

UPDATE**Can physical exercise in old age improve memory and hippocampal function?****Emrah Duzel,^{1,2,3} Henriette van Praag⁴ and Michael Sendtner⁵**

Physical exercise can convey a protective effect against cognitive decline in ageing and Alzheimer's disease. While the long-term health-promoting and protective effects of exercise are encouraging, it's potential to induce neuronal and vascular plasticity in the ageing brain is still poorly understood. It remains unclear whether exercise slows the trajectory of normal ageing by modifying vascular and metabolic risk factors and/or consistently boosts brain function by inducing structural and neurochemical changes in the hippocampus and related medial temporal lobe circuitry—brain areas that are important for learning and memory. Hence, it remains to be established to what extent exercise interventions in old age can improve brain plasticity above and beyond preservation of function. Existing data suggest that exercise trials aiming for improvement and preservation may require different outcome measures and that the balance between the two may depend on exercise intensity and duration, the presence of preclinical Alzheimer's disease pathology, vascular and metabolic risk factors and genetic variability.

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Introduction

Physical inactivity is an important risk factor for cognitive decline in ageing and for Alzheimer's disease (Norton *et al.*, 2014). Conversely, exercise can convey a protective effect (Ahlskog *et al.*, 2011; Geda *et al.*, 2012; Wirth *et al.*, 2014; Ngandu *et al.*, 2015; Prakash *et al.*, 2015; Tolppanen *et al.*, 2015) even if initiated after midlife (Tolppanen *et al.*, 2015). In this article we summarize current knowledge regarding exercise-induced hippocampal neural plasticity in animals

and humans with a focus on old age. Animal research of normal ageing and models of Alzheimer's disease generally support the notion that physical activity can prevent loss of neuroplasticity and maintain memory function. However, randomized controlled trials in older humans indicate that memory improvements after exercise interventions are highly variable. Understanding the possible sources of this variability will be important for tailored clinical prescriptions of exercise interventions, for preventing side-effects and treatment failures, and enhancing efficacy.

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We outline how research in this field can benefit from recent insights into the functional anatomical and cognitive organization of hippocampal circuits (Fig. 1). This brain region is critical for episodic memory, the ability to memorize and remember unique events and experiences (for review see Eichenbaum *et al.*, 2007). Together with its medial temporal lobe and subcortical circuits (Fig. 1A and B) the hippocampus is compromised early in ageing and neurodegenerative conditions, most notably in Alzheimer's disease and fronto-temporal dementias (Tan *et al.*, 2014; Braak and Del Tredici, 2015). We also consider how exercise may interact with preclinical Alzheimer's disease pathology, vascular and metabolic risk factors and genetic variability. Finally, we highlight questions that can be addressed in future studies.

Neural plasticity after exercise in animals

Voluntary wheel running upregulates expression of BDNF, IGF1 and VEGF (encoded by *VEGFA*) and modulates plasticity in the hippocampus and cortex (Box 2) (for reviews see Cotman *et al.*, 2007; Vivar *et al.*, 2013; Prakash *et al.*, 2015; Sleiman and Chao, 2015). BDNF is a major regulator of synaptic plasticity (Park and Poo, 2013) and lowering BDNF levels results in dysfunction, such as decreased synaptic plasticity not only in the hippocampus (Korte *et al.*, 1995; Patterson *et al.*, 1996) but also other brain regions that are affected during ageing such as cortex, the extra-hippocampal limbic system and the striatum (Rauskolb *et al.*, 2010). In mice lacking BDNF in the post-natal brain, survival of hippocampal neurons is not affected (Rauskolb *et al.*, 2010). Thus exercise-induced upregulation of BDNF expression in hippocampal and cortical neurons (Neeper *et al.*, 1995; 1996; Hopkins and Bucci, 2010) may promote synaptic remodelling and morphological complexity rather than cell survival.

Running increases dendritic complexity and the number of dendritic spines in the dentate gyrus (Eadie *et al.*, 2005), CA1 and entorhinal cortex (Stranahan *et al.*, 2007; Siette *et al.*, 2013; for review see Opendak and Gould, 2015). Aerobic exercise also increases resting state perfusion in the hippocampus in rodents and young/middle-aged humans (Pereira *et al.*, 2007), which could be mediated by exercise-induced angiogenesis. Animal studies suggest that angiogenesis is closely linked to adult neurogenesis (Palmer *et al.*, 2000; Louissaint *et al.*, 2002; Pereira *et al.*, 2007). Running-induced adult hippocampal neurogenesis is positively correlated with increased synaptic plasticity, spatial memory and pattern separation in adult animals. In addition, exercise can reverse declining neurogenesis and memory function in aged rodents (van Praag, 2008; Marlatt *et al.*, 2010; Vivar *et al.*, 2013; Opendak and Gould, 2015), (Figs 1C and 2).

It is important to consider that new hippocampal neurons are a functional and integral part of brain circuitry rather than just a local hippocampal phenomenon. Under sedentary conditions, substantial input to new neurons originates from perirhinal and lateral entorhinal cortex (Vivar *et al.*, 2012), areas that are considered important for object and object-in-context information processing (Knierim *et al.*, 2014). Lesion of this projection to new neurons results in deficient pattern separation (Vivar *et al.*, 2012). Running increases fine discrimination (Creer *et al.*, 2010; Bolz *et al.*, 2015) and results in enhanced short-term plasticity and increased input from lateral entorhinal cortex, as well as recruitment of caudo-medial entorhinal cortex to the circuitry of new neurons (Vivar *et al.*, 2015), (Fig. 2). Consistently, recent research in humans revealed a positive association between entorhinal cortex grey matter volume, cardiovascular fitness and memory function in young adults (Whiteman *et al.*, 2015).

