PL01

Healthy cognitive ageing

I. Deary

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Scotland tested the intelligence of a whole year-of-birth, twice. On 1st June 1932 almost every child born in 1921 took the same general mental ability test. The exercise was repeated on 4th June 1947. These were the Scottish Mental Surveys of 1932 and 1947. They were largely unused between the late 1960s and the late 1990s. Beginning in the late 1990s, our teams of researchers have been following up some people who took part in the Scottish Mental Surveys to conduct studies in cognitive ageing and cognitive epidemiology. Following up the individuals who took part in these surveys and now live in the Edinburgh area—the Lothian Birth Cohort studies of 1921 and 1936—has offered an opportunity to study the determinants of lifetime cognitive ageing differences. This talk will outline how participants of the original surveys were re-contacted, and concentrate on some of the recent results which their follow up has produced. Among the factors that will be considered with respect to people's differences in cognitive ageing will be social, health, fitness, brain imaging, and genetic factors.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

SA01

Ageing, exercise and recovery of motor and cognitive function following stroke

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Unlike "overt" stroke which affects the large vessels and produces paralysis or weakness, "covert stroke" arises from small vessel disease often as a result of hypertension, that eventually leads to diffuse white matter injury, small lacunar infarcts and vascular cognitive impairment (VCI). A barrier to the development of treatments for covert stroke and the associated VCI is the lack of an animal model. Such a model could pave the way for testing interventions such as exercise or drug therapies to slow or prevent cognitive decline. We describe a model of VCI that incorporates several key clinical pathological features, namely white matter damage, lacunar infarcts, dietary co-morbidity factors and cognitive impairment. We have used this model to assess novel regimens of physical activity (PA) and cognitive activity (CA) in attempts to attenuate cognitive dysfunction. In Experiment 1 we exposed 6 mo old rats to a high fat, high sugar diet (HFS) prior to permanent bilateral common artery occlusion (2-VO) under isoflurane anesthesia

(4.0% induction, 2.5% maintenance) followed by topical 2.0% xylocaine. Following recovery from surgery the rats were randomized to 5 groups: Sham + control diet (n=6); Sham + HFS (N=6); 2-VO + control diet (n=12); 2-VO + HFS (n=10) and 2-VO + PA (wheel running) + CA (exposure to Hebb-Williams maze) (n=11) 5 days per week. All groups were tested on the Morris water maze 4, 8, 16 and 24 weeks post-surgery. At the end of behavioural testing rats were humanely killed under 4.0% isoflurane anesthesia by exsanguination. Perfused brains were removed and processed for quantification of hippocampal CA1 cells using unbiased stereological procedures. At 16 weeks post surgery, 2-VO animals showed significant learning and memory deficits in the Morris water maze, independent of diet. These impairments were associated with CA1 hypertrophy. Rehabilitation, consisting of PA + CA, significantly attenuated cognitive deficits at 16 and 24 weeks. Interestingly, rehabilitation also normalized hippocampal CA1 soma size (area and volume) to that of control animals, independent of cell number. These results suggest that a combination of physical and cognitive exercise may be helpful in slowing the progression of VCI. In Experiment 2, we sought to further refine this 2-VO VCI model by introducing a small lacunar stroke in the mediodorsal thalamic (MD) nucleus using intracerebral injections of Endothelin-1 (0.25μl, 400pmol/μl) in middle-aged rats (n=150) using the same anesthetic and surgical procedures as in Experiment 1. Executive function was assessed using an attention set-shifting paradigm (Birrell & Brown 2000) at intervals post-surgery. Blood pressure (BP) and glucose tolerance were examined during this time period and microvascular function was determined using 2-photon imaging. Lesions of MD resulted in deficits in extradimensional set shifting strategy while HFS animals (diet exposure of 9 months) showed impairments in intra- and extradimenional set shifting ability, elevated BP ($p<0.03$), altered glucose homeostasis ($p<0.02$) and increased blockage of red blood cells in small cerebral vessels ($p<0.05$). There was also white matter atrophy in HFS exposed rats ($p<0.04$). Results show that chronic HFS diets in middle-aged rats causes hypertension, decreased cerebrovascular compliance and white matter atrophy. These effects manifested as general impairments in set shifting ability and perseverative errors. In contrast, the MD lacunes produced a selective impairment in extradimensional set shifting. In summary, we have described an animal model of VCI that includes aspects of aging, metabolic disturbances, cardiovascular and small vessel disease. Importantly, these animals experience profound executive dysfunction following a unilateral, small (0.363 mm^3) lacunar infarct in the MD, an area commonly affected in humans with small vessel disease (Longstreth et al., 1998; Carey et al., 2008). This animal model, including the co-morbidities, may be useful in developing treatment approaches to slow or offset the development of executive dysfunction arising from silent stroke.

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SA02

Enhancing cognition in aging and vascular disease

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A decline in cognitive abilities is common with aging, yet there is much variation in the rate of decline among individuals. This talk will highlight a number of factors that have been identified to be associated with cognitive function, including physical function, vascular health, and cognitive engagement. We previously reported that physical fitness, cardiovascular reserve and diversity of cognitive activities were significantly related to overall cognitive function, attention and executive function in a retrospective analysis of neuropsychological test performance in post-menopausal healthy female adults (Eskes et al., 2010). In addition, cognitive function was better predicted from the combination of these factors, compared to any factor alone. Thus it appears from our work and others that cognitive function with aging is multi-determined and may be mediated, at least in part, through effects on cerebrovascular health (Davenport et al., 2012). We will review these associations and link them to further results from a prospective study (*Brain in Motion* Study; Tyndall et al., 2013) now underway to further examine the synergy and underlying mechanisms of these factors on neuropsychological function in a healthy aging population. In this study, we are examining how certain factors, (e.g., daily cognitive activities, cerebrovascular function) modulate the impact of a six month physical exercise program on changes in neuropsychological test performance. Thus, the association between changes in physical fitness (i.e., assessed by VO_2max testing), cerebrovascular blood flow regulation (i.e., assessed by resting state, cerebrovascular responses to hypercapnia, cerebrobascular responses during submaximal exercise), cognitive activities and neuropsychological test performance will be presented. Finally, the evidence for whether specific cognitive training can directly impact aging-related cognitive decline in older adults with and without vascular disease will be reviewed and preliminary data presented.

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Tyndall AV, Davenport MH, Wilson BJ, Burek GM, Arsenault-Lapierre G, et al. 2013. The brain-in-motion study: effect of a 6-month aerobic exercise intervention on cerebrovascular regulation and cognitive function in older adults. *BMC Geriatrics* 13: 21-31

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SA03

Effects of exercise on the hippocampus and memory in older adults

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A growing body of evidence from neuroscience, epidemiology, and kinesiology suggests that physical activity is effective for preventing, delaying, and potentially treating neurocognitive problems throughout the lifespan. Despite the emerging recognition of physical activity as a powerful method to enhance brain health, there is continued confusion from both the public and scientific communities about what the extant research has discovered about the potential for physical activity to improve neurocognitive health and which questions remain unanswered. From this perspective, I will discuss the current research on exercise, fitness, and brain health and focus on several potential moderators of the effects of exercise on neurocognitive function. I will conclude that physical activity decreases the risk for brain diseases and disorders, ameliorates symptoms, improves function, and increases regional brain volume – especially in the frontal cortex and hippocampus - and that we are beginning to have a better understanding of the factors that moderate and mediate these associations. Overall, physical activity is an important modifiable lifestyle that carries significant consequences for learning, memory, and brain health for people of all ages.

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SA04

Role of nutritional supplementation on brain health in older adults

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In the UK the population is ageing and living longer than ever before. Cognitive function naturally declines with age and has been attributed to a number of factors including reduced synaptic plasticity, increased oxidative damage and reduced cerebral blood flow which has been consistently observed in both normal ageing and dementia. In functional terms ageing is associated with decrements in working memory and top-down control in selective attention. There is growing evidence to suggest that various lifestyle factors can either promote or attenuate cognitive ageing including smoking, alcohol consumption, exercise and diet. Dietary supplements such as vitamins, minerals or other food components is one approach to better nutrition and potentially better cognitive function adopted by 40% older adults aged 55+ in the UK (1) and novel supplements and functional foods are continually under development to meet this growing demand. The below study is an example of a human efficacy intervention trial for one such novel supplement that was investigated for its effects on cognitive function.

Neuravena® is an extract of wild green oats (*Avena sativa*) containing a range of potentially bioactive constituents including avenanthramides, saponins, phytoalexin and flavonoids such as vitexin and isovitexin, developed with reference to its inhibitory effect on the enzymes monoamine oxidase B (MAO-B) and phosphodiesterase 4 (PDE 4)(2). Beneficial effects of the extract on cognitive function have previously been demonstrated in both animal (3) and human trials (4). In addition, acute modulatory effects of the extract on cerebro-electrical activity (as measured by EEG) have been demonstrated (5), and chronic administration of 1500 mg extract per day has also been shown to improve peripheral and cerebral vasodilation (6) although this was not associated with any effects on cognitive function (7). The current study investigated the effects of separate single doses of Neuravena® on the performance of a wide range of computerised cognitive tasks selected to assess global functioning (speed, accuracy), and attention, working memory, episodic memory, and executive function. Forty-two healthy adults aged 40-65 years who self-reported memory decline took part. The study employed a double-blind, placebo-controlled, cross-over design with cognitive performance/mood being assessed prior to (Baseline) and 1, 2.5, 4 and 6 hours after the consumption of placebo and two separate doses of Neuravena® (800 mg, 1600 mg). Each treatment was taken on two occasions (i.e. a total of 6 assessments). The assessments were separated by a 7 day wash-out period.

Data were analysed using a linear mixed models; significant main effects of treatment or interactions with treatment were analysed further using post hoc pairwise

comparisons. The data indicate that the ingestion of single doses of 800 mg of Neuravena® was associated with a number of significant benefits to cognitive function. Most notably, 800 mg led to a significant improvement on a global 'Speed of Performance' measure which incorporated reaction times from all of the timed computerised tasks within the task battery ($p = 0.019$). However, in terms of individual tasks, this dose was also associated with some evidence of improved executive function [Peg and Ball planning time ($p = 0.002$) and completion time ($p = 0.005$)], improved working memory performance [Corsi blocks tasks, Visit 2 only ($p = 0.022$)] and improved episodic memory [Delayed word recall ($p = 0.021$)]. The pattern for the 1600 mg dose of Neuravena® was less pronounced with both improvements and decrements being observed across a small number of tasks.
In conclusion, the lower (800 mg) of two doses of Neuravena® administered here to older adults who self-reported memory decline resulted in broad improvements to cognitive function. The persistence of these effects following chronic supplementation warrents further investigation.

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SA05

Cardiorespiratory fitness, exercise training, cerebrovascular function and oxidative stress in older adults / animals

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Problem Statement: Vascular brain lesions share pathological hallmarks with atherosclerosis, such as increased inflammation and oxidative stress. In addition, increasing evidence suggests an important role for oxidative stress in the pathogenesis and progression of hypertension with age via a decrease of NO production. These pathophysiological features are increased in older women because of menopause. Conversely, regular physical training has been shown to reduce these risk factors by upregulating antioxidant enzymatic systems and anti-inflammatory processes, which may slow down the usual increase in oxidative stress and inflammation during aging. However, the effect of regular physical activity and fitness level on cerebrovascular health is not well documented.
The purpose of this research was i) to determine the beneficial effects of exercise on oxidative stress and inflammation in the brain using a mouse model of atherosclerosis associated with aging, ii) to test the impact of fitness status on enzymatic antioxidant efficiency, oxidative stress, and NO metabolism, and iii) to determine the associations among oxidative stress, and NO metabolism and cerebrovascular conductance (CVC) in postmenopausal women.
Methods: For the animal study, 70 week old $ApoE^{-/-}$ mice under high fat - high cholesterol diet and C57Bl6 mice on a standard diet were divided into 4 groups: C57 and $ApoE^{-/-}$ exercise trained (ExT; cage with running wheel) and C57 and $ApoE^{-/-}$ untrained mice (UT; standard cage). Metabolic assessments (plasma cholesterol level and insulin tolerance) and brain imaging (gadolinium and USPIO contrast-enhanced MRI for blood brain barrier leakage and macrophages accumulation) were performed after 12 weeks of exercise training. After sacrificing the animals, lipid (malondialdehyde, MDA) and protein oxidation (advanced oxidation protein products, AOPP) and inflammation (TNFα and IL-1β) markers in the brain were assessed. For the human study, physical fitness, physical activity and resting CVC were measured in postmenopausal women (50 to 90 years). NO metabolites, lipid oxidation (MDA and 8-iso-prostaglandin F2α, F2-iso), DNA oxidation (8-hydroxy-2'-deoxyguanosine, 8OHdG), protein nitration (nitrotyrosine), antioxidant glutathione peroxidase, and catalase activities were measured in the plasma at rest.
Results: In old $ApoE^{-/-}$ mice, 12 weeks of training was able to significantly reduce blood brain barrier leakage and brain macrophages accumulation (present in 71% of untrained vs. 14% of exercise trained $ApoE^{-/-}$ mice and not present in C57 mice). Similarly, exercise training decreased markers of oxidative stress (MDA: -43%, $p<0.01$, AOPP: -21%, $p<0.05$) and inflammation (TNFα: -17%, $p<0.05$ and

IL-1β: -20%, p<0.05) in the brain of ApoE$^{-/-}$ mice. In parallel, exercise decreased insulin resistance and plasma cholesterol and significantly improved survival (77 vs. 49%, p<0.05).
In postmenopausal women, we identified significant negative associations between oxidative stress and indices of physical fitness (MDA: r=-0.33, p<0.05; 8-iso-prostaglandin F2α: r=-0.39, p<0.05; 8OHdG: r=-0.35, p<0.05) and physical activity (MDA: r=-0.30, p<0.05; F2-iso: r=-0.41, p<0.01; 8-hydroxy-2'-deoxyguanosine: r=-0.39, p<0.05). Conversely, glutathione peroxidase was positively correlated with fitness level (r=0.55; p<0.01). Finally, CVC was significantly associated with 8OHdG (r=-0.36, p<0.05), nitrotyrosine (r=-0.32, p<0.05), and the end product of NO (r=0.44, p<0.01).
Conclusion: The animal study demonstrated the occurrence of vascular brain damage in an aging model of atherosclerosis and showed that exercise training is able to partially reverse this outcome. In parallel, exercise decreased oxidative stress and inflammation directly in the brain.
The human study findings demonstrated that, after menopause, fitness level and regular physical activity mediate against oxidative stress by maintaining antioxidant enzyme efficiency. Furthermore, these results suggest that oxidative stress and NO production modulate CVC.
On the whole, these studies suggest that regular physical activity can improve neurovascular health of older women and animals through vascular function and inflammation. In addition, the decrease in oxidative stress resulting from this physical activity is likely involved as part of the underlying mechanisms.

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SA06

Pathophysiology of falls, balance and fall prevention

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Poor balance, the inability to control the position of the body, is a significant contributor to of falls in older people. Balance requires the complex integration of sensory information regarding the position of the body relative to the surroundings, and the ability to generate appropriate motor responses to control body movement. The sensory component calls upon contributions from vision, peripheral sensation and vestibular sense, while the motor component requires muscle strength, neuromuscular control and reaction time. Linking these two components together are the higher level neurological processes enabling anticipatory mechanisms responsible for planning a movement, and adaptive mechanisms responsible

for the ability to react to changing demands of the particular task. With increased age, there is a progressive loss of functioning of sensory, motor and central processing systems and an increased likelihood of falls. Instability and falls in older people can result from impairment in any of these systems. These physiological risk factors have been adapted into assessment tools and have been either directly or indirectly addressed in many successful fall prevention trials. These interventions include: exercise to promote strength and balance, interventions to maximise vision, cognitive training to improve central processing and executive functioning, strategies for reducing hazardous medication use and podiatric interventions to maximise foot and ankle stability. Core themes that have emerged from this research are: (a) falls provide a unique physiological window into brain function, ageing and neurodegeneration, (b) Valuable information about both fall prediction and prevention has literally come from top to toe (c) interventions that maximise physiological function and reduce motor impairment are effective in preventing falls.

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SA07

Stepping for stability: A physiological protection against falls in ageing

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Physiological and degenerative changes involving multiple systems underlying the control of human standing balance are major contributors to falls and mobility disability with ageing. During actual or anticipated imbalance, multi-segmental postural movements of the limbs such as stepping are commonly executed and powerful protective actions for preserving balance by reconfiguring the body center of mass (CoM)-base of support (BoS) relationship. This requires that the stepping limb motion be appropriately directed, timed, and scaled in magnitude to match the ongoing motion of the whole body. Although age-related deficits in balance recovery during protective stepping have generally been identified, an impaired ability to control lateral balance is particularly relevant to the problem of falling among older people. In a series of studies investigating the impairments in physiological and mechanical mechanisms underlying lateral balance instability as a risk factor for falls, we have focused on two primary types of protective stepping involving different forms of neuromotor control: 1) externally induced *reactive stepping,* and 2) rapid *voluntary stepping*. Both models involve a rapid weight transfer sequence from bipedal to single-limb to bipedal support under the different control conditions. The methods have employed biomechanical movement analysis, kinetic recordings, electromyography, and electrophysiological and acoustic stimulation. Reactive stepping was evoked mainly by a motorized position-controlled waist-pull device. A directional vulnerability to loss of balance and falls was systematically

identified in community living adults by randomly delivering waist-pulls in 12 different directions at 30 deg. intervals. Younger participants mainly recovered balance with single steps in all directions while older groups predominantly took multiple steps that were least for forward-backward directions and greatest laterally with multiple interlimb collisions especially for prospectively identified fallers. Directional differences in adapting stepping parameters were also observed in relation to age and fall risk that further indicated particular difficulties with lateral balance recovery. An important determinant for successfully recovering reactive lateral balance appears to be the motor output generated by hip joint abductor (AB)-adductor (AD) torque and power production (and postural movements of the trunk) that underlie inter-limb postural weight transfer affecting the types of stepping strategies engaged. For example, when perturbed to the side, a passive increase in weight bearing load beneath the leg nearest to the side of destabilization occurs with a concomitant reduction in contralateral load. While younger adults often engage a single and more biomechanically stable loaded-limb sidestep by actively unloading and advancing the limb, older adults use less stabilizing and precarious multiple unloaded limb crossover and medial steps. These differences in first-step recovery patterns appear to involve ageing decrements in hip AB-AD joint torque and power production. Collectively, the use of multiple recovery steps in 100% of lateral perturbation trials, reduced maximum isokinetic hip AB torque and axial motion of the trunk, and shorter global first step length, significantly predict future falls among community living adults. The use of multiple steps, possibly reflecting reduced functional limits of dynamic stability involving the center of pressure position with respect to the BoS to regulate CoM momentum prior to stepping, is a comparatively robust performance variable for identifying future risk of falls. To gain further insights into why lateral challenges to balance stability linked with falls are especially challenging with ageing, we examined whether well-known sarcopenic and composition changes among lower limb muscles with different functional roles are equivalently degraded with older age. Using computed tomography (CT), the muscle cross-sectional area (CSA), intramuscular adipose tissue (IMAT) content, and muscle attenuation (density of the skeletal muscle fibers) were determined for six hip and knee muscles together with measures of muscle performance (isokinetic testing). Intermuscular comparisons indicated that gluteal muscles (gluteus maximus and gluteus medius/minimus) had the lowest muscle attenuation and highest IMAT infiltration, and that fallers were differentiated from nonfallers by lower muscle attenuation and higher IMAT infiltration despite comparable CSAs with the gluteal muscles being the most affected. The strongest associations were found between gluteus medius/minimus and hip abduction strength and power. These regionally disparate changes in muscle composition and performance may influence directional changes in lateral balance function. This possibility also has relevance for rapid *voluntary stepping* where anticipatory postural adjustments for lateral weight transfer normally precede step execution and choice reaction time performance is an independent discriminator between older fallers and nonfallers. These lateral balance factors have been incorporated into currently ongoing

intervention trials designed to use progressive high intensity step training and resistance exercise training to enhance lateral balance function and prevent falls.

