Chapter 166

Optimizing cognition in older adults: lifestyle factors, neuroplasticity, cognitive reserve.

Nicoletta Berardi[1,2], Alessandro Sale[2], Lamberto Maffei[2,3]

(1) Florence University, Department of Neuroscience, Psychology, Drug Research, Child Health (NEUROFARBA), Florence; (2) Institute of Neuroscience CNR, Pisa; (3) Scuola Normale Superiore, Pisa, ITALY

Key words: cognitive decline; cognitive activity; exercise; learning and memory; enriched environment; synaptic plasticity; hippocampal neurogenesis;

Abstract: Cognitive decline with age shows strong interindividual variance. Several epidemiological studies have shown that some of the factors associated with maintaining a good cognitive performance with age are lifestyle factors, such as practicing physical activity and being engaged in cognively stimulating activities, which are potentially modifiable even in old age. In parallel, studies in animal models have shown that physical exercise and environmental stimulation result in better cognitive performance, potentiation of neural plasticity, neuroprotection. More recently, intervention studies in humans begin to show that training based on cognitive or physical activity enhance cognitive performance in older adults. At the core of lifestyle effects on cognitive aging is neural plasticity and the action of multiple molecular factors which translate physical and cognitive activity into adaptive and protective changes in the brain, allowing elders to better face aging related cognitive changes.

Introduction

Aging is a physiological condition, characterized by multiple changes in the environment and in sensory, motor and cognitive functions. There is considerable variance in the degree of cognitive decline associated with non pathological aging, with some individuals maintaining strikingly effective intellectual abilities even beyond their nineties. While some of the factors associated with graceful aging seem to be linked to the individual genetic endowment or to aspects of childhood and youth experience, such as education, others are linked to chronic disease states and lifestyle factors. These include nutritional intake, smoking status, physical activity and being engaged in cognively stimulating activities. Importantly, many of these factors and even chronic disease status could be modifiable even in middle or old age to promote a successful aging. According to Norton et al., (2014), a third of Alzheimer's disease cases worldwide are estimated to be attributable to seven modifiable factors (**see Table 1**), some of which could be modified even in mid and late life. In this chapter we shall outline the human and animal literature which has provided evidence for the effects and mechanisms of action of lifestyle protective factors on age related cognitive decline and on age-related neurodegenerative dementia, concentrating on physical activity and cognitive activity, and the paradigm of Enriched Environment. We will also describe the core lifestyle effects on cognitive aging, including neural plasticity and the action of multiple molecular factors, which translate physical and cognitive activity into adaptive and protective changes in the brain.

Cognitive aging and neural plasticity

Neural plasticity is the capacity of neurons and of neural circuits to change, structurally and functionally, in response to experience. This property is fundamental for brain development, for the flexibility of our behavior, for learning new information and skills, for remembering the past and for brain repair. Within neural circuits, experience is translated in patterns of electrical activity, which drive the different forms of functional and structural plasticity through the spatially and temporally coordinated action of specific cellular and molecular factors. Synaptic plasticity is the major component of neural plasticity, and may involve changes in the efficacy of already existing synaptic contacts, formation of new synaptic contacts or elimination of existing ones. Moreover, neural plasticity includes production of new neurons in the hippocampus.

When we learn, synaptic efficacy changes take place in neural structures within the memory system specific for that form of learning and memory, such as sensory cortices for perceptual learning and hippocampus for spatial memory. The steps leading to the formation of long term memories involve forms of long term synaptic plasticity such as Long Term Potentiation (LTP) and Long Term Depression (LTD). Induction, consolidation and maintenance of LTP and LTD rely on

the coordination of multiple plasticity factors, including glutamate NMDA receptors, intracellular signalling pathways and transcription factors, such as ERK and CREB, epigenetic factors, such as histone acetylation, neurotrophic factors such as BDNF, and neuromodulators such as acetylcholine, noradrenaline, dopamine. For declarative memories, memories for facts and episodes, after the initial formation and consolidation in the hippocampus, memory traces are transferred/copied to neocortical structures, thus involving cortical synaptic plasticity factors. Alterations in synaptic plasticity mechanisms impair learning and memory processes (Mayford et al., 2012). Also, hippocampal neurogenesis, present in the Dentate Gyrus (DG) of the adult hippocampus (Spalding et al., 2013) is important for learning and memory. Newly generated neurons integrate with local circuits, receiving and establishing synaptic contacts, and are particularly susceptible to synaptic plasticity. Hippocampal neurogenesis seems to contribute to DG role in pattern separation, separating and differentiating between overlapping contextual representations (see Aimone et al., 2014).

Cognitive aging

Age-related cognitive decline in humans is much greater for some tasks than for others (Park and Reuter, 2009). Decrements are typically slight in implicit memory tasks or verbal ability, while age-related losses are substantial in tasks of declarative memory, particularly spatial and episodic memory tasks, requiring recollection of the original spatial and temporal context in which an event occurred. These tasks involve the hippocampus and other medial temporal lobe (MTL) structures. Also performance in processing speed, inhibitory functions and working memory tasks, which rely on prefrontal cortex, decline with age (Park and Reuter Lorenz, 2009). Similarly, animal models of aging show a decline in memory tasks dependent on MTL and prefrontal cortex (Burke and Barnes 2006).

Several papers have investigated the alterations in MTL and prefrontal cortex accompaniyng normal aging and have discussed how these age-associated alterations might contribute to the selective cognitive impairments occurring with advancing age (Burke and Barnes, 2006; Park and Reuter Lorenz 2009; Holden and Gilbert, 2012). Many of these studies point out that age-related changes in cognition cannot be accounted for by a generalized loss of neurons. With the exception of neurons from the monoamine cell groups in the midbrain and basal forebrain and of some areas of dorsolateral prefrontal cortex, significant reduction of cell number in the brain is not typical of normal aging; rather, specific changes in neuronal physiology and synaptic function, density and plasticity are found (see Burke and Barnes, 2006). Different brain regions and subregsions are

differentially affected by normal and pathological aging. This is evident at the level of the hippocampus, where DG is particularly affected by the aging process (Small et al., 2011).