Neurovascular plasticity and neurotrophins in humans

Human post-mortem studies using environmentally mediated ¹⁴C labelling support earlier research (Eriksson *et al.*, 1998) that hippocampal neurogenesis continuously occurs until very advanced age (Spalding *et al.*, 2013; Bergmann *et al.*, 2015). In the absence of *in vivo* imaging markers for human neurogenesis, exercise studies have used indirect indices of plasticity including morphometric measures such as magnetic resonance volumetry of grey matter and diffusion tensor imaging of white matter, functional and perfusion imaging of the hippocampus (for a review see Thomas *et al.*, 2012), as well as PET (for a review of PET studies see Boecker and Drzezga, 2015).

Although several randomized controlled exercise interventions have been conducted in old age (Colcombe *et al.*, 2004; Lautenschlager *et al.*, 2008; Muscari *et al.*, 2010; Anderson-Hanley *et al.*, 2012; Barnes *et al.*, 2013; Suzuki *et al.*, 2013) these have not assessed the relationship between improvements in cardiovascular fitness and morphometric, functional and perfusion-based brain changes, and memory performance. Also, in some of these studies outcome measures were primarily cognitive scores used in clinical Alzheimer's disease trials [Mini-Mental State Examination (Muscari *et al.*, 2010); Alzheimer Disease Assessment Scale (ADAS-Cog; Lautenschlager *et al.*, 2008; Suzuki *et al.*, 2013), Cognitive Battery of the Consortium to Establish a Registry for Alzheimer Disease words recall (Lautenschlager *et al.*, 2008; Suzuki *et al.*, 2013)] and hence not designed to be sensitive to specific plasticity-related mechanisms.

Few intervention trials (Colcombe *et al.*, 2006; Erickson *et al.*, 2011; Ruscheweyh *et al.*, 2011; Dery *et al.*, 2013; Maass *et al.*, 2015b, c) did relate fitness changes to hippocampal and/or serum biomarkers of plasticity in a way that