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SA08

Age-related changes in balance control during walking

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Most falls in older people occur during daily activities. To work on fall prevention, we need to find those people who have impaired balance control and have a high risk of falling. One way to identify people at risk is by challenging their balance control, for example by provoking them with balance perturbations. To be able to prevent a fall, one must quickly and adequately respond to balance perturbations, such as trips and slips. Balance recovery requires fast and powerful reactions. Especially in older adults, these reactions might be affected by physiological limitations such as muscle strength decline. Our experimental studies on tripping over an obstacle showed that the support limb plays an important role in balance recovery by generating the appropriate joint moments during push-off, necessary to restrain the forward angular momentum. Older adults showed similar onsets of muscle activity and joint moments as young adults. However, they had insufficient reduction of the angular rotation during push-off and poorer placement of the recovery limb. This was due to lower rates of moment generation in all support limb joints and a lower peak ankle moment. These results underline that a decline in rate of force generation in older people, due to age-related changes in muscle, tendon and neural properties, can impede fall avoidance and recovery strategies. Besides measuring ones physical capacities, we might also screen peoples balance control and fall risk based on their daily physical activities. Ambulatory measurements of trunk accelerations can provide valuable information on the quality and amount of daily life activities and contribute to the identification of individuals at risk of falls. We investigated the predictive value for prospective falls over a follow-up period of 6 months of parameters on the amount and quality of daily life gait in 169 older adults. We found that the predictive ability of commonly used questionnaires (area under the receiver operating curve (AUC) of 0.68) improved significantly by accelerometry-derived parameters of gait quality (local dynamic stability, intensity, smoothness), quantity (number of strides) and their interactions (AUC of 0.81). Daily-life accelerometry therefore contributes substantially to the identification of individuals at risk of falls and can predict falls with good accuracy.

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SA09

Brain imaging and the neuropsychology of risk factors for falls

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Balance control is a complex skill that requires coordination of peripheral sensorimotor systems and higher-level cognitive input. Ageing is associated with a decline in balance control and consequent increased risk of falling, particularly in challenging situations that require a person to react quickly and appropriately in order to prevent a fall. This reduced balance control may be partly explained by one or more sensorimotor deficits. Recent evidence also suggests the important role of higher order cognitive processing, i.e. executive functioning and attentional resources, in predisposing older people to falls. Impaired executive functioning may reduce the ability of an individual to attend to relevant sensory information required for maintaining balance when walking. The effect of attentional limitation on balance and gait is especially apparent during dual-tasking when motor and cognitive tasks are required to be performed concurrently (e.g., walking when talking) or when walking in busy or complex environments (e.g., when walking in crowded areas). Overall, there is ample evidence indicating that balance control utilizes higher cognitive processing, and impaired executive function and attention may lead to increased risk of falling.

Balance requires the structural and functional integrity of neural networks to process sensorimotor input. Structural changes of the brain occur with ageing, particularly in the prefrontal area that has been associated with executive function. Both brain grey matter and white matter are essential for fast and efficient operation of the neural networks, but it is primarily white matter that reflects the integrity of the connectivity of brain systems. Changes in white matter have been associated with several fall risk factors including impaired executive functioning, poor balance and slow gait, and also with falls themselves. Subcortical infarcts and large volumes of white matter hyperintensities have been associated with an increased risk of multiple falls. Both subcortical infarcts and white matter hyperintensities are commonly found in frontal and subcortical areas and could disrupt the integrity of neural networks including the long descending motor fibers and frontal-subcortical circuits that are important for control of motor and cognitive function. In recent years, advances in brain imaging techniques (e.g. Diffusion Tensor Imaging Tractography) have allowed us to look white matter integrity directly based on the strength and direction of water diffusivity in white matter. Disruption in white matter integrity, especially in the corpus callosum and longitudinal association fibres, has been associated to gait and balance impairments. Compromised white matter integrity leads to impairments in brain connectivity. This may have an important effect on processing speed which in turn impacts both motor and cognitive functions. Further, the ability to process and integrate information from sensory, visual and

motor domains – essential for balance and gait – are compromised as a result of white matter damage.
Looking at interrelationships between brain imaging and the neuropsychology of risk factors for falls helps to advance our understanding of the mechanisms underpinning physical impairments in older people. Poorer performance in measures of executive and sensorimotor function may reflect early brain structural changes, which could impact on physical and cognitive function, falls and fractures in older people. Interventions targeting physical fall risk factors along with strategies to prevent or slow the development of small vessel disease may reduce the risk of falls.

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SA10

Walking towards a healthier brain & mind

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In my presentation I will review research conducted in our laboratory, and the field in general, which has examined the extent to which fitness training and physical activity enhances cognition and brain structure and function of older adults. The presentation will cover both cross-sectional and intervention studies of fitness differences and fitness and physical activity training. Studies which assess cognition via both behavioral measures and non-invasive neuroimaging measures, such as magnetic resonance imaging, functional magnetic resonance imaging, event-related brain potentials, and the event-related optical signal, will be reviewed and discussed. Finally, I will explore the gaps in the human and animal literature on cognitive and brain health and the manner in which they can be addressed in future research.

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SA11

Skeletal muscle blood flow supply in aged individuals

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The regulation of skeletal muscle blood flow and oxygen delivery to contracting skeletal muscle is complex and involves the mechanical effects of muscle contraction, local metabolic and endothelial-derived substances, and the sympathetic

nervous system (SNS). With advancing age in humans, skeletal muscle blood flow is reduced during dynamic exercise and this is due to a lower vascular conductance, which could ultimately contribute to age-associated reductions in aerobic exercise capacity, a primary predictor of mortality in both healthy and diseased ageing populations. Recent advances in our understanding of vascular control during exercise in older humans indicate that the normal contribution of endothelium-derived substances (e.g. nitric oxide and prostaglandins) is impaired with age as would be predicted by age-related endothelial dysfunction. Additionally, evidence from our laboratory and others indicate that the ability to limit SNS-mediated vasoconstriction ("functional sympatholysis") is also impaired with advancing age, which could further reduce skeletal muscle perfusion during high intensity and/or large muscle mass exercise. Most recently, our laboratory has demonstrated that intravascular adenosine triphosphate (ATP) draining active skeletal muscle does not significantly increase during exercise in older adults, and given the dual vasoactive nature of ATP in the human circulation, could potentially explain impaired local vasodilatation and impaired functional sympatholysis with advancing age in humans.

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SA12

Reduced skeletal muscle blood flow and oxygen uptake in ageing: is it all an effect of sand through the hourglass?

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Peak aerobic exercise capacity and the ability to sustain a given absolute submaximal workload decline with advancing age. Ageing is also associated with a lower level of blood flow and oxygen delivery to the exercising muscles; however, to what extent this attenuated exercise hyperaemia in aged has functional consequences remains undisclosed. Furthermore, given that physical inactivity can mimic many of the physiological changes associated with aging a fundamental understanding of the influences of primary ageing versus physical inactivity is still lacking. Separating the effects of ageing and physical activity is challenging due to the complex interplay between these physiological stimuli; still, observations from cross-sectional and longitudinal studies have provided some insight. Physical activity appears to have the potential to offset the decline in blood flow to contracting skeletal muscle normally observed in aged individuals during submaximal loads, thus ensuring adequate oxygen delivery to meet the metabolic demand. This essential aspect of oxidative metabolism is likely to be of paramount importance for functional capacity. The mechanisms underlying the effects of physical activity are likely to include improved vascular function and ability for functional sympatholysis. The latter is defined as the attenuation of the vasoconstrictor effect of sympathetic

nervous activity in contracting skeletal muscle which is thought to be important for adequate perfusion of the contracting fibers. Collectively, the magnitude of blood flow and oxygen uptake in active skeletal muscle of aged individuals seems to a large extent to be related to the level of physical activity.

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SA13

Angiogenic potential and capillary growth in response to training in ageing

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It remains unclear if the age-related decline in physical health mainly is related to ageing per se or to long term inactivity but both inactivity and ageing are associated with a decline in physical performance and reduced capillary supply to skeletal muscle. An optimized capillary network is an important variable for optimal diffusion conditions for oxygen and nutrients from the blood to the muscle, thus interventions that can enhance peripheral adaptation, such as capillary growth, are important in maintaining cardiovascular and metabolic health and functional independence of aged individuals.
The process of capillary growth depends on the mechanical or chemical stimuli specific to the mode of exercise and the subsequent up-regulation of specific pro-angiogenic and angiostatic factors. When exercise is repeated for weeks or months, it is the balance of these angio-regulatory factors that determines if and when capillary growth occurs. Reports from studies on aged individuals have suggested that the angiogenic potential and acute response to exercise is reduced in aged compared to young. One important impairment in the aged is the much reduced exercise induced secretion of VEGF from skeletal muscle, which we propose is a central component in angiogenesis. The capacity of secreting VEGF from muscle appears to be improved by regular physical activity which may explain why capillary growth in response to a period of regular exercise appears to be similar in aged as in young individuals.

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SA14

The brain-muscle axis in human ageing

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Increased focus on ageing and the muscle-brain axis is appropriate not only because of the growing numbers of the aged but because we have increasing understanding of the malleability and limits of elements which compose it. This understanding is fueled by new sophisticated, often minimally invasive, ways to assess the brain and muscle. All types of movement from locomotion to fine manipulation require an interplay between sensory input and motor output that is controlled by the central nervous system. Failure within the brain-muscle axis is a direct result of ageing and this produces the major motor impairments which frequently accompany ageing, from falling to weakness. These impairments are also an end stage causing physical disability in many diseases. One impairment on which I will focus is the muscle weakness and reduced physical performance that typifies ageing. Here the impairment is related to serial changes along the axis from the muscle and related musculoskeletal mechanics, to the spinal cord and then to motor cortical and other supraspinal levels. Many of the age-related motor impairments can be investigated by acute reductions in physical exercise (disuse models) or acute exercise interventions which improve the impairment. New information about exercise prescription, muscle and brain plasticity, and even in the future adult neurogenesis, should provide ways to mitigate the deleterious physical effects of ageing.

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SA15

Age-related changes in the interactions between nerve and muscle

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The reduction in muscle mass and strength that occur during ageing can have a major impact on the quality of life of older individuals. Older people demonstrate reduced mobility which in turn leads to loss of independence, falls and social isolation. These changes occur partly because a large proportion of the muscle fibres are lost, but also the fibres that are retained are weak. It is currently unknown how muscle fibres are lost during ageing, but when these fibres are lost, the nerves that normally control the activity of these fibres are also lost. Age-related changes in

the interactions between nerves and muscles are poorly understood but appear to play a major role in development of muscle weakness and physical frailty in older people.
We have studied age-related structural changes in neuromuscular junctions (NMJs) using *thy1*-YFP transgenic mice that only express YFP in neuronal cells and permit ready localisation of the motor neurons and NMJs and staining with α-bungarotoxin to visualise the acetylcholine receptors (AChR). Comparison of NMJs from adult and old mice revealed a variety of age-related structural alterations, swellings, partial or complete withdrawal of axons from some postsynaptic motor endplates, and fragmentation of the postsynaptic organisation.
We have also examined the pattern of structural changes in motor neurons and NMJs following a protocol of damaging lengthening contractions to determine whether this process was defective in muscles of old mice. Structural changes in NMJs as well as the loss and regrowth of peripheral motor neurons were examined by fluorescence microscopy. Three days after injury, muscles from adult and old mice showed widespread necrosis. By 28 days, muscles from adult mice appeared histologically normal, whereas muscles from old mice showed multiple small atrophic fibres and fibres with central nuclei. Major disruption of the NMJs was seen at 3 days following damage in both adult and old mice, followed by re-innervation of the muscle that was completed by 28 days in adult mice (96% of the NMJs in EDL muscles from adult mice appeared to be normal with only 2% showing full denervation), but which remained sub-optimal in muscles of old mice.
Thus, data indicate that skeletal muscle ageing influences muscle regeneration, muscle innervation and neuromuscular junction plasticity.

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SA16

The impact of age on cerebral perfusion, oxygenation and metabolism during exercise in humans

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Cerebral perfusion increases during low-to-moderate intensity dynamic exercise by ≈10-30% in regions such as the motor-sensory cortex and supplementary motor area where cerebral neuronal activity and metabolism are elevated. Beyond ≈60% maximal oxygen uptake, cerebral vasoconstriction occurs and cerebral perfusion declines towards resting levels, substantively due to a hyperventilation mediated reduction in the partial pressure of arterial carbon dioxide ($PaCO_2$). A lower cerebral perfusion is observed in older individuals, both at rest and during incremental

dynamic exercise (Fisher at al., 2008, 2013). While a host of factors likely contribute (e.g., brain atrophy), an age-related reduction in $PaCO_2$ during exercise has been noted, which when corrected for by the provision of supplementary CO_2 ≈50% of the difference in cerebral perfusion between young and older individuals is removed (Fluck et al., 2014). The arterial-jugular venous differences for oxygen, glucose, lactate, and the molar ratio between cerebral uptake of O_2 versus carbohydrate (O_2–carbohydrate index; O_2/[glucose + 1/2 lactate]) are similar in young and older individuals exercising at an equivalent submaximal workload (i.e., matched relative intensity) (Fisher at al., 2013). Thus, despite the reduction in cerebral perfusion during exercise the healthy elderly brain appears to maintain its ability to take up nutrients. Intriguingly, during fatiguing dynamic exercise reductions in cerebral oxygenation are similar in young and older despite the much lower maximal workload in the older group. A caveat to the published studies examining the influence of age on cerebral perfusion during exercise is that volumetric flow has not been described and instead a reliance has been placed upon transcranial Doppler ultrasound derived middle cerebral artery blood velocity to index cerebral perfusion. Further studies are required to address this, and to provide a more detailed assessment of the regional influence of age on cerebral perfusion, oxygenation and metabolism during exercise. Such investigations may further our understanding of the mechanisms for the purported benefits of physical activity on cerebrovascular health in the elderly (e.g., shear stress) and support the utility of acute exercise as a means of identifying the existence of age-related deficits in the brain.

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SA17

Targeting the cAMP pathway in Chronic Lymphocytic leukaemia

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Chronic lymphocytic leukaemia (CLL), the most common adult leukaemia in Western societies, is more prevalent in the aging population; the average age at the time of diagnosis is ~70 years old. CLL is characterized by accumulation of mature $CD5^+$ B-cells, primarily as a consequence of impaired apoptosis. Patients with CLL can have indolent disease with minimal clinical manifestations or an aggressive form characterized by high mortality. Prolonged elevation of the second messenger cyclic AMP (cAMP) promotes apoptosis in lymphoid cells, including CLL cells (Zhang *et al*., 2008). Since the level of cAMP and activity of protein kinase A

(PKA) are lower in CLL-cells than in normal B-cells, these data suggest a disease-related defect in cAMP formation, degradation or both in the disease (Zhang *et al.,* 2008). The intracellular level and duration of cAMP is governed by its formation by adenylyl cyclases (ACs), which are primarily regulated by G protein-coupled receptor (GPCR) agonists and degradation by cyclic nucleotide phosphodiesterases (PDEs). The actions of cAMP are largely mediated by PKA and exchange protein directly activated by cAMP (Epac). Compartmentalization of components of cAMP signalling, by bringing cAMP close to specific targets, is also important in shaping functional responses. We hypothesised that analysis of components that mediate cAMP accumulation and signalling in CLL-cells (using peripheral blood mononuclear cells and B-cells isolated from normal- and CLL-patients, together with real-time PCR, immunoblotting and Immunofluorescence) and investigating the mechanisms that contribute to cAMP-promoted apoptosis (using FACS and annexin 5 staining) (methods in Zhang *et al*., 2008) would highlight ways to selectively increase cAMP and apoptosis in the CLL-cells relative to normal B-cells. This "cAMP-pathway approach" revealed signalling components involved in the progression of the disease and identified GPCR agonists/antagonists, AC isoform activators (e.g., of AC7), PDE inhibitors (e.g., of PDE7B), activators or inhibitors of downstream mediators (PKA and Epac, respectively) and regulators of subcellular microdomains (caveolin-1), which might be utilized for the treatment of CLL. These data provide insight into the pathophysiology and progression of CLL and identify novel drug targets for CLL. Our findings suggest the diagnostic and therapeutic potential of a pathway analysis of the expression and localisation of mediators of cAMP signalling in human disease.

Zhang L, Murray F, Kanter JR, Zahno A, Chou D, Suda R, Fenlon M, Rassenti L, Cottam H, Kipps TJ and Insel PA. Cyclic nucleotide phosphodiesterase profiling reveals selectively increased expression of phosphodiesterase 7B in chronic lymphocytic leukemia. *Proc Natl Acad Sci, USA* 105: 19532-7, 2008

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SA18

MLR, Cav-1, and neurorepair

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Membrane/lipid rafts (MLR) in neuronal plasma membrane establish cell polarity by clustering pro-growth receptors and tethering cytoskeletal machinery necessary for neuronal sprouting. MLR are essential for initiating growth in response to extracellular cues. Here we show that neuron-targeted overexpression of a MLR scaffold protein, caveolin-1 (*SynCav1*), increases MLR, MLR-localization of Cav-1 and

increases neurite growth in the adult mouse hippocampus *in vivo*. *SynCav1* overexpression in 6-month-old mice enhances dendritic arborization within the apical and basal dendrites of hippocampal neurons with corresponding increases in hippocampal theta burst induced long-term potentiation (LTP), indicating improved structural and functional plasticity of hippocampal neurons. *SynCav1* overexpression in 10-month-old mice increased dendritic arborization within the apical dendrites of hippocampal neurons with corresponding enhancement in contextual fear memory demonstrating improved hippocampal function at 20 months of age. Our study demonstrates that neuron-targeted overexpression of caveolin-1 in the adult hippocampus enhances structural and functional neuroplasticity *in vivo* and improves learning and memory in aged mice.