Aging and neural plasticity

Normal aging causes evident changes in neural plasticity, such as in hippocampal LTP maintenance (Burke and Barnes, 2006). Since LTP maintenance requires gene transcription, it is not surprising that these processes are altered in aged animals: region specific gene expression changes in the course of normal brain aging have been documented also in humans, with gender differences (Burke and Barnes, 2006; Berchtold et al., 2008). In particular Berchtold et al found that the sixth to seventh decades were a period of robust gene changes across cortical regions, suggesting that this period is a critical transition point in brain aging, particularly in males. Down-regulated genes in the male brain showed a broad enrichment of energy-related categories, which was not seen in the female brain, where down-regulated genes showed unique enrichment in categories of neuronal morphogenesis, intracellular signaling and signal transduction. On the contrary, genes showing increased expression with age across the brain were of similar categories in both sexes; in particular, inflammation and immune function genes emerged as the top enriched category for both sexes (Berchtold et al., 2006)

Studies detailing how aging might affect gene expression via epigenetic mechanisms and e causal linkage to age related memory impairment have been published. Peleg et al. (2010) found that at age 16 months (roughly 50 human years), mice exhibit clear deficits in hippocampus dependent memory, and there is a lack of the learning induced initiation of the hippocampal gene expression program and memory consolidation compared to younger mice. This failure of starting the experience-dependent gene expression pattern necessary for consolidation is due to a specific failure of epigenetic control over gene transcription. Specifically, there is a lack of learning induced histone acetylation, which prevents learning induced gene transcription. Pharmacologically enhancing histone acetylation restores learning induced plasticity gene expression and promotes memory consolidation, rescueing the memory impairments.

Aging also reduces hippocampal neurogenesis across several species (Kempermann, Gast and Gage 2002). In humans, direct evidence for reduced neurogenesis in aging has been provided by Spalding et al., (2013), which estimate a more modest 4-fold age related decline in humans comparaed to the nearly 10-fold decrease between young and middle-aged mice in neurogenesis. Reduced neurogenesis might contribute to hippocampal atrophy and to deficits in pattern separation with aging.

Compensatory plasticity in aging

In parallel to diminished neural plasticity, there are several examples of what can be considered compensatory plasticity during the aging process. This shows up mostly in terms of a larger and more elaborate pattern of activation of brain areas, and in particular of the prefrontal cortex, in aged with respect to young subjects performing the same task; interestingly, this more extensive activation correlates with better performance in the elders (Park and Reuter-Lorenz 2009). Cabeza et al. (2002) studied prefrontal cortex activation during recall and source memory of recently studied words in younger adults, low-performing older adults, and high-performing older adults and found that only old subjects with a good performance showed additional activity in the left prefrontal cortex with respect to young subjects; old subjects with poor performance did not.

Lifestyle effects on cognitive decline and dementia in aging: epidemiological studies

On the basis of epidemiological studies in humans, risk and protective factors for major cognitive decline and for developing dementia with age have been pointed out, which include genetic factors, such as the presence of the apolipoprotein E ε4 allele (APOE4), and environmentally influenced/lifestyle factors, such as: education, diet, diabetes mellitus, hypertension, obesity, being engaged in cognitively stimulating and social activities and practicing physical exercise (e.g. Fratiglioni et al., 2004; Norton et al., 2014; Wang et al., 2015) .

Data from observational studies exploring the association between elevated levels of blood pressure in midlife and late-life cognitive impairment have proved to be relatively consistent across cohorts; also cerebrovascular disease increases the risk of dementia (see Reitz et al., 2011). Transition from healthy aging to cognitive impairment to AD seems to be accompanied by a complex pattern of changes in the pattern of Cerebral Blood Flow (CBF). Diminished CBF reduces brain supply of oxygen, energy substrates and nutrients, impairs the clearance of neurotoxic molecules, and contributes to neuronal dysfunction found in neurodegenerative disorders. It has been suggested that reduced CBF might directly contribute to brain beta-amyloidosis (Zlokovitch, 2011). Epidemiological studies have also shown that diabetes mellitus (DM) nearly doubles the risk of AD and that midlife central obesity does the same by nearly 60% (see Reitz et al., 2011; Norton et al., 2014). These factors interact with each other: for instance, in a 2 years prospective study in cognitively unimpaired middle-age and elders, not only cognitve status deteriorated only in subjects with DM but only in these subjects global and regional cerebral vasoreactivity decreased and inflammatory biomarkers increased (Chung et al., 2015).

Amongst the risk factors, genetic risk factors, to date, cannot be modified. Environmental factors can be modified, and can be targets of interventions, both preventive and ameliorating with respect to age related cognitive decline (see Table 1).

Of these environmental, modifiable life-style factors, some are related to early environment, such as education. It is possibile to intervene on this factor, and, as pointed out in Norton et al (2014), AD incidence might indeed be reduced through improved access to education; however, increased educational attainment over the next few years would apply to a younger generation than those at risk of dementia by 2050. Beneficial effects of improved education access will be evident when the current young generation will become old. On the other hand, other lifestyle risk factors are modifiable even in old age, as introduced in Table 1, and interventions on these factors might yield beneficial effects in those which are now at risk for major cognitive decline and dementia or will be by 2050: if obesity, diabetes mellitus, physical inactivity, hypertension, low cognitive activity are risk factors for dementia and cognitive decline with age, then diet, physical activity, cognitive activity and strategies to control chronic disease and vascular factors should result protective factors. This is indeed what emerges form the literature, with some factors having accumulated particular wealth of data.

Here we shall briefly report the effects of nutrition as protective factor in cognitive aging. We shall then move to discuss in more detail the literature on the effects and mechanisms of action of protective factors cognitive reserve, physical activity and cognitive activity.