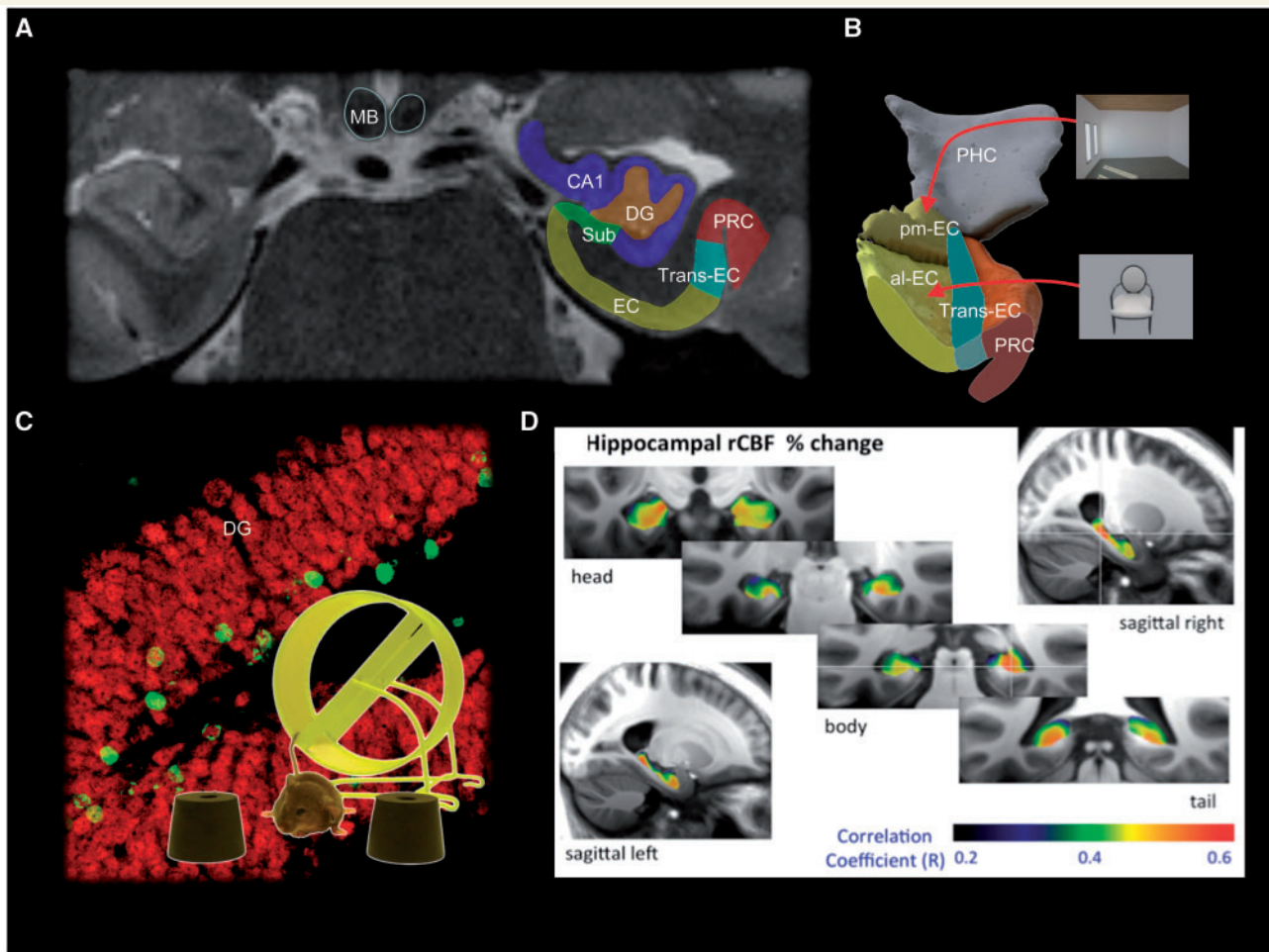


Figure 1 Brain regions and networks that are affected by exercise. **(A)** Subfields of the hippocampus (HC) and adjacent medial temporal lobe. The entorhinal cortex (EC) is a major gateway for hippocampus (for review see van Strien *et al.*, 2009). The dentate gyrus (DG) seems to be important for pattern separation of novel information (Leutgeb *et al.*, 2007; Neunuebel and Knierim, 2014), whereas CA3 (not visible in this section) is implicated in pattern completion. Pattern separation dissociates different memories to non-overlapping neural codes so that they are not confused with each other even if similar. Pattern completion, on the other hand, associates different memories to overlapping and linked neural codes such that a full episodic experience can be remembered from a partial memory (Neunuebel and Knierim, 2014). CA1 probably remaps memory representations back to their cortical topography (Kumaran and McClelland, 2012). **(B)** The entorhinal cortex receives inputs about object representations from perirhinal (PRC) and space/scene representations from parahippocampal cortices (PHC) (Witter *et al.*, 2014). In humans, the anterior-lateral (al) entorhinal cortex is functionally associated with the perirhinal cortex (Maass *et al.*, 2015a) and object processing (Navarro Schroder *et al.*, 2015) whereas the posterior-medial (pm) entorhinal cortex is functionally associated with the parahippocampal cortex (Maass *et al.*, 2015a) and scene processing (Navarro Schroder *et al.*, 2015). The mammillary bodies (MB) are a major subcortical hub for the hippocampus. Trans-EC = transentorhinal cortex, a transition zone between lateral entorhinal cortex and perirhinal cortex affected early in Alzheimer's disease by tau pathology. MB = mammillary bodies. Atrophy of the mammillary bodies can be seen in ~60% of patients with Alzheimer's disease (Hornberger *et al.*, 2012) and correlates with impaired recollection (Tsivilis *et al.*, 2008; Vann *et al.*, 2009). In animals running can enhance the connectivity between the mammillary bodies and new neurons in the dentate gyrus (Vivar *et al.*, 2015). **(C)** Running increases adult neurogenesis in the dentate gyrus and improves discrimination between similar stimuli (such as the two brown conical shapes on either side of the mouse). In the background is a photomicrograph of a coronal section through the mouse dentate gyrus double-labelled with the neuronal nuclei marker NeuN (red) and bromodeoxyuridine (BrdU, green), a thymidine analogue that labels dividing cells. Cells that show an overlap of red and green labels are considered to be newly born neurons in the adult mouse brain. **(D)** Voxel-based multiple regression analyses between changes in hippocampal regional cerebral blood flow (rCBF) changes after exercise in old age and changes in hippocampal grey matter density (with 7 T MRI, adapted from Maass *et al.*, 2015b). Sub = subiculum.

allowed more direct contact with the animal physiology of exercise-induced plasticity. Mild-to-moderate exercise over a period of 1 year appears to prevent hippocampal volume atrophy (Erickson *et al.*, 2011). Another study (Maass

et al., 2015c) of older individuals using very high-resolution (0.6 mm isotropic) structural imaging with high field MRI (7 T) did not observe a volume difference between moderate-to-intensive exercisers and controls over a period of 3