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SA19

Non-canonical roles for caveolin in cell growth and survival

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Caveolin is a membrane scaffolding protein that is traditionally considered a marker of plasma membrane caveolae, membrane microdomains rich in cholesterol and glycosphingolipids. Originally regarded as fixation artifacts of electron microscopy, the functional role for caveolae has taken decades to unravel. The discovery of the caveolin protein in 1992 (by the late Richard G.W. Anderson) accelerated progress in defining the contribution of caveolae to cellular physiology and pathophysiology. The three isoforms of caveolin (caveolin-1, -2 and -3) appear to be ubiquitously expressed and regulate a variety of functions in many organs. A PubMed search for "caveolae" reveals ~280 publications from their discovery in the 1950s to the early 1990s whereas a search for "caveolae or caveolin" after 1990, identifies ~7400 entries. Most work on the regulation of biological responses by caveolae and caveolin since 1990 has focused on caveolae as plasma membrane microdomains and the function of caveolin proteins at the plasma membrane. Recent evidence from our group as well as others has localized caveolin to many other cellular organelles (e.g., endoplasmic reticulum, Golgi, mitochondria, and nucleus) and shown that the protein is active at these sites. Organelle specific caveolin localization appears to be critical for regulation of cellular physiology. The mitochondria are one such organelle that are critical to the regulation of cell death and survival. We show that caveolin localizes to outer and inner mitochondrial membrane, regulates mitochondrial structure, and is a major regulator of mitochondrial function under various stress conditions. We further show that mice overexpressing caveolin are adapted to a variety of acute and chronic physiological stressors and have limited age-associated decline of function. Both mice and C.

elegans engineered to overexpress caveolin show increased lifespan and healthy aging. This preservation of function with age is dependent on regulated cycling of caveolin from membrane to mitochondria to maintain homeostasis. Importantly, the critical link between membrane caveolae, caveolin, and mitochondria appears to be a generalized, evolutionarily conserved mechanism of stress adaptation. Caveolin may be a major regulatory point for cell growth, survival, and death.

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SA20

Adenylyl cyclase-centred signalling microdomains

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Ca^{2+}-regulated adenylyl cyclases (ACs) are involved in many of the most sophisticated physiological events including, cardiac contraction, hormone secretion and neuronal function. Their ability to interact with Ca^{2+} allows discrete local feedback mechanisms that yield the pulsatility and rhythmicity that is a characteristic of elaborate homeostatic functions. The sensitivity of the ACs to Ca^{2+} is no passive by-product of responsiveness to generically elevated cellular Ca^{2+}, but instead is an elaborately orchestrated result of adjacency to Ca^{2+}-channels, which is brought about both by direct binding with channel elements and recruiting of other cellular factors.

I will summarize evidence for the direct binding of the Ca^{2+}-stimulated AC8 to the store-operated Ca^{2+}-entry channel, Orai1, using both biochemical and cell biological methods, such as pull-down, peptide array, FRAP and FRET studies. The ability of these ACs to sculpt their microenvironment will also be demonstrated by their recruitment of the actin cytoskeleton and lipid rafts. Additionally, the value of using AC-targeted sensors for measuring both Ca^{2+} and cAMP will be shown in exploring the dynamics of these second messengers in AC microdomains. New sensors for measuring AC microdomains in excitable cells will also be described.

The overall summary of these results is that ACs should be considered to be central scaffolding proteins which not only generate cAMP, but also actively recruit both their targets and their regulators to create a microenvironment in which the most delicate aspects of cAMP signaling occur. These AC microdomains may provide the most insightful level at which to address cAMP dynamics.

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SA21

Glutamate transporters and ataxia: Zonal susceptibility of Purkinje cells to loss of EAAT4 and GLAST

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Mutations in the gene encoding b-III spectrin, highly expressed in Purkinje cells, lead to spinocerebellar ataxia type 5 (SCA5) and spectrin-associated autosomal recessive cerebellar ataxia type-1 (SPARCA1). Loss of b-III spectrin (b-III$^{-/-}$) in mice has been shown to mirror the clinical phenotypes of both diseases and has revealed considerable Purkinje cell dysfunction prior to cell loss, including larger parallel fiber-Purkinje cell excitatory postsynaptic currents (PF-PC EPSCs). Reduction of the two most abundant cerebellar glutamate transporters (EAAT4 and GLAST) is also observed in b-III$^{-/-}$ mice, EAAT4 already reduced at 3 weeks of age, correlating with Purkinje cell hyperexcitability, whereas GLAST levels progressively drop from 3 months onwards. Involvement of these two glutamate transporters in cerebellar pathogenesis has been investigated using mice lacking either EAAT4 or GLAST. This has revealed that loss of EAAT4 can account for the initial hyperexcitability of Purkinje cells lacking b-III spectrin and that complete loss of either one of the two primary cerebellar glutamate uptake mechanisms is sufficient to cause progressive ataxia. However the physiological effect of either EAAT4 or GLAST loss on Purkinje cell activity and survival depends on the cells' cerebellar localization. Furthermore, combined loss of EAAT4 and GLAST has been found to have a profound effect on Purkinje cells within the posterior cerebellum. The discovery that the posterior cerebellum is the first area affected pathologically in b-III$^{-/-}$ mice suggests an important role for this region in the pathogenesis of SCA5 and SPARCA1.

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SA22

The Kv3.3 potassium channel triggers Arp2/3-dependent actin nucleation to regulate inactivation and cell survival

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The Kv3.3 potassium channel is expressed at high levels in the cerebellum and in auditory brainstem nuclei. Human mutations in Kv3.3 result in Spinocerebellar Ataxia 13 (SCA13), a condition associated with cerebellar atrophy and impaired auditory processing. The cytoplasmic C-terminus of Kv3.3 contains a proline-rich

domain that is conserved in proteins that activate actin nucleation through the Arp2/3 complex. In addition to binding to the Arp2/3 complex, Kv3.3 channels interact directly with Hax-1, an apoptotic protein that regulates Arp2/3 actin nucleation. Wild-type Kv3.3 channels recruit Arp2/3 to the plasma membrane, resulting in the formation of a relatively stable cortical actin filament network. These Kv3.3-associated actin structures are required to prevent very rapid N-type channel inactivation during short depolarizations of the plasma membrane. In contrast, a human Kv3.3 SCA13 mutation within the proline-rich domain produce functional channels that fail to recruit Arp2/3 to the plasma membrane, resulting in growth cones with deficient actin veils in stem cell-derived neurons. In transfected cells, this mutation also results in abnormal trafficking of Hax-1 into multivesicular bodies and an increased rate of cell death. Our findings suggest that the Kv3.3 interaction with the Arp2/3 complex and Hax-1 generates stable actin structures that control ion channel inactivation gating and link the channel to signaling pathways that protect cerebellar neurons from apoptosis.

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SA23

Cannabinoid signalling and cerebellar ataxia

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Cerebellar ataxias comprise a group of progressive neurological diseases associated with deficits in motor coordination and are typically associated with dysfunction and/or degeneration of Purkinje cells (PCs), the sole efferent output of the cerebellar cortex. Cannabinoid CB_1 receptors (CB_1Rs) represent the most widespread G-protein-coupled receptor population in the mammalian cerebellum. CB_1Rs are present on inhibitory, predominantly basket cell and stellate cell, interneurons (INs) and excitatory, predominantly parallel fibre and climbing fibre, presynaptic terminals supplying PCs. Activation of CB_1Rs by endogenous cannabinoids (endocannabinoids) suppress neurotransmitter release and have been widely associated with a number of different forms of short- and long-term synaptic plasticities. Importantly, activation of presynaptic CB_1Rs has been shown to promote cerebellar dysfunction, causing severe motor incoordination (Patel & Hillard, 2001), which models the ataxic condition. Of related interest is that whilst CB_1R knock-out animals do not exhibit gross defects in motor co-ordination, deficits in eyeblink conditioning, a discrete cerebellar-dependent, motor learning process, have been reported (Kishimoto & Kano, 2006). Together, these data suggest that CB_1Rs may modulate cerebellar circuitry in ataxic disease. We (and others) have shown that activation of CB_1Rs at IN-PC synapses causes a reduction in the frequency of spontaneous and miniature inhibitory postsynaptic currents, and that CB_1R antagonist

action is consistent with the presence of a significant endocannabinergic tone in the cerebellar cortex (Ma *et al*., 2008). We have also used multi-electrode array recording to demonstrate that CB_1R ligand-induced changes to cerebellar cortex network activity are mediated via effects on inhibitory synaptic transmission (Ma *et al*., 2008). It is likely that CB_1Rs couple to presynaptic $Ca_V2.1$ (P/Q-type) voltage-dependent calcium channels at IN-PC synapses and also have direct effects on the synaptic vesicle machinery to mediate reductions in quantal GABA release (as discussed in Wang *et al*., 2013). We have also shown that the allosteric CB_1R antagonist PSNCBAM-1 has differential, CB_1R agonist-dependent actions at IN-PC synapses (Wang *et al*., 2011). These data point to functional selectivity of allosteric antagonists in the cerebellum and suggest that CB_1Rs contain both orthosteric and allosteric sites that may be targeted in disease.

A number of mouse mutant models with specific ion channel subunit deficits exhibit different forms of ataxia. A well-described mouse mutant is the 'ducky2J' (du^{2J}) model, which has a 2 base pair deletion in exon 9 of the *Cacna2d2* gene, which results in the complete ablation of $\alpha2\delta2$ accessory voltage-dependent calcium channel subunits in the cerebellar cortex (Brodbeck *et al*., 2002). du^{2J} mice typically exhibit smaller than normal size, an ataxia phenotype, absence seizures and paroxysmal dyskinesia and are associated with reduced Cav2.1 current and, in common, with other ataxic mutants, an increased irregularity of PC firing (Brodbeck *et al*., 2002; Donato *et al.* 2006). We have shown that du^{2J} mice exhibit increased irregularity of PC and, to a lesser extent, granule cell, firing in multi-electrode array recordings from cerebellar brain slices (Wang *et al*., 2013). Of note was that clear effects on PC firing regularity in du^{2J}/du^{2J} mice were not seen in heterozygous +/du2J mice, the latter also lack a clear behavioural ataxic phenotype. Importantly, the CB_1R-mediated presynaptic inhibition at IN-PC synapses seen in litter-matched controls was completely absent in both +/du2J and du^{2J}/du^{2J} mice. These data demonstrate that ataxic $\alpha2\delta2$-deficient mice have aberrant CB_1R-mediated signalling that could contribute to disease and that progressive deficits may underlie the ataxic phenotype (Wang *et al*. 2013). Deficient CB_1R-mediated signalling occurred in the absence of gross changes to CB_1R expression in the cerebellar cortex and is suggested to occur due to compromised calcium channel activity consequential to reduced $\alpha2\delta2$ expression in du^{2J} mice. In the future, it will be of interest to determine if deficits in CB_1R-mediated signalling are hallmark characteristics of different forms of ataxia and if aberrant cannabinergic signalling represents a useful biomarker for early or asymptomatic cerebellar dysfunction.

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SA24

Moderation of enhanced metabotropic glutamate receptor (mGluR1) mediated synaptic signalling restores motor learning in a mouse model of human spinocerebellar ataxia type 1, SCA1

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Cerebellar ataxias are a rare and incurable group of neurodegenerative disorders. Several ataxias, including SCA1, are inherited polyQ disorders caused by expansion of unstable CAG repeats. Improved understanding of the cellular mechanisms that drive the early stages of ataxia progression is therefore critical for identifying new therapeutic leads. However, interpretation can be complicated by adaptive structural changes if disease progression also occurs during the critical period of brain development. Here we take advantage of a conditional (doxycycline repressible), Purkinje neuron (PN)-specific mouse model of human ataxia, SCA1 (82Q expansion in the gene for ataxin-1) to determine specific changes in mature PN function during SCA1 progression distinct from wider structural disruption to PNs caused by 82Q during the critical period of cerebellar development.

We used SCA1 mice at 6 and 12 weeks of age (82Q ON) and mice where 82Q was turned OFF by doxycycline (200mg/kg in feed) during gestation to age 6 weeks, but then turned ON by removal of doxycycline from 6-12 weeks (82Q OFF-82Q ON). In this way 82Q OFF-82Q ON mice received the same period of 82Q as the ataxic 6 week old 82Q ON mice but AFTER the critical period of cerebellar development. Motor performance and gait analysis revealed mild ataxia in 6 and 12 week old 82Q ON mice ($P < 0.01$, one and two-way ANOVAs) whereas 12 week old 82Q OFF-82Q ON mice behaved normally. PN electrical input resistance, action potential firing frequency, molecular layer thickness and climbing fibre extension were reduced in all 82Q ON mice ($P < 0.0001$, one-way ANOVAs) consistent with structural and functional disruption of the cerebellum, but all these parameters were normal in the pre-symptomatic 82Q OFF-82Q ON mice.

In contrast, PNs from pre-symptomatic 82Q OFF-82Q ON mice and all ataxic 82Q ON mice exhibited abnormal, long-lasting parallel fibre (PF)-evoked mGluR1 mediated synaptic currents ($P < 0.0001$, two-way ANOVAs). This result suggests that

enhanced mGluR1 signalling occurs before the onset of ataxia and independent of cerebellar structural disruption. mGluR1 activation can also mobilise PN calcium and we observed enhanced synaptic calcium responses in the PN outer dendrites ($P < 0.05$, one-way ANOVA) from 12 week 82Q ON PNs, but otherwise calcium handling was remarkably intact.

To determine the functional significance of the enhanced mGluR1 synaptic current we administered a very low dose of the potent, negative allosteric modulator of mGluR1, JNJ 16259685 (0.03 mg/kg, sub cutaneous) to mice prior to an acute motor learning test. Remarkably, JNJ-treated 6 week and 12 week 82Q ON mice exhibited significantly improved performance compared with vehicle-treated 82Q ON mice ($P < 0.0001$, two way ANOVAs) whilst the performance of JNJ and vehicle-treated wild type mice was unaffected.

Our results show that developing cerebellar PNs are more susceptible than mature PNs to structural and functional disruption caused by 82Q expansion in ataxin-1. We identified prolonged mGluR1 currents at the PF-PN synapse as an early cellular mechanism that drives SCA1 progression in this model, independent of complications from developmental structural disruption, and that may mark the beginning of PN degeneration. Furthermore, mild pharmacological moderation of mGluR1 partially restored motor learning in SCA1 mice and provides a potential new therapeutic lead for treating the early stages of ataxia.

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PC01

Anticoagulation and injurious falls in the elderly: A review

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Oral anticoagulants are a very commonly used class of medication in the elderly. Traditional oral anticoagulants belong to three main categories, namely the coumarin derivatives, aspirin and clopidogrel. Coumarins include warfarin, acenocoumarol and phenprocoumon, which all inhibit vitamin K availability.

This paper reviews the current knowledge relating to fall-related mortality as a result of TBI in elderly patients on oral anticoagulation (OAC). Several articles report that anticoagulant use does not adversely affect the outcomes of severe head injuries after a fall in elderly patients. [1-5]

Fortuna *et al.* compared 416 younger (50 years of age and younger) and older (70 years of age and older) patients with blunt haemorrhagic brain injuries who used clopidogrel, aspirin, or warfarin prior to injury with those who did not.[1] While the use of clopidogrel, aspirin, or warfarin was higher in the older patient group, it did not increase or change the mortality in elderly users of anticoagulation as compared to the younger group that used these anticoagulants. However, mortality in the older patient group who were not using clopidogrel, aspirin, or warfarin prior to injury was significantly increased as compared to the younger non-anticoagulant user group.[1] In addition, mortality was actually lower in the over-70 patient group who were using oral anticoagulants as compared to those who were not. Authors have suggested a beneficial effect of anticoagulant use secondary to a reduction in the incidence of thromboembolic injury following severe head trauma, which is known to induce a hypercoagulable state.[1][2]

A very recent meta-analysis of the effect of pre-injury anticoagulant use found a trend towards worse outcome.[3] However, due to the disparity between the types of anticoagulants used and the patient populations, no firm conclusions could be drawn as to the impact of use of OAC on mortality and recovery.

Much work remains to be done in determining the exact significance of the association observed in some studies. The use of different anticoagulants and different protocols, with variations in the INR allows for the limiting effect of many confounding factors. Future studies need to study the individual anticoagulants in specific protocols with sufficient sample size to allow valid conclusions to be drawn, and a valid control group.

The INR at admission should be monitored to allow clinical protocols to evolve with the least risk of hemorrhagic complications following trauma. An admission CT might be advisable in all patients with a GCS between 13-15 and repeated if any worsening of the neurological status is observed, in view of the risk of worsening of trivial TBI with a paradoxically high mortality rate reported in several studies [1-5]. These steps need to be studied and their value reported on to begin reducing the dismal outcome of TBI in this group.

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PC02

Relationship between tendon stiffness and metabolic cost of walking in young and older adult humans

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Introduction: Tendon mechanical properties may affect metabolic cost of locomotion via influence on muscle efficiency (1) and elastic energy utilisation (2). Here, we examine whether there is a relationship between gastrocnemius tendon stiffness (TS) and metabolic cost of walking (C_W) in young and older adults to explore whether age-related changes in TS (3) may contribute to age-related changes in C_W (4). **Methods:** Participants were 15 young adults (YA; aged 18-40 years) and 20 older adults (OA; aged 60-77 years) recruited from the community. We had excluded any participants with diseases thought to influence gait or muscle function. Following familiarisation, participants walked on a treadmill at up to four different speeds (3, 4, 5, 6 km/hr; 5 min per speed). Oxygen uptake was measured using a portable system (Cosmed K4b^2). Recordings in the final two minutes at each speed were used for analysis. C_W was expressed as net (above standing) oxygen uptake per kg body mass per m travelled. On a separate occasion, Gastrocnemius TS was determined as previously described (5). Briefly, a slow ramp

isometric plantar-flexion was performed with the knee at 180 and ankle at 90. Ankle torque (dynamometer) and tendon elongation (ultrasound imaging of gastrocnemius medialis myotendinous junction) were recorded synchronously. Tendon force was estimated using measured tendon moment arm, and by accounting for synergist and antagonist contributions to torque (5). TS was estimated using the tangent of a curve fitted to tendon elongation plotted against tendon force. The tangent was at 207 N (maximum voluntary contraction force in the weakest participant). Differences between groups were assessed using independent sample t-tests. Correlations were assessed using Pearson's r. Data are expressed as mean ± SD. TS, but not C_W, data from this study have been published previously (5). **Results:** Averaged across speeds, C_W (ml/kg/m) was 30% higher ($p < .01$) in OA (0.152 ± 0.031) than in YA (0.116 ± 0.016). TS (N/mm) was 41% lower ($p < .01$) in OA (30 ± 14) than in YA (51 ± 29). There was no significant correlation between TS & C_W at any walking speed when YA & OA were combined into a single group ($r = -0.07$ to -0.18; $p > .22$) or when OA was considered alone ($r = -0.18$ to -0.25; $p > .31$). In YA, there was a significant positive correlation between TS and C_W at 3 km/hr ($r = 0.52$; $p = .047$) but not at the three faster speeds ($r = 0.37$ to 0.42; $p > .12$). **Conclusion:** These data do not support a significant link between gastrocnemius TS and C_W within the range encountered across healthy young and older adult humans. Hence a decreased TS alone does not seem to account for increased C_W in old age.

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PC03

Relationship between sway components of static balance and cognitive impairment in older people

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Background and aim

It has been demonstrated that there is a significant impairment in some balance measures in people with diagnosed Alzheimer's disease (AD) and mild cognitive impairment (MCI) compared to age matched normals, implicating damage to the vestibular pathways as the most probable cause (Leandri et al, 2009). This study extends this to examining the relationship between cognitive ability and the vestibular component of balance in a population of older women with no definite AD or MCI diagnosis, no complaint of memory loss, and without impairment of daily activity, with a view to future consideration of balance as a possible diagnostic or prognostic indicator

Methods

70 physically active women with a mean age of 73 (sd=9) years were given the Italian version of the MoCA test and their static balance parameters (AP and ML total sway path length) were measured on a balance platform with and without a 30mm rubber mat. This paper only considers those measurements made with closed eyes to exclude visual balance components.

