, therapeutic window (personalized medicine)

For instance, what is the best exercise modality, aerobic or aerobic plus resistance training? Does the acute response to exercise predict the chronic response to exercise? How do age, sex, trained vs. untrained, or other covariates influence exercise outcomes? Can we perform dose-response trials? Are there non-responder biological characteristics?

2. What are good proxy measures for effects of exercise on the brain?

What are the readouts from blood, muscle, imaging CSF, brain tissue? Are there outcome anchors that can be standardized, e.g. Dual-energy X-ray absorptiometry (DXA), VO2max, strength test, blood or muscle biomarkers? PD is a good example with Unified Parkinson's Disease Rating Scale (UPDRS) which is an anchor.

3. Larger scale trials / pragmatic trials that are needed because they allow for more inclusion of subjects and therefore lessen the impact of interindividual variability (and for intervention to rise above the noise)

4. Exercise has multipotent systemic effects that provide feedback to the brain – animal and human studies need to understand the inter-organ interactions mediated by exosomes and exerkines.

5. How do you propose an exercise trial? How do you get reviewers of NIH grants to appreciate the value of the trial?

6. Animal exercise studies: which transgenic mouse models for AD and PD are optimal? Both mice and rats can serve as exercise models. Can we create better models?

7. Team science: collaborations are needed so we can pool data, share resources, samples and models to keep moving the field forward.

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CONFLICTS OF INTEREST

None to declare.

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