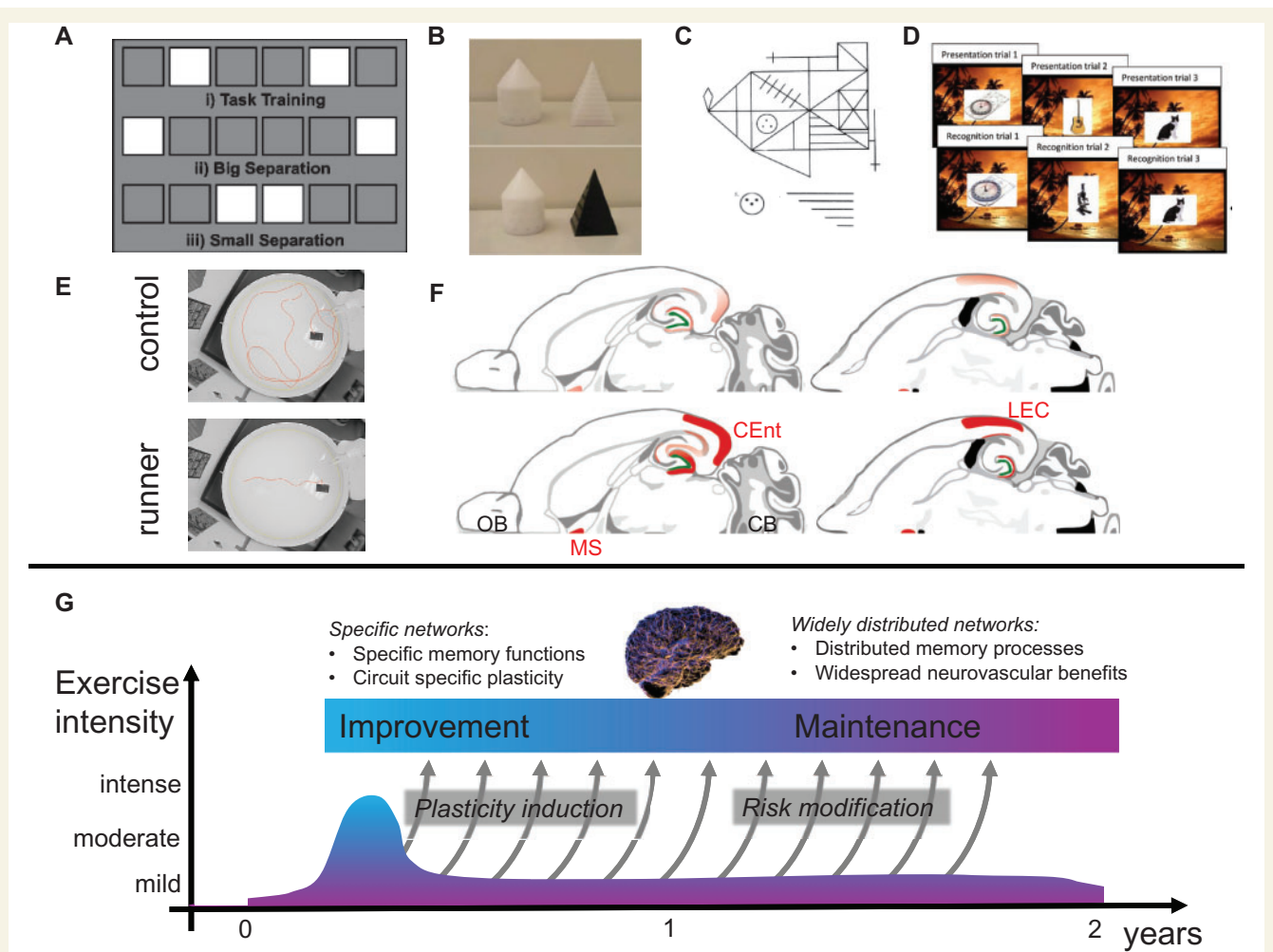


Figure 2 Effects of exercise on spatial memory, pattern separation and hippocampal circuitry. (A–D) Examples of tasks that tap into pattern separation and are influenced by exercise in animals (A, Creer *et al.*, 2010 and B, Bolz *et al.*, 2015) and old (C, Maass *et al.*, 2015c) and young (D, Dery *et al.*, 2015) human adults. (E) Running reduces latency and path-length in the Morris water maze in aged male mice. (F, Vivar *et al.*, 2015) Horizontal sections modified from the mouse brain atlas (Paxinos and Franklin, 2007) under sedentary (*top* sections) and running (*bottom* sections) conditions. Running increased innervation (red) from both caudomedial entorhinal cortex (CEnt) and lateral entorhinal cortex (LEC), proportionate to the increase in adult hippocampal neurogenesis (Vivar *et al.*, 2015). MS = medial septum; OB = olfactory bulb; CB = cerebellum. (G) A hypothetical relationship between exercise duration/intensity and improvement and preservation of cognitive function.

months. However, both studies found that hippocampal volume changes were correlated with cardio-vascular fitness changes and with changes in memory scores. Another study of mild-to-moderate exercise (Ruscheweyh *et al.*, 2011) did not observe fitness-related hippocampal changes after 6 months. A recent meta-analysis of exercise-related white matter changes (white matter volume, lesions, microstructure) as measured with MRI showed that there are modest beneficial effects, which are not consistent across studies (Sexton *et al.*, 2015).

Gadolinium contrast imaging in humans revealed hippocampal perfusion changes after exercise in young (Pereira *et al.*, 2007) and older adults (Maass *et al.*, 2015c). In the older adults, again the exercise group did not show an improvement of perfusion but instead a correlation

between changes in fitness levels and perfusion changes, hippocampal head volumes, and grey matter density (Fig. 1D) within the hippocampus.

It is unclear how exercise-induced changes in levels of growth and neurotrophic factors relate to volumetric and perfusion changes. In a 1-year intervention study (Erickson *et al.*, 2011) changes in serum BDNF were correlated with increases in hippocampal volume (exercise group only) and functional connectivity between the bilateral parahippocampal and bilateral middle temporal gyrus (Voss *et al.*, 2013). Another study showed that aerobic exercise did not elevate serum BDNF levels, whereas exhaustive physical exercise only induced BDNF serum changes that lasted for a few minutes (Berg and Bang, 2004; Rojas Vega *et al.*, 2006). In healthy older humans there was no increase in

the serum concentration of BDNF, VEGF or IGF1 (Box 2) by moderate-to-intensive exercise for 3 months (Maass *et al.*, 2015b) or mild-to-moderate exercise for a year (Voss *et al.*, 2013). One obvious limitation of such studies is that serum sampling pre- and post-intervention may miss the dynamic time course of growth factor upregulation, which, as outlined above, might be fast and transient (Berg and Bang, 2004; Rojas Vega *et al.*, 2006).