Results

30 (43%) of participants had total adjusted MoCA scores below the normal range (<26). The range of MoCA scores recorded was 19-30. A multiple regression model (forced entry) showed that only the AP sway on a firm surface was a significant predictor of the total adjusted MoCA score (R^2=0.172). Age was not a significant predictor. Although the AP sway (eyes closed) by itself accounts for less than a fifth of the total variation in cognition as measured by the MoCA, it does show a positive association and is likely to make a significant improvement in any existing risk model for cognitive impairment.

An independent-samples median test was used to compare the AP sway, eyes closed values between those with normal and below normal MoCA scores. There was a statistically significant difference ($p<0.001$) between the groups, with the group with lower MoCA score having greater sway. The AP sway measure in the lower MoCA score group is also more variable than in the normal score group

Conclusions

The antero-posterior sway component of static balance was demonstrated to be the best predictor of the MoCA overall score in physically active older women. As visual and proprioceptive components of balance were excluded in our assessments, the vestibular system is to be considered as a putative link between balance and cognitive impairment.

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PC04

Changes in pattern completion: A key mechanism to explain age-related recognition memory deficits?

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Accurate memory retrieval from partial or degraded input – such as recognizing a person when they have drastically changed their hairstyle – requires the reactivation of memory traces, via a hippocampal-based mechanism known as pattern completion. Given its extensive excitatory recurrent connections, sub-region CA3 within the hippocampus has been identified as a likely candidate to execute the auto-associative processing essential for pattern completion (Marr, 1971).
Age-related changes in hippocampal integrity have been hypothesized to shift the balance of memory processes in favour of the retrieval of previously stored information (pattern completion), to the detriment of encoding new events (pattern separation). In this study, we (i) established a novel paradigm providing a behavioural marker for hippocampal pattern completion, and (ii) examined how memory retrieval, and the process of hippocampal pattern completion in particular, is affected by cognitive aging.
Healthy younger and older adults were required to identify previously learned scenes among new ones. Additionally, all stimuli were presented in gradually masked versions to alter stimulus completeness. For both groups, recognition accuracy was reduced with decreasing stimulus completeness. This effect, however, was much more pronounced in older adults, suggesting that pattern completion is adversely affected by aging. Intriguingly, despite this substantial age-related performance decline, when novel scenes were shown, only the older adults showed an increased tendency to identify these as familiar scenes – revealing a clear bias toward pattern completion.
These results provide much needed empirical support for theoretical models of age-related changes in hippocampal function, and inform our understanding of (i) how partial information influences recognition memory (i.e. pattern completion), (ii) how cognitive aging shifts mnemonic processing in favour of the retrieval of previously stored information and to the detriment of encoding new events, and (iii) how age-related memory impairments can be understood in the context of environmentally aided (recognition) vs. more self-initiated (free recall) processing.

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PC05

Measurement of maximal isometric torque and muscle quality of the knee extensors and flexors in healthy 50 – 70y women

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The measurement of muscle quality (strength per unit tissue) of the major muscle groups in the appendages can contribute to the diagnosis of sarcopenia and be used in the evaluation of therapeutic intervention to reduce physical frailty. Maximal voluntary contraction (MVC) and dual energy x-ray absorptiometry (DXA) are criterion measures of muscle strength and lean tissue mass. The aim of this study was to measure the maximal voluntary isometric torque of the knee extensor and flexor muscle groups in healthy older women and to develop an index of muscle quality based on the combined knee extensor and flexor torque per unit LTM of the upper leg. Following habituation to the test protocol one hundred and thirty six healthy 50 – 70y women completed an initial measurement of isometric peak torque of the knee extensors and flexors (Con-Trex MJ; CMV AG, Dubendorf, Switzerland) that was repeated 7 days later. Subsequently, 131 women returned for whole and regional body composition analysis (iDXA^{TM}; GE Healthcare, Chalfont St Giles, Bucks., UK). Isometric peak torque demonstrated excellent within-assessment reliability for both the knee extensors and flexors (ICC range: 0.991 – 1.000). Test-retest reliability was lower (ICC range: 0.777 – 0.828) with an observed mean increase of 5% in peak torque (6.2 (17.2) Nm) on the second day of assessment ($p<.001$). The observed learning effect in the measurement of MVC is almost 50% of the cross-sectional change in isometric strength (-12.2%) between the 5th and 6th decade. Therefore, it is recommended that the measurement of MVC in healthy older women require a minimum of two testing sessions. Though cross-sectional in nature, the relative mean decrease in combined isometric peak torque (-12.2%; $p=.001$) was double that of the relative, non-significant, median change in upper leg LTM (-5.3%; $p=.102$) (Table 1). Isometric peak torque normalised for upper leg LTM (muscle quality) was 8% lower for those in the 6th decade of life compared with those in the 5th. This suggests that muscle strength may provide an earlier indicator of changes in muscle quality than LTM.

Age-related change in upper leg LTM, strength and muscle quality in healthy women (50 – 70y).

	50 - 70y	50 - 59y	60 - 70y	△ 8.6y
Upper Leg LTM (kg)	3.7 (0.8)	3.8 (0.8)	3.6 (0.8)*	0.2; p=.102
	2.8 - 6.1	2.9 - 6.1	2.8 - 4.8	
Knee Extensors (N●m)	88.3 (23.1)	96.2 (24.3)	81.2 (23.1)	15.1 (3.8); p<.001
	29.0 - 182.5	51.0 - 182.5	29.0 - 127.0	CI: 7.5 - 22.7
Knee Flexors (N●m)	46.5 (11.4)	47.8 (11.6)	45.4 (11.4)	2.4 (2.0); p=.234
	19.0 - 81.0	23.0 - 81.0	19.0 - 74.8	CI: -1.6 - 6.3
Combined Torque (N●m)	134.8 (30.8)	144.0 (31.3)	126.6 (30.8)	17.5 (5.2); p=.001
	50.7 - 246.5	77.9 - 246.5	50.7 - 198.7	CI: 7.2 - 27.7
Muscle Quality (N●m/kg)	35.8 (7.8)	37.4 (8.3)	34.4 (7.8)	3.0 (1.3); p=.029
	15.7 - 59.3	20.3 - 59.3	15.7 - 50.1	CI: 0.3 - 5.6

Values are reported as Mean (SD), Median (IQR), Min-Max and CI (95% Confidence Interval). *=non-normal data.

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PC06

Local and systemic effects of high intensity interval resistance training (HIIRT) in a population of older adults

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It is well known that the constant practise of Resistance Training (RT) could contrast sarcopenia (Skelton 1995), improve cardiovascular fitness and body composition (Steib 2010, Raymond 2013). It has been largely demonstrated that RT exerts anabolic effects but, considering the numerous variables of RT (Paoli 2012), the differences between training modalities has been till now poorly investigated. The aim of this study was to asses the effects of two different intensity of RT on muscle strength, body composition and some blood parameters in older adults. After 4 month of progressive RT protocol, 37 subjects were randomly divided in two groups: High Intensity Interval Resistance Training (HIIRT) and Traditional Resistance Training (TRT). HIIRT protocol consisted in performing 2 sets of 6/2/2 reps with incomplete rest between (20") sets at 85% 1RM while TRT consisted of 3 sets x 8 reps with 1'30" of rest between sets at 75% 1RM. Before and after 24 weeks of training body composition was measured by BIA and blood samples were collected. 1RM were determined at baseline, before the division in two groups and at the end of the experiment. Values are expressed as percentage, compared by repeated two-way ANOVA. Both groups increase strength (knee extension HIIRT +25% vs TRT +35%; chest press HIIRT +32% vs TRT +33%) but no differences were found between training methods ($p>0.05$). No change in body composition was found in HIIRT group, whilst in TRT fat free mass decreased (-5%) significantly ($p<0.05$). In both groups the anabolic hormones (IGF-1, GH and testosterone) decreased and cortisol increased significantly ($p<0.05$). Total cholesterol improved in both group, but HIIRT group showed a greater decrease in LDL value compared to TRT (HIIRT

-11% vs TRT –10%). Our findings suggest that a less time commitment resistance training technique is, at least, equally effective to induce an increase in strength in older adult, but is seems to has greater effects on muscle mass conservation. Moreover, high intensity resistance training improves lipid profile more than a traditional resistance training protocol.

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PC07

Larger age-related decline in vertebral than in internal carotid artery flow in men: relationship to blood pressure

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Objective: Increased vertebral artery vascular resistance is proposed to affect neural activity in centers of the brain stem implicated in autonomic control and may lead to arterial hypertension (1, 2*).* Atheroma of the vertebral rather than of the internal carotid artery is associated with hypertension (2). We hypothesized that *i*) age-related reductions in flow would be greater in the vertebral artery than in the internal carotid artery, *ii*) orthostatic stress reduces internal carotid but not vertebral artery flow, and *iii*) CBF is related to maximal oxygen uptake (VO_{2max}) as an indication for effect of aerobic fitness on "brain health".

Methods: The study included young (n = 22; 24 ± 1 yrs.; MAP 78 ± 2 mmHg (mean ± SE)) and elderly men (n = 16; 70 ± 1 yrs.; MAP 94 ± 4 mmHg) and measurements were conducted during supine and semi-seated rest and during submaximal exercise. MAP, heart rate and cardiac output were determined non-invasively by pulse-contour analysis (Modelflow). Near-infrared spectroscopy was used to determine frontal lobe oxygenation (S_cO_2) and middle cerebral artery mean flow velocity (MCA V_{mean}) was evaluated by transcranial Doppler sonography. Bilateral internal carotid and vertebral artery blood flow was determined by duplex ultrasound. Analysis of variables was by two-way ANOVA with the main factors age (young *vs.* elderly), intervention (supine and semi-seated rest, 15 W exercise, and peak workload) and their interaction. Differences between the two age groups were evaluated by a two-tailed *t*-test. Linear regression evaluated an association between CBF and VO_{2max}.

Results: During supine rest S_cO_2 (77 ± 2% *vs.* 68 ± 1%; *P* = 0.0002), MCA V_{mean} (60 ± 3 *vs.* 48 ± 3 cm/s; *P* = 0.0047), bilateral internal carotid (680 ± 26 *vs.* 607 ± 26 ml/min; *P* = 0.0593; 11 ± 6%) and vertebral artery flow (219 ± 11 *vs.* 136 ± 17 ml/min; *P* < 0.0001; 38 ± 9%), and thus CBF (900 ± 31 *vs.* 734 ± 37 ml/min; *P* = 0.0019) were lower in the elderly. CBF was associated with estimated VO_{2max} in the elderly (*P* = 0.0406). In a semi-seated position internal carotid (-9 ± 2%; *P* < 0.0001) but not vertebral artery flow decreased.

Conclusion: CBF is better preserved in aerobically conditioned elderly individuals supporting importance of exercise for "brain health", while the age-related decrease in CBF affects vertebral more than internal carotid artery flow which may have implications for blood pressure regulation. Preserved vertebral artery flow during orthostatic stress suggests an importance for cardiovascular control.

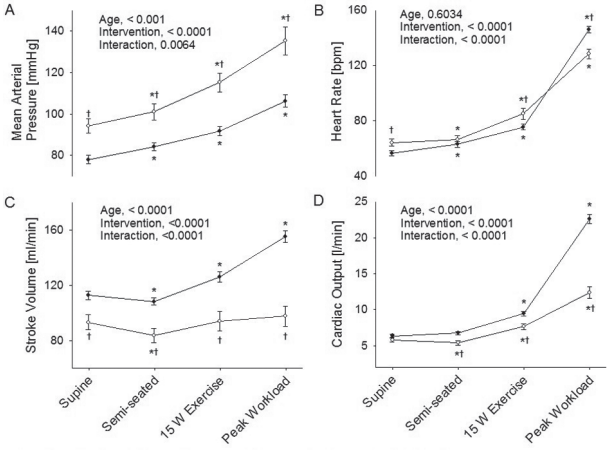

Fig. 1. Central cardiovascular variables at rest and during exercise. Young (●) and elderly (○) men.

Values are mean ± SE. *$P < 0.05$ *vs.* supine rest. †$P < 0.05$ *vs.* young (ANOVA).

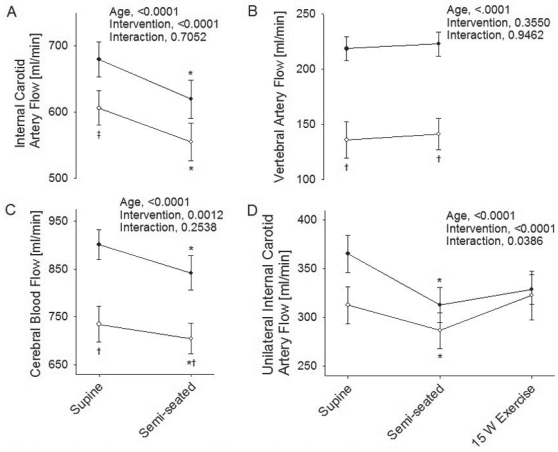

Fig. 2. Cerebrovascular variables at rest and during exercise. Young (●) and elderly (○) men.

Values are mean ± SE. *$P < 0.05$ *vs.* supine rest. †$P < 0.05$ *vs.* young. ‡$P = 0.0593$ (ANOVA).

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PC08

The potential mechanism of bilateral human symmetric parts interaction for the degenerative and oncological diseases

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Objectives

Ou MC decrescendo phenomenon (OuDP) is induced by interaction between human bilateral features and has shown to alleviate or cure infections and non-infectious diseases. The resolution of non-infectious disease with OuDP is consistent with the restoration of normal tissue function. The previous study showed that OuDP ameliorates degenerative diseases (Proc Physiol Soc, 2014; NS, 2014). This

study is to further approach the mechanism of OuDP with the cases of human oncologic diseases.

Methods

Ou MC handing remedy (HR) was availed to induce OuDP with hand to contralateral body part (AJEM, 2012; Proc Physiol Soc, 2014). Four female patients received HR for their oncologic diseases. Case 3 was treated with oral ergonovine maleate and tranexamic acid for the initial 5 days of HR treatment and case 4 had undgone treatment with Glivec for 2 years, while The other 2 patients have not received other treatments (Table 1). Though complementary therapy is exempt from informed consent by the law in Taiwan (Department Health, ROC. (1993) No.82075656), all patients agreed and provided consent for participation in this study.

Results

The OuDP showed to ameliorate oncologic changes of the four patients (Table 1). The uterine endometrioid cancer regressed from stage IIIB to IA with 5 months HR. The pancreatic isodense lesion of suspicious pancreatic cancer decreased from 1.6. x 1.7 to 1.0 x 1.0 cm in size with CA199 descending from 1090.0 to 136.5 (Unit/ml) associating with the main pancreatic duct diameter decreasing from 0.39 to 0.14 cm with tortuosity disappearance after 4 months treatment. (Fig. 1) The frequent profuse bleeding by uterine leiomyosarcoma prominently decreased immediately with HR and subsequent HR was also effective at minimizing heavy uterine bleeding in 3 weeks treatment. The gluteal macular lesion with chronic myeolgenous leukemia eliminated after 2 weeks treatment with HR. (Proc Physiol Soc, 2014, NS, 2015).

Conclusions

It reveals OuDP may normalize the tumor cells and microenvironmental function, which makes tumor cells conform to the regulations with apoptosis, metastasis suppression, preventing uninhibited proliferation, and supervision by host immunological systems.

Table 1 The effect of Ou MC decrescendo phenomenon (OuDP)

Case	Disease	Age	Diagnosis	Ou MC handing remedy (HR)	duraion	Short term effect	Long term effect
1	Uterine endometrioid cancer, stage IIIB	49	Pahology	Press hand on bilateral lower abdomen and perineum in first 2 months; then, press hand deeply into bilateral pelvis and press hand on bilateral perineum and whole abdomen occasionally.	5 months	Heavy uterine bleeding diminishing to trace and never recurred up to date	a. Slow tumor regression for first 2 months. b. Stage IIIB regressing to stage IA in the next 3 months.
2	Suspicious pancreatic cancer IA with isodense lesion in pancreatic tail	51	Radiology	Press hand deeply into epigastric area bilaterally and occasionally on bilateral costovertebral angles and whole abdomen.	4 months	Not observed.	a. Lesion size decreasing from 1.6 x 1.7 to 1.0 x 1.0 cm. b. Main pancreatic duct diameter decreasing from 0.39 cm to 0.14 cm. c. CA 199 descending from 1090 to 136.5 (Unit/ml). CA 125 from 50.2 to 25.4 (Unit/ml).
3	Uterine leiomyosarcoma, stage IB	59	Pathology	Press hand on bilateral lower abdomen.	3 weeks	Stopping active uterine bleeding immediately.	Trace uterine bleeding with following HR.
4	Perineal macular lesion with CML	39	Inspection	Place finger directly on the lesion	2 weeks	Not observed.	Lesion resolved.

Ou decrescendo phenomenon is induced by Ou MC handing remedy. CML, chronic myelogenous leukemia

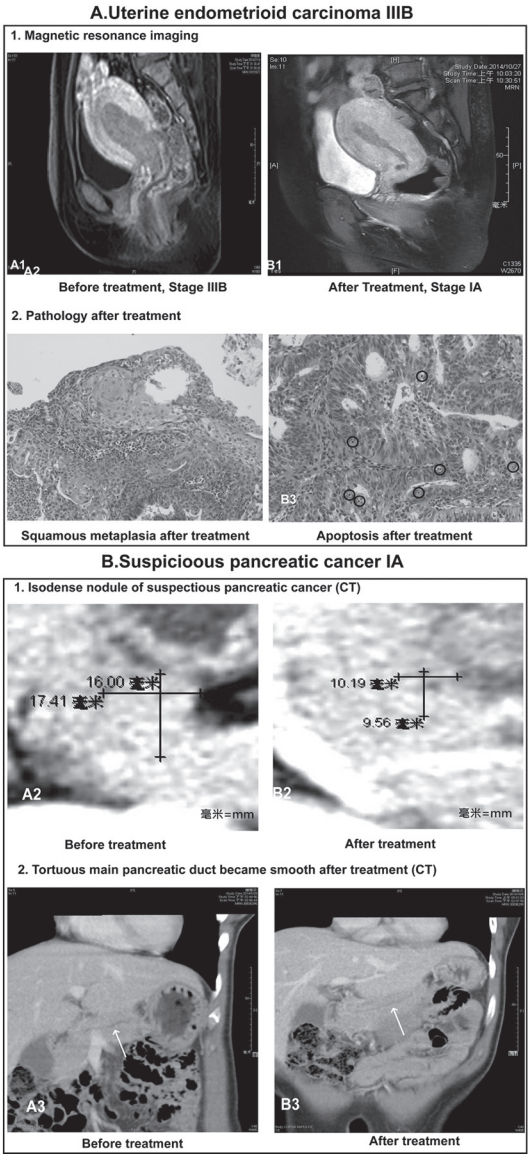

Fig. 1 A. Uterine endometrioid carcinoma. 1. Stage IIIB regressed to IA. (Magnetic resonance imaging) 2. No definite squamous or apoptosis before treatment and manifested with squamous and apoptotic changes with treatment. (hematoxylin and eosin staining, magnification, 100X). B. Suspicious pancreatic cancer IA. 1. Isodense nodule became smaller after treatment. 2. Tortuous main pancreatic duct became smooth and with decreased diameter after treatment, computed tomography (CT).

