Rethinking the reserve with a translational approach: novel ideas on the construct and the interventions

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Abstract

The concept of *brain, cognitive,* and *neural reserves* has been introduced to account for the apparent discrepancies between neurological damage and clinical manifestations. However, these ideas are yet theoretical suggestions that are not completely assimilated in the clinical routine. The mechanisms of the reserves have been extensively studied in the neurodegenerative pathologies, first of all the Alzheimer's disease. Both human and animal studies addressed this topic by following two parallel pathways. Specific aim of the present review is to attempt to combine the suggestions derived from the two different research fields to deepen the knowledge about reserves. In fact, the achievement of a comprehensive theoretical framework on reserve mechanisms is an essential step to propose well-timed interventions tailored on the clinical characteristics of patients. The present review highlights the importance of addressing three main aspects: the definition of reserve proxy measures, the interaction between reserve level and therapeutic interventions, and the specific time-window of reserve efficacy.

Key-words: Reserve mechanisms; human studies; animal studies; Alzheimer's disease; MRI; environmental enrichment.

INTRODUCTION

In Alzheimer's disease (AD) [1], there is not a clear correlation between neuropathology and cognitive decline [2, 3]. Indeed, patients with an apparent same level of neurological damage (e.g. hippocampal atrophy, global grey matter atrophy, etc.) can show different level of cognitive impairment. Several years ago, the "reserve" concept [2, 3] has been introduced to account for this contradiction.

Brain reserve (BR) is related to the quantitative aspects of the brain (e.g. number of neurons/synapses, brain volumetrics) that may account for differences in the cognitive, behavioural and functional decline observed in patients [4]. Classical studies of Katzman et al. [5] and Mortimer [6] revealed that patients with larger brains were less affected by dementia, or showed a lower level of cognitive decline. The BR implies that a larger brain can support more neurological damage before it shows clinical and cognitive decline. It is likely that a "clinical threshold" has to be achieved before the appearance of clinical symptoms [4].

Conversely, the cognitive reserve (CR) refers to the differences in cognitive processing, and it is related to the lifetime physical, intellectual and social activities [4]. The CR implies that the brain actively copes with neurological damages by using compensatory mechanisms or some still available cognitive abilities (such as memory, executive functions or general intellectual abilities) [3, 7, 8].

BR and CR concepts have been extensively studied both in humans and in animal models. Specifically, Stern and co-workers [9] addressed CR in a study involving patients with AD and subjects without AD symptomatology. The authors showed that individuals with greater reserves are able to tolerate AD pathology better than those with a lower level of CR. As a consequence, in subjects with high reserve the clinical manifestation of AD results to be delayed, although their cognitive decline is faster after the clinical diagnosis. A classical *post-mortem* study showed that CR is more able than BR to resist to AD neuropathological process

[6]. However, more recently it is becoming clear that the CR depends on the efficiency of neural activity in terms of brain network functioning [4, 8], which in turn is due to cognitive, social and physical activities experienced during lifespan. Therefore, the integrity of functional brain networks, rather than on the brain structure seems to be more important to explain the individual differences in tolerating neurodegeneration. More recently, to explain this issue the "neural reserve" (NR) hypothesis has been proposed [4, 10]. NR is a concept related to the efficiency of neural circuiting and to the ability to process information. Nevertheless, NR may provide the neural basis of CR, focalising the attention on brain networks functioning.

The human studies that investigate the effects of experience on cognitive functions are paralleled by animal studies mainly based on the effects of environmental enrichment (EE). An enriched environment is defined as a combination of complex inanimate and social stimulations [11]. Classically, for rodents it is realized by rearing the animals in cages wider and in groups larger than those generally used. The cages in which the animals are reared contain running wheels and numerous stimulating objects regularly changed and moved, to encourage exploration and physical activity [12-14]. The enhanced sensorimotor and cognitive stimulation has a valid control condition in the standard rearing, according to which laboratory rodents are usually housed in small groups (one or two rats; three or four mice) and in standard-size cages provided with bedding and *ad libitum* food and water [15].

The experimental paradigm of the EE provides a useful and controllable means to investigate the mechanisms underlying structural and functional effects of experience. EE represents a good experimental model for the human lifelong experience that provokes the development of BR, CR, and NR [13, 16]. Anyway, it can be also a model for any experiential treatment provided to patients after the occurrence of damage [17]. Moreover, EE allows overcoming some limitations of the human studies. Studying the effects of the enhanced experience in human individuals entails difficulties in comparing subjects in terms of the outcomes of well-

defined factors, since they are basically characterized by different genetic patterns and multifarious life experiences. Moreover, directly investigating a number of brain cellular and molecular indices of reserve in living human subjects is not yet possible. By using animals, EE model ensures comparable background before the exposure to the enhanced stimulation and allows the analysis of a large number of cellular and molecular indexes in the brain [13].