Nutrition and cognitive aging

There is a wealth of epidemiological evidence supporting a relationship between diet, age-related cognitive decline and AD, and suggesting that the risk of cognitive decline may be reduced by dietary interventions (e.g. Eskelinen et al., 2011). It has been proposed that adopting a healthy diet and lifestyle that improves cardiovascular function may help delaying AD onset due to its potential association with vascular disease. In addition, diet will impact obesity, another risk factor for cognitive decline and dementia. However, the effects of diet are not simply linked to reduced food intake or reduced cardiovascular risks, but are linked to the effects of specific components of the diet. Several nutrients, dietary components, supplements and dietary patterns have been reported in relation to their association with cognition and with the development of cognitive decline and AD (Dominguez and Barbagallo, 2016). Among the various dietary patterns that were tested for their effects on cognition, the traditional Mediterranean Diet (MeDi) a diet characterized by a high intake of plant foods and fish (with olive oil as the primary source of monounsaturated fat), a moderate

intake of wine and a low intake of red meat and poultry—reduced the incidence of AD and showed a trend towards reducing the risk of major cognitive decline (Safouris et al., 2015)

MeDi seems effective also in cognitively unimpaired subjects. As an example, in asymptomatic subjects at high cardiovascular risk (age 55-80 years) enrolled in the PREDIMED study, a primary prevention dietary-intervention trial, authors found that consumption of some foods was independently related to better cognitive function. Some specific associations were: total olive oil with immediate verbal memory, virgin olive oil and coffee with delayed verbal memory; walnuts with working memory (Valls-Pedret et al., 2012). The effectiveness of MeDi supplemented with olive oil was further shown by Martinez-Lapiscina et al., (2013), again within the PREDIMED project, who found better post-trial cognitive performance versus control (low-fat diet) in all cognitive domains tested.

Nutrition effects extend to include changes in expression of multiple genes, and responses to nutrition are in turn affected by individual genetic variability. Here again, an important component of regulation is provided by the epigenome (see Dauncey et al., 2014). Particularly interesting are Mediterranean diet effects on biomarkers of subclinical inflammation.

The beneficial effects of a MeDi has been confirmed also in non mediterranean countries. A particularly interesting study is that by Crous-Bou et al., (2014), which examined the effects of the diet on a general marker of aging, namely telomere length, within the Nurses' Health Study. The results show that greater adherence to MeDi was associated with longer telomeres, further supporting the benefits of adherence to the MeDi for promoting healthy aging and longevity.

Cognitive reserve

The concept of cognitive reserve has been proposed in order to explain the discrepancy between the degree of brain damage and the extent of clinical manifestations (Stern, 2009). This hypothesis has been supported by studies showing that subjects with a greater cognitive reserve can tolerate a greater extent of brain damage before showing significant cognitive impairment (Stern 2009). Amongst the factors possibly contributing to cognitive reserve formation, education (Katzman 1993) and occupational attainments have been first identified, by epidemiological studies, to provide reserve capacity against the effects of aging and disease on brain function (Stern, 2009) .

Cognitive activity in middle and old age contributes to cognitive reserve

Another group of studies has shown that engaging in a variety of cognitively stimulating leisure activities in middle and old age is also associated with a significant reduction in major

cognitive decline and in dementia. A large meta-analysis in the field points out that for middle and old aged persons, being presently engaged in complex patterns of mental activity results a significant protective factor even after controlling for the effects of past factors (education, occupation, baseline cognition), and for cardiovascular risk factors (Valenzuela and Sachdev 2006, a,b).

A very interesting study (Carlson et al. 2008) examined male twins pairs who differed for dementia diagnosis or for age at dementia onset. The results show that "participation in a range of cognitively and socially engaging activities in midlife reduced risk for dementia and AD in twins discordant for onset, particularly among monozygotic twin pairs at elevated genetic risk".

Higher education, occupational attainment and leisure activities seem to independently contribute to cognitive reserve (Valenzuela and Sachdev, 2006). These findings have been confirmed by Yaffe et al. (2009), who followed the time-course of cognitive status of 2509 healthy elders enrolled in a prospective study for 7 years (Fig. 1). Participants were classified as cognitive maintainers, minor decliners or major decliners according to the slope of the curve describing cognitive score change with time. Characteristics of the cognitive reserve, such as education level, literacy and life style, emerged as significant predictors of being a maintainer vs. a minor decliner. Of particular interest is the study by Paillard-Borg et al. (2012) which, in a 9 years follow-up study, showed that an active lifestyle including mental, physical and social activities delays the onset of clinical condition in old subjects: when the three types of activities are combined to generate a single index, it emerges clearly that the broader the spectrum of participation in the activities, the later the onset of disease.

Beneficial effects of physical exercise on age-related cognitive decline and dementia

It has become evident that also physical exercise can attenuate age-related cognitive changes and deficits and reduce the risk for dementia. Among the earliest studies to investigate this relation are Laurin et al., (2001), Weuve et al. (2004) and Podewils et al. (2005). All these studies pointed out that the higher and more varied physical activity, the lower cognitive decline and dementia incidence.

Positive effects of being physically active on age related cognitive decline were subsequently confirmed in several studies; amongst them, the already mentioned Yaffe et al. (2009) study (Fig. 1), which found that engaging in weekly moderate to vigorous exercise was a significant predictor of being a maintainer vs. a minor decliner; Buchman et al. (2012), who found that a higher level of total daily physical activity was associated with a reduced risk of AD, even after taking into account other protective or risk factors.

Factors mediating the effects of cognitive activity and physical exercise on cognitive decline

How can previous cognitive activity contribute to slow down age related cognitive decline? And more puzzling, how can physical exercise benefit cognition and reduce its decline with age? Animal models, where lifestyle effects on age related decline in cognitive functions and in neuroplasticity have been modeled employing Enriched Environment (EE) paradigms, provides some compelling information. Defined by Rosenzweig as "a combination of complex inanimate and social stimulation", EE consists of wide and attractive cages where the animals are reared in large social groups and in the presence of a variety of objects to stimulate voluntary explorative behavior, curiosity, memory and attentional processes. An essential component of EE procedure is voluntary physical exercise made possible by the presence of one or more running wheels. Thus, EE key components are cognitive activity, physical activity, social interactions.