The cognitive effects of exercise in animals and humans

Hippocampal–medial temporal lobe memory circuits (Fig. 1) partly segregate modalities such as objects and scenes, and memory processes such as pattern separation and pattern completion (Treves *et al.*, 2008; Yassa and Stark, 2011; Kumaran and McClelland, 2012). Converging evidence suggests that running-induced or transgenic upregulation of adult neurogenesis is associated with improved pattern separation (Creer *et al.*, 2010; Sahay *et al.*, 2011; Bolz *et al.*, 2015) (Fig. 2A–D). Quantitative analysis of afferent innervation of new neurons under running conditions suggests there is a shift in network balance that may benefit pattern separation processes (Vivar *et al.*, 2015). In particular, exercise increased adult neurogenesis more than the expansion of afferent inputs. This may allow for a larger spread of incoming data over individual new neurons, and benefit sparse encoding.

In older humans, memory measures are not consistently improved in randomized controlled trials of physical exercise due to considerable interindividual variability (Erickson *et al.*, 2011; Maass *et al.*, 2015c). However, rather than being random, this variability appears to be linked to neurovascular plasticity. After 3 months of exercise, changes in complex object recognition memory, a task that poses high demands on pattern separation (Fig. 2D), were correlated with changes in fitness levels, gadolinium-contrast magnetic resonance–perfusion in the hippocampus and hippocampal head volumes (Maass *et al.*, 2015c). Another study in healthy older adults that did not assess pattern separation (Erickson *et al.*, 2011) found that changes in fitness and hippocampal volumes were correlated with performance in a short-delay spatial working memory task.

Preclinical Alzheimer's disease

A substantial proportion of older adults who perform normally on standard neuropsychological assessments of dementia show Alzheimer's disease pathology and this is referred to as the preclinical phase of Alzheimer's disease (Reiman *et al.*, 2016). Preclinical cerebral tau deposition

starts in the transentorhinal cortex (Fig. 1A and B) and propagates to the dentate gyrus, CA1 and other medial temporal lobe regions (Gallagher and Koh, 2011; Braak and Del Tredici, 2015) although there is a controversy as to whether this pathology is part of a normal ageing process (Duyckaerts *et al.*, 2015; Jellinger *et al.*, 2015). Preclinical amyloid deposition is primarily found in extra-medial temporal lobe regions such as the retrosplenial region (Buckner *et al.*, 2005; Bateman *et al.*, 2012).

There is some evidence that physical activity levels may modify disease pathology in preclinical Alzheimer's disease. Mouse models suggest that exercise may improve degradation and clearance of amyloid- β (Adlard *et al.*, 2005). In humans, habitual physical activity levels, as measured by self-report questionnaires, are associated with lower brain amyloid load (Brown *et al.*, 2013; Wirth *et al.*, 2014) lower insulin, triglyceride, amyloid- $\beta_{1-42/1-40}$ levels (Brown *et al.*, 2013), and higher brain glucose metabolism, immediate recall and visuospatial ability (Vidoni *et al.*, 2012; Okonkwo *et al.*, 2014). Equally important is the possibility that preclinical Alzheimer's disease pathology modifies the effects of exercise. Amyloid- β deposition may lead to insulin resistance in the brain and therefore cause metabolic dysfunction (Bomfim *et al.*, 2012).

Aside from these direct interactions, exercise also has the potential to influence the modifiable risk factors for Alzheimer's disease (Norton *et al.*, 2014; Cooper *et al.*, 2015), such as insulin-resistance (Yarchoan and Arnold, 2014). Insulin-resistance in middle-aged to older adults is associated with reduced glucose metabolism in the medial temporal lobe and this association is even stronger than with APOE4 status (Willette *et al.*, 2015), which is a risk factor for Alzheimer's disease and also associated with reduced brain glucose metabolism (Jagust *et al.*, 2012). Exercise can improve insulin sensitivity (Lucas *et al.*, 2015) and could thereby potentially contribute indirectly to improving memory function.

Can the effects of exercise be enhanced?

One possibility to enhance efficacy is to combine physical activity with cognitive stimulation (i.e. Anderson-Hanley *et al.*, 2012; Barnes *et al.*, 2013). Just like exercise (Erickson *et al.*, 2011), spatial navigation training in old age can prevent the hippocampus from shrinkage (Lovden *et al.*, 2012) and also has a modest preserving effect on the retrosplenial region (Wenger *et al.*, 2012). A combination of exercise and cognitive enrichment in mice increases protective effects against synaptotoxicity of amyloid- β protein in the hippocampus (Li *et al.*, 2013).