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Department of Health, Executive Yuan, ROC. (1993) No.82075656, November 1993. http:// http://homepage.vghtpe.gov.tw/~ged/listn/listn_a122.htm.

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PC09

Ageing and gastrointestinal sensory function: altered colonic mechanosensory and chemosensory function in the aged mouse

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Ageing has a profound effect upon gastrointestinal function through mechanisms that are poorly understood. A feature of ageing is impaired sensory perception, including a diminished sensory response to inflammatory evoked gastrointestinal injury. However little is known about the mechanisms contributing towards the age-associated blunting of sensory perception. Here we study the effect of ageing upon colonic sensory signalling pathways in order to address this question. An in-vitro mouse colon preparation with attached lumbar colonic, inferior mesenteric ganglion and splanchnic nerves was used to study mechanosensory and chemosensory afferent function in young (3 m) and old (24 m) C57BL/6 animals. Mechanosensitivity was investigated by saline-induced ramp distensions of colonic segments (0- 60 mmHg), whilst chemosensitivity was determined by bath application of agonists. Calcium imaging experiments and real-time RT-PCR were used to investigate TRPV1 receptor function and mRNA expression in cultured dorsal root ganglion (DRG) cells (T9-L2) isolated from young and old animals. Data presented as mean ± SEM ($n \geq 8$). Data analysed by one or two way ANOVA or by Students t-test. $P < 0.05$ was taken as significant. Ramp distensions of colonic segments evoked increases

in afferent discharge via the activation of distinct subtypes of mechanosensitive afferents termed low threshold (LT), high threshold (HT) and wide dynamic range (WDR) fibres. Ageing affected colonic afferent mechanosensory function. Total afferent discharge in response to ramp distensions was attenuated in 24 m animals ($p<0.0001$ versus 3 m) in which significant differences were detected at ≥ 50 mmHg distension pressures ($p<0.05$). Analysis of individual subtype responses showed that the HT afferent response was significantly blunted ($p<0.0001$ versus 3m) in which significant differences were detected at ≥40mmHg distension pressures ($p<0.01$), whereas the LT and WDR responses were unaffected by ageing. Ageing also affected colonic afferent chemosensory function. HT afferent responses to 1 μM capsaicin was attenuated in 24 m animals ($p<0.05$ versus 3 m), and the peak response to capsaicin was also attenuated in aged colons (7.9±0.9 imp/s peak response in 3 m animals versus a 4.8± 0.7 imp/s peak response in 24 m animals, $p<0.05$). These results correlated with attenuated calcium signalling responses in cultured DRG neurons exposured to 300 nM and 1 μM capsaicin ($p<0.05$, 24 m versus 3 m). Ageing had no significant effect upon TRPV1 mRNA expression. Ageing is associated with decreased HT afferent mechanosensitivity in the mouse colon, and this appears to be associated with altered TRPV1 channel function. Since these units have the capacity to sensitise in response to injurious events, their loss in ageing may predispose the elderly to lower awareness of GI injury or disease.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

PC10

Physical activity and anterior hippocampal volume in older adults

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Introduction. There is currently great interest in the relationship between physical activity (PA) and anterior hippocampal volume, with cross-sectional magnetic resonance imaging (MRI) studies indicating that higher PA levels are associated with greater volumes[1,2], and interventional studies demonstrating that improving PA levels can lead to increases in volume[3,4]. However, replication of such positive findings in independent samples, the gold standard of the scientific process, is vital. Here, we use voxel-based morphometry (VBM) to examine the relationship

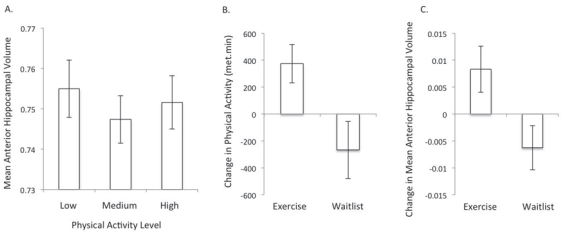
between PA levels and anterior hippocampal volume in a cross-sectional study of members of the Whitehall II Imaging Sub-Study[5] (Study 1) and, in a separate study, explore whether a twelve-week PA program can lead to increases in anterior hippocampal volume (Study 2).

Methods. Study 1 included 359 participants (75 females, age: 68.7 ± 5.0 years). PA was assessed using the CHAMPS questionnaire, with met.min in moderate-to-vigorous PA subsequently categorized into tertiles representing low, medium and high PA levels. Mean anterior hippocampal volume was calculated from T1-weighted MRI scans using FSL-VBM. An ANCOVA, with age and gender as covariates, was performed to test if anterior hippocampal volume differed with PA level.

Study 2 included 48 participants (30 females, age 66.7 ± 5.3) who were randomly assigned to supervised aerobic exercise sessions three times per week for 12-weeks or a waitlist. At baseline and after 12-weeks, PA was assessed using the CHAMPS questionnaire (met.min in moderate-to-vigorous PA) and mean anterior hippocampal volume calculated using FSL-VBM. ANCOVAs, with age and gender as covariates, were performed to examine if change in PA or change in anterior hippocampal volume differed between exercise and waitlist groups.

Results. In Study 1, anterior hippocampal volume was not significantly different between groups (Figure 1A; F = 0.52, p = 0.597). In Study 2, the PA intervention was associated with a significant increase in both PA levels (Figure 1B, F = 5.4, p = 0.024) and anterior hippocampal volume (Figure 1C, F = 4.3, p = 0.045).

Conclusions. Our results partly support the hypothesis that PA is associated with anterior hippocampal volume; however further work is required to explore the influence of age, gender and genotype on this relationship.



In a cross-sectional study, anterior hippocampal volume was not significantly different between high, medium and low PA groups (A). In an interventional study, change in PA (B) and change in anterior hippocampal volume (C) was significantly greater in the exercise group compared with the control group.

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Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

PC11

Age-associated alterations in mitochondrial architecture and motility in vascular smooth muscle

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The motility and architecture of mitochondria is central to cell function. Mitochondrial function declines with age, and may underlie the development of a diverse range of common diseases. Changes in mitochondrial structure and motility may also contribute to changes in function with age but are ill-defined due to challenges of imaging in native cells and tissues. We have developed methods to determine the structure and motility of mitochondria in live functional native cells based upon epifluorescence microscopy. To determine the spatial extent of individual, electrically-distinct mitochondria (i.e. their *functional* boundaries), stochastic transient "flickers" of mitochondrial membrane potential were induced and measured as fluctuations in cationic fluorophore intensity (Flicker-assisted Localization Microscopy, FaLM). Custom image analysis, written in Python, defined mitochondrial boundaries as having a strong positive spatio-temporal co-variance of fluorescence intensity changes, measured on a pixel-by-pixel basis around each mitochondrial centre. Single native smooth muscle cells isolated from cerebral resistance arteries from young (3 month) and aged (18 month) rats (humanely sacrificed in accord with UK legislation) were loaded with tetramethylrhodamine-ethyl ester (62.5 nM) and imaged at 37°C.

FaLM revealed a range of mitochondrial sizes in smooth muscle cells from young and aged rats. In young animals the majority of mitochondria were very small (most common size: mode area of 0.051 μm^2; geometric mean±s.d. of 0.35±3.08; n=19 cells/1259 mitochondria) when compared to older animals (mode 0.76 μm^2; geometric mean±s.d. of 1.38±2.44; n=12 cells/805 mitochondria; significantly different at the .05 α level by two-sample t-test with Welch correction for unequal variance). Interestingly, smooth muscle from older animals contained many more long mitochondria than from young (5.4% of mitochondria in young were > 1 μm vs. 39.5% in older; two-sample t-test between proportions significant at the .05 α level, $p<0.01$). Smooth muscle from older animals also contained a subpopula-

tion (4.2%) of highly-elongated, electrically-contiguous mitochondria (length:width ratio>3) not observed in younger animals (mean±s.d. length:width of 5% most elongated was 1.93±0.54 μm; two-sample t-test between proportions significant at the .05 α level, p<0.01). Additionally, mitochondria in smooth muscle from older animals were not observed to move. In the younger animals, both directed and Brownian-like mitochondrial motility occurred.
In conclusion, vascular smooth muscle from young animals contained small, motile mitochondria. In aged animals the mitochondria were larger, sometimes highly-elongated and were immobile. These age-associated alterations in mitochondrial behaviour may present a barrier for re-entry into the cell cycle and hence inhibit smooth muscle proliferation.

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PC12

Atrophic effects of IP10 on skeletal muscle primary cells

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Older people develop a loss a muscle mass and force, which is known as sarcopenia. Changes in the levels of pro-and anti-inflammatory cytokines are seen in serum and tissues of older people, reflecting the development of a chronic inflammation and this is proposed to be one of the major contributors to the development of sarcopenia.
Our laboratory has identified significant increases in the pro-inflammatory chemokine, IP10 in the serum of healthy older people (Ford et al, unpublished data). The aim of the current study was to determine the effect of IP10 on indices of atrophy in myotubes in culture.
Primary skeletal myoblasts from *Wistar* rats were isolated, cultured and differentiated into myotubes for 6 days. At this time point, myotubes were treated for either 1,3,5,7 or 10 days with IP10 at the average dose found in serum of older people (200pg/ml) or young adults (150pg/ml). Myotube diameter was assessed. Myotubes treated with IP10 were harvested and qPCR was used to analyse the mRNA expression of the atrophy gene, atrogin1. Values are means ± S.E.M compared by ttest.
Treatment of myotubes with 200pg/ml IP10 resulted in a significant increase in relative expression of atrogin1 mRNA (control: n=3, IP10:n=4 p<0.05) 24 hours following treatment and this was accompanied by a significant decrease in myotube diameter (control: 17±0.4 (n=18), IP10:15±0.3 (n=17) p<0.001). This decrease in myotube diameter became more apparent the longer lasting the IP10 treatment. (**3 day** control: 35±2 (n=10), IP10: 26±0.8 (n=15), **5 day** (control: 28±0.8 (n=22),

IP10: 23 ± 0.7 (n=27), **7 day** control: 28±2 n=15 IP10: 24±0.7 (n=17), **10 day** control: 28±2 (n=11), IP10: 18±1 (n=15)p<0.001).
Treatment of myotubes for 24 hours with 150pg/ml IP10 resulted in no significant changes to relative expression of atrogin1 mRNA (control:n=3, IP10:n=4 p>0.05) with only a non-significant 2% decrease from control in myotube diameter (control n=18, IP10:n=17 p>0.05) and only a transient reducion in myotube diameter at 3-7 days post-treatment.
The increase in atrogin1 and consistent decrease in myotube diameter induced by the levels of IP10 found in older people provides further evidence that an increased inflammatory environment is a likely contributor to sarcopenia. This is in agreement with current knowledge highlighting the importance of the environment on muscle viability and how this mechanism is severely compromised in older people and is a likely contributor to sarcopenia. Future work will examine the effect of nutritional interventions aimed at modifying systemic inflammation and the effects on cytokine-induced muscle atrophy.

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PC13

Sclerostin, Dickkopf-related protein 1 and Vitamin D are plasma-based markers associated with bone remodelling in healthy ageing

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Osteoporosis is characterized by low bone mass and deterioration of bone tissue that increase skeletal fragility and risk of fracture. Remodelling of skeletal tissue is related to biochemical processes that regulate osteoclastic and osteoblastic activity regukating bone mineral resorption and formation. The purpose of this study was to measure plasma-based markers of bone remodelling in relation to whole-body bone mineral density in humans. Healthy young (n=172 aged 18-30 yrs) and healthy older (n=283, aged 69-80 yrs) men and women were recruited as part of the EU FP7 project MYOAGE; a multi-centre and multi-national cross-sectional study of musculoskeletal ageing. All participants provided written informed consent to the study. Whole body bone mineral density was assessed in the fasted state by dual-energy x-ray absorptiometry (DEXA). Resting, fasted 10 ml blood samples were collated into EDTA tubes. Plasma concentrations of selected analytes were determined with the Multiplex xMAP "Human Bone Magnetic Bead" assay or ELISA and a Luminex 200 Bioanalyser. Multivariate ANOVA and regression analy-

ses were used to identify age- and sex-differences and correlations between analytes and bone mineral density. Regressions were adjusted for Country and Body Composition. Whole-body bone mineral density was significantly lower in women compared with men (11.4% difference) and lower in old compared with young (9.0% difference) ($p<0.001$). Older participants had significantly higher concentrations of Osteoprotegrin (OPG) (70% greater), Osteopontin (OPN) (3.2% greater) and Sclerostin (SOST) (83.7 % greater) compared with young. In young men and women, Dickkopf-1 (DKK1) and Vitamin D (Vit D) were significantly associated with bone mineral density. In older men, significant correlations were found for bone mineral density and DKK1 ($r=0.184$), OPN ($r=0.201$), SOST ($r=0.251$) and Vit D ($r=0.296$). In older women, associations were found for bone mineral density and DKK1 ($r=0.178$), SOST ($r=0.262$) and Vit D ($r=-0.233$). These results identify plasma-based markers of bone remodelling in healthy ageing. Vit D was associated with bone mineral density, although the association was positive in older men but inverse in older women. DKK1 and SOST were consistently associated with bone mineral density in older men and women. These proteins are Wnt-pathway inhibitors that are also up-regulated in bone diseases (Ke et al. Endocrinol Rev. 2012).

Ke HZ, Richards WG, Li X, Ominsky MS (2012) Sclerostin and Dickkopf-1 as therapeutic targets in bone diseases. *Endocrinology Review*. **(5)** 747-83.

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PC14

Accelerated vascular aging in aldosterone associated hypertension: role of NADPH oxidase 1 and implications for cardiovascular complications

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Endothelial dysfunction, vascular remodelling and pro-inflammatory responses are common features of vascular injury during hypertension and aging. Arterial modifications that are present in hypertensive subjects resemble those observed in aged individuals, suggesting that in hypertension, vessels may undergo premature aging. Increased reactive oxygen species (ROS) production is considered a hallmark of vascular aging, as well as for hypertension. Between the many sources of ROS, NADPH oxidase (Nox) is of interest and a major source of ROS in vascular cells. More specifically, Nox1 levels are increased in hypertension and are regulated by pro-hypertensive agents, such as aldosterone (aldo). Here, we postulated that aldo induces vascular damage through Nox1-ROS-dependent regulation of aging-asso-

ciated mechanisms, leading to hypertension. Levels of aging associated signalling molecules in arteries from stroke-prone spontaneously hypertensive rats (SHRSP) rats and Nox1 knockout mice infused with aldo (300ug/Kg/day) were studied. Gene expression was assessed by qPCR and protein levels by immunoblotting. Aldo levels were quantified by ELISA. In SHRSP rats, mRNA levels of Nox1 (4 fold), aging-associated inflammatory markers, such as RANTES (5- fold), MCP-1 (6-fold) and IL-6 (2-fold); as well as aldo levels (6-fold), H2AX (marker of aging-associated DNA damage – 1.5-fold) and cell cycle inhibitors, P27 (2-fold) and P21 (4-fold), were increased compared with control rats (WKY), $p<0.05$. In cultured vascular smooth muscle cells (VSMCs) from WKY and SHRSP rats, basal levels of P66shc activation was increased in cells from SHRSP (2.8-fold, $p<0.05$). Aldo stimulation increased p66shc phosphorylation in WKY (3.1-fold) and SHRSP (2-fold); an effect that was blocked by ML171 (Nox1 inhibitor). In mice treated with aldo, JNK (pro-inflammatory – 69%) and p66SHC (pro-senescence – 92%) activation were increased in mesenteric arteries ($p<0.05$); an effect blunted in vessels from Nox1 KO mice. In VSMCs from adult and aged control mice, as well as, from adult Nox-1 transgenic mice (VSMC specific overexpression) basal levels of p66SHC (39%) and OGG-1 (48%), markers of senescence, were increased in VSMCs from aged animals and; aldo effects on p66SHC activation were exacerbated in VSMCs from adult Nox1 transgenic mice. In conclusion, aldo may induce vascular injury through Nox1-p66shc-dependent mechanisms and regulation of pro-aging responses, which may be important to the pathogenesis of hypertension.

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PC15

Folate disruption in Normal Pressure Hydrocephalus patients

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As average lifespan increases, so too does the prevalence of neurodegenerative disorders such as Normal Pressure Hydrocephalus (NPH). NPH can result in dementia symptoms, gait disturbance and incontinence, however drainage of CSF through a lumbar peritoneal shunt can relieve these symptoms for some patients. Why this condition occurs, and how treatment brings about relief is still not clearly understood despite decades of research.
Folate has been shown to be correlated with several neurological disorders, and our previous work showed that there is evidence for changes in folate cycle com-

ponents in the CSF of NPH patients as a result of drainage (Miyan, *et al.,* 2013). The aim of this work is to further investigate the possible role of folate metabolism in NPH patients (n=5) relative to Controls (n=15) at the beginning of the drainage procedure.

CSF was collected from patients in accordance with the method published previously by Woodruff *et al.,* (2013) and analysed in triplicate for 5-methyltetrahydrofolate (5MTHF), B6, B12, Homocysteine, Cysteinebetasynthase (CBS) and Formyltetrahydrofolatedehydrogenase (FDH) using a standard dot blot technique. Both 5-MTHF and CBS levels were found to be reduced in NPH patients compared to controls, whereas B12 and B6 levels did not differ. Homocysteine was found to be increased along with FDH, which was found to be increased by up to tenfold in NPH patients when compared to controls.

Reduced 5-MTHF levels have been shown to result in hyperhomocysteinaemia, and Homocysteine has previously been shown to have a negative correlation with conditions including dementia and stroke (Smith *et al.,* 2010), CBS activity is closely related to Homocysteine, and this part of the folate pathway has been linked to neurotransmitter production eg. serotonin, and dopamine (Bottiglieri, *et* al., 2000). The results of this study confirm the CSF of NPH patients shows differences to that of normal patients, related to detrimental disruptions the folate pathway. These findings confirm the possibility of a link between folate metabolism and NPH. The role of FDH in NPH requires further investigation, if only as a possible marker for diagnosis of this condition.

Bottiglieri, T., Laundy, M., Crellin, R., Toone, B., Carney, M., Reynolds, E., (2000) Homocysteine, folate, methylation, and monoamine metabolism in depression. *Journal of Neurology Neurosurgery and Psychiatry* 69(2):228-32.

Miyan, J., Woodruff, K., Abraham, D., Lea, R. Allcock, R., Anser, M., Golash, A, Myers, M., (2013) A potential role for folate in normal pressure Hydrocephalus. *57th Annual Meeting Society for Research into Hydrocephalus and Spina Bifida.* Abstract 12.15 P20.

Woodruff, K., Abraham, D., Lea, R. Allcock, R., Anser, M., Golash, A, Myers, M., Miyan., J. (2013). A Screening Method for Blood Contamination in Cerebrospinal Fluid samples from Normal Pressure Hydrocephalus sufferers. British Neuroscience Association abstracts London.