In summary, in the last years several research papers and reviews appeared to address the "reserve question" by separately focusing on humans or animals. The present review specifically aims to combine together the knowledge derived from both clinical and basic research on reserves to obtain a more comprehensive theoretical framework.

LIFESTYLE ENRICHMENT INDEXES

In humans

Clinical research established that reserves can be built during life through enriching experiences [4, 18]. Such enriching experiences regard all the aspects of the individual's life. In humans, the formal education (expressed as years of schooling), occupational attainment, leisure activities, and cognitive performances have been traditionally considered the most important enrichment factors, and, as a consequence, they have been regarded as proxy measures of CR [4, 19]. An evolution in the CR proxies' measures is recently emerged. Currently, static and dynamic measures [20-23] have been postulated (see Table 1 panel A).

[Insert table 1 around here]

The years of schooling, occupational attainment (number of years and type of occupation), pre-morbid IQ and leisure activities (cognitive/social/physical) pursued during childhood-adolescence and early adulthood have been considered static measures. Indeed, these measures cannot directly catch the cognitive changes at individual level.

In humans, schooling is usually considered the most relevant factor impacting on brain resilience [4, 24]. Indeed, schooling may induce an increase of synaptic density in the neocortex promoting neural connectivity [25, 26]. Moreover, schooling appears to be an important environmental factor to drive the engagement in further cognitively stimulating activities during the lifespan [27] and to delay the AD symptom onset [25]. Indeed, it is likely that individuals with higher educational level are interested in more stimulating mental activities in the course of their life, and it may induce structural and functional brain changes and promote the brain resilience to neuronal damage. In addition, schooling can also be considered as a socialization process promoting more efficient learning strategies and responses to cognitive requirements [28]. More recently, by using a multistate survival analysis on six different longitudinal cohorts of patients, Robitaille and co-workers (2018) [29] showed a delay in cognitive decline due to schooling. Interestingly, the Authors reported a reduced risk of transition from normal level of cognitive functioning to mild level of cognitive decline for the individuals with high education, while no effect was reported in the transition from mild to moderate/severe level of cognitive decline [29].

Interestingly, several studies showed a decreased AD risk in subjects employed in highly mentally demanding occupation [9, 30, 31] and an increased risk of developing AD in individuals without a lifetime occupation [32]. It is possible to suggest that individuals such as company's managers, teachers, etc., who are involved in highly demanding works, may develop more flexible/efficient cognitive strategies to be spent when neurodegeneration occurs.

Recently, Soldan and co-workers [33] reviewed a large number of papers focalised on the longitudinal effects of CR, considered in terms of educational and occupational attainment. The Authors [33] hypothesised that CR may modify the rate of cognitive decline and the risk to dementia progression using four different pathways. In the first one, the CR should act directly without any interaction with other biomarkers (e.g., brain atrophy, brain or CSF levels of β-

amyloid/tau, ApoE genotype, etc.); through the second one, CR should moderate the relationship between biomarkers and clinical outcomes; through the third one, CR should act directly on biomarker levels modifying the amount of accumulation on neuropathology; and finally, through the fourth mechanism CR should change the relationship between demographical and genetics features and clinical outcomes [33]. From this revision of the literature it becomes clearer that CR considered in terms of static measures implies many complex factors directly or not interconnected each other. Clarifying the reciprocal relationships among factors seems to be essential.

However, the static measures do not assess directly patient's cognitive changes [20] and thus they provide an imprecise and scarcely sensitive estimate. To bypass this issue the concept of dynamic CR has been recently introduced [20-22]. In particular, some cognitive performances such as memory, executive functions and general cognitive abilities (see Table 1, panel A) reflect directly the cognitive functioning at a specific time-point, and therefore they can be considered dynamic indexes of CR [20-23]. More clearly, the patient's cognitive abilities that are measured in a specific moment can be considered as the residual cognitive abilities after statistically removing the effects of several incidental factors (such as demographic and brain features) [20-23]. However, the role of the residual cognitive abilities in withstanding dementia remains still unclear. It is possible to suppose that several cognitive abilities may counteract the onset of dementia.

Moreover, several activities have been considered in the literature as "reserve-builders" (Table 1, panel B). In particular, in several studies [4, 34-41], cognitive, social and physical activities pursued continuatively and intensely during the entire lifespan have been recognised as factors reducing the risk of AD. More recently, by using a comprehensive questionnaire investigating cognitive, social, physical and leisure activities, education years and type, and occupation years and type, we showed a higher AD risk in amnesic Mild Cognitive Impairment (a-MCI) patients