Pharmacological and dietary enhancements are other possibilities. The dietary flavanol epicatechin may enhance effects of running on retention of spatial memory in young rodents (van Praag, 2009) and may protect against

Alzheimer's disease (Cox *et al.*, 2015). Three months intake of a high flavanol drink in older humans enhanced reaction times in pattern separation but was independent of exercise (Brickman *et al.*, 2014). The flavanol epicatechin also has anxiolytic properties in rodents (Stringer *et al.*, 2015). Exercise has antidepressant effects (Ernst *et al.*, 2006; Ota and Duman, 2013) but serotonergic antidepressants do not seem to enhance the efficacy of exercise interventions in a mouse model of Alzheimer's disease (Marlatt *et al.*, 2013). Another possibility is that the administration of 'exercise-mimetics' that activate energy metabolism pathways in muscle affect brain function (Box 2). Furthermore, the importance of glucose metabolism in ageing and dementia (Wirth *et al.*, 2014) and the empirical observation that the insulin sensitizer pioglitazone is protective against Alzheimer's disease (Heneka *et al.*, 2015) raises the possibility that a combination of exercise and insulin sensitization may be effective (Yarchoan and Arnold, 2014). This approach may be particularly relevant for older adults with metabolic syndrome, a major risk factor for Alzheimer's disease (Norton *et al.*, 2014). More fundamentally, future studies will need to address the question whether exercise interventions should complement disease-modifying treatments of preclinical Alzheimer's disease which target amyloid (Sperling *et al.*, 2014) or, in future, tau deposition.

Interindividual variability: side effects and intermediate outcome markers

A number of vascular risk factors could compromise vascular plasticity after exercise, including metabolic syndrome, insulin resistance, hypertension, dyslipidaemia and recurrent strokes (Iadecola, 2013). Arteriogenesis and angiogenesis are stimulated not only by growth factors (i.e. VEGF) but also by mechanical factors such as fluid shear stress, which can be compromised by arteriosclerosis, and cerebral amyloid angiopathy (Charidimou *et al.*, 2012; Iadecola, 2013; Schmidt *et al.*, 2013). These factors can also limit adequate perfusion of the hippocampus during acute exercise (Schmidt *et al.*, 2013). In the Maass *et al.* (2015c) study reduced perfusion after exercise was observed in some individuals (particularly those older than 70) despite the fact that vascular risk factors were excluded. Indeed, more subtle factors could also compromise vascular plasticity. For instance, in ageing and MCI, leakage of gadolinium-contrast agent into CA1 and dentate gyrus suggests damage to the hippocampal blood–brain barrier that may be caused by pericyte injury (Iadecola, 2015; Montagne *et al.*, 2015). Finally, stress can suppress adult neurogenesis in animal models (Opendak and Gould, 2015), and elevated cortisol has a negative effect on verbal recall in old age (Maass *et al.*, 2015c). However, in one study, cortisol levels were unrelated to the vascular and

cognitive benefits of exercise in old age (Maass *et al.*, 2015c).

Until the sources of outcome variability (Freund *et al.*, 2013) are better understood, individuals at risk for adverse effects can be identified and criteria for either terminating or adapting intensity (Box 1) are developed, it seems premature to unrestrictedly prescribe moderate-to-intensive exercise interventions in old age. Moderate-to-intense exercise may have detrimental effects particularly in the presence of cerebrovascular and metabolic risk factors (Lucas *et al.*, 2015) when there is increased risk for Alzheimer's disease (Schmidt *et al.*, 2013; Norton *et al.*, 2014). Empirical data from the 'million women' study indicate that moderate activity was associated with lower risks for cerebrovascular events (haemorrhagic and ischaemic) than strenuous physical activity (Armstrong *et al.*, 2015).

Genetic factors may be another source of variability (Podewils *et al.*, 2005) pertaining to risk genes for Alzheimer's disease such as *APOE4* (Brown *et al.*, 2013; Jansen *et al.*, 2015) and genes that modify plasticity such as *BDNF* (Egan *et al.*, 2003; Rauskolb *et al.*, 2010). In a self-report study of habitual physical activity, *APOE4* carrying older adults in the highest tertile of physical activity had lower brain amyloid burden than those in the lowest exercise tertile (Brown *et al.*, 2013) while in non-carriers there was no difference.

Future outlook

It is now feasible to study the impact of exercise interventions on various aspects of vascular plasticity, connectivity, amyloid load, glucose metabolism and linking these effects to circuit-specific cognitive functions (Box 1 and Fig. 1B). Advances in brain imaging also allow investigating the effects of exercise on the function and structure of entorhinal cortex subregions (Maass *et al.*, 2014, 2015a).

In reviewing and discussing the effects of exercise, we see the need to highlight a distinction between preservation (or maintenance) and improvement of function (Box 1 and Fig. 2G). Improvement of function refers to plasticity in specific memory circuits (i.e. the dentate gyrus and entorhinal cortex) along with increased hippocampal perfusion and volume. Preservation, on the other hand, refers to the possibility that exercise interventions, particularly if they are prolonged, modify risk factors for cognitive decline and Alzheimer's disease, such as metabolic and vascular risk factors and amyloid deposition.

Although we do not yet understand the time courses of plasticity and risk modification this distinction may improve the selection of outcome measures in exercise interventions and thereby the consistency of results. Clinical outcome measures such as ADAS-Cog (for an overview see Andrieu *et al.*, 2015) tax widely distributed neural networks and may be suited in prevention trials aimed at preserving brain function. In contrast, they are likely to

Box 1 Preserving and improving brain function

Several studies provided cross-sectional support for the long-term preserving benefits of a physically lifestyle for the ageing brain (Colcombe et al., 2003; Erickson and Kramer, 2009; Honea et al., 2009; Flöel et al., 2010; Bugg and Head, 2011; Ho et al., 2011; Weinstein et al., 2012; Benedict et al., 2013).