EE starting from young or adult ages can be used to model the protective effects of cognitive reserve components stemming from early enriched cognitive activity (education) and engaging in satisfactory and rewarding activity, although EE contains a component of physical activity not necessarily present in subjects with a high cognitive reserve linked to education and occupational attaiments. EE starting later in life can be used to model the protective effects of physical and cognitive activities peformed in middle or old age. Although most of the studies have been conducted in aged rodents, EE providew cognitive benefits in other aged mammals (see Sale et al., 2014).

The results of the vast literature on EE effects in aged animals have shown that EE, or its sole physical exercise component, both early-onset and middle or old age onset, improves cognition in aged animals at several levels, from prefrontal cortex dependent working memory to hippocampal dependent spatial memory, and these positive effects have been related to EE/physical exercise increase of hippocampal neurogenesis, synaptic plasticity, neurotrophic factors (BDNF), IGF-1, neurotransmitter systems, epigenetic factors, and, more recently to a decrease of Aβ production/clearance and neuroinflammation (see Sale et al., 2014).

EE enhances neuroplasticity

Both early-onset and old age onset EE rescue age-related changes in plasticity factors crucial for induction, consolidation and maintenance of long term synaptic efficacy changes at hippocampal and cortical level (Sale et al., 2014). A particularly striking effect of EE/physical activity, both early- and late-onset, on aged animal neuroplasticity is the increase of hippocampal

neurogenesis (Kempermann et al., 2010). As in adult, the increase in BDNF caused by EE in aged animals, which counteracts age-related BDNF reduction, seems crucial for EE effects on neurogenesis (see Sale et al., 2014). Considered the lower baseline neurogenesis in old with respect to young animals, EE and physical exercise effects on hippocampal neurogenesis seems stronger in the former that in the latter.

As outlined before, the reduced efficiency in spatial pattern separation resulting from reduced neurogenesis may be a critical deficit contributing to episodic memory impairment associated with aging (Holden and Gilbert 2012). The increase in neurogenesis due to EE could contribute both to reduce the age-related decline in DG volume (Small et al., 2011), and to improve DG function in pattern separation. Interestingly, the effects of exercise and of the cognitive/social component of EE on adult neurogenesis seem to be additive (Fabel et al., 2009): sequentially combining the effects of physical activity and EE resulted more effective than EE or exercise alone in increasing neurogenesis. This is reminiscent of the stronger impact on dementia incidence of the combination of a variety of cognitive and physical activity shown in humans by Paillard Borg et al. 2012. Enhancement of neuroplasticity as a major mechanism underlying cognitive improvement or rescue caused by EE/physical exercise has also been found in animal models of Alzheimer's Disease (AD) (Nithianatharajah and Hannan 2009).

EE reduces brain Aβ contents

It has been shown that amongst the earliest effects of Aβ there is an impairment of neural plasticity: a reduction of brain Aβ would benefit cognition via an enhancement of neuroplasticity and would also possibly impact on the road towards AD (Shankar et al., 2008). The first studies concerning EE/physical exercise effects on Aβ brain contents were performed in mouse models of AD (Nithianatharajah and Hannan 2009), most studies employing protocols of EE starting before the onset of cognitive deficits. For instance, Lazarov et al. (2005) found pronounced reductions in hippocampal and cortical Aβ levels and amyloid deposits in EE mice, paralleled by an increase in the activity of an Aβ degrading enzyme, neprilysin. Berardi et al. (2007) found that EE starting from young adult age prevented the onset of memory deficits, reduced the presence of Aβ burden and rescued the cholinergic deficit. This study also addressed the long-term effects of EE exposure: beneficial effects of EE were still evident five months later, when animals had entered old age.

More recently, EE effects on Aβ are being investigated in animal models of physiological aging. Mainardi et al., 2014 analyzed the functional consequences of EE on molecular markers of neural plasticity and on the levels of soluble Aβ oligomers in aged mice, finding that EE enhanced

plasticity by an upward shift of the cortical excitation/inhibition balance, reduced brain Aβ oligomers and increased synthesis of the Aβ-degrading enzyme neprilysin.

These results point out to a strong effect of EE on Aβ processing, which could be due to alterations in Aβ production and degradation in enriched animals and to the increase of Aβ clearance from the brain.

An effect of lifestyle factors on Aβ is also suggested by a human epidemiological study. Landau et al. (2012) assessed whether the level of cognitive and physical exercise was associated with the extent of Aβ deposition in healthy elders; Aβ burden was determined using the 11–labeled Pittsburgh Compound B and positron emission tomography. The subjects were followed for 6 years. The results showed that lower Aβ burden was found in subjects more engaged in cognitively stimulating activities, particularly during early and middle life. Thus, there seems to be a direct correlation between cognitive activity and Aβ burden, suggesting that lifestyle factors might prevent or slow down Aβ deposition.

A recent finding in animal models of AD, which has been shown also in human patients, is that age-related cognitive impairments correlate with the presence of diffuse, low-weight Aβ oligomers, which are sufficient to impair synaptic plasticity and memory performance also when acutely administered to young normal animals (see Shankar et al., 2008), and are currently hypothesized to be the first pathogenic agents in AD. It has been shown (Li et al., 2013) that early exposure to EE completely prevented Aβ soluble oligomers extracted from human AD patient cortex from damaging hippocampal synaptic plasticity in young normal animals. Thus, lifestyle factors could not only reduce Aβ in the aged brain, but also make age-vulnerable brain structures, such as the hippocampus, resilient to Aβ negative effects.