with low CR level [41]. In addition, this study revealed that a-MCI patients with high CR and high scores in Mini Mental State Examination (MMSE), a test evaluating the level of general cognitive efficiency, remained free of AD symptomatology longer than a-MCI patients with high CR but low baseline MMSE scores. Remarkably, Valenzuela and co-workers [38] highlighted that the combination of different CR measures, instead of single CR measure is more effective in predicting AD risk. Among such cognitive abilities, the role of bilingualism should be better investigated. Indeed, individuals lifelong speaking two or more languages may be considered as living in a cognitively enriched environment. Several studies described the bilingualism as a protective factor against dementia onset [42-44]. More recently, the contribution of bilingualism to the enhancement of CR and the relationship between bilingualism and structural brain changes have been described [45]. In particular, in accordance with "reserve paradigm", it has been reported that bilingual patients with the same level of clinical AD symptoms significantly accumulated more atrophy of temporal lobe than monolingual patients [46]. Furthermore, bilingual and monolingual healthy elderly showed the same level of cognitive functioning, but bilinguals showed more microstructural damage than monolinguals in the white matter tracts, typically affected in AD patients [47]. In summary, the studies on bilingualism support the role of an "enriched language development" as reserve-promoting factor.

In the literature, there is an increasing interest for the effect of the "continuing education" on dementia prevention [48]. Continuing education comprises all structured learning activities provided to adults by formal and non-formal educational institutions [48]. It can be considered as a more organised set of cognitive tasks than cognitive leisure activities. It is possible to suppose that the continuing education may act as reserve-promoting factor, delaying the onset of dementia. However, it still remains unclear whether continuing education may prevent

dementia more than cognitive leisure activity. Further studies are needed to address this important issue.

Finally, not only cognitive/social/physical activities but also healthy life style (characterised by pursuing Mediterranean diet, drinking responsibly, limiting caffeine and nicotine, avoiding big-meals, maintaining sleep hygiene, etc.,) have been recognised as reserve-promoting factors [49].

As previously affirmed, the assessment of reserves in humans presents some limitations: i) the proxy measures used are only indirect indexes of BR and CR; ii) the measures considered as indexes cannot be experimentally manipulated by the examiner. The animal models allow overcoming, at least partially, these limitations.

In animals

A quite different framework has to be described for the reserve indexes considered in animal studies in comparison to the ones reported for humans. Namely, in the animal studies, the lifelong experiences considered "reserve-builders" in humans [41] become factors that may be actively manipulated by using the EE paradigm [13, 14, 50]. In applying this protocol, the researcher decides what variables to manipulate, and to what extent it occurs. Thus, the increased social interactions provided by the rearing in large groups parallel the amplified human social factors. The complex and frequently changing environment the animals are exposed to parallels the enriched human cognitive factors. Finally, the physical activity to explore the large cages and always-novel objects, the motor activity in the running wheels, the controlled diet, etc. parallel the human physical factor (Fig. 1). It is noteworthy that in EE paradigm the researcher may fix the age at which the animals begin to be enriched and the duration of such an enrichment in order to mimic differently lasting life experiences that in humans can occur in the early, adult, and even old ages [51]. Moreover, the researcher can

establish to enhance only one factor or different factors among those above described, given that it is possible to shape the complex environment to stimulate a single sensory channel or more than one [52, 53].

Animal studies mainly utilize two reserve measures, as the BR and CR [54]. While the BR is investigated by analysing molecular and supra-molecular biological factors [14], the CR is investigated by analysing the performance of the animals in a great number of cognitive tasks [13]. Anyway, inferences on the NR can be formulated by analysing the brain structural changes, such as neurogenesis, gliogenesis, angiogenesis, synaptogenesis, etc. [14, 55, 56]. In theory, these measures could be also used as dynamic reserve indexes *per se* of which to analyse the effects, just like in humans. However, since in the case of animal studies the experiential factors that build the reserves are established and controlled by the researcher, the subsequent identification of dynamic reserve indexes is less required. Thus, in animal designs the reserve measures are generally analysed as dependent variables. In any case, the analysis of the correlation between cerebral and cognitive measures of reserve could provide useful information on the biological mechanisms directly associated with successful performance.

[Please insert the Figure 1 in this point.]

STRUCTURAL AND FUNCTIONAL EFFECTS OF RESERVES

In humans

Behavioural studies investigating different aspects of reserves have shown that the combination of different factors may reduce the risk to develop dementia [38, 41, 57]. Specifically, Serra et al. [41] showed that a comprehensive CR questionnaire measuring leisure activities (cognitive, social and physical activities), years and type of formal education and occupational attainment was able to differentiate patients with high or low risk to develop AD. More recently, Cheng [58] highlighted the role of cognitive and physical activity in preventing dementia. In particular,

aerobic exercise is associated with reduced age-related grey and white matter loss and the cognitive training for executive functions improves the prefrontal network efficiency [58].