• What is the optimal exercise regime?

Preliminary data in humans and evidence from animal studies suggest that improving brain function would require 3–6 months of moderate to high intensity training. In contrast, preservation of function can be best demonstrated with prolonged regimes where mild-to-moderate levels are more practical. A combination of both approaches seems feasible but has not yet been tested.

	Exercise regime	Duration
Preserving function	Mild-to-moderate intensity, 50–70% of max. cardiac output, $\geq 3 \times$ weeks, 30–40-min sessions (Erickson et al., 2011)	≥ 12 months
Improving function	Moderate-to-high $> 75\%$ of max. cardiac output, $\geq 3 \times$ weeks, 30–40-min sessions with high intensity intervals of 4×5 min (Maass et al., 2015c)	3 to 6 months
Combined approach	Long-term mild-to-moderate intensity training with brief intervals (for instance 1 week every 4 weeks) of moderate-to-high intensity	≥ 12 months

• What are the optimal cognitive outcome markers?

It is unclear to what extent the memory effects of exercise in old age depend on modality (verbal, objects, spatial), retrieval demands (recall versus recognition) and delay (early versus late) and to what extent tests of spatial navigation are sensitive (analogous to spatial navigation in rodents; Fig. 2). Systematic comparisons of memory tasks that tap into pattern separation and pattern completion have not yet been conducted. The consequences on cognitive performance would be important; whereas pattern separation would improve the accuracy and precision of visual memory particularly in tests of recognition memory and visual discrimination, pattern completion would improve tests of recollection and recall. The following patterns of cognitive outcomes can be hypothesized:

Improving function in moderate-to-high intensity interventions:

- (i) Induction of circuit-specific plasticity improves circuit-specific memory processes such as pattern separation.
- (ii) Improving insulin resistance and thereby brain glucose metabolism improves function of different circuits and can therefore affect memory tasks that rely on distributed networks such as verbal delayed recall

Preserving function in prolonged mild-to-moderate intensity intervention:

- (i) Modifying risk factors of cognitive decline helps preserving brain function and this is associated with stable maintenance of memory tasks that rely on distributed networks

• Intermediate outcomes measures to detect adverse effects

For a timely identification of adverse effects of moderate-to-intensive exercise (drop in memory performance, drop in hippocampal perfusion) it seems necessary to use intermediate (i.e. 1–3 months) outcome markers, such as cognitive tests (i.e. those that tap into pattern separation) and non-invasive magnetic resonance-based perfusion measures such as arterial spin labelling (ASL). Perfusion measures immediately after acute exercise may yield information about vascular reactivity (Lucas et al., 2015). In one study (Ruscheweyh et al., 2011), a substantial proportion of older adults showed cortical volume loss after 6 months of moderate exercise training despite of a positive correlation between fitness change and volume. The inconsistent findings for growth factor levels suggest that they may not be reliable to monitor efficacy. In individuals who react adversely to moderate-to-intensive exercise it could be advisable to focus on preservation of function and continue with mild exercise in combination with other lifestyle modifications such as dietary and cognitive interventions (Ngandu et al., 2015).

• Recommended intensity of exercise in old age

The World Health Organization (WHO, 2012) recommends vigorous exercise levels in old age (75 min per week) that are similar to those levels with which some older adults show hippocampal perfusion and volume decreases (Maass et al., 2014). With the advance of neuroimaging methodology, it seems necessary to accumulate more data on potential physiological side effects of exercise on brain structure and function and adjust these recommendations accordingly.

• Standardizing randomized controlled proof-of-concept exercise trials

Prescription of exercise interventions in individuals at risk of cognitive decline will require a better understanding of the efficacy and risk profiles of different exercise regimes. To achieve this, it seems important that the field agrees on standardized core protocols for imaging, cognition and biomarker sampling. For instance, the Rey-Complex Figure recall and recognition test (Fig. 2) has been used in both cross-sectional (indexing preservation) (Brown et al., 2012) and interventional (Maass et al., 2014; 2015a) studies.

provide negative results in brief exercise interventions where the primary goal is to induce plasticity.

As adult neurogenesis declines with ageing (Seki and Arai, 1995) and mobility may be hampered by frailty, it

is important to explore the possibility of pharmacologically enhancing or substituting the effects of exercise (Box 2). Of equal importance is a better understanding of side effects of exercise, which may not be necessarily predicted by the

Box 2 The role of the muscle–brain axis

Substantial knowledge has been accumulated about the changes that exercise evokes in the brain in rodents and humans. However, the systemic, metabolic peripheral triggers that elicit these brain processes are virtually unknown. Recent research indicates that blood-borne systemic factors from young animals can counteract the age-related decline of adult neurogenesis and brain function (Villeda *et al.*, 2014). On activation by exercise, skeletal muscle may release such factors into the circulation to communicate with the brain. In addition, pharmacological activation and transgenic overexpression of muscle energy metabolism pathways can to some extent mimic effects of exercise on the brain (Kobilo *et al.*, 2011; Wrann *et al.*, 2013; Agudelo *et al.*, 2014; Moon and van Praag, 2014; Sleiman and Chao, 2015). As not everyone can exercise due to disease circumstances, or ageing senescence-related frailty, identification of peripheral factors and mechanisms that elicit the effects of exercise on the brain may lead to therapeutics that maintain and improve cognition.