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PC16

12 weeks of floorball training lowers body fat in elderly untrained men

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Aging is associated with adverse changes in body composition and physical function. Loss of muscle mass and a concomitant gain in body fat may consequently increase the risk of chronic diseases. However, it may be difficult to separate the effects of "true aging" (i.e. inherent aging) and a physical inactive lifestyle. This is supported by studies showing that life-long trained elderly subjects do not decline in physical function compared to age-matched sedentary counterparts (Lazarus and Harridge 2010). Furthermore, exercise training can reverse the physiological degeneration observed with aging (Melov et al. 2007). Typical exercise training interventions for an elderly population include aerobic activities, e.g. cycling, walking, or strength training activities. Results from recent studies suggest that small-sided football training may represent a motivating and health promoting exercise alternative (Krustrup 2010). However, none of these studies have so far investigated the effect of floorball training on body composition in elderly untrained men. Thus, the aim of the present study was to investigate the effects of floorball training on body composition in elderly untrained men.

Twenty untrained subjects aged 65-77 years took part in the first round of a 12-week training intervention study. Of note, the study is on-going and fifty subjects total are expected to complete the training intervention, hence, the present results are preliminary. Subjects were randomized to either a floorball group (FLO; n=10) or a control activity group playing petanque (CON; n=10). Whole body fat content and fat free mass were determined before and after the 12-week training intervention using Dual-energy X-ray Absorptiometry (DXA), and fat free mass to fat mass ratio was calculated. Data are presented as mean ± S.E.M compared by ANOVA. Visceral fat content and physical function, i.e. maximal oxygen uptake (VO_{2max}), time to exhaustion during incremental cycling, and 6 min maximal walking distance were also examined (results not shown in abstract).

In FLO, after 12 weeks of training, whole body fat content was 8.5% lower (25.8 ± 3.4 vs. 28.0 ± 3.3 kg, $P < 0.05$), whereas no change was observed in CON (24.9 ± 2.8 vs. 25.2 ± 2.8 kg). In FLO, fat free mass to fat mass ratio tended to be higher with a 10.1% increase (2.65 ± 0.54 vs. 2.40 ± 0.46, $P = 0.08$), with no change observed in CON (2.48 ± 0.29 vs. 2.44 ± 0.27). No change was observed in fat free mass in either FLO (57.8 ± 2.4 vs. 56.9 ± 2.1 kg) or CON (55.1 ± 1.6 vs. 55.4 ± 1.6 kg).

Preliminary results indicate that 12 weeks of floorball training lowers whole body fat content, leading to a more favorable body composition in elderly untrained men. The on-going intervention study will add more knowledge to whether floorball training also positively affects visceral fat content and physical function.

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Lazarus NR & Harridge SD (2010). Exercise, physiological function, and the selection of participants for aging research. *J Gerontol A Biol Sci Med Sci* **65**, 854-857.

Melov S, Tarnopolsky MA, Beckman K, Felkey K, & Hubbard A (2007). Resistance exercise reverses aging in human skeletal muscle. *PLoS One* **2**, e465.

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PC17

Age-related loss of motor units in the vastus lateralis

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A progressive loss of motor units has been documented in small and peripheral muscles, with around half of the motor unit pool lost by the age of around 80 yrs (Power et al. 2010) but very little is known about motor unit changes during healthy ageing in large locomotor muscles that are important for maintaining mobility. After ethical approval and with informed written consent, 29 active, healthy young men (age 26±5y) and 17 active, healthy older men (age 73±6y) were recruited. Proximal and distal motor points of the vastus lateralis muscle were identified by percutaneous electrical stimulation and the recoding of surface electromyographuic (SEMG) signals from those locations during isometric knee extension held at 25% of maximal voluntary contraction. Intramuscular EMG signals were also recorded close to the motor points at three depths within the muscle and turning the needle through 90º between contractions so that 12 separate recordings were made. Single motor unit potentials (SMUPs) were estimated from SEMG signals using a decomposition-enhanced spike-triggered averaging technique developed from that described by Parsaei et al (2012) and an average SMUP area determined using between 20-40 SMUPs for each subject. A motor unit number estimate (MUNE) was calculated by dividing the area of a compound surface muscle action potential, obtained by supra-maximal stimulation of the femoral nerve, by the average SMUP area.
MUNE in the older men was 75% of the value for the young (255±118 *vs* 339±128, $P = 0.02$). While it is possible for all fibres of a small distal muscle to make significant contributions to a recorded SEMG signal this is not likely with large muscles such as the quadriceps. If the SEMG signals were recorded from the same volume of muscle in each subject then it can be speculated that the total number of MUs in a muscle is proportional to the product of muscle volume and MUNE. We have recently shown that in older men of this age, quadriceps volume was approximately

70% that of the young (Maden-Wilkinson, 2014) suggesting that the total number of MUs in the older subjects relative to the younger subjects may be as low as 55%, depending on how much of the muscle wasting is due to fibre atrophy. Loss of MUs may contribute to the loss of strength which is characteristic of aging but the disruption of the normal recruitment patterns could also have important consequences for the ability to make smooth and coordinated movements.

Power GA, Dalton BH, Behm DG, Vandervoort AA, Doherty TJ, Rice CL (2010) Motor unit number estimates in masters runners: use it or lose it? Med Sci Sports Exerc 42 (9):1644-1650.

Parsaei H, Stashuk DW, Adel TM (2012) Decomposition of intramuscular EMG signals using a knowledge -based certainty classifier algorithm. IEEE Eng Med Biol Soc. 2012:6208-11

Maden-Wilkinson TM & McPhee JS, Rittweger J, Jones DA, Degens H (2014) Thigh muscle volume in relation to age, sex and femur volume AGE 36:383–393.

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PC18

Maximal oxygen uptake and fatty acid oxidation in athletic older men and women and healthy control

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Introduction: Cardiopulmonary and musculoskeletal systems deteriorate through middle and into older age. This has a negative impact on physical capability and energy metabolism. The purpose of the present study was to determine the effects of ageing and exercise on peak rates of oxygen uptake (VO_2peak) and fatty acid oxidation (PFO).

Methods: All participants provided written, informed consent. Masters Athletes (MA: n=40, aged 37-90) specialised in endurance (n=10) or sprint running (n=30) were recruited during the 2012 European MA Championships in Zittau, Germany. Untrained (n=42, aged 18-67; 23 men and 16 women) were recruited from the general Manchester population (UK). The untrained participants also completed 12 weeks very high intensity sprint cycle training (4* 20s at 170% VO_2max, 3/wk). VO_2max and PFO were assessed using indirect calorimetry and incremental cycle ergometry. Statistical significance was gained by independent samples t-tests using IBM SPSS v.20.

Results: The endurance and sprint trained MA were a similar age and had similar VO_2max (Endurance MA: 47.22 ml/kg/min (±4.15) vs Sprint MA: 43.52 ml/kg/min (±2.21) p=0.416). Both MA groups were significantly higher than untrained people

(38.86 ml/kg/min). MA sprinters and endurance runners had a VO_2max similar to 19 years younger untrained, healthy people. Regression analysis showed that VO_2max decreased by around 11% per decade after the age of 40 yrs in the MA group and 5% per decade after the age of 40 yrs in the untrained group. PFO was similar in endurance and sprint trained MA (Endurance: 8.09 mg/kg/min (±0.95) vs Sprint: 6.91 mg/kg/min (±0.53) p=0.284). In the untrained group, PFO was significantly lower than MA (p=0.006). Regression showed that PFO of MAs was similar to that of an untrained, healthy person 19 years younger. The sprint-training programme caused VO_2max to increase by 10% (Pre: 38.86 ml/kg/min (±1.31) vs Post: 42.84 ml/kg/min (±1.24) p<0.001) and PFO to increase by 18% (Pre: 5.57 mg/kg/min (±0.33) vs Post: 6.58 mg/kg/min (±0.41) p=0.050).

Conclusion: These results show that MAs have a cardiopulmonary and metabolic fitness at levels equivalent to someone almost 20 yrs younger. Previously untrained middle-aged people can achieve substantial gains in fitness by completing relatively short duration, but high intensity sprint training and reach levels similar to those observed in the master athletes.

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PC19

The effect of 'Walkactive' training on gait pattern and health-related indices in middle and senior aged people

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To promote and maintain health, older adults need moderate intensity aerobic physical activity for a minimum of 150 minutes per week[1,2]. Unfortunately, only 19% of over-65s comply with these guidelines[3] and this is more than likely the case also for the over-50s when walking is the only form of physical activity. In order to meet the energetic equivalent of the physical activity guidelines, the otherwise leisurely walker is thus required to increase their speed, or incorporate an additional task within their walking pattern[4]. A new walking technique has been developed. 'Walkactive' encourages walkers to walk while attending to specific mechanical elements within their gait. This technique anecdotally improves health and well-being and induces postural improvements. The purpose of the present study was to investigate whether participation in, and retention of an active walking profile beholds health improvements superior to what is otherwise regarded as 'normal' walking.

33 self-reported sedentary adults were assigned to either an experimental (EXP, *n*=24 [11M, 13F], mean ± SD: 53.6 ± 7.1 years; 27.1 ± 3.6 BMI) or control group (CON, *n*=9 [5M, 4F]: 56.0 ± 6.6 years, 25.4 ± 2.5 BMI). An A_1-B-A_2 experimental

design was adopted for the present study. A_1 consisted of baseline measurements comprising health-related indices and a full body gait analysis. Following this, EXP took part in one month's training of the 'Walkactive' technique (B). CON received no intervention (B) period and was instructed not to change their lifestyle in any way. Participants were then invited back to the laboratory for post-intervention measurements (A_2). A single factor (time) repeated measures ANOVA, with group as the between-subjects factor, was used to identify interaction and effect sizes (^{2}). Significant interaction effects were found for mass (P<0.01, η^2:0.24), body fat percentage (P<0.05, η^2:0.16) and supra-iliac skinfold site (P<0.01, η^2:0.30), being significantly lower in EXP post-intervention. There were no significant interaction effects (P>0.05) between the EXP and CON in any gait cycle spatio-temporal variable. However, interaction effects were found in whole body centre of mass range of motion (P<0.05); and in knee angular impulse (P<0.01, η^2:0.30), vertical ground reaction force (P<0.05, η^2:0.30) and the relative phase coordination between the lower limbs (P<0.05, η^2:0.13) all during mid-stance of the gait cycle.
The results suggest that EXP participants might not have fully ingrained the technicalities of the 'Walkactive' technique after only one month's training. Nonetheless, adopting a 'Walkactive' technique does improve general health and wellbeing and represents a more demanding and mechanically-efficient form of walking that may benefit the elderly walker in meeting the recommended physical activity guidelines.

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Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

PC20

Blueberry consumption enhances brain function in healthy elderly participants

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Blueberries are rich in flavonoids that possess antioxidant and anti-inflammatory properties, which in rodent models are neuro-protective. The risk of developing dementia is reduced in people habitually consuming high flavonoid intakes, but data from human intervention studies is sparse. We therefore investigated whether 12 weeks of blueberry concentrate supplementation improved cognitive function in healthy elderly via increased brain activation and perfusion. Twenty-six healthy elderly matched for Addenbrooke's Cognitive Examination score (ACE-III) were

block randomised to consume either 30 ml blueberry concentrate (5 female, 7 male, age 67.5±3.0y; BMI, 25.9±3.3kg.m^{-2}; ACE-III, 95±4) providing 12.9 mg.ml^{-1} anthocyanin or isoenergetic placebo (8 female and 6 male; age 69.0 ±3.3 y; BMI, 27.1±.4.0 kg.m^{-2}, ACE-III, 95±3) once per day for 12 weeks. The study was approved by the local University research ethics committee. Before and after supplementation, participants undertook a computer based battery of cognitive function tests and a numerical Stroop test within a 1.5T MRI scanner while functional magnetic resonance images were continuously acquired. In addition, quantitative resting brain perfusion was determined using an arterial spin labelling (ASL) technique. fMRI data were analysed based on massunivariate testing within the general linear model framework over the whole brain, treating each participant separately and constructing individual maps comparing the differences in response between visits. Group analysis was subsequently undertaken combining the individual responses, with differences between groups identified in regions with an uncorrected p-value < 0.001 and a cluster size threshold of 10 voxels. ASL data were analysed using the Oxford University FSL software library. Working memory (two back test) improved after blueberry versus placebo supplementation (pre-post change in response time: -1.0 ± 2.6 vs 0.4 ± 1.5%, p=0.09; accuracy 3.6 ± 9.0 vs -3.8 ± 9.0 %, p=0.05, mean±SD, unpaired t-test), but there were no significant differences between groups for the other cognitive function tests. The change in Stroop test performance was not different between conditions. However, significant increases in brain activity were observed in response to blueberry supplementation relative to the placebo group within Brodmann areas 4/6/10/21/40/44/45, the precuneus, anterior cingulate, and insula/thalamus (p=0.02), as well as significant improvements in grey matter perfusion in the parietal and occipital lobes (p<0.001). Collectively these data suggest that 12 weeks of supplementation with an anthocyanin rich blueberry concentrate improves active brain areas associated with cognitive function and brain perfusion in healthy elderly participants.

This study was funded in part by CherryActive Ltd.

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PC21

The effect of cardiovascular fitness training on cognition in older adults

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Introduction

Evidence from experimental RCTs of regular exercise programs in previously sedentary adults (Erickson et al. 2010) and cross-sectional studies of cardiorespiratory fitness (Barnes et al. 2003) have led to the view that engagement in regular aerobic exercise may both improve cognitive performance and even protect against

cognitive decline (Lytle et al. 2004). In a RCT designed to examine the effects of a 12-week aerobic exercise program on brain structure and cognitive health we aimed to investigate (1) Does aerobic fitness correlate with cognitive performance at baseline? (2) Do cognitive measures increase after an exercise intervention?

Methods

Fifty-one sedentary adults (33 female, age 66 ±5.5 years) were randomly assigned to an exercise or waitlist group. The exercise group underwent supervised aerobic exercise sessions three times per week for 12-weeks. The waitlist group underwent the same exercise sessions following a 12 week delayed start. Participants underwent tests of cardiovascular fitness (VO_{2max}) and a battery of neuropsychological tests at three time points; baseline, after 12 weeks and 24 weeks. The VO_{2max} test was a continuous, incremental test on a cycle ergometer. The neuropsychological tests included tests that spanned the three main cognitive domains; executive function (EF), processing speed (PS) and memory (MEM), with the full battery described in the Whitehall II Imaging Study (Filippini et al. 2014). Raw neuropsychological data were normalized into z-scores and composite scores for each cognitive domain created by summing individual tests by category. Correlations between variables were conducted with partial correlation controlling for age, gender and qualification level. Change in each cognitive domain was assessed using repeated measures ANOVA.

Results

Forty-one participants completed the intervention. Both groups increased VO_{2max} after the exercise intervention ($F_{(1,39)} = 22.65$, $P < .001$). There were no significant correlations between baseline VO_{2max} and cognitive domain scores; there was however a trend for a positive association between VO_{2max} and PS ($r = .270$, $P = .063$). When comparing change in each domain across time, there was a main effect of time for EF ($F_{(2,36)} = 23.81$, $P < .001$) and MEM ($F_{(2,26)} = 8.16$, $P = .001$), pairwise comparison identified an increase in EF and MEM between baseline and weeks 12 and 24. There was no main effect of group.

Conclusions

We observed a trend for a positive correlation between VO_{2max} and PS at baseline. Whilst we observed an increase in both EF and MEM performance between baseline and weeks 12 and 24 in both groups, there was no difference between groups. These results highlight that the relationship between aerobic fitness and cognitive performance remains equivocal and further research exploring the specific mechanisms and proposed exercise 'dose' for cognitive health is warranted.

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Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

PC22

The effect on increased IGF-I bioavailability on cardiovascular structure and function in normal aging

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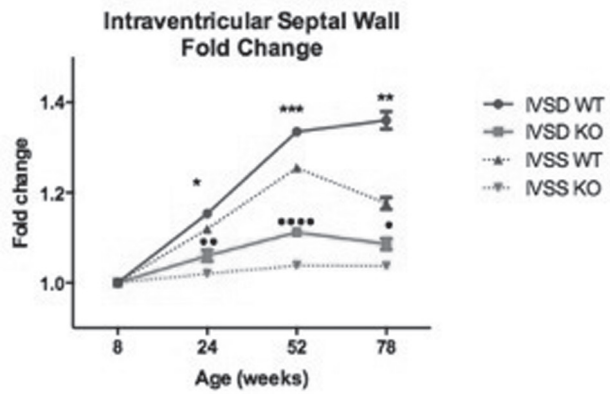
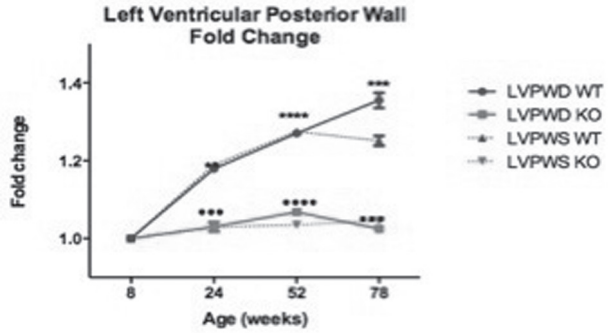
In cross sectional studies, low levels of insulin like growth factor I (IGF-I) have been identified as a risk factor for cardiovascular disease, the incidence of which is strongly age associated. In the current study, we have used mice deficient in IGFBP-1 as an animal model to study the effects of increased IGF-I bioavailability on cardiovascular structure and function in ageing mice.
Measurements of blood pressure in conscious mice (tail cuff photoplethysmography) and echocardiography in unconscious mice (under isoflourane anaesthesia) were recorded at 2, 6, 12 and 18 months of age (n=12-15). Mice were sacrificed and hearts used for left ventricular hypertrophy analysis by comparing cardiomyocyte cross-sectional area, fibrosis and apoptosis. Serum samples were used for total and free IGF-I and the Greiss reaction to estimate endogenous nitric oxide levels. Values are expressed as ±SEM and compared using student t-test or ANOVA. 8-12 week male IGFBP-1KO mice had an approx. 2.5 fold increase in free IGF-I compared to a matched WT cohort (WT 0.94±0.17ng/ml KO 2.58±0.34ng/ml $p<0.01$) with no change in circulating total IGF-I levels (WT 206.4±17.07ng/ml, 241.3±14.62ng/ml p=ns)
As the cohorts aged, there was a greater fold-increase in left ventricular wall size in WT 18m old mice in comparison to young 2m old mice (At 18m IVSD WT 1.36±.06-fold KO 1.09±.04-fold $p<0.01$; IVSS WT 1.18±0.04-fold KO 1.04+0.06-fold $P<0.05$; LVPWD WT 1.36±0.06-fold KO 1.03±.0.03-fold $p<0.001$; LVPWS WT 1.25±0.04-fold KO 1.05±0.02-fold $p<0.001$). At 18months, the measurements of diastolic function E/A ratio (WT 1.18±0.03 KO 1.32±0.04 $p<0.05$) IVRT/RR (WT 0.109±0.004ms/ms KO 0.094 ±0.002ms/ms $P<0.01$) IVCT/RR (WT 0.138±0.01ms/ms KO.113±.0.01ms/ms) were all preserved in the KO cohort compared to the WT. Ejection fraction, stroke volume and fractional shortening were all preserved in the KO cohort at 18m (EF WT 48.77±1.53% KO 53.50±1.03% $P<0.05$; SV WT 42.01±2.66ul KO 60.69±3.88ul $p<0.001$; FS WT 28.50±1.06 KO31.91±0.74 $p<0.05$).
KO mice were hypotensive at all time points compared to WT controls (at 2m WT 120.5±1.8mmHg KO 115.7±1.1mmHg $p<0.05$; 18m WT 123.5±2.6mmHg KO 114.5±2.2 $p<0.05$. This was abolished by chronic administration of L-NAME (at 2m WT 127.2±3.4mmHg KO 132.1±2.7 p2 KO 295.6±7.5um^2 $p<0.001$). WT mice had a greater increase in apoptopic cells per slide in aging mice compared to KO (2m WT 4.67±0.67 18m WT 11±2.24 $p<0.05$; KO 2m 5.2±1.16 18m 8.33±2.67 P=ns). Fibrosis measured by picrosirus red staining and hydroxyproline analysis

indicated that neither age nor genotype effected cardiovascular fibrosis. These results indicate that an increase in IGF-I bioavailability can help preserve cardiovascular structure and function in normal aging mice, possibly through increased nitric oxide production.