Reserve promoting factors cannot act alone, but they interact with several other biological factors. Significant interactions among promoting factors as levels of CR, CSF-biomarkers (amyloid-β and tau levels), ApoE status, and brain atrophy and risk to develop the clinical symptoms of AD as final outcome [59-62, 41] have been shown. Some procedures used routinely to diagnose AD in clinical setting are considered sensitive but also highly invasive (e.g. the use of CSF biomarkers). Conversely, quantitative magnetic resonance imaging (MRI) allows investigating *in vivo* and non-invasively the pathological processes underlying AD. In particular, metabolic [63-66], structural and functional MRI studies have provided *in vivo* evidence of BR and CR. For the purpose of the present review we focalised only on the structural and functional MRI studies. Structural MRI studies showed the relationship between CR levels and brain resilience. By using un-biased volumetric techniques, Serra and co-workers [60] showed in AD patients with high educational level (and high CR as a consequence) a significant grey matter (GM) atrophy in the entorhinal cortex and temporal pole, while AD patients with low CR level showed atrophy in the supramarginal gyrus, posterior cingulate cortex-PCC and precuneus. In addition, it is also shown in AD patients that education is able to counteract the effects both of hippocampal atrophy and of cerebrovascular diseases. Indeed, several studies [41, 67, 68] provided evidence that healthy elderly [68] and a-MCI and AD patients [41, 67] with high CR suffered from a severe white matter damage compared with those with low CR. Globally, in line with the reserve concept, these studies suggested that individuals with high CR need to accumulate more neuropathology to show a cognitive decline. However, the majority of studies focalised the impact of CR assessed by static measures on the brain. Conversely, Serra and co-workers [23] more recently investigated the impact of CR dynamic measures on brain structure. In particular, the Authors showed a significant association

between regional GM volumes and two measures of dynamic CR, one including the general cognitive efficiency scores (named the first latent variable) and one including memory score only (named dynamic CR index) in patients with a-MCI. We found volumetric reductions in the anterior cingulate cortex (ACC) and PCC, left hippocampus and parahippocampal gyrus associated with both dynamic CR measures. We hypothesised that these brain areas are likely involved both in memory and in the more general cognitive efficiency processes [23]. On the contrary, the finding that volumetric changes in the precuneus were associated with the first latent variable sustains the precuneus involvement in the general cognitive abilities [23]. Instead, the dynamic CR index was found associated with the atrophy of fronto-temporal brain regions (including the ACC). All these regions are considered involved in higher-level cognitive functions (as control and inhibition mechanisms) confirming the importance of the frontal cortices for an efficacious cognitive processing [23].

Several studies have addressed the relationship between CR and brain networks. Brain network and functional connectivity can be considered the most reliable representations of NR *in vivo*. A modulation of functional connectivity of the PCC has been recently found to be related to the CR levels in a-MCI patients [62]. PCC is a critical brain area for AD conversion, and functional disconnection between PCC and temporal lobe structures seems to be essential in AD conversion [62]. Bozzali and co-workers [62] sustained that the CR acts mainly through neural compensation mechanisms.

Very recently, by using the graph theory approach that allows a whole brain network investigation without an *a-priori* hypothesis [69, 70], Serra and co-workers [26] showed functional connectivity changes only in a-MCI patients categorized according to their CR level. Only a-MCI patients and neither healthy elderly nor AD patients showed modulation (seen as increase or decrease) of functional connectivity in different brain networks, supporting the assumption that NR is sustained by efficient neural networks. In particular, a recent review of

13 fMRI studies [71] reported that different brain networks are involved in NR and in neural compensation. Specifically, medial temporal regions and ACC and PCC are likely associated with NR, while frontal regions and dorsal attentional network are likely associated with neural compensation. Neural compensation is observed in the advanced stages of disease, while NR is likely observed in the early stages [71].

In animals

Several studies investigated the effects of lifelong exposure to EE in animal models of physiological or pathological aging. On the whole, these researches indicate that the exposure to complex stimulations provides the animals with CR and BR leading to efficient coping with aging [53].

As for CR, evidence indicates that rodents exposed to EE from weaning onwards or during adulthood show better performance in a lot of learning and memory tasks when aged [72, 73]. Mice reared in an enriched environment from weaning to twelve [74] or twenty [75] months of age showed increased learning and memory abilities in spatial and episodic-like memory tasks in comparison to control aged animals. Furthermore, in a couple of studies based on a model of senescence-accelerated prone mice (SAMP8), animals reared in an enriched environment from weaning to three months of age showed superior performance in comparison to controls in tasks requiring spatial and visual recognition memory [76, 77]. Also, mice and rats reared in enriched environment from young adulthood (two or three months of age) showed in aging better performance in spatial and visual recognition memory tasks in comparison to control animals [78, 79].