Effects of interventions based on physical exercise and cognitive activity on cognitive decline with age

Given the results outlined above, it is not surprising that the last few years have seen an increasing number of studies devoted to assess the effects of cognitive activity and physical exercise on age-related decline via intervention approaches. In this case, each subject is its own control and randomized trial with a control arm can be designed. The first studies which have followed this approach have been reviewed in Kramer and Erikson, 2007, where small groups of subjects underwent physical training consisting of controlled aerobic physical exercise for a few months. Cognitive performance was assessed before and after the training and in some cases was correlated with cortical activation, evaluated with fMRI. The results indicate that cognitive performance was

ameliorated in those subjects who performed aerobic training, in good correlation with the level of cardiovascular fitness and the pattern of brain activation. A Cochrane comprehensive survey (Angevaren et al., 2008) specifically reviewed the evidence that aerobic fitness is necessary for improved cognitive function and concluded that "aerobic physical activities which improve cardiorespiratory fitness are beneficial for cognitive function in healthy older adults".

In a randomized controlled trial in cognitively normal older adults, Erickson et al. (2011) showed that aerobic exercise training leads to improvements in spatial memory and is accompanied by a 2% increase in anterior hippocampal volume, which reverses age-related volume loss (Fig. 2). Caudate nucleus and thalamus volumes were unaffected by the intervention, showing that exercise effects are structure specific. They also demonstrated that increased hippocampal volume is associated with greater serum levels of BDNF. As we have seen, BDNF is a mediator of neurogenesis in the hippocampal dentate gyrus in response to physical exercise and EE.

The effectiveness of cognitive intervention on cognitive aging was reviewed in 2009 by Valenzuela and Sachdev who found only 7 studies qualifying as randomized control trials. The conclusion was that, despite the low quality of these trials, there was evidence for beneficial effects of cognitive training on healthy older adults' cognitive status. One notable study by Owen et al (2010) on cognitive training, tested the effects of computerized brain trainers. The results indicate that training did improve performance in every cognitive task in which subjects practiced, but "no evidence was found for transfer effects to untrained tasks, even when those tasks were cognitively closely related". This underlines the importance of testing cognitive improvement with standardized neuropsychological batteries and not in terms of improvement in the practiced tasks and also emphasises the unique nature of EE as a "multidomain training" not restricted to a single modality, process, or function. A very important study by Ngandu et al., 2015 (FINGER study) provides further rationale for this. More than 1250 elders, with cognition in the mean level for age, were randomized to a 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control. Findings show that global cognitive status, executive functions and processing speed improved more in the intervention than in the control group, suggesting that a multidomain intervention could indeed improve or maintain cognitive functioning.

Physical exercise or cognitive training based interventions in MCI or AD subjects.

The effects of cognitive and physical training, on elders with Mild Cognitive Impairment (MCI) subjects or subjects with AD are being investigated. MCI affects a vast number of people characterized by objective deficits in one single domain (e.g. memory) or multiple domains of

cognition, which do not yet configure as overt dementia (e.g Petersen 2004). The rate of yearly progression to dementia of MCI subjects is much higher than in non-MCI elderly: in particular, the amnestic subtype of MCI (aMCI) may represent a prodromal form of AD (Sperling et al., 2013).

Baker et al. (2009) investigated the effects of a 6 month program of aerobic exercise in thirty-three adults with aMCI ranging in age from 55 to 85 years. They found gender specific effects on cognition, with older women benefiting on a larger number of executive function tests than men, which had a limited benefit. In addition, physical exercise interventions has been shown to modulate the effects of diet on Aβ cerebrospinal fluid levels in MCI subjects: a healthy diet produced the strongest effects on Aβ when paired with physical exercise (Baker et al., 2012). Exercise and diet may thus interact in modifying the risk of AD. This underlines again the possibility that factors such as physical exercise, cognitive activity and other lifestyle factors might be additive in reducing the risk of severe cognitive decline and dementia.

Indeed, Gates and Sachdev, 2014, concluded that although the number of randomized controlled trials are limited, evidence suggests that cognitive training may provide immediate and longer term cognitive benefits which generalize to non-trained domains and non-cognitive functions, with supervised small group multi-domain training providing greatest benefits. Ohman et al., 2014, reviewed intervention studies based on physical training. While studies in MCI subjects were of moderate quality, most of the studies in AD subjects were found to be of poor quality. Cognitive improvement in MCI subjects were found in 3 out of five studies, and the pooled effect size was small. Taken in sum, this evidence provides strong rationale for the further development of the combination of physical and cognitive training interventions to attenuate cognitive decline and slow disease progession in the preclinical stage of dementia. A randomized trial on the effects of a combined physical and cognitive training on cognitive decline, brain volume and function in MCI subjects has been performed in Italy, (Train the Brain project). Over the 7 months of the intervention, global cognition in trained subjects significantly improved, while in control subjects significantly declined. Fiatarone-Singh et al (2014) found improved cognitive status following combined physical-cognitive intervention in MCI.

Conclusions

In summary, the current literature suggests a profound impact of lifestyle on physiological and pathological aging processes. A physically, cognitively and socially active lifestyle might be one of the keys to prevent major cognitive decline with age and to reduce dementia incidence. We would like to emphasize that physical exercise or cognitive exercise ability to impact on age related cognitive decline is likely mediated by their action on multiple molecular and cellular factors which

promote and sustain neuroplasticity. A few molecular pathways stand out as particularly important mediators of EE effects on aged brain plasticity, namely, BDNF, IGF-I, inhibition/excitation balance, epigenetic factors (Fig. 3). Application of paradigms akin to EE may open the way for new preventive or reparative intervention strategies, whereby stimulation of key molecular pathways involved in neural plasticity is obtained by using the potential of environmental stimulation, towards a graceful aging.

References

Aimone JB, Li Y, Lee SW et al. (2014) Regulation and function of adult neurogenesis: from genes to cognition. Physiol Rev. Oct;94(4):991-1026.

Angevaren M, Aufdemkampe G, Verhaar HJet al. (2008) Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. Cochrane Database Syst Rev CD005381.