Septal wall measurements in diastole and systole in aging WT and IGFBP-1KO mice at 2,6,12 and 18 months.



Left ventricular posterior wall measurements in diastole and systole in WT and IGFBP-1 KO mice in systole and diastole.

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PC23

Skeletal muscle myoblasts have a 'memory' of previous TNF-α insults: Role of DNA methylation

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Tumour-Necrosis Factor Alpha (TNF-α) is a pleiotropic cytokine that is chronically elevated in ageing/aged related disease states (Sarcopenia, Cachexia); where higher TNF-α levels are strongly correlated with morbidity and mortality in later life. We have extensively shown that TNF-α impairs regenerative capacity in mouse and human muscle cells (Meadows 2000; Foulstone 2001, 2004; Stewart 2004; Al-Shanti 2008; Saini, 2008; Sharples 2010). Recently, we have established a SIRT1 (histone deacetylase) mediated mechanism regulating survival of myoblasts in the presence of TNF-α (Saini, 2012). We therefore wished to extend this work and investigate the epigenetic consequences of repeated doses of TNF-α on DNA methylation. C2C12 myoblasts were cultured in the absence or presence of TNF-α (40 $ng.ml^{-1}$), followed by multiple population doublings (25 doublings; Sharples et al., 2011, 2012) in the absence of TNF-α, prior to the induction of differentiation in the absence or presence of a second dose of TNF-α (20 $ng.ml^{-1}$). Interestingly, the cells that received a pre- and post-population doubling dose of TNF-α were more susceptible to the cytokine and exhibited a larger reduction in morphological and biochemical (CK) differentiation vs. cells that had not been exposed to TNF-α previously. Interestingly, CpG island methylation of 3 different regions of myoD were increased in cells that have undergone the 'early life' TNF-α dose with corresponding reductions in myoD gene transcription. Overall, myoblasts seem to have a memory of earlier life encounters of TNF-α when exposed to a further catabolic stimulus in later life, potentially through increased CpG methylation of myoD.

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Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

PC24

Age associated motor unit remodelling in the vastus lateralis

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Denervation and remodeling of motor units (MU) of skeletal muscle is known to occur with ageing and has been demonstrated with EMG measurements of small peripheral muscles in humans (McNeil et al., 2005). However, there is less information about this process in large locomotor muscles that are important for mobility. In the present study, intramuscular EMG (iEMG) was used to examine motor unit potential (MUP) size and duration, in the vastus lateralis muscle. Thirteen active, healthy young men (mean age 26±5y) and 18 active, healthy older men (mean age 73±6y) gave signed, informed consent prior to participation in the study which had been approved by the local ethical committee. Proximal and distal motor points of the vastus lateralis were identified by percutaneous electrical stimulation and iEMG recorded around the motor point with a concentric needle electrode from 3 depths within the muscle and turning the needle through 90° between contractions so that 12 separate recordings were made. Offline analysis was performed on all detected MUPs using Decomposition-Enhanced EMG software (Parsaei et al., 2012). The mean number of MUPs identified and analysed in the young was 32(±9) and in the older subjects 29(±7). The mean area of the MUP was 1165±337 uV.ms for the young and significantly larger at 1690±614 uV.ms for the older subjects ($p=0.006$). MUP duration was 2.37±0.26 ms for the young and 3.19 ± 0.65 ms for the older subjects, the difference being significant ($p=0.002$).

These results are consistent with substantial motor unit loss (Ireland et al, 2015) and remodeling in the vastus lateralis during healthy ageing as a result of denervation and reinervation and slower propagation of action potentials, possibly associated with an increase in slow units. These changes in motor units may have consequences for motor unit recruitment and control of movements in old age.

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PC25

The role of SIRT1 in aged and glucose restricted skeletal muscle cells

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Calorie restriction (CR) is considered the only non-genetic dietary intervention implemented that increases lifespan and healthspan in a variety of species. Advancing age and malnutrition are however coupled with decreases in muscle mass (sarcopenia). We have previously shown Sirtuin1 (SIRT1) to be fundamental in muscle cell survival and regeneration in the presence of apoptotic cytokine TNF-α (Saini et al., 2012). Where loss of SIRT1 has also been shown to abrogate calorie restricted induced lifespan extension (Corbi et al., 2012). We therefore aimed to understand the role of SIRT1 in ameliorating the effect of calorie restriction (low glucose) in young and aged myoblasts originally derived by our group (Sharples et al. 2011, 2012, Deane et al., 2013). Preliminary data suggests low glucose (0.056g/L) reduced morphological and biochemical (CK) differentiation versus normal glucose (4.5g/L)in both young and aged myoblasts with reductions in corresponding myoD, myogenin, IGF-I, MGF mRNA. Aged myoblasts also experienced an increased susceptibility to these parameters in the presence of low glucose. We further confirmed that resveratrol (10uM) and SIRT inhibitor (EX-527, 100nM) were able to successfully activate and suppress respectively the activity of SIRT1 (pSIRT1) in both young and aged myoblasts. Further preliminary data suggests that when we co-incubated low glucose conditions in the absence/presence of SIRT activators/inhibitors that activation of SIRT1 ameliorated the impact of low glucose on differentiation, where resveratrol administration somewhat maintained normal differentiation in low glucose conditions. Interestingly, aged cells appear more responsive to these changes vs. young cells. We hypothesise that low glucose may induce increases in pAMPK and potentially TSC2 that maybe involved in the inhibition of mTOR/Akt /p70s6k and therefore the mechanisms that underpin reductions in muscle growth and differentiation.

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Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

PC26

The effects of age and physical fitness on an fMRI study of selective attention in older adults

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Introduction

Selective attention plays an important role in working memory (WM) performance. Top-down modulation is required to both enhance neural activity associated with relevant information and suppress that associated with irrelevant information, allowing an individual to restrict attention to relevant inputs and focus memory capacity appropriately. The prefrontal cortex (PFC) may play a key role, adjusting the strength of functional coupling between brain regions in accordance with stimulus relevance[1]. Age-related impairments in WM are thought to be associated with increased sensitivity to interference from distracting information and reduced ability to selectively attend to relevant information[2].

Physical fitness may be associated with the maintenance of cognitive function in older adults. Aerobic fitness training has been shown to improve performance in measures of selective attention[3] and greater physical fitness has been hypothesised to increase top-down modulation during task execution[4].

Here, we use fMRI to investigate the effects of age and cardiovascular (CV) fitness on the BOLD response to relevant and irrelevant face stimuli during a selective attention task. We hypothesise that individuals with lower age or greater CV fitness may show evidence of greater top-down modulation than those of higher age or lower fitness.

Methods

45 adults aged 60+ (66.80±5.76 yrs, 31 female) underwent BOLD fMRI while performing a selective attention task. Blocks of face and house stimuli were presented

in a random order, with repeats of some stimuli. In each block, either faces or houses were designated as 'relevant' and the other 'irrelevant'. Participants were asked to judge whether the relevant stimuli were novel or repeated and to ignore irrelevant stimuli. CV fitness (VO_2 max) was measured on a cycle ergometer. FEAT analysis[5] was used to analyse the fMRI response in each stimulus condition.

Results

Participants showed different activations when presented with face stimuli in irrelevant versus relevant conditions. We observed no effect of age. Preliminary analyses testing for a positive relationship between CV fitness and BOLD signal identified a positive association in the right frontal pole in the irrelevant>relevant condition (Fig1).

Conclusions

We have observed an effect of CV fitness on the BOLD response in a selective attention task in older adults. Higher fit individuals show signs of greater PFC demand in irrelevant conditions, possibly reflecting greater suppression of distracting information. Our results support the hypothesis that physical fitness may have an effect on top-down modulation in this population, though further work is required to explore this possibility.

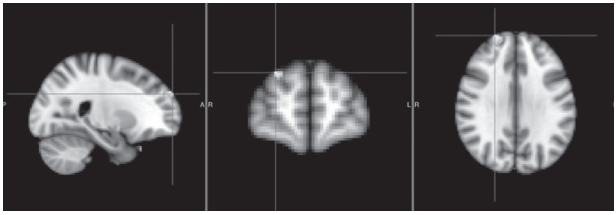

Figure 1. Positive association of VO_2 max with BOLD response in the irrelevant>relevant face condition. MNI coordinates of cluster max: x=24, y=60, z=30; right frontal pole. P<0.05.

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Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

PC27

Side effects of pharmacotherapy and cognitive impairment in Parkinson's disease: similar effect on generators of cognitive potentials P300

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Introduction

Parkinson's disease (PD) – human neurodegenerative disorder with dopamine deficit as major pathology. Primary symptom of PD is movement dysfunction but different other symptoms may be found in patients. Specific emphasis is directed at cognitive decline and harbingers of dementia. There are 5 main ways to correct functional activity of dopamine synapse: levodopa [1], dopamine agonists [1], amantadine [2], monoamine oxidase inhibitors [3], anticholinergic drugs [4]. We aimed to assess the possible side effects of these medications on cognitive functions in PD patients without dementia. Cognitive potential P300 is associated with information processing, memory, attention, and it's objective electroencephalography-based (EEG) approach for our goal.

Methods

92 PD humans (age 46-74, men and women, Hoehn-Yahr stage 2-3) and 26 healthy volunteers participated in present study. The study was approved in advance by the Ethical Committee of the Institute of Gerontology (Ukraine) and was in accordance with the Declaration of Helsinki. Cognitive dysfunctions in patients were evaluated on UPDRS-1 scale (The Unified Parkinson's Disease Rating Scale, part 1): 0-1 points for lower level and 2-4 points for higher level. All patients got their usual treatment; there were not additional prescriptions in connection with present study. Dosage of drugs per day: levodopa 150-375 mg – low dose, 400-887.5 – high; dopamine agonists 1.5-3 mg; amantadine 100-200 mg; monoamine oxidase inhibitors 6-7 mg; anticholinergic drugs 0,5-2 mg. Patients were divided into groups based on one of five types of medication, levodopa dosage and level of cognitive impairment (higher or lower). P300 was recorded in oddball paradigm task with auditory stimuli using NeuroCom Pro EEG system (XAI-Medica, Ukraine). We applied sLORETA (standardized low resolution brain electromagnetic tomography) [5] to identify the sources of P300 activity. Statistical analysis was performed by test for independent samples ($P < 0.05$, bootstrapping with 5000 samples).

Results

We have found increased activity of P300 sources in right middle frontal gyrus in patients with higher level of cognitive impairment (n=42). Similar differences in this area also were revealed in PD patients who didn't take dopamine agonist (n=52). Highest levodopa dosage leads to decreasing of P300 source's activity in same frontal region (n=23). In addition, PD subjects with greater doses of levodopa

(more 400 mg/day) demonstrated enhanced P300 generators in right parietal area (n=23). There were no significant differences in all other cases.

Conclusions

High levodopa dosage and absence of dopamine agonists in treatment regimen were associated with deviations in cognitive processes. These changes in P300 generators may serve as possible harbingers of future dementia in PD patients

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PC28

The effects of ageing on the excitatory and inhibitory presynaptic inputs to the neurones controlling micturition and continence in mice

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Incontinence or involuntary passing of urine remains a common and distressing problem in the elderly. Continence is influenced by the external urethral sphincter, but the urethral sphincter architecture and volume is unaltered in ageing (Russell et. al., 1996). We therefore hypothesised that there was a neural component contributing to reduced continence with age and examined the balance of excitatory and inhibitory influences on neurones involved in micturition. Ten wild-type mice C57BL6 female mice, age 3 month-old (n=5) and 24 month-old (n=5) were used. All mice were injected with Fluorogold i.p. to label motor and preganglionic neurones and 1 day later were anaesthetised with 80mg/kg pentobarbitone i.p, perfused

with 4% paraformaldehyde and spinal cords subsequently sectioned at 50μm. Triple labelling immunofluorescence with vesicular glutamate transporter 2 (VGLUT2), glutamic acid decarboxylase (GAD67) and glycine transporter 2 (GlyT2) was conducted on sections from L6-S1 for the dorsolateral nucleus (DLN, mouse homolog to Onuf's nucleus, which controls the urethral sphincter) and parasympathetic neurones (influence bladder emptying), and segment L1 for the sympathetic neurones (which relax the bladder to allow filling). Immunoreactive close appositions on neuronal soma were identified and analysed by confocal microscopy (Chang & Martin,2009), with differences examined using a t-test and significance at $p<0.05$. In aged mice DL motoneurones had significantly fewer glutamatergic appositions (12.24 ± 0.70 bouton/100μm, n= 33 cells) compared to young (22.98 ± 1.13 bouton/100μm, n= 30 cells); increased apposing GABAergic boutons (aged 7.68 ± 0.70 bouton/100μm; young 4.42 ± 0.61 bouton/100μm) and increased glycinergic terminals (aged 8.42 ± 0.63 bouton/100μm; young (3.37 ± 0.76 bouton/100μm). For sympathetic neurones, aged mice had a decreased number of glutamatergic terminals (9.49 ± 0.64 bouton/100μm, n= 37 cells) compared to young (12.32 ± 6.67 bouton/100μm, n= 41 cells) but did not demonstrate any changes in both inhibitory inputs. Compared to young adults parasympathetic neurones of aged mice had a significantly increased number of glutamatergic terminals (aged 11.00 ± 1.07 bouton/100μm, n= 33 cells; young 6.88 ± 0.51 bouton/100μm, n= 31 cells) and increased number of GABAergic terminals (aged 7.22 ± 0.58 bouton/100μm; young 4.70 ± 0.65 bouton/100μm) but did not show any significant changes in the inhibitory GlyT2 inputs. The overall pattern in ageing suggests a net increase in the inhibitory effects on the DLN (suggesting a reduction in tone of the urethral sphincter) and sympathetic neurones (reducing the capacity of the bladder). The alteration of the synaptic excitatory-inhibitory balance on the neurones controlling micturition and continence may therefore contribute to the incontinence in the elderly.

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PC29

Altered hemorheological indices in a Nigerian geriatrics population

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Aging is a normal process of adult life characterised by a gradual decline in the physiologic reserves. Physiologic functioning is probably a better measure of aging than chronological age. Elevated plasma fibrinogen concentration has been linked

severally with cardiovascular diseases and stroke in the elderlies and the influence of plasma Fibrinogen concentration on plasma viscosities is well understood.Our interest was primarily based at establishing Fibrinogen index in Geriatrics especially in the Nigeria and secondly to assess their rheological parameters as probable indices of their cardiovascular function. A total of 50 apparently healthy, elderly Nigerians with ages between 60 and 85 years comprising of 25 males and 25 females recruited from old people's home and some individuals around the southern area of Nigeria were studied for hemorheological parameters such as: Packed cell volume (PCV), Plasma and whole blood viscosity (PV and WBV respectively), Erythrocytes sedimentation rate (ESR), Plasma Fibrinogen concentration(PFC) and Euglobulin lysis time (ELT). They were compared with 50 healthy younger sex -matched subjects (controls).We observed statistically significant increases in the values of PV, PFC, ESR and ELT while PCV and WBV exhibited significant decreases when compared with controls ($P<0.05$, respectively). The increase in ELT is interpreted as a reduction in fibrinolytic activity.In conclusion, decreased haematocrit and lowered whole blood Viscosity coupled with hyperfibrinogenaemia with subsequent high plasma viscosity and hypofibrinolysis could be reflections of advanced age. The decreased parameters may favour improved hemorheology at the onset but the overwhelming influence of the elevated parameters are indicative of abnormal rheology and a predisposition to thrombotic tendencies and other cardiovascular complications at old age. The need for exercise and prophylactic antithrombotic therapy especially at advanced ages may be indicated.

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PC30

Assessing exercise capacity in older adults using a self-paced 6-minute stepper test (6-MST)

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Background
Exercise capacity is an important indicator of physical function in the aging population. Testing protocols are often ambulatory and require a long corridor (>30m). These protocols do not easily facilitate measurements of blood pressure or cardio-respiratory effort. Many studies also report poor acceptance from older adults. We assessed the feasibility of a 6-minute step test (6MST) for assessing exercise capacity in a tri-ethnic cohort of older adults. Test acceptability, sensitivity, reproducibility and agreement with a previously verified testing protocol were determined.
Method

Participants (n=181; 116=male, mean age 71±6years) were invited to undertake a 6MST on a stepper (Homcom, miniStepper) with hand-rail support provided. Number of steps, time stepping and perceived exertion were recorded, cardiorespiratory effort was monitored by portable gas analysis (K4b^2,Cosmed). A sub-set of participants completed a 6-minute walk test (6MWT) and a second 6MST.
Variables for all participants were compared by gender. Number of steps, perceived exertion and highest VO2 were compared between the first and second 6MST and between the first 6MST and the 6MWT. Data are means±SD or means±SD of differences (Δ) (6MST(2) - 6MST(1) or 6MST(1)-6MWT); a Student's t-test was used for comparisons.
Results
All participants agreed to undertake the 6-MST . 164 (91%) participants agreed to wear a mask to monitor cardiorespiratory effort and 121 (67%) completed 6 minutes of stepping. Overall men achieved a higher VO_2 than women (16.82±3.87 versus 14.20±3.26ml/l/kg, p<0.001). 10 participants completed a repeat 6MST and a 6MWT. On average participants completed 53 steps more in the second 6MST versus the first (p=0.02). There was no significant difference in perceived exertion (Δ=0.6±1.4, p=0.2), highest VO_2 (Δ=93.2 ±218ml/min, p=0.2) or heart rate (Δ=3±13bpm, p=0.5) between first and second step tests. Perceived exertion was similar in the first 6MST and the 6MWT (Δ=0.95±2.36, p=0.2) with no significant difference in highest VO_2 (Δ=73±401ml/min, p=0.6) or heart rate increase (Δ=9±21bpm, p=0.2) during the first 6MST and the 6MWT.
Conclusion
The 6-MST is a feasible and acceptable method for assessing exercise capacity in older adults. It is sensitive to expected gender differences in peak VO_2. The test is reproducible in terms of cardiorespiratory effort and perceived exertion but there is a 'learning effect' of ~15% improvement in steps achieved during the second step test. Measures of cardiorespiratory effort and perceived exertion showed acceptable agreement with a 6MWT but unlike a 6MWT, the 6MST permits continual BP measurements.