As for the BR, several studies indicate that the early exposure to EE provokes plastic modifications in the brain (both at molecular and supra-molecular levels) that support a successful coping with aging-related cognitive decline [14]. In rodent models of physiological

aging it has been demonstrated that the exposure to EE from young adulthood (one/three months of age) to aging (twelve/twenty-four months of age) is able to prevent the age-related damage to cholinergic system [79, 80], to increase hippocampal neurogenesis and volume [74, 78], to potentiate brain synaptic plasticity [74, 78], and to increase brain levels of neurotrophic factors [79]. Also, in the SAMP8 model the EE decreases neurodegeneration markers [76] and prevents epigenetic changes that promote oxidative stress and inflammation [77].

Notably, the beneficial effects of EE have been demonstrated also in models of pathological aging, such as AD. Studies on transgenic and non-transgenic models of AD reported that previous exposure to EE is able to diminish the cognitive decline and the brain pathological alterations [81]. Specifically, in transgenic murine models the exposure to EE before the appearance of symptoms provokes amelioration in spatial learning and memory tasks and in visual recognition memory performance [82, 83]. Similar results were obtained in a rat model of basal forebrain cholinergic damage, which mimics the early brain cholinergic dysfunction present in AD [84]. In this model, the animals exposed to EE from weaning (and lesioned after about three months) showed superior cognitive performance when compared to standard-reared lesioned rats. The improved behavioural performances were associated to normalization of the lesion-induced alteration of the neuronal morphology [84]. In fact, to compensate the cholinergic deafferentation the standard-reared lesioned rats showed a rearrangement of dendritic spine distribution in the neocortical pyramidal neurons, which was absent in the enriched-lesioned rats. Moreover, the increased cortical dendritic spine density exhibited by the enriched unlesioned rats was fully maintained in the enriched-lesioned animals. Presumably, the network connectivity potentiated by the exposure to EE was maintained also in the presence of the damage and allowed for a preserved cognitive performance. Accordingly, research on murine transgenic models demonstrated that the early exposure to EE is able to reduce AD

markers [82], to increase neurogenesis [85-87] and angiogenesis [88], and to augment neurotrophin levels in the brain [89].

NEUROREHABILITATION AND RESERVES

In humans

It is always more evident that healthy lifestyles beneficially impact on brain networks, but it remains to be demonstrated whether interventions later in life can modulate brain resilience.

In fact, an active cognitive stimulation can modulate brain changes, promote learning, and reinforce the neuronal connections, providing alternative cognitive strategies or recruiting different neural networks [4]. Several studies investigated cognitive rehabilitation in a-MCI and AD patients [90], but there are no studies directly investigating the relationship with the reserves. Only a study showed an increase in cognitive efficiency after training in a-MCI and AD patients with low CR level [91]. This result is in line with the "reserve paradigm": patients with high CR accumulate more AD neuropathology and therefore can benefit less of cognitive training in comparison to patients with low CR. A recent study on a group of patients at risk of dementia reported that the association between an active lifestyle and cognitive change over time was stronger than the one between short-term specific cognitive interventions and cognitive change over time [92].

While it is well known that physical exercise is able to prevent dementia in healthy subjects [93, 94], currently no studies investigated the efficacy of different levels of physical exercise in improving motor and/or cognitive outcome in patients with AD. As a consequence, the effects of CR on cognitive training, and their impact on the brain remain still under debate. Further studies assessing relationship between different CR levels and non-pharmacological treatments seem to be necessary and desirable in the immediate future.

In animals

EE paradigm can be used also to model cognitive and physical rehabilitation treatment applied to patients with evident symptoms of cognitive decline. Evidence on therapeutic effects of EE in aging rodents indicates the presence of a beneficial action on brain functionality [17, 72]. In eighteen month-aged rats, the exposure to six months of EE improved spatial learning performance. The functional amelioration was associated to increased hippocampal neurogenesis and synaptic plasticity, by up-regulating acetylation-associated events and epigenetic modulation of the *brain-derived neurotrophic factor* (*Bdnf*) gene [95]. Also, even the one-month exposure of twenty-two-month-old rats to EE induced significant amelioration in learning and memory performance, accompanied by enhancement of hippocampal LTP [93]. The exposure to only three weeks of EE was able to facilitate LTP as evaluated in hippocampal slices from twenty-one month-aged rats [96]. Finally, a two-month exposure to EE of nineteen month-aged rats potentiated gamma-aminobutyric acid (GABA)-ergic system [97].

Positive effects of the exposure to EE are reported also in models of AD. Arendash et al. [98] reported that the exposure of sixteen month-aged amyloid-β protein precursor (AβPP)sw transgenic mice to four months of EE resulted in a global improvement of cognitive functions. Paban et al. [99] found that in rats submitted to cholinergic depletion at three months of age, the post-lesional exposure to EE for one year induced amelioration in learning performance and decreased expression of genes involved in apoptosis and glial cell differentiation.