Baker LD, Frank LL, Foster-Schubert K, et al. (2009) Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch Neurol* 67:71-79.

Baker LD, Bayer-Carter JL, Skinner J et al. (2012) High-intensity physical activity modulates diet effects on cerebrospinal amyloid-beta levels in normal aging and mild cognitive impairment. *J Alzheimers Dis* 28:137-146.

Berardi N, Braschi C, Capsoni S et al. (2007) Environmental enrichment delays the onset of memory deficits and reduces neuropathological hallmarks in a mouse model of Alzheimer-like neurodegeneration. *J Alzheimers Dis* 11:359-370.

Berchtold NC, Cribbs DH, Coleman PD et al. (2008) Gene expression changes in the course of normal brain aging are sexually dimorphic. *Proceedings of the National Academy of Sciences of the United States of America* 105:15605-15610.

Buchman AS, Boyle PA, Yu L, et al. (2012) Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology* 78:1323-1329.

Burke SN and Barnes CA. (2006) Neural plasticity in the ageing brain. *Nature reviews* 7:30-40.

Cabeza R, Anderson ND, Locantore JK et al. (2002) Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage*. Nov;17(3):1394-402

Carlson MC, Helms MJ, Steffens DC et al. (2008) Midlife activity predicts risk of dementia in older male twin pairs. *Alzheimers Dement* 4:324-331.

Chung CC, Pimentel D, Jor'dan AJ, et al. (2015). Inflammation-associated declines in cerebral vasoreactivity and cognition in type 2 diabetes. *Neurology*. Aug 4;85(5):450-8.

Crous-Bou M, Fung TT, Prescott J et al. (2014). Mediterranean diet and telomere length in Nurses' Health Study: population based cohort study. *BMJ.* Dec 2;349:g6674.

Dauncey MJ. (2014). Nutrition, the brain and cognitive decline: insights from epigenetics. *Eur J Clin Nutr.* Nov;68(11):1179-85.

Dominguez LJ, Barbagallo M. (2016). Dietary Approaches and Supplements in the Prevention of Cognitive Decline and Alzheimer's Disease. *Curr Pharm Des*.;22(6):688-700.

Erickson KI, Voss MW, Prakash RS, et al. (2011) Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences of the United States of America* 108:3017-3022.

Eskelinen MH, Ngandu T, Tuomilehto J, et al. (2011) Midlife healthy-diet index and late-life dementia and Alzheimer's disease. *Dement Geriatr Cogn Disord Extra* 1(1):103–112.

Fabel K, Wolf SA, Ehninger D, et al. (2009) Additive effects of physical exercise and environmental enrichment on adult hippocampal neurogenesis in mice. *Front Neurosci* 3: 50.

Fiatarone Singh MA, Gates N, Saigal N, et al. (2014) The Study of Mental and Resistance Training (SMART) study—resistance training and/or cognitive training in mild cognitive impairment: a randomized, double-blind, double-sham controlled trial. J Am Med Dir Assoc. Dec;15(12):873-80.

Fratiglioni L, Paillard-Borg S, and Winblad B. (2004) An active and socially integrated lifestyle in late life might protect against dementia. *Lancet neurology* 3:343-353.

Gates NJ, Sachdev P. (2014) Is Cognitive Training an Effective Treatment for Preclinical and Early Alzheimer's Disease? J Alzheimers Dis. Aug 28.

Holden HM, and Gilbert PE. (2012) Less efficient pattern separation may contribute to age-related spatial memory deficits. *Front Aging Neurosci* 4:9.

Katzman R. (1993) Education and the prevalence of dementia and Alzheimer's disease. *Neurology* 43:13-20.

Kempermann G, Gast D, and Gage FH. (2002) Neuroplasticity in old age: sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. *Ann Neurol* 52:135-143.

Kempermann G, Fabel K, Ehninger D, et al. (2010) Why and how physical activity promotes experience-induced brain plasticity. *Front Neurosci* 4:189.

Kramer AF, and Erickson KI. (2007) Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function. *Trends Cogn Sci* 11:342-348.

Landau SM, Marks SM, Mormino EC, et al. (2012) Association of Lifetime Cognitive Engagement and Low beta-Amyloid Deposition. *Arch Neurol*. 69:623-629

Laurin D, Verreault R, Lindsay J, et al. (2001) Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol* 58:498-504.

Lazarov O, Robinson J, Tang YP, et al. (2005) Environmental enrichment reduces Abeta levels and amyloid deposition in transgenic mice. *Cell* 120:701-713.

Li S, Jin M, Zhang D, et al. (2013) Environmental Novelty Activates beta2-Adrenergic Signaling to Prevent the Impairment of Hippocampal LTP by Abeta Oligomers. *Neuron* 77:929-941.

Mainardi M, Di Garbo A, Caleo M, et al. (2014) Environmental enrichment strengthens corticocortical interactions and reduces amyloid-β oligomers in aged mice. Front Aging Neurosci. Jan 23;6:1.

Martínez-Lapiscina EH, Clavero P, Toledo E et al. (2013). Virgin olive oil supplementation and long-term cognition: the PREDIMED-NAVARRA randomized, trial. *J Nutr Health Aging.;*17(6):544-52.

Mayford M, Siegelbaum SA, and Kandel ER. (2012) Synapses and memory storage. Cold Spring Harb Perspect Biol 4.

Ngandu T, Lehtisalo J, Solomon A, et al. (2015). A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. Mar 11. pii:S0140-6736(15)60461-5.

Nithianantharajah J, and Hannan AJ. (2009) The neurobiology of brain and cognitive reserve: mental and physical activity as modulators of brain disorders. *Prog Neurobiol* 89:369-382.

Norton S, Matthews FE, Barnes DE, et al. (2014) Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol* 13:788–94.,

Ohman H1, Savikko N, Strandberg TE et al. (2014) Effect of Physical Exercise on Cognitive Performance in Older Adults with Mild Cognitive Impairment or Dementia: A Systematic Review. Dement Geriatr Cogn Disord. Aug 21;38(5-6):347-365.