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PC31

Subsarcolemmal lipid accumulation in ageing skeletal muscle

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Skeletal muscle insulin resistance associated with ageing may result from age-related intramyocellular lipid (IMCL) accumulation. Whether IMCL derived fatty acid oxidation is impaired during exercise in older individuals is unclear. Moreover,

there are disctinct pools of IMCL droplets localised to intermyofibrillar (IMF) and subsarcolemmal (SSL) regions of the myofibre, and little is known about the relative contribution of these pools to lipid use during exercise. To answer these questions, 14 healthy older (69 ± 1 yr, BMI 26.5 ± 0.8 kg/m^2) and 8 younger (22 ± 1 yr, BMI 24.0 ± 1.1 kg/m^2) men performed 1 hr of cycling at 50% maximal oxygen consumption and the contribution of plasma fatty acids and intramyocellular lipid (intermyofibrillar and subsarcolemmal) to total fat oxidation was determined using a combination of indirect calorimetry, intravenous [U-^{13}C]palmitate infusion, and electron microscopy of muscle biopsies. The study was approved by the University of Nottingham Medical School Ethics Committee. Two-way ANOVA was performed to detect within and between groups differences, with statistical significance declared at $P<0.05$ (all values represent mean ± standard error). There was no difference in the relative contribution of fat to total energy expenditure during exercise when comparing older and younger volunteers (41.2 ± 2.7 vs. 43.3 ± 6.1%, respectively), but the relative contribution of IMCL to total fat oxidation was 40% less in older subjects (42.0 ± 6.0 vs. 69.9 ± 3.5%, respectively; P<0.01). This difference was not attributable to reduced utilisation of IMF lipid droplets as the decrease in the % of IMF fibre area occupied by droplets after exercise was similar in between younger (0.65 ± 0.11 to 0.40 ± 0.09%; P<0.05) and old er(0.72 ± 0.09 to 0.57 ± 0.12%; P=0.07) subjects, and was predominantly due to a reduction in droplet number (22.2 ± 3.0 to 15.4 ± 2.7 and 23.3 ± 2.6 to 17.4 ± 2.9 droplets/mm^2 fibre for younger and older subjects, respectively; P<0.05). Indeed, average droplet size was unchanged by exercise in both age groups. Conversely, in the SSL region average droplet size (0.32 ± 0.04 to 0.40 ± 0.05 μm^2; P<0.05) increased in older, but not younger, subjects after exercise, such that the relative SSL fibre area occupied by droplets was ~3-fold greater in older compared to younger subjects (3.55 ± 0.66 vs. 1.26 ± 0.27%; P<0.05). Furthermore, the difference between rates of plasma fatty acid disappearance and oxidation was ~2 fold greater in older vs. younger subjects (16.2 ± 2.2 vs. 9.6 ± 1.7 μmol/kg lean mass/min, respectively; P<0.05). In conclusion, IMCL utilisation during exercise is blunted by age, which is localised to the SSL region and attributable to an imbalance between plasma fatty acid delivery and oxidation. SSL IMCL accumulation may explain age associated insulin resistance, particularly as this is the site of insulin action and glucose uptake.

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PC32

Step-test vs. six-minute walk test among active elderly undergoing functional training

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Prescription of Physical Exercise has become a professional challenge, involving professionals towards interdisciplinarity and the need of improving the elderly's functional fitness screening. The Senior fitness test (1) has been broadly used to test cardiovascular and muscular fitness under a functional approach, providing qualified and updated data about Elderly (2). However, some similarities have been found between tests like the Six-Minute Walk Test (6MWT) and the Two-Minute Step Test (2MST), both aimed at cardiovascular testing (3-5). Since multicomponent functional training programs have shown to improve strength and balance more than cardiovascular fitness, this study aims to investigate the level of association between these two tests in neuromuscular-oriented programs, and whether they should coexist in their fitness screening.

51 women and 8 men active elderly (72.02±5.22 years) undergoing a nine-month multi-component and cognitive functional-training program, volunteered to participate in this cross-sectional study, conducted in the second part of the program. Body composition (Tanita BC-545N: 68.30±8.98 Kg; 39.35±5.22 % Fat; 39.33±6.72 Kg of Muscle Mass) and Cardiovascular Fitness were measured (2MST: 64.61±19.88 steps; 6MWT: 583.47±55.72 m), in two testing sessions, counterbalanced, with 48 h of recovery. Participants were encouraged to play their best during testing. A Spearman's Rho Non Parametric correlation analysis was conducted, since data did not meet the normality assumption (Shapiro-Wilk's W test). Due to time-length differences between tests, the two first minutes of the 6MWT were considered, at least in one randomized mixed subgroup (n=17; 206.03±19.55 m).

Table 1 shows a medium correlation between the 6MWT and the 2MST ($r=0.37$; $p<0.05$) which gets lost when associated to the small sample accounted in the 6MWT_2min. Both, 6MWT and 2MST show a negative, medium to large, very significant correlation with age ($p<0.05$), bigger for 6MWT ($r=-0.66$ vs $r=-45$), but there is no association between body composition and the cardiovascular outputs. The 6MWT_2min is only associated to the 6MWT, although very significant and strongly ($r=0.93$).

Our results suggest the presence of different mechanisms underlying the performance in the 6MWT and the 2MST despite sharing cardiovascular components. Strength and balance gains may be responsible of a better performance in the 2MST in active Elderly, highlighting its neuromuscular content. The absence of association between muscle mass and 2MST triggers the importance of coordina-

tion. Fitness testing should therefore include both tests, although larger studies may elucidate if the stronger association between age and the 6MWT is due to a higher N in our test, or the consequence of functional training.

	Age	Weight (kg)	Fat Mass %	Muscle Mass (Kg)	2MST (nº of steps)	6MWT (m)	6MWT_2min (m)
Age	1.000 *59*	.159 *56*	.220 *56*	-.063 *56*	-.448** *45*	-.663** *54*	-.440 *17*
Weight (kg)	.159 *56*	1.000 *56*	.176 *56*	.778** *56*	-.088 *42*	-.223 *51*	-.150 *16*
Fat Mass %	.220 *56*	.176 *56*	1.000 *56*	-.325* *56*	-.051 *42*	-.493** *51*	-.452 *16*
Muscle Mass (Kg)	-.063 *56*	.778** *56*	-.325* *56*	1.000 *56*	-.074 *42*	.074 *51*	.082 *16*
2MST (nº of steps)	-.448** *45*	-.088 *42*	-.051 *42*	-.074 *42*	1.000 *46*	.373* *41*	-.015 *13*
6MWT (m)	-.663** *54*	-.223 *51*	-.493** *51*	.074 *51*	.373* *41*	1.000 *55*	.928** *17*
6MWT_2min (m)	-.440 *17*	-.150 *16*	-.452 *16*	.082 *16*	-.015 *13*	.928** *17*	1.000 *17*

Table 1. Correlations between the 6MWT, the 2MST and the first 2 minutes in the 6MWT (Rho of Spearman).

N in the inner corner. ** $\alpha < 0.01$; * $\alpha < 0.05$

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PC33

Age-related changes in glia-neuron communication in neocortex: implication for synaptic plasticity

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Maintaining brain function during the ageing is very important for the mental and physical health. Recent studies showed a crucial importance of communication between two major types of brain cells: neurons transmitting electrical signals and glial cells which maintain the wellbeing and function of neurons. Still, the study of age-related changes in the neuron-glia signaling is far from complete.
We studied the impact of physiological and pathological ageing on spontaneous and evoked Ca^{2+}-signalling in the astrocytes of mouse neocortex with particular focus on signals mediated by norepinephrine and endocannabinoid receptors. We observed the general trend of increase of astrocytic signaling with brain maturation (up to 6 month) followed by the considerable decrease towards old age (12-24 month). Our preliminary data showed the significant difference in the astrocytic signaling in neocortex of wild-type and AD model mice (line APP/PS1).
We have shown previously that cortical astrocytes are capable to release ATP, glutamate and D-Serine by Ca^{2+}-dependent mechanism. Release of gliotransmitters from cortical astrocytes can be activated via various pathways including direct UV-uncaging of intracellular Ca^{2+} or G-protein coupled receptors, such as α-adrenoreceptors or CB1 receptors. Importantly, release of both ATP and D-Serine from neocortical astrocytes was not observed in brain slice of dnSNARE mice, expressing dominant-negative SNARE domain selectively in astrocytes. We also discovered that astrocyte-derived ATP can facilitate the induction of long-term potentiation of synaptic plasticity in the neocortex. Additional stimulation of astrocytic Ca^{2+}-signalling via norepinephrine and endocannabinoid receptors did not facilitate LTP in the neocortex of dn-SNARE mice. The preliminary results of behavior experiments show that norepinephrine –mediated glial signaling can affect learning and memory.
Our recent data have shown that age-related decrease in the astroglial Ca^{2+} signalling can cause substantial decrease in the release of gliotransmitters.
Age-related impairment of gliotransmitter release from cortical astrocytes can compromise astroglial modulation of synaptic transmission in the neocortex and therefore can contribute to the age-related impairment of synaptic plasticity. We have also observed an alteration in the gliotransmitter release and astrocyte-neuron communications in the APP/PS1 mice, as compared to the wild-type littermates of the same age (12-14 months).
Combined, our data show that glia-neuron interaction can significantly decline with ageing and this decline in gliotransmission can contribute to age-related cognitive impairment. Also, our results strongly support the physiological relevance of glial exocytosis for glia neuron-communications and brain function.

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PC34

Unlocking vascular barriers to improved functional capacity in the elderly: A report from the PRIME trial

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Reduced functional ability with advancing age is, in part, due to decreased vascular reactivity and increased arterial stiffness. Lakatta (2003) theorizes such vascular changes contribute to greater myocardial work, lower skeletal muscle perfusion, and represents a significant risk factor for cardiovascular morbidity. Purpose: To determine effects of 8 wks of progressive whole-body training preceded by 4 wks of peripheral intermittent muscular exercise (PRIME) or aerobic training (AT) on flow mediated dilation (FMD), central blood pressures and functional ability. Methods: Subjects were over the age of 70, who walked between 218-490yards on a 6-minute walk test, without adverse responses. Subjects were randomized to AT or PRIME for the first 4 wks (Phase 1). AT consisted of 45 minutes of walking/biking at 40-60% of heart rate reserve, 3*wk. PRIME consisted of exercises specific to the calf, thigh, buttocks, arms, shoulders, and torso. Each exercise was performed for 3 to 5 minutes, at ~40-70% of the maximal voluntary strength of the primary muscle group of interest, for 45 minutes, 3*wk. Subjects in both groups were progressed as tolerated. Following the first 4 wks, all subjects were advanced to a well-rounded, whole-body exercise program using guidelines from ACSM (Phase 2). Before, after 4 and 12 wks, ultrasonography was used to determine brachial artery FMD, applanation tonometry to estimate central blood pressures, muscular strength determined from 1RM (Chest Press, Seated Row, Leg Press, and Handgrip (Total)), and functional ability from the Senior Fitness Test (SFT). Results: Using a repeated measure design, groups were similar in number (PRIME=48, 18 men; AT=48, 15 men), age (PRIME:76±4.29; AT:76±4.96 yrs), weight (PRIME:80.10±14.76; AET: 81.78±16.20Kg). Training resulted in significant improvements for FMD (↑50%; 4.43±2.83 to 6.53±2.64%, $p<0.05$), reductions in aortic BP (SBP: -4.41±11.72, DBP: -2.34± 7.53mmHg, $p<0.05$), increase in strength (Total: 74.46±75.16kg, $p<0.05$), and SFT (34.36±13.07 to 53.56±14.59%, $p<0.05$). Magnitude of change was significantly greater in PRIME ($p<0.10$) for aortic BP, and TOT ($p<0.05$), and similar for other variables. Conclusion: Twelve wks of training, resulted in significant reduction in cardiovascular morbidity risk and improvements in functional ability. Magnitude of improvement was greatest in those randomised to PRIME during Phase 1.

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PC35

Unlocking musculo-skeletal barriers to improved functional capacity in the elderly: A report from the PRIME trial

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Advancing age is associated with a decline in skeletal muscle mass and bone mineral density (BMD), These changes often result in a downward spiral, contributing to reduced functional ability and loss of independence. **Purpose:** To determine effects of 8 wks of progressive whole-body training preceded by 4 wks of peripheral intermittent muscular exercise (PRIME) or aerobic training (AT) on body composition, muscle strength and functional ability. **Methods:** Subjects over the age of 70, who scored between 218-490yards on a 6min walk test were included, and randomized to AT or PRIME for the first 4 wks (Phase 1). AT consisted of 45min of walking/biking at 40-60% of heart rate reserve, 3*wk. PRIME consisted of exercises specific to the calf, thigh, buttocks, arms, shoulders, and torso. Each exercise was performed for 3 to 5min, at ~40-70% of maximal voluntary strength of the primary muscle group, for 45min, 3*wk. Subjects in both groups were progressed as tolerated. Following phase 1, all subjects were advanced to a well-rounded exercise program using ACSM guidelines (Phase 2). Before, after 4 and 12 wks, body composition was determined from DXA scans (DXA; QDR 4500A, Hologic Inc., Bedford, MA), muscular strength assessed using 1RM (Chest Press, Seated Row, Leg Press, and Handgrip (Total)), and functional ability from the Senior Fitness Test (SFT). **Results:** Groups were similar in number (PRIME= 27, 9men; AT= 30,12 men), age (PRIME:75±3.96; AT:75±4.93 yrs), and weight (PRIME:80.84±15.06; AT: 82.93±17.25Kg). Using a repeated measure ANOVA, training revealed a main effect ($p<0.05$) for body weight (-0.62±0.21kg), body fat (-813±170.60g), leg lean mass (206±74.82g), thoracic (0.031±0.011g/cm^2), lumbar (0.021±0.01g/cm^2), and pelvic BMD (0.016±0.006g/cm^2), strength (Total: 83.02±10.93kg), and SFT (17.10±1.35%). Significant group*time interactions ($p<0.05$) were present for leg lean mass, thoracic and lumbar BMD, and strength, in favour of PRIME. Strength changes were correlated with changes in pelvic BMD and SFT. **Conclusion:** Twelve wks of training, resulted in significant increases in muscular strength, BMD, and functional ability, with those randomised to PRIME having the most favourable changes. Changes in strength were directly related to changes in BMD and functional ability, indicating an important strategy to prevent sarco- and osteopenia.

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PC36

Cardiometabolic risk factors clustered around metabolic syndrome and apolipoprotein E genotype predict cerebrovascular health in older adults: results from the *Brain in Motion study*

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Background: When clustered together, risk factors for cardiovascular disease, stroke, and type 2 diabetes mellitus (*e.g.*, hypertension and dyslipidemia) are called metabolic syndrome (MetS).[1] In the Canadian Health Measures Survey, 21% of Canadians between the ages of 18 and 79 were classified as having MetS[2] while the prevalence in the European population is about one-quarter.[3] With the rising worldwide prevalence of MetS, it is important to determine the extent to which MetS affects cerebrovascular health. In addition, apolipoprotein E (APOE) plays a role in lipid metabolism as it serves as a transport molecule of triglyceride-rich particles and high density lipoprotein cholesterol.[4] Since MetS is associated with an imbalance in lipid and lipoprotein metabolism, the role of the *APOE* genotype may be associated with MetS and cerebrovascular outcomes. The purpose of this study was to examine the effect of MetS on cerebrovascular health indices in healthy older adults and determine the influence of apolipoprotein E (*APOE*) ε4 expression. Methods: Participants included 258 healthy, sedentary older adults (122 men, 136 postmenopausal women) aged 54 to 93 yrs (65.9±6.3 yrs, mean±SD), who volunteered for a longitudinal exercise intervention study titled the *Brain in Motion* study.[5] In a cross-sectional study of baseline, pre-intervention, data we investigated the association between cerebrovascular health indices, MetS, and *APOE* genotype. MetS was determined using standard diagnostic criteria.[1] *APOE* genotyping was conducted on 242 samples and sequence data were generated using PCR-amplification followed by Sanger sequencing. Seventy-seven participants (29.8%) met

criteria for MetS. To model the association between cerebrovascular outcomes and MetS after controlling for *APOE* genotype, age, sex, education, and behavioural outcomes, ordinary linear regression analysis based on M-estimator was used. Results: Compared to participants without MetS, participants with MetS had lower resting cerebral blood flow (CBF) peak velocity (P) $p<0.01$, cerebrovascular conductance (CVC) $p<0.0001$, P-reactivity (change in P divided by the change in PETCO2 from +1 mmHg to +8 mmHg) $p=0.03$, and CVC-reactivity (change in CVC divided by the change in PETCO2) $p=0.01$. *APOE* ε4 carriers had higher CVC ($p=0.03$) and P-reactivity ($p=0.037$) than non-carriers. Conclusion: These results provide evidence that after adjusting for sociodemographic & lifestyle factors and *APOE* genotype, cardiometabolic risk factors clustered together as MetS predict cerebrovascular health indices in older adults. Furthermore, *APOE* ε4 carrier had higher CVC and P-reactivity, suggesting that compensatory mechanisms to protect the vulnerable brain may underlie the associations between cerebrovascular health and *APOE* genotype.

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Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

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Executive function and sensorimotor skill in older adults: An intervention study

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Background: The increasing number of elderly people is a societal challenge that is exacerbated by reducing cognitive ability, even in healthy ageing. Traditionally, cognitive impairment was ascribed to loss of frontal lobe function. The recent interest in cerebellar and striatal contributions to cognitive function, allied to the established volume reductions in cerebellum and basal ganglia, and the known impairments in sensorimotor functioning, indicate possible subcortical contributions to the cognitive decline. Recent intervention studies have highlighted the

importance of exercise, coordinative as well as aerobic, in increasing both hippocampal and cerebellar volume, with corresponding improvements in both physical and mental performance. The present study investigated further the link between subcortical and cortical function in the elderly by undertaking a coordinative exercise intervention.
Method: 98 healthy older adult volunteers (mean age 68.2, S.D 6.6) participated and were split into control and intervention groups. All participants undertook an initial series of pre-tests designed to evaluate Physical Coordination, Memory, Language Dexterity, Fluid Thinking and Affect, with identical post-tests around two months later. The intervention group undertook an 8 week internet-based coordinative exercise intervention, while the control group continued 'life as normal.'
Results: The intervention group showed significant pre- to post improvements in 12 of the 18 tests, whereas the controls improved significantly on one only. Effect sizes ranged from 0.1 to 0.6. MANOVA revealed significant between-group differences for the physical tasks and for the declarative memory tasks. Individual ANOVAs indicated that the intervention group improved significantly more than the controls on three tests - Balance, Peg Assembly and Delayed Picture Recall.
Conclusions: The results are consistent with studies indicating the benefits of exercise for the elderly, but to our knowledge this is the first study that has investigated a range of attributes from affective to cognitive to sensorimotor skills. The findings indicate that it is both feasible and beneficial to deliver an internet-based balance and coordination program to older adults, and highlight the opportunities for larger studies.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

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