In conclusion, the experimental studies on EE can provide useful suggestions for the managing of potentiation and/or rehabilitation of cognitive functions in old subjects and/or patients. Firstly, it has been demonstrated that the effects of EE are different if the exposure is performed before or after the decline occurs. In twenty-four month-aged rats the preventive exposure to EE from young adulthood makes the successive (therapeutic) exposure not necessary for spatial memory maintenance. Instead, the therapeutic exposure is required to ameliorate the

performance of aged rats previously unexposed to EE [100]. Accordingly, it has been suggested that the effects of preventive (pre-lesional) and therapeutic (post-lesional) EE are mediated by distinct molecular pathways [101]. This evidence supports the idea that the rehabilitation of elderly patients with different levels of BR and CR should be based on tailored strategies. This idea is even strengthened by the evidence that different protocols of EE induce different effects [102]. In eleven month-old AβPP-23 mice Wolf et al. [103] demonstrated that the cognitive stimulation provided by nine months of EE induced improvement of spatial performance, up-regulation of hippocampal growth factors, and increment in hippocampal neurogenesis. Conversely, the only physical stimulation (motor activity on running wheels) did not change spatial performance and hippocampal neurogenesis, although it induced down-regulation of hippocampal and cortical growth factors. Similarly, Cortese et al. [93] demonstrated that while the exposure of twenty-two-month-aged rats to a procedure of complex EE induced amelioration in learning and memory and hippocampal LTP, the only social enrichment failed in supporting it.

THE TIME-WINDOW OF RESERVE ACTION

In humans

One of the most intriguing issues about the reserve effect is to address the existence of specific time-windows in which BR, CR or NR may preferentially act, although in humans the exact time-window of BR/CR action is hardly identifiable because of the variability in the trend of AD neuropathology. A study showed that CR acts mainly in the a-MCI stage, succeeding in postponing the decline to dementia of almost two years [41]. In this study CR was assessed in terms of global enrichment index using a devoted questionnaire, based on formal education, occupational attainment and leisure activities. The Authors showed that the CR level was differently distributed in a-MCI, AD and healthy subjects, and it not follows the Gaussian

distribution reinforcing the Stern's hypothesis [3, 4]. According to Stern [3, 4] the level of CR is not randomly distributed in a population, but it is related to neuro-pathological mechanisms. Therefore, it is possible that CR has no influence on cognitive performance of the yet healthy older adults as well as paradoxically during the most advanced stages of AD neuropathology. Instead, CR can play a protective role during the early stages of dementia. By using the graph theory [69, 70], Serra and co-workers [26] showed connectivity differences only in a-MCI patients with high or low CR, confirming the hypothesis that CR impacts on neurodegenerative processes only in the early phase of AD. More recently, this hypothesis has been confirmed also by other studies highlighting a specific disease stage for the CR action [29, 104].

In animals

Animal studies emphasized that EE effects are age-dependent and not equally evident at different ages [105-110], even though some evidence is also present in favour of similar efficacy in young and aged rodents [111]. Studies on transgenic murine models of AD suggest that the beneficial effects of EE are more evident at a milder stage of the pathology [112, 113]. In addition, animal studies suggest that the effects of the exposure to EE are long-lasting [114-116], even though the exact extent of the efficacy duration has yet to be defined. Longitudinal studies on physiological and pathological aging models could provide insights on the action time-window of reserves and aid in identifying the ideal period to efficiently treat patients with high levels of BR and CR, before the cerebral damage (so far compensated) becomes devastating.

CONCLUSIONS

Since BR and CR might remain indeterminate concepts with limited usefulness in clinical settings, it appears mandatory the identification of sensitive and specific proxy measures of

reserves. A differentiation between static and dynamic CR measures has been recently proposed in the literature on human studies. Animal studies may contribute to the evaluation of the effect of well-defined "reserve-builders" providing a high-level experimental control.

The present review of the literature shows the necessity of extensive scientific evidence on the interaction between the different typologies/levels of reserve and the cognitive and/or non-cognitive therapeutic interventions. Animal studies offer the ideal tool to systematically address this issue through the manipulation of the involved variables and the highly controlled experimental designs.

The requirement of identifying the time-window of reserve efficacy arises to propose well-timed rehabilitation/potentiation interventions tailored on the clinical characteristics of patients with different reserve levels. Also in this case, animal models allow designing experiments specifically aimed to analysed well-defined phases of reserve efficacy.

In conclusion, the integration between clinical and animal investigation offers a unique opportunity to disentangle the multiple features of reserve concept, each with its own specific peculiarities (Fig. 2). Future studies based on such an integrated approach may enlighten the controversial issue of reserve implication in coping with the cognitive decline in the presence of neurodegeneration.

[Please insert the Figure 2 in this point.]

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Declarations of interest

The authors have no conflict of interest to report.

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Captions

Figure 1. Lifestyle enrichment indexes in humans and in animals. The panel represents the parallelism between the lifestyle enrichment indexes that are classically considered in humans (on the left) and the environmental enrichment variables that are manipulated in animal models (on the right).