Owen AM, Hampshire A, Grahn JAet al. (2010) Putting brain training to the test. *Nature* 465:775-778.

Paillard-Borg S, Fratiglioni L, Xu W et al. (2012) An active lifestyle postpones dementia onset by more than one year in very old adults. *J Alzheimers Dis* 31:835-842.

Park DC and Reuter-Lorenz P. (2009) The adaptive brain: aging and neurocognitive scaffolding. Annu Rev Psychol 60:173-196.

Peleg S, Sananbenesi F, Zovoilis A et al. (2010) Altered histone acetylation is associated with age-dependent memory impairment in mice. *Science (New York, NY* 328:753-756.

Petersen RC. (2004) Mild cognitive impairment as a diagnostic entity. *J Intern Med* 256:183-194.

Podewils LJ, Guallar E, Kuller LH et al. (2005) Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. *Am J Epidemiol* 161:639-651.

Reitz, C., Brayne, C. and Mayeux, R. (2001). Epidemiology of Alzheimer disease. *Nat Rev Neurol.* 2011 Mar; 7(3):137–152

Safouris A, Tsivgoulis G, Sergentanis TN et al. (2015) Mediterranean Diet and Risk of Dementia. *Curr Alzheimer Res.*12(8):736-44.

Sale A, Berardi N, Maffei L. (2014) Environment and brain plasticity: towards an endogenous pharmacotherapy. Physiol Rev. Jan;94(1):189-234).

Shankar GM, Li S, Mehta TH et al. (2008) Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nature medicine* 14:837-842.

Small SA, Schobel SA, Buxton RB et al. (2011) A pathophysiological framework of hippocampal dysfunction in ageing and disease. Nat Rev Neurosci. Sep 7;12(10):585-601.

Spalding KL, Bergmann O, Alkass K et al. (2013) Dynamics of hippocampal neurogenesis in adult humans. Cell. Jun 6;153(6):1219-27.

Sperling RA, Karlawish J, Johnson KA. (2013) Preclinical Alzheimer disease-the challenges ahead. Nat Rev Neurol. Jan;9(1):54-8.

Stern Y. (2009) Cognitive reserve. *Neuropsychologia* 47:2015-2028.

Valenzuela M, and Sachdev P. (2009) Can cognitive exercise prevent the onset of dementia? Systematic review of randomized clinical trials with longitudinal follow-up. *Am J Geriatr Psychiatry* 17:179-187.

Valenzuela MJ, and Sachdev P. (2006a) Brain reserve and cognitive decline: a non-parametric systematic review. *Psychol Med* 36:1065-1073.

Valenzuela MJ, and Sachdev P. (2006b) Brain reserve and dementia: a systematic review. *Psychol Med* 36:441-454.

Valls-Pedret C, Lamuela-Raventós RM, Medina-Remón A et al. (2012). Polyphenol-rich foods in the Mediterranean diet are associated with better cognitive function in elderly subjects at high cardiovascular risk. *J Alzheimers Dis*.;29(4):773-82.

Wang et al., (2015) Effects of vascular risk factors and APOE e4 on white matter integrity and cognitive decline. Neurology 84:1128–1135

Weuve J, Kang JH, Manson JE et al. (2004) Physical activity, including walking, and cognitive function in older women. *Jama* 292: 1454-1461.

Yaffe K, Fiocco AJ, Lindquist K et al. (2009) Predictors of maintaining cognitive function in older adults: the Health ABC study. *Neurology* 72: 2029-2035.

Zlokovic BV (2011) Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci* 12: 723-738.

Major modifiable Risk factors for Alzheimer's Disease
Diabetes mellitus
Midlife hyperthension
Midlife obesity
Physical inactivity
Depression
Smoking
Low education

Recent evidence suggest that reducing the prevalence of each of the risk factors listed on the left by 10% or 20% per decade would potentially reduce the worldwide prevalence of Alzheimer's disease in 2050 by between 8.8 million and 16.2 million cases. Of the seven risk factors, the largest proportion of cases of Alzheimer's disease in the USA, Europe, and the UK could be attributed to physical inactivity (Norton et al., 2014).

Table 1: Major factors associated with risk for developing Alzheimer disease with age which can be modified by preventive interventions (source: Reitz et al., 2011; Norton et al., 2014). In bold those which could be modified even in mid and late life through public health interventions. While low education attainments cannot be modified in old people, ample literature, discussed later in the Chapter, suggests that being engaged in cognitively stimulating activity is a protective factor, hence we might consider the inclusion of low cognitive activity in the list of risk factors modifiable even in mid and late life.

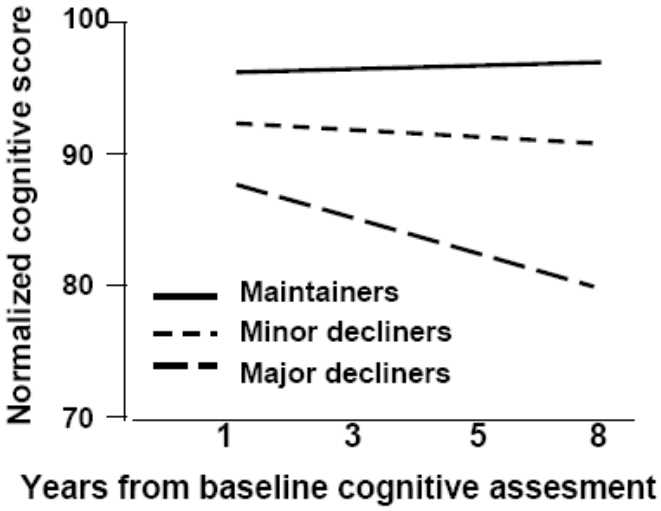

Fig. 1. Yaffe et al., 2009, followed the time-course of cognitive status of 2509 healthy elders enrolled in a prospective study for 7 years. Participants were classified as cognitive maintainers, minor decliners or major decliners according to the slope of the curve describing cognitive score change with time. Significant predictors of being a maintainer were age, having a high school education level or greater and a ninth grade literacy level or greater, engaging in weekly moderate to vigorous exercise, and not smoking at baseline.