• IGF1 (a Janus-faced molecule)

Growth factors in the periphery and brain have been closely linked to neural plasticity. These include the neurotrophin family (Dekkers *et al.*, 2013; Park and Poo, 2013), with brain-derived neurotrophic factor (BDNF), the neurocytokine family with ciliary neurotrophic factor (CNTF) and leukaemia inhibitory factor (LIF) (Sendtner, 2014) as well as pluripotent growth factors such as insulin-like growth factor I (IGF1) and the vascular endothelial growth factor (VEGF) family, hypoxia-inducible proteins promoting the formation and growth of blood vessels and neurogenesis (Greenberg and Jin, 2005). Reduced levels of IGF1 in the ageing brain have been proposed to contribute to age-associated decline in cognitive functions (Aleman and Torres-Aleman, 2009) and circulating IGF1 levels in healthy older adults show a modest positive correlation with hippocampal volumes and verbal free recall performance (Maass *et al.*, 2015b). During physical exercise, IGF1 levels in skeletal muscle are rapidly upregulated and peak transiently at ~5–10 min of training (Berg and Bang, 2004). Circulating IGF1 can be transported through the blood–brain barrier into the brain (Pardridge, 1993), and increased levels of circulating IGF1 also result in increased IGF1 levels in the brain (Carro *et al.*, 2000).

Plasticity promoting effects

Neutralizing IGF-1 antibodies block the effect of physical exercise on upregulation of hippocampal BDNF expression (Chen and Russo-Neustadt, 2007) and adult neurogenesis (Trejo *et al.*, 2001) in rodents. However, other mechanisms than IGF1 such as altered blood flow could also contribute to this effect (Davila *et al.*, 2007). In aged rodents, circulating IGF1 levels decrease (Breese *et al.*, 1991; Niblock *et al.*, 1998). In humans, basal circulating levels of IGF1 are lower in older individuals with high fitness than in those with lower fitness, but the transient IGF1 increases after exercise rise to significant levels only in those individuals with higher levels of fitness (Amir *et al.*, 2007). Nevertheless, progressive muscle training in aged humans has a significant effect on IGF1 upregulation in muscle that corresponds to musculoskeletal remodeling (Singh *et al.*, 1999).

Negative effects

IGF1 also seems to play a role in metabolism related to protein toxicity, and depletion of IGF1 apparently has a protective role (Cohen *et al.*, 2009; Gontier *et al.*, 2015) in mouse models of Alzheimer's disease. These data suggest that IGF1 cannot simply be considered as a mediator of neuroprotective effects of physical exercise on brain function. In fact, lower levels of IGF1 convey longevity (Longo *et al.*, 2015). Thus future studies have to define the conditions under which IGF1 can mediate neuroprotective effects of physical exercise or prevent acceleration of neurodegeneration during ageing.

• Are there exercise-mimetics?

Muscle energy metabolism is regulated by AMP-Kinase (Hardie, 2004). AMPK lies at the core of complex interconnected energy-sensing networks that include many other transcriptional co-activators such as peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1 α and sirtuin 1). This network is activated by a decrease in the ATP/AMP ratio within cells and increases catabolism, while reducing anabolic processes. Interestingly, over-expression of PGC-1 α in mouse muscle affects the kynurenine pathway and protects these mice from stress induced reduction of synaptic plasticity proteins in the brain, as well as from exhibiting depression-like behaviors (Agudelo *et al.*, 2014). Overexpression of PGC-1 α in muscle also has been reported to lead to increased production of Fibronectin type III domain containing 5 (FNDC5), a myokine that is released during exercise. Enzymatic cleavage of FNDC5 generates a peptide called irisin, which may enter the brain and induce hippocampal BDNF gene expression, and that is upregulated by an exercise intervention in humans (Wrann *et al.*, 2013; Sleiman and Chao, 2015; Wrann, 2015). Support for the idea that muscle energy metabolism affects brain function (Kobilo *et al.*, 2011) comes from studies showing that pharmacological activation of AMPK with the agonist 5-aminoimidazole-4-carboxamide 1- β -D-ribofuranoside (AICAR) can mimic effects of exercise on endurance (Narkar *et al.*, 2008), cognition, adult neurogenesis and hippocampal BDNF levels (Kobilo *et al.*, 2011; Guerrieri and van Praag, 2015). It is important to note that the beneficial effects of AICAR on the brain depend on the duration of administration (Kobilo *et al.*, 2011). Prolonged treatment (2 weeks) resulted in increased hippocampal and cortical expression of apoptotic genes, elevated markers of oxidative stress and inflammation (Guerrieri and van Praag, 2015), suggesting it may prove challenging to design pharmacological interventions that mimic exercise and are safe for humans.

presence of vascular risk factors. A concerted effort in which clinical prevention trials are complemented by trials designed to induce plasticity may offer the fastest way towards an optimal utilization and prescription of exercise interventions in old age and preclinical Alzheimer's disease, both as stand-alone intervention and as an add-on strategy to disease modification and prevention. To facilitate this research, there is an urgent need for the field to adjust and standardize protocols and outcome measures (Box 1).

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