Figure 2. Summary of the review. The panel represents the main topics that are addressed in the review. In green the main aspects arising from the "mash-up" between human (in red) and animal (in blue) studies are depicted. Abbreviations: BR: brain reserve; CR: cognitive reserve; NR: neural reserve.

Table 1. Cognitive reserve indexes and promoting factors

A) CR Proxy measures		
	Static indices	**Dynamic indices**
	Schooling (years and type of formal education)	Memory
	Occupational attainment (years and type)	Executive functions
	Pre-morbid IQ	General cognitive abilities
B) Reserve-builders		
Cognitive leisure activities	Reading books, magazines, newspapers; painting; poetry, sculpture, song writing; attending lectures or organized discussions	
Social leisure activities	Playing structured games; participating in hobbies; volunteering	
Physical leisure activities	Running, trekking, swimming, biking, skiing, dancing, yoga	
Other promoting factors	Bilingualism; continuing education; healthy life styles	

See text for further details.

Figure 1

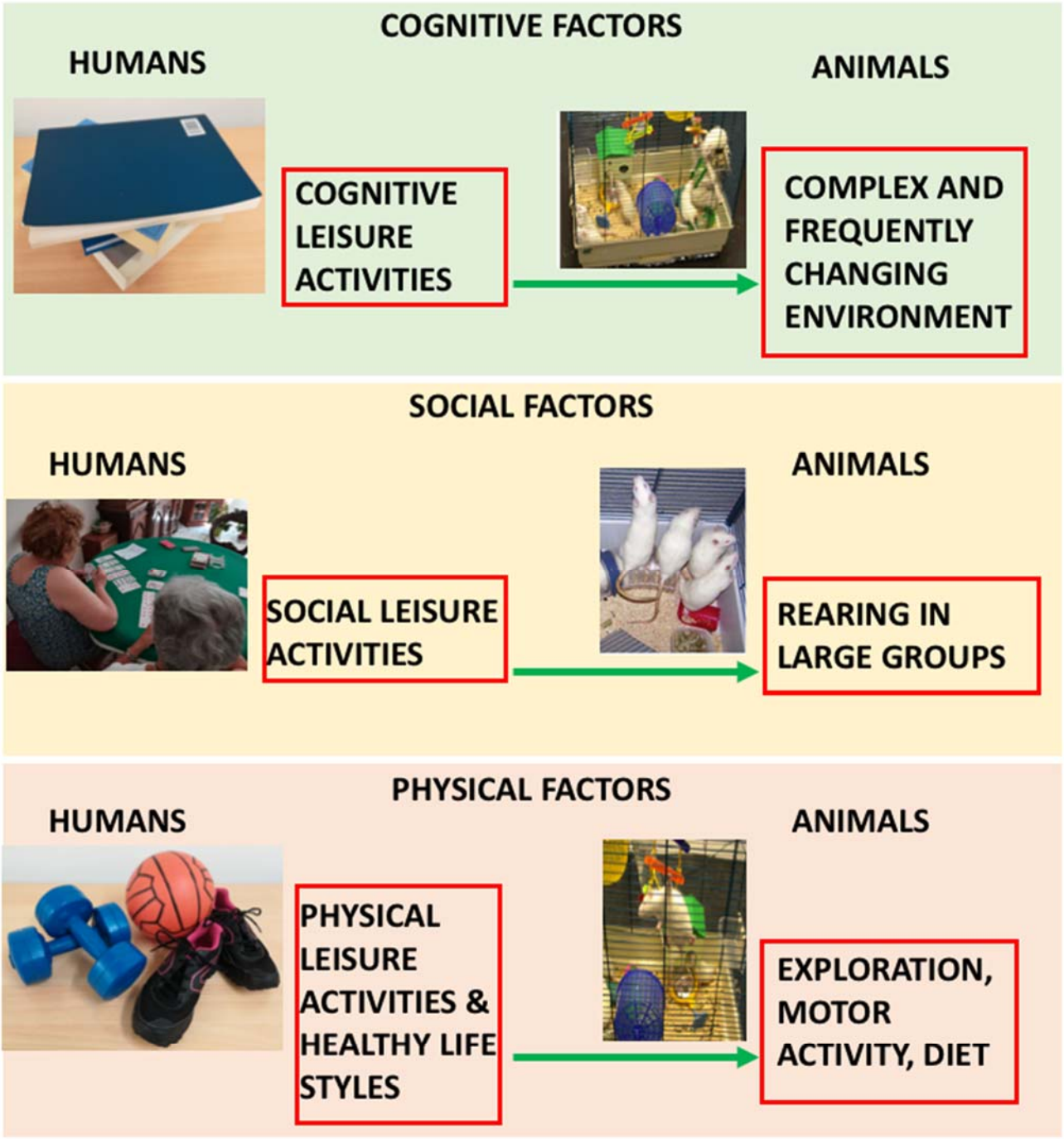
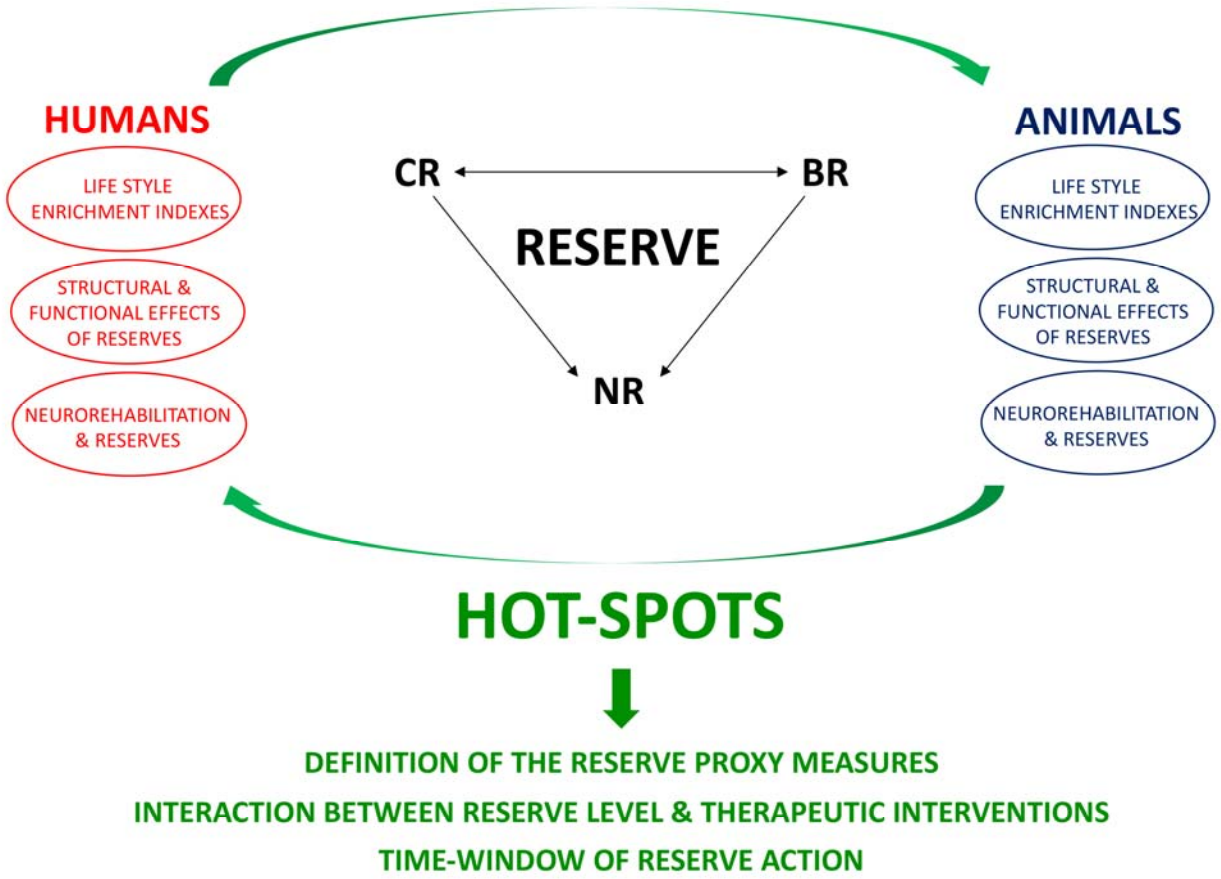

COGNITIVE FACTORS
HUMANS
ANIMALS
COGNITIVE LEISURE ACTIVITIES
COMPLEX AND FREQUENTLY CHANGING ENVIRONMENT
SOCIAL FACTORS
HUMANS
ANIMALS
SOCIAL LEISURE ACTIVITIES
REARING IN LARGE GROUPS
PHYSICAL FACTORS
HUMANS
ANIMALS
PHYSICAL LEISURE ACTIVITIES & HEALTHY LIFE STYLES
EXPLORATION, MOTOR ACTIVITY, DIET

Figure 2


HUMANS
LIFE STYLE ENRICHMENT INDEXES
STRUCTURAL & FUNCTIONAL EFFECTS OF RESERVES
NEUROREHABILITATION & RESERVES
CR
BR
RESERVE
NR
ANIMALS
LIFE STYLE ENRICHMENT INDEXES
STRUCTURAL & FUNCTIONAL EFFECTS OF RESERVES
NEUROREHABILITATION & RESERVES
HOT-SPOTS
DEFINITION OF THE RESERVE PROXY MEASURES
INTERACTION BETWEEN RESERVE LEVEL & THERAPEUTIC INTERVENTIONS
TIME-WINDOW OF RESERVE ACTION