Adapted from Yaffe et al., 2009

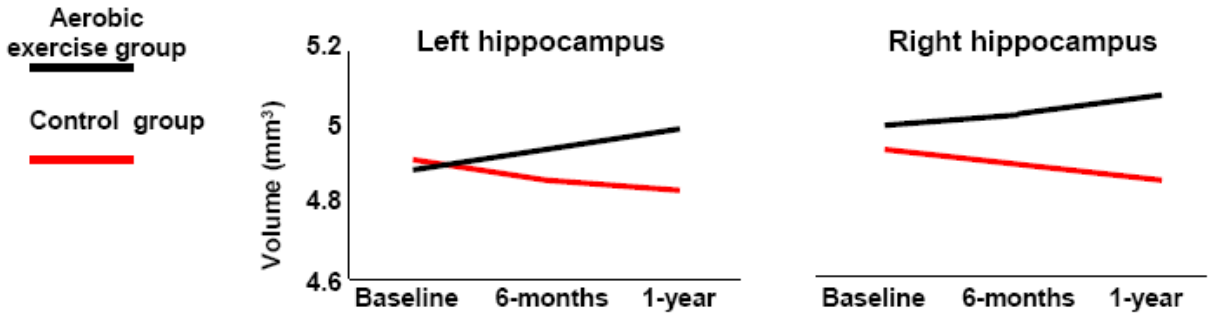

Fig. 2. Graphs demonstrating an increase in hippocampus volume for the aerobic exercise group and a decrease in volume for the stretching control group. The Time × Group interaction was significant ($P < 0.001$) for both left and right regions.

Modified from Erickson et al., 2011

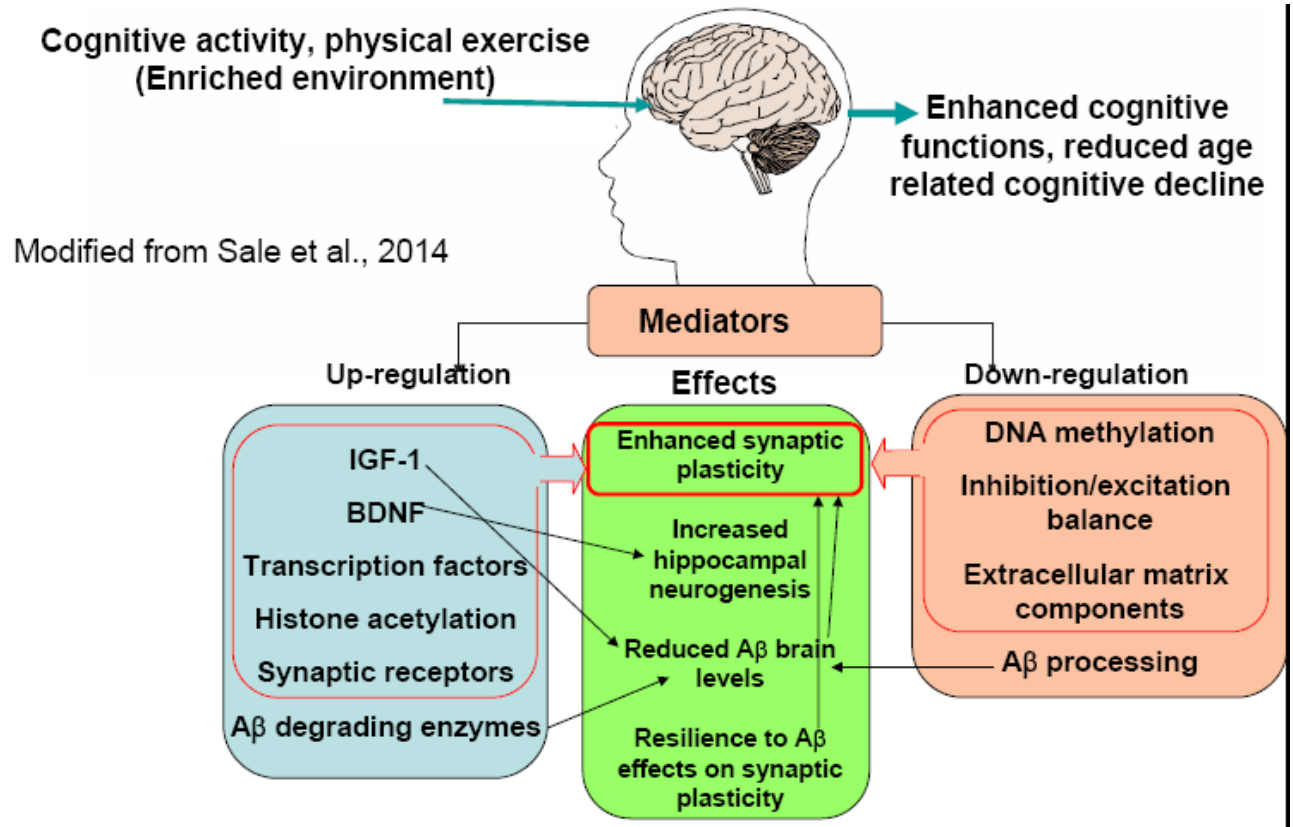

Fig. 3. The effects of Cognitive activity and physical exercise, key components of an Enriched Environment, on age related cognitive decline are mediated by several well-established key molecular factors. We have divided the factors through which EE acts into those that are upregulated and those that are downregulated. All factors within light red boxes enhance synaptic plasticity. In addition, BDNF increases hIppocampal neurogenesis and IGF-1 contributes to reduce Aβ levels. Reduced Aβ levels and resilience to Aβ effects further contribute to increase synaptic plasticity.